JOURNAL OF ADOLESCENT AND YOUNG ADULT ONCOLOGY
Volume 2, Number 4, 2013

DOI: 10.1089/jayao.2013.0012

Original Article

Fifteen Years' Experience of the Brazilian Osteosarcoma Treatment Group (BOTG): A Contribution from an Emerging Country

Antonio Sergio Petrilli, MD, PhD,[1] Algemir Lunardi Brunetto, MD, PhD,[2] Monica dos Santos Cypriano, MD,[1] Alexandre Archanjo Ferraro, MD, PhD,[3] Carla Renata Pacheco Donato Macedo, MD,[1] Andreza Almeida Senerchia, MD,[1] Maria Teresa Almeida, MD,[4] Cecilia Maria da Costa, MD,[5] Daniel Lustosa, MD,[6] Maria Luiza Borsato, MD,[7] Luiz Mario Calheiros, MD,[8] Jose Henrique Silva Barreto, MD,[9] Sidnei Epelman, MD,[10] Eny Carvalho, MD,[11] Maria Teresa Seixas Alves, MD, PhD,[1] Marcelo de Toledo Petrilli, MD,[1] Valter Penna, MD, PhD,[12] Pedro Pericles, MD,[7] Olavo Pires de Camargo, MD, PhD,[3] and Reynaldo Jesus Garcia-Filho, MD, PhD,[1] on behalf of the Brazilian Osteosarcoma Treatment Group

Purpose: Little information is available regarding the tumor features, prognostic factors, and treatment results in children and adolescents and young adults (AYAs) with osteosarcoma diagnosed in developing countries. We reviewed the results of three observational cohorts of osteosarcoma patients treated in an emerging country.
Methods: A total of 604 patients below the age of 30 years with high-grade osteosarcoma were prospectively enrolled in the Brazilian Osteosarcoma Treatment Group (BOTG) studies III, IV, and V. Gender, age, time from onset of symptoms to diagnosis, primary tumor site, presence or absence of metastases at diagnosis, tumor size, type of surgery (limb-sparing or amputation), treatment protocol, and histological response were correlated with survival.
Results: The estimated 5-year overall survival and event-free survival (EFS) rates for the 553 eligible patients were 49% and 39% respectively; of the 390 non-metastatic patients included in the total, overall- and event-free survival were 59% and 48% respectively. Metastases at diagnosis, primary tumor site, type of surgery, and histological response were significant predictors of overall survival and EFS in univariate and multivariate analysis, whereas tumor size and treatment protocol lost prognostic significance in multivariate analysis.
Conclusion: We report on the outcome of three consecutive studies for the treatment of osteosarcoma carried out in Brazil over 15 years. Although the survival rates presented are below those reported in current literature, it represents the result of a favorable experience gathered from the national collaborative work.

Keywords: osteosarcoma, survival, prognostic factors, emerging country, cooperative group

Adjuvant and neoadjuvant chemotherapy introduced in the early 1970s have significantly improved long-term outcomes for patients with osteosarcoma, resulting in 5-year survival rates of 55–77% in most North American and European countries.[1–9] Nevertheless, 15–20% of newly diagnosed osteosarcoma patients present with overt metastatic disease, and the prognosis in these cases remains poor, with a 5-year survival rate of around 20%.[5,10,11]

Further, scarce information is available regarding the tumor features, prognostic factors, and treatment results of

[1]Instituto de Oncologia Pediátrica/GRAACC—Universidade Federal de São Paulo, São Paulo, Brazil.
[2]Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil.
[3]Universidade de São Paulo, São Paulo, Brazil.
[4]Instituto da Criança—Universidade de São Paulo, São Paulo, Brazil.
[5]Hospital do Câncer A. C. Camargo, São Paulo, Brazil.
[6]Hospital do Câncer do Ceará, Ceará, Brazil.
[7]Santa Casa de Misericórdia de São Paulo, São Paulo, Brazil.
[8]Sociedade Pernambucana de Combate ao Câncer, Pernambuco, Brazil.
[9]Sociedade de Oncologia da Bahia, Bahia, Brazil.
[10]Hospital Santa Marcelina de Sao Paulo, São Paulo, Brazil.
[11]Hospital Pediátrico Martagão Gesteira, Bahia, Brazil.
[12]Hospital do Câncer de Barretos, São Paulo, Brazil.

osteosarcoma in children and adolescents and young adults (AYAs) in developing countries.[10,12,13] This is particularly disturbing considering that 70% of the world's youth with cancer are in these countries, and their survival rates are predictably inferior to those in countries with advanced healthcare systems.[14]

Brazil is a country of 190 million people with important social and economic disparities, and 43% of its population younger than 24 years of age.[15,16] An estimated 350 new cases of osteosarcoma are diagnosed in Brazil each year. The Brazilian Osteosarcoma Treatment Group (BOTG) was created in the 1980s to study the epidemiology and clinical features of osteosarcoma in our population and to develop treatment strategies that took local conditions into consideration. Five consecutive studies have now been completed by the group, which enrolled a total of 778 children, adolescents (aged 12–17), and young adults (aged 18–30) with osteosarcoma from across Brazil.[10,12,13,17]

We sought to describe our patient population by comparing and contrasting their demographics and treatment outcomes with those reported in the literature by other countries. The results of BOTG studies III and IV were previously published.[10] This article reports on study V, which was conducted in 25 institutions and enrolled 368 patients, and updates the data from the previous two studies (III and IV).These three successive protocols from the past 15 years, conducted from 1991 to 2005, provided a sufficient number of patients for meaningful analysis.

Methods

Participant selection

We prospectively enrolled 604 patients below the age of 30 years with high-grade metastatic and non-metastatic osteosarcoma in BOTG studies III, IV, and V. These protocols were introduced in a sequential stepwise manner building on experiences gained from each and discoveries reported at meetings and in journals. The studies were approved by the Institutional Review Board at each of the 25 participating institutions in 15 different cities; informed consent was obtained from the patients or their legal guardians for those under 18 years of age.

After histological confirmation of high-grade intramedullary osteosarcoma, an initial evaluation consisting of a complete medical history and physical examination; complete blood count; and full biochemistry including electrolytes, alkaline phosphatase, and lactic dehydrogenase were performed. Eligible patients were required to have normal renal, hepatic, and cardiac functions for their age; normal audiometric evaluation at diagnosis was also required for patients enrolled in studies IV and V. Imaging performed at diagnosis included plain radiograph of the chest and primary tumor site, computed tomography (CT) of the chest, radioisotope bone scan, and a CT scan or magnetic resonance imaging (MRI) of the primary site. These assessments were repeated just prior to surgery and at regular intervals thereafter, both during and after the completion of therapy, for at least 5 years.

BOTG studies III, IV, and V protocols

Chemotherapy. BOTG protocols (Fig. 1) were designed to be delivered in an outpatient setting. Study III started in 1991, closed in 1996, and enrolled a total of 117 patients. It was comprised of two chemotherapy arms: regimens A (standard risk patients) and B (high-risk patients). Regimen A consisted of epirubicin (75 mg/m^2 short-term intravenous [IV] infusion on day 1 of weeks 0, 6, 11, 17, 20, and 23); carboplatin (600 mg/m^2 IV on day 1 of weeks 3, 6, 14, and 17; and ifosfamide (3 g/m^2 with mesna on days 1, 2 and 3 of weeks 0, 3, 11, 14, 20, and 23; Fig. 1A). Thirty-three patients received two cycles of intra-arterial carboplatin as a single agent up front. Based on our previous studies,[12,13,17] it appeared that patients presenting with tumors larger than 12 cm and those requiring immediate or early amputation, as well as the ones presenting with metastasis, were considered to be at high risk of treatment failure, so they were additionally treated with high-dose methotrexate (HDMTX) 12 g/m^2 on weeks 11, 12, 19, 20, 27, and 28 (Fig. 1A, Regimen B).

Study IV, which enrolled 119 patients between 1996 and 1999, intensified therapy with platinum compounds (carboplatin and cisplatin). All patients received carboplatin (500 mg/m^2 IV on day 1 of weeks 0, 3, 6, 17, and 26) and cisplatin (100 mg/m^2 IV on day 1 of weeks 0, 3, 6, 11, and 20). Doxorubicin was initially administered at a dose of 30 mg/m^2 in short-term IV infusions on days 1 and 2 of weeks 0, 3, 6, 14, 17, and 23. After April 1998, the dose was changed to 35 mg/m^2 given with dexrazoxane, following the previously mentioned schedule. Ifosfamide 3 g/m^2 IV and mesna on days 1, 2, and 3 were administered on weeks 11, 14, 20, and 26 (Fig. 1B).

In study V, started in 2000 and closed in 2005 with an enrollment of 368, high-dose ifosfamide was added to the standard cisplatin/doxorubicin regimen. All patients received cisplatin 60 mg/m^2 IV over 4 hours combined with doxorubicin 40 mg/m^2 in short-term IV infusion on days 1 and 2 of weeks 0, 6, 15, and 21. High-dose ifosfamide 2.7 g/m^2 with mesna uroprotection was administered for days 1–5 of weeks 3, 9, 18, and 24 (total ifosfamide dose of 13.5 g/m^2; Fig. 1C). For metastatic patients, cyclophosphamide 2 g/m^2 was used as an upfront window therapy 6 and 3 weeks before starting on week 0.

Surgery. Definitive surgery was performed at week 9 in studies III and IV and week 12 in study V. The appropriate procedure for each case was chosen by the institutional orthopedic surgeon in collaboration with the pediatric oncology team. Limb preservation was encouraged whenever possible using a variety of techniques such as non-conventional endoprosthesis, resection of expendable bones, plates, and bone graft fixation (autograft or allograft). After primary tumor removal, global assessment of necrosis was made by the institutional pathologist using the scoring system designed by Huvos as follows: grade 1 = < 50% tumor necrosis, grade 2 = 50–90% tumor necrosis, grade 3 = ≥ 90% tumor necrosis, and grade 4 = 100% necrosis.[18]

All pulmonary metastases were surgically removed as soon as possible after resection of the primary tumor. Patients with non-metastatic disease were considered to be in complete remission on the date of the primary tumor resection, whereas patients with metastatic tumors were considered to be in complete remission on the date of the pulmonary metastases resection.

Statistical analysis

The following variables were evaluated and assessed for their association with survival: gender, age at enrollment

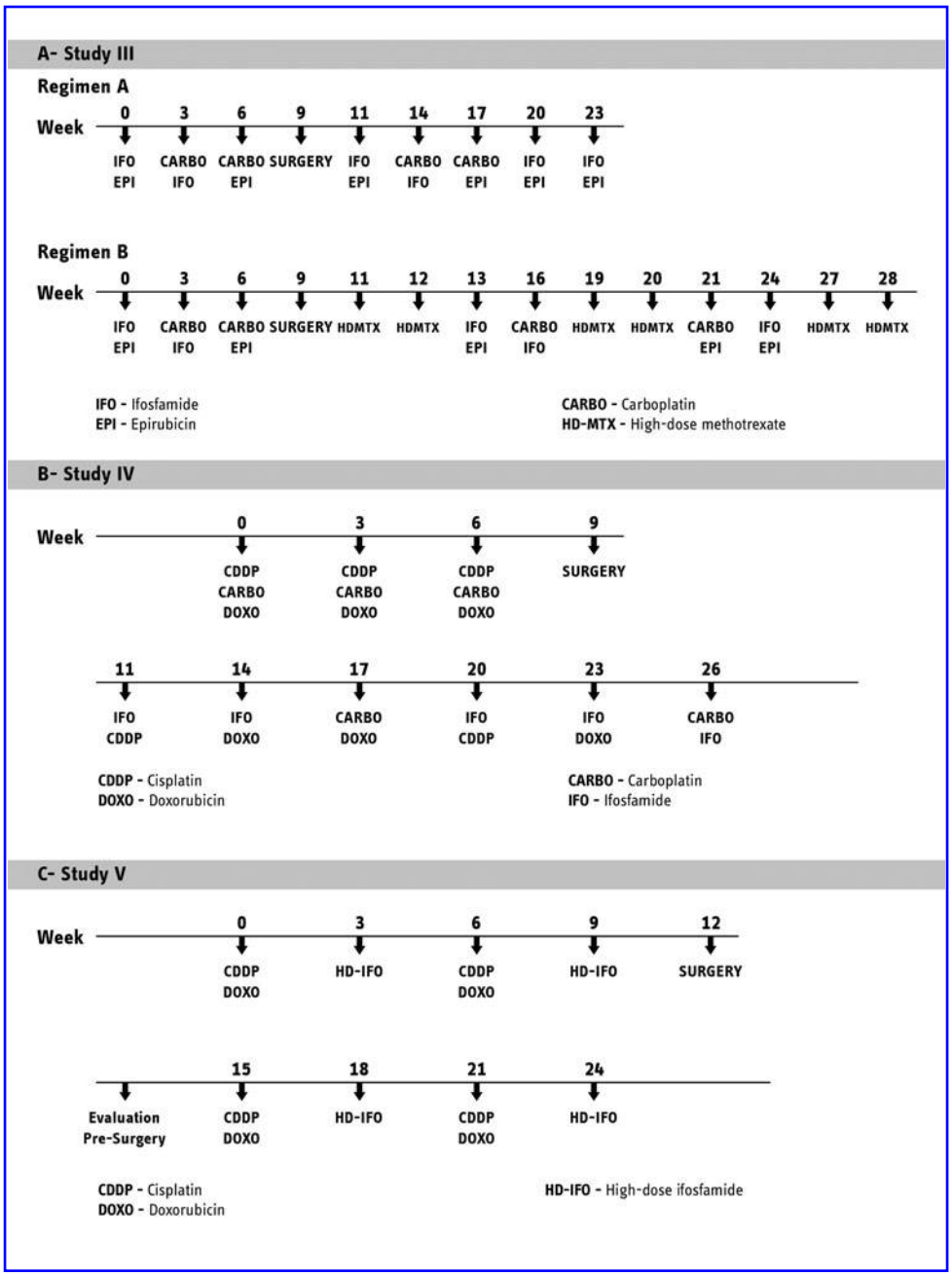

FIG. 1. Protocol design for BOTG studies III **(A)**, IV **(B)**, and V **(C)**. BOTG, Brazilian Osteosarcoma Treatment Group.

(stratified by age 14 as that is the line between attending a pediatric or adult institution in the majority of centers in Brazil), time from the onset of symptoms to diagnosis, primary tumor site, presence or absence of metastases at diagnosis, tumor size (≤12 cm or >12 cm), type of surgery (limb-sparing or amputation), treatment protocol, and histological response.

Overall survival was defined as the time interval between the date of study enrollment and either death from any cause or the most recent follow-up contact. Event-free survival (EFS) was defined as the time interval between study enrollment and disease relapse, death from any cause, or the most recent follow-up contact. The overall survival and EFS curves were created using the Kaplan–Meier method and log-rank tests were used to compare the curves. Hazard ratio estimates were calculated through univariate and multivariate Cox regression models. The probability of rejecting the null hypothesis was fixed at $p < 0.05$. The statistics software STATA v 10.0 was used in this study.

Results

Participant characteristics

A total of 604 patients were enrolled onto BOTG studies III ($n = 117$), IV ($n = 119$), and V ($n = 368$). Fifty-one (8.4%) patients were excluded from this analysis because of axial tumors ($n = 21$), refusal of surgery ($n = 20$), early discontinuation of treatment ($n = 7$), or unresectable tumor ($n = 3$). The remaining 553 patients were evaluated for overall survival and EFS. However, the entire population of 604 patients was included in demographic data (Table 1) and the osteosarcoma of the extremities (metastatic or non-metastatic) population in the intent-to-treat analysis. Patients ranged in age from 1 to 30

Table 1. Demographics, Tumor Characteristics, Surgery Type, and Histologic Response for Osteosarcoma Patients in BOTG Studies III, IV, and V

	BOTG study							
	III		IV		V		Total	
	n	%	n	%	n	%	n	%
Age (N = 604; range = 1–30)								
≤14 years	58	49.6	57	47.9	177	48.1	292	48.3
>14 years	59	50.4	62	52.1	191	51.9	312	51.7
Gender (N = 604)								
Male	63	53.8	74	62.2	198	53.8	335	55.5
Female	54	46.2	45	37.8	170	46.2	269	44.5
Metastases at diagnoses (N = 604)								
No	89	76.1	95	79.8	235	63.9	419	69.4
Yes	28	23.9	24	20.2	133	36.1	185	30.6
Primary tumor site (N = 604)								
Femur	64	54.7	63	52.9	191	51.9	318	52.6
Tibia	30	25.6	39	32.8	91	24.7	160	26.5
Humerus	8	6.8	12	10.1	44	12.0	64	10.6
Other	15	12.8	5	4.2	42	11.4	62	10.3
Tumor size (N = 410)								
≤12 cm	41	56.2	59	64.1	126	51.4	226	55.1
>12 cm	32	43.8	33	35.9	119	48.6	184	44.9
Type of surgery (N = 529)								
Limb-sparing	55	59.8	78	70.9	221	67.6	354	66.9
Amputation	37	40.2	32	29.1	106	32.4	175	33.1
Histological response to preoperative chemotherapy. Grade of necrosis (N = 395)								
Grade 1 or 2	34	53.1	79	82.3	151	64.3	264	66.8
Grade 3 or 4	30	46.9	17	17.7	84	35.7	131	33.2

Note: A total of 604 patients were enrolled onto BOTG studies III ($n = 117$), IV ($n = 119$), and V ($n = 368$). However, 51 (8.4%) patients were excluded from this analysis because of axial tumors ($n = 21$), refusal of surgery ($n = 20$), early discontinuation of treatment ($n = 7$), and or unresectable tumor ($n = 3$). All 604 were used for demographic and intent-to-treat analyses, but the number of patients in other analyses varied as shown above.

BOTG, Brazilian Osteosarcoma Treatment Group.

years old; the median age at study entry was 14.1 years. Of the 604 patients, 335 (55.5%) were male and 269 (44.5%) were female. The median time from onset of symptoms to diagnosis was 101 days (range = 2–758 days). Metastases at diagnosis were found in 185 patients (30.6%) as follows: pulmonary only = 85.6%, skeletal only = 2.9%, and pulmonary and skeletal = 11.5%. Femur was the most common primary tumor site.

Surgery

Twenty-four (4.3%) of the 553 eligible patients died before surgery: seven as a result of chemotherapy-related toxicity and 17 due to disease progression. Among the 529 patients who underwent surgical treatment, 354 (66.9%) had limb-sparing surgery and 175 (33.1%) had amputation (Table 1); 40 (7.6%) of those amputations were performed upfront before chemotherapy due to tumor size.

Local relapse occurred in 47 (8.9%) of the 529 patients; 42 underwent limb-sparing surgery and 5 had amputations. Fourteen (29.8%) of these patients were rescued and were alive without disease at a median follow-up time of 89.7 months after diagnosis.

Histological response to preoperative chemotherapy

Of the 488 patients who had a surgical procedure (limb-sparing or amputation) following chemotherapy, histological response was determined in 395 patients (80.7%; Table 1). The proportion of good responders (necrosis grade 3 or 4) in all studies combined was 33.2%. The proportion of patients achieving grade 3 or 4 necrosis in study III (46.9%) was higher than in study IV (17.7%; $p < 0.001$) or V (35.7%).

Survival outcomes

The median follow-up time from time of enrollment was 92.0 months (range = 35.3–209.2 months). Among the 553 patients evaluated for overall survival and EFS, 263 were alive at the time of the analysis, 284 had died, and 6 had been lost to follow-up. The causes of death were: disease relapse after attaining remission ($n = 170$; 30.7%), disease progression ($n = 62$; 11.2%), regimen-related toxicity ($n = 34$; 6.1%), second malignant neoplasm ($n = 3$; 0.5%), or other causes ($n = 2$; 0.4%). In 13 patients, the cause of death was not specified (2.4%).

Disease relapse or progression occurred in 281 cases (50.8%) after a mean time of 18.8 months following diagnosis;

Table 2. Overall- and Event-Free 5-Year Survival Based on Kaplan–Meier Estimates of Survival Curves and Log-Rank Tests for All Assessable Patients, by BOTG Study and According to Significant Prognostic Factors

		Overall survival			*Event-free survival*		
Factor	n	%	*(95% CI)*	p *(log-rank)*	%	*(95% CI)*	p *(log-rank)*
Overall	553	49	(44–52)		39	(42–51)	
Study (N = *550*)							
III	96	50	(40–59)		40	(31–50)	
IV	113	46	(37–55)	<0.0001[a]	39	(30–48)	<0.0001[b]
V	341	48	(43–54)		38	(33–43)	
Metastases at diagnosis (N = *550*)							
No	390	59	(54–64)	<0.0001	48	(43–53)	<0.0001
Yes	160	22	(16–29)		17	(11–23)	
Type of surgery (N = *550*)							
Limb-sparing	376	56	(51–61)	<0.0001	44	(39–50)	<0.0001
Amputation	174	32	(25–40)		27	(20–33)	
Tumor size (N = *407*)							
≤12 cm	224	64	(57–70)	<0.0001	51	(44–57)	<0.0001
>12 cm	183	41	(33–48)		31	(25–38)	
Histologic response to preoperative chemotherapy. Grade of necrosis (N = *393*)							
Grade 3 or 4	130	73	(64–80)	< 0.0001	58	(49–66)	0.0003
Grade 1 or 2	263	45	(39–51)		35	(29–41)	
Primary tumor site (N = *550*)							
Tibia	155	58	(50–65)	—	48	(40–56)	—
Femur	305	46	(40–51)	0.010	35	(29–40)	0.0064
Humerus	56	47	(33–59)	0.5760	38	(25–31)	0.3431
Other	34	34	(18–51)	0.2428	32	(16–49)	0.2647

[a]Study III > studies IV and V; study V > study IV.
[b]Study III = study IV; studies III and IV > study V.
BOTG, Brazilian Osteosarcoma Treatment Group; CI, confidence interval.

lungs were the most frequent site. Only 47 (16.7%) of these patients were rescued, while 232 (82.6%) died from disease and two (0.7%) were lost to follow-up.

The estimated 5-year overall survival and EFS rates for all eligible patients were 49% and 39% respectively (Table 2). For patients without metastases, overall survival and EFS at 5 years were 59% and 48% respectively (Table 2, Fig. 2A). However, patients with metastatic disease had only a 22% probability of overall survival and 17% of EFS at 5 years (Table 2, Fig. 2A).

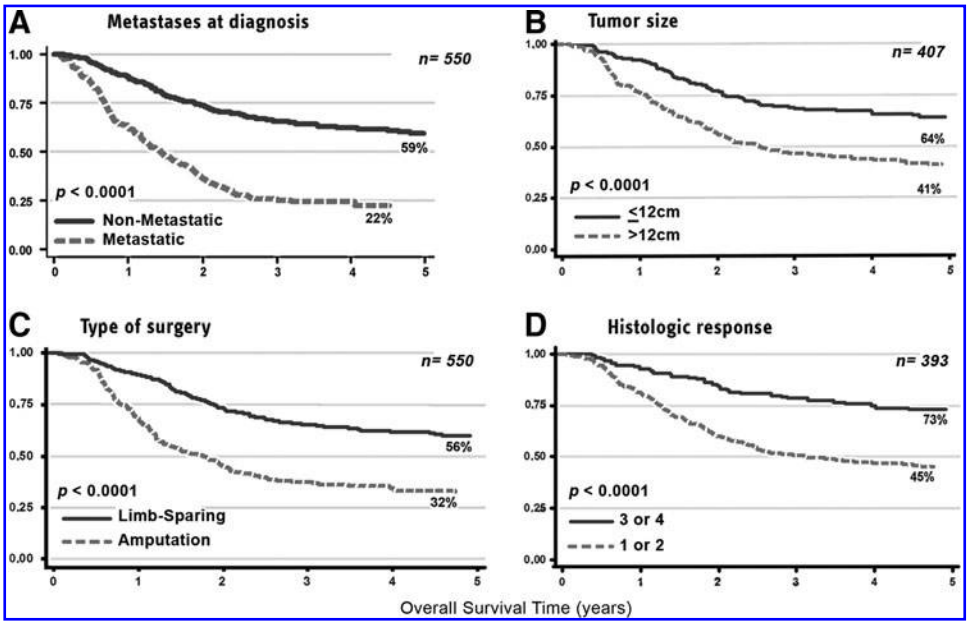

FIG. 2. Overall survival curves for assessable patients with osteosarcoma of the extremities in BOTG studies III, IV, and V by selected prognostic factors. BOTG, Brazilian Osteosarcoma Treatment Group.

Table 3. Prognostic Factors Associated with Event and Death in a Univariate Analysis

	Model	Hazard ratio	p	(95% CI)
Death				
Tumor size	≤12 cm	1.00	<0.001	(1.52–2.71)
	>12 cm	2.03		
Metastases at diagnosis	No	1.00	<0.001	(2.47–3.98)
	Yes	3.14		
Surgery	Limb-sparing	1.00	<0.001	(1.08–2.95)
	Amputation	2.30		
Grade of necrosis	3 or 4	1.00	<0.001	(1.74–3.63)
	1 or 2	2.52		
Primary tumor site	Tibia	1.00		
	Femur	1.40	0.020	(1.05–1.85)
	Humerus	1.30	0.242	(0.84–2.00)
	Other	1.79	0.020	(1.10–2.91)
Study	III	1.00		
	IV	1.11	0.576	(0.76–1.62)
	V	0.99	0.952	(0.72–1.36)
Event				
Tumor size	≤12 cm	1.00	<0.001	(1.39–2.34)
	>12 cm	1.81		
Metastases at diagnosis	No	1.00	<0.001	(2.14–3.34)
	Yes	2.67		
Surgery	Limb-sparing	1.00	<0.001	(1.53–2.42)
	Amputation	1.92		
Grade of necrosis	3 or 4	1.00	<0.001	(1.51–2.81)
	1 or 2	2.06		
Primary tumor	Tibia	1.00		
	Femur	1.45	0.005	(1.12–1.88)
	Humerus	1.36	0.129	(0.91–2.03)
	Other	1.67	0.033	(1.04–2.68)
Study	III	1.00		
	IV	1.03	0.851	(0.73–1.47)
	V	1.02	0.894	(0.76–1.37)

CI, confidence interval.

Table 4. Prognostic Factors Associated with Event and Death in a Multivariate Analysis

	Model	Hazard ratio	p	(95% CI)
Death				
Tumor size	≤12 cm	1.00	0.115	(0.94–1.70)
	>12 cm	1.27		
Metastases at diagnosis	No	1.00	<0.0001	(1.83–3.37)
	Yes	2.48		
Surgery	Limb-sparing	1.00	<0.0001	(1.35–2.58)
	Amputation	1.87		
Grade of necrosis	3 or 4	1.00	<0.0001	(1.47–2.92)
	1 or 2	2.08		
Primary tumor	Tibia	1.00		
	Femur	1.58	0.007	(1.13–2.23)
	Humerus	1.40	0.224	(0.81–2.42)
	Other	1.53	0.208	(0.79–2.97)
Event				
Tumor size	≤12 cm	1.00	0.369	(0.82–1.68)
	>12 cm	1.18		
Metastases at diagnosis	No	1.00	<0.0001	(1.97–3.99)
	Yes	2.8		
Surgery	Limb-sparing	1.00	<0.0001	(1.45–3.13)
	Amputation	2.13		
Grade of necrosis	3 or 4	1.00	<0.0001	(1.43–3.37)
	1 or 2	2.19		
Primary tumor site	Tibia	1.00		
	Femur	1.51	0.047	(1.00–2.29)
	Humerus	1.59	0.140	(0.85–2.98)
	Other	1.37	0.404	(0.65–2.87)

CI, confidence interval.

Prognostic factors

Age, gender, time from onset of symptoms to diagnosis, and treatment protocol were not associated with survival. In a univariate analysis (Table 3), the characteristics that were significantly associated with overall survival were: metastases at diagnosis (hazard ratio [HR] = 3.14; 95% confidence interval [CI]: 2.47–3.98), tumor size (HR = 2.03; 95% CI: 1.52–2.71), type of surgery (HR = 2.30; 95% CI: 1.08–2.95), histological response (HR = 2.52; 95% CI: 1.74–3.63), and primary tumor site (HR = 1.40; 95% CI: 1.05–1.85; Fig. 2A–D). The multivariate analysis for independent prognostic factors (Table 4) demonstrated that metastatic disease at diagnosis was the characteristic most significantly associated with EFS and overall survival. Grade of necrosis, surgery type, and tumor site were also independently associated with survival and EFS, whereas tumor size lost prognostic significance in the multivariate analysis.

Discussion

To the best of our knowledge, this report represents the largest osteosarcoma study from a developing country, and, as such, we expect to contribute to the best knowledge and management of this disease in other countries.

Our analysis attempted to compare our findings and results with those published in the literature. Prior to initiation of therapy, investigators visited prominent institutions to study prevailing methods of treatment. Treatment protocols were also gleaned from published reports and were similar—if not occasionally identical—to that published in the literature. Our patient population revealed a comparable list of parallels to that of published reports with an increase in several poor prognostic variables.

Metastases at diagnosis were present in 30% of our patients, which is higher than the frequency reported by other investigators.[19–21] While we had previously reported that only 21% of patients in BOTG studies III and IV had metastatic disease,[10] the increase seen in this analysis can be explained by the growth of the cooperative group, which increased the number of osteosarcoma Brazilian patients with access to a treatment protocol. For instance, while BOTG studies III and IV enrolled 30 patients per year from five institutions, the more recent study V enrolled 61 patients per year (368 patients over 6 years) from 25 institutions in 15 different cities, more accurately representing the Brazilian osteosarcoma population. Interestingly, there was no statistically significant relationship between this high incidence of metastatic disease and diagnostic delay, since the time from symptom onset to diagnosis did not correlate with the presence of metastases,

tumor size, or survival. The presence of metastatic disease at presentation may be more related to the tumor biology of individual patients than the interval from symptoms to diagnosis. The patient demographics were otherwise similar to those reported elsewhere in the literature.[2]

We recognize that the 5-year overall survival (49%) and EFS rates (39%) of our patients are below the 55–77% rates published by other groups.[1–7] This may be attributed to advanced stages of malignancy in patients presenting for treatment. When patients with metastatic disease are excluded from the analysis, the 5-year overall survival (59%) and EFS (48%) are similar to that reported by other cooperative groups.[1,3] Furthermore, our results were superior compared to our historical experience prior to the 1980s, when amputation was essentially the sole and "standard" treatment.[8,12] Also of note is that despite the large size of many tumors, limb salvage replaced amputation in the majority of patients, with the percentage of patients undergoing limb salvage increasing from study III (59.8%) to studies IV (70.9%) and V (67.6%), largely due to advances in orthopedic surgery nationwide.

Histological response was better in study III than in study IV or V. This finding is attributed to the use of intra-arterial carboplatin in the former study.[10,17] Other authors have already reported an improved response rate with the administration of intra-arterial chemotherapy.[22–25] Study III also had better 5-year overall survival (50%) and EFS rates (40%) when compared to studies IV (overall survival = 46%; EFS = 29%) and V (overall survival = 48%; EFS = 38%). In addition to the superior histological response in study III, it also had a lower proportion of metastatic patients (19.8%) than did study V (34.9%), which clearly contributes to the difference in survival curves.

Tumor size, which was significant in our previous studies if based on the cut-off of 12 cm,[10–12] was a significant prognostic factor in the univariate analysis, but lost its significance in the multivariate analysis. This may be secondary to the fact that we used absolute tumor size, whereas tumor size relative to bone length or patient size could be more accurate. Factors such as surgical resectability and grade of necrosis that account for response to neoadjuvant chemotherapy may be more important than size for outcome.

Conclusion

In conclusion, we report our experience treating osteosarcoma in three different multicenter Brazilian trials. Although the Brazilian survival rates presented in the past 15 years are lower than those reported in the current literature, this study represents the result of a favorable experience gathered from the national collaborative work. We have provided a reliable picture of our national reality and increased the number of osteosarcoma Brazilian patients with access to a treatment protocol.

Acknowledgments

We thank all the patients, physicians, nurses, data managers, and support staff at collaborating centers for their active participation in the BOTG studies. We acknowledge Drs. Leo Mascarenhas and Norman Jaffe for their contributions and friendship, as well as Mr. Arnaldo Pires, Ms. Ana Helena Dutra, and Ms. Mariana Grings for their invaluable contributions to data collection, monitoring, and management and formatting the tables and figures in this manuscript.

Disclaimer

Portions of this manuscript were previously presented at the ASCO 45th Annual Meeting, May 29–June 2, 2009, Orlando, Florida. Published as: Petrilli AS, de Camargo B, Odone Filho V, Lustosa D, Borsato ML, Calheiros LM, Brunetto AL, Barreto JH, Ferraro AA. Fifteen years experience of the Brazilian Osteosarcoma Treatment Group (BOTG). J Clin Oncol. 2009;27(15S):abstract 10039.

Author Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Antonio Sergio Petrilli, MD, PhD
Institute of Pediatric Oncology
Support Group for Children and Adolescents with Cancer (GRAACC)
Federal University of São Paulo (UNIFESP)
Rua Botucatu, 743
Vila Clementino
São Paulo, 04023-062
Brazil

Email: sergiopetrilli@graacc.org.br