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Pediatric Sarcoma in Central America: Outcomes, Challenges and Plans for Improvement

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Abstract

Background—Children with cancer in middle-income countries have inferior outcomes to those in high-income countries. The magnitude and drivers for this survival gap are not well understood. We sought to describe patterns of clinical presentation, magnitude of treatment abandonment, and survival in children with sarcoma in Central America.

Methods—Retrospective review of hospital-based registries from national pediatric oncology referral centers. Patients with newly diagnosed osteosarcoma, Ewing sarcoma (Ewing), rhabdomyosarcoma (RMS), and soft tissue sarcomas (STS) between 1/1/00-12/31/09 were included. Survival analysis was performed using standard definitions of overall and event-free survival (OS and EFS) and with abandonment included as an event (AOS and AEFS).

Results—A total of 785 new cases of pediatric sarcoma were reported (264 osteosarcoma, 175 Ewing, 240 RMS, and 106 STS). Metastatic disease at presentation was high (osteosarcoma 38%, Ewing 39%, RMS 29% and STS 21%). Treatment abandonment rate was high, particularly among patients with extremity bone sarcomas (osteosarcoma 30%, Ewing 15%, RMS 25% and STS 15%). Of 559 patients experiencing a first event, 59% had either relapse or progressive disease. The 4-year OS was 40% (SE±3%) and EFS was 30% (SE±2%), but further decreased to 31% (SE ±2%) and 24% (SE±2%), when abandonment was taken into account.

Conclusion—High rate of metastases and treatment abandonment, and difficulty with upfront treatment effectiveness are important contributors to poor survival of children with pediatric sarcomas in Central America. Initiatives for early diagnosis, psychosocial support, quality improvement, and multidisciplinary care are warranted to improve outcomes.

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Keywords

pediatric sarcoma; developing countries; treatment abandonment; outcomes research; international outreach

BACKGROUND

Eighty percent of children with cancer live in low-and middle-income countries (LMC)[1]. In developed countries, childhood cancer survival has steadily improved reaching 81% for all children with cancer and 70% for children with sarcoma[2, 3]. Improved survival for pediatric sarcoma in high income countries (HIC) reflects improved access to chemotherapy, surgery and radiation, as well as better diagnostic techniques, risk-adapted approaches and optimization of supportive care and palliation[4]. In developing countries, advances have been hampered by low socioeconomic conditions that result in delayed diagnosis and fractionated care. Information on clinical presentation, epidemiology, delivery of cancer care and outcomes for children with sarcoma in LMCs is scarce[5–8]; a detailed analysis of all these elements is needed. International organizations have called for action to address cancer in the developing world[9–11]. Great variability in cancer outcomes has been documented not only between developed and developing countries, but also between countries with similar government investment in health care[12, 13]; highlighting the need to improve our understanding of regional disparities and to develop new models of care for children with cancer in LMC. Successful models of care for treatment of childhood leukemia in resource-limited settings have been developed[14]. However, an expanded model that accounts for the complexity and multidisciplinary nature of solid tumor care is critically needed. Pediatric sarcomas collectively represent only between 6–16% of pediatric cancers[2, 3], however, due to the complexity of diagnostic and treatment, they can serve as a benchmark to study healthcare systems and the influence of quality improvement or multidisciplinary care paradigms on cancer outcomes in LMC.

The Central American Association of Pediatric Hematologists and Oncologists (AHOPCA) is a regional collaboration that has successfully implemented protocol-based treatment, studied causes of treatment abandonment, and improved survival in childhood leukemia in the region[15, 16]. However, despite parallel development of pediatric leukemia and solid tumor programs, improvements in outcomes for children with solid tumors, have not always matched those of children with pediatric leukemia.

In Guatemala, the implementation of a soft tissue sarcoma protocol based on IRS-IV proved deliverable, yet despite access to chemotherapy, surgery and radiation, the outcomes reported in developed countries were not reproducible in this lower-income setting[8, 17]. Similar challenges in matching published outcomes have been documented for treatment of rhabdomyosarcoma in Turkey[18], for treatment of osteosarcoma in Brazil[19] and other solid tumors in Nigeria, Morocco and South Africa[20–22].

The goal of this study was to describe patterns of clinical presentation, magnitude of treatment abandonment, and survival in children with sarcoma in Central America in order to document and guide development of focused initiatives aimed at addressing the expected survival gap.

METHODS

Study design

Retrospective review of previously collected de-identified data obtained from hospital-based registries from seven pediatric oncology centers in Central America. Based on nature of the data this study was reviewed and considered exempt from further review by the Office of Human Subject Research Studies at the Dana Farber Cancer Institute.

The centers

Six of seven pediatric oncology centers involved were pediatric cancer national referral centers and members of AHOPCA: *Hospital Nacional de Niños*, Costa Rica*, Hospital Nacional de Niños Benjamin Bloom*, El Salvador, *Unidad Nacional de Oncologia Pediatrica*, Guatemala, *Hospital Materno Infantil*, Honduras, *Hospital Infantil "La Mascota",* Nicaragua, and *Hospital del Niño de Panama (HNP)*, Panama. Centers serve the general population, including children from indigenous background, economically constrained households, and distant locations. Data from *Hospital de Especialidades Pediatricas (HEP),* the second largest center in Panama, was also included.

Data source

Hospital- based cancer registries stored in POND4KIDS[23]. Data collection and entry had been previously approved by local ethics committees. Data had been prospectively collected since 2005 and retrospectively collected for cases diagnosed before 2005. Data from HEP, Panama, was provided in Excel without linking identifiers.

Analytic cohort

Patients with newly diagnosed osteosarcoma, Ewing sarcoma (Ewing), rhabdomyosarcoma (RMS), and soft tissue sarcomas (STS) between Jan/1/00-Dec/31/09 were included. Patients with sarcoma as a secondary cancer were excluded. An age cut-off was not pre-established and all cases presenting to the pediatric oncology center and entered into the database were analyzed.

Oncology treatment

Patients had received multimodal treatment on a variety of published or regionally adapted protocols. Standard chemotherapy agents, pediatric surgeons, radiation therapy and subsidies for pediatric cancer care were available in all countries. For example, RMS treatment was based on IRS-IV and osteosarcoma treatment on amputation and chemotherapy with cisplatin, doxorubicin, ifosfamide, and etoposide. Limb-sparing procedures and high-dose methotrexate were only reliably available in Costa Rica.

Generalizability

Costa Rica is the only AHOPCA-member country with a national cancer registry. Therefore, the pediatric sarcoma incidence reported in Costa Rica (9.7 cases/million)[24] for the period of 1984–92 is the best regional estimate available. In the United States the incidence is reported to be higher (16 cases/million)[25]. Based on the population less than 15 years of age (14.8 million in 2009), between 143 and 237 new cases of pediatric sarcoma would be expected per year in the region during the analytic period. Because the incidence of sarcoma increases during adolescence, the number expected to present to a pediatric center could be higher and depend on the maximum age allowed at the center.

Outcomes and important definitions

AHOPCA-centers have shared agreement on cancer outcomes reported into POND4KIDS: treatment refusal, treatment abandonment, relapse, progressive disease, secondary malignancy, lost to follow-up and death[26]. *Treatment refusal* and *treatment abandonment* are not usually included in analysis of cancer outcomes in HICs, but are noteworthy outcomes in LMCs[27]. *Treatment refusal* involves upfront decline of treatment and does not allow initiation of therapy. *Treatment abandonment* occurs after initiation of treatment and has been defined in AHOPCA as missing 4 or more consecutive weeks of treatment. Refusal and abandonment were analyzed as one event ("abandonment") as recommended by the International Society of Pediatric Oncology Working Group on Treatment Abandonment[28]. *Date of abandonment* was the last date that the patient was known to participate in cancer care. Palliative care was considered continued care until death and was not counted as abandonment. Patients lost to follow-up after completion of therapy not counted as abandonment.

Subdivision of data

To evaluate changes over time, patients were divided into two treatment eras (2000–04 and 2005–09), based on existence of more mature twinning, more established psychosocial strategies and socioeconomic supports, and improved access to multimodal therapy in the second era. To evaluate the role of disease extent on outcomes, patients were divided based on presence or absence of metastases at diagnosis into *Localized* or *Metastatic*. To evaluate the role of disease location on outcomes, patients were divided into: *bone sarcoma* (osteosarcoma and Ewing of bone located in extremity or *other*- skull, chest wall, spine or pelvis), *soft-tissue sarcoma (*extra-osseous Ewing, rhabdomyosarcoma and STS in the extremity or *other*- located elsewhere).

Statistical Methods

Descriptive statistics were used to describe patient characteristics. A chi-square test was used to compare proportions. Cumulative incidence of abandonment curves were generated and Pepe-More test performed to test for statistically significant differences between the curves ($p<0.05$). Four survival analyses were performed: 1) Event-free survival (EFS) with events defined as relapse, progressive disease, secondary malignancy, or death; 2) Abandonment-sensitive event-free survival (AEFS) with events defined as abandonment of therapy, relapse, progressive disease, secondary malignancy, or death; 3) Overall survival (OS) with event defined as death, and 4) Abandonment-sensitive overall survival (AOS) with events defined as abandonment and death. Time to event was calculated from the time of diagnosis until the first event or until last contact if no event occurred. Survival results are presented as 4-year point estimate ± standard error due stability of the curves at that time point. Kaplan-Meier curves were generated and a Log rank test performed to test for statistically significant difference between the curves. P values of $p<0.05$ were considered significant.

RESULTS

Cohort

Seven hundred and ninety one (791) children were diagnosed with sarcoma in the seven pediatric oncology centers, between 1/1/2000 and 12/31/2009. Six patients (0.7%) were excluded because sarcoma represented a second malignancy. Among those included in the analysis, 323 (43%) were diagnosed between 2000–2004 and 458 (61%) between 2005–2009 (4 patients had missing data). Patients were from Costa Rica (115), El Salvador (102), Guatemala (259), Honduras (94), Nicaragua (151), and Panama (from HNP and 11 from

HEP). Of the 785 patients included in the analysis, 182 (23%) abandoned treatment. The summary of patient characteristics is presented in Table I by abandonment status. Median age of the cohort was 10.2 years (range 0.1–23.6 years). Mean age and age range were similar between the countries analyzed.

Burden of disease

A high proportion of patients presented with metastatic disease (osteosarcoma 38%, Ewing 39%, RMS 29% and STS 21% compared to in HICs (20%, 25%, 18%, and 15% respectively)[17, 29–31]. Decrease in metastatic disease was noted by era for all diagnoses, but trend was not statistically significant (osteosarcoma 39% to 38%, Ewing 42% to 37%, RMS 33% to 26%, and STS 25% to 19%). Only 17% of RMS were classified as surgical group I–II (compared to 33% in HIC)[17]. By histology, the proportion of alveolar subtype RMS (ARMS) was similar to that in HIC (30% vs 32% respectively)[17]. However, analysis by country revealed a higher rate of ARMS in Guatemala compared to the other countries (48% of RMS in Guatemala vs 17% in El Salvador, 22% in Nicaragua, 27% in Costa Rica, 28% in Honduras, and 29% in Panama).

Treatment abandonment

Twenty-three percent of patients abandoned treatment. Abandonment rate differed significantly by diagnosis (p=0.0094) and was higher for osteosarcoma and RMS (30% and 25% respectively) than for Ewing and STS (15% each). Abandonment rate decreased between the two eras (p=0.0193), but decrease was only significant for RMS and STS (p=0.011 and 0.0411, respectively, see Table II). Cumulative incidence (CI) of abandonment was not significantly different by era (p=0.2312; Figure 1a) or by disease extent (p=0.4760, Figure 1b). Pairwise comparisons between diagnoses revealed a higher CI of abandonment for osteosarcoma compared to Ewing (p=0.0008) or STS (p=0.0028), but not significantly different from RMS (Figure 1c). The CI of abandonment in the first six months was steeper for osteosarcoma compared to all other diagnoses, including RMS. Furthermore, 54% of patients with osteosarcoma and 56% of patients with Ewing who abandoned therapy did so in the first three months after diagnosis, compared to 30% for RMS and 41% for STS.

Pairwise comparisons by disease location showed higher CI of abandonment for patients with *bone sarcoma* located in the extremity compared to elsewhere (p=0.0006; Figure 1d). For sarcomas arising in soft tissues, CI of abandonment was not significantly different by disease location in the extremity vs. elsewhere (p=0.6880). CI of abandonment in the first six months was steeper for patients with *bone sarcoma* in the extremity than for tumors located elsewhere. Fifty-three percent of patients with *bone sarcoma* located in the extremity that abandoned therapy did so in the first three months after diagnosis compared to 45% for *soft-tissue sarcoma* located in the extremity, 34% for *soft-tissue sarcoma* located elsewhere, 22% for *bone sarcoma* located elsewhere.

Survival Analysis

Of 559 patients who experienced a first event: 329 (59%) experienced progressive disease or relapse, 161 (29%) abandoned therapy, 68 (12%) died and 1 developed a secondary malignancy. The median follow up for patients alive at last contact was 2.2 years (0 days -10.7 years). Of the 785 patients, 8 were excluded from the event-free survival (EFS) analysis and 7 from the overall survival (OS) analysis due to missing data.

Figure II shows the overview of survival analyses for pediatric sarcoma in Central America. The estimated 4-year OS and EFS were 40% (±3%) and 30% (±3%), respectively. With abandonment included as an event, estimated survival decreased to 31% (±2%) and 24% (±2%) respectively (AOS and AEFS). Four-year OS estimates by disease were 31% (±4%)

for osteosarcoma, 36% (±6%) for Ewing, 44% (±5%) for RMS, and 53% (±8%) for STS. By disease location, 4-year OS estimates were 32% (±4%) for *bone sarcomas* and 46% (±4%) for *soft-tissue sarcoma*. For contrast the 5-year survival in HIC is 68% for malignant bone tumors and 73% for soft-tissue sarcomas[3].

Significant differences in survival were noted by disease extent, diagnosis and disease location, but not by treatment era, even for patients with localized disease (See Table III and Figure III). Assuming negative outcome after abandonment, failing to include it as an event would have overestimated survival by 3–14% (see OS vs AOS and EFS vs AEFS). A difference ≥10% between OS and AOS was noted for localized disease, rhabdomyosarcoma, and STS. No differences ≥10% was observed between EFS and AEFS. Survival differed significantly by diagnosis. Patients with osteosarcoma and Ewing sarcoma experienced the poorest outcomes. In osteosarcoma, this was particularly strong when abandonment was included as an event (AOS for osteosarcoma vs RMS p=0.0007; vs STS p=0.0011; vs Ewing p=0.0669). Disease location in bone vs elsewhere was associated with decreased survival, particularly when abandonment was taken into account (AOS for *Extremity* vs *Other* was 28% vs 35%; p=0.0239 and EAFS for *Extremity* vs *Other* was 22% vs 27%; p=0.0376).

Analysis by country

Treatment abandonment and survival differed by country. Details of this analysis and correlation with cancer-infrastructure and health and economic indicators will be reported separately. In brief, treatment abandonment rate ranged from 1% in Costa Rica to 38% in Honduras. Abandonment-sensitive OS (AOS) ranged from 23.5% in Panama and 47.1% in Costa Rica.

DISCUSSION

This retrospective review of pediatric sarcoma outcomes in Central America documents a significant survival gap despite improved access to multimodal therapy and indicates that high burden of metastatic disease at diagnosis, high rate of treatment abandonment, and difficulty with upfront treatment effectiveness are likely drivers for the poor outcomes observed. To our knowledge, this study reviews the largest cohort of pediatric sarcoma cases from the developing world and provides relevant information for comprehensive cancer survival analysis in developing countries.

Due to lack of regional cancer registries, generalizability of our cohort cannot be fully ascertained. However, based on reported cancer incidence from Costa Rica, the cohort could represent up to two thirds of the expected cases, particularly during the second analytic period. Therefore, our results are likely the closest approximation to the true overall clinical presentation and outcomes of children with pediatric sarcoma in Central America.

One interesting variation in disease distribution was noted; while RMS histology for the cohort was similar compared to HIC, the proportion of alveolar RMS was notably higher (48%) in Guatemala. This supports prior observations of increased incidence of retinoblastoma, decreased incidence of neuroblastoma and high proportion of alveolar rhabdomyosarcoma in Guatemala[8, 32]. Comprehensive etiological studies merging cancer-epidemiology and tumor biology in LMCs are lacking and potential genetic and environmental modifiers of tumor behavior have not been fully explored. Studies confirming pathologic diagnostic accuracy, followed by studies integrating genetics, environment, and cancer biology would be of great value to the region.

A high proportion of patients presented with metastatic disease. In sarcomas, advanced disease translates into higher upfront risk-group assignment, more chemotherapy, difficulty

achieving complete surgical resection and increased reliance on radiation therapy to achieve adequate local control. Therefore, advanced disease impacts outcomes and imposes further pressure on already overburdened healthcare systems. Advanced disease at presentation is most often attributed to delayed diagnosis and this is the leading argument for national media and educational campaigns. Short term impact of such programs has been documented in Honduras, where a retinoblastoma education program linked to a national vaccination campaign increased referrals and decreased presentation with extraocular spread[33]. Bundled strategies that educate child advocates, the general public and health care providers on referral process, treatment availability and improved curability of low stage disease, has the potential to impact this driver of poor outcomes and merits further support.

Central America has pioneered research on delivery of pediatric cancer care in resource-limited settings and has shown great improvement in survival and treatment abandonment for children with leukemia[15, 16]. However, treatment abandonment in pediatric sarcoma remains a concern with rate consistently higher in pediatric sarcoma (average 20%) than for leukemia (average 6%) in recent years (AHOPCA unpublished data provided by Dr. Baez). This study shows that although the proportion of patients with pediatric sarcoma that abandon therapy has decreased over time, these patients remain at high-risk group for treatment abandonment. Also, that lack of inclusion of treatment abandonment as an event leads to overestimation of overall and event-free survival. Relevant socioeconomic and demographic drivers of abandonment have been described[15, 27, 34]. Our study focuses on clinical characteristics that influence abandonment. Occurrence and timing to abandonment appear to be mostly influenced by the primary diagnosis and disease location; not by age, gender, or disease extent. Patients with bone tumors of the extremities (particularly osteosarcoma) abandon treatment most frequently and do so earlier than patients with other types of sarcoma; presumably reflecting a rejection of amputation. Unfortunately, due to high cost of endo-prosthesis, lack of bone allografts and limited skilled personnel, amputation is the primary modality available for local control in all countries except Costa Rica. Strategies for strengthening of rehabilitation and reintegration programs for children that have sustained amputation and possibly increasing access to limb-sparing procedures could be of great impact.

Patients with rhabdomyosarcoma share similar long term incidence of abandonment as patients with osteosarcoma, but abandonment accumulates over longer period of time; suggesting that the drivers of early and late abandonment for bone and soft-tissue tumors are different. All in all, these findings suggest that abandonment is driven by factors beyond socio-demographics, are possibly disease/treatment specific, and that development of retention models designed for these high-risk patient populations is needed. However, metastatic disease and abandonment don’t fully explain the poor long-term outcomes observed. Survival did not significantly improve between eras, even for patients with localized disease and despite improved access to conventional therapy. Furthermore, 42% of all patients experienced progressive disease or relapse as first event, suggesting fundamental difficulty in effective delivery of upfront therapy. Focus on capacity building, quality improvement, communication, and coordination of multidisciplinary care is warranted to maximize upfront cancer care effectiveness and outcomes. This is particularly relevant in the management of solid malignancies, where sophisticated local control measures are at the core of therapy. Successful restructuring of care in order to effectively deliver complex frontline therapy has been reported for treatment of non-metastatic Ewing sarcoma[35] and osteosarcoma[36] in Chile.

In conclusion, we have identified high burden of metastatic disease, persistently high rate of treatment abandonment, and difficulty with upfront treatment effectiveness as major barriers to optimal care to children with sarcoma in Central America. While advances in care

delivery for children with hematologic malignancies have resulted in significant improvements in outcomes, children with sarcomas have not benefited from those gains, likely due to deficiencies in the delivery of multidisciplinary care that is key in the management of solid malignancies. Several initiatives are ongoing to address these issues. The Pan-American Health Organization is working regionally on general and health care provider education using the Integrated Management of Childhood Illness Method. Collaboration with major academic centers in the US, Italy and Brazil is allowing for further education and capacity building opportunities in limb-salvage surgery as well as early referral of selected cases for limb-sparing procedures. Finally, web-based case discussions, detailed infrastructure assessment, quality control initiatives, assessment of local control effectiveness, and further analysis of inherent drivers of abandonment in pediatric sarcoma are the focus of the current *AHOPCA Sarcoma Initiative* and the core of our future studies.

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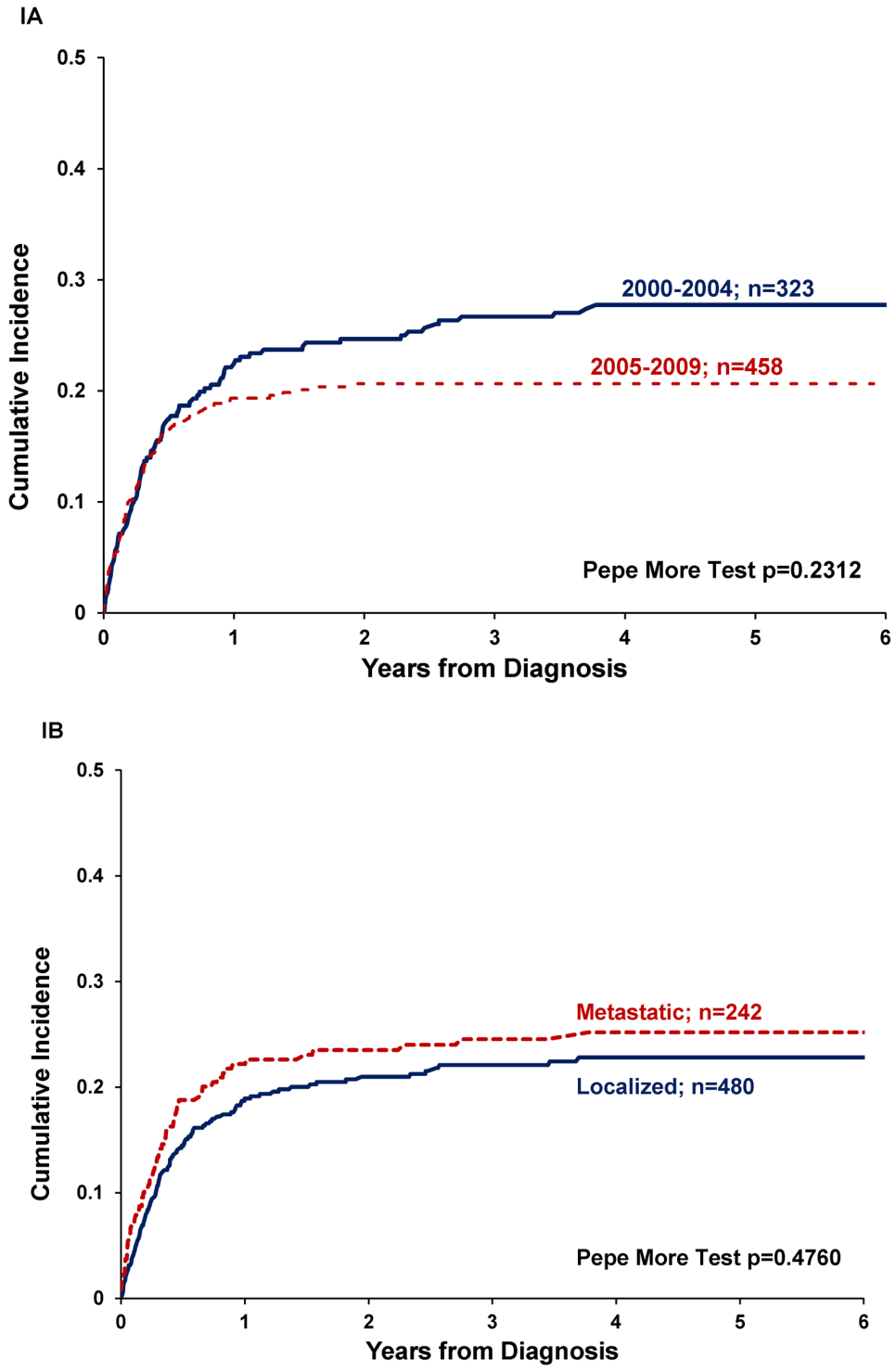


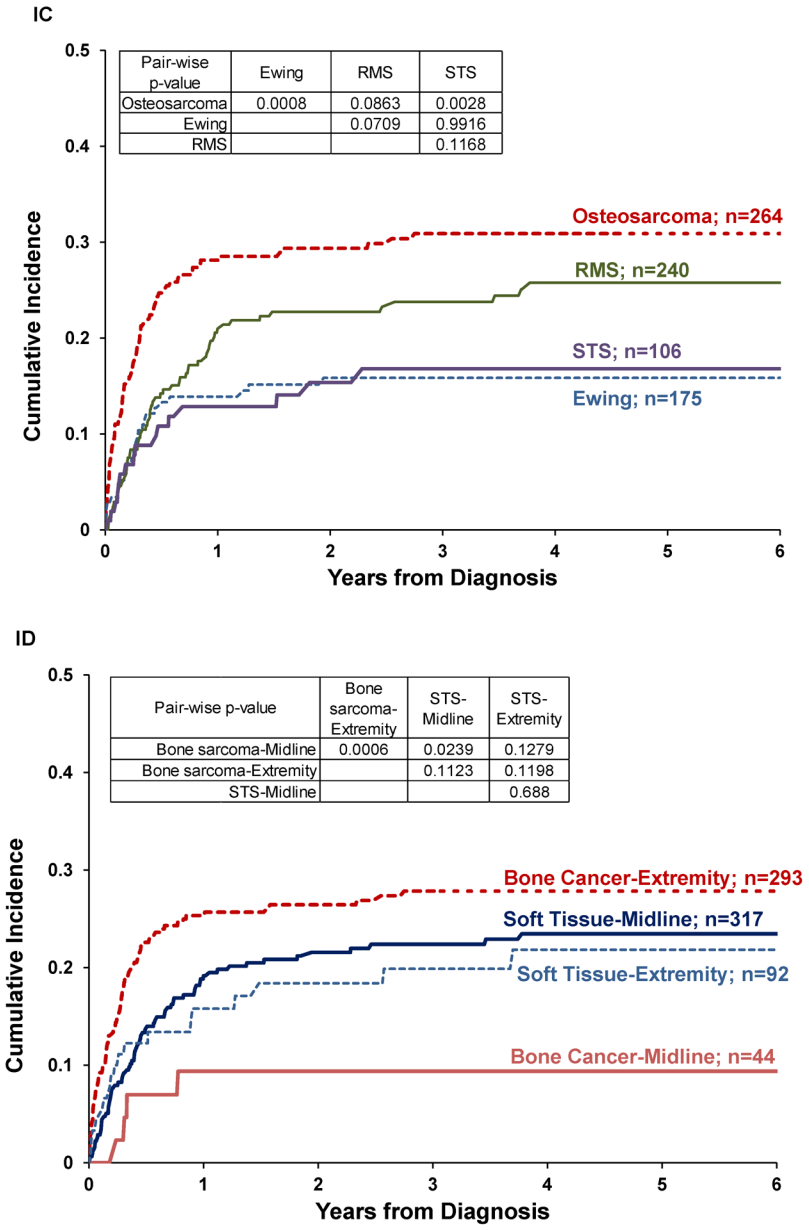


Figure I. Cumulative incidence of abandonment in pediatric sarcomas in Central America by (A) treatment era (n=781), (B) disease extent (n=722), (c) diagnosis (n=785), (D) disease location (n=746).

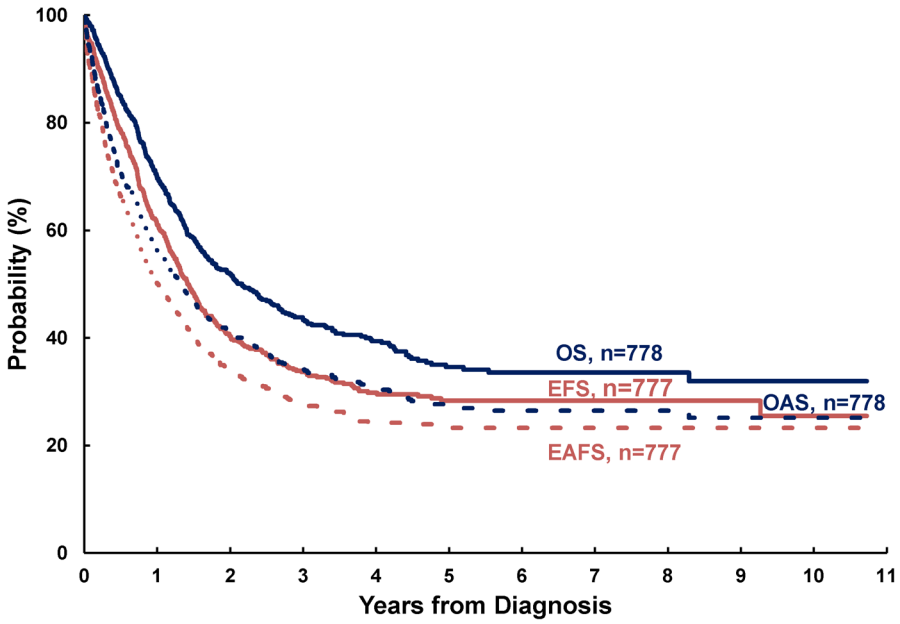
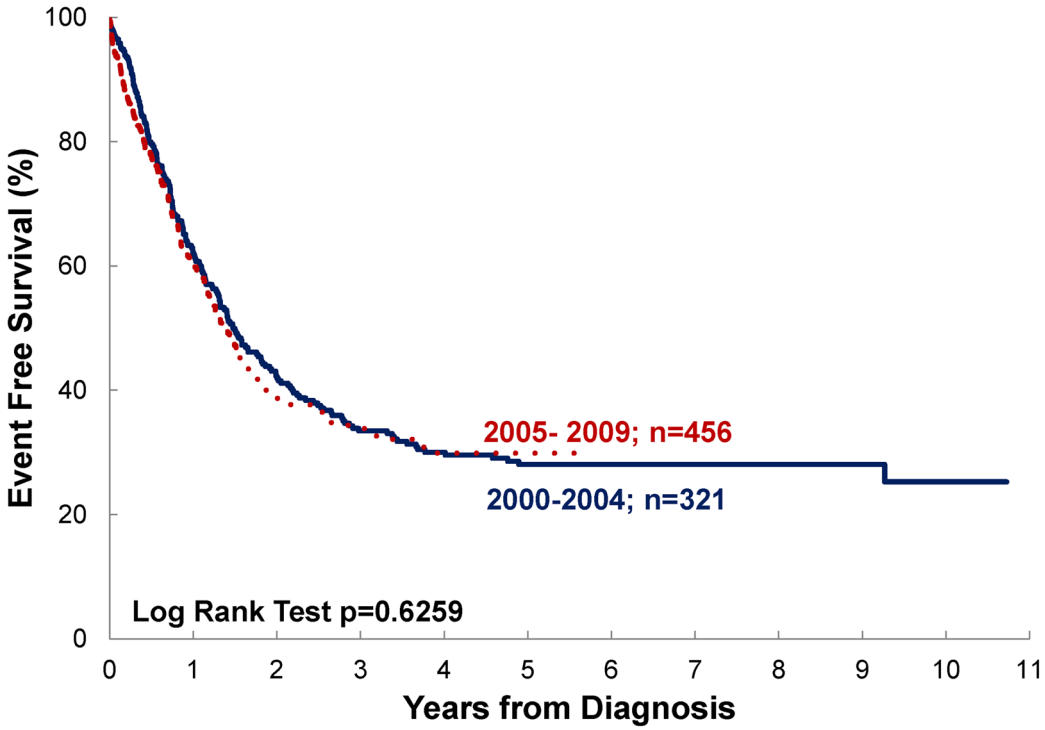


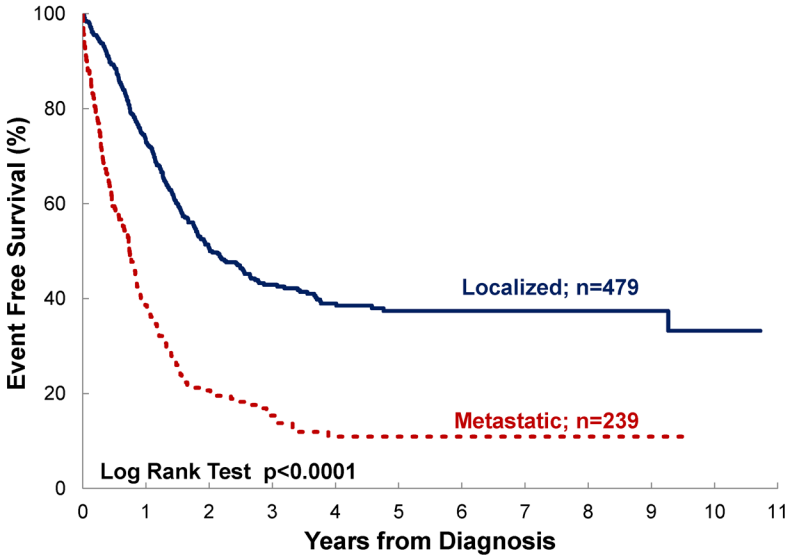
Figure II. Survival Analysis

Event-free survival (EFS), abandonment-sensitive event-free survival (AEFS), overall survival (OS) and abandonment-sensitive overall survival (AOS) for pediatric sarcoma in Central America.

IIA



IIB



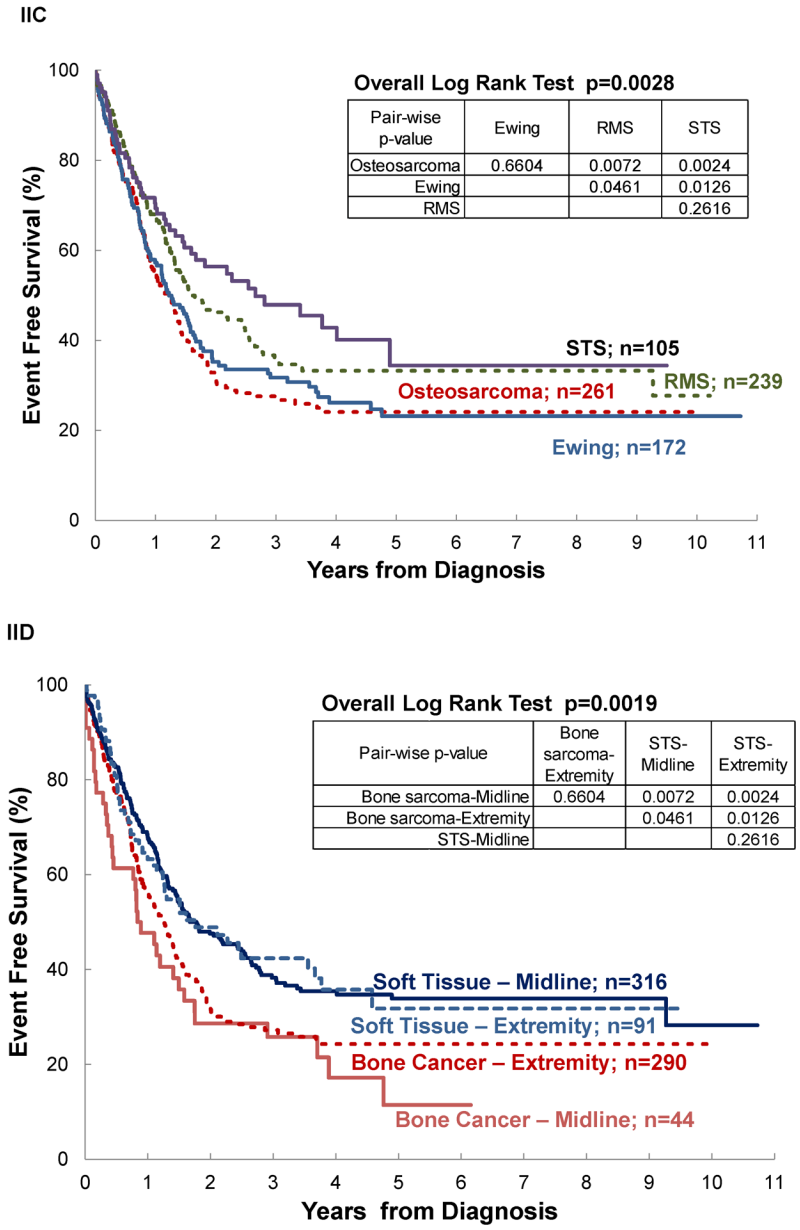


Figure III. Event-free survival of pediatric sarcoma in Central America
by: (A) treatment era, (B) disease extent, (C) diagnosis, and (D) disease location; (n=777).

Table I

Patient Characteristics by Treatment Abandonment Status

	Abandonment Status	Patients who did not abandon treatment	Patients who abandoned treatment
	n=785	**603**	**182**
Osteosarcoma	n	**184**	**80**
	Age (mean ±SD)	12.0 ±0.3	12.6 ±0.3
	Male	47%	51%
	Metastasis at Diagnosis	37%	42%
	Location in extremity	98%	97%
Ewing Sarcoma	n	**148**	**27**
	Age (mean ±SD)	9.6 ±0.3	8.6 ±1.0
	Male	50%	56%
	Metastasis at Diagnosis	41%	28%
	Primary bone, extremity	50%	71%
	Extraosseous, extremity	29%	25%
Rhabdomyosarcoma	n	**181**	**59**
	Age (mean ±SD)	6.4 ±0.3	5.9 ±0.7
	Male	55%	63%
	Metastasis at Diagnosis	28%	33%
	Surgical Group		
	I	7%	5%
	II	10%	12%
	III	52%	53%
	IV	24%	27%
	Not available	6%	3%
	Tumor Histology		
	Embryonal	60%	63%
	Alveolar	30%	27%
	Other	9%	8%
	Not available	1%	2%
	Location in extremity	17%	22%
Soft-Tissue Sarcoma	n	**90**	**16**
	Age (mean ±SD)	9.4 ±0.5	8.1±1.2
	Male	57%	44%
	Metastasis at Diagnosis	20%	29%
	Location in extremity	38%	23%

Table II

Proportion of Patients Who Abandoned Treatment by Disease and Treatment Era

		N	Patients who abandoned treatment (%)	p-value
All Diagnoses	2000–2004	323	27.0%	
	2005–2009	458	20.0%	0.0193
Osteosarcoma	2000–2004	107	32.0%	
	2005–2009	155	29.0%	0.6343
Ewing Sarcoma	2000–2004	68	13.0%	
	2005–2009	105	16.0%	0.5952
Rhabdomyosarcoma	2000–2004	112	32.0%	
	2005–2009	128	18.0%	0.011
Soft-Tissue Sarcoma	2000–2004	36	25.0%	
	2005–2009	70	10.0%	0.0411

Table III

Survival Analysis

			4-year OS		4-year AOS*			4-year EFS		4-year AEFS*	
		N	OS±SE (%)	p-value	AOS± SE (%)	p-value	N	EFS± SE (%)	p-value	AEFS ±SE (%)	p-value
	Overall	**778**	**40±3**		**31±2**		**777**	**30±3**		**24±2**	
Disease Extent	Localized Disease	479	52±3		42±3		479	39±3		33±3	
	Metastatic Disease	240	17±4	**<0.0001**	12±3	**<0.0001**	239	11±3	**<0.0001**	8±2	**<0.0001**
Treatment Era	2000–2004	321	41±3		30±3		321	30±3		23±3	
	2005–2009	457	39±5	0.41	32±4	0.92	456	30±4	0.63	26±4	0.93
Localized Disease, by treatment era	2000–2004	195	56±4		42±4		195	41±4		33±4	
	2005–2009	284	49±6	0.13	42±5	0.77	284	38±5	0.27	33±5	0.67
Diagnosis	Osteosarcoma	262	31±4		23±3		261	24±4		19±3	
	Ewing Sarcoma	173	36±6		31±5		172	26±5		23±5	
	Rhabdomyosarcoma	238	44±5		34±4		239	33±4		27±4	
	Soft-Tissue Sarcoma	105	53±8	**0.004****	42±8	**0.0007****	105	43±8	**0.0028****	35±7	**0.0005****
Disease Location#	Bone Sarcoma	335	32±4		25±3		334	23±4		20±3	
	Soft-Tissue Sarcoma	407	46±4	**0.0005**	36±3	**0.0006**	407	36±4	**0.0003**	29±3	**0.0004**
	Extremity	383	35±4		28±3		381	27±4		22±3	
	Other Location	359	44±4	**0.044**	35±4	**0.0239**	360	33±4	0.0727	27±3	**0.0376**

*AOS is abandonment-sensitive overall survival and AEFS is abandonment-sensitive event-free survival (see “Statistical Definitions” in methods for details)

**Global test for differences in survival curves across diagnoses. Pairwise analysis done (not shown) to detect individual differences.

#Disease Location (see “Subdivision of Data” in methods for details)