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Childhood osteosarcoma: Incidence and survival in Argentina. Report from the National Pediatric Cancer Registry, ROHA Network 2000–2013

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Abstract

Background: Differences in incidence and survival in osteosarcoma reports are considerable worldwide.

Purpose: This study describes the incidence and survival of patients with osteosarcoma in Argentina with data from the National Pediatric Cancer Registry (ROHA), and the impact of age, gender, stage, regional, and socioeconomic indicators on outcome.

Methods: Pediatric patients with osteosarcoma reported to ROHA from 2000 through 2013 were analyzed, the annual age-standardized incidence rate (ASR) was calculated using the National Vital Statistics, and survival was estimated. The extended human development index (EHDI) for each reporting region was used as an indicator of socioeconomic status.

Results: There were 515 cases of osteosarcoma identified, yielding an ASR of 3.2/1,000,000 children (0–14 years old). The ASR did not vary significantly by year of diagnosis but ranged from 4.0/1,000,000 in the Cuyo/Western Central region to 2.7/1,000,000 in the northeast region ($P < 0.000$). The estimated 5-year survival rate was 45% (95% confidence interval [CI] 44–51%), with no difference by sex, diagnosis year, region, or EHDI score ($P > 0.1$ in all cases). Survival rate for localized disease was 52% (95% CI 45–57%) and for metastatic 22% (95% CI 15–30%).

Conclusions: In Argentina, ASR of osteosarcoma is similar to that in high-income countries, but survival is lower in all regions. Future work will focus on identification and reduction of causes of preventable treatment failure.

KEYWORDS

Argentina, children, incidence, osteosarcoma, survival

1 | INTRODUCTION

Bone tumors account for 3–5% of pediatric cancers.[1] In the International Classification of Childhood Cancer (ICCC),[2] malignant bone tumors were classified into group VIII, of which osteosarcomas represent the majority.[3,4] Osteosarcoma is characterized by a broad histopathologic diversity,[4,5] and a varied geographical annual incidence[6] ranging from 5.1 in Portugal to 0.3 in African Americans, per 1,000,000 children aged 0–14 years. The tumor most frequently occurs in males and predominantly in the limbs.[7] It is rarely diagnosed before the age of 5, the incidence shows a peak with age until around puberty, this primary peak is followed by a decrease and plateau in incidence in individuals between 25 and 60 years old.[8] Risk factors include the following: (a) pre-existing bone conditions (Paget disease); (b) genetic-familial factors (hereditary retinoblastoma, Li–Fraumeni

Abbreviations: AAPC, average annual percentage change; ASR, age-standardized incidence rate; CI, confidence interval; DCO, death certificate only; EHDI, extended human development index; ES, Ewing sarcoma; ICCC, International Classification of Childhood Cancer; POU, Pediatric Oncology Unit; ROHA, National Pediatric Cancer Registry; SD, standard deviation; SEER, Surveillance, Epidemiology, and End Results

syndrome, Rothmund–Thompson syndrome, Bloom syndrome, familial osteosarcoma, and Diamond–Blackfan anemia); (c) chemical factors (antineoplastic drugs); and (d) physical factors (ionizing radiation).[8] Other factors studied remain controversial, such as parental occupation, rates of pre- and postpubertal growth, and fluoride in drinking water.[6]

Between 12 and 30% of osteosarcoma patients present with metastasis at diagnosis, predominantly in the lungs.[9] A strong correlation has been described between metastasis at diagnosis and a low extended human development index (EHDI) and socioeconomic status, respectively.[10,11]

International collaborative teams have shown that the most effective regimens of antineoplastic agents against osteosarcoma consist of a combination of doxorubicin, cisplatin, high-dose methotrexate, and ifosfamide. These drugs should be administered by experienced pediatric oncologists at institutions with the appropriate infrastructure and a multidisciplinary modality for the care for patients with these tumors.[4,12] Surgical treatment may be conservative or non-conservative depending on tumor location and size.[13]

Survival has remained unchanged over the past two decades.[3] According to the data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program, 5-year overall survival in patients with localized disease has been 70%, while 10-year survival for those with metastatic disease has been 20%.[3,9] Factors that have been described to have an impact on the survival of children with osteosarcoma are metastasis at diagnosis, location (axial vs. extremities), total resection of the tumor, and tumor response to preoperative chemotherapy.[9,14]

Here we describe incidence and survival rates of patients with osteosarcoma registered at the National Pediatric Cancer Registry (ROHA) over a 14-year period. Survival by sex, age, tumor stage and location, geographical region, and EHDI are reported. This is a study to provide incidence and survival data of patients with osteosarcoma at a national level in a Latin-American country.

2 | MATERIALS AND METHODS

2.1 | Country information

Argentina is a large country of 2.8 million square kilometers with a population of 40,117,096, mainly urban (90%) inhabitants. Data on the general population were obtained from the National Office of Statistic and Censuses (Instituto Nacional de Estadística y Censo—National Institute of Statistics and Census, Census 2010). Almost 46% of the population is concentrated in the capital and the province of Buenos Aires. Argentina is divided into 24 political units: 23 provinces plus the city of Buenos Aires, called the Federal District. Five main geographical regions are shown on the map in Figure 1. In 2010, there were 10.2 million children between 0 and 14 years of age in the following distribution: 60% in the Central region, 14% in the Northwest, 12% in the Northeast, 8% in the Cuyo/Western Central region, and 6% in the South. Throughout the country, there are 28 public hospitals that provide care for children with cancer at no cost to the patient.

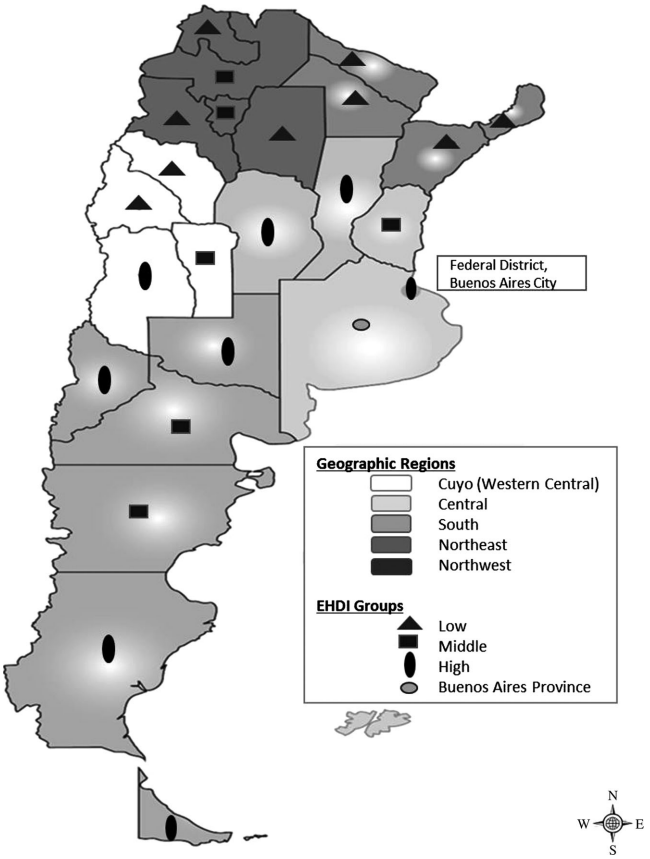

FIGURE 1 Map of Argentina. Geographic regions and groups of provinces by EHDI

2.2 | Data sources

The ROHA is a pediatric cancer registry with national coverage using active data collection since 2000 and is part of the National Institute of Cancer of the Ministry of Health. The data from the ROHA network come from different sources. Most cases are reported by Pediatric Oncology Units (POUs) from all regions of the country. Additionally, the ROHA receives information from 10 population-based cancer registries, centers for radiation therapy, and pathology departments. The data collected for each patient includes the name, identification number, date of birth, sex, home address (including geographical region), EHDI of the geographical region from which the patient comes, diagnosis date, histopathology, tumor sites, presence of metastases, stage, method of diagnostic confirmation (histologic, imaging diagnosis, or death certificate). Cases are codified according to the International Classification of Diseases for Oncology and the ICCC-3.[2,15]

2.3 | Case definition

A case was defined as a child younger than 15 years of age diagnosed with osteosarcoma from January 1, 2000, through December 31, 2013, living in Argentina at the time of diagnosis. The EHDI is

TABLE 1 Incidence rate of osteosarcoma in Argentina, 2000–2013

Morfology		Cases	Incidence[a]	IC 95%
Osteosarcoma		515	3.2	(2.9–3.5)
By sex				
Male		265	3.3	(2.9–3.7)
Female		250	3.1	(2.8–3.5)
By age				
< 1 year		0		
1–4 years		14	0.4	(0.2–0.6)
5–9 years		137	2.9	(2.4–3. 3)
10–14 years		364	7.5	(6.7–8.3)
By region				
Central	-EHDI: 0.774	286	3.0	(2.6–3.3)
Northwest	-EHDI: 0.673	85	3.9	(3.1–4.7)
Cuyo/Western Central	-EHDI: 0.718	53	4.0	(2.9-5.1)
Northeast	-EHDI: 0.653	51	2.7	(1.9–3.4)
South	-EHDI: 0.718	40	4.0	(2.7–5.2)
By EHDI groups[b]				
Buenos Aires		177	3.0	(2.6–3.5)
High		143	3.2	(2.7–3.7)
Low		125	3.5	(2.9–4.2)
Middle		70	3.2	(2.5–4.0)

[a]Age standardized rate per 1.000.000 population aged 0-14 years.
[b]Extended Human Development Index

a measure of levels of progress and well-being evaluated on three basic dimensions: the possibility of living a long and healthy life (life expectancy and preventable child mortality), education (literacy rate), and a decent standard of living (total family income per capita, employment rate). Provinces are classified into three EHDI groups: high (over 0.768), medium (between 0.752 and 0.703), and low (less than 0.700).[16] The average country-wide EHDI was 0.704; eight provinces had a high EHDI, seven a medium EHDI, and nine had a low EHDI (Fig. 1).[16]

2.4 | Analysis

Numerical variables were summarized using the median and standard deviation (SD), while categorical variables are presented as counts and percentages. Incidence and mortality rates were calculated using Epidat (version 3.1).[17] Annual standardized incidence rates per million children younger than 15 years (age-standardized incidence rate [ASRs]) for each age group are presented using the world standard population.[18] Average annual percentage change (AAPC) was analyzed based on estimated yearly ASR. Five-year survival was calculated with an actuarial using IBM SPSS Statistics, Version 21.0 (IBM Corp., 2012).[19] Overall survival was defined as the time from the date of diagnosis to the date of death, if the child died within 5 years of diagnosis, or were censored at 5 years if still living. Patients who lost contact with the treating center were classified as lost to follow-up on the date of the last visit. The date of incidence was defined as the date of confirmation of the diagnosis. For the cases that were identified through a death certificate only (DCO), the date of incidence was defined as the date of death.

3 | RESULTS

Osteosarcoma incidence rate and 5-year overall survival probabilities in Argentina for the period 2000–2013 are shown in Tables 1 and 2, respectively.

Overall, 18,909 children aged 0–14 years diagnosed with cancer were registered in the ROHA from 2000 through 2013 (mean: 1,350 cases per year). Over this period of 14 years, a total of 892 (4.7%) cases were in ICCC-group VIII; 515 patients had osteosarcoma and 311 patients had Ewing sarcoma (ES). Of the children with osteosarcoma, mean age was 10.9 years (2.8 SD) and of those with ES 9.3 years (3.6 SD). The diagnosis was confirmed by histology in 98.1% (n = 505) and by DCO in 1.9% (n = 10) of the cases. Tumor location was in the extremities in 93.6% (n = 482), axial in 4.1% (n = 21), and unknown in 2.3% (n = 12). Of 515 patients, tumors were metastatic in 130 (31%), localized in 294 (69%), and unknown in 91 (18%). Data on surgical treatment were available for 357 of 515 (70%), of whom 88 (25%) underwent nonconservative surgery.

Between 2000 and 2013, ASR at diagnosis was 3.2/million per year and this figure did not increase significantly over this period with an AAPC of 2.40% ($P < 0.08$; Fig. 2). The ASR was 3.1 (95% confidence

TABLE 2 Five-year global survival probabilities of osteosarcoma in Argentina, 2000–2013 by gender, age group, location, stage, geographical region, and EHDI

	Cases		Deaths	Global Survival 5 years	
Morfology	n	%	n	%	IC 95%
Osteosarcoma	515	57.7	283	44.1	(39.5–48.6)
By gender					
Female	250	48.5	136	42.6	(36.0–49.0)
Male	265	51.5	147	45.6	(39.2–51.7)
By age					
Under 10 years	151	29.3	88	43.1	(34.8–51.1)
10 - 14 years	364	70.7	195	44.5	(39.0–49.9)
Location					
Extremities	482	93.6	264	44.3	(39.6–48.9)
Axial	21	4.1	12	42.9	(21.9–62.3)
Unknown	12	2.3	7	41.7	(15.3–66.5)
By stage					
Localized	294	57.1	142	51.6	(45.4–57.4)
Metastatic	130	25.2	96	22.2	(14.9–30.4)
Unknown	91	17.7	45	51.3	(40.2–61.4)
By Geographic region					
Central	286	55.5	163	42.1	(36.0–48.0)
Northwest	85	16.5	51	35.9	(24.8–47.1)
Cuyo/Western Central	53	10.3	25	55.1	(40.4–67.6)
Northeast	51	9.9	26	48.8	(34.0–62.0)
South	40	7.8	18	53.0	(35.2–68.0)
By EHDI groups					
Buenos Aires	177	34.4	103	41.2	(33.6–48.7)
High	143	27.8	72	49.5	(40.6–57.8)
Middle	70	13.6	38	44.0	(31.6–55.7)
Low	125	24.3	70	42.0	(32.7–51.1)

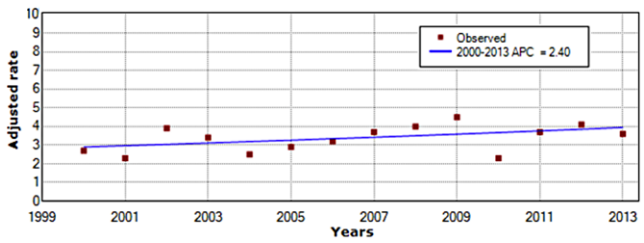

FIGURE 2 Osteosarcoma incidence trend in children under 15 years old, Argentina, 2000–2013. Age standardized rate per million. 0 joinpoints

interval [CI] 2.8–3.5) for females and 3.3 (95% CI 2.9–3.7) for males ($P < 0{,}50$). The incidence rate was higher in the second decade of life, as expected. There was considerable regional variation in incidence, with the highest incidence in the Cuyo/Western Central region (4.0; 2.9–5.1) and the lowest incidence in the Northeast (2.7; 1.9–5.2), but no differences in EHDI (Table 1).

Of all patients in ICCC group VIII (a), 98% (n = 503) could be evaluated for survival. Five-year survival was 44% (95% CI 40–49%), without significant sex differences. Localized tumors were found in 57% and metastatic disease in 25% of cases, the remaining 18% was unknown. In Table 2, deaths by sex, age group, tumor location and stage, geographic region, and EHDI are shown.

Of all patients with bone tumors, 49% had to travel to receive partial or total treatment at POUs in other provinces.

4 | DISCUSSION

4.1 | Incidence

The current study confirms that for osteosarcoma in Argentina, the ASR, sex ratio, the increased incidence around 10 years of age, and the earlier peak age in females compared with males are comparable to reports from SEER and in Europe.[20–23] The geographic disparity in the incidence of osteosarcoma has previously been described in European studies in Asia and some countries in Africa.[6,20] Table 3 shows incidence of osteosarcoma in Europe and two countries of South America. The data observed in this study show a considerable

TABLE 3 Incidence rate of osteosarcoma per million, and global 5-year survival probabilities in Argentina, Germany, United States, Europa, Uruguay, and Chile

	Argentina 2000-2013	Germany[21] 2004-2013	USA[22] 2007-2011	Europe [1] 1978-1997 2000/2007	Uruguay[a] 2003-2012	Chile[b] 2007-2012
Incidence rate (ASR)	3.2	3.1	4.2	2.8	4.2	3.9
Global Five-years-survival probabilities (%)	44.1	75	70.6	69.3[27]	-	-
EHDI	0.775	0.885	0.902	0.702	0.765	0.783

[a]Personal communication: August 2016. Registro Nacional de Cáncer. Comisión Honoraria de lucha contra el cáncer, Uruguay; Barrios E., Garau M, Alonso R, Musetti C.
[b]Personal communication: August 2016. Registro Nacional de Cáncer Infantil, Departamento de Epidemiología, Ministerio de Salud, Chile; Vallebuona Stagno C.

geographical variation in the incidence of osteosarcoma, with a higher incidence in the west of the country, the Cuyo/Western Central region, Patagonia, and the Northwest (Table 1 and Fig. 1). When analyzing incidence by EHDI, we observed a homogeneous distribution.

A difference in the prevalence of metastatic disease at the time of osteosarcoma diagnosis has been described in the literature[10,11] and attributed to progressive enlargement of microscopic lesions when diagnosis is delayed and potentially biologic differences by region.[24] Other important variables that play a role at the time of diagnosis of the disease and the finding of metastasis are axial location, tumor size, and older age.[10] Marko et al. have described a correlation between low EHDI and the increased incidence of metastatic osteosarcoma at diagnosis.[11] They reported a 30% rate of patients with metastasis at diagnosis compared to 19% in the United States and 39% in Central America. Unfortunately, in our study, it was not possible to analyze the correlation between metastasis at diagnosis and EHDI in the different regions of the country due to the lack of data on tumor stage and metastases.

4.2 | Survival

In Europe, accumulated 5-year survival increased significantly for all tumors from 54% in 1978–1982 to 75% in the period 1993–1997.[25] Five-year survival for osteosarcoma was 61% and ranged from 51% in Eastern Europe to 66% in Western Europe, over the period of 1993–1997.[26] Outcome was less favorable in the group of patients with metastatic disease, axial tumor location, and those who did not respond well to chemotherapy.[27] In Latin America, national data on survival for children younger than 15 years of age with osteosarcoma are scarce.

In Argentina, the 5-year survival rate is 44.1%, below the percentage that is reported for high-income countries. Although a difference in survival rate according sex in favor of females has been described,[27] this difference was not significant in our analysis. The decreased overall survival rate may be due to multiple factors: Argentina is a large country with profound sociocultural and economic differences. Making an early diagnosis, timely referral, performance of a biopsy, and adequate confirmation of the diagnosis by pathology studies still pose difficulties. The lack of standardized diagnostic and management practices also can affect survival.[5]

In European countries, the participation in cooperative groups has been associated with improved patient survival.[27] In Argentina, children with osteosarcoma are usually treated with pre- and postsurgical chemotherapy. Different regimens with or without high-dose methotrexate are used at different POUs, and currently there are no uniform treatment guidelines such that management varies. Some centers participate in the Latin-American Cooperative Group (Latin-American Pediatric Oncology Group) protocol, while others use institutional or individual treatment strategies.

This study has several limitations, most importantly the missing data on diagnostic delay, tumor size at diagnosis, and postchemotherapy tumor response.

In this study, we observed that the incidence of osteosarcoma has remained stable over the past 14 years. The incidence was higher in the west of the country, while it did not differ by EIDH, and the percentage of patients with metastatic disease was higher and survival was lower when compared with high-income countries.

A better understanding of the reason for the geographical variation, improvement of diagnostic and pathology study times, and the establishment of a uniform treatment (surgery–chemotherapy) protocol could improve the survival of these patients.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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