



Effective factors on clinical outcomes of children with osteosarcoma and Ewing bone tumors

Sasan Hejazi¹ , Mehran Noroozi¹ , Mohammad Amin Kuhestani², Farid Ghazizadeh¹ , Mohammad Karmiyar³, Ebrahim Sadeghi⁴ , Ahad Ghazavi⁴ , Hamidreza Houshmand⁵ 

¹Department of Pediatric Hematology and Oncology, Motahari Hospital, Urmia University of Medical Sciences, Urmia, Iran

²Urmia University of Medical Sciences, Urmia, Iran

³Department of Pediatric Infectious Disease, Motahari Hospital, Urmia University of Medical Sciences Urmia, Iran

⁴Associate Professor of Pediatric Neurology, Neurophysiology Research Center, Urmia University of Medical Sciences, Urmia, Iran

⁵Department of Pediatric Immunology and Allergy, Motahari Hospital, Urmia University of Medical Sciences, Urmia, Iran

*Correspondence to

Mehran Noroozi,

Email: mehranxnoroozi@gmail.com

Received 9 February 2020

Accepted 10 April 2020

Published online 23 May 2020

Keywords: Malignant bone tumors, Ewing sarcoma, Osteosarcoma, Survival, Metastasis

Abstract

Introduction: Malignant bone tumors account for 6% of childhood malignancies. The peak incidence rate for bone cancer is in adolescents. Geographic and race differences in incidence rate of bone tumors are important for correct diagnosis and treatment.

Objectives: This study aimed to investigate the demographic features of patients with malignant bone tumors and prognostic factors.

Patients and Methods: In a retrospective study, records of all patients diagnosed and treated for malignant bone tumor from March 1996 to February 2014 were investigated. Data were collected using checklists and analyzed using SPSS software.

Results: The most common type of bone tumor was Ewing sarcoma (73.7%) in patients who were over 10 years old (87.5%). Primary site of disease in most cases of osteosarcoma and Ewing sarcoma was distal femur (50% and 27.3%, respectively). Most common clinical manifestation was local pain and mass (88.5%). Regarding metastasis, 72.7% of osteosarcoma patients and 32.4% of Ewing sarcoma patients had metastasis. There was not statistically relationship between survival rate and gender, age group and stage of disease at diagnosis time. One, three and five-year survival rate was lower than the previous studies.

Conclusion: The incidence of Ewing sarcoma is more than osteosarcoma in West Azerbaijan. In our study there were no statistically important differences in survival rates of patients with metastasis at diagnosis time and those without metastasis.

Citation: Hejazi S, Noroozi M, Kuhestani MA, Ghazizadeh F, Karmiyar M, Sadeghi E, et al. Effective factors on clinical outcomes of children with osteosarcoma and Ewing bone tumors. *Immunopathol Persa*. 2020;6(2):e26. DOI:10.34172/ipp.2020.26.

Introduction

Malignant bone tumors account for about 6% of childhood malignancies (1). In the United States, the annual incidence of malignant bone tumors in children younger than 20 years is 7.8 per million. Malignant bone tumors in adults and children are mostly osteosarcoma (56%) and Ewing sarcoma (34%). Every year in the United States, 650-700 children are diagnosed with bone tumors (2). The peak of bone tumors is 15 years old, which is consistent with the sudden growth of adolescents. The incidence of osteosarcomas has two peaks in early adolescence and adults over 60 years old. Ewing sarcoma is a disease of young children and adults and is rare in older people. Generally, osteosarcoma happens in African American children more than white people (1).

Although the osteosarcoma etiology is unknown, certain factors are associated with

Key point

In a retrospective study, we found that the incidence of Ewing sarcoma is more than osteosarcoma in West Azerbaijan, Iran.

this event e.g. peak growth is associated with a developmental pubis mutation for pubic evolution (girls; 12 years/boys; 16 years), and height of patients, in which the height of patients with osteosarcoma is higher than the mean and the most common locations (distal femur, proximal humerus and proximal tibia) (3). Symptoms of osteosarcoma usually occur a few months (an average of 3 months) before the diagnosis. Patients usually have localized pain symptoms (90%), topical swelling (50%), decreased motion range (45%), pathologic fracture (8%) and rarely joint effusion (1). Treatment for osteosarcoma is surgery and chemotherapy. Complete relief from the



disease is 60%-80% for patients with non-metastatic osteosarcoma treated with chemotherapy as an adjuvant therapy; two-survival rate of patients with metastatic osteosarcoma is about 10%-30% (4,5).

Ewing sarcoma is the second primary malignant neoplasm prevalent in childhood. Approximately 80% of patients with Ewing sarcoma diagnosis were aged less than 20 years. In Asian and African-American children, the incidence of Ewing sarcoma is extremely low and does not correlate with familial cancers, and unlike osteosarcoma, the risk of Ewing sarcoma does not increase after exposure to radiation (1,6).

Metastasis is an important prognostic factor. Other factors include older age, axillary tumors, larger tumor size, and increased serum LDH levels (7,8). Gender and area of involvement are important factors for diagnosis (9). Geographic differences and race have a role in the incidence of bone tumors (9,10).

Femoral bone is one of the most common focal areas of primary involvement in Ewing sarcoma among Iranian children and the most common focal area is pelvis in Western countries (11). Ewing Sarcoma treatment involves surgery and radiotherapy for topical control of primary lesions and chemotherapy to eradicate subclinical micrometastases. Generally, the 5-year survival rate for a person suffering from Ewing sarcoma treated with radiotherapy and chemotherapy is approximately 60-70%. Metastatic patients have about 20-30% in their five-year survival rate. In Iran, unlike in western countries, the number of patients with Ewing sarcoma is more frequent than those with osteosarcoma, and Ewing sarcoma prognosis in Iran was better than in the West (11).

Objectives

This study aimed to clarify the status of patients with malignant bone tumors in the country and to investigate the relationship between demographic factors and other possible influencing factors with clinical outcomes of the disease.

Patients and Methods

Study design

In this analytical retrospective study, records of all patients diagnosed and treated for malignant bone tumor from March 1996 to February 2014 were investigated. Data were collected using checklists and analyzed using SPSS software. Sampling method was census. Inclusion criteria were all patients who had archived records and started to take curative measures with definite diagnosis. Exclusion criteria were incomplete and illegible records.

Ethical issues

The study was approved by the ethical committee of Shahid Beheshti University of Medical Sciences (#IR.UMSU.REC.1394.220). Written consent was obtained from each

patient before the study. In all stages of research, the tenets of the Declaration of Helsinki were observed. This study was extracted from the medical thesis of Mohammad Amin Kuhestani at this university (#94-0-32-1835).

Statistical analysis

The data were analyzed using SPSS software. The results were reported as frequency distribution for descriptive statistics. Analytical statistics (The Kaplan-Meier, Cox regression, Cox regression and chi-square) were performed to measure the variables affecting the clinical outcomes of patients.

Results

During the study, a total of 61 cases of patients with bone tumors, including 16 cases of osteosarcoma and 45 cases of Ewing sarcoma, were studied. Patients with osteosarcoma mostly lived in urban areas (68.8%) and children's place of birth in most cases was Urmia (62%) and Maku (12.5%); 63.6% of cases with Ewing sarcoma were born in urban areas and their place of birth was reported in most cases in Urmia (43.2%) and Khoy (11.4%). The minimum age of a person with osteosarcoma was 7 years and maximum age was 14 years and the mean age of patients was 12 ± 1.98 years. Most of the cases were over the age of 10 years (87.5%). The minimum age of the patients with Ewing Sarcoma was 1 year and the maximum age was 15 years and the mean age of the patients is 9.4 ± 3.9 years. Of these, 53.3% were older than 10 years old and 46.7% were less than 10 years old. Patients with osteosarcoma have a higher mean height than those with Ewing sarcoma. Most cases of bone tumors were presented with premature mass (42.6%) or pain (31.1%) or both (14.8%). Other clinical manifestations include fever, weight loss, and pathologic fracture. Several symptoms of pressure on the spinal canal, such as walking disorder and claudication, paraplegia, urinary and stool incontinence, muscle weakness were observed in the Ewing sarcoma (Table 1). Hemoglobin, white blood cell count (WBC), erythrocyte sedimentation rate (ESR), platelet and stage status by the type of tumor were compared (Table 2). Of the 16 cases of osteosarcoma, femur bone in the distal region is the most common focal area (50% of cases) and tibia proximal (25%). Of the 45 cases of Ewing sarcoma, femur bone was the most common bone (27.3%). Of the 16 patients with osteosarcoma, 7 patients had discontinued the follow up, and information about their outcome was unclear, and 6 patients died. One case was under treatment and in progress, and two patients fully recovered. One, three and five-year survival rates for osteosarcoma were 77.7%, 33.3% and 33.3%, respectively. According to the log-rank test, the survival time of patients with osteosarcoma was not significant regarding gender, stage of disease and age group ($P < 0.05$; Figure 1A and 1B). One, three and five-year survival rate of patients with Ewing sarcoma

Table 1. Primary manifestations of the disease by type of tumor

Primary manifestations		Osteosarcoma	Ewing
Mass	No.	4	22
	%	25.0	48.9
Pain	No.	6	13
	%	37.5	28.9
Fever	No.	1	0
	%	6.3	0.0
Wight loss	No.	1	0
	%	6.3	0.0
Pathologic fracture	No.	0	1
	%	0.0	2.2
Others	No.	0	3
	%	0.0	6.7
Pain and mass	No.	4	5
	%	25.0	11.1
Others and fever	No.	0	1
	%	0.0%	2.2

Table 2. Hemoglobin, ESR, platelet, WBC and stage status of the patients by type of tumor

Variable		Osteosarcoma	Ewing
WBC	<4000	No.	6
		%	37.5
	4000-11000	No.	10
		%	62.5
>11 000	No.	0	
	%	0.0	
Hemoglobin (g/dL)	<12	No.	9
		%	56.3
	>12	No.	7
		%	43.8
Platelets/ μ L	<150 000	No.	3
		%	20.0
	150 000-450 000	No.	12
		%	80.0
>450 000	No.	0	
	%	0.0	
ESR (mm/h)	<10	No.	2
		%	16.7
	>10	No.	10
		%	83.3
Stage	Stage I	No.	2
		%	13.3
	Stage II	No.	9
		%	60.0
	Stage III	No.	3
		%	20.0
	Stage IV	No.	1
		%	6.7

WBC, White blood cell count, ESR, erythrocyte sedimentation rate.

were 87.5%, 53.1% and 50%, respectively. According to the log-rank test, survival time of Ewing patients was not significant regarding gender, stage of disease and age group ($P < 0.05$; [Figure 2A](#) and [2B](#)).

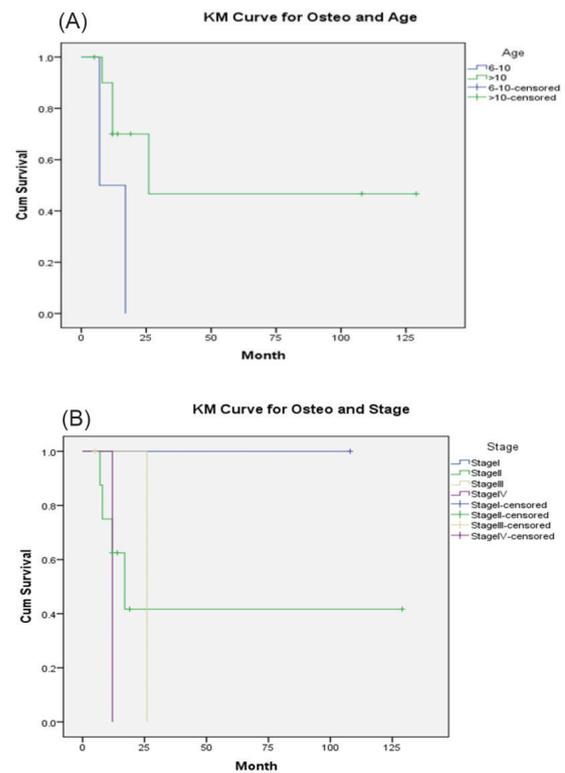


Figure 1. Survival curve of patients with osteosarcoma by (A) age group and (B) stage using log rank test

Discussion

Malignant bone tumors in adults and children are mostly osteosarcoma (56%) and Ewing sarcoma (34%). In the United States, every year, 650-700 children are diagnosed with bone tumors (1, 2). In a study in Pakistan, 280 cases of primary malignant tumors were studied. The highest was osteosarcoma (36.4%) and Ewing sarcoma (8.7%) among primary cancer tumors (12, 13). In our study, malignant bone tumors were mostly Ewing sarcoma (73.7%) versus osteosarcoma (26.3%). Unlike other countries that report the prevalence of osteosarcoma more than Ewing sarcoma, it seems in our country that Ewing sarcoma is more prevalent than osteosarcoma in the young age group.

The peak of bone cancer is 15 years old, which is consistent with the sudden growth of adolescents (1). In our study, 87.5% of patients with osteosarcoma at the time of diagnosis were more than 10 years old, which was associated with the age of adolescent, and 46.7% of cases with Ewing sarcoma were under the age of 10 years, which, unlike osteosarcoma, seems to be a significant prevalence of Ewing sarcoma throughout the life of an individual, and is consistent with previous studies. In a study by Aksnes et al on the state of health in the long-term follow up of patients treated for osteosarcoma and Ewing sarcoma, the prevalence of male and female patients were 52% and 48%, respectively (14). In our study, the prevalence of both types of tumors in males was slightly higher than females, which was consistent with other studies (15). In a study by Lofti

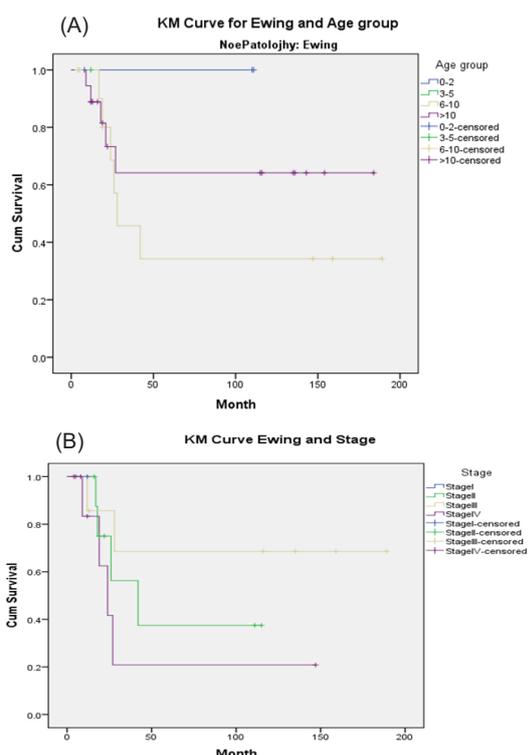


Figure 2. Survival curve of patients with Ewing sarcoma by (A) age group and (B) stage using log rank test

et al on the pathology of primary bone tumors, in all types of pathology including malignant, benign and pseudo-tumoral, female patients were more abundant than men (16).

In our study, most cases of bone tumors have been reported with pain or localized swelling or both. Other unidentified symptoms in previous studies include spinal cord symptoms such as walking disorder and claudication, paraplegia, urinary and stool incontinence, and muscle weakness. In a study by Bielack et al, prognostic factors in osteosarcoma were studied; the height of patients with osteosarcoma was higher than the mean, and the most common locations were distal femur, proximal humerus, and proximal tibia (3). In our study, distal femur (50% of cases) was the most common focal area of the involvement and proximal tibia in 25% of cases, which is consistent with the previous study. Ewing sarcoma involves commonly distals and the pelvis (1). In our study, the most common bone involved in Ewing sarcoma was femur bone (27.3%). The tumor has also affected other parts of the body including the spine, right and left hemithoraces, left ulnar, right iliac, mandibles, and deltoid right muscle.

In a retrospective study conducted by Iliæ et al, on osteosarcoma and Ewing sarcoma in children and adults, one, three and five-year survival rates were 100%, 86%, and 77.7%, respectively for osteosarcoma and 88.2%, 70.5% and 64.7%, respectively for Ewing sarcoma (17). In our study, one, three and five-year survival rates were 87.5%, 53.1% and 50%, respectively for Ewing sarcoma, and 77.7%,

33.3% and 33.3%, respectively for osteosarcoma. Low survival rates in our patients can be due to lack of timely follow up of patients for the advancement of treatment without appropriate social work practices and facilities for infectious care in immunocompromised patients such as proper isolation.

In the study of Iliæ et al, the survival rate was not related to age and gender for osteosarcoma and Ewing sarcoma. There was a statistically significant difference in the survival rate of patients with metastasis at diagnosis (stage 3) compared with non-metastatic patients (stage 2). There was no difference in survival rates in patients with lung metastasis and bone metastases in both sarcomas (17). In our study, the survival rate of patients with osteosarcoma or Ewing sarcoma was not significantly related to gender. The survival rate of patients with osteosarcoma and Ewing sarcoma was not significantly related to different age groups.

Conclusion

It is generally concluded that in West Azerbaijan, the most prevalent type of bone tumor is Ewing sarcoma (73.7%). Osteosarcoma was prevalent in patients over 10 years old (87.5%), in which, unlike in those suffering from Ewing sarcoma, the prevalence of Ewing sarcoma was almost the same throughout life. The primary site of involvement in most cases is osteosarcoma and Ewing sarcoma was femur (50% and 27.3%, respectively). Regarding ESR, it was increased considerably. There was no significant relationship between survival rates of patients with gender, age groups and stage of disease at diagnosis time. One, three and five-year survival rate in this study was lower than the previous studies.

Limitations of the study

Due to the rarity of the Ewing bone tumors in the general population, the sample size was relatively small.

Acknowledgments

This study was taken from the medical thesis with code 94-0-32-1835. The authors thank the research deputy of Urmia University of Medical Sciences and are also grateful to the Oncology department for helping with the study.

Authors' contribution

Study concept and design; SH, MN, MAK and HH. Collection of data; AG, ES and MAK. Interpretation of data; MN, FG and AG. Draft of the manuscript; MN, SH, HH and ES. Final revision; MN and SH. All authors approved the latest version of the article.

Conflicts of interest

The authors declared that there is no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

References

1. Lanzkowsky P, Lipton JM, Fish JD, editors. *Lanzkowsky's manual of pediatric hematology and oncology*. Academic Press; 2016.
2. Gurney JG, Swenson AR, Bulterys M. *Malignant bone tumors: cancer incidence and survival among children and adolescents: Unites States SEER Program 1975-1995*. SEER Program. Bethesda MD: National Cancer Institute; 1999.
3. Bielack SS, Kempf-Bielack B, Delling G, Exner GU, Flege S, Helmke K, 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*. 2002;20:776-90. doi: 10.1200/JCO.2002.20.3.776
4. Bielack SS, Marina N, Ferrari S, Helman LJ, Smeland S, Whelan JS, Reaman GH. Osteosarcoma: the same old drugs or more? *J Clin Oncol*. 2008;26:3102-3; author reply 3104-5. doi: 10.1200/JCO.2008.17.1108
5. Kager L, Zoubek A, Pötschger U, Kastner U, Flege S, Kempf-Bielack B, et al. Primary metastatic osteosarcoma: presentation and outcome of patients treated on neoadjuvant Cooperative Osteosarcoma Study Group protocols. *J Clin Oncol*. 2003; 21:2011-8. doi: 10.1200/JCO.2003.08.132
6. Cangir A, Vietti TJ, Gehan EA, Burgert Jr EO, Thomas P, Tefft M, et al. Ewing's sarcoma metastatic at diagnosis results and comparisons of two intergroup Ewing's sarcoma studies. *Cancer*. 1990;66:887-93. doi: 10.1002/1097-0142
7. Leavey PJ, Mascarenhas L, Marina N, Chen Z, Krailo M, Miser J, Brown K, Tarbell N, Bernstein ML, Granowetter L, Gebhardt M. Prognostic factors for patients with Ewing sarcoma (EWS) at first recurrence following multi-modality therapy: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2008;51:334-8. doi: 10.1002/pbc.21618
8. Shatkovskaia VV, Ladan AI. Factors of external environment and the incidence of malignant bone tumors. *Ortop Travmatol Protez*. 1983;(1):39-41.
9. Dahlin DC, Unni KK. *Bone tumours; general aspect and data on 8542 cases*. Charles C Thomas Pub Ltd; 1986.
10. Polednak AP. Primary bone cancer incidence in black and white residents of New York State. *Cancer*. 1985;55:2883-8. doi: 10.1002/1097-0142
11. Siegel RL, Miller KD, Jemal A. *Cancer statistics, 2019*. *CA Cancer J Clin*. 2019;69:7-34. doi: 10.3322/caac.21551.
12. Bahebeck J, Atangana R, Eyenga V, Pisoh A, Sando Z, Hoffmeyer P. Bone tumours in Cameroon: incidence, demography and histopathology. *Int Orthop*. 2003;27:315-7. doi: 10.1007/s00264-003-0480-7
13. Steward AG. Pattern of malignant bone tumour in Northern areas of Pakistan. *J Pak Med Assoc*. 1995;45:256.
14. Aksnes LH, Bauer HC, Dahl AA, Fosså SD, Hjorth L, Jebsen N, et al. Health status at long-term follow-up in patients treated for extremity localized Ewing sarcoma or osteosarcoma: A Scandinavian sarcoma group study. *Pediatr Blood Cancer*. 2009;53:84-9. doi: 10.1002/pbc.22027
15. Allen CE, Laetsch TW, Mody R, Irwin MS, Lim MS, Adamson PC, et al. Target and agent prioritization for the Children's Oncology Group—National Cancer Institute Pediatric MATCH Trial. *J Natl Cancer Inst*. 2017;109(5). doi: 10.1093/jnci/djw274.
16. Lotfi M. Frequency of Primary Bone Tumors Pathology in Kurdistan Province, from 1996 to 2000. *Sci J Kurdistan Univ Med Sci*. 2005;29:59-64.
17. Iliæ I, Manojloviæ S, Æepuliæ M, Orliaæ D, Seiwerth S. Osteosarcoma and Ewing's sarcoma in children and adolescents: retrospective clinicopathological study. *Croat Med J*. 2004;45:740-5.