RESEARCH ARTICLE

The Survival and Incidence Rate of Ewing Sarcoma; a National Population-based Study in Iran (2008-2015)

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Abstract

Background: The effect of race and ethnicity on some kind of malignant bone tumors including Ewing sarcoma has been proven in different studies. In order to evaluate the latter, national cancer registries may help to increase understanding about potential cancer causes, prevention and control strategies, and apply these findings to control health problems among populations with similar characteristics.

Methods: A national population-based cancer registry study based on all patients affected by Ewing Sarcoma was registered in the Iran National Cancer Registry (INCR) between 2008 and 2015 was designed. Demographic data of microscopically confirmed cases of bone Ewing sarcoma were registered. Patients with Ewing sarcoma were divided in groups to describe the primary site of the tumor (including axial or appendicular bones) and analyzed. In order to analyze the survival rate, randomized selection of the patient through the INCR data-base was performed.

Results: A total of 678 cases of malignant Ewing sarcoma of the bone were identified through the INCR. The mean age of Ewing sarcoma in Iran was 21.53 years. Nearly half of patients were observed at the age group of 15-24. The total crude incidence rate of Ewing sarcoma was 1.29 in 1 million. The mean 5 year survival rate was 47%. The Mean survival rate for study population was 5.53.

Conclusion: The crude incidence rate of Ewing sarcoma in Iran is relatively lower with respect to other registries. The majority of patients are in 15-25 years group and shows affection by Ewing sarcoma in an older age. Socioeconomic factors had direct influence on survival rate.

Level of evidence: IV

Keywords: Ewing sarcoma, Malignant bone tumors, Sarcoma

Introduction

Ewing sarcoma is a malignant tumor of the bone and soft tissue and was first described by James Ewing in 1921(1). Considering the childhood and adolescent population, Ewing sarcoma is the second most frequent bone malignancy following osteosarcoma while this malignancy is the most frequent bone sarcoma

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in children younger than 15 years (2). Generally, primary bone sarcomas include 0.2% of all malignancies. The incidence of Ewing sarcoma in industrialized western countries has been reported as 1.2-2.93 in one million population in different studies in England and united states; however, other geographical and ethnical registries including Africa and East Asia have reported lower incidence rates (2-4).

The aim of cancer epidemiology study is to increase the understanding about the potential cancer causes, prevention and control strategies, and application of these findings to control health problems. In some kinds of cancers including Ewing sarcoma the ethnic and race have strong influence on tumor epidemiology (3, 5)with a higher incidence noted in populations of European rather than African or Asian ancestry. The goal of the current study was to evaluate racial and ethnic differences in presentation and overall survival (OS. In order to evaluate the influence of ethnic and race on specific tumors the data base can be registered according to geographical zones and nations. In Iran and more comprehensively in the Middle East countries with nearly similar ethnical characteristics, there are few regional studies on the epidemiological aspects of bone cancers including Ewing sarcoma. Based on the data derived from Iran National Cancer Registry (INCR), this paper provides a detailed analysis of the incidence, demographic factors, and epidemiology of Ewing sarcoma of bone among the Iranian population (6). INCR is a preliminary registry of cancers in the territory of Iran based on the data provided by the ministry of health and medical education.

The aim of this study is to report epidemiological description of Ewing sarcoma according to available cancer registry in order to provide data for further oncology studies and improve the defects of cancer registry.

Materials and Methods

This was a national population-based cancer registry study based on all patients affected by Ewing Sarcoma registered in the INCR between March 20, 2008, and March 20, 2015. Only microscopically and pathologically confirmed cases of Ewing sarcoma in the territory of Iran were derived from data registry and enrolled in this study. Since the INCR in Iran is a subdivision of the ministry of health and medical education, registered data cover nearly all diagnosed cases of Iran population during these 7 years. Cases were excluded from the study when the case inquiry were not possible and when quality criteria standards did not met the entire time period. International Classification of Diseases for Oncology (ICD-O-3) were used to classify Ewing sarcoma of the bone (7). According to ICD-O-3, Ewing sarcoma of the bone with topography codes (C-code) C40.0-40.9 and C41.0-41.9 were divided in groups to describe the primary site of the tumor (including the axial or appendicular bones) and analyzed. C-code 40 contains malignant neoplasms of bone and articular cartilage of limbs with subtypes including: C40.0, scapula and long bones of upper limb; C40.1, short bones of upper limb; C40.2, long bones of lower limb; C40.3, short bones of lower limb; C40.8, overlapping lesion of bone and articular cartilage of limbs and C40.9, bone and articular cartilage of limb, unspecified. C-code 41 contains malignant neoplasm of bone and articular cartilage of other and unspecified sites in which subtypes C-code 41.2 include vertebral column and C-code 41.4 include pelvic bones, sacrum and coccyx bones. Histology codes were not available for the majority of patients and were consequently excluded completely from this study.

In the medical records of these patients, variables such as age, sex, location of cancer, and city of residence were recorded. In order to analyze the survival rate, randomized selection of the patient through the INCR data-base was made. The selected patients were communicated telephonically and the data regarding the survival were collected and registered using a questionnaire. Death due to Ewing sarcoma and the interval between diagnoses to death were registered as treatment failure and survival time, respectively. In order to evaluate the effect of socio-economic and cultural issues on survival and incidence of the disease, data were separately analyzed according to nine different geographic areas of Iran including north-west, mid-west, south-west, north, center-north, center, center-south, east, and south-east. The rate of literacy, employment, urban-rural population ratio, and family income for each geographical region of Iran (8,9) was derived from previously registered data and analyzed with survival rate data to understand the influence of socioeconomic factors on survival rate of Ewing sarcoma [Table 1].

Descriptive statistics mean ± standard deviation (SD) for continuous variables, and frequency (percentile for categorical variable) was used to summarize the variables information. The binominal proportion test was performed to compare the true proportion of two groups. The chi-square test of independence was used to determine the relationship between sex and C-code. Man-Whitney test was used to compare the mean age between two C-code classes (40 and 41). The Cox regression test was performed to assess the impact of variables on survival time and the Kaplan-Meier method was used to estimate the cumulative survival of Ewing sarcoma patients. The crude incidence rate, age-standardized incidence rate, mortality rate, and consequently survival rate were estimated. All analyzes were performed using the IBM SPSS, version 25, and the $P \leq 0.05$ was defined as significance level.

Results

Demographic and tumor characteristics of Ewing sarcoma of the bone diagnosed from March 20, 2008, and March 20, 2015 in Iran were summarized and analyzed. Out of 736 patients, 58 cases were excluded from the study due to incomplete information.

Through 678 enrolled patients with Ewing sarcoma, 425 (62.7%) were male and 253 (37.3%) were female. Among patients with c-code 40, 238 (61.20%) were male and 151 (38.80%) were female; among patients with c-code 41, 187 (64.70%) were male and 102

Table 1. Geographic Areas classification and socioeconomic factors

	Literacy (%)	Employment (%)	Popuation Urban/ rural (ratio)	Family income per year (Rials)
North	84.69	88.25	1.18	400432825
South west (upper)	84.26	85.35	1.47	469933897
Middle west	82.36	86.8	1.59	344053670
South west (lower)	82.35	84.85	1.15	212647199
North west	80.27	88.05	1.65	404110465
Center (north)	86.75	87.22	7.4	4092666719
Center (south)	75.41	86.07	1.18	156344174
East	82.14	90.6	1.80	139629736
Center (central)	86.4	86.2	3.65	275838949

Table 2. The frequency of Ewing Sarcoma based on the sex and C-subcode

	Frequency (Percentage)			ASR		
C-subcode	Male	Female	Total	Male	Female	Total
C40.0 (Scapula and long bones of upper limb)	40 (9.4)	29 (11.5)	69 (10.2)	0.15	0.12	0.14
C40.1 (Short bones of upper limb)	12 (2.8)	5 (2)	17 (2.5)	0.04	0.02	0.03
C40.2 (Long bones of lower limb)	150 (35.3)	92 (36.4)	242 (35.7)	0.53	0.38	0.46
C40.3 (Short bones of lower limb)	14 (3.3)	10 (4)	24 (3.5)	0.05	0.04	0.04
C40.9 (Bone and articular cartilage of limb, unspecified)	22 (5.2)	15 (5.9)	37 (5.5)	0.08	0.05	0.07
C41.0 (Bones of skull and face)	11 (2.6)	5 (2)	16 (2.4)	0.04	0.02	0.03
C41.1 (Mandible)	3 (0.7)	9 (3.6)	12 (1.8)	0.01	0.04	0.02
C41.2 (Vertebral column)	31 (7.3)	11 (4.3)	42 (6.2)	0.11	0.04	0.07
C41.3 (Ribs, sternum and clavicle)	16 (3.8)	11 (4.3)	27 (4)	0.05	0.05	0.05
C41.4 (Pelvic bones, sacrum and coccyx)	68 (16)	34 (13.4)	102 (15)	0.23	0.12	0.17
C41.9 (Bone and articular cartilage, unspecified)	58 (13.6)	32 (12.6)	90 (13.3)	0.21	0.13	0.17
Total	425 (100.0)	253 (100.0)	678 (100.0)	1.50	0.98	1.25

(35.30%) were female. Using binominal proportion test to assess the assumption of the equality of male and female in each c-code (40 and 41), the ratio of men in both c-codes was significantly higher (*P<0.001*). Evaluation of the total proportion of the population study showed that c-code 40 was significantly more frequent than the c-code 41. Using Chi-square test for independence, no relationship was found between sex and c-code 40 and 41 (*P=0.348*). Table 2 shows the frequency of tumor topography and sex according to c-code 40 and 41 subtypes.

The mean age of Ewing sarcoma was 21.53 years (range 0-80). Among male patients with Ewing sarcoma, the mean age was 21.74±12.46, while females showed the mean age of 21.17±14.38. However using independent T-Test, the mean age of patient with Ewing sarcoma was not affected by sex of the patient (*P=0.585*) [Table 3]. The mean age of patients with Ewing sarcoma in c-code 40 was 19.85 and in c-code 41 was 23.79. The mean age in c-code 41 was significantly higher than c-code 40 (*P<0.001*). Considering the gender, the results showed significant higher mean age in male and females for axial Ewing sarcoma (C-code 41) with respect to appendicular Ewing sarcoma (C code 40) [Table 3]. The mean age in axial Ewing sarcoma (C-code 41) (23.26) was significantly higher than appendicular Ewing sarcoma (C-code 40) (20.55). Among female patients, the results showed that the mean age in axial Ewing sarcoma (C-code 41) (24.75) was significantly higher than mean age in appendicular Ewing sarcoma (C-code 40) (18.75).

The highest rate of Ewing sarcoma was observed in males at the age group of 15-19 years (22.80%) followed by age group of 20-24 (22.10%). Among females affected by Ewing sarcoma, the highest rate of this disease was reported in the age group of 10-14 years (20.60%)

Table 3. The descriptive statistics of age by sex and c-code

Group	levels	Maximum	Minimum	Range	SD	Median	Mean	*P-value*
Sex	Male	80	0	80	12.46	20.00	21.74	0.585
	Female	75	1	74	14.38	18.00	21.17	
	Total	80	0	80	13.20	19.00	21.53	----
C-code	40	80	0	80	12.50	18.00	19.85	<0.001
	41	75	0	75	13.80	22.00	23.79	
	Total	80	0	80	13.20	19.00	21.53	----

Table 4. The Frequency (Percentage) and Age-Specific Rate (Per million Person-Years) based on different sexes

Age (years)	Frequency (Percentage)			Age-Specific Incidence		
	Male	Female	Total	Male	Female	Total
0-4	28 (6.6)	17 (6.7)	45 (6.6)	1.25	0.80	1.03
5-9	27 (6.4)	36 (14.2)	63 (9.3)	1.31	1.83	1.56
10-14	65 (15.3)	52 (20.6)	117 (17.3)	3.11	2.59	2.86
15-19	97 (22.8)	44 (17.4)	141 (20.8)	4.03	1.88	2.97
20-24	94 (22.1)	36 (14.2)	130 (19.2)	3.28	1.26	2.27
25-29	49 (11.5)	26 (10.3)	75 (11.1)	1.67	0.90	1.28
30-34	22 (5.2)	7 (2.8)	29 (4.3)	0.89	0.29	0.59
35-39	14 (3.3)	8 (3.2)	22 (3.2)	0.69	0.41	0.55
40-44	8 (1.9)	8 (3.2)	16 (2.4)	0.46	0.54	0.50
45-49	3 (0.7)	3 (1.2)	6 (0.9)	0.21	0.14	0.18
50-54	5 (1.2)	4 (1.6)	9 (1.3)	0.41	0.33	0.37
55-59	5 (1.2)	6 (2.4)	11 (1.6)	0.54	0.64	0.59
60-64	3 (0.7)	2 (0.8)	5 (0.7)	0.47	0.29	0.37
65-69	1 (0.2)	1 (0.4)	2 (0.3)	0.43	0.40	0.41
70-74	3 (0.7)	3 (1.2)	6 (0.9)	0.75	0.51	0.63
75-79	1 (0.2)	0 (0)	1 (0.1)	0.31	0.00	0.16
Total	425 (100)	253 (100)	678 (100)	1.60	0.97	1.29

and then in the age group of 19- 15 years (17.40%). In general, the highest number of patients were observed at the age group of 15-19 (20.80%) and then in the age group of 20-24 (19.20%) [Table 4]. Frequency distribution of Ewing Sarcoma, initially (0-4 years old), was homogeneous between male and females, while the number of patients between 5 to 14 years was higher among female patients. This proportion changed between 15 to 35 years with male predominance. In the range of 35 to 39 years the relation of male to female was almost identical, and among patients older than 40 year negligibly female predominance was seen [Figure 1]. Among patients with appendicular Ewing sarcoma (C-code 40), the age group of 15-19 years has the highest incidence of Ewing sarcoma (23.70%) while in axial Ewing sarcoma (C-code 41), the highest incidence was reported in the age group of 20-24 years (21.10%). The number of patients with Ewing sarcoma in the first four age groups (0 to 19 year) was higher in patients with appendicular Ewing sarcoma (c-code 40), while in the age group of 20 to 39 year range, patients with axial Ewing sarcoma (c-code 41) showed a higher incidence [Figure 2].

The crude incidence was 1.6 among males and 0.97 among females in one million according to our data. The total crude incidence rate was 1.29 in 1 million

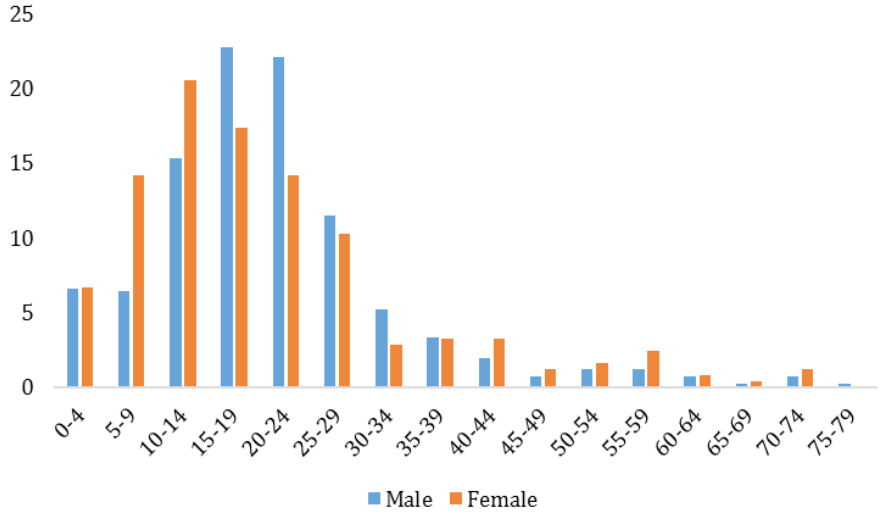

Figure 1. The percentage of Ewing Sarcoma based on Sex and Age.

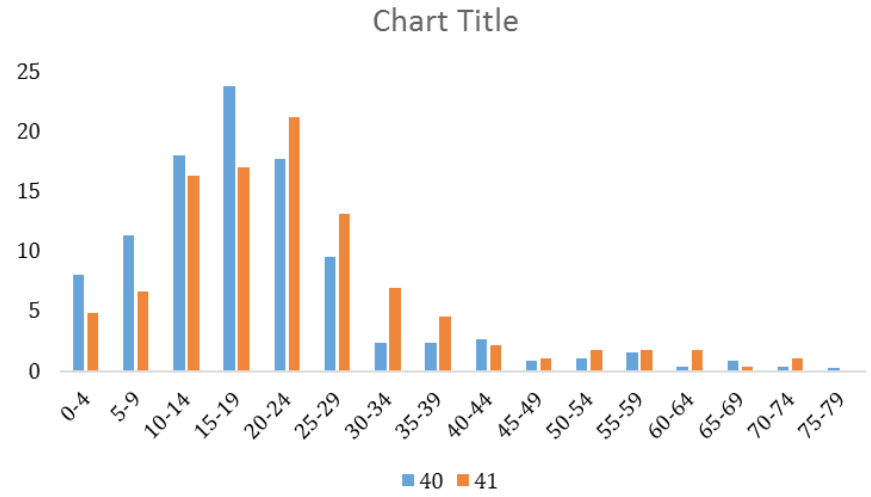

Figure 2. The percentage of Ewing Sarcoma based on C-Code (40 & 41) and Age.

[Table 4]. The crude incidence rate and age specific incidence rate (ASIR) of Ewing sarcoma by year is summarized in Table 5.

In order to analyze the survival rate of Ewing sarcoma, 161 patients were enrolled and considered in the study. One hundred and two patients dead and the rest were censored. According to Kaplan-Meier curve for total sample the survival rate after 9 years remained unchanged and was equal to 0.28. The survival rate was evaluated as one year, three years, five years and seven years. One year survival was 85.7% (confidence interval: (95%) 0.913-0.805). This means that the minimum and maximum annual survival rates were 80.5% and 91.3%, respectively. The mean 3-year survival rate was 61.5% and for five-year survival was 47%. The 7-year survival rate was 36%. A minimum survival rate of 7 years was 28.7% and maximum survival rate was 45.1%. The mean survival rate for study population was 5.53. Table 6 shows the survival rate data of Ewing sarcoma. The survival rate among male and female populations was not significant (*P=0.382*). Age range (higher survival range among younger patients) and C-codes (higher survival rate among appendicular Ewing sarcoma) were factors that influenced the survival rate (*P= 0.026* and *P=0.008*, respectively).

Results regarding the relation between the survival rate and socioeconomic factors showed that there is a positive significant correlation between the survival in nine regions and socioeconomic factors including literacy (r=0.645, *P<0.001*), employment (r=0.606, *P<0.001*), population urban rural (r=0.604, *P<0.001*) and family

Table 5. The Crude Incidence Rate and ASIR (per million person-years) over 2008 to 2014

Year	Crude incidence rate (Age standardize rate)		
	Total	Male	Female
2008	1.45 (1.36)	1.88 (1.75)	1.01 (0.96)
2009	1.60 (1.48)	1.92 (1.74)	1.27 (1.22)
2010	1.42 (1.35)	1.81 (1.71)	1.01 (0.99)
2011	1.17 (1.18)	1.45 (1.41)	0.89 (0.95)
2012	0.89 (0.91)	1.15 (1.15)	0.64 (0.66)
2013	1.17 (1.21)	1.44 (1.43)	0.89 (0.99)
2014	1.35 (1.41)	1.57 (1.57)	1.12 (1.24)

Table 6. The mean/median survival time and 1, 3, 5, and 7-years survival rate

Survival Rate				Mean Survival Time (year) 95% C.I	Median Survival Time (year) 95% C.I
1-Year Survival Rate 95% C.I	3-Year Survival Rate 95% C.I	5-Year Survival Rate 95% C.I	7-Year Survival Rate 95% C.I		
0.857 (0.805-0.913)	0.615 (0.544-0.695)	0.470 (0.399-0.554)	0.360 (0.287-0.451)	5.53 (4.87-6.18)	4.38 (3.45-6.30)

Table 7. Correlations between survival and socioeconomic factors

		Survival	Literacy	Employment	Population Urban Rural	Family Income
Survival	Correlation Coefficient	1.000	.645**	.606**	.604**	.207**
	Sig. (2-tailed)	.	.000	.000	.000	.008
	N	164	164	164	164	164
Literacy	Correlation Coefficient	.645**	1.000	.188*	.545**	.398**
	Sig. (2-tailed)	.000	.	.016	.000	.000
	N	164	164	164	164	164
Employment	Correlation Coefficient	.606**	.188*	1.000	.647**	.113
	Sig. (2-tailed)	.000	.016	.	.000	.151
	N	164	164	164	164	164
Population Urban Rural	Correlation Coefficient	.604**	.545**	.647**	1.000	.390**
	Sig. (2-tailed)	.000	.000	.000	.	.000
	N	164	164	164	164	164
Family Income	Correlation Coefficient	.207**	.398**	.113	.390**	1.000
	Sig. (2-tailed)	.008	.000	.151	.000	.
	N	164	164	164	164	164

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

income (r=0.207, *P<0.001*).

Discussion

Tumor registries provide valuable data allowing for the estimation of tumor incidence rates by patient age, sex, tumor location, and other factors such as social determinants of health. Some registries like the United States population-based cancer registry Surveillance, Epidemiology, and End Results (SEER) and the National Cancer Intelligence Network (NCIN) provide general papulation data (2, 3). But, in order to evaluate the influence of race and ethnicity, regional registries around the world help to study more genetically similar populations. In a study by Worch et al., they confirmed the existence of racial and ethnic factors in characteristics of patients with Ewing sarcoma (5)with a higher incidence noted in populations of European rather than African or Asian ancestry. The goal of the current study was to evaluate racial and ethnic differences in presentation and overall survival (OS. This confirms the importance of regional and national studies for each tumor separately.

To the best of our knowledge there are few limited studies about Ewing sarcoma in Iran and this is the first detailed descriptive demographic analysis of Ewing sarcoma among the Iranian population according to INCR (10)but their descriptive data in any region are important to reduce mortality rate and improve their management. Materials and Methods: Retrospectively, 426 pathologic reports from 1997 to 2008 were reviewed in Shiraz University Orthopedic Hospitals which are the main referral centers for musculoskeletal tumors in south of Iran. We collected and analyzed data on age, gender, anatomical site, and histopathologic types of musculoskeletal tumors. Results: Of the 426 cases, 60.1% were men and 39.9% were women. The commonest malignant bone tumors were osteosarcoma (89; 50.6%. This study was designed according to INCR registry from 2008 to 2015 to provide a national reference for Ewing sarcoma.

According to our registry, the total ASIR was 1.27 and 1.54 among males and 1.00 among females in one million. In comparison with microscopically diagnosed cases reported in the Cancer Incidence in Five Continents Vol X(CI5X) in which the incidence rate ranged from 2-4 per million in males and 1-4 per million in females, the ASIR in Iran showed a lower incidence. Even in comparison with the neighbor countries including Pakistan, Bahrain, Qatar, Saudi Arabia, and Turkey (range from 2-3) the Ewing sarcoma showed lower ASIR in Iran (4, 11–14)12 female.

Male predominance was observed both in appendicular (C-code 40) and axial (C-code 41) Ewing sarcoma; however, there was no relation between the sex and tumor location. This means that while male people were influenced more frequently by Ewing sarcoma, gender had no influence on the location of the tumor.

The mean age of Ewing sarcoma was slightly higher among male patients in comparison with females (21.74 versus 21.17), but, with no statistical significance (*P=0.585*). According to our data, axial Ewing sarcoma affected the patients in an older age compared to appendicular Ewing sarcoma. The mean age of patients with Ewing sarcoma in appendicular Ewing sarcoma (c-code 40) was 19.85 and in axial Ewing sarcoma (c-code 41) was 23.79 (*P<0.001*). The most frequent anatomical zones of Ewing sarcoma were long bones of lower limb (35.7%) followed by pelvis, sacrum and coccyx (15%), long bones of upper limb (10.2%), and vertebral column (6%). This was in accordance with other data registries which show similar anatomical distribution of Ewing sarcoma (1, 3, 12, 13, 15)India to provide incidence, patterns, and trends in the Indian population. Materials and Methods: The data of five Population Based Cancer Registries (PBCR.

Differences among age groups were observed among patients affected by Ewing sarcoma. It was generally more frequent among age group of 15-19 years (20.8%) followed by the age group of 20-25 years (19.2%). In comparison with near regional studies in India, Pakistan, Turkey, and Saudi Arabia almost half of the cases were in the age group 10-19 years while in Iran majority of the cases were in the age group 15-25 years (40%) (1, 11–13)India to provide incidence, patterns, and trends in the Indian population. Materials and Methods: The data of five Population Based Cancer Registries (PBCR. However, more precisely in Iran like other studies in the world, the most cases of Ewing sarcoma occured among patients in age group 15-19 years and rarely occured after 30 years of age (2, 3)the incidence and survival of all subtypes of MBS registered in England between 1979 and 2007 were analysed from patient registry data held by the National Cancer Intelligence Network (NCIN. Considering the gender, the highest number of patients with Ewing sarcoma was observed in males at the age group of 15-19 years while females showed the highest number of patients among the age group of 10-14. This showed that females were affected by Ewing sarcoma at a younger age than males. Despite different distribution of Ewing sarcoma according to sex and age groups, there was no significant relationship between the mean age of the patients and sex.

According to our data the mean survival rate for Ewing sarcoma was 47% and it was independent from the sex. Younger patients with Ewing sarcoma had higher survival rates. Appendicular tumors showed better prognosis and these patients had higher survival rates with respect to axial tumors. Socioeconomic factors had reverse influence on survival rates; in other word, social determinants of health influence this tumor. Esiashvili et al. showed that 5 years survival rate of patients with Ewing sarcoma was improved from 36.4% (1973-1982) to 60.2% (1993-2004) (16). They concluded that despite some progression in the treatment of Ewing sarcoma, in case of metastatic diseases, less evidence of improvement in treatment strategies are available. The lower survival rate in our registry may be due to the less effective treatment strategies or late diagnoses that increase the risk of metastasis at the time of diagnosis in areas with lower socioeconomic characteristics.

In conclusion, the crude incidence rate of Ewing sarcoma in Iran is significantly lower with respect to the neighbor countries in the Middle East zone. Unlike other studies, majority of the patients are in 15-25 years group and show affection by Ewing sarcoma in an older age. Despite the limitations of INCR that do not include microscopic, cytogenetic, and immunohistochemistry characteristic of the Ewing sarcoma, but, this study may provide a good regional descriptive epidemiology of this malignant tumor.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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