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Original Article

A clinicopathologic and survival study of patients with Ewing family of tumors: A retrospective-analytical study

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Abstract. With significant mortality among malignancies, Ewing's family of tumors stands out as one of the most malignant cancers in young patients. This study aims to investigate clinicopathological characteristics and the impact of demographic and treatment types on survival. This retrospective-analytical study was conducted using the census method at Shahid Sadoughi Hospital in Yazd. The study included all patients with Ewing's family of tumors referred to these hospitals from 2011 to 2018. Demographic and disease characteristics were collected from the registry and analyzed using SPSS v.17. Fifty patients were enrolled in the study, with a mean age of 19.14±15.92 years. The lower extremity (30%) and abdominopelvic (24%) were the most common sites of the primary tumor, respectively. The mean tumor size was 5.76 ± 3.92 cm, and metastasis occurred in 16% of patients. Among them, 42% underwent combination therapy (chemotherapy/radiotherapy/ surgery), and 40% underwent chemotherapy + surgery. The disease relapsed in 62% of patients, and the most common site of recurrence was the chest wall (38%). The mean overall survival was 87.82 ± 11.54 months. Tumor location was associated with overall survival. Gender, age group, tumor size, and treatment type did not affect overall survival (P> 0.05). The mean survival until disease recurrence was 57.74 ± 7.74 months. It was concluded that recurrence is common in Ewing sarcomas, with the chest wall being the most common site of recurrence. Overall survival is linked to tumor location.

Keywords: Ewing sarcoma, head and neck neoplasm, survival, primitive neuroectodermal tumor

Introduction

Ewing family tumors (EFT), one of the most malignant cancers, predominantly affect individuals under 20 years old. The prevalence of these tumors is estimated at 2-3 cases per million people per year. The family comprises three groups: Bone Ewing sarcoma, extra-skeletal Ewing sarcoma, and primitive neuroectodermal tumor. These tumors share clinical and pathological similarities, originating from embryonic neural crest cell debris. They are characterized by undifferentiated small round cells [1-4]. Lung, bone, and bone marrow metastases are observed in 25% of patients. Researchers have discovered similar DNA defects among Ewing tumor cells, EOE (Extraosseous Ewing tumor), and PNET, setting them apart from other cancers. The common origin of these three cancer cells from natural cells led to their classification as Ewing's family tumors.

Bone Ewing sarcoma constitutes 87% of the Ewing tumor family, EOE around 8%, and PNET 5%. [5-7]. Among the

Among them, bone Ewing sarcoma, Neuroepithelioma, Askin tumor within the chest wall, and PNET are included. [8]. PNET tumor originates from neuroepithelioma, displaying more neuronal differentiation in terms of pathology, immunohistochemistry and electron microscopy [9]. The differentiation process includes the presence of neuron-specific enolase, Rosette Homer Wright, the phenotype of ganglion cells, and in cases of good differentiation, neurofilament protein expression [10]. The neoplasm may be situated within the central or sympathetic nervous systems, which is typically the most prevalent location, or outside the CNS, referred to as peripheral PNET. pPNET constitutes approximately four percent of soft tissue tumors in juveniles, manifesting in proximity to the chest wall and head and neck regions, with equal incidence in both genders [11-13]. Stout reported the first case in the past century, located inside the ulnar nerve [14]. pPNET rarely

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occurs primarily in orbit. Up to 2015, only 26 cases of orbit pPNET had been reported, 65% of which were in children, and 2 cases (7% of the reported cases) were congenital.

Ewing's sarcoma family tumors are diagnosed based on the signs and symptoms found in this disease. A common symptom of EFT is bone pain, present in approximately 85% of sufferers. About 30% of bone tumors are warm and soft to touch, and youngsters often experience fever. Although these signs and symptoms can also be seen in cases of bruising and osteomyelitis, a diagnosis of cancer is only considered when the patient's condition does not quickly improve, or antibiotic treatment is ineffective [14, 15].

In pathology, small round cells with hyperchromatic nuclei, little cytoplasm, and high nucleus to the cytoplasm ratio with cell aggregation in cell nest and layers, sometimes with pseudo rosette or Homer-Wright rosette, is observed. From this point of view, 15 tumors are classified as tumors with small blue and round cells. Immunohistochemistry analysis shows that Ewing sarcoma family tumors, neuroblastoma, lymphoma, metastatic orbital retinoblastoma, hemangioblastoma, rhabdomyosarcoma, osteogenic sarcoma, and mesenchymal chondrosarcoma can be differentiated [16]. The study by immunohistochemistry is positive in 95 % of the tumors for CD99; however, this marker is not tumor-specific and is also found in lymphoblastic lymphoma, rhabdomyosarcoma, synovial sarcoma, and neuroblastoma. Though, the clear membrane staining pattern for small round and blue cell tumors is only seen in Ewing sarcoma and PNET.

Today, surgery, chemotherapy, and radiation therapy treat these tumors. The prognosis (outcome), with the initiation of chemotherapy, has increased significantly. If the tumor is confined to an area smaller than 10 cm (4 inches) and can be completely removed by surgery, the 5-year survival rate is 80%, and this amount can be increased with postoperative chemotherapy and radiation therapy. If the tumor is small but cannot be removed entirely, the survival rate is over 70%. If the tumor is large and cannot be fully removed, the 5-year survival rate is probably less than 60%, even with an excellent response to chemotherapy or radiation therapy [12].

Due to the challenging nature of diagnosing this disease, the absence of typical clinical symptoms at the time of diagnosis, a variety of differential diagnoses, and varying survival rates reported in other studies based on the timing of diagnosis and types of treatment, this study aims to study clinicopathologic and survival characteristics of patients with Ewing family of tumors in the pathology department of Shahid Sadoughi Hospital-Yazd Between 2011 to 2018.

Materials and Methods

The study population included Ewing's tumor patients who were referred to the pathology laboratory of the Yazd Mortaz Hospital between 2011 and 2018. Based on the information from the archives of Mortaz and Sadoughi hospitals, 50 patients from this cross-sectional study were selected as sample sizes for this study. Exclusion criteria included the presence of underlying diseases, certain medications, and inaccurate medical records. Patient demographics, clinical data, and survival information were collected from medical records and through telephone interviews with patients or their first-degree relatives. The information was recorded in an approved questionnaire prepared by the supervisor and advisor.

Statistical Analysis

Collected data were analyzed using the SPSS v. 17 (SPSS, Inc., Chicago, IL, USA) software. Log-rank and the Kaplan-Meier diagram (KM) were used for the survival analysis. A P-value less than 0.05 was considered a statistically significant level.

Ethical Considerations

After obtaining the necessary permissions to collect information, patient information was kept confidential and used solely for research purposes. The study was conducted in accordance with ethical standards and guidelines, and approval was obtained from the Biomedical Research Ethics Board (Code of Ethics: IR.IAU.KHUISF.REC.1400.105).

Results

In this study, 50 patients with EFT were studied. Of the samples, 19 (38%) were female, and 31 (62%) were male. The mean age was 19.14 ± 15.92 years, ranging from 1 to 61 years. The average tumor size was 5.76 ± 3.92 cm and ranged from 0.7 to 19 cm. Tumors were non-metastatic in 84% of cases (42 patients) and metastatic in 16% of cases (8 people). At the time of the study, 60% (30 patients) of the patients had died, and 40% (20 patients) were still alive. After treatment, in 62% (31 patients) of the cases, tumors relapsed, and 38% (19 patients) did not experience recurrence. The average overall survival was 87.82 ± 11.54 months, and the mean survival to recurrence was 57.74 ± 7.74 months.

The most common location of the tumor was the lower extremities, 30% (15 cases), followed by the abdomen and pelvis, 24% (12 patients), and the head and neck region, 10% (5 cases).

The treatment approaches are outlined in Table 1, with the most common approach being chemotherapy + radiation therapy + surgery 42% (21 cases).

The disease was associated with recurrence in 31 patients. There were chest wall metastases, according to Table 2, with 13 cases where the rarest sites of recurrence were the upper limbs, abdomen, and extremities, each with one case. The average survival time of the patients was 87/82 ± 11/54 months, with a 95% confidence interval ranging from 65/19 months to 110/45 months. In this study, 60% of the samples died from the EFT. As illustrated, the survival rate decreases to approximately 34% after about five years from diagnosis, after which the decrease is not significant.

Patients were divided into two age groups: 1 to 14 years and 15 to 61 years. The average survival duration in the age group 1 to 14 years age group was 80/30 ± 16/31 and in the age group of 15 to 61 years was 95/21 ± 16/26. The Kaplan-Meier curve indicated slightly lower average survival in the 1 to 14 years age group. The log-rank test revealed no significant difference in survival between the two age

TABLE 1

TYPE OF RECEIVED TREATMENT AND THE MEAN SURVIVAL TIME IN PATIENTS

Treatment Type	Case No (%)	Alive Case No (%)	Survival Time Mean± STD	P-Value*
Chemo+ Radio+ Surgery	21 (42)	6 (28.57)	44.81±3.97	0.3151
Chemo+ Radio	9 (18)	3 (33.33)	50.92±11.66	
Chemo+ Surgery	20 (40)	11 (55)	113.17±19.43	

*log-rank test. The average patient survival time by tumor size is shown

TABLE 2

FREQUENCY DISTRIBUTION OF THE TUMOR LOCATION AND MEAN SURVIVAL TIME IN PATIENTS

Tumor Location	Case No (%)	Alive Case No (%)	Survival Time Mean± STD	P-Value*	Recurrence Case No (%)
Head & neck	5 (10)	1 (20)	29.60±10.08	0.0398	5 (10)
Chest wall	7 (14)	3 (42.86)	54.93±2.99		13 (26)
Abdomino-pelvic	12 (24)	3 (25)	47.53±13.14		5 (10)
Upper extremity	11 (22)	9 (81.82)	159.04±20.74		1 (2)
Lower extremity	15 (30)	4 (26.67)	51.53±8.17		2 (4)

*log-rank test

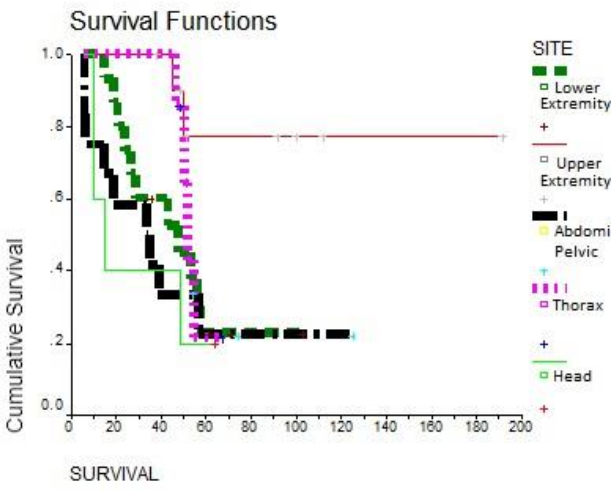

Figure 1 Kaplan-Meier survival curve according to the tumor location

TABLE 3

TUMOR SIZE AND THE MEAN SURVIVAL TIME IN PATIENTS

Tumor Size	Case No (%)	Alive Case No (%)	Survival Time Mean± STD	P-Value*
<5 cm	26 (52)	11 (42.41)	67.86±9.42	0.9616
5-10 cm	15 (30)	5 (33.33)	80.52±19.31	
>10 cm	9 (18)	4 (44.44)	87.09±29.74	

groups (P-value = 0.49898). The mean survival time for females and males was 82/02 ± 19/82 and 90/70 ± 14/26 months, respectively (P-value = 0.6695, log-rank test).

The average patient survival associated with treatment approaches is shown in Table 1, with the best outcomes seen with chemotherapy plus surgery. The log-rank test measured the survival probability, and since the P-value was 0.3151, the difference was not significant. The average survival time based on the tumor's location is shown in Table 2, with upper limb tumors demonstrating longer survival.

Measured by a survival probability based on tumor location with a log-rank test, a significant difference was observed (P-value =0.0398). Based on the Kaplan-Meier survival curve (Figure 1), the survival probability was higher than the other sites' tumors approximately five years after diagnosing patients with upper limb tumors. In contrast, the survival was not much different from other sites' tumor involvement.

The average patient survival time by tumor size is shown in Table 3. This difference was not statistically significant (P-value =0.9619, log-rank test). The mean survival time to recurrence was 57/74 ± 7/74 months, with a 95% confidence interval ranging from 42/56 to72/92 months. The Kaplan-Meier graph illustrates that the probability of survival until relapse decreases to around 45% after about 30 months from diagnosis, after which no significant decreases occur.

The average survival time to relapse in the age group of 1 to 14 years was 51/93 ± 10/73 months, and in the age group of 15 to 61 years, it was 53/45 ± 8/54 months. The probability of survival was not significant between the two age groups (P-value = 0.3151, log-rank test). The average survival time to relapse in men and women, respectively, was 63/17 ± 10/24 and 41/42 ± 7/73 months. The probability of survival to relapse difference was insignificant between the two gender groups (P-value = 0.6512, log-rank test).

Discussion

This study studied 50 patients with Ewing's sarcoma with an average age of 19.14 ± 15.92 years. Of the patients, 62% were male. The expected location of the primary tumor was in the lower extremities (30%). Tumor location was in the extremities for 52% of cases and in the axial region of the body for 48%. Among Ewing's family tumors, 82% were non-metastatic, and the majority of patients (84%) received chemotherapy as well as local surgical treatment. At the time of the study, only 40% of patients were alive, and 62% had a tumor recurrence. The chest wall was the expected location of the recurrence. The mean survival time for patients was 87/82 ± 11/54 months. There was no significant relationship between the age, gender, tumor size, or type of treatment with survival time, but it was related to the tumor location. The average survival relapse time was 57/74 ± 7/74 months, which was not significantly related to age or gender.

Ewing's sarcoma is the second malignant bone tumor in children and teenagers, with the highest incidence in the first 20 years of life and, like many children's tumors, somewhat common in the male gender [17, 18]. Chemotherapy, surgery, radiation therapy, or a combination of these methods is used to treat tumors. In the past, treatment was radiation-only, with an overall survival rate of 10% after five years. As the hybrid approach became more popular, this rate increased to 55-65% [19-21]. At the time of

diagnosis, about 20-25% of patients have metastasis. Lung metastases are common (70-80%) and do not involve bone (40-45%). Despite current aggressive treatment, 5-year survival is 20-35 percent after metastatic Ewing's sarcoma diagnosis [19-21]. In the first non-metastatic case, 30-40% of patients experience tumor recurrence during post-treatment follow-up. According to previous studies, the 5-year survival rate after recurrence varies between 15 and 25% [22-24]. The mean survival in our study was 87.82 months. For comparison, Verma et al. analyzed 1,870 patients with Ewing's sarcoma (976 children and 894 adults) and reported an average survival time of 103 months [25], which is notably higher than our findings. The survival rate of the study by Verma et al. was 66% [25], 65.2% in Friedman et al.'s study [26], 75% in Albergo study et al. [27] and 58/9% in Lee's study et al. [28]. These findings suggest that the survival rate in this study is significantly lower than in other studies. One of the reasons for this difference may be the small sample size of this study, which can affect the accuracy of survival determinations. Also, differences in survival may be due to racial differences, as investigated in previous studies [29, 30]. In this study, this difference is not statistically significant, even though males (38.7%) have lower survival rates than females (42/1%). In a study by Verma et al., gender affected overall survival in adult patients. However, there was no significant difference between males and females in terms of overall pediatric survival [25], which are consistent with the study's results. Bacci et al. examined 359 patients with non-metastatic Ewing's sarcoma and showed that male gender was associated with lower patient survival [31].

Similarly, Jawad et al. indicated that female gender (59% vs. 52%) was associated with improved patient survival [32]. Miller et al., in a study of 1031 patients with Ewing's sarcoma, found that men (62/9% vs. 71/5%) may experience worse survival. This study showed that females had higher survival rates at 2, 5, and 10 years than males, and the difference could be longer over time [33]. In Albergo et al., males had lower survival rates though the difference was not statistically significant [27]. Based on the above, the survival rate of males is slightly lower, as some studies report a significant difference, while others do not.

In the current study, there was no significant relationship between age and survival. This finding aligns with the results of a survey by Rodriguez Galindo et al., which also found no relationship between age and survival rate [23]. In Albergo et al. study on 293 cases, patients aged 16 years and older had lower survival rates [27]. In a survey by Bacci et al. and Cotterill et al., patients aged 12 or 15 years or older were associated with poor patient survival [25, 34], which is inconsistent with the results of this study. This difference may be due to the subjects' narrow age range, while our study's average age range was higher. Nevertheless, these earlier studies also encompassed adolescents over the age of 15, and thus, while they did not indicate a significant difference in younger age groups, they did show a decrease in survival with increasing age.

This study found no significant relationship between the treatment approach and patient survival. In Verma et al. study, a meaningful relationship was found between survival in patients with metastases, tumor location (axial bones or extremity bones), and type of treatment (surgery or radiation performed / not performed). Also, they showed that surgery in children with Ewing's sarcoma had a positive effect on survival, but radiation therapy did not improve survival [25]. Research by Miller et al. showed that radiation therapy alone compared to surgical treatment combined with radiation therapy (52.5% vs. 77/2%) could shorten patient survival [33]. Research by Jawad et al. revealed that surgery is associated with improved patient survival [32]. A study by Rodriguez Garindo et al. and Bacci et al. showed that those who received surgical treatment in addition to radiation therapy reported higher survival rates than those who received radiation therapy alone [23, 31]. In this study, the survival rates of patients who underwent surgery were higher than those who received radiation therapy. However, the combination of radiation therapy and surgery had worse survival than each of these methods alone. This can be due to the ominous condition of those who have undergone the hybrid approach.

In this study, it was observed that patient survival time was significantly related to tumor location. Upper limb tumors had a better prognosis than tumors of other sites; however, no significant relationship was seen between the tumor size and survival. Verma et al. also reported that tumor sites other than the limbs were less likely to result in survival [25]. Conversely, a survey by Kharoud et al. failed to reveal a relationship between the probability of survival in adult patients and tumor size or location [35].

Since patients with various types of sarcoma and Ewing family tumors participated in this study, differences in survival and gender distribution between these neoplasms could exist. Future studies should consider investigating each of these neoplasms separately. Due to the rarity of the disease, the number of patients who participated in the study was small, which could affect the results as the smaller sample size suggests further research to increase the sample size at multiple centers across the country for children and adult patients separately, to determine accurate survival. It is also recommended that factors influencing survival are investigated to determine short-term and long-term survival.

Conclusion

This study reveals relatively low survival rates for patients with Ewing's sarcoma, with survival being significantly associated with tumor location. The study did not find significant associations between survival and variables such as age, gender, tumor size, or treatment type. Additionally, survival until relapse did not appear to be significantly influenced by age or gender.

Conflict of Interest

The authors declare no conflict of interest.

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