# Outcomes of Ewing`s Sarcoma in Patients Admitted to Hospitals of a Medical University in South of Iran

**Abstract**

**Background**: Ewing's sarcoma is a primitive and malignant bone tumor that is a serious medical challenge in preserving the patient's life and choosing the appropriate treatment. The aim of this study was to consider the metastasis and survival rate after preoperative chemotherapy, surgery and postoperative chemotherapy as a treatment protocol.

**Methods**: In this study, 42 patients with Ewing's Sarcoma admitted to Chamran and Namazi Hospitals during 2005 to 2016 were enrolled. After considering inclusion and exclusion criteria, 27 patients were finally entered the study. Neo adjuvant chemotherapy and again restaging with MRI and chest CT scan was done. After restaging, treatment was selected. Treatments included amputation; only wide resection; wide resection and allograft; wide resection and prosthesis and only chemotherapy. After surgical treatments, patient had adjuvant chemotherapy.

**Results**: In this study, 42 patients were investigated of whom 29 (%69) were male and 13 (%31) female respectively. The age mean and standard deviation were 21.45± 7.69 and 16.23± 4.9 in the male and female in respect. Femur (%30) and tibia (%23.8), respectively, were the more commonly involved sites. The treatments of 27 cases in the study group were amputation (5 subjects), only wide resection (6 subjects), wide resection and allograft (8 subjects) and wide resection and prosthesis (3 subjects). Patients with pelvis involvement received only chemotherapy (5 subjects). 46.2% of subjects had a 5-year survival period.

**Conclusion**: Early diagnosis of Ewing's sarcoma and appropriate treatment using preoperative chemotherapy followed by, surgery through proper margin removal and then postoperative chemotherapy is highly recommended for this condition. Our study confirmed the above-mentioned points on preoperative chemotherapy followed by surgery and post operative chemotherapy.

**Keywords**: Ewing`s Sarcoma, Survival, Chemotherapy, Metastasis

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## Introduction

Ewing`s Sarcoma is one of the most malignant tumours in people below twenty years old which annually 2-3 cases in one million suffer [1-4]. It is more prevalent in Caucasians than East Asians and less prevalent in Africans. The male are more prone to experience Ewing`s Sarcoma [5]. Nearly %85 of these tumours originates from the bone and the rest from the soft tissue [6]. They are categorized in three groups according to their locations as bone sarcoma, extra skeletal and primitive neuroectodermal tumor (PPNET) which are the same clinically and pathologically and only differ in neuronal distinction. Ewing`s tumours are caused by the remaining fetal neural crest and are morphologically circular, small and undistinguished [7]. This is made of tiny blue cells with little intracellular matrix(2). Ewing`s Sarcoma has metastatic trend to other remote organs such as lungs. Metastasis to lungs, bones and bone marrow is seen in %25 of patients(5). Bone Ewing`s Sarcoma is the second primitive bone tumor in children and adults [8]. Pelvis and femur are the most common bones involved respectively [9]. Pain is the leading symptom. Other signs include fever, swelling, irritation, weight loss, anorexia, and pathologic fractures after cortical destruction and also low back pain and limb paralysis as a result of vertebral metastasis. It might increase ESR and leukocytosis [10]. Histologic and immunologic findings result in the diagnosis [5, 10]. It is known as a degenerative lesion of the long bone metaphysis radiating to diaphysis shown through plain radiography which is the most valued method in proper diagnosis. Onion skin appearance is the general radiographic finding attacking the metaphysis and diaphysis. Differential diagnosis consists of osteomyelitis, malignant lymphoma and histiocytosis. For instance, extracting abscess through needling might declare acute osteomyelitis and postpone the diagnosis that is averagely 4.7 months [10].

MRI is the most efficient instrument for monitoring bone and soft tissue tumor development and its relation to the neighbouring structures. Chest radiography and CT scan are carried out to consider pulmonary metastasis [11]. Bone scan is also needed as it is the second common site of metastasis. These tests should be performed before biopsy [10].

Ewing`s Sarcoma treatment has developed in recent decades. Systemic therapies have been less effective while local control procedures are of more and faster outcomes [1]. Today a blend of systemic and local treatments including surgery, chemotherapy and radiotherapy is provided. Chemotherapy is usually presented as a various combinations of the following six drugs: doxorubicin (DOX), cyclophosphamide (CPM), vincristine (VCR), actinomycin-D (ACT-D), ifosfamide (IFO), and etoposide (ETO) [10]. Necrosis of more than %90 of tumor cells resulting from chemotherapy is indicative of good prognosis [4]. %30-40 of patients experience local recurrence or metastasis or mixed lesion after removing or amputation. In local recurrence with poor prognosis, radical resection and chemotherapy are used [12]. Efficient chemotherapy has decreased metastasis and mortality. Moreover, imaging and prosthetic advancement has simplified decision on various treatments with more accuracy and less invasion[12]. There are a few studies on effects of chemotherapy before and after surgery [13] as well as studies on Ewing`s Sarcoma in Iran especially the effectiveness of treatments and survival afterwards. Given the low number of patients with Ewing`s Sarcoma and related studies on therapeutic outcomes in Iran, this study investigates the outcomes of Ewing`s Sarcoma according to presence of metastasis and survival based on preoperative chemotherapy, surgery and postoperative chemotherapy.

## Methods

In this retrospective study, patients with Ewing`s Sarcoma admitted to hospitals of a Medical University in south of Iran (Namazi and Chamran Hospitals in shiraz) from 2005 to 2016 for any diagnosis and treatment procedures including bone radiography and bone scan, MRI, chest imaging, biopsy, chemotherapy, radiotherapy and surgery have been considered. Patients were first referred to the clinic for having tumor signs. After imaging and pulmonary metastasis analysis, biopsy was carried out and admitted to Namazi Hospital for preoperative chemotherapy. Standard medication included vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide prescribed by an oncologist. After preoperative chemotherapy, total resection or amputation were applied. 2-5 cm of surrounding area was resected through surgery and referred to clinic for chemotherapy as confirming whole tumor disappearance. Chemotherapy regime was based on the guideline and not on size of the surgery. 42 patients were identified through monitoring the medical records from which 15 ones were excluded because of unavailability or dislike in participation and finally 27 were entered. From these, 13 patients were deceased whose records were evaluated for death time, diagnosis time, involved sites, treatments, surgery type, tumor progression, metastasis and survival. The remaining 14 ones were also interviewed. In case of children, parents were asked for gathering data. The participants ranged from 11 to 29 years old. They were explained of research goals, performance and confidentiality of information gathered. Informed and written consent of patients were obtained.

Subjects were assessed again through local and chest radiography. Bone scan was implemented for metastasis. Local MRI and pulmonary CT scan were applied for detecting pulmonary metastasis. The afore-mentioned procedures had no cost for subjects. In the present study, the average follow-up of patient for metastasis was 2 years. SPSS -21 was used for analyzing the data.

## Results

In this study 42 patients with Ewing`s Sarcoma were investigated of whom 29 (%69) were

male and 13 (%31) female. Men were 2.2 more involved than women.

The age mean and standard deviation in the time of diagnosis were 21.45± 7.69 and 16.23± 4.9 in the male and female in respect. The female age mean in the time of diagnosis was lower than the male. To compare the relationship between patient`s age mean and the diagnosis age in men and women, independent sample t-test was applied which resulted to no significant difference (P> 0/05).

Surgeries included amputation (9 subjects), only wide resection (8 subjects), wide resection and allograft (osteoplasty with allograft) and wide resection and prosthesis (3 subjects) of which osteoplasty with allograft has been the most common type (10 subjects). Only wide resection was operated for clavicle and fibula involvement. Patients with pelvis involvement with no surgical indication received only chemotherapy (5 subjects). Involved bones consisted of femur (13 subject), tibia (10 subject), humerus (5 subject), ilium (5 subject), fibula (4 subject), forearm (3 subject), scapula (1 subject) and clavicle (1 subject). Femur (%30) and tibia (%23.8) were of more involvement respectively.

Only one subject with forearm Ewing`s Sarcoma experienced local recurrence. Although amputation was suggested by the physician, however the patient did not agree this and was operated through radius wide resection at the beginning, and was amputated after 11 months due to local recurrence. Relationship between surgery type and survival was considered via chi-squared test which indicate no significance. Osteoplasty with allograft was done in 8 subjects of whom 2 were deceased. From 5 subjects receiving only chemotherapy, 3 died and one was followed having vertebral metastasis. Figure 1 illustrates data regarding surgery type and survival.

24 subjects (%88.88) had no local or remote metastasis at the beginning while 3 experienced pulmonary metastasis initially that led to death. In further follow-up 16 patients (%59.25) had remote metastasis including lung (8 cases), vertebra (2 cases), both lung and vertebra (2 cases), brain (1 case), eye (1 case), limb (1 case) and testis (1 case), 13 of whom (%81.25) have been deceased and 3 (%18.75) survived. The tumor and side effects of chemotherapy has been documented as the cause of death in forensic medicine. As mentioned earlier, remote metastasis led to death in all subjects except for 3 with pulmonary metastasis. Significant difference between pulmonary metastasis and other metastatic sites is shown in figure 2 (P< 0/05).

The age mean and standard deviation of survival before having metastasis were 20.5± 16.34 months. The age mean and standard deviation of tumor size in survivors and the deceased were 6.9± 3.26 months and 8.92± 2.75 months in respect. The bigger size tumours had earlier demise, although not statistically significant probably due to small sample size. Table 1 describes the 5-year survival of patients with at least 5 years follow-up.

Cumulative survival estimate and function are respectively presented in table 2 and figure 3.

**Table 1. The 5-year survival of patients with at least 5 years follow-up**

| % | frequency | variable |
|---|---|---|
| 53.8 | 7 | Deceased |
| 46.2 | 6 | Survivors |
| 100 | 13 | Total |

**Table 2. Cumulative 1, 3 and 5-year survival estimate**

| Standard error | Cumulative survival | survival |
|---|---|---|
| 0.03 | %96 | 0-1 year |
| 0.06 | %88 | 1-2 years |
| 0.06 | %62 | 2-3 years |
| 0.06 | %37 | 3-4 years |
| 0.08 | %25 | 4-5 years |
| 0.08 | %23 | 5 years> |

## Discussion

Ewing`s Sarcoma is a primitive and malignant bone tumor mostly present before adulthood whose prognosis has improved due to developed therapeutic protocols. It is mostly an invasive lesion in long bones metaphysis/diaphysis and lungs are the most common metastatic sites. In this study femur

and tibia were involved most and pulmonary metastasis as well which is in line with former

**Figure 1. Relationship between surgery type and survival**

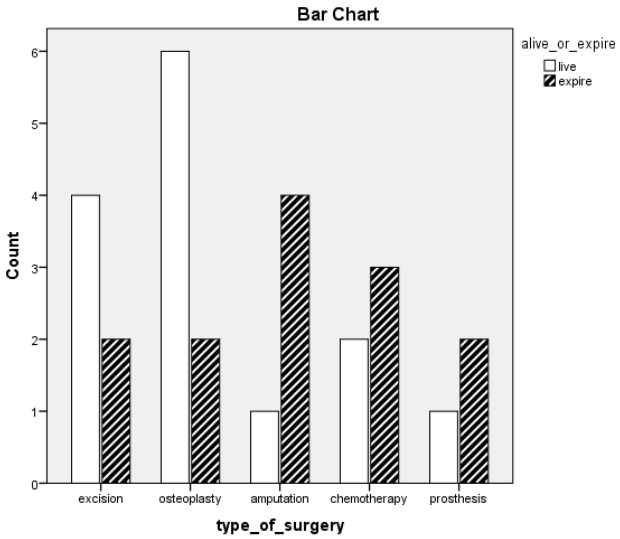



**Figure 2. Relationship between location of metastasis and survival**

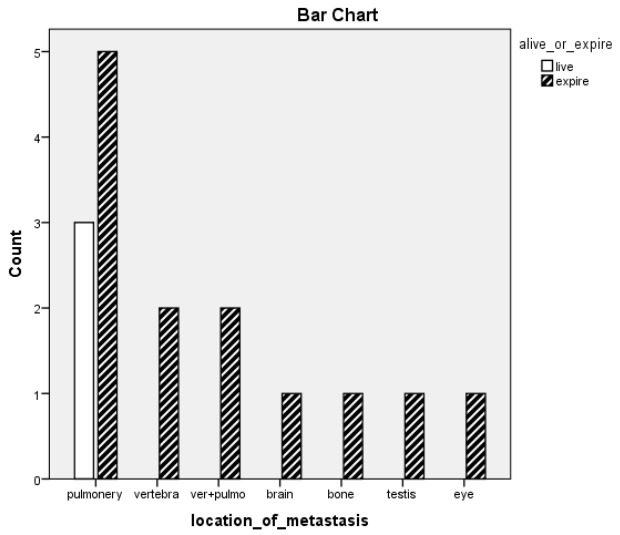
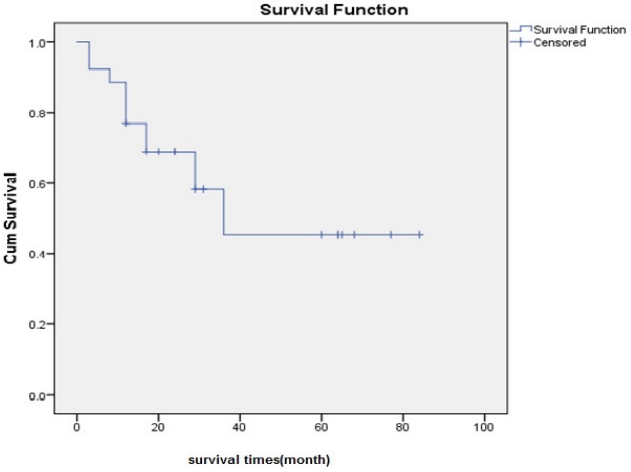



**Figure 3. Overall Cumulative survival function**



studies [1, 3, 10]. In a study femur was the second common site involved [10]. Several factors have been proven as the prognosis of Ewing`s Sarcoma. Indicators of poor diagnosis include exacerbation after primary treatment, remote metastasis (the worst prognosis), tumor size and location (larger and more proximal tumours have poorer diagnosis), being old and male [1, 4, 10]. Previous studies show that patients suffering remote metastasis with no pulmonary involvement, have poorer diagnosis than the ones with pulmonary metastasis [1, 4, 10]. In this study the only significant factors affecting survival were remote and pulmonary metastasis. All subjects without pulmonary involvement were deceased but 3 with pulmonary metastasis survived indicating better prognosis of lungs involvement than other metastasis. The mean age of male patients in the time of diagnosis was higher however, the age mean difference were of no significance. Moreover, gender was shown to have no effect on mortality. Higher prevalence of Ewing`s Sarcoma in the male has been also reported in former studies [4, 14]. In general, results of this study stated that age and gender were not influencing factors in metastasis rate and mortality and for prognosis as well. %88 of subjects entered with a primary bone lesion and %12 with primitive metastasis while in another study %25 enlisted with primitive metastasis probably due to younger subjects (<6 years old) [15]. According to previous studies %80 of patients have come to death in 2 years before chemotherapy and the survival has been less than %10 [1, 2, 10]. Thus, chemotherapy could chemotherapy before and after surgery could increase survival. In this study the survival of metastatic cases is %18.75 which is close to the results of other studies (%20-30) [1, 4].

%85.72 of patients had surgery and %14.28 received only chemotherapy because of pelvis involvement and surgical impossibility. From 5 patients having only chemotherapy, 3 died and two survived of whom one suffered vertebral metastasis. Osteoplasty with allograft has been stated as the most common surgery in various studies [10, 14] as done in 2 hospitals of the present study which might be due to prosthetic unavailability, high expenses and diaphysial location of tumours as well. Common surgical methods in former studies included wide resection and further chemotherapy [4, 14]. Preoperative chemotherapy was conducted alongside with standard guideline in this study. The present study showed the 5-year survival as %46.2. In other studies, 5-year survival without metastasis has been reported %60-70, and %20-30 in multiple bones involvement and metastatic cases %20-30 [16]. Long-term survival has been %43 [3]. Higher survival in the present study might be due to pre and post-surgical chemotherapy. Moreover, %70 of subjects without metastasis at the beginning experienced 2 years survival. In other words, only %30 without metastasis died in 2 years.

This retrospective study did not include information of precise size of surgery zone. So, no comparison conducted between surgery size and chemotherapy effect which is suggested for future studies.

## Conclusion

There have been many advancements in Ewing`s Sarcoma treatment since 30 years ago. Multidimensional approach in treating Ewing`s Sarcoma has made better prognosis and higher survival. The most efficient protocol seems to be conducted in specialized clinics supervised by tumor experts. Most patients admitted to hospitals in this study had low socio-economic status which might influence the process of treatment and follow-up. Making appropriate therapeutic policies facilitate receiving treatment for low-income population. Furthermore, socio-economic status could be investigated as an influencing factor in future studies. New effective medication is also needed for patients relapsed. One of the limitations of this study was medical records incompleteness that contributed to decline in number of participants. It is concluded that appropriate techniques, ongoing follow-up and interdisciplinary collaboration including orthopaedic surgeon, oncologist, radiologist,

counsellor, occupational therapist, nurse and psychologist will promote recovery process.

## Conflict of Interests

The authors declare that there is no conflict of interest.

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