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**Original Article / Orijinal Araştırma**

# Diagnosis and Treatment of Musculoskeletal Sarcoma in a Tertiary Reference Hospital

## *Üçüncü Basamak Bir Referans Hastanesinde Kas-İskelet Sistemi Sarkomlarının Tanısı ve Tedavisi*

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## ABSTRACT

**Objective:** Aim of study was to describe the clinical characteristics and short-term survival of adult patients diagnosed with skeletal Ewing sarcoma.

**Methods:** This descriptive study included 15 patients who underwent surgical treatment after being diagnosed with skeletal Ewing sarcoma and received perioperative treatment between January 2017 and February 2023. Patients were retrospectively evaluated for tumor recurrence, metastasis development, and survival.

**Results:** Of the 15 patients, 10 were men and 5 were women. At the time of diagnosis, 11 (73.33%) patients were found to be non-metastatic. Bone marrow transplantation was performed in 12 (80%) patients. Metastasis was detected during the follow-up period in 6 (40%) patients. Local recurrence developed in 10 (66.7%) patients, and additional surgeries were planned due to recurrence in 5 (33.3%). Second recurrence developed in 4 (26.67%) patients and 2 (13.3%) patients who required additional surgery. Overall, survival after surgical treatment was 4 years in 11 (73.33%) patients.

**Conclusion:** Treatment protocols applied to adult patients with Ewing sarcoma are often adapted from pediatric clinical studies or have been developed based on the experiences of the centers. Therefore, to achieve better outcomes, it is crucial to report the treatment protocols and patient outcomes of centers providing care for adult Ewing sarcoma patients and contribute these findings to the literature in order to develop an optimal treatment strategy.

**Keywords:** Epidemiology, bone tumor, Ewing sarcoma, survival

## ÖZ

**Amaç:** Bu çalışmanın amacı, kemik dokusu kaynaklı Ewing sarkomu tanısı alan erişkin hastaların klinik özelliklerini ve kısa süreli sağkalımlarını tanımlamaktır.

**Yöntem:** Tanımlayıcı tipteki bu çalışma, Ocak 2017 ile Şubat 2023 tarihleri arasında kemik dokusu kaynaklı Ewing sarkomu tanısı konulduktan sonra cerrahi tedavi uygulanan ve üçüncü basamak referans hastanede perioperatif tedavi gören 15 hastayı içermektedir. Hastalar tümör nüksü, metastaz gelişimi ve sağkalım açısından retrospektif olarak değerlendirildi.

**Bulgular:** Ewing sarkom tanısı konulan 15 hastanın 10'u (%66,7) erkek, 5'i (%33,3) kadındı. Tanı anında 11 (%73,33) hastada metastaz olmadığı belirlendi. Hastaların 12'sine (%80) kemik iliği nakli yapıldı. Takip döneminde 6 (%40) hastada metastaz tespit edildi. Hastaların 10'unda (%66,7) lokal nüks gelişti ve 5'inde (%33,3) nüks nedeniyle ek ameliyat planlandı. 4 (%26,67) hastada ikinci nüks gelişti ve 2 (%13,3) hastada ek ameliyat gerekti. Toplamda 11 (%73,33) hastada cerrahi tedavi sonrası sağkalım 4 yıl olarak belirlendi.

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**Sonuç:** Ewing sarkomlu yetişkin hastalara uygulanan tedavi protokolleri sıklıkla pediatrik klinik çalışmalardan uyarlanmıştır veya merkezlerin deneyimlerine dayanarak geliştirilmiştir. Bu nedenle, daha iyi sonuçlar elde etmek adına optimal bir tedavi stratejisi geliştirebilmek için, erişkin Ewing sarkomu hastalarına tedavi hizmeti veren merkezlerin tedavi protokolleri ve hasta sonuçlarının bildirilerek literatüre kazandırılması önemlidir.

**Anahtar Kelimeler:** Epidemiyoloji, kemik tümörü, Ewing sarkomu, sağkalım

## INTRODUCTION

Ewing sarcoma (ES) is the second most frequently observed malignant bone tumor after osteosarcoma. Histologically, it is a high-grade tumor formed from poorly differentiated small round cells.[1-3] It is usually observed in children and young adults. Although it usually originates from bones, it can also occur within soft tissues and visceral organs.[4] The most commonly involved anatomic localisations are the pelvic bones, axial skeleton and femur. The computerized tomography section in Figure 1 shows the iliac bone-located ES, and the magnetic resonance imaging view in Figure 2 demonstrates the scapula-located ES. Metastasis is observed at the initial stages in one in four cases.[3] The presence of metastasis at the time of diagnosis is the only universally accepted prognostic factor based on valid evidence.[5]

Diagnosis of ES, provision of appropriate and sufficient treatment, and continuity of follow-up is often difficult and complex. Although various treatment schemes are applied in different centers, a combination of neoadjuvant chemotherapy, surgery, radiotherapy and adjuvant chemotherapy is usually preferred.[6] Therefore, a multidisciplinary team approach in centers with experience of sarcoma treatment should manage the diagnosis process and treatment afterwards to provide appropriate and adequate care for better results.[7] In the pediatric population, the 5-year survival rate of patients with ES has been reported to be 60-80%.[8,9] Although studies evaluating the outcomes of adult patients with ES have reported different and conflicting results, the prognosis and survival rates are generally worse than those of the pediatric population.[10,11]

Another important point that must be taken into consideration is that ES is mainly observed in adolescents and young adults. There are few clinical studies of adult patients with ES, and these are generally retrospective studies with small sample sizes. Consequently, treatment protocols applied to adult patients with ES are often adapted from pediatric clinical studies or have been developed based on the experience of the treating centers. This is a significant shortcoming of the literature. The aim of this study was to describe the clinical characteristics and short-term survival of adult patients diagnosed with skeletal ES who received multimodality treatment at our center.

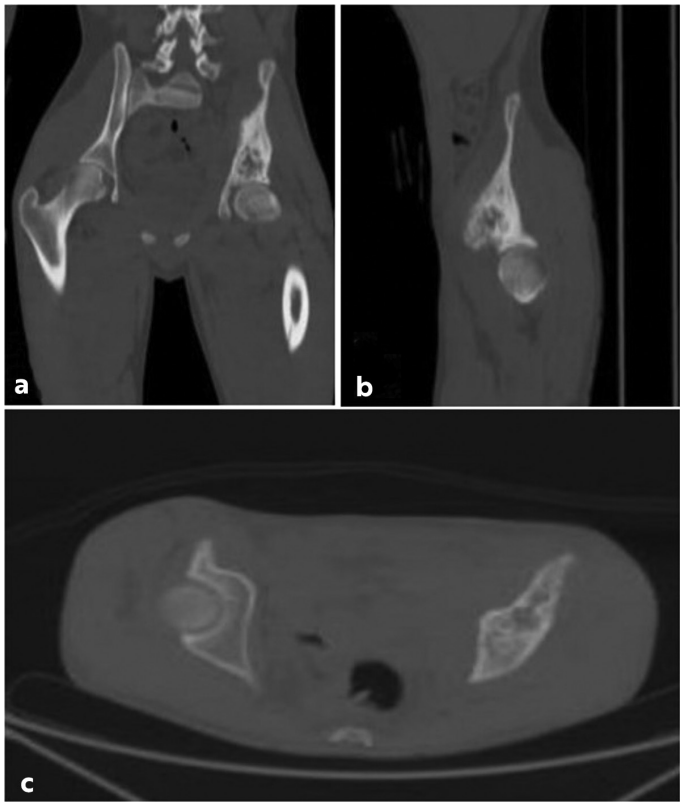


**Figure 1.** Pelvic CT of 23 year old male patient showing iliac wing-seated Ewing sarcoma

*CT: Computed tomography*

## METHODS

Approval for this retrospective study was granted by the University of Health Sciences Türkiye, Gülhane

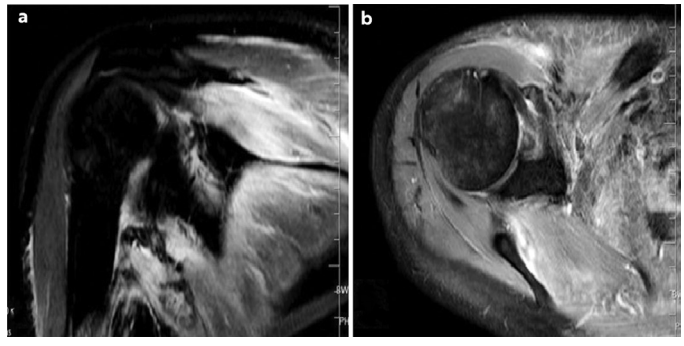


**Figure 2.** Shoulder MRI of 31 year old female patient with Ewing sarcoma located within the scapula

*MRI: Magnetic resonance imaging*

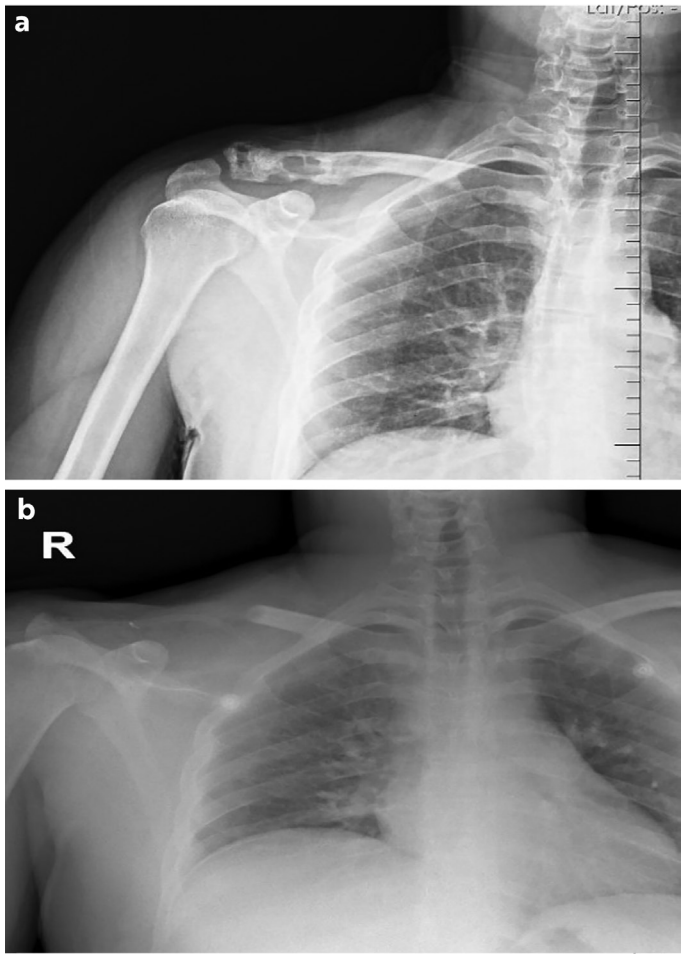


**Figure 3.** (a) Preoperative roentgenogram of 39 year old male patient with clavicle-originated Ewing sarcoma. (b) Postoperative roentgenogram shows wide resection of the clavicle performed

Training and Research Hospital Local Ethics Committee (approval number: 2024/196, date: 24/04/2024). The study included 15 adult patients who were diagnosed with histopathologically confirmed skeletal ES and underwent surgical treatment between January 2017 and February 2023. Figure 3a shows clavicle-originated ES and Figure 3b shows the postoperative radiograph. Patients were excluded from the study if they were aged 18 years, had not undergone an orthopedic surgical procedure for ES, or had a follow-up period shorter than 12 months.

Patients were staged according to the American Joint Committee on Cancer. All patients have received alternate vincristine, adriamycin, cyclophosphamide-ifosphamide-etoposide regimens every 14 days as the neoadjuvant and first-line metastatic regimen. After progression, they received gemcitabine, docetaxel, topotecan, endoksan, temozolamide, and irinotecan as further treatment regimens. All treatment protocols were suggested according to the National Comprehensive Cancer Network guidelines. Radiotherapy was given for local control either alone or after surgical resection using 3D conformal radiotherapy. Patients received an average total dose of 54 Gy (48-64 Gy) at 1.8 Gy daily doses. In routine follow-up examinations once every 3 months, the patients underwent physical examination, routine blood count, basic biochemistry tests, and whole body positron emission tomography-computed tomography.

All patients in this cohort were aged 40 years and had no comorbidities at the time of ES diagnosis. Approximately 60% of the patients had hematologic toxicities (50% grade 1 neutropenia, 10% grade 3 neutropenia, 30% grade 1-2 thrombocytopenia, 5% grade 3 thrombocytopenia). Fifty per cent had other adverse reactions due to the treatment initiated.

Medical and surgical treatment modalities were individualized for each patient based on demographic and epidemiological data, such as age, gender, bone involvement, tumor localization within the bone, and presence of metastasis at the time of diagnosis. Prospective data were collected on the development of recurrence during the follow-up period after the first treatment, the time to the development of recurrence, the development of metastasis, the number of secondary surgeries if performed, and the duration of overall survival after surgery. These data were evaluated retrospectively.

### Statistical Analysis

Data obtained in this study were statistically analyzed using IBM SPSS vn. 22.0 software (IBM Corporation, Armonk, NY, USA). Continuous variables were reported as mean±standard deviation values, and categorical variables were reported as frequency and percentage. The overall survival and survival probabilities according to gender were predicted using the Kaplan-Meier method. A value of $p<0.05$ was set as statistically significant.

## RESULTS

The 15 patients diagnosed with ES comprised 10 (66.7%) men and 5 (33.3%) women, with a mean age of 29.7 years. The histopathological diagnosis was established with examination of samples obtained via excisional biopsy in 14 patients and via tru-cut biopsy in 1 patient. The femur was most frequently involved bone (n=7, 46.6%) in our cohort. Tumors were most commonly localized within the diaphysis (66.7%, n=12). At the time of diagnosis, there was no metastasis in 11 (73.33%) patients. Metastasis was detected in 4 (26.67%) patients upon diagnosis (Table 1).

Details of the applied treatment protocols were reviewed, and it was observed that neoadjuvant chemotherapy

was provided to 14 (93.33%) patients, preoperative radiotherapy to 6 (40%), adjuvant chemotherapy to 12 (80%), postoperative radiotherapy to 4 (26.67%), and bone marrow transplantation to 12 (80%) (Table 2). The mean follow-up period of the patients was 62 months (range 52-96 months).

Local recurrence developed during the follow-up period in 10 (66.7%) patients, and 5 (33.3%) of these required additional surgery. A second recurrence developed in 4 (26.67%) patients, and additional surgery for a second time was deemed to be necessary in 2 (13.3%) patients. Metastasis was present at the time of diagnosis in 4 patients and developed during follow-up period in 2 patients. Thus, the presence of metastasis was determined in 6 (40%) patients. Overall 4-year survival was observed in 11 (73.33%) patients and 8-year survival was observed in 4 (26.67%) (Table 2).

## DISCUSSION

ES is most commonly observed in children and the young adult population, and it is extremely uncommon after the age of 40 years. In a study by Ashour et al.[12] involving 53 adult patients with ES, the mean age was 26.9 years, and Seker et al.[13] reported a median age of 27 years in a study evaluating 26 adult ES patients. In the current study, the mean age was 29.7 years. Therefore, when an ES-like tumor is diagnosed in patients aged >30 years, it would be appropriate to first consider other small round cell tumors, such as small-cell carcinoma or large-cell lymphoma.[14] In the current study, ES was found to originate from the femur most oftenly (n=7). Although most studies have indicated that axial skeleton and pelvis involvement is predominant[6,15], there are also studies in the literature showing that involvement of the long bones of the extremities is also common.[13]

Non-metastatic disease was detected in 11 (73.3%) patients, whereas metastasis at the time of diagnosis was present in 4 (26.6%) patients. In the literature that studied adult patients with ES, the rates of patients with metastatic disease were similar to the results of the current study. The rate of patients diagnosed with metastatic disease was reported to be 30% in a study of 53 patients by Ashour et al.,[12] 19% in a study of 26 patients by Seker et al.,[13] and 27% in a study of 77 patients by Rochefort et al.[16] In addition to the 4 patients that presented with metastatic disease in the

**Table 1. Demographics and epidemiological data**

| | | n | % |
|---|---|---|---|
| Gender | Male | 10 | 66.7 |
| | Female | 5 | 33.3 |
| Age (years) | Mean±SD | 29.74+10.15 | |
| Involved bone | Costa (6th costa) | 1 | 6.6 |
| | Femur | 7 | 46.6 |
| | Fibula | 1 | 6.6 |
| | Anterior chest wall | 1 | 6.6 |
| | Clavicle | 1 | 6.6 |
| | Sacroiliac region | 1 | 6.6 |
| | Scapula | 1 | 6.6 |
| | Vertebra (T12) | 1 | 6.6 |
| | Tibia | 1 | 6.6 |
| Localization of the tumor within the bone | Vertebra costa anterior chest wall, sacroiliac region,and scapula | 5 | 33.3 |
| | Diaphysis | 10 | 66.7 |
| Metastasis during diagnosis | Present | 4 | 26.67 |
| | Absent | 11 | 73.33 |

SD: Standard deviation

**Table 2. Details regarding treatment and survival of patients**

| | | n | % |
|---|---|---|---|
| Preoperative CT | Present | 14 | 93.33 |
| | Absent | 1 | 6.67 |
| Preoperative RT | Present | 6 | 40 |
| | Absent | 9 | 60 |
| Type of surgery | Amputation | 1 | 6.67 |
| | Excision | 13 | 93.33 |
| Bone-Marrow transplantation | Present<br>Absent | 12<br>3 | 80<br>20 |
| Postoperative CT | Present | 12 | 80 |
| | Absent | 3 | 20 |
| Postoperative RT | Present | 4 | 26.67 |
| | Absent | 11 | 73.33 |
| Metastasis | Present | 6 | 40 |
| | Absent | 9 | 60 |
| 1st Recurrence | Present | 10 | 66.7 |
| | Absent | 5 | 33.3 |
| 1st Additional surgery requirements: | Present | 5 | 33.3 |
| | Absent | 10 | 66.7 |
| 2nd Recurrence | Present | 4 | 26.67 |
| | Absent | 11 | 73.33 |
| 2nd Additional surgery requirements: | Present | 2 | 13.33 |
| | Absent | 13 | 86.67 |
| Survival | 4 Years | 11 | 73.33 |
| | 8 Years | 4 | 26.67 |

CT: Computed tomography, RT: Radiotherapy

current study, metastasis developed in 2 patients during the follow-up period. Metastatic lesions were found in the lungs of all patients with metastasis.

Local recurrence developed during the follow-up period in 10 (66.7%) patients (mean, 19.8 months. Additional surgery was required for recurrence in 5 (33.3%) patients. A second recurrence developed in 4 (26.67%) patients, and surgical intervention was scheduled for 2 (13.3%) patients. The local recurrence rates of ES in adults are highly variable. Ashour et al.[12] reported local recurrence in 20% of patients in a follow-up period of median 38 months, and recurrence with distant metastasis in 36%. In a series of 102 adult patients with ES, Ahmed et al.[15] reported a 5-year local and distant total recurrence rate of 14%, and stated that the recurrence usually occurred as distant metastatic involvement. Rochefort et al.[16] determined the development of recurrence in 43 of 77 patients, and reported that of these, the recurrence was metastasis in 58.1% and only local recurrence in 23.2%. What we observed in the current study was mainly local recurrence. However, large cohorts in the literature have indicated that recurrence usually occurs as metastatic involvement. The conflicting results in the current study can be explained by the small sample size.

Overall 4-year survival was observed in 11 (73.33%) patients and 8-year survival in 4 (26.67%) patients. Although the few studies that have included only adult patients with ES and evaluated survival have reported different results, there is consensus that the only evidence-based factor with an effect on survival is metastatic involvement. Seker et al.[13] reported disease-free survival of 72 months in non-metastatic patients and progression-free survival of 10 months in metastatic patients. In addition, it was also striking that disease-free survival was determined to be 83 months in non-metastatic patients aged <30 years, and median 22 months in non-metastatic patients aged >30 years. The overall survival was found to be a median of 19 months in metastatic patients. In a series of 102 patients, all of whom were non-metastatic, Ahmed et al.[15] reported a 5-year total survival rate of 60% and a disease-free survival rate of 52%. Rochefort et al.[16] reported a median total overall survival of 92.8 months in a series of patients aged >50 years. The median total survival of those with localized disease was 128 months, and a median total survival of 23 months was determined for patients with metastatic disease.

Current large cohort studies have indicated an association between increasing age and poor prognosis for adult patients with skeletal ES.[17-19] A multidisciplinary team approach for primary ES and its recurrences is crucial for combining different modalities to obtain better outcomes and achieve higher survival rates.[7]

## Study Limitations

Several limitations warrant consideration, particularly the retrospective study design. Moreover, the relatively short follow-up duration and the lack of a comparison group that can provide clinical progress in the diagnosis and treatment of the ES. Another limitation is that our study by design, did not include patients who did not receive surgical treatment. Therefore, we were unable to compare the outcomes of adult patients with ES who underwent surgical treatment with those who did not. Because our study was a descriptive study, we could not statistically evaluate the factors affecting survival. Finally, a larger number of patients are required to confirm our results.

## CONCLUSION

Our findings are consistent with the literature, except for the fact that recurrence was mainly local. The conflicting results in the current study can be explained by the small sample size.

## Ethics

**Ethics Committee Approval:** Approval for this retrospective study was granted by the University of Health Sciences Türkiye, Gülhane Training and Research Hospital Local Ethics Committee (approval number: 2024/196, date: 24/04/2024).

**Informed Consent:** Retrospective study.

## Footnotes

## Authorship Contributions

Surgical and Medical Practices: İ.E., N.K., Concept: M.A., İ.E., Design: İ.E., N.K., Data Collection or Processing: Ö.L.K., A.M.B., Analysis or Interpretation: B.A.K., N.K., Literature Search: Ö.L.K., A.M.B., Writing: M.A., B.A.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this studyreceived no financial support.

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