# Treatment of Extraosseous Ewing Sarcoma in Children: Single Center Experience

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**ABSTRACT**

Extraosseous Ewing sarcoma (EOES) is an infrequent type of soft tissue sarcoma, which is highly chemosensitive and radiosensitive. It resembles Ewing sarcoma (ES) of bone histopathologically. The purpose of this study was to demonstrate the characteristics and clinical outcomes of children with EOES treated in a single centre, the largest state hospital that accepts oncologic patients. Patients and Method: We analysed data from 13 pediatric patients who were diagnosed with EOES during the period between June 1992 and December 2007. Results: The median age was 12 years (3-16 years) and male/female ratio was 1.2/1. Surgery was planned as a first treatment modality in eight patients in other hospitals. All these patients were admitted to our hospital with local recurrent or progressive disease, except for one with a negative surgical margin. Definitive surgery was performed prior to chemotherapy in four patients and after chemotherapy in three patients. Eleven patients were treated with the EICESS-92 chemotherapy protocol. In 10 patients, radiotherapy was applied to the primary tumor site at a dose of 50-56 Gy. The median follow-up was 48 months (range, 12-103 months). The five-year estimate of failure free survival and overall survival was 67%. None of the patients died due to treatment toxicity. Conclusion: Patients with a diagnosis of EOES must be referred to oncology centers. Treatment must be planned by an oncology team consisting of a pediatric oncologist, an oncological surgeon, and a radiotherapist, in order to avoid mutilating surgery and delays in receiving chemotherapy.

**Key Words:** Extraosseous Ewing sarcoma, Surgery, Chemotherapy, Radiotherapy, Children

**ÖZET**

**Çocukluk Çağı Ekstraosseous Ewing Sarkomalı Hastaların Tedavisi: Tek Merkez Deneyimi**

Ekstraosseos Ewing sarcoma (EOES) çocukluk çağının nadir görünen yumuşak doku sarkomu olup kemoterapi ve radyoterapiye oldukça hassastır. Bu çalışmanın amacı tek merkezde EOES nedeniyle izlenen hastaların klinik özelliklerini ve tedavi sonuçlarını bildirmektir. Hastalar ve Yöntem: Haziran 1992 ile Aralık 2007 tarihleri arasında merkezimizde izlenen 18 yaşından küçük 13 çocuk hastanın dosyası retrospektif olarak incelendi. Hastaların klinik özellikleri, tedavileri ve sonuçları değerlendirildi. Bulgular: Ortanca yaş 12 (3-16 yaş) olup, erkek/kız oranı 1.2/1'dir. Önce dış merkezde değerlendirilen sekiz hastada cerrahi ilk tedavi yöntemi olarak seçilmiş olup yedi hasta merkezimize tekrarlayan veya ilerleyici lokal hastalık ile başvurdu. Merkezimizde tedavi amaçlı cerrahi dört hastada kemoterapiden önce, 3 hastada kemoterapiden sonra uygulandı. Onbir hastada kemoterapi olarak EICESS-92 tedavi protokolü uygulandı. On hastada primer bölgeye 50-56 Gy radyoterapi verildi. Ortanca izlem süresi 48 ay (12-103 ay) olup beş yıllık hastalıksız ve genel yaşam hızı %67 olarak bulundu. Hiçbir hasta tedaviye bağlı yan etkiler nedeniyle kaybedilmedi. Sonuç: Bu hastalar komplikasyon riski yüksek büyük ameliyatlardan kaçınmak, kemoterapiyi geciktirmemek ve hastalık tekrarını önlemek için öncelikli olarak onkoloji merkezlerine sevkedilmeli, tedavi çocuk onkoloğu, onkolojik cerrah ve radyoterapistin bulunduğu bir konsey tarafından planlanmalıdır.

**Anahtar Kelimeler:** Ekstraosseos Ewing sarkoma, Cerrahi, Kemoterapi, Radyoterapi, Çocuk

## INTRODUCTION

Ewing sarcoma (ES) of bone, extra-osseous Ewing sarcoma (EOES), Askin tumors of the thoracic wall, and peripheral primitive neuroectodermal tumors are highly aggressive and poorly differentiated neoplasms. The term "Ewing sarcoma family of tumors" (ESFT) is commonly used for this group of small round blue cell tumors.[1] Ewing sarcoma originating from soft tissue is histopathologically identical to ES of bone with prominent intracellular glycogen.[2] It is treated as ES of bone in some centers and as rhabdomyosarcoma in others. The purpose of this study is to demonstrate the characteristics and clinical outcomes of children with EOES treated in a single centre, the largest state hospital specialized in oncology in Turkey.

## PATIENTS AND METHODS

The study involved 13 patients younger than 18 years who were diagnosed with EOES during the period between June 1992 and December 2007. Their oncology files were reviewed retrospectively. Patients were evaluated using the following techniques: computed tomography (CT) or magnetic resonance imaging (MRI) of the primary site, thoracic CT for lung metastasis, Tc-99m bone scan for bone metastasis, and bone marrow aspiration at diagnosis. The patients were grouped into those with metastatic disease and those with non-metastatic disease. Several variables were analyzed including age, sex, primary tumor site and size, metastasis, treatment and outcome.

### Treatment

Eleven patients were treated with the EICESS-92 protocol. Details of the treatment plan and timing of the local control have been published elsewhere.[3] After diagnosis, patients were separated into two groups: standard risk, with a tumor volume <100 ml and no metastasis; or high risk, with a tumor volume >100 ml and with metastasis. Standard risk patients were treated with the VAIA, and the high risk patients were treated with the EVAIA chemotherapy protocol. Fourteen courses of therapy were carried out every three weeks for total treatment duration of 42 weeks.[3]

### Follow-up and Definitions

During the treatment, patients were evaluated after every four courses of therapy. Local or distant relapses, disease progression, resistant disease, second malignancy, and death were categorized as "events". "Event-free survival" (EFS) was defined as the time from diagnosis, till an event or final contact with the patient. "Overall survival" (OS) was defined as the time from diagnosis until death or final contact with the patient.

## RESULTS

In our center, 120 patients were diagnosed with PNET/Ewing sarcoma between the years of 1992 and 2007. The primary tumor site was extraosseous in 13 of these patients. In this subgroup, the male/female ratio was 1.2/1, with a median age of 12 years (ranging from 3 to 16 years). Pain and swelling were the main symptoms in eleven patients, and one patient presented with prominent neurological symptoms caused by an intracranial tumor. The tumor was localized to an extremity in seven patients, it was orbital in three patients, it was localized to subcutaneous tissue in two patients, and it was intracranial (extradural) in one patient. Symptoms had been present for an average of 3.5 months (range, 2 to 20 months) prior to diagnosis. The median tumor diameter was 6 cm (2 cm to 30 cm). Lung metastases were detected in two patients, lung and bone metastases in one, and regional lymph node metastases in two.

### Surgery

As shown in Table 1, surgery was planned as a first treatment modality in eight patients in other hospitals. All these patients were admitted to our hospital with local recurrent or progressive disease, except for one with a negative surgical margin. In our hospital, three patients were diagnosed with incisional biopsy. Definitive surgery was performed prior to chemotherapy in four patients (cases 3, 4, 6, and 9) and after chemotherapy in three patients (cases 3, 10, and 13). In patients in whom an extremity was the primary site, limb salvage surgery was performed in four patients (cases 7, 8, 9, and 10). Amputation was performed in one patient (case 13) after neoadjuvant chemotherapy and radiotherapy

**Table 1.** Demographic features of patients and details of surgeries

| Case | Age (years) /sex | Localization | Metastatic region | First surgery | | | Recurrence on admission | Second surgery | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Place* | Type | Surgical margin | | Place* | Time | Type | Surgical margin |
| 1 | 9/f | Intracranial (epidural) | | Outside | Total | + | + | Outside | Before chemotherapy | Subtotal | + |
| 2 | 9/f | Orbita | | Outside | Total | + | + | | | | |
| 3 | 5/m | Orbita | | Outside | Subtotal | + | + | Outside | Before chemotherapy | Subtotal | + |
| 4 | 9/m | Orbita | | Our hospital | Total | + | - | | | | |
| 5 | 3/m | Zygomatic Region (sct) | | Outside | Total | + | + | Outside | Before chemotherapy | Total | + |
| 6 | 15/m | Suboccipital Region (sct) | Lung | Outside | Total | + | + | Our hospital | Before chemotherapy | Total | + |
| 7 | 15/m | Deltoid Region | | Outside | Total | - | - | | | | |
| 8 | 14/m | Distal upper Extremity | | Our hospital | Biopsy | | - | Our hospital | After four courses of chemotherapy | Total | - |
| 9 | 13/f | Hand (sct) | | Outside | Total | + | + | Our hospital | Before chemotherapy | Total | - |
| 10 | 12/m | Cruris | | Our hospital | Biopsy | | | Our hospital | After four courses of chemotherapy | Total | - |
| 11 | 12/f | Cruris | Regional lymph nodes and lung | Our hospital | Biopsy | | | | | | |
| 12 | 9/f | Cruris | Regional lymph nodes, lung and bone | Our hospital | Biopsy | | | | | | |
| 13 | 16/f | Cruris | | Outside | Subtotal | + | + | Our hospital | After two courses of chemotherapy | Total | - |

* The hospital where the operation was performed

*Abbreviations*: sct, subcutaneous tissue; DOD, dead of disease; NED, no evidence of disease

**Table 2.** Chemotherapy protocols and radiotherapy doses of patients and outcomes

| Case | Chemotherapy | Radiotherapy dose (Gy) | Result of induction therapy | Outcome and Survival time (month) |
|---|---|---|---|---|
| 1 | CCNU, Vincristine, Cisplatin | 54 | Progression | DOD (42) |
| 2 | EVAIA | 54 | Remission | NED (51) |
| 3 | VAIA | - | Remission | NED (25) |
| 4 | VAIA | 50 | Remission | NED (12) |
| 5 | EVAC | 50 | Remission | NED (48) |
| 6 | EVAIA | 50 | Remission | NED (46) |
| 7 | EVAIA | 54 | Remission | NED(61) |
| 8 | VAIA | 50 | Remission | NED (62) |
| 9 | VACA | - | Remission | NED (44) |
| 10 | EVAIA | 54 | Remission | NED (103) |
| 11 | EVAIA | - | Progression | DOD (3) |
| 12 | EVAIA | 56 | Progression | DOD (17) |
| 13 | EVAIA | 54 | Progression | DOD (9) |

*Abbreviations:* DOD= dead of disease; NED= no evidence of disease

due to a progressive, large, and painful mass. In all five patients with extremity primary, the surgical margins were free of disease. In patients in whom the tumor was localized to the zygomatic region, the suboccipital subcutaneous region, or the orbita, gross total or partial resection was performed. In these patients, the surgical margins were positive.

### Chemotherapy

The EVAIA regimen was applied to seven patients, the VAIA regimen was used for three patients, and the others received VACA regimen, EVAC regimen, and combination of CCNU, vincristine, and cisplatin. The median number of courses was 14, ranging from four to 14 courses.

### Radiotherapy

In 10 patients, radiotherapy was applied to the primary tumor site at a dose of 50-56 Gy. Surgical margins were negative in three cases before radiotherapy. One of the patients died before radiotherapy. The family of the one case with an orbital lesion refused radiotherapy due to the risk of vision loss. In one of the patients with a hand lesion, radiotherapy was not indicated due to negative surgical margins.

### Survival

Nine patients were still alive and without disease at the completion of the study. The median follow-up time was 48 months (range, 12-103 months). The five-year estimate of FFS and OS is 67% (standard error, 13%). Four patients died of progressive disease in a median time of 18 months (3-42 months). The first patient with intracranial disease developed local recurrence after 30 months of diagnosis. In this case surgery and radiotherapy had been applied without chemotherapy as the first-line therapy in another hospital. After local recurrence a second surgery and chemotherapy was given in our center, but this patient died of progressive disease. Two patients diagnosed with lung and inguinal lymph node metastasis died at three and 17 months because of metastasis to the cranium. The last patient with a cruris lesion showed progression of the primary tu-

mor in spite of chemotherapy and radiotherapy. Amputation was performed, but she died of multiple bone metastases at nine months of disease. None of the patients died due to treatment toxicity. Table 2 provides the details of chemotherapy and radiotherapy, and the outcomes of patients.

## DISCUSSION

Extraosseous Ewing sarcoma was first described by Teff et al.[4], who analyzed four cases of paravertebral soft tissue sarcoma resembling Ewing sarcoma of bone. The first large series of EOES, involving 39 patients, was reported by Angervall and Enzinger.[5] Shimada et al.[6] reported histopathological findings of patients with EOES registered to Intergroup Rhabdomyosarcoma Study I and II. EOES commonly involves the lower extremities, paravertebral regions of the spine, retroperitoneum-pelvis, and the chest wall.[6,7] In rare cases, the central nervous system, orbit, diaphragm, vagina, larynx, nasal cavity, and the infratemporal fossa may be affected.[8-12] It can be seen in all age groups, but two-thirds of patients are younger than 30 years.[13] EOES must be differentiated from other small round blue cell tumors, especially from Ewing sarcoma of bone extending to surrounding soft tissue, from rhabdomyosarcoma, and from non-Hodgkin's lymphoma. In the current study, more than half of the cases were in the second decade of life and one third of the cases involved tumors localized to the lower extremity, as expected. Extremely rare sites were also seen in our series, such as the orbital and subcutaneous tissue.

Treatment of EOES involves a combination of surgery, chemotherapy, and radiotherapy. Unlike other non-rhabdoid soft tissue sarcomas, EOES is highly chemosensitive and radiosensitive.[1] Most of our patients had come first to the surgeon, and surgery was chosen as the first-line treatment. Inappropriate surgery done by a non-oncological surgeon resulted in local failure. Later these cases were evaluated by the pediatric oncologist, and more appropriate courses of chemotherapy and radiotherapy were planned.

Before 1970, EOES patients were treated with a single agent, dactinomycine, or with low doses of methotrexate, and amputation was the choice for surgery. After 1970, patients were treated according to the IRS protocol. The five-year survival rate has been reported as 28% for patients presenting before 1970, and 48% for those presenting after 1970.[13]

Raney et al. reported the largest series of patients with EOES, which were included in the IRS I-III. This series involved 130 patients younger than 21 years. After initial surgery, patients were grouped as rhabdomyosarcoma and treated according to the rhabdomyosarcoma protocol. Vincristine and dactinomycin (VA) were applied to some group I patients and all the group II patients. Some group III and IV patients received the VAC protocol. The other group III and IV patients were given VAC plus doxorubicin. Radiation therapy to the primary tumor bed was given to some group I patients and to all other patients. The overall 10-year survival rates increased from 62% and 61% in IRS I and II, respectively, to 77% in IRS III. Survival rates for clinical groups I-IV were 86%, 78%, 60%, and 25%, respectively. No apparent benefit was obtained by adding doxorubicin therapy to VAC.[7]

Krasin et al. from St. Jude Children's Research Hospital reported the results of localized ESFT treated with chemotherapy and surgery. Patients were treated with the VACA or VACA plus ifosfamide and etoposide. They reported 5-year estimates of 25% for the EFS of patients with localized EOES. This rate was lower than that of patients with Ewing sarcoma of bone (78.6%).[14] They also reported the results of patients treated with surgery, chemotherapy, and radiotherapy. For 18 patients with EOES, the 8-year survival estimate was reported to be 88%, and the local failure rate 6%. These authors concluded that local control with surgery and radiotherapy provides excellent results in patients with unfavorable prognostic factors.[15] Chow et al.[16] from the same hospital reported excellent results of nonmetastatic cutaneous and subcutaneous EOES with radiotherapy. They showed that treating patients with adjuvant radiotherapy, even if the surgical margin is free of disease, can increase the survival rate. In our center, patients were treated as in Ewing sarcoma of bone, and chemotherapy was carried out according to the EICESS-92 protocol. The difference between our approach and EICESS-92 protocol was that we applied radiotherapy to most of the patients, even when surgical margins were negative, because of local recurrences on admission.

In summary, EOES is an infrequent type of soft tissue sarcoma, which is highly chemosensitive and radiosensitive. These patients must be referred to oncology centers and treatment must be planned by an oncology team consisting of a pediatric oncologist, an oncological surgeon, and a radiotherapist, in order to avoid mutilating surgery and delays in chemotherapy. This approach also helps to ensure maximal treatment response. It appears that radiotherapy can increase the survival rate in patients with inadequate surgical margin, even if it is negative, or in patients with large and recurrent tumors.

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