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**Case Series**

# A single centre experience in challenging diagnosis and management of osseous and extraosseous Ewing sarcoma: a case series

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## ABSTRACT

Ewing sarcoma (ES) predominantly affects adolescents and young adults, commonly involving the pelvis, femur, and chest wall. This case series analysed the clinicopathological features and treatment profiles of 12 pediatric and adolescent ES patients treated at Tirunelveli Medical College Hospital, Tamil Nadu, from 2019 to 2023. The peak incidence occurred in the 6–15-year age group, with a female predominance. Osseous ES was the most common subtype, with most patients presenting with localised disease or lung metastases. Treatment included chemotherapy, surgery, and radiotherapy, delivered through a multidisciplinary approach. Survival outcomes varied based on disease extent and response to treatment. Advances in radiotherapy and surgical management of oligometastatic disease, along with multiple chemotherapy cycles, may enhance prognosis. The study highlights the importance of early detection, increased awareness, and structured follow-up protocols in improving outcomes. Tailored, comprehensive management strategies are crucial for addressing the clinical challenges of ES in resource-limited settings.

**Keywords:** Ewing sarcoma, Bone, Incidence, Early detection, IHC

## INTRODUCTION

The "Ewing family of tumours" includes a variety of neoplasms with shared characteristics, genetic features, and immunohistochemical profiles. This group consists of Ewing sarcoma of the bone, extra skeletal Ewing tumours, primitive neuroectodermal tumours, and skin sarcomas (originating in the chest wall). Ewing sarcoma (ES) is the second most common malignant primary bone tumour in children and teenagers, after osteosarcoma, and accounts for approximately 10-15% of all bone sarcomas. It is a rare and aggressive cancer that primarily affects children and young adults, and is characterized by small, round cells. ES typically develops in the bone marrow of the long bones, ribs, and pelvis, with the highest incidence in individuals aged 10 to 15 years, although approximately 30% of cases are diagnosed in adults over 20 years old.[1] Extraskeletal Ewing sarcoma (EES) is a rare form of Ewing sarcoma that occurs outside the bone, constituting about 20-30% of all Ewing sarcoma cases. EES is known for its aggressive nature and tendency to metastasize, presenting unique diagnostic and therapeutic challenges when it is found in soft tissues or extramedullary locations. The most common sites of EES include the trunk (32%), extremities (26%), head and neck (18%), and retroperitoneum (16%).[2] A significant number of Ewing sarcoma cases are associated with the chromosomal translocation t (11;22) (q24;12), resulting in the EWS-FLI-1 fusion protein present in approximately 85% of cases. Additionally, 10-15% of cases involve other translocations, such as t (21;12) (22;12), which create fusion genes, such as EWS-ERG.[3] Patients with ES may present with localized or metastatic disease, with approximately 30% having metastases. Pulmonary metastasis generally has a better prognosis than bone marrow involvement. The clinical presentation varies according to age, sex, stage, and tumour size; older patients (≥15 years) have a higher incidence of metastasis, whereas those under 9 years of age typically present with smaller tumours.[4] Symptoms often include fever and local manifestations depending on the location of the tumour. Overall, factors such as age and tumour characteristics

significantly influenced the clinical picture of Ewing sarcoma. An aggressive treatment approach for Ewing sarcoma involves intensive neoadjuvant and adjuvant chemotherapy, achieving a remission rate of nearly 65% in patients with localized disease. Factors such as large tumour size, older age, elevated lactic dehydrogenase levels, involvement of the axial skeleton, and poor chemotherapy response were correlated with worse outcomes.[5] The standard treatment combines chemotherapy with local therapies such as surgery and radiotherapy, with systemic therapy primarily consisting of a vincristine, doxorubicin, cyclophosphamide (VDC) regimen alternating with ifosfamide, etoposide (IE). Local therapy is typically recommended after induction chemotherapy. The five-year survival rate is approximately 75-80% for nonmetastatic disease, while it drops to approximately 30% for metastatic cases.[1]

## CASE SERIES

This case series reviews 12 patients diagnosed with Ewing sarcoma at a South Indian institution between January 2019 and February 2024. Patients of all ages with confirmed skeletal and extra skeletal Ewing's were included, with staging involving MRI/CECT and whole-body FDG-PET-CECT. After confirmation via histopathology and immunohistochemistry, the cases were discussed by a multidisciplinary tumour board. Seven patients with localized disease received curative treatment, whereas five patients with metastatic disease underwent palliative therapy. Treatment outcomes and follow-ups were recorded and analysed using hospital data and Microsoft Excel. The study found peak Ewing sarcoma incidence in the 6-10 and 11-15 age groups, accounting for 50% of cases, predominantly in females (75%). Most patients were students (66.66%) from the upper-lower socioeconomic stratum (58.33%) and lived in rural areas (75%). The pelvis was the most common tumour site (25%), with 75% of patients having osseous Ewing sarcoma. Painful swelling was the most frequent symptom (66.66%) and MRI was the primary diagnostic tool (66.66%). Limited-stage disease and lung metastases were also prevalent (Tables 1 and 2).

Survival outcomes showed that 75% of the patients were alive at the last follow-up, with 58.33% still receiving treatment. The treatment included systemic chemotherapy (91.66%), surgery (41.66%), and radiotherapy (33.33%). However, 33.33% were lost to follow-up, and 25% died during the study (Table 2).

**Table 1: Demographics and clinical features.**

| Parameter | | Count | % |
|---|---|---|---|
| **Age (in years)** | 0-5 | 1 | 8.33 |
| | 6 10 | 3 | 25 |
| | 11-15 | 3 | 25 |
| | 16-20 | 1 | 8.33 |
| | 21-30 | 1 | 8.33 |
| | 31-40 | 2 | 16.66 |
| | 40-50 | 1 | 8.33 |
| | >50 | - | - |
| **Gender** | Male | 3 | 25 |
| | Female | 9 | 75 |
| **Occupation** | Student | 8 | 66.66 |
| | Housewife | 4 | 33.33 |
| | Others | - | - |
| **Education** | School education | 11 | 91.66 |
| | Graduate | 1 | 8.33 |
| **Socio-economic position** | Upper-lower class | 7 | 58.33 |
| | Lower-middle class | 3 | 25 |
| | Upper-middle class | 2 | 16.66 |
| **Residence** | Rural | 9 | 75 |
| | Urban | 3 | 25 |

**Table 2: Patient clinical characteristics.**

| Parameter | | Count | % |
|---|---|---|---|
| **Primary tumor site** | Soft tissues | 3 | 25 |
| | Pelvis | 3 | 25 |
| | Extremities | 2 | 16.66 |
| | Scapula | 1 | 8.33 |
| | Rib | 1 | 8.33 |

Continued.

| Parameter | | | Count | % |
|---|---|---|---|---|
| | Axial skeleton (spine) | | 2 | 16.66 |
| **Tumor type** | Osseous ES | | 9 | 75 |
| | Extraosseous ES | | 3 | 25 |
| **IHC** | CD99 positivity | | 12 | 100 |
| | FLI-1 positivity | | 5 | 41.66 |
| **Stage** | IB | | 1 | 8.33 |
| | IIIA | | 2 | 16.66 |
| | IIIB | | 4 | 33.33 |
| | IV | | 5 | 41.66 |
| **Metastases** | None | | 7 | 58.33 |
| | Lung | | 4 | 33.33 |
| | Bone | | 1 | 8.33 |
| **Symptoms** | Painful swelling | | 8 | 66.66 |
| | Pain alone | | 5 | 41.66 |
| | Weakness of limbs | | 3 | 25 |
| | Fever | | 1 | 8.33 |
| | Abdominal distension | | 1 | 8.33 |
| **ECOG PS** | 1 | | 8 | 66.66 |
| | 2 | | 4 | 33.33 |
| **Diagnostic method** | MRI | | 8 | 66.66 |
| | PET CT | | 2 | 16.66 |
| | CECT | | 2 | 16.66 |
| **Treatment** | Chemotherapy | | 11 | 91.66 |
| | Surgery | | 5 | 41.66 |
| | Radiotherapy | | 4 | 33.33 |
| **Survival time (in months)** | 0-6 | | - | - |
| | 7-12 | | 1 | 8.33 |
| | 13-18 | | 1 | 8.33 |
| | 19-24 | | 1 | 8.33 |
| **Patient follow-up status** | Regular follow up | | 8 | 66.66 |
| | Lost to follow up | | 4 | 33.33 |
| **Patient status** | Alive | On treatment | 7 | 58.33 |
| | | Completed treatment | 2 | 16.66 |
| | Dead | | 3 | 25 |

**Table 3: Overview of treatment strategies.**

| Case | Treatment | Drug(s) used |
|---|---|---|
| **1** | Chemotherapy | VAC/IE |
| **2** | Chemotherapy | VAC/IE |
| **3** | Chemotherapy, surgery | VAC/IE |
| **4** | Chemotherapy | VAC/IE |
| **5** | Chemotherapy, radiotherapy | VAC/IE |
| **6** | Surgery, radiotherapy | - |
| **7** | Chemotherapy, surgery | VAC/IE |
| **8** | Chemotherapy, surgery | VAC/IE |
| **9** | Chemotherapy | VAC/IE |
| **10** | Chemotherapy, radiotherapy | VAC/IE |
| **11** | Chemotherapy, surgery | VAC/IE |
| **12** | Chemotherapy | VAC/IE |

## DISCUSSION

Ewing sarcoma accounts for approximately 15% of bone malignancies, with 68% of cases occurring in individuals aged 0–19 years. The highest incidence is seen in the 10–14 years age group, and 12% of cases affect individuals aged > 30 years. Incidence rates vary by population, with a higher occurrence in Indian than in Malay and Chinese groups. Limited global data exists, but this study shows

that 66% of cases occur in those aged 0–20 years, with peaks in the 6–10 and 11–15 age groups. Notably, 75% of cases involved females, consistent with the findings of Muralidhar et al.[6] Diagnosing pediatric malignancies, such as Ewing's sarcoma, is difficult due to vague symptoms such as pain or swelling, which are often mistaken for trauma or infection. In this study, 66.66% of the patients reported painful swelling and 41.66% experienced pain alone, highlighting the potential for misdiagnosis due to nonspecific symptoms. Immunohistochemistry and histopathological examinations are crucial for the diagnosis of ES. The common immunohistochemical markers include CD99 and FLI-1. CD99, although sensitive, is not specific to ES and can also be expressed in other soft tissue sarcomas. Approximately 95% of ES cases exhibit strong membranous CD99 expression, and a study by Chinchilla et al reported 100% positivity, which is consistent with the findings of this study.[7] FLI-1 were positive in 5 patients, but its use was limited due to practical challenges.

The diagnosis of ES in this study population was made using a combination of histopathological and available immunohistochemical markers. ES commonly affects the lower extremities (45%), pelvis (20%), and other bones, with the femur often involved. In this study, the pelvis was the most frequent site (25%), followed by the long bones and the spine (16.66%). EES accounts for 20% of cases and typically occurs in soft tissues of the trunk and extremities.8 In this study, 25% of the patients had extraosseous ES, while 75% had primary bony ES. Approximately 20% of Ewing sarcoma cases are diagnosed with distant metastasis, often involving the lungs or pleura. The disease has a strong tendency to metastasize, with the lungs, bones, and bone marrow being common sites. Grier et al, found that 23.1% of patients with ESFT had metastases at the time of diagnosis.[9]

In this study, 41% of the patients had metastasis upon diagnosis, with the lungs (33.33%) and bones (8.33%) being the primary sites of spread. Most patients were in the locally advanced stage, consistent with previous research highlighting the aggressive nature of Ewing sarcoma and its frequent metastatic presentation. Current chemotherapy for ES typically includes six drugs: doxorubicin, vincristine, cyclophosphamide, dactinomycin, ifosfamide, and etoposide. Localized ES is treated with surgery, radiotherapy, or both, and radiotherapy is often used when surgery is not feasible. Adding ifosfamide and etoposide to vincristine, doxorubicin, cyclophosphamide, and dactinomycin improved outcomes in patients with localized ES or related tumours.

However, for patients diagnosed with distant metastases, this addition did not improve the results, outcomes remained poor regardless of the treatment protocol used.[9] Effective treatment of metastatic ES remains challenging. In this series, the patients were treated with chemotherapy (91.66%), surgery (41.66%), and radiotherapy (33.33%). Combination chemotherapy has improved five-year survival rates for localized Ewing sarcoma from 10% to 60%.[10] However, metastatic cases have shown a decrease in survival to 25%. Of the 12 patients, 25% died and 75% survived.

## CONCLUSION

Ewing's is a highly aggressive cancer affecting bones and soft tissue, mainly in younger individuals, with an incidence of three cases per million globally. Its rapid onset, nonspecific symptoms, and limited awareness among primary care clinicians contribute to delayed diagnoses and poor outcomes. Early detection and treatment are critical to improve patient survival. This study addressed the limited literature on Ewing sarcoma, particularly focusing on its burden and incidence trends in India and globally.

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