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# Osseous Ewing's Sarcoma in Children: Challenges in Local Treatment and its Impact on Treatment Outcome

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**ABSTRACT**

**Background:** Ewing's sarcoma (ES) is the second most common primary malignant bone tumor in children. Treatment consists of systemic chemotherapy and local treatment either surgery, radiotherapy (RT) or both depending on various tumor characteristics. We evaluated the clinical characteristics and outcome of osseous ES in children. We tried to find out the limitations for providing the best possible local treatment and its impact on treatment outcome. **Methods:** All patients of ES ( ≤ 15 years of age at presentation) diagnosed between October 2016 to September 2019 were included in this retrospective analysis. Patients were followed up till February 2021. **Results:** Clinical characteristics analysis of the 39 cases of osseous ES showed 22 had a primary tumor in the axial skeleton, and 17 in the appendicular skeleton. Twenty-seven patients had localized disease, and 12 had metastasis at presentation. Thirty patients (22 localized, 8 metastatic) were treated with curative intent. Twenty-seven patients received RT. Eight among them had metastatic disease, 3 had chest wall ES who received RT after surgery, 9 received definitive RT for unresectable axial tumor, and 3 received RT for positive cut margin following LSS. Four patients had appendicular tumors, but could not undergo LSS because of logistic issues and received definitive RT. Only two patients could undergo LSS and didn't require postoperative RT. The overall survival (OS) and event-free survival (EFS) at 3 years were 71% and 60% respectively, which is comparable to historical control**. Conclusion:** Limb salvage surgery, though is the treatment of choice, is not always feasible in developing countries. Definitive RT can achieve effective local control with outcomes comparable to patients treated with surgery.

**Keywords**
Ewing's sarcoma, Local treatment, Definitive radiotherapy

## INTRODUCTION

Ewing's sarcoma (ES) is the second most frequent primary malignant bone tumor in children and young adults. It accounts for nearly 40% of all childhood (0-14 years) bone malignancies.[1,2]. The five-year survival rate for patients with a localized ES has improved from 10% with RT alone to 78% with multimodal treatment.[2-4]. Systemic chemotherapy along with timely local treatment is crucial for an optimal outcome. Decision regarding the modality of local treatment depends on tumor characteristics, possible side effects and benefits to the treatment, and personal preferences of the patient. Other factors include the availability of trained experts and the cost of therapy. There are no randomized trials comparing radiotherapy (RT) and limb salvage surgery (LSS) as local treatment in ES. Radiotherapy is easily available in most of the centres in India. Surgical experts for LSS are very few; and LSS is costly. Limited data is available from the eastern zone of India about ES in children.[5,6] We analyzed the clinical characteristics, challenges in ES local treatment and its impact on treatment outcome, from a newly established pediatric oncology unit in the eastern zone of India.

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## MATERIALS AND METHODS

All patients of osseous ES (≤ 15 years of age) registered to the pediatric oncology unit at "Institute of Medical Sciences and SUM Hospital" Bhubaneswar, between October 2016 to September 2019 were enrolled in this retrospective analysis. Data analysis was done with a follow up till February 2021. Patients who had not completed treatment were excluded. Medical records including outpatient notes, indoor charts, and discharge summaries were reviewed. The diagnosis was based on histopathology and immuno-histochemistry. Disease staging was done either by PET CT scan; or bone scan along with CT thorax and bone marrow examination. All patients treated at our centre received neoadjuvant chemotherapy (NACT) for 10-12 weeks followed by response assessment, local treatment LSS or RT, then adjuvant chemotherapy (ACT). Patients' families were counselled in details regarding the available modalities of local treatment, and they opted for the same as per their choice, based on various factors. The data regarding all events (treatment defaults, progression, relapse, or death) and the disease status at last follow up were recorded.

## STATISTICS

Standard statistical methodology was used to describe the patient clinical, demographic and socio-economic profile. Overall survival (OS) was defined as the time interval between the date of diagnosis and either the date of death from any cause or the date of the last follow-up. Event-free survival (EFS) was defined as the time interval between the date of diagnosis and the date of death, first relapse/progression, or the date of the last follow-up. Kaplan-Meier method was used for the estimation of survival curves.

## RESULTS

During the study period (36 months) 472 children with malignancies were registered. Hematolymphoid malignancies were in 290 and 182 had solid tumors. Forty-three (9%, n=472) had ES, among which 4 had extra-skeletal tumors and 39 had osseous tumors. Seventeen were male and 22 were female. Clinical characteristics are described in **Table 1**. The median age at diagnosis was 12 years and ranged from 4 to 15 years. In children with osseous ES 22 (56.5%) had an axial primary tumor, and 17 (43.5%) had a primary tumor in the appendicular skeleton. The most common site of the tumor was lower extremity (n=15, 38%); followed by pelvis (n=9, 23%). Common presenting symptoms were swelling (n=14, 36%), pain (n=13, 32%), walking difficulty (n=10, 26%), and respiratory symptoms (n=7, 19%). Fever or/and other constitutional symptoms were present in 6 (15%). Twenty-seven patients (69%) had localized disease, & 12 (31%) presented with metastasis. Four patients had only lung metastasis, 8 had involvement of bone/bone marrow with or without lung involvement. The consort diagram of the 39 registered patients with Ewing sarcoma is depicted in **(Fig. 1).** In our study group majority of the children (n=22, 56%) were from upper lower socio economic status (SES), followed by 10 (26%) from lower SES, 5 (13%) from upper middle and 2 (5%) were from upper SES (As per the Modified Kuppuswamy scale, updated-2019). Majority (n=32, 82%) were from rural area.

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| Patient and tumor characteristic | Total (n=39) | Percentage (%) |
|---|---|---|
| Sex | | |
| Male | 17 | 43 |
| Female | 22 | 57 |
| Tumor Site | | |
| Skull | 5 | 13 |
| Chest wall | 3 | 8 |
| Upper extremity | 2 | 5 |
| Lower extremity | 15 | 38 |
| Pelvis | 9 | 23 |
| Vertebra | 4 | 10 |
| Other | 1 | 3 |
| Presenting symptoms | | |
| Pain | 9 | 30 |
| Mass | 11 | 35 |
| Gait difficulty | 8 | 27 |
| Respiratory distress | 6 | 19 |
| Constitutional symptoms | 5 | 15 |
| Staging | | |
| Localized | 27 | 69 |
| Metastasis to only lung | 4 | 10 |
| Multiple metastasis: lung, bone, marrow | 8 | 21 |
| Intent of therapy | | |
| Curative | 30 | 77 |
| Palliative | 4 | 10 |
| Other | 5 | 13 |
| Local treatment in curative treatment(n=30) | | |
| Surgery only | 3 | 10 |
| Surgery + radiotherapy | 6 | 20 |
| Radiotherapy only | 21 | 70 |

**Table 1**. Baseline clinical characteristics and the local treatment modalities used (n=39)

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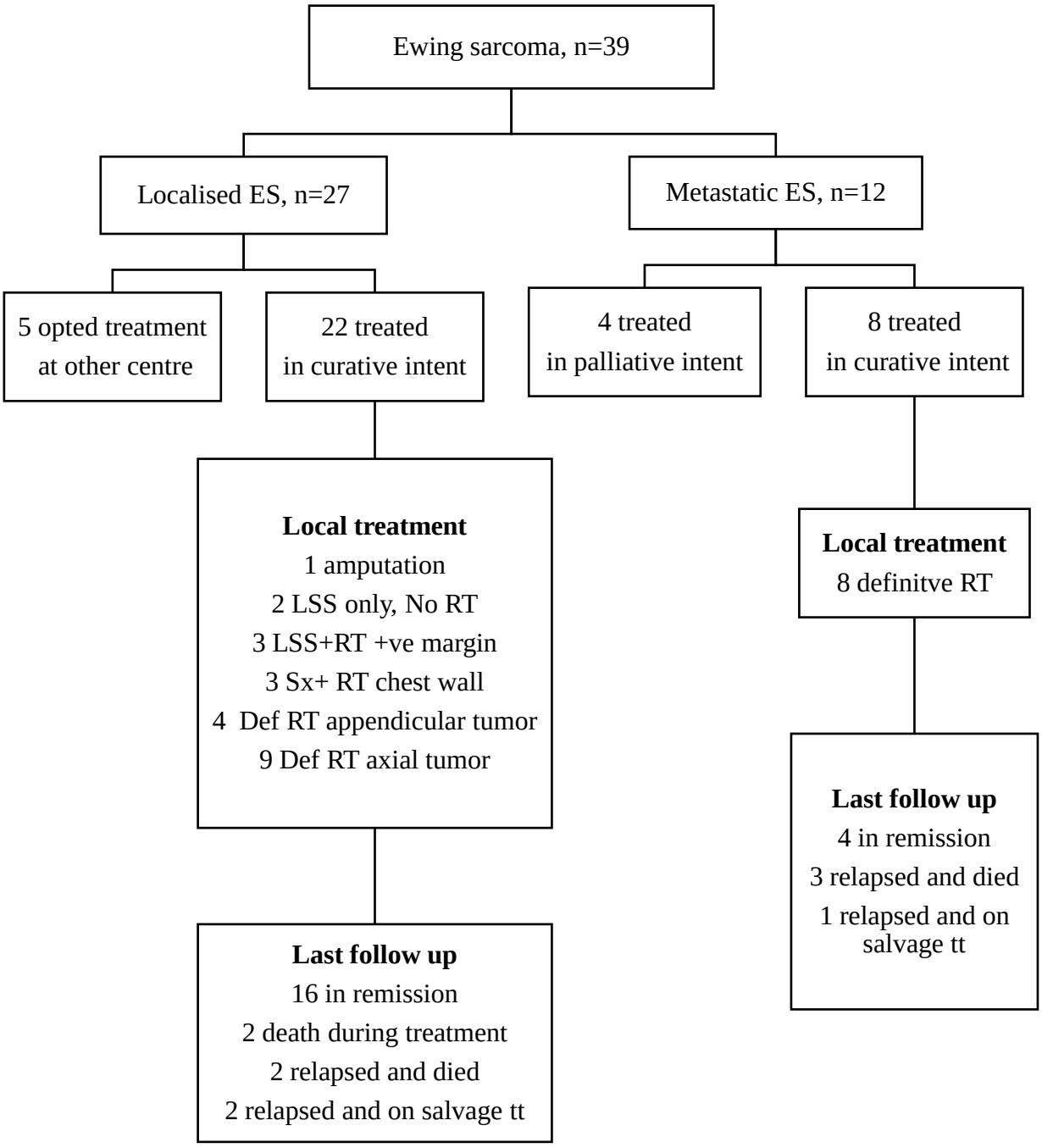


**Figure 1. Consort diagram of this retrospective study**

**Patients with Localized Disease (n=27)**

All patients with localized disease except one (she underwent upfront below-knee amputation for a fungating ulcerated painful mass) received neoadjuvant chemotherapy (NACT). Five patients opted for treatment at other institutions; they were excluded from outcome analysis. Twenty two patients continued treatment at our center. Twelve patients received modified intergroup study INT-0091 chemotherapy with alternating cycles of VDC (Vincristine 1.5mg/m$^2$, Doxorubicin

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75mg/$m^2$, Cyclophosphamide 1,200mg/$m^2$) and IE (Ifosfamide 1,800mg/ $m^2$/day for 5 days, Etoposide 100mg/$m^2$/day for 5 days) every 2weekly; and 10 patients received chemotherapy as per the Tata Memorial Hospital EFT 2001 protocol.[7,8] The median duration of NACT was 87 days. The average number of chemotherapy before local treatment was 5 cycles.

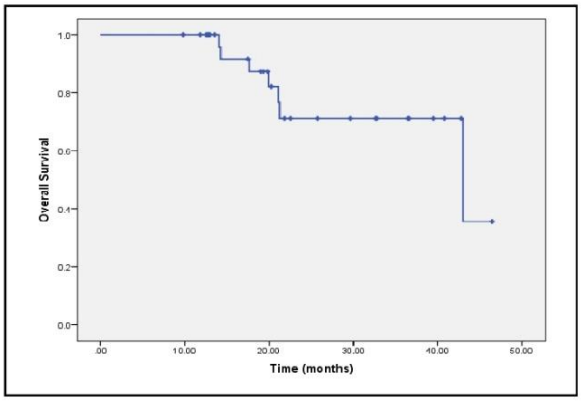
Nineteen patients received RT. Nine among them received definitive RT for unresectable axial tumor, 3 patients of chest wall ES received post surgery RT, 3 patients received RT for positive cut margin post limb salvage surgery, 4 patients had appendicular tumors, but could not undergo limb salvage surgery because of financial constrains, & logistic issues and received definitive RT. Only two patients could undergo limb salvage surgery and didn't require postoperative RT. One underwent upfront amputation. Till the time of the last data collection, 16 patients completed treatment and were in remission. Two patients died during treatment (1 due to infection, 1 due to dilated cardiomyopathy); 2 relapsed and died of disease, and 2 relapsed in lung and were on salvage therapy.

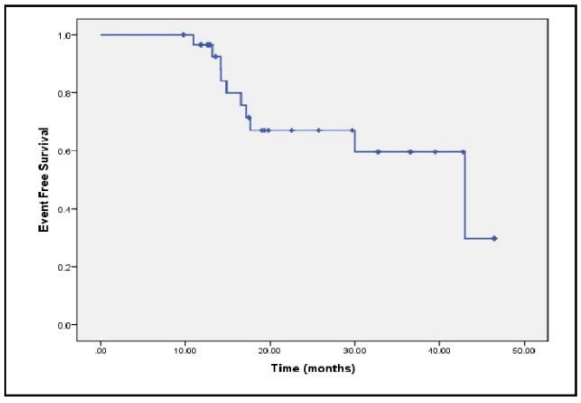
**Patients with metastatic disease (n=12)**

Four patients had isolated lung metastasis and 8 had additional bone/bone marrow involvement. Four patients with bone/bone marrow involvement opted for best supportive care, and they received metronomic oral chemotherapy in a palliative intent. Four patients with bone/BM involvement received curative-intent treatment with an explained guarded outcome. Four patients with isolated lung metastasis were treated with curative intent. A total of 8 patients with metastatic disease were treated in curative intent and completed treatment. All of them received VDC/IE 2 weekly NACT for 12 weeks followed by RT as local treatment. At last follow up, 4 patients were in remission. Four patients relapsed, among them 3 died of disease and 1was on salvage chemotherapy during the last data collection.

**Survival outcome**

Thirty patients (22 localized and 8 metastatic) were included for outcome analysis. For the whole group, OS was 71% and EFS was 60% at 3 years. For localized disease, OS and EFS were 79% and 71% respectively at 3 years. For metastatic disease, OS and EFS were 50% and 26% respectively at 3 years. The median follow-up period was 24 months (**Fig. 2).**



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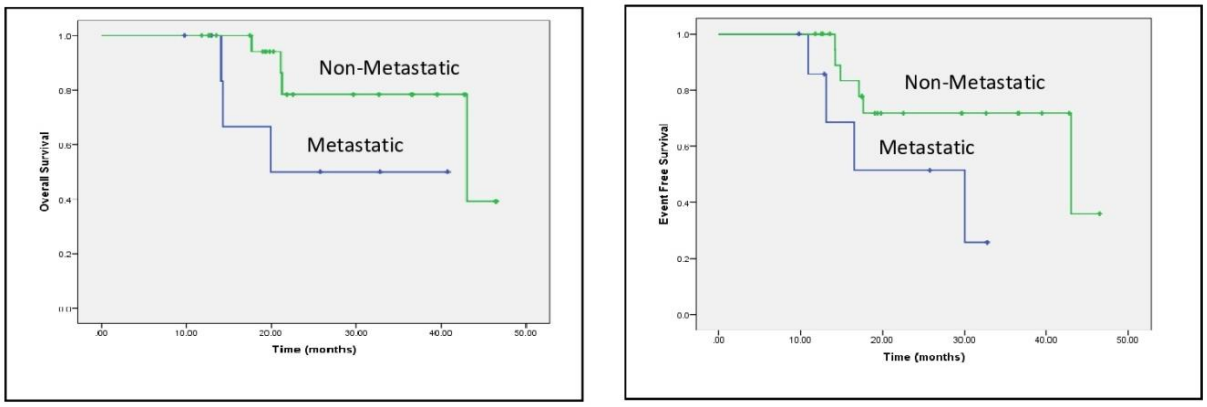


**Figure 2.**
Kaplan-Meier survival curve of pediatric Ewing's sarcoma. OS was 71 % and EFS 60% at 3 years. For localized disease, OS and EFS were 79% and 71% respectively at 3 years. For metastatic disease, OS and EFS were 50% and 26% respectively at 3 years

## DISCUSSION

The clinical profile and outcome of childhood bone tumors in eastern zone of India is unknown. There is no electronic medical data recording system in the majority of these hospitals. Our study is a preliminary step towards a better understanding of the clinical characteristic and the treatment outcome of childhood ES in our centre. In our study, patients' age ranged from 4 to 14 years, with slight female gender predominance. This gender bias, which is not in agreement with other studies, may be related to small sample size. Forty-six percent of the children (n=17) were under 10 years. Younger patients have a better prognosis than patients of 15 years and older.[9,10] The most common site was the lower extremity (38%), followed by the pelvis (23%) and other sites (skull, vertebra and chest wall); which is same as reported in the literature.[11] Ewing's sarcoma in the distal extremities has the best prognosis. Patients with Ewing's sarcoma in the proximal extremities have an intermediate prognosis, followed by patients with central or pelvic sites. At diagnosis, 27 patients (69%) had a localized disease; and 12 (31%) had metastasis. Majority of them had multiple site metastasis (n=8, 67%), followed by isolated lung metastasis (n=4,33%). Metastases at diagnosis are one of the poorest prognostic factors.[9-12]
Thirty children (22 localised, 8 metastatic) received curative-intent treatment at our centre. Twenty seven among them required RT in the local treatment. Ten patients of localised ES had a tumor in the appendicular skeleton. Two cases could be managed with limb salvage surgery only. Another 3 patients though underwent limb salvage surgery, had a positive cut margin necessitating post operative RT. Four patients , though had an extremity tumor received definitive RT, LSS was not feasible because of unavailability of surgical experts, financial limitations, or logistic issues of procuring custom made prosthesis.
OS and EFS for all the 30 patients were 71% and 60% respectively at 3 years. This outcome is comparable to historical data from developing countries.[5-7] The median follow up period was 24 months. We didn't ascertain statistical significance in outcome between RT and surgery treatment group because of the small number of patients.
Head to head comparison of surgery and RT in local control of ES by a well designed randomized control trial has not been done so far. Retrospective institutional series suggest lesser local toxicity, superior local control, and better survival with surgery than with radiation.[13-16] RT

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is recommended when the tumor is inoperable because of inaccessible location (like the spine, sometimes pelvis) or if the effect of surgery would significantly alter the quality of life.[17-19]But in developing countries, significant challenges are there. The availability of surgical experts in limb salvage surgery, financial constraint, and logistics for custom made prosthesis influence the decision for local treatment. Survival outcome with definitive RT in such a group of patients in our study seems comparable to historical data of patients treated with surgery.[5-7] A similar result for patients with pelvic primary Ewing's sarcoma from the North American intergroup trial had shown no difference in local control or survival based on local-control modality.[20] The limitation of our study is its retrospective design and small sample size.

## CONCLUSION

Multimodal treatment with chemotherapy, surgery, and RT is crucial in the management of ESFT. Local therapy is vital for an optimal outcome. Our study brings about an important understanding that successful treatment is challenging in resource-limited settings. Limb salvage surgery, though is the treatment of choice, is not always feasible even in localized extremity tumors because of the paucity of trained pediatric onco-surgeon, financial limitations, and logistic reasons. Definitive RT in such cases can achieve effective local control with outcomes comparable to patients treated with surgery.

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**Conflicts of interest**
There are no conflicts of interest

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