

Clinical Profile and Treatment Outcomes of Adult Ewing Sarcoma: A Tertiary Care Centre Study

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Abstract: Introduction: Ewing sarcoma (ES) is the second most common primary bone tumor. Ewing sarcoma (ES) is more common in children and relatively rare in adults. Adult ES has poor prognosis than children. Treatment approaches for adults have been extrapolated from paediatric experience. The inclusion of adults in pediatric trials was limited. Aims and Objectives: 1) To evaluate the clinical profile of Adult Ewing Sarcoma. 2) To identify risk factors for poor outcomes of Adult Ewing Sarcoma including patient, tumor, and treatment related variables. Materials and Methods: It is retrospective study. Medical records of 45 patients with age >18 years treated at our centre between 2014 and 2020, were retrospectively analysed. Survival analysis is done by plotting Kaplan–Meier curves. Results: Out of 45 patients 28 (62.2%) had localised disease, 17 (37.8%) had metastatic disease. Males were 27 (60%) and females were 18 (40%). Median age 23.6yrs. Pain (73.3%) was the most common symptom at presentation. Extremities were most common site (46.7%). Size < 8cm 28 (62.2%), > 8cm 17 (37.8%). The lung (70.6%) was the most common site of metastasis followed by the bone, bone marrow. The median number of chemotherapy cycles in the localized disease was 15 (range 1–17), and in metastatic disease, it was 8 (range 1–17). Local treatment modalities were Surgery in 9 (32.1%), RT in 19 (67.9%). Up front Surgery done in 2 patients, RT received by 3 patients. Recurrence occurred in 4 patients with localised disease. Univariate analysis was done with respect to age (< 25 vs. ≥25), gender, elevated or normal serum lactate dehydrogenase level, tumor size (< 8 cm versus ≥8 cm), site (axial versus extremity), and neoadjuvant chemotherapy (NACT) given or not. NACT had a significant impact on overall survival (OS) and the rest had no effect. At a median follow - up of 40 months, the 3 - year OS in localized disease was 80%. In metastatic disease, no one survived at 36 months. Conclusion: With the introduction of VDC/IE regimen, survival has dramatically improved. Outcomes of localized disease are similar to that of a paediatric patients with multimodality therapy in adult ES. Metastatic ES patients still have adverse outcomes, pressing the need for additional therapies in future.

Keywords: Adult Ewing sarcoma, multi - modality therapy, Neo adjuvant chemotherapy, OS

1. Introduction

Ewing's sarcoma (ES) family is a group of malignant small round cell tumors of neuroectodermal origin that vary in their neurogenic differentiation but share the same treatment and prognosis. ES is the second most frequent primary malignant bone tumor that affects mainly children and young adult and constitutes 3% of all paediatric malignancies [1]. It rarely occurs in adults. Approximately 70% are diagnosed in childhood, while the rest occur in adults. [2]

The gold standard for diagnosing ES is the demonstration of t (11; 22) by fluorescent in situ hybridization (FISH) or polymerase chain reaction (PCR). ES occurs in both osseous and extra osseous sites with poor survival outcomes in certain sites such as the pelvis. Currently, the standard practice is multimodality management, typically with induction chemotherapy, followed by definitive local therapy with surgery and/or radiotherapy. [4 - 15]

The survival rates in patients with ES have been markedly improved due to the advent of recent chemotherapy protocols, advanced radiotherapeutic techniques with accurate localization and delivery, and improved surgical techniques. [4-13] The prognosis of patients with ES depends on the age of the patient, stage of disease, primary tumor site, and tumor size. [17-19]

Historically, vincristine, doxorubicin, and cyclophosphamide (VDC) regimen was used. The introduction of ifosfamide and etoposide (IE) to the VDC regimen resulted in a significant improvement in the survival. [6] Further studies showed that intensification with 2 - weekly administration of VDC/IE regimen instead of conventional 3 - weekly regimen

has further improved survival in localized adult ES patients. [8]

Treatment for metastatic ES is mainly palliative in nature although a fraction of these patients may have a significantly long survival, especially those with limited metastasis in sites such as the lung. There are no specific management guidelines for adult ES. Treatment approaches for adults are based on paediatric protocols.

Despite growing literature evaluating the treatment effectiveness in patients with ES from the Western countries, data on adult ES from the Indian subcontinent are scant. Most of them are studies, case series, or case reports on paediatric ES. Thus, this study was designed to identify the clinicopathologic features and treatment results of patients with adult ES presented to our tertiary care centre.

2. Materials and Methods

It is retrospective, observational study. Medical records of 45 patients with age >18 years treated at our centre between 2014 and 2020, were analyzed for demographic and clinicopathologic features and survival outcomes. Patients who had incomplete information were excluded from the study. A total of 45 patients were included with a median follow- up duration of 40 months. Data regarding age at diagnosis, sex, site, and size (based on the greatest reported dimension) of the primary tumor, chemotherapy, surgery, radiotherapy, relapse, and survivals were extracted.

The diagnosis of ES was confirmed by local part imaging with MRI, biopsy, and IHC, FISH for ES breakpoint region 1 (EWSR1). The staging valuation included a bone marrow aspiration and biopsy, CT chest, and a bone scan.

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Most of the patients with the localized disease received neoadjuvant chemotherapy (NACT), followed by definitive surgery and/or radiation and adjuvant chemotherapy (ACT) thereafter. The chemotherapy regimen VDC/IE was given for a duration of 1 year. Some patients had surgery or radiotherapy upfront, followed by ACT. Patients with the metastatic disease received palliative chemotherapy with the VDC regimen. Palliative radiation was given to selected patients. Those patients with localized or metastatic disease who received treatment for at least one cycle of chemotherapy were analyzed for survival rates. Patients who lost to follow - up were censored. Overall survival (OS) was defined as the time from diagnosis to the time of death due to any cause or lost to follow - up.

Statistical Analysis

The clinic - pathological parameters were extracted and statistically analyzed with IBM SPSS Statistics, version 23.0 (IBM Corp. Released 2015. Armonk, NY, USA.). To describe about data descriptive statistics frequency analysis, percentage analysis were used for categorical variables, the mean & SD were used for continuous variables. Univariate analysis was done to assess the effect of age, gender, primary tissue type, primary site of the disease, and size of the primary tumor on OS in localized ES. Survival analysis was done by plotting Kaplan–Meier curves. In all the above statistical tools p value 0.05 is considered as significant level.

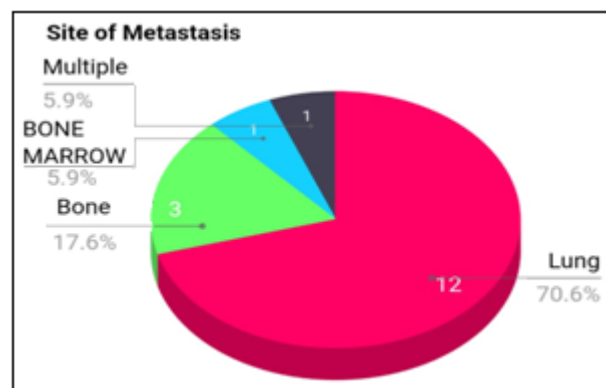
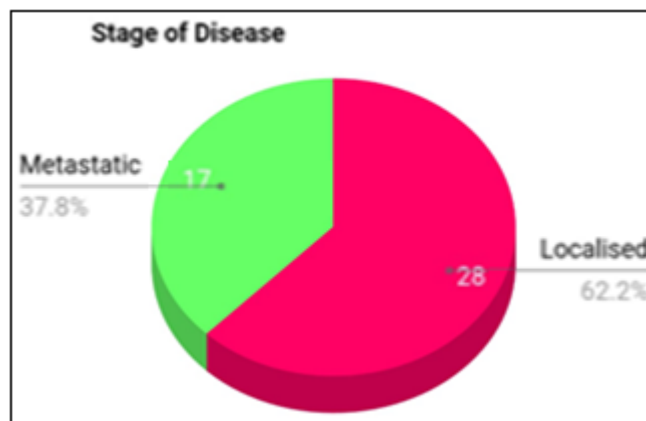
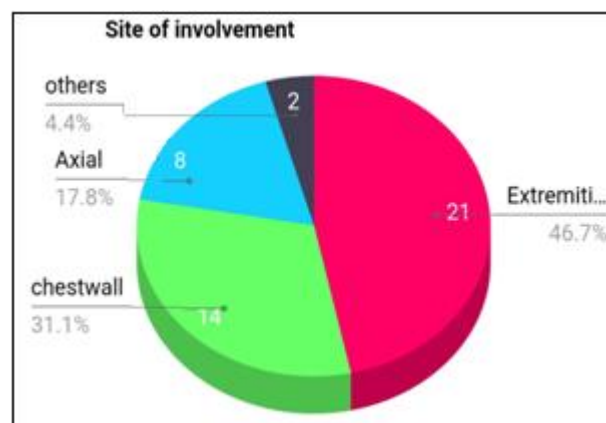
3. Results

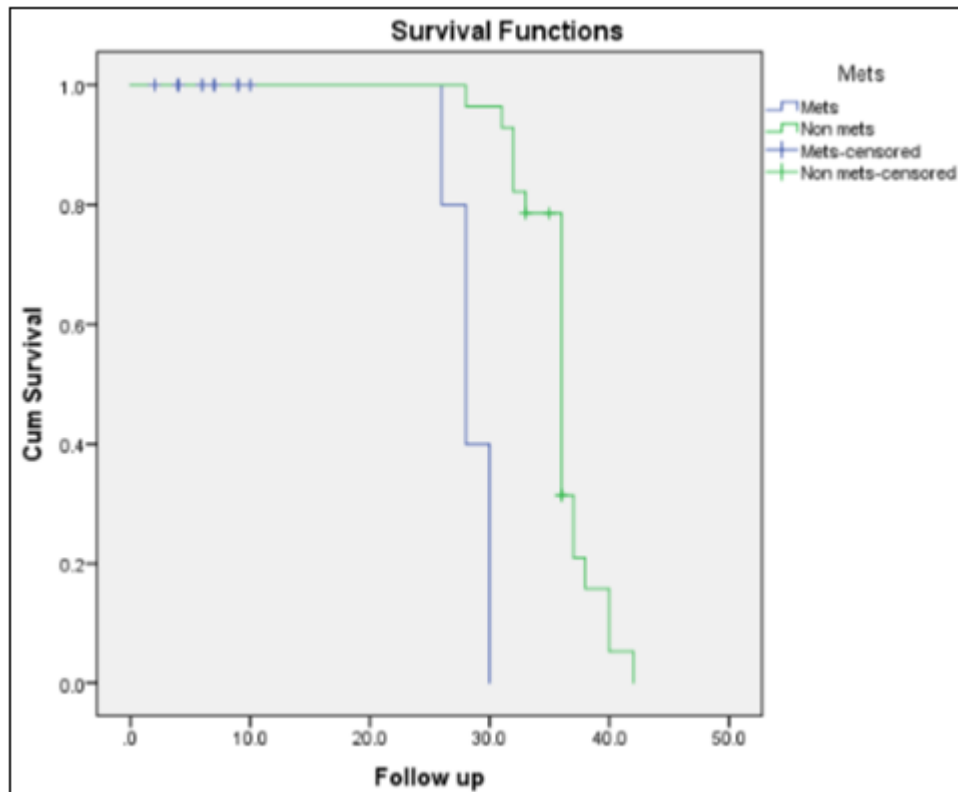
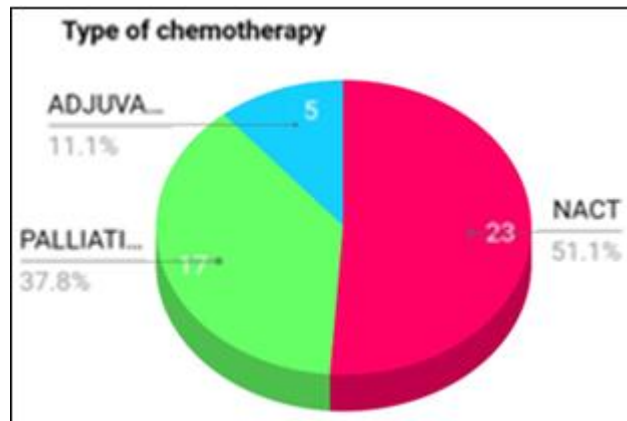
Patient’s characteristics

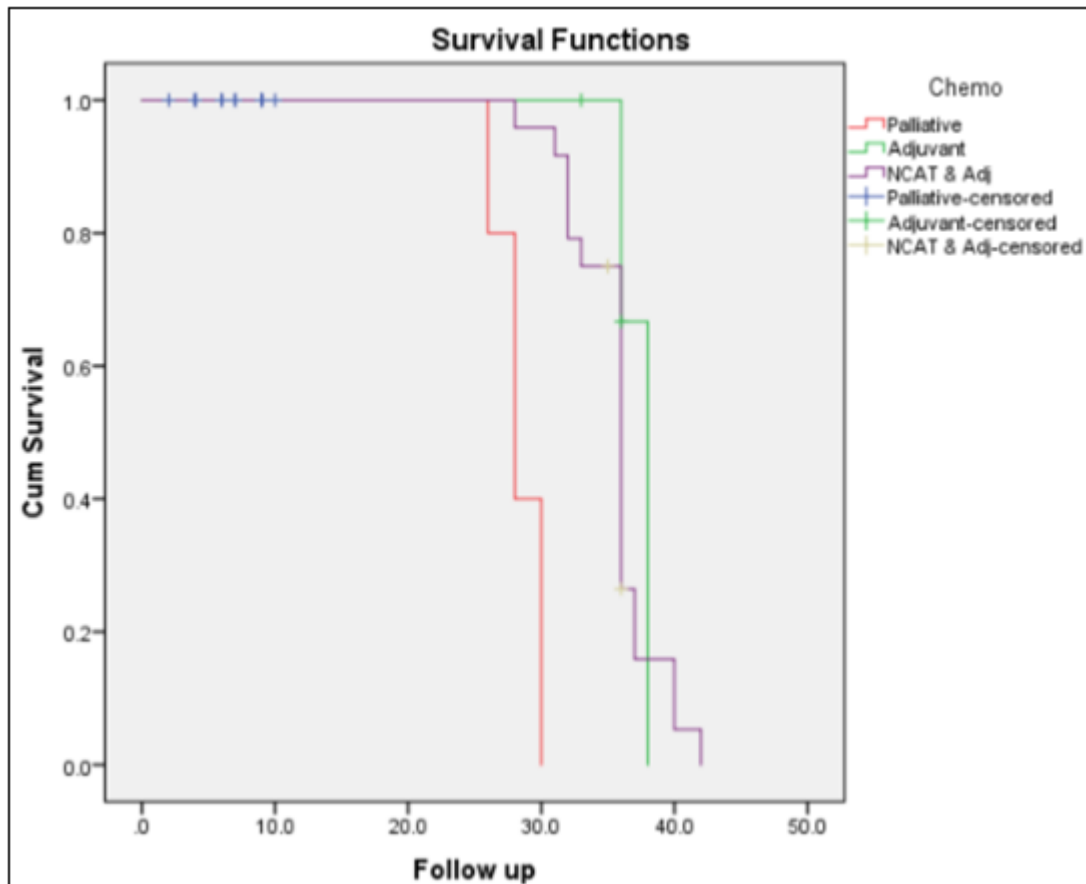
Out of 45 patients 28 (62.2%) had localised disease, 17 (37.8%) had metastatic disease. Median age of presentation is 23.6yrs. Males were 27 (60%) and females were 18 (40%). Pain (73.3%) was the most common symptom at presentation followed by swelling and both pain & swelling. Of 45 patients, 27 (60%) patients had an osseous origin of the primary tumor and the rest had an extra osseous origin. Sites of involvement were Extremities, most common site in 22 patients (46.7%) followed by chest wall in 13 (28.9%), axial in 8 (17.8%), other sites in 2 patients. Patients with tumor size < 8cm were 28 (62.2%), > 8cm 17 (37.8%). Out of 17 (37.8%) patients with metastatic disease, lung 12 (70.6%) was the most common site of metastasis followed by the bone, bone marrow. One patient had multiple metastases.

Parameters		n (%)	p value
Age	<25	26 (57.8)	0.74
	>25	19 (42.2)	
Gender	Male	27(60)	0.345
	Female	18 (40)	
Site	Extremities	21 (46.7)	0.49
	Chest Wall	14 (31.1)	
	Axial	8 (17.8)	
	Other	2 (4.4)	
Size	< 8cm	28 (62.2)	0.645
	> 8cm	17 (37.8)	

Primary Tissue	Osseous	22 (48.9)	0.23
	Extra Oss.	23 (51.1)	
Symptom	Pain	33 (73.3)	0.539
	Swelling	9 (20)	
	Both	3 (6.7)	
Sr. LDH	Elevated	26 (57.8)	0.0005
	Normal	19 (42.2)	
Stage	Localised	28 (62.2)	0.0005
	Metastatic	17 (37.8)	
Site of Mets	Lung	12 (70.6)	0.0005
	Bone	3 (17.6)	
	Bone Marrow	1 (5.9)	
	Multiple	1 (5.9)	
Type of Chemo	Palliative	17 (37.8)	0.0005
	NACT → Adjuvant	23 (51.1)	
	Adjuvant	5 (11.1)	







Treatment Modalities

Among 28 patients with localised disease, initial induction chemotherapy with VDC/IE regimen was given for 12 - 15 weeks in 23 patients. Doxorubicin was replaced by Actinomycin - D ($1.25\text{mg}/\text{m}^2$) once reaching a cumulative dose of $450\text{mg}/\text{m}^2$ or couldn't be tolerated by patients. Up front Surgery done in 2 patients, upfront RT received by 3 patients. The median number of chemotherapy cycles in the localized disease was 15 (range 1–17), and in metastatic disease, it was 8 (range 1–17). Local treatment modalities received were surgery in 9 (32.1%), RT in 19 (67.9%) patients with localised adult ES.

Variables Affecting Survival

Univariate analysis was done with respect to age (< 25 vs. ≥ 25), gender, elevated or normal serum lactate dehydrogenase level, tumor size (< 8 cm versus ≥ 8 cm), site (axial versus extremity), and neoadjuvant chemotherapy (NACT) given or not. NACT had a significant impact on overall survival (OS) and the rest had no effect survival.

Survival

Recurrence in localised disease was observed only in 2 patients. At a median follow - up of 40 months, the 3 - year OS in localized disease was 85.7%. In metastatic disease, no one survived at 36 months.

4. Discussion

ES is a very aggressive disease, and multimodality treatment approach that involves local control modality with attempts to preserve the function, and eradication of micro metastases using chemotherapy is the current standard treatment of ES.

We tried in this work to determine the clinicopathological features and treatment outcomes of patients with adult ES in tertiary care centre.

Similar to acute lymphoblastic leukaemia, the treatment protocols for the adult ES were inspired from paediatric ES studies. The inclusion of adults in paediatric trials was limited. Even though these landmark studies included patients aged > 18 years, they accounted for 9 to 15% only. [5 - 8]

In our study, the median age at the time of diagnosis was 23.6 years and males accounted for 60%. The largest series of ES was studied by Verma et al ($n = 1870$), who reported the median age as 29 years. [10] Other studies by Pretz et al, and Verrill et al, Ahmed et al, reported a median age of 28, 24 and 27.5 years, respectively. [11, 12, 15] In this study, there was a male predominance (60%), similar to that of the studies by Verma et al (60%), Ahmed et al (67.7%), and Verrill et al (62.7%). Pretz et al had a female predominance, accounting for 60%.

In this study, pain and swelling were the most common presenting complaints seen in 73.3% and 20% patients, respectively, which is similar to other studies. The extremity was the most common site in majority of studies except in the study by Verma et al where the axial skeleton was most commonly involved.

Neo adjuvant chemotherapy was given to 23 patients (82.1%) and 3 (10.7%) of the patients had received upfront radiotherapy, who were diagnosed with localised adult ES.

Two patients underwent upfront surgery. Our data reflected the real - world practice of localized ES patients.

For patients with localized disease who received multimodality therapy, the 3 - year OS was 80%. According to the historical data, before the introduction of VDC/IE regimen, the 5 - year OS was 20 to 60%. This increased to more than 80% with the adoption of the VDC/IE regimen. Ahmed et al studied this impact of the addition of therapy in their recent study, showing improvement of 5 - year OS from 49% to 73%, done between 1977 to 1992 and 1993 to 2007, respectively. [15] A similar study by Nasaka et al reported the impact of the chemotherapy regimen on ES. [17] She reported increased OS with the VDC/IE regimen. A recent study on adult ES by Pretz et al showed a 5 - year OS of 79%.

In this study, 37.8% of the patients were diagnosed with a metastatic disease, which is similar to the study reported by Verma et al (33%) and slightly higher compared to Verrill et al and Chandran et al (28.8%). Pretz, Chandran's and Varma's studies reported lung as the most common site of metastasis, as was found in this study. However, Verrill et al reported bone as the frequent metastatic site. All patients in this study were given VDC - based regimen and 29.4% required radiation for palliation of symptoms. For metastatic ES, the 3 - year OS was 0%, while it was 10% and 0% in studies by Verma et al and Verrill et al, respectively.

Retrospective nature, limited sample sizes are the limitations of this study. However, these problems reflect the ground reality of real - world scenario while treating patients with adult ES.

5. Conclusion

With the introduction of VDC/IE regimen, survival has dramatically improved. Outcomes of localized disease are similar to that of a paediatric patients with multimodality therapy in adult ES. Metastatic ES patients still have adverse outcomes, pressing the need for additional therapies in future. Adoption of dose - dense regimens in select patients may further increase the survival.

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Nil

Conflicts of Interest

There is no conflict of interest.

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