

Morphological Features of Ewing Sarcoma Post-Neoadjuvant Therapy and Their Impact on Prognosis

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ABSTRACT

Objective: To study the effect of chemotherapeutic response on resection specimens and to assess their effect on prognosis.

Study Design: Retrospective longitudinal study.

Place and Duration of Study: Shaukat Khanum Memorial Cancer Hospital and Research Centre, Peshawar Pakistan, from Jan 2010 to Mar 2018.

Methodology: This study included 42 cases of Ewing sarcoma diagnosed, treated and followed at our institute. Various diagnostic parameters were noted and were assessed for their impact on two-year overall survival, development of distant metastasis, recurrence and cancer-related death.

Results: This study included 28 males and 14 females. The majority involved long bones followed by the axial skeleton and soft tissue. Nine cases (9) were confirmed by molecular testing. On the post-neoadjuvant chemotherapy resection specimens, 45% cases had Huvos grade I necrosis, 17% had grade-II, 12% had grade-III and 26% cases had Huvos grade-IV necrosis. Increasing Huvos grade was associated with improved disease-free survival (21%, 43% and 69% for grades-I, II and III/IV respectively). The site and size did not significantly affect the development of recurrence, development of metastasis, or two-year survival ($p>0.05$).

Conclusion: Meticulous assessment of post neoadjuvant resection specimens for necrosis provides helpful information about the prognostic outcome. Increasing grade of tumour necrosis was associated with increasing disease-free survival. The response to chemotherapy in our study population was worse than Western data, which may be linked to a variety of factors.

Keywords: Ewing's sarcoma, Necrosis, Neoadjuvant therapy, Prognosis.

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INTRODUCTION

Ewing sarcoma is the second most common primary bone tumour in adolescents and young adults.^{1,2} In Pakistan, Ewing sarcoma constitutes 45% of primary malignant bone tumours in children and 5.04% of all the childhood malignancies.³ Ewing sarcoma can arise in any part of the body; long bones of the appendicular skeleton are the most frequently involved. Peak age is in the first and second decade of life with slight male predilection (1.5:1.0).⁴

Various prognostic factors have been studied to determine overall survival (OS) and disease-free survival (DFS) for patients with Ewing sarcoma. The percentage of post-NACT necrosis is a significant predictor of the outcome.^{5,6} Recent data has shown that NACT causes significant tumour regression and improves local control and long-term survival.^{7,8} Bosma *et al*,⁷ conducted a study on 792 patients with Ewing sarcoma. They identified histologic therapeutic res-

ponse in terms of necrosis and the presence or absence of distant metastasis as parameters that significantly affect prognosis. They highlighted the importance of recording the percentage of tumour necrosis in surgical resection specimens of patients receiving NACT. Localized complete therapeutic response was linked to a higher 5-year overall survival of 92% than 79% in partial therapeutic response.⁹ Ackerman (1997) applied the Huvos grading system on resection specimens of Ewing sarcoma patients treated with NACT. It was observed that increased necrosis grade was associated with better DFS (69% for grade-IV compared to 24% for grade-I).¹⁰

Upon the review of local scientific literature, limited work was found describing the outcome of Ewing sarcoma in our population. Our rationale was to study the effects of therapy response (described as a percentage of necrosis) in our hospital and to correlate this with disease-free and overall survival.

METHODOLOGY

This was a retrospective longitudinal study conducted at Shaukat Khanum Memorial Cancer Hospital, Peshawar Pakistan, from January 2010 and March

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2018. Permission for this study was obtained from Institutional Review Board (EX-27-04-20-01).

Inclusion Criteria: All the patients diagnosed with Ewing Sarcoma, treated and followed at our hospital were included in the study.

Exclusion Criteria: Patients with lost to follow-up before two years were excluded from this study.

All the patients were initially diagnosed on tissue biopsy followed by NACT. EuroEwing 99 protocol was followed with six cycles of neoadjuvant therapy with Vincristine, Ifosfamide, Doxorubicin, and Etoposide followed by surgical resection or amputation eight cycles of adjuvant therapy with vincristine, Actinomycin D and Ifosfamide. Their reports and follow-up notes were retrieved from the hospital information system, and histologic slides were retrieved from the laboratory record. A consultant and a resident histopathologist reviewed the slides. Age, gender, site, tumour size, percentage of necrosis post-chemotherapy, post-therapy grading, soft tissue involvement, margin status, CD99 positivity, FISH for EWSR1 gene rearrangement, development of recurrence or metastasis and two years follow up, were noted. The chemotherapy response was assessed using the HUVOS grading system. The most significant slice of the tumour was processed and studied microscopically, the percentage of tumour necrosis was noted. Tumours with less than 50% necrosis were assigned grade-I, 50-89% as grade-II, 90-99% as grade-III and 100% necrosis as grade-IV.^{11,12}

Statistical Package for Social Sciences (SPSS) version 20 was used for the data analysis. Descriptive statistics such as gender, site, soft tissue involvement, CD99 positivity, FISH study and recurrence and metastasis were described as frequencies and percentages. Chi-square test was applied to find out the difference in 2 years survival, recurrence, presence of distant metastasis among the four grades. The *p*-value of ≤ 0.05 was considered statistically significant.

RESULTS

Employing the inclusion and exclusion criteria, 42 patients were selected who were treated and diagnosed for Ewing sarcoma, from January 2010 to March 2018. They were aged 1-40 years (mean age = 14.1 ± 8.9 years) with 28 males (64%) and 14 females (36%). Twenty-six tumours arose in the long bones, ¹⁴ in the axial skeleton and 2 in soft tissue (Table-I).

The cases were first diagnosed on biopsy from the tumour site. All the tumours showed a small round blue cell morphology. The diagnosis was further sup-

ported by CD99 positivity in all the cases. Nine cases were confirmed using Fluorescent hybridization for EWSR1 gene rearrangement. NACT and later surgery followed the diagnosis. Nineteen patients underwent amputation, while 23 patients had a resection.

Table-I: Site wise distribution of ewing Sarcoma.

Site	Number of Cases (n=42)
Appendicular Skeleton	26
Tibia and Fibula	15
Femur	7
Humerus	4
Axial Skeleton	14
Scapula	5
Iliac crest	5
Chest wall	3
Mandible	1

On gross examination, the tumour size ranged from 3-21 cm in the tumours of long bones and 5-9.5 cm in the tumours of the axial skeleton. The surgical resection margin was positive in six cases, and lymphovascular invasion was seen in two cases. None of the reported neoplasms showed perineural invasion. Huvos grade-I was observed in 19 patients (45%), grade-II in 7 (17%), grade-III in 5 (12%) and grade-IV in 11 patients (Figure-1A-1D).

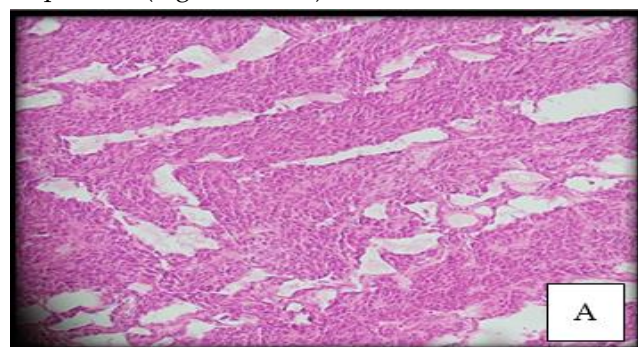


Figure-1A-AD: Morphological changes in post-therapy Ewing sarcoma. (10x magnification) (A), Poor response to chemo therapy. Completely viable tumour with no necrosis (Huvos Grade-1).

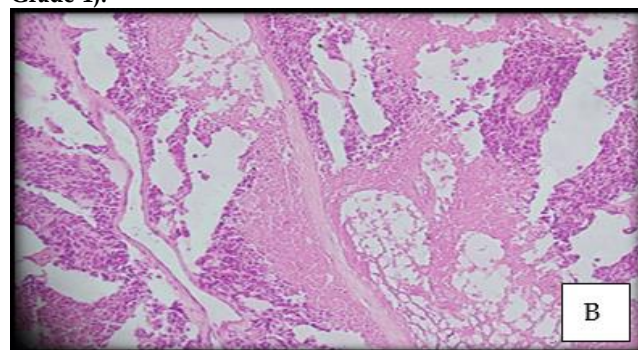


Figure-1B: Partial response with 50% necrosis (Huvos Grade-2).



Figure-1C: Few viable tumour clusters presents in a background of necrosis, 90% of tumour is necrotic (Huvos Grade-3).

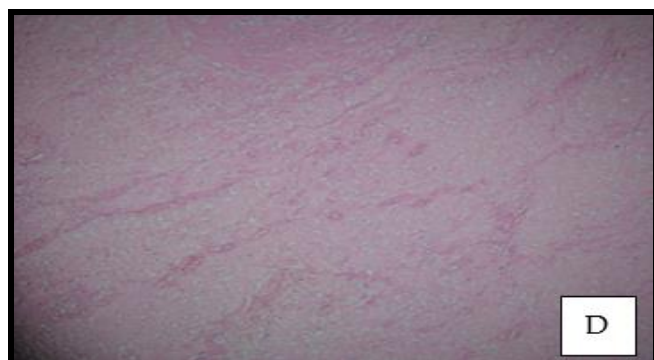


Figure-1D: Complete response; the entire tissue shows necrosis with no viable cells (Huvos Grade-4).

Eight cases showed recurrence among the patients with Huvos grade-I necrosis, 8 cases showed recurrence, and 7 exhibited distant metastasis within two years. Four of these patients died within two years of diagnosis. Among those with Huvos grade-II, 3 patients developed recurrence while 4 had distant metastasis within two years of diagnosis. All these patients were alive two years after diagnosis. In those patients with grades-III/IV necrosis, six patients developed recurrence and distant metastasis, and one patient died within two years of diagnosis.

DFS for grades-I, II and III/IV was 21%, 43% and 69%, respectively. Chi-square test was applied to find any significant difference between the grades for recurrence, two-year survival and distant metastasis. No statistically significant difference was observed between the grades for these factors (Table-II).

DISCUSSION

Ewing sarcoma is the second most primary malignant bone tumour in patients under the age of 20 years in our population and worldwide.^{13-15.}

Since the introduction of NACT, there has been a significant improvement in survival outcomes for non metastatic and metastatic Ewing Sarcoma. Over twenty years (between 1973 and 1993), the five-year OS has improved to 68% from 44% to 39% from 16% for localized and metastatic disease, respectively.¹⁶ In 1992, Huvos developed a grading system to assess the histologic response to NACT in terms of tumour necrosis. He assigned grades-I, II, III and IV to tumours that showed less than 50%, 50-89%, 90-99% and 100% necrosis, respectively.¹⁷ Numerous studies have been published to observe the prognostic impact of NACT. Wunder *et al*, (1998) studied 113 Ewing sarcoma patients, diagnosed between 1978 and 1989. Among these, 74 patients received NACT followed by surgical resection. They included 42(57%) males and 32 females (43%). Forty-two of these Ewing sarcoma cases were found in the long bones, whereas 32 arose in the axial skeleton. Lin *et al*,⁸ studied 64 patients with Ewing sarcoma who had undergone NACT followed by surgical resection between 1990 and 2001. These patients observed male predilection (66% males vs 34% females). Thirty-nine of these tumours developed in the long bones and 25 in the axial skeleton. In comparison, our study included 42 patients with a male: female ratio of 2:1 and a median age of 15 years. Twenty-six of these occurred in the long bones of the extremities, 14 in the axial skeleton and 2 in soft tissue.

Wunder *et al*,⁹ assessed the histologic response to NACT. He applied the Huvos grading system to the post-NACT resection specimens. The frequency was 19% (14), 22% (16), 18% (13) and 42% (31) for grades I-IV respectively. Picci *et al*,¹⁸ also studied 68 post-NACT resection specimens and observed that 37%, 34% and 29% specimens had absent, partial and complete necrosis, respectively. We observed in our study that 45% of patients had Huvos grade-I, 17% had grade-II, 12% had grade-III, and 26% had grade-IV. Compared to these studies, the response to NACT was poor in our

Table-II: Comparison of grades of necrosis.

Huvos Grade	Presence of Recurrence			Distant Metastasis			Two Year Survival		
	Present	Absent	p-value	Present	Absent	p-value	Alive	Deceased	p-value
I	8	11	0.796	8	11	0.946	14	4	0.165
II	3	4		4	3		7	-	
III	1	4		2	3		5	-	
IV	5	6		5	6		10	1	

population.

Wunder *et al.*⁹ concluded that response to NACT and tumour size had the greatest impact on the DFS ratio. The DFS ratio was 0% and 40% for grade-I and II tumours. It was 84% for grades-III, and grade-IV combined. Akermann 10 noted a DFS of 24%, 65%, 45% and 69% for grades I-IV respectively. In our study, the DFS was 21% for grade-I, 43% for grade-II and 69% for grades-III and IV.

The response of patients of Ewing sarcoma neoadjuvant chemotherapy in our population was poor compared to data from the Western world. It may be due to various socio-economic factors like poor health-care facilities, lack of awareness about the disease, late presentation. Broader studies on larger sample size are recommended to enhance our population's understanding of the disease prognosis and treatment response. There is also a need for wider availability of molecular testing to have a more accurate diagnosis because the molecular testing results may affect the treatment modalities.

LIMITATIONS OF STUDY

A limitation of our study was that not all our diagnoses were confirmed by molecular testing for EWSR-FLI1 translocation, so although some tumours may be true Ewing sarcomas, others may belong to Ewing like the family of tumours which may affect the treatment response.

CONCLUSION

Meticulous assessment of post neoadjuvant resection specimens for necrosis provide helpful information about the prognostic outcome. Increasing grade of tumour necrosis was associated with increasing disease-free survival. The response to chemotherapy in our study population was worse than Western data, which may be linked to a variety of factors.

Conflict of Interest: None.

Authors' Contribution

UA: Direct Contribution, SM:, IAR:, UH:, Data Conception & Interpretation.

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