

Clinical Outcome of paediatric ewing sarcoma and significance of pathological necrosis for mortality after neoadjuvant chemotherapy: Single institutional study

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Abstract

Objective: To determine the clinical outcome and significance of pathological necrosis after neoadjuvant chemotherapy.

Methods: The retrospective study was conducted in Shaukat Khanum Memorial Cancer Hospital and Research Center and comprised data from January 2010 to December 2015 related to young with newly diagnosed Ewing sarcoma on histopathology. Data was collected on patients aged <20 years of either gender along with primary tumour site, metastatic status, tumour volume, mode of local therapy, degree of necrosis post-surgery, tumour margins after resection, outcome at the end of treatment and at last follow-up visit. Tumours were categorised as grade I = little or no necrosis, grade II = 50-90% necrosis, grade III = 90-99% necrosis, and grade IV = 100% necrosis. Data was analysed using SPSS 20.

Results: Of the 124 patients, 89(72%) were non-metastatic; 35(28%) were metastatic; 37(29.8%) underwent surgery; 58(46%) received radiotherapy; 7(5.6%) received both surgery and radiotherapy; 22(17.7%) received no treatment. Histopathology report post-surgery showed little grade 1 necrosis in 10(8%) patients, grade II in 8(6.5%), grade III in 8(6.5%) and grade IV in 14(11%). Event-free survival in grade IV necrosis was 93% in 14 (11.3%) patients, EFS in grade III necrosis was 71% in 8(6.5%) patients, EFS in grade II necrosis was 22% seen in 9(7.3%) patients and EFS in grade- I necrosis was 35% seen in 14 (11.3%) patients. Overall survival in grade IV necrosis was 93% in 14 (11.3%) patients, OS in grade III 75% seen in 8(6.5%), OS in grade II 25% seen in 9(7.3%) and OS in grade I was 50% in 14(11.3%) patients. Event-free survival was 48 (38%) patients and overall survival of Ewing sarcoma patients was 52 (46.6%) patients respectively.

Conclusion: Tumour necrosis and histopathological changes post-surgery were found to have great impact on survival outcome in Ewing Sarcoma.

Keywords: Ewing sarcoma, Risk factors, Metastasis, Degree of necrosis, Local control, Event-free survival, Overall survival.

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Introduction

Ewing sarcoma is an aggressive primary bone tumour, most commonly affecting children and young adults.¹ About 20-25% patients present with metastases at the time of presentation in which pulmonary site involvement is in 70-80% cases, and osseous involvement in 40-45%.² A multidisciplinary treatment strategy dramatically improved the survival of patients with localised ES and 10-year overall survival has reached up to 55-65% nowadays. However, local recurrence and distant metastasis lead to poor 5-year overall survival (OS) of 20-35% in metastatic disease.³ Presence of metastasis at the time of diagnosis is one of strongest risk factors and other well-known risk factors are primary tumour site⁴ and tumour volume/size.⁵ ES treatment consists of induction chemotherapy followed by local treatment of the primary tumour either by surgery, radiotherapy or both, and ends with consolidation chemotherapy.⁶ Percentage of necrosis after giving induction chemotherapy is an additional prognostic factor for OS⁷ but impact of surgical margins on OS is

controversial; however, the risk of local relapse is significantly less after wide resection in comparison to marginal or intra-lesional resections.⁸ Postoperative radiotherapy in patients with close resection and intralesional margins increase the local control and event-free survival (EFS).⁹

The current study was planned to determine the clinical outcome and significance of pathological necrosis after neoadjuvant chemotherapy.

Patients and Methods

The retrospective descriptive study was conducted at Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore and comprised data from January 2010 to December 2015 of both non-metastatic and metastatic who were followed up until October 2019. After approval from the institutional ethics review committee, data was collected from patients aged <30 years of either gender related to primary tumour site, metastatic status, tumour volume, mode of local therapy, degree of necrosis post-surgery, tumour margins after resection, outcome at the end of treatment and at the last follow-up visit. Data of those who were lost to follow-up was excluded.

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The ES diagnosis was made by histopathologist on open biopsy and was considered confirmed on the presence of round blue cell tumour and clostridium difficile infection (CDI) antigen which was absent in lymphoma, rhabdomyosarcoma and neuroblastoma. All patients underwent complete history, thorough physical examination, blood tests, imaging of primary site with magnetic resonance imaging (MRI) scan, bone scan and bilateral bone marrow biopsy. To rule out pulmonary involvement in patients in whom thorax was the primary site, computed tomography (CT) scan was used.

Tumour volume was measured by recording the maximum dimensions in three planes. Tumour volume <200ml and > 200ml were included in the study.

Euro-Ewing 99 (EE-99)¹⁰ and AEWS 0031¹¹ protocols were used during treatment. EE-99 protocol comprised vincristine, ifosfamide, doxorubicin and etoposide (VIDE) and vincristine, actinomycin, ifosfamide (VAI) chemotherapy drugs. In AEWS 0031 protocol, compressed cycles of ifosfamide and etoposide alternated with vincristine, doxorubicin, cyclophosphamide chemotherapy drugs.

In EE-99 protocol, reassessment scans were done after the fourth cycle of VIDE chemotherapy and mode of local control was decided which was introduced after the sixth cycle. In AEWS 0031 protocol, reassessment scans were performed after the fifth cycle of chemotherapy and local control was introduced after the sixth cycle.

Local control in the form surgery had been given to the patients whose tumour was amenable to resection with adequate margins regardless of size, response to chemotherapy or location of tumour. However, in some patients it was based on the patient and tumour characteristics which standardised the choice of local control. Preoperative radiotherapy was given to patients who presented with spinal cord compression and in patients where complete resection of tumour was not possible after the induction chemotherapy. Postoperative radiotherapy had been given to patients in whom there was poor histological response <90% necrosis and resection margins positive of tumour. The dose of radiotherapy was 55.4 Gys in 30 fractions. After local control of tumour, the patients received consolidation cycles of chemotherapy in both non-metastatic and metastatic cases.

Histological response and resection margins were assessed on the surgical specimen by experienced pathologists. For tumour necrosis grading, Huvos system was used; grade I = little or no necrosis, grade II = 50-90% necrosis, grade III

= 90-99% necrosis and grade IV = 100% necrosis.¹²

Local disease relapse was defined as local site recurrence after initial complete treatment response and distant metastasis was defined as new metastatic disease after initial complete response.

The outcome of treatment was evaluated in terms of OS and EFS. OS was calculated from the date of start of treatment to the last follow-up. EFS was measured from the start of therapy to the end of treatment as disease progression, relapse and death.

Data was analysed using SPSS 20. Mean±standard deviation was used to summarise quantitative data, whereas frequencies and percentages were used to organise qualitative data. The association of explanatory variables in relation to status (alive or death) was determined by using chi-square test. Univariable and multivariable logistic regression (MLR) models were used to identify the independent risk factors associated with mortality. Kaplan-Meier survival curves were used to assess OS. Log-rank test was employed to compare OS. Statistical significance was defined as two-tailed $p < 0.05$.

Results

Of the 148 ES patients registered for treatment between 2010 and 2015, 24 went missing after baseline workup and before the start of treatment. The study sample comprised 124 patients; 71(57%) males and 53(43%) females. The mean age at presentation was 11.3 ± 4.27 years (range 1-18 years). The median follow-up of the cohort was 48 months and IQR was 36 months. There were 64(51.6%) limb tumours and 60(48.3%) were central tumours affecting the primary pelvis, head and neck, thorax, spine and abdomen (Table-1). Overall, 112(90%) patients were treated under EE-99 protocol and 12(10%) under the AEWS 0031 protocol. Local control in the form surgery was given to 37(30%) patients. Preoperative radiotherapy was given to 7(5.6%) patients who either presented with spinal cord compression or in whom complete resection of tumour was not possible after induction chemotherapy.

Four-year EFS in ES patients was 38% (Figure-1) and OS was 46.4% (Figure-2). On univariate analysis (Table-2), metastatic status ($p < 0.005$), effect of local control ($p < 0.005$), percentage of necrosis after neoadjuvant chemotherapy ($p = 0.001$), tumour margins ($p = 0.001$) and relapse status ($p = 0.001$) significantly affected OS (Figure 3) and EFS (Figure 4).

In multivariate analysis, four variables were identified as independent risk factors for mortality in ES: if disease was metastatic; if tumour margins were involved; if relapse status was positive; and if the gender was female (Table 3).

Table-1: Baseline characteristics.

Variables	n (%)
Age (years)	
Above 11 years	64(52%)
Less than 11 years	60(48%)
Sex	
Female	54 (43.5%)
Male	70 (56.5%)
Primary site of involvement	
Abdomen	5 (4.0%)
Spine	10 (8.1%)
Thorax	14 (11.3%)
Head and neck	15 (12.1%)
Pelvis	16 (12.9%)
Upper limb	25 (20.5%)
Lower limb	39 (31.5%)
Size of tumour	
Outside films	5 (4.0%)
Coming in SKM* after excision	7 (5.6%)
Up to 200ml	25 (20.2%)
Above 200ml	87 (70.2%)
Metastasis status	
Non-metastasis	90 (72.6%)
Metastasis	34 (27.4%)
• Bone marrow/bone scan/pulmonary Mets	1 (2.9%)
• Bone scan and pulmonary Mets	2 (5.9%)
• Bone marrow and bone scan	3 (8.8%)
• Bone marrow	4 (11.8%)
• Pulmonary Mets	11 (32.4%)
• Bone Mets	13 (38.2%)
Management	
Surgery	37 (29.8%)
Radiotherapy	58 (46.8%)
Combine	7 (5.6%)
Not done	22 (17.7%)
Histopathology report	
Necrosis of 50-90%	8 (6.5%)
Necrosis of 90-99%	8 (6.5%)
Necrosis of 100%	14 (11.3%)
Little or no necrosis	10 (8%)
Tumour margins	
Margin involved	21 (16.9%)
Margins not involved	23 (18.5%)
Relapse	
No	80 (64.5%)
Yes	44 (35.5%)
• Local	10 (22.7%)
• Distant	14 (31.8%)
• Both	20 (45.5%)
Survival	
Event free survival	48 (38%)
Overall Survival	52 (46.6%)

SKM:

Outcome at the end of treatment was 'alive' in 48(39%) patients, 'relapse' in 23(18.5%), 'disease progression' in 21(17%), 'death' in 20(16%); and 'abandonment' in 12(9.7%) patients. The causes of death were sepsis in 14(70%)

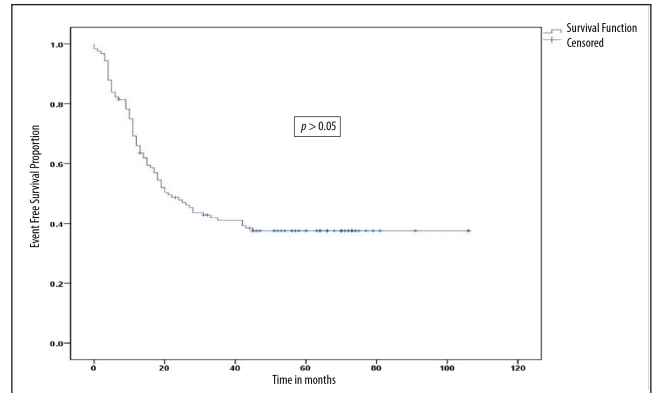


Figure-1: Event-free survival (EFS) in Ewing Sarcoma cases.

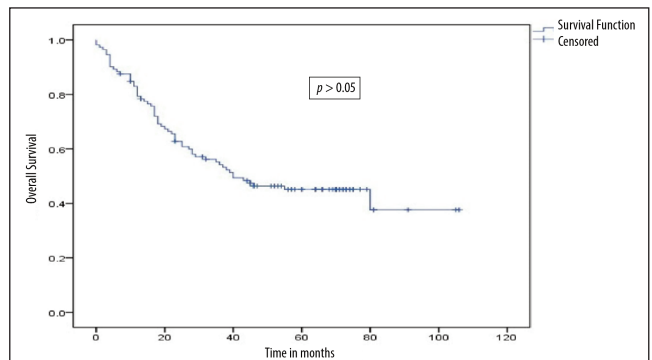


Figure-2: Overall survival in Ewing sarcoma cases.

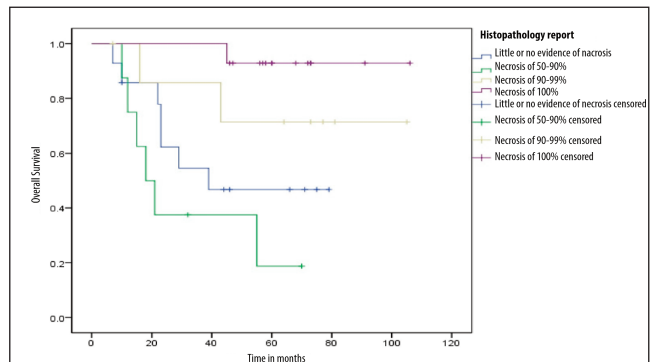


Figure-3: Overall survival with reference to pathological necrosis after neoadjuvant chemotherapy.

patients, therapy-related acute myeloid leukaemia (t-AML) in 4 (20%) and disease progression in 2(10%) patients. Of the patients who died due to sepsis, 13(93%) were treated under EE-99 protocol.

Disease relapse in 23 (18.5%) patients and disease progression in 21(17%) patients. Local site relapse in 10(8%) patients, in which 2 (20%) patients had spine disease, 4(40%) patients had disease in pelvis, 3 (30%) patients had disease in thorax and lower limb involvement in 1(10%) patient. Surgery was done as local therapy in 1 (10%) patient, radiotherapy in 7 (70%) patients and combination

Table-2: Descriptive statistics with univariate analysis.

Variables	Characteristics	Alive n (%)	Death n (%)	p-value
		52 (41.9)	72 (58.1)	
Age (years)	Less than 11 years	29 (55.8)	43 (59.7)	0.66
	Above 11 years	23 (44.2)	29 (40.3)	
Sex	Male	23 (44.2)	47 (65.3)	0.02
	Female	29 (55.8)	25 (34.7)	
Size of tumour	<200ml	30 (57.7)	57 (79.1)	0.04
	>200ml	15 (28.8)	10 (13.9)	
	unknown	7 (13.4)	5 (7.0)	
Metastatic status	No	46 (88.5)	44 (61.1)	0.001
	Yes	6 (11.5)	28 (38.9)	
Local control	Surgery	24 (46.2)	13 (18.1)	0.001
	Radiotherapy	24 (46.2)	34 (47.2)	
	Both	4 (7.7)	3 (4.2)	
	Not done	0 (0.0)	22 (30.6)	
Histopathology report				0.01
	Necrosis of 50-90%	2 (7.1)	6 (37.5)	
	Necrosis of 90-99%	6 (21.4)	2 (12.5)	
	Necrosis of 100%	13 (46.4)	1 (6.2)	
	Little or no necrosis	3 (25.0)	7 (43.8)	
Tumour margins	Margins not involved	19 (36.5)	4 (5.6)	0.001
	Margins involved	9 (17.3)	12 (16.7)	
Relapse status	No	48 (92.3)	32 (44.4)	0.001
	Yes	4 (7.7)	40 (55.6)	

Table-3: Risk factors of mortality.

Variables	Characteristics	Unadjusted OR (CI), p-value	Adjusted OR (CI), p-value
Sex	Male	Ref	Ref
	Female	0.42 (0.20 0.90), 0.02	0.33 (0.13 0.90), 0.03
Metastatic status	No	Ref	Ref
	Yes	4.90 (1.84 12.92), 0.001	2.73 (0.90 8.25), 0.08
Tumour Margins	Not involved	Ref	Ref
	Involved	1.75 (0.65 4.70), 0.09	3.63 (1.01 14.42), 0.004
Relapse status	No	Ref	Ref
	Yes	15.00 (4.89 46.01), 0.001	16.20 (4.65 58.50), 0.001

OR: Odds ratio, CI: Confidence interval.

therapy was given to 2 (20%) patients.

Distant site relapse in 14(11.3%) patients, in which spine involvement was in 2(14%) patients, pelvis 3(21%) patients, thorax in 1(7%) patient, head and neck in 2(14%) patients, upper limb in 4 (28%) patients and lower limb in 2 (14%) patients were involved. Surgery was done in 3 (21%) patients, radiotherapy in 10 (70%) patients, surgery along with radiotherapy were done in 1 (7%) patient. Local and distant relapse in 20 (16%) patients, in which pelvis was involved in 5 (25%) patients, Thorax in 1(5%) patient, lower limb in 9 (45%) patients, upper limb in 4(20%) patients, head and neck in 2 (10%) and spine in n=1 (5%)patient. Surgery was done in 7 (35%) patients, radiotherapy in 12 (60%) patients and combination therapy was given in 1 (5%) patient.

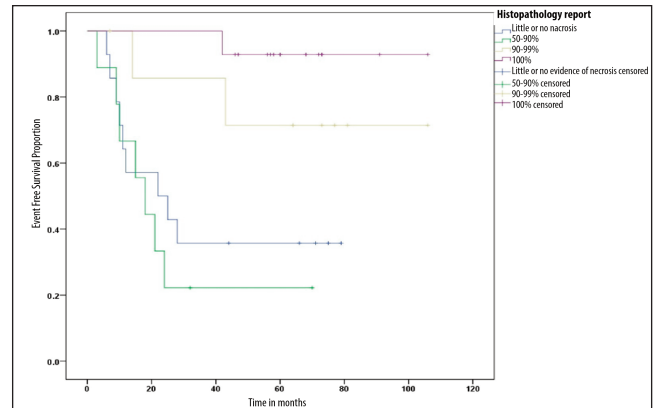


Figure-4: Event-free survival (EFS) with reference to pathological necrosis after neoadjuvant chemotherapy.

Different chemotherapy agents such as vincristine, topotecan, cyclophosphamide, ifosfamide, carboplatin, etoposide, gemcitabine, oxaliplatin and irinotecan were given either alone or in combination with radiotherapy and surgery. Forty (91%) patients died due to disease progression and only 4 (9%) patients were alive.

Discussion

Paediatric sarcoma is the third most common malignancy in the paediatric age group and, among them, ES is the second most prevalent bone tumour in children and adolescents. In developing countries, like Pakistan, there are few tertiary care oncology centres in which paediatric ES treatment is offered and that explains the scarcity of published data on paediatric ES outcome from Pakistan. The Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH&RC) is a tertiary care cancer hospital in which specific ES management is available. The current single-centre study revealed the risk factors and predictors of survival outcome in paediatric ES.

During the last three decades, there is improvement in survival outcome of ES patients due to advancement of chemotherapy agents. However, in low-income countries, such as Pakistan, EFS and OS are still <50%. There are multiple pre-treatment risk factors which affect survival in ES.

Paediatric ES frequency is more common in the 2nd decade of life, and only 15% patients have age <10 years.¹³ However, in the current study about half the patients were aged <11 years. In a previous study, survival outcome of paediatric ES was better than adult population¹⁴ which is contrary to the current findings.

There is no impact of difference in gender on treatment

efficacy and drug toxicity, as shown by Van den Berg H et al.¹⁵ However, further studies are needed to prove the difference in enzyme metabolism for ifosfamide and cyclophosphamide between males and females. In the current study, female patients were less in number compared to male patients and death also occurred less in female patients. In previous studies, baseline tumour volume had impact on disease outcome, as in our study, but the most important factor to consider was the estimation of tumour volume response to initial chemotherapy and histological response after surgery on the survival outcome.^{16,17}

Metastatic ES is a very aggressive systemic disease and presents with a wide spectrum ranging from solitary lung metastasis to widely disseminated multi-organ disease with different disease outcome.¹⁸ Isolated pulmonary metastatic disease outcome is always better than bone and bone marrow disease despite treatment with high-dose chemotherapy along with stem cell transplant. In the current study, metastatic disease had dismal outcome whether it was isolated or combined metastasis, and, unfortunately, no patient survived.

ES management included systemic chemotherapy and local control either by surgery, or radiotherapy or surgery followed by radiotherapy. In the systemic chemotherapy there are multiple chemotherapy drugs used in combination in initiation and consolidation chemotherapy. Initiation chemotherapy was done with vincristine, doxorubicin, cyclophosphamide/ifosfamide, etoposide (VDC/IE) and continuation phase with ifosfamide, etoposide/vincristine, cyclophosphamide (IE/VC) is better than VIDE/VAI/ vincristine, ifosfamide, doxorubicin, etoposide, actinomycin and cyclophosphamide (VAC).¹⁹ However, in the current study most patients were treated with VIDE/VAI chemotherapy and almost all patients who died due to sepsis received this chemotherapy, and therapy-related complications were also common.

The decision on local control in the current study depended on the plan made in the multidisciplinary team (MDT) meeting. MDT decisions based on site, size of tumour along with patient and family preference were also considered in the final decision. In the current study, 16% patients absconded during the treatment. However, most patients left treatment at the time of local control.

As in a previous study,²⁰ best outcome was achieved in the current study with surgery followed by post-operative radiotherapy. Almost all patients with pelvis as the primary site were treated with radiotherapy solely. After surgery two most important risk factors for local and distant relapse were surgical margins and percentage of necrosis on

histology after chemotherapy.²¹ In the current study, patients whose percentage of necrosis on histology was 100% had approximately more than 90% EFS compared to those who had no necrosis on histology.

The role of postoperative radiotherapy seemed to be protective in patients in which margins were involved to reduce the risk of local relapse and it was also helpful in pelvic or axial skeleton ES. Unfortunately, all patients with pelvic ES in the current study died due to local disease recurrence. Radiotherapy was associated with the development of secondary malignancies, growth retardation and post-operative complications in limb salvage reconstructive surgeries.

In ES patients, about 70% relapse happened within 2 years of completion of treatment and very rarely patients relapsed after 2-5 years of completion of treatment.²² In the current study, half of relapsed patients presented with both local and distant relapse and most of the patients were identified on follow-up imaging and very few presented with clinical signs and symptoms. There was a multiple chemotherapy drugs regimen used for treating recurrent ES and a study is currently being performed to evaluate the best regimen; temozolamide/irinotecan combination regimen holds 47% cumulative response rate compared to another regimen. Clinical trials, including cytotoxic chemotherapy, agents targeting pathways specific to tumour cells and immunotherapy, are going on and these are essential for treating resistant systemic disease.^{23,24}

The current study showed the most important risk factors for mortality in ES were gender, metastatic status of disease at baseline, tumour margins post-surgery and relapse status after treatment completion. The most important factor to reduce the mortality and abandonment is educating the general physicians and paediatricians regarding early referral to paediatric oncologists along with psychosocial support by developing support groups for poor patients.

The main limitation of the current study was its retrospective nature alongside being a single-centre experience. Also, there was no follow-up of patients who absconded the ES treatment protocol.

Conclusion

Tumour necrosis and histopathological changes post-surgery were found to have great impact on survival outcome in ES. Knowledge of prognostic factors in ES patients helps to guide treatment planning and there is a need for close collaboration between paediatric and adult sarcoma centres around the world to develop curative therapy in recurrent ES.

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