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Original Article

Oncological And Functional Outcome Of Patients Suffering From Ewing's Sarcoma Family Of Tumors (ESFT), Treated By Chemotherapy And Limb Salvage Surgery.

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Abstract

Background: The Oncological and functional outcome of patients suffering from nonmetastatic, non-axial Ewing's sarcoma treated with chemotherapy and limb salvage surgery in two institutions are reported.

Patients and Methods: A retrospective review of 32 patients with Ewing's sarcoma (ES) and peripheral neuroectodermal tumor of the bone. All patients were nonmetastatic, non-axial at diagnosis. They were treated at two institutions (Department of Clinical Oncology - Menufeya University and Orthopedic Department - Cairo University) with the same chemotherapy regimen and all had limb-salvage surgery between march 1994 and end of april 2005. The median age at diagnosis was 14.7 years; 15 patients were males and 17 were females.

Results: At a median follow up of 36 months, patients had an overall survival of 60%. Local recurrence was seen in 15.6%, whereas lung metastasis was seen in 31.25% of patients, both at a median survival of 27 months. While univariate analysis showed that local recurrence and the occurence of lung metastasis have an adverse effect on survival, multivariate analysis proved that none of these factors have an independent significant impact on survival. Patients who suffered from metastatic lung nodules had a much worse survival rate (29.6%) than those who did not (75.4%, $p < 0.05$). 68.7% of patients had a "Good" response to preoperative chemotherapy with an increase in survival probability to 82.2%, while those having a "fair" response, or "progressive" disease had a survival of 14.8% ($P<0.001$). The average functional outcome following limb salvage surgery and chemotherapy was 70% (range 62-90%).

Conclusion: Overall survival of patients receiving chemotherapy followed by limb-salvage surgery alone as local control is comparable to patients reported in literature treated by chemotherapy and having surgery and/or radiation therapy as local control. Response to preoperative chemotherapy is a powerful prognostic factor that had an impact on survival and this observation points out the importance of further stratification of patients based on this response. Limb salvage surgery by itself had no impact on incidence of local recurrence or systemic relapse, and gave a good functional outcome.

Key words: *Ewing's sarcoma family tumors, Limb salvage surgery, Chemotherapy.*

Introduction:

The Ewing's sarcoma family of tumors (ESFT) includes Ewing's sarcoma of bone, extraosseous Ewing's sarcoma, peripheral neuroectodermal tumor, Askin tumor and neuroepithelioma, all known as the Ewing's sarcoma family of tumors (ESFT). The identification non-random t (11; 22) (q24; q12) chromosome rearrangement in these aggressive malignant tumors arising in bone and soft tissue is evidence of their common histogenesis [6].

The introduction of multimodal treatment, including multiagent chemotherapy, more precise radiation therapy, and more aggressive surgery has led to substantial improvement in the prognosis of these patients [5], with a disease free survival (DFS)

of (60% -70%) for newly diagnosed patients with localized disease [2].

Although more patients with Ewing's sarcoma of bone (ESB) are being treated by surgery, the relative role of surgery, radiotherapy or using them both in the local control of this tumor has yet to be determined. The outcome of ESFT may differ; as patients with axial, large -sized tumors and clinically detectable metastasis at diagnosis have a much worse prognosis [24]. This study reports the outcome of a group of patients suffering from nonmetastatic, non-axial Ewing's sarcoma or peripheral neuroectodermal tumors treated with chemotherapy and limb salvage surgery only.

Patients and Methods:

We carried out a retrospective review of 32 patients diagnosed as Ewing's sarcoma (ES) and PNET of bone treated in two institutions in Egypt (Department of Clinical Oncology -Menufeya University and Department of Bone and Orthopedic Surgery - Cairo University). This review included all newly diagnosed patients suffering from this tumor (non metastatic and non axial) at both centers and treated with chemotherapy and limb salvage surgery alone as local control with no radiation therapy given locally. The patients were treated at both centers during the period between March 1994 and end of April 2005. The median age at diagnosis was 14.7 years (Range, 6-32 years); 15 patients were males and 17 were females with 1: 1.13 sex ratio. The median follow up was 36 months from surgery (range, 6-120 Months). Only 9 patients (28.1%) were less than or equal to 10 years of age at diagnosis while 23 patients (71.9%) were older than 10 years. Primary tumors involved the femur in 21 patients (65.6%), humerus in 7 patients (21.8%), and tibia in 4 patients (12.5%). The diagnosis, according to the histologic definition of Ewing family of tumors, was Ewing sarcoma of bone in 29 cases (90.6%), malignant peripheral primitive neuroectodermal tumor (PNET) in 3 cases (9.4%).

Pretreatment Staging:

1. Computed tomography (CT) and/or magnetic resonance imaging of the primary site.
2. CT scan of the chest (and/or abdomen and pelvis, where appropriate).
3. Technetium-99m bone scan.
4. Base line echocardiogram was performed as well as a follow up one before each dose of anthracycline.

Initial patient evaluation included medical history, physical examination, hematologic studies, and several chemical laboratory tests, including serum lactate dehydrogenase (LDH). Bone marrow biopsy to determine presence of occult metastatic disease was not performed routinely for all patients. Tumor size was estimated by CT scan measures of the lesion's three dimensions and calculated accordingly.

The patients were assigned to receive standard chemotherapy regimen which included doxorubicin, vincristine, cyclophosphamide, alternating with ifosfamide and etoposide, the courses of therapy consisted of 1.5 mg of vincristine per square meter of body-surface area (maximal dose, 2 mg), doxorubicin given at a dose of 25 mg per square meter per day for three successive days as a bolus I.V infusion, and 1200 mg of cyclophosphamide per square meter surface area I.V, followed by mesna to prevent hemorrhagic cystitis caused by cyclophosphamide. Dactinomycin at 1.5 mg per square meter per dose was substituted for doxorubicin when the cumulative doxorubicin dose reached 375 mg per square meter. For the alternate ifosfamide and etoposide course, 1800 mg of ifosfamide per square meter per day was given as I.V infusion for five days with mesna, and 100 mg of etoposide per square meter I.V per day over the same five days.

The courses of chemotherapy were administered every three weeks for a total of 17 courses .The duration of chemotherapy was planned for 48 weeks. Hematopoietic cytokines were available at the discretion of the treating physicians. Before surgery, second evaluation studies were done, MRI of the lesion site as well as CT chest and a bone scan for all patients with a reported estimation of degree of tumor size reduction by the radiologist.

Local control consisted of limb salvage surgery alone with no radiation therapy given to tumor site twelve weeks from the start of therapy.

Surgery consisted of resection with wide margins and reconstruction of the resultant defect. The method of reconstruction was chosen according to the age of the patient, size of the defect and amount of available muscles after resection. Patients were evaluated functionally during their follow up visits using the musculoskeletal tumor society scoring system [34] (appendix 1). Regarding the age, our patients were divided into 2 categories, less than 10 years of age and more than 10 years of age.

Statistical Analysis:

Statistical analysis was performed using SPSS for Windows version 11.0 (SPSS Inc., Chicago, IL, USA). Association between outcome and some clinico-demographic parameters were analyzed by Fisher exact test. For survival analysis Cox univariate, and multivariate regression models were used to evaluate the Hazard Ratio (HR). Confidence intervals for relative risks were derived from the proportional-hazards regression model. Kaplan-Meier survival analysis was used to construct survival probability curves and log-rank test used for comparing survival probability of two groups. The level of significance was set as P-value <0.05.The primary end point of our study was disease-free survival.

Results:

At a median follow-up of 36 months (range 6-120 Month), 10 patients (31.3%) were dead, 3 patients (9.4%) had disease progression, while 18 patients (56.3%) had no evidence of disease, only one patient had controlled stationary disease after upgrading his chemotherapy. Overall survival was 60% for patients after limb-salvage surgery with chemotherapy which continued for a total of 48 weeks from the start of therapy. Free or pedicled vascularized fibular graft was used in 18 patients, vascularized pedicled scapular crest in 2, modular prosthesis in 5, rotationplasty in 6 and no reconstruction (suspension) in one patient.

Local recurrence was seen in 5 patients (15.6%), while lung metastasis was seen in 10 (31.25%). Males had a slightly better survival probability (0.66, 95 % CI=0.38-0.94) than females (0.55, 95 % CI=0.26-0.82) but this was statistically insignificant. Although patients less than 10 years old showed lower (0.58%, 95 % CI=0.18-0.98) survival probability than older children (0.61, 95 % CI=0.37-0.84), yet this difference was also not statistically significant (P>0.05). Patients who had lung metastasis had a much lesser survival (0.29, 95 % CI=0.03-0.62) than those who did not have any recurrence through their disease history (0.75, 95 % CI=0.53-0.97) at a median survival of 27 months (P =0.015).

Evaluation results of patients after preoperative chemotherapy significantly correlated with patients' survival. They were divided into 2 categories, those who had 50% or more reduction in tumor size described as "Good" response had a survival probability of (0.82, 95 % CI=0.64-1.0), while those with poor response, stationary or progressive disease had a much less survival probability (0.15, 95 % CI=0.11-0.41) at 27 months median survival time. This finding was of significance (p<0.001).

Patients had an average functional outcome of 70% (range 62 - 90%) according to the musculoskeletal tumor society scoring system [34]. The scoring evaluation of all our patients was done at follow up clinics and a percent score was given to each patient to evaluate functional outcome (see appendix 1).

Table (1). Different characteristics of studied patients.

Character	Number	Percent
Age in years (X±SD)= 14.7+5.8 (Range 6-32)		
< 10	9	28.1%
> 10	23	71.9%
Sex		
Male	15	46.9%
Female	17	53.1%
Tumor Site		
Femur	21	56.6%
Humerus	7	21.8%
Tibia	4	12.5%
Lung Metastasis		
Positive	10	31.2%
Negative	22	68.8%
Evaluation of response after Chemotherapy:		
Good=More than 50%reduction in size of tumor	22	68.8%
Fair=Less than 50% reduction in tumor size	8	25.0%
Stationary Disease=No reduction in tumor size	1	3.1%
Progressive Disease=Increase in tumor size	1	3.1%

Table (2): Univariate and Multivariate Hazard Ratio (HR) of all Prognostic factors in Studied patients.

	Univariate HP	95% C.I	Multivariate HR	95% C.I
Age (Year)				
< 10	1.0	0.4-6.0	0.84	0.1-7.63
> 10	1.5			
Sex				
Male	1.0	0.51-6.4	3.5	0.46-25.81
Female	1.8			
Site of Tumor				
Around Knee	1.0	0.51-7.72	1.33	0.23-7.58
Other Sites	2.0			
Lung Metastasis				
Negative	1.0	1.17-15.0	0.91	0.06-12.42
Positive	4.2			
Local Recurrence				
Negative	1.0	1.63-20.63	4.45	0.63-31.3
Positive	5.8			

Table (3): Evaluation before Local control in Relation to Outcome of Disease

Evaluation after preoperative chemotherapy	Outcome: No evidence of disease/stationary N=19 No	%	Outcome: Dead/progressive N=13 No	%	p
Good Responders	18	82%	4	18 %	
Fair/stationary/progressive	1	10%	9	90 %	<0.001
Total	19	59.3%	13	40.7%	

Fig (1) Overall survival of Ewing's sarcoma patients

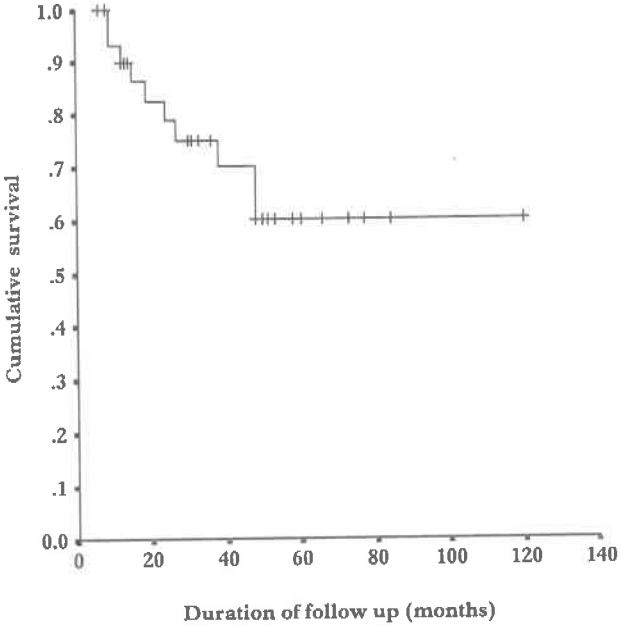


Fig (2): Kaplan - Meier survival curve of Ewing's sarcoma patients by local recurrence.

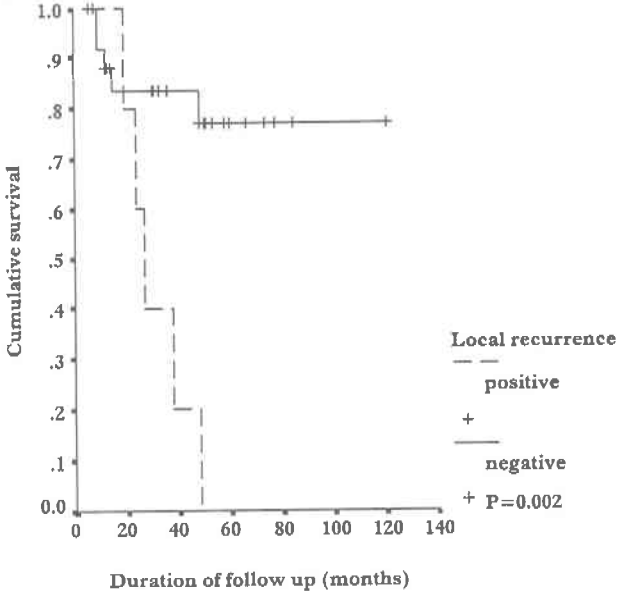
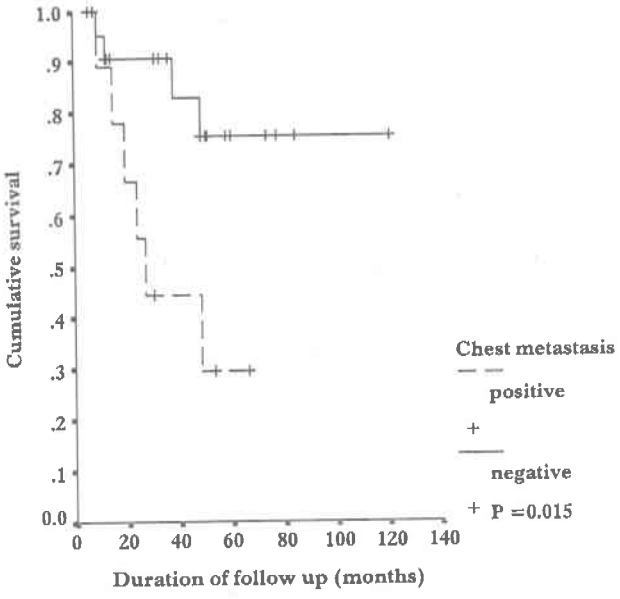


Fig (3) Kaplan-Meier survival curve of Ewing's sarcoma patients who had lung metastasis



Fig(4) Kaplan - Meier curve of patients' response before surgery

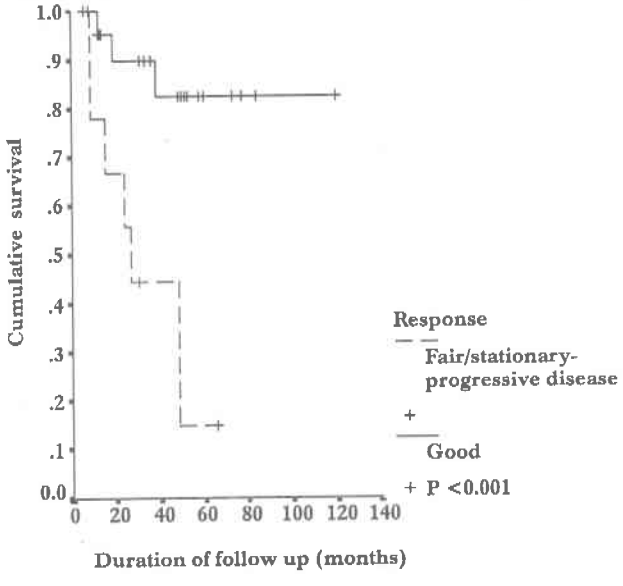
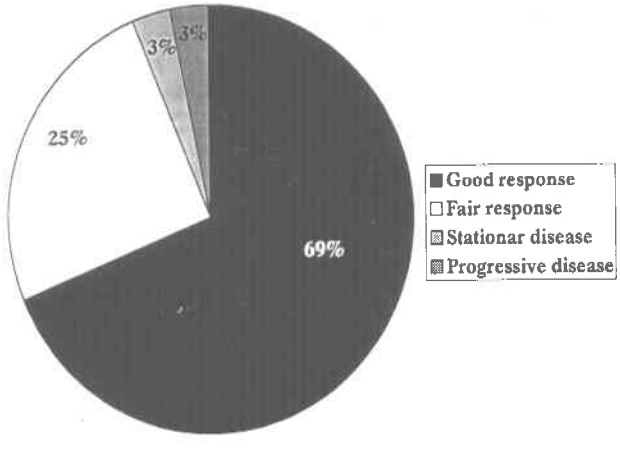


Fig (5): Pie chart dividing patients according to response to presurgery neoadjuvant chemotherapy.



Appendix 1: Musculoskeletal Tumor Society scoring System [34]

Functional Evaluation - lower extremities

Hospital number:. . . . . .
Name:. . . . . .
Date of evaluation: . . . . . .

	Pain	Functional activities	Acceptance
5	No Pain (No medicate)	No restriction (no disability)	Enthused (would recommend to others)
4	Intermediate	Intermediate	Intermediate
3	Modest/Non/disabling (non-Narcotic analgestics)	Recreational restriction (Minor disability)	Satisfied (would do again)
2	Intermediate	Intermediate	Intermediate
1	Moderate/Intermittently Disabling (Intermittent narcotics)	Partial occupational restriction (major disability)	Accepts (would repeat reluctantly)
0	Severe/Continuously disabling (Continuous narcotics)	Total Occupational restriction (complete disability)	Dislikes (would not repeat)

	Supports	Walking ability	Gait
5	None (No support)	Unlimited(same as preop)	Normal (no alteration)
4	Intermediate (occasional use brace)	Intermediate	Intermediate
3	Brace (mostly barce)	Limited (Significantly less)	Minor cosmetic (cosmetic alteration only)
2	Intermediate	Intermediate	Intermediate
1	Once cane or crutch (mostly cane/crutch)	Inside only (can not walk outside)	Major cosmetic (minor functional deficit)
0	Two canes or crutches (Always canes/crutches)	Not independently (can walk only with assistance or wheelchair bound)	Major handicap (major functional deficit)

Discussion:

The advent of limb salvage surgery in the treatment of primary malignant bone tumors has renewed interest in the surgical treatment of Ewing's sarcoma. ESFT is the second primary bone malignancy in childhood. Its 5-year survival has significantly increased from less than 10% (during 1960's) to 60 - 70% [19, 26, 27] and 10-year event-free survival is approximately 50% [2]. The successful treatment of patients with tumors of the Ewing's family (EFTs) requires now the use of multidrug chemotherapy, in addition to radiation therapy and/or surgical therapy to the primary tumor [17, 1, 18]. The results of this study showed an overall survival of 60% at a median follow up of 36 months for patients suffering from non-axial, non-metastatic tumors treated with limb-salvage surgery and chemotherapy only. This was comparable to various studies using surgery and/or radiation therapy, as some reported 5-years survival of 53% while for others, a higher chance of survival (68%) after first complete remission was reported due to an earlier local control [4]. An Italian study reported the overall survival (OS) at real follow-ups of 5-, 10-, 15- and 20-years to be 57.2, 49.3, 44.9 and 38.4%, respectively treated with chemotherapy, surgery and/or radiation therapy [1]. This observation of comparable results in overall survival to patients having both modalities surgery and radiation therapy for their local control has led us to think that this might be attributed to the use of neoadjuvant chemotherapy and wide surgical resection margins.

The choice of local therapy for the treatment of Ewing's sarcoma of bone remains controversial [19]. Several retrospective studies have reported a survival advantage with surgery over radiotherapy. Wilkins et al (1986) [31] reported 5 years survival of 74% in patients receiving surgical resection versus 34% in patients treated by radiotherapy. Other multi-center studies reported similar outcomes. However none of these studies randomized the selection of local therapy leading to the conclusion that a selection bias may have influenced these results.

Although Jereb et al (1986) [33] indicated that local recurrence rate after limb salvage surgery is high without postoperative radiotherapy ($>$ 50%), this was not the case for patients in this study as local recurrence occurred only in 5 patients (15.6%). Limb salvage surgery in which resection margins are wide offers the same oncologic safety as amputation with the advantage of providing a better functional outcome. It is believed that the functional outcome after surgery may be inferior to the function following radiotherapy. This was not observed in the current study as the patients in our series had an average functional outcome of 70% (range 62 - 90%) according to the musculoskeletal tumor society scoring system [34], while another study evaluating eighty-nine survivors of ESFT treated at the National Cancer Institute-USA between 1965 and 1992 showed a significantly lower functional outcome measured by Karnofsky index (KI) (50-80) in comparison to controls. The majority of these cases (89%) received external beam irradiation for local tumor control. Treatment-related variables that might have affected functional status of subjects and the effect of functional status on employment, health care, and health-insurance coverage were also addressed in that study [36].

On the other hand, radiation therapy is associated with various complications especially in skeletally immature patients. Paulino (2004) [32] reported

atrophy in 80%, bone growth abnormalities in 67%, fracture in 33%, limitation of movement in 13%, and secondary malignancy in 20%. He stated that although most children treated with radiation therapy for a pediatric extremity sarcoma have minimal late toxicity by LENT-SOMA scale, approximately half required a surgical procedure to correct a late effect [32]. The oncogenic potential of radiotherapy is well-known, especially sarcomas induced by radiation therapy for Ewing's sarcoma [25]. These secondary tumors are classified as sarcomas or malignant fibrohistiocytomas. Their progression is fast with a very poor prognosis [28]. In the previous CESS 81 and CESS 86 studies, radiation-induced second cancers were cumulatively observed in up to 5% of patients within 15 years [7]. Other studies reporting the rate of second malignancies to be 3% for 371 survivors at 5 years, 6.5% for 219 survivors at 10 years, and 12.7% for 91 survivors at 20 years or more. The authors found that the risk of secondary malignancy is higher only after radiotherapy [28]. Multivariate analyses in an Italian study of 402 ESFT patients showed male gender, age older than 14 years, high serum lactate dehydrogenase (LDH) level, axial location of the tumor, use of radiotherapy alone as a local treatment, and poor histological response to chemotherapy, to be independent, adverse prognostic factors for event-free survival (EFS) [1].

Also the local failure after radiation therapy was within the irradiated volume in 62% of patients, outside the irradiated volume in 24% of cases, while the precise location could not be determined in the remaining 14% [35]. While a higher survival of 86.9% was reported in an American study of 23 ESFT patients at a minimum of 5 years follow up was attributed to wide surgical margins attempted in all patients which reflects the role of surgical procedure in local control [29]. These findings drew more attention to the efficacy of surgery for local control for localized ESFT of bone. The ESMO report (2005) stated that despite Ewing's sarcoma being a radiosensitive tumor, surgery is the preferred treatment for local control. A wide surgical margin should be attempted, and radiation therapy should only be given to patients with marginal or intralesional surgery, or with inoperable tumors. Radiation dose will depend on tumor site [26].

In the current available international data, the majority of patients were treated with radiation therapy alone before 1982, while after 1982, surgery has been used more commonly, but still not often enough to allow a direct comparison [30]. All our patients had successful primary limb-salvage surgery with 15.6% having local recurrence and no major surgical revisions. Early complications were limited to the allograft reconstruction and were either delayed union or an allograft fracture. There was no infection reported in those patients and no neurovascular compromise.

It is our impression, supported by the study's results, that non-axial Ewing's sarcoma of bone is particularly suitable for surgical treatment. This might be due to the fact that it frequently does not involve the epiphyseal areas of the long bones and that it, not uncommonly, occurs in expendable bone.

Current standard chemotherapy protocol includes vincristin, doxorubicin, and cyclophosphamide, alternating with ifosfamide and etoposide [2]. The combination of ifosfamide and etoposide has shown activity in Ewing's tumor of bone [15]. The number of courses is 12-15 and total treatment time 8-12 months. Treatment is divided into induction chemotherapy (3-6 courses) followed by local therapy and consolidation chemotherapy (8-10 courses) [26].

It was found in the early 90s that histologic response to chemotherapy is a valuable prognostic indicator for patients undergoing surgery [20]. Since then other studies reported that the response to induction chemotherapy is a strong prognostic factor and that event-free survival rate for "good responders" was better (57%) than that for "bad responders" (9%) [8, 30]. The survival probability of our patients who had "Good" response was (0.82, 95 % CI=0.64-1.0), while those with a poor response, stationary or progressive disease had a much less survival probability (0.15, 95 % CI=0.11-0.41) with a 27 months median survival time. This finding was statistically significant ($p<0.001$). Multiple studies have shown that patients with minimal or no residual tumor after pre-surgical chemotherapy have a significantly better event-free survival compared to patients with larger amounts of viable tumor [12,11,13]. Massive tumor necrosis after induction chemotherapy is a very favorable sign [8,14]. Using pathologic evaluation after neoadjuvant chemotherapy (good pathologic response if less than 10% of viable cells), the German Cooperative Group reported a 10-year event-free survival of 64% for good responders dropping to 38% for poor responders ($P = 0.0007$) [11], while in the French EW 88 study,

which used different histological criteria, disease-free survival was 75% for good responders (less than 5% viable tumor cells), 48% for intermediate responders, and 20% for poor responders (> or =30% viable tumor cells, P <0.0001) [13].

In another series of population, 5-year PFS (Progression-free survival) was 71% in good responders and 44% in poor responders (P = 0.012) [22].

The evaluation of patients in this study after neoadjuvant chemotherapy was performed for all of them, with a survival rate of (82.2%) for those having a "Good" response [More than 50% reduction in size of tumor after 5 cycles of neoadjuvant chemotherapy], 94.7% of those patients having no evidence of disease till last follow up, while the survival rate dropped to less than (14.8%) for those patients having a fair response or progressive disease, with 69.2% of them died or had advanced progressive disease during their follow up. This was shown at a median survival follow up of 27 months and it was statistically significant (p<0.001). The discrepancy between those two groups of patients in their survival rates not only manifested the importance of response to therapy and evaluation before local control of tumor, but also more importantly stressed the need for adopting a more aggressive approach for those who showed poor response to initial chemotherapy.

Univariate analysis of our data had shown recurrence either local (HR 5.8, and 95% C.I 1.63-20.63) or systemic (H.R 4.2, and 95% C.I 1.17-15) and response to neoadjuvant chemotherapy (H.R 6.9 and 95% C.I 1.78-27.03) to have an impact on survival (Table 4), although Multivariate analysis failed to show that any of these variables had an independent effect on survival. The response after neoadjuvant therapy (whether regarding size reduction measured radiologically or histopathologic response with the percent degree of necrosis) to survival, detected here and in other studies, may point out the importance of standardization of evaluation before local control therapy, and as mentioned before, further stratification of patients according to their response to neoadjuvant chemotherapy is needed.

In the ESMO guidelines and therapy recommendations (2005), there was no mention of stratification of patients after evaluation before local control therapy, but it stated that despite Ewing's sarcoma being a radiosensitive tumor, surgery is the preferred treatment for local control. A wide surgical margin should be attempted, and radiation therapy should be given to patients with marginal or intralesional surgery, or with inoperable tumors [26]. This coincides also with the current recommendations of the Intergroup Ewing's Sarcoma Study (IESS) that no radiation therapy should be recommended for those who have no evidence of microscopic residual disease following surgical resection [9]. In this study we report a local recurrence rate of 15.6% and systemic relapse of 31.2% at a median follow up of 36 months which is also comparable to other studies using both surgery and radiation therapy for local tumor control.

An American study, evaluating recurrent ESFT patients stated that local recurrence, either isolated in (35%) or combined local and distant in (17%) may have been due to the routine use of radiotherapy alone for local control (especially radiotherapy doses < 35 Gy), which also may have contributed to the relatively high local failure in earlier studies [21]. Our results showed that 11 patients had relapsed (34.3%) after response to initial therapy, 10 of them (31.3%) died of disease progression or treatment consequences, 3 patients (9.4%) had advanced disease progression, while 18 patients (56.3%) had no evidence of disease all through their follow up. Males in this study showed higher survival rates than females 65.8% Vs 58.3% but this was statistically insignificant (p>0.05), but there was a statistically significant difference in survival outcome between patients who developed lung metastatic lesions or those having local recurrences (29.6%) and other patients who did not show any evidence of relapse through their follow up time (75.4%) with (P<0.05). Age, sex, site of tumor or type of operation did not have any impact on survival. In the present study, patients who did not respond to first line therapy or relapsed on treatment did not benefit much from upgrading chemotherapy. Accordingly as agreed by other studies, even with improved primary treatment for ESFT, recurrent disease remains a significant clinical problem for pediatric and medical oncologists [21].

In conclusion, we found that overall survival of patients with localized, non axial ESFT that underwent limb-salvage surgery and received neoadjuvant as well as adjuvant chemotherapy is comparable with the use of chemotherapy, surgery and/or radiation therapy. We believe that surgical resection should be considered for all patients with Ewing's sarcoma family tumors when the surgeon can achieve a wide resection margin. If it is judged during preoperative staging that surgical

resection would be associated with inadequate margins, radiation therapy should be used either alone or post surgery. Also this study showed that the response to neoadjuvant chemotherapy was a significant prognostic factor. We feel that patients must be evaluated histologically as well as radiologically before local control and to further stratify patients into two groups according to their response. This is based on an observation of a statistically significant difference of survival between patients with good response (>50% reduction in size of tumor mass) who achieved more than 82.2 % and those who had fair response, or progressive disease survival reached (14.81%) with p value <0.001. The patients in this study reported a good comparable functional outcome of average 70% after limb-salvage surgery and chemotherapy.

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