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Prognosis and Outcome of Adult Patients with Ewing Sarcoma (Local Experience)

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Abstract

Objective: Aim of this work is to assess clinical features, outcome and prognosis of adult patients diagnosed with Ewing Sarcoma (ES). **Patients, Methods and Results:** The records of 53 adult patients treated with Euro-Ewing protocol at Kuwait cancer control center (KCCC) over a period of 5 years were reviewed. Mean age was 26.9 ± 1.25 years. Thirty percent of patients presented with metastatic disease, and 65% of tumors were centrally located and 50% were ≥ 8 cm. All patients received initially VIDE protocol. 13.5% achieved complete remission (CR), and 57.7% achieved partial response (PR). Approximately 1/3 of patients underwent surgery which was adequate in 76% of them, and all patients received local radiotherapy. Post local treatment 56% of patients received VAC and 44% received VAI protocol. Mean treatment duration was 11 months ± 0.54. Median follow-up duration was 38.39 (33.49 - 43.28) months At the end of follow up 20% of patients relapsed locally and 36% distally. Median PFS was 46.9 months (95% CI 41.42 - 52.39), Median OS was 55.43 ms (95% CI 30.71 - 75.74); survivals at 3 and 5 years were 88%, 46% respectively. **Conclusion:** In this series metastases at presentation and wide surgical margins were the most important prognostic factors. Multimodality therapy is necessary for this rare disease.

Keywords

Adult, Ewing, Sarcoma, Treatment

1. Introduction

ES is one of the most common malignancies during childhood and adolescence.

It is considered the second most common primary bone malignancy during this period, with frequency approximately 2.9 per million in the population younger than 20 years, mostly among age group between 15 and 17 [1].

Approximately 95% of patients with ES have a characteristic t (11; 22) (q24; q12) or t (21; 22) (q22; q12) chromosomal translocation, which gives rise to fusion of the EWS gene on chromosome 22 and the FLI-1 gene on chromosome 11 or the ERG gene on chromosome 21 [2].

Few studies have investigated adult outcomes, and regarding the existing studies, there are ongoing controversies regarding prognosis. In some series, adults have worse outcomes while in others, outcomes are similar to those among children and adolescents [3] [4].

The importance of age on ES prognosis remains debatable, but in most trials older age has been associated with an inferior clinical outcome. The exact reason of the poor prognostic effect of age is not clearly understood till now, however it may be due to the fact that most adult cases present with pelvic disease and other biological factories [5] [6].

There is debate about the optimal modality of local control for Ewing sarcoma. Some centers prefer to use surgery and others use radiotherapy or both modalities. Actually the site of primary disease and the response to chemotherapy may help in choosing the optimal way of management.

There were many studies demonstrating the prognostic factors as tumor stage, size, surgical margin, high lactate dehydrogenase, and achievement of CR after initial treatment [7] [8] [9].

Therapy for pediatric patients is usually based on clinical trial protocols; however adult treatment is often extrapolated from pediatric protocols or is institutional based. The main concern regarding the use of pediatric protocols is the tolerance of adult patients to therapy that obligates most of centers to modify their regimens to better suit this older population. Thus, the ideal treatment strategy for adults with ES remains undefined due to the lack of well-designed prospective clinical trials to solve this problem.

Our trial tried to explore our center strategy for treatment of adult patients with ES.

2. Patients and Methods

The records of 53 adult patients treated with Euro-Ewing protocol at Kuwait cancer control center (KCCC) over a period of 5 years were reviewed. We started collecting and analyzing patients' data after approval of the ministry of health ethical committee.

The diagnosis of all cases was based on biopsy specimens either true cut needle or open biopsy. All biopsies were reviewed by a sarcoma specialized pathologist at KCCC. Diagnosis was confirmed by immunohistochemical markers as positive CD99 and occasionally genetic detection of t (11; 22) (q24; q12) or t (21; 22) (q22; q12) to exclude other round cell tumor (lymphoma, rhabdomyosarcoma or neuroblastoma).

The following data were collected; patient's age, gender, site and size of the primary tumor, presence and sites of metastases. The management including the different treatment modalities received (chemotherapeutic, surgery and radiotherapy), treatment outcome, time to progression and survival.

Most patients received Euro-Ewing protocol; Patients received VIDE (vincristine, ifosfamide, doxorubicin, etoposide) as induction chemotherapy. One third of the patients underwent surgical resection of the tumor. Radiotherapy was given for local control either alone or post-surgical resection using 3D conformal radiotherapy. Patients received an average total dose of 54 Gy (48 - 64 Gy) at 1.8 Gy daily doses. The planning target volume encompassed the prechemotherapy tumor volume plus a minimum of 2.5 cm margins all around.

Post local treatment most of the patients received vincristine IV on day 1& dactinomycin and ifosfamide IV on days 1 and 2 (VAI) for 5 - 6 courses. Treatment was repeats every 21 days. Some of our patients received VAC (vincristine, actinomycin, cyclophosphamide).

Patients were regularly evaluated during their treatment course by physical examination, complete blood count, serum chemistry and CT chest, abdomen and pelvis. The diagnosis of recurrence was made on the basis of physical examination, radiological evidence and pathology, if required.

WHO response criteria were used for response assessment, CR was defined as complete disappearance of the soft tissue mass and sclerosis of the lytic bone lesion. PR was defined as >50% reduction in the sum of the products of the diameters of all measured lesions, no increase in the size of any previous lesion and no new lesion. Progressive disease (PD) was defined as >25% increase in the sum of the products of the diameters of any measurable lesion or the appearance of a new lesion.

After the completion of therapy, patients were followed-up every 3 months with proper history, physical examination, chest X-ray and complete blood count. CT scans of the primary tumor location and chest were performed every 6 months for 5 years and yearly afterwards.

3. Statistical Methods

Data were analyzed using SPSS version 20. Categorical data were summarized as percentages. Numerical data were summarized as mean ± standard deviation or median and range if skewed. Chi-square test and fisher exact test were used to examine the relation between qualitative variables

Overall survival (OS) was defined as the time from diagnosis to the time of death from any cause. Patients who were alive on the date of last follow-up were censored on that date. Progression free survival (PFS) was defined as the time from diagnosis until documented progression or death. For patients without disease progression at the time of analysis, the date of last follow-up was considered right-censored. OS and PFS were estimated using the Kaplan-Meier analysis. Log rank test was used to compare survival curves. All tests of hypotheses were conducted at the alpha of 0.05 level, with a 95% confidence interval.

4. Results

The records of 53 adult patients diagnosed with ES seen in KCCC over a period of 5 years were reviewed. Mean age at diagnosis was 26.9 ± 1.25 years, with 6 patients above 40 years. Sixty six percent of the patients were females. Seventy percent had localized disease while 30% had metastatic disease out of which 11 patients has lung only metastasis. Approximately 65% of tumors were centrally located, the most common primary sites being the pelvis and spine. Fifty percent of tumors were 8 cm or more in maximum dimension at diagnosis (Table 1).

No standard treatment model is established for ES. The management is different from one center to the other. In this series patients were treated using EURO-EWING protocol. Mean time to starting treatment from diagnosis was 1.6 ± 0.37 ms. All patients received initially VIDE protocol. 13.5% of patients

Table 1. Patients and tumor characteristics.

Patients characteristics	n	%
Mean age	26.89	±1.25
Sex		
Female	18	(34)
Male	35	(66)
PS		
0	11	(20.8)
1	24	(45.3)
2	15	(28.3)
3	3	(5.7)
Fever	20	(38.5)
No fever	32	(61.5)
Mean LDH level	336.9	±32.2
Mean hemoglobin level	11.2	±0.25
Tumor size		
≥8	26	(50)
<8	26	(50)
Tumor site		
Central	34	(65.4)
Peripheral	18	(34.6)
No metastatsis	36	(67.9)
Metastasis to lung	8	(15)
Metastasis to other sites	6	(11.3)
Bone marrow infiltration		
Infiltrated	16	(30.8)
Not infiltrated	36	(69.2)

achieved CR, 57.7% PR, 13.5% SD and 15.4% progressed. Median number of cycles received was 6 (range 2 - 8). Seven patients needed dose reduction. 25 (37.5%) patients underwent surgery which was adequate in 19 of them (76%), all patients received local radiotherapy. They received a median total dose of 54 Gy (48 - 64 Gy) at 1.8 Gy daily doses. The planning target volume encompassed the prechemotherapy tumor volume plus a minimum of 2.5 cm margins all around.

Patient then continued to receive chemotherapy. Twenty eight patients (56%) received VAC protocol and 22 (44%) received VAI protocol. Mean treatment duration was 11 months ± 0.54. Response to treatment is shown in Table 2. Median follow-up duration was 38.39 (33.49 - 43.28) months. At the end of follow up 20% of patients relapsed locally and 36% distally. Median PFS was 46.9 months (95% CI 41.42 - 52.39) (Figure 1). There was no effect of age at diagnosis (<30 and ≥30), tumor size (<8 cm and ≥8 cm) or high LDH level (<280 and ≥280) on PFS, P = (0.078, 0.925, and 0.25 respectively).

Median OS was 55.43 ms (95% CI 30.71 - 75.74); survival at 3 years and 5 years were 88%, and 46% respectively (Figure 2). Cases presenting with metastatic disease had a statistically significant lower PFS and OS (P = 0.002, 0.001) respectively. Patients achieving wide surgical margin did better than those not.

Table 2. Response to therapy.

Response	n	(%)
CR	7	(13.5)
PR	30	(57.7)
SD	7	(13.5)
DP	8	(15.4)

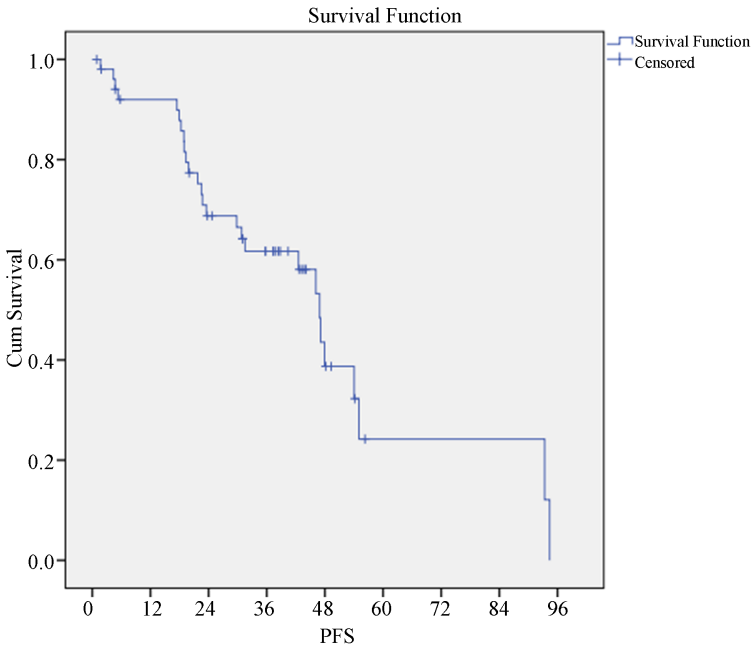

Figure 1. Progression free Survival for all cases.

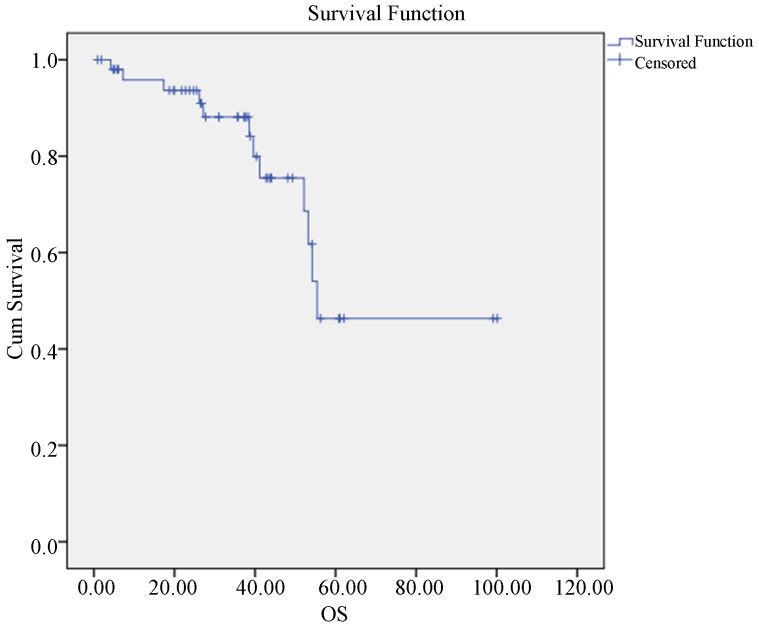

Figure 2. Overall survival for all cases.

No statistically significant effect of age, tumor size or LDH level on OS, P = (0.084, 0.973, 0.89 respectively).

5. Discussion

ES is more common in children and adolescents. Many studies dealt with treatment of adult patients with Ewing sarcoma using multiagents chemotherapy and aggressive local treatment. The outcomes of children with localized ES have improved greatly, with survival now ranging from 60% to 80% at 5 year [10] [11]. The available clinical trials for adult are limited, on small number of patients and retrospective. Most of management usually follows pediatric protocols. In our series we tried to collect and analyses data of adult patients presented to our center treated by the same concepts and protocols of pediatric group.

The mean age of patients in our study was 26.9 ± 1.25 years, with 6 patients above 40. Mehmet *et al.* in his study reported a median age of 27; 3.8% of patients (n = 1) were older than 40 year, and 19% of the patients (n = 5) were older than 30 years. This observation was also consistent with observations from other centers [8] [12] [13].

In our series 70% of patients presented with localized disease while 30% had metastasis. Approximately 65% of tumors were centrally located, the most common primary sites were the pelvis and spine. These findings were consistent with that reported by other investigators one of which is Mehmet *et al.* who reported localized disease in 81% and metastatic disease in 19% of patients at the time of diagnosis. Most of cases were at extremities or thorax (31% each) [12] [14] [15].

There were many risk factors widely investigated like age, sex, LDH, size, and presence or absence of metastasis. Most of results of these studies were not ho-

mogenous and conflicting [1] [16] [17].

In our study there was no effect of age at diagnosis (<30 and ≥30), tumor size (< 8 cm and ≥ 8 cm), and high LDH level (<280 and ≥280) on PFS, P (0.078, 0.925, and 0.25 respectively) or OS, P (0.084, 0.973, and 0.89 respectively). The only risk factor in our study that translated to significant PFS and OS difference was presence of metastasis (P = 0.002, 0.001) respectively. This is consistent with the evidence-based prognostic factor accepted by all authors [6] [18] [19].

The effect of adequate surgical resection was also a determinant factor of good prognosis in our series. This observation was similar to that reported by Balamuth and Womer, 2010 [15].

Many studies like Mehmet *et al.*, showed that patients with localized disease and younger than 30 years have better DFS and OS. This difference has not been seen in metastatic patients. Baldini *et al.* reported that patients older than 26 years have a worse survival rate [20]. Similar data were reported by Grier *et al.* [17]. In contrast some studies did not observe the effect of age on outcome [19] [21]. These controversies may be attributed to the retrospective nature of available data; better designed studies are needed to ensure the result.

Currently, many centers use different treatment schedules, but generally they have agreement that treatment of adult ES needs to be aggressive including local modalities and intensive systemic chemotherapy. In our series we used EURO-EWING protocol. Daniz T. *et al.* used vincristine, doxorubicin, cyclophosphamide and actinomycin-D (VACA) alternating with ifosfamide, etoposide (IE). Cycles were administered every 3 weeks to complete a total of 52 weeks, while Grier *et al.* used doxorubicin, vincristine, cyclophosphamide and dactinomycin [17] [22]. These multimodality forms of treatment have much better survival than single modality either surgery, radiotherapy or chemotherapy [21] [23].

The 5-year survival have shown marked improvement from 36% to 56% in periods from 1975 to1984 and 1985 to 1994 [24]. This benefit is clear in non-metastatic patients who received doxorubicin, vincristine, cyclophosphamide and dactinomycin. Patients who received these four drugs alternating with courses of ifosfamide and etoposide (IE), had better 5-year survival (72% vs 61%, P = 0.01] [22]. In our series we reported close 5 years survival of 46% in metastatic and non-metastatic patients. Deniz *et al.* reported a 5-year survival of 64.5% in patient with localized disease [22]. Similarly Smith etal reported 5-year survival of 60% [24]. The 5 year EFS was 59.7% and 52% in Deniz *et al.* and Safia *et al.* respectively [22] [25] values which are close to what we reported in our study.

6. Conclusion

In this series metastases at presentation and wide surgical margins were the most important prognostic factors. Multimodality therapy is necessary for this rare disease.

Conflict of Interest

The author(s) declare(s) that there is no conflict of interest regarding the publi-

cation of this paper."

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