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ORGINAL ARICLE

Ewing Sarcoma outcome of 60 cases: Single institution experience

***MW Hegazy*[1, 2], *M Rizwanullah*[1] ,*Nabila Hefzi*[2]**

1Department of Radiation Oncology, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia
2 Department of Clinical Oncology & Nuclear Medicine, Zagazig College of Medicine, Egypt

Corresponding Author:
Nabila Hefzi
Associate Professor
Clinical Oncology & Nuclear Medicine, Zagazig College of Medicine, Egypt

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ABSTRACT

Background: Ewing sarcoma (ES) is most common in adolescents and young adults with tendency to affect any bone especially pelvic, femur and chest wall bones. Multimodality approach (multiagent chemotherapy, surgery and/or radiotherapy) is the standard of care in treating localized ES.**Purpose of this study:** was to present our institution experience in ES treatment and evaluate the clinical outcome including survival and prognostic factors.

Patients and methods: This was a retrospective study including 60 patients with primary Ewing Sarcoma (ES) treated at radiation Oncology section – King Faisal Specialist Hospital and Research Centre (KFSH & RC) – Riyadh, Saudi Arabia between Jan 2005 and April 2018.**Results:** At diagnosis, median age was 20 (range 14-70) years, thirty five(58.3%) patients were male. Forty one (68.3%) patients had localized disease; extremities were commonest primary site in 29(48.4%) patients. Surgery performed in35 (58.3%) patients and 51(85%) patients received radiation therapy (RT). Median follow-up was 31 months (8-160). Forty four patients had disease progression. Site of first failure was local for ten patients, local and distant failure for ten patients, and distant for Twenty four patients. Five year LRFS, DMFS, PFS,andOS were 69.8%, 35.8% ,26.7% and 60.7% respectively.

Conclusion: The best outcome of ES can be achieved through multidisciplinary team where the upfront step and whole treatment plan are properly selected. Multiple lines of chemotherapy, recent advances of irradiation and surgery of oligometastatic sites may play a role in improving the treatment outcome.

Key Word: Ewing sarcoma, Treatment, Prognostic factors

INTRODUCTION

Ewing sarcoma (ES) is a bone cancer that commonly affects adolescents and young adults, with a proclivity to affect any bone, particularly the pelvic, femur, and chest wall bones [1]. The diaphysis is a common location for long bone inclusion. The lungs and bone are the most common sites of metastasis. [2,3]. It is a highly aggressive tumor with suspected distant micrometastases, and all patients require multiagent chemotherapy to control the potential systemic disease [4]. In the treatment of localized ES, a multimodality approach (systemic chemotherapy, local treatment, surgery, and/or radiotherapy) is the standard of care [5-10].

With advances in chemotherapy regimens, the five-year overall survival of localized disease reached up to 83% [9], compared to 20-40% for metastatic disease [1,3,6,7].

The purpose of this retrospective study was to present our institution's experience with ES treatment and to evaluate clinical outcomes such as survival and prognostic factors.

PATIENTS AND METHODS

A database of 60ES patients referred to the radiation Oncology section of King Faisal Specialist Hospital and Research Centre (KFSH & RC) in Riyadh, Saudi Arabia between January 2005 and April 2018 was reviewed. This retrospective study was approved by the institution's research ethics committee. The described work was done in accordance with the World Medical Association's Code of Ethics (Declaration of Helsinki) for human experimentation.

Cohort selection

On initial staging and serial follow-up visits, all patients had biopsy-proven ES, local MRI and/or CT scans, and a whole-body PET/CT scan or bone scan.

Chemotherapy regimens

Vincristine, Doxorubicin, Dactinomycin, and If osfamide were the first-line drugs (VAID).

Etoposide, Cisplatin, and Ifosfamide comprised the second line. Irinotecan and Temozolomide were the third line of treatment.

Radiotherapy technique

In the case of the radical course, a dose of 55.8Gy was administered in 31 fractions, whereas the adjuvant course received a dose of 45-50.4Gy in 25-28 fractions. 3D-CRT, IMRT, VMAT, and Helical Tomotherapy were the techniques used. The same protocols were used for irradiating solitary or oligo-metastasis as for primary site irradiation. 15Gy was delivered in ten fractions during whole-lung irradiation. Palliative regimens ranging from 30 Gy in 10 fractions to 20 Gy in 5 fractions to 8 Gy in a single fraction were used.

STATISTICAL ANALYSIS

Continuous variables were expressed as the mean ± SD & median (range), and the categorical variables were expressed as a number(percentage). Percent of categorical variables were compared using Pearson's Chi-square test or Fisher's exact test when was appropriate. Recurrence Free Survival (RFS) was calculated as the time from date of surgery to date of recurrence or the most recent follow-up contact that patient was known as recurrence free. Distant Metastasis Free Survival (DMFS) was calculated as the time from date of diagnosis to date of distant metastasis or the most recent follow-up contact that patient was known as distant metastasis free. Progression Free Survival (PFS) was calculated as the time from date of start of treatment to date of progression or the most recent follow-up contact that patient was known as progression free. Overall Survival (OS) was calculated as the time from date of diagnosis to date of death or the most recent follow-up contact. These time-to-event distributions were estimated using the method of Kaplan-Meier plot, and compared using two-sided exact log-rank test. All tests were two sided. A p-value <0.05 was considered significant. All statistics were performed using SPSS 22.0 for windows (IBM Inc., Chicago, IL, USA) and MedCalc 13 for windows (MedCalc Software bvba, Ostend, Belgium).

RESULTS

Thirty-five (58.3%) of the sixty patients treated and followed up at (KFSH & RC) were males. The median age was 20 years (range 14-70 years), and 33 (55%) of the patients were over the age of 18. Out of nineteen patients with distant metastasis at diagnosis, nine (45%) had lung metastasis, and six (30%) had bone metastasis, 41 (68.3%) had localized disease. The extremities were the most common primary site in 29 (38.4%) of patients, followed by the pelvis in 13 (21.7%).Surgery was performed on 35 patients (58.3%), thirteen of whom were operated on immediately and the remaining after induction chemotherapy. Fifty-one patients (85%) received radiation therapy (RT), with thirty-four (66.7%) receiving radical doses, fifteen (29.4%) receiving adjuvant RT, and only two receiving preoperative RT. On describing chemotherapy regimens given for 59 cases, you described treatment of only 56, so, what was given the the other 3 patients.l. The median duration of follow-up was 31 (8-160) months. One patient (2%) had a complete response CR, twenty-one patients had a partial response PR, and 29 patients (56.9%) had stable disease. Local recurrence occurred in ten of the 35 patients who underwent surgery.Out of 41 patients with localised disease at diagnosis, 24 (58.5%) developed distant metastasis. The disease progressed in 44 patients. The location of the first failure was local for ten people, local and distant for ten people, and distant for twenty-four people. Distant metastasis was found to be significantly related to chemotherapy timing and regimen (P values 0.023 and 0.001, respectively). Table 4. Progression was significantly correlated with stage at presentation as well as chemotherapy regimen (P value 0.001), while total RT dose and incidence of local failure were significantly correlated with treatment progression (P value 0.001). (P value 0.034).Progression was strongly associated with the presence of distant metastasis (P value 0.001), according to Table5. The average LRFS was 93.09 (74.85-111.33) months. The two-year, five-year, and ten-year LRFS were all 69.8%. Sex, stage at diagnosis, primary site, lung metastasis at any time, chemotherapy, RT, lung RT, response to treatment did not have a significant effect on LRFS, whereas age 18 years, upfront surgery, and total dose of RT did (P value 0.043,0.049,0.034 respectively) Table 6 and Figure A. The mean DMFS was 56.85 months (40.14-73.58), with 2-year, 5-year, and 10-year DMFS of 52.1%, 35.8%, and 35.8%, respectively. Age, gender, primary site, chemotherapy (use and timing), RT (timing dose), and treatment response had no significant effect on DMFS. However, lung metastasis at any time, chemotherapy regimen 1, use of RT, lung irradiation, and the absence of local failure all have a significant effect on DMFS (P values of 0.009,0.001,0.04,0.007,0.001, and 0.001 respectively). Table 7&figure 1 B. PFS (95% CI) 54.79 (40.41-69.17) months, age, sex, primary site, metastasis site, surgery, CT (use, timing), treatment response did not have a significant effect on PFS. While in the localized stage, lung metastasis at any time, chemotherapy regimen1,

use of RT, RT timing, RT dose to PTV1,2, total RT dose,lung irradiation, local recurrence, and distant metastasis were all associated with a significant effect on PFS (P value 0.001, 0.004, 0.001, 0.001, 0.001, 0.001, 0.001, 0.001, 0.001, 0.001, 0.001, 0.00). Table 8 & fig.1C shows that the 2-year, 5-year, and 10-year PFS were 55%, 26.7%, and 23.4%, respectively.As regard overall survival (95%CI) 107.77 (87.21 – 128.34)months, 2-years OS: 78.8%,5-years OS: 60.7% and10-years OS: 60.7%,Fig.1 D.

Table (1): Basic characteristics and outcome of 60 patients with Ewing's Sarcoma.

Parameters	All patients (N=60)		Parameters	All patients (N=60)	
	No.	%		No.	%
Sex			Radiotherapy		
Male	35	58.3%	No	9	15%
Female	25	41.7%	Yes	51	85%
Age (years)			RT timing	(N=51)	
Mean ± SD	23.83 ± 12.04		Radical	34	66.7%
Median (Range)	20 (14 – 70)		Preoperative	2	3.9%
≤18 years	27	45%	Adjuvant	15	29.4%
>18 years	33	55%	RT dose to PTV1	(N=51)	
Stage			40 Gy	3	5.9%
Localized	41	68.3%	45 Gy	10	19.6%
Metastatic	19	31.7%	50 Gy	13	25.5%
Primary			54 Gy	7	13.7%
Skull	4	6.7%	56 Gy	18	35.3%
Chest wall	6	10%	RT dose to PTV2	(N=6)	
Upper extremity	10	16.7%	No	1	16.7%
Spine	8	13.3%	Yes	5	83.3%
Pelvis	13	21.7%	Total RT dose	(N=51)	
Lower extremity	19	31.7%	40 Gy	3	5.9%
Site of metastasis	(N=20)		45 Gy	10	19.6%
Bone	6	30%	50 Gy	7	13.7%
Lung	9	45%	54 Gy	7	13.7%
Lymph node	2	10%	56 Gy	18	35.3%
Multiple sites	3	15%	66 Gy	1	2%
Lung DM at any time			58 Gy	5	9.8%
No	25	41.7%	Lung XRT	(N=35)	
Yes	35	58.3%	No	18	51.4%
Surgery			Yes	17	48.6%
No	25	41.7%	Response	(N=51)	
Yes	35	58.3%	CR	1	2%
Surgery timing	(N=35)		PR	21	41.2%
Upfront	13	37.1%	SD	29	56.9%
Postchemotherapy	22	62.9%	FU duration (months)		
Chemotherapy			Mean ± SD	42.98±36.67	
No	1	1.7%	Median (Range)	31 (8-160)	
Yes	59	98.3%	Local recurrence	(N=35)	
Chemotherapy timing	(N=59)		Absent	25	71.4%
Pre-operative/RT	20	33.9%	Present	10	28.6%
Post-operative/RT	4	6.8%	Distant metastasis	(N=41)	
Peri-operative/RT	35	59.3%	Absent	17	41.5%
Chemotherapy regimen	(N=59)		Present	24	58.5%
Regimen 1	21	35.6%	Progression		
Regimen 2	33	55.9%	Absent	16	26.7%
Regimen 3	5	8.5%	Present	44	73.3%

Continuous variables were expressed as mean±SD and median (range); categorical variables were expressed as number (percentage).

Table (2): Relationship between clinicopathological parameters/treatment and response to treatment among the studied patients (N=51).

Parameters	All patients (N=51)		Response						p-value[a]
			CR (N=1)		PR (N=21)		SD (N=29)		
	No.	%	No.	%	No.	%	No.	%	
Age									
≤18 years	20	39.2%	0	0%	10	50%	10	50%	0.463
>18 years	31	60.8%	1	3.2%	11	35.5%	19	61.3%	
Sex									
Male	30	58.8%	0	0%	12	40%	18	60%	0.454
Female	21	41.2%	1	4.8%	9	42.9%	11	52.4%	
Stage									
Localized	37	72.5%	1	2.7%	16	43.2%	20	54.1%	0.703
Metastatic	14	27.5%	0	0%	5	35.7%	9	64.3%	
Primary									
Skull	4	7.8%	0	0%	0	0%	4	100%	0.179
Chest wall	5	9.8%	0	0%	1	20%	4	80%	
Upper extremity	7	13.7%	0	0%	2	28.6%	5	71.4%	
Spine	8	15.7%	0	0%	2	25%	6	75%	
Pelvis	13	25.5%	1	7.7%	9	69.2%	3	23.1%	
Lower extremity	14	27.5%	0	0%	7	50%	7	50%	
Site of metastatsis	(N=15)		(N=0)		(N=5)		(N=10)		
Bone	5	33.3%	0	0%	2	40%	3	60%	0.596
Lung	7	46.7%	0	0%	3	42.9%	4	57.1%	
Lymph node	2	13.3%	0	0%	0	0%	2	100%	
Multiple sites	1	6.7%	0	0%	0	0%	1	100%	
Lung metastatsis									
No	25	49%	1	4%	10	40%	14	56%	0.588
Yes	26	51%	0	0%	11	42.3%	15	57.7%	
Surgery									
No	23	45.1%	1	4.3%	10	43.5%	12	52.2%	0.488
Yes	28	54.9%	0	0%	11	39.3%	17	60.7%	
Surgery timing	(N=28)		(N=0)		(N=11)		(N=17)		
Upfront	13	46.4%	0	0%	3	23.1%	10	76.9%	0.102
Post-chemotherapy	15	53.6%	0	0%	8	53.3%	7	46.7%	
Chemotherapy									
No	1	2%	0	0%	1	100%	0	0%	0.483
Yes	50	98%	1	2%	20	40%	29	58%	
Chemotherapy timing	(N=50)		(N=1)		(N=20)		(N=29)		
Pre-operative/RT	18	36%	1	5.6%	10	55.6%	7	38.9%	0.129
Post-operative/RT	4	8%	0	0%	0	0%	4	100%	
Peri-operative/RT	28	56%	0	0%	10	35.7%	18	64.3%	

Parameters	All patients (N=51)		Response						p-value[a]
			CR (N=1)		PR (N=21)		SD (N=29)		
	No.	%	No.	%	No.	%	No.	%	
Chemotherapy regimen	(N=50)		(N=1)		(N=20)		(N=29)		
Regimen 1	19	38%	1	5.3%	7	36.8%	11	57.9%	0.788
Regimen 2	26	52%	0	0%	11	42.3%	15	57.7%	
Regimen 3	5	10%	0	0%	2	40%	3	60%	
Radiotherapy timing									
Radical	34	66.7%	1	2.9%	18	52.9%	15	44.1%	0.129
Preoperative	2	3.9%	0	0%	0	0%	2	100%	
Adjuvant	15	29.4%	0	0%	3	20%	12	80%	
Parameters	All patients (N=51)		Response						p-value[a]
			CR (N=1)		PR (N=21)		SD (N=29)		
	No.	%	No.	%	No.	%	No.	%	
RT dose to PTV1									
40 Gy	3	5.9%	0	0%	1	33.3%	2	66.7%	0.409
45 Gy	10	19.6%	0	0%	1	10%	9	90%	
50 Gy	13	25.5%	0	0%	6	46.2%	7	53.8%	
54 Gy	7	13.7%	0	0%	3	42.9%	4	57.1%	
56 Gy	18	35.3%	1	5.6%	10	55.6%	7	38.9%	
RT dose to PTV2	(N=6)		(N=0)		(N=5)		(N=1)		
16 Gy	1	16.7%	0	0%	0	0%	1	100%	0.167
18 Gy	5	83.3%	0	0%	5	100%	0	0%	
Total RT dose									
40 Gy	3	5.9%	0	0%	1	33.3%	2	66.7%	0.110
45 Gy	10	19.6%	0	0%	1	10%	9	90%	
50 Gy	7	13.7%	0	0%	1	14.3%	6	85.7%	
54 Gy	7	13.7%	0	0%	3	42.9%	4	57.1%	
56 Gy	18	35.3%	1	5.6%	10	55.6%	7	38.9%	
66 Gy	1	2%	0	0%	0	0%	1	100%	
68 Gy	5	9.8%	0	0%	5	100%	0	0%	
Lung XRT	(N=26)		(N=0)		(N=11)		(N=15)		
No	12	46.2%	0	0%	3	25%	9	75%	0.130
Yes	14	53.8%	0	0%	8	57.1%	6	42.9%	

Categorical variables were expressed as number (percentage); a: Chi-square test;p-value<0.05 is significant.

Table (3): Relationship between clinicopathological parameters/treatment and local recurrence among the studied patients (N=35).

Parameters	All patients (N=35)		Local recurrence				p-value[a]
			Absent (N=25)		Present (N=10)		
	No.	%	No.	%	No.	%	
Age							
≤18 years	12	34.3%	11	91.7%	1	8.3%	0.113
>18 years	23	65.7%	14	60.9%	9	39.1%	
Sex							
Male	20	57.1%	14	70%	6	30%	1.000
Female	15	42.9%	11	73.3%	4	26.7%	
Stage							
Localized	28	80%	22	78.6%	6	21.4%	0.155

Parameters	All patients (N=35)		Local recurrence				p-value[a]
			Absent (N=25)		Present (N=10)		
	No.	%	No.	%	No.	%	
Metastatic	7	20%	3	42.9%	4	57.1%	
Primary							
Chest wall	6	17.1%	4	66.7%	2	33.3%	0.719
Upper extremity	8	22.9%	5	62.5%	3	37.5%	
Spine	5	14.3%	3	60%	2	40%	
Pelvis	3	8.6%	3	100%	0	0%	
Lower extremity	13	37.1%	10	76.9%	3	23.1%	
Site of metastatsis	(N=8)		(N=3)		(N=5)		
Bone	4	50%	1	25%	3	75%	0.376
Lung	3	37.5%	2	66.7%	1	33.3%	
Multiple sites	1	12.5%	0	0%	1	100%	
Lung metastatsis							
No	11	31.4%	9	81.8%	2	18.2%	0.447
Yes	24	68.6%	16	66.7%	8	33.3%	
Surgery timing							
Upfront	13	37.1%	12	92.3%	1	7.7%	0.055
Post-chemotherapy	22	62.9%	13	59.1%	9	40.9%	
Chemotherapy							
No	1	2.9%	1	100%	0	0%	1.000
Yes	34	97.1%	24	70.6%	10	29.4%	
Chemotherapy timing							
Pre-operative/RT	7	20.6%	5	71.4%	2	28.6%	0.987
Post-operative/RT	3	8.8%	2	66.7%	1	33.3%	
Peri-operative/RT	24	70.6%	17	70.8%	7	29.2%	
Chemotherapy regimen							
Regimen 1	8	23.5%	7	87.5%	1	12.5%	0.082
Regimen 2	21	61.8%	12	57.1%	9	42.9%	
Regimen 3	5	14.7%	5	100%	0	0%	
Radiotherapy							
No	7	20%	5	71.4%	2	28.6%	1.000
Yes	28	80%	20	71.4%	8	28.6%	
Radiotherapy timing	(N=28)		(N=20)		(N=8)		
Radical	13		8	61.5%	5	38.5%	0.410
Adjuvant	15		12	80%	3	20%	
Parameters	All patients		Local recurrence				p-value[a]
			Absent		Present		
	No.	%	No.	%	No.	%	
RT dose to PTV1	(N=28)		(N=20)		(N=8)		
40 Gy	1	3.6%	1	100%	0	0%	0.446
45 Gy	7	25%	5	71.4%	2	28.6%	
50 Gy	11	39.3%	6	54.5%	5	45.5%	
54 Gy	5	17.9%	4	80%	1	20%	
56 Gy	4	14.3%	4	100%	0	0%	
Total RT dose	(N=28)		(N=20)		(N=8)		
40 Gy	1	3.6%	1	100%	0	0%	0.106
45 Gy	7	25%	5	71.4%	2	28.6%	
50 Gy	6	21.4%	5	83.3%	1	16.7%	
54 Gy	5	17.9%	4	80%	1	20%	

Parameters	All patients (N=35)		Local recurrence				p-value[a]
			Absent (N=25)		Present (N=10)		
	No.	%	No.	%	No.	%	
56 Gy	4	14.3%	4	100%	0	0%	
68 Gy	5	17.9%	1	20%	4	80%	
Lung XRT	(N=24)		(N=16)		(N=8)		
No	10	41.7%	6	60%	4	40%	0.673
Yes	14	58.3%	10	71.4%	4	28.6%	
Response	(N=28)		(N=20)		(N=8)		
PR	11	39.3%	7	63.6%	4	36.4%	0.671
SD	17	60.7%	13	76.5%	4	23.5%	

Categorical variables were expressed as number (percentage); a: Chi-square test;p-value<0.05 is significant.

Table (4): Relationship between clinicopathological parameters/treatment and distant metastasis among the studied patients (N=35).

Parameters	All patients (N=41)		Distant metastasis				p-value[a]
			Absent (N=17)		Present (N=24)		
	No.	%	No.	%	No.	%	
Age							
≤18 years	16	39%	9	56.2%	7	43.8%	0.195
>18 years	25	61%	8	32%	17	68%	
Sex							
Male	22	53.7%	10	45.5%	12	54.5%	0.577
Female	19	46.3%	7	36.8%	12	63.2%	
Primary							
Skull	4	9.8%	1	25%	3	75%	0.467
Chest wall	4	9.8%	2	50%	2	50%	
Upper extremity	5	12.2%	1	20%	4	80%	
Spine	6	14.6%	1	16.7%	5	83.3%	
Pelvis	9	22%	5	55.6%	4	44.4%	
Lower extremity	13	31.7%	7	53.8%	6	46.2%	
Surgery							
No	13	31.7%	7	53.8%	6	46.2%	0.273
Yes	28	68.3%	10	35.7%	18	64.3%	
Surgery timing	(N=28)		(N=10)		(N=18)		
Upfront	13	46.4%	6	46.2%	7	53.8%	0.433
Post-chemotherapy	15	53.6%	4	26.7%	11	73.3%	
Chemotherapy							
No	1	2.4%	0	0%	1	100%	1.000
Yes	40	97.6%	17	42.5%	23	57.5%	
Chemotherapy timing	(N=40)		(N=17)		(N=23)		
Pre-operative/RT	13	32.5%	9	69.2%	4	30.8%	**0.023**
Post-operative/RT	3	7.5%	2	66.7%	1	33.3%	
Peri-operative/RT	24	60%	6	25%	18	75%	
Chemotherapy regimen	(N=40)		(N=17)		(N=23)		
Regimen 1	15	37.5%	10	66.7%	5	33.3%	**<0.001**
Regimen 2	21	52.5%	3	14.3%	18	85.7%	
Regimen 3	4	10%	4	100%	0	0%	
Radiotherapy							
No	4	9.8%	0	0%	4	100%	0.128

Parameters	All patients (N=41)		Distant metastasis				p-value[a]
			Absent (N=17)		Present (N=24)		
	No.	%	No.	%	No.	%	
Yes	37	90.2%	17	45.9%	20	54.1%	
Radiotherapy timing							
Radical	22	59.5%	10	45.5%	12	54.5%	0.942
Adjuvant	15	40.5%	7	46.7%	8	53.3%	
RT dose to PTV1	(N=37)		(N=17)		(N=20)		
40 Gy	2	5.4%	0	0%	2	100%	0.107
45 Gy	6	16.2%	1	16.7%	5	83.3%	
50 Gy	10	27%	4	40%	6	60%	
54 Gy	6	16.2%	5	83.3%	1	16.7%	
56 Gy	13	35.1%	7	53.8%	6	46.2%	
Total RT dose	(N=37)		(N=17)		(N=20)		
40 Gy	2	5.4%	0	0%	2	100%	0.064
45 Gy	6	16.2%	1	16.7%	5	83.3%	
50 Gy	6	16.2%	4	66.7%	2	33.3%	
54 Gy	6	16.2%	5	83.3%	1	16.7%	
56 Gy	13	35.1%	7	53.8%	6	46.2%	
66 Gy	1	2.7%	0	0%	1	100%	
68 Gy	3	8.1%	0	0%	3	100%	
Lung XRT	(N=18)		(N=3)		(N=5)		
No	8	44.4%	0	0%	8	100%	0.216
Yes	10	55.6%	3	30%	7	70%	
Response	(N=37)		(N=17)		(N=20)		
CR	1	2.7%	1	100%	0	0%	0.457
PR	16	43.2%	8	50%	8	50%	
SD	20	54.1%	8	40%	12	60%	
Local recurrence	(N=28)		(N=10)		(N=18)		
No	22	78.6%	10	45.5%	12	54.5%	0.062
Yes	6	21.4%	0	0%	6	100%	

Categorical variables were expressed as number (percentage); a: Chi-square test;p-value<0.05 is significant.

Table (5): Relationship between clinicopathological parameters/treatment and progression among the studied patients (N=60).

Parameters	All patients (N=60)		Progression				p-value[a]
			Absent (N=16)		Present (N=44)		
	No.	%	No.	%	No.	%	
Age							
≤18 years	27	45%	8	29.6%	19	70.4%	0.771
>18 years	33	55%	8	24.2%	25	75.8%	
Sex							
Male	35	58.3%	10	28.6%	25	71.4%	0.693
Female	25	41.7%	6	24%	19	76%	
Stage							
Localized	41	68.3%	16	39%	25	61%	**0.001**
Metastatsic	19	31.7%	0	0%	19	100%	
Primary							
Skull	4	6.7%	0	0%	4	100%	0.330

Parameters	All patients (N=60)		Progression				p-value[a]
			Absent (N=16)		Present (N=44)		
	No.	%	No.	%	No.	%	
Chest wall	6	10%	2	33.3%	4	66.7%	
Upper extremity	10	16.7%	1	10%	9	90%	
Spine	8	13.3%	1	12.5%	7	87.5%	
Pelvis	13	21.7%	5	38.5%	8	61.5%	
Lower extremity	19	31.7%	7	36.8%	12	63.2%	
Lung DM at any time							
No	25	41.7%	13	52%	12	48%	**<0.001**
Yes	35	58.3%	3	8.6%	32	91	
Surgery							
No	25	41.7%	6	24%	19	76%	0.693
Yes	35	58.3%	10	28.6%	25	71.4%	
Surgery timing							
Upfront	13	37.1%	6	46.2%	7	53.8%	0.123
Post-chemotherapy	22	62.9%	4	18.2%	18	81.8%	
Chemotherapy							
No	1	1.7%	0	0%	1	100%	1.000
Yes	59	98.3%	16	27.1%	43	72.9%	
Chemotherapy timing	(N=59)		(N=16)		(N=43)		
Pre-operative/RT	20	33.9%	8	40%	12	60%	0.105
Post-operative/RT	4	6.8%	2	50%	2	50%	
Peri-operative/RT	35	59.3%	6	17.1%	29	82.9%	
Chemotherapy regimen	(N=59)		(N=16)		(N=43)		
Regimen 1	21	35.6%	9	42.9%	12	57.1%	**0.001**
Regimen 2	33	55.9%	3	9.1%	30	90.9%	
Regimen 3	5	8.5%	4	80%	1	20%	
Radiotherapy							
No	9	15%	0	0%	9	100%	0.096
Yes	51	85%	16	31.4%	35	68.6%	
Radiotherapy timing							
Radical	34	66.7%	9	26.5%	25	73.5%	0.232
Preoperative	2	3.9%	0	0%	2	100%	
Adjuvant	15	29.4%	7	46.7%	8	53.3%	

Table (5): Continue

Parameters	All patients (N=60)		Progression				p-value[a]
			Absent (N=16)		Present (N=44)		
	No.	%	No.	%	No.	%	
RT dose to PTV1	(N=51)		(N=16)		(N=35)		
40 Gy	3	5.9%	0	0%	3	100%	0.068
45 Gy	10	19.6%	1	10%	9	90%	
50 Gy	13	25.5%	4	30.8%	9	69.2%	
54 Gy	7	13.7%	5	71.4%	2	28.6%	
56 Gy	18	35.3%	6	33.3%	12	66.7%	
Total RT dose	(N=51)		(N=16)		(N=35)		
40 Gy	3	5.9%	0	0%	3	100%	**0.034**
45 Gy	10	19.6%	1	10%	9	90%	
50 Gy	7	13.7%	4	57.1%	3	42.9%	

Parameters	All patients (N=60)		Progression				p-value[a]
			Absent (N=16)		Present (N=44)		
	No.	%	No.	%	No.	%	
54 Gy	7	13.7%	5	71.4%	2	28.6%	
56 Gy	18	35.3%	6	33.3%	12	66.7%	
66 Gy	1	2%	0	0%	1	100%	
68 Gy	5	9.8%	0	0%	5	100%	
Lung XRT	(N=35)		(N=3)		(N=32)		
No	18	51.4%	0	0%	18	100%	0.104
Yes	17	48.6%	3	17.6%	14	82.4%	
Response							
CR	1	2%	1	100%	0	0%	0.189
PR	21	41.2%	8	38.1%	13	61.9%	
SD	29	56.9%	7	24.1%	22	75.9%	
Local recurrence	(N=35)		(N=10)		(N=25)		
No	25	71.4%	10	40%	15	60%	**0.034**
Yes	10	28.6%	0	0%	10	100%	
Distant metastasis	(N=41)		(N=16)		(N=25)		
No	17	41.5%	16	94.1%	1	5.9%	**<0.001**
Yes	24	58.5%	0	0%	24	100%	

Categorical variables were expressed as number (percentage); a: Chi-square test;p-value<0.05 is significant.

Table (6): Local Recurrence Free Survival.

	N	Local Recurrence Free Survival (LRFS)						p-value[b]
		Mean	(months)	(95%CI)	2-years	5-years	10-years	
All patients	35	93.09	months	(74.85 – 111.33)	69.8%	69.8%	69.8%	-------
Age group								
≤18 years	12	118.09	months	(99.57 – 136.06)	90.9%	90.9%	90.9%	**0.043**
>18 years	23	63.22	months	(44.53 – 81.90)	58.4%	58.4%	------	
Sex								
Male	20	91.84	months	(67.73 – 115.95)	68.6%	68.6%	68.6%	0.940
Female	15	83.80	months	(60.17 – 107.43)	72%	72%	------	
Stage								
Localized	28	102.29	months	(84.06 – 120.52)	78%	78%	78%	0.080
Metastatic	7	19.92	months	(13.33 – 26.52)	35.7%	------	------	
Primary								
Chest wall	6	75.95	months	(35.89 – 116.02)	62.5%	62.5%	-----	0.713
Upper extremity	8	39.43	months	(21.45 – 57.42)	56.3%	56.3%	-----	
Spine	5	24.40	months	(15.13 – 33.67)	60%	-----	-----	
Pelvis	3	78	months		100%	-----	-----	
Lower extremity	13	100.76	months	(73.71 – 127.82)	76.9%	76.9%	76.9%	
Site of metastasis								
Bone	4	11.75	months	(8.25 – 15.24)	-----	-----	-----	0.098
Lung	3	26.33	months	(20.46 – 32.20)	66.7%	-----	-----	
Multiple sites	1	19	months		0%	0%	0%	
Lung DM at any time								
No	11	106.72	months	(80.05 – 133.39)	81.8%	81.8%	81.8%	0.378
Yes	24	76.55	months	(56.65 – 96.45)	64.3%	64.3%	64.3%	
Surgery timing								
Upfront	13	119.15	months	(102.49 – 135.81)	92.3%	92.3%	92.3%	**0.049**
Post-chemotherapy	22	54.74	months	(39.08 – 70.40)	57.7%	57.7%	-----	

	N	Local Recurrence Free Survival (LRFS)						p-value[b]
		Mean	(months)	(95%CI)	2-years	5-years	10-years	
Chemotherapy								
No	1	27	months		100%	-----	-----	0.543
Yes	34	91.98	months	(73.28 – 110.68)	68.9%	68.9%	68.9%	
Chemotherapy timing								
Pre-operative/RT	7	93.85	months	(53.86 – 133.85)	71.4%	71.4%	71.4%	0.996
Post-operative/RT	3	65.66	months	(23.52 – 107.80)	66.7%	66.7%	-----	
Peri-operative/RT	24	80.40	months	(60.88 – 99.93)	68%	68%	-----	
Chemotherapy regimen								
Regimen 1	8	113.62	months	(87.27 – 139.98)	87.5%	87.5%	87.5%	0.074
Regimen 2	21	23.26	months	(18.44 – 28.07)	52.4%	-----	-----	
Regimen 3	5	112	months		100%	100%	-----	
Radiotherapy								
No	7	41.14	months	(30.76 – 51.51)	71.4%	-----	-----	0.739
Yes	28	93.69	months	(73.60 – 113.78)	70.8%	70.8%	70.8%	
RT timing								
Radical	13	51.61	months	(33.42 – 69.80)	61.5%	61.5%	-----	0.258
Adjuvant	15	104.73	months	(81.18 – 128.28)	80%	80%	80%	
RT dose to PTV1								
40 Gy	1	22	months		100%	-----	-----	0.504
45 Gy	7	46	months	(29.59 – 62.40)	71.4%	71.4%	-----	
50 Gy	11	74.54	months	(39.90 – 109.19)	54.5%	54.5%	54.5%	
54 Gy	5	70.40	months	(43.05 – 97.74)	80%	80%	-----	
56 Gy	4	78	months		100%	-----	-----	
	N	Local Recurrence Free Survival (LRFS)						p-value[b]
		Mean	(month)	(95%CI)	2-years	5-years	10-years	
Total RT dose								
40 Gy	1	22	months		100%	-----	-----	**0.034**
45 Gy	7	46	months	(29.59 – 62.40)	71.4%	71.4%	-----	
50 Gy	6	108.83	months	(74.54 – 143.12)	83.3%	83.3%	83.3%	
54 Gy	5	70.40	months	(43.05 – 97.74)	80%	80%	-----	
56 Gy	4	78	months		100%	-----	-----	
68 Gy	5	13.20	months	(6.22 – 20.17)	20%	-----	-----	
Lung XRT								
No	10	33.80	months	(21.47 – 46.12)	60%	-----	-----	0.361
Yes	14	82.61	months	(58.50 – 106.72)	69.6%	69.6%	-----	
Response								
PR	11	52.39	months	(32.43 – 72.35)	62.3%	62.3%	-----	0.428
SD	17	100.41	months	(76.76 – 124.05)	76.5%	76.5%	76.5%	

95%CI: 95%Confidence Interval;b:Log-rank test; p-value<0.05 is significant.

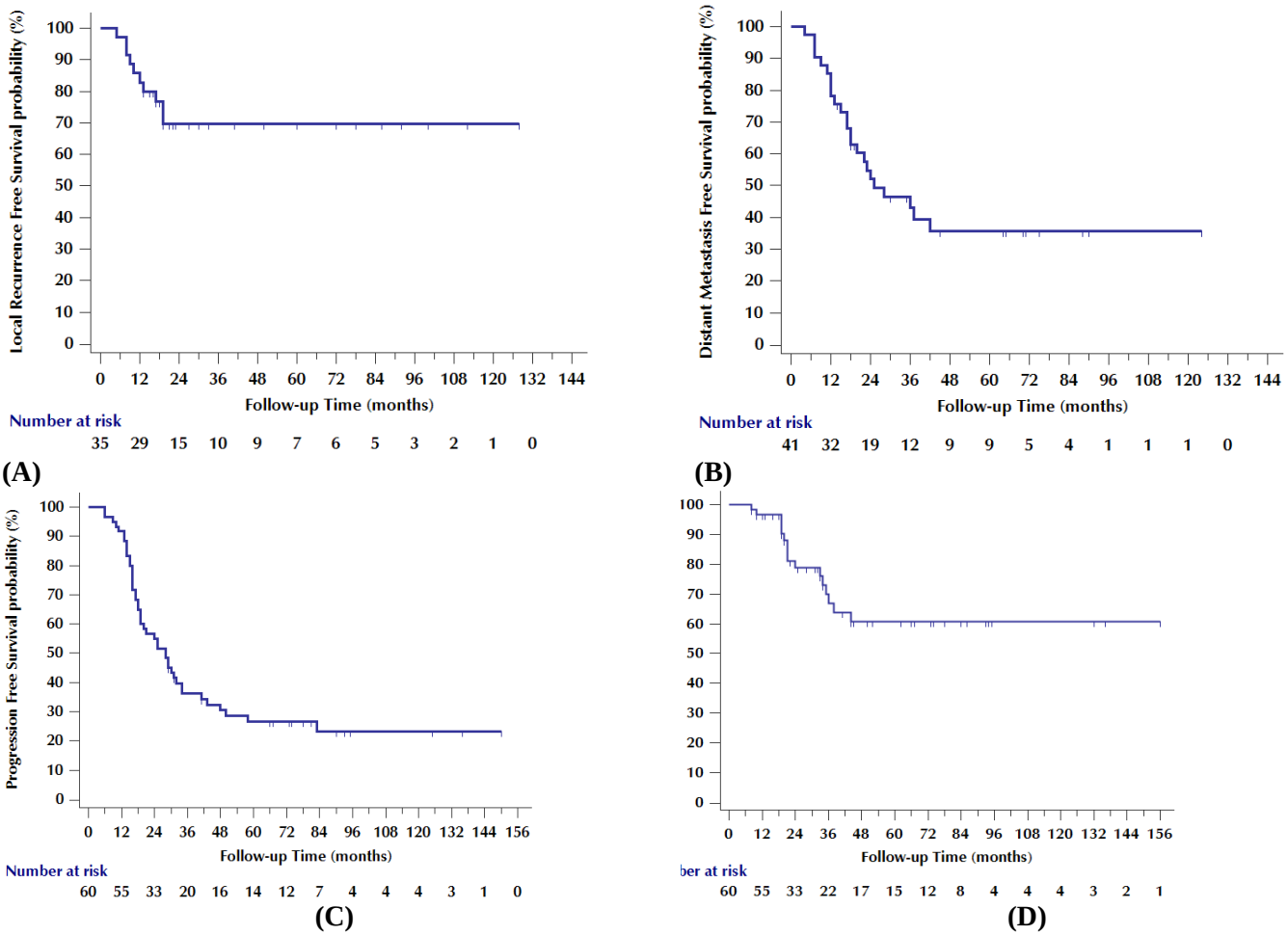

Figure (1): Kaplan Meier plot of the studied Ewing's sarcoma patients; (A) Local Recurrence Free Survival (B) Distant Metastasis Free Survival, (C)Progression Free Survival, (D) Overall Survival.

DISCUSSION

Ewing sarcoma (ES) is a bone cancer that commonly affects adolescents and young adults, with a proclivity to affect any bone, particularly the pelvic, femur, and chest wall bones [1]. When it comes to long bones, the diaphysis is the most commonly affected site [1]. In the current study, sixty patients were treated and followed up on at (KFSH & RC), with thirty-five (58.3%) of them being men. The median age was 20 years (range 14-70 years), and 33 patients (55%) were over the age of 18. Out of nineteen patients with distant metastasis at diagnosis, 41 (68.3%) had localized disease, nine (45%) had lung metastasis, and six (30%) had bone metastasis.In this study, one patient (2%) had a complete response (CR), twenty-one patients had a partial response (PR), and 29 patients (56.9%) had stable disease. Local recurrence occurred in ten of the 35 patients who underwent surgery. Out of 41 patients with localized disease at diagnosis, 24 (58.5%) developed distant metastasis. The disease progressed in 44 patients. The location of the first failure was local for ten people, local and distant for ten people, and distant for twenty-four people.The current study revealed a poor prognostic value of age >18 years, delayed surgery, and total dose of radiation on local control, as well as favourable effects of absence of lung metastasis, use of regimen 1 of chemotherapy, use and total dose of radiation therapy, use of total lung irradiation, and absence of local recurrence on distant metastasis free survival, as well as a significant prognostic value of localized stage at diagnosis, occurrence of lung metastasis.a study of 98 ESFT patients aged 18 years, 52 had a primary lesion confined to the limbs [11], and in the study of ***Uyeturk et al,*** extremity accounts for 25.7% [12]. In line with this, the current study found 19 patients with a primary lesion in the lower extremity (31.7%). ES has a high proclivity to spread. Metastases most commonly occur in the lungs and bone [13]. At the time of diagnosis, more than 10% of patients have multiple bone metastases. Although metastases to the lungs, bone, bone marrow, or a combination of these are found in 25% of patients, metastases to the lymph nodes are uncommon

[14].***Grier et al.*** found that 23.1% of EFST patients had metastasis, with the lungs, bones, and bone marrow being the most common metastatic sites [6]. ***Kutluket et al.*** reported a 34% rate of metastasis at the time of diagnosis [15]. The lungs and bone were found to be the most common sites of metastasis by ***Smorenburg et al.*** [16]. Patients in the current study had metastasis at the time of diagnosis (31.7%), which was consistent with previous studies, and the most common metastatic sites were the lungs and bones. After a biopsy, the standard of care for ES is 3-6 cycles of induction multi-agent chemotherapy, followed by surgery and/or local radiotherapy, and then 6-10 cycles of chemotherapy [9, 17].With the use of combination chemotherapies, the 5-year survival rate among patients with ESFT, particularly those with localised disease, has increased from 10% to 60%. Adriamycin, vincristine, ifosfamide, etoposide, dactinomycin, and cyclophosphamide are the most commonly used chemotherapeutic drugs [18,19, 20, 1, 6, 5, 21,22,23]. Preoperative radiotherapy can be combined with surgery as part of the local control method to avoid intralesional resection and achieve negative surgical margins. If surgery is not possible or is refused by the patient, definitive radiotherapy can be used instead. Postoperative radiotherapy should be considered in patients with inadequate surgical margins and if the surgical specimen has a poor histological response to initial chemotherapy [24, 25, 26]. When considering surgery, make every effort to perform limb-sparing surgery [1]. In another study, the authors discovered that patients who underwent surgery had better local control [27]. Furthermore, ***Haueslerat al.*** reported that local treatment was a poor predictor of survival [28]. Because of its tumour volume-depleting effects, systemic chemotherapy is effective for both microscopic and macroscopic metastases. Non-metastatic ESTF patients in an INT-0091 study conducted by the Pediatric Oncology Group Children's Cancer Group received cyclophosphamide-adriamycin-vincristine-dactinomycin (CAVD) chemotherapy or alternating CAVD and IE chemotherapies.The chemotherapy had no effect on the 5-year disease-free survival (DFS) or overall survival (OS) in the metastatic group. In the non-metastatic group, however, intensive chemotherapy increased the rates of both DFS and OS [29]. According to the ESMO guidelines, chemotherapy should be used in patients with metastatic disease, as opposed to those with localised disease. The combination of total lung irradiation and thoracotomy is critical in patients with lung metastasis for achieving complete remission and controlling localised residual microscopic disease. Palliative radiotherapy should be administered in addition to chemotherapy to patients with bone metastasis [19].The combination of temozolomide and irinotecan was a well-tolerated and dependable palliative treatment regimen in advanced stage ES [30, 31]. Racibborka et al. demonstrated that temozolomide/irinotecan plus vincristine was effective and well tolerated in patients with relapsed or refractory ES [32&33]. In the current study, we used a chemotherapy protocol in which most patients received local control methods regardless of their metastatic status at the time of diagnosis. The presence of metastatic disease at the time of diagnosis, tumours arising from extra-osseous rather than osseous tissue, and a diagnosis age of 26 years have all been reported to be poor prognostic factors for survival [5,34].In their study, ***Uyeturk et al*** found that centrally localized tumours in osseous primary sites, metastasis at the time of diagnosis, and non-bone metastasis had a negative impact on survival[12].

CONCLUSION

The best outcome of ES can be achieved through multidisciplinary team where the upfront step and whole treatment plan are properly selected. Multiple lines of chemotherapy, recent advances of irradiation and surgery of oligometastatic sites may play a role in improving the treatment outcome.

Declaration of interest **and** Funding information.

The authors report no conflicts of interest.

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