|| Print ISSN: 2589-7837 || Online ISSN: 2581-3935 ||
International Journal of Medical Science and Diagnosis Research (IJMSDR)
Available Online at www.ijmsdr.com
PubMed (National Library of Medicine ID: 101738824)
Original Research Article
Volume 4, Issue 3; March: 2020; Page No. 13-19

CLINICAL PROFILE OF EWING'S SARCOMA/ PRIMITIVE NEUROECTODERMAL TUMORS IN A DEVELOPING COUNTRY, AN INSTITUTIONAL EXPERIENCE.

Dr. Javvid Muzamil[1], Dr. Shiekh Zahoor Ahmed[2], Dr. Gull Mohammed Bhat[3], Dr. Nazir Ahmed Khan[4]

[1]MD, DM, consultant medical oncologist, Sheri Kashmir Institute of Medical Sciences, Soura, Srinagar.
[2]MS, DNB, Associate professor Surgical Oncology, Sheri Kashmir Institute of Medical Sciences, Soura, Srinagar
[3]MD, DM, Professor and Head Medical Oncology, Sheri Kashmir Institute of Medical Sciences, Soura, Srinagar
[4]MD, Professor Radiation Oncology, Sheri Kashmir Institute of Medical Sciences, Soura, Srinagar

Conflicts of Interest: Nil

Corresponding author: Dr. Javvid Muzamil

Abstract:

Ewing's sarcoma is the second most common bone tumor among children. The present study is an observational study started from 2008 till 2017 at one regional cancer centre of north India.

Purpose of study: To record clinical profile of EWING'S SARCOMA/PNET patients, the impact of prognostic factors on outcome, and to see overall outcome in localized, metastatic and recurrent disease.

Materials and Methods: A detailed data was recorded regarding demography, clinical characteristics, imaging details, laboratory investigations and treatment received, from Regional cancer centre registry data base. Only histologically proven Ewing sarcoma/Primitive neuroectodermal tumor patients were taken and recorded. Standard operating procedures were used in evaluation and staging of disease.

Results: Most common site was pelvic bones, followed by Tibia, chest wall ribs and then by femur. Sixty percent had localized disease and 40% had metastatic disease. Most common site of metastasis was lungs (31.4%), followed by bone marrow (29.6%). The optimum duration of chemotherapy received by only 24.7% of patients. 67% patients received local control treatment. Mean OS was 2.3(27.6 M) years and median OS was 2.0(24 M) years, with a range of 0.7(8.4 M) to 8.9(106.8 M) years. The 3year OS was 26.5% and 5-year OS was 7%. In univariate analysis, gander had significant impact on PFS, while as LDH, age, ESR had significant impact on OS.

Conclusion: There are still unmet needs in our part of world, which can be looked on very low over all survivals compared to rest of world.

Key words: OS- Overall survival, DFS- Disease free survival, PFS-Progression free survival, ES-Ewing's sarcoma, PNET-Primitive neuroectodermal tumor, CR- complete response, PR- partial response, PD- Progressive disease, SD- stable disease.

Introduction

Ewing sarcoma was named after James R. Ewing, an eminent American pathologist at Cornell who described the first cases in 1921[1]. The annual incidence of ES in the population younger than 20 years is approximately 2.9 per million [2]. The oldest patient reported in literature is 86 years old [3]. In India, there are no uniform cancer reporting registries available, still the proportion of childhood cancers (0-14) relative to all cancers reported by Indian cancer registries varied from 0.8% to 5.8% in boys, and from 0.5% to 3.4% in girls, the proportion of Ewing Sarcoma is 6% (National Cancer Registry Programme, India, 2013).

Majority of patients (85%) harbor a reciprocal chromosomal translocation between chromosomes 11 and 22, the t (11;22) (q24;q12), and is therefore considered pathognomonic for the disease. A recent hypothesis regarding the histogenesis of ES is that it might arise from mesenchymal stem cells [4-6].

ES can arise in almost every age group, the median age being 15 years. Diagnostic staging at presentation must include appropriate evaluation for metastases, which will be detected in about 25% of patients. The most common metastatic sites are the lungs, bones, bone marrow, or combinations thereof. Imaging studies are mandatory to reveal parenchymal lung or pleural metastases and bone metastases at distant sites [7-8].

Ewing sarcoma is managed by multispecialty. For localized disease, it needs good local care either by surgery or radiotherapy, plus systemic chemotherapy. With application of modern multimodal therapeutic regimens including combination chemotherapy, surgery, and RT, cure rates of 60% and more can be achieved [9-

23]. Recurrences come within 2 years in 80% of patients, however late recurrences have been seen. Recurrent tumors are incurable. There is also survival difference in children and adult cases, due to more aggressive nature in adults than children. As there was no such study in our part of country, we made an attempt to study the nature of Ewing's sarcoma in our patients.

Methods and Materials

The present study is an observational study started from 2008 till 2017 in the Department of Medical Oncology and regional cancer centre registry at SKIMS Srinagar.

After the clearance from institutional ethical committee, a detailed data was recorded regarding demography, clinical characteristics, imaging details, laboratory investigations and treatment received, from Regional cancer centre registry data base. Only histologically proven Ewing sarcoma/Primitive neuroectodermal tumor patients were taken and recorded. The following investigations were carried out which were as per standard operating procedure in this disease.

1. Routine tests

CBC with PBF, LFT, KFT, blood sugar, LDH, Uric acid, ECG, Chest X-ray, Urine examination, Hepatitis and HIV serology, electrolytes

2. Bone marrow aspiration and biopsy
3. Biopsy with review and IHC.
4. Imaging of local area and CECT chest
5. Bone scan
6. ECG and echocardiography.
7. Optional tests were PET, FISH etc.

Patients received standard treatment in the form of systemic chemotherapy along with local treatment either radiotherapy or surgery. These patients were followed from cancer registry and timely data was recorded. At the end, each variable was analyzed and the final outcome was recorded.

Statistical Analysis:

Data was entered in MS excel spread system, and was analyzed using SPSS software for windows version 22. The categorical variables were summarized as percentages and the continuous variables were summarized as mean and standard deviation. Univariate analysis was done for variables using Chi square test, to see significant impact on outcome. A "p" value of < 0.05 was taken as significant. Multivariate analysis was done to find out the prognostic impact of different variables on survival of patients. Survival analysis was carried out using the Kaplan-Meier method. Survival curves were compared using Log Rank test.

Observations and results

The data of Ninety-seven patients was recorded who were registered in the Regional Cancer Centre 2008 to 2017. Only 89 patients who received some form of treatment were analysed for final outcome.

Males out-numbered females very slightly with male: female ratio of 1.1: 1. The mean and median age of presentation was 20.27±11.87 and 18.0 respectively with range of 2 to 65 years. The maximum patients were under 30 years of age.

The most common symptom being swelling (63%), pain (62%), followed by fever (21%). Multiple symptoms were in an individual patient. We observed some atypical symptoms in our patients, like haematuria in a patient who had renal ES, and loss of vision in 2 patients, which was due to optic atrophy because of tumor infiltration, not due to paraneoplastic manifestation. The mean and median duration of symptoms were 2.39 and 2 months respectively, with range of 2 to 30 months.

In our patient population, around 63% had high LDH. LDH correlated well with the stage of the disease, patients having metastatic disease had high LDH as compared to normal LDH in localised disease, ESR was found to be high in 40 % and normal in 60 %.

Out of 97 patients, 55 (56.7%) were osseous and 42 (43.3%) were extra-osseous. Among these patients, 33% had axial site of origin, with majority of appendicular in origin. In appendicular system (N=49), 65.0% had primary disease in distal limbs than 14.2% in proximal limbs, besides limb girdles and 20 % having central primaries**.** Among the osseous primaries, most common site was pelvic bones, followed by Tibia, chest wall ribs and then by femur**.** Among the 42 patients of extra-skeletal Ewing sarcoma, most common site of primary was soft tissues of lower limbs, followed by soft tissues of chest wall and para-spinal region, followed by scapular area**.** There were some rare atypical sites like kidney, Breast, brain, oral cavity and peritoneal sarcomatosis (Fig.1A).

Fifty percent of patients had disease less than 8 cm's and 4% had no measurable disease. As for volume of disease was concerned at primary site, imaging was utilized for same. Forty-one percent had less than 200 ml volume. Physical measurements and volume of disease were more or less equal with slight variation. The sensitivity of FNAC was 69%. Biopsy was available in 99% of patients, 2% it was reported as normal, 10% it was reported as soft tissue sarcoma other than ES and in 87% it was diagnostic of ES. The sensitivity of biopsy was 87%. Bone marrow was available in 93% of patients, 20.5% had bone marrow involvement on aspiration and trephine. IHC was available in 94%, only 6% had histopathological diagnosis. In 2% patients, IHC was not suggestive of ES, in whom FISH

confirmed t(11;22). So the sensitivity of IHC was 97% vs 87% with biopsy.

We had 60% localized disease and 40% metastatic disease. Among 40% metastatic disease, lungs constitute 17.5%, bone marrow 16.4% and bones 7% as metastatic sites in whole case study. We observed atypical sites of metastasis like mesocolon, nodes, pleura and peritoneum (Fig.1B).

Out of 97 patients, only 89 patients received some form of treatment. Only records of 89 patients were utilized for assessment of final outcome. Overall, 87% patients received chemotherapy, 50.4% underwent some form of surgery and 42.2% received radiotherapy with other modalities in neoadjuvant setting. Most common chemotherapy regimen given was VAC/IE, both in localized or metastatic disease. Second common regimen given in localized disease was EFT2001 and VAC in metastatic disease. In localized disease, median chemotherapy cycles and weeks received were 12.0 and 36.0 respectively (range 2 to 17 cycles). For metastatic disease median chemotherapy cycles and weeks received were 9.0 and 27.0 respectively (range 3 to 48weeks). Over all, optimum chemotherapy of 48 or more weeks was received by 24.7% only.

In local treatment 49 (50.5%) patients underwent surgery, most common surgery being wide local excision/Limb salvage (81.6%) followed by laminectomy (14.2%). The surgical results were excellent with R0 resection in 41(84%), R1 resection in 7(14%) and R2 in 1(2%). Around 41(42.3%) patients received radiotherapy, 82.9% received primary site RT and 17% received both metastatic site and primary site RT. The mean and median RT received was 47.5 and 50.0 Gy respectively (range 15 to 65Gy).

Post primary/upfront treatment, 82 patients out of 89 were available for assessment (Table1). Patients who progressed, primary site progression were in 11%, rest had distant site progression. In progression, most common chemotherapeutic regimen used was VAC, Irinotican/Temozolomide and ICE. Median number of chemotherapy weeks received in progression was 12.0 (range of 1 to 36) weeks. Median and mean RT dose in progression delivered was 37.5 and 33.75 Gy respectively.

Disease free survival was noted down in patients who had achieved complete response (CR). DFI was defines as time interval in months from the date of documentation of CR till first event in the form of relapse or death, whichever comes first. In our 45 evaluable patients, mean and median DFI was 22.9 and 22.0 months respectively, (range of 4 to 66 months). Out of 45 patients,17 patients relapsed, rest had sustained CR. Most patients had multiple site relapses. The most common pattern of failure was primary site, followed by lungs, bones, skin, liver and peritoneum. The most common regimen received in relapse was Irinotican/ Temozolomide followed by VAC. The average number of chemotherapy weeks received in relapse was 12 weeks (range 6 to 42weeks), average dose of RT received was 25 Gy (range 15 to 40 Gy).

Progression free survival (PFS) ranged from 3 to 35 months, with median of 6.0 month and mean PFS of 8.5±6.9SD months (Fig. 2A). Disease free survival (DFS) ranged from 4 to 92 months, with mean DFS of 24.45 months and median of 20 months (Fig.2B).

Out of 89 patients, 43(44.3%) patients were fully treated as per protocol, 8(8.25%) patients were on active treatment at the time of last follow up, in this 4 patients were on primary treatment and 4 patients on relapse treatment. Our 17(17.5%) patients expired while they were on treatment. On last follow up, 46(47.4%) patients had expired, 34(35.1%) were living, and 17(17.5%) had unknown (defaulted) status. Median follow up period was 24 months with range of 8.4 to 108.4 months. Mean OS was 2.3±1.6SD years and median OS was 2.0 years (range of 0.7 to 8.9 year) (Fig. 2C). The 3-year OS was 26.5% and 5-year OS is 7%. The OS in metastatic disease ranged from 0.7 years to 5 years, with median and mean OS of 1.0 and 1.77 years respectively. In localized stage, OS ranged from 0.9 to 8.9 years, with mean and median OS of 2.6 and 2.2 years respectively. The 3year OS in localized disease was 32.7% and in metastatic disease was 17.9%.

In univariate analysis, all prognostic factors like hemoglobulin, platelet count, LDH, ESR, site of lesion, stage of disease and volume of disease had no significant impact on PFS, DFS and OS, except gender, which had significant (p=0.025) impact on PFS. Similarly, in univariate analysis, age (p=0.017) and ESR (p=0.002) had significant impact on OS. In multivariate analysis, same thing was not reproduced. There was no significant impact of any prognostic variable on PFS, while as ESR (P=0.023) had significant impact on DFS (P=0.016) and Platelet count had significant impact on OS. We studied the impact of different parameters on OS, each variable had statistical insignificant impact on OS, except age, LDH and ESR with 'P' value of 0.02, 0.03 & 0.002 respectively (Fig.3A-C). At present 34 patients are on follow up (Fig.4).

Table 1: Chemotherapy regimen in upfront treatment

	Frequency	Percent
VAC/IE	58	68.2
VAC	16	18.8
EFT2001	6	7.0
POG PROTOCOL	1	1.1
GEMCITABINE/DOCETAXEL	1	1.1
VAC/IE FOLLOWED BY VAC	3	3.5
Total	85	100.0

Table 2: Status of patients post primary treatment

Response status	Number of patients	Percentage of patients
Complete response(CR)	45	46.4
Partial response(PR)	6	6.2
Stable disease(SD)	4	4.1
Progressive dise2se(PD)	27	27.8
Defaulted	7	7.7
Not treated at all	8	7.7
Total	97	100

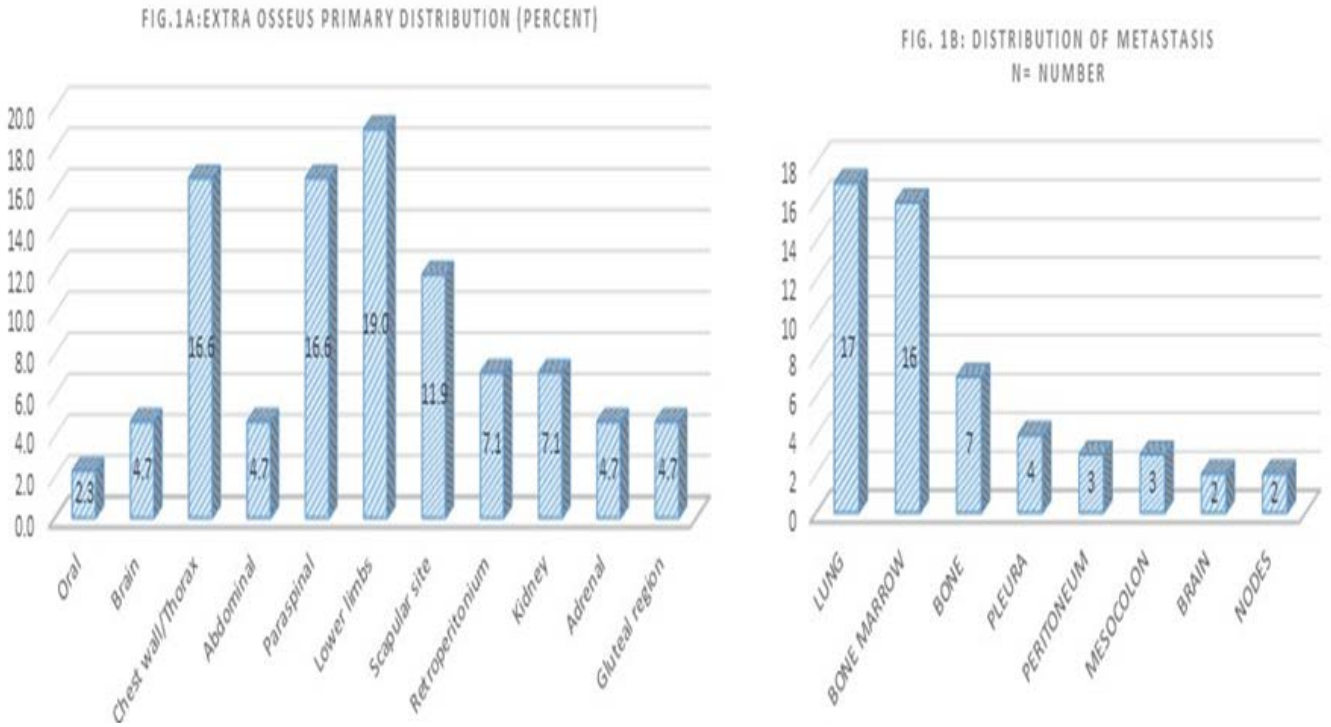
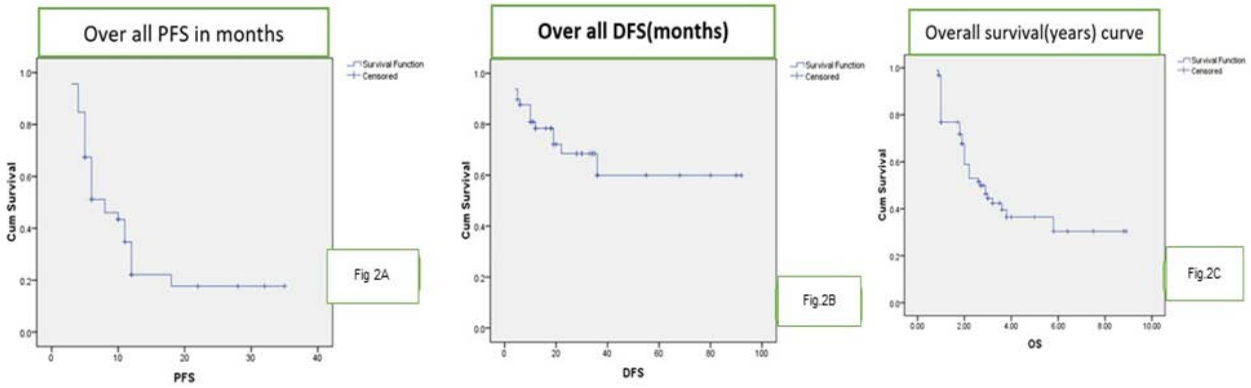


Figure 1:



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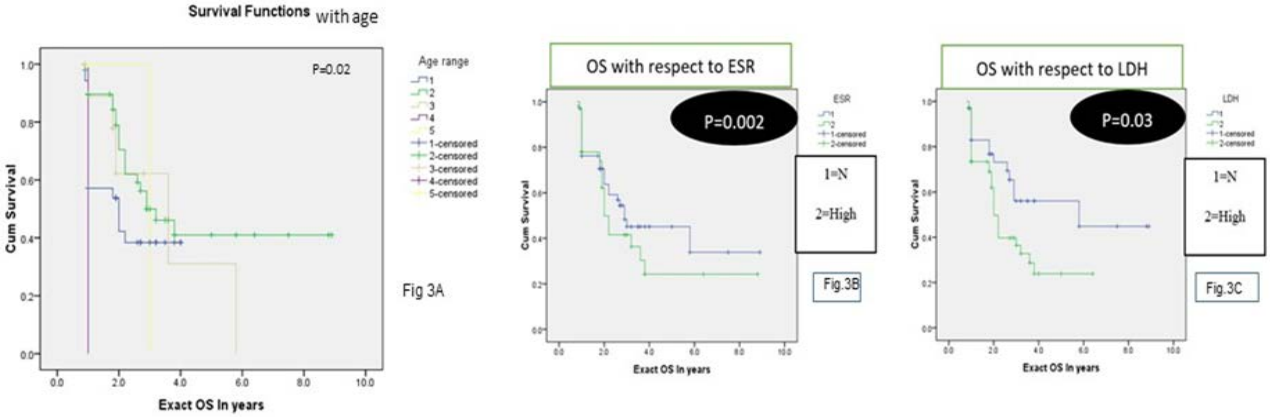

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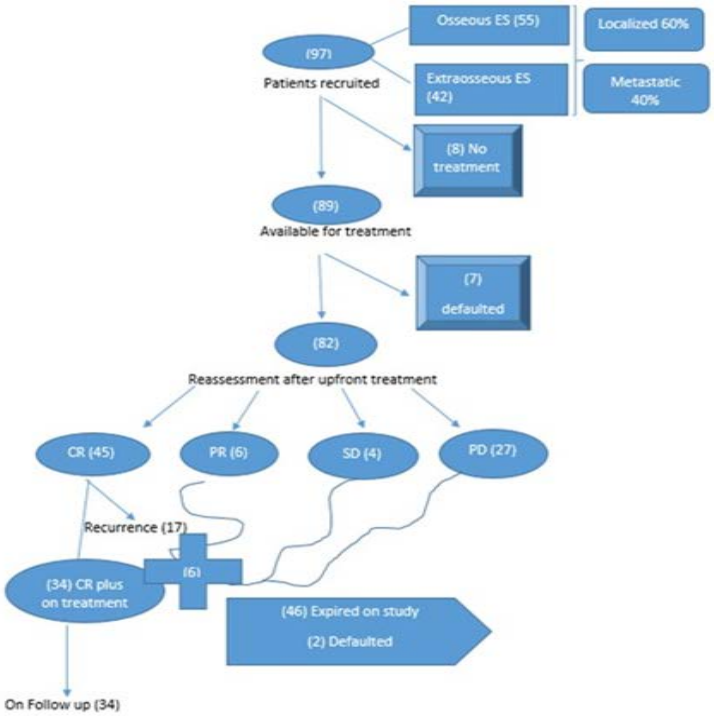

The 3-year OS 26.5% and 5-year OS 7%

CONSORT DIAGRAM OF STUDY (Fig.4)

Discussion

This study spanned over a period of ten years in the department of medical oncology Sheri- Kashmir- Institute of medical Sciences, with collaboration of Surgical and Radiation Oncology departments. This is first kind of study reported from this institute since the inception of oncology departments.

In our 97 patients, around 20 % patient were urban dwellers, rest were rural residents, making this disease more common in such areas, probably due to more population in rural set up.

Our study had slight male dominance, while as study reported by Biswas et al, the male to female ratio was 2.7: 1 [24]. The difference is huge, possibly due to demographic/ genetics differences. Other possibility could be that here medical access is equal for both genders, which is not true in study of Biswas et al, where males are given more attention than females. In another study reported by Mark A. Applebaum et al, the ratio was 1.4: 1 between male and female [25].

In one northern Indian study, Biswas et al reported the mean age of presentation of 15.1 to 15.5 years [24]. In another study reported by Nazeer et al, median age was13 years, with around 80% of patients below 15 years of age, which is again much lower than from our patient cohort [26]. In one western study, Mark A. Applebaum et al reported mean age of 17 to 18.3 years, with age range of 0-39 years [25]. We had slightly older patients as compared to these two studies. The study reported by Biswas et al, mean duration of symptoms was 6.5 months. Most of our patients had lag period of 2-4 months (36%) followed by 0-2 months (27%). So, again our patients presented earlier than other reported studies [24].

In our patient population, around 63% had high LD and most of them were metastatic. The study reported by Biswas et al, found 53% had high LDH, the variation was because of stage, as they had more localized disease contrary to our study [24].

The study reported by Biswas et al, had 16% extra-skeletal (soft tissue) ES, against ours 43.3%. In both Skeletal and Extra-skeletal ES, 40% were metastatic at beginning, 60% were localized, which is same as that of study reported by Biswas et al. In our axial/appendicular relation, 33% had axial origin, against 54-77% (SES-EES) in study reported by Biswas et al [24]. Similarly, we had higher appendicular patients; the reasons are unknown for such disparity.

Forty-one percent had less than 200 ml volume of disease and rest had more than 200 ml. In a study reported by Nazeer et al, 56.4% had disease less than 8cm, in contrast to 50% in our study.[25] In a study reported by H. Juergens, 11% had volume of disease less than 200ml [27].

The sensitivity of FNAC and biopsy was 69% and 87% respectively. In a study reported by Ahmed Mohamed Aly et al, FNAC accuracy was 91% [28]. In another study, Open surgical biopsy was 100% accurate, fine-needle aspiration and core biopsy had 79.17% and 79.2% sensitivity, 72.7% and 81.8% specificity, 67.9% and 76% positive predictive value, 82.8% and 84.4% negative predictive value, and an overall accuracy of 75.4% and 80.7%, respectively [29].

In a study reported by M. Ashour et al, the localized disease was seen in 67.9% and metastatic disease was seen in 32.1%, against our study 60% & 40% respectively. The most common site of metastasis was in lungs (30.8%) followed by bone marrow (15% [30]. Our results are matching with this study.

In regard to treatment, chemo-radiotherapy with or without surgery is standard of care, depending upon the site or stage of disease. We treated our localized disease patients with VAC/IE mostly followed by EFT 2001. In metastatic disease, treatment delivered was VAC/IE mostly followed by VAC. In a trial conducted between 1988-1992, POG CESS INT 0091, localized patients were treated with VAC/IE and metastatic patients were treated with VAC only, they did not find any advantage of adding IE in metastatic patients [31]. In a study from middle east, M. Ashour et al reported the median number of chemotherapy cycles received were 6 (range 2 - 8), which is inferior to our study [30].

The mean and median RT received was 47.5 and 50.0 Gy respectively (range 15 to 65Gy), at 1.8 Gy daily dose. In a study reported by M. Ashour et al, 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. With our initial treatment 46.4% achieved CR, 6.2% achieved PR and 27.8% had PD against 13.5%, 57.5% and 15.4% respectively in M. Ashour et al study [30].

In the study reported by M. Ashour et al, the relapse was seen in 56%, with local relapses of 20% and distal relapses of 36%. In another study reported by Biswas et al, relapse was noted in 42% who attained initial CR against 37% in our study.

On comparing our OS results, the median OS was 55.4 months vs 24 months in ours, OS at 3 years was 88% vs 26.5% (17.9%localised-32.7%metastatic) in ours, 3-year OS of 43.9% vs 26.5% in ours. [24] The differences in OS might be either due to higher default rates after attaining CR, without further continuing full one-year treatment, or could be due to genetic differences or more metastatic disease. The study reported by Nazeer et al, found that the age of presentation, site of disease and volume of disease had significant impact on EFS and OS. In another study reported by M. Ashour et al, metastatic disease had a

statistically significant lower PFS and OS (P <0.05). Patients achieving wide surgical margin did better than those not, and there was no statistically significant effect of age, tumor size or LDH level on OS (P>0.05).

Conclusion

Our study had almost equal sex distribution, with slightly older age, with some atypical sites of presentation. Majority had higher LDH, high volume of disease and skeletal Ewing's sarcoma. Optimum duration of chemotherapy was received by one quarter of patients, 34% progressed and 37% relapsed, with 3year OS of 26.5% and 5-year OS of 7%, which is remarkably very low as compared to national/international studies. Need of the hour is to collaborate with different centers and see the biological nature of this disease at our place and to make more adherence to treatment by providing free treatment to very poor privileged patients.

Acknowledgement:

This study is acknowledged by all authors and I am thankful to all regional cancer centre employees, radiation and surgical oncologist team.

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