



Ewing Sarcoma/Peripheral Neuroectodermal Tumor of Bone and Soft Tissue in Infants: A Report from Children Cancer Hospital of Egypt

Enas El Nadi^{1, 2, *}, Ahmed El Ghoneimy³, Maged El Shafiey^{4, 5}, Hala Taha^{6, 7},
Mohamed Saad Zaghlool^{8, 9}, Iman Zaki^{10, 11}, Nehal Kamal¹², Nada Mounir¹², Manal Amin^{2, 13}

¹Department of Clinical Oncology, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt

²Pediatric Oncology Department, Children Cancer Hospital of Egypt, Cairo, Egypt

³Orthopedics, Children Cancer Hospital of Egypt, Cairo, Egypt

⁴Surgical Oncology, Children Cancer Hospital of Egypt, Cairo, Egypt

⁵Surgical Oncology National Cancer Institute, Cairo, Egypt

⁶Surgical Pathology, Children Cancer Hospital of Egypt, Cairo, Egypt

⁷Surgical Pathology National Cancer Institute, Cairo, Egypt

⁸Radiotherapy Department, Children Cancer Hospital of Egypt, Cairo, Egypt

⁹Radiotherapy Department, National Cancer Institute, Cairo, Egypt

¹⁰Radiology Department, Children Cancer Hospital of Egypt, Cairo, Egypt

¹¹Radiology Department, National Cancer Institute, Cairo, Egypt

¹²Clinical Research Department, Children Cancer Hospital of Egypt, Cairo, Egypt

¹³Pediatric Oncology Department, National Cancer Institute, Cairo, Egypt

Email address:

inas.mohsen@57357.com (E. El Nadi)

*Corresponding author

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Abstract: *Introduction:* Ewing sarcoma is an aggressive malignancy of bone and soft tissue. It is rare in children under age 5 years. Ewing's sarcoma family tumors include classic Ewing's sarcoma, primitive neuroectodermal tumour and Askin tumor. ES is the second most common variety of primary bone cancer in adolescents and young adults. The treatment strategy for ES is characterized by multi-disciplinary collaboration between pediatric oncologists, radiation oncologists, and orthopedic surgeons. Although the survival rate of ES patients has improved, their prognosis remains unsatisfactory. The treatment of ES is still challenging specially in age group below 3 years. *Patients and methods:* A Retrospective study of children below 3 years with a diagnosis Ewing Sarcoma/PNET presented to CCHE from July 2009 till December 2018. *Results:* A review of 46 patients with age ranged from 3 months to 3 years with Mean of age was 1.8. Primary site was Osseous and extraosseous in 23 infant patients for each. Main site was mainly axial in 28 cases (60.8%). Cases were treated according to COG protocol. Infantile Ewing sarcoma OS and EFS at 5-years OS were 75.5% and 66.7%. *Conclusion:* Patients below 3 years represent an unusual young age group. *Conclusion:* ES/PNET in age below 3 years is a unique age group with a different management and outcome.

Keywords: Ewing Sarcoma, Survival, Infants

Figure 1. Neoadjuvant chemotherapy protocol Adapted from COG (AEWS0031).

3. Pathology

3.1. Microscopic Picture

ES has sheets of uniform small round tumor cells with round nuclei and little cytoplasm with no matrix formation. ES tumor cells have uniform findings with few mitoses. ES also demonstrates morphological features showing neural differentiation, as rosette formation.

3.2. Immunohistochemistry

In over 90% of ES cases, positivity for CD99, a product of the MIC2 gene, is detected on the cytoplasmic membrane.

Positivity for neural markers such as S-100 protein and PGP9.5 is sometimes detected, and vimentin positivity is also commonly observed. Atypical ES, a variant of ES composed of large cells, has also been reported. In addition, ES composed of spindle-shaped and adamantinoma-like cells, as well as other variants have also been reported.

3.3. Molecular Diagnosis

The EWS-FLI1 fusion gene, which is caused by the t (11; 22) (q24; q12) translocation, is the most common type of fusion gene (85% of ES tumors).

4. Results

Table 1. Patients demographics and clinical characteristics.

Age		
< 1 year (< 3months)	7	15.2%
1-3 years	39	84.8%
Sex		
Male	39	84.8%
Female	7	15.2%
Localized		
Metastatic		
Chest metastasis (5)	39	84.8%
Chest and bone mets (1) Soft tissue (1)	7	15.2%
Osseus	23	50%
Soft tissue	23	50%
Site		
Axial	28	60.8%
Peripheral	18	39.1%
Lower limb	12	26.1%
Upper limb	6	13%
Head and neck	9	19.6%
Chest and chest wall	12	26.1%
Pelvis	4	
Vertebral spine	3	
Local control		
Surgery	18	
Radiotherapy	16	
Both	9	
Pathological response		
Good responder	11	
Poor responder	8	
Outcome		
Alive	25	
Deaths	7	
Lost follow up	1	

A review to patients with a diagnosis of Ewing's Sarcoma below 3 years enrolled from 2009 till December 2018. Forty six patients were studied. They presented 8.3% of the whole Ewing's Sarcoma patients in CCHE: {n=554}) in the study period.

Patient demographics and clinical characteristics (shown in table 1) as sex, primary tumor site (head, neck, upper limb, lower limb, pelvis, chest/thorax, abdomen, vertebral column/spinal cord) Figure 1 showing the sites of ES patients below 3 years.

Primary tumor localization (axial vs. appendicular; tissue origin (skeletal vs. soft tissue); histology classical Ewing sarcoma vs. PNET (coded as either PNET or Askin tumor). Tumor volume and stage (metastatic vs. localized) were also collected, when available.

Age of patients ranged from 3 months to 3 years, 7 patients (15.6%) were below 1 year. The mean of age was 1.8 and median was 1.91. A male predominance ((n=27) 58.7% were found.

Tumor Volume were collected in 35 patients, {11 don't have 3 dimensions for volume tumor}. Sixteen patients had a tumor volume < 100 cm³ (34.8% of patients) and 19 had ≥ 100 cm³ (41.3%).

Twenty one had tumor volume < 200 cm³ (45.7%) and 14 patients had, ≥ 200 cm³ (30.4%).

Primary site was mainly osseous in patients above 3 years osseous (n= 383) 75.6% and extra-osseous (Soft tissue) (n= 125) but in patients below 3 years were equally distributed in osseous ES and extraosseus ES with 23 patients for each.

Osseous (n=23)

Cranium5 cases (2 Mandible, 2 Orbit, 1 Temporal bone)

Trunk 8 cases (5 Chest wall/Ribs, 1 Vertebra, 1 Paravertebral, 1 Scapula)

Upper extremities 2 cases (1 Metacarpal, 1 Radius)

Lower Extremities 8 cases (Femur)

Extra-osseous (n=23)

Head & Neck

4 cases (1 Posterior aspect of Neck, 1 Orbit, 1 Left External Auditory Canal, 1 LNs: Cervical & Supra-clavicular)

Trunk

13 cases (2 Mediastinum, 4 Chest wall/Ribs, 1 Abdomen, 3 Pelvic, 1 Inguinal, 1 Paravertebral, 1 Shoulder)

Upper extremities 2 (1 Wrist, 1 forearm)

Lower Extremities 4 (1 thigh, 2 Ankle, 1 Metatarsal)

EWSR1 t (11; 22) (q24; q12) translocation was done in 20 cases out of the 46 cases found to be positive in 9 cases, negative in 3 cases and failed in 8 cases. Main site was the extremity 18 cases (12 cases of lower limb and 6 cases in upper limb) followed by chest wall (12 cases), pelvis 4 cases and 9 Cases head and neck. Vertebral spine 3 cases

In the adult cases 508 cases above 3 years Lower Limbs were the most common → 156 cases (30.7%) but still axial sites is more than peripheral 342 cases out of the 508 cases (distributed in chest, chest wall, head and neck and vertebral column).

Most of the cases (39 cases) were localized to primary site with 7 cases metastatic.

Eighteen cases (39.1%) had surgery at local control, sixteen cases had Radiotherapy (34.8%) and nine cases (19.8%) had both.

The outcome of the whole group was studied after exclusion to 13 patient (only 27 patients were studied).

Upfront surgery	8
Secondary Malignancy over ALL	1
Died before Starting Chemotherapy (due to disease Progression)	1
Died post week 1	2
Died before Local Control	1

Figure 2. Status of the whole studied patients.

The 3 Years Overall Survival (figure 2) of 33 patients was 75.5% and 5 Years Overall Survival was 75.5%.

Twenty five cases were alive, 7 cases were dead and one case Lost FU.

The 3 & 5 Years Event-Free Survival (figure 3) = 68.2% Events (n = 9).

The 3 years overall Survival of the age group below 3 years was compared to patients above 3 years it was slightly better 76.7% in comparison to 72.7% but difference was insignificant (P-value = 0.151). comparing the EFS of age group below 3 years to older age group (68.2% in comparison to 59.7% difference was still insignificant P-value = 0.112).

Patient were treated according to COG study chemotherapy protocol was shown in table 1.

Seven patients relapsed one patient had Local recurrence and another one with both systemic and local. Five patients had systemic relapse (3 cases in lung, one case in bone, and another case in brain).

One case died from toxicity and another one died out of secondary malignancy (n = 1).

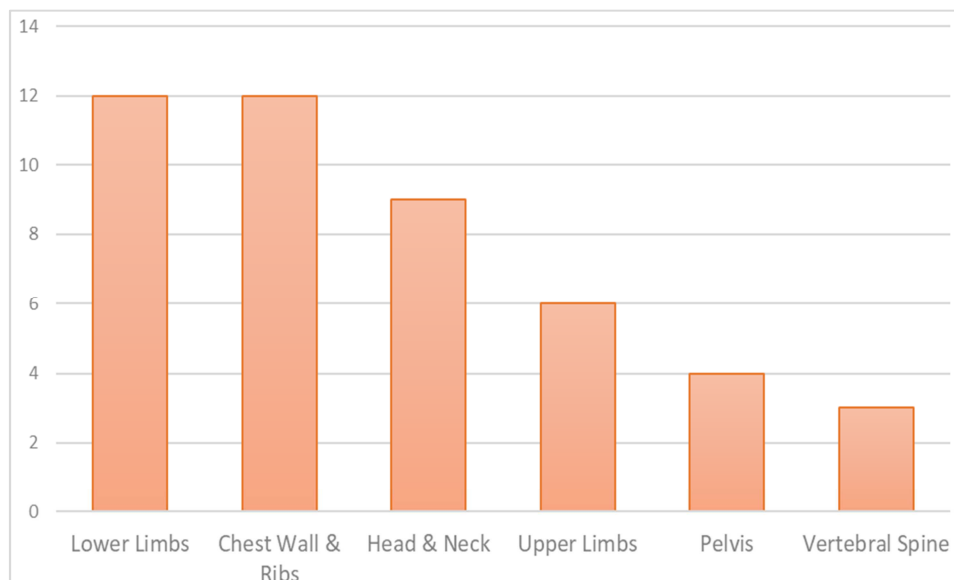


Figure 3. Sites of ES patients below 3 years of age.

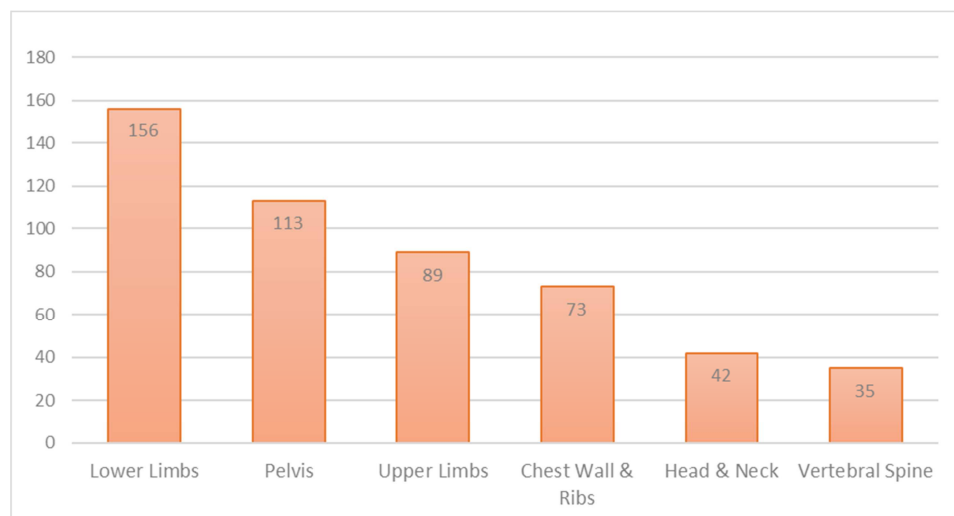


Figure 4. Sites of ES patients above 3 years of age.

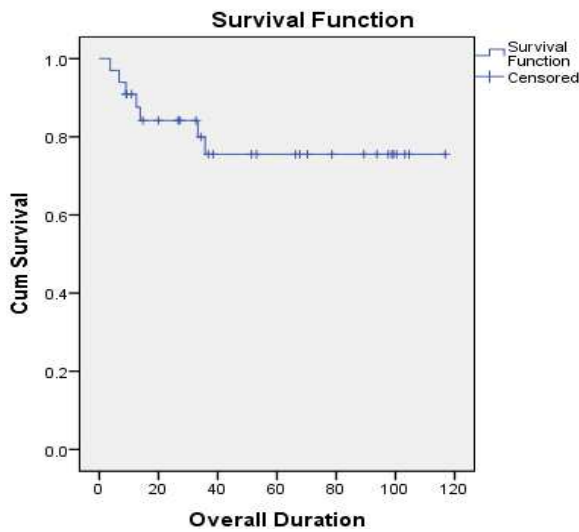


Figure 5. The 3 Years Overall Survival of 33 patients was 75.5%.

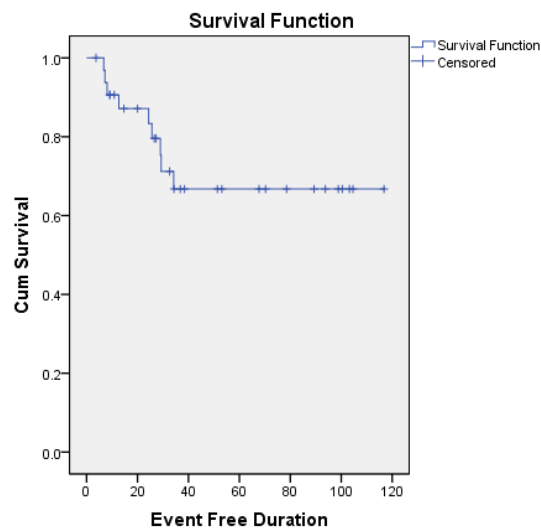


Figure 6. The 3 & 5 Years Event-Free Survival = 68.2%.

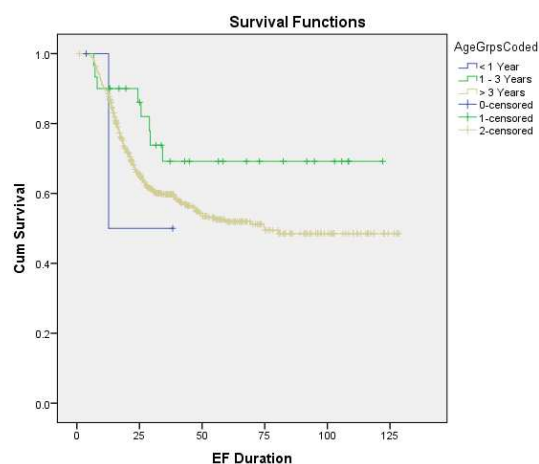


Figure 7. 3 & 5 Years Event-Free Survival according to age was not significant < 1Year (n=3) → 1 event 50%, 1-3 years (n=30) → 8 events 69.2% > 3 years (n=446) → 190 events 59.7% (3years) 1.9% (5years), P-value = 0.206.

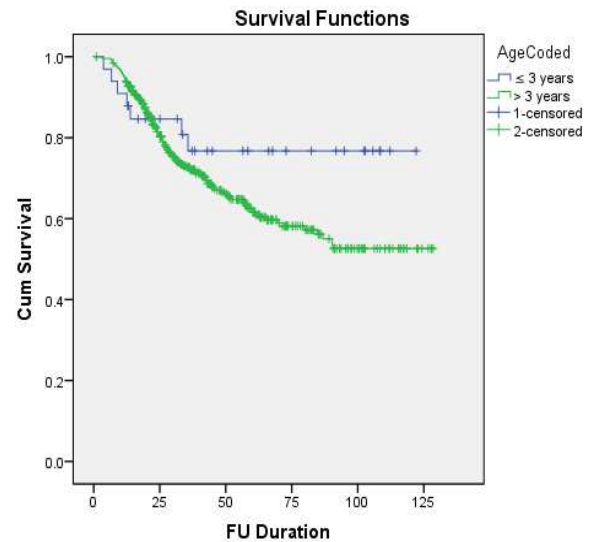


Figure 8. Osseous (n=17) → 5 events 66%, Extra-osseous (n=16) → 4 events 68.9%, (P-value = 0.9).

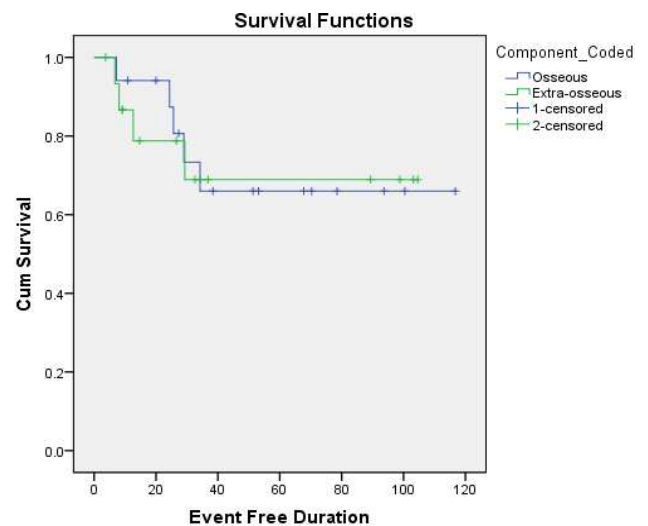
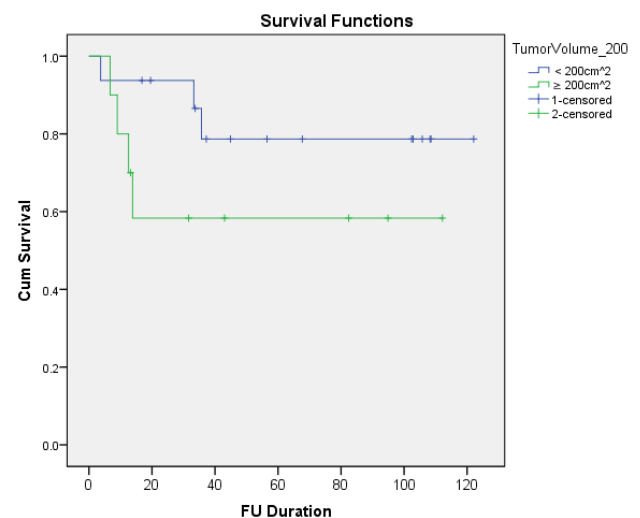


Figure 9. < 200 (n=16) → 3 events 78.7%, ≥ 200 (n=10) → 4 events 58.3%, When correlated to survival it was insignificant (P-value = 0.166).



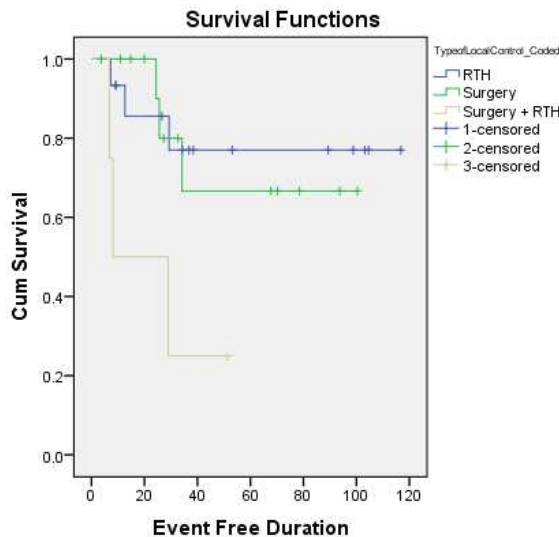


Figure 10. Patients received RTH (n=15) → 3 events 77%, Patients had Surgery (n=14), → 3 events 66.7%, Patients received both Surgery + RTH (n=4) → 3 events 25%, (P-value = 0.035).

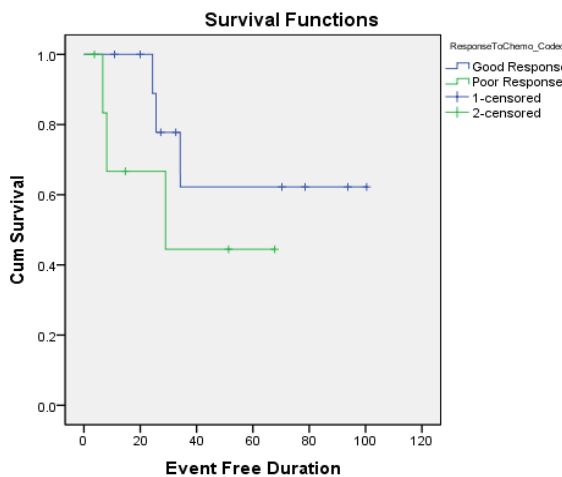


Figure 11. Pathological examination was done postoperatively in 18 patients, Good Responders (n=11), → 3 events 62.2%, Poor Responders (n=7), → 3 events 44.4%, P-value = (0.287).

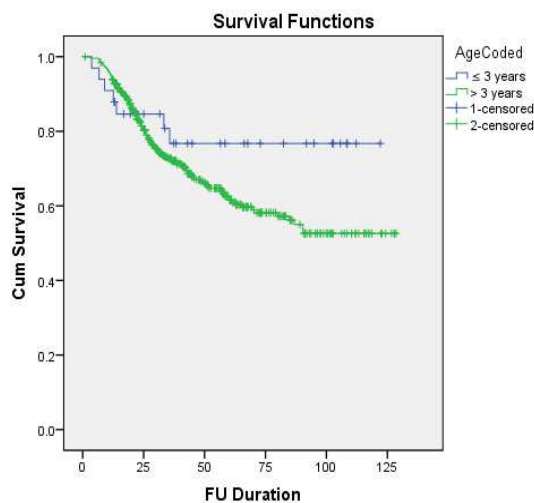


Figure 12. ≥ 3 years (n= 33) 3 Years Overall Survival = 76.7%, 5 Years Overall Survival = 76.7% Dead (n = 7) > 3 years (n= 446) 3 Years Overall Survival = 72.7%, 5 Years Overall Survival = 61.5% Dead (n = 143).

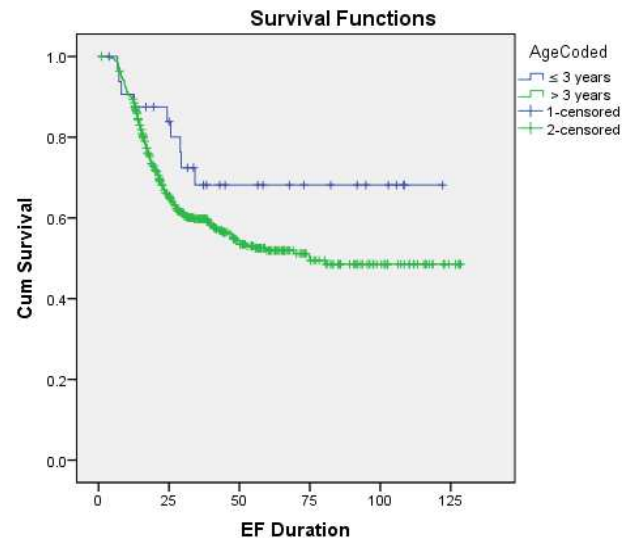


Figure 13. 3 years (n= 33) 3 & 5 Years Event- Free Survival = 68.2% (9 event) > 3 years (n= 446) 3 Years EF Survival = 59.7%, 5 Years EF Survival = 51.9%.

5. Statistical Methods

A Retrospective review of the medical records was conducted to identify all the patients aged 18 or less, with pathologically-confirmed Ewing's Sarcoma/PNET, treated at the Children Cancer Hospital-Egypt, with registration date between July 2007 and December 2018.

The Overall survival was defined as the time interval from the date of registration to the date of death from any cause or last follow-up.

The Event-free survival was defined as the time interval from the date of registration to the date of the first event (disease progression or recurrence, diagnosis of a secondary malignancy, or death).

Differences in the Overall & the Event-free survival between age groups were estimated according to the Kaplan–Meier method with 95% confidence interval (CI), and the p-values were reported from the two-sided log rank test. The statistical significance threshold was determined at a p-value < 0.05.

All statistical calculations were performed using SPSS program, version 20.

6. Discussion

Ewing sarcoma peaks in incidence in adolescence. Infants <12 months old have rarely been reported [4]. It was found ES can occur at all ages, the peak age of onset ranges from puberty to early adulthood but reports of this disease in infants are also rare [10].

In a study The median age at diagnosis was 13.7 years (range, 1.1–25.2 years) [13]. We aimed to study clinical features, treatment, and survival of infants < 3 years and to compare those with older pediatric patients with Ewing sarcoma.

Malignancies in infancy are extremely rare. Ewing tumors are hardly ever noted in these children. Since it is generally assumed that malignancies in infancy have an extremely poor

outcome, we wanted to investigate whether this was also the case in Ewing tumors [14].

Total number of patients enrolled from 2009 till December 2018 and below 3 years of age was 46 Patients who constituted 8.3% of all Ewing's Sarcoma patients in CCHE with 1.5% of the patients were below 12 months. This is lower than literature a, it found that infants below one year represent 2.6% of all patients registered in the Intergroup Ewing's Sarcoma Study (IESS) [8].

Significant differences in clinical characteristics between infants and older patients were observed for primary tumor site, tissue origin, and histological diagnosis. Primary tumor site was mainly axial 28 cases (39.1%) in infants in contrast to tumors in children above 3 years which mainly had ES in the pelvis and lower extremity.

Ewing's sarcoma of the bone commonly occurs in the long bones of the limbs and the pelvis but rarely in the head and neck region [10]. In another study infants had a different distribution of primary tumor sites, with lower extremity tumors under represented. An axial primary localization was present in 66% of patients with the primary site in the chest wall in 34% Compared to older patients, infants were more likely to have soft tissue tumors [4]. This is contrary to what we found an equal distribution of soft tissue and bony lesion. This may be explained by the rarity of disease in this age group thus increasing the sample size is needed.

In our study tumor volume of the lesion was calculated and was correlated to survival, twelve patients had tumor volume $< 100 \text{ cm}^3$ (n=12) \rightarrow 3 events with OS 73.3% and $\geq 100 \text{ cm}^3$ (n=14) \rightarrow 4 events with OS 70.7%.

We studied also lesions $< 200 \text{ cm}^3$ (n=16) \rightarrow 3 events 78.7% ≥ 200 (n=10) \rightarrow 4 events 58.3%.

When correlated to survival both were insignificant (P-value = 0.166 and 0.675) may be due to small number of patients this is contrary to literature. In another study, tumor volume of 100 ml did not distinguish groups of patients with different prognosis. However, the prognosis of patients with tumors $>200 \text{ ml}$ (8-year EFS rate: 42%) was significantly inferior compared to patients with tumors both of 100 to 200 ml (70%) and of $<100 \text{ ml}$ (63%) [19].

We studied Response to chemotherapy in 18 cases after neoadjuvant chemotherapy and survival of the two groups was calculated. Good Responders (n=11) had DFS 62.2% and Poor Responders (n=7) DFS was 44.4% but correlation was insignificant with (P-value = 0.287. This was the same as Ahrens, 1999 where they found the histological response to chemotherapy was no longer a significant prognostic factor (EFS: 64% for good and 50% for poor responders, respectively). This is in contrast to CESS 81 which found disease free survival for patients with a tumor volume less than 100 ml was 75% after 41 months compared to 10% for patients with a tumor volume greater than or equal to 100 m^3 .

Most current therapies call for multidrug chemotherapy, consisting of cycles of varied combinations of Vincristine, Doxorubicin, Cyclophosphamide, Etoposide, Ifosfamide,

Actinomycin D, and Topotecan, followed by local therapies radiation and/or surgery [9].

Patients with localized tumors to the primary site without systemic metastasis in a pilot study of COG reported favorable outcomes [10].

In this study, The 3 Years Overall Survival of 33 patients was 75.5% and 5 Years Overall Survival was 75.5%. The 3 & 5 Years Event-Free Survival was 68.2%.

In patients with metastatic ESFT, the 5-year EFS was 22%, even after VDC-IE therapy with alternating cycles. Thus, such patients still have poor prognoses [10]. In the current study EFS was 30% in patients initially presented with metastasis relation was significant when correlated to EFS.

Surgical resection may be particularly preferable in younger patients, as radiotherapy to the developing skeleton can result in skeletal deformities and attenuated bone growth [4].

In the current study 18 cases had surgery as local control measure, 16 patients had radiotherapy and 9 patients had both. Method of local control was not significant in relation to EFS but patients who had radiotherapy as local control showed improved survival than those had surgery as local control 77% versus 66.7%. This may be due to including the 8 cases who had initial surgery to patients received radiotherapy as local control. This contrary to Salah, et al 2020 who stated Inferior OS was predicted in patients with definitive radiation as opposed to definitive surgery (5-year OS 25% vs. 79%, respectively, $p = 0.041$) and tumor necrosis $<90\%$ as opposed to $\geq 90\%$ (5-year OS 55% vs. 90%, respectively, $p = 0.01$).

Infants and younger patients have a better prognosis than do patients aged 15 years and older, as noted in the following studies [15, 16].

Review of the SEER database from 1973 to 2011 identified 1,957 patients with Ewing sarcoma. Thirty-nine of these patients (2%) were younger than 12 months at diagnosis. Infants were less likely to receive radiation therapy and more likely to have soft tissue primary sites. Early death was more common in infants, but the overall survival (OS) did not differ significantly from that of older patients [17].

In the current study the 3 years overall Survival of the age group below 3 years was compared to patients above 3 years it was slightly better 76.7% in comparison to 72.7% but difference was insignificant (P-value = 0.151). comparing the EFS of age group below 3 years to older age group (68.2% in comparison to 59.7% difference was still insignificant P-value = 0.112). so survival of that age group was better may be due to encouraging the local control 16 patient received radiotherapy but still number of patient in comparison to that age group (46 (9%) in comparison to whole patients 508).

7. Conclusion

ES in age below 3 years is a unique age group with a different management and outcome. Increasing the study

number of patients and duration of the study should be done to assess late effects in this young age group.

Children Cancer Hospital of Egypt, Sayeda Zeinab, Cairo

ES EWING SARCOMA
PNET PRIMITIVE NEUROECTODREMA TUMOR
CCHE CHILDREN CANCER HOSPITAL OF EGYPT
OS OVERALL SURVIVAL
EFS EVENT FREE SURVIVAL
VTC vincristine, Topotecan, and Cyclophosphamide

Conflict of Interest

The author declares that he has no conflict of interest.

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