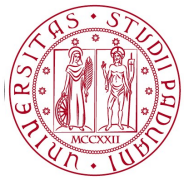

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Dipartimento di Onco-Ematologia Pediatrica

SCUOLA DI DOTTORATO DI RICERCA IN MEDICINA DELLO SVILUPPO E SCIENZE DELLA PROGRAMMAZIONE
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CICLO XXII

TITOLO TESI

SARCOMA DI EWING IN ETA' PRE-SCOLARE: ESPERIENZA Associazione Italiana EmatoOncologia Pediatrica (AIEOP)

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EWING SARCOMA OF THE BONE IN PRE-SCHOLAR CHILDREN : THE AIEOP EXPERIENCE

INTRODUCTION

PATIENTS AND METHOD

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CONCLUSION

INTRODUCTION

The Ewing's Sarcoma Family Tumours (ESFT) is an aggressive form of childhood cancer characterized by a group of small round cell neoplasm of neuroectodermal origin which include classic Ewing's Sarcoma, Askin tumour and peripheral primitive neuroectodemal tumour (PNET) (1,2). In 25% of cases, ESFT arise in soft tissue rather than bone and represent the second most common bone tumours in children and adolescents accounting for 3% of all paediatric tumours (1, 2).

The ESFT are characterized by the presence of a chimeric transcript resulting from the fusion of the EWS gene with the genes that encode for structurally related transcription factors, usually FLI1 or ERG 2 (3).

Metastatic spread is detectable in 25 % of new patients at diagnosis; the lungs are the most common site (50%) followed by bone (25%) and bone marrow (20%) (1,2). Significant progress has been made in the diagnosis and treatment of localised disease over the past 30 years. Before the chemotherapy era, only 10% of patients with Ewing's sarcoma survived. The overall survival (OS) is approximately 70% for patients with localized ESFT and only 20% to 30% in metastatic disease (1, 2, 4-6).

Many clinical variables have been investigated as prognostic indicators, in order to tailor the treatment. Evidence of metastatic disease at the time of diagnosis is the worst prognostic factor, in particular for patients with extrapulmonary metastasis (4). Adverse outcome has also been associated with older age at presentation (age ≥14 years or ≥18 years) (4, 6, 7), larger tumour volume (6, 8,

9), poor response to induction therapy (6), axial tumour location (4,6), elevated lactate dehydrogenase (10), secondary cytogenetic abnormalities (11), deletion of p16 (12), and mutation of p53 (13,14).

ESFT and osteosarcoma represent the most frequent bone tumour in childhood; both tumours had their highest incidence in late childhood or early adolescence while the occurrence in early childhood is rare (15). The aim of this study is to investigate the clinical characteristics and outcome of pre-scholar children affected by ESFT of bone.

PATIENT AND METHODS

The Associazione Italiana Emato-Oncologia Pediatrica (AIEOP) database was checked in order to identify patients affected by EFST of bone and diagnosed before 6 years of age. Between January 1982 and March 2008, ninety patients were identified while the total number ESFT of bone was 783. Therefore the prevalence of pre-scholar ESFT of bone in the AIEOP series is 11, 5% (90/783). A medical record revision for each patient was requested and CRF were sent to be completed by the reference centre; for 16 patients, the CRF were not completed. Therefore, this study concerns a series of 74, previously untreated, ESFT patients diagnosed before 6 years of age and treated in the AIEOP centres during 26 years period.

Medical records of all 74 patients were retrospectively reviewed and data regarding sex, age, tumour localization at diagnosis, presence of metastasis, site of metastasis, tumour dimension, treatment protocol, treatment details of surgery, chemotherapy and radiotherapy, histology with necrosis after surgery and outcome were collected. The occurrence of relapse and death from any cause was registered.

Statistical methods

Overall survival (OS) was defined as the time interval between the date of diagnosis and the date of death from any cause or the date of last follow-up. Progression free survival (PFS) was defined as the time interval between the date of diagnosis and the date of first relapse or the date of last follow-up. The

Kaplan–Meier method was used for the estimation of survival curves (16), while the log-rank test was used to compare differences between groups.

Multivariate analyses were performed using Cox proportional hazards regression model for OS and PFS. Variables that reached a p-value of 0.20 after univariate analysis were included in the initial model and variables were eliminated one at a time in a stepwise fashion to only keep variables that reached a p-value of 0.05 or less into the final models. All P-values were 2-sided, with a type I error rate fixed at 0.05. Variables considered in risk factor analysis for OS and PFS were period of diagnosis (1980-1989; 1990-1999; 2000-2008), gender, primary site (extremities, skull, pelvis, chest wall and spine), presence of metastasis, site of metastasis (lung only, bone/bone marrow $\pm$ lung, other sites), tumour size (< 8 cm, $\geq$ 8cm); type of local control (none, radiotherapy alone, surgery alone, surgery plus radiotherapy) , response to chemotherapy (in patients with evaluable tumour burden), radiotherapy, surgery, definitive surgery, necrosis after surgery (100%; less than 100%); high dose chemotherapy and tumour status at the end of treatment. Analyses were performed using the Stata 9.0 statistical software package (StatCorp LP, Texas, USA).

RESULTS

Patients Characteristics and Treatment

This study concerns 74 patients affected by ESFT of bone diagnosed before 6 years of age in 10 different AIEOP centres. Patient characteristics are summarized in Table 1.

The median age was 48 months (range 1-72) and 82% of patients were older than 24 months. The presenting symptoms (full data available for 47 patients) were pain (32%), palpable lesion (36%), walk disorder or neurologic impairment (32%), respiratory symptoms (19%) and fever or/and anorexia (8).

Table 1: Patient characteristics

			No	%
Age	Median (months) Range (months)	48 1-72		
Sex	Male		36	49
	Female		38	51
Stage of disease	Localized		56	75
	Metastatic		18	25
Site of Metastasis	Lung		11	60
	Bone/Bone Marrow + Lung		5	22
	Others		2	18
Tumour Size (data recorded for 39 pts)	< 8 cm		23	59
	≥ 8 cm		16	41
Primary Sites	Extremity		23	31
	Skull		7	9
	Pelvis		8	11
	Chest Wall		27	37
	Spine		9	12

Thirty-seven patients were prospectively enrolled in the national protocols, ongoing at the time of diagnosis; 10 patients were treated at the Istituto Nazionale Tumouri (INT) in Milan and 9 patients at the Ospedale Pediatrico Bambino Gesù in Rome with a local protocol, four patients was treated with POG/CCSG, Euro Ewing 99, SIOP RMS stage IV and CESS 91, respectively; 14 were treated at AIEOP centres using different protocols.

In this series most patients had an axial primary 69% and 37% had a chest wall primary; the prevalence of axial site was 70% in localized and 67% in metastatic patients (See Figure 1-3).

Eighteen (25%) patients presented a metastatic spread; 13 patients had metastasis in the lung (lung only, 11), 5 patients in the bone/bone marrow and 2 patients in other site (in lung plus lymph- nodes and in the pleura, respectively).

Figure 1: Primay sites in whole population

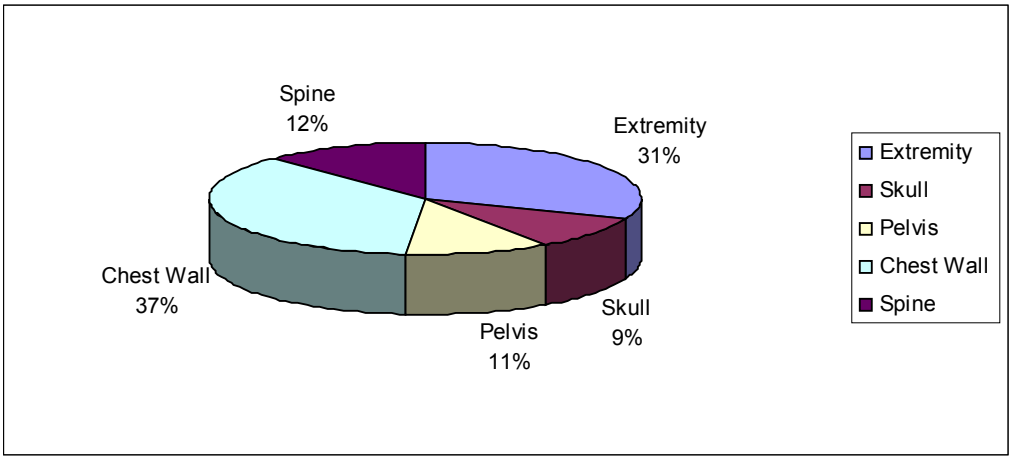


Figure 2: Primay sites in localized patients

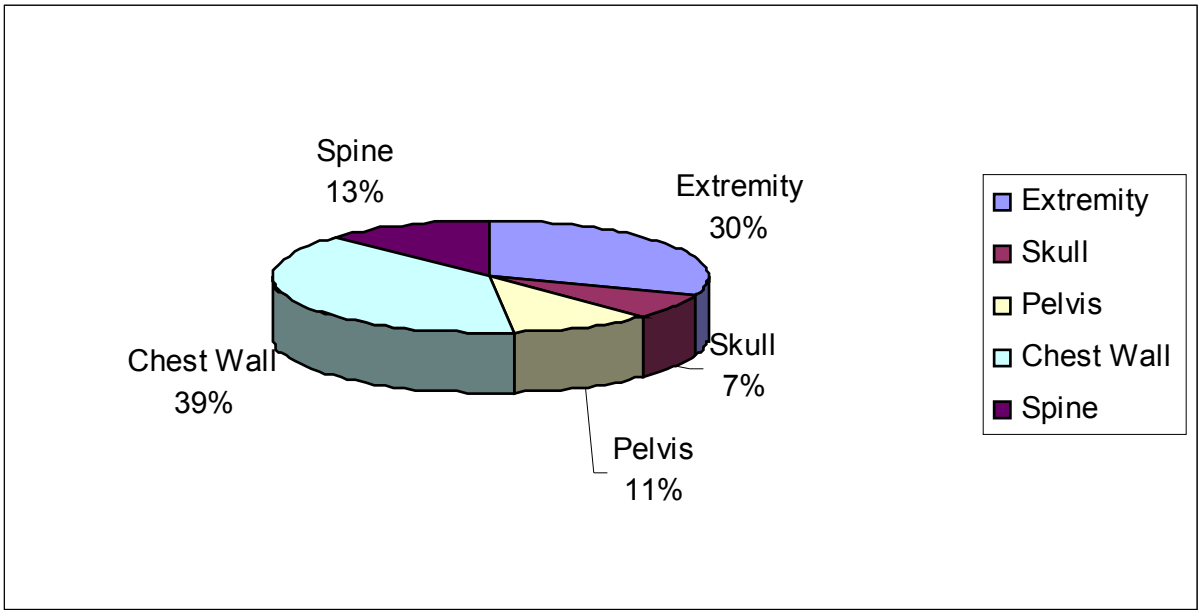


Figure 3: Primay sites in metastatic patients

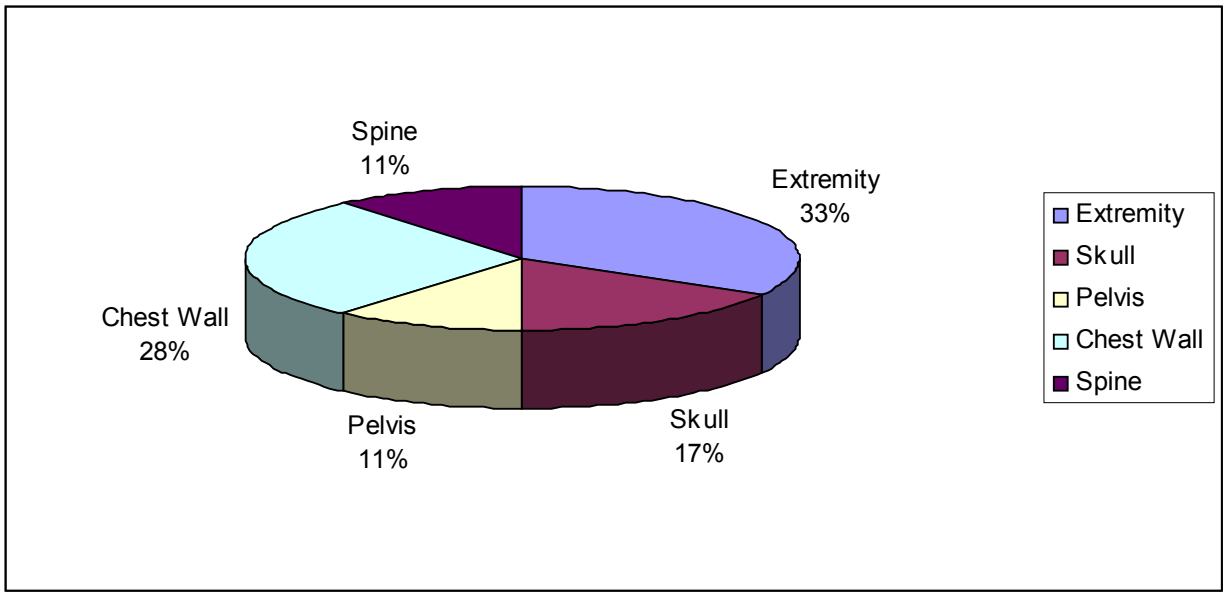
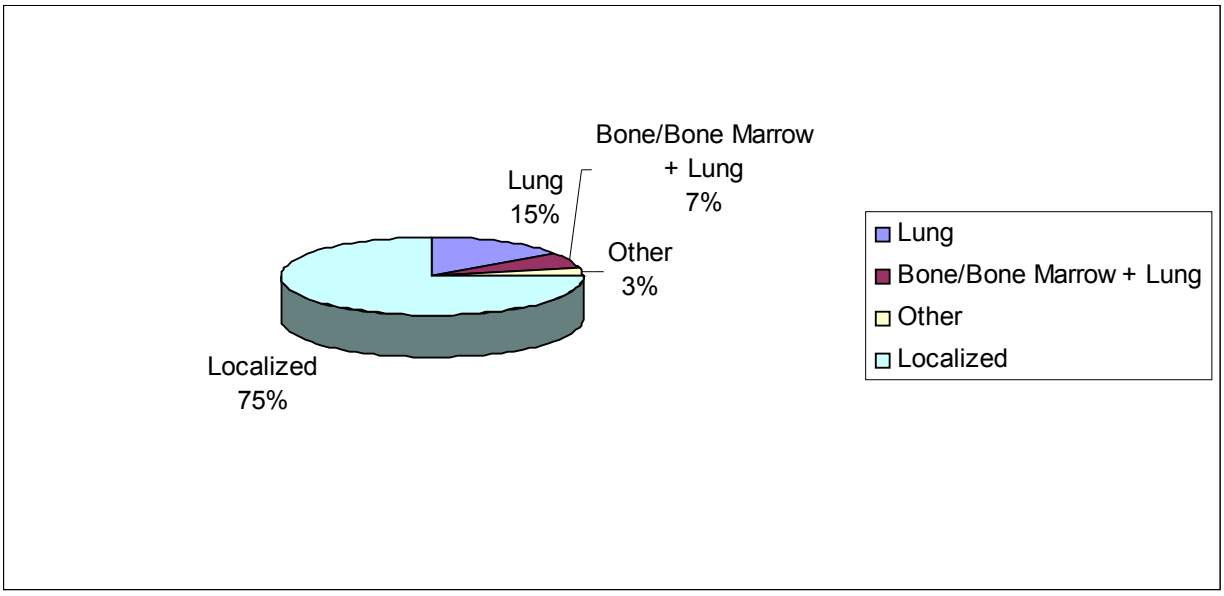


Figure 4: Stage of disease



Tumour size was only available for 39 patients (53%) while the histological response after chemotherapy was available for 32 out of 36 patients (89%). A large tumours (> 8 cm) was evident in 17 patients (46%) while a complete necrosis after surgery was achieved in 17 (47%) of patients.

Primary surgery was performed in 19 patients while 36 patients received surgery after chemotherapy. A definitive surgery was achieved in 40 patients. In all patients conventional chemotherapy was administered; of them 65 patients presented a tumour burden and were evaluable for response. A complete response was achieved in 8 patients and a partial response in 50 while 7 patients progressed during chemotherapy.

Nearly all patients (94%) received a local control treatment (two patients were excluded from the analysis for incomplete data): surgery alone in 36 patients (50%); radiotherapy alone in 13 (18%) and surgery plus radiotherapy in 19 (26%).

High dose chemotherapy followed by autologous rescue was performed in 25 patients (34%) and in a third (8 patients) the conditioning regimen was busulfan plus L-PAM.

At the end of treatment, 53 patients achieved a complete remission of disease both at local and metastatic sites while 7 patients presented a residual disease. Overall, 11 patients progressed during first line treatment; seven of them were metastatic. Three patients were not evaluable for disease status: one patient died after the second course for toxicity while in two patients the data were incomplete.

Outcome

The median follow-up of the entire cohort was 62 months (range 1 months-25 years). Of 74 patients, 28 (38%) died; 27 of relapsed/resistant disease and the last one due to treatment-related toxicity (severe infection) after the second course of chemotherapy. Relapse occurred in 31/74 (42%) patients after a median time from diagnosis of 19 months (range 1-120 months); in 26/31 (84%) patients relapses occurred before 36 months from diagnosis.

Of 18 metastatic patients, 12 (67%) died for a relapsed disease. Relapse occurred in 15/18 patients (83%) after a median time from diagnosis of 17 months (range 1-61 months).

The 5-year Kaplan-Meier estimates of OS and PFS were 65% (95% confidence interval (CI) 53-75%) and 61% (95% CI 48-71%) while the 10-year Kaplan-Meier estimates of OS and PFS were 59% (95% CI 45-70%) and 48% (95% CI 32-62%), respectively. The 5-year OS and PFS for localized patients were 73%

(95% CI 58-83%) and 72% (95% CI 57-83%), respectively while the 5 –year OS and PFS for metastatic patients were 38 (95% CI 17-60%) and 17% (95% CI 4-37%) (Figure1 and 2). The difference in OS and PFS between the two patient groups was statistically significant only for PFS ($p < 0.05$).

Figure 1: PFS metastatic versus localized patients

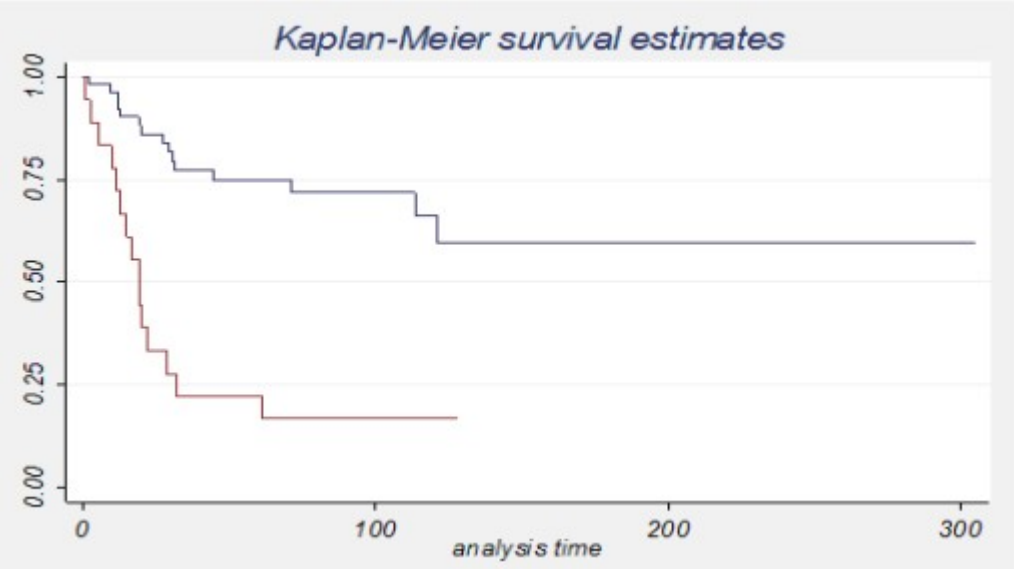
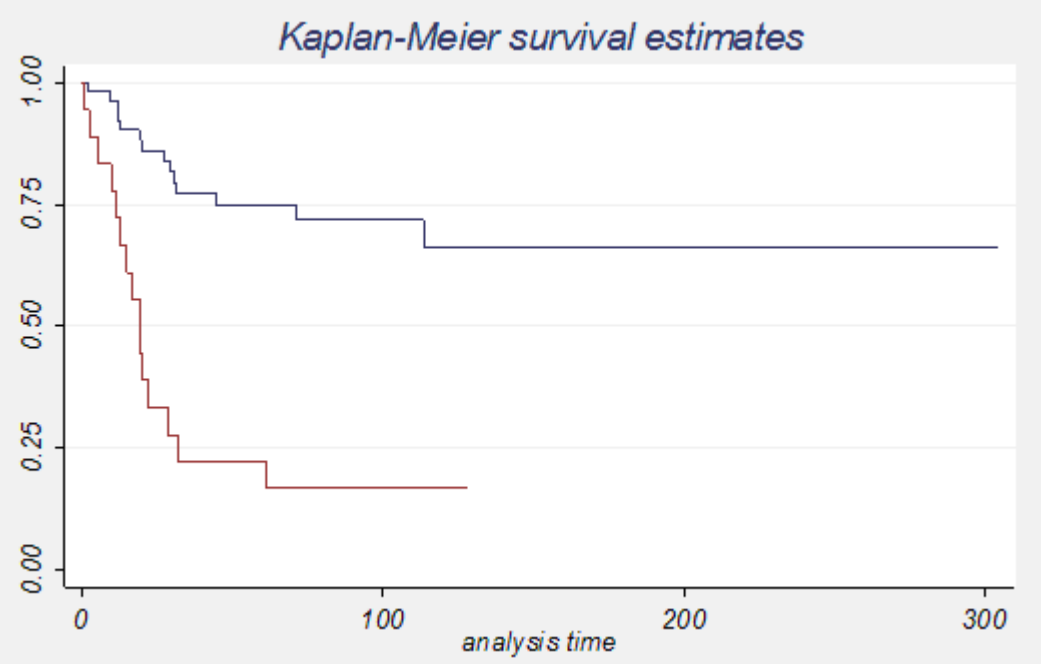


Figure 1: OS metastatic versus localized patients



Second malignancies were not recorded in this series of patients.

Seven patients progressed during chemotherapy and all died. At the end of treatment 53 patients achieved a complete remission of disease while 7 patients presented a residual disease. Six out seven patients with residual disease died for progression; the alive patient presented a primary of the spine and received surgery plus radiotherapy for local control. All 11 patients who presented a progression during first line treatment died.

Analysis of Prognostic Factors

The tables 2 and 3 summarizes the univariate analysis of predictive factors. Metastatic spread at the time of diagnosis ($P < 0.01$), extra lung metastasis ($P < 0.0001$) and a primary tumour localized in the skull, pelvis or chest wall ($P < 0.01$) were found to be associated with worse OS and PFS. A poor histological response -considered as necrosis less than 100% - was associated with a significant worse OS (P 0.0025), however the PFS difference (60% versus 88% at 5-year) between the poor and good histological responders was no longer significant (P 0.102). Surprisingly larger tumours were no associated with a worse prognosis, probably this result was due to the incomplete data (only 39 patients with tumour size data were included in the analysis).

Patients who received treatment with surgery or surgery plus radiotherapy were found to have better outcomes than those who were treated with radiotherapy only or without any local control.

As expected, a progressive disease during first line treatment represented a major prognostic both for OS and PFS ($P < 0.01$). Patients with a residual disease at the end of treatment presented a worse OS and PFS ($P < 0.01$).

Table 2: Univariate Analysis of Factors Predictive for Outcome

		Pts	PFS 5 yr %	95 % CI	Univariate analysis P value	OS 5 yr %	95 % CI	Univar analy P val
Sex	Male	36	58	39-73	0.99	67	48-80	0.9
	Female	38	63	44-76		64	46-77	
Stage of disease	Localized	56	72	57-83	**< 0.0001**	73	58-83	**0.00**
	Metastatic	18	17	4-37		38	17-60	
Site of Metastasis	Lung	11	25	6-51	**< 0.0001**	50	21-74	**< 0.0**
	Bone/Bone Marrow + Lung	5	0			25	9-66	
	Other	2	0			0		
Tumour Size	< 8 cm	23	65	35-84		76	47-90	
	≥ 8 cm	16	65	37-82		81	51-90	
Primary Sites	Extremity	23	75	50-89	**0.009**	72	49-87	**0.01**
	Skull	7	43	10-73		54	13-83	
	Pelvis	8	25	4-56		38	9-67	
	Chest Wall	27	64	41-79		75	53-88	
	Spine	9	70	22-92		53	18-80	
Treatment Era			46	17-61	**0.004**	41	15-67	**0.01**
	1982-1989	12						
	1990-1999	32	39	22-57		52	33-67	
	2000-2008	30	86	66-94		89	71-96	
Histological Response			88	60-97	0.102	100		**0.00**
	100% necrosis	17						
	< 100%	17	60	32-80		74	44-90	

Table 3: Univariate Analysis of Factors Predictive for Outcome

		Pts	PFS 5 yr %	95 % CI	**Univariate analysis P value**	OS 5 yr %	95 % CI	**Uni ana P v**
Surgery	No	19	24	7-45	**< 0.001**	32	12-53	**< 0**
	Yes	55	71	56-82		78	63-87	
Definitive Surgery	No	32	38	21-55	**< 0.001**	42	25-58	**< 0**
	Yes	40	75	58-86		84	67-92	
Response to CT	PD	7	0		**< 0.0001**	0		**< 0**
	PR	50	66	51-78		50	15-77	
	CR	8	50	15-77		77	62-86	
Local Control	None	5	0		**< 0.001**	0		**< 0**
	RT alone	13	33	10-59		38	14-63	
	Surgery alone	35	67	49-80		75	57-87	
	Surgery + RT	19	70	43-87		77	49-90	
RT	No	41	61	51-81	0.761	62	44-75	0.
	Yes	32	60	40-75		55	35-71	
HD CT	No	47	60	43-73	0.79	62	46-75	0.
	Yes	25	63	41-75		75	52-88	
Status at the end of TT	PD	11	0		**0.003**	0		**< 0**
	Residual disease	7	14	7-46		29	41-61	
	CR	53	76	61-85		85	71-93	

Legend: PD, progressive disease; PR, partial response; CR, complete response; RT, radiotherapy

In the final model of multivariate analysis, the presence of metastasis was a significant prognostic factors ($p<0.01$) with a hazard ratio (HR) of 8 for recurrence while the HR was not significant for OS. The site of the primary was confirmed to be associated with a worse prognosis with an HR of 8 for skull primary (P 0.026), an HR of 43 for pelvic primary (P 0.006) and an HR of 6 (P 0,011) for chest wall primary. However the risk in term of survival was no longer

significant for skull and chest wall primary; only the presence of pelvic tumour presented a significant HR of 27 (P 0.029). The presence of a progressive disease during treatment represented a strong risk factor both for recurrence and for survival with an HR of 15 and 2249 (P 0.001), respectively. As suggested in the univariate analysis, the presence of a residual disease at the end of treatment was associated with a worse prognosis with an HR of 15 for recurrence and an HR of 67 for survival (P < 0.001). The Table 3 summarizes the multivariate analysis.

Table 4: Multivariate Analysis of Prognostic Factors.

		Pts	PFS 5 yr	95 % CI	HR	P	OS 5 yr	95 % CI	HR	P
Stage of disease	Metastatic	18	17	4-37	8	0.003	38	17-60		
Primary Sites	Skull	7	43	10-73	8	0.26	54	13-83		
	Pelvis	8	25	4-56	43	0.006	38	9-67	27	0.029
	Chest Wall	27	64	41-79	6	0.011	75	53-88		
Surgery	No	19	24	7-45			32	12-53	74	0.02
Status at the end of TT	PD	11	0		15	0.001	0		2249	< 0.001
	Residual disease	7	14	7-46	15		29	41-61	65	< 0.001

Legend: PD, progressive disease; TT, treatment; Pts, patients; HR, hazard ratio.

Only significant HR was indicated

DISCUSSION

ESFT represents the second bone tumour after osteosarcoma with the highest incidence in late childhood and adolescence (16). The occurrence in early childhood is rare accounting for less than 10 cases per million each year, while the incidence is about 30-40 cases per million between 11 and 18 years of age (16). Moreover, there are limited data about the clinical characteristics of ESFT in early childhood. Recently, Van der Berg reported a series of 14 infant: all patients had an axial tumours and most of them were PNETs (17).The age is a well known prognostic factors (4,6,7) as confirmed recently by Ladenstein in multifocal disseminated ESFT enrolled in EUROEWING 99 Protocol. Moreover, the age was taken into account in the risk stratification based on simple clinical features proposed by Rodriguez Galindo (4).

The aim of this study was to report on the clinical characteristics and outcome of pre-scholar children affected by ESFT of the bone.

The prevalence of ESFT of the bone in the AIEOP series was 11, 5% and the occurrence below the age of two years was rare with only a 20% of cases. In this series most patients had an axial primary 69% (70% in localized patients and 67% in metastatic patients) while in the large population, the axial site represents the 50% (7-9, 19-21) of the population. As observed in infant (17), the axial site seems to be a characteristic of the younger age.

Also the chest wall tumours seem a characteristic of the younger age. We reported a prevalence of 37% while a prevalence of less than 20% is usually reported (7-9; 19-21).

The pelvis tumours occur in only 11% of patients. As observed in the large series, the prevalence of pelvis tumours increase with increasing age (17, 21).

The survival both in term of OS and PFS is comparable with the older patients. The 5-year OS and PFS were 73% and 72% for the localized patients while for the metastatic patients were 38% and 17% (4, 7-9, 15, 19-21). Furthermore the survival presented an impressive improvement in the last decades with an OS a PFS that exceed the 80% (P 0.004) in the localized patients. This favourable outcome confirms a better overall survival of the younger patients affected by ESFT and this result is more impressive considering the high prevalence of axial site always associated with a worse prognosis (4, 6).

Prognostic factors seem the same of general cohort of ESFT patients. Pelvic tumour, poor histological response, presence of metastasis, bone/bone marrow involvement, surgery, quality of local control and response to treatment influence the outcome. Nevertheless, only the site of primary, presence of metastasis, surgery and response to treatment result to have an impact on survival in the multivariate analysis. In contrast tumours size don't influence outcome but this result presents some limitation due to the incomplete data (tumour size reported in only 39 patients). In contrast to Van den Berg et al. (17), our data confirm the role of the general accepted prognostic factors and of age in the pre-scholar ESFT of the bone .

The axis localization is more frequent in this age group with a higher prevalence of the chest wall tumours. Further biological studies are needed to identify the causes of this prevalence.

CONCLUSION

The axis localization is more frequent in pre-scholar children affected by ESFT of the bone with a higher prevalence of the chest wall tumours. Further biological studies are needed to identify the causes of this prevalence.

The outcome of the pre-scholar children affected by ESFT is better than the general population with a significant improvement of survival in the last decade confirming the favourable prognosis of this age group. Further staging system will strictly take in to account the age as prognostic factors.

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