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Unusual sites of Ewing sarcoma (ES): A retrospective multicenter 30-year experience of the Italian Association of Pediatric Hematology and Oncology (AIEOP) and Italian Sarcoma Group (ISG) ☆

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Abstract ***Purpose:*** The aim of this study was to describe the Italian Association of Pediatric Hematology and Oncology (AIEOP) and Italian Sarcoma Group (ISG) experience from 1980 to 2009 on 112 patients with Ewing sarcoma (ES) occurring in unusual sites such as the craniofacial bones (CF), hands or feet (HF), or the mobile spine. These sites were grouped because their rarity as ES localisations.

Patient and methods: Twenty-six patients had CF ES (23%), 37 patients had HF ES (33%) and 49 patients had mobile spine ES (44%). A total of 26 patients presented with synchronous metastatic disease (23%). The local treatment with surgery and/or radiotherapy differed among ES sites. Systemic therapy was administrated according to the protocols in use over the years.

Results: From the data available, the histological/radiological response was higher for HF-patients even not statistical significant (good responders: CF 41%, HF 65% and mobile spine 39%, $P = 0.$NS) and the probability of achieving complete response was similar among the three sites (CF 87%, HF 83% and spine 74%, $P = 0.44$). Ten year overall survival (OS) was

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61% (95% confidence interval [CI] 39–82), 63% (95% CI 37–89) and 64% (95% CI 49–79) for CF, HF or vertebral ES, respectively (P = NS). Ten year OS for non-metastatic patients was 60% (95% CI 36–83), 75% (95% CI 56–94) and 67% (95% CI 47–89) for CF, HF and mobile spine patients respectively (P = NS). Ten year OS was 45% (95% CI, 31–84) and 70% (95% CI, 61–85, [$p = 0.01$]) for metastatic and localised ES, respectively.

Conclusions: The probability of successful treatment did not differ from ES of the extremities. Furthermore, our series confirm the poor prognosis for patients with metastatic disease. Our data do not strengthen the need for a specific protocol for unusual site ES.

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1. Introduction

Ewing sarcoma (ES)/primitive neuroectodermal tumours (PNET, together defined as Ewing sarcoma [ES]) of the bone are the second most common primary malignant bone cancers in children and adolescents. Its incidence is around 0.3/100,000 white Caucasians, while it is very rare in African and Asian populations.[1,2] In Italy, approximately 100 paediatric patients are diagnosed with ES per year. 20% of patients have ES diagnosed in the pelvic bones, 50% show extremity tumours, while, for the remaining patients, this tumour may involve any other bone or soft tissue. Between 20% and 25% of patients have synchronous metastatic disease.

With most modern treatment regimens, the overall survival (OS) for ES of the extremities is around 80% for patients with localised disease, while event-free survival (EFS) may approach 70%.[3,4] Disease-Free Survival (DFS) is lower for patients with lung metastases at presentation (around 40%) and is dismal for patients with multicentric ES.[5,6]

For decades, chemotherapy for ES has been based on a four-drug combination of vincristine, doxorubicin, cyclophosphamide and actinomycin-D (VACAc regimen).[4,5] More recent studies replaced cyclophosphamide with ifosfamide and others added ifosfamide and/or etoposide.[7–9]

The literature is poor about the outcome of unusual sites of ES, since most authors report the outcomes of single case or, by contrast, including unusual sites together with ES of the extremities. In order to understand whether unusual sites are favourable or unfavourable localisations, here we report the experience of the Italian Association of Pediatric Hematology and Oncology (AIEOP) and Italian Sarcoma Group (ISG) with ES occurring in the craniofacial bones (CF), hands or feet (HF) bones or mobile spine in children and young adults. Clearly these sites have different local approaches (both surgery and radiotherapy [RT]), however their systemic treatment was the same according to the given protocol so the histological or radiological response could be compared.

2. Patient and methods

Data of patients with ES occurring in CF, HF bones and mobile spine were retrieved from AIEOP and ISG registries.

The patient's medical records were retrospectively reviewed and data regarding gender, age, presence of metastases, tumour dimension, tumour necrosis by histological or radiological assessment after primary chemotherapy and outcome were collected. Informed written consent was obtained from parents or guardians at the time of diagnosis.

Patients were prospectively enroled in the national protocols ongoing at the time of diagnosis, however some regimens were unique to an institution.[4,10–18] Primary chemotherapy was recommended in all cases, followed by surgery and/or radiotherapy (RT) on the primary site and further chemotherapy as consolidation treatment. The policy for the choice of timing and modality of the local treatment remained unmodified throughout the study period. The response (histological and/or radiological) to primary chemotherapy was evaluated according to established criteria available over the years.[19–21] Briefly the histological response was defined as: grade I when evidence of macroscopic foci of viable tumour cells were found; grade II if only isolated microscopic nodules of viable tumour cells were found and grade III if no nodules of viable tumour cells were found. The radiological response assessment after induction chemotherapy distinguished patients with complete disappearance of the disease involving the soft tissues compared with patients with persistent disease of the soft tissues. The complete response was defined as the complete disappearance of tumour at the end of the given treatment.

2.1. Statistical analysis

The statistical analysis of patient-related factors and treatment-related factors were studied with the Fisher exact test or χ^2 test for dichotomical variables, while the Student's T-test or the Mann Whitney tests was used for continuous variables. All tests were two-sided.

Overall survival (OS) was calculated from diagnosis to death or to the last follow-up irrespective of whether relapse occurred. The event-free survival (EFS) was calculated as the time from diagnosis to relapse or to death from treatment-related complications or secondary malignancy or to the last follow-up whichever occurred first. Both OS and EFS were calculated by Kaplan–Meier statistics,[22] while differences among curves were calculated by the log-rank test.[23]

Factors considered in univariate analysis for each ES site and OS or EFS as end-points were: gender, age at diagnosis, period of diagnosis (before 2000 versus after January 2000), tumour volume, metastatic versus localised disease, time lapse from symptoms to diagnosis, histological or radiological response (good response versus poor response), chemotherapy protocols (national versus local) and finally the achievement of complete response (yes versus no). Factors having a P value less than 0.2 in univariate analysis for the EFS as end-point were run in multivariate analysis by the Cox regression model.[24]

3. Results

A total of 112 patients treated in 11 different centres were eligible and were included in this study.

As reported in Table 1, 26 patients had CF ES (23%), 37 had HF ES (33%) and 49 patients had mobile spine ES (44%). Patients' details are outlined in Table 1. Table 2 describes the local treatments by site of occurrence.

At the time of writing this paper (April 2013), among the 112 patients, 52 are alive with no evidence of disease (NED), 13 are still alive after relapse, while 37 died of progression of the disease and one patient died of congestive heart failure. One patient developed an acute myeloid leukaemia (AML M2) 4 years after ES diagnosis (alive at 3 years from AML diagnosis). Ten patients were lost at follow-up. The median follow-up for surviving patients was 59 months (8–87 months), for deceased patients it was 21 months (3–189).

The OS and EFS for all ES were 64% (95% CI 53–74) and 63% (95% CI 56–70). The OS was 66% (95% CI 52–79) and 72% (95% CI 54–90, $P = \text{NS}$) for males and females respectively. OS according to the median age at diagnosis ($\geqslant$13 years) was 64% (95% CI, 52–84) versus 58% (95% CI 42–73, $P = \text{NS}$) for patients younger than 13 years. The 10-year OS was 70% (95% CI 61–85) and 45% (31–84, $P = 0.01$) while the EFS was 64% (49–77) and 42% (31–53, $P = 0.03$) for localised and metastatic patients, respectively (Fig. 1).

According to the period of treatment OS was 68% (95% CI 58–82) in patients treated after 2000 versus45%

Table 1
Clinical details of ES patients at diagnosis. ES = Ewing sarcoma; ml = millilitres; PNET = primitive neuroectodermal tumours. The p value reports the Fisher's exact test or χ^2 test.

Characteristics		Total	Craniofacial	Hands or feet	Mobile spine	P
Patients		112	26	37	49	
Sex	Male	74 (66%)	16 (61%)	28 (76%)	30 (61%)	NS
	Female	38 (34%)	10 (38%)	9 (24%)	19 (39)	
Age years (range)		11 (1–39)	10 (1.6–18.4)	9 (5.4–30.1)	15 (1–39)	<0.001
Diagnosis	Ewing	99 (88%)	21 (81%)	34 (92%)	44 (90%)	NS
	PNET	13 (12%)	5 (19%)	3 (8%)	5 (10%)	
Symptoms-diagnosis Interval in weeks (range)		8 (0–54)	18 (0–28)	12 (2–54)	8 (1–36)	NS
Asthenia	No	58 (52%)	20 (77%)	12 (92%)	26 (53%)	0.038
	Yes	24 (21%)	3 (11%)	3 (8%)	18 (49%)	
	Not known	30 (27%)	3 (11%)	22 (59%)	5 (10%)	
Weight loss	No	73 (65%)	23 (88%)	13 (35%)	37 (75%)	NS
	Yes	9 (8%)	0	2 (5%)	7 (14%)	
	Not known	30 (27%)	3 (11%)	22 (59%)	5 (10%)	
Fever	No	79 (70%)	15 (58%)	28 (76%)	36 (73%)	NS
	Yes	19 (17%)	8 (31%)	4 (11%)	7 (14%)	
	Not known	14 (12%)	3 (11%)	5 (13%)	6 (12%)	
LDH	Normal	60 (53%)	8 (31%)	20 (54%)	32 (65%)	NS
	High	23 (20%)	8 (31%)	6 (16%)	9 (18%)	
	Not known	29 (26%)	10 (38%)	11 (30%)	8 (16%)	
Median volume ml (range)		27 (1–240)	33 (1–240)	17 (1–236)	28 (1–210)	NS
Metastatic disease	Yes	26 (23%)	5 (19%)	10 (27%)	11 (22%)	NS
	No	86 (77%)	21 (81%)	27 (73%)	38 (77%)	

LDH=Lactate Dehydrogenase

Table 2
Details of local therapy given. The p value was calculated according to the Fisher's exact test.

Local treatment	Craniofacial, $N = 26$	Hands and feet, $N = 37$	Mobile spine, $N = 49$	P
Surgery alone	5 (19%)	14 (38%)	4 (8%)	0.0022
Surgery & radiotherapy	8 (31%)	9 (24%)	15 (31%)	
Radiotherapy alone	9 (35%)	6 (16%)	23 (47%)	
Not known	4 (15%)	8 (22%)	7 (14%)	

(95% CI 21–68, P = NS) for those treated before 2000 (Fig. 2). Among poor responder patients, despite not achieving the statistical significance (a total of 37 poor responder patients were analysed: 7 patients before and 30 patients after 2000) a trend for a better outcome was observed in patients treated in the last period (10 year-OS 60% [95% CI 41–80] after 2000 versus 44% [95% CI 10–87) before 2000, $P = 0.07$) whereas no differences were observed in good-responder patients (OS was 73% (95% CI 51–95) and 73% (95% CI 47–99). The OS according to time to diagnosis (> versus ⩽8 weeks) was 63% (95% CI 48–77) and 57% (95% CI 34–80, P = NS), respectively. Tables 3 and 4 provide details of the histological/radiological responses and the likelihood to achieving the complete response according the three sites. Finally Table 5 reports the outcome of patients according to given protocols over the years.

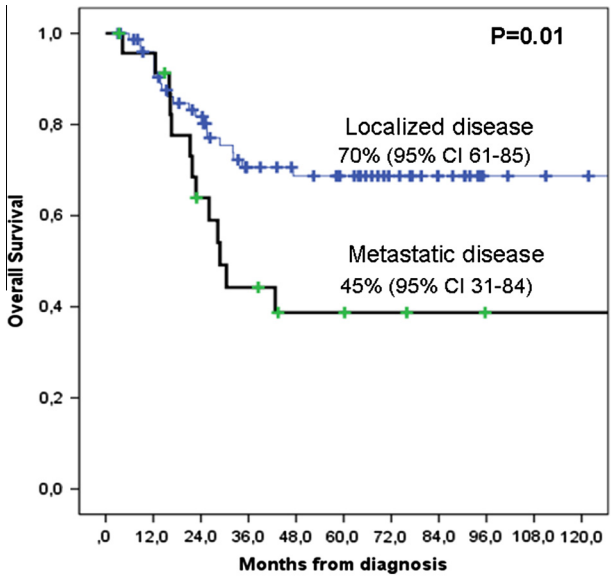

Fig. 1. Overall survival for localised and metastatic patients. All Ewing sarcoma (ES) sites were analysed.

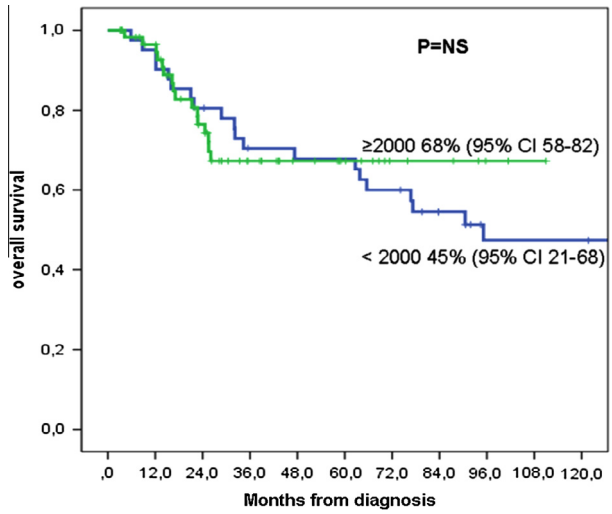

Fig. 2. Overall survival for patients diagnosed before and after 2000. All Ewing sarcoma (ES) sites were analysed.

3.1. Craniofacial ES

Twenty-one patients had classical ES (80%), while 5 had PNET. The majority of patients were males (16, 61%), their median age was 10 years (range 1–18). Five out of 26 CF ES were metastatic at diagnosis (19%), one patient had lung metastasis (4%), 3 patients had bone metastases (11%) while one patient had both lung and bone metastases at presentation (4%). The median tumour volume was 33 ml (1.2–240), and the delay between the onset of symptoms and diagnosis was 8 weeks (0–28). Surgery was the local treatment in 13 patients (54%) and 8 received also RT (69%). Nine patients received only radiation therapy (RT) as the local therapy (35%). Eight patients underwent high dose Busulfan–Melphalan (HDCT) followed by autologous haematopoietic stem cell transplantation (HSCT, 30%).

Ten year OS and EFS rates were 63% (95% CI 37–89) and 52% (95% CI 26–78), respectively (Fig. 3). OS and EFS were 64% (95% CI 40–88), 58% (95% CI 34–82, P = NS) and 50% (95% CI 31–88) and 20% (95% CI 0–88, $P = 0.03$) for localised or metastatic ES patients, respectively. Twenty patients achieved complete response (77%), their EFS was 57% (95% CI 10–64) while no patients survived if complete response was not achieved ($P < 0.001$). The EFS was 57% (95% CI 17–74) and 50% (95% CI 10–75) for patients undergoing surgery compared to others (P = NS). Among available data, seven patients (27%) were good-responders and 10 patients (37%) were poor-responders. The EFS was 57% (95% CI 10–81) and 44% (95% CI 10–64, P = NS). Among the poor-responder group only two out of 10

Table 3
Histological/radiological response. The p value was calculated according to the Fisher's exact test.

Histological/ radiological response	Craniofacial, $N = 26$	Hands and feet, $N = 37$	Mobile spine, $N = 49$	P
Good responders	7 (27%)	13 (35%)	13 (26%)	0.16
Poor responders	10 (38%)	7 (19%)	20 (41%)	
Not known	9 (35%)	17 (46%)	16 (33%)	

Table 4
Remission achieved after the conclusion of the first line therapy for unusual EFTs. The p value was calculated by Fisher's exact test or χ^2 test.

Complete response	Craniofacial, $N = 26$	Hands and feet, $N = 37$	Mobile spine, $N = 49$	P
Yes	20 (77%)	15 (40%)	28 (57%)	0.44
No	3 (11%)	3 (8%)	10 (20%)	
Not known	3 (11%)	19 (51%)	11 (22%)	

Table 5
Details of treatment results by protocols for Ewing Sarcoma patients with typical and unusual sites.

Protocols	Protocol EFS	Patients at study outcome	Histological or radiological response	Complete response at the end of treatment**
AIEOP CNR 88	42%	3 patients: 2 patients CF 1 relapsed, 1 patient HF no relapse.	3: NK	3: 100%
AIEOP CNR 91	77.8%	7 patients: 2 patients CF, 1 lost al last FUP, 1 patient relapsed, 5 patients HF, 2 relapsed, 1 dead for cardiac failure, 1 patient lost at FUP	1 GR 7: NK	2: 100%
AIEOP CNR 93	21%	3 patients: 2 HF 2 relapsed, 1 patient mobile spine no relapse	1 GR 2: NK	3: 100%
IOR/Ew1	55.1%	8 patients: 4 HF relapsed, 4 mobile spine relapsed	1: GR 7: NK	8: NK
IOR/Ew2	60.7%	3 patients: 1 patient HF no relapsed, 2 patients mobile spine 1 relapsed	2: GR 1: NK	2: 100%
IOR/Ew3	79%	5 patients: 4 HF, 1 patient relapsed, 1 patient lost at follow-up, 2 patients NED	3: GR 1: PR 1: NK	1: 100% 7: NK
Local INT	56% GM-CSF arm 51% no GM-CSF arm	11 patients: 6 patients CF, 2 relapsed, 2 patients HF: 1 patient relapsed, 3 patients mobile spine: 2 relapsed	5: GR 6: PR	11: 91%
AIEOP ISG/SSG III	43%	5 patients CF: no relapse, 7 patients HF: 2 relapsed, 18 patients mobile spine: 5 patients relapsed, 1 patients lost at FUP	8: GR 14: PR 8: NK	18: 75%
AIEOP ISG/SSG IV	37%	11 patients: 3 patients CF 2 relapsed, 6 patients HF 3 relapse, 2 patients mobile spine, no relapse	5: GR 2: PR 4: NK	7: 87%
AIEOP ISG/SSG VHR	43%	4 patients: 1 CF relapsed, 1 patient HF relapsed, 2 patients mobile spine 2 relapsed	0: GR 3: PR 1: NK	2: 50%
CCGS 7781/POG	Not known	6 patients: 2 patients CF, 1 relapsed, 1 patient HF no relapse, 3 patients mobile spine, no relapse	2: GR 2: PR 2: NK	6: 83%
Local OPBG	ICE-CAV regimen 67% Other regimens 22%	8 patients: 3 patients CF 2 relapsed, 1 patient HF no relapse, 4 patients mobile spine 2 relapsed	1: GR 7: PR	8: 75%
EuroEwing99	27%	1 patient mobile spine, no relapse	1: PR	1: 100%
EpSSG 2005	Ongoing	1 patient mobile spine, no relapse	1: GR	1: 100%
AIEOP RMS 99	35.3%	1 patient mobile spine relapsed	1: PR	1: 0%
Other/not known	NA	6 patients: 2 patients mobile spine 2 relapsed, 1 patient CF no relapse	3: GR 3: NK	2: 100%

Abbreviations: EFS, event-free survival; AIEOP, Associazione Italiana di Ematologia Oncologia Pediatrica; CNR, Centro Nazionale Ricerche; IOR, Istituti Ortopedici Rizzoli; INT, Istituto Nazionale dei Tumori, Milan, Italy; OPBG, Ospedale Pediatrico Bambin Gesù, Rome, Italy; ISG, Italian Sarcoma Group; SSG, Scandinavian Sarcoma Group; ICE, Ifosfamide, Carboplatin, Etoposide-Cyclophosphamide, Adryamicin, Vincristine; CF, craniofacial; HF, hands or feet; NED, no evidence of disease; FUP, follow-up; GR, good-responder; PR, poor-responder; NK, not known.
** Number of evaluated patients and percentage of evaluable patients having reached complete response at the end of treatment.

patients were metastatic at presentation and both relapsed at 16 and 38 months from diagnosis. The EFS of patients treated before 2000 was 43% (95% CI 9–77) versus 61% (95% CI 35–88, P = NS) for patients treated after 2000.

3.2. Hands and feet ES

Thirty-four patients had classical ES (92%), while 3 patients had PNET (8%). The majority of patients were males (28, 76%), their median age was 9 years (5–30). Ten out of 37 patients were metastatic at diagnosis (27%): five patients had lung metastasis (13%), 4 patients had bone metastasis (11%) and one patient had both lung and bone metastasis (3%). The median tumour volume was 17 ml (1–236) and the delay before diagnosis was 12 weeks (2–54). A total of 23 patients had surgery as the local therapy (62%), while 9 patients received also RT (24%). Six patients received only RT as the local treatment (16%). Ten patients received HDCT (27%).

Ten year OS and EFS were 61% (95% CI 39–82, Fig. 3) and 59% (95% CI 35–74). The OS and EFS were 66% (95% CI 41–91, $P = 0.02$) and 65% (95% CI 36–80, $P = 0.02$) versus 44% (95% CI 30–100) and 43% (95% CI 30–100) and for localised or metastatic ES patients, respectively.

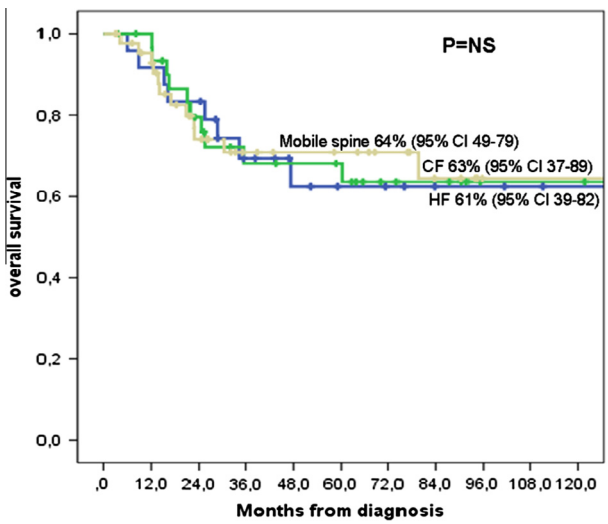

Fig. 3. Overall survival for craniofacial, hands or feet and mobile spine Ewing sarcoma (ES).

The EFS was 61% (95% CI 34–88) for patients achieving a complete response, while no patients survived if the complete response was not reached ($P < 0.001$). The EFS was 77% (95% CI 47–90) and 33% (95% CI 0–52) for patients undergoing surgery compared to others ($P = 0.03$). Among available data, 13 patients were good responders (35%), 7 patients were poor-responders (19%). A total of 15 patients achieved complete response after the end of treatment (41%), while 3 did not.

For 19 patients (51%) these data were not available.

There were no differences in the EFS probability among good-responder or poor-responder patients. Among the seven poor-responder patients, two were metastatic at presentation (one with bone metastasis and one with lung metastasis) and finally relapsed at 29 months. The EFS of patients treated before 2000 was 64% (95% CI 28–82) versus 54% (95% CI 16–74, $P =$ NS) for patients treated after 2000.

3.3. Mobile spine ES

Forty-four patients (90%) had classical ES while 5 patients had PNET (10%). The majority of patients were males (30, 61%), their median age was 15 years (1–39). Eleven patients (22%) were metastatic at presentation. Five patients had lung metastasis (10%), two patients had bone metastases (4%) and four patients had both bone and lung metastases at diagnosis. A total of 19 patients had surgery as the local therapy (39%), while 15 patients also received RT (31%). A total of 23 patients received RT as the only local treatment (47%). Nineteen patients received HDCT (39%).

The 10 year OS and EFS of this subgroup were 64% (95% CI 49–79) and 61% (95% CI 39–75). The EFS was 50% (95% CI 22–100) and 76% (95% CI 51–88, $P < 0.001$) for metastatic or localised ES patients, respectively. Thirteen patients were good-responders (27%), 20 patients were poor-responders (41%), these data were not available for other patients (16 patients, 32%). A total of 28 patients achieved a complete response (57%), their EFS was 71% (95% CI 51–91), while it was 20% (95% CI 0–50) for those who did achieve the complete response at the end of treatment. Among these 10 patients who never achieve the complete response after the end of treatment, three patients are alive without ES relapse or progression. Two of them underwent surgery combined with RT, while one patient received only RT. Their median follow-up was 21 months (3–64). A total of 23 patients were evaluable for EFS according their histological response. EFS was the same (66% [95% CI 25–85]) for both good-responder and poor responder patients. EFS of patients treated before 2000 was 55% (95% CI 28–82) versus 60% (95% CI 16–84, $P =$ NS) for patients treated after 2000.

4. Discussion

The aim of this study was to analyse the characteristics and the outcome of ES localised in sites other than the extremities or pelvic bones, such as the craniofacial, hand/feet bones and the mobile spine. As the number of papers published to date on this topic is somewhat limited[7,25–30] we decided to retrieve data of these unusual presentations and to analyse their characteristics and outcome.

Three major points can be extrapolated from our study.

Point 1: Patients with ES of the mobile spine were older than those with CF or HF location and, more commonly, had asthenia at presentation and a shorter median interval between symptoms onset and diagnosis. The LDH level was significantly higher in CF patients. The tumour volume was higher for CF and mobile spine ES compared to HF ones (27 ml versus 33 ml versus 17 ml), however, when we then compare the tumour size of these unusual sites to classical ES, their median volume was significantly lower,[29,30] Regarding other variables, such as gender, age, LDH serum level, no differences were observed. Finally, we found a similar proportion of metastatic versus non-metastatic patients compared to ES of the extremities.[4]

Point 2: The modality of local control differed according to the site of tumours. Patients with a mobile spine tumour were mainly treated with RT (91% of patients according to the available data), sometimes combined with surgery often given upfront. It has to be noted that patients were often treated with decompressive surgery at diagnosis and then, in this particular case, as local therapy they receive RT. The initial surgical approach may have a role in the local control of the disease. According to this a recent French study showed

that 69% of patients received decompressive surgery at diagnosis and, subsequently, as a local treatment, 92% had received treatments including RT. In particular, patients who received surgery as the only local treatment, presented a lower probability of 5-year local control (50%), compared to those who received both surgery and RT (83%) or RT alone (74%).[30]

In the case of CF patients, surgery ± RT was given to 50% of patients and in the case of HF location, surgery ± RT was used in 62% of cases. In patients with CF ES the percentage of patients treated with only RT was 35%, for HF patients it was 16% and finally it was 47% for mobile spine patients. However it has to be stated that the local treatment for 19 patients is unknown.

Point 3: The probability of survival of the patients with non-metastatic ES included in the present study was 70% (95% CI 61–85) at 10 years with survival substantially unmodified in those patients treated in the last decade. Starting from 1999, for all patients the chemotherapy was tailored according to patient-specific histological and/or radiological responses. In particular, the poor-responder patients were candidates for intensification with Busulfan and Melphalan.[34–36] In this analysis we observed that the prognosis of good-responders was very similar among patients treated before and after 2000, while, an observed better OS was observed in poor-responder patients treated after 2000,[4] probably also given by an improvement of surgical or RT techniques. It is interesting to notice that in other experiences[29,33] patients with ES located to HF, mobile spine and CF had a lower probability of survival. All our patients received systemic chemotherapies. The OS for non-metastatic patients was 60% (CI 95% 36–83), 75% (CI 95% 56–94) and 67% (CI 95% 47–89) for CF, HF and mobile spine patients, respectively (data not shown).

Despite these considerations and together with the lacking data in a 30-year study, the probability of achieve the complete response at the end of the treatment was surprisingly high (around 80% for all three sites). If we consider the outcome of patients who only received local therapies such as surgery or RT or a combination of both (before 1980), the long-term benefit of systemic chemotherapy cannot be denied.[10,11]

In ES of the extremities, a continuous improvement for localised EFS from 60% to above 70% was observed, while a significantly lower probability of survival for metastatic patients is observed to date.[15,16,31,32] Although we are not able to distinguish a different prognosis throughout the study period, the differences in EFS probabilities between localised and metastatic disease has also been confirmed in our cohort. Overall, the probability of survival was quite satisfactory and we observed a trend for an improved survival over the years for poor-responders. Our results also do suggest that the ES of unusual locations are on average small in volume and this is a well known favourable prognostic factor. These data should be taken into consideration when we analyse the role of high dose chemotherapy if we consider that the most recent and intensive protocols designed for metastatic patients can offer around 40% of a 5 year-EFS.

In conclusion, while we are aware that the results of this Italian experience on ES in unusual sites might be related to the long-term duration of the study and the retrospective analysis, this report is the largest experience on unusual site ES, and does add some new information to the present literature. Furthermore, while we do not recommend the need for specific protocols for the unusual sites of occurrence of these tumours, and despite not achieving statistical differences, our data do show an improved outcome for poor-responders over the last years.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2013.06.045.

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