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Original Research

Extraskeletal osteosarcoma: A European Musculoskeletal Oncology Society study on 266 patients☆

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KEYWORDS
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Abstract ***Purpose:*** Prognosis of extraskeletal osteosarcoma (ESOS) is reported to be poorer than that of skeletal osteosarcoma. This multicenter retrospective study aimed to evaluate factors influencing ESOS prognosis.

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Localised osteosarcoma; EMSOS

Patients and methods: Members of the European Musculoskeletal Oncology Society (EMSOS) submitted institutional data on patients with ESOS.

Results: Data from 274 patients treated from 1981 to 2014 were collected from 16 EMSOS centres; 266 patients were eligible. Fifty (18.7%) had metastases at diagnosis. Of 216 patients with localised disease, 211 (98%) underwent surgery (R0 = 70.6%, R1 = 27%). Five-year overall survival (OS) for all 266 patients was 47% (95% CI 40–54%). Five-year OS for metastatic patients was 27% (95% CI 13–41%). In the analysis restricted to the 211 localised patients who achieved complete remission after surgery 5-year OS was 51.4% (95% CI 44–59%) and 5-year disease-free survival (DFS) was 43% (95% CI 35–51%). One hundred twenty-one patients (57.3%) received adjuvant or neoadjuvant chemotherapy and 80 patients (37.9%) received radiotherapy. A favourable trend was seen for osteosarcoma-type chemotherapy versus soft tissue sarcoma-type (doxorubicin ± ifosfamide) regimens. For the 211 patients in complete remission after surgery, patient age, tumour size, margins and chemotherapy were positive prognostic factors for DFS and OS by univariate analysis.

At multivariate analysis, patient age (≤40 years versus >40 years) (P = 0.05), tumour size (P = 0.0001) and receipt of chemotherapy (P = 0.006) were statistically significant prognostic factors for survival.

Conclusion: Patient age and tumour size are factors influencing ESOS prognosis. Higher survival was observed in patients who received perioperative chemotherapy with a trend in favour of multiagent osteosarcoma-type regimen which included doxorubicin, ifosfamide and cisplatin.

1. Introduction

First reported in 1941, extraskeletal osteosarcoma (ESOS) is a rare mesenchymal tumour arising in soft tissue accounting for 1% of all soft tissue sarcomas and 4% of all osteosarcomas [1–3]. Several retrospective series have been reported, mostly with less than 50 patients. The largest series are shown in Table 1. Median age at diagnosis is in the fifth and sixth decade of life. In children, ESOS are much rarer than skeletal osteosarcoma [11]. Males prevail in all but one cohort. Aetiology is unknown, although 5–10% occur after radiotherapy (RT) and preceding trauma is reported in 12–13% [7]. An association with previous myositis ossificans has also been postulated [12].

ESOS usually occurs as a slow growing mass with a longer interval between symptom onset and diagnosis compared to skeletal osteosarcoma (median 6 versus 2 months) [4–8,14]. Common sites are limbs, retroperitoneum and chest wall [7], but 50 cases arising in the breast have been described [15]. These must be distinguished from matrix-producing epithelial breast carcinomas. Recommended criteria for ESOS of the breast include absence of an epithelial component and presence of malignant osteoid [15,16]. Histologically ESOS presents similar characteristics to those of skeletal osteosarcoma with a differing proportion of osteoid and cartilaginous and fibrous tissue [13]. It is high grade though exceptionally may be well differentiated [1].

ESOS relapse rate is over 75% [13]. Distant metastases occur most frequently in lungs, lymph nodes and bone [7].

Surgical resection is the standard treatment. ESOS are considered poorly responsive to chemotherapy: Ahmad *et al.* [6] reported only 19% response (complete remission [CR]+ partial remission [PR] to doxorubicin-based chemotherapy and 13% to cisplatin-based chemotherapy. However, because of the perceived similarities to skeletal osteosarcoma, the role of chemotherapy is debated.

This retrospective study, performed under the auspices of EMSOS, aimed to improve knowledge on the natural history of ESOS, identify prognostic factors and inform on the role of chemotherapy treatment.

Table 1
ESOS larger cohort studies.

Author (year)	Total no. of patients (localised)	Outcome
Lee (1995) [8]	40	5-year OS 37%
Ahmad (2002) [6]	60 (38)	5-year DFS 46% (localised)
Choi (2014) [9]	53 (42)	3-year OS 61% (localised)
Thampi (2014) [10]	256 (188)	5-year OS 37% (47% in localised)
Longhi (2017)	266 (211)	5-year OS 47% (51.4% in localised)

ESOS = extraskeletal osteosarcoma; OS = overall survival; DFS = disease free survival.

2. Patients and methods

A request was sent to EMSOS members to participate in the study with study information available on the society website (www.emsos.org). All participating centres obtained ethical approval. All centres were provided

with a case report form for collection of anonymised data.

From March 2014 to December 2015 data for 274 patients treated from 1981 to 2014 from 16 centres or cooperative groups were submitted for analysis. For this study we accepted a time lapse of 33 years due to rarity of the disease and considering that not many changes occurred in this period for ESOS treatment. Analyses were performed by descriptive statistics. Median follow up for the 266 patients was 22.5 months (range 1–384 months).

Overall survival (OS) was calculated from diagnosis to death or last follow up, disease-free survival (DFS) was calculated from date of surgery to relapse/progression or last follow up by the Kaplan–Meier method. The time scale was extended to the last follow up if none of these events were observed. Log-rank test was used to compare survival curves for the different subgroups of patients. Statistical significance of each variable was then tested by multivariate analysis using the stepwise model and Cox regression analysis. Osteosarcoma-type chemotherapy corresponds to the multidrug regimen similar to that used for bone osteosarcoma with cisplatin, doxorubicin, ifosfamide, methotrexate and sometimes etoposide. Soft tissue sarcoma-type chemotherapy corresponds to a regimen similar to that used for soft tissue sarcomas (an anthracycline with or without ifosfamide).

3. Results

Two hundred sixty-six patients had adequate data for analysis. Patient characteristics are reported in Table 2. There was a higher incidence of male gender (M:F = 1.5:1). Median age was 57 years (range, 12–91). The median interval from symptom onset to diagnosis was 5 months (range 0–130 months) with some cases of very late diagnosis. Median tumour size was 10 cm (range 2–50 cm). Histologic subtype distribution was similar to that of skeletal osteosarcoma [1]. Most cases were categorised as high grade osteosarcoma without specification of subtype. Three patients had a previous diagnosis of myositis ossificans in the site where ESOS occurred. Twelve patients had 13 different previous malignancies. ESOS was a radiotherapy-induced secondary malignancy in 5 of these 12 patients: 1 non-Hodgkin lymphoma, 1 fibrosarcoma, 1 rhabdomyosarcoma and 2 Ewing sarcomas, after a mean interval of 17.7 years (7–38 yrs). Five-year OS for the 266 patients was 47% (95% CI 40–54%) and 51.4% (95% CI 44–59%) for the 211 patients with localised disease ($P < 0.0001$) after surgical excision (Fig. 1).

Six patients developed a second malignancy after ESOS (two kidney carcinoma, one bladder carcinoma, one prostate cancer and two acute myeloid leukaemia [AML]). The 2 patients (15-year old male and 54-year old female) who developed AML received osteosarcoma-type chemotherapy and no RT and AML was probably in correlation with chemotherapy. The other tumours occurred in patients over 70 years of age. The 2 patients with secondary kidney carcinoma and the patient with prostate cancer received only chemotherapy. The patient of 73 with ESOS of shoulder treated with local RT developed a bladder cancer 13 years later. So apart from AML, the other secondary cancers could be related more to age of patients.

Table 2
Patient characteristics; all 266 pts (left) and 211 pts with localised ESOS (right).

	All patients (266)	Pts with localised disease (211)
Median age years	57 (12–91)	57 (12–91)
Gender		
- Male	162 M:F = 1.5:1	128 M:F = 1.5:1
- Female	104	83
Stage		
- Localised	216 (80.8%)	211
- *Metastatic	50 (18.7%)	–
Site of primary tumour		
- Extremity	221 (83%)	180 (85.7%)
- Non-extremity	45 (16.9%)	31 (14.3%)
Chest	25	17
Abdomen	8	3
Viscera	6	5
Breast	6	6

ESOS = extraskeletal osteosarcoma; Pts = patients; *Metastatic at diagnosis.

3.1. Patients with metastases

Fifty patients had metastases at diagnosis: median age 58.5 years (range, 13–87 years), 32 male and 18 female, 40 patients had one metastatic site, ten had multiple sites. Lung metastases were reported in 42/50 patients, bone in four, lymph nodes in six, abdominal metastases

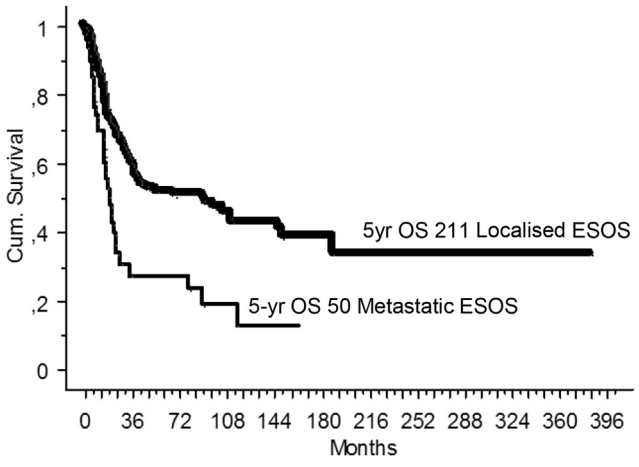

Fig. 1. 5-year overall survival of localised versus metastatic extraskeletal osteosarcoma ($P < 0.0001$).

in three (1 in omentum, 2 abdomen not otherwise specified), liver metastases in two and brain metastases in 1 patient.

Chemotherapy was administered in 36 of the 50 metastatic patients at presentation. 28/36 (77.7%) received an osteosarcoma-type regimen: five received doxorubicin–cisplatin, 11 doxorubicin–cisplatin–ifosfamide, nine doxorubicin–cisplatin–ifosfamide–methotrexate, two doxorubicin–cisplatin–ifosfamide–etoposide and one doxorubicin–cisplatin–ifosfamide–methotrexate–etoposide. Eight patients received a soft tissue sarcoma-type scheme: four a combination of doxorubicin + ifosfamide, three doxorubicin alone and one only high dose ifosfamide. RT was given to 14 patients, in 11 it was associated with chemotherapy. Two patients received only best supportive care. Thirty-three of 50 patients were already dead at the onset of the study, with a median follow up of 19 months (range, 1–142 months), the 5-year OS for the 50 metastatic patients was 27% (95% CI 13–41%).

3.2. Patients with localised disease

Of the 216 patients with localised disease at diagnosis, 211 underwent surgical resection of the primary tumour, in 5/216 (2.3%) no surgery was performed (primary site: 1 neck, 1 chest, 1 thigh, 2 pelvises). Of these patients, three received only local palliative RT, the other two received chemotherapy alone. Data of 211 localised patients are reported in Table 3.

Forty-six (21.8%) had surgery alone, 43 (20.3%) had surgery + RT, 83 (39.3%) had surgery + chemotherapy and 37 (17.5%) received surgery + RT + chemotherapy. In two cases treatment was unknown. Surgical margins were reported as R0 in 149 (70.6%) patients, R1 in 57 (27%) and unknown in five. In this group of 211 patients with resected localised disease, 5-year OS and 5-year DFS were 51.4% (95% CI 44–59%) and 43% (95% CI 35–51%), respectively (Fig. 2). One hundred twenty-one of 211 (57.3%) patients with localised disease were alive at time of data lock; 77/90 (85.5%) died of ESOS; 13 patients died of causes unrelated to ESOS treatment (12 of whom had no recurrence reported): 2/13 died of a haematologic second malignancy (one AML and one myelodysplastic syndrome (MDS) which progressed to AML). The 2 patients who developed an AML received chemotherapy osteosarcoma-type and no RT. One case was a 15-year old male, who after 2 years from diagnosis of ESOS developed AML, the other was a 54 year old female, who developed a MDS 3 years after ESOS treatment and after another 4 months MDS turned into AML.

Table 3
5-year DFS and 5-year OS in 211 patients with localised ESOS.

		No. of Pts	5-year DFS (95% CI)	5-year OS (95% CI)
		211	43% (35–51)	51.4% (44–59)
Gender	Male	128 (60.6%)	40% (31–50)	48% (39–58)
	Female	83 (39.3%)	46% (33–59)	56.5% (44–69)
			P = 0.2	P = 0.9
Age	≤18 years	16 (7.5%)	67% (43–91)	58% (32–84)
	19–40 years	32 (15.1%)	65% (46–84)	71% (52–89)
	41–65 years	98 (46.4%)	45% (33–56)	57% (46–68)
	>65 years	65 (30.8%)	18% (6–31)	29% (16–43)
			P = 0.0003	P = 0.0001
Size	≤5 cm	42 (19.9%)	74% (59–90)	78% (64–92)
	5–10 cm	80 (37.9%)	34% (22–45)	46% (34–58)
	>10 cm	72 (42.1%)	30% (16–44)	34% (21–47)
	Unknown	17	P = 0.0001	P = 0.0001
Margins	R0	149 (70.6%)	51% (42–61)	58% (48–67)
	R1	57 (27%)	24% (10–37)	37% (23–52)
	Unknown	5	P = 0.002	P = 0.006
RT	Yes	80 (37.9%)	46% (36–56)	52% (40–65)
	No	128 (60.6%)	40% (28–52)	52% (42–62)
	Unknown	3	P = 0.3	P = 0.5
Treatment	Surgery alone	46 (21.8%)	26% (10–42)	37% (21–53)
	Surgery + CT	83 (39,3%)	56% (44–68)	60% (48–73)
	Surgery + RT	43 (20.3%)	27.5% (12–43)	40% (24–56)
	Surgery + CT + RT	37 (17.5%)	52% (35–69)	64% (46–81)
	Unknown	2	P = 0.02	P = 0.002
Chemo	Yes	121 (57.3%)	55% (45–65)	62% (51–72)
	No	86 (40.7%)	27% (16–38)	38% (26–49)
	Unknown	4	P = 0.003	P = 0.0002
Chemo type	Osteo-type	69 (57.5%)	62% (49–75)	65% (52–79)
	STS-type	43 (35.8%)	48% (32–64)	59% (42–75)
	Unknown	9	P = 0.05	P = 0.08

ESOS = extraskeletal osteosarcoma DFS = disease-free survival; OS = overall survival.

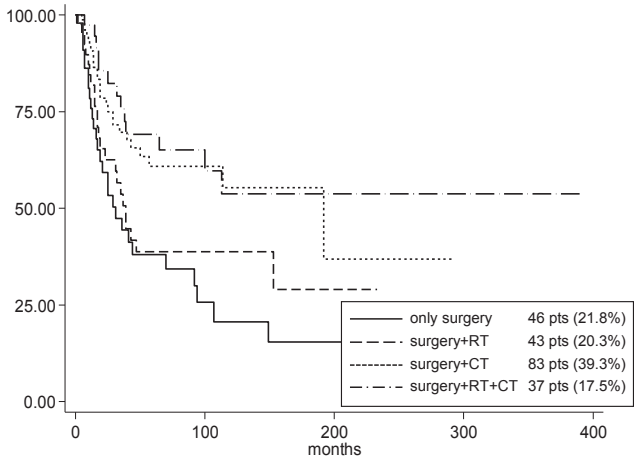

Fig. 2. 5-year overall survival and treatment (P = 0.002).

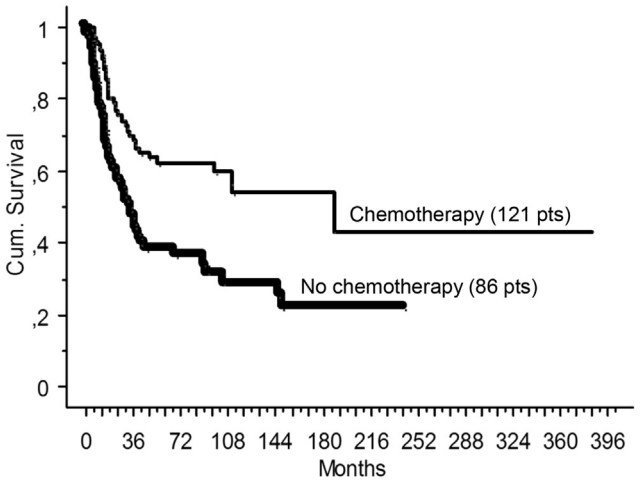

Fig. 3. 5-year overall survival for chemotherapy versus no chemotherapy (P = 0.0002).

Radiation therapy was administered in 80 (37.9%) patients. In 55 (68.7%) RT was administered post-operatively, in 5 (6%) preoperatively, in 3 (4%) RT was palliative, in the remaining 17 (21%) timing of RT was unknown. Median dose was 58 Gy (36–79 Gy).

Chemotherapy was administered in 121 (57.3%) patients. In 32/121 as neoadjuvant (preoperative), in 75 as adjuvant and in the remaining 14 it was not specified an osteosarcoma-type regimen of chemotherapy was administered in 69 (57.5%) patients. A soft tissue-type regimen was administered to 43 patients (35.8%). In the remaining 9 patients (7.4%) the type of chemotherapy was unknown. All together 68/69 received doxorubicin, 65/69 received cisplatin; 58/69 received ifosfamide and 27 received methotrexate. The combinations were the following: 10 patients received cisplatin and doxorubicin, 28 doxorubicin–cisplatin–ifosfamide, 23 doxorubicin–cisplatin–ifosfamide–methotrexate, four doxorubicin–cisplatin–ifosfamide–methotrexate-etoposide and carboplatin and three received VIDE (vincristine, ifosfamide, doxorubicin, etoposide) chemotherapy.

Median number of cycles for patients treated with osteosarcoma-type chemotherapy was 5 (range 2–20).

Thirty-six patients treated with soft tissue sarcoma-type chemotherapy received a combination of an anthracycline associated with ifosfamide. Only 5 patients received anthracycline as single agent, 2 received etoposide and ifosfamide without anthracycline. The median number of chemotherapy cycles per patient was 3 (range 1–12).

Table 3 reports the 5-year DFS and OS according to patient characteristics and treatment. Five-year DFS and OS were significantly better (P = 0.003 and P = 0.0002, respectively) in patients selected to receive chemotherapy (Fig. 3).

3.3. Distribution of treatment according to patient age, tumour margins and size

These data are reported in Table 4. Chemotherapy was given to 52.3% patients with tumours <5 cm, in 57.5% in tumour ≥5–10 cm and in 61.3% when the tumour was >10 cm (P = 0.64). Chemotherapy was administered more frequently in patients younger than 65 years (P = 0.0001). The use of chemotherapy in tumours >5 cm was a significant prognostic factor for 5-year DFS (Fig. 4). Median DFS of patients who received an osteosarcoma-type regimen was 31.2 months (2–184) compared to 14.9 months (2–384) of those who received an soft tissue sarcoma (STS) type chemotherapy (P = 0.003). Patients treated with adjuvant osteosarcoma-type chemotherapy reported a 5-year DFS of 62% (95% CI 49–75%) versus 48% (95% CI 32–64%) in STS-type chemotherapy with a trend of statistical significance in favour of osteosarcoma-type chemotherapy (P = 0.05) (Fig. 5). There was no difference in choice of administration of RT according to tumour size or surgical margins.

3.4. Relapse

104/211 (49.2%) patients relapsed: 52 relapsed locally, 88 had distant metastases, 36 relapsed both locally and

Table 4
Distribution of treatment in 211 patients with localised ESOS according to age, margins, size.

	Surgery (%)	Surgery and RT (%)	Surgery + Chemo ± RT (%)	P value
Age				P = 0.0001
≤18	6.2	6.2	87	
19–40	9.3	12.5	78	
41–65	17.3	13.2	69	
>65	39.6	39.6	20.6	
Margins				P = 0.01
R0	20.9	16.2	62	
R1	26.7	32.1	41	
Size				P = 0.69
≤5 cm	23.8	26.1	50	
5–10 cm	18.8	24	56.9	
>10 cm	23.9	16.9	59.1	

ESOS = extraskeletal osteosarcoma; RT = radiotherapy.

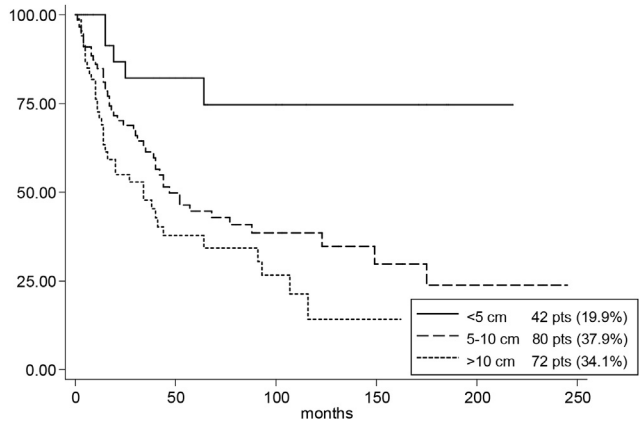

Fig. 4. 5-year disease-free survival and size (P = 0.0002).

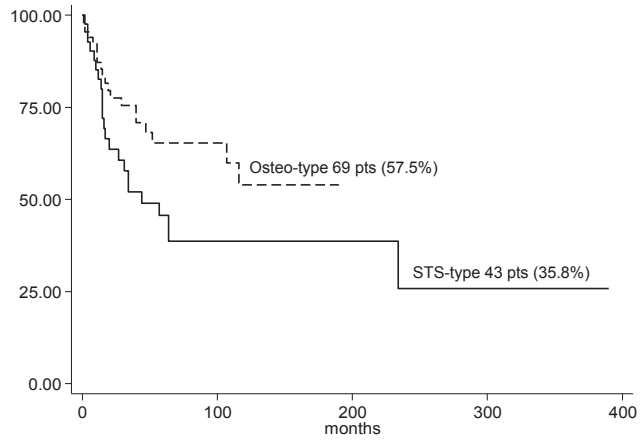

Fig. 5. 5-year disease-free survival and type of chemotherapy: osteosarcoma-type versus soft tissue-type chemotherapy (P = 0.05).

distantly and 10 of these being simultaneous. Median time to relapse was 12 months (1–185), median time to local relapse was 13 months (2–116) and median time to distant metastases was 11 months (2–185). Twelve patients had more than one distant metastatic site. Sites of metastases were: lung in 64 patients, bone in 7, lymph node in 5, soft tissue in 4, brain in 3, liver in 2, abdomen in 2 and breast in 1.

For local relapse 22/52 patients received surgery alone, six received surgery + RT, six received surgery + chemotherapy, 1 surgery + RT + chemotherapy, 2 chemotherapy alone and 3 as palliative treatment. In 12 patients treatment was not reported.

Treatment for distant relapse was unknown in 27/88 cases, treatment was surgery alone in 18, chemotherapy alone in 16, surgery + chemotherapy in ten, surgery + RT in four, chemotherapy + RT in three and best support in ten.

For the few patients with clinical data after local or distant relapse the majority received gemcitabine-based chemotherapy which is used in STS and as well in osteosarcoma.

A further subanalysis of local relapse free survival (LRFS) of the 31/52 patients with local relapse as only site or first site of relapse (6 months before any further relapse) showed a 5-year LRFS of 77% (95% CI 69–85%). Positive prognostic factors for LRFS were: margins (P = 0.05) and chemotherapy (P = 0.04). At multivariate analysis chemotherapy was the most important prognostic factor for LRFS (P = 0.004), RT (P = 0.07) was not significant.

Distant metastases free survival (DMFS) on 78 patients with distant metastases as unique or first site of relapse had a 5-year DMFS of 55% (95% CI 47–64%). Significant prognostic factors were size (P = 0.002), margins (P = 0.004) and chemotherapy (P = 0.004). At multivariate analyses only size (P = 0.003) and chemotherapy (P = 0.001) were significant.

All these results should be taken cautiously because the cohort is small and heterogeneous.

3.5. Radiotherapy and local relapse (Table 5)

Local relapse rate was not statistically different for patients who received RT (P = 0.7). RT decreased the incidence of local relapse for patients with tumour >5 cm (P = 0.054) and in patients with tumour >5 cm and R0 margins: local relapse occurred in 17/61 (28%) in the no RT group versus 4/37(11%) in the RT group (P = 0.05). For patients with tumour >5 cm and R1 margins no statistically significant difference was

Table 5
Radiotherapy and local relapse.

Radiotherapy	# Patients	No local relapse	Local relapse	P value
No RT in tumours >5 cm	87	59 (68%)	28 (32%)	0.054
Yes RT in tumours >5 cm	61	50 (82%)	11 (18%)	
No RT in tumours >10 cm	40	28 (70%)	12 (30%)	0.1
Yes RT in tumours >10 cm	29	25 (86%)	4 (14%)	
No RT in tumour margin R1	32	20 (62.5%)	12 (37.5%)	0.9
Yes RT in tumour margin R1	29	18 (86%)	11 (38%)	
No RT in R0 only T > 5 cm	61	44 (72%)	17 (28%)	0.05
Yes RT in R0 only T > 5 cm	37	33 (89%)	4 (11%)	
No RT in R1 only T > 5 cm	26	15 (58%)	11 (42%)	0.3
Yes RT in R1 only T > 5 cm	24	17 (71%)	7 (29%)	

RT = radiotherapy; T = tumour; R0 and R1 margin according to Union for International Cancer Control (UICC) margin classification.

Table 6
Multivariate analysis.

Variable	Relative risk	P value
Age		
≤40 yrs	1	
>40 yrs	0.49 (95% CI 0.25–0.99)	P = 0.05
Size		
>10 cm	1	
≤10 cm	0.38 (95% CI 0.24–0.6)	P = 0.0001
Chemotherapy		
Yes CT	1	
No CT	1.92 (95% CI 1.2–3.1)	P = 0.006
Margins		
R1	1	
R0	0.65 (95% CI 0.4–1.1)	P = 0.075

observed for local relapse in relation to RT (P = 0.3). Seen the paucity of patients who underwent adjuvant RT its role in ESOS must be further examined.

At univariate analysis for 5-year DFS the significant prognostic factors were size, age, margins, chemotherapy and type of chemotherapy for the 211 patients with localised resected disease. Size, age, margins and chemotherapy use were statistically significant for 5-year OS. Sex, RT and type of chemotherapy were not statistically significant (Table 3). At multivariate analysis: size, age and chemotherapy were statistically significant prognostic factors (Table 6).

3.6. Chemotherapy and radiotherapy choice according to EMSOS centers

The use of chemotherapy and RT as adjuvant treatment varied between centres. Some centres administered chemotherapy in 80–90% of patients and RT in no more than 20%. In other centres there was a prevalent use of RT (maximum in 48%) and chemotherapy was employed only in 30% of patients. Patients treated with osteosarcoma-type regimens were given less RT compared to those treated with STS-type regimens (respectively, 11% and 66.6%).

4. Discussion

This study reports the largest cohort of this rare sarcoma subtype and is notable for management having been undertaken in specialist centres defined by membership of EMSOS. While reinforcing information about the clinical features, it is most valuable in highlighting the uncertainties about best management of ESOS, illustrated by the variation in use of different treatment modalities between centres. The data presented about a potential value for adjuvant chemotherapy is stimulating but should be considered with caution.

The major limitations of the study are that it is retrospective and the heterogeneity in treatment strategy observed between participating centres. That said, to gather adequate amount of data on such a rare disease would not have been possible without a multicenter effort carried out by several referral centres throughout Europe.

In this cohort of ESOS, as seen in other studies with a population of similar age, 5-year DFS is less than 50% (47%) compared to that of about 60–65% [17,18] in localised skeletal osteosarcoma patients under 40 years. A previous EMSOS study on 481 patients older than 40 years with localised skeletal osteosarcoma by Grimer [19] reported a 5-year OS of 46% similar to the 5-year OS of 51.4% reported in this study.

Although ESOS is classified as a soft tissue sarcoma there is a significant trend of greater responsiveness to osteosarcoma-type chemotherapy (methotrexate, cisplatin, doxorubicin, ifosfamide) compared to only anthracycline-based ± ifosfamide chemotherapy as usually employed in soft tissue sarcoma. Other papers [5,20,21] have reported response to regimens including cisplatin. A recent study on 55 patients with ESOS reported an advantage in OS and progression free survival for patients who received chemotherapy including cisplatin versus those treated without cisplatin [20]. Another study on 17 patients from the Cooperative Osteosarcoma Study Group (COSS) reported a favourable 3- and 5-year estimated DFS of 77% after multimodal treatment including osteosarcoma-type chemotherapy (doxorubicin, cisplatin, ifosfamide, methotrexate) [21].

RT was administered in a small group of patients, about one third (80/211). It was mainly adjuvant, and used more frequently in patients with R1 margins and in those who received STS-type chemotherapy. There was no difference in the choice of RT administration according to age, size of primary tumour. Notably, RT seems to give an advantage in those patients with tumour >5 cm and R0 margins, whereas no benefit was seen in patients with R1 margins confirming that inadequate surgery cannot be overcome by RT. It seems that those centres which treated ESOS as a soft tissue sarcoma were more likely to use RT compared to those who treated ESOS with osteosarcoma-type chemotherapy. In this series adjuvant chemotherapy was a positive prognostic factor for both OS and DFS. The positive trend for an osteosarcoma-type chemotherapy regimen was observed for DFS but not for OS.

For patients with localised ESOS, complete surgical resection is necessary. The role of adjuvant RT and chemotherapy remains unclear from this study and argues for prospective randomised allocation but such a study is likely to prove impossible to conduct. In the meantime, selection of patients for multiagent chemotherapy and RT should be strongly considered, preferably by multidisciplinary teams working in specialist referral centres.

Conflict of interest

None declared.

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