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Ewing's sarcoma family of tumors in Finland during 1990–2009: A population-based study

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Abstract

Background. Ewing's sarcoma family of tumors (ESFTs) are rare bone and soft tissue tumors characterized by specific genetic alterations. Our aim was to carry out a nationwide analysis of ESFT, to survey the treatments used and to report the five-year disease specific and event-free survival rates (EFS and DSS). *Material and methods.* The study data was gathered from the Finnish National Cancer Registry and all five University Hospitals and consisted of 76 bone and soft tissue ESFT patients diagnosed during 1990–2009. Their medical records were reviewed and data on their disease, treatments, complications and outcome were analyzed. *Results.* The five-year EFS and DSS of patients with localized disease at diagnosis (n = 57) were 70% and 60%, respectively. Factors contributing to DSS and EFS were the axial vs. peripheral site of primary tumor and adequate surgical resection of the primary tumor. DSS was also affected by patient's age at diagnosis and the treatment employed. The five-year DSS of patients with metastatic disease at diagnosis (n = 19) was 33% and both preoperative and high dose chemotherapy were associated with improved survival. *Conclusion.* Population-based studies including both bone and soft tissue ESFTs are few. In this nationwide, population-based study on Finnish bone and soft tissue ESFT patients, we find their treatment successful and results comparable to those previously published. Absence of metastases, young age at diagnosis and a peripheral primary tumor site were associated with a better prognosis. It seems that surgical resection of the primary tumor should be performed whenever adequate resection margins can be achieved. The role of high dose chemotherapy merits further studies in this setting.

Ewing's sarcoma family of tumors (ESFTs) is a group of rare bone and soft tissue tumors consisting of small round blue cells. Genetically they are characterized by a translocation involving the *EWS* gene and one of the several *ETS* domains. The most common translocation is t(11;22)(q24;q12) which creates a functional *EWS-FLI1* fusion gene [1]. The presenting symptoms are most often local pain and a palpable mass [2]. Fever and other non-specific symptoms may also occur and are more common in a metastatic or advanced disease. Findings in plain radiographs include osteolysis, cortical destruction and an "onion skin" bone formation. Magnetic resonance imaging (MRI) images show a soft tissue expansion typical for a Ewing's sarcoma of bone [3]. The MRI findings in a soft tissue ESFT

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are non-specific and similar to other soft tissue malignancies [4].

The treatment protocols for ESFTs include chemotherapy with surgery and/or radiation therapy (RT) as primary local treatment. Yet, the details of optimal local treatment remain controversial [5,6]. When at least a marginal resection is feasible, surgery remains a key contributor to the successful local control of the disease [7,8]. The prognosis of patients with ESFTs has improved during the last decades. In a population-based report from Northern England, the five-year survival of pediatric patients with Ewing's sarcoma of bone improved from 37.5% (1981–1987) to 70% (1995–2000) [9]. With modern chemotherapy protocols, the five-year event-free survival (EFS) reported for patients with no detectable metastases at diagnosis is greater than 50% [10]. The prognosis is significantly worse in primary metastatic disease, as well as when the location of the primary tumor is particularly challenging, e.g. the spine [11].

A significant proportion of the studies of outcome in ESFTs are register-based and therefore the details of surgical treatment and complications of cancer therapy may remain unreported. Most commonly, the studies of ESFTs also include only bone or soft tissue tumors. Therefore, population-based reports on patients with ESFTs including both bone and soft tissue tumors are few. In this retrospective, nationwide study our goal was to find out how the treatment of Finnish patients with bone and soft tissue ESFTs was carried out, establish the five-year EFS and disease-specific survival (DSS) rates and assess prognostic factors.

Materials and methods

Data

The core of the data was collected from the Finnish National Cancer Registry of reported bone sarcomas during 1991–2006. To search for possible missing cases, to obtain a wider material and to include also soft tissue tumors, all five Finnish university hospitals were contacted and data was collected for bone and soft tissue ESFTs during 1990–2009. A total of 88 patients were identified and their medical records reviewed for the diagnostics, treatment, possible complications and follow-up. Survival data was updated by using the nationwide death records from the Finnish Population Register Center.

Eight patients with a final diagnosis other than ESFT and four patients with limited patient information were excluded, leaving 76 patients for the study. The numbers of patients treated in each university hospital were: Helsinki 34 patients, Tampere 19 patients, Turku 16 patients, Kuopio five patients and Oulu two patients. This is based on which hospital was mainly responsible for the treatment. The numbers do not represent regional differences in incidence since the university hospitals collaborate in treating these patients. Forty-eight patients had a primary tumor of bone, 27 of soft tissue and one a multifocal disease with both bone and soft tissue tumors. Three patients (4%) died in less than three months after the diagnosis. All these had axial primaries, two with metastases at diagnosis and the third was diagnosed with a metastatic disease during the first two months after diagnosis. The three were excluded from all analyses on the treatments and the prognostic effectors.

Confirmation of the diagnoses was based on the original pathology reports; no histological re-evaluation was performed. Also the response to preoperative chemotherapy and data on the surgical margins were based on original reports from the resection samples. The response to preoperative chemotherapy was graded as good or poor according to the judgment recorded on the patient records by the pathologist and the sarcoma groups treating the patient. In this study, the response was graded as "good response" when the percentage of viable cells was less than 10%. The resection margins were considered adequate (radical, wide or marginal resection margins) if the entire tumor was removed and the margins were free of tumor cells.

Data on adverse effects of chemotherapy and surgical complications was not systematically collected during the treatment but retrospectively from the medical records. Relapses and second malignancies were regarded as events in the analysis of the EFS. In the DSS analysis only death due to ESFT was regarded as an event. In case of a death due to other reasons the patient was censored at the date of death. Median follow-up time for patients that did not die due to disease was 7.0 years (range 1.3–19.0).

Treatment protocols

The protocols used included the US National Cancer Institute protocol INT-0091 (CCG-7881/POG-8850) [12] and the Scandinavian and Italian Sarcoma Group study protocols, SSG IX [13], ISG/SSG III [14] and ISG/SSG IV [15]. All these include pre- and postoperative chemotherapy with surgery and/or RT as the local treatment of the primary tumor. The chemotherapeutic agents vincristine, adriamycin and ifosfamide are included in all of these protocols. In addition to these, ISG/SSG IV includes also etoposide and cyclophosphamide, whereas ISG/SSG III and INT-0091 include etoposide, cyclophosphamide and actinomycin-D.

SSG IX is the only protocol including cisplatin. ISG/SSG IV is a protocol for patients with metastatic disease confined to lungs and/or maximum one bone metastasis and includes high dose chemotherapy with autologous stem cell rescue (HDT) and total lung irradiation as standard treatment. In other protocols HDT is considered when response to preoperative chemotherapy is poor or the disease progresses in spite of active standard therapy.

Statistics

To compare differences between two groups, χ^2 and Fisher's exact-tests were used for nominal variables and Mann-Whitney U-test for non-parametric continuous variables. Survival analysis was performed using the Kaplan-Meier analysis and log rank-test. Cox regression analysis was used for multivariate survival analysis as well as for survival analyses of continuous variables. SPSS 19 was used for all statistical analyses. Results with $p < 0.05$ were considered statistically significant.

Results

At the time of the diagnosis, 19 of the 76 patients (25%) had a metastatic disease. This group was analyzed separately from the group with a non-metastatic disease. There were no differences between these two groups regarding sex, age, tumor size or the site of the primary tumor (Table I). The most frequent primary sites were the pelvic bones (n = 16), soft tissues of the thigh (n = 10), the femur (n = 8) and the thoracic cage (ribs or intercostal muscles, n = 7) in the 76 patients. There were eight patients whose primary tumors involved the spine: three in the sacrum, two in the vertebras of the mobile spine and three in the paraspinal muscles. Two patients were considered to have a multifocal disease. One of them had two separate tumors: one in the proximal radius and another in the L II -vertebra. The other patient had a widely disseminated disease with multiple lesions in bone and lungs at diagnosis without a discernible primary mass. The diagnostics included molecular genetic testing in 45 (59%) of the 76 patients. Of these, 30 samples (67%) were positive for *EWS-FLI1* and five (11%) carried other, more complex genetic alterations that had been evaluated to fit the ESFT diagnosis.

Table I. Patient characteristics.

	No. patients		
	Local	Metastatic	All
All	57	19	76
Age (median)	16.1	18.6	17.8
Sex			
Male	35	15	50
Female	22	4	26
Site of tumor as axial or distal			
Distal	29	9	38
Axial	28	10	38
Site of tumor as bone or soft tissue*			
Bone	38	11	49
Soft tissue	19	8	27
Largest diameter of the primary tumor in cm**			
< 8 cm	26	9	35
> 8 cm	31	8	39
Year of diagnosis			
1990–1999	27	6	33
2000–2009	30	13	43
Molecular genetic analysis†			
Positive	26	9	35
Negative	9	1	10

* Multifocal disease was classified as bone tumor if bone lesions were present.
** Data not available for two patients.
† Molecular genetic analysis was not performed in 31 patients.

Local disease at diagnosis

Chemotherapy. Of the 57 patients with local disease at diagnosis one did not receive chemotherapy as part of the primary therapy and one died shortly after the diagnosis. INT-0091 was the most frequent protocol used (24 patients). The protocol chosen was affected by age: younger patients were more often treated according to the INT-0091 protocol and those older according to SSG IX. High dose chemotherapy with autologous stem cell rescue was part of the primary therapy in 13 patients (23%) who either had a poor response to primary chemotherapy or were considered to have a high-risk disease by the treating physicians.

Forty-seven of the 57 patients (82%) received chemotherapy before surgery and/or RT of the primary tumor. Histological response to chemotherapy was reported for 38 of the 41 patients who received preoperative chemotherapy and whose local treatment included surgical resection. The response was graded as good in 27 (71%) and poor in 11 (29%) patients. There was no difference between the chemotherapy protocols employed.

Severe immediate treatment complications related to chemotherapy were observed in four patients. These included severe renal failure, heart failure, polyneuropathy, and delirium (n = 1 each). Neutropenic infections grade III or IV (CTCAE version 4.0) were very common and not analyzed in the present study, nor were mild symptoms that did not require any special treatment other than rehydration or

delaying the following chemotherapy treatment. Anemia and thrombocytopenia were also common and were not registered in this study.

Late adverse effects putatively related to chemotherapy were reported in 11 of the 45 patients (24%) who had received chemotherapy and survived at least two years from diagnosis. These included reduced renal function (n = 5), cardiomyopathy (n = 2, one remains on medication for heart failure) and endocrine impairments: hypogonadism (n = 4), azoospermia (n = 1) and osteoporosis (n = 2).

Surgical treatment. Local treatment included surgery in 48 patients (86%) of the 57 without metastases at diagnosis. The margins of the resection were considered adequate in 45 of these (94%) while three of the operations were considered intralesional. For those with adequate resection margins, the operation was limb sparing in 24 patients, a resection of the tumor in the trunk for 18 patients, and for three an amputation at or proximal to the level of wrist or foot. There were two amputations of singular digits and these were considered limb-sparing. Two patients of those operated in a limb-sparing manner with adequate margins (8%) eventually had to go through an amputation because of a local relapse.

Immediate complications related to surgical resection of the primary tumor occurred in eight patients (17%). These included wound infection (n = 5), wound necrosis (n = 3), neurologic defect (n = 2), systemic infection and muscle necrosis (n = 1 each). Four patients (8%) had to be reoperated because of immediate complications. Late complications occurred in 10 patients (21%) and included fractures of allo- or vascularized fibulografts (n = 4) and endoprostheses (n = 1), ossification problems (n = 2), a luxation of an endoprosthesis, a prolonged wound infection and an avascular necrosis in the caput of the femur.

Radiation therapy. Twenty-four patients received RT for the primary tumor. For six of them it was the only local treatment with the median dose of 57.9 Gy (range 42.0–67.0 Gy). Four patients received preoperative (median 43.5 Gy, 42.0–60.0 Gy) and 11 postoperative (median 42.0 Gy, 20.0–61.0 Gy) RT in addition to surgical resection with at least marginal margins. All those with an intralesional resection received RT with a median dose of 54.0 Gy (42.0–64.5 Gy). No serious complications related to RT occurred. There were two patients (8%) with notable skin and bowel irritation resolving shortly after the RT. In addition, one patient developed a notable upper limb length discrepancy after surgery and postoperative radiotherapy.

Survival. The five-year EFS and DSS for the 57 patients with a localized disease at diagnosis were 60% and 70%, respectively. Factors that contributed to the five-year DSS and EFS included the site of the primary tumor and a surgery with adequate margins (Figure 1a, Table II). The five-year DSS, but not EFS, was also affected by age at diagnosis (HR 1.03 per year of age at diagnosis, 95% CI 1.00–1.06, p = 0.031) (Figure 1b) and the treatment protocol: five-year DSS was 82% with INT-0091 (n = 24) and ISG/SSG III (n = 11), 56% with SSG IX (n = 19) and 0% with ISG/SSG IV (n = 1), p = 0.012. Adding pre- or postoperative RT to a surgical resection with at least a marginal margin did not improve outcome

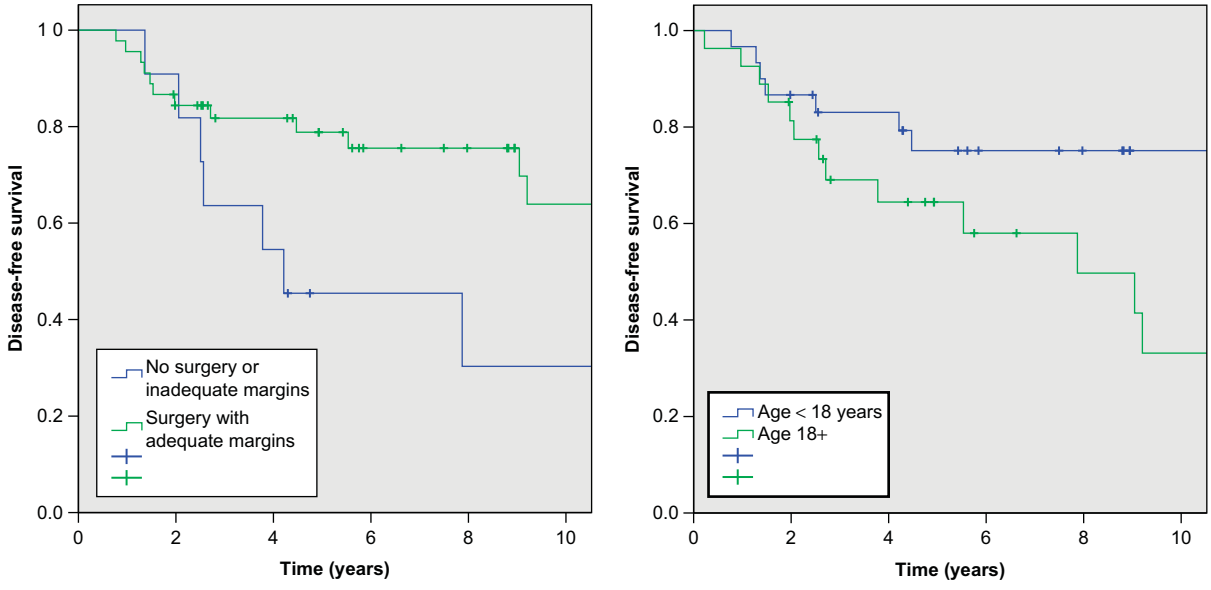

Figure 1. Five-year disease-free survival of patients with localized disease according to a) surgical local control and b) age at diagnosis.

Table II. The five-year EFS and DSS of patients with localized ESFTs.

	No. patients	EFS		DSS	
		%	p	%	p
Sex					
Male	35	64%	0.370	72%	0.750
Female	22	54%		67%	
Age at diagnosis*					
0–18 years	30	66%	0.154	75%	**0.051***
>18 years	27	53%		64%	
Site of primary tumor					
Axial	28	50%	**0.046**	54%	**0.016**
Peripheral	29	70%		85%	
Bone or soft tissue tumor					
Bone	38	59%	0.886	67%	0.597
Soft tissue	19	63%		78%	
Size					
0–8 cm	26	69%	0.425	76%	0.202
>8 cm	31	53%		65%	
Neoadjuvant chemotherapy**					
No	7	65%	0.516	80%	0.201
Yes	47	60%		69%	
Response to neoadjuvant therapy†					
Poor	11	72%	0.941	68%	0.347
Good	27	70%		81%	
High dose chemotherapy††					
No	43	59%	0.817	71%	0.662
Yes	13	67%		67%	
Surgical resection with at least marginal margins††					
No	11	46%	**0.040**	46%	**0.033**
Yes	45	65%		79%	
Time of diagnosis					
1990–1999	27	56%	0.465	63%	0.210
2000–2009	30	66%		79%	

*In Cox regression analysis the risk for death due to disease increases 1.03-fold for every year of age at diagnosis (95% CI 1.00–1.06, p = 0.031)

**N = 54, two patients had no local treatment and one died in <3 months

†Those who received neoadjuvant therapy and were operated and the data was available.

††The patient who died in less than 3 months was not included.

CI, confidence interval; DSS, disease-specific survival; EFS, event-free survival; ESFT, Ewing's sarcoma family of tumors.

(EFS was 60% for these and 68% for those whose tumor was resected but received no RT, p = 0.335). Local relapse-free survival, however, varied among different local treatment approaches (Table III).

Treatment and prognosis after relapse. There were altogether 24 patients whose disease relapsed or progressed. Eleven patients had a local recurrence and 19 patients developed distant metastases at some point (of the 11 patients who had a local recurrence three had simultaneous distant metastases and three had distant metastases later on). Median time to first relapse from diagnosis was 1.4 years (range 0.1–6.6 years); in 21 of the 24 patients (88%) the first relapse appeared in less than three years from diagnosis. The most frequent metastatic sites were lungs (n = 11) and bones (n = 10), of which spinal column was most common (n = 8). In addition, one patient was diagnosed with a malignant phylloid tumor of the breast. It was the only secondary malignancy and diagnosed more than 10 years after the ESFT diagnosis; the patient had not received RT to the area of the breast.

Chemotherapy was given to all but two of the 24 patients. It consisted of various combinations and single-agent therapies, such as topotecan, irinotecan, high dose ifosfamide and p.o. etoposide. Five patients received also high dose chemotherapy with peripheral stem cell rescue. Four of the 11 patients with local recurrence were operated: two of them had an amputation, one a re-resection of thoracic wall and one a second limb-sparing resection. Three of them also received RT to the local recurrence. In four patients the local treatment was radiation only and in three patients the local relapse was not locally treated. Surgical metastasectomies were performed

Table III. The local treatment of the primary tumor and five-year local relapse-free survival (LRFS).

	No. patients	5-year LRFS	p	5-year LRFS	p
Local treatment					
No surgical resection or intralesional margins	11			53%	
No local treatment	2	50%			
RT only	6	44%			
Intralesional resection and postoperative RT	3	67%			
Surgical resection with at least marginal margins	45			83%	**0.021****
with no RT	30	87%			
with preoperative RT	4	38%			
with postoperative RT	11	90%	**0.050***		
Site					
Axial	28	70%			
Peripheral	29	82%	0.193		
Bone or soft tissue tumor					
Bone tumor	38	75%			
Soft tissue tumor	19	82%	0.814		
Size of primary tumor					
0–8 cm	26	92%			
>8 cm	31	66%	0.066		
Neoadjuvant chemotherapy					
No	9	65%			
Yes	47	80%	0.356		

RT, radiation therapy.
*The borderline p = 0.050 applies to the differences between the six subgroups of local treatments.
**The p = 0.021 applies to the difference between the two main groups "No surgical resection or intralesional margins" and "Surgical resection with at least marginal margins".

for seven of the 19 patients with distant metastases and RT was given to seven.

Five of the patients were alive at time of analyses with two of them alive after five or more years from the relapse. The five-year DSS was 15% for those with a local recurrence (n = 8), 15% for those with metastatic relapse (n = 13) and 33% for those with both local and distant relapse (n = 3), however, all three patients in the last group eventually died due to the disease and there was no statistical difference between the groups (p = 0.657). Among the 19 patients with distant metastases the five-year DSS was significantly better for the seven patients whose treatment included surgical metastasectomies (33%) compared to those 12 who did not (8%, p = 0.036).

Metastatic disease at diagnosis

The most frequent sites for metastases were lungs (n = 12) and bones (n = 9) for all the patients with radiologically detectable metastases at diagnosis (n = 19). Three of these also had bone marrow involvement.

Treatment. The treatment of a primary metastatic disease followed the same principles as for localized disease. Of the 19 patients, all 17 that lived longer than three months from diagnosis received chemotherapy with curative intention. The most frequent protocol was ISG/SSG IV (n = 8). Other protocols included SSG IX (n = 6) and INT-0091 (n = 3). The primary tumor was operated in 10 patients and in seven of these the resection margins were at least marginal. All three with intralesional resections received RT as well as one of those whose resection margins were free of tumor. RT was the

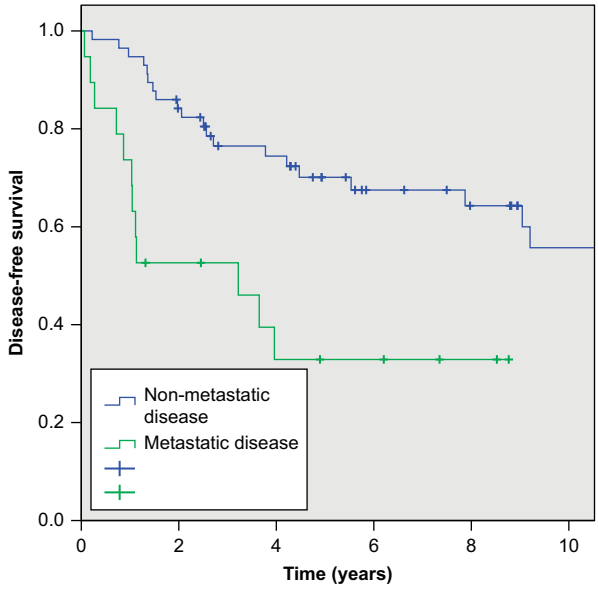

Figure 2. Five-year disease-free survival according to presence of metastases at diagnosis.

only local treatment in four patients. Three patients received total lung irradiation (TLI) with a dose of 15 Gy.

Survival. The five-year DSS of the 19 patients with a metastatic disease at diagnosis was 33%, which was significantly poorer compared to the 70% of those with localized disease (p = 0.001, Figure 2). The only factors contributing to survival of these patients were preoperative chemotherapy (when primary tumor was treated with surgery or RT, n = 14) and HDT (Table IV). The positive effect of surgical resection with at least marginal margins did not quite reach statistical significance (p=0.052).

Discussion

The main goal of this study was to assess the five-year survival rates of Finnish patients with ESFT. Using the Finnish National Cancer Registry, which has a close 100% correct and complete registration [16] and local registries in university hospitals we achieved study data covering the registered patients with ESFT diagnosed in Finland during 1990–2009. The five-year EFS and DSS rates of the patients with primary localized disease were 60% and 70%, respectively. The rates are comparable to those reported in another national study with both bone and soft tissue ESFTs [17]. The key prognostic factors for patients with localized ESFTs included the site of the primary tumor, adequate surgical resection of the primary tumor, age at diagnosis and the chemotherapy employed. The same have also been reported as prognostic factors in large studies for Ewing's sarcoma of bone [7,10]. As also previously reported [18], the prognosis of soft tissue ESFTs did not differ from bone tumors, but dissimilar results have also been reported [19].

Table IV. The five-year DSS of patients with metastatic ESFT.

	No. pts.	5-year DSS	p
Sex			
Male	15	36%	0.742
Female	4	25%	
Age at diagnosis			
0–18 years	9	53%	0.089
>18 years	10	13%	
Site of primary tumor			
Axial	10	30%	0.301
Peripheral	9	31%	
Bone or soft tissue tumor			
Bone	11	55%	0.121
Soft tissue	8	0%	
Size (n = 17)			
0–8 cm	9	53%	0.194
>8 cm	8	17%	
Neoadjuvant chemotherapy (n = 14)*			
No	3	0%	**0.008**
Yes	11	58%	
Response to neoadjuvant therapy (n = 7)**			
Poor	4	50%	0.919
Good	3	67%	
HD-chemotherapy (n = 17)†			
No	8	0%	**<0.001**
Yes	9	74%	
Total lung irradiation†			
No	14	25%	0.074
Yes	3	100%	
Surgical resection with at least marginal margins (n = 17)†			
No	10	20%	0.052
Yes	7	64%	
Time of diagnosis			
1990–1999	6	17%	0.492
2000–2009	13	46%	

*N = 14, two patients died in <3 months and three did not receive local treatment for primary treatment.
**Those who received neoadjuvant therapy and were operated and the data was available.
†The two patients who died in less than 3 months were not included.
DSS, disease-specific survival; ESFT, Ewing's sarcoma family of tumors.

The lack of prognostic value of response to preoperative chemotherapy could be due to the small number of patients for whom this information was available. Furthermore, the evaluation of the response by different pathologists may cause lack of unity in the grading. Finally, as the study time period was long, the preferred grading criteria have changed as the Picci grading system [20] has substituted the Huvos grading system [21]. Possible defects in diagnostic accuracy over time also constitute a potential pitfall [22].

The LRFS of patients whose tumor was surgically resected with at least marginal margins was clearly better than that of those not. Based on our material it is difficult to say if postoperative RT after a surgical resection with at least marginal margins is profitable. The finding that the combination of pre- or postoperative RT to surgical resection did not improve EFS in our material may relate to pre- or postoperative RT being given when the disease was more aggressive or the width of the surgical resection was suspected to be inadequate. As the best LRFS rates were achieved in those patients whose tumor was resected with at least marginal margins whether they received postoperative RT or not and those who received postoperative RT after intralesional resection, we feel that RT should be considered when surgical resection with at least a marginal margin is not feasible or the resection margins are intralesional. However, the few patients who received preoperative RT fared even worse than those whose only local treatment was RT. The results may be confounded by the limited number of patients in some of our subgroups and selection bias: preoperative RT was deemed necessary for tumors in which adequate surgical margins seemed difficult to accomplish.

The five-year DSS of patients with a primarily metastatic disease in our cohort was 33% which is also comparable to previous reports [17]. Chemotherapy prior to local treatment and high dose chemotherapy with autologous stem cell rescue seemed to improve prognosis. The role of HDT remains controversial: There are reports suggesting that HDT improves survival in poor responders to conventional chemotherapy [14] and patients with recurrent or progressive disease [23] but also of HDT not improving outcome in patients with poor prognosis [24]. In a study with 281 patients with primary disseminated multifocal Ewing's Sarcoma [25], the authors reported three-year EFS of 27% for all study patients. The estimated three-year EFS after HDT was 45% for 46 patients less than 14 years old and the factors contributing to survival included patient age, primary tumor volume, sites of metastases and number of bone lesions.

In our study the five-year post relapse DSS of patients with a relapse after treatment of a localized ESFT was 18%. Both poorer and better results have been reported: Bacci et al. reported a five-year postrelapse OS of 7.9% and reported surgical local treatment as a significant prognostic factor [26]. Barker et al. reported the five-year OS after relapse to be 31% for patients who initially had a local disease [27] and HDT to be associated with improved overall survival.

In conclusion, the treatment of patients with Ewing's sarcoma family of tumors in Finland is generally in line with established recommendations and the survival rates of the patients are comparable to published reports. Younger patients and patients with peripheral primary tumors have a better prognosis. The therapy of these patients should follow modern treatment protocols including pre- and postoperative chemotherapy with surgical resection with at least marginal margins being the preferable local treatment option. In the case of a primarily metastatic disease, HDT can be considered. This is one of the few population-based studies including both bone and soft tissue ESFTs. In addition, it also stands out from many population-based ESFT studies by including data from the original medical records instead of leaning solely on register-based data.

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