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Impact of Single Center Treatment on Ewing Sarcoma 10-Year Long Term Survival Rates

Léčba Ewingova sarkomu soustředěná do jednoho centra ovlivňuje desetileté dlouhodobé přežití

A. H. KRIEG[1,2], S. GEHMERT[2], R. ANGST[1,3], J. R. RISCHEWSKI[1,4], T. KÜHNE[1,5], F. HEFTI[1,2]

[1] Bone and Soft Tissue Tumour Center of the University of Basel (KWUB), Switzerland
[2] Orthopaedic Department, University Children s Hospital, Basel (UKBB), Switzerland
[3] Paediatric Oncology Department Childrens Hospital, Aarau, Switzerland
[4] Paediatric Oncology Department Childrens Hospital, Lucerne, Switzerland
[5] Paediatric Oncology Department, University Children s Hospital, Basel (UKBB), Switzerland

ABSTRACT

PURPOSE OF THE STUDY
Ewing sarcomas (ES) are the second most common solid malignant bone tumors in both, children and adolescents, and systemic chemotherapy protocols were established during the last 3 decades which proved to be a successful approach in addition to local treatment. The purpose of the present study is (i) to provide survival rates and prognostic factors for patients with ES which received treatment in a single center and (ii) to compare data with results of multicenter studies.

MATERIALS AND METHODS
Patients (n = 38) were treated by the same surgeon whereas surgery was combined with radiotherapy in 55.3% of the patients (n = 21). Median age at diagnosis was 17.5 years (4.7–60) and the median follow-up time for all patients was 8.2 years (9.8 years for survivors, 3.2 years for non-survivors).

RESULTS
The survival rate for metastasis free sarcoma decreases from 90.5% to 50% for patients diagnosed with disseminated disease stage. Patients with a good response to chemotherapy survived in 83.3% of the cases. In addition, a higher OS was found for patients younger than 15 years (82.4%) when compared to patients older than 15 years (73.3%). In contrast, multicenter studies reported lower survival rates for metastasis free (~60%) and metastasis stages (< 40%).

DISCUSSION
The survival rates in the present single center study are higher than the rates reported from multi-center studies although same chemotherapy protocols were used and no substantially difference are apparent for patient population.

CONCLUSIONS
Based on the present data we re-emphasize that patients with Ewing sarcoma receive appropriate treatment in a large and qualified center particularly considering the survival rates. In addition, our data underline that a close collaboration between the oncological team and the experienced surgeon is crucial for patient's care.

Key words: Ewing sarcoma, survival rate, single center, prognostic factors, chemotherapy, surgery, multi center, single center.

INTRODUCTION

Ewing sarcomas (ES) are the second most common solid malignant bone tumors in both, children and adolescents, and are known for their poor prognosis in the past (6, 12, 13). However, systemic chemotherapy protocols were established as a standard during the last 3 decades and proved to be a successful approach in addition to local treatment of ES. Overall survival rate and event free survival significantly improved (10, 21) whereas recent studies report survival rates of 50–70% for local disease and 20–30% for disseminated disease (12, 18, 19). Various therapy optimization studies paved the way to the most actual treatment recommendations and protocols. The most important in Europe are: CESS86, EICESS92, Euro-EWING 99 and the EWING 2008 as current state of research. All of these studies evaluated the efficacy of new chemotherapeutic strategies in comparison to the best available standard therapy (16, 17).

Prognostic factors are still under a partially controversial debate. Metastatic disease at diagnosis and the response to neo-adjuvant and adjuvant chemotherapy are significant indicators for the survival rate as reported in various multicenter studies (15, 16). However, age and site of the tumor did not prove to be independent prognostic factors (3, 5, 23). Tumor volume, has been shown to be prognostic factor in some studies (1, 8, 16, 22) but evidence is not consistent for all data (3, 14). Other factors such as lactate dehydrogenase (LDH) levels in

serum, radiotherapy for local treatment or tumor free margins after resection are also considered to be prognostic factors in some studies (3) but large multivariate analyses did not confirm their predictive value concerning survival (4, 14).

The purpose of this study was to (i) obtain the survival rates of patients with Ewing sarcoma of the bone and to identify potential prognostic factors affecting the survival of these patients. Moreover, we aimed to report data from a single center where patients were operated or supervised by one experienced surgeon. In addition, (ii) the results of the present study were compared to survival rates reported in previous multicenter studies.

MATERIAL AND METHODS

We performed a retrospective analysis of 38 patients who were treated for Ewing sarcoma in our hospital between 1990 and 2010. The chemotherapy or combined chemo-radiotherapy was carried out either in our center or in a pediatric oncologic facility close to patients living area. Ethics approval for the study was obtained from the Ethics Committee beider Basel (EKBB, ref: 2012/41).

All patients received an initial biopsy prior to treatment. The diagnosis was based on the local histological analysis of the biopsy samples, and confirmed by a centralized reference pathologist. Lesions included conventional ES and atypical ES, peripheral primitive neuroectodermal tumours of bone (pPNET) and Askin's tumours of the thoracic wall. The median age at diagnosis was 17.5 years (range 4.7–60.0 years) with a median follow up time of 8.2 year (range 0.6–19.1 years). The median follow-up time for survivors was 9.8 years (range 2–19.1), and for non-survivors 3.2 years (range 0.5–10.5). The minimum follow-up time for survivors was 2 years. Primary tumor location at the trunk was present in twenty patients (52.6%) and 18 patients (47.4%) were diagnosed with ES at the extremities. The most common tumor-localizations were the pelvis with 11 (28.9%) and the femur with 8 cases (21%). 50% of the patients (19) were male, and 44.7% (17 patients) were under the age of 15 years. Further patients' data are reported in table1.

Informed consent was obtained either from patient or from the legal guardian. Four patients with ES were excluded due to the following criterias: initially defined best supportive care situations (n = 2), primary operation outside of our center and case of relapse (n = 1) and another patient dropped out of follow up due to migration.

The staging procedure for all patients included conventional radiography, magnetic resonance imaging of the primary site, a computer tomography of the chest (and/or abdomen and pelvis, when appropriate) and a whole body technetium-99m bone scan. In addition, histo-pathological, histo-chemical and in selected cases molecular biological evaluation of bone marrow aspirates was carried out. Patients with loco-regional disease had tumors confined to the region of the primary site of disease. Patients with distant metastases had radiographic or pathologic evidence of tumor at least one site distant from the primary location. Twelve patients had metastases, whereas 10 patients were diagnosed with lung metastases, and two with bone and lung metastases. The tumor volume was estimated by determining the three dimensions of the primary bone tumor and of the soft tissue mass on the MRI prior to treatment. The tumor volume was calculated (< 200 ml vs. > 200 ml) according to the formula: volume = a × b × c × 0.52 for 'ellipsoidal tumors' and a × b × c × 0.785 for 'cylindrical tumors' (a: the maximal tumor dimension; b: tumor dimension perpendicular to a; c: the longitudinal maximum tumor dimension) (20). Primary tumors of the rib, even with malignant pleural effusion, were considered as localized disease.

Table 1. Patients' data

		N	5y (%)	10y (%)	p-value
Total survival		29/38	81.2	77.3	
Localized/Metastatic	Local	26	96.2	90.5	<0.001
	Metastatic	12	50.0	50.0	
Local Therapy	Wide	31	85.7	85.7	0.641
	Non-wide	7	80.1	75.6	
Age	<15	17	82.4	82.4	0.497
	> = 15	21	80.0	73.3	
Response	Cr	29	86.2	81.1	0.08
	Nr	9	62.5	62.5	
Tumour size	<200	18	83.3	72.9	0.934
	> = 200	20	78.9	78.9	
Trunk / extremity	Trunk	20	85.0	85.0	0.644
	Extremity	18	76.4	68.8	
Radiation	No	21	94.1	84.7	0.146
	Yes	17	71.4	71.4	
Recurrence	Yes	3	1	0.5	0.263
	No	35	79.1		

Chemotherapy was administered according to three different consecutive protocols, CESS86 (n = 12; 31.6%), EICESS92 (n = 8; 21.1%), Euro-EWING 99 (n = 18; 47.4%). Depending on the date of diagnosis we applied the most recent and updated treatment protocol.

Every patient received local surgical resection after neoadjuvant chemotherapy. All resections had been carried out or supervised by the senior author (FH). More than the half (55.3%, n = 21) of all patients received additional radiotherapy as local treatment. None of the patients received radiotherapy alone or no local treatment. Surgery was performed in all cases with the intent of a wide resection to obtain clear margins. Biological reconstruction or implantation of a tumor prosthesis was discussed with the patient prior to surgery depending on the staging results and severity. Patients were subjected to radiotherapy after resection was not possible or tumor free margins were not present in histo-pathological findings (R1-resection). One patient received a second-look resection followed by radiotherapy since the primarily resection confirmed only intralesional excision.

Surgical resection was scheduled after recovery from the last course of neoadjuvant chemotherapy whenever applicable. Radiotherapy (RT) was applied using 45 to 50.4 Gy for microscopic margins, and 55.8 Gy for gross disease following to the indication protocols (6).

All surgical excised specimens were examined by a specialized bone pathologist (who is also head of the Bone Tumor Registry). The evaluation of the response is based on the regression grade according to Salzer-Kuntschik (21). Response was assessed according to 2 stages: good responder (no evidence of viable tumor or less than 10% of residual tumor cells, regression grade 1–3) or poor responder (> 10% of visible residual tumor cells, regression grade 4–6 according to Salzer-Kuntschik). In addition, the margins of the specimen were always carefully examined regarding residual tumor cells.

The data were analyzed using the survival package for R (Therneau 2012), and R 2.12.0 (R Development Core Team 2010). Kaplan-Meier survival curves were computed and compared among prognostic factors using log-rank tests.

RESULTS

Twenty-nine patients (76.3%) survived and nine patients (23.7%) died despite the treatment. One patient died due to side-effects of the administered chemotherapy. The survival rate of patients without metastasis after 10 years was significantly higher (90.5%) when compared to patient with metastatic disease (50%) ($p < 0.001$). The Kaplan-Meier analysis clearly displays a significant difference for the variable metastasis (Fig. 1). Patients who did not survived (n = 9) had metastases (lungs alone or lungs and bone, n = 7, 77.8%) when diagnosed for ES. The remaining other two patients were good responders to the chemotherapy. One of these patients had an extremity tumor and secondary lung metastases. The other one had a localized ES at the axial skeleton. Five out of 9 patients (55.6%) who died during ES treatment showed good response to chemotherapy. In addition, the resected tissue did not show tumor-free margins for 2 patients (22.2%) and 4 non-survivors (55.6%) were diagnosed with ES at the trunk.

Local treatment: Surgery

Tumor free margins were achieved by surgical resection in 31 (81.6%) patients. Clear margins were not obtained for the remaining 7 patients (18.4%) whereas the tumor was located at the trunk in 5 patients and at the femur in 2 patients. Interestingly, tumors located at the trunk did not affect the 10-year survival rate as it might be expected. The 10-year survival rate of 85% for trunk tumors was higher than for extremity tumors (68.8%). No case of local recurrence occurred.

A primary tumor volume higher than 200 ml was found in 20 patients (52.6%) and associated with a 10-year survival rate of 78.9%. Eighteen patients (47.4%) had a tumor volume of less than 200 ml which was associated with a survival rate of 72.9%. However, the initial tumor volume did not seem to affect the results of the treatment.

Local treatment: Radiotherapy

A total of 21 patients received radiation as an adjuvant treatment but radiotherapy decreased since the beginning of the study. Irradiation was applied to 9 out of 12 patients (75%) which were included in the CESS86 study and only to 7 out of 18 patients (38.9%) which were assigned to the most recent protocol (Euro-EWING 99). 15 patients with a trunk located tumor and 6 patients with a tumor at their extremities received radiotherapy. A marginal resection of the tumor was another primary indication for radiotherapy; R1 for 5 patients and R2 in 1 case, 4 of these 6 (66.7%) patients are still alive and with no evidence of disease after 6.67 years of their initial diagnosis. The remaining 2 other patients did not survive due to poor chemotherapy response.

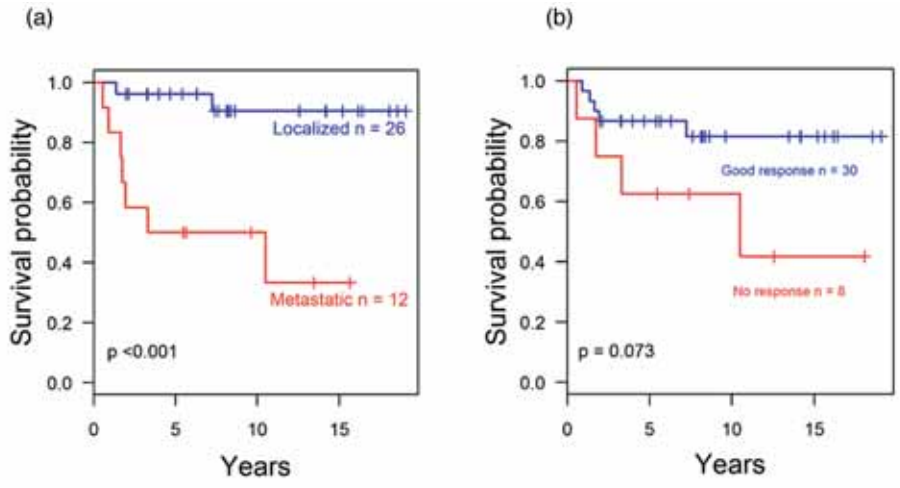

Fig. 1. The Kaplan-Meier analysis displays the survival rates for (a) the metastatic status and for (b) the response to chemotherapy. The survival rate of patients without metastases at diagnosis was significantly higher (90.5%) when compared to patients with metastases 50% (a). Overall survival in the group of poor responders (NR) was significantly decreased to 50% (5-year survival: 62.5%) when compared to 83.3% (5-year survival: 86.7%) for patients with a good response to chemotherapy (p = 0.07)(b).

Age

Survival rates were calculated for two groups separated by the age of 15 with 17 patients under the age of 15 years (44.7%) and 21 patients (55.3%) with the age above 15 years. The 10-year survival rate was marginally better in patients younger than 15 years (82.4%) when compared to older patients (73.3%). However, the difference regarding the survival rate between the two age groups was not significant suggesting that age might not be a relevant prognostic factor.

Systemic treatment

Patient received chemotherapy either in our Oncology Department or in the Pediatric Oncological Units associated to our hospital but located near to patient's residence (n = 11). The overall survival rates, according to the different protocols, are presented in Table 2. Noteworthy, the survival increased during the study period most likely due to the difference of the chemotherapeutic strategy accompanied with a decreased radiotherapy rate. The response to chemotherapy has been evaluated in every patient based on histology. The overall survival for poor responders (NR) was significantly worse with 50% (5-year-survival: 62.5%) compared to 83.3% (5-year-survival: 86.7%) for patients who had a good response to chemotherapy (p = 0.07).

Table 2. Survival rates for each treatment protocol that were used in the study

Protocol	Total (n =)	Failure (n =)	Survival (n =)	Percent
CESS 1986	12	4	8	66.7%
EICESS 1992	8	2	6	75%
EuroEWING 99	18	3	15	83.3%
Overall	38	9	29	76.3%

Table 3. Comparison of 10-year survival rates between the current study and data from literature (4,11,24)

	10-year OS-Study	10-year OS-Literature
Local disease	90.5%	60%
Disseminated	50%	<40%

Secondary metastases

Secondary metastases at the time of follow-up (median 5.53 years) were present in 3 (7.9%) patients. One patient is still alive with no evidence of disease after resection of the metastases but 2 patients with metastases died. All metastases were distant to the primary site with no local recurrences. Only 1 patient with metastases showed a poor response to chemotherapy. The same patient was diagnosed with an axial manifestation of ES which was impossible to remove by a wide resection. The remaining 2 patients with metastases had tumours at the extremities that presented clear margins after surgical resection.

DISCUSSION

The purpose of this study was to assess survival rates and to identify prognostic factors for patients diagnosed for ES who were surgically treated in a single center institution. In addition, it was of interest to compare present survival rates with reports of multicenter studies. One limitation of this study is the small number of patients. Furthermore, patients were treated according to different protocols which might cause a bias. However, the patients were offered the most recent and activated treatment protocol depending on the time of diagnosis. The strength of our study is the long follow-up time and the clinical details of each patient. Evaluation of late complications such as drug toxicity, second neoplasms and relapses, which can also appear up to fifteen years or more after the successful end of the treatment (3) underline the importance of a long-term follow-up time.

The survival rate in the present study is similar or superior to those reported from multicenter studies (18, 19), especially for patients without metastases at diagnosis (Table 3). Prognostic factors of ES are a subject of controversy in the literature. Our results show that metastatic disease at initial diagnosis and poor response to chemotherapy are correlated with poor prognosis. This is in line with findings in multicenter studies. However, prognostic factors such as tumour volume (< 200 ml, > 200 ml) and tumour localisation (axial vs. extremities) are not supported by our data. The 10-year survival rates in the two groups axial and extremity-tumours did not show a significant difference, despite the fact that in the seven cases of resection without clear margins five were in the group of axial tumours (3, 4, 14).

We could not provide an analysis of radiotherapy's efficacy since radiotherapy is not an independent risk factor. The survival rate of patients with radiotherapy is quite poor compared to patients without receiving radiation owing to the higher risk category. Thus, radiotherapy can not be defined as a poor outcome marker. Noteworthy, radiotherapy as a local treatment option was applied to a lesser extent during the study period. With reference to our data some other criteria cannot be listed as prognostic factors probably based by the small number of patients. Nevertheless, age (< 15, > 15 years) and chemotherapy protocol are most likely relevant to patients outcome. In particular, patients younger than 15 years at time of diagnosis have been reported with higher survival rates in previous studies (3, 4). In addition, the most recent chemotherapy regimen apparently is more effective than previous protocols (17).

An additional purpose of this study was to compare treatment results of a single center with multicenter studies. There are only few other reports on a single center experience in patients with ES (3, 9). The survival rates in our cohort are higher than those described in multicenter studies using the same international treatment protocols within a comparable patient collective. The high percentage of clear margins resection in our study might be the reason for these higher rates as reported from multicenter trials (16). Thus, we assume that the higher survival rates are an indicator of high surgical quality. Taken together, we suggest that all surgical interventions (including the diagnostic biopsy) are performed in a multidisciplinary center by an experienced surgeon with a fully-fledged team. Although the surgical treatment and postoperative phase is relatively short compared to the period of chemotherapy treatment it is crucial and important. The systemic treatment can be carried out in paediatric oncologic centres close to the patients' family preventing additional stress with long journeys and lack of contact with peers and other important relatives.

The present data underline the importance of experience in the treatment of ES, not only for the precise diagnostic evaluation and for the most actual systemic treatment

but also for the surgical treatment. Moreover, the study confirms that the metastatic status at diagnosis and the response to chemotherapy are prognostic factors in Ewing sarcoma patients (4, 14). In contrast, age, tumour volume and localisation were not associated with a prognostic value in our study as previously reported by various studies (1, 3, 20).

CONCLUSIONS

Based on the present data we re-emphasize that patients with Ewing sarcoma receive appropriate treatment in a large and qualified center particularly considering the survival rates. In addition, our data underline that a close collaboration between the oncological team and the experienced surgeon is crucial for patient's care.

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Corresponding author:
Andreas H. Krieg
Orthopaedic Department, University Children's Hospital (UKBB)
Bone and Soft Tissue Tumour Center of the University of Basel (KWUB)
Spitalstrasse 33
4053 Basel, Switzerland
E-mail: Andreas.krieg@ukbb.ch