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Metastatic soft tissue sarcomas in children – a remaining challenge for paediatric oncology. A retrospective multicenter study from the Polish Pediatric Solid Tumors' Group

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Introduction. *Soft tissue sarcomas (STS) in children and adolescents account for approximately 5% of all malignant neoplasms diagnosed in Poland each year. Histologically and clinically they are a heterogeneous group of malignant solid tumours. Although we have observed a remarkable progress in the therapy of childhood STS in recent decades there remain many controversies as to how STS-patients with distant metastases should be stratified and treated. The aim of this study was to present the 12-years experiences of the Polish Paediatric Solid Tumors Group in the treatment of children suffering from metastatic soft tissue sarcomas.*

Material and methods. *All patients were enrolled into the study between 1991 and 2002 in 11 centres belonging to the PPSTG. The children were treated according to the SIOP-MMT-91 protocol (23 patients) or according to CWS-96 protocol (35 patients). Their age ranged between 1 and 217 months. The diagnosis was undifferentiated rhabdomyosarcoma in 4 cases, 23 embryonal rhabdomyosarcoma in 4 cases, alveolar rhabdomyosarcoma in 18 cases, PNET in 9 cases, EES in 1 case and sarcoma synoviale in 2 cases. The most common localisations of distant metastases were non-regional lymph nodes and lungs. Median follow up for all patients was 36 months (range: 22 to 118 months) and for surviving patients - 35 months (range: 25 to 118 months).*

Results. *Estimated 5-year event free survival for all patients was 0.26 and estimated 5-year overall survival was 0.33. Complete remission was achieved by 37 patients (63.8%). The comparison of EFS between the patients treated with different protocols revealed significantly better results for the CWS-96 protocol (p<0.005). Prognosis was also evaluated according to diagnosis, age, localisation and number of metastases. Although no parameter did significantly influence the patient outcome alone, we did observe that patients with RME, below 10 years of age and with solitary metastases, but with the exception of patients with bone and bone marrow metastases, had better prognosis when all these parameters were considered together (p=0.03).*

Conclusions. *We were able to demonstrate that patients with metastatic sarcomas could be subdivided according to prognosis, and therefore a new stratification system should be developed for this group of patients. Patients with very poor prognosis need new therapy strategies as those currently employed are totally ineffective.*

Słowa kluczowe: soft tissue sarcomas, metastases, treatment, results, children

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Introduction

Soft tissue sarcomas (STS) in children and adolescents account for approximately 5% of all malignant neoplasms diagnosed in Poland each year in Poland [1]. This number has practically remained unchanged over the past several years, as sarcomas continue to account for 1% of all newly diagnosed adult cancers. Unfortunately, for patients who have metastatic disease at diagnosis the outlook remains poor despite the use of contemporary multiagent chemotherapy, radiotherapy, and surgery and the addition of new agents and intensification of therapy with known active agents [2]. Disease-free survival and overall survivalremain disappointing in the case of children with metastatic STS at diagnosis.

The current classification system for sarcomas is still a work in progress covering a heterogenous group of malignant solid tumors. Newer classification systems seek to identify the cell of origin (ie, adipocytic, myogenic, vascular, neural, fibroblastic, chondrocytic, osteogenic, or other). But in the long run, does this serve any useful purpose? Tuveson and Fletcher contend that there are distinct differences in outcome between myogenic and nonmyogenic tumors [3]. Histologic grades within a specific subtype, namely liposarcomas, have a significant bearing on 5-year survival outcomes, 90% for patients with well-differentiated tumors vs 20% for those with pleomorphic liposarcomas.

According to the response to therapy, this very heteregenous group of malignancies has, from the clinical point of view, been divided into 2 subgroups. Survival is still the ultimate proof of treatment efficacy. The following tumours are listed as chemosensitive neoplasms by some authors: rhabdomyosarcoma (RMS), Ewing family tumors (extraosseus Ewing's sarcoma – EES, and peripheral neuroectodermal tumor – PNET) including synovial sarcoma (SS) [2] while the STS are considered chemotherapy-resistant and usually chemotherapy is not used as a first line treatment in this subpopulation of patients [2].

Here, we present the 12-year experience of the Polish Paediatric Solid Tumors Group (PPSTG), analysing the patterns of disease extent, response to treatment, and survival rates in children with chemosensitive STS in stage IV. The study was undertaken in order to evaluate the results of treatment and to define the clinical factors

Table I. Clinical characteristics of studied patients

Characteristics	All patients N (%)	SIOP-MMT-91 N (%)	CWS-96 N (%)
Age:			
≤10 years	23 (39.7)	10 (43.5)	13 (37.1)
>10 years	35 (60.3)	13 (56.5)	22 (62.9)
Gender:			
Males	32 (55.2)	12 (52.2)	20 (57.1)
Females	26 (44.8)	11 (47.8)	15 (42.9)
Diagnosis:			
RMU	4 (6.9)	0 (0)	4 (11.4)
RME	23 (39.7)	13 (56.4)	10 (28.6)
RMA	18 (31.0)	7 (30.4)	11 (31.4)
PNET	9 (15.5)	1 (4.4)	8 (22.9)
EES	1 (1.7)	1 (4.4)	0 (0)
SS	3 (5.2)	1 (4.4)	2 (5.7)
Primary localization:			
orbit	1 (1.7)	0 (0)	1 (2.8)
head/neck parameningeal	10 (17.2)	8 (34.8)	2 (5.7)
head/neck non-parameningeal	1 (1.7)	1 (4.4)	0 (0)
bladder/prostate	5 (8.6)	0 (0)	5 (14.3)
genito-urinary tract without bladder/prostate	6 (10.3)	3 (13.0)	3 (8.6)
extremities	19 (32.8)	8 (34.8)	11 (31.4)
others	16 (27.6)	3 (13.0)	13 (37.2)
Tumor status (T):			
T1	8 (13.8)	5 (21.7)	3 (8.6)
T2	47 (81.0)	16 (69.6)	31 (88.6)
TX	3 (5.2)	2 (8.7)	1 (2.8)
Tumor size:			
a (<5 cm)	10 (17.2)	4 (17.4)	6 (17.1)
b (≥5 cm)	45 (77.6)	18 (78.2)	27 (77.2)
x	3 (5.2)	1 (4.4)	2 (5.7)
Regional lymphnode status:			
N0	20 (34.4)	6 (26.1)	14 (40.0)
N1	27 (46.6)	14 (60.9)	13 (37.1)
NX	11 (19.0)	3 (13.0)	8 (22.9)

RMU – undifferentiated rhabdomyosarcoma, RME – embryonal rhabdomyosarcoma, RMA – alveolar rhabdomyosarcoma, PNET – primary neuroectodermal tumor, EES – extraosseus Ewing's sarcoma, SS – synovial sarcoma influencing the prognosis in the management of STS patients with distant metastases.

Material and method

Patients

Patients below 19 years of age diagnosed in 11 pediatric oncology centres belonging to the PPSTG were eligible for study entry if they had newly diagnosed, histologically proven distant metastatic STS on presentation. The histologic diagnosis was confirmed by two independent pathologists. Protocol treatment was required to begin within 28 days of the definitive surgical procedure (eg, biopsy). Patients were treated mainly using multimodality therapeutic approaches, including surgery, chemotherapy and radiotherapy. The reatment protocol scheduled for 23 patients was the SIOP-MMT-91 (used between 1991 and 1996) [4], while the remaining 35 patients were treated according to the CWS-96 protocol (between 1996 and 2002) [5]. Patients treated according to the SIOP-MMT-91 protocol received chemotherapy including: carboplatin, epirubicin, vincristine, ifosfamide, actonomycin D and etoposide. The response to primary chemotherapy was evaluated after 9 weeks of treatment and second surgery was recommended if a residual tumour had been found. Radiotherapy was administered, concomitantly with chemotherapy in patients with micro- or macroscopically incomplete resection in a recommended dose of 40 Gy or 54.5 Gy using a hyperfractionated, accelerated modality. High-dose chemotherapy with melphalan, followed by haemopoietic stem cell rescue has been used in all metastatic patients. In the CWS-96 protocol these patients received the 6-drug regimen CEVAIE (carboplatin, epirubicin, vincristine, ifosfamide, actonomycin D and etoposide). After local therapy (second surgery and/or radiotherapy- 45 Gy) in 10-13 weeks the patients were randomized to receive either a 6-month maintenance oral therapy with trofosfamide/epirubicin/etoposide or a double high-dose consolidation with etoposide/melphalan or cyclophosphamide/thiothepa.

From January 1991 through December 2002 – 58 patients were enrolled, 32 boys and 26 girls. The characteristics of the eligible patients are depicted in Table I. Median age at diagnosis was 141 months, range: 1 – 217 months, accounting for 18.9% of all patients with STS registered in the study. Almost half of the patients had RMS (4 patients – 6.9% undifferentiated rhabdomyosarcoma (RMU), 23 patients – 39.7% – embryonal rhabdomyosarcoma (RME), 18 patients – 31% alveolar rhabdomyosarcoma (RMA), 9 patients (15.5%) PNET, 1 patient (1.7%) EES, and 3 patients (5.2%) SS. Major sites of metastatic disease at diagnosis included: non-regional – distant nodes (n=21), lung (n=20), bone (n=17), bone marrow (n=11) and pleura (n=4). Approximately 80% of the patients presented with tumors of more than 5 cm in diameter. More than 80% of these patients had two or more metastatic sites at the time of diagnosis (Table II).

The median follow-up for all patients was 36 months (ranging from 22 to 118 months) and for surviving patients – 35 months (ranging from 25 to 118 months).

Statistical considerations

Data available by May 2002 was retrospectively analysed using the *Statistica® 97 PL* for Windows software. All patients were followed-up for survival (time from start of treatment to death) and failure-free survival (FFS; time from start of treatment to the first occurrence of progression, relapse after response, or death from any cause). Estimates of the time-to-event distributions were calculated using the Kaplan-Meier method, and confidence intervals (CIs) for specific estimates of time-to-event distributions were calculated using Greenwood's formula for the variance of the estimates. Comparisons of outcome among responders and nonresponders were made using the log-rank test. For mulivariative analysis, Cox's regression model was used. A p value of less than 0.5 was considered statistically significant [6, 7].

Table II. Localization of distant metastases

Localization	Number of patients
Non-regional lymphnodes	21
Lungs	20
Bones	17
Bone marrow	11
Liver	4
Pleura	4
Subcutaneous	3
Central nervous system	2
Peritoneal	1
Mediastinal	1
Pelvic	1

Results

The estimated 5-year event free survival for all patients was 0.26 (Figure 1) and estimated 5-year overall survival was 0.33. Complete remission was achieved by 37 patients (63.8%) (Table III). The percentage of children who achieved complete remission was similar in both protocol groups (SIOP-MMT-91 and CWS-96). However, the comparison of EFS between the patients treated with different protocols revealed significantly better results of therapy in the group treated according to the CWS-96 protocol (EFS estimated after 50 months were 0.13 for the SIOP-MMT-91 group and 0.32 for the CWS-96 group, $p<0.005$) (Figure 2). Of the 58 patients, 13 individuals (22.4%) did not respond to the therapy (7/23 in the SIOP-MMT-91 subgroup and 6/35 in the CWS-96 subgroup)

Table III. Treatment results of children with soft tissue sarcomas in stage IV

N (%)	All patients N (%)	SIOP MMT-91 N (%)	CWS-96
Number of patients	58 (100)	23 (100)	35 (100)
Complete remission CR	37 (63.8)	14 (60.9)	23 (65.7)
Relapse (all):	17* (45.9)	10* (71.5)	7* (30.4)
– local	5* (13.5)	4* (28.6)	1* (4.3)
– metastatic	4* (10.8)	2* (14.3)	2* (8.7)
– mixed	8* (21.6)	4* (28.6)	4* (17.4)
Patients alive in CR1	19* (51.4)	3* (21.4)	16* (69.6)
Tumour progression	13 (22.4)	7 (30.4)	6 (17.1)
Partial remission	8 (13.8)	2 (8.7)	6 (17.1)
Toxic death	6** (10.3)	4 (17.4)	2 (5.7)
Patients alive	26 (44.8)	4 (17.4)	22 (62.9)

* Percentage of patients who achieved complete remission;
** Causes of death: intracranial bleeding (1 patient), acute cardiotoxicity (1 patient), cerebral oedema (1 patient), death after implantation of Pudenze valve (1 patient), acute respiratory distress syndrom (1 patient), septicaemia (1 patient)

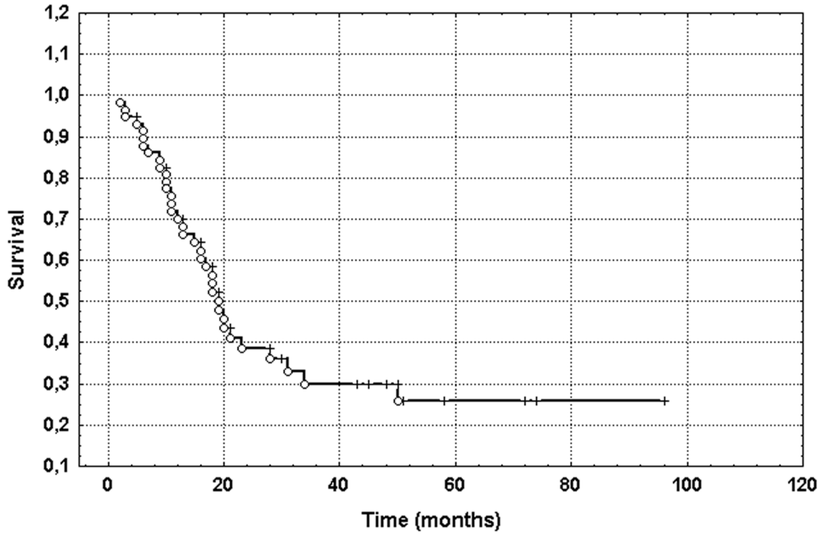

Figure 1. Event free survival of children suffering from soft tissue sarcomas with distant metastases

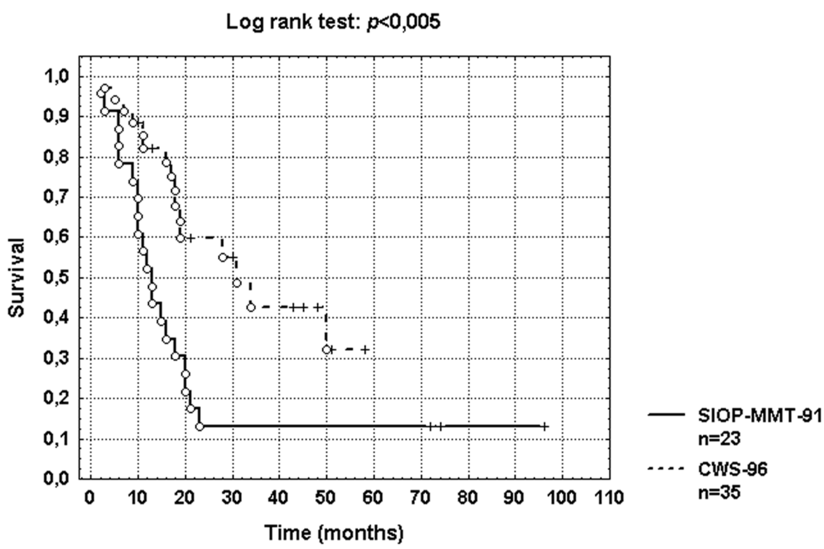

Figure 2. Comparison of event free survival between patients treated according to the SIOP-MMT-91 protocol and the CWS-96 protocol

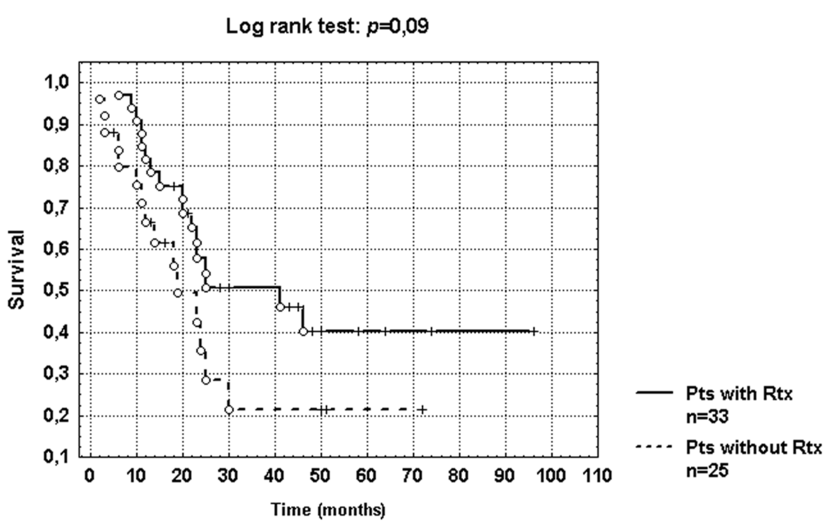

Figure 3. Influence of radiotherapy on the final treatment results. Rtx – radiotherapy

and died due to disease progression (Table III). It must be stressed that radiotherapy seemed to be an important component of successful therapy (Figure 3).

Interestingly, parameters which are normally regarded as prognostic indicators for localised STS, did not influence the prognosis of patients with distant metastases: primary tumor size (<5 cm vs. ≥5 cm, 5-years EFS: 0.31 vs. 0.27 respectively; p=0.85), regional lymphnode involvement (regional lymphnodes involved vs. regional lymphnodes not involved, 5-years EFS 0.25 vs. 0.26: respectively; p=0.51), resection of primary tumor (biopsy vs. primary resection, 5 years EFS: 0.22 vs. 0.38 respectively; p=0.28), and primary localisation of tumor (none primary localisation had better outcome than others – data not shown). As the standard stratification parameters were not well suited for patients in stage IV, we attempted to assesswhether these patients were a homogenous group with generally poor prognosis or if the patients could have been divided into subgroups with better and poorer outcome. For this reason we employed a stratification system proposed by Klingebiel [9] with some modifications (Table IV). The prognosis was evaluated according to histology, age, and localisation and number of metastases. Although no parameter did significantly influence patient outcome alone, it was observed, that patients with RME (Figure 4), aged below 10 years (Figure 5) and with solitary metastases, except

Table IV. Risk factors in patients with distant metastases

Parameter	Score 0	Score 1
Histology	RME N=23	Other than RME N=35
Age	≤10 years old N=23	>10 years old N=35
Localization of metastases	Solitary metastases (except bone and bone marrow metastases) N=24	Bones, bone marrow or multiple metastases N=34

RME – embryonal rhabdomyosarcoma

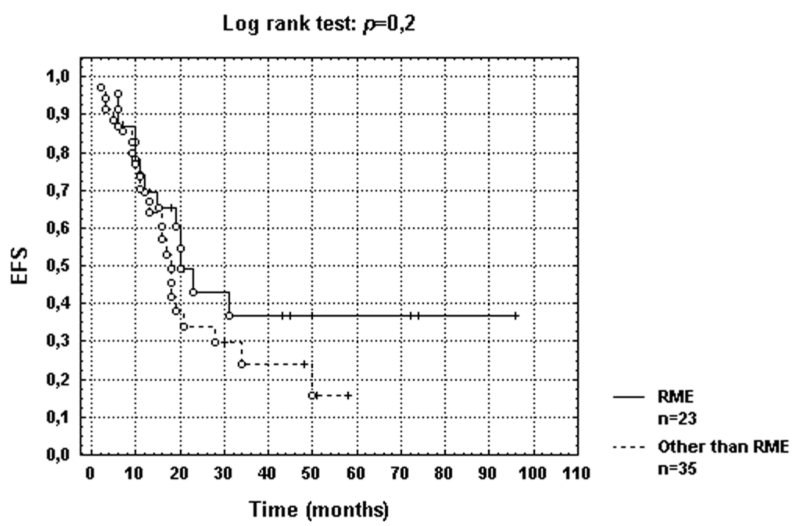

Figure 4. Outcome of children with metastatic sarcomas according to the histology.
RME – embryonal rhabdomyosarcoma

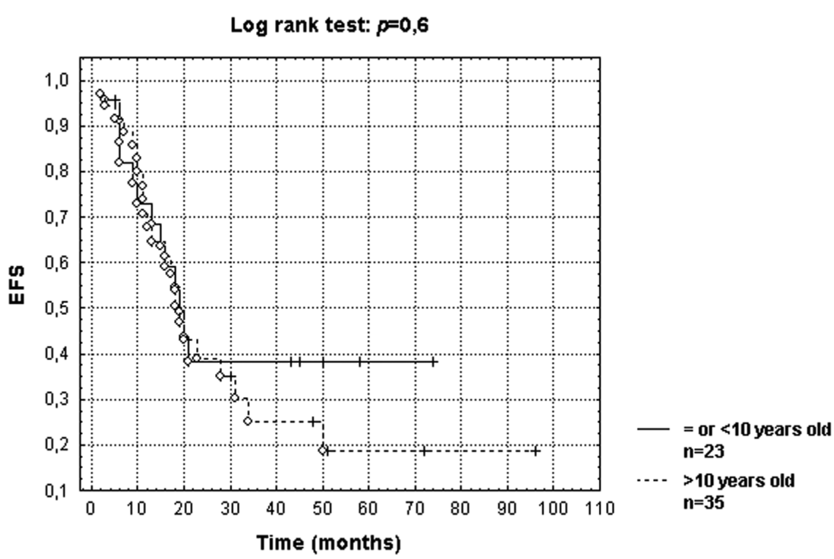

Figure 5. Outcome of children with metastatic sarcomas according to patient age

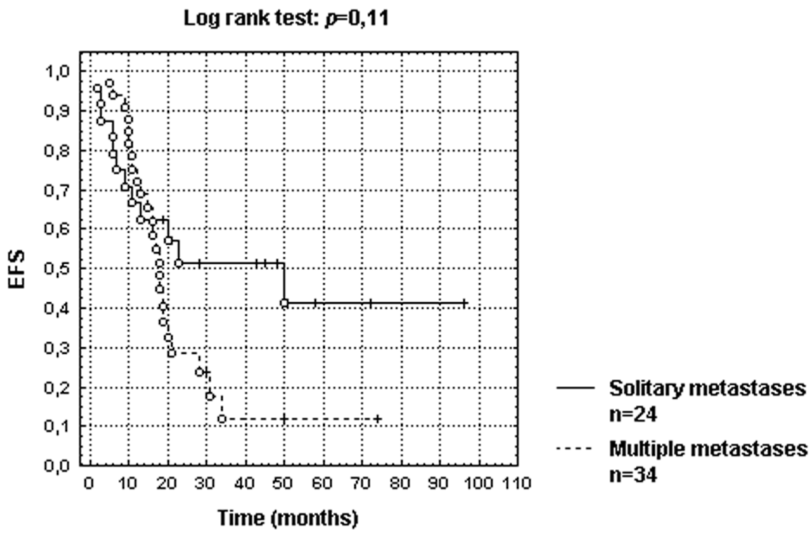

Figure 6. Outcome of children with metastatic sarcomas according to the number and localizations of metastases

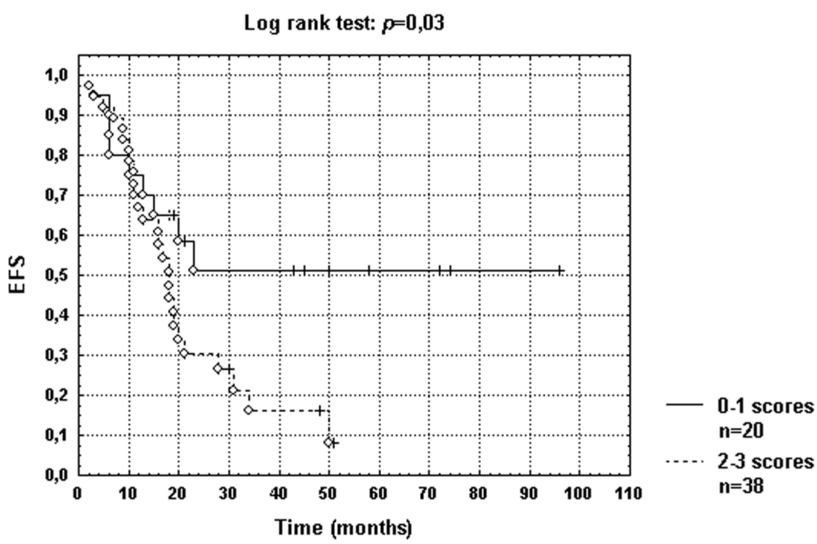

Figure 7. Event-free survival for children divided in 2 subgroups according to the stratification system presented in Table IV

for patients with bone and bone marrow metastases (Figure 6), had better prognosis. Moreover, when all these parameters were considered simultaneously, it was noted that patients with 2 (23 patients) or 3 (15 patients) of the disadvantageous clinical factors mentioned above had significantly poorer prognosis than patients with none (6 patients) or with only one (14 patients) disadvantageous parameter (estimated EFS after 50 months of observations: 0.08 vs. 0.51 respectively; p=0.03) (Figure 7).

Multivariative analysis

The type of protocol (SIOP-MMT-91 *versus* CWS-96), the stratification system (0-1 score *versus* 2-3 scores) and treatment with radiotherapy (given *versus* not given) were entered as covariates in Cox's regression model for EFS. The model revealed type of treatment and scoring achieved in the new stratification system as significant independent prognostic factors (Table V). When the parameters included in the stratification system were added to the Cox's regression model, they were all not statistically significant, and the type of treatment and scoring remained independent prognostic factors (data not shown).

Table V. Multivariative analysis of event-free survival (Cox regression model)

Covariate		β	p
Applied therapy	SIOP-MMT-91 vs. CWS-96	-1.31	0.0003
Stratification system	0-1 score vs. 2-3 scores	1.23	0.003
Radiotherapy	Given vs. not given	-0.31	0.37

Discussion

Although paediatric STS has a more favorable prognosis than its adult counterpart, still the treatment results in patients with distant metastases remain unsatisfactory. In this series, the tumor size correlated with metastatic disease at the onset and is the major factor influencing survival. Surgery is the mainstay of therapy. The effectiveness of adjuvant therapy remains to be established, though radiotherapy may be advisable in cases of inadequate surgery.

EFS reported for children and adolescence with metastatic STS is not better than 26-28% after a 5-year observation period [8-11], which corresponds with our results achieved by the PPSTG. Although the different long term outcomes with the CWS-96 protocol for STS in stage IV could not be definitely assessed because of the relatively short follow-up time, some preliminary observations could be made. A comparison of these two treatment protocols (SIOP-MMT-91 and CWS-96) reveals significantly better results in patients tretated with the CWS-96 protocol. Speculating as the cause of this discrepancy one could explain it by another strategy employed after the initial phase of intense chemotherapy. Patients treated according to the SIOP-MMT-91 protocol were stipulated to go through autogenic bone marrow transplantation (ABMT) or peripheral blood stem cell transplantation (auto-PBSCT) after high dose chemotherapy (HDC/T). Such a treatment caused deep immunosupression by ablating all inherited and acquired anti-tumor immunity. Presuming that high dose chemotherapy is not able to destroy all the tumor cells, a single surviving malignant cell had a good chance to develop during this deep immunosupression. The observation that most relapses occurred within 8 months after ABMT or auto-PBSCT, is in favour of this hypothesis. Similar facts were reported by other authors [12-17]. Most patients treated with the CWS-96 protocol were after intensive chemotherapy treated with so-called low-dose intensity maintainance chemotherapy [5]. Such a treatment could prolong EFS in metastatic STS. However, these observations are restricted to a relatively short follow-up time and final conclusions will be available after a longer period.

Patients with metastatic sarcomas are generally considered to be a homogenous group with a very poor prognosis. We were able to demonstrate that this population could be further divided into two subpopulations with relatively better outcomes a 5-year EFS estimate of approx. 50%) or with a very poor prognosis having a survival ratio below 10% after a 5-year observation time. Such a stratification system could be a useful tool for the further assessment of children with metastatic soft tissue sarcomas. In the group with relatively good prognosis optimising the therapy could reduce the early and late side-effects [18-20]. Neoadjuvant chemotherapy and/or radiation therapy confers to substantial benefit following complete surgical resection of localized disease. The management goals of metastatic sarcomas was claimed to be palliative, since these advanced malignancies are virtually always incurable, in spite of high-dose chemotherapy, highly toxic combination chemotherapy, and surgical intervention. It is very important to underline, that there is an urgent need to search for other therapy methods for patients with 2 or 3 unfavourable scores. For this subgroup of patients the currently used treatment regimens are ineffective and new drugs or a different approach is needed. Agents that have shown the most activity in treating STS include doxorubicin and ifosfamide. Topotecan, vinblastine, paclitaxel, docetaxel, dacarbazine, gemcitabine, and carboplatin have also shown some degree of efficacy [21]. The targeted molecular therapies of the present may be well suited for treating sarcomas, given the fact that many sarcoma-linked oncogenes appear to be triggered by viruses, including the Rous sarcoma virus. The sequencing of these viruses may allow to develop specific antibodies against oncogenic activation. Probably the most exciting recent advance in the treatment of sarcomas has been the effect of imatinib/STI571 on GISTs, which, heretofore, have been notoriously resistant to chemotherapy [22]. The expression of platelet-derived growth factor beta in dermatofibrosarcoma tuberans is also being investigated as a target for imatinib/STI571 therapy [22, 23]. The rapid identification and testing of promising new therapies is urgently needed to improve the outcomes of children with disseminated disease. We have a long way to go before the lethal natural histories of these tumors are radically altered.

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