Eur J Orthop Surg Traumatol (2018) 28:1–7
https://doi.org/10.1007/s00590-017-2019-4

ORIGINAL ARTICLE • TUMORS - PAEDIATRICS

Pediatric soft tissue sarcoma of the limbs: clinical outcome of 97 patients

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Received: 27 May 2017 / Accepted: 19 July 2017 / Published online: 1 August 2017

Abstract
Purpose Soft tissue sarcomas (STS) of the extremities in children are a heterogeneous group of tumors with a very different prognosis for which optimal treatment remains controversial.
Patients and methods We retrospectively evaluated 97 patients younger than 15 years old affected by limb soft tissue sarcomas. All cases were histologically revised, and tumor grade was assessed according to the FNLCC system. Thirty-two were rhabdomyosarcoma (RMS) and 65 non-rhabdomyosarcoma (NRMSTS); among these, 40 (61.5%) were grade 3 according to FNLCC classification. Overall survival, local recurrence and distant metastasis were analyzed.
Results Overall survival was 77.8% at 5 years and 69.7% at 10 years. Among grade 3 tumors, RMS had a worse prognosis over NRSTS. Similarly, tumors larger than 5 cm had a worse prognosis compared to smaller ones. Local recurrence-free survival was 90.7% at 5 years and 87.1% at 10 years with a better local control in grade 3 NRSTS over RMS and in tumors smaller than 2 cm.
Conclusion Children affected by extremities RMS were confirmed to have the worst prognosis, in particular in case of metastasis at presentation. Differently from adult patients, hand and feet locations are frequent site for STS and 2 cm diameter should be taken as cut off for higher risk of LR. Similarly to adulthood STS, grading correlates with prognosis in NRSTS. The identification of prognostic variables should enable risk-adapted therapies to be planned.

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Keywords Pediatric · Childhood · Soft tissue sarcoma · Limbs · Extremities

Introduction

Soft tissue sarcomas (STS) represent a heterogeneous group of mesenchymal malignancies that account for about 8% of all neoplasms in childhood and adolescence. Approximately 50–60% of STS are rhabdomyosarcoma (RMS), while the remainder forms varied group of the so-called non-rhabdomyosarcoma soft tissue sarcomas (NRSTS).

Rhabdomyosarcoma is the most common STS in children younger than 14 years, and it is further divided into 3 histologic subtypes (embryonal, alveolar, pleomorphic). The most common sites of primary RMS are the head, the genitourinary tract and the limbs [1, 2]. In particular, those RMS affecting limbs and girdles are more likely to display alveolar histology and metastatic spread [3].

Non-rhabdomyosarcoma soft tissue sarcomas are a heterogeneous group of adult-type STS encompassing more than 50 different histologic diagnoses arising from primitive mesenchymal tissue, which occur in children and adolescents [4–7]. They generally affect older children, increasing in incidence throughout adolescent years [8]. More frequently NRSTS arise in the extremities (limbs and girdles), although they can develop anywhere in the body, and are characterized by local aggressiveness and a propensity to metastasize that is correlated with their grade of malignancy [4, 9, 10].

The prognosis of pediatric STS has improved significantly during the past three decades thanks to a multidisciplinary therapeutic approach [11–13].

Surgery provides the best choice of local control of small resectable tumors in order to obtain margins free of tumor

and to achieve local control and hopefully to improve the likelihood of survival [14].

Nowadays chemotherapy (CMT) protocols for RMS generally include a combination of vincristine, actinomycin D and cyclophosphamide. Radiotherapy (RT) is generally used as additional therapy with excellent local control rates in addition to surgery [15, 16].

In NRSTS, most of data on the treatment come from adult studies and these suggest that patients with high-risk extremity sarcomas can benefit from intensified adjuvant CMT [9, 17, 18].

In general, similarly to adults STS, RT is indicated for patients with inadequate surgical margins and for larger and high-grade tumors [19]. With combined surgery and RT, local control of the primary tumor can be achieved in more than 80% of patients [10].

The aim of this study was to evaluate the prognosis of pediatric STS affecting girdles and limbs.

Patients and methods

From March 1990 to September 2015, a total of 105 pediatric (<15 years old) patients received diagnosis of STS of the limbs/girdles at our Institution. Seven metastatic patients who received only palliative CMT and 1 patient who refused surgery were excluded from the study population; therefore, 97 patients were included in this study.

Tumor size was assessed on surgical specimens using the larger diameter as a reference, and depths were divided into superficial and deep (above or below the fascia, respectively), according to preoperative imaging (computerized axial tomography scan or magnetic resonance imaging).

All patients underwent operation in order to obtain limb-sparing, function-sparing surgery with wide surgical margins [20].

The use of RT and CMT was decided at the discretion of a multidisciplinary team (orthopedic surgeon, radiotherapist and oncologist), basing on the ongoing protocols at the time of diagnosis.

All cases were histologically revised and classified according to the 2013 World Health Organization classification of STS [21] by experienced sarcoma pathologist of our Institute (MG).

A three-step system (FNCLCC) was used to assess NRSTS grade [22]. According to FNLCC classification, all RMS was considered grade 3.

Patients' characteristics are presented by frequencies and percentages for categorical variables, median and range for continuous variables. According to previous studies, a cutoff of 5 cm was used as a reference for the size of the tumor [9, 23]. Similarly, since RMS was reported to have a worse prognosis in children <1 year or >10 years old, a cutoff of 10 years old was used as a reference [24]. The sites of the tumors were divided in "girdles", "proximal limb" (arm and thigh), "distal limb" (forearm and hand, leg and foot).

Median age at the time of surgery was 10 years (range 4 months–15 years); 50 (51.5%) patients were female 47 (48.5%) were male.

Thirty-two (33%) STS were RMS, whereas most of them were NRMSTS (65, 67%); among these, 40 tumors (61.5%) were grade 3 according to FNLCC classification. (Table 1) A significant difference in the age at presentation was found between RMS and NRSTS ($p < 0.001$), with RMS being more frequent in patients aged <10 years.

The majority (68, 70%) of STS had not been previously treated; 18 (19%) were local relapses (>3 months after primary tumor excision), whereas 11 (11%) were previously unplanned excisions ("re-excisions", lesion excised with inadequate margins ≤3 months earlier) [25]. All previously inadequately excised tumors were smaller than 5 cm ($p = 0.007$).

Fourteen (14%) tumors were localized in the girdles, 83 (86%) tumors in the limbs; 15 of these (18%) were in the hand or foot.

Most of STS were deep (93, 96%); only 4 (4%) were superficial. Fifty-four (56%) were <5 cm (20 smaller than 2 cm), 43 (44%) >5 cm (12 larger than 10 cm).

Twenty-two patients (23%) had metastasis at presentation (13 to the lungs, in one case associated with lymphnodes, in 6 to the lymphnodes alone, in 3 cases bone metastasis), with a positive correlation with STS larger than 5 cm ($p = 0.010$) and those localized in the girdles ($p = 0.049$).

Among grade 3 tumors, metastases at presentation were mostly seen in RMS ($p = 0.007$).

The Kaplan–Meier method was used to estimate overall sarcoma-specific survival (OS), local recurrence (LR)-free survival and distant metastasis (DM)-free survival.

Local recurrence-free survival and DM-free survival intervals were defined as the time between surgery and the first LR or DM, respectively, or last follow-up available. Similarly, OS interval was defined as the time between surgery and death or last follow-up. Patients who died of other causes were censored. Differences in survival rates were assessed by the log-rank test.

Multivariable analysis of OS and LR was based on cause-specific hazards and therefore carried out by Cox regression models. p values < 0.05 were considered significant.

All analysis was completed using the Statistical Package for Social Science (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

Table 1 Patients' characteristics

	RMS ($n = 32$)	NRSTS ($n = 65$)	p*
Sex			
Female	17	33	0.827
Male	15	32	
Age			
<10 years	24	21	<0.001
≥10 years	8	44	
Histotype	Embryonal ($n = 14$) Alveolar ($n = 17$) Pleomorphic ($n = 1$)	Synovial sarcoma ($n = 20$) Ewing sarcoma ($n = 10$) Spindle cell sarcoma ($n = 10$) Fibrosarcoma ($n = 8$) Epithelioid sarcoma ($n = 5$) MPNST** (= 5) Myxofibrosarcoma ($n = 3$) Leiomyosarcoma ($n = 3$) Liposarcoma ($n = 1$)	
Size			
<5 cm	15	39	0.221
>5 cm	17	26	
Depth			
Superficial	1	3	0.729
Deep	31	62	
Grade	3 ($n = 32$)	1 ($n = 8$) 2 ($n = 17$) 3 ($n = 40$)	
Metastasis at presentation			
No	18	57	0.001
Yes	14	8	
Presentation			
Primary	24	44	0.534
Local recurrence	6	12	
Unplanned	2	9	
RT			
No	16	46	0.045
Yes	16	19	
CT			
No	0	31	<0.001
Yes	32	34	
Site			
Limb	30	53	0.108
Girdle	2	12	

* Chi square test, comparison between RMS and NRSTS group characteristics at baseline. A p value < 0.05 was considered significant

** *MPSNT* Malignant Peripheral Nerve Sheath Tumors

Results

In 14 patients (15%), an amputation was necessary, whereas in 83 (85%) excision was possible (11 scar re-excision). Amputation was more frequently performed in local relapses ($p = 0.028$).

Among 11 re-excised tumors, only 1 case had microscopic residual of the disease; in 10 cases no residual disease was found in the analyzed specimen.

Excluding those patients with no residual disease in the re-excised specimen, an adequate margin was achieved in 60 cases (in 14 cases a radical, wide in 46), while in 27 cases

the quality of the margins was inadequate (marginal in 17 and intralesional in 10 cases).

Chemotherapy was used in all RMS. Among NRSTS, CMT was given in 25 grade 3 and in 8 grade 2 tumors, with no significant difference between groups ($p = 0.254$).

Regardless the histology, the use of CMT was more common in large tumors ($p = 0.004$) and in not previously treated patients ($p = 0.017$).

In 35 cases, RT was added to surgery as part of primary treatment, in particular in RMS ($p = 0.045$), grade 3 tumors ($p = 0.027$) and those with inadequate margins ($p = 0.047$).

Two patients were lost to follow-up since they returned to their own country after surgery and were therefore excluded from survival analysis. At the last follow-up (median 96 months, range 2–305), 69 patients are alive with no evidence of disease and 26 died of the disease. In particular, among patients with metastasis at diagnosis, 13 died of the disease after a median time of 19 months (range 2–135); 9 patients are alive with no evidence of the disease after surgical metastasis removal.

Specific sarcoma survival

Kaplan–Meier analysis with OS as a primary endpoint showed an estimated survival of 77.8% (CI 95% 76.9–78.7%) at 5 years and 69.7% (CI 95% 68.7–70.7%) at 10 years.

By considering only patients affected by grade 3 STS, RMS had a worse prognosis over NRSTS (41.9 vs 83.4% at 10 years, $p = 0.001$) (Fig. 1). Similarly, tumors larger than 5 cm had a worse prognosis compared to smaller ones (54.1 vs 82.1% at 10 years, $p < 0.001$) (Fig. 2).

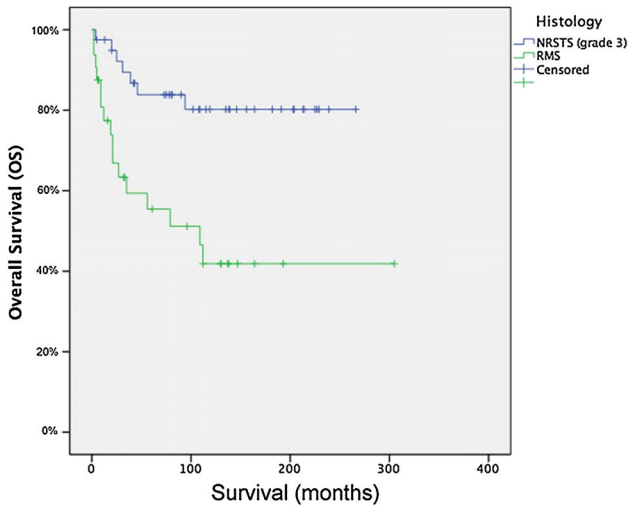

Fig. 1 Kaplan–Meier overall survival (OS) curve according to histology. Patients affected by RMS (*green line*) and grade 3 NRSTS (*blue line*) are represented in this curve (color figure online)

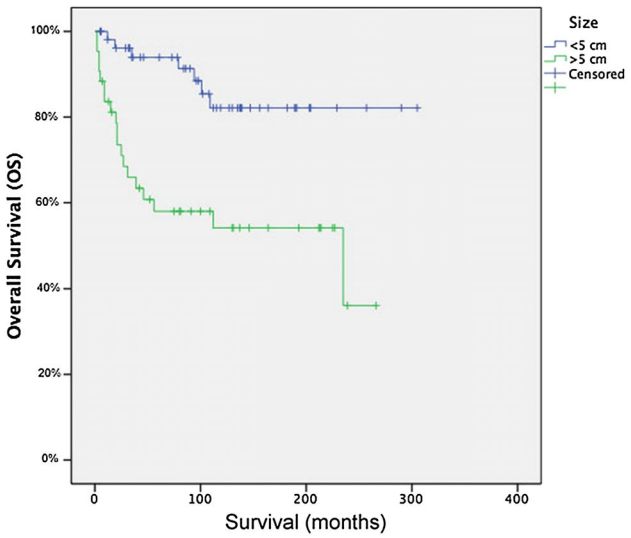

Fig. 2 Kaplan–Meier overall survival (OS) curve according to the size of the tumor. Patients affected by STS smaller than 5 cm (*blue line*) and larger than 5 cm (*green line*) are represented in this curve (color figure online)

No correlation was found between the 2-cm cutoff for the size of the tumor and OS ($p = 0.220$). Similarly, no differences were found in prognosis for patients younger and older than 10 years ($p = 0.652$), even when RMS and NRSTS were considered separately ($p = 0.149$ and $p = 0.117$, respectively). The distal localization of the tumor was found to be a positive prognostic factor for OS ($p = 0.023$).

Patients with metastasis at the diagnosis had the worst prognosis 41.1 versus 77.9% at 10 years, $p = 0.002$); nevertheless, in multivariate analysis only size of the tumor (>5 cm) and Rhabdo/Non-rhabdo histology were confirmed to be significant independent prognostic factors.

A further survival analysis was performed considering only NRMST. All patients affected by grade 1 NRMST were alive at latest follow-up available (median 119 months, range 36–257). Similarly, no patient affected by superficial NRSTS died of the disease.

Among patients affected by grade 2 and 3 NRMST, grade 2 had a higher survival rate at 5 years (93.8 vs 83.7% at 5 years) with no significant difference at longer follow-up (82.0 vs 80.1% at 10 years, $p = 0.946$) (Fig 3).

Patients with small NRSTS (<5 cm) and those with the tumor in the limb had a better prognosis at 10 years (90.7 vs 68.0%, $p = 0.010$ and 86.3 vs 50.8%, $p = 0.004$, respectively).

In the multivariate setting, size of the tumor and limb localization were confirmed to be favorable prognostic factors.

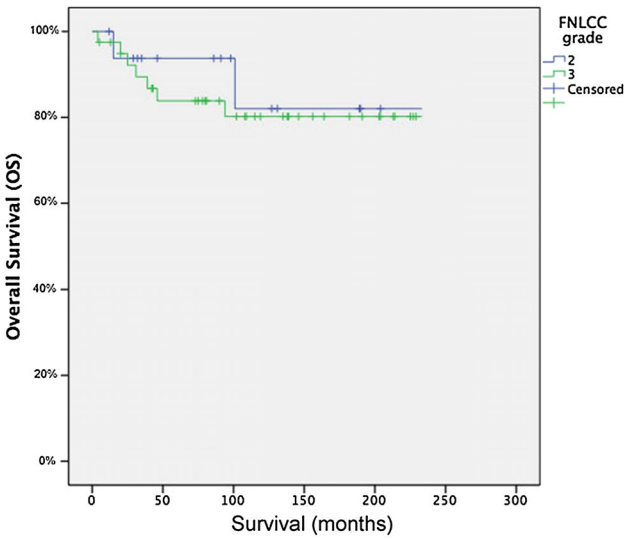

Fig. 3 Kaplan–Meier overall survival (OS) curve according to FNLCC grade of the tumor in NRSTS group. Patients affected by grade 2 NRSTS (*blue line*) and grade 3 NRSTS (*green line*) are represented in this curve (color figure online)

Distant metastasis

Among localized STS at the time of diagnosis, 10 patients (5 RMS and 5 NRSTS) developed DM after a median of 33 months (range 5–96) (5 to the lungs, 1 to soft tissues, 1 to bone, 1 to lungs and lymphnodes and 2 to lymphnodes).

All these patients but 1 died of the disease after a median of 6 months (range 3–74 months).

Kaplan–Meier analysis carried out considering DM as a primary endpoint showed a DM-free survival was 91.9% (CI 95% 91.2–92.6%) at 5 years and 87% (CI 95% 86.7–88.5%) at 10 years.

Local recurrence

In 12 cases (12%), LR occurred after a median period of 14 months (range 3–124 months).

Kaplan–Meier analysis considering LR as primary endpoint showed a LR-free rate of 90.7% (CI 95% 90.1–91.3%) at 5 and 87.1% (CI 95% 86.3–87.9%) at 10 years.

Among grade 3 tumors, RMS had a higher LR rate compared to NRSTS ($p = 0.008$).

Patients presenting with LR and those with a previous unplanned excision had a worse local control compared to not previously treated STS. (75.0 vs 90.0% at 10 years, $p = 0.047$).

No significant correlation was found neither between the quality of margins nor the size of the tumor (<5cm vs >5 cm) and the risk for LR. Nevertheless, STS smaller than 2 cm had a decrease LR risk among larger tumors ($p = 0.031$). A tendency toward a better local control was also found in those patients receiving RT ($p = 0.127$).

In multivariate analysis, STS smaller than 2 cm and NRSTS histology were confirmed to be protective independent prognostic factors for LR.

Discussion

Even though STS are not uncommon during childhood as they account for up to 8% of tumor during this age, they encounter a very heterogeneous group of histologies ranging from RMS to other histotypes which are generally enclosed in the group of NRSTS: For this reason, the prognosis is very variable. In addition the localization in the extremities is not so common as for STS in adult age.

In particular, STS affecting limbs and girdles generally have a very different behavior respect to those in other anatomic sites. Furthermore, STS in extremities may be surgically treated in different ways when compared to other sites (e.g., excision, amputation).

To the best of our knowledge, all previous series in the literature analyzed separately RMS and NRSTS but considering different localizations (extremities and non-extremities) together.

This study retrospectively analyzes the clinical features, treatment, and outcome of a large single-institution series of pediatric patients affected by STS of the girdles and limbs.

Our findings confirm the known epidemiologic data with one-third of STS being RMS and two-thirds NRSTS. In addition, RMS mostly affects younger patients, while NRSTS are prevalent during adolescence. In particular synovial sarcoma (Fig. 4) is one of the most frequent histotypes in adolescents and young adults. Furthermore, this histotype in young patients seems to have a good prognosis when compared to adult ones [26].

In the present series, we report 11% of previously inadequately excised tumors, which is lower than reported for adult STS [27]. In addition, only one of these had residual disease in the re-excised specimen thus suggesting that even when unplanned excised, the whole tumor is generally removed completely probably due to their small size.

Interestingly, those patients presenting at our center with a local relapse of the disease underwent an amputation. An amputation was necessary in most of these cases either because the large size of the tumor or the invasion of neurovascular bundle. The high rate of amputation might also be a consequence of the high rate of STS localized in the hand and foot compared to adulthood counterpart, as in these peripheral sites a proper excision is more difficult due to the closeness to vessels and nerves.

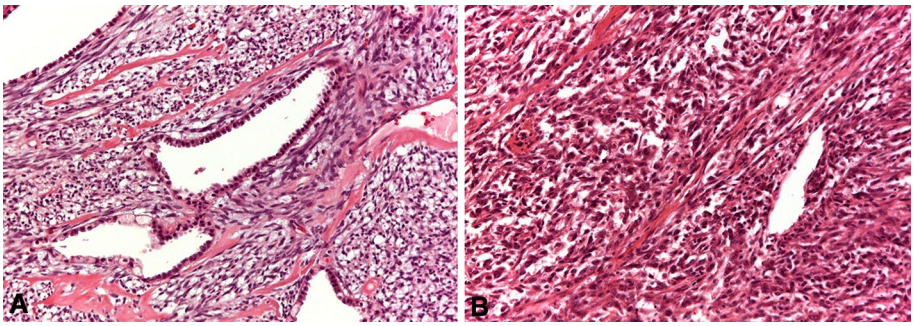

Fig. 4 On hematoxylin and eosin staining, an example of synovial sarcoma in the children. (×50 of magnification). **a** The biphasic type, with epithelial cells arranged in glandular structures and uniform spindle cells; **b** the monophasic type, entirely composed of spindle cells

All the patients affected by RMS in this series underwent CMT, as it is well known that it is a chemosensitive histotype [9]. Even though all these patients received CMT, we found that RMS of the extremities has a significant worse prognosis when compared to grade 3 NRSTS [5, 8].

Considering only NRSTS patients, we confirm a better prognosis for lower grade over higher-grade NRSTS [28]. This confirmed that FNLCC grading plays an important prognostic factor when dealing with NRSTS as for adult-type STS, as previously reported by Khoury et al. [29]. However, when compared to their adulthood counterpart, NRSTS had a better prognosis. This is partially explainable by different histologies prevalence but also by a different behavior of the same histotype, as reported for synovial sarcoma [26, 30].

In addition, FNLCC grading system is a three-tier system that grades sarcomas by summing scores assigned to each of the following: histologic subtype/differentiation, amount of tumor necrosis and mitotic count. Therefore, some sarcomas such as synovial sarcoma can have a differentiation score of 3 and can be therefore always a high-grade sarcoma (grade 2 or 3) [31] underlying the importance of a careful pathological diagnosis.

As reported by Spunt et al. [32], we found a better prognosis in children with tumor smaller than 5 cm; however, we did not find any significant correlation between the age at the time of diagnosis and prognosis, neither for RMS nor NRSTS. This data differ from those previously reported [33–35].

Patients affected by RMS had a higher incidence of metastasis, both at the time of diagnosis and after surgery.

Regarding LR, we found a LR rate lower than data reported on adult STS [30].

A higher LR was found in RMS even though they received CMT more frequently. Interestingly, no correlation was found between the 5-cm cutoff of the size of the tumor and LR but a lower LR was found in STS smaller than 2 cm. The risk associated with a given tumor size is not the same in patients of different body size, so that it may be wrong to use the same 5-cm cutoff for tumor size in risk stratification.

A few limitations of the present study must be addressed, as it is a retrospective study. Furthermore, the wide period in which patients were treated does not allow drawing any definitive conclusion on the possible role of RT and CMT for STS of the extremities. Nevertheless, we report data from a selected cohort of patients including only pediatric patients affected by STS of the girdles and limbs.

In conclusion, childhood STS of the limbs and girdles are a very heterogeneous group of tumors that should be considered separately than other sites. In particular, RMS is confirmed to have a very different prognosis with respect to other histotypes. In addition, NRSTS cannot be considered in the same way as their adulthood counterpart since different prevalence of histologies and different behavior of the same histologic subtype in different ages.

Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflict of interest. This study complies with the current laws of the country in which it was conducted.

Ethical standard The study was approved by the local Ethic committee.

Informed consent All patients signed an informed consent.

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