

Synovial sarcoma in children and adolescents: the European pediatric Soft tissue sarcoma Study Group prospective trial (EpSSG NRSTS 2005)

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Key message

The paper report the results of the first European prospective non-randomized trial dedicated to pediatric synovial sarcoma. The study included 138 patients treated from 2005 to 2012 with a multimodal therapeutic approach. The overall treatment results were higher than those previously published by pediatric groups.

ABSTRACT

Background

To report the results of the first European prospective non-randomized trial dedicated to pediatric synovial sarcoma.

Patients and Methods

From August 2005 to August 2012, 138 patients <21 years old with non-metastatic synovial sarcoma were registered in 9 different countries (and 60 centers). Patients were treated with a multimodal therapy including ifosfamide-doxorubicin chemotherapy and radiotherapy, according to a risk stratification based on surgical stage, tumor size and site, and nodal involvement.

Results

With a median follow-up of 52.1 months (range 13.8-104.4), event-free survival (EFS) was 81.9% and 80.7%, and overall survival (OS) was 97.2% and 90.7%, at 3 and 5 years, respectively. The only significant prognostic variable at univariate analysis was the risk group: 3-year EFS was 91.7% for low-risk, 91.2% for intermediate-risk, and 74.4% for high-risk cases. In 24 low-risk patients (completely resected tumor ≤ 5 cm in size) treated with surgery alone, there were 2 local relapses and no metastatic recurrences. Among 67 high-risk patients (unresected, or axial tumor or nodal involvement), 66 underwent surgery after neoadjuvant chemotherapy. Response to chemotherapy was 55.2%, including 22.4% cases with complete or major partial remissions, and 32.8% with minor partial remissions.

Conclusion

This study demonstrates that collaborative prospective studies on rare pediatric sarcomas are feasible even on a European scale, with excellent treatment compliance. The overall results of treatment were satisfactory, with higher survival rates than those previously published by pediatric groups. Nonetheless, larger, international projects are needed, based on a cooperative effort of pediatric and adult oncologists.

Keywords

Synovial sarcoma, pediatric sarcoma, children, adolescents, clinical trial, cooperative groups

Clinical Trials number

European Union Drug Regulating Authorities Clinical Trials No. 2005-001139-31

INTRODUCTION

Synovial sarcoma (SS) is a malignant mesenchymal tumor characterized by local invasiveness and a propensity to metastasize [1]. Its hallmark is a specific t(X;18)(p11.2;q11.2) chromosomal translocation and the SYT-SSX transcript (in its various forms) [2]. It is a type of tumor that occurs in both the pediatric and adult age range, and the most common non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) in childhood. The prognosis for SS patients depends largely on the presence of any metastases, the feasibility of surgical resection, and tumor size and site [3-7].

The optimal treatment for SS remains to be established, also due to the rarity of the disease and the consequent difficulty of conducting randomized clinical trials. Given pediatric series [3-7] reporting a relatively high rates of response to chemotherapy (in particular to ifosfamide-based regimen), SS has traditionally been considered chemosensitive and treated according to rhabdomyosarcoma protocols by pediatric oncologists, particularly in Europe [8]. In contrast, adult cases of SS have generally been treated like other adult soft tissue sarcomas with limited chemosensitivity, focusing on local control with a limited use of chemotherapy [9-11].

In the last decade, reports from retrospective pediatric series have supported the potential efficacy of chemotherapy on the one hand [5-7], while suggesting on the other that adjuvant chemotherapy could be omitted for low-risk patients [12]. European pediatric oncologists have consequently moved away from their “rhabdomyosarcoma-like” strategy towards a dedicated treatment approach that more closely resembles the one usually adopted in adults, ranging from full-dose ifosfamide-doxorubicin chemotherapy to no chemotherapy at all for completely resected tumors <5 cm in size, depending on the patient’s risk stratification [8].

The International Society of Pediatric Oncology – Malignant Mesenchymal Tumour Committee (SIOP-MMT) and the Associazione Italiana Ematologia Oncologia Pediatrica – Soft Tissue Sarcoma Committee (AIEOP-STSC, previously called the Italian Cooperative Group, ICG) founded the European pediatric Soft tissue sarcoma Study Group (EpSSG) in 2005, and started the NRSTS 2005 study with the goal to make uniform the treatment of pediatric NRSTS patients across Europe;

the study included a trial on SS, a trial on adult-type NRSTS and treatment guidelines for other rare pediatric histotypes [8]. The present paper reports the results of the prospective non-randomized trial on localized SS.

MATERIAL AND METHODS

The EpSSG NRSTS 2005 study began to enroll SS patients in August 2005. The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines, the EU Clinical Directive 2001/20/EC for non-commercial clinical trials (European Union Drug Regulating Authorities Clinical Trials No. 2005-001139-31).

Main objectives were to assess: a) survival rates and treatment failure patterns; b) the role of ifosfamide-doxorubicin chemotherapy in improving response rates in patients with unresectable SS; c) the impact of omitting adjuvant chemotherapy in patients with low-risk SS.

The inclusion criteria were: 1) a pathologically proven diagnosis of SS; 2) age under 21 years; 3) no evidence of metastatic disease; 4) no previous treatment except for primary surgery; 5) no pre-existing illness preventing treatment; 6) no previous malignant tumors; 7) diagnostic specimens available for central pathological review; 8) written consent for data management, treatment and sample collection signed by patients, parents and/or guardians; 9) patients' availability for long-term follow-up.

Inclusion in the protocol was based on the local pathologist's diagnosis, although pathology review by a EpSSG panel was encouraged, as was an assessment of the specific translocation t(X;18) and its transcripts. Tumors were graded according to the French Federation of Cancer Centres Sarcoma Group's (FNCLCC) grading system [13].

The protocol required local tumor assessment with computerized tomography (CT) and/or magnetic resonance imaging (MRI). Pre-treatment investigations included the search for distant metastases (chest CT scanning, Technetium bone scanning, and abdominal ultrasound).

Post-surgical staging was classified according to the Intergroup Rhabdomyosarcoma Study (IRS) grouping system, in relation to the extent of residual tumor after initial surgery: group I – initial complete resection (also called R0 resection), group II - grossly-resected tumors with suspected microscopic residual disease (R1), group III - macroscopic residual disease (R2) or biopsy only (unresected disease) [14]. Patients were stratified according to surgical stage, tumor size and nodal involvement, as follows: “low-risk” (IRS group I, ≤ 5 cm in size), “intermediate-risk” (IRS group I, > 5 cm, and all IRS group II) and “high-risk” (all IRS group III or any N1 tumor). After September 2009 (amendment 1.1), tumor site was included as one of the variables for risk stratification purposes, based on the publication of the Italian series [7], and tumors arising from axial sites (i.e. head-neck, trunk, lung-pleura, retroperitoneum) were classed as “high-risk” regardless of any other clinical parameters. Multimodal treatment was indicated depending on the risk category (Figure 1): “low-risk” patients were treated with surgery alone, “intermediate-risk” patients had 3-6 courses of orubicin adjuvant chemotherapy \pm radiotherapy; “high-risk” patients had 6 courses of chemotherapy, delayed surgery (when feasible) and radiotherapy (local treatment had to be planned after 3 cycles of neoadjuvant chemotherapy). The main chemotherapy regimen was ifosfamide 3 g/m²/day, for 3 days + doxorubicin 37.5 mg/m²/day, for 2 days, and was given for a maximum of 4 cycles (doxorubicin cumulative dose 300 mg/m²). Two cycles of ifosfamide 3 g/m²/day for 2 days, was given concomitantly with radiotherapy to IRS group II, > 5 cm patients and to IRS group III patients.

Toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0 (<http://ctep.cancer.gov/reporting/ctc.html>).

In patients with measurable disease, response to chemotherapy was assessed after 3 cycles of chemotherapy in terms of radiologically-identified tumor volume reduction: i.e. complete response (CR) = complete disappearance of visible tumor with no residual disease; major partial response (PR $\geq 2/3$) = volume response in the range of 66-99%; minor partial response (PR $< 2/3$) = volume response in the range of 34-65%; stable disease (SD) = $< 33\%$ reduction in tumor volume;

progressive disease (PD) = a more than 40% increase of tumor volume, or the appearance of new lesions.

Radiotherapy was administered using a conventional fractionation (1.8 Gy daily fractions) and was indicated in IRS group II and III patients, with different doses according to the degree of surgery and tumor size (Figure 1). The protocol allowed for irradiation to be avoided for group II limb cases in younger patients (<6 years old) with tumors smaller than 5 cm in size.

Statistical analysis

Data were collected using a web-based system and analyzed at the Istituto Oncologico Veneto (Padova, Italy), considering information reported up to 25th May 2014. Continuous variables were summarized as median, minimum, and maximum values, and categorical variables were reported as counts and percentages. Survival time was calculated from the date of diagnosis to that of the latest follow-up or event. Tumor progression, relapse, second malignancies or death due to any cause were considered in calculating event-free survival (EFS). Overall survival (OS) was measured from the date of diagnosis to death due to any cause. Patients still alive at the end of the study were censored at the date of latest follow-up. The survival probability was computed using the Kaplan Meier method and heterogeneity in survival rates among strata of selected variables was assessed using the log-rank test. The 3-year EFS and OS were reported along with their 95% confidence intervals (CI). A p-value of less than 0.05 was considered statistically significant. Gender, age group (<10 years; ≥10 years), tumor size (≤5 cm; >5 cm), primary site (axial, extremities), IRS group and risk group (low, intermediate and high) were considered for their impact on EFS and OS. All data analyses were performed using the SAS statistical package (SAS, rel. 9.2; SAS Institute Inc., Cary, NC).

RESULTS

From August, 2005 to August, 2012, 138 patients <21 years old with non-metastatic SS were registered from 9 European countries (and 60 different centers). Median age at diagnosis was 13.7

years. Forty-one patients were classified as IRS group I (of whom 32 had had a primary re-excision after initial incomplete surgical excision), 30 as group II, 67 as group III. Most patients (72%) had tumors of the extremities. Only 5 cases had nodal involvement at diagnosis. Supplementary Table S1 shows the clinical characteristics of the series.

Histology review was performed for 94 cases, and changed the diagnosis in 2: from SS to malignant peripheral nerve sheath tumor (MPNST) in one, and to undifferentiated sarcoma in the other. These patients were nonetheless considered in the analysis based on the intention-to-treat principle. The specific translocation and its transcripts were analyzed in 123 (89%) cases, of which 111 (90%) were positive (SYT–SSX1 in 37 cases, SYT–SSX2 in 12, t(X;18) in 62); translocation analysis was non informative in 12.

Treatment and outcome

The treatment protocol was strictly followed for the majority of patients: major violations were registered in only 6 cases (4%): 4 patients were not given the chemotherapy recommended in the protocol, and this was at their physician's discretion in 3 cases and due to the patient's or parents' refusal in 1 case; 2 patients were given radiotherapy despite the protocol not recommending it, at the attending physician's discretion. Minor modifications (e.g. delays in administering chemotherapy, omitting a dose of chemotherapy, small changes to radiotherapy doses) were reported in another 11 cases (8%).

Tumor progression or relapse occurred in 27 patients after a median time to progression of 22.0 months (1.9-78.8): 2 had local progression, 10 relapsed locally, 1 experienced concurrent local and metastatic relapse, 2 had regional lymph node spread, and 12 had an isolated metastatic recurrence (lung metastases) as the first event. Among the 27 patients who relapsed, 8 died of disease a median 37.8 months (28.6-60.0) after their diagnosis. Nineteen were alive at the time of this analysis (May 2014), 15 of them in second or subsequent remissions after salvage therapy (with

1.12-79.63 months elapsing between these events and the latest follow-up, median 14.36 months), and 4 with disease.

With a median follow-up of 52.1 months (range 13.8-104.4), EFS was 81.9% (95% CI 73.9-87.6) and 80.7% (95% CI 72.5-86.7) at 3 and 5 years, respectively, and OS was 97.2% (95% CI 91.5-99.1) and 90.7% (95% CI 82.0-95.3) (**Figure 2**).

Low-risk patients

Twenty-four patients with extremity tumors ≤ 5 cm were completely resected at diagnosis (17.3% of the whole series). Surgical resection was conservative in all but one patient whose foot was amputated. This group of patients was treated with surgery alone, without any adjuvant therapy.

There were 2 local relapses; both the patients involved were alive in second remission at the time of this report (Supplementary Table S2). There were no cases of metastatic relapse. The EFS and OS at 3 years were 91.7% (95% CI 70.6-97.8) and 100%, respectively.

Intermediate-risk patients

There were 37 patients classified as intermediate-risk (26.8%).

Thirteen were IRS group I, >5 cm tumor: they received adjuvant chemotherapy without radiotherapy. Among them, there was one case of regional lymph node relapse.

Twenty-four patients were IRS group II (16 with tumors ≤ 5 cm and 8 with tumors >5 cm).

Radiotherapy was administered to 20/24 cases. There were 4 local relapses (Supplementary Table S2), involving 3/20 patients who had radiotherapy and 1/4 who did not. One case with regional lymph node relapse was reclassified as MPNST at national pathological review.

The 3-year EFS and OS for the intermediate-risk patients were 91.2% (95% CI 75.1-97.1) and 100%, respectively.

High-risk patients

There were 77 cases classified as high-risk patients (55.7%): 67 were IRS group III (58 underwent biopsy, and 9 had an initial resection with macroscopic residual disease), 44 with limb tumors and 23 with axial tumors. Ten more cases were classified as high-risk because they were axial tumors (4 IRS group I, 6 group II).

All 67 IRS group III patients received neoadjuvant chemotherapy with ifosfamide and doxorubicin. Response to chemotherapy after three cycles was as follows: 4 CR (6%), 11 PR $\geq 2/3$ (16.4%), 22 PR $< 2/3$ (32.8%); 28 SD (41.8%); and 2 PD (3%). The overall response rate was 55.2%. No correlation was seen between the degree of tumor response to chemotherapy and subsequent events: relapse occurred in which were seen in 3/15 (20%) cases achieving CR/major PR, 7/22 (32%) with minor PR and 3/28 (11%) with SD.

Supplementary Figure S1 shows the different local treatment performed after chemotherapy, and the treatment failures by type of local therapy. Local relapse occurred in 2/12 patients treated without radiotherapy and in 3/55 patients treated with post-operative irradiation.

The 3-year EFS and OS for IRS group III patients were 77.3 (95% CI 64.6-86.0) and 94.3 (95% CI 83.4-98.1).

Overall, there were 39 patients with axial tumors, 33 of them treated as high-risk; one was classified as low-risk and 5 as intermediate-risk before the protocol amendment. Chemotherapy was given to 36/39 patients, radiotherapy to 32/39. The 3-year EFS was 77.7% (95% CI 60.2 – 88.2), OS was 100%.

Univariate analysis

Table 1 shows the estimated 3-year EFS and OS by patients' main characteristics. The only significant prognostic variable was the risk group. The *p*-value became more significant when high-risk patients were compared with low- and intermediate-risk patients pooled together, i.e. 74.4% (95% CI 62.4-83.1) versus 91.5% (95% CI 80.7-96.4), *p*-value 0.0065.

As for nodal involvement, only 5 patients were classified as N1, and no events were registered among them.

DISCUSSION

This study is the first report of a European-based prospective trial dedicated to pediatric SS.

Importantly, this series demonstrates that pan-European collaborative prospective studies in rare pediatric sarcomas are feasible. The very good compliance with treatment (major protocol deviation was reported in <5% patients) in the different European countries involved shows that the goal to standardize the treatment of SS children in Europe was achieved.

The overall results of the treatments were satisfactory. Although a statistical comparison was not feasible, with a descriptive intent we may remark that the current study achieved higher survival rates than those historically reported in adult [9-11,15,16] and in pediatric series [3-7], with a marked improvement for the categories with unfavorable outcome (Supplementary Table S3). In particular, the decision to intensify the treatment for axial tumors seemed to improve their outcome. In patients with measurable disease, response to neoadjuvant ifosfamide-doxorubicin chemotherapy was 55.2% (22.4% with CR/major PR, and 32.8% with minor PR). Historical retrospective pediatric series [3] reported a 60% response rate, but this finding is not comparable with that from our study, which demanded a careful assessment of tumor response in terms of changes in tumor volume, which differs from cross-sectional area or diameter. Our results are similar, however, to those of the joint European-American retrospective study on unresected NRSTS, which reported 40% of major responses for SS, or 59% if minor responses were considered too [17]. It is noteworthy that we observed 55.2% of cases that responded to treatment in our series, plus 41.8% of cases with stable disease, amounting to 97% of cases experiencing no progression. Moreover, no correlation emerged between the degree of response and tumor recurrence (tumor response after three courses of chemotherapy was not a prognostic variable). These findings might shed doubts on whether dimensional criteria should be used to assess tumor response, or whether other changes in tumor

tissue characteristics (e.g. tumor density on CT scan or signal intensity on MRI) would be better indicators of response to treatment, even in the absence of tumor shrinkage.

In our study, the absence of random assignment of subjects to treatments represents a selection bias that may confound the relationship between treatments and outcomes. Further limitation to the interpretation of the data may be the small numbers of patients for each category. However, the risk grouping being found significantly associated with outcome was a strength of the study.

Our protocol established that adjuvant chemotherapy could be omitted for low-risk patients. This was a substantial change vis-à-vis previous European pediatric SS studies, which adopted rhabdomyosarcoma-like protocols [5-7]. In the previous Italian study, for instance, low-risk patients received 9 courses of chemotherapy [5]. In the present series, we identified 2 local relapses in this subgroup and no metastatic relapses among 24 cases. The number of cases was relatively small and caution is needed: however, this finding might suggest that adjuvant chemotherapy might be safely omitted for such patients without jeopardizing their outcome.

No definitive conclusions can be drawn from our series regarding the role of radiotherapy; however, no local relapses were observed in 13 patients in IRS group I (completely resected) with tumors >5 cm, treated with chemotherapy but without RT, suggesting that it might be acceptable to omit radiotherapy in this group in the future.

Although this study confirmed its initial goal to standardize treatment for SS across an international European group, it is also clear that the number of patients in each of the risk groups would be too small, to undertake a randomized clinical trial (for example, to ascertain the role of adjuvant chemotherapy). This highlights the need to create opportunities for larger, international, prospective projects. In view of the peak age range for the occurrence of SS, pediatric oncologists should collaborate with oncologists treating adult patients with SS to develop cooperative studies spanning different ages, integrating the same treatment concepts regardless of age. Such a cooperation might also investigate whether reported differences in outcome [1] are related to differences in delivered treatment (i.e. different use of chemotherapy) or differences in tumor biology across ages. New

comprehensive strategies may also facilitate collaborations with biologists to improve our understanding of the biology of SS and hopefully identify new targets for novel therapies.

Disclosure / Conflict of Interest statement

The authors have declared no conflicts of interest

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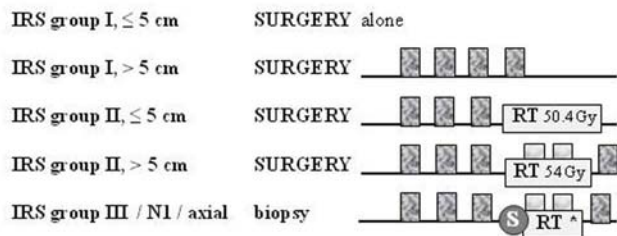
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Table 1 – Estimated 3-year event-free survival (EFS) and overall survival (OS) by patients' characteristics (univariate analysis)

Figure 1. The risk-adapted treatment program for synovial sarcoma in the EpSSG NRSTS 2005 trial. Low-risk patients were treated with surgery alone (no adjuvant therapy); intermediate-risk patients had 3-6 courses of adjuvant chemotherapy ± radiotherapy; high-risk patients had 6 courses of chemotherapy, delayed surgery (when feasible) and radiotherapy (local treatment had to be planned after 3 cycles of neoadjuvant chemotherapy).

* **radiotherapy doses in IRS group III tumors:** 59.4 Gy in case without the option of secondary resection; 50.4 Gy as preoperative radiotherapy; 50.4, 54 Gy and 59.4 Gy as postoperative radiotherapy, in the case of R0, R1, R2 resections, respectively (no additional radiotherapy in the case of secondary complete resections with free margins, in children under 6 years old).

Figure 2. EFS and OS for the whole series and EFS by risk group



-  chemotherapy with ifosfamide and doxorubicin
-  chemotherapy with ifosfamide
-  radiotherapy
-  surgery

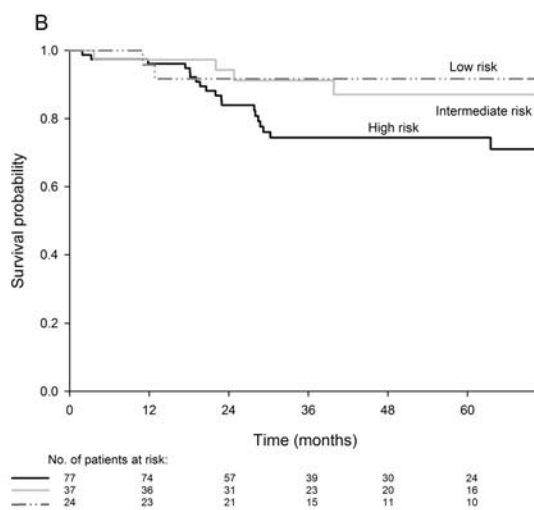
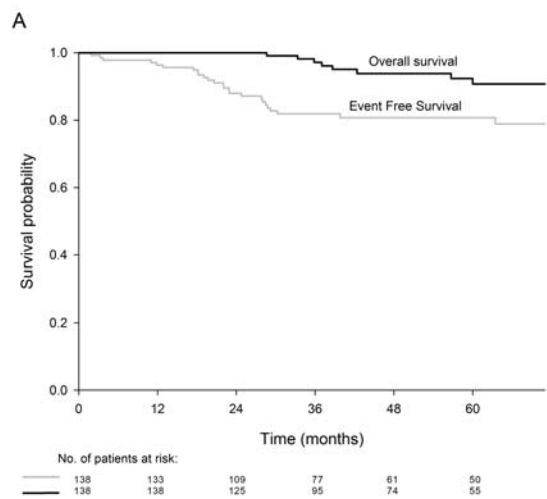


Table 1 – Estimated 3-year event-free survival (EFS) and overall survival (OS) by patients' characteristics (univariate analysis)

Characteristic	<i>N</i>	<i>N. events</i>	<i>N. deaths</i>	3-yr EFS (95%CI)	<i>p</i> -value	3-yr OS (95%CI)	<i>p</i> -value
Age, years							
<10	29	4	2	89.2 (70.2–96.4)	0.3594	100 (-)	0.7827
≥10	109	23	6	79.8 (70.3–86.5)		96.4 (89.2-98.8)	
Gender							
Male	77	13	4	83.4 (72.5–90.2)	0.3684	95.1 (85.5–98.4)	0.7269
Female	61	14	4	79.8 (66.3–88.3)		100 (-)	
Size, cm*							
≤5	62	9	1	87.8 (76.1–94.0)	0.1360	100 (-)	0.0638
>5	74	18	7	76.5 (64.4–84.9)		94.9 (84.9-98.3)	
Primary site							
Axial	39	10	3	77.7 (60.2–88.2)	0.3232	100 (-)	0.5094
Extremities	99	17	5	83.8 (74.4–89.9)		96.0 (88.2-98.7)	
Risk group							
Low	24	2	-	91.7 (70.6-97.8)		100 (-)	
Intermediate	37	6	-	91.2 (75.1-97.1)	0.1859	100 (-)	0.0246
High	77	19	8	74.4 (62.4-83.1)		95.0 (85.1-98.3)	
IRS group							
I	41	4	1	89.5 (74.2-95.9)	0.1961	100 (-)	0.0657
II	30	8	-	81.8 (61.6-92.0)		100 (-)	
III	67	15	7	77.3 (64.6-86.0)		94.3 (83.4-98.1)	
Grading*							
1/2	69	10	2	87.6 (76.7–93.6)	0.3705	100 (-)	0.3583
3	35	7	2	81.4 (63.1–91.2)		92.7 (73.7-98.1)	
Transcript*							
SSX1	37	4	1	90.2 (72.5–96.8)	0.4556	100 (-)	0.5541
SSX2	12	2	0	75.0 (29.8–93.4)		100 (-)	

*The sum does not add up to the total because some values were missing.