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RESEARCH ARTICLE

Treatment at relapse for synovial sarcoma of children and adolescents: A multi-institutional European retrospective analysis

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Abstract

Purpose: Though the prognosis for pediatric patients with localised synovial sarcoma (SS) is generally good, the chances of being cured after relapse are limited. This study describes a retrospective multi-institutional series of relapsing SS patients treated at six selected European referral centers for pediatric sarcoma.

Patients and methods: The study included 41 patients <21 years with relapsing SS, treated between 2002 and 2022. The analysis included patient's characteristics at first diagnosis, first-line treatments, clinical findings at relapse, and second-line treatment modalities.

Abbreviations: CI, confidence interval; EFS, event-free survival; EpSSG, European paediatric Soft tissue sarcoma Study Group; HR, hazard ratio; IRS, Intergroup Rhabdomyosarcoma Study; MAGE-A4, melanoma-associated antigen 4; NRSTS, nonrhabdomyosarcoma soft tissue sarcomas; OS, overall survival; SS, synovial sarcoma; TCR, T-cell receptor.

Results: The first relapse occurred within 3–132 months (median 18 months) after first diagnosis and was local in 34%, metastatic in 54%, and both in 12%. Treatment at first relapse included surgery in 56% of cases, radiotherapy in 34%, and systemic therapy in 88%. In all, 36 patients received second-line medical treatment, that was chemotherapy in 32 cases (with 10 different regimens) and targeted therapy in four. No patient was included in an early-phase clinical trial as second-line therapy-line therapy. Overall response rate was 42%. Median event-free survival (EFS) was 12 months, postrelapse 5-year EFS was 15.8%. Median overall survival (OS) was 30 months, postrelapse 5-year OS was 22.2%. At the Cox's multivariable regression analysis, OS was significantly associated with time and type of relapse.

Conclusion: Pediatric patients with relapsed SS have a poor prognosis and generally receive an individualized approach, due to the lack of a uniform standardized approach. New comprehensive strategies are needed to improve the knowledge on the biologic landscape of SS and develop tailored prospective clinical trials.

KEYWORDS
adolescents, children, outcome, prognostic factors relapse, synovial sarcoma, treatment

1 | INTRODUCTION

Synovial sarcoma (SS) is a high-grade mesenchymal tumor with the specific chromosomal translocation t(X;18)(p11.2;q11.2) as molecular hallmark.[1] In various international series, SS has been reported as the most common nonrhabdomyosarcoma soft tissue sarcoma (NRSTS) in childhood and adolescence.[2–4]

SS is generally characterized by local invasiveness and the potential to metastasize. It is considered to have intermediate sensitivity to chemotherapy, with a reported response rate in the 45−60% range (less than that observed in rhabdomyosarcoma but generally higher than reported for other adult-type sarcomas).[5–10] According to the last protocols developed by European and American pediatric cooperative groups,[3,4] children and adolescents with SS are treated with a multimodal risk-adapted strategy developed considering from previous pediatric studies[5–10] but also experience coming from adults.[11–13] More than three in four pediatric patients with localized SS can be cured with the current standard approach that includes surgery, radiotherapy, and chemotherapy, depending on the risk factors (i.e. extent of disease at diagnosis and quality of surgical margins, tumor size, tumor site).[14,15]

Conversely, the outcome remains poor for patients after relapse. Three retrospective studies were published some years ago on pediatric patients with relapsed SS, with 5-year postrelapse survival ranging from 30 to 46%.[16–18]

As a matter of fact, patients with relapsed SS generally receive an individualized approach, as there is still a lack of consensus regarding standard treatment approaches.[19]

The present study aims to describe a retrospective multi-institutional series of relapsing SS patients treated at selected European referral centers for pediatric sarcoma, with a specific focus on the administered individual postrelapse treatment and subsequent response. As secondary aim, the study investigates clinical findings and treatment-related variables (at first diagnosis and at the time of relapse) associated with survival.

2 | METHODS

For this retrospective multicenter international study, patients were collected from six selected European referral centers for pediatric sarcoma, that is, Istituto Nazionale dei Tumori, Milan (Italy), University of Padova (Italy), Ospedale Bambino Gesù, Rome (Italy), Princess Maxima Center, Utrecht (the Netherlands), Institut Curie, Paris (France), and Centre Leon Berard, Lyon (France).

Inclusion criteria were as follows: (a) a diagnosis of SS with molecular confirmation; (b) treatment at first diagnosis between 2002 and 2022; (c) age 21 years or younger at first diagnosis; (d) nonmetastatic disease at first diagnosis; (e) tumor relapse or progression after first therapy; (f) details available on patients' clinical data, treatment modalities, and outcome. The study was exempted from ethical approval by the medical research ethics committee of the Istituto Nazionale dei Tumori, Milan. All participating centers obtained informed consent from patients and/or their parents or legal guardians. Most patients were treated according to the European paediatric Soft tissue sarcoma Study Group (EpSSG) NRSTS 2005 protocol (EUDRACT No 2005-001139e31), a prospective non-randomized study for patients < 21 years old with localized adult-type NRSTS and localized SS (conducted from 2005 to 2016).[3,14]

The following variables were collected:

1. Clinical findings at first diagnosis: sex, age, tumor grade (assigned according to the French Federation of Cancer Centers Sarcoma Group's grading system),[20] tumor site, tumor size (diameter ≤5 cm

or >5 cm), presence or absence of regional lymph nodal metastases, surgical stage according to the Intergroup Rhabdomyosarcoma Study (IRS) grouping system[21];

2. First-line treatment modalities: surgery, radiotherapy, chemotherapy; response to chemotherapy (assessed after three cycles) according to the tumor volume reduction (complete response = clinically or histologically confirmed complete disappearance of disease, major partial response = volume reduction in the range of 66–99%, minor partial response = reduction in the range of 33–65%); histological margins in relation to the maximum degree of surgical resection, considering both first surgical approach and delayed surgery (after primary chemotherapy), when done (R0, R1, R2);
3. Clinical findings at the time of first relapse: local or metastatic relapse (including nodal metastases), time to recurrence, site and number of metastases;
4. Second-line treatment modalities and response to systemic therapy (assessed after three cycles of second-line therapy); achievement of second remission with second-line therapy, defined as the absence of disease after surgery, or complete tumor remission after chemotherapy and/or radiotherapy, persisting for at least 6 months after the end of the treatment.

2.1 | Statistical analysis

Survival after relapse was calculated from the time of the first disease progression/recurrence to the latest uneventful follow-up, further disease progression or relapse, or death from any cause for event-free survival (EFS), and to death or latest contact with patients who were still alive for overall survival (OS).

The different clinical and therapeutic variables were examined using univariable analyses to ascertain their potential role as prognostic factors: OS after first relapse was estimated with the Kaplan-Meier method,[22] and the log-rank test was used to compare the survival curves for patient subgroups.[23] The multivariable analysis focusing on the variables at relapse was developed for OS using Cox's proportional hazards regression method (with a backward variable selection procedure applied to the covariates with a p value of at least < .02 in the univariable analysis).[24] All data analyses were performed using the SPSS R statistical software, version 15.0.

3 | RESULTS

In total, 41 patients aged 3–20 years (median 15 years) were included in the study. Table 1 shows their main clinical findings at the time of first diagnosis and details on first-line treatments. Around half of the cases arose in axial sites, most had tumor larger than 5 cm at diagnosis and none had nodal involvement. All but three patients had received chemotherapy as part of their initial treatment, according to the ongoing protocols: 29 patients received the ifosfamide–doxorubicin

TABLE 1 Patients' characteristics at first diagnosis and first-line treatments

Clinical findings at diagnosis	Patients	%
Gender		
Female	15	36%
Male	26	64%
Age		
<15 years	17	42%
≥15 years	24	58%
Tumor grade		
G2	14	34%
G3	16	39%
Unspecified	11	27%
Tumor site		
Extremities	21	51%
Axial sites[a]	20	49%
Tumor size		
≤5 cm	10	24%
>5 cm	31	76%
IRS group[b]		
I	5	12%
II	12	29%
III	24	59%
First-line treatments	**Patients**	**%**
Type of surgery		
R0	13	32%
R1	23	56%
R2/biopsy	5	12%
Radiotherapy		
No	7	17%
Yes	34	83%
Chemotherapy		
No	3	7%
Ifosfamide–doxorubicin	29	71%
Other regimens[c]	9	22%
Response to chemotherapy[d]		
No response	7	30%
Objective response[e]	16	70%

[a]Axial sites = seven superficial trunk, six lung/pleurea, three head–neck, two retroperitoneum, one pelvis, one mediastinum.
[b]IRS, Intergroup Rhabdomyosarcoma Study (group I—complete resection at first surgical approach, group II—microscopic residual disease, group III—macroscopic residual disease).
[c]Other regimens = six vincristine, actinomycin-D, ifosfamide, adriamycin (VAIA), two ifosfamide, vincristine, actinomycin-D (IVA), one high-dose ifosfamide.
[d]Evaluable in 23 patients.
[e]Objective response = complete response (clinically or histologically confirmed complete disappearance of disease), major partial response (volume reduction in the range of 66–99%), minor partial response (reduction in the range of 33–65%).

combination, while nine had other regimens (all including ifosfamide, as reported in the legend of Table 1).

At the time of the relapse, patient's age ranged from 6 to 25 years (median 17 years), with 16 patients being > 18 years old. The first relapse occurred within 3–132 months (median 18 months) after the patients' first diagnosis. Four recurrences (one local, two metastatic, and one both) occurred more than 5 years after the initial diagnosis. Relapses were local in 14 cases, metastatic in 22, and combined local plus concomitant metastatic relapse in five (Table 2). The median time to local relapse was 15 months, while it was 21 months for metastatic relapse (with or without concomitant local recurrence).

Among the 19 cases with local recurrences (five with concomitant metastases), 16 had received radiotherapy as first line treatment: in 13 of them, the relapse occurred within the previous radiation field. Considering the 27 patients who had metastatic relapse (five with concomitant local relapse), seven had a single lesion (six single pulmonary metastasis, one single bone metastasis), while 20 had multiple lesions. Site of metastases were lungs alone in 20 cases, two lungs and bone, two lungs and lymph nodes, one brain, one liver, one bone.

3.1 | Treatment at relapse

Treatment at first relapse included surgery in 23 cases, radiotherapy in 14, and systemic therapy in 36. The surgical procedures were resections for local relapse in 13 cases (eight defined as R0, including one amputation, and five as R1) and the surgical removal of metastases in 10. Radiotherapy was performed in 11 cases on a local relapse and in three as whole lung irradiation.

Second-line systemic therapy was chemotherapy in 32 cases and targeted therapy in four. Chemotherapy included ifosfamide–doxorubicin in 10 cases, high-dose ifosfamide in 13 cases (in 10 it was given as a prolonged continuous infusion, that is, 1 g/m^2/day on 14 consecutive days by elastomeric pump infusion), and other different regimens in nine (two trabectedin, one ifosfamide–cyclophosphamide, one cisplatin–etoposide, one cisplatin–doxorubicin, one cisplatin plus other drugs, one gemcitabine–docetaxel, one vinorelbine, one temozolomide). Four patients had targeted therapy as second-line medical treatment: one pazopanib, one regorafenib, one BRAF inhibitor (this was a 15-year-old male with relapsing intrathoracic SS harboring a BRAF V600E mutation).[25] No any patient was included in a formal early-phase clinical trial.

Response to systemic therapy was available in 31 cases: nine major and four minor partial responses were reported, with an overall response rate of 42%. Responses were observed in five out of nine cases who had ifosfamide–doxorubicin, seven out of 13 who had high-dose ifosfamide, zero out of six who had other chemotherapy regimens, and one out of three who had target therapy (the patient treated with BRAF inhibitor).

In all, 18 out of 40 patients (one unknown) (45%) achieved a complete secondary remission with second-line therapy (i.e., absence of disease after surgery, or complete remission after chemotherapy and/or radiotherapy).

TABLE 2 Clinical characteristics at time of first relapse and second-line treatments.

Clinical findings at relapse	Patients	%
Time of relapse		
≤12 months	7	17%
13–24 months	17	41%
>24 months	17	41%
Type of relapse		
Local	14	34%
Local and metastatic	5	12%
Metastatic	22	54%
Type of metastatic relapse (1)		
Single lesions	7	26%
Multiple lesions	20	74%
Type of metastatic relapse (2)		
Lungs only	20	74%
Others	7	26%
Second-line treatments	**Patients**	**%**
Surgery		
No	18	44%
Yes	23	56%
Radiotherapy		
No	27	66%
Yes	14	34%
Systemic therapy		
No	5	12%
Yes	36	88%
Type of systemic therapy		
Ifosfamide–doxorubicin	10	28%
High-dose ifosfamide	13	36%
Other chemotherapy	9	25%
Targeted therapy	4	11%
Response to systemic therapy[a]		
No response	18	58%
Objective response[b]	13	43%
Secondary remission[c]		
No	22	55%
Yes	18	45%

[a]Evaluable in 31 patients.
[b]Objective response = complete response (clinically or histologically confirmed complete disappearance of disease), major partial response (volume reduction in the range of 66–99%), minor partial response (reduction in the range of 33–65%).
[c]One unknown.

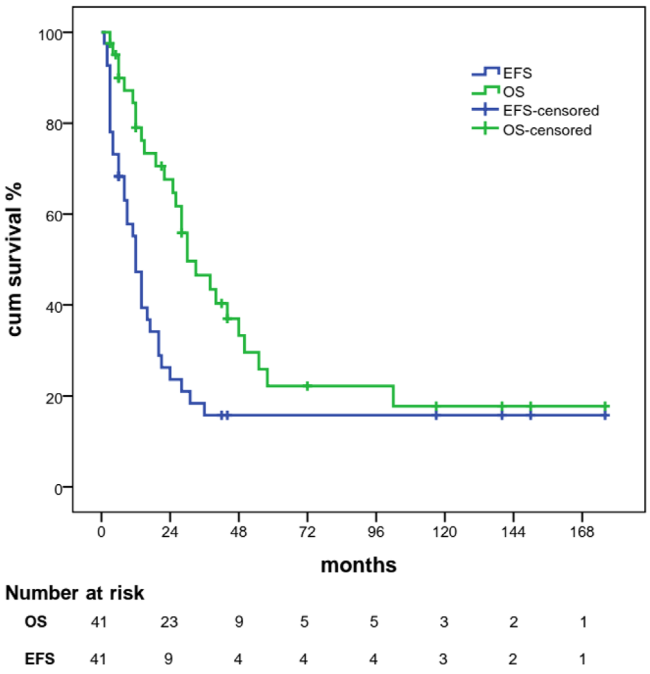

FIGURE 1 Postrelapse event-free survival (EFS) and overall survival (OS).

Further progression/relapse occurred in 32 cases, local in three, metastatic in 24, and combined local plus metastatic in five. Further-line treatment included surgery in three cases and radiotherapy in four. Systemic therapy, given as third- and fourth-line, included: vinorelbine (± oral cyclophosphamide) in six cases (two minor responses), five trabectedin, two high-dose ifosfamide (one major response), one gemcitabine–docetaxel (one minor response), two dacarbazine, two oral etoposide; 11 patients received pazopanib (one major and three minor responses),[26] one sorafenib, one vemurafenib; three patients were enrolled in early-phase trials with experimental therapies; one additional patient received adoptive immunotherapy with melanoma-associated antigen 4 (MAGE-A4) specific T-cell receptor (TCR)-T cells within a specific study.

3.2 | Patient outcome

With a median follow-up of 40 months (range 3–176), the median postrelapse EFS was 12 months (95% confidence interval [CI] 9.1–14.9). EFS was 23.6% at 2 years and 15.8% at 5 years. The median OS after relapse was 30 months (95% confidence interval 16.6–43.4), with OS rates of 67.6% at 2 years and 22.2% at 5 years, respectively (Figure 1).

Table 3 shows the 5-year OS according to the univariable analysis. Considering the patients' characteristics at the time of first diagnosis, OS was associated with gender, patients' age, and IRS group, with a trend of worse survival for tumors larger than 5 cm. As concerns initial treatments, patients who had not been given radiotherapy as part of their first-line therapy showed a better outcome.

Considering the clinical findings at the time of relapse, OS was significantly associated with time and type of recurrence. Survival was better for patients with a late relapse (>24 months) and those with local relapse only. In the subgroup of patients with a metastatic relapse, OS was better for patients with single lesion versus those with multiple lesions. As for the second-line treatment modalities, the feasibility of surgery and the chances of achieving secondary remission were associated with significantly better OS, with a trend of better outcome for patients who received ifosfamide-based chemotherapy and those who responded to second-line medical treatment.

In a Cox multivariable regression analysis focusing on variables at relapse (Supplementary Table S1), OS was significantly associated with type of relapse, with hazard ratio (HR) 0.27 (95% CI 0.09–0.83) for local relapses (*p* value .022), and time to relapse, with HR 0.23 (95% CI 0.08–0.66) for late relapses (*p* value .006).

4 | DISCUSSION

This study describes second-line treatment and postrelapse outcome of relapsing SS patients.

As first finding, the study confirmed that the chances of survival for this patient category remain largely unsatisfactory. The outcome did not change over the study period. Survival was particularly poor for older patients; other published SS series already reported a progressively worsening survival with age,[2,6,11,27] and a possible explanation for the differences in outcome was suggested by some studies reporting differences in the genomic instability between older and younger patients with SS.[28,29]

Our study described the pattern of relapse and enabled to identify variables influencing the outcome. Focusing in particular on the clinical characteristics and treatment at the time of relapse, our analysis showed that survival was significantly better for patients who had local relapses or late relapses (occurring more than 24 months after first diagnosis) Univariable analysis showed also better OS for patients who could undergo tumor resection and achieve a secondary remission. These findings were similar to those already reported in other studies[16–18] and are useful to guide the approach to second-line treatment, to distinguish between patients with some prospects of cure (with currently available therapeutic options) and patients with little chance of salvage, who should be considered for experimental therapy.[16,19,30]

The evidence that patients who succeeded in undergoing surgery had a better outcome would indicate that an aggressive surgical approach may be justified or, better, recommended, when feasible. For example, while amputation should generally not be considered as a standard procedure for newly diagnosed patients with extremity SS (with a few exceptions), it might be an option for locally relapsing limb tumor. Aggressive surgery should likewise be recommended for metastases, as well aggressive focal therapy like pulmonary stereotactic-guided radiotherapy or cryoablation.[18,19]

Our analysis showed also a trend of better survival for patients who received ifosfamide-based chemotherapy and those who responded

TABLE 3 Postrelapse overall survival (OS) and log-rank test for univariable analysis by patients' characteristics.

Category	*N*	Groups	*N*	5-year OS (%)	*p* Value
Clinical findings at diagnosis					
Gender	41	Female	15	38.7%	.041
		Male	26	12.6%	
Age	41	<15 years	17	41.8%	.004
		≥15 years	24	10.3%	
Year of diagnosis	41	2002–2012	23	25.6%	.720
		2013–2022	18	16.4%	
Grade	30	G2	14	38.5%	.203
		G3	16	9.3%	
Tumor site	41	Extremities	21	28.7%	.295
		Axial sites	20	13.9%	
Tumor size	41	≤5 cm	10	61.7%	.079
		>5 cm	31	13.2%	
IRS group[a]	41	I	5	100.0%	.020
		II	12	0.0%	
		III	24	14.8%	
First-line treatment					
Type of surgery	41	R0	13	36.4%	.622
		R1	23	7.8%	
		R2	5	40.0%	
Radiotherapy	41	No	7	66.7%	.040
		Yes	34	10.5%	
Chemotherapy	38	Ifosfamide–doxorubicin	29	11.8%	.666
		Other regimens	9	33.3%	
Response to chemotherapy	23	No response	7	0.0%	.984
		Objective response	16	17.8%	
Clinical findings at relapse					
Time of relapse	41	≤24 months	24	8.0%	.026
		>24 months	17	38.0%	
Type of relapse	41	Local only	14	39.2%	.027
		Metastatic ± local	27	12.0%	
Type of metastatic relapse (1)	27	Single lesions	7	44.4%	.007
		Multiple lesions	20	0.0%	
Type of metastatic relapse (2)	27	Lungs only	20	15.2%	.887
		Others	7	0.0%	
Second-line treatment					
Surgery	41	No	18	14.9%	.027
		Yes	23	27.8%	
Radiotherapy	41	No	27	17.5%	.968
		Yes	14	29.0%	
Systemic treatment	41	No	5	26.7%	.883
		Yes	36	21.7%	
Type of systemic treatment	36	Ifosfamide-based chemotherapy	24	27.5%	.071
		Others	12	13.6%	

(Continues)

TABLE 3 (Continued)

Category	N	Groups	N	5-year OS (%)	p Value
Response to systemic therapy	31	No response	18	19.0%	.079
		Objective response	13	34.6%	
Secondary remission	40	No	22	7.2%	.003
		Yes	18	39.7%	

[a]IRS, Intergroup Rhabdomyosarcoma Study.

to second-line systemic treatment, findings that would emphasize the importance to find more effective medical therapies.

It is exactly on the topic of medical treatment that our study offers the most interesting insights. The wide and heterogeneous list of different regimens utilized as second or further line of therapy clearly demonstrates the lack of a uniform standardized approach to treat young patients with relapsed SS, whose treatment is still based, as a general rule, on an individualized approach. This finding appears even more relevant (or alarming) if we consider that our cohort included patients treated in six selected European referral centers for pediatric sarcoma. In our series, 32out of 36 patients received conventional chemotherapy as second-line systemic therapy, with 10 different regimens; targeted therapy was given to four cases; none was included in a formal early-phase clinical trial. Concerning third- and fourth-line medical treatment, it was reported that 19 patients had chemotherapy and 13 targeted therapy; three patients were included in early-phase trials with experimental therapies; one patient received MAGE-A4 TCR-T cells therapy.

Noteworthy, while the EpSSG NRSTS 2005 study[3] and the ARST0332 study developed by the Children's Oncology Group[4] were able to establish the risk-adapted front-line standard of care for pediatric patients with newly diagnosed localized SS and NRSTS, both the protocols did not include definitive treatment recommendations for patients at relapse. For these patients, a clear standard of care has not yet been defined.

Despite its limitations (i.e. the retrospective design and the limited sample size, as is usually the case in studies on such a rare tumor), we believe that our study might have the value of improving the awareness of the pediatric sarcoma community on the importance of dedicating any possible effort to develop prospective studies for patients with relapsing SS (and NRSTS in general).[19,31,32] New comprehensive multifaceted approaches are needed. If the development of tailored prospective clinical trials—and the wide involvement of patients in such protocols—is the challenging goal, studies aiming to improve our knowledge on the biologic landscape of SS are needful. Young patients with relapsed SS should be always offered a deep molecular profiling (after tumor biopsy) to implement genomic information and potentially drive suggestions on targeted therapies. While various molecular profiling programs on relapsed/refractory pediatric tumors have been conducted or are ongoing in Europe,[33–36] it is worth mentioning that the EpSSG is ready to open, at the time of writing the current manuscript, the MYKIDS study ("Molecular Identification and Characterization of non-Rhabdomyosarcoma Soft Tissue Sarcoma in Kids, Adolescents and Young Adults"), which implies a systematic multicenter molecular and epigenetic characterization of newly diagnosed NRSTS cases (and SS among them).[31]

The arrival point of the better understanding of tumorigenesis and the identification of new targets relevant to tumor growth is the development of new dedicated early-phase clinical trials. The historical limitations in the availability of new drugs for pediatric patients (due to the rarity of the diseases, the difficulty of establishing safe doses in children, the ethical and regulatory barriers) should be overcome by broader networking and global-scale collaboration, including also a greater and more effective cooperation between pediatric and adult sarcoma groups.[37] Joint pediatric/adult research trials based on the molecular target and mechanism of action rather than age (and therefore spanning both pediatric and adult populations) is the ideal goal (Table S1).

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to disclose.

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DATA AVAILABILITY STATEMENT

Data for this study are available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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