Salvage rates and prognostic factors after relapse in children and adolescents with initially localised synovial sarcoma

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Abstract ***Background:*** Previous studies have reported a poor outcome for synovial sarcoma patients whose tumours relapse.

Methods: This study analysed 44 relapsing cases in a series of 118 consecutive patients <21 yr of age with non-metastatic synovial sarcoma prospectively enrolled in Italian paediatric protocols between 1979 and 2006. In an effort to identify a possible risk-adapted stratification enabling a better planning of second-line treatment, the relapsing patients' outcome was analysed vis-à-vis their clinical picture at onset, first-line treatments, clinical findings at the time of first relapse and second-line treatment modalities.

Results: The first event was a local recurrence in only 15 cases, and metastatic in 29 (associated with local relapse too in 7 cases). The time to relapse ranged from 4 to 108 months (median 20 months). Overall survival was 29.7% and 21.0% five and ten years after relapsing, respectively.

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The variables influencing survival were the timing and type of relapse (combined) and the chances of a secondary remission, which correlated strongly with the feasibility of complete surgery.

Conclusions: Our study confirmed a largely unsatisfactory prognosis after recurrences in children and adolescents with synovial sarcoma: the chances of survival can be estimated on the basis of several variables for the purposes of planning risk-adapted salvage protocols. An aggressive surgical approach should be recommended. New effective systemic agents are warranted, and experimental therapies can be offered to patients with little chance of salvage.

1. Introduction

Synovial sarcoma (SS) is a high-grade sarcoma characterised by local invasiveness and a propensity to metastasise. It accounts for about 8% of all soft tissue sarcomas and shows a peak incidence in the third decade of life: it is the most common non-rhabdomyosarcoma soft tissue sarcoma in childhood and adolescence (approximately one third of cases occurring in patients under twenty years of age).[1,2]

The prognosis for SS patients depends largely on the feasibility of surgical resection, any presence of metastases and the tumour's size and site. Around three in four patients with SS can currently be cured using a risk-adapted multimodal treatment approach that includes surgery plus radiotherapy and/or chemotherapy (depending on the risk factors).[3–10] The Associazione Italiana Ematologia Oncologia Pediatrica – Soft Tissue Sarcoma Committee (AIEOP-STSC) (previously called the Italian Cooperative Group - ICG) has already reported the clinical results in a series of 115 patients (age range 1–20 yr) with a diagnosis of SS who were treated according to Italian paediatric protocols: tumours progressed or recurred in 40% of these cases, with 5-year event-free survival (EFS) and overall survival (OS) rates of 62.8% and 76.9%, respectively.[6] The report described a narrow 'salvage gap' (defined as the difference between EFS and OS), suggesting a limited ability of further treatment to cure patients who progressed or relapsed.

In the current analysis, we aimed to identify which clinical findings (at diagnosis or at the time of first relapse) or treatment-related variables (first- or second-line therapies) might influence the outcome of relapsing patients, with a view to possibly arriving at their risk-adapted stratification for a better planning of their second-line treatment.

2. Materials and methods

The study group included 44 patients with SS, who were under 21 yr when they were first diagnosed, and who were prospectively enrolled in Italian paediatric protocols (AIEOP-STSC trials and the protocol of the Istituto Nazionale Tumori of Milan) between 1979 and 2006, who experienced tumour relapse after first therapy. This cohort was part of a series of 118 consecutive, previously-untreated patients with localised tumours at diagnosis; patients who already had metastatic disease were ruled out.

The histological slides of all patients enrolled in the AIEOP protocols were reviewed by the same national pathology panel at the time of diagnosis.[6] Cases from the Istituto Nazionale Tumori of Milan (25 patients) were subsequently reviewed (for inclusion in a previous publication).[4] Results of t(x;18) and SYT-SSX transcript analyses were only available for 16 cases.

All patients or their guardians had given their informed consent to their enrolment in studies and to the management of their data according to the rules adopted over the years.

The present analysis focused on how the following variables correlated with the pattern of relapse and patients' survival after their first relapse:

1) clinical findings at onset: age; gender; histological subtype (biphasic, monophasic and poorly-differentiated) and grade; tumour site (axial sites, i.e. head and neck, lung and pleura, retroperitoneum, thoracic and abdominal wall; extremities, including limb girdles like the inguinal region, hip, buttock, shoulder and axillary region); T stage (in relation to local invasiveness and tumour diameter $\leqslant$ or >5 cm)[11] and nodal involvement; surgical stage according to the Intergroup Rhabdomyosarcoma Study (IRS) grouping system (group I – complete resection, group II – microscopic residual disease, group III – macroscopic residual disease)[12];

2) first-line treatment modalities: surgery and histological margins, radiotherapy, chemotherapy and response to chemotherapy; on the whole, the front-line treatment strategies did not change substantially over the years for this patient cohort;

3) clinical findings at the time of the first relapse: local or metastatic relapse (including nodal metastases); time to recurrence (interval between first diagnosis and recurrence, arbitrarily defined as early or late when less or more than 18 months, respectively); size of local relapse and site in relation to any previous radiotherapy fields; site and number of metastases;

4) second-line treatment modalities: surgery and degree of resection, radiotherapy, chemotherapy and response to chemotherapy; achievement of second remission with second-line therapy and further events.

Response to second-line chemotherapy in patients with measurable disease was evaluated after three cycles and was based on the radiologically detectable reduction in the sum of the products of the perpendicular diameters of all measurable lesions. Response was defined as: complete (CR) = complete disappearance of disease; partial (PR) = tumour reduction >50%; minor (MR) = reduction between 25% and 50%. Stable disease or a tumour reduction <25% was classified as no response, while an increase in the tumour's size or the detection of new lesions was considered as tumour progression.

Secondary remission was defined as absence of disease after surgery, complete remission after chemotherapy and/or radiotherapy, or steady residual images after chemotherapy and/or radiotherapy, that remained stable for at least 6 months after the end of therapy. Tumour recurrence was the evidence of new lesions after the achievement of remission.

2.1. Statistical analysis

Survival after relapse was measured from the time of the first progression or recurrence of the disease until death, or until the latest contact with patients who were still alive. All deaths were counted as failures irrespective of whether or not they were disease-related. The survival distribution after the first relapse was estimated using the Kaplan–Meier method, and confidence intervals for the 5- and 10-year survival estimates were calculated using Grenwood's formula. The log-rank test was used to compare the survival curves for patient subgroups by univariate analysis to ascertain the potential role of prognostic factors.

Multivariate analysis was conducted using Cox's proportional hazards regression method to establish the independent prognostic significance of the clinical factors considered. A backward variable selection procedure was applied to the covariates with a *p*-value of at least 0.2 at univariate analysis. Hazard ratios (HRs) with 95% confidence intervals, calculated according to the Wald method, are reported for the significant variables.

All data analyses were performed using the SAS statistical package (SAS, rel. 9.2; SAS Institute Inc, Cary, NC).

3. Results

Table 1 shows the characteristics of the 44 relapsing patients.

Concerning their clinical findings at first diagnosis, the initial tumour was more than 5 cm in size in most cases,

while the IRS stages were equally distributed. All but 6 patients had received chemotherapy as part of their initial treatment, according to the ongoing protocols: all the regimens adopted had included ifosfamide or cyclophosphamide. For the relapsing patients with evaluable disease, response to initial chemotherapy had been as follows: 8 major responses, 2 minor responses and 4 no responses. Most patients (72.7%) had also received radiotherapy.

The first event was a local recurrence in 15 cases, metastatic in 22 and combined local plus concomitant metastatic relapse in 7. The time to relapse ranged from 4 to 108 months after the first diagnosis (median 20 months): the median time to local relapse was 24 months (95% confidential interval (CI) 13–34), while for metastatic relapse it was 18 months (95% CI 14–32). Five recurrences (2 local and 3 metastatic) occurred more than 5 yr after the initial diagnosis.

Among the 22 cases with local recurrences, the relapse occurred within the previous radiation field in 14 cases (in 2 this aspect was not known). The locally relapsing tumours were 2–15 cm in size (median 7 cm). The pattern of metastatic recurrences (29 cases, 7 with concomitant local relapse) was as follows: 12 unique metastases site (4 lymph nodal, 7 isolated lung metastases and one single bone metastasis), 17 multiple metastatic sites (15 cases of multiple pulmonary lesions, 2 of multiple skeletal metastases).

3.1. Treatment at relapse

The treatment modalities used at relapse varied, as detailed in Table 1. Overall, chemotherapy was administered to 24 patients, according to various different regimens (ifosfamide-doxorubicin in 5, high-dose ifosfamide in 5, carboplatin-etoposide ± other drugs in 5, cisplatin-based regimens in 3, dacarbazine in 3, other regimens in 3). Response to second-line chemotherapy was evaluable in 19 cases and involved: 8 PR, 3 MR, 5 no responses and 3 tumour progressions. Radiotherapy was administered to 11 patients.

Twenty-one patients were able to undergo complete resection of their relapsing tumours, which involved local recurrences in 9 cases, metastatic sites in 8 (i.e. pulmonary metastasectomy, lymph nodal dissection) and both in 4. Surgery for local relapse meant limb amputation in 6 cases. Overall, 25 patients achieved a secondary complete remission of the disease. There was a strong association between secondary remission and complete surgery, i.e. 21 of the 25 patients achieving a complete remission had undergone complete tumour resection. Four additional patients achieved remission with chemotherapy and radiotherapy.

3.2. Outcome

At the time of this report, 10 patients were alive, and 8 of them in remission (5 in second remission and 3 in

Table 1
Patients' characteristics at first diagnosis, first-line treatments, clinical characteristics at the time of first relapse and second-line treatments.

Clinical findings at onset		No. of patients[a]	%
Age	⩽10 yr	9	20.4
	>10 yr	35	79.6
Gender	Male	27	61.4
	Female	17	38.6
Histological subtype	Biphasic	17	38.6
	Monophasic	19	43.2
	Poorly-differentiated	2	4.6
	NOS	6	13.6
Grade	G2	11	50.0
	G3	11	50.0
Tumour site	Axial	16	36.36
	Limbs	28	63.64
Local invasiveness	T1	9	20.4
	T2	35	79.6
Tumour size	⩽5 cm	7	15.9
	>5 cm	37	84.1
Nodal status	N0	43	97.7
	N1	1	2.3
IRS group	I	13	29.6
	II	14	31.8
	III	17	38.6
First-line treatment			
Type of surgery	Complete	21	47.7
	Microscopic residuals	14	31.8
	Macroscopic residuals	9	20.5
Radiotherapy	Given	32	72.7
	Not given	12	27.3
Chemotherapy	Given	38	86.4
	Not given	6	13.6
Chemotherapy response	Complete response	2	14.3
	Partial response	6	42.8
	Minor response	2	14.3
	No response	4	28.6
Clinical findings at relapse		No. of patients[a]	%
Type of relapse	Local	15	34.1
	Metastatic	22	50.0
	Local plus metastatic	7	15.9
Metastases	Unique site	12	41.4
	Multiple site	17	58.6
	Metastatic	29	65.9
Relapse in the RT field	No	6	27.3
	Yes	14	63.6
	Unknown	2	9.1
Time to relapse	Early (⩽18 months)	21	47.7
	Late (>18 months)	23	52.3
Second-line treatment			
Surgery	Complete	21	47.7
	Microscopic residuals	6	13.6
	Not performed	14	31.8
	Unknown	3	6.8
Chemotherapy	Yes	24	54.5
	No	16	36.4
	Unknown	4	9.1

Table 1 (continued)

Chemotherapy response	Partial response	8	42.1
	Minor response	3	15.5
	No response	8	42.1
Radiotherapy	Yes	11	25.0
	No	30	68.2
	Unknown	3	6.8
Overall treatment	Surgery alone	10	22.7
	CT only	7	15.9
	Surgery and CT	7	15.9
	Surgery and RT	3	6.8
	Surgery, CT, RT	7	15.9
	CT and RT	4	9.1
	Palliative	3	6.8
	Unknown	3	6.8
Status	Alive in remission	8	18.1
	Alive with disease	2	4.6
	Dead	34	77.3

Legend: NOS = not otherwise specified, RT = radiotherapy; CT = chemotherapy.
[a] The sum of the patients is not always the same due to values being unavailable for some variables.

third or further remissions) 14–143 months (median 99 months) after relapsing (Table 2), while 2 patients were alive with disease and still on treatment. A further event occurred in 20 out of the 25 patients who had achieved a secondary complete remission: 2 had further local relapse (Table 2), 18 had metastatic recurrence, 3–48 months (median 8 months) after secondary remission. The overall survival (OS) rates were 29.7% (16.8–43.9) and 21.0% (10.0–34.9) five and ten years after relapsing, respectively; the median follow-up for the patients who were still alive was 8.2 yr, interquantile (IQ) range 4.1–11.9 yr (Fig. 1).

Table 3 shows the 5- and 10-year OS by patients' characteristics in univariate analysis. As concerns their initial clinical characteristics and treatments, a trend towards a better survival was seen for patients with young age at diagnosis and small-sized tumours (though it was not statistically significant). Patients who had not been given chemotherapy and radiotherapy as part of their first-line treatment showed a slight trend towards a better survival.

Statistically significant factors associated with survival were the time to relapse and the type of recurrence. When these two variables were considered together, a subset of patients with a relatively good survival rate emerged, i.e. patients with local and late relapses had a 10-year OS rate of 68.6% (30.5–88.7).

As for the second-line treatment modalities, patients who responded to second-line chemotherapy had a statistically significant better survival. The two most significant variables, however, were the feasibility of complete surgery and the chances of achieving secondary remission.

On Cox's multivariate regression analysis (performed on 41 cases with a complete data set available), two factors remained significantly associated with the risk of

Table 2
Clinical characteristics of patients alive in remission.

Clinical findings at onset	Initial treatment	Relapse	Treatment at relapse	Further events	Outcome
F, 8 yr, T2A, IRS III, head-neck	CT (PR), incomplete surgery, RT	Single bone M, at 41 mos	CT (IFO-DOXO) with PR, RT	–	Alive in 2nd remission, 19 mos after relapse
F, 3 yr, T2A, IRS II, lower extremity	Incomplete surgery, CT, RT	Local relapse (4 cm, within the RT field), at 36 mos	Amputation, CT (IFO-DOXO)	–	Alive in 2nd remission, 104 mos after relapse
F, 16 yr, T1B, IRS I, upper extremity	Complete surgery, CT, RT	Local relapse (3 cm, within the RT field), at 36 mos	Amputation, CT (CARBO-CYC-ETO)	–	Alive in 2nd remission, 96 mos after relapse
M, 4 yr, T1A, IRS III, upper extremity	CT (CR), RT	Local relapse (2 cm, within the RT field), at 21 mos	CT (CARBO-ETO-IFO-DOXO) with PR, complete resection, CT	–	alive in 2nd remission, 102 mos after relapse
M, 15 yr, T2B, IRS II, lower extremity	Incomplete surgery, RT	Single pulmonary M, at 87 mos	Complete resection (lobectomy)	–	Alive in 2nd remission, 143 mos after relapse
M, 13 yr, T2A, IRS I, lower extremity	Complete surgery	Local relapse (4 cm, out of the RT field), at 34 mos	Complete resection	Further local recurrence 70 mos after first relapse, treated with amputation	Alive in 3rd remission, 114 mos after 2nd relapse
M, 16 yr, T2B, IRS II, upper extremity	Incomplete surgery, CT, RT	Local relapse (2 cm, within the RT field), at 75 mos	Complete resection	Further local recurrence 12 mos after first relapse, treated with amputation	Alive in 3rd remission, 54 mos after 2nd relapse
M, 10 yr, T2B, IRS II, lower extremity	Incomplete surgery, CT, RT	Regional lymph node M, at 56 mos	Complete resection, CT (IFO)	Lung metastases, treated with surgery and further CT	Alive in 5th remission, 14 mos after last lung relapse

Legend: F = female; M = male; yr = years of age; T = tumour stage; IRS = Intergroup Rhabdomyosarcoma Study; CT = chemotherapy; RT = radiotherapy; CR = complete remission; PR = partial remission; M = metastasis; mos = months; IFO = ifosfamide; DOXO = doxorubicin; CARBO = carboplatin; CYC = cyclophosphamide; ETO = etoposide.

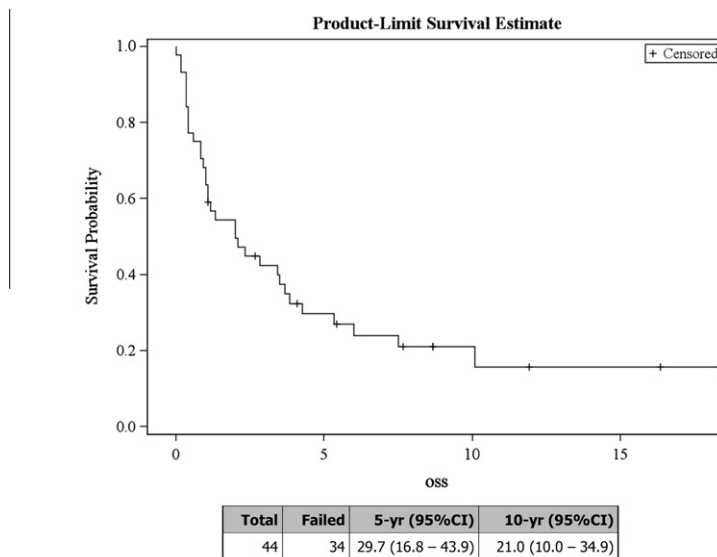| Total	Failed	5-yr (95%CI)	10-yr (95%CI)
44	34	29.7 (16.8 – 43.9)	21.0 (10.0 – 34.9)

Fig. 1. Overall survival of the whole sample of patients with synovial sarcoma after relapse (median follow-up for patients who were still alive: 8.2 yr, IQ range 4.1–11.9 yr).

death, i.e. secondary remission and the combination of time and type of relapse considered together (Table 4). Time and type of relapse were combined in only one variable since they were both slightly significant when indi-vidually considered in the multivariate model; when recoding these two factors in only one variable with two strata (one represented by patients with a local and late relapse, the other one constituted by patients with

Table 3
Estimated overall survival (OS) after relapse by patient characteristics (univariate analysis).

Characteristics		No.	No. of failures	5-yr OS (95%CI)	10-yr OS (95%CI)	P-value
Gender	Female	17	13	30.2 (10.1–53.6)	22.6 (5.8–46.0)	0.898
	Male	27	22	29.2 (13.6–46.7)	19.4 (6.7–37.1)	
Age at diagnosis	≤10 yr	9	4	48.6 (12.8–77.6)	48.6 (12.8–77.6)	0.089
	>10 yr	35	30	25.7 (12.8–40.8)	15.0 (5.2–29.6)	
Histotype	Biphasic	17	12	33.6 (12.9–56.0)	26.9 (8.7–49.4)	0.851
	Monophasic	19	16	30.7 (12.0–51.7)	15.3 (2.9–37.2)	
	Poorly-diff.	2	1	–	–	
	NOS	6	5	16.7 (0.7–51.7)	16.7 (0.7–51.7)	
Initial T-stage	T1	9	6	27.8 (4.4–59.1)	–	0.544
	T2	35	28	29.8 (15.6–45.6)	18.9 (7.5 – 34.4)	
Initial tumour size	≤5 cm	7	3	57.1 (17.2–83.7)	57.1 (17.2–83.7)	0.144
	>5 cm	37	31	25.6 (12.7–40.6)	14.9 (5.2–29.5)	
IRS group	I	13	11	30.8 (9.5–55.4)	23.1 (5.6–47.4)	0.203
	II	14	9	40.8 (15.6–64.9)	32.6 (10.4–57.4)	
	III	17	14	19.8 (5.0–41.8)	–	
Initial surgery	Macro-incomplete	9	8	11.1 (0.6–38.8)	–	0.0417
	Micro-incomplete	14	8	37.5 (12.5–62.9)	37.5 (12.5–62.9)	
	Complete	21	18	32.6 (14.1–52.7)	16.3 (4.1–35.5)	
First-line chemotherapy	No	6	4	50.0 (11.1–80.4)	33.3 (4.6–67.5)	0.1951
	Yes	38	30	26.4 (13.3–41.6)	19.3 (7.9–34.3)	
First-line radiotherapy	No	12	11	31.5 (15.9–48.3)	27.0 (12.3–44.0)	0.278
	Yes	32	23	25.0 (6.0–50.5)	8.3 (0.5–31.1)	
Timing of relapse	Early	21	21	14.3 (3.6–32.1)	0 (–)	0.001
	Late	23	13	44.2 (22.8–63.7)	44.2 (22.8–63.7)	
Type of relapse	Local	15	8	59.3 (30.7–79.3)	40.6 (14.7–65.6)	0.0046
	Single meta	12	9	38.1 (12.1–64.3)	28.6 (7.0–55.5)	
	Multiple meta	17	17	0 (–)	0 (–)	
Relapse vis-à-vis RT field	Outside	6	5	33.3 (4.6–67.5)	16.7 (0.8–51.7)	0.8078
	Within	14	9	41.7 (16.4–65.4)	–	
Surgery at relapse	Incomplete	6	6	16.7 (0.8–51.7)	0 (–)	<0.0001
	Complete	21	13	51.9 (29.1–70.6)	40.9 (19.8–61.1)	
	No surgery	14	13	0 (–)	0 (–)	
Chemotherapy at relapse	No	16	11	50.0 (24.5–71.0)	25.7 (6.9–50.1)	0.3198
	Yes	24	20	17.9 (5.6–35.7)	17.9 (5.6–35.7)	
Chemotherapy response	No response	8	8	0 (–)	0 (–)	0.0122
	Objective response	11	9	10.4 (0.6–36.7)	0 (–)	
Radiotherapy at relapse	No	30	22	29.6 (14.6–46.3)	25.9 (11.9–42.5)	0.7882
	Yes	11	11	31.2 (7.5–59.1)	10.4 (0.6–36.8)	
Secondary remission	No	17	17	0 (–)	0 (–)	<0.0001
	Yes	25	16	50.0 (29.0–67.9)	35.4 (16.7–54.7)	

Legend: OS = overall survival; NOS = not otherwise specified; T = tumour stage; RT = radiotherapy.

Table 4
Cox regression analysis: secondary remission and time and type of relapse combined in one variable were significantly associated with the risk of death.

Characteristics		HR	HR 95% CI	P-value
Secondary remission	No	1		<0.0001
	yes	9.9	3.7–26.4	
Time and type of relapse	Late (>18 months) and local	1		0.039
	Early (≤18 months) and/or metastatic	4.7	1.1–20.5	

a metastatic and/or an early relapse), the model resulted statistically significant. For patients who did not achieve secondary remission, the HR for death was 9.9 (95% CI 3.7–26.4) ($p < 0.0001$); for patients who had a metastatic and/or early relapse the HR for death was 4.7 (95% CI 1.1–20.5). Response to second line chemotherapy was not considered in the multivariate analysis as it was available in only 19 patients.

The results of the multivariate analysis were used to calculate the overall survival on the basis of the number of prognostic factors for each patient. The 5-year OS for the 7 patients without any risk factor was 85.7% (95%
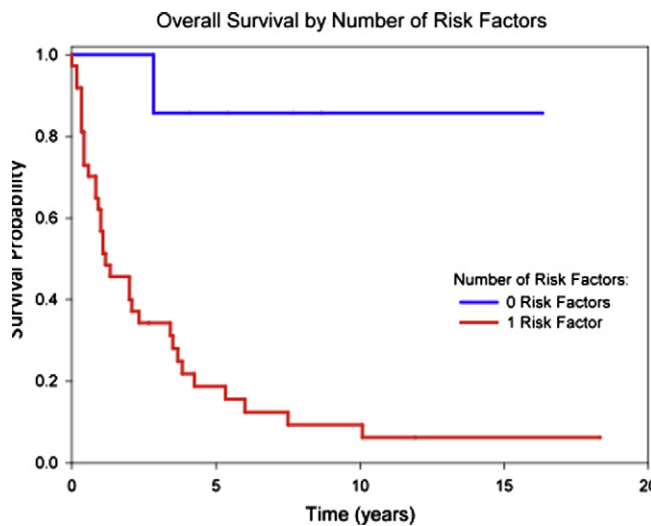
Fig. 2. Overall survival on the basis of the number of prognostic factors emerged in the multivariate analysis. In the subset of patients without any risk factor (7 cases), 5-year OS was 85.7%; when one factor was present, 5-year OS was 18.7%.

CI 33.4–97.8), as compared to 18.7% (95% CI 7.7–33.6) for the 36 patients with one risk factor (Fig. 2).

4. Discussion

This report describes the pattern of recurrence, the salvage rates and the prognostic variables influencing the survival of a subset of relapsing SS patients treated at Italian paediatric centers. To our knowledge, no such analyses have been published in the literature to date.

A first finding of our study was that survival after recurrence was largely unsatisfactory for children and adolescents with SS, suggesting the urgent need for new salvage treatment approaches. Our goal was to identify the factors correlating with final outcome with a view to defining a risk-adapted approach to patients, distinguishing between those with realistic prospects of cure (using currently available therapeutic options) and those with little chance of salvage, who might – in principle – be offered experimental therapy (or palliative care).[13]

Though our sample was drawn from a series of 118 patients collected by means of a national-scale cooperation, the relatively small number of events represents a limitation of this study. Some interesting results emerged nevertheless: univariate analysis showed that patients whose relapse was local and occurred later on (more than 18 months after their first diagnosis) had a reasonable chance of cure, particularly when these two variables were combined (10-year OS 68.6%), whereas patients with multiple metastases had a dismal outcome. Concerning initial tumour's characteristics, no other variable was significantly related with outcome after relapse. Initial tumour size showed a statistically not-significant trend (the 10-year OS rate was 57% and 15% for tumours larger or smaller than 5 cm, respectively), that might suggest in principle that a larger initial tumour may be a sign of a biologically more aggressive disease.[14,15]

The effectiveness of second-line therapy strongly influenced the final outcome of our patients. There was a chance of cure for patients who responded well to salvage chemotherapy and for those whose recurrences (at both local and distant sites) were amenable to complete surgical resection. Finding that patients who succeeded in undergoing complete surgery had a better outcome would indicate that an aggressive surgical approach is justified. While amputation should generally not be considered as a standard procedure for patients at first onset (with a few exceptions), every effort should be made to achieve secondary remission at the time of any relapse, and amputation for locally relapsing limb disease may be a valid option. Aggressive surgery should likewise be recommended for metastases.

Systemic therapy may have a role in achieving tumour shrinkage and enabling a delayed resection, as well as preventing further events. In the current series, final outcome correlated with response to second-line chemotherapy: this would support the indication for intensive chemotherapy (e.g. high-dose ifosfamide, even as a re-challenge),[16] but also means that efforts should be made to explore new, more effective combined strategies and novel agents with alternative mechanisms of action.[17,18] The specific chromosomal translocations and fusion proteins, and the proteins overexpressed by the tumour cells (epidermal growth factor receptor EGFR, human epidermal growth factor receptor 2 HER-2/neu, Bcl-2)[19–22] make SS a promising tumour type for targeted therapy. Investigations are underway on the role of new drugs, such as trabectidine, multi-target anti-tyrosine kinases inhibitors, Bcl-2 antisense oligonucleotide,[23–25] and on monoclonal antibody against frizzled homologue 10 (FZD10), a cell-surface receptor in the Wnt pathway,[26] or adoptive immunotherapy using tumour-infiltrating lymphocytes against NY-ESO-1 cancer/testis antigen (expressed in 80% of SS).[27] Relapsing SS patients who have little chance of cure, judging from our analysis (e.g. with early and metastatic recurrences) could be offered experimental therapies.

Conflict of interest statement

The authors do not have any conflict of interest to be disclosed.

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