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Original Research

Surgery alone is sufficient therapy for children and adolescents with low-risk synovial sarcoma: A joint analysis from the European paediatric soft tissue sarcoma Study Group and the Children's Oncology Group

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Abstract ***Background:*** Multimodal risk-adapted treatment is used in paediatric protocols for synovial sarcoma (SS). Retrospective analyses suggest that low-risk SS patients can be safely treated with surgery alone, but no prospective studies have confirmed the safety of this approach. This analysis pooled data from the two prospective clinical trials to assess outcomes in SS patients treated with a surgery-only approach and to identify predictors of treatment failure.

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Methods: Patients with localised SS enrolled on the European paediatric Soft tissue sarcoma Study Group (EpSSG) NRSTS2005 and on the Children Oncology Group (COG) ARST0332 trials, treated with surgery alone were eligible for this analysis. Patients must have undergone initial complete resection with histologically free margins, with a grade 2 tumour of any size or a grade 3 tumour ≤5 cm.

Results: Sixty patients under 21 years of age were eligible for the analysis; 36 enrolled in the COG (from 2007 to 2012) and 24 in the EpSSG study (from 2005 to 2012). The 3-year event-free survival was 90% (median follow-up 5.2 years, range 1.9–9.1). All eight events were local tumour recurrence, whereas no metastatic recurrences were seen. All patients with recurrence were effectively salvaged, resulting in 100% overall survival.

Conclusion: This joint prospective analysis showed that patients with adequately resected ≤5 cm SS, regardless of grade, can be safely treated with a surgery-only approach. Avoiding the use of adjuvant chemotherapy and radiotherapy in this low-risk patient population may decrease both short- and long-term morbidity and mortality.

1. Introduction

Synovial sarcoma (SS) is a malignant mesenchymal tumour characterised by a specific t(X; 18) (p11.2; q11.2) chromosomal translocation that results in several different SYT-SSX fusion proteins, thought to be responsible for the malignant phenotype. SS occurs in both adult and paediatric patients, but is most common in adolescents and young adults [1]. In childhood and adolescence, it is generally included by paediatric oncologists in the large and heterogeneous group of non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), which are distinguished from rhabdomyosarcoma (RMS) by their relative insensitivity to chemotherapy and radiotherapy. Although SS is the most common of the NRSTS in paediatric patients, its rarity has limited the available data on its natural history and treatment [2–5]. Historically, treatment of SS was based on principles deriving from the management of RMS or, alternatively, from the treatment of adult soft tissue sarcomas. However, these approaches are problematic since SS is less sensitive to chemotherapy and radiotherapy than RMS and certain soft tissue sarcoma histotypes behave differently in different age groups [6,7]. More recently, both the North American Children Oncology Group (COG) and the European paediatric Soft tissue sarcoma Study Group (EpSSG) launched clinical trials specifically tailored to NRSTS. In both of these protocols, a multimodal risk-adapted treatment program was defined according to features previously identified to predict outcome in paediatric NRSTS: the extent of disease, histologic grade and size of the primary tumour and the extent of surgical resection [8–12]. Both studies identified a group of low-risk SS cases to be treated with surgery alone. This treatment strategy was based on retrospective analyses suggesting that adjuvant chemotherapy and radiotherapy might be omitted in low-risk SS [13–15], but no prospective series have confirmed the safety of this approach.

The current analysis pooled data from the two prospective COG and EpSSG clinical trials to assess outcomes in low-risk localised SS patients treated with a surgery-only approach and to identify predictors of treatment failure.

2. Material and methods

Newly diagnosed patients under 30 years of age with SS enrolled on one of two prospective clinical trials (EpSSG NRSTS 2005 or COG ARST0332) were eligible for this subset analysis if they were treated with surgery alone. Diagnosis and histologic tumour grade were confirmed in all cases by the central review of submitted tumour tissue by expert paediatric soft tissue pathologists.

The criteria for treatment with surgery alone differed slightly on the 2 studies. The NRSTS 2005 protocol [16] recommended a surgery-only approach for SS patients with tumours ≤5 cm in maximal diameter who had initial microscopically complete resection with histologically free margins (i.e. group I according to the paediatric Intergroup Rhabdomyosarcoma Study [IRS] post-surgical staging system [17], "wide resection" or R0 resection according to Enneking criteria [18]), regardless of the tumour grade established according to the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system [19]. The ARST0332 protocol prescribed surgery only for patients with Pediatric Oncology Group (POG) [20] grade 2 tumours of any size that were widely (IRS group I or R0 resection) or marginally (IRS group II or R1 resection) excised and for POG grade 3 tumours ≤5 cm in maximal diameter. In the ARST0332 protocol, treatment assignment was based on POG grading system, but tumour grade was also evaluated according to the FNCLCC system. For the purpose of the current analysis, the FNCLCC system was used to align with both the series.

Patients with marginally excised grade 2 tumours were excluded from this analysis. Therefore, patients

included in the current study had completely resected tumours (IRS group I and R0 resection) with size ≤5 cm, any grade, or with grade 2 tumour and any size.

Assessment of tumour features including anatomic site, maximal tumour diameter, translocation status and extent of surgery differed for the two clinical trials. The EpSSG NRSTS 2005 trial required local tumour assessment with computerised tomography (CT) and/or magnetic resonance imaging. Pre-treatment investigations included the search for distant metastases (chest CT scanning, technetium [Tc]^{99m} bone scanning and abdominal ultrasound). No centralised review for radiology was required. Histological diagnosis was confirmed in all cases by a national pathology panel and in most of them by a second review performed by the EpSSG pathology panel. All the clinical data were reviewed by the EpSSG NRSTS Committee. In the ARST0332 study, anatomic site and maximal tumour diameter were independently evaluated based on the review of baseline imaging studies by two paediatric radiologists; discrepancies were resolved by consensus review. For patients without baseline imaging, these features were assigned by review of operative notes by orthopaedic and paediatric surgeons. Operative notes and pathology reports were evaluated by the same surgeons and the study chair to determine the surgical procedures performed and the translocation status of each tumour. Each tumour arising in the extremity was categorised as proximal (axilla, arm, inguinal, thigh, knee) or distal (forearm, wrist, hand, finger, leg, ankle, foot, toe).

Descriptive statistics (frequency and percentage for categorical characteristics; median and range for numerical characteristics) were used. The Kaplan–Meier method was used to construct the event-free survival (EFS) curve, with the standard error computed using the Peto–Pike method. The log-rank test was performed to compare EFS distribution.

3. Results

Sixty patients were eligible for this analysis: 36 patients were enrolled in the ARST0332 (from February, 2007 to February, 2012) and 24 patients were enrolled in the EpSSG 2005 study (from August, 2005 to August, 2012). The latter were included in a previous EpSSG publication on 138 SS patients [16]. The clinical features of the study cohort are shown in Table 1. The median age at study enrolment was 12.3 years; age range was 1–20 years, with only five patients older than 18 years. Sixty percent of patients were male. Eighty-eight percent of the tumours arose in the extremity; slightly more than half were in the distal extremity. The median tumour size was 3 cm, with only four patients (all from ARST0332) with tumors >5 cm in maximum diameter. Most patients (87%) had tumour classified as FNCLCC grade 2. An SYT rearrangement was detected in 98% of the tumours evaluated, but 17% were not tested.

Table 1
Patient characteristics and treatment.

Characteristic	Number (%)
Age	
Median	12.3 years
Range	0.4–20.9 years
Sex	
Male	36 (60%)
Female	24 (40%)
Primary tumour site	
Distal extremity	29 (48%)
Proximal extremity	24 (40%)
Other	7 (12%)
FNCLCC grade	
2	45 (86.5%)
3	7 (13.5%)
Translocation status	
SYT rearrangement	31 (52%)
SYT-SSX1	14 (23%)
SYT-SSX2	4 (7%)
SYT not rearranged	1 (2%)
Unknown	10 (16%)
Maximal tumour diameter	
Median	3 cm
Range	0.6–7.8 cm
Initial operation	
Resection	55 (92%)
Biopsy	5 (8%)
Primary re-excision procedure	
No	19 (32%)
Yes, no tumour found	19 (32%)
Yes, tumour found and completely resected	22 (36%)

All patients underwent complete tumour resection before study enrolment. Eight percent of patients had a biopsy before the surgical resection. About two-thirds (68%) underwent a primary re-excision procedure. Tumour was found (and completely excised) in 54% of patients who underwent a primary re-excision; no residual tumour was found in the remaining 46%.

All patients were alive at the time of this analysis, with a median follow-up of 5.2 years (range, 1.9–9.1 years). At 3 years, EFS and OS were 90% (95% confident interval 81.9%, 98%) and 100%, respectively. There were eight events reported, all of which were local tumour recurrence. The median time to relapse was 18.5 months (range 8.8–74.4 months). Of note, there was one late local recurrence at 6.2 years. All patients with tumour recurrence were alive at the time of the analysis, after second-line treatment, consisting in surgery, chemotherapy and radiotherapy in three cases, surgery plus radiotherapy in three cases, surgery plus chemotherapy in one case and surgery alone in one case.

Log-rank test analysis showed that clinical trial (ARST0332 versus NRSTS2005), age (≤10 years versus >10 years), gender (male versus female) and FNCLCC grade (2 versus 3) and anatomic site (proximal versus distal extremity) were not significant predictors of EFS. Patients with larger tumours (>3 cm) fared better than those with ≤3 cm tumours ($p = 0.03$) (Table 2).

Table 2
Analysis of predictors of event-free survival (EFS).

Characteristic	3-year EFS (95% CI)	Log-rank test p value
Clinical trial		
NRSTS2005	91.7% (79.4%, 100%)	0.34
ARST0332	88.8% (78.2%, 99.4%)	
Age		
≤10 years	82.4% (63.6%, 100%)	0.19
>10 years	93.0% (84.9%, 100%)	
Gender		
Male	86.1% (74.0%, 98.2%)	0.10
Female	95.7% (87.1%, 100%)	
FNCLCC grade[a]		
2	88.8% (79.0%, 98.7%)	0.19
3	100%	
Maximal tumour diameter[b]		
≤3 cm	86.5% (73.3%, 99.8%)	0.03
>3 cm	100%	
Anatomic site (extremity only)		
Proximal extremity	91.7% (79.4%, 100%)	0.22
Distal extremity	86.2% (73.1%, 99.3%)	

[a] 8 with missing data.
[b] 9 with missing data.

4. Discussion

This joint analysis of data from two prospective trials for paediatric patients with NRSTS shows that children and adolescents with small and adequately resected localised SS can be safely treated with a surgery-only approach. Importantly, there were no metastatic recurrences despite the omission of systemic chemotherapy and the 3-year EFS was 90%. Patients with local tumour recurrence were effectively salvaged, resulting in 100% overall survival.

These findings are of great importance because the optimal treatment for paediatric SS remains unclear. Various published series indicate that the prognosis depends largely on the presence or absence of metastases, the feasibility of surgical resection and tumour size and site [2–5,8–12]. However, the rarity of the disease and the consequent difficulty of conducting randomised clinical trials have resulted in considerable heterogeneity in the treatment approach. The roles of both adjuvant chemotherapy and adjuvant radiotherapy are still debated.

Paediatric oncologists have traditionally considered SS a chemosensitive tumour, according to the relatively high rates of response to chemotherapy (around 60%) reported in historical paediatric series. Until recently, European paediatric protocols defined SS as an "RMS-like" tumour and at least nine courses of adjuvant chemotherapy were recommended for all SS patients, even for those with completely excised small tumours. More recently, though, this approach has changed. An Italian and German paediatric retrospective study of initially grossly resected SS (most also treated with adjuvant chemotherapy) suggested that patients with completely resected tumors <5 cm in size had a very low risk of metastasis: in a cohort of 48 cases, four developed local relapse and none experienced metastatic relapse [13]. On the basis of this finding, adjuvant chemotherapy was omitted in such low-risk cases in the following generation of European paediatric protocols dedicated to SS.

As data on the long-term toxicity of radiotherapy in paediatric patients has accrued, paediatric oncologists have also sought to avoid the use of adjuvant radiotherapy in low-risk patients. Several retrospective analyses in adults with soft tissue sarcomas indicate that adjuvant radiotherapy is not necessary for patients whose tumour can be adequately excised, even when the tumour is high grade or >5 cm in maximal diameter [14,15,21]. An analysis of paediatric SS patients treated on three prospective European studies showed that a significant proportion could be cured without radiotherapy when a strategy of omitting radiotherapy for those with a complete response to surgery and chemotherapy was utilized [5]. These observations led both the COG and the EpSSG to omit radiotherapy in low-risk patients with SS whose tumour could be completely resected. The demonstration that long-term EFS can be achieved in these patients with surgery alone will minimise the number of survivors with radiotherapy-related long-term toxicities.

Our analysis demonstrated that surgery alone was sufficient therapy for children and adolescents with low-risk SS; however, an important observation was that about two-thirds of patients underwent a primary re-excision procedure. It may be suspected that the rate of primary re-excision was high because malignancy was not suspected in many cases at the time of initial surgery and there was uncertainty about the adequacy of the surgical margins. Indeed, 54% of patients who underwent primary re-excision had residual tumour found, which was quite similar to the rate previously reported in both paediatric and adult patients with soft tissue sarcomas [22–24]. The fact that few local recurrences occurred in patients who had undergone primary re-excision suggests that the need to do two operations is not, per se, a contraindication to omission of adjuvant therapy. Rather, our data suggest that primary re-excision is effective in ensuring the removal of residual tumour remaining after an unplanned excision. This observation is in keeping with an analysis in adult soft tissue sarcomas where patients who underwent primary re-excision fared as well as those who underwent a single definitive resection [25].

Interestingly, our study found no relationship between high grade as well as large tumour and the likelihood of local recurrence. Certainly, this might be related, at least in part, to the small sample size and the small number of events. Noteworthy, patients with tumour size >3 cm had a better outcome than those with tumours ≤3. Though it is difficult to find an explanation

for this finding, it is relevant to note that, however, our series included only four patients with tumours >5 cm (and all of these had grade 2 tumours). The small number of patients with tumours >5 cm limits our ability to provide a strong recommendation about the optimal management of patients with larger but resected tumours. Additional data are needed to confirm that radiotherapy can be omitted in those with larger tumours, since tumour size larger than 5 cm had been shown to be of prognostic value in various paediatric SS series [3–5,26].

As no metastatic relapses occurred in this low-risk patient category, it might be possible to speculate also on tumour surveillance for metastatic relapse based on the risk of recurrence: to limit unnecessary ionising radiation exposures, in principle, thorax X-ray for detecting lung metastases may be sufficient for these patients (with the omission of CT scan) [27].

Based on this joint prospective series, we conclude that the use of adjuvant chemotherapy and radiotherapy may be avoided in paediatric patients with adequately excised ≤5 cm SS without jeopardising their outcome. Omission of adjuvant therapy in these patients may also decrease short- and long-term complications of treatment. Further research is needed to determine whether adjuvant radiotherapy may be eliminated in those with adequately excised >5 cm tumours.

Conflict of interest statement

None declared.

Clinical trials registration number

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

COG ARST0332: ClinicalTrials.gov Identifier: NCT00346164.

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