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

Andrea Ferrari a,*, Yueh-Yun Chi b, Gian Luca De Salvo c, Daniel Orbach d, Bernadette Brennan e, R. Lor Randall f, M. Beth McCarville g, Jennifer O. Black h, Rita Alaggio i, Douglas S. Hawkins j, Gianni Bisogno k, Sheri L. Spunt l

a Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy
b Department of Biostatistics, University of Florida, Gainesville, FL, USA
c Clinical Trials and Biostatistics Unit, IRCCS Istituto Oncologico Veneto, Padova, Italy
d Department of Pediatric, Adolescent and Young Adult Oncology, Institut Curie, Paris, France
e Department of Pediatric Oncology, Royal Manchester Children’s Hospital, Manchester, United Kingdom
f Pediatric Orthopaedics, Primary Children’s Hospital, Salt Lake City, UT, USA
g Department of Diagnostic Imaging, St. Jude Children’s Research Hospital, Memphis, TN, USA
h Pediatric Pathology, Children’s Hospital Colorado, Aurora, CO, USA
i Pathology Department, Padova University, Padova, Italy
j Hematology/Oncology, Seattle Children’s Hospital, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
k Pediatric Hematology and Oncology Division, Padova University, Padova, Italy
l Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA, USA

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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.
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.

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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 NRSTS2005 and COG ARST0332 protocols 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
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