AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

NRSTS

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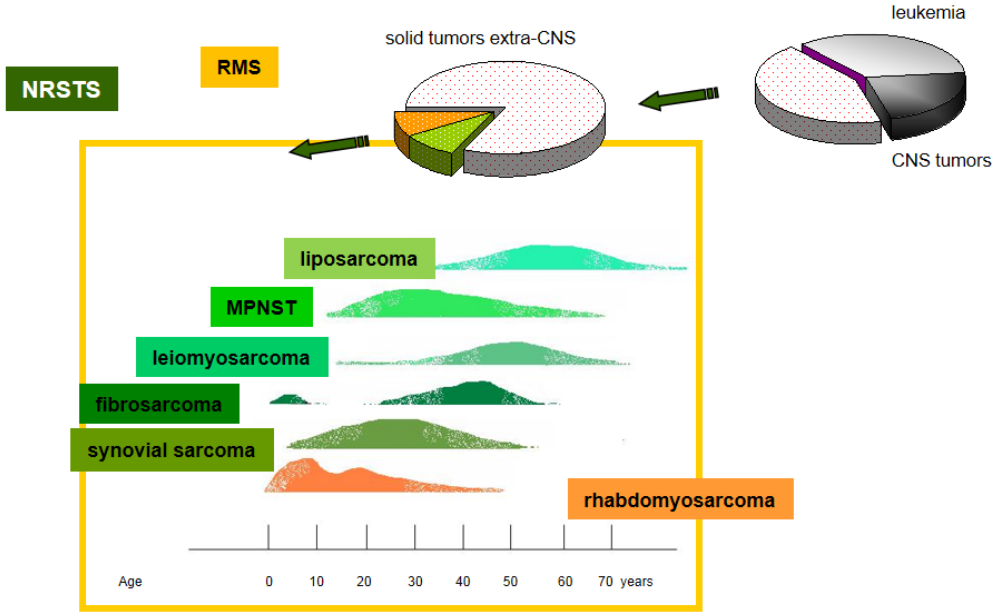
Il sottoscritto Andrea Ferrari
ai sensi dell'art. 3.3 sul Conflitto di Interessi,
pag. 17 del Reg. Applicativo dell'Accordo
Stato-Regione del 5 novembre 2009,

dichiara *che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario*



RMS

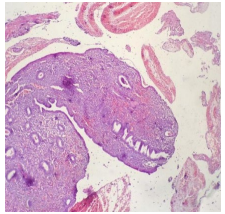
- typical embryonal tumor of childhood
- high grade of malignancy, local invasiveness and a marked propensity to metastasize…

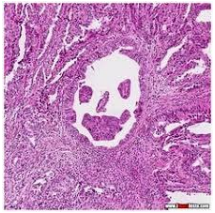
  …all RMS patients should be assumed to have micrometastatic disease at diagnosis, so systemic therapy is definitely recommended for all patients
- (generally) good response to chemotherapy (90% response rate) and radiotherapy

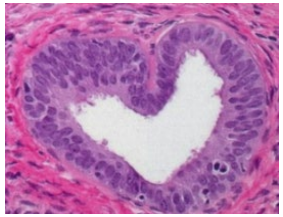
NRSTS

- rare tumors
- most are tumor entities typically found in adults
- extremely heterogeneus tumors
- scarcely sensitive to chemotherapy

Different histology







Different histology

Different biology

Histotypes	Pick of incidence	Molecular finding	Clinical characteristics
Synovial sarcoma	2°-3°decade	t(X;18)(p11;q11) SYT-SSX1, SYT-SSX2, SYT-SSX4	extremity site (most frequent subtype in lung, pleura and mediastinum) - , 60% response rate to chemotherapy
Malignant peripheral nerve sheath tumor (MPNST)	3-4° decade	loss or rearrangement of 10p, 11q, 17q and 22q	30% associated to NF-1, trunk poor response to chemotherapy, poor prognosis
Infantile fibrosarcoma	1° year	t(12;15;)(p13;q25) ETVG(TEL)-NTRK3 *(as mesoblastic nephroma)*	rapid growth, high chemosensitiveness overall good prognosis
Adult-type fibrosarcoma	4°-5° decade	t(2,5) and t(7,22)	tendency to metastatic spread according to tumor grade
Epithelioid sarcoma	3° decade	SMARCB/INI1 lost expression in 85-93% P13 K – AKT – MTOR signaling pathway	superficial distant site (fingers), indolent course, lymph nodal spread
Liposarcoma	6°-7° decade	myxoid liposarcoma: t(12;16)(q13;p11) t(12;22)(q13;q12) FUS-CHOP	different subtypes, i.e. well-diff, dediff or myxoid/round cell subtype - retroperitoneal location
Leiomyosarcoma	6° decade	-	retroperitoneum immunocompromised patients
Alveolar soft part sarcoma	3° decade	t(X;17)(p11.2;q25) TFE3-ASPL	poor response to chemotherapy poor prognosis
Clear cell sarcoma	3-4° decade	t(12;22)(q13;q12) t(9;22)(q22;q12) ATF1-EWS	poor response to chemotherapy poor prognosis
Angiosarcoma	4°-6° decade	-	poor prognosis associated with lymphedema, after radiotherapy
Dermatofibrosarcoma protuberans	3°-5° decade	t(17;22) t(2;17)(p23;q23) ALK-CLTC PDGFβ-COL1A1	Subcutaneous, indolent growth
Extraskeletal myxoid chondrosarcoma	5°-6° decade	t(9;22)(q22;q12) t(9;17)(q22;q11.2) EWS-CHN	slow-growing tumor of extremity
Extraskeletal mesenchymal chondrosarcoma	2°-3° decade	complex cytogenetic alteration t(11;22) (q24;q12) (as Ewing family tumors)	head-neck region (orbit) highly aggressive tumor
Desmoplastic small round cell tumor	2°-3° decade	t(11;22) (p13;q12) EWS-WT1	abdominal mass widely disseminated at onset, peritoneal seeding, metastases, poor outcome
Extracranial extrarenal rhabdoid tumor	infants and young children	mutated hSNF5/INI 1 gene	poor prognosis

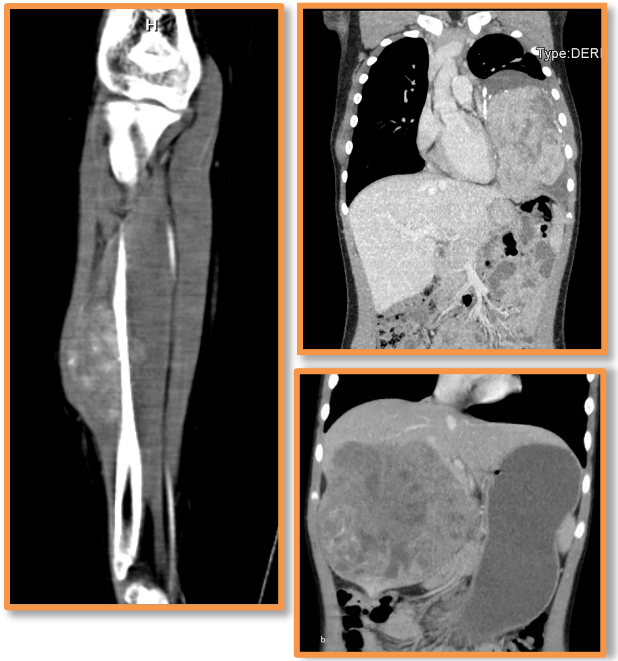
As a general view, borderline and low-grade tumors may be locally aggressive, but unlikely to metastasize: the growth rate may be indolent and sometimes the diagnosis is done after removing a small swelling that has existed for several years. High-grade tumors are more aggressive and can have a strong propensity to metastasize, particularly to the lung.

Different histology

Different biology

Different clinical aspects

- **MPNST** are generally axial and aggressiveness disease, characterised by poor prognosis, particularly when associated to neurofibromatosis type 1 (NF1)
- **epithelioid sarcomas** present typical features such as peculiar superficial distal location (i.e. hand, fingers), indolent growth and tendency for lymph node involvement
- **infantile fibrosarcomas** is a peculiar subtype that may have initial rapid growth and metastatic spread, but also indolent evolution (and also spontaneous regressions have been described)
- **desmoplastic small round cell tumors (DSRCT)** usually present as large abdominal masses generally disseminated at the time of diagnosis, with extensive spread to regional lymph nodes, peritoneal seeding, and distant metastases; the outcome is extremely poor despite intensive multimodality treatment approaches



Different histology

Different biology

Different clinical aspects

Different outcome

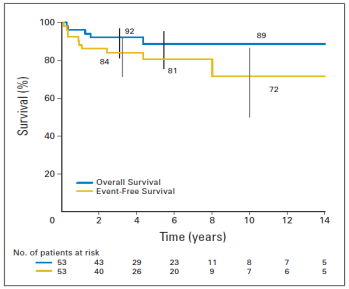


Fig 1. Overall survival and event-free survival of patients with localized infantile fibrosarcoma. Vertical bars indicate standard deviation.

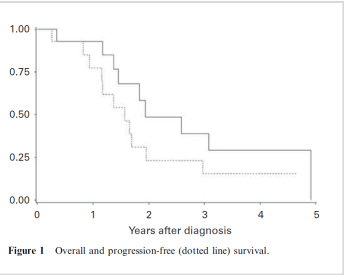


Figure 1 Overall and progression-free (dotted line) survival.

Turning points in the management of pediatric NRSTS

2005

2015

In the past, NRSTS = **orphan diseases**

Very few trials

- *Pratt, JCO1999 - only NRSTS randomised study in pediatric age (most pts refused randomization, i.e. 51/81)*
- *Pappo, JCO 2005 - phase 2 trial with IFO-DOXO-VCR in advance disease -39 cases*

The two largest reported series of pediatric NRSTS were single-institution experiences

- *St Jude – Spunt, JCO 1999 – 121 cases*
- *INT Milan - Ferrari, JCO 2005 – 182 cases*

NRSTS were often treated, in Europe at least, with RMS protocols

The different NRSTS entities were often treated all together, including in the same approach (and in the same analysis) very different entities as adult-type STS and extraosseous Ewing or DSRCT; or truly malignant tumors and soft tissue tumors with intermediate malignancies

Pediatric cooperative groups started to develop clinical trials specifically tailored to NRSTS, i.e. **COG ARST0332 study** (conducted from 2007 to 2012), **EpSSG NRSTS 2005 study** (2005-2016).

These multimodal risk-adapted studies were very similar in terms of their rationale, patient stratification and treatment programs

The two publications represent the benchmark for this tumor group, and defines the risk-adapted standard of care

- *Spunt, Lancet Oncol 2020 – 529 cases*
- *Ferrari, Lancet Child Adolesc Health 2021 – 569 cases*

ARST1321 study

first study with a target therapy in front-line in NRSTS

first study with adults (cooperation embracing nearly the whole age spectrum are feasible... maybe)

- Weiss *Lancet Oncol 2020*

Turning points in the management of pediatric NRSTS

2005 — 2015

synovial sarcoma
angiosarcoma
epithelioid hemangioendothelioma
desmoid-type fibromatosis
MPNST
epithelioid sarcoma
alveolar soft part sarcoma
rhabdoid tumor
inflammatory myofibroblastic tumors
undifferentiated soft part sarcoma
INFANTILE FIBROSARCOMA
leiomyosarcoma
LIPOSARCOMA
adult-type fibrosarcoma
desmoplastic small round cell tumor
clear cell sarcoma
extraosseous Ewing sarcoma
undifferentiated sarcoma of the liver
dermatofibrosarcoma protuberans

Adult-type NRSTS

undifferentiated high-grade pleomorphic sarcoma
BCOR family / CIC-rearranged undifferentiated sarcomas

The different NRSTS entities were often treated all together, including in the same approach (and in the same analysis) very different entities as adult-type STS and extraosseous Ewing or DSRCT; or truly malignant tumors and soft tissue tumors with intermediate malignancies

molecular advancements
more sophisticated understanding of biology
refinement of diagnostic criteria
biological stratification
biologic targets
re-delineation of treatment strategies
novel agents

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Synovial sarcoma in children and adolescents: the European Pediatric Soft Tissue Sarcoma Study Group prospective trial (EpSSG NRSTS 2005)

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Original research

Conservative strategy in infantile fibrosarcoma is possible: The European paediatric Soft tissue sarcoma Study Group experience

Daniel Orbach [a,*], Bernadette Brennan [b], Angela De Paoli [c], Soledad Gallego [d], Peter Mudry [e], Nadine Francotte [f], Max van Noesel [g], Anna Kelsey [h], Rita Alaggio [i], Dominique Ranchère [j], Gian Luca De Salvo [c], Michela Casanova [k], Christophe Bergeron [l], Johannes H.M. Merks [m], Meriel Jenney [n], Michael C.G. Stevens [o], Gianni Bisogno [p], Andrea Ferrari [k]

Clinical Trial

Outcome of extracranial malignant rhabdoid tumours in children registered in the European Paediatric Soft Tissue Sarcoma Study Group Non-Rhabdomyosarcoma Soft Tissue Sarcoma 2005 Study—EpSSG NRSTS 2005

Bernadette Brennan [a,*], Gian Luca De Salvo [b], Daniel Orbach [c], Angela De Paoli [b], Anna Kelsey [d], Peter Mudry [e], Nadine Francotte [f], Max Van Noesel [g], Gianni Bisogno [h], Michela Casanova [i], Andrea Ferrari [i]

RESEARCH ARTICLE

WILEY Pediatric Blood & Cancer | SIOP | aspho

Alveolar soft part sarcoma in children and adolescents: The European Paediatric Soft Tissue Sarcoma study group prospective trial (EpSSG NRSTS 2005)

Bernadette Brennan[1] | Ilaria Zanetti[2] | Daniel Orbach[3] | Soledad Gallego[4] | Nadine Francotte[5] | Max Van Noesel[6] | Anna Kelsey[7] | Michela Casanova[8] | Gian Luca De Salvo[2] | Gianni Bisogno[9] | Andrea Ferrari[8]

The EpSSG NRSTS 2005 treatment protocol for desmoid-type fibromatosis in children: an international prospective case series

Daniel Orbach, Bernadette Brennan, Gianni Bisogno, Max Van Noesel, Véronique Minard-Colin, Julia Daragjati, Michela Casanova, Nadege Corradini, Ilaria Zanetti, Gian Luca De Salvo, Anne Sophie Defachelles, Anna Kelsey, Myriam Ben Arush, Nadine Francotte, Andrea Ferrari

Cancer Medicine

ORIGINAL RESEARCH | Open Access

Genomic complexity in pediatric synovial sarcomas (Synobio study): the European pediatric soft tissue sarcoma group (EpSSG) experience

Daniel Orbach[1], Véronique Mosseri[2], Daniel Pissaloux[3], Gaelle Pierron[4], Bernadette Brennan[5], Andrea Ferrari[6], Frederic Chibon[7], Gianni Bisogno[8], Gian Luca De Salvo[9], Camille Chakiba[3], Nadège Corradini[10], Véronique Minard-Colin[11], Anna Kelsey[12] & Dominique Ranchère-Vince[3]

Dermatofibrosarcoma protuberans in children and adolescents: The European Paediatric Soft Tissue Sarcoma Study Group prospective trial (EpSSG NRSTS 2005)

Bernadette Brennan[1] | Ilaria Zanetti[2] | Gian Luca De Salvo[2] | Daniel Orbach[3] | Soledad Gallego[4] | Nadine Francotte[5] | Stefan Schifflers[5] | Max Van Noesel[6] | Anna Kelsey[7] | Michela Casanova[8] | Gian Paolo [illegible] | Paola Collini[9] | Angelica Zin[10] | Luisa Santoro[11] | Andrea Ferrari[8]

Outcome and prognostic factors in pediatric malignant peripheral nerve sheath tumors: An analysis of the European Pediatric Soft Tissue Sarcoma Group (EpSSG) NRSTS-2005 prospective study

Max M. van Noesel[1] | Daniel Orbach[2] | Bernadette Brennan[3] | Anna Kelsey[4] | Ilaria Zanetti[5] | Gian Luca de Salvo[6] | Mark N. Gaze[7] | Ross J. Craigie[8] | Kieran McHugh[9] | Nadine Francotte[10] | Paola Collini[11] | Gianni Bisogno[12] | Michela Casanova[13] | Andrea Ferrari[13]

Original Research

Clinical features and outcomes of young patients with epithelioid sarcoma: an analysis from the Children's Oncology Group and the European paediatric soft tissue Sarcoma Study Group prospective clinical trials

Sheri L. Spunt [a,*], Nadine Francotte [b], Gian Luca De Salvo [c], Yueh-Yun Chi [d], Ilaria Zanetti [c], Andrea Hayes-Jordan [e], Simon C. Kao [a], Daniel Orbach [b], Bernadette Brennan [e], Aaron R. Weiss [f], Max M. van Noesel [g], Lynn Million [a], Rita Alaggio [h], David M. Parham [i], Anna Kelsey [e], R. Lor Randall [j], M. Beth McCarville [k], Gianni Bisogno [c], Douglas S. Hawkins [f], Andrea Ferrari [c]

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

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 [f], Gianni Bisogno [k], Sheri L. Spunt [f]

Original Research

Outcomes of metastatic non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) treated within the BERNIE study: a randomised, phase II study evaluating the addition of bevacizumab to chemotherapy

Andrea Ferrari [a,*], Johannes H.M. Merks [b,c], Julia C. Chisholm [d], Daniel Orbach [e], Bernadette Brennan [f], Soledad Gallego [g], Max M. van Noesel [b], Kieran McHugh [b], Rick R. van Rijn [b], Mark N. Gaze [i], Helene Martelli [j], Christophe Bergeron [k], Nadege Corradini [k], Veronique Minard-Colin [l], Gianni Bisogno [m], Birgit Geoerger [l], Hubert N. Caron [n], Gian Luca De Salvo [o], Michela Casanova [a]

Inflammatory myofibroblastic tumor: The experience of the European pediatric Soft Tissue Sarcoma Study Group (EpSSG)

Michela Casanova [a], Bernadette Brennan [b], Rita Alaggio [c], Anna Kelsey [d], Daniel Orbach [e], Max M. van Noesel [f], Nadege Corradini [g], Veronique Minard-Colin [h], Ilaria Zanetti [i], Gianni Bisogno [j], Soledad Gallego [j], Johannes H.M. Merks [f,k], Gian Luca De Salvo [l], Andrea Ferrari [a,*]

Articles

Paediatric non-rhabdomyosarcoma soft tissue sarcomas: the prospective NRSTS 2005 study by the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG)

Andrea Ferrari, Max M van Noesel, Bernadette Brennan, Ilaria Zanetti, Nadege Corradini, Michela Casanova, Pablo Berlanga, Johannes H M Merks, Rita Alaggio, Stefan Schifflers, Gema L Ramirez-Villar, Chiara Girardo, Gabriela Guillen Burrieza, Akmal Safwat, Gianni Bisogno, Gian Luca De Salvo, Daniel Orbach

Summary

Background A standardised approach to treatment of paediatric non-rhabdomyosarcoma soft tissue sarcomas (NRSTS), which account for about 4% of childhood cancers, is still lacking. We report the results of the NRSTS 2005 protocol developed specifically by the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) to determine a risk-adapted multimodal standard of care for this group of tumours.

Methods The EpSSG NRSTS 2005 study included two prospective, non-randomised, historically controlled trials (one on localised adult-type NRSTS and the other on localised synovial sarcoma) done at 100 academic centres and hospitals in 14 countries. Patients younger than 21 years with a pathologically proven diagnosis of synovial sarcoma or an adult-type NRSTS, no evidence of metastatic disease, no previous treatment other than primary surgery, and diagnostic specimens available for pathological review were included. Patients were stratified by surgical stage, tumour size, nodal involvement, tumour grade (for adult-type NRSTS), and tumour site (for synovial sarcoma). Patients were then divided into four treatment groups: surgery alone, adjuvant radiotherapy, adjuvant chemotherapy (with or without radiotherapy), or neoadjuvant chemotherapy (with or without radiotherapy). The main chemotherapy regimen was ifosfamide (3·0 g/m² intravenously per day for 3 days) plus doxorubicin (37·5 mg/m² intravenously per day for 2 days); only ifosfamide (3·0 g/m² intravenously per day for 2 days) was given concomitantly with radiotherapy (delivered with three-dimensional conformal external beam technique, using conventional fractionation [1·8 daily fractions, 5 days per week] at a dose of 50·4 Gy or 54·0 Gy, to a maximum of 59·4 Gy). The number of chemotherapy cycles ranged from three to seven depending on the stage of the disease. The primary outcomes were event-free survival and overall survival. This study has been completed, and is registered under EudraCT, 2005-001139-31.

Findings Between May 31, 2005, and Dec 31, 2016, 1321 patients were enrolled, of whom 569 (206 with synovial sarcoma and 363 with adult-type NRSTS), with a median age of 12·6 years (IQR 8·2–14·9), were included in this analysis. With a median follow-up of 80·0 months (IQR 54·3–111·3) for the 467 patients alive, 5-year event-free survival was 73·7% (95% CI 69·7–77·2) and 5-year overall survival was 83·8% (95% CI 80·3–86·7). 5-year event-free survival was 91·4% (95% CI 87·0–94·4) and 5-year overall survival was 98·1% (95% CI 95·0–99·3) in the surgery alone group (n=250); 75·5% (46·9–90·1) and 88·2% (60·6–96·9) in the adjuvant radiotherapy group (n=17); 65·6% (54·8–74·5) and 75·8% (65·3–83·5) in the adjuvant chemotherapy group (n=93); and 56·4% (49·3–63·0) and 70·4% (63·3–76·4) in the neoadjuvant chemotherapy group (n=209). Reported severe adverse events included one case of generalised seizures (probably related to ifosfamide) and six cases of secondary tumours.

Interpretation Findings from the EpSSG NRSTS 2005 study help to define the risk-adapted standard of care for this patient population. Adjuvant treatment can be safely omitted in the low-risk population (classified here as the surgery alone group). Improving the outcome for patients with high-risk, initially resected adult-type NRSTS and those with initially unresectable disease remains a major clinical challenge.

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Lancet Child Adolesc Health 2021

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A risk-based treatment strategy for non-rhabdomyosarcoma soft-tissue sarcomas in patients younger than 30 years (ARST0332): a Children's Oncology Group prospective study

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Summary

Background Tumour grade, tumour size, resection potential, and extent of disease affect outcome in paediatric non-rhabdomyosarcoma soft-tissue sarcoma (NRSTS), but no risk stratification systems exist and the standard of care is poorly defined. We developed a risk stratification system from known prognostic factors and assessed it in the context of risk-adapted therapy for young patients with NRSTS.

Methods In this prospective study, eligible patients enrolled in 159 hospitals in three countries were younger than 30 years, had a Lansky (patients ≤16 years) or Karnofsky (patients >16 years) performance status score of at least 50, and a new diagnosis of a WHO (2002 criteria) intermediate (rarely metastasising) or malignant soft-tissue tumour (apart from tumour types eligible for other Children's Oncology Group studies and tumours for which the therapy in this trial was deemed inappropriate), malignant peripheral nerve sheath tumour, non-metastatic and grossly resected dermatofibrosarcoma protuberans, undifferentiated embryonal sarcoma of the liver, or unclassified malignant soft-tissue sarcoma. Each patient was assigned to one of three risk groups and one of four treatment groups. Risk groups were: low (non-metastatic R0 or R1 low-grade, or ≤5 cm R1 high-grade tumour); intermediate (non-metastatic R0 or R1 >5 cm high-grade, or unresected tumour of any size or grade); or high (metastatic tumour). The treatment groups were surgery alone, radiotherapy (55·8 Gy), chemoradiotherapy (chemotherapy and 55·8 Gy radiotherapy), and neoadjuvant chemoradiotherapy (chemotherapy and 45 Gy radiotherapy, then surgery and radiotherapy boost based on margins with continued chemotherapy). Chemotherapy included six cycles of ifosfamide 3 g/m² per dose intravenously on days 1–3 and five cycles of doxorubicin 37·5 mg/m² per dose intravenously on days 1–2 every 3 weeks with sequence adjusted on the basis of timing of surgery or radiotherapy. The primary outcomes were event-free survival, overall survival, and the pattern of treatment failure. Analysis was done per protocol. This study has been completed and is registered with ClinicalTrials.gov, NCT00346164.

Findings Between Feb 5, 2007, and Feb 10, 2012, 550 eligible patients were enrolled, of whom 21 were treated in the incorrect group and excluded from this analysis. 529 evaluable patients were included in the analysis: low-risk (n=222), intermediate-risk (n=227), high-risk (n=80); surgery alone (n=205), radiotherapy (n=17), chemoradiotherapy (n=111), and neoadjuvant chemoradiotherapy (n=196). At a median follow-up of 6·5 years (IQR 4·9–7·9), 5-year event-free survival and overall survival were: 88·9% (95% CI 84·0–93·8) and 96·2% (93·2–99·2) in the low-risk group; 65·0% (58·2–71·8) and 79·2% (73·4–85·0) in the intermediate-risk group; and 21·2% (11·4–31·1) and 35·5% (23·6–47·4) in the high-risk group, respectively. Risk group predicted event-free survival and overall survival (p<0·0001). No deaths from toxic events during treatment were reported. Nine patients had unexpected grade 4 adverse events (chemoradiotherapy group, n=2; neoadjuvant chemoradiotherapy group, n=7), including three wound complications that required surgery (all in the neoadjuvant chemoradiotherapy group).

Interpretation Pre-treatment clinical features can be used to effectively define treatment failure risk and to stratify young patients with NRSTS for risk-adapted therapy. Most low-risk patients can be cured without adjuvant therapy, thereby avoiding known long-term treatment complications. Survival remains suboptimal for intermediate-risk and high-risk patients and novel therapies are needed.

Funding National Institutes of Health, St Baldrick's Foundation, Seattle Children's Foundation, American Lebanese Syrian Associated Charities.

Introduction

Long-term survival in childhood rhabdomyosarcoma improved from about 35% in the 1960s to nearly 70% by 2000.[1] This improvement was partly because of the

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Summary

Background A standardised approach to treatment of paediatric non-rhabdomyosarcoma soft tissue sarcomas (NRSTS), which account for about 4% of childhood cancers, is still lacking. We report the results of the NRSTS 2005 protocol developed specifically by the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) to determine a risk-adapted multimodal standard of care for this group of tumours.

Methods The EpSSG NRSTS 2005 study included two prospective, non-randomised, historically controlled trials (one on localised adult-type NRSTS and the other on localised synovial sarcoma) done at 100 academic centres and hospitals in 14 countries. Patients younger than 21 years with a pathologically proven diagnosis of synovial sarcoma or an adult-type NRSTS, no evidence of metastatic disease, no previous treatment other than primary surgery, and diagnostic specimens available for pathological review were included. Patients were stratified by surgical stage, tumour size, nodal involvement, tumour grade (for adult-type NRSTS), and tumour site (for synovial sarcoma). Patients were then divided into four treatment groups: surgery alone, adjuvant radiotherapy, adjuvant chemotherapy (with or without radiotherapy), or neoadjuvant chemotherapy (with or without radiotherapy). The main chemotherapy regimen was ifosfamide (3·0 g/m² intravenously per day for 3 days) plus doxorubicin (37·5 mg/m² intravenously per day for 2 days); only ifosfamide (3·0 g/m² intravenously per day for 2 days) was given concomitantly with radiotherapy (delivered with three-dimensional conformal external beam technique, using conventional fractionation [1·8 daily fractions, 5 days per week] at a dose of 50·4 Gy or 54·0 Gy, to a maximum of 59·4 Gy). The number of chemotherapy cycles ranged from three to seven depending on the stage of the disease. The primary outcomes were event-free survival and overall survival. This study has been completed, and is registered under EudraCT, 2005-001139-31.

Findings Between May 31, 2005, and Dec 31, 2016, 1321 patients were enrolled, of whom 569 (206 with synovial sarcoma and 363 with adult-type NRSTS), with a median age of 12·6 years (IQR 8·2–14·9), were included in this analysis. With a median follow-up of 80·0 months (IQR 54·3–111·3) for the 467 patients alive, 5-year event-free survival was 73·7% (95% CI 69·7–77·2) and 5-year overall survival was 83·8% (95% CI 80·3–86·7). 5-year event-free survival was 91·4% (95% CI 87·0–94·4) and 5-year overall survival was 98·1% (95% CI 95·0–99·3) in the surgery alone group (n=250); 75·5% (46·9–90·1) and 88·2% (60·6–96·9) in the adjuvant radiotherapy group (n=17); 65·6% (54·8–74·5) and 75·8% (65·3–83·5) in the adjuvant chemotherapy group (n=93); and 56·4% (49·3–63·0) and 70·4% (63·3–76·4) in the neoadjuvant chemotherapy group (n=209). Reported severe adverse events included one case of generalised seizures (probably related to ifosfamide) and six cases of secondary tumours.

Interpretation Findings from the EpSSG NRSTS 2005 study help to define the risk-adapted standard of care for this patient population. Adjuvant treatment can be safely omitted in the low-risk population (classified here as the surgery alone group). Improving the outcome for patients with high-risk, initially resected adult-type NRSTS and those with initially unresectable disease remains a major clinical challenge.

Funding Fondazione Città della Speranza.

Introduction

The tumours collectively known as non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) form a heterogeneous group of malignant extraskeletal mesenchymal neoplasms accounting for about 4% of childhood cancers. More than 50 distinct histological subtypes have been described, with biological and clinical characteristics varying from relatively benign to highly malignant. Although some NRSTS histotypes are specific to infants and young children (younger than 3 years), most are more common in adults and rare in children.[1] Given this rarity, data on the disease course and treatment of paediatric NRSTS remain scarce.[2–11] In the past, these tumours were managed with prolonged chemotherapy,

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See Online/Comment https://doi.org/10.1016/S2352-4642(21)00178-4

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Lancet Child Adolesc Health 2022

Controversies and challenges in the management of paediatric non-rhabdomyosarcoma soft tissue sarcomas

*Andrea Ferrari, Sheri L Spunt, Monika Sparber-Sauer, David O Walterhouse, Kristian W Pajtler, William H Meyer, Daniel Orbach, Aaron Weiss

European Journal of Cancer 169 (2022) 10–19

The treatment approach to pediatric non-rhabdomyosarcoma soft tissue sarcomas: a critical review from the INternational Soft Tissue SaRcoma ConsorTium

Andrea Ferrari [a,*], Daniel Orbach [b], Monika Sparber-Sauer [c,d], David O. Walterhouse [e], Kristian W. Pajtler [f,g,h], William H. Meyer [i], Sheri L. Spunt [j], Aaron R. Weiss [k]

Table 1
Main findings of the COG ARST0332 and the EpSSG NRSTS 2005 studies.

	COG ARST 0332 *Spunt SL, et al. Lancet Oncol.* 2020 Jan; 21(1):145-161	EpSSG NRSTS 2005 Ferrari A, *et al.* Lancet Child Adolesc Health. 2021 Aug; 5(8):546–558.
Study period	Feb 2007–Feb 2012	May 2005–Dec 2016
Participating centres	159 centres from 3 countries	100 centres in 14 countries
Inclusion criteria		
Age	<30 years	<21 years
Histotypes	Intermediate, rarely metastasising[a] and malignant tumours[b]	Malignant tumours including synovial sarcoma and 'adult-type' NRSTS[c]
Tumour stage	All stages	Localised disease (metastatic disease excluded)[d]
Treatment grouping		
Risk factors	Presence of metastases, surgical stage (IRS group), tumour grade (POG system), tumour size (≤ or >5 cm)	Surgical stage (IRS group), tumour grade (FNCLCC system), tumour size (≤ or >5 cm), nodal involvement, and (for synovial sarcoma) tumour site
Groups	1. Low-risk (1a. surgery alone, 1b. radiotherapy) 2. Intermediate-risk (2a. chemoradiotherapy, 2b. neoadjuvant chemoradiotherapy) 3. High-risk (3a. chemoradiotherapy, 3b. neo-adjuvant chemoradiotherapy)	1. Surgery alone 2. Adjuvant radiotherapy 3. Adjuvant chemotherapy (with or without radiotherapy) 4. Neoadjuvant chemotherapy (with or without radiotherapy)
Systemic therapy	Ifosfamide-doxorubicin chemotherapy and local treatment according to IRS group (radiotherapy mainly pre-operative)	Ifosfamide-doxorubicin chemotherapy and local treatment according to IRS group (radiotherapy mainly post-operative)
Results	529 evaluable patients	569 evaluable patients
Outcomes	5-year EFS 68.0%, 5-year 79.4% (including metastatic patients)	5-year EFS 73.7%, 5-year OS 83.8% (not including metastatic patients)
Main conclusions	• risk stratification system separated patients effectively into prognostic subgroups • Radiotherapy can be safely omitted in some low-risk clinical settings • A lower radiotherapy dose than is typically used produced high rates of local tumour control • Neoadjuvant dose-intensive ifosfamide plus doxorubicin chemotherapy combined with radiotherapy is feasible and produced a high proportion of delayed gross resection	• Adjuvant chemotherapy and radiotherapy can be safely omitted in low-risk NRSTS • The chances of investigating the role of adjuvant chemotherapy in preventing distant recurrences in patients with high-risk, initially-resected NRSTS were hindered by the limited sample size • Better results than in historical series for unresected cases; neo-adjuvant ifosfamide-doxorubicin chemotherapy improved the resectability

- the COG ARST0332 trial and the EpSSG NRSTS 2005 study represent the **benchmark** for this tumor group, and defines the risk-adapted standard of care

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REVIEW

Pediatric Non-Rhabdomyosarcoma Soft Tissue Sarcomas: Standard of Care and Treatment Recommendations from the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG)

Andrea Ferrari[1], Bernadette Brennan[2], Michela Casanova[1], Nadege Corradini[3], Pablo Berlanga[4], Reineke A Schoot[5], Gema L Ramirez-Villar[6], Akmal Safwat[7], Gabriela Guillen Burrieza[8], Patrizia Dall'Igna[9], Rita Alaggio[10], Lisa Lyngsie Hjalgrim[11], Susanne Andrea Gatz[12], Daniel Orbach[13], Max M van Noesel[5]

Table 2. A practical classification of the main pediatric NRSTS histotypes

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  - dermatofibrosarcoma protuberans
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  - desmoplastic small round cell tumor
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  - undifferentiated sarcoma of the liver
  - BCOR family / CIC-rearranged undifferentiated sarcomas
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Adult-type NRSTS

"definitely malignant soft tissue tumors occurring mainly in adult age and characterized by a closer morphological resemblance of differentiated/mature tissues and an uncertain response to chemotherapy"

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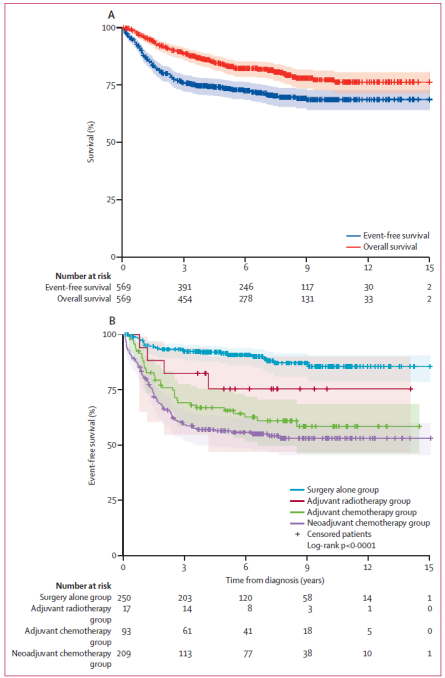
  - inflammatory myofibroblastic tumors
  - epithelioid hemangioendothelioma

Surgery alone group		
Synovial sarcoma	IRS group I, tumour size ≤5 cm	Initial resection only, no adjuvant treatment
Adult-type non-rhabdomyosarcoma soft tissue sarcomas	IRS group I, tumour size ≤5 cm, any tumour grade	
	IRS group I, tumour size >5 cm, tumour grade 1	
	IRS group II, any size tumour, tumour grade 1	
Adjuvant radiotherapy group		
Adult-type non-rhabdomyosarcoma soft tissue sarcomas	IRS group I, tumour size >5 cm, tumour grade 2	Radiotherapy 50·4 Gy
	IRS group II, tumour size ≤5 cm, tumour grade 2–3	Radiotherapy 54·0 Gy
	IRS group II, tumour size >5 cm, tumour grade 2	
Adjuvant chemotherapy group (with or without radiotherapy)		
Synovial sarcoma	IRS group I, tumour size >5 cm	I+D I+D I+D I+D
	IRS group II, tumour size ≤5 cm	I+D I+D I+D Radiotherapy 50·4 Gy
	IRS group II, tumour size >5 cm	I+D I+D I+D I I Radiotherapy 54·0 Gy I+D
	Axial site or resected N1	
Adult-type non-rhabdomyosarcoma soft tissue sarcomas	IRS group I–II, tumour size >5 cm, tumour grade 3 or resected N1	
Neoadjuvant chemotherapy group (with or without radiotherapy)		
Synovial sarcoma	IRS group III (unresected disease) or unresected N1	S I I I+D I+D I+D Radiotherapy 50·4–59·4 Gy I+D ± I+D
Adult-type non-rhabdomyosarcoma soft tissue sarcomas		

Paediatric non-rhabdomyosarcoma soft tissue sarcomas: the prospective NRSTS 2005 study by the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG)

Andrea Ferrari, Max M van Noesel, Bernadette Brennan, Ilaria Zanetti, Nadege Corradini, Michela Casanova, Pablo Berlanga, Johannes H M Merks, Rita Alaggio, Stefan Schifflers, Gema L Ramirez-Villar, Chiara Giraudo, Gabriela Guillen Burrieza, Akmal Safwat, Gianni Bisogno, Gian Luca De Salvo, Daniel Orbach



5-year EFS 73.7%
5-year OS 83.8%

OS 98.1%

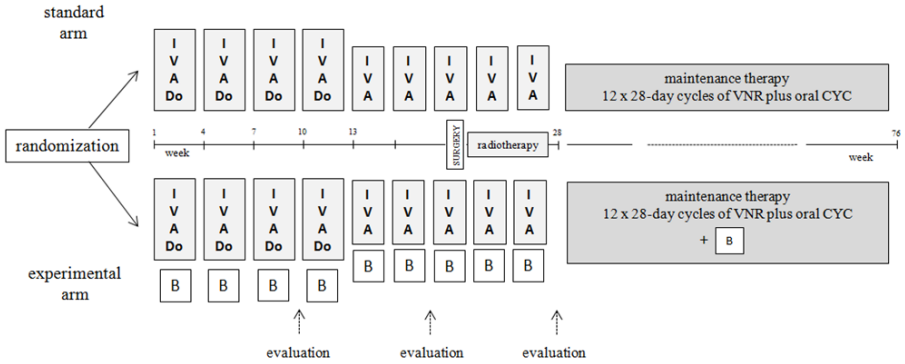
OS 70.4%

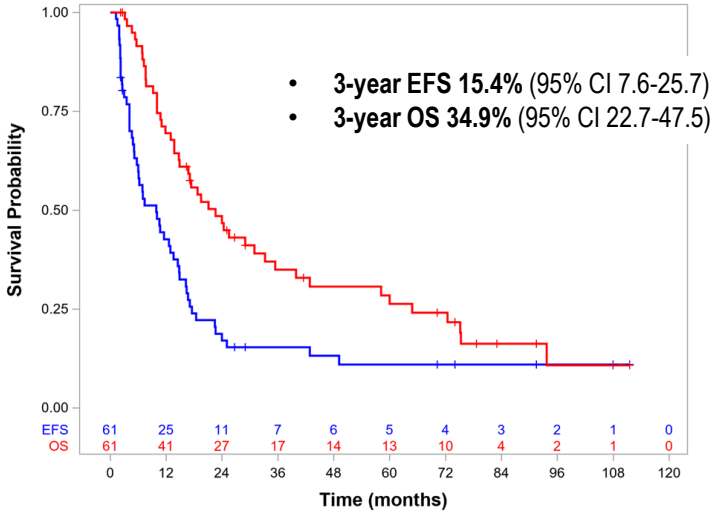
Received: 16 January 2023 | Revised: 1 March 2023 | Accepted: 22 March 2023
DOI: 10.1002/cncr.34814

ORIGINAL ARTICLE

Metastatic adult-type non-rhabdomyosarcoma soft tissue sarcomas in children and adolescents: A cohort study from the European paediatric Soft tissue sarcoma Study Group

Andrea Ferrari MD[1] | Daniel Orbach MD[2] | Michela Casanova MD[1] | Max M. van Noesel MD[3] | Pablo Berlanga MD[4] | Bernadette Brennan MD[5] | Nadege Corradini MD[6] | Reineke A. Schoot MD[3] | Gema L. Ramirez-Villar MD[7] | Lisa Lyngsie Hjalgrim MD[8] | Rita Alaggio MD[9] | Gabriela Guillen Burrieza MD[10] | Akmal Safwat MD[11] | Alison L. Cameron MD[12] | Rick R. van Rijn MD[13] | Veronique Minard-Colin MD[4] | Ilaria Zanetti BSc[14] | Gianni Bisogno MD[14,15] | Julia C. Chisholm MD[16] | Johannes H. M. Merks MD[3,17]





- **3-year EFS 15.4%** (95% CI 7.6-25.7)
- **3-year OS 34.9%** (95% CI 22.7-47.5)

European Journal of Cancer 169 (2022) 179–187

Adult-type non-rhabdomyosarcoma soft tissue sarcomas in pediatric age: Salvage rates and prognostic factors after relapse

Stefano Chiaravalli [a,1], Luca Bergamaschi [a,1], Virginia Livellara [a], Giovanna Sironi [a], Nadia Puma [a], Olga Nigro [a], Giovanna Gattuso [a], Roberto Luksch [a], Monica Terenziani [a], Filippo Spreafico [a], Cristina Meazza [a], Marta Podda [a], Veronica Biassoni [a], Elisabetta Schiavello [a], Carlo Morosi [b], Maura Massimino [a], Michela Casanova [a,2], Andrea Ferrari [a,*,2]

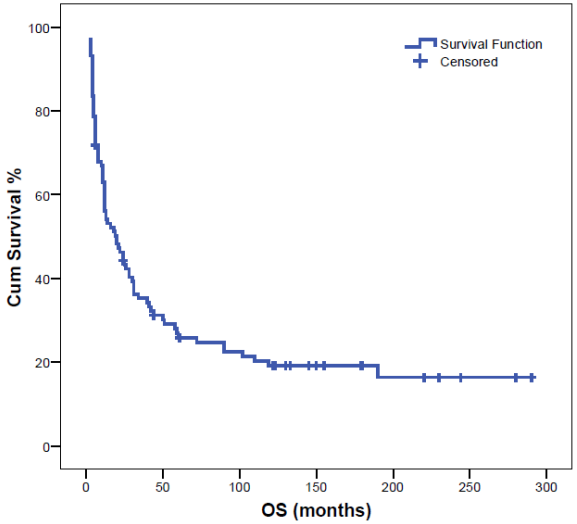


Fig. 1. Overall survival (OS) of the whole sample of patients with NRSTS after a first relapse.

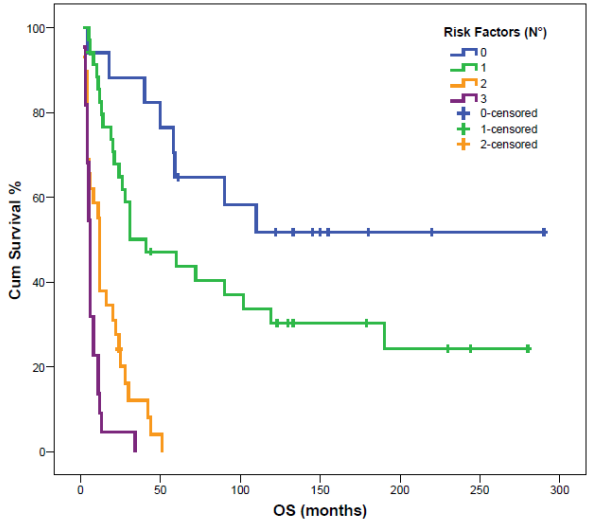


Fig. 2. Overall survival (OS) based on the number of patients' prognostic risk factors emerging from the multivariable analysis (type of relapse, time to relapse, and whether or not a secondary complete remission was achieved).

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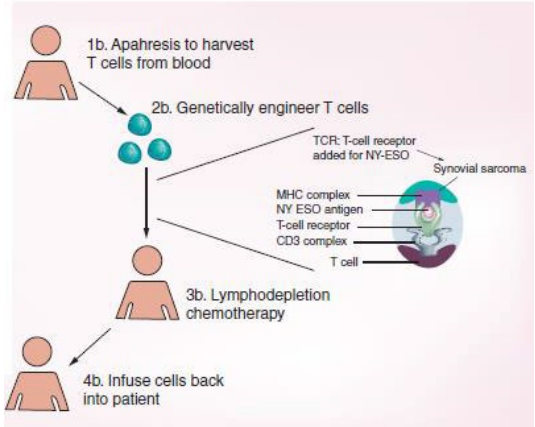
In press

Treatment at relapse for synovial sarcoma of children, adolescents and young adults: from the state of art to future clinical perspectives

Andrea Ferrari, MD1, Pablo Berlanga, MD, PhD2, Susanne Andrea Gatz, MD, PhD3, Reineke A. Schoot, MD, PhD4, Max M van Noesel, MD, PhD4,5, Shushan Hovsepyan, MD6, Stefano Chiaravalli, MD1, Luca Bergamaschi, MD1, Veronique Minard-Colin, MD, PhD2; Nadege Corradini, MD7, Rita Alaggio, MD8, Patrizia Gasparini, PhD9, Bernadette Brennan, MD10, Michela Casanova, MD1, Sandro Pasquali, MD, PhD11,12, Daniel Orbach, MD13

Adoptive immunotherapy with T-cell therapy (TCR-T cells) targeting cancer testis antigens (CTAs, i.e. NY-ESO-1, MAGE-A4, and PRAME



MAGE-A4 in synovial sarcoma (ADP-A2M4 SPEAR T, NCT04044768)
Proposed roadmap!

1. **Synovial sarcoma first relapse**
   - Phone call with treating physician, then with patient/gardians
   - Pre-screening performed remotely: buccal swab (HLA sample)
2. **If HLAA*02:01 positive (ca 40%)**
   - Archival/fresh tissue sent for MAGE-A4 analysis
3. **If HLA-A*A02:01, MAGE-A4+, relapse/progression (ca 20%)**
   - Confirmatory HLA blood sample prior to leukaferesis
   - Lymphodepleting chemotherapy + infusion (6 weeks)
4. **Patient back home**

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- ASPS - Targeted agents (sunitinib, cediranib, pazopanib, tivantinib or bevacizumab) in case of unresectable/metastatic disease. Promising data on immune checkpoint inhibitors (PD1/PDL1 inhibitors)
- CCS - Promising results with immunotherapy (PD1/PDL1 inhibitors)
- DFSPT - Imatinib

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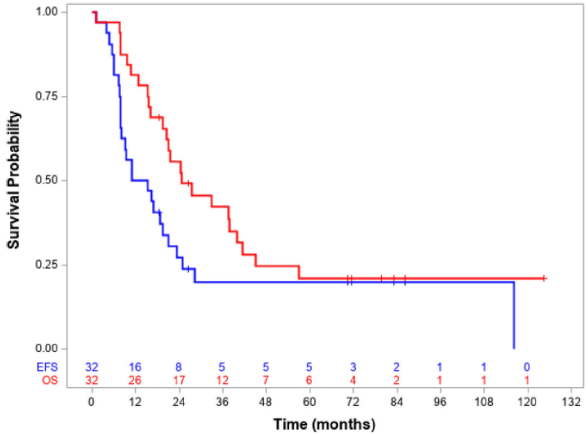
DOI: 10.1002/pbc.30447

Pediatric Blood & Cancer

RESEARCH ARTICLE

Intra-abdominal desmoplastic small round cell tumor: The European *pediatric* Soft tissue sarcoma Study Group (EpSSG) experience

Pablo Berlanga[1] | Daniel Orbach[2] | Reineke A. Schoot[3] | Michela Casanova[4] | Rita Alaggio[5] | Nadege Corradini[6] | Bernadette Brennan[7] | Gema L. Ramirez-Villar[8] | Lisa Lyngsie Hjalgrim[9] | Julia C. Chisholm[10] | Gianni Bisogno[11,12] | Beatrice Coppadoro[11] | Akmal Safwat[13] | Johannes H. M. Merks[3,14] | Gabriela Guillen Burrieza[15] | Max M. van Noesel[3,14] | Andrea Ferrari[4]



All patients	N	Failed	5-yr Survival (95%CI)
EFS	32	26	19.7 (7.9-35.5)
OS	32	24	21.0 (8.7-37.0)

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EXPERT REVIEW OF ANTICANCER THERAPY
https://doi.org/10.1080/14737140.2023.2200171

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REVIEW

Check for updates

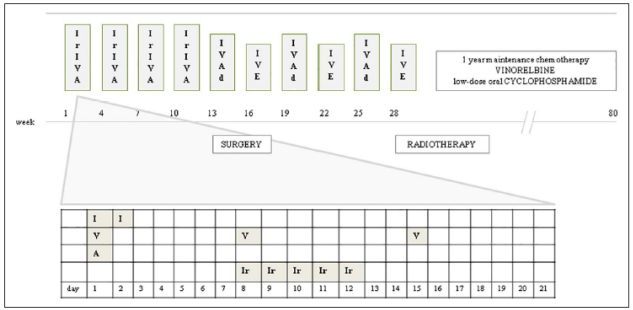
Desmoplastic small round cell tumor: from state of the art to future clinical prospects

Shushan Hovsepyan[a*], Claudia Giani[b*], Sandro Pasquali[c,d], Angela Di Giannatale[e], Stefano Chiaravalli[f], Chiara Colombo[d], Daniel Orbach[g], Luca Bergamaschi[c], Sabina Vennarini[h], Susanne Andrea Gatz[i], Patrizia Gasparini[j], Pablo Berlanga[k], Michela Casanova[f] and Andrea Ferrari[f]

TJ Tumori Journal

Multiagent chemotherapy including IrIVA regimen and maintenance therapy in the treatment of desmoplastic small round cell tumor

Andrea Ferrari[1], Luca Bergamaschi[1], Stefano Chiaravalli[1], Emilia Pecori[2], Barbara Diletto[2], Ombretta Alessandro[2], Tommaso Giandini[3], Livellara Virginia[1], Giovanna Sironi[1] and Michela Casanova[1]



JOURNAL OF CHEMOTHERAPY
https://doi.org/10.1080/1120009X.2022.2067706

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BRIEF COMMUNICATION

Check for updates

Trabectedin-irinotecan, a potentially promising combination in relapsed desmoplastic small round cell tumor: report of two cases

Andrea Ferrari[a], Stefano Chiaravalli[a], Luca Bergamaschi[a], Olga Nigro[a], Virginia Livellara[a], Giovanna Sironi[a], Patrizia Gasparini[b], Sandro Pasquali[c,d], Nadia Zaffaroni[c], Silvia Stacchiotti[e], Carlo Morosi[f], Maura Massimino[a] and Michela Casanova[a]

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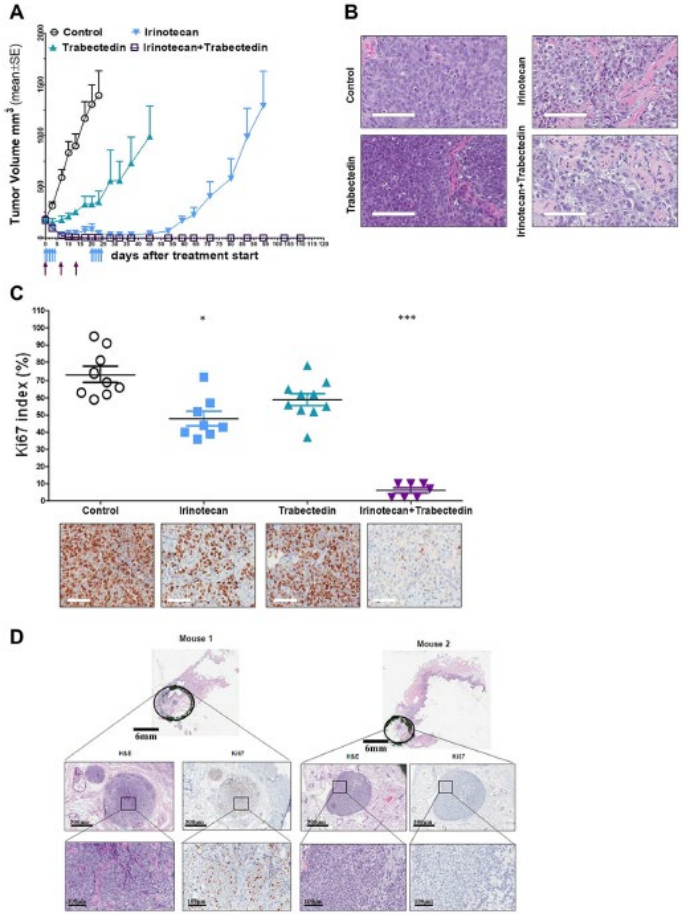
The Company of Biologists

RESEARCH ARTICLE

Effectiveness of irinotecan plus trabectedin on a desmoplastic small round cell tumor patient-derived xenograft

Valentina Zuco[1,*], Sandro Pasquali[1,2,*], Monica Tortoreto[1], Stefano Percio[1], Valentina Doldi[1], Marta Barisella[3], Paola Collini[3], Gian Paolo Dagrada[3], Silvia Brich[3], Patrizia Gasparini[4], Marco Fiore[2], Michela Casanova[5], Anna Maria Frezza[6], Alessandro Gronchi[2], Silvia Stacchiotti[6,*], Andrea Ferrari[5,*] and Nadia Zaffaroni[1,*,‡]



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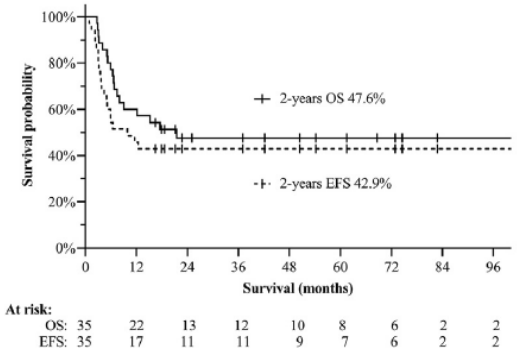
European Journal of Cancer 161 (2022) 64–78

Extracranial rhabdoid tumours: Results of a SFCE series of patients treated with a dose compression strategy according to European Paediatric Soft tissue sarcoma Study Group recommendations

Maxime Enault [a,b], Véronique Minard-Colin [c], Nadège Corradini [d], Guy Leverger [e], Estelle Thebaud [f], Angélique Rome [g], Stéphanie Proust [h], Aude Marie-Cardine [i], Anne-Sophie Defachelles [j], Sabine Sarnacki [k], Pascale Philippe-Chomette [l], Olivier Delattre [b,m], Julien Masliah-Planchon [n], Brigitte Lacour [o], Andrea Ferrari [p], Bernadette Brennan [q], Daniel Orbach [b], Franck Bourdeaut [b,r,*]



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REVIEW

Pediatric Non-Rhabdomyosarcoma Soft Tissue Sarcomas: Standard of Care and Treatment Recommendations from the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG)

Andrea Ferrari[1], Bernadette Brennan[2], Michela Casanova[1], Nadege Corradini[3], Pablo Berlanga[4], Reineke A Schoot[5], Gema L Ramirez-Villar[6], Akmal Safwat[7], Gabriela Guillen Burrieza[8], Patrizia Dall'Igna[9], Rita Alaggio[10], Lisa Lyngsie Hjalgrim[11], Susanne Andrea Gatz[12], Daniel Orbach[13], Max M van Noesel[5]

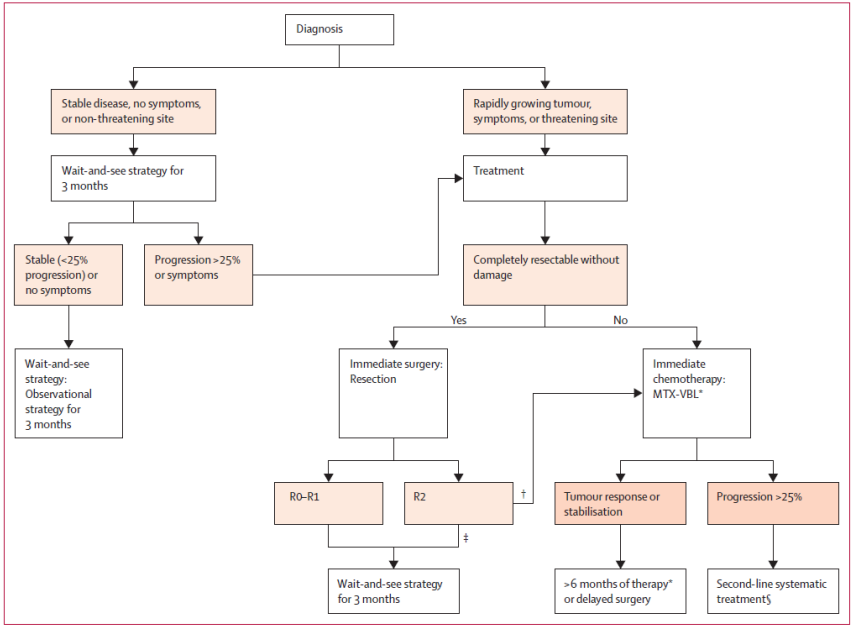
Table 2. A practical classification of the main pediatric NRSTS histotypes

- Adult-type NRSTS requiring the same therapeutic approach
  - synovial sarcoma
  - malignant peripheral nerve sheath tumor
  - adult-type fibrosarcoma
  - epithelioid sarcoma
  - leiomyosarcoma
  - liposarcoma
  - angiosarcoma
  - undifferentiated high-grade pleomorphic sarcoma
- Adult-type NRSTS requiring a specific therapeutic approach
  - alveolar soft part sarcoma
  - clear cell sarcoma
  - dermatofibrosarcoma protuberans
- Malignant soft tissue tumors requiring a specific therapeutic approach
  - rhabdoid tumor
  - desmoplastic small round cell tumor
  - undifferentiated soft part sarcoma
  - undifferentiated sarcoma of the liver
  - BCOR family / CIC-rearranged undifferentiated sarcomas
- Soft tissue tumors of intermediate malignancy requiring specific therapeutic approaches
  - desmoid-type fibromatosis
  - infantile fibrosarcoma
  - inflammatory myofibroblastic tumors
  - epithelioid hemangioendothelioma

Lancet Child Adolesc Health
2017; 1: 284–92

The EpSSG NRSTS 2005 treatment protocol for desmoid-type fibromatosis in children: an international prospective case series

Daniel Orbach, Bernadette Brennan, Gianni Bisogno, Max Van Noesel, Véronique Minard-Colin, Julia Daragjati, Michela Casanova, Nadege Corradini, Ilaria Zanetti, Gian Luca De Salvo, Anne Sophie Defachelles, Anna Kelsey, Myriam Ben Arush, Nadine Francotte, Andrea Ferrari



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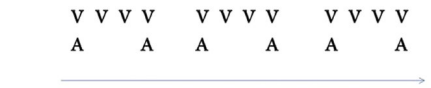
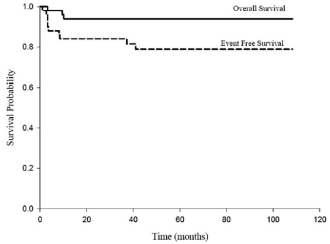
Original research

Conservative strategy in infantile fibrosarcoma is possible: The European paediatric Soft tissue sarcoma Study Group experience

Daniel Orbach [a,*], Bernadette Brennan [b], Angela De Paoli [c], Soledad Gallego [d], Peter Mudry [e], Nadine Francotte [f], Max van Noesel [g], Anna Kelsey [h], Rita Alaggio [i], Dominique Ranchère [j], Gian Luca De Salvo [c], Michela Casanova [k], Christophe Bergeron [l], Johannes H.M. Merks [m], Meriel Jenney [n], Michael C.G. Stevens [o], Gianni Bisogno [p], Andrea Ferrari [k]





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European Journal of Cancer 127 (2020) 123–129

Inflammatory myofibroblastic tumor: The experience of the European pediatric Soft Tissue Sarcoma Study Group (EpSSG)

Michela Casanova [a], Bernadette Brennan [b], Rita Alaggio [c], Anna Kelsey [d], Daniel Orbach [e], Max M. van Noesel [f], Nadege Corradini [g], Veronique Minard-Colin [h], Ilaria Zanetti [i], Gianni Bisogno [i], Soledad Gallego [j], Johannes H.M. Merks [f,k], Gian Luca De Salvo [l], Andrea Ferrari [a,*]

Original research

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BJC British Journal of Cancer
www.nature.com/bjc

PERSPECTIVE

Rationale for the use of tyrosine kinase inhibitors in the treatment of paediatric desmoid-type fibromatosis

Monika Sparber-Sauer[1], Daniel Orbach[2], Fariba Navid[3], Simone Hettmer[4], Stephen Skapek[5,6], Nadège Corradini[7], Michela Casanova[8], Aaron Weiss[9], Matthias Schwab[10,11] and Andrea Ferrari[8]

Contents lists available at ScienceDirect

Current Problems in Cancer

journal homepage: www.elsevier.com/locate/cpcancer

Inflammatory myofibroblastic tumor: molecular landscape, targeted therapeutics, and remaining challenges

Priya Mahajan[a], Michela Casanova[b], Andrea Ferrari[b], Ashleigh Fordham[c], Toby Trahair[c,d,e], Rajkumar Venkatramani[a,*]

Current Perspective

European Journal of Cancer 137 (2020) 183–192

Spotlight on the treatment of infantile fibrosarcoma in the era of neurotrophic tropomyosin receptor kinase inhibitors: International consensus and remaining controversies

Daniel Orbach [a,*,1], Monika Sparber-Sauer [b,1], Theodore W. Laetsch [c], Veronique Minard-Colin [d], Stefan S. Bielack [b,e], Michela Casanova [f], Nadege Corradini [g], Ewa Koscielniak [b,h], Monika Scheer [b], Simone Hettmer [i], Gianni Bisogno [j], Douglas S. Hawkins [k], Andrea Ferrari [f]

TRK inhibitors

Potency(IC50, nM)	Crizotinib Xalorki®	Entrectinib Rozlytrek®	Larotrectinib Vitrakvi®	Repotrectinib
≤ 10	HGFR (c-Met)	TRK, ROS1	TRK	TRK, ROS1, ALK
11-100	ALK	ALK, JAK2, ACK1		
101-1000	TRK, RON, AXL, TIE2	JAK1, IGF1R, FAK, FLT3, BRK, IR, AUR2, JAK3, RET	TNK2	

- **Larotrectinib** FDA approval 2018 and 2019 EMA; all age; capsule, liquide
- **Entrectinib** FDA 2019 and Japan 2019 ; ≥ 12 years ; capsule

Zarrinkar. Blood. 2009. Menichincheri. J Med Chem. 2016. Zou. Cancer Res. 2007. Doebele. Cancer Discovery. 2015.

Overall, conventional conservative strategies before the era of targeted therapy, even in the case of extensive tumours, demonstrate efficacy in IFS, but are associated with acute and some chronic side effects.
TRKI have demonstrated very rapid responses in the vast majority of children with IFS with limited acute toxicity (but with few available data on long-term toxicity).

With the current state of our knowledge, both conventional chemotherapy and TRKI should be regarded as options for patients with localized disease at the physician's and parent's discretion.
TRKI should be considered in patients with metastatic disease, and before mutilating surgery when conventional chemotherapy fails.
Outside a clinical trial, additional data are needed to resolve the lack of consensus about front-line use of conventional chemotherapy versus TRKI in patients with localised disease.

Current Perspective

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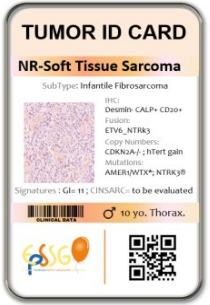
Association
EpSSG
European Paediatric Soft Tissue Sarcoma Study Group

THE NEXT GENERATION
STARFLEET
UNITED FEDERATION OF PLANETS
Star Trek

MYCKIDS: Molecular Identification and Characterization of non-Rhabdomyosarcoma Soft Tissue Sarcoma in Kids, Adolescents and Young Adults: an EpSSG NRSTS study

International sponsorship: Prinses Máxima Center, Utrecht

PI's: M van Noesel, D Orbach, A Ferrari



- to lead to an integrated diagnosis, and a comprehensive understanding of the treatment options for a given patient
- to characterize as yet unknown or unclassified sarcomas using whole-exome sequencing (WES), mRNA sequencing (mRNAseq), and DNA methylation profiling
- to identify novel translocations and genetic drivers
- to identify new, reproducible molecular signatures for predicting outcome and refine risk stratification (in particular, the predictive role of chromosomal instability, assessed with a genomic index or a more complex biological signature known as CINSARC
- other working packages within the MYKIDS study focus on liquid biopsy, the development of faithful tumor models such as organoids, and post-treatment molecular changes.

MYKIDS
EpSSG-non-rhabdomyosarcoma soft tissue sarcoma study
Molecular identification and characterization of tissues

Work packages	Material	Number of cases	Investigations	Coordinators
WP1	Fresh frozen tissue or DNA & RNA	200	WES mRNAseq DNAmeth	Prinses Máxima Center, Utrecht, Netherlands *Bas Tops, Michael Meister*
WP2	FFPE-paraffin embedded tissue	250	GI vs CINSARC vs grading	Centre Léon Bérard, Lyon, France *Franck Tirod, Marie Karanian*
WP3	Fresh viable tissue	30	organoids	Prinses Máxima Center, Utrecht, Netherlands *Bas Tops, Michael Meister*
WP4	Blood plasma	100	liquid biopsies	Royal Marsden, Sutton, UK *Janet Shipley*
WP5	FFPE Posttreatment tissue	40	WES mRNAseq DNAmeth	OPBG Roma + Padova, Italia *Rita Alaggio, Giuseppe Maria Milano*

REACH

(**RE**gorafenib in young adults, **A**dolescents and **C**hildren with **H**igh-risk non-rhabdomyosarcoma soft tissue sarcoma)

Andrea Ferrari, Michela Casanova, Reineke Shoot, Pablo Berlanga,
Max M van Noesel, Daniel Orbach, Bernadette Brennan, Susanne Gatz

Statisticians: Piers Gaunt & Laura Kirton

Trial question:

Can addition of **Regorafenib** to standard Ifosfamide-Doxorubicine chemotherapy improve outcome in children, adolescents and young adults with high-risk NRSTS?