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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]

[1]Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy

[2]SIREDO Oncology Center, Institut Curie, PSL University, Paris, France

[3]Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands

[4]Department of Pediatric and Adolescent Oncology, Gustave-Roussy, Cancer Campus, Université Paris-Saclay, Villejuif, France

[5]Pediatric Oncology, Royal Manchester Children's Hospital, Manchester, UK

[6]Department of Pediatric Oncology, Institut d'Hematologie et d'Oncologie Pédiatrique,/Centre Léon Bérard, Lyon, France

[7]Pediatric Oncology Unit, Hospital Universitario Virgen del Rocío, Sevilla, Spain

[8]Department of Pediatrics and Adolescent Medicine, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

[9]Pathology Department, Ospedale Pediatrico Bambino Gesù IRCCS, Rome, Italy

[10]Surgical Oncology and Neonatal Surgery, Pediatric Surgery Department, Hospital Infantil Universitari Vall d'Hebron, Barcelona, Spain

[11]Oncology Department and Danish Center for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark

[12]Bristol Haematology and Oncology Centre, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK

[13]Department of Radiology and Nuclear Medicine, UMC University of Amsterdam, Amsterdam, Netherlands

[14]Pediatric Hematology Oncology Division, University Hospital of Padua, Padua, Italy

[15]Department of Women's and Children's Health, University of Padua, Padua, Italy

[16]Children and Young People's Unit, The Royal Marsden Hospital and Institute of Cancer Research, Sutton, UK

[17]Division of Imaging and Oncology, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

Correspondence
Andrea Ferrari, Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori Via G. Venezian, Milano, MI 1 20133, Italy.
Email: andrea.ferrari@istitutotumori.mi.it

Abstract

Background: Limited data exist on the clinical behavior of pediatric non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) with distant metastases at onset, and a clear standard of care has not yet been defined.

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Methods: This cohort study reports on pediatric adult-type metastatic NRSTS enrolled in two concurrent prospective European studies, i.e., the randomized BERNIE study and the single-arm MTS 2008 study developed by the European paediatric Soft tissue sarcoma Study Group. Treatment programs were originally designed for patients with metastatic rhabdomyosarcoma, i.e., nine courses of multidrug chemotherapy (with or without bevacizumab in the BERNIE study), followed by 12 cycles of maintenance therapy, whereas radiotherapy and/or surgery (on primary tumor and/or metastases) were delayed until after seven courses of chemotherapy had been administered.

Results: The study included 61 patients <21 years old treated from July 2008 to December 2016. The lung was the site of metastases in 75% of the cases. All patients received multi-agent chemotherapy, 44% had local therapy to primary tumor, and 18% had treatment of metastases. Median time to progression/relapse was 6 months. A high rate of tumor progression was observed during the initial part of the chemotherapy program. With a median follow-up of 41.5 months (range, 2–111 months), 3-year event-free survival and overall survival were 15.4% (95% confidence interval [CI], 7.6–25.7) and 34.9% (95% CI, 22.7–47.5), respectively. There were no statistically significant differences in outcome depending on the type of treatment administered.

Conclusions: The study confirmed the overall poor outcome for patients with metastatic NRSTS, whose treatment remains a challenge.

Plain Language Summary

- Pediatric non-rhabdomyosarcoma soft tissue sarcomas form a heterogeneous group of rare tumors.
- Although recent international studies have defined the standard of care for patients with localized disease, limited data are available on the clinical behavior of patients with distant metastases.
- This study on 61 metastatic cases treated on two prospective European protocols confirms that the chances of survival of such patients are often dismal and a standard treatment is still lacking.

KEYWORDS
adolescents, children, metastases, non-rhabdomyosarcoma soft tissue sarcomas, outcome, prognostic factors, treatment

INTRODUCTION

Pediatric non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) form a heterogeneous group of extra skeletal mesenchymal malignancies, many of which are more common in adults and very rare in children.[1] The definition of NRSTS generally includes several different histological subtypes whose clinical behavior may vary from relatively benign to highly malignant.[2,3]

Tailored, risk-adapted multimodal therapies have been used in two recent large cooperative efforts, the ARST0332 study (ClinicalTrials.gov identifier: NCT00346164)[4] conducted by the Children's Oncology Group (COG) and the NRSTS 2005 study (EUDRACT, 2005-001139-31) conducted by the European paediatric Soft tissue sarcoma Study Group (EpSSG).[5] These two studies were able to define the standard of care for patients with localized NRSTS.[6] The reported outcome for patients with nonmetastatic disease was similar in the two trials, the 5-year event-free survival (EFS) and overall survival (OS) rates being respectively 76.5% and 87.4% in the COG study,[4] and 73.7% and 83.8% in the EpSSG study.[5]

The prognosis for NRSTS patients is influenced by several variables (such as histotype and grade, tumor size, and extent of surgical resection).[7–12] The presence of distant metastases at onset is the most important prognostic factor, however, and results in a dismal outcome.[9,13,14] Very limited data are available on the clinical behavior of metastatic NRSTS.[13,14] The COG's ARST0332 study was a nonrandomized phase 3 study conducted between 2007 and 2012,

recruiting 529 evaluable patients less than 30 years old. It included a subgroup of 80 patients with metastatic NRSTS (15% of the whole series), with a reported 5-year OS of 35.5%.[4]

Within the EpSSG framework, patients with metastatic NRSTS were included in the BERNIE study or the concurrent MTS 2008 study. The BERNIE study (BO20924/ITCC-006; ClinicalTrials.gov identifier: NCT00643565) was developed by the EpSSG in cooperation with the European Innovative Therapies for Children with Cancer (ITCC) Consortium, and it was sponsored by Roche. The study was conducted between July 2008 and October 2013 at a limited number of EpSSG centers. It was an open-label, multicenter, phase 2 study aiming to evaluate the randomized addition of bevacizumab—a monoclonal antibody against vascular endothelial growth factor (VEGF)—to the conventional intensive multi-drug chemotherapy used to treat rhabdomyosarcoma (RMS). Both RMS and NRSTS patients were included. The main results of the BERNIE study have already been published, showing that EFS did not benefit from adding bevacizumab.[15,16]

Because the BERNIE study only involved a limited number of centers and had stringent inclusion/exclusion criteria, the single-arm EpSSG MTS 2008 study (ClinicalTrials.gov identifier: NCT00379457)—using the same chemotherapy backbone as the BERNIE study, but without bevacizumab—was started to obtain data on patients with metastatic NRSTS and RMS who did not enter the BERNIE study. The study was conducted from June 2010 to December 2016.

This study reports the treatment and outcomes of patients with adult-type NRSTS metastatic at onset, treated within the BERNIE or concurrent MTS 2008 studies.

MATERIALS AND METHODS

Study design and participants

This cohort study included patients enrolled in two different EpSSG trials. The inclusion criteria were: age from 6 months to 18 years for BERNIE, and <21 years for MTS 2008; no more than 8 weeks elapsing between diagnostic surgery/biopsy and the start of chemotherapy; no previous treatment (chemotherapy and/or radiotherapy) other than initial surgery; details available on clinical condition, treatment modalities, and outcome; and written consent to enrollment in the present study. Both studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and all participating centers obtained approval from their local administrations and ethics committees.

Only patients with a diagnosis of adult-type NRSTS were selected for the present analysis. The term "adult-type NRSTS" identified "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".[9] This definition, which was used in the EpSSG NRSTS 2005 study as well, aimed to identify a relatively homogeneous group of histological subtypes, excluding small round-cell tumors (e.g., desmoplastic small round-cell tumor or extraosseous Ewing sarcoma), tumors typical of young children (e.g., rhabdoid tumor, infantile fibrosarcoma), and tumors of intermediate malignancy (e.g., hemangioendothelioma or myofibroblastic tumors). The list included synovial sarcoma, malignant peripheral nerve sheath tumor (MPNST), liposarcoma, epithelioid sarcoma, leiomyosarcoma, adult-type fibrosarcoma, myxoid chondrosarcoma, clear-cell sarcoma, alveolar soft part sarcoma, angiosarcoma, and malignant fibrous histiocytoma (or what is now called undifferentiated pleomorphic sarcoma [UPS]). Patients with undifferentiated sarcoma and "not otherwise specified" (NOS) sarcoma were also included. Histological diagnoses were based on local pathologists' diagnoses; then national and/or international pathology panels reviewed all cases.

Treatment

In the BERNIE study, patients were randomized 1:1, and the experimental arm was given bevacizumab whereas the control arm was not. The control arm received induction chemotherapy, maintenance therapy and local treatment. Induction therapy included nine courses of chemotherapy given every 21 days, i.e., four consecutive courses of the IVADo regimen (ifosfamide, 3 g/m^2 on days 1 and 2; vincristine, 1.5 mg/m^2 [max 2 mg] weekly during the first 7 weeks, then on day 1 of each cycle; actinomycin-D, 1.5 mg/m^2 [max 2 mg] on day 1; and doxorubicin, 30 mg/m^2 on days 1 and 2), followed by five courses of the IVA regimen (ifosfamide, vincristine and actinomycin-D, given at the same doses as IVADo). Maintenance therapy included 12 28-day cycles of intravenous vinorelbine (25 mg/m^2 on days 1, 8, and 15 of each cycle), and low-dose cyclophosphamide (25 mg/m^2 orally every day), for a total duration of 18 months of chemotherapy.[15,16] Surgery to the primary tumor was indicated, if feasible without mutilation and with the expectation of an R0/R1 resection, after the seventh cycle of chemotherapy had been administered. The indication for resecting metastases was at the physician's discretion. It was suggested that radiotherapy to the primary tumor start concomitantly with cycle 7 or 8 of chemotherapy. For NRSTS, doses ranged from 50.4 to 59.4 Gy. Radiotherapy to all metastatic sites was recommended, if feasible. Multidisciplinary discussion and individual tailored approaches were suggested because the site, number, and size of metastases varied from one patient to another.

In the experimental arm, bevacizumab was given intravenously at doses of 7.5 mg/kg every 3 weeks on day 1 of each cycle during the induction phase and 5.0 mg/kg every 2 weeks (on days 1 and 15 of each cycle) in the maintenance phase. The protocol established how to synchronize bevacizumab and local therapy: a time window of 4 weeks after bevacizumab administration was required for both surgery and radiotherapy.[15]

In the MTS 2008 study, the chemotherapy protocol was the same as for the control arm of the BERNIE study.[17]

Response to chemotherapy was assessed after three cycles of chemotherapy, according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.0.[18]

Statistical methods

The primary aim of the BERNIE study was to test the efficacy of adding bevacizumab to standard chemotherapy (the primary end point was EFS); the main results already have been published.[15]

For the present analysis, differences in the distribution of clinical characteristics by group were investigated with χ^2 tests or Fisher's exact test (depending on the frequencies). Survival probabilities were estimated using the Kaplan–Meier method and the log-rank test. EFS was defined as the time elapsing between diagnosis and disease progression, recurrence, refusal of therapy, or death due to any cause. OS was defined as the time elapsing from the date of diagnosis up to death for any reason. Patients still alive at the end of the study or lost to follow-up were censored, in both the EFS and the OS analyses, at the date of latest observation. Five-year EFS and OS rates with 95% confidence intervals (CIs) were calculated using the Greenwood method. All prognostic factors were considered for their effect on EFS and OS using Cox's univariable models to assess hazard ratios (HRs) throughout the follow-up. A p value of less than .05 was considered significant.

To better examine the impact of local treatment (on both primary tumors and metastases) and maintenance chemotherapy, a landmark analysis[19] was used to adjust for the fact that some diseases progressed before any local treatment or maintenance chemotherapy had been administered. The analysis only included patients who were alive without progression on day 221, which was the scheduled end of cycle 9 plus a 1-month grace period. Patients who had an event before day 221 were excluded.

Data collected as at September 10, 2022 were analyzed with the SAS statistical packages (version 9.4).

RESULTS

The study cohort included a total of 61 cases, 35 from the BERNIE study, and 26 from the MTS 2008 study. Supplementary Figure 1 shows the study flow diagram. Table 1 gives the clinical characteristics of the series. The median age of the whole cohort was 13 years (interquartile range, 1.9–20.2). Undifferentiated soft tissue sarcoma (14 cases) and MPNST (10 cases, five with neurofibromatosis type 1) were the most frequent histotypes, followed by synovial sarcoma, alveolar soft part sarcoma, epithelioid sarcoma, and NOS sarcoma (six cases each).

The most frequent site of distant metastases was the lung, which was involved in 46 cases (75%): the lung alone in 25, plus other metastases in 21. Bone metastases were reported in 14 cases.

Table 2 shows the treatments administered. Induction chemotherapy consisted of IVADo-IVA in 43 cases. Instead of the recommended treatment, 16 patients received ifosfamide-doxorubicin for seven courses, as given for high-risk localized NRSTS in the EpSSG NRSTS 2005 protocol.[5] Maintenance chemotherapy with vinorelbine and low-dose cyclophosphamide for 12 cycles was given to 17 of 61 patients (28%); 31 patients (51%) had disease progression before starting maintenance therapy. Table 2 also shows patients' response to chemotherapy (after three cycles). The overall objective response rate was 35% (two complete and 15 partial responses out of 48 evaluable cases): 38% for patients who received IVADo-IVA, and 31% for those given ifosfamide-doxorubicin. Calculated by histological subtype, the objective response rate was 54% in patients with undifferentiated soft tissue sarcoma, 25% in those with MPNST, and 35% in those with other histotypes.

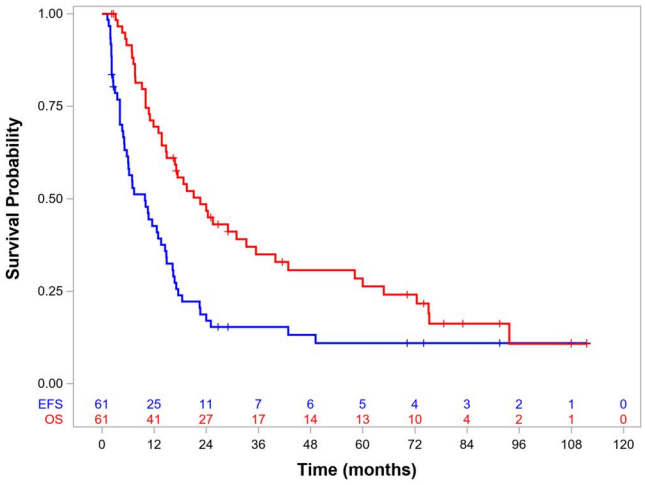

FIGURE 1 For the whole cohort, the 3-year EFS and OS rates were 15.4% (95% CI, 7.6–25.7) and 34.9% (95% CI, 22.7–47.5), respectively. CI indicates confidence interval; EFS, event-free survival; OS, overall survival.

Local therapy consisted of surgical resection of the primary tumor in seven cases, definitive radiotherapy in 12, and surgery plus radiotherapy in eight cases. No local treatment was administered in 34 cases (56%), and this was due to early disease progression in 23 of them.

Metastases were treated in 11 cases (18%), involving radiotherapy in three patients, surgery in five patients, and both surgery and radiotherapy in three patients. Five of these 11 patients had lung metastases alone, six had metastases to the lung and other sites. No treatment of metastases was performed in 50 cases (82%), and this was due to early disease progression in 28 of them.

Outcome

Overall, 52 of 61 patients (85%) had an event, which was tumor progression in 40 cases (local in four, metastatic in four, both in eight, unspecified in 24), and relapse in 12 (local in three, metastatic in seven, both in one, unspecified in one). Time to progression/relapse ranged from 1 to 49 months, median 6 months. In 31 cases (51%), tumor progression occurred before day 221.

At latest follow-up, 15 patients were alive and 46 had died. The median follow-up for patients still alive was 41.5 months, with a range of 2–111 months. For the whole series, the 3-year EFS and OS rates were 15.4% (95% CI, 7.6–25.7) and 34.9% (95% CI, 22.7–47.5), respectively (Figure 1).

TABLE 1 Patients distribution by clinical characteristics.

	MTS 2008, No. (%), *n* = 26	BERNIE, No. (%), *n* = 35	Total, No. (%) *n* = 61
Age at diagnosis, years			
<15	20 (76.9)	20 (57.1)	40 (65.6)
≥15	6 (23.1)	15 (42.9)	21 (34.4)
Median age in years (range)	12.0 (1.9–20.2)	14.0 (2.0–17.7)	13.0 (1.9–20.2)
Gender			
Male	17 (65.4)	16 (45.7)	33 (54.1)
Female	9 (34.6)	19 (54.3)	28 (45.9)
Histology			
Alveolar soft part sarcoma	2 (7.7)	4 (11.4)	6 (9.8)
Angiosarcoma	3 (11.5)	1 (2.9)	4 (6.6)
Clear cell sarcoma	2 (7.7)	2 (5.7)	4 (6.6)
Epithelioid sarcoma	5 (19.2)	1 (2.9)	6 (9.8)
Adult-type fibrosarcoma	—	1 (2.9)	1 (1.6)
Leiomyosarcoma	—	1 (2.9)	1 (1.6)
MPNST	1 (3.9)	9 (25.7)	10 (16.4)
Myxoid chondrosarcoma	1 (3.9)	1 (2.9)	2 (3.3)
UPS	—	1 (2.9)	1 (1.6)
Sarcoma NOS	3 (11.5)	3 (8.6)	6 (9.8)
Synovial sarcoma	4 (15.4)	2 (5.7)	6 (9.8)
Undifferentiated soft tissue sarcoma	5 (19.2)	9 (25.7)	14 (23.0)
Primary tumor site			
Head-neck region	2 (7.7)	2 (5.7)	4 (6.6)
Superficial trunk	4 (15.4)	6 (17.1)	10 (16.4)
Intra-abdominal	6 (23.1)	8 (22.9)	14 (23.0)
Extremities	14 (53.9)	18 (51.4)	32 (52.5)
Unknown	-	1 (2.9)	1 (1.6)
Tumor size			
a: ≤5 cm	5 (19.2)	NA	
b: >5 cm	21 (80.8)		
Loco-regional N			
N0	13 (50.0)	29 (82.9)	42 (68.9)
N1	9 (34.6)	6 (17.1)	15 (24.6)
N unspecified	4 (15.4)	—	4 (6.6)
Metastases			
No. of metastatic sites			
Single site	15 (57.7)	19 (54.3)	34 (55.7)
Multiple sites	11 (42.3)	16 (45.7)	27 (44.3)
Metastatic sites			
Lung metastases	21 (80.8)	25 (71.4)	46 (75.4)
Alone	13 (61.9)	12 (48.0)	25 (54.3)

TABLE 1 (Continued)

	MTS 2008, No. (%), $n = 26$	BERNIE, No. (%), $n = 35$	Total, No. (%) $n = 61$
With other metastases	8 (38.1)	13 (52.0)	21 (45.7)
Pleural metastases	2 (7.7)	4 (11.4)	6 (9.8)
Alone	–	–	–
With other metastases	2 (100)	4 (100)	6 (100)
Bone metastases	4 (15.4)	10 (28.6)	14 (23.0)
Alone	1 (25.0)	2 (20.0)	3 (21.4)
With other metastases	3 (75.0)	8 (80.0)	11 (78.6)
Bone marrow metastases	–	1 (2.9)	1 (1.6)
Alone	–	–	–
With other metastases	–	1 (100)	1 (100)
Liver metastases	2 (7.7)	5 (14.3)	7 (11.5)
Alone	1 (50.0)	–	1 (14.3)
With other metastases	1 (50.0)	5 (100)	6 (85.7)
Peritoneal metastases	3 (11.5)	4 (14.3)	7 (11.5)
Alone	–	1 (25.0)	1 (14.3)
With other metastases	3 (100)	3 (75.0)	6 (85.7)
Subcutaneous metastases	1 (3.8)	–	1 (1.6)
Alone	–	–	–
With other metastases	1 (100.0)		1 (100)
Distant N metastases	6 (23.1)	6 (17.1)	12 (19.7)
Alone	–	3 (50.0)	3 (25.0)
With other metastases	6 (100)	3 (50.0)	9 (75.0)

Abbreviations: MPNST, malignant peripheral nerve sheath tumor; N, lymph nodes; NA, not available; NOS, not otherwise specified; UPS, undifferentiated pleomorphic sarcoma.

Table 3 gives the results of the univariable analysis with the different clinical variables. Histological subtype correlated with EFS but not with OS, which was not influenced by any of the clinical variables considered. In particular, no statistically significant differences emerged by number of metastatic sites, or for patients with lung metastases alone versus those with other sites of metastases as well.

Table 4 shows the survival rates by type of treatment administered (i.e., chemotherapy, local therapy to primary tumor, and treatment of metastases). No statistically significant differences in outcome by type of treatment were observed.

DISCUSSION

The present analysis pooled patients enrolled in two concurrent prospective European studies on pediatric metastatic soft tissue sarcomas (the BERNIE and the EpSSG MTS 2008 study) to describe a relatively large series of children and adolescents with adult-type NRSTS with metastases at diagnosis.

This series of 61 cases is comparable with the subgroup of 80 metastatic patients enrolled in the COG ARST0332 study. The histological subtypes included in the COG series were almost the same as those included in the EpSSG cohort, but the upper age limits were 30 years in the former and 21 years in the latter. The survival rates were similar, with 3-year EFS and OS of 15.4% and 34.9%, respectively, in the EpSSG series, and 5-year EFS and OS of 21.2% and 35.5%, respectively, in the COG cohort.[4] Taken together, these two series may represent the reference for this disease category and serve as the starting point for developing future dedicated investigational trials.

In our series, undifferentiated soft tissue sarcoma and MPNST are the most frequent histotypes, followed by alveolar soft part sarcoma and epithelioid sarcoma (together with synovial sarcoma). The pattern of histologic subtypes differed from that generally observed in localized NRSTS.[5] This is related to the different biologic aggressiveness of the different specific histotypes (i.e., the diverse occurrence of initial metastatic disease in each histologic category).

Our study confirmed that the outcome of metastatic NRSTS is often—but not always—dismal. Our analysis found no clinical

TABLE 2 Systemic and local treatment administered.

	MTS2008, No. (%), *N* = 26	Bernie, No. (%), *N* = 35	Total, No. (%), *N* = 61
Systemic treatment			
4 IVADo + 5 IVA + bevacizumab	—	11 (31.4)	11 (18.0)
4 IVADo + 5 IVA + maintenance + bevacizumab	—	7 (20.0)	7 (11.5)
4 IVADo + 5 IVA	4 (15.4)	14 (40.0)	18 (29.5)
4 IVADo + 5 IVA + maintenance	4 (15.4)	3 (8.6)	7 (11.5)
Ifosfamide-doxorubicin	13 (50.0)	—	13 (21.3)
Ifosfamide-doxorubicin + maintenance	3 (11.5)	—	3 (4.9)
Other regimens[a]	2 (7.7)	—	2 (3.3)
Response to systemic treatment			
Complete response	2 (7.7)	—	2 (3.3)
Partial response	6 (23.1)	9 (25.7)	15 (24.6)
Stable disease	8 (30.8)	16 (45.7)	24 (39.3)
Progressive disease	5 (19.2)	2 (5.7)	7 (11.5)
Unable to assess	5 (19.2)	4 (11.4)	9 (14.8)
Missing data	—	4 (11.4)	4 (6.5)
Local treatment on primary tumor			
Radiotherapy only	8 (30.8)	4 (11.4)	12 (19.7)
Surgery only	2 (7.7)	5 (14.3)	7 (11.5)
Surgery and radiotherapy	6 (23.1)	2 (5.7)	8 (13.1)
No treatment on primary tumor	10 (38.5)	24 (68.6)	34 (55.7)
Treatment on metastases			
Radiotherapy	1 (3.8)	2 (5.7)	3 (4.9)
Surgery	2 (7.7)	3 (8.6)	5 (8.2)
Surgery and radiotherapy	2 (7.7)	1 (2.9)	3 (4.9)
No treatment on metastases	21 (80.8)	29 (82.9)	50 (82.0)

Abbreviations: IVA, ifosfamide, vincristine and actinomycin-D; IVADo, ifosfamide, vincristine, actinomycin-D, and doxorubicin.

[a]One patient received six cycles of ifosfamide, and one patient received chemotherapy according to Ewing sarcoma protocol (vincristine, ifosfamide, doxorubicin alternated to cyclophosphamide, etoposide).

characteristics (other than metastatic disease) correlating with OS, and no statistically significant differences in outcome depending on the treatment administered.

The chances of identifying prognostic variables were limited by the nature of our cohort, the relatively small sample size (reflecting the rarity of metastatic NRSTS in pediatric age) and marked heterogeneity, with mixed histotypes and very few cases in each histological category. Another limitation of the study was the lack of genomic analyses to better characterize the group of soft tissue sarcomas classified here as undifferentiated. In the present sample, these undifferentiated soft tissue sarcomas accounted for 23% of patients, who showed a better response to chemotherapy and had a better EFS.

These limitations make it difficult to draw any conclusions on the potential role of different types of treatment, such as maintenance chemotherapy or local therapy. The treatment of metastatic NRSTS remains a major challenge, and a clear standard of care has yet to be established. Similarly, in the adult population, a demonstration that multi-agent chemotherapy is superior in survival terms to single-agent doxorubicin is still lacking (although higher response rates and a longer progression-free survival have been reported).[20,21] Because many histotypes show a limited sensitivity to medical treatments, experts on metastatic adult sarcoma tend to focus mainly on aggressive surgery and radiotherapy for both the primary tumor and metastatic sites.[22]

Given the lack of dedicated protocols or even a standard of care for pediatric patients with metastatic NRSTS, the BERNIE and EpSSG MTS 2008 studies recommended a treatment program based on the one for metastatic RMS. This included nine courses of intensive multidrug chemotherapy, followed by the maintenance therapy used in EpSSG RMS trials,[23] for a total duration of 18 months. Radiotherapy and/or surgery (to the primary tumor or metastases) were

TABLE 3 Univariate analyses considering the different clinical variables.

	No.	Failed	3-year EFS (95% CI)	*p*	Deaths	3-year OS (95% CI)	*p*
All patients	61	52	15.4 (7.6–25.7)	—	46	34.9 (22.7–47.5)	—
Age at diagnosis, years							
<15	40	34	15.5 (6.3-28.4)	.6602	30	36.3 (21.2-51.6)	.4187
≥15	21	18	15.2 (3.8-33.9)		16	33.0 (13.8-53.7)	
Histology							
MPNST	10	8	20.0 (3.1-47.5)	.0278	8	20.0 (3.1-47.5)	.5166
Undifferentiated soft tissue sarcomas	14	7	41.7 (15.2–66.5)		7	41.7 (15.2–66.5)	
Other histology	37	37	5.4 (1.0–15.9)		31	37.6 (21.8–53.4)	
Tumor primary site[a]							
Intra-abdominal	14	11	28.6 (8.8–52.4)	.1559	11	25.7 (6.7–50.6)	.4958
Extremity	32	30	6.5 (1.2–18.8)		25	42.9 (24.9–59.7)	
Trunk and head-neck	14	11	15.4 (2.5–38.8)		10	23.1 (5.6–47.5)	
No. of metastatic sites							
Single	34	29	15.3 (5.6–29.4)	.1816	26	38.2 (21.8–54.5)	.7315
Multiple	27	23	15.5 (4.9–31.6)		20	29.7 (12.8–48.8)	
Lung metastases							
Only lung metastases	26	23	15.4 (4.8–31.5)	.5168	20	40.6 (21.6–58.8)	.3400
All other metastases	35	29	15.4 (5.6–29.6)		26	30.1 (15.0–46.7)	

Abbreviations: CI, confidence interval; EFS, event-free survival; MPNST, malignant peripheral nerve sheath tumor; OS, overall survival.
[a]One patient with unknown tumor primary site was excluded.

delayed until after seven courses of chemotherapy had been administered to enable an adequate dose intensity of chemotherapy during the first cycles. The fact that this treatment was originally designed for RMS patients reflects the decision often made by local physicians to adopt the ifosfamide-doxorubicin regimen generally used for children and adolescents with advanced adult-type NRSTS.[5]

The different induction chemotherapy regimens or the treatments' duration made no apparent difference to the outcomes. The results of treatment in our patients given nine courses of IVADo-IVA and 1 year of maintenance therapy were very similar to those seen in the COG ARST0332 study after seven courses of chemotherapy altogether (four courses of ifosfamide-doxorubicin, two courses of ifosfamide alone, and one course of doxorubicin alone).[4]

Local treatment represents a major challenge in the treatment of patients with metastatic NRSTS. Tumors progressed before day 221 (the scheduled end of cycle 9 plus a 1-month grace period) in half of the patients in our series. The type of tumor progression was not collected for many patients. This represented a limitation of our study and limited the possibility to compare our data to the COG ARST0332 experience, that showed more frequent metastatic progression (alone or in combination with local progression) rather than local progression alone.[4] However, the decision to postpone local treatment until after the seventh cycle of chemotherapy might at least partly account for this high number of early progressions. It is noteworthy that 56% of patients had no local treatment on their primary tumor (usually due to early disease progression), and metastases were treated locally in only 18% of cases. Similarly, in the COG ARST0332 study, only 22% of patients with metastatic NRSTS underwent gross resection of the primary tumor and metastases.[4]

Further investigations are needed on the role of local therapies to the primary tumor and/or metastases to ascertain the best timing, modality, and aggressiveness of these treatments, which might differ from those established for RMS. An interesting comparison may be drawn between the metastatic NRSTS cohort discussed here and the group of patients with metastatic RMS treated using the same protocol in the BERNIE and the EpSSG MTS 2008 studies.[17] The median time to progression was 6 months for NRSTS and 11.5 months for RMS. Tumor progression during treatment occurred in 66% of NRSTS patients and 46% of those with RMS. In the RMS series, 78% of patients received radiotherapy to the primary tumor and 33% had radiotherapy to metastatic sites.[17] These different findings are likely to correlate with the different sensitivity to chemotherapy of NRSTS and RMS and might support the argument for local therapy to be delivered earlier in patients with NRSTS.

Radiotherapy is becoming increasingly important in adult soft tissue sarcomas, particularly in the treatment of patients with low-volume metastatic disease. Adult patients with metastatic soft tissue sarcomas have a poor prognosis overall, but there is evidence of local therapy—including surgery, ablation, embolization, and

TABLE 4 Survival rates according to administered treatment.

	No.	Failed	3-year EFS (95% CI)	*p*	Deaths	3-year OS (95% CI)	*p*
All patients	61	52	13.7 (6.4–23.7)	—	46	34.9 (22.7–47.5)	—
Protocol							
Bernie study	35	27	21.7 (9.6–36.9)	.3320	22	36.4 (19.9–53.2)	.7229
MTS 2008 study	26	25	7.7 (1.3–21.7)		24	34.6 (17.5–52.5)	
Local treatment on primary tumor (Landmark analysis)							
No treatment	9	7	33.3 (7.8–62.3)	.5738	6	41.7 (10.9–70.8)	.6530
Surgery and/or RXT	21	16	28.6 (11.7–48.2)		13	58.4 (33.3–76.8)	
Treatment on metastases (Landmark analysis)							
No treatment	20	16	30.0 (12.3–50.1)	.8678	13	57.4 (32.2–76.1)	.4887
Surgery and/or RXT	10	7	30.0 (7.1–57.8)		6	50.0 (18.4–75.3)	
Chemotherapy regimen							
Ifosfamide-doxorubicin	16	16	0	.2026	16	25.0 (7.8–47.2)	.2737
IVADo-IVA	25	20	22.3 (8.2–40.7)		17	37.5 (18.2–56.8)	
IVADo-IVA + bevacizumab	18	14	22.2 (6.9–42.9)		11	40.7 (17.4–63.1)	
Maintenance chemotherapy (Landmark analysis)							
No maintenance	13	11	23.1 (5.6–47.6)	.4191	10	49.5 (19.5–73.8)	.1949
Yes maintenance	17	12	35.3 (14.5–57.0)		9	55.7 (28.6–76.1)	
Response to systemic treatment							
CR/PR	17	12	31.4 (11.4–53.8)	.1460	11	55.6 (28.6–75.9)	.2125
SD	24	22	8.8 (1.5–24.5)		19	32.8 (14.8–52.1)	

Abbreviations: CI, confidence interval; CR, complete response; EFS, event-free survival; IVA, ifosfamide, vincristine and actinomycin-D; IVADo, ifosfamide, vincristine, actinomycin-D and doxorubicin; MPNST, malignant peripheral nerve sheath tumor; OS, overall survival; PR, partial response; RXT, radiotherapy; SD, stable disease.

radiotherapy—improving progression-free survival and possibly also overall outcome.[24,25] Stereotactic body radiation therapy (SBRT), for example, could be an alternative to pulmonary metastasectomy and may improve survival in selected patients.[26–29] Interesting findings have been published on SBRT in pediatric patients.[30]

As already described, in contrast to the policy generally adopted in adult sarcoma, a high percentage of patients in our studies received no local treatment to the primary tumor (56%) and metastases (82%). We believe that an earlier and more rigorous application of local treatment to primary tumor and metastases should be considered in future studies to potentially improve survival.

Novel agents are needed for children and adolescents with metastatic NRSTS that can effectively target the multiple signaling pathways involved in tumorigenesis across NRSTS subtypes and might enhance the efficacy of conventional cytotoxic chemotherapy.

The BERNIE study did not show any significant benefit of adding an anti-VEGF antibody to standard chemotherapy.[16] Pediatric sarcoma experts should nonetheless make every effort to include NRSTS with a poor prognosis in specific clinical trials. Given the difficulties of developing dedicated early-phase trials and accessing new targeted agents for the pediatric sarcoma population, more intense cooperation with the adult sarcoma community is needed. This could prove a key step toward enabling children and adolescents to benefit from agents that have already proved effective in adult patients.[31,32]

Although some might suggest including adolescents with NRSTS in clinical trials on adult patients,[33] the ultimate goal should be to conduct shared clinical trials for children, adolescents and adults with the same type of disease. Age limits should be abandoned, and the only criterion should be that a patient be fit enough to be given the therapy under study. An example is the COG ARST1321 trial on pediatric and adult NRSTS patients (conducted from 2014 to 2018), in which pazopanib was added to the standard treatment with ifosfamide-doxorubicin chemotherapy. Although the near-complete pathological response rate was significantly higher with the addition of pazopanib,[12] patient outcomes did not differ significantly between the experimental and control arms of the study.[34]

Alongside efforts to establish a stronger cooperation with the adult sarcoma community, the EpSSG is currently developing a program to complete the systematic molecular and epigenetic characterization of NRSTS cases called the MYKIDS (molecular identification and characterization of non-rhabdomyosarcoma soft tissue sarcoma in kids, adolescents and young adults) study.[6] A more sophisticated understanding of tumor biology and an effective

integration between histological diagnosis and molecular characterization will lead to better diagnosis and better treatment strategies, with the identification of new biomarkers and molecular-based NRSTS stratification and the identification of molecular alterations as targets for novel therapies.

AUTHOR CONTRIBUTIONS

Andrea Ferrari: Conceptualization, study design, literature search, data analysis, and writing–original draft. **Daniel Orbach:** Literature search. **Michela Casanova:** Conceptualization and study design. **Max M. van Noesel:** Literature search. **Pablo Berlanga:** Literature search. **Ilaria Zanetti:** Data analysis. **Gianni Bisogno:** Data analysis. **Julia C. Chisholm:** Conceptualization and study design. **Johannes H. M. Merks:** Conceptualization, study design, data analysis, and writing–original draft. All the authors made substantial contributions to data collection, data interpretation, editing, and final approval. Andrea Ferrari, Ilaria Zanetti, Julia C. Chisholm, and Johannes H. M. Merks had full access to the raw data and were responsible for the decision to submit the present article for publication on behalf of the European paediatric Soft tissue sarcoma Study Group board members. The corresponding author confirms that all authors have seen and approved the final text.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data on individual participants are not publicly available because this requirement was not anticipated in the study protocol. The study protocols can be requested through the European paediatric Soft tissue sarcoma Study Group website (https://www.epssgassociation.it/en/).

ORCID

Andrea Ferrari https://orcid.org/0000-0002-4724-0517
Daniel Orbach https://orcid.org/0000-0002-2520-139X
Veronique Minard-Colin https://orcid.org/0000-0002-0296-5207
Gianni Bisogno https://orcid.org/0000-0003-4462-5523

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SUPPORTING INFORMATION

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

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