ANNUAL REPORT 2022

The European Paediatric Soft tissue sarcoma Study Group

INDEX

THE EpSSG ASSOCIATION

The European Paediatric Soft tissue sarcoma Study Group (EpSSG) is an international organisation for professionals devoted to the care and treatment of children and young people with cancers known as soft tissue sarcoma (STS). This includes the most common STS, rhabdomyosarcoma (RMS), and a wide range of other cancers known collectively, as Non Rhabdomyosarcoma or Adult-type Soft Tissue Sarcomas (NRSTS).

The legal entity for EpSSG activities is the EpSSG Association. This exists to promote and manage clinical trials, encourage and facilitate clinical and basic science research, foster optimal standards of care, organise educational meetings for its members and other professionals, and advocate for patients with STS.

It collaborates with other similar groups in Europe, North America and elsewhere.

EpSSG has its administrative and legal home in Padua, Italy. An elected board manages it, and its membership is open, by application, to professionals who have an interest in the research or treatment of these diseases when they occur in children, teenagers and young adults.

This report summarises the main EpSSG activities for 2022. Importantly, we have had the opportunity since 2016, to welcome parents of sarcoma patients to collaborate with us and support the development of our activities.

Further information is available on the EpSSG website: www.epssgassociation.it

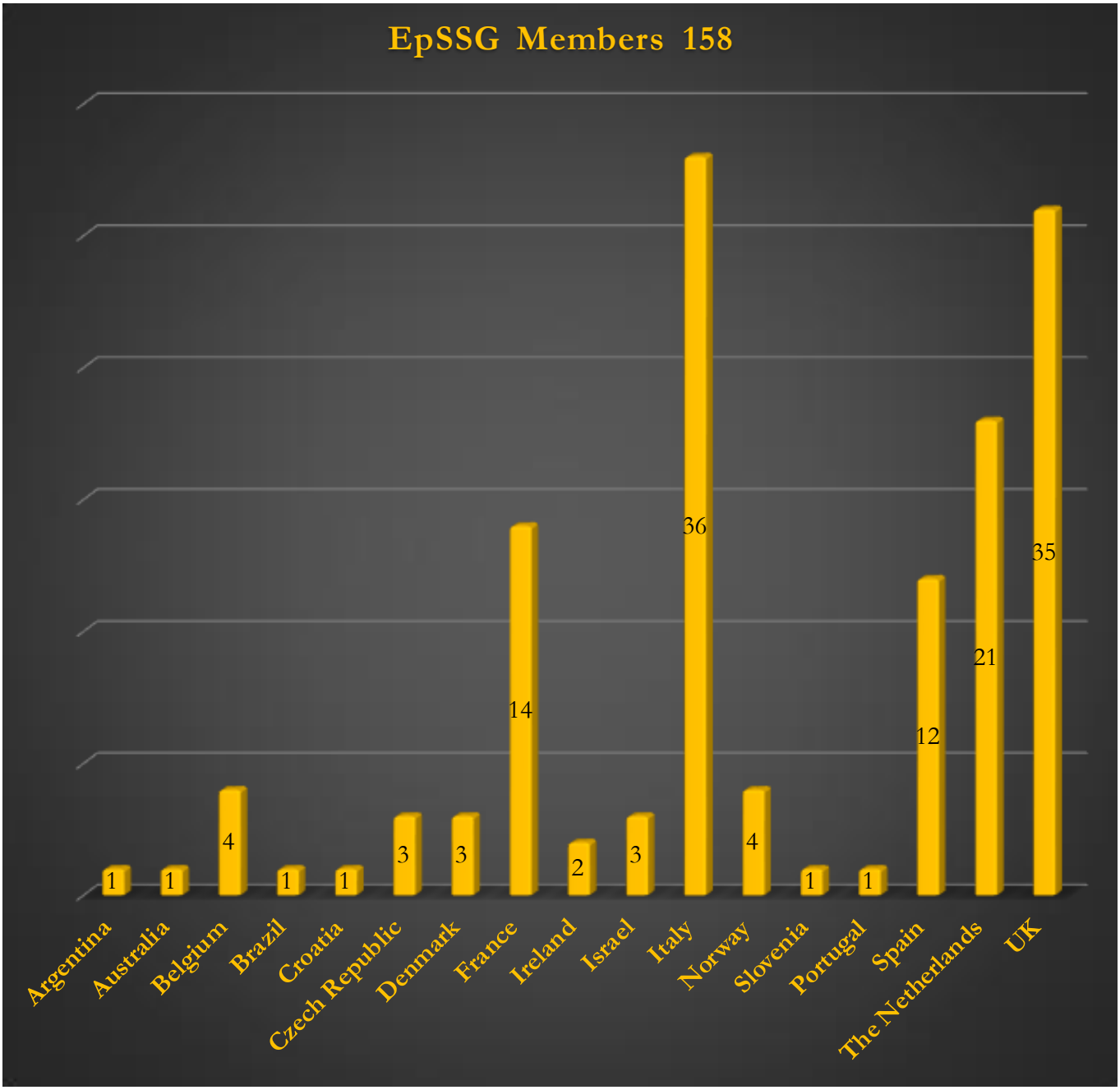
EpSSG BOARD

Prof. Hans Merks	• Chairman - Utrecht, The Netherlands
Dr. Timothy Rogers	• Treasurer, Bristol, UK
Prof. Veronique Minard-Colin	• Paris, France
Dr. Michela Casanova	• Milan, Italy
Dr. Henry Mandeville	• Sutton, UK
Dr. Andrea Ferrari	• Milan. Italy
Dr. Gabriela Guillén Burrieza	• Barcelona, Spain
Dr. Nadège Corradini	• Lyon, France
Dr. Lisa Hjalgrim	• Copenhagen, Denmark

Board meetings were mostly held virtually in 2022 each second Monday of the month: January 10th , February 14th, March 9th , April 11th , May 9th , June 21st , September 12nd , October 13th and November 14th . The board has organized meetings with Discipline Panel Committees in order to be updated on the work of Committees. In particular the meetings were organized in March 23rd-25th and in September 12-23 and October 13th.

EpSSG MEMBERSHIP

EpSSG members represent mostly: Italy, UK, The Netherlands, France, Spain, Portugal, Belgium, Ireland, Denmark, Norway, Czech Republic, Croatia, Slovenia, Israel, Argentina, Brazil, Greece, Australia and Iran**.** In 2022, there were 158 individual members of the EpSSG from 20 different countries comparing to last year that we had 144 members. These two years we welcomed new members from Iran, UK, and Greece.


EpSSG Members 158
1
1
4
1
1
3
3
14
2
3
36
4
1
1
12
21
35
Argentina
Australia
Belgium
Brazil
Croatia
Czech Republic
Denmark
France
Ireland
Israel
Italy
Norway
Slovenia
Portugal
Spain
The Netherlands
UK

EpSSG COMMITTEES

Chair

Biology	Prof. Beat Schaefer, Zürich, Switzerland
Pathology	Dr. Rita Alaggio, Rome, Italy
Radiology	Prof. Rick R. van Rijn, Amsterdam, The Netherlands
Surgery	Dr. Sheila Terwisscha van Scheltinga, Utrecht, The Netherlands
Radiotherapy	Dr. Raquel Davila Fajardo, Utrecht, The Netherlands
Phase I/II trials	Dr. Susanne Gatz, Birmingham, UK

EpSSG MEETINGS 2022

The Spring meeting in 2022 was organized virtually because of the COVID Pandemic during the 3rd Annual Meeting of SIOP Europe. In particular EpSSG had joint meetings with ExPERT group, Cooperative Weichteilsarkom Study (CWS-german group) and the Innovative Therapies for Children with Cancer in Europe (ITCC group).

In addition, we had a very successful EpSSG Winter meeting which took place finally live in Rome on 1st and 2nd of December, 2022 supported by Bambino Gesù Hospital Rome. It was hosted by Dr. Giuseppe Maria Milano. During this meeting we had outstanding presentations from clinicians, biologists and parents.

The discipline panel groups for biology, radiotherapy, NRSTS TMC, surgery, pathology, phase I/II, and radiology, met separately in the week leading to the main meeting.

Almost, 130 delegates from all over Europe and across the Atlantic were present in Rome for the EpSSG Winter meeting.

THE NEW FRONTLINE AND RELAPSE STUDY IN RHABDOMYOSARCOMA

(BY PROF. MERIEL JENNEY AND DR. JULIA CHISHOLM on behalf of the CRCTU team)

Trial Update March 2023

An overarching study for children and adults with Frontline and Relapsed RhabdoMyoSarcoma

The FaR-RMS trial is an overarching trial for all patients with newly diagnosed and relapsed paediatric-type rhabdomyosarcoma and is open to patients of all ages. The trial has an innovative multi-arm, multi-stage design that allows the testing of new combinations of therapy in upfront and relapsed settings in phase Ib, phase II and phase III.

The trial has now been open for over two years. It is recruiting well and we are pleased to announce the relapse research question opened in March 2022, funded by Bayer.

We are delighted that there is wide international interest, and that in the last year, several new countries have opened the trial. The current recruiting countries are:

Country	Number of open sites
Australia	11
Czech Republic	1
Denmark	2
France	9
Greece	8
Ireland	0
Israel	6
Netherlands	2
New Zealand	2
Norway	5
Slovenia	1
Spain	10
Switzerland	10
United Kingdom	25

Countries still in set-up since last update:
Austria, Belgium, Canada, Croatia, Germany, Italy, Portugal, Slovakia, Sweden.

Map of Open and Set-up Countries

Phase 1b Dose Escalation Study

To find the dose of irinotecan in combination with ifosfamide, vincristine and actinomycin-D. This question is open at ITCC and early phase approved centres.

14 patients have been recruited to Phase 1b.

The study is currently recruiting at dose level 3.

Induction Chemotherapy (CT1a/b)

The CT1 randomisations will open at all participating centres, upon completion of the Phase 1b question. These questions will compare the determined dose of irinotecan in combination with ifosfamide, vincristine and actinomycin-D, against the current standard of care for patients with High Risk and Very High Risk disease.

Radiotherapy (RT1a/b/c, RT2)

All sites delivering radiotherapy are approved by QUARTET (Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials) and all radiotherapy plans for patients randomized to a radiotherapy question are prospectively reviewed by QUARTET. Prospective review aims to help standardise the radiotherapy being delivered within the FaR-RMS trial

The Radiotherapy randomisations are open to recruitment. The radiotherapy questions are pre vs post-operative radiotherapy (RT1a), dose-escalation in patients at higher risk of local failure (RT1b for patients

with resectable disease, RT1c for non-resectable) and comparing limited vs extensive radiotherapy for patients with extensive metastatic disease (RT2). An important aspect of the study focusses on the Quality of Life of patients when receiving radiotherapy.
So far, 73 patients have been recruited to the Radiotherapy questions.

Maintenance Chemotherapy (CT2a/b)

The purpose of the CT2 questions is to extend the number of maintenance chemotherapy cycles for patients with HR and VHR disease compared to the current standard of care i.e. 6 vs 12 cycles and 12 vs 24 cycles respectively. Please note that some younger patients may not be able to swallow cyclophosphamide capsules. Where centres need access to oral liquid formulations, this should be discussed with the National Coordinating Centres.
So far, 19 patients have been recruited to the Maintenance questions.

Relapse RMS (CT3)

The randomisation for patients with relapsed RMS opened in March 2022. The first new combination to be tested is vincristine, irinotecan (VI) + regorafenib, a multityrosine kinase inhibitor, vs VI + Temozolomide (VIT) as the control arm. The relapse study is an investigator-led collaboration between EpSSG and Bayer, the manufacturer of regorafenib. Quality of life questionnaires are collected for all CT3 patients.
So far, 11 patients have been recruited to the CT3 question.

FaR-RMS Expected vs Actual Recruitment. By Trial Question

Pathology

Risk group assignment and fusion status are integral part of the trial, molecular diagnostics for all cases of RMS should be carried out at the local centre. All samples will be centrally reviewed in each Country by the national pathology coordinator. An international review of scanned slides is ongoing with over 136 cases having international review.

FDG-PET Sub-Study

If FDG PET-CT or FDG PET-MRI scanning is available at diagnosis & facilities allow, there is the option to take part in this sub study where an additional scan after 3 courses of induction chemotherapy is undertaken to determine the prognostic value of FDG-PET imaging response for EFS and local failure free survival. The collection of scans will be started n 2023.

DW-MRI Sub-Study:

The aim of this sub-study is to investigate the prognostic value of DW-MRI imaging response by comparing DW-MRI at diagnosis and at reassessment (After 3 cycles of chemotherapy for patients with localised disease).
Centres are encouraged to include diffusion-weighted series in their standard soft tissue sarcoma MRI protocols. Prinses Maxima and the EpSSG imaging group are leading this sub-study. The collection of scans will be started n 2023.

Quality of Life (QoL)

The TMG is working closely with the EpSSG PPI group to develop a more detailed assessment of QoL within the FaR-RMS study. The FaR-RMS study provides a unique platform to understand better the experience of patients of all ages, and their families. The aim is to extend quality of life study within FAR-RMS to correlate with a focus on the impact of local therapy (short- and longer-term outcomes) and to extend follow up duration to ensure long term QoL scores are measured. This will allow a more detailed understanding of the impact of local therapy for RMS for patients in the medium and long term. Currently quality of life data is collected for patients entering RT1a, RT2 and CT3.

Surgery

Impact of surgery (as part of local control) on short term and late toxicity and QoL. A surgical review of the data entry has recently stated.

Biology

To establish a virtual biobank for samples, including liquid biopsies, to evaluate prognostic factors at diagnosis, response to treatment and disease recurrence. The preferred storage of samples in is the VIVO biobank, Newcastle UK but some countries will use national biobanks.

Vinorelbine Phamacokinetic (PK) Study

To investigate the PK of IV and oral vinorelbine and explore opportunities for the more extensive use of oral vinorelbine within the FaR-RMS trial.

Sponsor

The Study Sponsor is the University of Birmingham Cancer Research Clinical Trials, UK
EudraCT Number: 2018-000515-24

FaR-RMS
Frontline and Relapse
RhabdoMyoSarcoma study

PARENTS AND EpSSG 2022

(By SARA WAKELING, DELPHINE HEENEN and ANGELIKA SANDAKLY)

FOCUS ON PATIENT/PARENTS GROUP

The parent group comprises individuals across EpSSG countries (active parents come from France, Belgium and UK) and those with a mixture of paediatric sarcoma experiences and outcomes. The group strives to ensure that the patient/parent view is represented in the development and management of paediatric sarcoma clinical trials and research. In addition, the group seeks to establish communications between the EpSSG and parent/patient community regarding the clinical trials and their outputs. It also aims to further develop the role of patient advocates and the invaluable role they can play within the organisation.

During this time period, the group has primarily been involved in highlighting the role that advocacy can play and defining a strategy for parent/patient involvement within the EpSSG group.

Below is a summary of ongoing and new activities.

1 - Involvement in clinical trials/Research

- FaR-RMS Trial - Attendance at the trial steering group meetings.

Commencing work to create a video explainer for the parent/patient community regarding the trial goals and experience from the patient perspective. This is being conducted by a collaboration of young cancer survivors at the Royal Marsden and parent-led rhabdomyosarcoma children's charity, Alice's Arc. This group are contributing to the script development, video style and character development. The goal is to ensure that this is accessible across multiple trial locations with multi-language versions available.

- MyKids Trial - Attendance at the trial steering group meetings.

2 - Rome Winter Meeting 2022

This included a parent-led session with two presentations.

- Delphine Heenen gave an overview of the Fight Kids Cancer grant process with emphasis on the quality/quantity of applications booked down by paediatric cancer type. She encouraged EpSSG members to apply for the first sarcoma only grant call in 2025.

- Sara Wakeling provided a summary of the cancer grand challenge, NexTGen and the role that patient advocates are playing as part of this five year project aiming to devise new generation T-cell therapy for children with solid tumours.

- The team also attended a Board meeting to identify priorities for the Parent group moving forward.

3 - Developing a parent section on the EpSSG Website

The team commenced a project to design a parent-focused page on the website. This will provide parents with user-friendly information regarding paediatric sarcoma and clinical trial data.

4 - Alice's Arc funding

Alice's Arc, children's cancer charity focused on research into rhabdomyosarcoma, provided funding for two roles within the EpSSG – Scientific Project Manager and Statistician. These

roles aim to enhance the efficient running of the organisation and ensure that data generated from clinical trials such as RMS 2005 are analysed in order to inform new research and to publish across academic publications and relevant parent/patient platforms.

5- Informing articles with the parent/patient perspective

Sara Wakeling participated as a co-author providing the parent perspective on an article entitled "Patient Reported Outcomes and Measures in children with Rhabdomyosarcoma" published in Cancers in November 2022.

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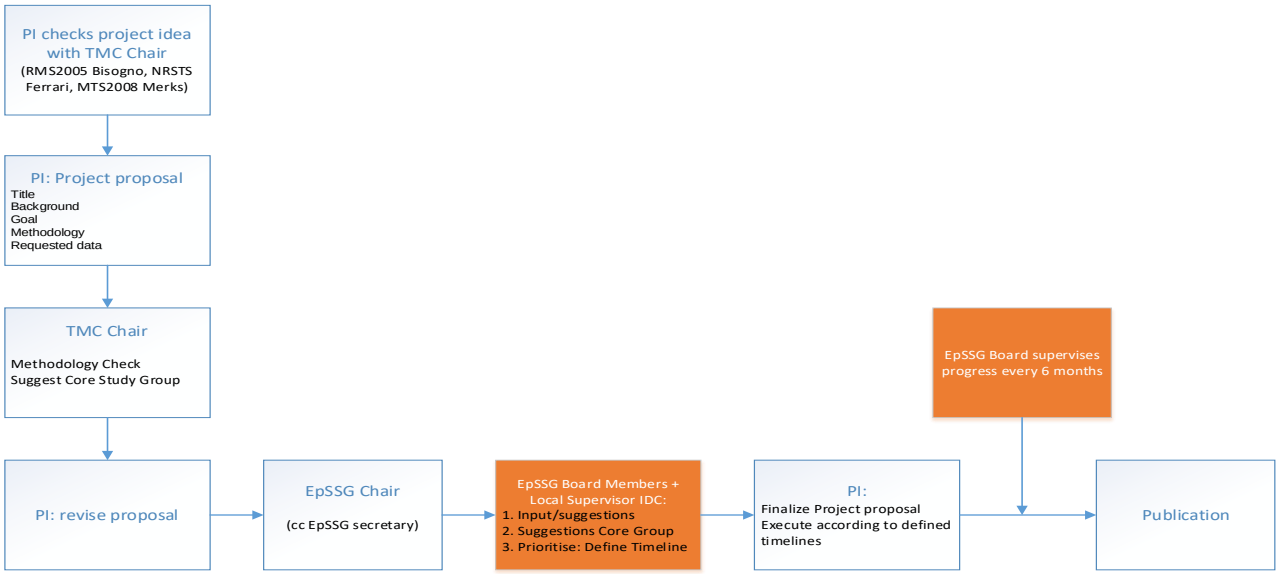
6 - The future

The voice of parents and patients is becoming increasingly recognised in the formation of patient-centric research questions. We will explore and define how this role can have more impact within the EpSSG setting. Additionally, we hope to involve some paediatric sarcoma cancer survivors within the group in the future. There are challenges associated to the level of impact the patient/parent group can have and these involve identifying patients/parents who have sufficient time to carry out the tasks and ensuring the best levels of collaboration between the patients/parents and the EpSSG medical community.

We are proud to be a part of the EpSSG and look forward to the year ahead!

NEW STUDY PROPOSALS ARE WELCOME

The International Data Center (IDC) together with different PI's are working on many analyses in parallel to translate all the knowledge we gathered through our clinical trials into publications in peer reviewed journal to share this with professionals across the globe. In particular, a scheme is reported below. This explains the steps every PI should take before starting a project/analyses.



PAPERS IN 2022

1. **Slater O**, Gains J, Kelsey A, De Corti F, Zanetti I, Coppadoro B, Jorgensen M, Gallego S, Orbach D, Glosli H, Cesen M, Gaze MN, Smeulders N, Ferrari A, Jenney M, Minard-Colin V, Bisogno G, .Merks JHM for the European paediatric Soft tissue sarcoma Study Group **Localised rhabdomyosarcoma in infants (< 12 months) and young children (12-36 months of age) treated on the EpSSG RMS 2005 study** Eur J Cancer. 2022 Jan;160:206-214. doi: 10.1016/j.ejca.2021.10.031. Epub 2021 Dec 2.

   Babies under 1 year of age with rhabdomyosarcoma have traditionally been considered to have a very poor survival when compared to the older age groups. The reason behind this were thought to be difficulties in delivering chemotherapy to young babies as they organs such as liver and kidney were considered not to be able to clear the chemotherapy drugs appropriately. Also, radiotherapy was often not used in very young children due to its lasting long-term effects in terms of growth and development of the irradiated and surrounding tissues.
   We analysed to outcomes for 110 babies enrolled into the EpSSG 2005 Localised Rhabdomyosarcoma study and compared their survival with 380 slightly older children aged 1-3 years.
   The survival was measured as overall survival – this is proportion of patients who survive the disease 5 years since the diagnosis. Comparing the overall survival between these two groups we have found that babies have achieved favourable survival (the survival rate was 88.4% compared to 78.0% in 1-3 year old children). We went on to try to understand this better. We have found that the babies received chemotherapy according to the appropriate schedule. We also found that we have increased the use of radiotherapy in young children, but with almost half of the children receiving localised radiotherapy called brachytherapy which is less damaging to surrounding tissues.
   All this put together gives a promise that babies under 1 year of age who have rhabdomyosarcoma might have better outcome in the future.

2. **Terwisscha van Scheltinga CEJ**, Wijnen MHWA, Martelli H, Guerin F, Rogers T, Craigie RJ, Guillén Burrieza G, Dall'Igna P, De Corti F, Smeulders N, van Rijn RR, Dávila Fajardo R, Mandeville HC, Zanetti I, Coppadoro B, Minard-Colin V, Jenney M, Bisogno G, van Noesel MM, van der Steeg AFW, Merks JHM. **In transit metastases in children, adolescents and young adults with localized rhabdomyosarcoma of the distal extremities: Analysis of the EpSSG RMS 2005 study**. March 2022, European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology Follow journal, doi: 10.1016/j.ejso.2022.03.001

In transit metastases are tumor deposits between the primary tumor and the regional nodal basin. We included 109 distal extremity RMS patients included in the EpSSG2005-study. Lymph node metastases were present at diagnosis in 37/109 (34%) of patients, and 19/37 (51%) had in transit metastases (ITM) especially in lower extremity RMS. The 5-yr EFS of patients with ITM vs proximal lymph nodes vs combined proximal and ITM was 88.9% vs 21.4% vs 20% , respectively (p=0.01) and 5-yr OS was 100% vs 25.2% vs 15%, respectively (p=0.003).
In the distal extremity, popliteal nodes should be considered as regional (first echelon) nodes. In these patients positive inguinal nodes are metastatic second echelon nodes. In case only the inguinal nodes are biopsied, it is unknown if these are regional (first echelon) or metastatic (second echelon nodes). In the distal upper extremity, epitrochlear nodes should be considered as regional, first echelon nodes. Axillary nodes can be first or second echelon nodes (in case of positive epitrochlear nodes). Patients with proximal (axillary or inguinal) lymph node involvement have a worse prognosis.

3. **Rogers T**, Zanetti I, Coppadoro B, Martelli H, Jenney M, Minard-Colin V, Terwisscha van Scheltinga SEJ, Skerritt C, Dávila Fajardo R, Guérin F, Kelsey A, Merks JHM, Mandeville H, Guillén G, Glosli H, Bisogno G. **Perianal/perineal rhabdomyosarcoma: results of the SIOP MMT-95, ITALIAN RMS-96, and EpSSG RMS-2005 studies** Pediatr Blood Cancer 2022 Apr 23;e29739. doi: 10.1002/pbc.29739. Online ahead of print.

   Rhabdomyosarcoma of the perianal/perineal region is rare, with poor survival and limited understanding of the functional consequences of treatment. Fifty patients from three European trials were analysed to identify factors that impacted their survival. Two-thirds of patients had large tumours, and similarly two-thirds had the less favourable alveolar subtype with three-quarters of these having a genetic fusion. Nearly half had lymph node tumour spread at diagnosis, emphasising the importance of identifying tumour spread to the lymph nodes. Attempt at complete surgical removal of the tumour at diagnosis was seldom possible, indicating biopsy as the best initial procedure. Tumour removal after chemotherapy was followed by radiotherapy in two-thirds of patients, most with external beam radiotherapy, and a few with local techniques (brachytherapy). Despite treatment, progression or relapse of disease occurred in nearly a half of patients after five years follow-up, resulting in death in most of these patients. About 60% of patients survived with one-third having faecal incontinence or urinary symptoms. Quality of life and functional studies are needed to better understand the consequences of treatment.

4. **Ferrari A**, Chisholm J, Jenney M, Minard-Colin V, Orbach D, Casanova M, Guillen G, Glosli H, van Rijn RR, Schoot RA, Cameron AL, Rogers T, Alaggio R, Ben-Arush M, Mandeville HC, Devalck C, Defachelles AS, Coppadoro B, Bisogno G, Merks JHM. **Adolescents and young adults with rhabdomyosarcoma treated in the European paediatric Soft tissue sarcoma Study Group (EpSSG) protocols: a cohort study.** Lancet Child Adolesc Health. 2022 Jun 8;S2352-4642(22)00121-3. doi: 10.1016/S2352-4642(22)00121-3. Online ahead of print.
   Several studies have reported that adolescent and young adult (AYA) patients with rhabdomyosarcoma (RMS) are characterised by poorer survival when compared to younger

patients. This inferior outcome is likely to be multifactorial; however, differences in clinical management – including lack of referral to experienced centres, lack of inclusion into clinical trials, or less intensive treatments because of decreased tolerance to chemotherapy in older patients – have been suggested to play a role.

This study aimed to compare clinical findings, treatment data, toxicity and outcome of RMS patients aged 15-21 years (AYA), with children <15 years enrolled in two EpSSG prospective clinical protocols, i.e. RMS2005 for patients with localised and MTS2008 for metastatic disease.

The added value of this study is that it focused on RMS patients enrolled into EpSSG trials - so enrolled in the same clinical trials and receiving similar treatment - therefore eliminating the potential impact on survival of a lower recruitment of AYA patients into clinical protocols.

The study cohort included 1977 patients, 1720 children and 257 AYA.

As first finding, the study showed that AYA patients were more likely than children to have metastatic tumours, unfavourable histological subtypes, large tumours, and regional lymph node involvement. AYA patients had significantly lower survival: 5-year EFS 52.6% and 67.8% in patients aged ≥15 and <15 years, respectively (p-value <0.0001), while 5-year OS was 57.1% and 77.9% (p-value <0.0001). Outcomes remained statistically worse for AYA patients when different subgroups were analysed, with the exception of patients with non-metastatic favourable histotypes, that achieved similar results to children with the inclusion in a paediatric trial.

The multivariable analysis confirmed the prognostic value of age ≥15 years.

A further aim of our study was to compare the treatment administered and treatment toxicity in AYA patients and children. In our study, we did not observe major toxicity and major protocol modifications in AYA patients compared to children. Modifications of administered chemotherapy occurred in 15.3% and 21.3% of patients ≥15 years and <15 years, respectively. Grade 3-4 haematological toxicity and infection were observed more frequently in children.

In conclusion, the study demonstrated better results for AYA patients than those reported in epidemiological studies (e.g. the EUROCARE-5 study, that reported 5-year OS of 39.6% for patients 15–19 years in the 2000–2007 study period), supporting their inclusion in paediatric RMS trials. It suggests that AYA patients, at least up to 21 years old, can be treated with intensive therapies originally designed for children, with no major tolerability issues. However, our study showed that treatment results were inferior in AYA patients than in children, despite receiving similar therapy. This may suggest that a tailored and intensive treatment strategy may be warranted for these patients. Our findings also suggest that in older patients, more aggressive tumour biology may play an important role in the different outcomes.

5. **Schoot RA**, Chisholm JC, Casanova M, Minard-Colin V, Geoerger B, Cameron AL, Coppadoro B, Zanetti I, Orbach D, Kelsey A, Rogers T, Guizani C, Elze M, Ben-Arush M, McHugh K, van Rijn RR, Ferman S, Gallego S, Ferrari A, Jenney M, Bisogno G, Merks JHM **Metastatic Rhabdomyosarcoma: Results of the European *Paediatric* Soft Tissue Sarcoma Study Group MTS 2008 Study and Pooled Analysis With the Concurrent BERNIE Study.** J Clin Oncol. 2022 Jun 16:JCO2102981. doi: 10.1200/JCO.21.02981. Online ahead of print.PMID: 35709412

   Outcome for children with metastatic rhabdomyosarcoma remains poor with survival rates between 34-56%. The EpSSG conducted two different studies between 2005 and 2016 in

children with metastatic rhabdomyosarcoma: the MTS2008 study and the BERNIE study. In the MTS2008 study, two treatment changes were introduced compared to the previous treatment: doxorubicin was added to the chemotherapy treatment with ifosfamide, vincristine, and actinomycine (IVADo courses). Secondly, a year of maintenance treatment was added to the IVADo treatment. The BERNIE study was conducted in collaboration with Hoffmann-La Roche. In this study the same treatment regimen from the MTS2008 study (IVADo plus one year of maintenance) was randomized against the same treatment approach with the addition of bevacizumab during IVADo and maintenance courses. The results of these two studies were combined in a pooled analysis. The MTS2008 study included 270 patients with metastatic rhabdomyosarcoma. The 3 year event free survival (EFS) and overall survival (OS) were 34.9% and 47.9% respectively for patients treated according to the MTS2008 study. Another 102 patients were treated within the BERNIE study (50 received additional bevacizumab, 52 did not). The 3-year EFS and OS for the pooled cohort (372 patients) were 35.5% and 49.3% respectively.
The outcome for patients with metastatic rhabdomyosarcoma remains poor. Nevertheless, in comparison to historical cohorts, this study suggests moderate improvement in outcome for this patient population. Due to the design of the studies it is not possible to determine whether the addition of doxorubicin or the introduction of maintenance treatment contributed to the apparent improvement in outcome. Potentially, improvement in diagnostics and/or supportive care also contributed to better survival rates.

6. **Ben Arush M**, Minard-Colin V, Scarzello G, Davila Fajardo, R, Terwisscha Van Scheltinga S, Bernier-Chastagner V, Jenney M, Gallego S, Zanetti I, Česen M, Merks JHM, G. Bisogno **Therapy and Prognostic Significance of Regional Lymph node involvement in Embryonal Rhabdomyosarcoma: a Report from the European paediatric Soft tissue Sarcoma Study Group European Journal of Cancer** Eur J Cancer 2022 Jun 25;172:119-129. doi: 10.1016/j.ejca.2022.05.033.

   Rhabdomyosarcoma with node involvement has been considered with a worse prognosis. One hundred and forty-three children with embryonal rhabdomyosarcoma and nodal involvement enrolled in the European pediatric soft tissue sarcoma RMS2005 were analyzed for event free and overall survival and identification of prognostic factors. Most pts had tumors with unfavorable characteristics including parameningeal site in 40%. Five-year event-free survival and overall survival was respectively 65.2% and 70%. The results were similar to the other high risk patients group without node involvement. On univariate analysis, larger tumor, unfavorable site, invasiveness, IRS group III, correlated with worse prognosis. On multivariate analysis, IRS Group remained as the only significant prognostic variable but it does not seem to be a consistent estimator. The role of radiotherapy to nodes has to be reconsidered in a larger prospective study.

7. Orbach D, van Noesel MM, Brennan B, Corradini N, Alaggio R, Ben Arush M, Schoot RA, Berlanga P, Zanetti I, Lyngsie Hjalgrim L, De Corti F, Ramirez G, Casanova M, Ferrari A. **Epithelioid hemangioendothelioma in Children: the European pediatric soft tissue sarcoma study group (EpSSG) Experience** Pediatr Blood Cancer 2022 Jul 16;e29882. doi: 10.1002/pbc.29882. Online ahead of print.

Epithelioid hemangioendothelioma (EHE) is a malignant vascular sarcoma (ICD-O-3.2: 9133/3) composed of epithelioid endothelial cells within a distinctive myxo-hyaline stroma. Most cases are characterized by the presence of a WWTR1::CAMTA1 gene fusion in tumor cells. A small subset of tumors, characterized by a YAP1::TFE3 gene fusion, show a distinctive morphology with nests of cells with prominent eosinophilic cytoplasm and tendency to form vascular spaces and are more frequent in younger patients. The EpSSG analysed the clinical outcome of patients registered with an EHE. This analysis was based on all patients registered within the EpSSG NRSTS05 trial and the EpSSG MTS2008 study. Among the 1356 patients registered in both studies, 11 patients had EHE (0.8%). Median age was 14.3 years (range, 9.0–18.8). Primary site was mainly limbs (six cases), than trunk (four cases) and one patient had a metastatic disease with bone, lung, liver and meningeal involvement. Nine patients are alive off therapy: eight in complete remission and one with a stable residual disease 5 years after diagnosis. One patient with a localized thoracic tumor developed bone metastasis and died 10.3 months after initial diagnosis. Five-year PFS and OS are, respectively, 77.1% (95% confidence interval [CI]: 34.5–93.9) and 74.1% (95% CI: 28.1–93.0). In conclusion, this pediatric experience on these exceptional entities confirms the overall favorable course of these tumors with exclusive surgery for localized diseases. In the case of diffuse progressive disease, patients should be included in trials to validate the value of new drugs. The precise role of these treatments needs further exploration in larger international cohorts of pediatric and adult patients in collaboration with medical oncologists.

8. Affinita MC, Merks JHM, Chisholm JC, Haouy S, Rome A, Rabusin M, Brennan B, Bisogno G. **Rhabdomyosarcoma with unknown primary tumor site: A report from European pediatric Soft tissue sarcoma Study Group (EpSSG).** Pediatr Blood Cancer. 2022 Sep 12:e29967. doi: 10.1002/pbc.29967.

Rhabdomyosarcoma (RMS) is an aggressive malignancy, and 20% of children present with metastases at diagnosis. Patients presenting with disseminated disease very occasionally have no clear evidence of a primary tumor mass. As these patients have rarely been investigated, this study reported on a series of patients with RMS and unknown primary tumor site registered in the Metastatic (MTS) RMS 2008 protocol (October 2008 to December 2016) coordinated by the European pediatric Soft tissue sarcoma Study Group. There were identified 10 patients with RMS and unknown primary site, most of them adolescents (median age 15.8 years, range: 4.6-20.4). Nine had fusion-positive alveolar RMS. Multiple organ involvement was identified in seven patients, two only had bone marrow disease, and one only had leptomeningeal dissemination. All patients were given chemotherapy, four were irradiated, and none had surgery. Three patients underwent allergenic bone marrow transplantation.
At the time of this analysis, only two patients are alive in complete remission: one had received radiotherapy; and one had a bone marrow transplant.
Conclusion of the paper reported that RMS with unknown primary tumor occurs mainly in adolescents and is typically fusion-positive alveolar. Radiotherapy may be important, but survival is poor and patients should be offered enrollment in investigational trials.

9. **Ferrari A**, Brennan B, Casanova M, Corradini N, Berlanga P, Schoot RA, Ramirez-Villar GL, Safwat A, Guillen Burrieza G, Dall'Igna P, Alaggio R, Lyngsie Hjalgrim L, Gatz SA, Orbach D, van Noesel MM
Pediatric Non-Rhabdomyosarcoma Soft Tissue Sarcomas: Standard of Care and Treatment Recommendations from the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) Cancer Manag Res. 2022 Sep 23;14:2885-2902. doi: 10.2147/CMAR.S368381. eCollection 2022.

   This is a review paper describing the standard of care for patients with non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) and the therapeutic recommendations developed by the EpSSG.
   The rarity, heterogeneity, and aggressiveness of NRSTS make the management of children and adolescents with these tumors complex and challenging. The overall cure rate for patients with NRSTS is around 70%, but survival depends on several prognostic variables, such as histotype and tumor grade, extent of disease and stage, tumor size, and tumor site. While surgery remains the mainstay of treatment for most of these tumors, a multimodal therapeutic approach including radiotherapy and chemotherapy is required in many cases.
   The EpSSG NRSTS 2005 study was the first prospective protocol tailored specifically to NRSTS, and - together with the COG ARST0332 study - represents the benchmark for these tumors, establishing risk-adapted standards of care.
   The paper describes the EpSSG recommendations developed for the large group of adult-type NRSTS (including synovial sarcoma), and the specific treatment recommendations tailored for other particular adult-type histologies. The need of new effective drugs for patients at worse prognosis is discussed.

10. **Ferrari A**, Gatz SA, Minard-Colin V, Alaggio R, Hovsepyan S, Orbach D, Gasparini P, Defachelles AS, Casanova M, Milano GM, Chisholm JC, Jenney M, Bisogno G, Rogers T, Mandeville H, Shipley J, Miah A, Merks JHM, van der Graaf WTA. **Shedding a Light on the Challenges of Adolescents and Young Adults with Rhabdomyosarcoma.** Review Cancers (Basel). 2022 Dec 9;14(24):6060. doi: 10.3390/cancers14246060.

    Rhabdomyosarcoma (RMS) is a typical tumour of childhood but can occur at any age. Several studies have reported that adolescent and young adult (AYA) patients with RMS have poorer survival than do younger patients. This review discusses the specific challenges in AYA patients with RMS, exploring possible underlying factors which may influence different outcomes. Reasons for AYA survival gap are likely multifactorial, and might be related to differences in tumor biology and intrinsic aggressiveness, or differences in clinical management (that could include patient referral patterns, time to diagnosis, enrolment into clinical trials, the adequacy and intensity of treatment), as well as patient factors (including physiology and comorbidity that may influence treatment tolerability, drug pharmacokinetics and efficacy).
    This paper describes how improved survival has been reported in the most recent studies for AYA patients treated on pediatric RMS protocols. Different strategies that may help to further improve outcome are discussed, such as trans-age academic societies and national/international cooperation, the definition of integrated biologic and genomic approach, and the development of collaborative rhabdomyosarcoma clinical trials without upper age limit.

COLLABORATION WITH OTHER GROUPS:

11. Whittle S, Venkatramani R, Schönstein A, et al., **Congenital spindle cell rhabdomyosarcoma: An international cooperative analysis.** Eur J Cancer 2022 Jun;168:56-64. doi: 10.1016/j.ejca.2022.03.022. Epub 2022 Apr 19.
12. **Hettmer S, Linardic CM, Kelsey A,** Molecular testing of rhabdomyosarcoma in clinical trials to improve risk stratification and outcome: A consensus view from European paediatric Soft tissue sarcoma Study Group, Children's Oncology Group and Cooperative Weichteilsarkom-Studiengruppe. Eur J Cancer. 2022 Sep;172:367-386. doi: 10.1016/j.ejca.2022.05.036. Epub 2022 Jul 12.
13. **Bisogno** G, Fuchs J, Dasgupta R, et al., . **Patients with completely resected nongenitourinary low-risk embryonal rhabdomyosarcoma are candidates for reduced duration low-intensity chemotherapy.** Cancer. 2022 Dec 1;128(23):4150-4156. doi: 10.1002/cncr.34497. Epub 2022 Oct 17.

NRSTS PROJECTS

(by Dr. Andrea Ferrari & Dr. Daniel Orbach)

THE EPSSG NRSTS COMMITTEE IS WORKING ON THE DEVELOPMENT OF NEW STUDIES DEDICATED TO NRSTS ACROSS EUROPE.

The EpSSG NRSTS Committee is soon to start new protocol dedicated to NRSTS, called **MYKIDS - Molecular Identification and Characterization of non-Rhabdomyosarcoma Soft Tissue Sarcoma in Kids, Adolescents and Young Adults: an EpSSG NRSTS study.**
The MYKIDS study is designed to better understand the molecular diagnosis of pediatric NRSTS in view of optimal treatment. In particular, to a) understand the role of molecular profiling in pediatric NRSTS, b) enable a comprehensive decision on the treatment for individual patients, c) compare molecular profiles to histological grading for prognostification, and d) use molecular diagnostics to study non-invasive diagnosis (liquid biopsies).
Co-principal investigators of the study are Max van Noesel (Princess Máxima Center, Utrecht), Daniel Orbach (Institut Curie, Paris) and Andrea Ferrari (Istituto Nazionale Tumori, Milan).

In parallel, the NRSTS Committe is working on two other prospective therapeutic projects:
joining forces with the CWS group to develop a randomised phase II trial dedicted to pediatric desmoid-type fibromatosis, aiming to evaluate efficacy and safety of the oral combination vinorelbine- methotrexate
(**Desmover** study, PI – Nadege Corradini, Leon Berard, Lyon).
REACH NRSTS project - REgorafenib in young adults, **A**dolescents and **C**hildren with **H**igh-risk **NRSTS** – exploring whether the

addition of **Regorafenib** to standard Ifosfamide-Doxorubicine chemotherapy improve outcome in high-risk NRSTS (PIs – Susanne Gatz, Andrea Ferrari).

The NRSTS committee continues to collaborate within the **INSTRUCT project** (INternational Soft Tissue SaRcoma ConsorTium) to promote transatlantic cooperation and data sharing on pediatric soft part sarcomas. Clinical data from previous European (SIOP MMT, EpSSG, ICG, CWS) and American (COG) NRSTS studies will soon be ready to be analyzed to improve knowledge on such rare sarcomas. Projects are on going on "Challenging and controversies in pediatric soft part sarcomas" and "Consensual definitions on NRSTS margins".

FINANCIAL STATEMENT 2022

(by T. Rogers, H. Merks)

An accountancy and treasurer's Report of the final year's account was presented and approved during the EpSSG Spring meeting Assembly held in May 11, 2023 during the 4th SIOPE Annual Meeting in Valencia.

Total income for the association in 2022 was €60.413,40, mainly from members' fees, meeting registration and donations from Alice's Arc.
Total expenses were almost €65.746,35.

For 2023 we expect income from EpSSG membership fees and meeting fees from our Winter meeting; we aim to negotiate with Pharma whenever we substantially invest our expertise and network into Paediatric Investigation.

Plans or other work. As our association is vital to maintain both expertise and the clinical network this justifies financial support from parties that need substantial input from EpSSG members.
Funding Sources for 2023: EpSSG will receive financial support from Alice's Arc Foundation to support our EpSSG scientific project manager and statistician for the year 2023. We are grateful to Sara Wakeling and the trustees of Alice's Arc for the support so crucial for our scientific network organization.
Grateful to those who help implementing work resources in research.

WORK PLAN IN 2023

Continue to open the FaR-RMS study in countries and centers not open yet. Promote patient participation in the randomized trial questions; this includes support from our parents organization to optimize explanation of these questions to patients and parents.
Implement and optimize participation in sub-studies to FaR-RMS including Imaging and Biology Biomarker studies and studies on Quality of Life
Open the MYKIDS Study and initiate the study across EpSSG countries.
Efficient preparation of reports by the International Data Center (IDC) in close collaboration with PI of each project leading to timely delivery of manuscripts to be published in peer reviewed journals.
Consolidate funding for EpSSG IDC and secretariat activities essential for our network organization of professionals to optimally function and create scientific reports.
Optimize collaboration with parents through involvement at meetings and in projects.
Optimize communication with members through our refreshed-EpSSG website and mailings on important EpSSG developments
Continue the good work of the EpSSG Discipline Panels to deliver and update practice guidelines, initiate important analyses and new research.
Have our twice yearly EpSSG live meetings; first the spring at the SIOPE meeting in Valencia, then our EpSSG Winter meeting this year kindly hosted by the Barcelona team led by Dr Gabriela Guillen-Burrieza and Dr. Raquel Hladun.

WE HAVE A DONATION BUTTON ON OUR WEBSITE! HELP US SPREAD THE WORD!

The EpSSG coordinates European international clinical trials aimed at improving the treatment of soft tissue sarcoma (STS). Through research our goal is to improve the quality of care offered to children, teenagers and young adults with STS and to improve the outcomes of treatment.

Your donation will help to support the team of clinicians, scientists, statisticians and data managers in developing and running new clinical trials in paediatric STS in order to help future generations of children with STS.

ASSOCIATION PAST MEETINGS

CALENDAR 2022

DATE	MEETING	LOCATION	NOTES
2022			
March 23-25 (Wed-Fri)	EpSSG Spring Meeting & Association Assembly	SIOP Europe 2021 3rd Annual Meeting Virtual	Virtual Meeting
December 1-2(Th-Fri)	EpSSG Winter Meeting & Association Assembly	Rome	Performed

ASSOCIATION FUTURE MEETINGS

CALENDAR 2023-2025

DATE	MEETING	LOCATION	NOTES
2023			
May 8-12(Mon-Fri)	EpSSG Spring Meeting & Association Assembly	SIOP Europe 2023 4th Annual Meeting Valencia	Confirmed
November 30-December 1 (Thu-Fri)	EpSSG Winter Meeting & Association Assembly	Barcelona	Confirmed
2024			
May 13-17 (Mon-Fri)	EpSSG Spring Meeting & Association Assembly	SIOP Europe 2024 5th Annual Meeting Milano	Confirmed
December 5-6 (Thu-Fri)	EpSSG Winter Meeting & Association Assembly	Paris	Confirmed
2025			
May (Mon-Fri)	EpSSG Spring Meeting & Association Assembly	SIOP Europe 2025 6th Annual Meeting	TBD
December 4-5(Thurs-Fri)	EpSSG Winter Meeting & Association Assembly	Athens	TBD

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and with the great
collaboration of all
EpSSG Members