EPSSG ASSOCIATION

THE EUROPEAN PAEDIATRIC SOFT TISSUE SARCOMA STUDY GROUP

ANNUAL REPORT 2018

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 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. It is managed by an elected board, 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 that have been developed in 2018. Importantly, we have had the opportunity to welcome parents of sarcoma patients to collaborate with us and support the development of our activities since 2016.

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

EpSSG Board (By dr Julia Chisholm)

Prof. Gianni Bisogno	•Chairman - Padua, Italy
Dr. Hans Merks	•Treasurer, Chair Elect- Utrecht, The Netherlands
Dr. Julia Chisholm	•Sutton, UK
Dr. Soledad Gallego	•Barcelona, Spain
Dr. Heidi Glosli	•Oslo, Norway
Dr. Daniel Orbach	•Paris, France
Dr. Meriel Jenney	•Cardiff, UK
Dr. Christophe Bergeron	•Lyon, France
Dr. Andrea Ferrari	•Milan, Italy

Board meetings were held on the following dates in 2018:
May 9th, 11th, October 10th, December 5th, 7th
TCs were held on: February 26th, March 20th, June 26th, August 23rd.

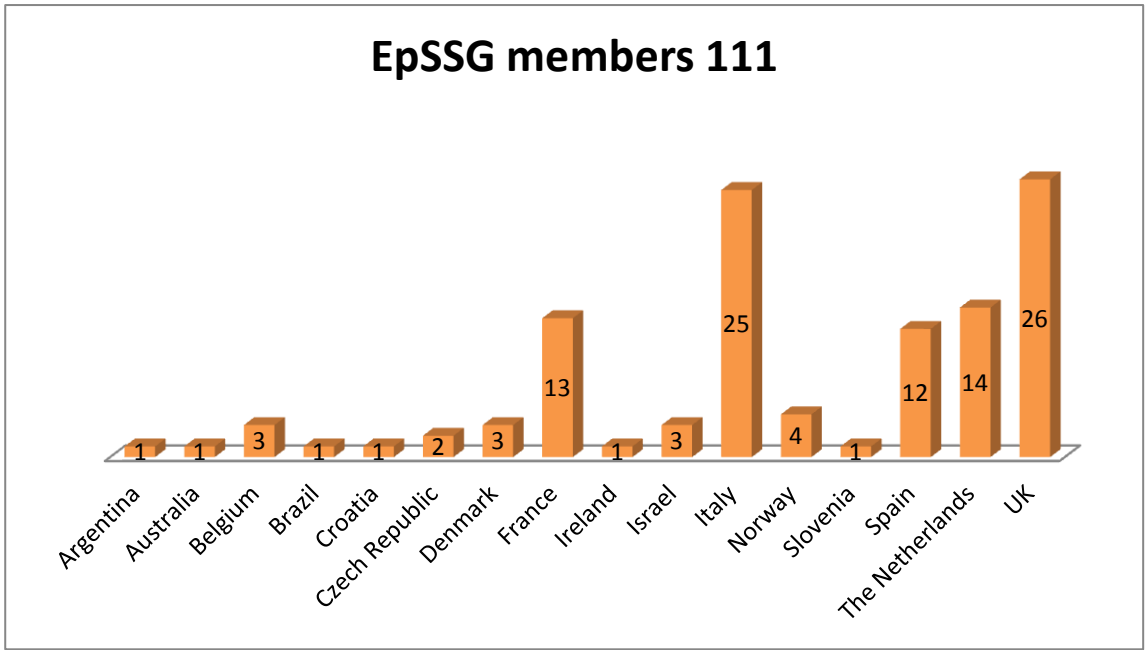
We are extremely grateful to Dr Jenney, Dr Bergeron and Dr Ferrari for their major contributions to the board. These members rotated off the Board in December 2018 and in their place Dr Henry Mandeville, Dr Michela Casanova and Dr Veronique Minard-Colin were elected (see below).

Hans Merks will remain in the board as chair elect of the EpSSG Association until December 2019, when he will be the New Chair.

EpSSG MEMBERSHIP (BY DR JULIA DARAGJATI)

EpSSG studies are undertaken in the following countries: Italy, France, UK, The Netherlands, Spain, Belgium, Ireland, Denmark, Norway, Czech Republic, Slovenia, Israel, Argentina, Brazil and one centre from Australia. Each country has an EpSSG National Coordinator.

In 2018 there were 111 individual members of the EpSSG from 16 different countries.



EpSSG SUBCOMMITTEES

	Chair
Biology	Prof Janet Shipley, Sutton, UK
Pathology	Dr Anna Kelsey, Manchester, UK
Radiology	Prof Rick R. van Rijn, Amsterdam, The Netherlands
Surgery	Dr Timothy Rogers, Bristol, UK
Radiotherapy	Dr Henry Mandeville, Sutton, UK
Phase I/II trials	Dr Michela Casanova, Milan, Italy
Biostatistics/Data management	Dr Gian Luca De Salvo, Padua, Italy

EpSSG Meetings 2018 (By Dr Julia Daragjati)

The Spring meeting took place on 10th - 11th May 2018 at the Thon Opera Hotel, in Oslo, Norway. The meeting was hosted by Dr. Heidi Glosli, the meeting included discipline panel meetings on surgery, biology-pathology, phase II, radiotherapy. Other topics meetings of interests were the FaR-RMS update and a symposium entitled: "*Indications of the different radiotherapy techniques in the new protocol*".

The Winter meeting took place the 6th and 7th of December at the Universitair Medisch Centrum in Utrecht, The Netherlands. It was hosted by Dr Hans Merks and included discipline panel meetings on biology, radiotherapy, NRSTS TMC, surgery, pathology, phase I/II, radiology, and an International Symposium on the "*Infant Rhabdomyosarcoma*". Our meetings are growing and welcoming more than

100 participants. In Utrecht we had 125 participants! Moreover, a half day of the INTERNATIONAL SOFT TISSUE SARCOMA CONSORTIUM (INSTRuCT) meeting was held. This consortium developed to share data from soft tissue sarcoma trials, focused on either RMS rhabdomyosarcoma or on NRSTS non-rhabdomyosarcoma soft tissue sarcomas, has resulted in sharing of data from thousands of children within the EpSSG, RMS and MTS 2008 protocols, CWS and COG group. The first aim is to develop international guidelines for risk stratification in RMS.

The New **F**rontline **a**nd **R**elapse study in **R**habdo**M**yo**S**arcoma

(by Dr. Meriel Jenney and Dr. Julia Chisholm)

The New Frontline and Relapse study in RhabdoMyoSarcoma (FaR-RMS) is an overarching trial for all patients with newly diagnosed and relapsed paediatric-type rhabdomyosarcoma and will be 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 study is due to open in the UK in the summer of 2019 and will roll out to other countries across the EpSSG subsequently. The Study is coordinated through the Cancer Research Clinical Trials Unit in Birmingham UK and is due to open to recruitment in the summer of 2019.

All tumours are planned to be assessed for "fusion status": this discriminate between fusion positive tumours (that have a translocation of chromosomes involving the FOXO-1 and (usually) PAX 3 or PAX7 gene) and fusion negative tumours that do not. This is very important in assigning risk status – fusion positive tumours are considered higher risk. It is also strongly recommended that tumour is taken and stored so that it is available to be used, with informed consent, for future research studies as well as for the patient's own benefit

When the trial first opens there will be a number of different trial questions:

For frontline chemotherapy aspects the trial will start with a dose finding (phase 1b) study of the combination of irinotecan with the standard IVA chemotherapy for "high risk" rhabdmomyosarcoma (ifosfamide, vincristine and actinomycin D). Once the safe dose of irinotecan with IVA has been found (IrIVA), the study will proceed to a randomization between IrIVA and doxorubicin (IVADo) in very high risk patients (ie those with metastatic disease (disease that has spread) or "fusion positive" tumours with lymph node involvement) and between IrIVA and IVA in "high risk" patients. At the same time there will be randomisations for the duration of the low dose maintenance chemotherapy that follows on from the more intensive induction treatment in "high risk" (6 versus 12 months) and "very high risk" (12 versus 24 months) in very high risk patients. These randomisations will start as phase II studies of effectiveness and can move to phase III to give better evidence about which treatment is best. We aim to introduce new therapies for relapsed patients in the future but the will be no initial trial question for relapsed patients.

Importantly the study has 3 radiotherapy questions: preoperative versus post operative radiotherapy for patients with resectable tumours, standard versus higher dose of radiotherapy for patients at higher risk of tumour recurrence, and also a radiotherapy question in patients with metastatic disease.

PARENTS AND EpSSG

PARENTS AND EPSSG 2018 (BY DR. JULIA CHISHOLM AND ANGELIKA SANDAKLY)

We welcomed four parents, including two local parents from Oslo, to the Spring meeting in May 2018 and six parents to the Winter meeting in December 2018, including a mother of a child being treated in Princess Maxima Hospital. To date 10 parents in total have attended EpSSG meetings and 6 EpSSG countries are now represented (France, Italy, NL, Norway, Denmark, Belgium) . For the first time, the parent group had its own session at the 2018 Winter meeting and used this time to identify priorities to discuss with the board. The EpSSG board has met with parents at the end of both meetings .

During 2018 the parent group has kindly reviewed the parent information sheets for the FaR-RMS study.

The new EpSSG website is now up and running with a "parent corner". A top priority in 2019 will be to produce information for parents relevant to the opening of the FaR-RMS study.

From a parent's point of view:

Both meetings in 2018, first in Oslo and then in Utrecht, made us feel that we start to be a group with some (brief) history, some of us have attended the EpSSG meetings for more than 2 years now. I would like to thank EpSSG, for that opportunity.

To get an insight in your work and to mirror our - sometimes very personal - experiences with your - sometimes very scientific – approach seems to be helpful for both sides.

On the administrative side we have overcome some funding issues by involving our local associations. We do our best to progress on the gathering of relevant information for the website project.

We continue to be available for all review activity related to the FaR-RMS study. Gaining more understanding for the interest of the participation in clinical studies in general and in the Far-RMS study in particular is one of the priorities for 2019.

We are looking forward to enlarging our activities to turn our experience into something beneficial for EpSSG and its public. It's good to know that our contribution might be useful for your work, it's a very small give back for the efforts you do for our children.

REPORTS FROM TRIAL COMMITTEES

(BY PROF. GIANNI BISOGNO /IDC)

a) RMS 2005

This was the first International EpSSG trial for children and adolescents with localized rhabdomyosarcoma. Patients were included in 4 different risk groups according to 6 prognostic factors (result of initial surgery, histology subtype, tumour site and size, nodal involvement and patient age). Overall, 1762 patients were enrolled from 134 centres in 14 countries.

Low risk Group

75 patients were enrolled and treated with vincristine and actinomycin D for 22 weeks. Results are very satisfying with 5-year Event Free Survival (EFS) of 94.4% (CI95% 85.8-97.9) and 5-year Overall Survival (OS) of 100%.

Standard risk group

628 patients were enrolled and treated with ifosfamide, vincristine and actinomycin D (IVA) but with a higher ifosfamide cumulative dose if patients had not received radiotherapy. 5-year Event Free Survival (EFS) was 77.9% (CI95% 74.2-81.2) and 5-year Overall Survival (OS) was 91.0% (CI95% 88.0-93.2).

High Risk Group

855 enrolled patients are in the high risk group. 5-year Event Free Survival (EFS) of the entire cohort was 66.7% (CI95% 63.3-69.9) and 5-year Overall Survival (OS) was 75.5% (CI95% 72.2-78.4).

In the first randomized question there were 645 eligible patients were and in the second there were 670 eligible patients. In the 1st question 484 patients were randomized to receive ifosfamide, actinomycin D and vincristine with or without doxorubicin given in the first 4 courses: no benefit from the addition of doxorubicin was documented.
5-year Event Free Survival (EFS) of the IVA arm was 59.6% (CI95% 52.9-65.7) and 5-year Overall Survival (OS) was 76.0% (CI95% 69.8-81.1). 5-year Event Free Survival (EFS) of the IVADo arm is 65.4% (CI95% 58.9-71.2) and 5-year Overall Survival (OS) was 72.3% (CI95% 65.8-77.7). These results have already been published (Bisogno et al., Lancet Oncology, 2018). In the second randomised question 371 patients in complete remission after 9xIVA cycles were randomised to stop treatment or to continue with low dose maintenance therapy with a combination of cyclophosphamide and vinorelbine. Initial analysis showed benefit of maintenance chemotherapy and the results were presented at the American Society of Clinical Oncology (ASCO) meeting in June 2018, raising sufficient interest to be included in the plenary session. The full paper has been submitted for journal publication., .

Very High Risk Group

144 patients with alveolar RMS and nodal involvement were included in this group: 5-year EFS and OS were 52.0 (CI95% 42.7-60.6) and 50.5 (CI95% 40.4-59.7), respectively.
Overall, the EpSSG RMS2005 trial showed an improvement in survival for patients with RMS when compared with previous European experiences. This study has been published (Gallego et al., Cancer 2018).

NRSTS 2005 (BY DR. ANDREA FERRARI)

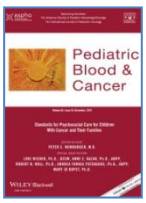
The EpSSG NRSTS Committee is working on the development of a new protocol dedicated to NRSTS. Meanwhile, the group continues the analysis of selected series of NRSTS histotypes. In particular, in 2018 we published the series on alveolar soft part sarcoma (Brennan B et al. Pediatr Blood Cancer 65(4), 2018) and the SYNOBIO study (Orbach D et al. Cancer Medicine 7(4):1384-1393, 2018). The SYNOBIO study aimed to assess genomic index (GI) in pediatric patients with synovial sarcoma, to determine its value as a prognostic factor. The study included 61 pediatric patients from the EpSSG-NRSTS 2005 protocol: 5-year EFS were 93.8% in cases with GI-1 (flat profile, no copy number alterations) vs. 64.9% in those with GI-2 (rearranged profile, one or more copy number alterations).

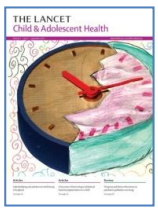
GI status remained an independent prognostic for EFS also in multivariate analysis, suggesting it could be a good tool to predict the metastatic behavior of pediatric synovial sarcoma.

Very recently, the joint EpSSG-COG study on epithelioid sarcoma has been accepted for publication on European Journa Eur J Cancer (Spunt SL et al).

Further analyses ongoing are on malignant peripheral nerve sheath tumor, inflammatory myofibroblastic tumor, dermatofibrosarcoma protuberans and metastatic NRSTSs included in the Bernie study.

PAPERS IN 2018





1. **ALVEOLAR SOFT PART SARCOMA IN CHILDREN AND ADOLESCENTS: THE EUROPEAN PAEDIATRIC SOFT TISSUE SARCOMA STUDY GROUP PROSPECTIVE TRIAL (EPSSG NRSTS 2005).** . Pediatr Blood Cancer. 2017 Dec 29. doi: 10.1002/pbc.26942

   Brennan B, Zanetti I, Gallego S, Francotte N, Van Noesel M, Kelsey A, Casanova M, De Salvo GL, Bisogno G, Ferrari A

   -22 patients with ASPS were enrolled into the EpSSG NRSTS 2005 study. After surgical resection, subsequent treatment depended on the stratification of patients for IRS) stage, size, and grade. Chemotherapy using ifosfamide and doxorubicin was performed in IRS group III. Radiotherapy was performed in IRS groups II and III, and grades 2 and 3 tumors.

   -The majority in the series had localized disease (20 cases), with small IRS I tumors (12 cases), and in total 19 had surgical resection upfront. Of the four patients who received conventional chemotherapy, there were no responses. Concerning the outcome, 3/20 patients with localized tumors and all metastatic patients developed metastases. The 5-year EFS of patients with localized disease is 94.7% and the OS is 100%.

   -In conclusion, this report demonstrates the ability to run prospective pediatric studies in NRSTS in multiple European countries, despite the small numbers of ASPS patients. We can conclude that for the majority with small resected tumors, there were few events and no deaths.

2. **GENOMIC COMPLEXITY IN PEDIATRIC SYNOVIAL SARCOMAS (SYNOBIO STUDY): THE EUROPEAN PEDIATRIC SOFT TISSUE SARCOMA GROUP (EpSSG) EXPERIENCE** Cancer Med. 2018 Mar 13. doi: 10.1002/cam4.1415

Orbach D, Mosseri V, Pissaloux D, Pierron G, Brennan B, Ferrari A, Chibon F, Bisogno G, De Salvo GL, Chakiba C, MD, Corradini N, Minard-Colin V, Kelsey A,Ranchère-Vince D.

-A genomic index (GI) tool using array comparative genomic hybridization (aCGH) on tumor cells has emerged as independent prognostic factor associated with the risk of metastatic relapse in synovial sarcoma. The aim of this tudy was to assess GI in pediatric patients with SS, to determine its value as a prognostic factor.

-61 patients <25 years) with localized SS prospectively included in the European EpSSG-NRSTS05 protocol with a contributive aCGH were selected.

-Definition of GI was A2/C, where A is the total number of alterations (segmental gains and losses) and C is the number of involved chromosomes on aCGH results.

-GI1 group corresponds to cases with no copy number alterations (flat profile, GI=0) and GI2 group cases with at least one or more copy number alterations (rearranged profile; GI≥1).

-Overall, 55.7% were GI1 group, and 44.3% GI2. Respectively for GI1 vs. GI2 groups, 5-year EFS were 93.8 vs. 64.9 (P<0.006) and 5-year-MFS 93.8 vs. 72.9 (P<0.04). In multivariate analysis, GI status as adjusted for IRS group, patient age, site and tumor size remains independent prognostic for EFS with a relative risk (RR) of 6.4 (p<0.01) and for MFS with a RR of 4.8 (p<0.05).

-In conclusions, genomic complexity evaluated through GI may explain the metastatic behavior of pediatric SS.

3. **ADDITION OF DOSE-INTENSIFIED DOXORUBICIN TO STANDARD CHEMOTHERAPY FOR RHABDOMYOSARCOMA (EPSSG RMS 2005): A MULTICENTER, OPEN-LABEL, RANDOMIZED CONTROLLED, PHASE 3 TRIAL.** Lancet Oncol. 2018. DOI: 10.1016/S1470-2045(18)30337-1

Bisogno G, Jenney M, Bergeron C, Gallego Melcón S, Ferrari A, Oberlin O, Carli M, Stevens M, Kelsey A, De Paoli A, Gaze MN, Martelli H, Devalck C, Merks JH, Ben-Arush M, Glosli H, Chisholm J, Orbach D, Minard-Colin V, De Salvo GL, for the EpSSG

Rhabdomyosarcoma is an aggressive tumour that can develop in almost any part of the body. Doxorubicin is an effective drug against rhabdomyosarcoma, but its role in combination with an established multidrug regimen remains controversial. Therefore, we aimed to evaluate the possible benefit of early dose intensification with doxorubicin in patients with non-metastatic rhabdomyosarcoma.

We did a multicentre, open-label, randomised controlled, phase 3 trial involving 108 hospitals from 14 countries. We included patients older than 6 months but younger than 21 years with a pathologically proven diagnosis of rhabdomyosarcoma. We assigned each patient to a specific subgroup according to the EpSSG stratification system. Those with embryonal rhabdomyosarcoma incompletely resected and localised at unfavourable sites with or without nodal involvement, or those with alveolar rhabdomyosarcoma without nodal involvement were considered at high risk of relapse. These high-risk patients were randomly assigned (1:1) to receive either nine cycles of IVA (ifosfamide 3 g/m2 given as a 3-h intravenous infusion on days 1 and 2, vincristine 1.5 mg/m2 weekly during the first 7 weeks then only on day 1 of each cycle [given as a single intravenous injection], and dactinomycin 1.5 mg/m2 on day 1 given as a single intravenous injection) or four cycles of IVA with doxorubicin 30 mg/m2 given as a 4-h intravenous infusion on days 1 and 2 followed by five cycles of IVA. The interval between cycles was 3 weeks. Randomisation was done using a web-based system and was stratified (block sizes of four) by enrolling country and risk subgroup. Neither investigators nor patients were masked to treatment allocation. The primary endpoint was 3-year event-free survival assessed by the investigator at each centre in the intention-to-treat population. Patients who received at least one dose of study treatment were considered in the safety analysis. In agreement with the independent data monitoring committee, the study was closed to patient entry on Dec 16, 2013, after futility analysis. This trial is registered with EudraCT, number 2005-000217-35, and is currently in follow-up.

Between Oct 1, 2005, and Dec 16, 2013, 484 patients were randomly assigned to receive each chemotherapy regimen (242 in the IVA group and 242 in the IVA plus doxorubicin group). Median follow-up was 63.9 months (IQR 44.6-78.9). The 3-year event-free survival was 67.5% (95% CI 61.2-73.1) in the IVA plus doxorubicin group and 63.3% (56.8-69.0) in the IVA group (hazard ratio 0.87, 95% CI 0.65-1.16; p=0.33). Grade 3-4 leucopenia (232 [93%] of 249 patients in the IVA plus doxorubicin group vs 194 [85%] of 227 in the IVA group; p=0•0061), anaemia (195 [78%] vs 111 [49%]; p<0.0001), thrombocytopenia (168 [67%] vs 59 [26%]; p<0.0001), and gastrointestinal adverse events (78 [31%] vs 19 [8%]; p<0•0001) were significantly more common in the IVA plus doxorubicin group than in the IVA group. Grade 3-5 infections (198 [79%] vs 128 [56%]; p<0.0001) were also significantly more common in the IVA plus doxorubicin group than in the IVA group, in which one patient had grade 5 infection. Two treatment-related deaths were reported (one patient developed septic shock and one affected by Goldenhar syndrome developed intractable seizures) in the IVA plus doxorubicin group, both occurring after the first cycle of treatment, and none were reported in the IVA group.

INTERPRETATIONS: The addition of dose-intensified doxorubicin to standard IVA chemotherapy did not show a significant improvement in the outcome of patients with high-risk non-metastatic rhabdomyosarcoma. Therefore, the IVA chemotherapy regimen should remain the standard of care for patients with localised rhabdomyosarcoma in Europe.

4. **FUSION STATUS IN NODE-POSITIVE (N1) ALVEOLAR RHABDOMYOSARCOMA IS A POWERFUL PREDICTOR OF PROGNOSIS: THE EXPERIENCE OF THE EUROPEAN PAEDIATRIC SOFT TISSUE SARCOMA STUDY GROUP (EPSSG).** Cancer. 2018. Aug 1;124(15):3201-3209. doi: 10.1002/cncr.31553.

Gallego Melcón S, Zanetti I, Orbach D, Ranchère D, Shipley J, Zin A, Bergeron C, De Salvo GL, Chisholm J, Ferrari A, Jenney M, Mandeville HC, Rogers T, Merks JH, Mudry P, Glosli H, Milano GM, Ferman S, Bisogno G, on behalf of the EpSSG (European Paediatric Soft Tissue Sarcoma Study Group),

BACKGROUND: Alveolar rhabdomyosarcoma (aRMS) with lymph node involvement (N1 classification) accounts for up to 10% of all cases of RMS. The prognosis is poor, and is comparable to that of distant metastatic disease. In the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) RMS2005 protocol, patients with a histologic diagnosis of aRMS/N1 received intensified chemotherapy with systematic locoregional treatment.

METHODS: Patients with aRMS/N1 were enrolled prospectively after primary surgery/biopsy and fusion status was assessed in tumor samples. All patients received 9 cycles of induction chemotherapy and 6 months of maintenance therapy. Local treatment included radiotherapy to the primary site and lymph nodes with or without secondary surgical resection.

RESULTS:A total of 103 patients were enrolled. The clinical characteristics of the patients were predominantly unfavorable: 90% had macroscopic residual disease after initial surgery/biopsy, 63% had locally invasive tumors, 77% had a tumor measuring >5 cm, and 81% had disease at unfavorable sites. Fusion genes involving forkhead box protein O1 (FOXO1) were detected in 56 of 84 patients. Events occurred in 52 patients: 43 developed disease recurrence, 7 had disease that was refractory to treatment, and 2 patients developed second neoplasms. On univariate analysis, unfavorable disease site, tumor invasiveness, Intergroup Rhabdomyosarcoma Study group III, and fusion-positive status correlated with worse prognosis. The 5-year event-free survival rate of patients with fusion-positive tumors was 43% compared with 74% in patients with fusion-negative tumors (P = .01). On multivariate analysis, fusion positivity and tumor invasiveness proved to be unfavorable prognostic markers.

CONCLUSIONS: Fusion status and tumor invasiveness appear to have a strong impact on prognosis in patients with aRMS/N1. Fusion status will be used to stratify these patients in the next EpSSG RMS study, and treatment will be intensified in patients with fusion-positive tumors. Cancer 2018. © 2018 American Cancer Society.

5. **LOCALIZED VAGINAL/UTERINE RHABDOMYOSARCOMA-RESULTS OF A POOLED ANALYSIS FROM FOUR INTERNATIONAL COOPERATIVE GROUPS.** Pediatr Blood Cancer. 2018 Sep;65(9):e27096. doi: 10.1002/pbc.27096. Epub 2018 May 21.

Minard-Colin V, Walterhouse D, Bisogno G, Martelli H, Anderson J, Rodeberg DA, Ferrari A, Jenney M, Wolden S, De Salvo G, ArndtC, Merks JHM, Gallego S, Schwob D, Haie-Meder C, Bergeron C, Stevens MCG, Oberlin O, Hawkins D;

International Society of Pediatric Oncology Sarcoma Committee, the Children's Oncology Group, the Italian Cooperative Soft Tissue Sarcoma Group, and the European pediatric Soft tissue sarcoma Study Group.

Background: Vaginal/uterine rhabdomyosarcoma (VU RMS) is one of the most favorable RMS sites. To determine the optimal therapy, the experience of four cooperative groups (Children's Oncology Group [COG], International Society of PediatricOncology (SIOP)Malignant Mesenchymal Tumor Group [MMT], Italian Cooperative Soft Tissue Sarcoma Group [ICG], and European pediatric Soft tissue sarcoma Study Group [EpSSG]) was analyzed.
Procedure: From 1981 to 2009, 237 patients were identified. Median age (years) at diagnosis differed by tumor location; it was 1.9 for vagina (n = 160), 2.7 for uterus corpus (n = 26), and 13.5 for uterus cervix (n =51). Twenty-eight percent of patients received radiation therapy (RT) as part of primary therapy (23% COG, 27% MMT, 46% ICG, and 42% EpSSG), with significant differences in the use of brachytherapy between the cooperative groups (23% COG, 76% MMT, 64% ICG, and 88% EpSSG).
Results: Ten-year event-free (EFS) and overall survival (OS)were 74% (95% CI, 67–79%) and 92% (95% CI, 88–96%), respectively. In univariate analysis, OS was inferior for patients with uterine RMS and for those with regional lymph node involvement. Although EFS was slightly lower in patients without initial RT (71% without RT vs. 81% with RT; P = 0.08), there was no difference in OS (94% without RT vs. 89% with RT; P = 0.18). Local control using brachytherapy was excellent (93%). Fifty-one (51.5%) of the 99 survivors with known primary therapy and treatment for relapse were cured with chemotherapy with or without conservative surgery.
Conclusions: About half of all patients with VU RMS can be cured without systematic RT or radical surgery. When RT is indicated, modalities that limit sequelae should be considered, such as brachytherapy.

6. **DEMOGRAPHIC AND TREATMENT VARIABLES INFLUENCING OUTCOME FOR LOCALIZED PARATESTICULAR RHABDOMYOSARCOMA: RESULTS FROM A POOLED-ANALYSIS OF NORTH AMERICAN AND EUROPEAN COOPERATIVE GROUPS** *J Clin Oncol*. 2018 Oct 23:JCO2018789388. doi: 10.1200/JCO.2018.78.9388.

Walterhouse D, Barkauskas DA, Hall D, Ferrari A, De Salvo GL, Koscielniak E, Stevens MCG, Martelli H, Seitz G, Rodeberg DA, Shnorhavorian M, Dasgupta R, Breneman JC, Anderson J, Bergeron C, Bisogno G, Meyer WH, Hawkins D, Minard-Colin V.

PURPOSE: Treatment recommendations for localized paratesticular rhabdomyosarcoma (PT RMS) differ in North America and Europe. We conducted a pooled analysis to identify demographic features and treatment choices that affect outcome.
PATIENTS AND METHODS: We retrospectively analyzed the effect of nine demographic variables and four treatment choices on event-free survival (EFS) and overall survival (OS) from 12 studies conducted by five cooperative groups.
RESULTS: Eight hundred forty-two patients with localized PT RMS who enrolled from 1988 to 2013 were included. Patients age ≥ 10 years were more likely than younger patients to have tumors that were > 5 cm, enlarged nodes (N1), or pathologically involved nodes (P ≤ .05 each). With a median follow-up of 7.5 years, Kaplan-Meier estimates for 5-year EFS and OS were 87.7% and 94.8%, respectively. Of demographic variables, cooperative group, era of enrollment, age category, tumor size, Intergroup Rhabdomyosarcoma Study group, and T stage affected EFS (P ≤ .05 each). Surgical assessment of regional nodes, which was performed in 23.5% of patients-usually in those age ≥ 10 years or with suspicious or N1 nodes-was the only treatment variable associated with EFS by univariable and multivariable analyses (P ≤ .05 each) in patients age ≥ 1 year. A variable selection procedure on a proportional hazards regression model selected era of enrollment, age, tumor size, and surgical assessment of regional nodes as significant (P ≤ .05 each) in the EFS model, and era of enrollment, age, tumor size, and histology (P ≤ .05 each) in the OS model.
CONCLUSION: Localized PT RMS has a favorable prognosis. Age ≥ 10 years at diagnosis and tumor size larger than 5 cm are unfavorable prognostic features. Surgical assessment of regional nodes is important in patients age ≥ 10 years and in those with N1 nodes as it affects EFS.

EARLY PHASE TRIALS (BY DR. MICHELA CASANOVA)

BERNIE

The BERNIE study was a joint EpSSG/ITCC randomized phase II study of standard chemotherapy +/- bevacizumab in paediatric metastatic soft tissue sarcoma, sponsored by F Hoffman la Roche.
The results of the study were published on Eur J Cancer in 2017; additional analysis on the role of radiotherapy and on the NRSTS patients are ongoing.

VIT 0910

The VIT 0910 study (randomised phase II study of vincristine and irinotecan (VI) +/- temozolomide (T) in refractory/relapsed RMS) is a joint ITCC/EpSSG investigator initiated study sponsored in Lille, France. The Principal Investigator is Dr Anne-Sophie Defachelles.

The trial was opened in 37 centres, from five countries (France, UK, Italy, the Netherlands and Spain). Firstly, 80 patients were included between 14.03.2012 and 19.06.2014. As preliminary results indicated that more precision was needed, 40 additional patients in the relapse status have been enrolled between 17.06.2016 and 06.04.2018, up to 120 patients (60 patients in the VI arm and 60 patients in the VIT arm).

The main objective of the study was to evaluate the efficacy of VI and VIT regimens in terms of objective response rate after2 courses of treatment in patients with recurrent or refractory rhabdomyosarcoma, separately in each treatment arm. The trial was initially designed as a randomised Phase II trial, with no comparison between randomized treatment arms. This latter objective has been added in an amendment.
Preliminary results of the final analysis showing a better response rate for the VIT arm were discussed in the Utrecht meeting. The complete data will be presented at ASCO 2019.

REGORAFENIB

The phase 1b expansion cohort to evaluate safety and tolerability of regorafenib combined with vincristine/irinotecan (VI) in patients with relapsed/refractory RMS and other solid tumors (Ewing sarcoma, hepatoblastoma, Wilms tumor and neuroblastoma) was introduced as an amendment in the regorafenib pediatric phase 1 study, sponsored by Bayer.
In monotherapy regorafenib in pediatric subjects resulted to be tolerable across dose levels and the safety was consistent with the known safety profile in adults. The RP2D of regorafenib as a single agent in children and adolescents with solid tumors is 82 mg/m2 taken orally qd in a 3 weeks on/1 week off schedule. The only partial response observed was in a patient with an alveolar rhabdomyosarcoma.
The dose expansion phase 1b is ongoing and it is active in 25 centres, from 4 countries (France, UK, Italy, and Spain). The expansion phase study design was agreed with PDCO in the context of Stivarga PIP.

If the combination of regorafenib and VI will result to be feasible and of interest, it will be incorporated in the relapsed randomized phase II study part of FaR-RMS.

The early phase trials committee continues to work with pharma and the EpSSG Biology Committee to facilitate access to new agents for the FaR-RMS trial and other indications. There are ongoing efforts on the proposal to include volasertib in FaR-RMS.

- During the recent SIOP congress 2018 held in Kyoto, Japan the following abstracts were presented by EpSSG members:

1. INDETERMINATE PULMONARY NODULES AT DIAGNOSIS IN PEDIATRIC RHABDOMYOSARCOMA: ARE WE UNDERTREATING PATIENTS? A REPORT FROM THE EUROPEAN PAEDIATRIC SOFT TISSUE SARCOMA STUDY GROUP-RMS-2005 STUDY

B. Vaarwerk, I. Zanetti, G.L. De Salvo, N. Corradini, M. Jenney, D. Orbach, J. Chisholm, A. Ferrari, C. Morosi, H. Brisse, K. McHugh, G. Bisogno, R. van Rijn, H. Merks.

2. SOFT TISSUE SARCOMA: 18 YEARS SINGLE CENTER EXPERIENCE

M. Mikeskova, I. Beder, A. Kolenova, S. Jakesova

3. DOES EARLY DETECTION WITH OFF-THERAPY SURVEILLANCE IMAGING IMPROVE SURVIVAL IN PEDIATRIC RHABDOMYOSARCOMA PATIENTS? THE EUROPEAN EXPERIENCE

B. Vaarwerk, C. Mallebranche, M.R. Adams, M. Jenney, M. C. Affinita, G. Bisogno, K. McHugh, R. R. van Rijn, D. Orbach, J. H.M. Merks.

- During the recent ASCO meeting 2018 the following abstract was presented in the plenary session the 3rd of June the EpSSG chair.

1. MAINTENANCE LOW-DOSE CHEMOTHERAPY IN PATIENTS WITH HIGH-RISK (HR) RHABDOMYOSARCOMA (RMS): A REPORT FROM THE EUROPEAN PAEDIATRIC SOFT TISSUE SARCOMA STUDY GROUP **(EpSSG).**

B. Bisogno, G.L. De Salvo, C. Bergeron, M. Jenney, J.H. Merks, V. Minard-Colin, D. Orbach, H. Glossli, J. Chisholm, M. Casanova, S. Gallego, A. Ferrari.

FINANCIAL STATEMENT 2018 (BY DR. J.H.M. MERKS)

Total income for the association in 2018 was €7.800, mainly from members' fees and meeting registration. Interest on accounts and investments was €500,00.

Total expenses were €29.616; Datamanager/statistician salary (€15.000) annual and Board meeting costs (€4.491) accountant's costs (€1125) Travel costs (€2000) and website costs (€7000).

For 2019 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.

An accountancy report was presented during the EpSSG general assembly held at the Oslo spring meeting in 2018. A Treasurer's Report of the final year's account was presented and approved during the EpSSG Winter meeting held in Utrecht 2018.

Funding Sources: The EpSSG is indebted to the Kick Cancer Foundation, founded by one of our parents, Delphine Heenen and King Baudouin Foundation for supporting a new EpSSG data manager and for supporting preclinical pilot research directly supporting the biological studies planned within the EpSSG FaR-RMS study.

WORKPLAN IN 2019

1. Increased communication with members through the use of our New EpSSG Website and emails, increased networking time at meetings.
2. Enhanced EpSSG Subcommittee activities and involvement
3. "Maintaining a constant and programmed" data delivery from the International data Centre
4. Increased and consolidated EpSSG analysis (IDC) and publications
5. 4rth EpSSG Report: finalize and share Report 2018
6. New FaR RMS protocol: prepare for the launch of the new protocol in 2019
7. Funds for EpSSG projects
8. Increased EpSSG collaboration with Parents: gathered ideas for a "Parents corner" to be setup in the New EpSSG Website.

Help support the EpSSG Association

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.

photograph taken by dr. Andrea Ferrari

DONATE to EpSSG

Association meetings - Calendar 2018-2019

DATE	MEETING	LOCATION	NOTES
2018			
May 10-11 (Th-Fr)	EpSSG Spring Meeting & Association Assembly	Oslo Local organizer: Heidi Glosli	PERFORMED
December 6-7 (Th-Fr)	EpSSG Winter Meeting & Association Assembly	Utrecht Local organizer: Hans Merks	PERFORMED
2019			
May 20-25 (Mo-Sat)	EpSSG Spring Meeting & Association Assembly	SIOPE Congress, Prague, Czech Republic	CONFIRMED
December 5-6 (Th-Fr)	EpSSG Winter Meeting & Association Assembly	London	CONFIRMED