E*p*SSG
NRSTS 2005

a protocol for

Localized Non-Rhabdomyosarcoma Soft Tissue Sarcomas

VERSION 1.2

JANUARY 2014

Contents

1. Administrative organisation

1.1 PROTOCOL SPONSOR

It is responsibility of each participating national Group or Institutions to arrange sponsorship in line with the requirements of the European Union directive on Good Clinical Practice in Clinical Trials.

1.2 PROTOCOL COORDINATION

The protocol is co-ordinated by a Trial Monitoring Committee under the supervision of **European paediatric Soft Tissue Sarcoma Study Group** (in its abbreviated form **E*p*SSG**) Board.

This study will not introduce or try to license chemotherapeutic agents for treatment of paediatric sarcoma. Treatment will rely on already licensed and introduced chemotherapeutic drugs. Therefore, chemotherapeutic agents and other therapeutic substances needed for treatment in EpSSG NRSTS 2005 will not be paid for by the study nor will these substances be provided by pharmaceutical companies.

Important note:
It is emphasised that no legal responsibility for possible consequences resulting from the application of recommendations from this protocol will be taken by the members of the EpSSG. Treatment and follow-up of patients with soft tissue sarcoma requires a high degree of medical competence and humane presence existing only in hospitals with adequate infra-structure. A state of emergency due to complications from the underlying disease or from its treatment can develop in every patient at any time. Children with soft tissue sarcomas should thus be treated by an experienced team with multidisciplinary competences.

1.3 EPSSG AND NRSTS 2005 STRUCTURE

EpSSG BOARD

Dr. Christophe Bergeron Institut d'Hémato-Oncologie Pédiatrique (IHOP) 28 rue Laennec, 69800 Lyon, France Tel 33 (0)4 78 78 26 06 Fax 33 (0)4 78 78 27 03 E-mail: bergeron@lyon.fnclcc.fr	***Dr. Gianni Bisogno*** Haematology/Oncology Division Department of Paediatric, Via Giustiniani, 3 - 35128 Padova, Italy Tel +39 049 8211481 Fax +39 049 8211462 E-mail: gianni.bisogno@unipd.it
Dr. Julia Chisholm Department of Haematology and Oncology, Great Ormond Street Hospital for children London, WC1N 3JH, UK Tel.: + 44 (0) 20 7829 8832 Fax: + 44 (0) 20 7813 8588 E-mail: chishj@gosh.nhs.uk	***Dr. Gian Luca De Salvo*** International Data Centre Clinical trials and Biostatistics Unit "Istituto Oncologico Veneto" Via Gattamelata 64 - 35128 Padova, Italy Tel +39 049 8215704 Fax +39 049 8215706 E-mail: gianluca.desalvo@ioveneto.it; epssg@ioveneto.it
Dr. Andrea Ferrari Pediatric Oncology Unit, Istituto Nazionale Tumori, Via G. Venezian 1, 20133 Milano, Italy Tel +39 02 23902588 Fax +39 02 23902648 E-mail: andrea.ferrari@istitutotumori.mi.it	***Dr. Soledad Gallego*** *Paediatric Oncology,* *Hospital Universitario Vall d´Hebron* *Pº Vall d´Hebron 119-129, 08035 Barcelona, Spain* *Tel +34 93 4893090* *E-mail: sgallego@vhebron.net*
Dr. Meriel Jenney Children Hospital for Wales Cardiff and Vale NHS Trust Heath Park Cardiff CF 14 4XW Tel +44 29 2074 2107 E-mail: meriel.jenney@wales.nhs.uk	***Dr. Hans Merks*** Department of Pediatric Oncology Emma Children's Hospital - Academic Medical Center - University of Amsterdam Floor F8-Room 245 Meibergdreef 9 Tel +31 20 5663050 Fax +31 20 6912231 E-mail: j.h.merks@amc.uva.nl
Dr. Daniel Orbach Department of children, adolescents and young adults, Institut Curie 26 rue d'Ulm - 75995 Paris, France Tel +33 (0)1 44 32 45 51 Fax +33 (0)1 53 10 40 05 E-mail: daniel.orbach@curie.fr	

E*p*SSG NRSTS 2005 TRIAL MANAGEMENT COMMITTEE

Dr. Andrea Ferrari (Coordinating Investigator) Pediatric Oncology Unit, Istituto Nazionale Tumori, Via G. Venezian 1, 20133 Milano, Italy Tel +39 02 23902588 Fax +39 02 23902648 E-mail: andrea.ferrari@istitutotumori.mi.it	***Dr. Gianni Bisogno*** Haematology/Oncology Division Department of Paediatric, Via Giustiniani, 3 - 35128 Padova, Italy Tel +39 049 8211481 Fax +39 049 8211462 E-mail: gianni.bisogno@unipd.it
Dr. Bernadette Brennan Royal Manchester Children's Hospital, Hospital Road, Manchester, M27 4HA Tel +44 161 922 2227 Fax +44 161 728 3529 E-mail: bernadette.brennan@cmft.nhs.uk	***Dr. Michela Casanova*** Pediatric Oncology Unit, Istituto Nazionale Tumori, Milano Via G. Venezian 1, 20133 Milano, Italy Tel +39 02 23902588 Fax +39 02 23902648 E-mail: michela.casanova@istitutotumori.mi.it
Dr. Gian Luca De Salvo International Data Centre Clinical trials and Biostatistics Unit "Istituto Oncologico Veneto" Via Gattamelata 64 - 35128 Padova, Italy Tel +39 049 8215704 Fax +39 049 8215706 ***E-mail:*** *epssg@ioveneto.it*	***Dr. Nadine Francotte*** Département de Pédiatrie CHC-Clin Espérance - rue Saint Nicolas B.4420 Montegnée Tel 3242249111/ 3242249140 E-mail: nadine.francotte@chc.be
Dr. Anna Kelsey Department of Diagnostic Paediatric Histopathology Royal Manchester Childrens Hospital - 4th Floor Oxford Road Manchester M13 9WL Tel 0161 701 2247 Fax. 0161 701 2249 E-mail: anna.kelsey@cmft.nhs.uk	***Dr. Daniel Orbach*** Department of children, adolescents and young adults, Institut Curie 26 rue d'Ulm - 75995 Paris, France Tel +33 (0)1 44 32 45 51 Fax +33 (0)1 53 10 40 05 E-mail: daniel.orbach@curie.fr
Dr. Max Van Noesel Erasmus MC/Sophia Children's Hospital Dept. of Pediatric Oncology-Hematology Dr. Molewaterplein 60 3015 GJ Rotterdam, The Netherlands Tel +31-10-463 2073/6691 Fax +31-10-463 6801 E-mail: m.vannoesel@erasmusmc.nl	

E*p*SSG PANEL COORDINATORS

Surgery	***Prof. Helene Martelli*** Service de Chirurgie Pédiatrique, Hôpital de Bicêtre, 78, rue du Général Leclerc 94275 Le Kremlin-Bicetre, Cedex, France Tel 33 (0)1 45 21 20 92 Fax 33 (0)1 45213189 E-mail: helene.martelli@bct.ap-hop-paris.fr
Radiotherapy	***Dr Henry C. Mandeville*** Consultant Clinical Oncologist Children's & Young Person's Unit & Haemato-oncology Unit The Royal Marsden NHS Foundation Trust T: 0208 661 3329 (CYPU)/ 0208 661 3272 (Haem) F: 0208 661 3617 (CYPU)/ 0208 915 6791 (Haem) E-mail: Henry.Mandeville@rmh.nhs.uk
Pathology	***Dr. Anna Kelsey*** Department of Diagnostic Paediatric Histopathology Royal Manchester Childrens Hospital - 4th Floor Oxford Road - Manchester M13 9WL Tel 0161 701 2247 Fax. 0161 701 2249 E-mail: anna.kelsey@cmft.nhs.uk
Biology	***Dr. Janet Shipley*** Unit of Molecular Haematology Inst. of Child Health and Great Ormond Street Hospital 30 Guilford Street, London WC1N 1EH, UK Tel +44 (0)207 905 2265 Fax +44 (0)207 813 8100 E-mail: Janet.Shipley@icr.ac.uk
Radiology	***Dr. Kieran McHugh*** Radiology Department, Great Ormond Street Hospital London WC1N 3JH, UK Tel 00442074059200 Fax 00442078298665 E-mail: kmchugh@gosh.nhs.uk
Biostatistics	***Dr. Gian Luca De Salvo*** International Data Centre Clinical trials and Biostatistics Unit "Istituto Oncologico Veneto" Via Gattamelata 64 - 35128 Padova, Italy Tel +39 049 8215704 Fax +39 049 8215706 E-mail: epssg@ioveneto.it

EPSSG INTERNATIONAL DATA CENTRE

Dr. Angela De Paoli International Data Centre: Clinical trials and Biostatistics Unit "Istituto Oncologico Veneto" Via Gattamelata 64 - 35128 Padova, Italy Tel +39 049 8215704 Fax +39 049 8215706 E-mail: angela.depaoli@ioveneto.it; epssg@ioveneto.it	*Dr. Ilaria Zanetti* Haematology/Oncology Division Department of Paediatric, Via Giustiniani, 3 - 35128 Padova, Italy Tel +39 049 8215465 Fax +39 049 8213166 E-mail: ilaria.zanetti@unipd.it; epssg@ioveneto.it

REMOTE DATA ENTRY SYSTEM

Dr. Marisa De Rosa Systems and Services for Health CINECA - www.cineca.it Via Magnanelli 6/3, 40033 Casalecchio di Reno, Bologna, Italy Tel +39 051 6171411 Fax +39 051 6132198 E-mail: m.derosa@cineca.it	*Dr. Anna Covezzoli* Systems and Services for Health CINECA - www.cineca.it Via Magnanelli 6/3, 40033 Casalecchio di Reno, Bologna, Italy Tel +39 051 6171411 Fax +39 051 6132198 E-mail: a.covezzoli@cineca.it

Protocol NRSTS 2005 – National Coordinators

COUNTRY	*NATIONAL COORDINATOR*	*ADDRESS*
Argentina	*Marcelo Scopinaro*	Hospital de Pediatria "Prof. Dr. Juan P. Garrahan" Calle Pichincha 1890, 1245 Buenos Aires mscopinaro@intramed.net.ar
Belgium	*Nadine Francotte*	SUHOPL (Service Interhospitalier Univeritaire d'Hématologie et d'Oncologie Pédiatrique Liégeois) - rue Saint Nicolas 447-449 B 4420 Montegnée Tel 3242249111/ 3242249139 nadine.francotte@chc.be
Czech Rep	*Peter Mudry*	Department of Pediatric Oncology University Children´s Hospital Brno Cernopolni 9 - 662 63 Brno Tel +420 532 234 614 Fax + 420 532 234 614 pmudry@fnbrno.cz
Denmark	*Niels Clausen*	Dept of Pediatrics, Skejby hospital, DK-8200 Aarhus Tel +45-89 49 68 58 nc@dadlnet.dk
France	*Daniel Orbach*	Department of children, adolescents and young adults, Institut Curie 26 rue d'Ulm - 75995 Paris, France Tel +33 (0)1 44 32 45 51 Fax +33 (0)1 53 10 40 05 E-mail: daniel.orbach@curie.fr
Israel	*Myriam Weyl Ben Arush*	Pediatric Hematology Oncology Department Meyer Children's Hospital Rambam Medical Center Bat Galim Street Haifa 31096, Israel Tel 48543002 Fax 48542007 m_benarush@rambam.health.gov.il
Italy	*Andrea Ferrari*	Pediatric Oncology Unit, Istituto Nazionale Tumori Milano Via G. Venezian 1 - 20133 Milano Tel +39 02 23902588 Fax +39 02 23902648 andrea.ferrari@istitutotumori.mi.it
Norway	*Heidi Glosli*	Department of Pediatrics Rikshospitalet-Radiumhospitalet HF, N-0027 Oslo Tel +47 23 07 45 93 heidi.glosli@rikshospitalet.no

Slovakia	*Daniela Sejnova*	University children's Hospital Limbova, 1 833 40 Bratislava, Slovakia Tel / Fax +421 2 59371 583 sejnova@dfnsp.sk
Slovenia	*Maja Česen Mazić*	Pediatrična Klinika Univerzitetni Klinični Center Ljubljana Bohoričeva 20, 1525 Ljubljana Phone: +38641365384 Fax: +38615224036 maja.cesenmazic@kclj.si majacesen@yahoo.com
Spain	*Soledad Gallego*	Paediatric Oncology, Hospital Universitario Vall d´Hebron Pº Vall d´Hebron 119-129, 08035 Barcelona Tel +34 93 4893090 sgallego@vhebron.net
Switzerland	*Felix Niggli*	Paediatric Oncology University Children's Hospital Steinwiesstrasse 75 - CH-8032 Zürich Tel +41 44 266 7823 Fax +41 44 266 7171 felix.niggli@kispi.unizh.ch
The Netherlands	*Max van Noesel*	Dept of Pediatric Oncology-Hematology Erasmus MC-Sophia Children's Hospital Dr. Molewaterplein 60 - 3015 GJ Rotterdam Tel 31-10-463 2073/6691 Fax 31-10-463 6801 m.vannoesel@erasmusmc.nl
United Kingdom and Ireland	*Bernadette Brennan*	Royal Manchester Children's Hospital, Hospital Road, Manchester M27 4HA Tel +44 161 922 2227 Fax +44 161 728 3529 bernadette.brennan@cmmc.nhs.uk

2. Abbreviations

EpSSG = European paediatric Soft Tissue Sarcoma Study Group
CWS, GPOH = Co-operative Weichteilsarkom Studie, Gesellschaft für pädiatrische Onkologie und Hämatologie
ICG, AIEOP-STSC = Italian Cooperative Group, Associazione Italiana Ematologia Oncologia Pediatrica – Soft Tissue Sarcoma Committee
SIOP-MMT = Societè Internationale d'Oncologie Pediatrique / International Society of Paediatric Oncology - Malignant Mesenchimal Tumour Committee
UKCCSG = United Kingdom Children's Cancer Study Group
SFCE = Societè Francaise des Cancers d'Enfants
SEOP = Sociedad Espanola de Oncologia Pediàtrica
NOPHO = Nordic Organisation of Pediatric Hematology and Oncology
BSPHO = Belgian Society of Paediatric Hematology Oncology
DCOG = Dutch Childhood Oncology Group
IRS = Intergroup Rhabdomyosarcoma Study
POG = Pediatric Oncology Group
COG = Children Oncology Group
NCI = National Cancer Institute

RMS = rhabdomyosarcoma
NRSTS = non-rhabdomyosarcoma soft tissue sarcomas
STS = soft tissue sarcomas
pPNET = peripheral primitive neuroectodermal tumour
MPNST = malignant peripheral nerve sheath tumour
NF1 = neurofibromatosis type 1
GIST = gastro-intestinal stromal tumour
DSRCT = desmplastic small round cell tumour

TNM = tumour – node – metastasis
FNCLCC = French Federation of Cancer Centers Sarcoma Group
OS = overall survival
EFS = event-free survival
LRFS = local relapse-free survival
MFS = metastases-free survival
CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease

S = surgery
RT / RXT = radiotherapy
GTV = gross tumour volume
CTV = clinical target volume
PTV = planning target volume
CT= chemotherapy
IFO = ifosfamide
DOXO = doxorubicin
G-CSF = granulocyte colony stimulating factor
VA = vincristine-actinomycin
VAC = vincristine-actinomycin-cyclophosphamide
VAdrC = vincristine-adriamycin-cyclophosphamide
VACA = vincristine-actinomycin-cyclophosphamide-adriamycin
VAIA = vincristine-actinomycin-ifosfamide-adriamycin
CEVAIE = carboplatin-etoposide-vincristine-actinomycin-ifosfamide-epirubicin
CT-scan = computed tomography scan
MRI = magnetic resonance imaging
CTC = common toxicity criteria
IDMC = International Data Monitoring Committee
RDE = Remote Data Entry

3. Summary

The NRSTS 2005 protocol addresses the treatment of children and young people presenting with non-metastatic non-rhabdomyosarcoma soft tissue sarcomas (NRSTS).

Soft tissue sarcomas (STS) are rare, with an annual incidence around 2-3/100,000: they account for less than 1% of all malignant tumours and 2% of all cancer-related deaths. In paediatric age, however, about 8% of all malignancies are STS, with RMS representing approximately 55-60% of them. The so called "non-rhabdomyosarcoma" soft tissue sarcomas (NRSTS) account for about 3-4% of paediatric cancers and constitute a very heterogeneous group of tumours with a variety of histotypes with different origins, biology and natural history, some of which are more common in adults.
Most of the experience of treatment for paediatric NRSTS derives from the experience of managing the same diseases in adults or is based on the principles derived from the management of RMS.
Despite the global incidence of NRSTS is not so far from that of RMS, the large heterogeneity of this group and the rarity of each single histoptype prevents the performance of clinical trials on a single tumour type, and NRSTS consequently have to be treated and studied as a group.

The E*p*SSG NRSTS protocol is completely dedicated to NRSTS, with three separate sections:

1. A prospective non-randomized historically-controlled trials for **synovial sarcoma**
2. A prospective non-randomized historically-controlled trials for **"adult-type" soft tissue sarcomas**
3. General considerations and suggestions forthe so-called **"other histotypes"** (reported in the appendix)

Patients with **undifferentiated sarcomas and malignant ectomesenchymoma** are registered in the NRSTS protocol, but they need to be treated according to the E*p*SSG RMS 2005 protocol. These patients should be treated according to the RMS guidelines, but they should not be included in the RMS protocol (i.e. they should not be randomized)

Patients with **extraosseous pPNET/Ewing sarcomas** are not included in the E*p*SSG NRSTS 2005 study. However, these patients can be registered in the EpSSG website.

The E*p*SSG NRSTS 2005 protocol is a protocol for non-metastatic patients.
NRSTS patients with metastases should be included in stage IV protocol of E*p*SSG or according to specific EpSSG recommendations and should be registred in the Cineca databe.
An exception is represented by **rhabdoid tumours**: patients with metastatic rhabdoid tumours should be treated according to the guidelines defined for localised disease (see 19.2 and appendix)

3.1 Objectives:

First objective of the study is to make uniform the treatment of NRSTS patients in Europe.
Patients will be treated with a risk-adapted multidisciplinary treatment approach.

In particular, the protocol aims to investigate, as main objectives:

- the survival rates (event-free survival EFS and overall survival OS) and the pattern of treatment failure in patients with synovial sarcoma and adult-type sarcomas
- for synovial sarcoma: a) the role of high-dose ifosfamide in improving response rate in patients with unresectable disease (efficacy question); b) the possibility to reduce toxicity (no anthracyclines, less hematological toxicity), reduce costs and improve quality of life (no hospitalization) without jeopardizing the results utilizing high-dose ifosfamide instead of ifosfamide-doxorubicin chemotherapy in those cases requiring chemotherapy according to the risk stratification (toxicity question)
- for adult-type soft tissue sarcomas: the role of an ifosfamide-doxorubicin regimen in improving the response rate in patients with unresectable disease

Secondary objectives will be:

- the prospective evaluation of clinical/pathological prognostic factors,
- the impact of the omission of adjuvant chemotherapy in synovial sarcoma patients with tumour smaller than 5 cm
- the role of adjuvant chemotherapy in IRS group I-II, G3, size > 5 cm adult-type soft tissue sarcoma patients in improving the metastases-free survival (MRS) and the OS

Moreover, the study aims to improve the biological studies and samples collection of these malignancies.

3.2 Patients eligibility

Registration is recommended for all patients with diagnosis of NRSTS
Inclusion in the prospective non-randomized historically-controlled trial require:

- Pathologically proven diagnosis of synovial sacomas or adult-type soft tissue sarcomas
- Age less than 21 years
- No evidence of metastatic disease
- No previous treatment except for primary surgery
- Diagnostic specimens available for pathological review
- Written consent

3.3 Patients stratification

Adult Oncology Groups utilised different staging systems for soft tissue sarcomas, including histological grading, tumour size, tumour depth, degree of surgical resection and sometimes age.
In agreement with previous paediatric studies, stage of disease will be defined according to both

1. the clinical tumour-node-metastases (TNM) staging classification
2. the Intergroup Rhabdomyosarcoma Study (IRS) post-surgical grouping system.

For adult-type NRSTS, patients stratification needs to be performed according to

- IRS group
- tumour size
- tumour grade

Tumour grade, assessed according to the FNCLCC System, is required in all cases, regardless of its predictability of the clinical/biological outcome, because for the NRSTS 2005 protocol is a parameter that guides the choice of treatment (and in particular the indication to adjuvant chemotherapy).

For synovial sarcoma, patients stratification needs to be performed according to

- IRS group
- tumour size
- tumor sites (patients with tumor arising at axial sites should be treated as those with group III or N1 tumor)

(synovial sarcoma has to be considered as a high grade tumour in all cases)

3.4 Pathology and biology

The sample collection of NRSTS needs to be improved and this is one of the aim of this protocol.
For the pathologists, one of the most debated and complex subject on NRSTS concerns the definition of tumour grade, which is predictive for clinical outcome and essential to guide the treatment choice. It is well know that different grading systems are available (NCI, POG, FNCLCC), but unfortunately an universally accepted system does not exist still today.

For the E*p*SSG NRSTS protocol, the **FNCLCC grading system** will be adopted to give to the clinicans the tumour grade essential to define the treatment choice.

Translational research on NRSTS will be strengthened.

3.5 Statistical considerations

The study on synovial sarcomas and adult-type soft tissue sarcomas is a prospective, non-randomised, observational, international, multi-institutional, and historically-controlled study.

For “other histotypes”, only general considerations and suggestions are provided.

3.6 Organization of the study

The E*p*SSG is an inter-group structure which is based on the already existing national and international organisations. The existing national coordinating centers will continue their work ensuring pathology review, clinical advice and data quality control.
New clinical centres, whose national group does not take part as a whole, who wish to participate must demonstrate their ability to participate in the study and must link to one of the existing co-operative Groups.
The E*p*SSG Co-ordinating Centre will supervise the data collection and data quality and will be responsible for the statistical analysis within the trial at given time periods in collaboration with the panel of statisticians from individual groups.

3.7 Data mangement and analysis

The E*p*SSG NRSTS trial will be managed via a web based system provided by **CINECA** (Casalecchio, Italy). Standard Operative Procedures for the electronic data management will be agreed on and followed by the Co-ordinating Centres.
Reports on the study progress will be prepared twice yearly, describing accrual of the patients, group allocations, local therapy modalities and toxicity of the treatments given. This report will be circulated to the Principal Investigators.
The international study committee shall meet as appropriate to consider patient accrual, eligibility, treatment allocation and outcome and ensure a smooth conduct of the study.
An International Data Monitoring Committee (IDMC) is not required because the trial is not an investigational trial.

3.8 Ethical considerations

The E*p*SSG NRSTS 2005 protocol follows the EU Clinical Directive 2001/20/EC for non-commercial clinical trials, in according to the Good Clinical Practice guidelines. National implementation of the directives is a matter of current debate, and possibly divergent views between Member States could be present. As a consequence, different national groups may need deal differently with the protocol in order to address relevant ethical and insurance requirements.
The protocol is not an investigational trial: therefore, the decision to submit it, before patients enrolment, to the Ethics Committee of each centre for review and approval according to in force law depends to the each national group.
The patient’s and/or parent’s written consent is required for data management and for collecting samples for biological studies (sending diagnostic material to reference institutions, which in all participating countries has to conform to the national data protection legislation). The need for a written consent for participating in the study depends on the indication of each national group.

TREATMENT SUMMARY

SYNOVIAL SARCOMA

- limbs, IRS group I, ≤ 5 cm → surgery only
- limbs, IRS group I, > 5 cm → high-dose IFO x 3
- limbs, IRS group II, ≤ 5 cm → surgery ± RXT 50.4 Gy *
- limbs, IRS group II, > 5 cm → high-dose IFO x 4 ± RXT 54 Gy*

  * RXT could be avoided in selected cases (option B)

- IRS group III or N1 or axial sites → high-dose IFO x 5+ best local treatment (S ± RXT)

ADULT-TYPE STS

- group I, ≤ 5cm → surgery alone
- group I, > 5cm
  - G1 → surgery alone
  - G2 → RXT 50.4 Gy
  - G3 → IFO-DOXO x 3 - IFO x 2 + RXT 50.4 Gy – IFO-DOXO x 1
- IRS Group II / N0
  - G1 → surgery alone
  - G2-G3, ≤ 5 cm → RXT 54 Gy
  - G2, > 5 cm → RXT 54 Gy
  - G3, > 5 cm → IFO-DOXO x 3 - IFO x 2 + RXT 54 Gy - IFO-DOXO x 1
- IRS III & N1 → IFO-DOXO x 3 – best local treatment (S ± RXT ± IFO x 2) ± IFO-DOXO x 2

4. Background

Soft tissue sarcomas are a very heterogeneous group of non-epithelial extraskeletal malignancies that are classified on a histogenic basis according to the adult tissue they resemble. Different histotypes with different biology and clinical behaviour are included in the group of NRSTS. Some of these tumours are more frequently found in adult age and many of which are very rare in childhood.
NRSTS can arise, generally as a soft part enlarging mass, anywhere in the body (most frequently in the muscles of extremities, less usually in the trunk or head and neck region). They occur at any age, but some subtypes are particularly typical of adolescents, i.e. synovial sarcoma, malignant peripheral nerve sheath tumours (MPNST) and fibrosarcoma (liposarcoma and malignant fibrous histiocytoma the most common histotypes in adult age).
Usually, they are characterized by local aggressiveness; their propensity to metastasize is directly correlated to their grade of malignancy. Different histotypes with the same grade of malignancy could display the same clinical behaviour. Generally, low-grade tumours usually may have local aggressiveness but low tendency to metastatic spread. High-grade tumours are more frequent and have a more invasive behaviour with high propensity to metastasize (in particular at the lung).

Overall, the survival rate for soft tissue sarcomas averages 60%, with substantial differences according to the different histotypes, the degree of malignancy, and the stage of the disease. The treatment of patients with soft tissue sarcomas is complex and necessitates multidisciplinary approach.
Surgery is the mainstay of treatment in NRSTS. Quality of surgery is critical, and it is felt that soft tissue sarcoma patients should be referred to specialist centers for local treatment, preferably prior to undergoing biopsy. In particular, deep and large (i.e. in excess of 5 cm) soft tissue lesions are highly suspicious for sarcomas, and they should be referred to centers of excellence.
Inadequate surgical margins adversely affect the local outcome, and - as a consequence – the overall survival, although some experiences in adult soft tissue sarcomas failed to find a strong correlation between quality of surgery and final outcome (various studies showed that what was relevant for distant metastases and therefore disease-specific survival was the intrinsic biological aggressiveness of the tumour, as defined by size, depth, malignancy grade and histotype, whereas, in this sense, the quality of surgical margins and the local recurrence might be well regarded as an additional biological marker of aggressiveness, i.e. a result rather than a cause).

With the exception of pPNET/Ewing sarcomas (and partially of synovial sarcomas), NRSTS are generally considered poorly chemosensitive tumours. However, knowledge regarding chemotherapy responsiveness is clearly incomplete and must be improved. In addition, prognostic factors in paediatric NRSTS are not completely defined and it is uncertain whether they are the same of those identified in adult sarcomas.
Despite the global incidence of NRSTS being not so far from that of RMS, the published studies available on paediatric NRSTS are definitely less than those on RMS.

The only published multicenter study is that of Pediatric Oncology Group (POG) that reported the results of a prospective randomised trail of adjuvant chemotherapy in patients with surgically resected NRSTS. The trial was conducted from 1986 to 1992: IRS group I patients were randomized to be observed or to receive adjuvant chemotherapy (VAC/VAdrC), group II patients received radiotherapy and then were randomly assigned to receive or not chemotherapy. Unfortunately, only 30 out of the 81 eligible patients accepted randomization: therefore, only 15 patients were assigned to each arm. For the whole series, 5-year EFS and OS were 72.2% and

84.5%, respectively. No statistically significant differences were observed between patients treated or not treated with chemotherapy. Tumour grade was identified as the most important predictor of outcome *(Pratt CB, 1999).*

The St Jude Children's Research Hospital reported a large single-institution experience with surgically-resected *(Spunt SL, 1999)* and initially unresected non-metastatic NRSTS *(Spunt SL, 2002).* In the series of 121 IRS group I-II patients, 5-year EFS and OS were 77% and 89% respectively. Statistical analysis confirmed the prognostic role of surgical margins, local invasiveness, tumour grade and, in particular, tumour size *(Spunt SL, 1999)*.

In the series of 40 initially-unresected patients, 5-year EFS and OS were 33% and 56% respectively. These patients presented high-risk features at diagnosis. Response rate to primary chemotherapy was 37%, but the response to therapy did not predict the outcome. Most treatment failures were local, and post-relapse survival was poor (19%) *(Spunt SL, 2002).*

More recently, the retrospectively-analysed single-institution series from the Istituto Nazionale Tumori of Milan, Italy, parallels the two studies reported by the St Jude *(Ferrari A, J Clin Oncol, 2005)*.

The series includes 182 patients aged less than 18 years treated between 1977 and 2003: the most frequent histotype was synovial sarcoma (32% of cases), followed by MPNST (17%). Overall, 102 patients received complete resection at diagnosis. Radiotherapy was given to 73 patients. Chemotherapy was administered to 114 patients, 70 of them as adjuvant therapy. Reported survival rates at 5 years were as follow: EFS 63%, LRFS 75%, MFS 72%, OS 76%. Local invasiveness and tumour size represented the most significant prognostic factors.

In patients with grossly-resected disease (136 patients, 5-year EFS and OS 72% and 86%), adjuvant chemotherapy was given to 52% of cases. The authors reported the analysis of patients with adult-type STS (excluding synovial sarcomas) at high risk of metastatic failure (i.e. IRS group I-II, size > 5 cm, G3): in this subset of 15 patients, 5-year MFS was 36%, and it was 53% in patients treated with adjuvant chemotherapy (11 cases) and 0% in those treated without chemotherapy (4 cases). Post-operative radiotherapy seemed to have an impact on local control and outcome in IRS group I patients considered at high-risk of local control due to large tumour size and in IRS group II patients.

In patients with initially unresected disease (40 cases – EFS and OS 45% and 52%, respectively), the overall response rate was 39% in terms of complete and partial response (CR+PR), but it was 58% when minor responses were included (some cases - initially considered unresectable - had complete delayed surgery after minor response to chemotherapy; in these tumours, generally regarded as poor responders to chemotherapy, also minor tumour shrinkage may have a significant value). Response rate was better in those cases treated with regimens including ifosfamide and antracyclines. The outcome was directly influenced by the response to primary chemotherapy and the possibility to obtain complete tumour resection *(Ferrari A, J Clin Oncol, 2005)*.

4.1 References

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5. Study structure

The protocol containes three separate sections:
1 – synovial sarcoma
2 – "adult-type" soft tissue sarcomas
3 – "other histotypes"

6. Patient eligibility

Eligibility criteria for the prospective non-randomized historically-controlled trials are the following:

- A pathologically proven diagnosis of **synovial sarcoma** and **adult-type soft tissue sarcomas**
- **No** evidence of metastatic lesions
- Age less than **21 years** (20 years and 364 days) of age
- No previous treatment except for primary surgery
- No previous malignancy
  Patients with post-irradiation soft part sarcomas could be registered and treated according to the protocol guidelines, but they will be analysed separately
- For patients who require adjuvant chemotherapy according to protocol guidelines, no pre-existing illness preventing treatment (in particular renal function must be equivalent to grade 0-1 nephrotoxicity, no prior history of cardiac disease and normal shortening fraction [> 28%] and ejection fraction [> 47%])
- Diagnostic material available for pathology review
- Available for long term follow up through the treatment centre
- Written informed consent for treatment available.

Note:
A limit of interval between the diagnostic surgical approach and the start of chemotherapy (for those patients who require chemotherapy according to protocol guidelines) is not required for patient eligibility. All the NRSTS cases will be considered eligible regardless of the time occurring between diagnosis and start of therapy. This factor will be considered at the time of analysing the final results, in order to investigate its impact on outcome.
Of course, this does not mean that patients can be referred without any urgency and that chemotherapy may be delivered when possible.
Chemotherapy must be started as soon as possible, preferably within 6 weeks from diagnostic procedure.

7. Pre-treatment investigations

With the pre-treatment investigations a patient will be tested for eligibility and staging criteria. The pre-treatment investigations must be performed **no more than 4 weeks before the beginning of chemotherapy**; otherwise they need to be repeated

7.1 Histological diagnosis

The diagnosis must be established pathologically.
Open surgical biopsy is the preferred approach as this maximises the tissue available for diagnostic procedures, biological studies and central pathology review. Open biopsy is essential if initial needle biopsy is non-diagnostic or equivocal. (*See the paragraph of Surgical Guidelines for biopsy techniques and of Pathology Guidelines for details about tissue handling and diagnostic pathology techniques*)

7.2 Clinical assessment

- Weight, Height and Body Surface Area
- Blood pressure, pulse
- Site and clinical extent of the tumour
- Regional lymph node involvement should be clinico-radiologically assessed and recorded in all cases. Lymph node biopsy is required when nodal involvement is suspected.

7.3 Laboratory investigations

- Blood: Full Blood Count, Differential WBC and Platelet Count, Creatinine (and formal GFR measurement if possible), Na, K, Ca, Mg, PO_4, Cl and HCO_3 or Total CO_2, LDH, Liver function including ALT / AST, Bilirubin and Alkaline Phosphatase
- Early Morning Urine sample for Phosphate, Creatinine, Osmolarity and routine urinalysis (included as baseline for Ifosfamide nephrotoxicity evaluation)
- Bone Marrow: the evaluation of bone marrow (bilateral aspirates and trephines) is required only for patients with extraossues pPNET/Ewing sarcoma.
- Cerebrospinal fluid examination for cytospin and cell count is required only for patients with parameningeal tumours with high risk of meningeal involvement (i.e. cranial nerve palsy, skull base bone erosion, intracranial tumour extension)

And

- **Echocardiogram**: baseline assessment is required in all patients who are to receive anthracycline chemotherapy according to protocol guidelines

7.4 Radiological investigations

(see also Appendix: Radiological Guidelines)

- Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI) of the primary site. **Volume estimation** should be attempted by providing the maximum sagittal, coronal and axial diameters.
  MRI: Intravenous **gadolinium** administration (0,2 ml/kg - 0,1 mmol/kg) is mandatory for all MRI examinations (post-contrast T1-weighted sequences should ideally be performed with fat saturation). MRI is particularly recommended for limb, head/neck, pelvic and paraspinal masses. MRI appears to be superior to CT scan in defining soft tissue extension.
  CT scan: it is superior to MRI in the evaluation of possible bone erosion and could be indicated for nasopharyngeal masses, and also for the assessment of abdominal lymphadenopathy and pulmonary metastases.
  It is generally advised to follow treatment response with the same imaging technique (CT or MRI) particularly where measurement is required. Imaging of the primary site should include examination of regional lymph nodes if not evaluable clinically or if clinically suspicious.

  ► It is important to note that radiological primary tumour assessment should precede the biopsy (this can significantly modify initial tumour volume) or/and be repeated in case of primary partial surgery (or large biopsy) to have an accurate initial tumor volume assessment.

  ► All imaging data should be **stored in DICOM** format for further review (on CDROM if PACS is not locally available)

- Chest CT scan: the presence of lung metastases must be evaluated by CT scan. Chest CT scan is mandatory for patients with tumour larger than 5 cm and suggested for the other cases (it may be potentially omitted for synovial sarcomas less than 5 cm and for G1 adult-type STS less than 5 cm)
- Chest X-Ray Postero-Anterior and Lateral, if no Chest CT scan is performed
- Tc Bone Scan (with plain X rays and / or MRI of any isolated abnormal site): it can be avoided in G1 tumours and in synovial sarcoma less than 5 cm in size
- Bone plain films (± CT/MRI): for differential diagnosis if isolated bone uptake on bone scan.
- Abdominal Ultrasonography (US)
- Abdomen-pelvic CT scan with intravenous contrast enhancement: for abdominal or lower limbs primaries, to evaluate the lymph nodes.
- Upper Limb tumours must have radiological evaluation (US) of axillary nodes.
- Positron emission tomography (PET) scans may be used in synovial sarcoma patients with measurable disease as base-line investigation and then after three courses of chemotherapy to evaluate possible changes in tumor tissue characteristics, as indicators of therapeutic response even in the absence of tumor shrinkage (the dimensional criterion alone can underestimate tumor response)

(Semen storage should be considered in post-pubertal boys before commencing chemotherapy).

7.5 Tumour measurements

Tumour dimensions should be recorded in three diameters choosing, as far as possible, the three maximum diameters.

With MRI, tumour **measurements** should be performed on post-gadolinium T1 or T2-weighted sequences (but not on STIR or non-enhanced T1-weighted sequences).

The tumour volume will be calculated according to the following:

Tumour volume (V) calculation:

a= length (in cm)
b= width (in cm)
c= thickness (in cm)

$\mathbf{V} = \pi/\mathbf{6} \times \mathbf{a} \times \mathbf{b} \times \mathbf{c} = \mathbf{0.52} \times \mathbf{a} \times \mathbf{b} \times \mathbf{c}$ in cm^3

7.6 Lung lesions

At Chest CT scan (when required), the differentiation between metastatic or benign nodules may be sometimes very difficult (benign lesions may be, for example, granulomatous disease, intrapulmonary lymph nodes, bronchiolitis).
Several criteria may be used for the differential diagnosis, i.e. number, size, morphology (non-calcified, round and well-defined) and location (inferior lobes, subpleural spaces, vessels-branching). Actually, no radiological criterion has a 100% specificity.

For EpSSG studies, the following patterns will be arbitrarly considered as **metastatic pulmonary disease** (assuming there is no other clear medical explanation for these lesions) :

- One or more pulmonary nodules of 10 mm or more diameter
- *or* two or more well-defined nodules of 5 to 10 mm diameter
- *or* 5 or more well-defined nodules of less than 5 mm

Hence, 4 or less small nodules (< 5mm) at diagnosis will not be considered as pulmonary metastatic disease and should be classified only as "non-specific pulmonary lesions".

Note:
The same lung window settings should be used when pulmonary nodules are being measured at diagnosis and follow-up.

8. Staging Systems

Adult Oncology Groups utilised different staging systems for soft tissue sarcomas, including histological grading, tumour size, tumour depth, degree of surgical resection and sometimes age *(Wunder JS, 2000*).
In agreement with previous pediatric studies, stage of disease will be defined according to both

1. the clinical tumour-node-metastases (TNM) staging classification *(Harmer MH, 1982*)
2. the Intergroup Rhabdomyosarcoma Study (IRS) post-surgical grouping system *(Maurer HM, 1988)*.

The **TNM** T1 definition applies to tumours confined to the organ or tissue of origin, while T2 lesions invade contiguous structures;
T1 and T2 groups are further classified as A or B according to tumour diameter, ≤ or > 5 cm respectively.
Regional node involvement was designated as N1 (no node involvement - N0)
Distant metastases at onset as M1 (no metastases - M0).

After initial surgery, patients were classified according to the **IRS system**:

- group I includes completely-excised tumours
- group II indicates grossly-resected tumours with microscopic residual disease and/or regional lymph nodal spread
- group III includes patients with gross residual disease after incomplete resection or biopsy
- group IV comprises patients with metastases at onset.

8.1 References

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9. Surgical guidelines

Local treatment is essential in non-metastatic NRSTS as chemosensitivity is uncertain for most of them. It can be achieved by surgery, radiotherapy or both.

The aim of local treatment is to cure the patient with no or minimal long term sequelae. The choice of local treatment will depend on the site and the size of the primary tumour, the age of the patient and the possible response to neoadjuvant chemotherapy. Surgical planning should include all reconstructive procedures with optimal timing of possible additional radiotherapy.

Surgical guidelines for NRSTS are necessarily partially different from those proposed for RMS, due to some relevant differences between the two subsets of tumours. In particular, surgical discussion for NRSTS would be influenced (in comparison to those for RMS) by the higher proportion of tumours localized at extremities, the median higher age of patients, the lower chemo-radio-responsiveness and the lower tendency to lymph-nodal spread (NRSTS patients are often adolescents with localized extremities tumours with uncertain possibilities to obtain tumour shrinkage with pre-operative chemotherapy).

In this group of patients, the mainstay of therapy, as in adults, remains conservative surgical resection. The possibility to achieve a surgical complete excision of the tumour is the most critical prognostic factor.

9.1 Definitions

The quality of the resection is defined by its worst margin and is usually classified as follows for extremity tumours but definitions can be extended to other sites whenever possible.

- **R0 resection (= microscopically complete resection = radical resection)**

  - Wide
  It is an en-bloc resection through normal tissue, beyond the reactive zone, with the removal of the tumour with its pseudocapsule and a margin of normal tissue; a resection could be defined as "wide" when the tumour is covered at every point by healthy tissue (muscle, subcutaneous tissue, thick fascia or intermuscular septum) according to the growth pattern of the tumour.
  When the tumour involves more than one anatomical compartment, the wide resection may include adjacent muscle compartment, bone, blood vessels or nerves and should be immediately followed by reconstructive surgery.

  – **Compartmental surgery**
  When the tumour is removed en-bloc with the entire muscular or anatomical compartment and is covered by intact deep fascia. This surgery is feasible when tumour is entirely anatomically confined.

- **R1 resection (= micoscopically incomplete resection = marginal resection)**

  When the tumour surface emerges macroscopically at the resection surface (e.g. surgical plane through the reactive zone or pseudo-capsule), or when microscopic tumour extension is present at the margin of resection, but without evidence of macroscopic disease residue.

Surgery is defined **contaminated** when accidental rupture of the tumour pseudocapsule with spillage of material into the operating field occurs, and also when the pseudocapsule has simply emerged at the margin of resection. In these cases spillage of material must be controlled by all means, and then the operating field must be rapidly washed and the resection margins widened. The contamination must be reported in the description of the surgical procedure and will be followed by complementary radiotherapy.

- **R2 resection (= macroscopically incomplete resection = intralesional resection)**

  When macroscopic tumour residue is left in situ.

Primary resection is recommended when complete and non-mutilating resection is considered feasible, otherwise a biopsy is absolutely required.

9.2 Biopsy

Aim: *to provide enough material for histology, grading, immunochemistry, cytogenetics, central pathology review and spare of tissues for biological studies and frozen storage.*

Biopsy should be the initial surgical procedure in all patients. Also when primary excision with adequate margins seems possible, the biopsy could be considered to avoid inadequate surgery performed according to a mistaken presumptive clinical diagnosis.

Open biopsy is recommended and should be **incisional**, although ultrasound or CT scan guided core needle biopies (tru-cut) may be appropriate in difficult or inaccessible sites.
Fine needle aspiration biopsy is not recommended. Endoscopic biopsies are appropriate for bladder, prostate or vaginal tumours.

In planning the surgical approach for biopsy it must be kept in mind that:

- **Incisional biopsy:**
  - The scar and the biopsy track must be included en bloc in the subsequent definitive surgical procedure (this also applies to needle biopsy)
  - In case of sarcoma of the extremities, the incision must always be longitudinal to the limb (transverse and inappropriately placed incisions that traverse multiple tissue compartments must be avoided, because they interfere with the further delayed surgery)
  - Very careful hemostasis must be ensured, to avoid post-surgical hematoma. If drains are used (not recommended), the tract of the drain must be in-line with the skin incision and as close as possible from it.

- **Tru-cut biopsy:**
  - The biopsy track must always go directly to the tumour, through the muscle fibers with minimal use of retractors
  - The biopsy track must contaminate only the anatomical compartment in which the tumour is situated, avoiding major neurovascular structures.

Tissue should always be sent fresh to the laboratory if possible. If fixative has to be used it should be formalin based.

9.3 Primary resection

Aim: *to achieve complete resection (R0: microscopically complete resection), without danger or mutilation.*

Primary resection is indicated:

1. if there is no clear clinical evidence of lymph node or metastatic disease
2. if the tumour can be excised with adequate margins and without danger or mutilation.

Adequate margins
The pathologic assessment of the quality of resection margin status is regarded as the benchmark, though imperfect, for determining the quality of local treatment.
A layer of healthy tissue between tumour and resection margins should exist. This layer of healthy tissue is defined as a "*safety distance"*, and depends on the type of the tissue.
In the recent Milan Consensus Conference on Adult Soft Tissue Sarcomas (June 2004), **adequate margins** have been defined as: *> 1 cm of healthy tissue around the tumour in all directions (when the tissue is a muscle), > 1 mm of healthy tissue around the tumour when the tissue is periostium, vessel sheath, epineurium, muscular fascia*.
The metric definition of the safety distance cannot be easily used in paediatric tumour surgery. However, it is important to have well-defined criteria to standardize the language and the definitions. Therefore, for the E*p*SSG NRSTS protocol, we decide to arbitrarily adopt the above mentioned definition of **adequate margins,** as those more commonly adopted in adult surgical oncology.
It is important to note that the layer of healthy tissue can show a shrinkage from *in vivo* to the subsequent pathological evaluation. Surgeons and pathologists must take this possibility into account.
The kind of tumour growth has to be settled as well-defined with pseudocapsule or locally infiltrating, and should be documented. These information are important to characterize the biological behaviour of the tumour, and thus contribute to the evaluation of further local therapeutical measures.

In order to ensure the evaluation concerning complete resection, the risk stratification, and therefore further treatment, a close **cooperation between surgeon and pathologist** is necessary. The surgeon should perform an exact drawing of the tumour, including resection margins being important for the evaluation of safety distance (also marked at the tumour). It should be possible for the pathologist to reconstruct the tumour and biopsies taken from the resection margins according to the surgeon`s drawing and information. An agreement between surgeon and pathologist concerning TNM-status should be achieved. It will be important for the pathologist to examine the specimen with the surgeon so that correct orientation is ensured for accurate evaluation of the margins. The surgeon must help the pathologist to identify the most critical resection margin and likewise must ensure that points where the tumour emerges only due to muscle retraction following surgical removal are not identified as critical margins.

According to adult oncology orthopedic surgical guidelines, only R0 resections, as above defined, are considered adequate. The feasibility of primary resection should be carefully evaluated with

radiologists. Irrespective of the site, surgery will be largely planned on the basis of imaging findings (CT, MRI) and the least favorable intraoperative situations will be hypothesized.

Extensive, "mutilating" operations should never be considered at primary resection.

"Mutilating" is defined as: leading to significant long term anatomical, functional or cosmetic impairment; e.g. extremity amputation or extensive muscular resection, orbital exenteration, major resection of the face, pneumonectomy, pelvic exenteration with definitive intestinal or urinary diversion, total cystectomy, total prostatectomy, hysterectomy.
However, the terms "resectability" and "mutilation" have to be understood under consideration of the possible reconstructive techniques of plastic surgery, microsurgery and the cooperation of different surgical disciplines in tumour surgery.

It is of note that in some younger cases, amputation may be preferable to radiotherapy, given the severe radiotherapy late-effects on growth and function.

9.4 Primary re-operation

Aim: *To achieve complete resection (R0) in patients with microscopic (certain or doubtful) residue after primary operation, before other therapies, if this can be done without danger or mutilation*

If a primary marginal excision or excisional biopsy (not recommended) has already been done, or where histological evaluation is inadequate, then primary re-excision should be considered (*Hays, 1989; Cecchetto, 2001*). This applies particularly to trunk, limb and paratesticular tumours.
The interval between initial surgical approach and primary reexcision should be as short as possible, and should never exceed 8 weeks. Similarly, the interval between the "adequate" surgery (first surgery or primary re-excision) should not exceed 8 weeks. In case of adequate margins (or no tumour) on specimen from primary re-excision, patient should be classified as IRS Group I only if the description of first surgery allows to be confident that no tumour spill and contamination has occurred.

9.5 Secondary operation (delayed surgery, post-chemotherapy)

Aim: *to achieve complete resection (R0) of a residual mass after neoadjuvant chemotherapy*.

Secondary operations and even multiple biopsies for verification of local control are not indicated if clinically, endoscopically and on CT or MRI scanning there is no visible tumour (*Godzinski, 1994*).

Where a residual mass is demonstrated or in cases of doubt, surgical resection should be done, although there may be certain anatomical sites, particularly in the head and neck, where this may not be feasible and the final indication in these cases is left to the decision of the individual surgeon. It should however be remembered that negative biopsies of the residual mass, even if multiple, may be unrepresentative.
It is important to note that in patients considered unresectable at diagnosis, the outcome strongly correlate with the achievement of complete delayed resection. In the series from INT Milan (40 IRS group III patients with adult-type STS), 5-year OS was 80% and 86% in patients who underwent

complete delayed surgery and complete delayed surgery plus radiotherapy, whereas it was 36% and 14% in those who did not undergo complete resection (with or without radiotherapy, respectively) (*Ferrari A, 2004)*

Marginal resections (R1 resections) in sites where R0 resection is not possible may also be acceptable, provided they are always followed by radiotherapy.
If residual mass is not completely resected, radiotherapy should be given.

Secondary operations should, as a rule, be conservative, anticipating local radiotherapy for residual disease, but "mutilating" operations may be appropriate in certain circumstances, after unsuccessful neo-adjuvant chemotherapy or radiotherapy or in patients under 3 years.

"Debulking" procedures are not recommended.

9.6 Reconstructive surgery and local control

Reconstructive measures have to be included early enough in the planning of the resection and can be most often performed during the same operation as the resection of the tumour.
Pre or post operative irradiation has to be considered depending on the necessary reconstructive measures:

- Bone reconstruction (microvascular transfers of fibula or iliac bone is incompatible with post-operative irradiation)
- Free flaps for soft tissue replacement can help lymphatic reconstruction only if they are not irradiated (proximal part of arm or thigh tumours)
- The integration of metal implants in general for joint replacement may be disturbed by radiation.

9.7 Lymph nodes

Aim: *to confirm nodal involvement with nodal sampling, avoiding radical lymph node dissection*.

Clinically or radiologically suspicious regional lymph nodes should be sampled on initial presentation and at relapse. Cytology may be useful to confirm nodal involvement but only if a conventional biopsy of the primary tumour has been obtained for diagnostic purposes.

Nodal spread is less frequent in NRSTS as compared to RMS, and therefore surgical recommendations are partially different.
In RMS arising at extremities, systematic biopsy of regional nodes may be recommended and a technique of sentinel lymph node mapping may be useful *(McMulkin, 2003)*. This procedure is not standardized in adult soft tissue sarcomas (with partial exception for some particular histotypes, i.e. epithelioid sarcomas, clear cell sarcomas or vascular sarcomas). Therefore, also in paediatric adult-type sarcomas systematic biopsy would be not required in absence of clinico-radiological suspicion.
In RMS, radical lymph node dissections are not indicated and involved lymph nodes should be irradiated. In NRSTS (generally less sensitive to chemotherapy and radiotherapy), lymph node dissection may be considered.

It should be remembered that the combination of radiation therapy and radical lymph node dissection should be avoided as it can induce severe lymphoedema.

9.8 Specific sites

Parameningeal site

Complete surgical resection is difficult and generally not possible. Radiotherapy is always necessary in patients over 3 years and should be given at week 9 regardless of response to initial chemotherapy.

An initial resection will not be accepted if permanent severe functional dysfunction or mutilation results. In all cases where resectability is uncertain a resection should not be attempted and only a biopsy taken. Neck dissections should not be performed initially.

Only after radiotherapy a secondary resection is acceptable. Secondary resections in this site should only be performed in centres with experience in this field. A combination of surgery and brachytherapy ("AMORE" technique) is practised in some Centres (*Buwalda 2003*).

Orbit

Biopsy is usually the only surgical procedure required for orbital tumours. Secondary resections are not recommended. Enucleation or exenteration are very rarely indicated *(Oberlin, 2001)*.

Depending on the age of the child microsurgical reconstruction with a free flap or forearm flap in combination with an appropriate prosthetic device are recommended after exenteration of the orbit.

Head and Neck

Complete surgical excision is difficult but major resections with reconstruction may be appropriate in some circumstances, after neoadjuvant chemotherapy. Such operations should only be realised in centres with an interdisciplinary surgical team and with experience in microsurgical free flap reconstruction.

The "AMORE" technique could be considered in some Centres (*Buwalda 2003*).

Bladder/Prostate

Cystoscopy should be done at diagnosis and during follow up.

Initial resection (rather than biopsy alone) should only be done in the case of very small tumours arising in the fundus of the bladder, far from the trigone.

Secondary operations :

Conservative surgery of bladder /prostate tumours could be done where feasible (partial cystectomy and/or partial prostatectomy) in conjunction with brachytherapy particularly in very young boys *(Haie-Meder, 2000; Martelli, 2003)* or external beam radiotherapy.

Partial prostatectomy, without radiotherapy, carries a high risk of local relapse *(Audry, 1998)*

Where conservative treatment is not feasible, the treatment will include total cystectomy and/or total prostatectomy with or without post-operative radiotherapy.

Vagina

Partial vaginectomy may be feasible after chemotherapy but brachytherapy is often preferable after ovarian transposition *(Martelli, 1999).*

Paratesticular

These should be excised via an inguinal incision, first ligating the cord at the internal inguinal ring. Orchidectomy is essential. In rare cases, if the tumour is very large and delivery into the groin would be difficult or traumatic, it is better to make a scrotal incision (keeping the tunica vaginalis intact) and deliver the testis and cord via this.
Retroperitoneal lymphadenectomy or nodal sampling at diagnosis is not recommended unless there is uncertainity on imaging *(Olive, 1984; Ferrari A, 2002)*

If the initial operation before referral was scrotal then primary re-operation should be done to excise the cord at the internal ring. When there is a doubt about scrotal contamination, hemiscrotectomy should be performed.

Extremities

At secondary operation, formal compartmental resection (en bloc resection of the tumour and the entire compartment of origin, where tumour was entirely anatomically confined) may be appropriate for some tumours but less "anatomical" wide resections (en bloc resection through normal tissue, beyond the reactive zone, with the removal of the tumour with its pseudocapsule and a margin of normal tissue) is usually sufficient, providing an adequate margin of normal tissue.

A wide cutaneous incision will be made along traditional lines (along the major axis of the tumour-bearing anatomical compartment), and must include en bloc the scar and the holes-track of previous biopsies or surgery. Once the skin-fat flaps have been prepared the tumour will be isolated within the tumour-bearing structure, with prompt recognition and careful dissection of the main vascular structures and motor nerves (femoral, sciatic, external/internal sciatic-popliteal, median, ulnar and radial). These structures must not show tumour infiltration. Should doubt arise about a possible edema or suspect thickening of the delimiting fascia (vascular external tunica, perineurium), it will be prudent to perform frozen section biopsy.

Care must be taken to avoid contamination of the surgical field, which can also occur if the tumour is allowed to emerge on the surface of resection. When minimal contamination has occurred at primary surgery, the patient will be classified as IRS group II, and complementary radiation therapy will have to be planned in any case. Once the malignancy has been isolated, it must be removed en bloc with the surrounding soft tissue, covered at every point by at least one centimeter of healthy tissue.

Compartmental operations will be performed only if made necessary by the site and dimensions of the tumour. If the lesion is near structures such as the vascular-nervous fascia or bone, it must be cautiously prepared by also removing the fascia covering said structures (vascular external tunica, perineurium or periostium). If these structures are also found to be infiltrated, they must be resected en bloc with the tumour, assessing the possibility of performing vascular, neurological or bone reconstruction as an alternative to mutilating procedures.

Specific problems which can arise from the combination with the irradiation should be considered already at the operation planning. These are:

- disturbance of growth because of irradiation of growth plates
- pathological fractures after marginal bone resection
- lymph edema after regional lymph node dissection and nevertheless necessary irradiation, especially in the region of the shoulder and groin
- scarred contracture.

When considering radiotherapy, it should be remembered that amputation may be preferable in young children, bearing in mind the serious effects of radiations on growth and function.

Abdomen/Pelvis

If radiotherapy is anticipated for pelvic tumour the surgeon should consider exclusion of the ovaries from the radiotherapy field by transposition and could consider exclusion of small bowel from the pelvis by insertion of a tissue expander or absorbable mesh.

9.9 Surgery for relapse

This depends on the treatment used during primary treatment, but "mutilating" operations may be justified, particularly if radiotherapy options have already been exhausted.
It is to note that the long term salvage in relapsing patients is generally confined to those patients who can undergo surgical resection of relapsing disease (*Zagars, 2003).*

9.10 Marker clips

If it is considered necessary to mark the tumour bed for post operative radiotherapy, titanium rather than stainless steel clips should be used so as not to interfere with CT or MRI scans.

9.11 Histology

Whenever possible, the case should be discussed with the pathologist pre-operatively and the tissue sent fresh from the operating theatre to the laboratory. Marker sutures should be inserted to help in orientation and show crucial resection margins. If the tissue has to be sent fixed rather than fresh, a formalin based fixative is preferred.

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10. Radiotherapy guidelines

Radiotherapy is an essential component of the treatment strategy for NRSTS.
The use of radiotherapy is a balance between the prognostic improvement due to radiotherapy and the potential side effects of the treatment. In adults, radiotherapy is required in most patients after wide excision, especially in large tumours, and irradiation is considered always unnecessary only after compartment resection. The situation in children and adolescents is different: the morbidity of radiotherapy is clearly much greater than in adults (depending on the site that require irradiation) since these patients are growing and physical development can be disturbed.
In adult studies, relatively high total dose of conventional fractionated external beam irradiation are recommended to achieve local control: doses of 60-64 Gy are used, sometimes with 50 Gy on a large first volume and a boost on a smaller one. Radiotherapy is usually delivered following surgery (post-operative radiotherapy), but excellent results have been reported with pre-operative irradiation. For children and adolescents, so far lower radiation doses of about 50 Gy have been used in the CWS-trials.
The rationale, indications and doses of radiotherapy in synovial sarcoma and adult type NRSTS are given below.

10.1 Equipment

► Megavoltage equipment

All patients will be treated with megavoltage equipment (4-20 MV linear accelerator preferably). For extremity tumours photons of 4 to 6 MV are recommended. Care must be taken to ensure an adequate skin dose in high risk areas when high energy photons are used. For tumours of the trunk, photons of 6 to 20 MV energy are recommended.

► Electrons

Electrons are allowed for superficial and moderately infiltrating tumours (to a maximum depth of 5 cm) either as an electron field matching on, or as boost to, linear accelerator planned fields. The use of electron fields alone should be avoided because of the late effects.

► Brachytherapy

Brachytherapy may be used in cases of incompletely resected tumours of vagina, perineum, bladder, prostate and orbit. It may be used as boost technique before or after external beam irradiation or may in some cases replace external beam irradiation. This must be discussed with the reference centre for each individual patient. The dose for brachytherapy and external beam radiotherapy must take into account radiation-tolerance of adjacent tissue and should be calculated individually in each case.

10.2 Treatment planning

3-D-conformal radiotherapy planning is recommended when critical structures lie in or nearby the target volume. The dose is prescribed according to ICRU 50.

10.3 Fractionation

Treatment is applied in **conventional fractionation with 1.8 Gy per day, 5 day per week**. In patients with large fields, smaller fractions may be used. In patients < 3 years of age, smaller fractions may be given as well (1.6 Gy). The radiation dose is prescribed according to ICRU 50.

► Compensation for treatment breaks

Standard fractionation is 5 days per week. If there is a treatment interruption, 2 fractions with an interval of at least 6 hours between fractions should be given to enable completion of treatment within the same overall time, if fesible from the surrounding critical structures.

10.4 Target volume definition for primary tumour

- The target volume is chosen according to the initial tumour volume (gross tumour volume - GTV). The pre-therapeutic T1 MRI image with contrast is usually the optimal imaging study.
    - Exceptions: intrathoracic or pelvic tumour bulk
- The clinical target volume (CTV) is defined as the GTV + 1 cm
    - Exception limbs: 2 cm in longitudinal direction
- Additionally, scars of the biopsy, of the initial surgery, of the second look surgery and of drain sites have to be included in the CTV. Furthermore all tissues that were potentially tumour-contaminated during surgery need to be included in the CTV.
- The planning target volume (PTV) is defined as the CTV + 1 cm
    - Exception chest wall: 2 cm
- In patients receiving a boost after 50.4 Gy, the PTV of the boost is the residual tumour at the start of radiotherapy plus a margin of 1-2 cm.
- In growing patients, a radiation dose gradient through the epiphyseal growth plates should be avoided because of the risk of asymmetric growth. The growth plates should either be included in or, if feasible from the tumour extension, be excluded from the radiation fields. The same should be observed for vertebral bodies in order to avoid scoliosis.

Summary:
The PTV consists of the initial tumour volume + 2 cm except for limb and chest wall tumours (+ 3 cm). Areas contaminated during surgery including scars and drainage sites must be included in the PTV. If more than 50.4 Gy need to be applied, the PTV of the boost is the residual tumour at the start of radiotherapy plus a margin of 1-2 cm.

10.5 Target volume definition for lymph nodes

In case of involved lymph nodes:

1. Radiotherapy could be avoided in case of radical lymphadenectomy (surgical removal of all the lymph nodes of the involved site).

2. After biopsy or non-radical resection (surgical removal of the involved nodes but not of all the lymph nodes of the involved site) radiotherapy is required. The dose of **50.4 Gy** is applied to the entire lymph node site (axilla, groin, paraaortic lymph nodes etc.). When that approach results in very large radiation fields, this extent can be reduced to the involved lymph nodes plus a PTV margin of 3 cm at the discretion of the treating radiation oncologist.
3. In case of still enlarged lymph nodes at the time of radiotherapy, lymph nodes receive an additional boost up to a total dose of **59.4 Gy** if feasible from the surrounding critical structures (PTV definition for the boost as for the boost of primary tumour).

If possible the draining lymphatic vessels between the primary tumour and the involved lymph node site should be irradiated. However, in some cases this would result in unacceptable large radiation fields. In these patients, two separate radiation fields have to be used to treat the primary tumour and the lymph node site excluding draining lymphatic vessels.

Note:
no systematic prophylactic nodal irradiation should be delivered

10.6 Timing of radiotherapy

Since the value of chemotherapy is not clear, radiotherapy should not be delayed when radiotherapy and chemotherapy are given.
In patients submitted to initial gross resection, radiotherapy should start at least after 3 cycles of chemotherapy. Radiotherapy plans should be performed during the 7° week, with the aim to start the irradiation at **week 9**, at the resolution of the toxicity of the third cycle of chemotherapy.
During the administration of radiotherapy (5-6 weeks, overlapping with 2 chemotherapy cycles) chemotherapy will be given with ifosfamide alone.

In patients with IRS group III (macroscopical residual disease), the option for second surgery must be checked before the onset of radiotherapy.
In patients receiving **no second surgery**, radiotherapy is performed at **week 9**.
When second surgery is planned, there are 3 treatment options:

- preoperative radiotherapy
- postoperative radiotherapy
- no radiotherapy

When radiotherapy is performed before second surgery (**pre-operative radiotherapy**), irradiation starts at **week 9**. Surgery should be performed 5 weeks after the end of radiotherapy (and after the last chemotherapy cycle) to avoid surgical complications.
When **postoperative radiotherapy** is given, radiotherapy should be started within 21 days except when there are postoperative complications.

10.7 Indications and doses

► **Synovial sarcoma:**

IRS group I → no RXT

IRS group II **≤ 5 cm** → **option 1**: 50.4 Gy (1.8 Gy/d) – **option 2:** NO RXT
> 5 cm → **option 1**: 54 Gy (1.8 Gy/d) - **option 2:** NO RXT

IRS III / axial

different options in relation to delayed surgery
(and to age and initial tumour size)

- no RXT
- pre-op RXT 50.4 Gy
- post-op RXT 50.4 Gy ("R0")
- post-op RXT 54 Gy ("R1")
- definitive RXT 59.4 Gy

► **Adult type NRSTS:**

IRS group I **≤ 5 cm** → no RXT

> 5 cm **G1** → no RXT
G2 → RXT 50.4 Gy
G3 → RXT 50.4 Gy

IRS group II **G1** → no RXT
G2 → 54 Gy
G3 → 54 Gy

IRS III

different options in relation to delayed surgery
(and to age and initial tumour size)

- no RXT
- pre-op RXT 50.4 Gy
- post-op RXT 50.4 Gy ("R0")
- post-op RXT 54 Gy ("R1")
- definitive RXT 59.4 Gy

10.8 Normal tissue tolerance guidelines

	Conventional fractionation (F:fraction)
Heart	**30.6** Gy; 17 F
whole liver	**19.8** Gy; 11 F
whole kidney	**14.4** Gy; 8 F
spinal cord (part)	**41.4** Gy; 23 F
spinal cord in pts. with residual paraspinal tumour (on MRI)	**50** Gy; 28 F
optic nerve/optic chiasm	**45** Gy; 25 F

10.9 Treatment guidelines for special sites

Parameningeal tumours

In case of skull base erosion and cranial nerve palsy, the PTV will be that required to treat the primary tumour (initial tumour volume + 2 cm). Radiation fields must adequately cover the initial skull base erosion but there is no routine whole brain irradiation.

Extremities

Extremity tumours should be treated according to the general guidelines described above. Tissue contaminated during surgery must be included in the CTV. After surgical procedures, all scars and drainage sites should be irradiated with a safety margin of 1 - 2 cm. Circumferential radiotherapy must be avoided because of the danger of constrictive fibrosis and lymphedema. In growing patients, a radiation dose gradient through the epiphyseal growth plates should be avoided because of the risk of asymmetric growth. The growth plates should either be included in or, if feasible from the tumour extension, be excluded from the radiation fields.

Urogenital Site

The doses and target volume definitions follow the general guidelines. Gonads should be positioned out of the treatment volume if possible (in girls oophoropexy must be discussed!). Individual planning and discussion with the respective reference centre is advised.

Abdomen

The kidney and liver tolerance doses have to be respected. In growing patients, a radiation dose gradient through vertebral bodies should be avoided because of the risk of scoliosis. Vertebral bodies and pedicles should either be included in or, if feasible from the tumour extension, be excluded from the radiation fields.

Pelvis

Small bowel/iliocoecal bowel may be displaced from the pelvis by treating the patient in prone position and by using a belly board. In some cases, bowel can be spared with special surgical techniques using a spacer. Tumours with non-infiltrating extension into the preformed pelvic cavity often show a large intrapelvic mass. Irradiating the pre-treatment volume would mean that large volumes of normal tissue (bowel and bladder) are in the radiation field. In these cases, the target volume in the areas of non-infiltrating tumour encompasses only the residual mass after surgery/chemotherapy at the beginning of radiotherapy and a 2 cm safety margin. For all other parts of the tumour (infiltrated muscle, bone or organs), the general safety margins according to the initial tumour extension are to be applied.

Retroperitoneum

Tolerance doses of organs in this region need to be respected (i.e. kidneys, bowel, spinal cord). Dose volume histograms for these organs are strongly recommended. In order to avoid scoliosis in growing patients the vertebral bodies should either be irradiated symmetrically or shielded.

Chest wall

The doses and target volume definitions follow the general guidelines. Tumours with non-infiltrating extension into the preformed thoracic cavity often show a large intrathoracic mass. Irradiating the pre-treatment volume would mean that large volumes of lung tissue are in the radiation field. In these cases, the target volume in the areas of non-infiltrating tumour encompasses only the residual mass after surgery/chemotherapy at the beginning of radiotherapy and a 3 cm safety margin. For all other parts of the tumour (infiltrated muscle or bone), the general safety margins according to the initial tumour extension are to be applied.

10.10 Quality assurance of radiotherapy

Radiotherapy documentation forms will be completed and submitted via the relevant data office for review by the Radiotherapy Committee. Simulator films, plans and diagnostic films which determined treatment volume will be requested in all cases who fail locally after radiotherapy and in randomly selected cases of those who do not fail as part of a quality assurance assessment. This will be co-ordinated by the Radiotherapy Committee who will contact centres for films from individual patients as requested.

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11. Chemotherapy guidelines

It is well-know that the role of chemotherapy in the treatment of adult and childhood NRSTS continues to be controversial.
NRSTS are generally considered tumours with uncertain sensitivity to chemotherapy.
Synovial sarcoma represents a partial exception; its chemosensitiveness has long been appreciated by paediatricians, who often included synovial sarcoma patients in the same protocols as for RMS. In recent years, adult oncologists have increased their use of chemotherapy in synovial sarcomas; as for chemotherapy responsiveness, this histotype probably comes somewhere between most typical adult soft tissue sarcomas and "paediatric" small round cell sarcomas, generally characterized by high response to chemotherapy.

In paediatric age, few studies reported data on the efficacy of chemotherapy in NRSTS. Paediatric NRSTS were generally treated with the same chemotherapy regimens adopted for RMS (cyclophosphamide/ifosfamide, vincristine, actinomycin-D as standard treatment).
In patients with measurable disease, the overall response rate to chemotherapy was in the 30-50% range, but it may be superior when one consider also the minor response (that in some cases could permit however a delayed surgery considered unfeasible at diagnosis) or consider only the chemotherapy regimen including ifosfamide and doxorubicin (in the series from Istituto Nazionale Tumori of Milan the overall response rate was 39% in term of CR+PR, 58% in term of CR+PR+MR, and 80% for CR+PR+MR considering only ifosfamide-doxorubicin treatment) (*Ferrari A, J Clin Oncol 2005*).
The role of adjuvant chemotherapy was explored by POG trial that compared a regimen with cyclophosphamide, vincristine, doxorubicin and actinomycin-D to observation. The study failed in its aim because 51 out of 81 patients refused randomization (*Pratt, 1999).*

More data could be collected by adult literature. Several randomized adjuvant chemotherapy trials have been performed over the years in adult soft tissue sarcomas. To date, only a minority of them have shown a significant survival advantage for chemotherapy. Nevertheless, more recent data would seem to suggest some different considerations. In fact, 14 randomized trials comprising 1,568 adult patients with NRSTS were included in a meta-analysis that demonstrated a reduction in the risk of local and distant failures at 10 years in the group treated with intensified doxorubicin-based chemotherapy, with an advantage of 10% in recurrence-free survival and of 4% in overall survival (*Thierny JF. Sarcoma meta-analysis collaboration 1997*). Moreover, an Italian randomized trial on adjuvant full-dose doxorubicin + ifosfamide was closed in advance due to an early striking benefit in overall survival in favour of the chemotherapy arm. Long-term results of this trial are still consistent with a benefit *(Frustaci S, 2001).*
Therefore, though adjuvant chemotherapy is yet not currently standard treatment for adult soft tissue sarcomas, more hints of efficacy have been provided, and chemotherapy is often suggested in high-risk cases (high-grade, large size) or considered for a shared decision-making in conditions of uncertainty *(Bramwell VHC, 2001).* However, it is of note a recently-published study from the M.D.Anderson and the Memorial Sloan Kettering Cancer Centers, that reported a benefit for adjuvant doxorubicin-based chemotherapy during the first year only: this initial clinical benefit seems not be sustained over time (beyond one year of follow-up) (*Cormier, J Clin Oncol 2004*).

In conclusion, the role of chemotherapy is yet unclear, but some findings would seem to suggest a more relevant effect when a fair selection of high risk and high-grade cases is provided, and when a high-dose intensity chemotherapy including the most active drugs is delivered.

Various data from adult trials have shown that in adult-type soft tissue sarcomas: 1) ifosfamide may be more effective than cyclophosphamide against these tumours, 2) increased doses of ifosfamide improves the benefit, 3) the association ifosfamide-doxorubicin constitutes the regimen with the higher response rate, and 4) the higher doses of doxorubicin are associated with the improvement of response rate and disease-free survival.

For synovial sarcoma, high dose of ifosfamide showed improved response rate, suggesting that this drug may be considered the most active agent in this tumor type.
Recently, a regimen with **high dose ifosfamide** (14 g/m^2 ifosfamide given in continuous infusion via ambulatory external portable pump over 14 days) has been shown to be active in soft tissue sarcomas, and in particular in synovial sarcoma, with an excellent toxicity profile.
Various adult series have been reported on this regimen.
In pediatric age, a single-institutional series has been published (Meazza C et al. Prolonged 14-Day Continuous Infusion of High-Dose Ifosfamide With an External Portable Pump: Feasibility and Efficacy in Refractory Pediatric Sarcoma. Pediatr Blood Cancer 2010;55:617–620):

> 14 pre-treated pediatric patients (4 synovial sarcoma)
> *Toxicity*: grade 3 hematological toxicity in 19.6% of cycles. There were no cases of grade 4 hematological toxicity. No GCSF was administered. No grades 3–4 non-hematological toxicity.
> *Efficacy*: overall response rate was 35% (plus 28% of stable disease).
> For synovial sarcoma: 2/4 partial response and 2 stable disease (all patients pre-treated with ifosfamde)

This regimen has been defined as "a new metric of continuos improvement in quality of care (Anderson P. Continuously Improving Ifosfamide/Mesna: A Winning Combination Pediatr Blood Cancer 2010;55:599–600)

From 2014 (version 1.2), the **high dose ifosfamide** regimen will substitute the classic ifosfamide-doxorubicin regimen in patients with synovial sarcoma.
This change may be of interest for:

a) **efficacy question**: a more intensive use of most active drug in synovial sarcoma, with the hope to increase chemotherapy-response rate in unresected cases; the question is whether high-doses of ifosfamide may be better than standard dose
b) **toxicity question**: whether high-doses ifosfamide may be as efficient as ifo–doxo regimen; this regimen may permit the omission of anthracyclines and so the removal of potential late cardiotoxicity; moreover, this regimen has been reported to have less hematological toxicity than the classic ifosfamide-doxorubicin chemotherapy, it may reduce costs and improve quality of life (no hospitalization)
c) a trail with the same regimen is currently ongoing in some European centers for adult synovial sarcoma; there may be a particular interest, therefore, to compare therapeutic results with adult data.

11.1 Chemotherapy regimen

All the drugs used are licensed in Europe and have passed clinical phase II trials.

The use of central lines is recommended

The **administration of chemotherapy** courses should not be started unless all these conditions are present:

- 1.500/ μl WBC, or 800/μl neutrophils
- 80.000/μl platelets are reached.
- absence of any relevant organs dysfunction
  - in particular: → adequate cardiac function (ejection fraction EF ≥ 47%) for patients receiving doxorubicn
    → adequate renal function (creatinine < 1.5 X Normal value)
    → adequate hepatic function (bilirubin < 17 μmol/l, transaminases < 2 x normal value)

A) ifosfamide 3 g/m^2/day, for 3 days + doxorubicin 37.5 mg/m^2/day, for 2 days

for adult-type soft tissue sarcomas
to be given every 21 days
for 3, 4 or 5 cycles according to the risk-group

DOXORUBICIN (ADRIAMYCIN)

- Mechanism of action: inhibition of DNA synthesis
- Side effects: bone marrow depression, acute and late cardiotoxicity, gastrointestinal irritation (nausea, vomiting, ulceration), allergic reactions with skin rash and fever, alopecia. Local ulceration with extravasation.

- *Dose and mode of administration in this protocol:*
  - Doxorubicin: 37.5 mg/m^2 day 1, and 2 (75 g/m^2 total for cycle)
  - 10 mg/hour infusion (longer infusion does not seem cardioprotective and may increase the risk of mucositis)
  - The drug can be given by peripheral iv. cannula or central line with appropriate precautions against extravasation.

IFOSFAMIDE

- Mechanism of action: alkylating agent (IFO has to be activated hepatic hydroxylation)

- Side effects: haemorrhagic cystitis (Mesna uroprotection is required), nephrotoxicity (tubulopathy with glucosuria, aminoaciduria, loss of phosphate and Ca, full range of tubulopathies from subclinical changes to a full Franconi syndrome), bone marrow depression, gastrointestinal irritation (nausea, vomiting, diarrhoea, stomatitis), alopecia, neurotoxicity with transient somnolence and mental disturbance, infertility, immunosuppression

- *Dose and mode of administration in this protocol:*
  - Ifosfamide: 3 g/m²/day 1, 2 and 3 (9 g/m^2 total for cycle)
  - 3 hours infusio
  - Hyperhydration (3 L/m²/day) and Mesna (3 g/m²/day 1, 2 and 3) are required until 12 hrs after completion of IFO .

B) <u>ifosfamide alone at 3 g/m^2/day, for 2 days, concomitantly to radiotherapy</u>

for adult-type soft tissue sarcomas
to be given every 21 days
for 2 cycles concomitantly to radiotherapy

- *Dose and mode of administration in this protocol:*
  - Ifosfamide: 3 g/m²/day 1 and 2 (6 g/m^2 total for cycle)
  - 3 hours infusio
  - Hyperhydration (3 L/m²/day) and Mesna (3 g/m²/day 1, 2 and 3) are required until 12 hrs after completion of IFO .

In *high grade adult-type soft tissue sarcomas, group II > 5 cm, and group III* patients that need to receive both chemotherapy and radiotherapy, it is important to avoid the concomitant administration of doxorubicin and radiotherapy, due to the radio-synergistic effects of doxorubicin that could increase the acute side effects of irradiation.
Since radiotherapy will be given in conventional fractionation, it will last 5-6 weeks and overlap with 2 chemotherapy cycles. These 2 cycles will be given with ifosfamide alone, at the dose of 3 g/m^2/day, for 2 days.

Note:
*after the first three courses of ifosfamide-doxorubicin and the tumour re-assessment, radiotherapy should start at week 9th, then the fourth chemotherapy cycle would start at week 10th and should be **ifosfamide** alone; the fifth cycle would be at week 13° (**ifosfamide** alone), and the sixth (**ifosfamide-doxorubicin**) could therefore be planned at least 2 weeks after the completion of radiotherapy.*
*In case of some delay in radiotherapy start, it could be better to give **ifosfamide-doxorubicin** as fourth cycle, and utilize **ifosfamide** alone in the subsequent courses, considering that the sixth chemotherapy could probably overlap the radiotherapy or be administered few days after the end of irradiation.*

C) ifosfamide 14 g/m^2 in 14 days

for synovial sarcomas
to be given every 21 days
for 3,4 or 5 cycles according to the risk-group

- 14 g/m^2 ifosfamide plus 14 g/m^2 Mesna (mixed 1:1 in normal saline, total volume up to 275 ml) in continuous infusion, delivered via ambulatory external portable pump, over 14 days
- dose of 1 g/m^2/day, over 14 days the multi-day infusion pump had to be replaced after 1 week of therapy (because no data are available on ifosfamide stability beyond 9 days): ifosfamide 7 g/m^2 in 7-day infusion for first week, 7 g/m^2 in 7-day infusion for second week, then the infusion is stopped at day 14
- no hyperhydration is required (only oral hydration with 1.5 L/day is recommended)
- antiemetic prophylaxis (oral ondansetron or granisetron) may be given, but is generally unnecessary
- no growth factors are generally needed
- no hospitalization is required

Dose modifications

Age < 3 months - Anthracyclines should be avoided in the initial(s) cycle(s), but should be administered when the child is >3 months old with doses calculated *by weight*.

Age > 3 months and < 12 months (or < 10 kg body weight) -
Drug dose should be calculated *by weight* without further reduction.

For example, for the ifosfamide (3 g/m^2/day, for 3 days) + doxorubicin (37.5 mg/m^2/day, for 2 days) regimen, it should be:
DOXO 1.25 mg/kg/dose
IFOSFAMIDE 100 mg/kg/dose

Note: when the drug doses are initially calculated by weight, in absence of important toxicity they have to be gradually increased (by 30%) at each cycle up to dose calculated by body surface area.

In patients with body surface area (BSA) > 2 m^2 , the chemotherapy dose should not exceed the dose calculated for a BSA of 2 m^2.
The dose given to obese patients should be calculated based on regular body weight.
The chemotherapy doses must be recalculated for each course of chemotherapy according to the actual weight and surface area.

If count recovery is delayed more than 2 weeks after the planned start of the next course of chemotherapy, consider dose reduction of all drugs in the subsequent course to 66% of previous dose.

11.2 Chemotherapy toxicity

HAEMATOLOGICAL TOXICITY

Recovery of neutrophils > 1.0 x 10^9/l and Platelets > 80 x 10^9/l is required before the start of each course of chemotherapy.
If count recovery is delayed more than 2 weeks after the planned start of the next course of chemotherapy, a dose reduction of all drugs in the subsequent course to 66% of previous dose could be considered.

BLADDER TOXICITY

Haemorrhagic cystitis with ifosfamide is rare if hydration and mesna are utilised appropriately. Microhaematuria can usually be tolerated. In case of macrohaematuria it is important to continue (or re-implement) hydration. In case of cystic bleeding under or within 24 hours of completion of IFO-infusion mesna protection should be continued or started again.
Only recurrent macroscopic haematuria is an indication for discontinuing IFO, in which case cyclophosphamide at a dose of 1500 mg/m² per course may be substituted.

RENAL TOXICITY

Serious renal toxicity may occur with exposure to IFO. A prospective monitoring is therefore necessary and is more likely to occur with an increasing cumulative dose.
If nephrotoxicity occurs discontinue IFO and substitute with cyclophosphamide at a dose of 1500 mg/m² per course for the remaining courses of treatment.
Be careful because increased excretions of tubular enzymes, amino acid or proteins may be evident shortly after IFO infusion. This is tubular dysfunction, is usually transient, and does not require dose modification.

CARDIOTOXICITY

In this protocol the maximum cumulative dose of doxorubicin is 375 mg/m^2, therefore at the limit of the threshold dose for late cardiotoxicity reported in most studies. A very-careful monitoring for possible acute or late cardiotoxicity is recommended. The echocardiogram is required in all patients who have to receive chemotherapy, 1) as baseline assessment, 2) after 3 cycles of IFO-DOXO and 3) at the end of the treatment.
Significant deterioration in cardiac function is indicated by a shortening fraction (SF) <28%. In this event, doxorubicin must be withdrawn.
A fall in shortening fraction by an absolute value of >10 percentile units but with an actual SF value >28% (i.e. from SF 42% to SF 31%) may also represent a significant deterioration in function. Also in this event, doxorubicin must be omitted.

NEUROLOGICAL TOXICITY

Serious neurological toxicity from IFO is rare but more likely to occur in patients with impaired renal excretion of the drug, either from an obstructed urinary tract at initial diagnosis or from renal impairment later in treatment. Evidence of IFO encephalopathy may be mild initially but should be considered in any patient who demonstrates altered level of consciousness during or shortly after the drug infusion.

In case seizures occur, methylen-blue may be given: 30 mg/m^2 (max 50 mg) as a 2% aqueous solution, give by slow i.v. injection. The reversal of encephalopathic features should occur over the next 30-60 minutes.
If grade 3 or 4 central neurotoxicity occurs (somnolence > 30% of the time, disorientation / hallucination / echolalia / perseveration / coma) consider to avoid further ifosfamide and substitute with cyclophosphamide 1500 mg/ m^2 per cycles.

TOXICITY MONITORING

This protocol should be regarded as "therapeutic recommendations" and not at all as an "investigational protocol".
Therefore, the toxicity monitoring must be quite different of an investigational protocol (as the E*p*SSG RMS 2005), for which all adverse events (AE) must be registered.

Definitions:
Adverse events (AE) are illnesses, signs of illnesses or symptoms which occur or aggravate after the patient has been included in protocol.
The investigator must try to assess the relationship of any adverse event to the use of study drugs, based on available information, using the following guidelines:

1. not connected to the Protocol treatment = Unlikely-no temporal association, or the cause of the event has been identified, or the drugs cannot be implicated
2. possibly connected to Protocol treatment = Possible-temporal association, but other aetiologies are likely to be the cause; however involvement of the drug cannot be excluded
3. definitely or most probably connected to Protocol treatment = Probable-temporal association, other aetiologies are possible, but unlikely to be the cause of the event.

Severity of adverse event must be classified as

- *Mild:* Awareness of any sign, symptom or event, but easily tolerated, and not requiring intervention.
- *Moderate:* Discomfort enough to cause interference with usual activity and may warrant intervention
- *Severe:* Incapacitating with inability to do usual activities or significantly affecting clinical status, and warrants intervention.
- *Life threatening:* Serious adverse event

A serious adverse event (SAE) is any event that:

- Is fatal
- Is life threatening
- Is significantly or permanently disabling
- Is a congenital anomaly or birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse drug experience when, based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalisation, or the

development of drug dependency or drug abuse. In addition, laboratory value(s) changes may require reporting unless otherwise specified in the protocol.

- Second malignancy

For this protocol, only **very severe and /or unexpected adverse events** must be reported. The Remote Data Entry System provides a special form denominate "SAE form" that should be completed and will be sent to the national and protocol coordinators.

In case the system is not used the notification must be done by fax to the national coordinator that will be in charge to inform the protocol coordinator.

11.3 Supportive care

The treatment of patients with NRSTS require a multidisciplinary approach with a high degree of medical competence existing only in institutions familiar with the administration of intensive chemotherapy and adequate infrastructure to provide the necessary supportive care.

NAUSEA AND VOMITING

Antiemetic therapy according to the institutional policy should be given with each major block of therapy.

HEMATOLOGICAL TOXICITY

- Anemia should be treated by transfusion if necessary (Hb 7-8 g/l) according to national or centre guidelines but is not an indication to modify the treatment schedule.

- Thrombocytopenia: should be treated by transfusion if platelets count >10.000/mmc or in hemorragic patients with thrombocytopenia.

- Use of **G-CSF**: according to centre guidelines

  Primary prophylaxis with G-CSF is not required but is advised for the IFO-DOXO regimen. If infection complications (neutropenic fever) or prolonged neutropenia develops, administration of growth factors will be recommended.
  G-CSF should be given at a dose of 5 µg/kg (maximum dose 300 µg) and should be continued until WBC > 1000 x 10^9 for 3 days.
  Chemotherapy must not be resumed until 48 hours after the end of G-CSF.

INFECTIONS

Neutropenic Fever - Episodes of neutropenic infection are likely to occur after chemotherapy. All participating Institutions must be familiar with managing such problems instituting promptly all necessary investigations (e.g. blood culture) and empiric antibiotic treatment according centre guidelines. Note: neutropenic fever is not a serious adverse event.

Pneumocystis carinii pneumonia - Patients could be treated with cotrimoxazole according to the centre guidelines for prophylaxis. The usual dose is 5 mg trimethoprim/kg/day in two divided doses or 10 mg trimethoprim/kg (in two divided doses per day) given twice weekly.

Varicella or herpes - Patients who develop varicella or herpes should receive Aciclovir and chemotherapy should not be restarted until one week after the resolution of the rash.

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12. Investigation during and at the end of treatment

12.1 Investigation during treatment

Physical Examination

A thorough physical examination should be performed prior to every block of chemotherapy.

Laboratory Investigations

- Full blood count (including differential white cell count and platelets) before each course of chemotherapy (neutrophils > 1.0 x 10^9/l and platelets > 100 x 10^9/l is required before the start of each course of chemotherapy).
- Serum creatinine, electrolytes and liver function tests: before each block of chemotherapy
- *Ifosfamide Nephrotoxicity Monitoring:* ifosfamide nephrotoxicity needs to be monitored periodically. Monitoring must include:
  - Blood for Na, K, Ca, Mg, PO_4, Cl, Total CO_2/HCO_3 and AP
  - Early morning urine sample for PO_4, Creatinine and Osmolarity
  - GFR
  - Renal Tubular Threshold for Phosphate (Tm_p/GFR)

Echocardiogram

It is required in all patients who receive chemotherapy after 3 cycles of IFO-DOXO and at the end of the treatment.

12.2 Tumour reassessment

If no signs of progression are present, a formal tumour reevaluation is advised at the end of treatment in patients without measurable disease, and at 9th week in IRS group III patients (after 3 cycles of chemotherapy).
A clinical assessment of tumour response should be made at each visit in order to detect tumour progression at any point during treatment. This should be supplemented by radiological examination as appropriate.
The radiological reassessement must use comparable techniques to those used at diagnosis (MRI and/or CT scan).

Note
If the lesion can be completely analysed with **ultrasonography** (for example, a limb primary), then ultrasound may be used instead of MRI or CT to study the response rate during neoadjuvant chemotherapy.
MR or CT remains necessary prior to surgery.

As at diagnosis, tumour dimensions should be recorded in three diameters and can be compared choosing, as far as possible, the diameters selected at diagnosis.

Tumour volume (V) calculation:

a= length (in cm)
b= width (in cm)
c= thickness (in cm)

$$\mathbf{V} = \pi/\mathbf{6} \times \mathbf{a} \times \mathbf{b} \times \mathbf{c} = \mathbf{0.52} \times \mathbf{a} \times \mathbf{b} \times \mathbf{c} \text{ in } cm^3$$

12.3 Response evaluation criteria

Response in patients with macroscopic residual disease after initial surgery (IRS group III) will be evaluated as follow:

All response must last at least 4 weeks without evidence of tumour progression or relapse

Complete Response ***(CR)***	Complete disappearance of all visible disease, complete disappearance of tumour with no residual disease **
Very Good Partial Response ***(VGPR)***	≥ 90% reduction of tumour volume (volume response between 90-99%)
Partial Response ***(PR>2/3)***	≥ 66% reduction of tumour volume (volume response between 66-90%)
Minor Partial Response ***(PR<2/3)***	Volume response between 34-65%
Stable Disease ***(SD)***	< 33% reduction of tumour volume (no criteria for PR or PD)
Progressive Disease ***(PD)***	Any increase of more than 40% in the sum of volumes of all measurable lesions, or appearance of new lesions.

** ***Residual disease*** *should be defined as macroscopic measurable residue. Residual ill-defined areas of high density on CT-scan, or residual signal abnormalities on MR such as low intensity on T1WI, high intensity on T2WI and ill-defined margins of enhancement areas are commonly observed after chemotherapy. If no measurable mass, these may be regarded as post-therapeutic residue, and should not exclude the classification as CR.*

Note:
Positron emission tomography (PET) scans may be used in synovial sarcoma patients with measurable disease as base-line investigation and then after three courses of chemotherapy to evaluate possible changes in tumor tissue characteristics, as indicators of therapeutic response

even in the absence of tumor shrinkage (the dimensional criterion alone can underestimate tumor response)

12.4 Investigations at the end of treatment

Investigations required at this point are:

- Thorough physical and neurological examination (weight, height, pubertal status)
- Blood: Full Blood Count, liver enzymes, K, Na, Ca, PO_4, Cl, Mg, Glucose, AP, H_2CO_3, creatinine.
- Urine: Na, Ca, Glucose, PO_4, Creatinine, pH, Total Protein; 24 h urine: Calculate GFR, 24 h Ca, PO_4 and Glucose loss, max. PO_4 reabsorption/GFR.
- MRI/CT/ultrasound of primary tumour site
- Other investigations if previously abnormal may be indicated but are not generally recommended.

12.5 Investigations during follow-up

Post therapy, all patients should be followed for possible tumour relapse and treatment side effects monitoring.

► **TUMOUR RELAPSE SURVEILLANCE**

Patients should be evaluated with:

- Clinical examination
- Ultrasound ± CT scan or MNR of the primary tumour site
- Chest X-ray

with these recommended interval periods:

- every 3 months during the 1st year of follow-up
- every 4 months during the 2nd and 3rd year
- every 6 months during the 4th and 5th year
- then every 12 months up to 10 year from diagnosis.

► **LATE EFFECTS SURVEILLANCE**

Height and weight at 6 months to 1 year intervals. Any child showing a growth deceleration of 20-25 percentile units on standard growth charts from the pretreatment height, should be eva1uated for thyroid and pituitary function.

Annual blood pressure measurement.

Annual Tanner Staging for girls and boys till maturity. If there is delayed, the patient warrants eva1uation of gonadotrophins values, i.e., at 12-14 years for girls (FSH, LH and estradiol) and boys (FSH, LH and testosterone).

Record annual measurement of testicular size in boys using volume measured by Prader orchidometer if possible. The vast majority of patients on this study will receive alkylating agents and may accrue damage to the germinal epithelium of the testis. Surveillance of testicular growth in boys at annual visits and initial screening of gonadal hormone values at 14 years of age (FSH, LH and testosterone). Adult values for these hormones are expected at 16-17 years of age. High FSH values suggest damage to the germinal epithelium. Semen analysis can be done if requested by the patient or if the patient is receptive to the suggestion by a physician.

Record the onset of menses in girls and regularity of periods. IN case of pelvic radiotherapy or alkylating agents therapy, ovarian failure may occur in some patients.

History should include **school performance and behavioural disturbances** so that early intervention can be made for recognized problems.

Cardiac surveillance. Annual evaluation of cardiac function should be made for at least 5 years in case of history of anthracyclin administration. Histories should include reference to exercise tolerance or shortness of breath.

Particular studies for specific primary sites:

- **Head and neck NRSTS:**

    - **Annual growth measurements** plotted on standard growth curves for all patients
    - **Annual ophthalmologic exam** by an ophthalmologist if eye was in radiotherapy field
    - **Annual dental exam** if maxillary/mandibular sites were in radiotherapy field
    - **Auditory examination every year** if the ears were in the irradiated field
    - If radiotherapy was given to the primary site, get **bone X-Rays of the primary site** every 1-2 years till maturity. Include opposing normal side for comparison of degree of bone hypoplasia
    - **Thyroid function** (TSH, T3, T4) must be verified every 2 years in case of irradiation on the neck.

- **Trunk**

    - If radiotherapy was given to primary tumours of the chest or to pulmonary metastases, take **history for exercise intolerance or shortness of breath**.

    - If part of heart was in radiotherapy field and patient also received doxorubicin, follow for cardiac toxicity (see 2.a.).

    - **X-Rays of the bone in the primary site** with the opposite normal side for evaluation of bone hypoplasia - facultative

    - Studies appropriate to investigate problems fol1owing **abdominal/pelvic irradiation** which may include bowel obstruction, chronic diarrhea, inadequate absorption, recta1 stenosis, and sphincter problems.

- **Kidney function** should be followed annually in patients receiving para-aortic node irradiation or other abdominal sites encroaching on the kidneys.

- If radiotherapy port included the **upper femurs/hip joints**, slipped capita1 femora1 epiphyses may occur severa1 years after therapy. Symptoms are limp or pain.

- Extremities

- If limb or pelvic radiotherapy was given, appropriate **bilateral limb length measurements** should be done annually.
- **X-Rays of primary sites for bone growth-abnormalities –** facultative. Get normal side for comparison.
- History should address **limp, evidence of pain and other dysfunction** of the involved extremity.

♠ **Pain in the primary site 5-10 years after therapy** warrants investigation for the development of secondary bone tumours. This is applicable to all radiation treated sites.

♠ The development of **a second malignant neoplasm,** either leukaemia, lymphoma or solid tumour, should be reported immediately.

13. SYNOVIAL SARCOMA

Synovial sarcoma is the most common NRSTS in childhood. It occurs mostly in extremities of adolescents, marked by the presence of both epithelial-like and spindle cells, with a biphasic aspect, or a monophasic, or a poorly differentiated one. The specific translocation t(X;18) has been found in more than 90% of cases. Though it could be graded according to mitotic index, differentiation and percent of necrosis, synovial sarcoma needs to be considered as a high-grade tumour.

Recently published pediatric series on synovial sarcomas:

Okcu F, 2003 - multicenter study (MDACC, SJCRH, INT Milan, CWS) 219 pts < 20 years, 5-year OS 80% 84% received chemotherapy rate of response to chemotherapy – 60%
Brecht IB, 2005 - CWS, AIEOP-STSC 150 pts < 18 years, IRS groups I-II (initial gross resection), nearly all treated with chemotherapy, 5-yrea OS 89% identification of low-risk patients (group I, ≤ 5 cm) for which chemotherapy might be omitted
Ferrari A, 2009 - AIEOP-STSC 115 patients < 20 years, 5-year OS 76.9%, nearly all patients received chemotherapy worse outcome for non-extremity sites vs limbs (OS 55.1% vs 84.0%)
Brennan B, 2010 - UK CCLG 77 patients < 18 years, 5-year EFS and OS 72% and 76% prognostic factors: T stage and IRS group
Orbach D, 2011 - SIOP-MMT 88 patients < 18 years, 5-year EFS and OS 68% and 85% omission of radiotherapy in many cases (e.g. tumors < 5 cm, after marginal resection; complete remission after primary chemotherapy)
Ferrari A, 2012 - European join series critical reappraisal of staging investigations in relation to the rate of metastatic involvement at diagnosis 258 patients - tumor diameter to warrant more accurate radiological investigations
Ferrari A, 2012 - AIEOP-STSC Salvage rates and prognostic factors after relapse - 44 relapsing cases - 10 year survival 21% variables influencing survival: timing and type of relapse, complete surgery

EpSSG series *from August 2005 to August 2012*
Preliminary data

136 patients enrolled
40 IRS group I, 29 group II, 67 group III
5 N1
70% extremity, 30% axial

Median follow-up 44 months (7.4-93.1)
3-yr EFS = 80.7 (95%CI 72.1-86.9) - 5-yr EFS = 79.5 (95%CI 70.6-85.9)
3-yr OS = 97.8 (95%CI 91.5-99.5) - 5-yr OS = 89.6 (95%CI 78.6-95.1)

Response to chemotherapy in patients with measurable disease:
CR+VGPR+PR = 21.6%
CR+VGPR+PR+MR = 53.3%
CR+VGPR+PR+MR+stable disease = 95%

G4 hematological toxicity = 46%

Events in patients with tumour less than 5 cm:
IRS group I <5 cm (24 pts) → 2 local relapse
IRS group II <5 cm (17 pts) → 2 local + 1 N relapse

13.1 Chemotherapy for synovial sarcoma

The optimal treatment approach to synovial sarcoma remains to be determined, and over the years different strategies have been used in paediatric oncology protocol as compared to the adults. Adult patients have been treated within trials including all soft tissue sarcoma histotypes, generally with an adjuvant chemotherapy and a no-therapy arm. Concerning its chemoresponsiveness, only recently has synovial sarcoma been recognized to stand halfway between most typical adult soft tissue sarcomas and paediatric small round cell tumours.
On the contrary, paediatricians have long appreciated that this tumour needs to be considered a "quite" chemoresponsive tumour, borrowing their approach from RMS. Thus, in previous European protocols synovial sarcoma was considered as a "RMS-like" tumour and included in RMS treatment study: all paediatric patients with synovial sarcoma received chemotherapy (with the same regimen in use for RMS), regardless of surgery and size (i.e. also in case of small tumour completely resected). The role of adjuvant chemotherapy is however still uncertain, and up to now a randomized trial has been considered unfeasible due to the low accrual even in national cooperative studies.
Recently-reported studies would seem unable to definitely clarify the need to adjuvant chemotherapy in synovial sarcomas.
On the one hand, the multicenter multivariate analysis coordinated by the M.D.Anderson (with German and Italian cases), suggested that adjuvant chemotherapy did not seem to have an impact on survival in IRS Group I-II patients. In this series, 5-yr OS was 80%, and tumour size appeared to be the most relevant prognostic factor. Event-free survival (EFS) was 84% in the subset of 37 IRS group I-II patients treated without adjuvant chemotherapy and 78% in the subset of 122 group I-II patients who received it. In IRS group III cases, however, the response rate to chemotherapy was quite high (60%) *(Okcu F, J Clin Oncol 2003)*. These results would seem to suggest to avoid adjuvant chemotherapy in resected patients.

On the other hand, various data suggest continuing to treat all synovial sarcomas with chemotherapy.

In a retrospective single-institutional analysis (271 patients of all ages) (*Ferrari A, Cancer 2004),* the outcome was clearly better in paediatric than in adult cases. This could be related on the different incidence of adverse prognostic factors (i.e. size) in the different age groups, but also to the different use of chemotherapy.

Age-groups	% adjuvant chemotherapy	5yr EFS
0-16 years	78%	66%
17-30 years	20%	40%
> 30 years	14%	31%

Moreover, adjuvant chemotherapy would seem to improve the outcome, with benefit in high risk cases (adults, tumour larger than 5 cm) but even in the low-risk subgroup (completely resected, size less than 5 cm). MFS was 47% in group I-II, > 5 cm patients receiving adjuvant chemotherapy and 27% in those who did not receive adjuvant chemotherapy.
Far from a demonstration of efficacy of adjuvant chemotherapy in synovial sarcomas, these data would seem suggestive of a role of it.

Thereafter, the issue of the role of adjuvant chemotherapy in synovial sarcomas still remains unclear.
An open question concerns the possibility to avoid chemotherapy in tumours smaller than 5 cm after initial resection. A study from CWS and AIEOP STSC on 150 grossly-resected synovial sarcoma patients (group I-II) showed good overall results, with 5-year EFS and OS of 77% and 89%, respectively *(Brecht IB, Pediatr Blood Cancer 2006).* Survival rates did not depend on the surgical margins (IRS group I and II patients have similar outcomes), but on tumour size and local invasiveness. The T2B subset of patients shows 5-year EFS and OS of 41% and 67% respectively.

	5yr EFS	5yr OS
IRS group I	79%	90%
IRS group II	75%	98%
≤ 5 cm	92%	98%
> 5 cm	56%	78%

The rate of metastases in patients with tumour ≤ 5 cm (both group I and II) was really small (in that series, all but very-few patients received adjuvant chemotherapy)

Pattern of relapse:

	L	L+M	M
group I, ≤ 5 cm (48 pts) 4	0	0	
group I, > 5 cm (27 pts)	3	1	7
group II, ≤ 5 cm (43 pts)	3	0	1
group II, > 5 cm (30 pts)	2	3	9

The good outcome of group I patients is confirmed by the SIOP MMT experience (66 patients: EFS and OS at 5 years were 67% and 81%, respectively, being 5-year EFS 73% in cases with tumour size less than 5 cm, and 62% in those with tumour larger than 5 cm). When we consider only patients submitted to complete resection at diagnosis (16 cases), all were alive at the time of the analysis, 13 in first remission and 3 in second remission (at more than 5 years from relapse, that was local in all cases); no metastatic relapse was observed.

The preliminary EpSSG data confirmed the very low risk of metastatic spread of initially resected patients with tumour smaller than 5 cm.

According to these findings, from January 2014 the EpSSG protocol (version 1.2) requires the **omission of chemotherapy in group I-II, ≤ 5 cm patients**
A careful monitoring of relapse rate will be performed to periodically re-consider this indication.

In relation to data suggesting that high dose of ifosfamide might improve response rate in synovial sarcoma, from January 2014 the EpSSG protocol (version 1.2) replaces the classic ifosfamide-doxorubicin regimen with a regimen with **high dose ifosfamide (14 g/m^2 ifosfamide given in continuous infusion via ambulatory external portable pump over 14 days).** This regimen has been shown to be active in pediatric soft tissue sarcomas, and in particular in synovial sarcoma, with an excellent toxicity profile (*Meazza C et al. Prolonged 14-Day Continuous Infusion of High-Dose Ifosfamide With an External Portable Pump: Feasibility and Efficacy in Refractory Pediatric Sarcoma. Pediatr Blood Cancer 2010;55:617–620*).

This change may be of interest for:

a) **efficacy question**: a more intensive use of most active drug in synovial sarcoma, with the hope to increase chemotherapy-response rate in unresected cases; the question is whether high-doses of ifosfamide may be better than standard dose
b) **toxicity question**: whether high-doses ifosfamide may be as efficient as ifo–doxo regimen; this regimen may permit the omission of anthracyclines and so the removal of potential late cardiotoxicity; moreover, this regimen has been reported to have less hematological toxicity than the classic ifosfamide-doxorubicin chemotherapy, it may reduce costs and improve quality of life (no hospitalization)
c) a trial with the same regimen is currently ongoing in some European centers for adult synovial sarcoma; there may be a particular interest, therefore, to compare therapeutic results with adult data.

For patients considered unresectable at diagnosis, 3 cycles of neo-adjuvant chemotherapy are required. After the assessment of chemotherapy response, the best local treatment approach should be performed.

- In case of complete remission, partial remission and stable disease at the evaluation after 3 courses, a total of 5 chemotherapy cycles need to be given.
- In case of progression of disease after the 3 courses, if the patient receive deleyed complete surgery (± radiotherapy), NO further chemotherapy should be given; if the patient cannot undergo surgery, alternative chemotherapy may be considered.

The **chemotherapy response** is evaluated according to the **radiological** response.

*Complete Response **(CR)***	Complete disappearance of all visible disease, complete disappearance of tumour with no residual disease
*Very Good Partial Response **(VGPR)***	≥ 90% reduction of tumour volume (volume response between 90-99%)
*Partial Response **(PR>2/3)***	≥ 66% reduction of tumour volume

	(volume response between 66-90%)
Minor Partial Response ***(PR<2/3)***	Volume response between 34-65%
Stable Disease ***(SD)***	< 33% reduction of tumour volume (no criteria for PR or PD)
Progressive Disease ***(PD)***	Any increase of more than 40% in the sum of volumes of all measurable lesions, or appearance of new lesions.

13.2 Radiotherapy for synovial sarcoma

Concerning radiotherapy, as for other STS, it will be given as conventional fractionation of 1.8 Gy/day. The total dose will range between 50.4 and 59.4 Gy.

► IRS Group I (initial complete resection, R0):

The INT Milan series seemed to suggest a favourable trend for post-operative radiotherapy in patients previously submitted to complete resection (with no statistically significant difference).

		post-operative radiotherapy	
		yes	no
5 year LRFS	complete resection (n.patients 144)	77.8% (n.51)	66.9% (n.93)
	complete resection, tumour ≤ 5 cm (n.63)	100% (n.19)	75.9% (n.44)
	complete resection, tumour > 5 cm (n.72)	73.1% (n.30)	60.9% (n.42)
5 year LRFS	marginal resection (n.71)	57.4% (n.56)	**7.1%** (n.15)

In the common ICG-CWS analysis, no benefit of adding radiotherapy in IRS group I patients (complete macroscopic and microscopic resection) was observed, independent on the initial tumour size. So far there is no clear evidence of the role of radiotherapy in these patients.

► IRS group II (microscopic residual disease at initial resection or positive lymph nodes):

Important note:
Every effort should be done by the surgeon to avoid IRS group II patients (the use of primary re-excision is recommended, when feasible).

There is a debate on the indication of radiotherapy in group II synovial sarcoma, and opposing hints would come from previous studies.

The multicenter analysis from the M.D. Anderson *(Okcu F, J Clin Oncol 2003)* showed the benefit of post-operative radiotherapy on LRFS and OS in group I-II patients (93 group I and 66 group II cases, analysed together: 5-year EFS and OS 83% and 91% in cases treated and 73% and 83% in cases not treated with radiotherapy)..
In the analysis of the INT Milan data (most patients being adults), a clear benefit was observed for group II patients who received radiotherapy: 5-year LRFS was 57% for patients receiving radiotherapy (56 cases) and 7% for those not receiving it (15 cases) *(Ferrari A, Cancer 2004).*
These findings would suggest the use of radiotherapy after marginal resection.
In the CWS-ICG-analysis *(Brecht IB, Pediatr Blood Cancer 2006)*, the treatment results for patients in IRS group II were comparable to those in IRS group I. These results were obtained with nearly all patients in IRS II receiving radiotherapy.
Data from the SIOP-MMT series (89 patients, from MMT 84-89-95 studies), showed opposite findings: in the subset of 27 IRS group II cases (6 received radiotherapy, 21 did not), outcome was similar regardless of irradiation, thus suggesting that radiotherapy may not be necessary after microscopic incomplete surgery at diagnosis as first line therapy. Similar findings would emerge from a joint SIOP-AIEOP analysis (57 group II cases).
The reasons that may partially explain these differences in results are not clear, and might probably related, at least in part, to the difficulty in give a precise definition of IRS group II and adequate surgical margins.
The debate on indication for radiotherapy in IRS II patients has its background on the different philosophies adopted over the years by the different groups, i.e. the concept of the "total burden of therapy" experienced by a given patient and the predicted sequelae that treatments may have. In particular, the philosophy behind the SIOP-MMT studies has pointed to a lesser use of radiotherapy in selected subsets of patients, generally produced worse local relapse rates than those reported elsewhere, but the overall survival was often superimposable, since a significant number of locally relapsing patients were cured by salvage treatments (including aggressive surgery and radiotherapy); on the other hand, a significant proportion of patients could be cured without radiotherapy.

Since a complete agreement was unreachable within the E*p*SSG, the NRSTS 2005 protocol presents **two alternative options for group II extremity synovial sarcomas**:

a) **to administer radiotherapy in IRS group II synovial sarcomas (option A)**
b) **to avoid irradiation in IRS group II synovial sarcomas (option B), in particular for younger patients and cases with tumour size smaller than 5 cm**

Note:
For the AIEOP STSC, the decision should be on a "*national-basis*", i.e. all group II synovial sarcomas should be irradiated.

In case of indication for RXT:
Radiotherapy need to be applied in conventional fractionation. The total radiation dose for patients with tumours $\leq$ 5 cm in diameter is **50.4 Gy** in 1.8 Gy fractions. Because of a higher local failure risk in patients with larger tumours, **54 Gy** are given in patients with > 5 cm initial tumour size.
Radiotherapy should be planned at 9-12th week of treatment. High-dose ifosfamide may be ivem concomitantly to radiotherapy.

► IRS group III (macroscopic residual disease at initial resection):

After the initial 3 cycles of chemotherapy, tumour-reassessment and then local treatment need to be planned.
Four different options are possible:

a. Patients with the option of secondary complete resection:

Surgery remains the mainstay of treatment for synovial sarcomas.
The use of radiotherapy is a matter of debate in patients with secondary complete resection.
In the CWS group, nearly all patients treated with complete second surgery received radiotherapy.
In INT Milan series, 30 out of 40 IRS group III patients had delayed complete resection: 11 of them received radiotherapy, 19 did not, and no difference was observed on the outcome. Survival rates strongly correlated with the chances to achieving complete surgery (5-year EFS 42% vs 10%), though metastases (and not the local relapse) were the main cause of treatment failure (5-year LRFS 80%, MFS 34%) *(Ferrari A, Cancer 2004)*.
In the E*p*SSG centers, there is no a consensus on:
1) the necessity to give radiotherapy after delayed complete surgery; it is not clear whether the use of radiotherapy in these patients results in improved survival
2) what is the best option, when the decision to give radiotherapy has been taken, between pre-operative and post-operative radiotherapy
(pre-operative irradiation can improve the chance to perform a complete secondary resection; moreover, pre-operative radiotherapy could be more effective in non-hypoxic tissues, may reduce the risk of intra-operative contamination, and could use smaller radiotherapy fields; post-operative radiotherapy has a small risk of wound complication).

Therefore, there are three treatment options for patients with the option of secondary complete resection:

a1. Preoperative RXT with **50.4 Gy** in 1.8 Gy daily fractions

a2. No additional RXT following secondary complete resection

a3. Postoperative RXT with **50.4 Gy** in 1.8 Gy daily fraction

The decision may depend also to the physician's preference.
However, possible suggestions are:

- to avoid RXT in younger patients after delayed complete surgery (< 6 years)
- to give RXT in case of initial large tumour size (> 10 cm) and in case on first surgical approach (biopsy) that could have caused tissue contamination.

The results of the different local modality groups will be compared

a.4 Following secondary incomplete resection, **54 Gy** have to be given with microscopical residual disease. In case of macroscopic residual disease, radiotherapy has to be given according to patients with no second surgery (see below)

b. Patients without the option of secondary complete resection:

In IRS group III patients who cannot have a complete secondary resection, radiotherapy is then the only local therapy modality and should be given with high doses. The recommended dose is **59.4 Gy**.
An additional boost of 5.4 Gy can be given when there is residual disease at the end of radiotherapy. The dose recommendation may need modification depending on the age of the patient and the tumour site.

Note:
High-dose ifosfamide may be ivem concomitantly to radiotherapy.

►►► Timing of radiotherapy

IRS group II:
Radiotherapy plans should be performed during the 7th week, with the aim to start the irradiation at **week 9**

IRS group III:
In patients receiving **no second surgery**, radiotherapy is performed at **week 9**.
When second surgery is planned, there are 3 treatment options:

- preoperative radiotherapy
- postoperative radiotherapy
- no radiotherapy

When radiotherapy is performed before second surgery (**pre-operative radiotherapy**), irradiation starts at **week 9**. Surgery should be performed 5 weeks after the end of radiotherapy (and after the last chemotherapy cycle) to avoid surgical complications.
When **postoperative radiotherapy** is given, radiotherapy should be started within 21 days except when there are postoperative complications.

►►► Radiotherapy in younger children

Children < 3 years of age

Radiotherapy is only given when there is residual tumour after primary or secondary resection. For patients in IRS group III without an option of secondary complete resection, the dose is reduced to 50.4 Gy

- IRS group I: no RXT
- IRS group II: no RXT
- IRS group III, secondary complete resection: no RT
- IRS group III, no complete secondary surgery: 50.4 Gy

Note:

Synovial sarcomas of AXIAL sites

Although the most common clinical presentation of synovial sarcoma is a slow-growing mass in the soft tissues of the lower extremities, especially around the knee and ankle (associated with joints, tendons and bursal structures), sites of origin other than the extremities are more common than generally believed (1 in 4 of all cases). Synovial sarcoma can arise in the head and neck, in the chest and abdominal wall, in the retroperitoneum and mediastinum, in the lung and pleura, and at other visceral locations. In these less common sites, synovial sarcoma is often diagnosed late or not at all, and its treatment may be more of a challenge, particularly as concerns local therapies (resection with clear histological margins is usually more difficult to achieve, and full-dose radiotherapy may also be more difficult to administer). The outcome of patients with non-extremity synovial sarcoma is consequently generally worse than for patients with limb tumors.

The Italian series (*Ferrari, Eur J Cancer 2008*) confirmed the worse prognosis of synovial sarcoma originating at axial locations: 115 cases, 30 arising from "axial" sites; 5-year OS was 55% for axial cases and 84% for extremity cases. The study found that the chances of initial gross resection were strongly influenced by tumor site, but on the other hand final outcome was not satisfactory also in patients achieving initial gross resection too (possibly suggesting a more aggressive clinical course - and biology - of non-extremity cases). In conclusion, the Italian study suggested that tumor site should be considered when defining a risk-adapted treatment strategy for synovial sarcomas.

Similar findings are confirmed emerged from the SIOP analysis (Orbach, 2011): 89 cases from MMT 84-89-95, of which 30 from axial sites, 5-year OS 89% vs 73%.

As a consequence, it has been decided to consider tumor site as a variable for defining treatment intensity: patients with tumor arising from axial sites (i.e. head-neck, trunk, lung-pleura, retroperitoneum) should be always treated in the higher risk group (as group III and N1 patients), in order to benefit from the most aggressive therapy i.e. in terms of number of chemotherapy cycles and systematic radiotherapy.

13.3 Risk-adapted treatment program for synovial sarcoma

Limbs, IRS group I, ≤ 5 cm

→ surgery only

NO adjuvant chemotherapy, NO radiotherapy

Limbs, IRS group II, ≤ 5 cm

→ surgery ± radiotherapy 50.4 Gy (1.8 Gy/d)

Limbs, IRS group I, > 5 cm

→ high dose IFOSFAMIDE x 3 cycles
(cumulative IFO 42 g/m^2)
NO radiotherapy

Limbs, IRS group II, > 5 cm

→ high dose IFOSFAMIDE x 4 cycles
(cumulative IFO 56 g/m^2)

± Radiotherapy 54 Gy (1.8 Gy/d)
starting at 9th week

IRS group III or N1 or axial sites

→ high dose IFOSFAMIDE x 5 cycles
(cumulative IFO 70 g/m^2)

then evaluation of tumour response (week 9th) and local treatment:

- delayed complete surgery, no RXT
- pre-op RXT 50.4 Gy, then surgery
- delayed complete surgery, then post-op RXT 50.4 Gy
- delayed incomplete surgery, then RXT 54-59.4 Gy
- RXT 59.4 Gy

► Limbs, IRS group I, > 5 cm

	1°	4°	7°	weeks
S	*high-dose* IFO	*high-dose* IFO	*high-dose* IFO	

► Limbs, IRS group II, > 5 cm

	1°	4°	7°	10°	weeks °
S	*high-dose* IFO	*high-dose* IFO	*high-dose* IFO	*high-dose* IFO	

⇒ ± **RADIOTHERAPY** 54 Gy

► IRS group III or N1 or axial sites

	1°	4°	7°	9°	tumour re-assessment
biopsy	*high-dose* IFO	*high-dose* IFO	*high-dose* IFO		

a)

10°	13°	16°	weeks
high-dose IFO	*high-dose* IFO	**S**	

⇒ pre-op **RADIOTHERAPY** 50.4 Gy

b)

10°	12°	15°	weeks
S	*high-dose* IFO	*high-dose* IFO	

c)

10°	12°	15°	18°	weeks
S	*high-dose* IFO	*high-dose* IFO		

⇒ post-op **RXT** 50.4 Gy (or 54–59.4 Gy)

d)

10°	13°	16°	weeks
high-dose IFO	*high-dose* IFO		

⇒ **RADIOTHERAPY** 59.4 Gy

after the first three courses of chemotherapy, continuation of chemotherapy is indicated in the case of complete remission, partial remission or stable disease to primary chemotherapy

S = surgery
high-dose IFO = ifosfamide 14 g/m^2 in 14 days

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14. ADULT-TYPE SOFT TISSUE SARCOMAS

We have defined as "adult-type" soft tissue sarcomas those NRSTS that are:

- typical of adulthood (excluding infantile fibrosarcoma)
- definitely malignant (excluding borderline tumours, i.e. hemangioendothelioma)
- with morphological features resembling differentiated/mature tissues (excluding small round cell tumours, i.e. extraosseues pPNET/Ewing's sarcoma and desmoplastic small round cell tumour).

Therefore, the following histotypes are included in this group:

- fibrosarcoma (adult-type)
- malignant peripheral nerve sheath tumour (malignant schwannoma, neurofibrosarcoma)
- epithelioid sarcoma
- leiomyosarcoma
- clear cell sarcoma
- liposarcoma
- alveolar soft part sarcoma
- malignant fibrous histiocytoma
- hemangiopericytoma (adult-type)
- angiosarcoma
- dermatofibrosarcoma protuberans

The definition of this group tries to respond to the necessity of the identification of a relatively "homogeneous" group of NRSTS. This definition is arbitrary and is based on clinical consideration more than histological ones.

14.1 Chemotherapy for adult-type soft tissue sarcomas

This group includes the large proportion of NRSTS, generally considered as characterized by uncertain response to chemotherapy.
As in adults, conservative surgical resection remains the unquestionable mainstay of therapy, and radiotherapy is considered important in case of incomplete resection or, after wide excision, in case of large tumours.
Surgery (IRS group), tumour size and tumour grade represent the most important prognostic factors, as reported by paediatric and adult published series.
There is a general agreement that patients with small and low-grade tumour, who underwent complete surgical resection, can be cured without adjuvant therapies.
Differently, patients with large tumour and/or high-grade tumour had a high risk of metastatic spread. Therefore, a relevant question concerns the role of **adjuvant chemotherapy** in these patients.

Though several adult studies did not demonstrate any advantage for chemotherapy (while the only one randomized trial on adjuvant chemotherapy performed in paediatric age failed in its aim because the majority of patients refused randomization), various recent hints would suggest that chemotherapy might have a more significant role in high-risk cases (i.e. large tumour, high-grade) than is generally believed.
A large meta-analysis (including trials on intensified doxorubicin-based chemotherapy) demonstrated a reduction in the risk of local and distant failures in the chemotherapy-group (*The Sarcoma Meta-analysis Collaboration, Lancet 1997*).
Moreover, the Italian randomized trial on high risk patients (high-grade, large, deep, extremities site) was closed in advance due to an early striking benefit in EFS and OS for patients who received intensive ifosfamide-doxorubicin chemotherapy (with G-CSF support) versus those treated with local therapy only (*Frustaci, J Clin Oncol 2001*). IFO-DOXO regimen needs to be considered the most effective chemotherapy and several suggestions have prompted that the dose intensification has been associated with the improvement of response rate and disease-free survival.

More recently, the M.D.Anderson and the Memorial Sloan Kettering Cancer Centers published a common retrospective analysis on localized, high-risk (high-grade, deep, size > 5 cm) STS of extremities, with the aim to evaluate the impact of doxorubicin-based chemotherapy on outcomes. This reports showed a time-varying effect associated with chemotherapy: during the first year, chemotherapy seemed to improve the outcome, but thereafter the clinical benefits are not sustained over time *(Cormier, J Clin Oncol, 2004).*

In summary, the role of adjuvant chemotherapy remains controversial in these tumours. Caution should be used in interpreting both the negative results from the previous randomized studies (that in most cases used "old" regimens in unselected groups of patients), and the apparently more satisfactory recent findings *(Frustaci, J Clin Oncol 2001; Brodowicz, Sarcoma 2000; Petrioli, Am J Clin Oncol 2002).*
Henceforward, it is clear that clinical trials should properly:
1) target high-risk patients, with a fair selection of the cases,
2) deliver full-dose intensity chemotherapy including the most active drugs.

Currently, **it is clear that we cannot yet define intensive adjuvant IFO-DOXO chemotherapy as "standard of care" in high-risk resected soft tissue sarcomas**.
Moreover, various data would seem to suggest that about 50% of NRSTS with measurable disease might respond to chemotherapy, in particular when minor response are considered too.
In grossly-resected, large, G3 cases, a quite large percentage of patients might have in principle a benefit from the addition of adjuvant chemotherapy, especially when an intensive ifosfamide-doxorubicin regimen is adopted.

In the single-institution series from the Istituto Nazionale Tumori of Milan, *(Ferrari A, J Clin Oncol 2005),* the authors reported the analysis of patients with adult-type STS (excluding synovial sarcomas) considered at high risk of metastatic failure (i.e. IRS group I-II, size > 5 cm, G3): in this subset of 15 patients, 5-year MFS was 36%, and it was 53% in patients treated with adjuvant chemotherapy (11 cases) and 0% in those treated without chemotherapy (4 cases).

Focusing on these subset of patients (IRS group I-II, high risk of metastatic failure due to large size and high-grade), a retrospective analysis has been performed within the ICG-CWS groups (*Ferrari A, Ped Blood Cancer 2005*).

Though grade evaluation was not available for the majority of patients enrolled in previous European protocols, **36** patients (age 3-20 years, median 13) with **group I-II, > 5cm, G3** tumour have been found in the ICG-CWS protocols.

The patients' characteristics were the following:
Histotypes: 14 MPNST, 4 epithelioid sarcoma, 3 clear cell sarcoma, 3 liposarcoma 3 leiomyosarcoma, 3 fibrosarcoma, 1 alveolar soft part sarcoma, 1 chondrosarcoma, 1 malignant hemagiopericytoma, 1 malignant fibrous histiocytoma, 2 not-otherwise specified.
Tumour site: 20 extremities, 8 trunk, 5 abdomen, 3 head and neck.
Stage: 9 T1B, 27 T2B; 3 N1; 23 IRS group I, 13 group II.
After primary resection, 11 patients received radiotherapy and 21 had adjuvant chemotherapy (11 VACA, 8 VAIA, 1 CEVAIE regimen).
Median follow-up was 75 months (range 11-240).
The analysis showed poor survival rates and, in particular, a high proportion of metastatic failures. The time from diagnosis to relapse was 2-59 months, median 6 months. The median time to relapse was 13 months for the "chemotherapy group" and 3 months for the "no chemotherapy group" *(Ferrari A, Ped Blood Cancer 2005)*.

5yr EFS = 26.2% 5yr LRFS = 46.8% **5yr MFS = 34.0%** 5yr OS = 37.5%

patients treated with adjuvant chemotherapy (no.21)
→ 5yr EFS = 36.7%, LRFS = 56.9%, **MFS = 49.5%**, OS = 41.5%

patients treated without chemotherapy (no.15)
→ 5yr EFS = 0%, LRFS = 33.3%, **MFS = 0%**, OS = 23.8%

It is clear that the very-small number of patients strongly limits the value of this analysis.
Nevertheless, the combination of the two variables (G3 and size > 5 cm) seems to bestow a high risk of metastatic spread: large size and high-grade probably define the intrinsic biological aggressiveness of the tumour, that affects the survival despite of the initial surgery. This may suggest in principle the use of systemic therapies.
Moreover, adjuvant chemotherapy seems to have an impact on survival rates.

The results of this analysis are not comparable with the other reported in literature.
Various paediatric and adult series showed EFS rate in the 50% range for large tumours and for G3 tumours, but analyses of large and G3 (considering the two variables together) are not available.
As for paediatric series, the POG study reported a 5-year EFS of 52% for group I-II, G3 patients, but they did not report the outcome of G3 and tumour > 5 cm (*Pratt, J Clin Oncol 1999*). The St. Jude series reported by Sheri Spunt noted that, in the group of IRS group I-II children, > 5 cm cases had a 5-year EFS of 55%, while G3 cases had a 5-year EFS of 65% (no data on > 5 cm and G3) (*Spunt et al, J Clin Oncol 17:3697-3705, 1999*). In an older series reported by Rao et al, T2G3 cases had a 10-year OS of 10% *(Rao et al. Semin Surg Oncol 9:524-531, 1993)*.

Other findings from the ICG and SIOP cases confirm the EFS in the range of 50% for patients with large tumour (and a trend of benefit for patients treated with chemotherapy).

ICG: 23 group I-II, > 5 cm patients		chemotherapy (19 pts)	NO chemotherapy (4)
5yr EFS	50.2%	57.9%	0%
5yr OS	50.2%	57.9%	0%
SIOP: 15 group II, > 5 cm patients		(11)	(4)
5yr EFS	50.9%	63.6%	0%
5yr OS	70.5%	72.7%	50.0%

Similarly, the SIOP MMT95 study analysed the outcome of NRSTS according to tumour grade.
In the last MMT trial, 149 patients with NRSTS were included: 68 of them were graded according to the FNCLCC system: 5-year EFS was 74% for G1-G2 patients (44 cases) and 50% for G3, respectively; MFS figure was superimposable.

► As a consequence of these considerations, and without the possibility to have the patients accrual necessary to a randomized study, the role of adjuvant chemotherapy will be explored in high-risk adult-type NRSTS (IRS group I-II, G3, tumour > 5 cm) within the E*p*SSG protocol.
Adjuvant chemotherapy will be required in these patients: 4 cycles of ifosfamide-doxorubicin plus 2 additional cycles of ifosfamide concomitantly to radiotherapy.
Though adjuvant chemotherapy is not "standard" in these histotypes, the poor MFS of this selected group suggest its use: this recommendation could be considered questionable in patients with no evidence of disease (and therefore without a parameter of measuring response, that would implicate the risk of a subset of patients pointlessly receiving full courses of such a toxic treatment). However, overall chemotherapy response rate has been reported to be around 40%, but up to 55-60% when minor responses were considered too (*Ferrari, J Clin Oncol 2004*). So, a potential benefit for about half of cases might be considered acceptable.

Important note:
The chemosensitivity of the different histotypes will be evaluated prospectively in IRS group III patients. Interim analyses *will be performed considering chemotherapy response rate of each histotype. These results will be considered and – in case of very poor response rate for some particular histotypes - could lead to change the indication for adjuvant chemotherapy with amendments.*

► For patients considered unresectable at diagnosis, 3 cycles of neo-adjuvant chemotherapy with ifosfamide-doxorubicin will be required.

Response rate will be assessed after three courses, then patients will receive local treatment. Additional chemotherapy (2 cycles of ifosfamide concomitantly to radiotherapy, and 2 additional cycles of ifosfamide-doxorubicin) will be required in case of radiological response to the first three cycles (also "minor partial response will be considered sufficient).
Chemotherapy will be avoided in case of stable disease and progression of disease.

Two cycles of ifosfamide alone will be added also to those patients whose local treatment will be surgery alone, to uniform the systemic treatment in the IRS group III patients.

Response evaluation:

Complete Response ***(CR)***	Complete disappearance of all visible disease, complete disappearance of tumour with no residual disease
Very Good Partial Response ***(VGPR)***	≥ 90% reduction of tumour volume (volume response between 90-99%)
Partial Response ***(PR>2/3)***	≥ 66% reduction of tumour volume (volume response between 66-90%)
Minor Partial Response ***(PR<2/3)***	Volume response between 34-65%
Stable Disease ***(SD)***	< 33% reduction of tumour volume (no criteria for PR or PD)
Progressive Disease ***(PD)***	Any increase of more than 40% in the sum of volumes of all measurable lesions, or appearance of new lesions.

Important note:

Neo-adjuvant (pre-operative) chemotherapy *could be proposed with a cytoreductive aim:*
- when a patient is considered unresectable at diagnosis, and may be converted to conservative resectability after tumour shrinkage
but also
- in those cases with large tumour size and a biopsy showing a G3 tumour (for these patients adjuvant chemotherapy will be required), in which the surgeon is not sure to obtain a complete resection (histologically free margins), i.e. he might try a resection, with a risk of infiltrated margins. "IRS group II-resections" should be avoided.
- the multidisciplinary evaluation could be lead to consider, in selected cases, the individually-based decision to use primary chemotherapy also in G3, >5 cm cases considered resectable by surgeons. Surgery remains the mainstay of treatment for NRSTS, but high-risk "adult-type" STS fare poor for metastatic dissemination, independently to surgical margins and local control. Neo-adjuvant chemotherapy could be given as front-line, with a) the aim to treat early the micro-metastases, b) the opportunity to evaluate the response to chemotherapy given the measurable disease. In these situations, very careful evaluation of tumour extension and dimensions is necessary at any cycles, in order to avoid local progression that could make the potential delayed resection unfeasible.

► Cumulative dose of doxorubicin will be 300 mg/m^2 in IRS group I-II patients who receive adjuvant chemotherapy, and 375 mg/m^2 in IRS III patients who respond well to primary chemotherapy and therefore continue with the full program.

14.2 Radiotherapy for adult-type soft tissue sarcomas

► IRS Group I (initial complete resection, R0):

In adult patients with soft tissue sarcoma, radiotherapy is required after incomplete resection, but often also after wide excision, especially in case of large tumour. In children with a higher risk of severe late effects of radiotherapy, the indication has to be stricter than in adults.
There is little data about the impact of radiotherapy in IRS group I patients in paediatric age. In the analysis of the St. Judes experience of patients with at least grossly resected tumours, univariate analysis of factors associated with improved local control included the use of radiotherapy. It is of note, though, that the majority of irradiated patients belonged to IRS group II. (*Spunt S, 2002*).
In the INT Milan series, 100 paediatric patients were classified as IRS group I: 22 received post-operative radiotherapy and 78 did not. LRFS at 5 years was 95.2% in the group of patients who had radiotherapy and 84.4% in the second group, without statistically significant difference. When only patients with tumour larger than 5 cm were considered, 5-year LRFS and OS were 91.7% and 90.0% for patients treated with radiotherapy (13 cases) and 69.8% and 53.8%, respectively, for those who were not irradiated (23 cases), and the p value was significant for OS (though the OS results may be influenced by the different use of chemotherapy in this two groups, the percentage of patients who had also chemotherapy being higher in the first group) (*Ferrari A, J Clin Oncol 2005*).

However:

- because of the low risk of local failure in patients with small tumours, no radiotherapy is given in patients in IRS group I with < 5 cm tumour diameter at diagnosis.
- in IRS group I patients with tumours > 5 cm, radiotherapy is given in G2 and G3 tumours (no in G1 tumour). In case of local relapses, these patients are at risk of metastatic relapse and consequently impaired prognosis. The radiation dose of adjuvant radiotherapy is **50.4 Gy** in 1.8 Gy fractions.

► IRS group II (microscopic residual disease at initial resection):

Patients with microscopic residual disease following secondary complete resection are at a considerable risk to develop local recurrences. In the INT Milan series, 5-year LRFS was 75.7% in patients who had radiotherapy (n = 27) and 55.6% in those who did not receive it (n = 9) (*Ferrari A,J Clin Oncol 2005*)
An exception is low-grade tumours. The risk of relapse is lower, and furthermore local recurrences are usually again low-grade, are hardly ever associated with systemic failure, and could be treated with success with re-surgery and eventual radiotherapy. COG (Children's Oncology group) series included 4 IRS group II G1 patients treated without radiotherapy who did not relapse (*unpublished data*). In the INT Mila series, 3 patients were classified as group II/G1: two received radiotherapy, and one did not; this patient relapsed locally, but he was salvage with surgery and radiotherapy.
Therefore, no radiotherapy is recommended in patients with IRS group II G1 tumours.
An exception is patients in whom surgery of local recurrence would be problematic because of tumour site or because of the extent of primary surgery. In these cases, radiotherapy should be given at primary treatment (54 Gy).
In patients IRS group II G2-3, radiotherapy is given with **54 Gy**, 1.8 Gy daily fractions.

► IRS group III (macroscopic residual disease at initial resection):

As for synovial sarcoma, after the initial 3 cycles of chemotherapy, tumour-reassessment and then local treatment need to be planned.

a. Patients with the option of secondary complete resection:

Patients with initially unresectable tumour are at high risk of local failure. In the St. Jude's experience, local failure rate was 44 % at 5 years (*Spunt S, 2002*.). The mainstay of treatment is to obtain a secondary complete resection. Initial incomplete resection should be followed by immediate re-resection if expected to be complete and non-mutilating. In all other patients, chemotherapy is administered before second surgery is attempted. The use of radiotherapy is a matter of debate in patients with secondary complete resection. In the paediatric series from the INT Milan, the 5-year OS of the 40 group III patients was 52%, and correlated with the chance to undergo delayed surgery with histologically free margins. No major differences were observed according to the administration of post-operative radiotherapy: 5-year OS was 80% in the 11 patients who had delayed complete surgery alone, and 86% in the 8 patients who had delayed complete surgery followed by radiotherapy (*Ferrari A, J Clin Oncol 2005*).

Similarly to IRS group III synovial sarcomas, there is no a consensus about a common approach concerning radiotherapy, in particular on:
1) the necessity to give radiotherapy after delayed complete surgery
2) what is the best option, when the decision to give radiotherapy has been taken, between pre-operative and post-operative radiotherapy
(pre-operative irradiation can improve the chance to perform a complete secondary resection; moreover, pre-operative radiotherapy could be more effective in non-hypoxic tissues, may reduce the risk of intra-operative contamination, and could use smaller radiotherapy fields; post-operative radiotherapy has a small risk of wound complication).

Therefore, there are three treatment options for patients with the option of secondary complete resection:

a1. Preoperative RXT with **50.4 Gy** in 1.8 Gy daily fractions

a2. No additional RXT following secondary complete resection

a3. Postoperative RXT with **50.4 Gy** in 1.8 Gy daily fraction

The decision may depend also to the physician's preference.
However, possible suggestions are:

- to avoid RXT in younger patients after delayed complete surgery (< 6 years)
- to give RXT in case of initial large tumour size (> 10 cm) and in case on first surgical approach (biopsy) that could have caused tissue contamination.

The results of the different local modality groups will be compared

a.4 Following secondary incomplete resection, **54 Gy** have to be given with microscopical residual disease. In case of macroscopic residual disease, radiotherapy has to be given according to patients with no second surgery (see below)

b. Patients without the option of secondary complete resection:

Radiotherapy is then the only local therapy modality and should be given with high doses. The recommended dose is **59.4 Gy**. An additional boost of 5.4 Gy can be given when there is residual disease at the end of radiotherapy. The dose recommendation may need modification depending on the age of the patient and the tumour site.

►►► Timing of radiotherapy

IRS group I (> 5 cm) and group II:
Radiotherapy (when indicated) should start after 3 cycles of chemotherapy. Radiotherapy plans should be performed during the 7° week, with the aim to start the irradiation at **week 9**, at the resolution of the toxicity of the third cycle of chemotherapy.
During the administration of radiotherapy (5-6 weeks, overlapping with 2 chemotherapy cycles) chemotherapy will be given with ifosfamide alone.

IRS group III:
The option for second surgery must be checked before the onset of radiotherapy.
In patients receiving **no second surgery**, radiotherapy is performed at **week 9**.
When second surgery is planned, there are 3 treatment options:

- preoperative radiotherapy
- postoperative radiotherapy
- no radiotherapy

When radiotherapy is performed before second surgery (**pre-operative radiotherapy**), irradiation starts at **week 9**. Surgery should be performed 5 weeks after the end of radiotherapy to avoid surgical complications. The sixth cycle of chemotherapy should be given after the end of radiotherapy and before surgery, the last cycle after surgery.
When **postoperative radiotherapy** is given, radiotherapy should be started within 21 days except when there are postoperative complications.

►►► Radiotherapy in younger children

Children < 3 years of age

IRS group I independent of size:	no RXT
IRS group II G1:	no RXT
IRS group II G2 and G3:	50.4 Gy
IRS group III and delayed complete resection	no RXT
IRS group III, no second surgery possible:	50.4 Gy

14.3 Risk-adapted treatment program for adult-type soft tissue sarcomas

IRS Group I ≤ 5cm

→ SURGERY alone
no chemotherapy, no radiotherapy

IRS Group I > 5cm

- **G1** → SURGERY alone
- **G2** → radiotherapy 50.4 Gy
- **G3** → IFO-DOXO x 3 cycles – IFO x 2 – IFO-DOXO x 1
  (cumulative IFO 48 g/m^2, cumulative DOXO 300 mg/m^2)

  Radiotherapy 50.4 Gy (1.8 Gy/d)
  starting at 9th week, concomitantly to 4th and 5th cycles

IRS Group II N0

- **G1** → SURGERY alone
- **G2-G3, ≤ 5 cm** → radiotherapy 54 Gy
- **G2, > 5 cm** → radiotherapy 54 Gy

- **G3, > 5 cm**

  → IFO-DOXO x 3 cycles – IFO x 2 – IFO-DOXO x 1
  (cumulative IFO 48 g/m^2, cumulative DOXO 300 mg/m^2)

  Radiotherapy 54 Gy (1.8 Gy/d)
  starting at 9th week, concomitantly to 4th and 5th cycles

IRS III & N1

→ IFO-DOXO x 3 cycles

then evaluation of tumour response (week 9th) and local treatment:

- delayed complete surgery, no RXT
- pre-op RXT 50.4 Gy, then surgery
- delayed complete surgery, then post-op RXT 50.4 Gy
- delayed incomplete surgery, then RXT 54-59.4 Gy
- RXT 59.4 Gy

in case of major or at least minor response to chemotherapy:
IFO x 2 during RXT, then IFO-DOXO x 2
(cumulative IFO 57 g/m^2, cumulative DOXO 375 mg/m^2)
(no further chemo in case of stable disease)

IRS group I - II, G3, > 5 cm

	1°	4°	7°	9°	10°	13°	17°	weeks
S	IFO-DOXO	IFO-DOXO	IFO-DOXO		IFO	IFO	IFO-DOXO	

⇒ **RADIOTHERAPY** 50.4-54 Gy

IRS group III

	1°	4°	7°	9°	tumour re-assessment
biopsy	IFO-DOXO	IFO-DOXO	IFO-DOXO		

→ **a)**

10°	13°	16°	18°	20°	weeks
IFO	IFO	IFO-DOXO	**S**	IFO-DOXO	

⇒ pre-op **RADIOTHERAPY** 50.4 Gy

→ **b)**

10°	12°	15°	18°	21°	weeks
S	IFO-DOXO	IFO-DOXO	IFO	IFO	

→ **c)**

10°	12°	15°	18°	21°	weeks
S	IFO-DOXO	IFO	IFO	IFO-DOXO	

⇒ post-op **RXT** 50.4 Gy (54-59.4 Gy)

→ **d)**

10°	13°	16°	21°	weeks
IFO	IFO	IFO-DOXO	IFO-DOXO	

⇒ **RADIOTHERAPY** 59.4 Gy

*** in case of no response to primary chemotherapy → local treatment only**

S = surgery
IFO-DOXO = ifosfamide 3 g/m^2/day, for 3 days + doxorubicin 37.5 mg/m^2/day, for 2 days
IFO = ifosfamide 3 g/m^2/day x 2 days

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15. Statistical considerations

The EpSSG NRSTS includes a prospective trial for synovial sarcomas and adult-type sarcomas, and general considerations and suggestions only for the so-called "other histotypes"

SYNOVIAL SARCOMA AND "ADULT TYPE" SOFT TISSUE SARCOMAS

Design of the trial

This study is a prospective, non randomised, international, multi-institutional and historically controlled clinical trial.

First objective of the study is to make uniform the treatment of NRSTS patients in Europe.
Patients will be treated with a risk-adapted multidisciplinary treatment approach.

In particular, the protocol aims to investigate, as main objectives:

- the survival rates (event-free survival EFS and overall survival OS) and the pattern of treatment failure in patients with synovial sarcoma and adult-type sarcomas
- for synovial sarcoma: a) the role of high-dose ifosfamide in improving response rate in patients with unresectable disease (efficacy question); b) the possibility to reduce toxicity (no anthracyclines, less hematological toxicity), reduce costs and improve quality of life (no hospitalization) without jeopardizing the results utilizing high-dose ifosfamide instead of ifosfamide-doxorubicin chemotherapy in those cases requiring chemotherapy according to the risk stratification (toxicity question)
- for adult-type soft tissue sarcomas: the role of an ifosfamide-doxorubicin regimen in improving the response rate in patients with unresectable disease

Secondary objectives will be:

- the prospective evaluation of clinical/pathological prognostic factors,
- the impact of the omission of adjuvant chemotherapy in synovial sarcoma patients with tumour smaller than 5 cm
- the role of adjuvant chemotherapy in IRS group I-II, G3, size > 5 cm adult-type soft tissue sarcoma patients in improving the metastases-free survival (MRS) and the OS

Moreover, the study aims to improve the biological studies and samples collection of these malignancies.

The study patients with the same subtype of sarcoma, enrolled into the previous European studies RMS96, CWS-96 and SIOP-MMT95 trials, are defined as the historical control group.

End points

The objectives of the study are:

- Event free survival (EFS), measured as time from histological diagnosis (first surgical approach – biopsy or resection – that leads to histological diagnosis) up to an event. Event is defined as:

death for all reasons, progression of a residual tumour, relapse following previous complete remission, appearance of a new tumour. Patients without an event at the end of the study or lost to follow up will be censored at the date of last observation.

- Local relapse free survival (LRFS), measured as time from histological diagnosis up to local progression or local relapse. Patients without local failure at the end of the study or lost to follow up will be censored at the date of last observation.
- Metastases free survival (MFS), measured as time from histological diagnosis up to appearance of metastasis. Patients without metastasis at the end of the study or lost to follow up will be censored at the date of last observation.
- Overall survival (OS), measured as time from histological diagnosis up to death for all reasons. Patients still alive at the end of the study or lost to follow up will be censored at the date of last observation.
- Response rate in according to classification criteria reported in chapter 16. Complete response, very good partial response, partial response, minor partial response and stable disease will be considered responses in this study.

Analysis Population

All efficacy analysis will be carried out according to the intention to treat principle. It foresees that all subjects, whether or not they received any study medication, will be analysed.

Patients will be also analysed according to the treatment they actually received. This per-protocol population is defined as all subjects who fulfil all inclusion and exclusion criteria and who receive the planned doses of chemotherapy and radiotherapy according to protocol indications for dose delivery and modifications (i.e., patients who were eligible and who received treatment as planned).

Analysis of toxicity will be based on the safety population that consists of all the subjects who received at least one dose of chemotherapy analysed according to the actual treatment received.

All analyses will be performed exploratively. Therefore the p-values are regarded as descriptive.

Description of patient population

The number and percentage of patients included, completed, withdrawn and lost to follow-up will be summarised using descriptive statistics.

The patient population will be described by descriptive statistics as follows:

1. Demography Variables
   - Co-operative group and Country of provenience
   - Age (<10 years, ≥10 years)
   - Gender
2. Prognostic Factors
   - Tumour size
   - Tumour grade
   - Site of disease
   - Extent of the tumour (TNM classification and IRS post-surgical grouping system)

Description of treatment exposure

- Surgical resection
- Radiotherapy
- Chemotherapy

The number of treatment cycles administered will be summarised using descriptive statistics. Treatment delays will be summarised using counts and percentages. The cumulative dose and actual dose intensity ($mg/m^2/wk$) and the relative dose intensity (actual dose/planned dose) of Doxorubicin and Ifosfamide regimen will be summarised using descriptive statistics (median, range).

Survival and prognostic analyses

EFS, LRFS, MFS and OS will be plotted as a function of time using Kaplan-Meier product limit method. The two-sided log rank test will be used to compare the treatment arms with the historical control population. Summary statistics (3-yr and 5-yr, EFS, LRFS, MFS and OS) will be reported together with their 95% confidence interval.
In addition, the Cox regression model, whenever all assumptions will be satisfied, will be used to check the influence on EFS, LRFS, MFS and OS of the prognostic variables as defined above.

Response rate analysis

The frequencies of responses will be reported with 95% confidence intervals. Comparisons will be analysed by a two-side chi-squared test.

Safety evaluation and analysis

The safety evaluation will be based on the NCI-CTC Version 3 and will be displayed in summary tables according to NCI CTC Version 3 category and grade (all grades, grade 3 and grade 4) for the worst grade documented.

16. Organisational and administrative issues

The E*p*SSG is an inter-group structure which represents an evolution of a well established situation in Europe. It is based on the already existing national and international organisations built with the efforts of the participants to CWS, ICG and SIOP MMT studies over many years.
The E*p*SSG takes into account the differences in the study management and regulations that may exist in the different European countries and co-operative Groups and try to harmonise them.

PARTICIPATING CENTRES
All clinical centres previously part of the SIOP and ICG Co-operative Group are expected to participate in the E*p*SSG study.
New clinical centres, whose national group does not take part as a whole, who wish to participate must demonstrate their ability to participate in the study and must link to one of the existing co-operative Groups.

All participating centres are expected to:
- confirm in writing the intention to participate before starting to recruit patients
- name a clinician who will be responsible for communication with the data office.
- obtain patient's/parents' written consent to data processing and sending diagnostic material to reference institution
- register all patients with non-metastatic NRSTS
- timely and accurate submit clinical data on paper to their reference Co-ordinating Centres or directly via a Remote Data Entry System
- provide diagnostic material for central pathology review, and for related biological studies

According to the European rules, this trial (considered as therapeutic guidelines) does not need a formal approval from the Research Ethical Committees.

CO-OPERATIVE GROUP AND CO-ORDINATING CENTRES

Each Co-operative Group will keep its existent Co-ordinating Centre.

All existing Co-ordinating Centres are expected to:
- promote the study within their group and obtain specific study commitment by the clinical centres
- distribute the protocol, the forms and all pertinent material to the participating centres within their Group
- manage the data collection and implement procedures for data quality control within their group
- be a referring Centre for the Clinicians from participating centres to address clinical questions
- collaborate with the E*p*SSG Co-ordinating Centre to update regularly the data

Other National Co-ordinating Centres may be added or created on purpose to support the work of E*p*SSG if reputed necessary.

CO-ORDINATING CENTRE

The E*p*SSG Co-ordinating Centre is the trial unit in charge of harmonisation and co-ordination of the study related activity of each Group.

In detail it is expected to:

- co-ordinate the development of the common data base in co-operation with CINECA (Bologna, Italy) and the Co-ordinating Centres
- guarantee the functionality of the data base during the whole study period
- supervise the data collection and data quality to ensure the validity of interim and final analyses on the common data
- be a referring Centre for the Co-ordinating Centres to address technical and operative questions regarding the data management of the study
- be responsible for the statistical analysis within the trial at given time periods in collaboration with the panel of statisticians from individual groups
- update regularly the protocol committees on the ongoing trial

The **E*p*SSG Co-ordinating Centre** is located at the:

Clinical Epidemiology Unit	Tel: 0039-0498215704
Regional Cancer Centre	Fax: 0039-0498215706
Via Gattamelata 64	Email: cor.epiclin@unipd.it
35128 Padova	Website: www.corpadova.it
ITALY	

PROTOCOL AND FORMS

One common protocol will be used by the three Groups and all participating Centres. The master protocol will be in English. Translations of the master protocol will be prepared ifrequired by each Co-ordinating Centre.

Any amendments to the protocol must be agreed by all the participants Groups and notified in writing. Addenda may be added independently by any of the national groups to address local needs, provided they have no bearing on the essential aims of the international protocol and they have been previously discussed and approved by the protocol Committee.

Each Co-ordinating Centre will be responsible for distribution of protocols to the Institutions within their Group.

The protocol with all the amendments will be accessible online via the E*p*SSG website to all the participating Investigators.

Identical data forms will be used by all co-operative groups. The master version will be in English and each Co-ordinating Centre is responsible for translating the document for the national Centres. Additional forms may be produced within each Co-operative group for data collection that are specific for that group and exceed the international data set.

DATA MANAGEMENT

Data flow

The E*p*SSG NRSTS 2005 trial will be managed via a web based system. It is expected that each Co-ordinating centre will utilise the Remote Data Entry system hosted at CINECA to perform the data management of the study. At the moment it has not yet established if the Co-ordinating centres will allow their local sites to enter directly the data into the electronic data base via Internet or if they will choose the traditional paper based flow of data within their group.
If paper based flow is chosen, forms returned from the treating Institutions will be stored at the respective Co-ordinating Centres for time periods conforming to national law.
On receipt of forms at each Co-ordinating centre, common range and logical checks will be carried out on the data prior to entering into the web-based national database.
Errors noted in the national and/or master data base will be reported back to the Co-ordinating centre or to the institution of origin.
Standard Operative Procedures for the electronic data management will be agreed on and followed by the Co-ordinating Centres. These SOPS will be described in a specific document.

Patient Registration procedure

Patients with a diagnosis of localised NRSTS must be registered only after he/she and/or his/her legal guardian has consented to registration and data handling. Patients must be registered before treatment is started by the participating Institutions using the Remote Data Entry (RDE) system.
If the access to the RDE system is not possible for whatever reason a fax must be sent to the corresponding Co-ordinating Centre. The Co-ordinating Centre will register the patient using the RDE system.

Access to data from E*p*SSG Central Database

The collected data will be available to all the research staff involved in the trial with different access profiles, in real time and with the possibility of multiple concurrent accesses, despite geographical location.
The Co-ordinating Centre of each group, for example, could have access to all data from its Clinical Centres; instead the principle investigator of each participating Centre may have access only to his centre's data.
Data relating to the present study must not be reported or published without prior consultation of the Protocol Committee.

Data analysis and monitoring

Reports on the study progress will be prepared twice yearly, describing accrual of the patients, group allocations, local therapy modalities and toxicity of the treatments given. This report will be circulated to the Principal Investigators. Data will be published as abstracts at each SIOP meeting if considered appropriate.

The international study committee shall meet as appropriate to consider patient accrual, eligibility, treatment allocation and outcome and ensure a smooth conduct of the study.

According to the European rules, this trial does not need an International Data Monitoring Committee (IDMC) as scheduled for investigational randomised studies (i.e. RMS protocol).

Protocol modification

Any modification which may have an impact on the conduct of the study, or may affect patient safety, including changes of study objectives, study design, patient population, sample size, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by the Protocol Committee and reviewed prior to implementation.
A formal approval by the Ethics Committees for minor administrative changes of the protocol which have no impact on the conduction of the study will not be required.

INSURANCE

The decision whether the study needs to be covered by a specific insurance against damage ensuing from the organisation of the study depends on the indication of each national group.

FINANCING

Each Co-operative Group and Co-ordinating Centre will provide its own financing. E*p*SSG will not pay for the expenses sustained by the clinicians involved in the study.
The E*p*SSG Co-ordinating Data Centre and the Remote Data Entry system (provided by CINECA) will be supported by a Research Grant from the Fondazione Città della Speranza ONLUS, via Pasubio 17 - 36034 Malo (Vicenza), www.cittadellasperanza.org**.**

PUBLICATION POLICY

Participating centres or national Groups may publish details of their own cases but will agree to allow the committee the exclusive right to publish the results of the E*p*SSG NRSTS 2005 Protocol, in part or in total.
Similarly each Cooperative Group forming the E*p*SSG agrees that the results of the Protocol should not be published separately.

All publications using data from the E*p*SSG central data bank are considered to be official E*p*SSG papers and these should be agreed by the main author of the project with the E*p*SSG NRSTS 2005 Protocol Committee before starting the work, so that authorship can be discussed within this group prior to preparation of any publication.
All such publications will be presented on behalf of the E*p*SSG and will acknowledge the contribution of the participating clinicians.
All persons designated as authors should qualify for authorship. Every other author should have participated sufficiently in the work to take public responsibility for the content.

All manuscripts and abstracts (including abstracts for presentation at meetings) and other documents that contain data from the central E*p*SSG data bank must be submitted to the E*p*SSG NRSTS committee at least 21 days prior to the deadline for conference submission.
All abstracts must have written approval from the executive committee prior to final submission.

ETHICAL ISSUES

The E*p*SSG NRSTS 2005 protocol follows the EU Clinical Directive 2001/20/EC for non-commercial clinical trials, in according to the Good Clinical Practice guidelines. National implementation of the directives is a matter of current debate, and possibly divergent views between

Member States could be present. As a consequence, different national groups may need deal differently with the protocol in order to address relevant ethical and insurance requirements.
The protocol is not an investigational trial: therefore, the decision to submit it, before patients' enrolment, to the Ethics Committee of each centre for review and approval according to in force law depends to the each national group.
The patient's and/or parent's written consent is required for data management and for collecting samples for biological studies (sending diagnostic material to reference institutions, which in all participating countries has to conform to the national data protection legislation). The need for a written consent for participating in the study depends on the indication of each national group.

INFORMED CONSENT
The patient's and/or parent's written consent is needed for data management and biology material handling. The need for a written consent for participation in the study depends on the indication of each national group. If the patient is a minor, consent should be received from his/her guardian. Adequate explanation on treatment options must be given, also to the child according to his/her means of understanding. Enough time and the opportunity to discuss participation before the decision for and start of treatment have to be given. The right of a patient to refuse to participate withour giving reasons must be respected.
The patient must remain free to withdraw at any time from the study or to withdraw his/her data from the study, without giving reasons and without prejudicing further treatment.
Administrative documents, consent forms and copies of the study documentation have to be kept according to set archival terms.
Exmples of Consent Forms are provided in Appendix.

DECLARATION OF HELSINKI
The investigator agrees, by signing the protocol, to adhere to the principles of Good Clinical Practice. A copy of the Declaration of Helsinki in its latest form is provided in Appendix .

CONFIDENTIALITY/SECURITY
A high standard level of data confidentiality and security should be guaranteed throughout the study.
In detail:

- The International common data base will not contain individual personal information
- Patients will be identified by a code, not by full name
- All traffic with the server will be encrypted.
- Each user at each site will have a personal User ID and Password.

The system will ensure:

- appropriate and regular backup on electronic media of all data, to permit restoration in case of loss or damage of the data base,
- operation tracking log (for each user: registration of any operation),
- electronic data audit trails (creation of a data base of original entries/modifications with identification of date, time, source and user identity),
- disaster recovery procedures.

Appendix

TNM CLASSIFICATION AND GROUPING

Pre treatment TNM

Tumour:

T0:	No evidence of tumour	
T1:	Tumour confined to organ or tissue of origin	T1a: Tumour ≤ 5 cm in greatest dimension T1b: Tumour > 5 cm in greatest dimension
T2:	Tumour not confined to organ or tissue of origin	T2a: Tumour ≤ 5 cm in greatest dimension T2b: Tumour > 5 cm in greatest dimension
TX:	No information on size and tumour invasiveness	

Lymph nodes:

N0:	No evidence of lymph node involvement
N1:	Evidence of regional lymph node involvement
NX:	No information on lymph node involvement

Metastasis:

M0:	No evidence of metastases or non-regional lymphnodes
M1:	Evidence of distant metastasis or involvement of non-regional lymphnodes
MX:	No information on metastasis

pTNM: Post surgical TNM classification

pT

pT0: No evidence of tumour found on histological examination of specimen.
pT1: Tumour limited to organ or tissue of origin.
Excision complete and margins histologically free.
pT2: Tumour with invasion beyond the organ or tissue of origin.
Excision complete and margins histologically free.
pT3 Tumour with or without invasion beyond the organ or tissue of origin.
Excision incomplete.
- pT3a: Evidence of microscopic residual tumour.
- pT3b: Evidence of macroscopic residual tumour.
- pT3c: Adjacent malignant effusion regardless of size.

pTX: Tumour status may not be assessed.

pN

pN0: No evidence of tumour found on histological examination of regional lymph nodes
pN1: Evidence of invasion of regional lymph nodes
- pN1a: Evidence of invasion of regional lymph nodes
  Involved nodes considered to be completely resected
- pN1b: Evidence of invasion of regional lymph nodes
  Involved nodes considered not to be completely resected

pNX: N status may not be assessed due to lack of pathological examination or inadequate information on pathological findings.

pM

pM0: No evidence of metastasis found on histological examination of regional lymph nodes
pM1: Evidence of metastasis on histological examination
pMX: M status may not be assessed due to lack of pathological examination or inadequate information on pathological findings.

For evaluations NX and pNX will be regarded as N0 and pNX, MX and pMX will be regarded as M0 and pM0

IRS CLINICAL GROUPING CLASSIFICATION

Group I: Localized disease, completely resected

(Regional nodes not involved – lymph node biopsy or dissection is required except for head and neck lesions)

(a) Confined to muscle or organ of origin

(b) Contiguous involvement – infiltration outside the muscle or organ of origin, as through facial planes.

Notation: This includes both gross inspection and microscopic confirmation of complete resection. Any nodes that may be inadvertently taken with the specimen must be negative. If the latter should be involved microscopically, then the patient is placed in Group IIb or IIc (See Below).

Group II: Total gross resection with evidence of regional spread

a) Grossly resected tumour with microscopic residual disease.
(Surgeon believes that he has removed all of the tumour, but the pathologist finds tumour at the margin of resection and additional resection to achieve clean margin is not feasible.) No evidence of gross residual tumour. No evidence of regional node involvement. Once radiotherapy and/or chemotherapy have been started, re-exploration and removal of the area microscopic residual does not change the patient's group.

b) Regional disease with involved nodes, completely resected with no microscopic residual.

Notation: Complete resection with microscopic confirmation of no residual disease makes this different from Groups IIa and IIc.
Additionally, in contrast to Group IIa, regional nodes (wich are completely resected, however) are involved, but the most distal node is histologically negative.

c) Regional disease with involved nodes, grossly resected, but with evidence of microscpic residual and/or histologic involvement of the most distal regional node (from the primary site) in the dissection.

Notation: The presence of microscopic residual disease makes this group different from Group IIb, and nodal involvement makes this group different from Group IIa.

Group III: Incomplete resection with gross residual disease

a) After biopsy only

b) After gross or major resection of the primary (>50%)

Group IV: Distant metastasic disease present at onest
(Lung, liver, bones, bone marrow, brain, and distant muscle and nodes)

Notation: The above excludes regional nodes and adjacent organ infiltration which places the patient in a more favorable grouping (as noted above under Group II).

The presence of positive cytology in CSF, pleural or abdominal fluids as well as implants on pleural or peritoneal surfaces are regarded as indications for placing the patient in Group IV.

pTNM and Grouping System

Group	Definition	pTNM
I	Tumour macroscopically and microscopically removed	
(IA)	Tumour confined to organ or tissue of origin	pT1
(IB)	Tumour not confined to organ or tissue of origin	pT2
II IIA IIB	Macroscopic complete resection but microscopic residuals Lymphnodes not affected Lymphnodes affected but removed	pT3a
III	Macroscopic complete resection but microscopic residuals and lymphnodes affected and not removed	pT3a
	Macroscopic residuals after resection or biopsy With malignant effusion	pT3b pT3c
IV	Metastasis present or non-regional lymphnodes involved	pT4

DEFINITION OF SITES

To define the site of origin may be difficult in some cases of NRSTS. A correct site assignation is of importance in the choice of treatment. The following definitions are given to facilitate the clinician in the appropriate site classification.
We achnowledge the permission given by the IRSG to modify and use their original document on site definitions,

ORBIT

1. Eyelid
This site is sometimes erroneously designated as "eye". Although there may occasionally be a case arising from the conjunctiva of the eye, the globe itself is not a primary site. The eyelid is much less frequent than the orbit itself.

2. Orbit
This refers to the bony cavity, which contains the globe, nerve and vessels and the extra-ocular muscles. Tumour in this site will only rarely invade the bony walls and extend into the adjacent sinuses. This is why this tumour which is clearly adjacent to the skull base and its meninges is not by its natural history appropriate to include in the parameningeal sites unless there is invasion of bone at the base of the skull.

PARAMENINGEAL

1. Middle ear
This refers to a primary that begins medial to the tympanic membrane. This tumour is often advanced at presentation and because of extension laterally may present with a mass in front of or under the ear suggesting a parotid origin. It may also extend through the tympanic membrane and appear to be arising in the ear canal. When there is doubt about the site of origin, the "middle ear" designation should be picked as it implies the more aggressive therapy required of parameningeal sites.

2. Nasal Cavity and Paranasal Sinuses
The three paranasal sinuses are the maxillary sinuses, the ethmoid sinuses, and the sphenoid sinus. These surround the nasal cavity, and a primary in one will frequently extend to another. It can be difficult to determine the exact site of origin, but the choice is academic as the treatement is not affected. The site designation will have a bearing on the design of radiotherapy portals. Tumour arising in the maxillary or the ethmoid sinuses may invade the orbit. This is much more likely than a primary in the orbit invading one of the sinuses. When the distinction between orbit and paranasal sinus is unclear, the site selected should be paranasal sinus as it is the more likely primary site and requires appropriately more aggressive therapy. A primary arising in the sphenoid sinus (rare) may extend inferiorly to involve the nasopharynx.

3. Nasopharynx

This refers to the superior portion of the pharynx which is bounded anteriorly by the back of the nasal septum, superiorly by the sphenoid sinus, inferiorly by a level corresponding to the soft palate, and laterally and posteriorly by the pharyngeal walls.

4. Infratemporal Fossa/Pterygopalative and Parapharyngeal Area

This refers to the tissues bounded laterally by the medial lobe of the parotid gland and medially by the pharynx. Large tumours in this region may extend through the parotid gland and present as a mass of the lateral face, sometimes extending even to the cheek. Where there is doubt as to the primary, the parameningeal designation should be chosen as it confers appropriately more aggressive treatment. The superior boundary of this tissue volume is the base of skull just under the temporal lobe, hence the term "infratemporal". The distinction between this and the "parapharyngeal" area is academic.

5. Orbital tumours with bone erosion
Tumours arising in the orbit but with intracranial extension or important bone erosion are included in the parameningeal group.

In addition the following are classified as parameningeal tumours:
Tumours involving vessels or nerves with direct intracranial connection (Arteria carotis interna, vertebralis, N. opticus, trigeminus, facialis etc).
All intracranial and intraspinal tumours (but tumours arising from the paraspinal muscles with intraspinal extension should be designated as paraspinal, see "Other site" definition)
All tumours with cranial nerve paresis
CSF tumour cell positive patients

HEAD AND NECK

1. Scalp
This site includes primaries arising apparently in, or just below, the skin of all the tissues of the face and head that are not otherwise specified below. This usually means the scalp, external ear and pinna, the nose and the forehead, but not the eyelids or cheek.

2. Parotid
The parotid gland lies just in front of, and under, the ear and may surround both sides of the posterior aspect of the ascending ramus of the mandible. As noted above, large primaries in the infratemporal fossa may erode through the parotid. A true parotid primary should not, on radiographic studies, reveal a mass in the infratemporal fossa.

3. Oral Cavity
This includes the floor of the mouth, the buccal mucosa, the upper and lower gum, the hard palate, the oral tongue (that portion of the tongue anterior to the circumvallate papillae). A primary arising in the buccal mucosa can be impossible to distinguish from one arising in the cheek, but the distinction is academic. This would also include those lesions arising in or near the lips.

4. Larynx
This refers to primaries arising in the subglottic, glottic, or supraglottic tissues. Tumours of the aryepiglottic folds can be impossible to distinguish from the hypopharynx, but the distinction is academic.

5. Oropharynx
This includes tumours arising from the anterior tonsillar pillars, the soft palate, the base of the tongue, the tonsillar fossa, and oropharyngeal walls. Tumours arising in the parapharyngeal space may indent the oropharyngeal wall. In this circumstance, the primary should be considered parameningeal. If the mucosa of the oropharynx actually contains visible tumour as opposed to being bulged by it, the primary would be oropharynx. Primaries arising in the tongue base, soft palate, or tonsillar region may extend into the oral cavity. The oropharynx designation is preferred.

6. Cheek
This refers to the soft tissues of the face that surround the oral cavity. Tumours arising in the parotid may invade the cheek. As noted above, the distinction between this and the buccal mucosa is academic.

7. Hypopharynx
This refers to the pyriform sinus and may be difficult to distinguish from larynx although the designation is academic.

8. Thyroid and Parathyroid
Primaries arising in these two sites are exceedingly rare, if they exist at all, and should those structures be involved, it would more likely be from a primary arising in an adjacent structure such as the neck or, rarely, the trachea.

9. Neck
This refers to the soft tissues of the lateral neck between the mastoid tip and the clavicle. It does not include those medial structures such as hypopharynx and larynx noted above. Unfortunately this site overlaps with the designation "paraspinal" included under the site group "trunk". Primaries arising in the neck can and frequently do behave as a paraspinal primary with direct invasion into the spinal extra dural space, especially if posteriorly placed.

GENITO-URINARY BLADDER AND PROSTATE

1. Bladder
Our criteria for identifying the bladder as a primary site has included the appearance of tumour within the bladder cavity, which can be biopsied under cystoscopy or occasionally at laparotomy. We do not recognize as primary bladder tumours those that simply displace the bladder or distort its shape. The latter are ordinarily primary pelvic tumours, unless otherwise specified.

2. *Prostate*
It is important to differentiate true prostatic tumours from pelvic tumours.

3. Bladder/Prostate
In approximately 20% of males with bladder or prostatic tumours, the precise site cannot be determined even at autopsy. The histologic features are similar. Although it is desirable to have an indication of the "most probable" site from the institution, and one should to get this, it may not be possible.

GENITO-URINARY NON BLADDER AND PROSTATE

1. Paratesticular
The tumours arises from mesenchymal elements of the spermatic cord, epididymis, and testicular envelopes, producing a painless scrotal mass.

2. Testis
This designation is usually wrong because the tumours arise from paratesticular structures.

3. Uterus
A tumour in this primary site may be difficult to differentiate from a primary vaginal site, because a tumour originating in the uterus may fill the vagina. After a therapeutic response, the distinction is usually clear. In

general there is a wide separation of age range between these two groups, with the vaginal cases occurring in infancy or early childhood and uterine primaries in adolescents or young adults.

4. Vagina
A patient with a primary vaginal lesion must have evidence of a visible tumour on the vaginal surfaces which can be biopsied through the vagina. Displacement or distortion of the vagina is not sufficient.

5. Vulva
Primary lesions in this site arise in the labia minora or majora.

EXTREMITIES

1. Hand
Refers to the area from the top of the fingers to the wrist

2. Forearm
Refers to the area from the wrist to the elbow joint

3. Arm
Refers to the area from the elbow joint to the shoulder joint. Tumours arising in the axilla are considered as extremity lesions.

4. Shoulder
The posterior aspect of the shoulder, i.e., the scapular area, is an extremity site.

5. Foot
Refers to the area from the top of the toes to the ankle

6. Leg
Refers to the area from the ankle to the knee

7. Thigh
Refers from the area from the knee to the hip joint

8. Buttocks
These are extremity lesions.

OTHER SITES

This term conventionally groups tumours originating from the sites not mentioned above. Prognosis is similar and usually not satisfying.
The following specific sites have been defined:

Thorax
Includes tumours arising in the following sites:

a) Thoracic wall:
includes tumours arising from the thoracic muscles and the parietal pleura

b) Mediastinum
Occasionally a primary rhabdomyosarcoma may arise form thrachea, heart or nearby areas.

c) Lung:
includes tumours arising form the lung parechyma, brochus and visceral pleura

Diaphragm

Abdominal Wall (including Lumbar or lumbo-sacral wall)
This refers to the anterior abdominal wall from the inferior costal margins superiorly to the inguinal ligaments and symphysis pubis, inferiorly, and extends laterally between the costal margin and posterior iliac crests to the paraspinal region.

Paraspinal
When tumours are described as adjacent to the vertebral column, arising from the paraspinal muscles. This designation is preferable to "abdominal wall" or "trunk" or "neck". They often show an intraspinal component and this should be specified.

Abdomen - Intraperitoneal

a) Liver
True liver rhabdomyosarcoma are less frequent than bile ducts tumours.

b) Bile duct
Bile Duct is a specific site and can be recognised as such at surgery. This might also be called "choledochus" or "biliary tract". There is probably no way one can distinguish an intrahepatic bile duct site from a primary liver site except by examining the excised specimen.

c) Pancreas

d) Bowel

e) Abdomen
The term abdominal refers to tumours arising in the intraperitoneal cavity, when a specific organ of origin such as liver, bile duct, pancreas or intestine cannot be determined.

Abdomen - Retroperitoneal
The term retroperitoneal is reserved for those posteriorly situated abdominal tumours in which there does not seem to be a more specific site. Tumours in a retroperitoneal site are in the posterior aspect of the abdominal and/or pelvis. The term "psoas" as a site is not very specific, as the muscle extends through the posterior lower abdomen, pelvis and into the leg.

Pelvis
It is difficult to define the site of origin when there is a large tumour in the abdomen. The pelvis designation is reserved for lesions involving the lower part of the abdomen when no more specific site is appropriate.

Perianal
These sites are ordinarily "perirectal" or "perianal". They are distinguished with difficulty from perineal and vulval sites; but the latter distinction is important.

Perineum
This should include the site which appear the anus posterior to the scrotum in males and posterior to the labia in females. It extends anteriorly to the base of the scrotum in males and to the introitus in females. It must be distinguished from labial and sites.

REGIONAL LYMPH NODES DEFINITION

Regional lymph node involvement is defined N1 according to TNM system.
Regional lymph nodes are defined as those appropriate to the site of the primary tumour, for example:

Head & Neck :	ipsilateral cervical and supraclavicular lymph nodes; bilateral adenopathy may be present with centrally situated tumours
Orbit :	ipsilateral jugular, pre-auricular, cervical
Intrathoracic:	internal mammary, mediastinal nodes
Thoracic wall:	axillary, internal mammary, infraclavicular nodes

Intraabdominal & Pelvic : Sub diaphragmatic, intra abdominal and iliac lymph nodes according to site.

Abdominal wall:	inguinal, femoral nodes
Genito-urinary:	
Bladder Prostate:	iliac nodes at renal artery or below (lumboaortic nodes are second level nodes).
Cervix and Uterus	iliac nodes at renal artery or below
Paratesticular :	external iliac and para- aortic lymph nodes at renal artery or below
Vagina:	retroperitoneal, pelvic nodes at or below common iliacs inguinal nodes
Vulva:	inguinal nodes
Perineum:	inguinal and iliac (may be bilateral)
Upper Limbs :	axillary lymph nodes (epitrochlear rarely involved)
Lower Limbs :	inguinal lymph nodes (popliteal rarely involved)

Evidence of nodal involvement different than those listed above must be interpreted as distant metastatis and the patient must be treated according to the protocol for patients with metastatis at diagnosis .
Examples:

- perineal tumour with nodes above the pelvis
- thigh tumour with iliac or periaortic nodes
- intrathoracic tumour with subdiaphragmatic nodes
- paratesticular tumour with inguinal nodes regional
- Unilateral tumour with controlateral involved lymph nodes (except in the head and neck).

TOXICITY GRADING

This is a short version of the NCI CTC only containing the most common side effects. The full text vesion can be downloaded from: http://ctep.cancer.gov/reporting/ctc.html.

Grade Toxicity	0	1	2	3	4
ALLERGY/IMMUNOLOGY					
Allergic reaction/ hypersensitivity (including drug fever)	none	transient rash, drug fever < 38°C (<100.4°F)	urticaria, drug fever ≥ 38°C (≥100.4°F), and/or asymptomatic bronchospasm	symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema	anaphylaxis
Note: Isolated urticaria, in the absence of other manifestations of an allergic or hypersensitivity reaction, is graded in the DERMATOLOGY/SKIN category.					
BLOOD/BONE MARROW					
Hemoglobin (Hgb)	WNL	< LLN - 10.0 g/dl < LLN - 100 g/L < LLN - 6.2 mmol/L	8.0 - < 10.0 g/dl 80 - < 100 g/L 4.9 - < 6.2 mmol/L	6.5 - < 8.0 g/dl 65 - 80 g/L 4.0 - < 4.9 mmol/L	< 6.5 g/dl < 65 g/L < 4.0 mmol/L
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis, other)	none	only laboratory evidence of hemolysis [e.g., direct antiglobulin test (DAT, Coombs') schistocytes]	evidence of red cell destruction and ≥ 2gm decrease in hemoglobin, no transfusion	requiring transfusion and/or medical intervention (e.g., steroids)	catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)
Also consider Haptoglobin, Hgb.					
Leukocytes (total WBC)	WNL	< LLN - 3.0 x 10^9 /L < LLN - 3000/mm^3	≥2.0 - < 3.0 x 10^9 /L ≥2000 - < 3000/mm^3	≥1.0 - < 2.0 x 10^9 /L ≥1000 - < 2000/mm^3	< 1.0 x 10^9 /L < 1000/mm^3
Lymphopenia	WNL	<LLN - 1.0 x 10^9 /L <LLN - 1000/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3	-
Note: The following criteria using age, race, and sex normal values may be used for pediatric studies if the protocol so specifies.		*≥75-<100%LLN*	*≥50-<75%LLN*	*≥25-<50%LLN*	*<25%LLN*
Neutrophils/granulocytes (ANC/AGC)	WNL	≥1.5 - <2.0 x 10^9 /L ≥1500 - <2000/mm^3	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	< 0.5 x 10^9 /L < 500/mm^3
Platelets	WNL	< LLN - <75.0 x 10^9 /L < LLN - 75000/mm^3	≥50.0 - < 75.0 x 10^9 /L ≥50000 - < 75000/mm^3	≥10.0 - < 50.0 x 10^9 /L ≥10000 - < 50000/mm^3	< 10.0 x 10^9 /L < 10000/mm^3
Transfusion: Platelets	none	-	-	yes	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
Also consider Platelets.					
Transfusion: pRBCs Also consider Hemoglobin.	none	-	-	Yes	-
CONSTITUTIONAL SYMPTOMS					
Fatigue (lethargy, malaise, asthenia)	none	increased fatigue over baseline, but not altering normal activities	moderate (e.g., decrease in performance status by 1 ECOG level or 20% Karnofsky or *Lansky*) or causing difficulty performing some activities	severe (e.g., decrease in performance status by ≥2 ECOG levels or 40% Karnofsky or *Lansky*) or loss of ability to perform some activities	bedridden or disabling
Note: See Appendix III for performance status scales.					
Fever (in the absence of neutropenia, where neutropenia is defined as AGC < 1.0 x 10^9/L) Also consider Allergic reaction/hypersensitivity. Note: The temperature measurements listed above are oral or tympanic.	none	38.0 - 39.0°C (100.4 - 102.2°F)	39.1 - 40.0°C (102.3 - 104.0°F)	> 40.0°C (>104.0°F) for < 24hrs	> 40.0°C (>104.0°F) for > 24hrs
Hot flashes/flushes are graded in the ENDOCRINE category.					
Rigors, chills	none	mild, requiring symptomatic treatment (e.g., blanket) or non-narcotic medication	severe and/or prolonged, requiring narcotic medication	not responsive to narcotic medication	-
Sweating (diaphoresis)	normal	mild and occasional	frequent or drenching	-	-
Weight gain Also consider Ascites, Edema, Pleural effusion.	< 5%	5 - <10%	10 - <20%	≥ 20%	-

Grade Toxicity	0	1	2	3	4
Weight gain - veno-occlusive disease (VOD) Note: The following criteria is to be used ONLY for weight gain associated with Veno-Occlusive Disease.	<2%	≥2 - <5%	≥5 - <10%	≥10% or as ascities	≥10% or fluid retention resulting in pulmonary failure
Weight loss Also consider Vomiting, Dehydration, Diarrhea.	< 5%	5 - <10%	10 - <20%	≥20%	-
Constitutional Symptoms-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
DERMATOLOGY/SKIN					
Alopecia	normal	mild hair loss	pronounced hair loss	-	-
Dry skin	normal	controlled with emollients	not controlled with emollients	-	-
Flushing	absent	present	-	-	-
Injection site reaction	none	pain or itching or erythema	pain or swelling, with inflammation or phlebitis	ulceration or necrosis that is severe or prolonged, or requiring surgery	-
Pruritus	none	mild or localized, relieved spontaneously or by local measures	intense or widespread, relieved spontaneously or by systemic measures	intense or widespread and poorly controlled despite treatment	-
Rash/desquamation Also consider Allergic reaction/hypersensitivity. Note: Erythema multiforme (Stevens-Johnson syndrome) is graded separately as Erythema multiforme.	none	macular or papular eruption or erythema without associated symptoms	macular or papular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface area	symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis
Urticaria (hives, welts, wheals)	none	requiring no medication	requiring PO or topical treatment or IV medication or steroids for <24 hours	requiring IV medication or steroids for ≥24 hours	-
ENDOCRINE					
Hot flashes/flushes	none	mild or no more than 1 per day	moderate and greater than 1 per day	-	-
SIADH (syndrome of inappropriate antidiuretic hormone)	absent	-	-	present	-
GASTROINTESTINAL					
Anorexia	none	loss of appetite	oral intake significantly decreased	requiring IV fluids	requiring feeding tube or parenteral nutrition
Ascites (non-malignant)	none	asymptomatic	symptomatic, requiring diuretics	symptomatic, requiring therapeutic paracentesis	life-threatening physiologic consequences
Colitis Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Melena/GI bleeding, Rectal bleeding/hematochezia, Hypotension.	none	-	abdominal pain with mucus and/or blood in stool	abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation	perforation or requiring surgery or toxic megacolon
Constipation	none	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Dehydration Also consider Hypotension, Diarrhea, Vomiting, Stomatitis/pharyngitis (oral/pharyngeal mucositis).	none	dry mucous membranes and/or diminished skin turgor	requiring IV fluid replacement (brief)	requiring IV fluid replacement (sustained)	physiologic consequences requiring intensive care; hemodynamic collapse
Diarrhea Patients without colostomy: Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Pain, Dehydration, Hypotension.	none	increase of < 4 stools/day over pre-treatment	increase of 4-6 stools/day, or nocturnal stools	increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration	physiologic consequences requiring intensive care; or hemodynamic collapse
Gastritis	none	-	requiring medical management or non-surgical treatment	uncontrolled by out-patient medical management; requiring hospitalization or surgery	life-threatening bleeding, requiring emergency surgery
Mouth dryness	normal	mild	moderate	-	-
Mucositis Note: Mucositis not due to radiation is graded in the GASTROINTESTINAL category for specific sites: Colitis, Esophagitis, Gastritis, Stomatitis/pharyngitis (oral/pharyngeal mucositis), and Typhlitis; or the RENAL/GENITOURINARY category for Vaginititis. Radiation-related mucositis is graded as Mucositis due to radiation.					

Grade Toxicity	0	1	2	3	4
Nausea	none	able to eat	oral intake significantly decreased	no significant intake, requiring IV fluids	-
Stomatitis/pharyngitis (oral/pharyngeal mucositis) Note: Radiation-related mucositis is graded as Mucositis due to radiation.	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swallow	painful erythema, edema, or ulcers requiring IV hydration	severe ulceration or requires parenteral or enteral nutritional support or prophylatic intubation
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hypotension, Febrile/neutropenia.					
Vomiting Also consider Dehydration.	none	1 episode in 24 hours over pretreatment	2-5 episodes in 24 hours over pretreatment	≥6 episodes in 24 hours over pretreatment; or need for IV fluids	Requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse
HEPATIC					
Alkaline phosphatase	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Bilirubin	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
GGT (γ - Glutamyl transpeptidase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic enlargement Note: Grade Hepatic enlargement only for changes related to VOD or other treatment related toxicity.	absent	-	-	present	-
Hypoalbuminemia	WNL	<LLN - 3 g/dl	≥2 - <3 g/dl	<2 g/dl	-
Liver dysfunction/failure (clinical) Note: Documented viral hepatitis is graded in the INFECTION category.	normal	-	-	asterixis	encephalopathy or coma
Portal vein flow	normal	-	decreased portal vein flow	reversal/retrograde portal vein flow	-
SGOT (AST) (serum glutamic oxaloacetic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
SGPT (ALT) (serum glutamic pyruvic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
INFECTION/FEBRILE NEUTROPENIA					
Catheter-related infection	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment or hospitalization	life-threatening sepsis (e.g., septic shock)
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC < 1.0 x 10^9/L, fever ≥38.5°C) Note: Hypothermia instead of fever may be associated with neutropenia and is graded here.	none	-	-	Present	Life-threatening sepsis (e.g., septic shock)
Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC < 1.0 x 10^9/L) Note: Hypothermia instead of fever may be associated with neutropenia and is graded here. In the absence of documented infection with grade 3 or 4 neutropenia, grade as Febrile neutropenia.	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Infection with unknown ANC Note: This toxicity criterion is used in the rare case when ANC is unknown.	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Infection without neutropenia	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment, or hospitalization	life-threatening sepsis (e.g., septic shock)
Infection/Febrile Neutropenia-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
METABOLIC/LABORATORY					

Grade Toxicity	0	1	2	3	4
Acidosis (metabolic or respiratory)	normal	pH < normal, but ≥7.3	-	pH < 7.3	pH < 7.3 with life-threatening physiologic consequences
Alkalosis (metabolic or respiratory)	normal	pH > normal, but ≤7.5	-	pH > 7.5	pH > 7.5 with life-threatening physiologic consequences
Hyperkalemia	WNL	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Hypernatremia	WNL	> ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Hypoglycemia	WNL	<LLN - 55 mg/dl <LLN - 3.0 mmol/L	40 - < 55 mg/dl 2.2 - < 3.0 mmol/L	30 - < 40 mg/dl 1.7 - < 2.2 mmol/L	< 30 mg/dl < 1.7 mmol/L
Hypokalemia	WNL	<LLN - 3.0 mmol/L	-	2.5 - <3.0 mmol/L	<2.5 mmol/L
Hypomagnesemia	WNL	<LLN - 1.2 mg/dl <LLN - 0.5 mmol/L	0.9 - <1.2 mg/dl 0.4 - < 0.5 mmol/L	0.7 - < 0.9 mg/dl 0.3 - < 0.4 mmol/L	< 0.7 mg/dl < 0.3 mmol/L
Hyponatremia	WNL	<LLN - 130 mmol/L	-	120 - <130 mmol/L	<120 mmol/L
Hypophosphatemia	WNL	<LLN -2.5 mg/dl <LLN - 0.8 mmol/L	≥2.0 - <2.5 mg/dl ≥0.6 - <0.8 mmol/L	≥1.0 - <2.0 mg/dl ≥0.3 - <0.6 mmol/L	< 1.0 mg/dl <0.3 mmol/L
OCULAR/VISUAL					
Dry eye	normal	mild, not requiring treatment	moderate or requiring artificial tears	-	-
Tearing (watery eyes)	none	mild: not interfering with function	moderate: interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	-
Vision- blurred vision	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Ocular/Visual-Other (Specify, _____)	normal	mild	moderate	severe	unilateral or bilateral loss of vision (blindness)
PAIN					
Abdominal pain or cramping	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Headache	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Hepatic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Rectal or perirectal pain (proctalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
RENAL/GENITOURINARY					
Bladder spasms	absent	mild symptoms, not requiring intervention	symptoms requiring antispasmotic	severe symptoms requiring narcotic	-
Creatinine	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Note: Adjust to age-appropriate levels for pediatric patients.					

NEPHROTOXICITY GRADING

Table 1: Nephrotoxicity Grading: Values

Toxicity Grade	GFR	Tm_p/GFR		HCO_3		EMUO
		Age <1 yr	Age ≥1 yr	Age <1 yr	Age ≥1 yr	
0	≥ 90	≥ 1.10	≥ 1.00	≥ 18	≥ 20	≥ 600 or normal response to DDAVP if tested
1	60-89	0.90 – 1.09	0.80 – 0.99	15.0 – 17.9	17.0 – 19.9	500 – 599
2	40-59	0.70 – 0.89	0.60 – 0.79	12.0 – 14.9	14.0 – 16.9	400 – 499
3	20-39	No symptoms but 0.60 – 0.69	0.50 – 0.59	No symptoms but 10.0 – 11.9	12.0 – 13.9	No symptoms 300 – 399 with no response to DDAVP if tested
4	≤ 19	HR or Myopathy or < 0.60	< 0.50	HCMA or < 10	< 12	NDI or < 300 with no response to DDAVP if tested

Tm_p/GFR = Renal threshold for Phosphate (mmol/l) which is calculated as

$$Tm_p / GFR = PO_{4(Plasma)} - \frac{PO_{4(Urine)} \times Creatinine_{(Plasma)}}{Creatinine_{(Plasma)}}$$

EMOU: Early Morning Urine Osmolarity (mOsm/kg)

HR: Hypophosphatemic Rickets: Defined by biochemistry (moderate or severs hypophosphatemia: < 0.90 mmol/l at < 1 year of age, < 0.80 at ≥ 1 year) with either clinical signs (genu valgus, bow legs, rickets rosary, cranial tabes, swollen wrists and ankles, abnormal gait, painful limb) or radiological features (wide epiphysal plate, expanded metaphysis, reduced bone density, secondary hyperparathyreoidism with subperiostal erosion) or with both.

HCMA: Hyperchloremic Metabolic Acidosis: Defined by biochemistry (moderate or severe metabloc acidosis: HCO_3 < 15.0 at < 1 year of age, < 17.0 at ≥ 1 year; usually with moderate or severe hyperchloremia ≥ 112 mmol/l) with or without clinical symptoms (e.g. Kussmal respiration)

NDI: Nephrogenic Diabetes Insipidus: Defined by clinical symptoms/sings (polyuria, polydipsia, dehydration) with or wtihout biochemistry (moderate or sever hypernatremia < 150 mmol/l) with lack of response to DDAVP (a normal response is defined as a urine osmolality ≥ 800 mOsm/kg).

Table 2: Nephrotoxicity Grading: Total Score

Sum scores	Total Score	Extent of nephrotoxicity
GFR + Tm_p/GFR + HCO_3 + EMUO	0	No nephrotoxicity
	1-3	Mild nephrotoxicity
	4-7	Moderate nephrotoxicity
	≥ 8	Severe nephrotoxicity

OTHER HISTOTYPES

For the so-called "other histotypes", the E*p*SSG NRSTS protocol provides **general suggestions** only.

1. Infantile Fibrosarcoma

Infantile fibrosarcoma is the most common soft tissue sarcoma under 1 year of age and is identified by the t(12;15) translocation. The clinical behaviour of this tumour may be peculiar, and the overall prognosis is very good.
The so called "infantile fibrosarcoma" (in general clinically defined with a cut off of 2 years) shows peculiar clinical characteristics: it could have initial rapid growth, but also indolent evolution; metastatic spread is uncommon (1-13%) but local recurrence after surgery alone is possible (17-43%). Spontaneous regressions in congenital cases have been described.
The overall prognosis is good with survival rates between 80-100%.

Surgery is the mainstay of treatment, and wide resection represents the adequate treatment strategy in most of patients. However, infantile fibrosarcoma is generally regarded as a chemosensitive tumour (complete remission could be achieved with chemotherapy alone). As a consequence, surgery need to be proposed only if it can be done simply without mutilation; immediate re-excision is required in case of initial incomplete surgery (in case if initial wrong diagnosis).

Surgery alone could be considered the appropriate treatment approach not only for patients who underwent complete resection (histological free margins), but also for IRS group II patients (the salvage rate after local relapse has been reported as more than 80%). Given the age of the patients, radiotherapy is not usually recommended.

Chemotherapy is the initial treatment in cases of inoperable tumours (preoperatively) to permit the tumour shrinkage and the subsequent conservative surgery. Adjuvant chemotherapy following gross-resection, instead, is not established.
The most common chemotherapy regimen used in the literature is VAC (or VadC), while IVA is the standard in Europe.
The **VA regimen** (vincristine plus actinomycinD, avoiding alkylating agents and anthracyclines) have demonstrated its efficacy. Due to the reported good response to chemotherapy, the good overall outcome, and the age of the patients, this regimen is considered the first treatment of choice in this protocol.

Treatment options:

- IRS group I and group II:
  - Only surgery – no further therapy

- patients with unresectable disease (IRS group III):
  - VA chemotherapy

VA regimen is the treatment of choice in patients with unresectable disease, although congenital cases could be differentiated from the others:

- in congenital patients (defines as age less than 3 months), a "wait and see" strategy could be considered, in the view to evaluate possible spontaneous regression or the baby's growth (that can facilitate a subsequent surgery). The patient needs to be carefully monitored. In case of progression, VA chemotherapy needs to be started.

- older patients (> 3 months of age) need to be treated with VA chemotherapy for 6 months. If the tumour responds to VA, and surgery could become feasible without antracyclines and alkylating agents, VA is to be continued up to the surgery; chemotherapy will be stopped after surgery. Response to chemotherapy could be delayed and chemotherapy should be going on at least for 6 months in the absence of possible surgery.

- If the response if not sufficient to permit a conservative surgery (but an initial tumour shrinkage appears evident), IFO could be add (IVA regimen).
  In case of no response to VA, IFO-DOXO regimen will be required.

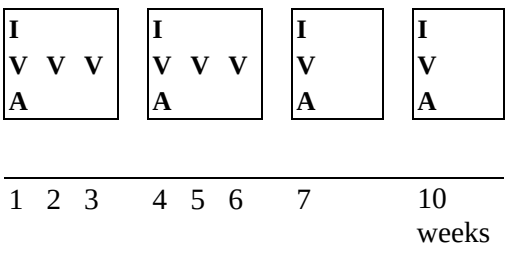
VA regimen (Vincristine + Actinomycin-D)

	V		**V**	**V**			**V**	**V**	**V**	**V**			**V**	**V**	**V**	**V**			**V**	**V**	**V**	**V**
	A			**A**			**A**			**A**			**A**			**A**			**A**			**A**
Weeks	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*21*	*22*
Cycle no.	1			2			3			4			5			6			7			8

Vincristine and actinomycin –D doses:

Age 0-6 months or weight < 5 kg → 50 µg/kg. First injections should be delivered at 30 µg/kg then 40µg/kg then 50µg/kg to check to overall tolerance in babies.
Age 6-12 months or weight < 10 kg → 50 µg/kg
Age > 12 months and weight > 10 kg → 1.5 mg/m² (maximum 2 mg/injection)

IVA regimen:



For a total of 9 courses (25 weeks)
IFOSFAMIDE:
- no alkylating agent before 1 month,
- ifosfamide 50 mg/kg/d x 2 days in patients aged 1-3 months or with weight < 5 kg, First injections should be delivered at 50% then 75% then 100% to check to overall tolerance in babies.
- ifosfamide 100 mg/kg/d x 2 days in patients > 3 months and < 1 year (or > 5 kg and < 10 kg)

► for vincristine and actinomycin-D: see above

IFO-DOXO regimen:

► IFOSFAMIDE:
no alkylating agent before 1 month,
ifosfamide 50 mg/kg x 3 days in patients aged 1-3 months or with weight < 5 kg,
ifosfamide 100 mg/kg x 3 days in patients > 3 months and < 1 year (or > 5 kg and < 10 kg)
► DOXORUBICIN:
no anthracyclin before 3 months
doxorubicin 1 mg/kg x 2 days in patients > 3 months and < 1 year (or > 5 kg and < 10 kg)

References:

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- *Shetty AK, YU LC, Gardner RV, Warrier RP. Role of chemotherapy in the treatment of infantile fibrosarcoma. Med Pediatr Oncol. 33:425-427 (1999)*
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2. Desmoplastic small round cell tumour

Desmoplastic small round cell tumour (DSRCT) is an aggressive neoplasm that has an extremely poor outcome despite an intensive multimodality treatment approach. Since its first description in 1989 by Gerald and Rosai (*Gerald WL, 1989*), DSRCT is being increasingly identified, but its histogenesis remains uncertain. The specific translocation t(11;22)(p13;q12), with the chimeric transcript EWS-WT1, characterises this tumour.
The tumour predominantly affects young males, usually in their second decade of life (*Leuschner I, 1996*). DSRCT typically presents as a large abdominal mass already widely disseminated at the time of diagnosis, with extensive spread to regional lymph nodes, peritoneal seeding, and distant metastases to the lungs, liver and bones. Other, less frequent primary sites are the paratesticular region, the thoracic cavity, sometimes extensive involvement of pleura (*Parkash B, 1995*). Intracranial origin has also been described (*Tyson V, 1996*).

Several small series have now been published examining upfront chemotherapy, +/- aggressive local and metastatic control with surgery and radiotherapy (*Kushner, 1996; Bisogno G, 2000; La Quaglia; 2000*) and specifically high dose chemotherapy with stem cell rescue (*Bertuzzi A, 2003*).
Several factors seem to be emerging which may be important in achieving CR and hence a chance of cure in the long term. Firstly dose intensive and upfront chemotherapy may be important for cure. The P6 regimen of high dose alkylating base chemotherapy Kushner describes achieves more PR's with the chemotherapy alone compared to lower dose regimens such as ICG group based on ifosfamide, vincristine and actinomycin. This, however, may be at a cost, certainly in terms of toxic deaths and also in the median term the risk of developing AML on Kushner's P6 regimen is greater than expected (*Kushner, 1998*).
Secondly, the role of surgery: the patients in the Kushner series and Bisogno's series who were in CR after surgery at diagnosis had no events at the time of publication of their papers and therefore appear to be survivors. Furthermore there are no survivors in any chemotherapy series who do not achieve CR following chemo with surgery.
The role of radiation is difficult to assess. Whole abdominal radiotherapy (up to 30 Gy) has been proposed (*Goodman, 2002).* Certainly in the Kushner series *(Kushner, 1996)* and the ICG (*Bisogno G, 2000*) series, some patients with microscopic residual disease prior to radiotherapy survived. No patient, however, with bulky disease was converted to CR after radiotherapy and hence its role maybe with aggressive surgery in the minimal residual disease setting.
Lastly, the Bertuzzi paper does not support the use of high dose therapy and stem cell rescue (*Bertuzzi A, 2003*). The study does demonstrate, however, the possible role of graft versus tumour effect in apparently clearing the hybrid transcript from peripheral blood in a progressing patient. This should be explored further in any prospective biological study.

The E*p*SSG NRSTS Committee suggest to treat DSRCT patients according to the EpSSG protocol for stage IV RMS
(i.e. Bernie study or IVADo-based program)

Rererences

- *Gerald WL, Rosai J. Case 2. Desmoplastic small cell tumor with divergent differentiation.Paediatric Pathology 1989;9:177-183*

- *Gerald WL, Miller HK, Battifora H, Miettinen M, Silva EG, Rosai J. Intra-abdominal desmoplastic small round-cell tumor. Report of 19 cases of a distinctive type of high-grade polyphenotypic malignancy affecting young individuals. Am J Surg Pathol. 1991 Jun;15(6):499-513.*
- *Kushner B H, Heller G, Cheung N V, et al. High Risk of Leukaemia After Short-Term Dose-Intensive Chemotherapy in Young Patients With Solid Tumors. J Clin Oncol 1998;16: 3016-3020*
- *Bisogno G, Roganovich J, Sotti G, et al. Desmoplastic Small Round Cell Tumor in Children and Adolescents. Med Ped Oncol 2000;34: 338-342*
- *Kushner B H, LaQuaglia M P, Wollner N, et al. Desmoplastic Small Round-Cell Tumor: Prolonged Progression-Free Survival With Aggressive Multimodality Therapy. J Clin Oncol 1996;14: 1526-1531*
- *Bertuzzi A, Castagna L, Quagliuolo V, et al Prospective study of high-dose chemotherapy and autologous peripheral stem cell transplantation in adult patients with advanced desmoplatic small round-cell tumor. Br J Cancer 2003;89**:** 1159-1161*
- *Goodman KA, Wolden SL, La Quaglia MP, Kushner BH. Whole abdominopelvic radiotherapy for desmoplastic small round-cell tumor. Int J Radiation Oncol Biol Phys, 2002;54:170-176*
- *Schwarz RE, Gerald WL, Kushner BH, Coit DG, Brennan MF, La Quaglia MP. Desmoplastic small round cell tumors: prognostic indicators and results of surgical management. Ann Surg Oncol 1998, 5: 416-422.*
- *Leuschner I, Radig K, Harms D, Desmoplastic small rouind cell tumor. Semin Diagn Pathol 1996;13: 204-211*

3. Undifferentiated sarcoma of the liver

note:
undifferentiated sarcoma of the liver and undifferentiated sarcoma of soft part are two distinct entities

Undifferentiated (embryonal) sarcoma of the liver (UESL) is an uncommon hepatic tumour of mesenchymal origin, recognized as a unique clinicopathologic entity in 1978 (*Stocker, 1978*). It accounts for 9-13% of paediatric hepatic tumours, occurring mainly between 5 and 10 years of age, without gender predilection. Clinical presentation is typically an abdominal mass. Malignant mesenchymal elements without any evidence of specific differentiation are observed on histology.

The old reported series described an aggressive neoplasm with poor outcome.
More recently, a high rate of long-term survivors after multidisciplinary treatment approach have been described. In particular, the Italian and German groups reported the experience on 17 children, with 70% of long-term survivors (*Bisogno, 2002*). As expected, in this series surgery continued to play a crucial role in the outcome (all patients with localized, completely resected tumours were cured), but partially unexpected good responses to chemotherapy were observed (tumour shrinkage was evident in 6 out of 9 cases with measurable disease). Others confirmed the same findings, pointed out the efficacy of chemotherapy regimens usually adopted for rhabdomyosarcomas. The role of adjuvant chemotherapy, after initial complete resection, is debatable: however, the overall good outcome reported in patients treated with adjuvant chemotherapy would support its use.

Possible future collaboration with cooperative groups involved in the treated of paediatric liver tumours (SIOPEL) could be welcome and might open the opportunity to design a protocol specifically tailored for UESL.

The current suggestions within the E*p*SSG protocol are the following:

- Surgery remains the mainstay of treatment and aggressive surgical approach should be suggested
- Patients with tumour considered unresectable at the time of diagnosis may benefit from chemotherapy, according to the regimens used for RMS (i.e. IVA, or VAIA regimen including also anthracyclines)
- Also without strong evidence, adjuvant chemotherapy should be recommended.
- The role of radiotherapy in case of incomplete resection is still unclear.

References:

- *Stocker JT, Ishak KG. Undifferentiated (embryonal) sarcoma of the liver. Cancer 1978;42:336-348.*
- *Horowitz ME, et al. Hepatic undifferentiated (embryonal) sarcoma and rhabdomyosarcoma in children. Cancer 1987;59:396-402.*
- *Bisogno G, Pilz T, Perilongo G, et al. Undifferentiated sarcoma of the liver in childhood. A curable disease. Cancer 2002;94:252-257.*
- *Urban, et al. Undifferentiated (embryonal) sarcoma of the liver in childhood. Successful combined-modality therapy in four patients. Cancer 1993;72:2511-2516.*

4. Malignant ectomesenchymoma

It is a very rare tumour comprised of ganglion cells or neuroblasts and one of more malignant mesenchymal elements including rhabdomyosarcoma (as indicated by its alternative designation "gangliorhabdomyosarcoma"). Molecular findings suggest that malignant ectomesenchymoma could be another member of the Ewing's sarcoma/PNET family (EWS/FLI-1 was found in some cases) and may also overlap with alveolar rhabdomyosarcoma (t(2;13)-encoded PAX3/FKHR), as a polyphenotypic small round cell tumour capable of multidirectional differentiation.
This tumour is usually diagnosed in the first 3 years of life, and may arise anywhere in the body.
Complete surgical resection is theainstay of treatment, but chemotherapy probably need to be used.
Overall survival is around 60%, and correlates with resectability.

The E*p*SSG committee suggests to treat malignant ectomesenchymoma as high-risk rhabdomyosarcoma, but patients will not be included in the RMS protocol (i.e. not randomized).

References:

- *Coffin CM, Dehner LP, Neurogenic tumors of soft tissue, in Coffin CM, Dehner LP, O'Shea PA (eds) Pediatric soft tissue tumours: a clinical, pathological, and therapeutic approach. Williams & Wilkins, 1997.*
- *Kawamoto EH, Weidner N, Agostini RM, et al. Malignant ectomesenchymoma of soft tissue: report of two cases and review of the literature. Cancer 1987;59:1791-1802.*
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5. Mesenchymal Chondrosarcoma

Mesenchymal chondrosarcoma (MCS) is a rare malignancy characterized by a biphasic histologic pattern of small undifferentiated round cells intermixed with islands of well-differentiated cartilaginous matrix. Because of its aggressive clinical behavior, MCS should be always regarded as a high-grade sarcoma.

MCS is a rare tumor. In comparison to the most frequent classic chondrosarcoma, MCS typically occurs in young adults (whereas most classic chondrosarcoma patients are >50 years old), it is highly malignant, and has a high proportion of extraskeletal tumors (about 1/3 of MCS occur in soft tissues, whereas extraosseous classic chondrosarcoma account for <1% of all cases.

A CWS retrospective study reported on 15 cases aged 0-25 years, 4 osseous and 11 extraosseous, 1 M1 at diagnosis. Tumor sites were head/neck (n = 6), paravertebral (n = 3), pelvis (n = 3), limbs (n = 2), and kidney (n = 1). All tumors were resected, but only 8 completely. Thirteen individuals received chemotherapy, 6 were irradiated. Actuarial 10-year event-free and overall survival rates were 53% and 67%, respectively.

MCS should be considered a part from adult-type NRSTS. Emerging cytogenetic data, in fact, have raised the idea that this tumor may be closely related to extraskeletal Ewing's sarcoma/pPNET; patients with MCS should be treated with multimodal regimens, probably following Ewing's sarcoma protocols.

References

- *Dantonello T et al. Mesenchymal chondrosarcoma of soft tissues and bone in children, adolescents, and young adults: experiences of the CWS and COSS study groups. Cancer. 2008;112(11):2424-31*

6. Epithelioid hemangioendothelioma

The term **hemangioendothelioma (HE**) included different soft part neoplasms of vascular origin:

- malignant HE should probably considered as angiosarcomas
- kaposiform HE, spindle cells HE and retiform HE are low-grade tumours, that need to be treated with surgery alone
- epithelioid HE represents a more difficult entity with peculiar clinical features, and needs a particular treatment approach. It is a intermediate or borderline tumour, and could include two distinct subtypes:
    - epithelioid HE of soft part: usually presents as a unique lesion localized at extremities or cervical district; and rarely metastasizes or causes patient's death. Surgery is the only treatment for these patients.
    - epithelioid HE of bone, lung and liver

Epithelioid hemangioendotelioma of bone, lung and liver is often metastatic or multifocal, could have indolent course, but the death rate is around 35-65% (*Bollinger et al. Cancer 1994;73:610-615*). The optimal treatment approach is not clear: different data (including ICG-CWS cases), however, underlined a significant role for alpha-interferon (α-IFN), probably due to an anti-angiogenic effect *(Ferrari et al. Ital J Pediatr 2001;27:774-778*). On the contrary, the absence of response to chemotherapy (regimen in use for soft tissue sarcomas) has been reported.

These cases are not so infrequent. Thereafter, ESSG NRSTS Committee could gather all cases and standardize the treatment, with the opportunity to define the role of interferon.
The use of α-IFN is generally suggested (in Italy, both in adult and paediatric cases), but not filed.
We can propose, in all cases with multifocal or unresectable hemangioendothelioma:

- **α-IFN** at the starting dose of **3 x 10^6 U x 3 / week SC**

- if well tolerated, the dose may be increased to 6 and then to 9 x 10^6 U x 3 / week

- in case of response (or stable disease?), the treatment should be continued for 9-12 months

References:

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7. Myofibroblastic lesions and aggressive fibromatosis/desmoid tumours

7.a

Infantile myofibroma (solitary) and **myofibromatosis** (multicentric) are benign neoplasms originating from contractile myoid cells around thin walled blood vessels.

Myofibroma probably forms a morphological continuum with myopericytoma and infantile hemangiopericytoma.

Three entities could be described: 1) solitary myofibroma (most common: >50%), 2) multicentric myofibromatosis (less common), and 3) multicentric myofibromatosis with visceral involvement (<15%). No specific translocations or genetic aberration are known for this entity.

Solitary or multicentric myofibroma are most commonly found in subcutaneous tissue or bone of the head and neck, less frequently in extremities and trunk. Visceral lesions can involve central nervous system, lungs, heart, gastro-intestinal tract, liver, or kidney (*Behar PM, 1998; Fletcher CDM, 2002).* The natural course often involves rapid initial growth, then a stable phase, often followed by spontaneous regression.

Complete excision is often curative, with a low local recurrence rate (<10%). In the absence of visceral involvement, the prognosis is excellent and spontaneous regression is common. Visceral involvement is prognostically unfavorable, with reported survival of 0-25% (*Davies RS, 1994*).

The role of chemotherapy is uncertain (*Palumbo JS, 1999; Williams W, 2002*).However, its use is generally recommended for patients with visceral involvement or multicentric lesions that compromise normal function and involve mutilating surgery. Low-dose chemotherapy with vinblastine plus methotrexate may be the treatment of choice.(*Day M 2002 ; Gandhi M 2003*)

7.b

Inflammatory myofibroblastic neoplasms (IMT) (inflammatory pseudotumour and inflammatory fibrosarcoma are considered to be synonymous) generally follow a benign course. Predominantly, they most commonly occur in lungs and abdomen, but can arise in many other areas of the body. Associated symptoms include mass, fever, pain, weight loss, malaise or growth failure, anemia, thrombocytosis, polyclonal hyperglobulinaemia and/or elevated erythrocyte sedimentation rate. Although generally benign, IMT can be locally invasive and the local recurrence rate is reported between 15-35%, especially for abdominal localization.

Wide resection is the mainstay of treatment.

However, some IMT tumours have a more aggressive behaviour, including multiple recurrences and/or metastases. Little is described about the management of these aggressive IMTs.

Radiation therapy has been reported to be of use, but others have reported little effect (*Dishop MK, 2003).* Immunosuppressive treatment with corticosteroids has also met with variable results. Chemotherapy has been utilized (cyclophosphamide, actinomycin-D, adriamycin, 5-fluorouracil, cisplatin, ifosfamide, etoposide, and carboplatin), but its role is unclear. Overall, the benefit of chemotherapy, radiotherapy or other therapies not been established yet.

Use of these additional treatments in addition to the surgical resection however is advised in locally recurrent histologically malignant tumours not amenable to complete resection (*Janinis J, 2003).*

7.c

AGGRESSIVE FIBROMATOSIS

Aggressive fibromatosis (AF), also known as **desmoid tumor**, is a rare, deep-seated, muscoloaponeurotic, tumor of borderline malignancy with an incidence of 0.2-0.4 per 100,000 population/year, and two relative peaks in incidence among 6-15 year-olds and between puberty and the age of forty in women.
AF is a fibroblastic proliferation with a monoclonal pattern arising from fascial planes and muscoloaponeurotic structures, with a marked local aggressiveness. Its growth may be fairly slow, spreading over several years; it has a strong tendency for local recurrence, but does not metastasize to other organs as truly malignant tumors do.
The pathogenesis of AF is most likely multifactorial and genetic predisposition, endocrine factors and trauma all seem to play an important part. The incidence is higher in families with familial AF, familial adenomatous polyposis (FAP), and Gardner syndrome: in particular, intra-abdominal fibromatosis has a distinct behaviour, being primarily associated with FAP and mutations of the APC gene on chromosome 5q21 (Gardner's syndrome).
Extra-abdominal fibromatosis arise in musculo-aponeurotic structures, mainly in extremities and girdles, chest and abdominal wall, and neck. The propensity of AF to grow diffusely along muscle bundles and fascial planes, and the lacks of a pseudocapule contributes to the difficulty to define the border of the tumour at resection.

The biological and clinical patterns in AF in children are generally considered the same as in adults and treatment recommendations are usually similar.

Although surgery is generally considered the mainstay of treatment, a high local recurrence rate is reported, ranging from 24-77% at 10 years, while overall survival is generally over 90% at 10 years *(Mendez-Fernandez MA, 1991; Catton CN, 1995; Gronchi A, 2003)*. The best predictors of local recurrence are microscopically positive margins, negative margins that fall close to the tumour and large tumours located at the extremities or girdles, regardless of positive or negative margins *(Gronchi A, 2003*).

Radiation therapy has a well-established role in adult AF, in case of microscopically positive margins *(Ballo MT, 1998; Plukker JT, et al. 1995*). Its associated, potentially long-term cosmetic or functional morbidity limits its use in children.

The pharmacological treatment of AF can involve non-cytotoxic and cytotoxic agents.
Non-cytotoxic agents include hormonal treatment, NSAIDs/anti-inflammatory agents, and IFN-alfa *(Janinis J, et al. 2003*). Most commonly used cytotoxic drug regimens are doxorubicin-based, in combination with dacarbazine or cyclophosphamide and vincristine, actinomycin D-based treatment (vincristine, actinomycin D and cyclophosphamide), or a combination of weekly low-dose methotrexate with vinca alkaloid (vinblastine or vinorelbine). The effectiveness of the different regimens is comparable to that in adult STS, with a chemo-responsiveness around 50%. However, since AF is a slow growing tumour with a slow response to chemotherapy, prolonged exposure of at least 6 months or even 12-18 month is generally recommended.

Other open questions relating to treatment strategy concern the possibility of a no-treatment approach in cases of non-evolving disease, and the search for prognostic indicators for the purpose of patients' risk stratification

The Italian pediatric group recently reviewed a large series of 94 patients < 21 years with AF (7 abdominal). Five-year event-free survival and overall survival rates were 44% and 99%, respectively. Local relapse occurred in 22% patients in IRS group I, 76% in group II and 76% in group III (*Meazza 2009*). The main findings of the Italian series were:

- extra-abdominal AF in children has much the same clinical course and natural history as in adults: at extra-abdominal sites, AF is a slow-growing disease with a marked tendency for local recurrence, but a very low risk of affecting survival (the prognosis of abdominal fibromatosis remains uncertain; i.e. 2 out of 7 cases died of disease)
- local relapse did not change neither the possibility of responding to systemic therapy nor survival
- disease control after marginal resection was similar to that observed in case of intralesional surgery/biopsy, thus suggesting that primary surgical attempt would be indicated *only* when complete and non mutilating excision is considered feasible
- interesting response to chemotherapy were reported (49% CR/PR/MR, 38% stable disease), in particular to low-dose chemotherapy (methotrexate and vinblastine/vinorelbine); in patients with initially unresectable disease, best outcome was achieved by those patients receiving systemic treatment followed by delayed surgery
- the observation that desmoid tumors can remain stable for a long time, with or without primary treatment, prompts the suggestion that a "wait-and-see" strategy (clinical-radiological monitoring alone) might be suitable in cases of non-evolving disease, and therapies should be given only in the event of tumor growth.
- a precise stratification pointing to risk-adapted treatments seems less readily applicable to desmoid tumors than to truly malignant mesenchymal neoplasms, and the particular natural history of AF would suggest that we take another approach to measuring outcome - not just in terms of EFS, but as a combination of survival rates, total burden of therapy and functional-cosmetic iatrogenic sequelae. The clinical management of patients with AF often needs to be customized. It is difficult to establish a treatment flow-chart based, for instance, on factors such as IRS group and tumor size, because individual, less easily quantified variables may have a significant impact both on the risk of failure and on the functional fallout (including the patient's age and the tumor's location - not in terms of anatomic site, but of its interaction with adjacent anatomical structures, and even the surgeon's experience).

Paediatric French cases were included in a series of 112 adult-pediatric cases (*Bonvalot, 2008*) that investigated the role non-aggressive surgical approach and watchful waiting strategy, suggesting that therapeutic recommendations should be given only in case of progressive disease. The availability of relatively-effective drugs is shifting the focus on AF treatment from a strategy of aggressive surgery to a multidisciplinary approach that takes the functional and cosmetic sequelae of treatments into account too.

Pediatrics French cases were also reviewed in a retrospective bicentric analysis (Institut Gustave Roussy Villejuif, Institut Curie Paris) including 59 children treated between 1976 and 2005. The first treatment was surgery in 80% of cases and chemotherapy in 15% because of unresectable lesion; 2 patients were under medical surveillance without treatment. Thirty-nine patients had developed one or more recurrences or progressions (66%, median interval of first recurrence/progression 3.3 years, range, 0.2-5.2), while 20 (34%) never relapsed after initial treatment and were in persistent CR (n=13) or minimal disease (n=7). A measurable response (CR and PR) was documented in 32% of cases (48% after vinblastine-methotrexate); stable disease was documented as the best response to treatment in 50% of cases. Ten-year DFS rate of these 59 patients was 32% and 10 year OS rate was 83%.

The genetic predisposition of this tumor should be considered, suggesting the need for adequate genetic counselling and the investigations for detecting Familial Adenomatous Polyposis or colon carcinoma. Desmoid fibromatoses belong to the familial adenomatous polyposis (FAP) and Gardner syndrome spectrum. The exact frequency of Gardner syndrome revealed by desmoid fibromatosis in childhood is unknown. The absence of a family history cannot eliminate this diagnosis, as de novo mutations are observed in about 30% of cases of FAP. The FAP spectrum comprises, in addition to colonic polyps and gastrointestinal cancers, congenital hypertrophy of the retinal pigment epithelium (70%), desmoid tumours (6-15%), very specific osteomas of the face (90%), epidermoid cysts (60%), supernumerary teeth (40%), and other tumours (< 5%): medulloblastoma, hepatoblastoma, thyroid cancer.

It is therefore proposed to assess the family history and systematically propose a genetic information consultation (study of the APC gene) with assessment at adolescence comprising:

- Skull x-ray looking for osteomas of the skull and mandible
- Panoramic dental x-rays
- Fundus examination
- Colonoscopy and gastroscopy at the age of 20 years (after puberty)
- Dermatological examination

The significance of a negative APC study has not been determined in this disease.

► The E*p*SSG NRSTS Committee strongly wants to encourage the registration of patients with AF in the protocol, for standardizing their treatment based on a minimally-aggressive strategy (considering "wait-and-see" strategy, avoiding repeated resections or destructive surgery, adopting low-dose chemotherapy when systemic treatment is required).

<u>Treatment proposal</u>

The therapeutic strategy must be defined by a multidisciplinary approach with a surgeon, radiotherapist and paediatric oncologist. The diagnosis must be based on histological examination usually after biopsy.

- when AF is diagnosed, a possible **first approach** should be to consider the **wait-and-see strategy**, to understand tumor growth rapidity (AF may remain stable for long periods);
  in no-threatening site (i.e. extremity) treatment should be considered only in case of tumor growth (> 25%); even when the lesion appears to be operable with no risk to vital structures, simple surveillance can be proposed after biopsy, with surgical resection only in the case of progression demonstrated on repeated examinations.

- **primary resection** should be considered as first approach only in case of:
  a. **tumor progression** or
  b. **symptoms** or
  c. **threatening site**

  and

d. if **completely possible, without mutilation** (otherwise first treatment should be medical treatment with low dose chemotherapy)
there is no indication for partial resection in desmoid tumors

- in case of 1) tumor progression, symptoms or threatening site, and 2) complete resection considered unfeasible, **minimal-morbidity systemic therapy** should be given:
chemotherapy with low-dose methotrexate plus vinblastine should be the first option
vinblastine 6 mg/m^2 (max: 10 mg) IV on day1 once a week
methotrexate 30 mg/m^2 IV day1 once a week

- The goal of **systemic therapy** in AF should not be only the tumor shrinkage to permit a subsequent resection, but also the induction of growth arrest and tumor stabilization
After chemotherapy response, delayed resection could be proposed (if complete and non-mutilating), but also wait-and –see after tumor stabilization may be considered
The proposed **duration of chemotherapy** should be 6 months with full doses, followed by 6 months spacing the administration (doubling the time between injections)
The efficacy of treatment is assessed on surveillance examinations, to be performed every 3 months (not too frequently). Radiological assessment should be primarily based on MRI. Only frank tumor progression (> 25%) should be considered as treatment failure to suggest **second-line treatment**

- no adjuvant therapy is required after complete or microscopically-incomplete resection at first approach or at delayed surgery
post-operative chemotherapy after macroscopically-incomplete resection may be considered, but also careful surveillance may be proposed (and systemic treatment given only in the case of marked progression of the residual tumor)

- in the case of local recurrence, another surgical resection can be proposed if it is likely to be complete. In the case of tumor progression despite two surgical resections, medical treatment must be considered also when complete resection seems feasible. Repeated surgery may be a risk factor for recurrence.

- **radiotherapy** may have a role after failure to chemotherapy, in case of progression despite multiple surgeries, as alternative to mutilating surgery
Target doses can be 50 Gy in the case of microscopically complete resection and 55 Gy in the case of macroscopic residual disease.

Chemotherapy options:

First option:

Methotrexate 30 mg/m^2/week iv + Vinblastine 6 mg/m^2(max 10 mg)/week iv

Other options:

- **Methotrexate 30 mg/m^2/week iv + Vinorelbine 20 mg/m^2/week iv**
- **Vinorelbine 25 mg/m^2/iv** (or alternatively, **60 mg/ m^2 oral) day 1, 8, 15**

plus oral Cyclophosphamide 25 mg/m^2/day (every day)

- **IVA regimen** (Vincristine 1.5 mg/m^2 day 1, Actinomycin 1.5 mg/m^2 day 1, Ifosfamide 3 g/m^2 day1-2) or **VAC regimen** (Vincristine 1.5 mg/m^2 day 1, Actinomycin 1.5 mg/m^2 day 1, Cyclophosphamide 1.2 g/m^2 day 1), or **VA regimen** (Vincristine 1.5 mg/m2 and Actinomycine 1.5 mg/m2) every 21 days.

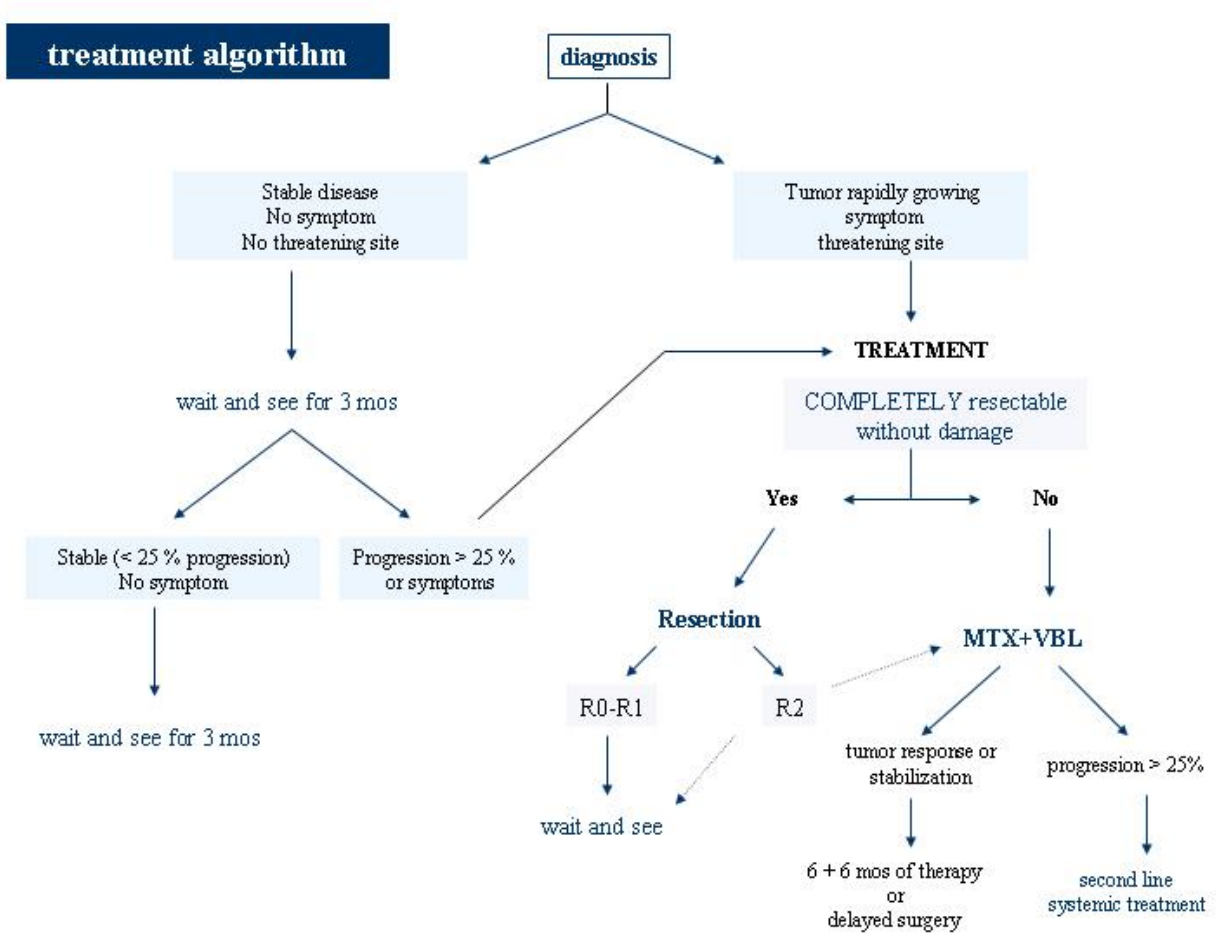
- **Tamoxifene 5 mg x 2/day if age < 10 years, 10 mg x 2/day if > 10 years**

  Tamoxifen may be administered alone or combination with other treatments.
  Note that experience of treatment in prepubescent children is very limited and this treatment should probably be administered very cautiously. Tamoxifen is a clomid-like product with an oestrogen antagonist activity on mammary receptors and an agonist activity on bone and endometrial receptors. An effect on closure of the epiphyseal growth plate therefore cannot be excluded. A variable effect is observed on menstruation: amenorrhoea in 1/3 of cases, polymenorrhoea in 1/3 of case, no change in 1/3 of cases. It is a potentially teratogenic agent: patients of childbearing potential must use contraception especially as tamoxifen stimulates ovulation. Increased risk of deep vein thrombosis: treatment should be stopped in the case of prolonged bed-rest and is contraindicated in patients with a family or personal history of deep vein thrombosis. Other known adverse effects in adults: myalgia and weight gain. No expected specific adverse effects in adolescent boys. Specialist gynaecological follow-up looking for signs of peripheral hyperoestrogenism must be ensured regularly (endometrial hyperplasia, menstrual disorders). There is a risk of functional ovarian cyst (abdominal pain, torsion of appendages): half-yearly abdominal ultrasound

- **Non-steroidal anti-inflammatory drug**

  - Sundilac-Arthrocine® (100-200 mg tablets) at the dose of 4 mg/kg x 2 /day (100-200 mg twice daily) or 4 mg/kg twice daily or Celecoxib-Celebrex® (100-200 mg capsules): 100 mg twice daily in adolescents or young adults or another NSAID in younger patients.
  - The usual precautions with long-term NSAIDs must be observed: antacids or proton pump inhibitor, renal function tests, the patient must consult immediately in the case of abdominal pain, avoid concomitant nephrotoxic drugs, temporary discontinuation in the case of dehydration (vomiting, diarrhoea).

- There are some recent data (2009) of the efficacy of **Hydroxyurea** (20 mg/kg/day to start and then 30 mg/kg/day)



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8. Extra-cranial malignant rhabdoid tumour

Note:
All extra-cranial rhabdoid tumours, including stage IV tumours, are eligible for registration on the EpSSG NRSTS 2005 protocol

At the present, centres participating to the EpSSG NRSTS protocol are invited to register patients with rhabdoid tumour in the NRSTS data-base.

The following treatment plans must be considered as suggestions only.

Summary
Extra-cranial rhabdoid tumours are rare, and often occur in infants (Brennan, 2013). While the kidney is the commonest site, they can occur at any anatomical site. The vast majority contain a bi-allelic inactivating mutation in the *SMARCB1* gene, which is part of the chromatin remodelling complex SWI/SNF, important in cell cycle control, and functions as a classic tumour suppressor gene. Despite multimodal therapy, outcome in rhabdoid tumours remains poor with a 1 year survival of only 31%, the young age of patients limiting the use of radiotherapy which with age, remain important prognostic factors. Given their rarity, there is no standard therapeutic pathway, and there have been no randomised clinical trials examining the role of new therapeutic approaches. The better understanding of the biology and role of the *SMARCB1* gene has, and will be able to identify new targets for small molecule inhibitors, to hopefully add to chemotherapy back bones we may establish from the current EpSSG study.

Introduction
Extra-cranial rhabdoid tumours were first described as a distinct pathological entity in 1978 by Beckwith and Colleagues. Haas et al, in 1981, recognised rhabdoid tumour of the kidney as a separate tumour, not a variant of Wilms' and introduced the term 'rhabdoid' because of the close histological resemblance of the tumour cells to rhabdomyoblasts. Subsequent studies, however, have failed to confirm a myogenic origin of the tumour cells, but the term is still used for this entity. It was not, however, until 1989, when Weeks et al published 111 cases of rhabdoid tumour of the kidneys from the National Wilms' Tumour Study (NWTS) Pathology Centre, that the tumour was recognised as a distinct entity (Weeks et al, 1989). *SMARCB1*-deficient tumours is an increasing family of tumours; within this family, rhabdoid tumours, which are a kind of historical leader, show specific clinical and histological features, usually containing the classic rhabdoid cell with vesicular and eccentrically placed nuclei containing a single prominent nucleolus, and eosinophilic inclusions in the cytoplasm. This distinguishes them from other *SMARCB1*–deficient tumours, and hence makes them an entity of specific interest.

Biology-genetics
The first genetic feature identified in rhabdoid tumours, whatever their anatomic location, was monosomy 22, and subsequently translocations and deletions of the 22q11.2 cytoband were identified (Severnet et al, 1999). Positional cloning, subsequently allowed identification of the bi-allelic inactivation of the *SMARCB1* (*INI1/hSNF5*) gene, located at 22q11.2, as the main oncogenic event in rhabdoid tumours (Verteege et al, 1998). The complete inactivation of this tumour suppressor gene results from various combinations of i) large interstitial chromosome 22q deletions

encompassing the whole gene (about half of the cases), ii) whole exons duplication or deletion, iii) oligonucleotides insertions or deletions, leading to frameshift and subsequent premature stop codons, or iii) nonsense mutations (about 25% of cases) (Biegel etal, 1999, Sevenet et al, 1998, Jackson et al 2007). Homozygous deletions may be more frequent in extra-cranial tumours. Missense mutations seem to be exceptional. In some rare cases, the second hit remains unknown when searched for by classical analysis of the coding sequence (i.e. direct sequencing and quantitative PCR). Base pair substitutions in the 3' UTR have offered putative explanations in some cases; otherwise, intronic base pair variations leading to the illegitimate insertion of a pseudo-exon in the transcript might also account for the full inactivation of *SMARCB1* in rare rhabdoid tumours. In all cases, the genetic abnormalities lead to a total loss of protein expression, as assessed by immunohistochemistry (Hoot et al, 2004 and Bourdeaut et al, 2007).

Genetic counsuelling should be proposed to families.

Survival

Rhabdoid tumours are often described as lethal, with little evidence of improvement in survival over recent years. Among the 106 children diagnosed with extra-cranial rhabdoid tumour in the UK population during 1993-2010, 1-year survival was only 31%.

The Society of Paediatric Oncology (SIOP) intermediate nephroblastoma series, published in 1996, found twenty two cases of rhabdoid tumour of the kidney out of 2,392 renal tumours in children. Metastases developed in 82%, either from diagnosis, or developed from two weeks to nine months after the initial diagnosis. Only two of the series survived and both had localised disease (Stage II) (Vujanic et al, 1996).

In the NWTS series of one hundred and forty two renal rhabdoid tumours over a period between 1969 and 2002, overall survival (OS) at four years was 23.2% (Tomlinson et al, 2005) . Important factors for outcome were stage at diagnosis, with a 41.8% four year OS for stage I to II tumours compared 15.9% in those with stage III, IV or V disease. Sultan et al publication from the SEER program again confirms stage as an important prognostic factor for outcome. In a multivariate model applied only to children and adolescents with extra-cranial rhabdoid tumours tumour stage remains a significant predictor of survival (P = 0.00014) (Sultan at al, 2010).

A further prognostic factor is age at presentation. In Tomlinson et al series from NWTS of renal rhabdoid tumours, survival increased with age with a four year OS of 8·8% for infants aged 0 to 5 months and a OS of 41·1% in children greater than 24 months of age. This is confirmed in the SEER program where all sites are included – cranial, renal and extra-renal – with the worst outcome for those less than 2 years of age or greater than 18 years of age (H.R 1·79 and 1·83 respectively) (Sultan et al, 2010). In the UK population, infants with extra-cranial rhabdoid tumours had a lower 1-year survival (17%) than older children (54%).

Disappointingly, the NWTS series and the population-based series from the UK and the SEER program all showed no improvement in outcome with time. One-year survival among children in the UK was 32% in 1993-2000, 31% in 2001-2005 and 30% in 2006-2010. In the SEER data, there was no improvement in survival of patients diagnosed during the last 5 years of the study period (2001 – 2005) compared with those diagnosed in 1986 – 2000 (p = 0·78) (Sultan et al, 2010).

Small series which either focus on extra-renal non-cranial rhabdoid tumours or liver only as a site demonstrate an even poorer survival (Bourdeaut et al, 2008, Trobaugh et al, 2011) . In Bourdeaut et

al series of extra renal non-cranial rhabdoid tumours, the median time to progression was 5 months (0 – 44), with only one patient remaining free of disease at seven years. Trobaugh-Lotrario et al reviewed 34 cases of liver rhabdoid tumours identified by a literature search using PUBMED from 1970 to 2010. The mean age at presentation of the subjects was eight months. Thirty patients went on to die, either of disease or treatment complications with the majority (21) having metastases. In the UK population, one-year survival of children by primary site ranged from 14% for liver to 25% for kidney, 33% for head and neck and 50% for other sites.

Role of chemotherapy

Given the rarity of extra-cranial rhabdoid tumours, there is no standard therapeutic pathway and there have been no randomised trials examining the role of chemotherapy combinations or addition of new agents. Instead we rely on often historical single arm series from single institutions. Two case reports including two and one patients respectively with metastatic renal rhabdoid tumours are often cited in view of their successful outcome (Waldron et al, 1999 and wagner et al, 2002). The chemotherapy they describe forms the basis for the current Children's Oncology Group (COG) study [www.childrensoncologygroup.org] in high risk kidney tumours, which includes extra-cranial rhabdoid tumours, and this European Paediatric Soft Tissue Sarcoma Group (EpSSG) protocol. In both protocols the philosophy of treatment indicates early surgical resection of the primary tumour if feasible, intensive multi agent chemotherapy, derived from the case reports of Waldron et al and Wagner et al, and local radiotherapy to all sites of disease.)

In the case reported by Waldron et al, they alternated courses of vincristine, doxorubicin, cyclophosphamide (VDC) chemotherapy with ifosfamide, etoposide (IE) in intensive 2-weekly schedule in a child with a metastatic renal rhabdoid tumour, the patient remaining disease free five years out from diagnosis. Similarly, Wagner et al described again successful outcome for two cases of metastatic renal rhabdoid tumours using ifosfamide, cyclophospamide, etoposide (ICE) alternating with vincristine, doxorubicin and cyclophosphamide (VDC). The inclusion of doxorubicin in chemotherapy combinations is suggested as important for survival in extra-cranial rhabdoid tumours. In Tomlinson et al series from NWTS 58% of the renal rhabdoid tumours received doxorubicin but there was no difference in survival between those who did and did not receive it. The lack of information on the type and use of chemotherapy from the SEER program in the Sultan et al series of rhabdoid tumours did not allow them to explore this factor any further in relation to outcome and prognosis.

Further possible evidence for the role of chemotherapy in particular ifosfamide comes from a single historical institutional series from St Jude's (Gururangan et al, 1993). This, however, included only 13 children with extra-cranial rhabdoid tumours, but those patients who responded to chemotherapy had regimens containing ifosfamide and hence they argue its role in treating rhabdoid tumours. It was noteworthy, however, that all patients died.

Although not regarded as standard of care in extra-cranial rhabdoid tumours high dose chemotherapy with stem cell rescue is very well reported in intra-cranial rhabdoid tumours either following relapse or as part of up front therapy to delay irradiation in younger children. It remains to be seen, however, what its role is in extra-cranial rhabdoid tumours although there has been a single report of its use in two children with renal rhabdoids (Koga et al, 2009).

The series discussed so far illustrate the difficulty in either recommending a standard treatment or indeed generating a hypothesis to test additional chemotherapy regimens or agents. In particular there is a complete paucity of published phase II chemotherapy studies in rhabdoid tumours.

Role of radiotherapy

The role of radiotherapy in local control of extra-cranial rhabdoid tumours is suggested from a small series of renal rhabdoid tumours from NWTS (Palmer et al, 1983). In a later series from NWTS where larger numbers of renal rhabdoid tumours were analysed, 100 of the 142 patients in the series received radiotherapy (Tomlinson et al, 2005). The overall survival at 4 years was 28.5% amongst the irradiated patients and 12 % among the un-irradiated patients ($p = 0.25$). This effect of radiation was difficult to analyse because radiation tended to be given to those with a higher stage and in an older age group, furthermore the older patients were more likely to receive a higher radiation dose. The positive effect of radiotherapy, and in particular of radiotherapy greater than 25 Gy, was thus confounded by age. This effect was lost when the infants under one year of age were analysed. Only one infant received a dose greater than 25 Gy. Therefore, after adjusting for age and stage, known prognostic factors, the relative risk (RR) of death comparing 25 Gy with no radiotherapy was 0.85 ($p = 0.83$), and hence the apparent effect of radiotherapy on survival was much reduced and no longer significant.

In a multivariate model that was applied to the SEER program series, three factors remained significant of which one was the use of radiotherapy. In particular, if the multivariate model was only applied to children and adolescents (less than 18 years old) in the extra-cranial rhabdoid tumours, the use of radiotherapy remained a significant predictor of survival ($p = 0.0006$). Radiotherapy was only used in 35% of patients in total, but there was no significant difference in its use at the different primary tumour sites ($p = 0.90$). However, only 23% of children younger than 3 years received radiotherapy which was significantly lower than for the older patients (46% in patients greater than or equal to 3 years old) ($p= 0.0085$). The SEER program does not include data on the dose and volume of the radiotherapy so further analysis could not be performed with regard to this (Sultan et al, 2010).

Rationale for interval compressed chemotherapy VDC alternating with IE

At SIOP 2012 we presented the outcome on Extra-cranial rhabdoid tumours registerd on the EpSSSG NRSTS 2005 study. Treatment recommended consisted of upfront or early surgical resection of the primary tumour, chemotherapy with 5 cycles of vincristine, doxorubicin and cyclophosphamide, and 5 cycles of cyclophosphamide, carboplatin and etoposide, with radiotherapy to the primary tumour and metastatic sites following surgery.
53 patients from 7 European countries were registered from 2005 to 2012. 20 pts were ≤ 1 year of age, with a median age of 18.4 (range 0.4-131.2) months. Post surgical staging at diagnosis was IRS I in 9 patients, IRS II in 7 and IRS III in 37, the commonest site was liver (no= 9) with 50% of tumours extending beyond the tissue of origin. Complete treatment data was available in 45 pts with 21 receiving chemotherapy as described and radiotherapy, and 24 receiving chemotherapy alone. Radiotherapy dose was ≤ 45.0 Gy for 13 patients, and > 45.0 Gy for remaining patients. The median follow-up is 34.5 (range 0.6-60.7) months, with a 3 year EFS of 31.6 % (95% CI 17.5-46.9) %. Twenty patients stopped treatment prematurely, 3 due to death, 15 due to progression and 2 due to physician's choice.
The recommended chemotherapy could be delivered to children with extra-cranial rhabdoid tumours but it was noteworthy that a proportion will progress before treatment is finished. The data is currently being updated and will include an analysis of a further 25 stage IV patients, as well a total now of 61 localised tumours. While this data maybe encouraging as it contains a cohort of patients in less favourable sites it may not be a significant improvement compared to historical smaller series.

In the original case report by Waldron and colleagues IE chemotherapy was alternated with VDCy to cure a patient with a Stage IV rhabdoid tumour of the kidney with metastases to the lung (*Waldron et al, 1999*). At the time this regimen was being piloted for Ewings sarcoma and subsequently was one of the arms in a randomised COG study in localised Ewings sarcoma of interval compressed chemotherapy – AEWS0031. This study demonstrated that 2 weekly chemotherapy was more effective, with no added toxicity. There are other examples of studies which follow Norton's dose intensity model, maintaining doses while decreasing intervals between them, which have led to better outcomes such as in paediatric AML and breast cancer (Norton et al, 1997, Woods et el 1996, Citron et al, 2003). It may also be more pertinent in tumours like rhabdoids who progress during chemotherapy as demonstrated in the early analysis of our series. Therefore, in the absence of new effective agents in rhabdoid tumours available to test in either a phase II or III setting we propose to determine if interval compressed chemotherapy of VDCy alternating with IE improves the outcome of patients with extra-cranial rhabdoid tumour as compared to historical controls, recommending this treatment arm for all extra-cranial rhabdoid tumours, including stage IV disease. This may allow us data to establish a more successful backbone of chemotherapy to add a small molecule against what we know or establish from phase I studies, against the known targets in ERT.

Histological Diagnosis

The diagnosis must be established pathologically. If feasible and safe, the tumour whether renal or extra renal should be completely resected with good margins when first encountered. Failing complete surgical removal, open surgical biopsy is the preferred approach as this maximises the tissue available for diagnostic procedures, biological studies and central pathology review. Open biopsy is essential if initial needle biopsy is non-diagnostic or equivocal (see surgical guidelines below). Patients with renal rhabdoid tumour who have received prior chemotherapy of vincristine, actinomycin +/- doxorubicin pre nephrectomy, will still be eligible. It is recommended that an MR scan of the head is performed in addition to other radiological investigations.

Staging systems

Renal Rhabdoid Tumour

Criteria for staging- in renal tumours who have not received preoperative chemotherapy

Stage I

a) The tumour is limited to kidney or surrounded with a fibrous pseudocapsule if outside of the normal contours of the kidney. The renal capsule or pseudocapsule may be infiltrated with the tumour but it does not reach the outer surface, and it is completely resected (resection margins 'clear').

b) The tumour may be protruding ('bulging') into the pelvic system and 'dipping' into the ureter (but is not infiltrating their walls).

c) The vessels of the renal sinus are not involved.

d) Intrarenal vessel involvement may be present.

Stage II

a) The tumour extends beyond kidney or penetrates through the renal capsule and/or fibrous pseudocapsule into peri-renal fat but is completely resected (resection margins 'clear').

b) Tumour infiltrates the renal sinus and/or invades blood and lymphatic vessels outside the renal parenchyma but it is completely resected.

c) Tumour infiltrates adjacent organs or vena cava but is completely resected.

Stage III

a) Incomplete excision of the tumour which extends beyond resection margins (gross or microscopical tumour remains post-operatively).

b) Any abdominal lymph nodes are involved.

c) Tumour rupture before or intra-operatively (irrespective of other criteria for staging).

d) The tumour has penetrated through the peritoneal surface.

e) Tumour implants are found on the peritoneal surface.

f) Tumour thrombi is present at the resection margins of vessels or ureter, transsected or removed piecemeal by surgeon.

Stage IV

Haemotogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdomino-pelvic region.

Stage V

Bilateral renal tumours at diagnosis. Each side should be substaged according to above classifications.

Extrarenal Rhabdoid Tumour

In keeping with paediatric soft tissue sarcomas, stage of disease will be defined according to both

1. the clinical tumour-node-metastases (TNM) staging classification (Harmer MH, 1982).
2. the Intergroup Rhabdomyosarcoma Study (IRS) post-surgical grouping system (Maurer HM et al, 1988).

The TNM T1 definition applies to tumours confined to the organ or tissue of origin, while T2 lesions invade contiguous structures;
T1 and T2 groups are further classified as A or B according to tumour diameter, ≤ or > 5 cm respectively.
Regional node involvement was designated as N1 (no node involvement - N0)
Distant metastases at onset as M1 (no metastases - M0).

After initial surgery, patients will be classified according to the IRS system:

- group I includes completely-excised tumours
- group II indicates grossly-resected tumours with microscopic residual disease and/or regional lymph nodal spread
- group III includes patients with gross residual disease after incomplete resection or biopsy
- group IV comprises patients with metastases at onset.

TREATMENT PLAN

Overview of Treatment plan

Week

1	2	3	4	5	6	7	8	9	10	11	12				
V		I		V		I		V		I					
D		E		D		E		D		E					
Cy				Cy				Cy							
13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
V		I		V		I		V		I		V		I	
D		E		D		E		C		E		C		E	
Cy				Cy											

V	**Vincristine**	0.025mg/kg/day IV x 1 as bolus for infants < 12 month 0.05mg/kg/day IV x 1 as bolus for children 12 mo.-3 yr 1.5 mg/m^2/day x1 as bolus for children ≥ 3 years old
D	**Doxorubicin**	1.25mg/kg/day IV x 2 days over 15 minutes for infants <12 month or < 10 kg in weight 37.5mg/m^2/day IV x 2 days over 15 minutes for children ≥ 12 months
Cy	**Cyclophosphamide**	40 mg/kg/day IV x 1 day over 1 hour for infants < 12 months or < 10 kg in weight, 1200 mg/m^2/day IV x 1 day over 1 hour for children ≥ 12 months
I	**Ifosfamide**	900 mg/m^2/day IV over 1 hour x 5 days for infants < 12 months or < 10 kg in weight 1800 mg/m^2 day IV over 1 hour x 5 days for children ≥12 months
E	**Etoposide**	3.3mg/kg/day IV over 1 hour x 5 days for infants < 12 months or < 10 kg in weight 100mg/m^2/day IV over 1 hour x 5 days for children ≥ 12 months

Note:
Chemotherapy in infants should be delivered very carefuly and increased following patients' age and height.
It may be considered to administer first cycle with reduced doses and increase them according to the toxicity in the subsequent courses.

Suggested starting dose for infants < 6 month or < 5 kg:
Vincristine = 0.025mg/kg/day IV x 1 as bolus
Doxorubicin = 62.5 µg/kg/day IV x 2 days over 2 – 4 hours
Cyclophosphamide = 20 mg/kg/day IV x 1 day over 1 hour
Ifosfamide = 450 mg/m^2/day IV over 1 hour x 5 days
Etoposide = 1.65 mg/kg/day IV over 1 hour x 5 days

G-CSF Treatment intensity is essential in this interval compresed. G-CSF support is essential following VDC/IE chemotherapy. The dose or type of G-CSF i.e. daily G-CSF or PEG-filgrastim is according to institutional guidelines. Daily G-CSF 5 µg/kg/d SC should be started 48hours after end of chemotherapy and must be stopped 24 hours prior to chemotherapy commencing.

Chemotherapy should be delivered in case of neutrophils > 0.75 x 10^9/l and platelets > 75 x 10^9/l

Co-trimoxazole prophylaxis is recommended

If patient has already received other neoadjuvant chemotherapy for initial wrong diagnosis (as for example VA for nephroblastome or PLADO for hepatoblastoma), chemotherapy should nevertheless re-start at week 1 of the protocol but total cumulative dosage must be calculated to avoid overall overdosage.

As soon as work-up is completed and the tumour has been completely excised or biopsied and the diagnosis of rhabdoid tumour has been made, chemotherapy should be given to the patient. Patients with initially unresectable or incompletely resected tumours will receive chemotherapy and undergo reassessment after 6 cycles - approximately week 12 onwards.
Delayed surgical resection should then take place to remove primary tumour and any residual resectable metastases.
Radiation will begin at week 1 for those patients whose tumours were resected initially, if possible immediately after the first course of VDCy chemotherapy. For patients with delayed tumour resection, radiation therapy should begin after the primary tumour is resected, usually at week 13. During radiation doxorubicin should be ommitted and given during a later cycle of VC at week 21

Administration schedule for cycle VDCy

Drug	Route	Dose	Day(s)
Vincristine	**IV over 1 minute**	0.025mg/kg/day for infants < 12 months 0.05mg/kg/day for children 12 mo.-3 yrs 1.5 mg/m^2/day for children ≥ 3 years old	**1**
Doxorubicin	**IV over 15 minutes**	1.25mg/kg/day for infants <12 month or < 10 kg in weight 37.5mg/m^2/day for children ≥ 12 months Individual groups may prefer to infuse over 1 – 24 hours.	**1-2**
Cyclophosphamide With MESNA hydration*	**IV over 1 hour**	40 mg/kg/day for infants < 12 months or < 10 kg in weight 1200mg/m^2/day for children ≥ 12 months	**1**

*Mesna and hydration guidelines: MESNA 1440 mg/m^2/dose (48mg/kg/dose for infants <12 months old) should be added to the hydration (2000ml/m^2/16 hours) of 0.45% saline/2.5% dextrose and run for 3 hours pre- and with cyclophosphamide, and at least 12 hours post cyclophosphamide – total 16 hours. Urine output at least 3ml/kg/hour.

Administration schedule for cycle IE

Drug	Route	Dose	Day(s)
Ifosfamide With MESNA hydration	**IV over 1 hour**	900 mg/m^2/day IV over 1 hour x 5 days for infants < 12 months or < 10 kg in weight 1800 mg/m^2/day IV over 1 hour x 5 days for children ≥12 months	**1-5**
Etoposide	**IV over 1 hour**	3.3mg/kg/day for infants < 12 months or < 10 kg in weight 100mg/m^2/day for children ≥ 12 months	**1-5**

Hydration: prehydrate with 0.45 % saline/ 2.5 % dextrose at 125 ml/m^2/hour for 2 hours. Then continue at 125ml/m^2/hr for 2 hours following completion chemotherapy- total fluids 3000 ml / m^2/d with 2200 mg/m^2 (1100 mg/m^2 for infants < 12 months) of MESNA added over 24 hrs after the last ifosfamide dose administration.

Dose Modifications For Toxicity

Haematological Toxicity

Recovery of neutrophils > **0.75** x 10^9/l and Platelets > **75** x 10^9/l is required before the start of each course of chemotherapy.

Infection and Fever

Dose reductions of myelosuppressive agents should occur if the chemotherapy combination results in a life threatening infection (Grade 4) or a complicated episode of febrile neutropenia regardless of a positive bacterial culture or not. However, uncomplicated bacteremia is not an indication to reduce doses of chemotherapy. The dose reduction schedule is as for haematological toxicity.

Haematuria

Transient haematuria requires no modification. Persistent haematuria –micro-or macroscopic- ensure compliance with mesna hydration. Increase hydration rate to at least 4000ml/m^2/day with

mesna at a dose of at least 150 % of the cyclophosphamide/ ifosfamide dose. If the haematuria is macroscopic withhold the cyclophosphamide/ifosfamide until haematuria is microscopic.

Mucositis

Mucositis that interferes with oral intake necessitating IV fluids should result in 25 % dose reduction of doxorubicin or etoposide with the next course of chemotherapy. Doses may be escalated back up to 100 % if subsequent doses are not associated with significant mucositis as haematological toxicity section above.

GI toxicity (Diarrhea and Typhilitis)

Severe treatment related diarrhea is an indication to interrupt temporarily a course of abdominal radiation therapy if underway, or delay a scheduled dose of doxorubicin.

Radiation Dermatitis and Radiation recall risk

If a patient has moist skin desquamation after radiation therapy, doxorubicin doses should be omitted and made up later when it clears. If a patient has erythema or dry desquamation the dose of doxorubicin should be reduced by 50 %. Children who are to receive whole abdominal or lung irradiation should have their dose of doxorubicin reduced by 50 % if to be given within 6 weeks of the completion of radiotherapy.
Some centers may prefer to avoid doxorubicin during or within the the first three weeks after radiotherapy and catch up with the doxorubicin course later on.

Vincristine related toxicity

Significant toxicities – jaw pain uncontrolled with analgesia, cranial nerve palsies and peripheral neuropathies which interfere with daily activities are an indication to omit 1 or 2 doses of vincristine. Once the neuropathies have resolved vincristine should be recommenced at 50 % of the previous dose with increments for further doses by 25 % until the full dose is reached.

Cardiac abnormalities

Cardiac abnormalities not previously present including an ejection fraction of < 50% or fractional shortening of < 28 % are indications for delaying doxorubicin regimen by 1 week. If repeat studies are normal then the full dose of doxorubicin may be given. If the abnormalities persist omit the dose of doxorubicin.
Overt cardiac failure is an indication for permanent discontinuation of doxorubicin.
Cyclophosphamide in a VDCy cycle should also be reduced by 25 % but escalated back up to full dose if there is no worsening of symptoms or echocardiogram.

Pulmonary abnormalities

The acute onset of tachypnoea following doxorubicin and after whole lung radiotherapy may represent radiation pneumonitis. Unless radiation pneumonitis can be excluded due to infective causes, further doses of doxorubicin should be withheld until the tachypnoea and respiratory symptoms have improved.

Hepatic function

Doses of etoposide and doxorubicin should be modified for above grade 2-3 toxicity after discussion with trial coordinator. The dose should be withheld for grade 4 toxicity.

Renal toxicity

Extra GFR tests should be performed if the serum creatinine increases by 100% of the baseline value or exceeds the upper limit of normal for age.

Infections

Episodes of *neutropenic infection* are likely to occur after chemotherapy. All participating institutions must be familiar with managing such problems instituting promptly all necessary investigations (e.g. blood culture) and empiric antibiotic treatment according to centre guidelines.

Pneumocystis carinii pneumonia - Patients should be treated with co-trimoxazole according to the centre guidelines for prophylaxis.

A recommended schedule is as follows:

Co-trimoxazole 2 days per week twice per day, dose for surface area;

S.A.	Co-trimoxazole
0.5-0.75 m^2	240mg b.d.
0.76-1 m^2	360mg b.d.
> 1m^2	480mg b.d.

Varicella or herpes - Patients who develop varicella or herpes should receive Aciclovir and chemotherapy should not be restarted until one week after the resolution of the rash.

INVESTIGATIONS DURING AND AT THE END OF TREATMENT

Summary

	Before week															
	1	2	4	6	8	10	12	13	15	17	19	21	23	25	26	27
History/examination	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
FBC, Electrolytes, liver function	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
CT/MRI primary site							X*									
Chest XRay							X									
GFR (a as per institutional practice)	X				X					X				X		
Echo	X				X					X					X	

* for patients with biopsy or incomplete resection at diagnosis

Investigation during treatment

Physical Examination

A thorough physical examination should be performed prior to every block of chemotherapy.

Laboratory Investigations

- Full blood count (including differential white cell count and platelets) before each course of chemotherapy (neutrophils > 0.75 x 10^9/l and platelets > 75 x 10^9/l is required before the start of each course of chemotherapy).
- Serum creatinine, electrolytes- including Ca, Po_4, Mg and liver function tests and renal tubular function: before each block of chemotherapy.
- **GFR before week 4 and 19**

Echocardiogram

- Before week 1 and 9, 17, and at the end of treatment.

Tumour reassessment

If no signs of progression are present, a formal tumour re-evaluation is advised at the end of treatment in patients without measurable disease, and at the 12^{th} week in patients with either measurable disease or who did not receive surgery at diagnosis, prior to surgery at week 13 onwards.

A clinical assessment of tumour response should be made at each visit in order to detect tumour progression at any point during treatment. This should be supplemented by radiological examination as appropriate.

The radiological reassessment must use comparable techniques to those used at diagnosis (MRI and/or CT scan) and include all sites of disease.

As at diagnosis, tumour dimensions should be recorded in three diameters and can be compared choosing, as far as possible, the diameters selected at diagnosis.

Tumour volume (V) calculation:

a= length (in cm)
b= width (in cm) $\mathbf{V} = \pi/\mathbf{6} \times \mathbf{a} \times \mathbf{b} \times \mathbf{c} = \mathbf{0.52} \times \mathbf{a} \times \mathbf{b} \times \mathbf{c}$ in cm^3
c= thickness (in cm)

Investigations at the end of treatment

Investigations required at this point are:

- Thorough physical examination (weight, height, pubertal status)
- Blood: Full Blood Count, liver enzymes, K, Na, Ca, PO_4, Cl, Mg, Glucose, AP, H_2CO_3, creatinine and GFR, and renal tubular function. (as per institutional guidelines)
- MRI/CT of primary tumour site and all measurable disease, CT chest if metastases present at diagnnosis
- echocardiogram

Investigations during follow-up

Post therapy, all patients should be followed for possible tumour relapse and treatment side effects monitoring.

► **TUMOUR RELAPSE SURVEILLANCE**

The following is recommended

- Clinical examination
- Ultrasound/ CT scan or MRI of the primary tumour site
- Chest X-ray

Primary Surgery of Rhabdoid Tumours

The recommendations for primary surgery of renal tumours are described in the SIOP Wilms tumour protocol - SIOP WT 2001. Tumour banking for all resected tumour specimens should be done as per individual tumour banking protocols.

Delayed surgical management of initially unresectable tumours

Patients should receive 11 weeks of preoperative chemotherapy followed by the appropriate imaging and surgery to resect residual tumour at week 13.

Definition of Unresectable tumours

- Tumour thrombus extending into the IVC above the level of the hepatic veins
- Tumours that involve contiguous structures whereby the only means of removal would involve removal of the contiguous structure (excluding the adrenal gland)
- Tumours that would result in tumour spillage if resected before chemotherapy
- Patients with pulmonary compromise due to extensive pulmonary metatases

Surgical management of metastases

Intra-abdominal metastases

If residual intra-abdominal metastatic disease remains after 11 weeks of chemotherapy, it should be resected if feasible. If complete resection is not feasible, then continue chemotherapy until week 25, assessing resectability at that point

Pulmonary metastases

If residual pulmonary metastases remain after 11 weeks of chemotherapy, they should be resected if feasible. If not feasible resection after assessment at week 25 should be attempted.

Bone Metastases

Surgery is rarely recommended for boney metastases and should only be considered if results in resection of all known disease. Radiation is recommended instead.

Brain Metastases

Surgical resection of brain metastases may be considered before chemotherapy if feasible. Cerebral tumors may sometime be considered as multifocal primaries, in a context of constitutionnal INI -1 mutation, in the overall therapeutic strategy.

Surgical Management of Extra-renal rhabdoid tumour

Extra-renal rhabdoid tumours can be found in a variety of locations including soft tissues of the trunk, the extremities, head and neck, abdomen, pelvis and retroperitoneum , as well as a variety of organs – thymus, liver, heart and bladder. The same general surgical principles apply as those to rhabdoid tumours occurring in the kidney i.e. complete surgical resection at diagnosis unless this is associated with significant morbidity – resection of organs or amputations - adjuvant chemotherapy should then be given to shrink the tumour with reassessment and possible surgery at week 13 or if still not feasible assessment and surgery at week 25.

RADIOTHERAPY GUIDELINES

Renal Rhabdoid Tumours

Indications for post-operative flank radiotherapy

- Stage I-III renal rhabdoid tumour (19.8 Gy in 11 fractions of 1.8 Gy over 2 weeks for patients ≥ 12 months; 10.5 Gy in 7 fractions of 1.5 Gy over 9 days for patients < 12 months)

Indications for whole abdominal and pelvic radiotherapy

- Stage III with cytology positive ascites
- Preoperative intraperitoneal rupture
- Diffuse operative spill and peritoneal seeding
  (19.5 Gy in 13 fractions of 1.5 Gy over 17 days for patients ≥ 12 months; 10.5 Gy in 7 fractions of 1.5 Gy over 9 days in the case of patients < 12 months

Indications for pulmonary radiotherapy

- Lung metastases (15 Gy with lung correction in 10 fractions of 1.5 Gy over 12-14 days for patients ≥ 12 months; 10.5 Gy in 7 fractions of 1.5 Gy over 9 days for patients < 12 months)

Indications for liver radiotherapy

- Liver metastases (19.8 Gy in 11 fractions of 1.8 Gy for patients ≥ 12 months; 15 Gy in 10 fractions of 1.5 Gy for patients < 12 months.)

Indications for whole brain radiotherapy

- brain metastases (21.6 Gy in 12 fractions of 1.8 Gy) + boost of 10.6 Gy

Indications for bone metastases radiotherapy

- bone metastases (25.2 Gy in 14 fractions of 1.8 Gy)

Timing of Radiation therapy

All radiation therapy should begin as soon as it is logistically possible concurrent with the initiation of chemotherapy after surgery which is either upfront or after 12 weeks of chemotherapy.

Equipment

All patients will be treated with megavoltage equipment (4-20 MV linear accelerator. The use of colbalt-60 equipment is not acceptable for radical therapy.)

Treatment planning

All patients should have a planning CT scan to enable 3-D-conformal planning, generation of dose volume histograms for organs at risk, and lung correction where necessary. The dose is prescribed according to ICRU 50.

Fractionation

Treatment is given with conventional fractionation, treating all fields each day, with one treatment daily, five days a week. The fraction size should be 1.8 Gy except with large fields (whole abdominal and pelvic radiotherapy, and whole lung irradiation) and in infants. Once treatment is started, there will be no interruptions in treatment unless absolutely necessary. It is not necessary to suspend treatment because of uncomplicated myelosuppression, supportive care should be given for neutropenia and thrombocytopenia according to local protocols. Haemoglobin levels should be maintained at 12 g/dl^{-1} or above during the time of radiotherapy.

►►► Compensation for treatment breaks

Standard fractionation is one treatment per day, five days each week. If a treatment interruption is unavoidable, this should be compensated for. Ideally, two fractions per day with a minimum interfraction interval of 6 hours should be given to enable treatment to be completed within the same overall time as was originally intended. If this is not possible, for example in the case of a child requiring general anaesthesia, one or two additional fractions should be given according to the COG guidelines below.

Or as per COG protocol

The total number of fractions or total radiotherapy dose to be delivered according to the duration of interruptions is indicated below;

Patients prescribed 10.8 Gy

Timing	Fx size	# Fx	Total dose (Gy)
Normal and/or up to 3 day split	1.8	6	10.8
4-7 day split	1.8	7	12.6
> 7 day split	1.8	8	14.4

Patients prescribed 19.8 Gy

Timing	Fx size	# Fx	Total dose (Gy)
Normal and/or up to 3 day split	1.8	11	19.8
4-7 day split	1.8	12	21.6
> 7 day split	1.8	13	23.4

Target volume definition for primary tumour

- The target volume is chosen according to the initial tumour volume (gross tumour volume - GTV). The pretherapeutic CT is usually the optimal imaging study.
- The clinical target volume (CTV) is defined as the GTV + 1 cm extended medially (and superiorly and inferiorly as appropriate) to encompass vertebral bodies in their entirety.
- The planning target volume (PTV) is defined as the CTV + 1 cm unless departmental quality control data indicate that a different margin is appropriate.

Flank irradiation

The GTV is determined by the preoperative CT scan and it is defined as the outline of the kidney with the associated tumour. The PTV should not extend more than 2cm beyond the defined GTV, except where necessary to allow the superior and inferior field borders to lie within an intervertebral space, and the medial border to fully encompass the entire vertebral width without significantly overlapping the contra lateral kidney. In patients where the tumour prior to resection bulged into the contra lateral flank without tumour invasion into the contra lateral kidney, it is not necessary for the CTV to encompass the medial extent of the GTV, and so the PTV can lie so that the full vertebral width is covered without overlap of the contra lateral kidney. In most patients the superior border of the radiation therapy field will be well below the diaphragmatic dome. The radiation therapy field should not be extended to the dome of the diaphragm unless there is tumour extension to that height. When there are positive lymph nodes that have been surgically removed, the entire length of the para-aortic chain of lymph nodes should be included in the radiotherapy field. An antero-posterior parallel-opposed technique (AP-PA) is recommended for flank irradiation. The borders of the radiation fields should be placed so that the PTV is encompassed by the 95% isodose. The flank irradiation dose is 19.5 Gy in 13 fractions of 1.5 Gy over 17 days for those 12 months or older, and 10.5 Gy in 7 fractions of 1.5 Gy over 9 days in the case of infants. Dose volume histograms should be performed for liver and the remaining kidney to ensure that the doses to these organs at risk are kept within tolerance levels. At least two thirds of the remaining kidney should not receive a dose greater than 14.4 Gy, and at least half the liver should not receive a dose greater than 19.8 Gy.

Whole Abdominal and Pelvic Irradiation

For whole abdominal and pelvic radiotherapy the clinical target volume (CTV) will be the entire peritoneal cavity that extends from the dome of the diaphragm superiorly to the pelvic diaphragm inferiorly and laterally from the right to the left lateral abdominal wall. The superior border of the whole abdominal and pelvic field will be placed approximately 1 cm above the dome of the diaphragm. The inferior border of the field will be placed at the bottom of the obturator foramen. The lateral borders of the field will be placed approximately 1 cm beyond the lateral abdominal wall. The femoral heads should be shielded during radiotherapy. An antero-posterior parallel opposed technique (AP-PA) is recommended for whole abdominal and pelvic irradiation. The dose/fractionation schedule for whole abdominal and pelvic radiotherapy is 19.5 Gy in 13 fractions

of 1.5 Gy over 17 days for those 12 months or older. For these patients the remaining kidney should be shielded to limit the dose to 14.4 Gy. In the case of infants, the whole abdominal and pelvic dose is 10.5 Gy in 7 fractions of 1.5 Gy over 9 days. This treatment should be CT planned to allow dose volume histograms to be generated for organs at risk. This is especially important if a second phase of treatment to boost the dose to macroscopic residual disease is being contemplated (Section 9.1.8).

Boost for gross residual disease

Patients with gross residual disease after surgery may receive a second phase of treatment after flank or whole abdominal and pelvic radiotherapy. This requires individualised consideration. Depending on factors such as the volume which would require treatment, and the age of the patient, a lower dose may be deemed safer, or the boost may be omitted. The GTV will be defined on the postoperative planning CT scan used for planning the first phase of treatment. The CTV will usually be the same as the GTV, but may be extended to ensure uniform irradiation of vertebral bodies. The PTV will be the CTV + 1cm unless departmental quality control data indicate that a different margin is appropriate. The organs at risk will already have been delineated on the planning CT scan. Fields will be shaped with MLC or customised blocks to conform to the PTV. The most appropriate field arrangement will be selected by the clinician taking into account the composite dose volume histograms for phase 1 and phase 2 combined, with respect to coverage of the PTV and the dose constraints to organs at risk as stated in section 9.1.6. The dose will usually be 10.8 Gy in six fractions of 1.8 Gy over eight days, but 10.5Gy in seven fractions over nine days may be more appropriate in infants or if the volume is large.

Whole Lung Irradiation (WLI)

Both lungs are irradiated regardless of the number and location of the metastases. Treatment should be CT planned with patient lying supine with the arms to the side, slightly away from the body. The CTV includes the entire lungs, mediastinum and the pleural recesses. The CTV to PTV margin should take account of respiratory movement and is likely to be about 1 cm superiorly and laterally and 2 cm inferiorly. Anterior and posterior parallel opposed field will be used such that the PTV is encompassed with the 95% isodose. CT planning will take into account and correct the increased transmission through lung tissue. The inferior border of the field should lie in an intervertebral space, often below L1. The shoulder joints should be protected by MLC or cerrobend shielding. The WLI dose/fractionation schedule for those aged 12 months or over is 15 Gy with lung correction in 10 fractions of 1.5 Gy over 12-14 days. For infants it is 10.5 Gy in 7 fractions of 1.5 Gy over 9 days. If patients require both whole lung and infra-diaphragmatic irradiation, then both fields should be treated simultaneously whenever possible. As the volumes for WLI often abut or overlap with the volumes for flank or whole abdominal and pelvic radiotherapy, the contiguous areas should be treated in the first instance as a single volume with a single pair of appropriately shaped anterior and posterior parallel opposed fields. For such a large volume a fraction size of 1.5 Gy will be used. The fields will be reduced in size (off the lungs) after 10 fractions (15 Gy) to cover only the infra diaphragmatic volume. If the WLI volume and the flank volume appear well separated, they may be treated simultaneously as two separate areas, but great care must be taken when planning to ensure an adequate gap so that there is no overlap. Similarly, if WLI and infra diaphragmatic radiotherapy are given at different times, care must be taken to ensure that there is no overlap.

Localized foci of lung disease persisting two weeks after the delivery of WLI may either be excised or given an additional 7.5 Gy in 5 fractions. The volume of the lungs included in this boost irradiation field should be <30% in order to limit the acute and long-term pulmonary complications that could result from higher doses of irradiation.

Liver Irradiation

The entire liver is included in the irradiation portal only if the liver is diffusely involved (19.8 Gy in 11 fractions of 1.8 Gy.) In infants the dose/fractionation schedule should be 15 Gy in 10 fractions of 1.5 Gy). If the entire liver volume is not involved, then only the metastases with a margin of 2 cm is irradiated. Additional boost irradiation doses of 5.4 to 10.8 Gy may be administered to limited volumes (<75% of the entire liver) at the discretion of the clinical oncologist. While irradiating the liver, the dose to the upper pole of the remaining kidney should be monitored. A posterior kidney block may be inserted in order to limit the remaining kidney to ≤ 14.4 Gy. An antero-posterior parallel opposed technique (AP-PA) is recommended for liver irradiation.

Brain Irradiation

In patients with brain metastases, the whole brain is included in the irradiation field to a dose of 21.6 Gy in 12 fractions of 1.8 Gy. A boost of at least 10.8 Gy is required to site of metastases. In patients with ≤ 3 circumscribed lesions especially in patients younger than 3 years, a limited volume (tumour, or tumour bed only with 0-1 cm margin) boost dose of 10.8 Gy in 6 fractions using IMRT or sterotactic radiotherapy may be administered after whole brain irradiation to 21.6 Gy.

A lateral parallel opposed technique (right and left lateral) is recommended for whole brain irradiation.

Bone Irradiation

In patients with bone metastases, the GTV is the lesion as shown on appropriate imaging, which may include skeletal scintiography, plain radiographs MRI and CT. The clinical target volume will usually include a margin of apparently healthy bone up to 2cm. A narrower margin may be appropriate where the metastasis is close to the edge of the bone. Irradiation of the epiphyses should be avoided where possible to diminish late effects. An appropriate margin should be added for the PTV, taking into account the technique of immobilisation used. The entire bone need not be irradiated. An antero-posterior parallel opposed technique (AP-PA) is usually recommended for bone irradiation, depending on the anatomical site. The bone irradiation dose is 25.2 Gy in 14 fractions of 1.8 Gy, but may be modified if appropriate.

Lymph Node Irradiation

Lymph nodes with metastatic tumour that have not been surgically removed should receive radiation therapy. Groups of lymph nodes which were involved at presentation should be irradiated in their entirety. The GTV will be the nodal area including any residual mass after chemotherapy as defined on the planning CT scan. The CTV will usually be a 1 cm margin around the GTV. The margin for PTV definition will depend on immobilisation and individual departmental data. If vertebrae are to be irradiated, the whole vertebral body shall be included in the fields. For

mediastinal and abdominal nodes a parallel opposed field arrangement usually gives best coverage of the PTV. Where possible, nodal areas will be treated in continuity with the primary tumour site or other metastatic sites requiring irradiation. The dose will usually be 19.8 Gy in 11 fractions of 1.8 Gy.

Target Dose

The daily dose to ICRU prescription points shall be 1.8 Gy, except in younger children (e.g. under three years of age) or when large volumes (e.g. whole lung or whole abdomen and pelvis) are to be treated.

Extra-Renal Non-CNS Rhabdoid Tumour

All patients should have a consultation by a radiation oncologist at the time of study entry so that the radiation oncologist can assist in providing appropriate staging/grouping of the patient and review the adequacy of the initial diagnostic imaging studies for subsequent local control treatment with RT.

Extra-renal non-CNS Rhaboid Tumours

Gross total resection with no residual disease (microscopic negative margins) (Group I)	36 Gy in 20 fractions
Gross total resection with microscopic residual disease (microscopic positive margins) (Group II)	45 Gy in 25 fractions
Biopsy only or gross residual disease (Group III)	50.4 Gy in 28 fractions

These total doses and fractionation schedules may need to be modified taking into account factors including the age of the child, the volume requiring irradiation, critical normal structures and co-morbidity.

Equipment

Treatment will usually be with x-ray photons of 4-20 MV from a linear accelerator. The use of cobalt teletherapy is not acceptable.
In some circumstances, the use of electrons may result in a more favourable dose distribution.
Similarly, interstitial or intacavitary brachytherapy may be preferable in certain circumstances, such as with tumours at gynaecological, extremity and some non-parameningeal head and neck primary

sites. Brachytherapy should not be used without careful discussion, and is only appropriate in specialised treatment centres.
Proton therapy is permitted in this study in specialised treatment centres.

Protocol Target Volumes

Three-dimensional treatment planning is strongly encouraged for patients treated on this study.
All treatment planning, regardless of whether it is standard or 3D conformal/IMRT, will be based upon the following target definitions. Treatment will be prescribed to the PTV, which will be derived from the GTV and CTV as follows:

GTV

The GTV is defined as the pre-treatment visible and/or palpable disease defined by physical examination, operative surgical findings, computer tomography, or magnetic resonance imaging. The T_1 MR image with contrast is usually optimal imaging study. In special circumstances, changes can be made in this definition based upon the post-operative geometry of the target volume. In patients who have undergone primary surgical tumour resection, the entire surgical scar should be included in the GTV. However, in general, the GTV does not change based on any surgical resection or chemotherapy response.

CTV

For all Clinical Groups, the CTV is defined as the GTV + 1.5 cm (but not extending outside of the patient). For some sites, the definition of the CTV is modified to account for specific anatomic barriers to tumour spread. The CTV will always include the entire draining lymph nodes chain if the regional nodes are clinically or pathologically involved with tumour. Patients with gross residual disease and primary sites in the head and neck and vulva/uterus who do not undergo second look operations may have second CTV and PTV defined for a cone down boost. The patients will receive a total dose of 50.4 Gy given to the PTV.

PTV

For all Clinical Groups, the PTV is defined as the CTV plus an institution specific margin to account for day to day setup variation related to the ability to immobilize the patient and physiologic motion of the CTV.

PRV (Planning Organ at Risk Volume)
Planning Organ at Risk Volumes (PRV) will be defined for each organ-at-risk defined in section 14, Radiotherapy Guidelines, and for any other organ that the treating clinical oncologist wishes to limit to a specific dose. The PRV is defined as the volume of the organ at risk plus a margin to account for that organ's positional uncertainty.

Special Modifications of GTV and CTV for Certain Sites

- **Orbit:**

For orbit primaries, the CTV will not extend outside the bony orbit, providing there is no bone erosion of the orbit

- **Thorax:**

Tumours which have displaced a significant amount of lung parenchyma which has subsequently returned to normal anatomic position following surgical debulking will have the GTV defined as the pre-operative tumour volume excluding the intra-thoracic tumour which was debulked. However, all areas of preoperative involvement of the pleura will be included in the GTV.

- **Bladder/Prostate, Perineum, Pelvis, Biliary tree and Abdomen:**

Tumours which have displaced a significant amount of bowel which has subsequently returned to normal anatomic position following surgical debulking will have the GTV defined as the pre-operative tumour volume excluding the intra-abdominal or intra-pelvic tumour which was debulked. However, all areas of preoperative involvement of the peritoneum or mesentery, and the site of origin, will be included in the GTV.

Timing of Radiotherapy:

All patients who require radiation therapy shall begin treatment concurrent with the initiation of chemotherapy after surgery. If surgery is performed up-front, radiation therapy should begin as close to the beginning of chemotherapy as possible. If surgery is delayed, radiation therapy should begin after recovery from surgery when chemotherapy is reinitiated. Chemotherapy will be given concurrent with radiotherapy. The regimen is designed so that doxorubicin is avoided during the six weeks following irradiation.

Prescribed Dose and Fractionation

The total radiotherapy dose for the various clinical Groups are indicated in the table below:

Gross total resection with no residual disease (negative margins) (Group I)	36 Gy in 20 fractions
Gross total resection with microscopic residual disease (positive margins) (Group II)	45 Gy in 25 fractions
Biopsy only or gross residual disease (Group III)	50.4 Gy in 28 fractions

All radiation should be given at 1.8 Gy per fraction with one fraction given per day. Five fractions should be given per week.

Interruptions

Patients requiring an interruption in radiotherapy (i.e., for low counts, infection, toxicity) will receive a modification in the schedule as shown in the tables below

Patients prescribed 36 Gy (Gp I)

Timing	Fx Size (GY)	# Fx	Total Dose (Gy)	Total Time
Normal and/or up to 2 wk split	1.8	20	36	4 – 6 wks
2 -3 wk split	1.8	21	37.8	6 – 7 wks
> 3 wk split	1.8	22	39.6	> 7 wks

Patients prescribed 45.00 Gy (Gp II)

Timing	Fx Size (GY)	# Fx	Total Dose (Gy)	Total Time
Normal and/or up to 2 wk split	1.8	25	45	5 - 7 wks
2 -3 wk split	1.8	26	46.8	7 – 8.4 wks
> 3 wk split	1.8	27	48.6	> 8.4 wks

Patients prescribed 50.40 Gy (Gp III)

Timing	Fx Size (GY)	# Fx	Total Dose (Gy)	Total Time
Normal and/or up to 2 wk split	1.8	28	50.4	5.4 – 7.3 wks
2 -3 wk split	1.8	29	52.2	7.4 - 8.4 wks
> 3 wk split	1.8	30	54.0	> 8.4 wks

Normal tissue Sparing

It is important to protect normal vital structures whenever possible. Such shielding must be weighed against the possibility of under treatment of known tumour-bearing tissue.

The recommended upper dose limits for different organs are shown in the table below. These limits are the same as, or less than, those used in the previous IRS studies and have not been associated with excessive toxicity when used with chemotherapy.

Normal tissue Tolerance

Organ	Dose Limit (Gy)
Optic Nerve and Chiasm	50
Lacrimal Gland	41.4
Small Bowel	45.0
Spinal Cord	45.0
Lung (when > ⅓ but <½ of total lung volume is in the PTV)	18.0
Lung (when > ½ of total lung volume is in the PTV)	15.0
Whole Kidney	19.8
Whole Liver*	23.4

*Tolerance for partial liver radiation: when ⅔ of the liver volume is included in the initial radiation port and > ⅓ of the liver requires a boost beyond the maximum whole liver dose (23.4), the total dose to the boost volume may be limited to a maximum of 30 Gy. The boost volume should not exceed ⅔ of the total liver volume.

Genetic Study

INI1 Mutation Analysis

Established methods in Dr. Jaclyn Biegel's laboratory will be utilized for molecular genetic testing of rhabdoid tumours *(Biegel, 1999)*. Tumours will be analyzed for an INI1 deletion by interphase fluorescence in situ hybridization, using an INI1 probe from 22q11.2 and an EWS control probe that maps to 22q12. Tumours that are not deleted by FISH will be analyzed by microsatellite analysis to detect loss of heterozygosity. Tumours with one or two copies of INI1 will be screened by reverse transcriptase- polymerase chain reaction (RT-PCR) to determine expression of the INI1 gene. RT-PCR products will be sequenced to detect mutations. Heteroduplex analysis and direct sequencing will be employed to detect mutations at the DNA level. If mutations are demonstrated in the tumour tissue, DNA from blood from the patient will be sequenced to identify a germline mutation. Parental blood specimens will be analyzed to detect inherited versus de novo mutations. As newer methods for detecting alterations of the INI1 gene at the DNA, RNA and protein level are developed, they will be incorporated into these studies.

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SECOND-LINE THERAPIES

Note:
the following chapter must be considered as **general considerations and suggestions**, and not as therapeutic guidelines.

It is important to underline that in relasing NRSTS patients, surgery must be considered as the first choice. For local relapse, mutilating surgery must be considered. Surgery is regarded as the mainstay of treatment also in case of distant relapse when the lung is the only site and in particular when the number of metastases is low. Nevertheless, the prognosis of relapsing patients is generally poor, and consequently with the exception of selected cases, chemotherapy could be required.

In adult or adult-type soft tissue sarcomas, few drugs have demonstrated to be effective.

- **The ifosfamide-doxorubicin regimen is the most effective combination, and must be the chemotherapy of choice in patients previously treated with surgery (± radiotherapy) alone.**
- **In patients previously treated with ifosfamide-doxorubicin as first therapy, standardized second-line chemotherapy is not available.**
- **The inclusion of the patients in phase I-II studies should be considered and/or recommended.**

However, some possible suggestions for relapsing patients are herein reported.
In fact, various hints are coming, in particular from adult groups, and the concept of the histotype-driven chemotherapy is emerging: drugs other than the ifosfamide-doxorubicin combination have proved fairly active against particular histotypes, and the new efforts are in the direction of exploring new therapeutic approaches tailored to each histological subtype. More than for new cytotoxic drugs, the main expections are for the development of new targeted therapies. The success of anti-tyrosine kinase imatinib mesylate in treating c-kit-positive gastrointestinal mesenchymal tumors has provided important insight for the development of new molecular therapies specifically designed to reach targets crucial to a given tumor's biology. Various targeted drugs are currently under investigation in adult sarcomas.

► Vinorelbine

Vinorelbine as a single agent and in combination with low-dose oral cyclophosphamide showed high response rate in already heavily-treated patients with recurrent RMS (and a possible anti-angiogenic effect has been hypothesized). Few data are available on the efficacy of vinorelbine in NRSTS: some responses have been seen in **synovial sarcoma** and **DSRCT**. Further evaluation might be useful to define its role in NRSTS.

Patients could be treated with:
vinorelbine 30 mg/m^2/iv (or alternatively, **80 mg/ m^2 oral**)
day 1, 8, 21, 28
or
vinorelbine 25 mg/m^2/ev (or alternatively, **60 mg/ m^2 oral) day 1, 8, 15**
+ **oral cyclophosphamide 25 mg/m^2/day (every day)**

► High-dose ifosfamide

High dose ifosfamide (defined as doses ≥ 12-14 g/m^2) has shown satisfactory response rate in patients (in particular with **synovial sarcoma**) that did not respond to conventional-dose ifosfamide (9 g/m^2), or relapsed after ifosfamide-doxorubicin regimen. Therefore, these patients might be successfully treated with high-dose ifosfamide, especially when they relapsed more than 1 year after the end of the first treatment.
High-dose ifosfamide can be administered in 4-5 day infusion; this administration is generally associated with important neutropenia, and this side effect must be considered in relapsing patients when the quality of life represents an important goal.
Recently, ifosfamide has been proposed at the dose of 14 g/m^2, given in 14-day infusion by external pump. This administration has been proven to be safe and well-tolerated, with the same activity of 4 or 5-day infusion. The drug has been demonstrated to be stable in solution for 7 days, so the pump must be renewed after one week of therapy. A prospective phase II trial is open in the adult Italian Sarcoma Group (ISG): this study schedules the administration of continuous infusion ifosfamide as follow:

Ifosfamide 14 g/m^2 day 1-14
corresponding to 1 g/m^2/day for 14 consecutive days, given by external pump in 7-day infusion, with Uromitexan at the same dose (oral hydration of 1.5 l/day)

Alternatively, **ifosfamide at 14-15 g/m^2** may be given in 4-5-day infusion (2.8-3 g/m^2/day).

► Gemcitabine in leiomyosarcoma

Gemcitabine and, more recently, gemcitabine associated with docetaxel have proved to be effective against **leiomyosarcoma** (objective response around 40-50%).
A prospective phase II trial is ongoing within the adult Italian Sarcoma Group (ISG), with this schedula: **Gemcitabine 1000 mg/mq, day 1-8-15 – second cycle at 28th day.**

► Gemcitabine and docetaxel

This combination has been compared to gemcitabine alone in metastatic soft tissue sarcomas in a phase II randomized study of the Sarcoma Alliance for Research Through Collaboration SARC, including 122 cases (Maki RG, et al. J Clin Oncol 2007;25(19):2755-63).

In the gemcitabine-only arm, gemcitabine was administered as a fixed dose rate of 10 mg/m^2/min during a 120-minute intravenous infusion, at 1,200 mg/m^2 days 1 and 8, every 21 days.

In the gemcitabine-docetaxel arm, the gemcitabine dose was a fixed dose rate 900 mg/m^2 intravenous infusion during 90 minutes days 1 and 8, with docetaxel 100 mg/m^2 intravenously during 60 minutes day 8, every 21 days.

The objective RECIST response rates were 16% (gemcitabine-docetaxel) and 8% (gemcitabine).

► Gemcitabine plus Vinorelbine

A recent report from the Dana-Farber Cancer Institute, Boston (*Dileo O, et al, Cancer 2007; 109:1863-9*) suggested a possible role for this combination: **Gemcitabine 800 mg/m2 was given over 90 minutes on Days 1 and 8 of a 21-day cycle after administration of vinorelbine 25 mg/m2**.

This study (including 40 patients) reported 1 CR lasting >1 year in a patient with high-grade pleomorphic spindle-cell sarcoma.

► Taxanes in angiosarcoma

The experience reported by the MSKCC has opened the question on the role of paclitaxel in the treatment on malignant vascular tumours, with results superior to any other drugs never used in angiosarcoma: paclitaxel as a single agent achieved 8 objective responses (4 CR, 4 PR) in 9 adult patients with cutaneous angiosarcoma of the scalp and face.

Possible schedula: **Paclitaxel 80 mg/m^2 1-hour infusion, day 1,8,15.**

► Trabectidine in myxoid/round cell liposarcoma

Trabectedine has recently revealed an impressive activity in **myxoid/round cell liposarcoma** (with a possible direct effect on the products of the histotype-specific FUS-CHOP translocation) and the potential for an effect on **leiomyosarcoma** and **Ewing's sarcoma** too.

► Imatinib in dermatofibrosarcoma protuberans

Imatinib has proved effective against, possibly by deregulating the platelet-derived growth factor-B (PDGFB) resulting from the specific t(17,22) translocation.

► Sorafenib for vascular sarcomas and leiomyosarcoma

Preliminary data are available on the effects of vascular endothelial growth factor (VEGF) inhibitors, as Sorafinib, in vascular sarcomas and leiomyosarcoma

► Mammalian targets of rapamycin (mTOR) inhibitors (AP23673) in leiomyosarcoma

► Temodal-Topotecan regimen

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Isolated limb perfusion (chemo-hyperthermic perfusion)

Isolated limb perfusion is not included in the E*p*SSG NRSTS therapy plan, as routine treatment procedure. Nevertheless, centers that have the experience on this technique could decide to utilize this procedure as part of the treatment in selected cases.
Possible indications for isolated limb perfusion could be multifocal recurrence, or recurrence in irradiated areas (patients who probably require amputation), although in some cases this procedure is utilized also as front-line treatment, in patients who are still not eligible for conservative surgery after pre-operative chemo-radiotherapy.

Technique: Isolated limb perfusion (ILP) surgically isolates the main limb vessels in order to deliver high concentrations of anti-tumour drugs to a limb-threatening tumour. ILP can achieve regional concentrations in the tumour-bearing limb 5-25 times higher than achieved after systemic administration and without systemic side-effects. Isolation of the limb circulation is achieved by clamping and cannulation of the main artery and vein followed by connection to an extracorporeal circuit, ligation of collateral vessels, and application of a tourniquet. After isolation, drugs can be injected into the isolated perfusion circuit, together with radiolabelled albumin and erythrocytes for monitoring of systemic leakage by using a precordial scintillation probe. After 60-90 minutes of perfusion, the limb is rinsed with an electrolyte solution, the cannulae are removed and the vessels repaired. Delayed surgery of the tumour is usually feasible 6-8 weeks after ILP.

Specific Side effects:
1. Acute tissue reactions must be monitored and classified *(I: No reaction, II: Erythema and/or oedema, III: Substantial oedema and/or erythema, with some blistering, slightly disturbed motility, IV: Extensive epidermolysis and/or obvious damage to the deep tissue with functional disturbances; threatening or manifest compartmental syndrome, V: Reactions that may necessitate amputation*). Grade IV and V acute tissue reactions occur in a small minority of ILP.
2. Toxicity to the growth plates should be considered and joints/growth plates are preferentially kept out of the perfused area.
3. Postoperative morbidity described in ~2% of cases is arterial thrombosis at the arteriotomy site, which can be resolved by prompt thrombectomy.
4. Hematologic toxicity in case systemic leakage of anti-cancer drugs occurs. TNF-α can induce septic shock syndrome and the use of high concentrations of TNF-α also necessitates the monitoring for systemic leakage during the procedure.

Hyperthermia and drugs:

Hyperthermia is applied to prevent vasoconstriction and increase perfusion in (sub)cutis for superficial tumours. Secondly, tumour cells are sensitive to heat and uptake of drugs is increased at higher temperatures. True hyperthermia (>41° C) yields high CR rates, but is also associated with unacceptable regional toxicity. Mild hyperthermia (39-40° C) is probably no more effective than normothermia (37-38° C), and borderline true hyperthermia (40-41° C) seems to increase the tumour response rate, but possibly also increases regional toxicity. Most current studies in adults with soft tissue sarcomas (STS) use borderline true hyperthermia.

Melphalan: Melphalan has proven to be an effective drug for local perfusion with low regional toxicity, most commonly used at a dose of 10 mg/L perfused tissue for the leg and 13 mg/L for the arm.

Doxorubicin: Doxo is the most effective single agent in STS. However, it may induce more local toxicity than melphalan. MTD of Doxo was established at 0.7 and 1.4 mg/kg for upper and lower limb, respectively.

TNF-α: The use of TNF-α has strongly increased the effectiveness of ILP. It seems to increase the tissue delivery of chemotherapy, it has a direct cytotoxic effect and it has a damaging effect on the tumour vascularity. Dose-limiting toxicity in ILP is achieved at concentrations 10-50 times higher as systemic doses. Most studies use 3-4 mg in adult patients.

Indications for use of ILP:

ILP should be considered in patients with limb-threatening primary or recurrent STS, when an adequate tissue reconstruction is considered feasible after ILP and tumour excision. Usually it concerns bulky, unresectable tumours and/or tumours close to important structures (nerve, vessels, interosseous membrane). Encouraging results have also been achieved in non-STS tumours, such as advanced osteosarcoma, desmoid tumours, kaposi sarcoma. In adults, ILP alone, or in combination with surgery (usually after 6-8 weeks) improves local control, by induction of tumour shrinkage, and induction of tumour necrosis. ILP has also been used for the management of local tumour recurrence of previously irradiated limbs. Multiple treatments with ILP can be applied to improve local control if the desired effect has not been achieved after one treatment, or in the management of local recurrences that had responded previously to ILP. The use of irradiation as adjuvant treatment after ILP and marginal tumour excision is controversial. The addition of radiotherapy will increase local control, but there have been contradictory reports concerning the additional toxicity.

Treatment results:

In adults, ILP is a treatment of choice in *in-transit* metastases of melanoma. Response rates are significantly improved in studies with melphalan with TNF-α (CR 64%) versus melphalan alone (CR 17%) in bulky (sarcoma-like) melanomas. ILP improves local control and is limb-sparing in 74-87% of adult melanoma patients who would normally have been managed by amputation. Similarly, in adult STS, limb amputation could be avoided in 73-86%. Local control was reported as high as 57%. However, ILP did not improve outcome in adult patients with melanoma or STS, . The use of ILP in paediatric STS patients is anecdotal, but seems to be no different from the adult patient groups.

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Metastatic NRSTS

The E*p*SSG NRSTS 2005 protocol is a protocol for non-metastatic patients

NRSTS patients (including DSRCT) with metastases should be included in stage IV protocol of E*p*SSG

An exception is represented by rhabdoid tumours: patients with metastatic rhabdoid tumours should be treated according to the guidelines defined for localised disease (see 19.2 and appendix)

E*p*SSG European paediatric Soft Tissue Sarcoma Study Group

RMS & NRSTS 2005
Radiological guidelines

1. Objectives of imaging

- Assessment of **tumour extent** and possible dissemination
- **Biopsy guidance**: to define biopsy tract and to choose viable, vascularised tumour, avoiding necrotic areas.
- Defining or excluding **residual tumour** after surgical excision biopsy: imaging permits depiction of macroscopic residue (imaging cannot accurately depict microspic residue [1]).
- Assessment of initial **volume**: prognostic value, baseline for further evaluations during chemotherapy.
- Assessment of **residual disease** after neoadjuvant chemotherapy.
- Assessment for **radiotherapy planning**.

2. Pre-treatment Evaluation

2.1 Imaging-guided biopsy

- Surgical open biopsy is recommended, but, according to local procedures, US or CT scan-guided core needle biopsies may be appropriate, especially **in difficult or inaccessible sites**, whereas endoscopic biopsies are appropriate for bladder, prostate or vaginal tumours.
- 18 or 16 Gauge (1.2 – 1.6 mm) needles may be used depending of local procedures. Fine needle aspiration (22 Gauge-0.7 mm) *only* is not recommended, but additional FNA may provide additional cellular material which can be used for genetical examinations (i.e. DNA ploidy and chromosomal analysis) [2].
- For limb primaries in particular the **biopsy tract** must contaminate **only the anatomical compartment** in which the tumour is situated, avoiding major neurovascular structures. Useful anatomical landmarks may be found in the following reference [3].
- For limb or superficial primaries it is recommended the **biopsy tract is marked** e.g. with ink (tattooing), at the time of biopsy to allow later surgical excision of the tract.
- Local arrangements with the histopathology department should be in place regarding **fast transport of fresh tumour biopsy specimens**.
- Direct **fixation must be avoided** since no cytogenetic studies are possible when a specimen is placed in formaldehyde, but **RPMI medium** (Roswel Park Memorial Institute 1640) may be used for specimen transport without jeopardizing genetic studies.

2.2 Imaging techniques and indications

- First locoregional evaluation should be made with **MRI**. The choice between CT and MR depends also on local availability.
- **MRI is preferable for most locations** [4, 5], other than the chest [6], including head and neck tumours with possible skull base invasion [7].

- MRI is mandatory for genito-urinary primaries.
- CT is occasionally useful for assessing subtle bone destruction but MRI is sufficient for most head and neck lesions.
- Pre-treatment **re-evaluation must be performed after excision biopsy** since this can significantly modify initial tumour volume.
- All imaging data should be **stored in DICOM** format for further review (on CDROM if PACS is not locally available)
- Data transfer on the website (www.essg.cineca.org) is not yet available but is planned to be implemented.

TECHNIQUES	Comments
MRI (or CT) of primary tumour site **+ initial US if follow-up with US is possible**	Will need to be performed (again) after surgical excision biopsy if significant volume resected
Chest CT	Mandatory in all patients at diagnosis. Intravenous-contrast enhancement is mandatory for limb or abdominal primaries (and ideally for other primaries)
Abdomen-pelvic CT **(during same acquisition as chest CT)**	For abdominal, pelvic, paratesticular or lower limb primaries Intravenous-contrast enhancement is mandatory
Abdomen US	If abdominal CT is equivocal regarding lymphadenopathy or liver metastases
Radionuclide bone scan	Mandatory in all patients at diagnosis.
Bone plain films (+/- CT or MRI)	For differential diagnosis if isolated bone uptake on bone scan
Craniospinal MR	If intraspinal extension or suspected meningeal involvement
PET-CT	According to local availability and local protocols

2.3 MRI protocol

- Intravenous **gadolinium** administration (0,2 ml/kg - 0,1 mmol/kg) is mandatory for all MRI examinations (post-contrast T1-weighted sequences should ideally be performed with fat saturation)
- Tumour **measurements** should be performed on post-gadolinium T1 or T2-weighted sequences (but not on STIR or non-enhanced T1-weighted sequences).
- Fast **dynamic sequences** (e.g. spoiler 3D T1 : FLASH 3D, VIBE, FSPGR, 3D-FFE, volume RF-FAST) to assess early tumour vascularity are recommended at diagnosis (can help differentiation between vascularized and necrotic areas), after biopsy (helps differentiation between residual disease and fibrosis), and also after chemotherapy (depiction of residual disease) and for suspected relapse (helps differentiation between residual disease and fibrosis) [8].
- **Sedation** or general anaesthesia for children 6 months-5 years according to local procedures.
- A **cutaneous localiser** for small superficial lesions or in front of scars on limbs is good practice.

- Additional recommendations according to primary location :

Orbit	Bilateral study Thin slice width 2-4 mm
Head and Neck	No sedation if airway obstruction
Limbs	Surface coil Cutaneous localiser
Cranio-spinal MR	from C0 to S3 Anterior presaturation

2.4 Technical recommendations for CT scanning

- Apnea if possible for chest and abdominal CT
- 3 to 5 mm reconstruction slice width
- 100 - 120 kV
- mAs adjusted according to patient size, pitch and rotation time
- Recommended **CTDI vol** : 5 to 15 mGy according to age, location and local technical options
- Reconstruction filters for soft tissue, bone and lung
- Oral contrast opacification is recommended for all abdominal and pelvic studies.
- **Intravenous contrast** injection : 1,5-2ml/Kg of iodinated agent (300 or 350 mg Iodine/l); rate : 0,7 to 2 cc/sec, scan delay: 35 - 40 sec.

2.5 Evaluate according to primary location

2.5.1 Initial primary tumour volume

3D tumoural measurements are mandatory (sagittal, coronal and axial)

Tumour volume is calculated as follows : a x b x c x 0.52

2.5.2 Locoregional analysis

- **Head and neck primaries: parameningeal extent** should be specified. Parameningeal tumours are those invading one or more of the following structures: **skull base, orbital roof, paranasal sinuses, nasal cavity, nasopharynx, infratemporal fossa, pterygopalatine fossa, parapharyngeal space, middle ear or mastoid**. *In addition the following are also classified as parameningeal tumours :*
  - Tumours involving vessels or nerves with direct intracranial connection (internal carotid or vertebral artery, optic, trigeminal or facial nerve etc).
  - All intracranial and intraspinal tumours (but tumours arising from the paraspinal muscles with intraspinal extension should be designated as paraspinal)
  - All tumours with cranial nerve paresis
  - CSF tumour cell positive patients

- **Genito-urinary primaries :** assess bladder wall extension, prostatic, vaginal, uterine, ischio-rectal fossa spread [9]

- **Paraspinal locations** : Intraspinal evaluation mandatory: perform craniospinal MR.

2.5.3 Lymph nodes.

Comment: Defining lymph nodal spread of tumour is critical to staging [10], although accurately evaluating pathological lymph node (LN) extension of tumour can be problematic.

- Oval shaped nodes (with a preserved hilum at sonography) and a short axis diameter of less than 1cm are considered normal nodes.
- Locoregional nodes which show only peripheral enhancement on CT or MRI (probable necrotic centres) are likely to be involved by tumour also, even if less than 1 cm axis.
- Mildly enlarged locoregional nodes pose a diagnostic challenge but when round in shape, over 1.5-2 cm in short axis with a heterogenous appearance are likely invaded by tumour.
- All suspicious lymph nodes merit biopsy or another form of nodal sampling.
- Sampling of loco-regional nodes is mandatory for all limb primaries (regardless of imaging findings).

Regional lymph nodes are defined as those appropriate to the site of the primary tumour:

Head & Neck	ipsilateral cervical and supraclavicular lymph nodes bilateral adenopathy may be present with centrally situated tumours
Orbit	ipsilateral jugular, pre-auricular, cervical
Intrathoracic	internal mammary, mediastinal nodes
Thoracic wall	axillary, internal mammary, infraclavicular nodes
Intraabdominal & Pelvic	Sub diaphragmatic, intra abdominal and iliac lymph nodes according to site.
Abdominal wall	inguinal, femoral nodes
Bladder Prostate	iliac nodes (external, internal and common chains; note that paraaortic nodes are second level nodes).
Cervix and Uterus	iliac nodes (external, internal and common chains)
Paratesticular	external iliac and para-aortic (retroperitoneal) lymph nodes at renal artery or below (inguinal if the scrotum is involved)
Vagina	iliac nodes (external, internal and common chains; note that paraaortic nodes are second level nodes).
Vulva	inguinal nodes
Perineum	inguinal and iliac (may be bilateral)
Upper Limbs	axillary lymph nodes (epitrochlear rarely involved)
Lower Limbs	inguinal lymph nodes (popliteal rarely involved)

Locoregional LN extension should be differentiated from distant LN which are considered as true metastases. (Regional lymph node involvement is defined N1 according to TNM system).

Evidence of nodal involvement different than those listed above must be interpreted as distant metastasis and the patient must be treated according to the protocol for patients with metastases at diagnosis .
Examples:
- perineal tumour with nodes above the pelvis
- thigh tumour with iliac or periaortic nodes
- intrathoracic tumour with subdiaphragmatic nodes
- Unilateral tumour with contralateral involved lymph nodes (except in the head and neck).

2.5.4 Pulmonary metastases

Comment: Defining pulmonary spread of tumour is critical to staging, although differentiation between metastatic or benign nodules (i.e. granulomatous disease, hamartoma, intrapulmonary lymph nodes, bronchiolitis…) can be impossible [11-17]. Several criteria are commonly used to diagnose metastastic lesions : number, size, morphology (non-calcified, round and well-defined) and location (inferior lobes, subpleural spaces, vessels-branching). Actually, no radiological criterion has a 100% specificity.

For EpSSG studies, the following patterns will be considered as **metastatic pulmonary disease** (assuming there is no other clear medical explanation for these lesions) :

- One or more pulmonary nodules of 10 mm or more diameter
- *Or* : two or more well-defined nodules of 5 to 10 mm diameter
- *Or* : 5 or more well-defined nodules of less than 5 mm

Hence, 4 or less small nodules (< 5mm) at diagnosis will not be considered as pulmonary metastatic disease and should be classified only as "non-specific pulmonary lesions".

The same lung window settings should be used when pulmonary nodules are being measured at diagnosis and follow-up.

3. Recommendation for imaging dedicated to radiotherapy treatment planning

Pre-radiotherapy scanning with quality assurance assessment will be performed under local arangements.

4. Imaging during chemotherapy

- Evaluation during treatment should be performed when possible **with the same techniques** as initially used.
- If the lesion can be completely analysed with **sonography** (for example, a limb primary), then ultrasound may be used instead of MRI or CT to study the response rate during neoadjuvant chemotherapy.
- **MR or CT remains necessary prior to surgery** [18-20].

5. Radiological response criteria

- A choice has been made for this study to rely on volume measurements for tumour response assessment. Tumours do not necessarily grow or shrink in a rounded fashion and 3D evaluation may be more accurate than uni or bidimensional criteria [21].
- It is planned to also measure the maximum unidimensional measurement as suggested by the RECIST guidelines and later compare the volume with unidimensional measurements in terms of tumour response [22, 23]. The maximum lesion diameter in any plane should be recorded as the longest tumour diameter, and measurements may be taken from CT or MRI (contrary to the formal RECIST guidance) but the maximum tumour measurement must always be in the same plane (axial, coronal or sagittal).
- The presence or absence of a post-therapeutic residue should be stated in the radiology report [24-26].
- Very good partial response and minor partial response criteria are not recognised international criteria but have been added for this protocol.

Response levels have been adapted to 3D measurements according to published criteria [22].

		Criteria
Complete response	**CR**	Complete disappearance of tumour with no residual disease (*)
Very good partial response	**VGPR**	Volume reponse between **90-99%**
Partial response	**PR**	Volume response of **65-90%**
Minor partial response	**Minor PR**	Volume reponse between **34% and 65%**
Stable disease	**SD**	No criteria for PR or PD
Progressive disease	**PD**	Volume increase of more than **40%** and/or new lesions

*** Note :**
Residual disease should be defined as macroscopic measurable residue. Residual ill-defined areas of high density on CT-scan, or residual signal abnormalities on MR such as low intensity on T1WI, high intensity on T2WI and ill-defined margins of enhancement areas are commonly observed after chemotherapy. If no measurable mass, these may be regarded as post-therapeutic residue, and should not exclude the classification as CR.

Note : Relationship between change in diameter, product and volume (from [22])

	Diameter ($2r$)	Product $[(2r)^2]$	Volume $(4/3\pi r^3)$
Response	Decrease	Decrease	Decrease
	30%	50%	65%
	50%	75%	87%
Disease progression	Increase	Increase	Increase
	12%	25%	40%
	20%	44%	73%
	25%	56%	95%
	30%	69%	120%

6. Investigations at the end of treatment
Chest X-ray
initial location : CT or MR (and US for abdominal primaries)

7. Follow-up after the end of treatment

First year :
Every 3 months: Chest X-ray, initial location CT or MR

Note : using MR, T2-weighted and post-contrast T1-weighted sequences are of important predictive values for local relapse depiction [27]

2nd and 3rd year :

Every 4 months : Chest X-ray, initial location CT or MR

4th and 5th years :

Every 6 months: Chest X-ray, initial location CT or MR or US

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EpSSG NRSTS 2005 Protocol : Pathology guidelines

1. GENERAL REMARKS

Role of the pathologist in a participating centre:

The local pathologist has an essential role in both the clinical trial and the prospective study.
The correct histopathological classification is crucial for the appropriate treatment of patients

1. The diagnosis of Soft Tissue Sarcoma (STS) and subtyping is made by the local pathologist.

2. The local pathologist needs to consider the appropriate handling and triage for diagnosis, assessment of prognosis, determination of pathologic stage, and the assessment of therapeutic response.

3. The pathologist needs to liaise with the molecular biology laboratories so that appropriate molecular diagnostics are carried out.

4. The local pathologist has a key role in coordinating tissue banking.

5. Material needs to be sent to the national coordinator as soon as possible following biopsy or resection.

The national coordinators and the E*p*SSG panel of pathologists are willing to offer real time review for all STS. In cases where there is a discrepancy between the local pathology diagnosis and the molecular diagnostic result, rapid central review is mandatory.

2. CLASSIFICATION AND DIAGNOSIS OF SOFT TISSUE SARCOMAS

This is not meant to be a conprehensive review.
For full description refer to the following texts:
1. Soft Tissue Tumours, Enzinger & Weiss, 4th. Edition.
2. Diagnostic Soft Tissue Pathology, Markku Miettinen
3. Pathology and Genetics. Tumours of Soft Tissue and Bone. WHO Classification of Tumours.

Soft Tissue Tumours are a diverse group of benign, malignant and borderline malignant (intermediate malignant) tumours. Most of them arise from, or show differentiation towards, mesenchymal cells, but some are of neuroectodermal, epithelial or haematolymphatic origin. The accepted basis for soft tissue tumour classification is the World Health Organisation.

2.1. WHO Classification of Soft Tissue Tumours

(from the Working Group of the Editorial and Consensus Conference, Lyon, France, April 24-28, 2002)

ADIPOCYTIC TUMOURS

Benign
Lipoma
Lipomatosis
Lipomatosis of nerve
Lipoblastoma / Lipoblastomatosis
Angiolipoma
Myolipoma
Chondroid lipoma
Extrarenal angiomyolipoma
Extra-adrenal myelolipoma
Spindle cell / Pleomorphic lipoma
Hibernoma

Intermediate
Atypical lipomatous tumour / Well differentiated liposarcoma

Malignant
Dedifferentiated liposarcoma
Myxoid liposarcoma
Round cell liposarcoma
Pleomorphic liposarcoma
Mixed-type liposarcoma
Liposarcoma, not otherwise specified

FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS

Benign
Nodular fasciitis
Proliferative fasciitis
Proliferative myositis
Myositis ossificans
Fibro-osseous pseudotumour of digits
Ischaemic fasciitis
Elastofibroma
Fibrous hamartoma of infancy
Myofibroma / Myofibromatosis
Fibromatosis colli
Juvenile hyaline fibromatosis
Inclusion body fibromatosis
Fibroma of tendon sheath
Desmoplastic fibroblastoma
Mammary-type myofibroblastoma
Calcifying aponeurotic fibroma
Angiomyofibroblastoma
Cellular angiofibroma
Nuchal-type fibroma

Gardner fibroma
Calcifying fibrous tumour
Giant cell angiofibroma

Intermediate (locally aggressive)
Superficial fibromatoses (palmar / plantar)
Desmoid-type fibromatoses
Lipofibromatosis

Intermediate (rarely metastasizing)
Solitary fibrous tumour and haemangiopericytoma (incl. lipomatous haemangiopericytoma)
Inflammatory myofibroblastic tumour
Low grade myofibroblastic sarcoma
Myxoinflammatory fibroblastic sarcoma
Infantile fibrosarcoma

Malignant
Adult fibrosarcoma
Myxofibrosarcoma
Low grade fibromyxoid sarcoma / hyalinizing spindle cell tumour
Sclerosing epithelioid fibrosarcoma

SO-CALLED FIBROHISTIOCYTIC TUMOURS

Benign
Giant cell tumour of tendon sheath
Diffuse-type giant cell tumour
Deep benign fibrous histiocytoma

Intermediate (rarely metastasizing)
Plexiform fibrohistiocytic tumour
Giant cell tumour of soft tissues

Malignant
Pleomorphic 'MFH' / Undifferentiated pleomorphic sarcoma
Giant cell 'MFH' / Undifferentiated pleomorphic sarcoma with giant cell
Inflammatory 'MFH' / Undifferentiated pleomorphic sarcoma with prominent inflammation

SMOOTH MUSCLE TUMOURS

Benign
Angioleiomyoma
Deep leiomyoma
Genital leiomyoma

Malignant
Leiomyosarcoma

PERICYTIC (PERIVASCULAR) TUMOURS

Benign
Glomus tumour (and variants)

Intermediate
Myopericytoma

Malignant
Malignant glomus tumour

SKELETAL MUSCLE TUMOURS

Benign
Rhabdomyoma (adult type, fetal type, genital type)

Malignant
Embryonal rhabdomyosarcoma (incl. spindle cell, botryoid, anaplastic)
Alveolar rhabdomyosarcoma (incl. solid, anaplastic)
Pleomorphic rhabdomyosarcoma

VASCULAR TUMOURS

Benign
Haemangiomas (of subcut/deep soft tissue, capillary, cavernous, arteriovenous, venous, intramuscular, synovial)
Epithelioid haemangioma
Angiomatosis
Lymphangioma

Intermediate (locally aggressive)
Kaposiform haemangioendothelioma

Intermediate (rarely metastasizing)
Retiform haemangioendothelioma
Papillary intralymphatic angioendothelioma
Composite haemangioendothelioma
Kaposi sarcoma

Malignant
Epithelioid haemangioendothelioma
Angiosarcoma of soft tissue

CHONDRO-OSSEUS TUMOURS

Benign
Soft tissue chondroma

Malignant
Mesenchymal chondrosarcoma
Extraskeletal osteosarcoma

TUMOURS OF UNCERTAIN DIFFERENTIATION

Benign
Intramuscular myxoma (incl. cellular variant)
Juxta-articular myxoma
Deep (‘aggressive’) angiomyxoma
Pleomorphic hyalinizing angiectatic tumour
Ectopic hamartomatous thymoma

Intermediate (rarely metastasizing)
Angiomatoid fibrous histiocytoma
Ossifying fibromyxoid tumour (incl. atypical / malignant)
Mixed tumour / Myoepithelioma / Parachordoma

Malignant
Synovial sarcoma

Epithelioid sarcoma
Alveolar soft part sarcoma
Clear cell sarcoma of soft tissue
Extraskeletal myxoid chondrosarcoma ("chordoid" type)
Extraskeletal Ewing tumour / pPNET
Desmoplastic small round cell tumour
Extra-renal rhabdoid tumour
Malignant mesenchymoma
Neoplasms with perivascular epithelioid cell differentiation (PEComa) / clear cell myomelanocytic tumour
Intimal sarcoma.

2.2. HISTOTYPES

The following is a brief review of the most common and sometimes challenging soft tissue sarcomas.

Synovial sarcoma

These tumours account for 5-10% of soft tissue sarcomas and 42% of paediatric non-rhabdomyosarcoma soft tissue sarcomas. 85-95% of all synovial sarcomas arise in the extremities with the second most common site being the head and neck region. Synovial sarcomas also arise in the trunk including the chest wall and abdominal wall. However, synovial sarcomas have been described at virtually every anatomic site including the skin, heart, kidney and lung. The peak incidence is in the second decade.

In its classical form synovial sarcoma is biphasic and consists of clearly distinguishable spindle cell and epithelial or glandular areas. Monophasic either spindle or epithelial patterns are recognised. Poorly differentiated synovial sarcomas may have a spindle cell appearance or a round/oval cell pattern that mimics other 'small blue cell neoplasms'.

The diagnosis of biphasic synovial sarcoma does not pose a problem, but the diagnostic challenges increase when dealing with the monophasic spectrum and poorly differentiated subtypes and in limited biopsy material. The immunohistochemistry profile does overlap with malignant peripheral nerve sheath tumour and primitive neuroectodermal tumour.

The spindle cell component of synovial sarcoma can be immunoreactive for CD57, CD56, S100, Cytokeratin and Epithelial Membrane Antigen (EMA). The epithelial or glandular areas are immunoreactive for high and low weight Cytokeratin and EMA. As some synovial sarcomas stain for EMA but not Cytokeratin and vice versa, both markers should be used. In some monophasic synovial sarcomas it may be necessary to stain multiple sections for those markers. CD99 can be detected in the cytoplasm or membrane of cells in 60-70% of synovial sarcomas and bcl-2 protein has been reported in 75-100% of cases.

Synovial sarcoma is characterised by a translocation t(X;18)(p11.2; q11.2) which is found in more than 90% of cases. There are three possible transcripts, SYT-SSX1, SYT-SSX2 and SYT-SSX4. The SYT-SSX2 has been recently associated with better survival.

Malignant peripheral nerve sheath tumour (MPNST)

This diagnosis has always been regarded as 'difficult' due to the lack of standardised diagnostic criteria. However, it is now considered essential that one of the following criteria is met:

a. the tumour arises from a peripheral nerve

b. arises in a pre-existing benign nerve sheath tumour, usually a neurofibroma, or in connection with NF1.

c. the tumour shows histologic features that are seen in the above tumours and reflects schwann cell differentiation.

The tumour occurs in all ages from early childhood but is most common in middle age. Grossly the tumour has an oval or fusiform mass arising from a nerve and usually measures more than 10 cm. Histologically, MPNSTs are high-grade tumours with high mitotic rate and necrosis. A number of patterns are recognised, the most common being a high-grade fibro-sarcomatous pattern. Many tumours have large irregular areas of necrosis and vascular proliferation, the tumour cells forming perivascular collars. Few cases of MPNST show extensive S100 positivity, many show focal positivity. The presence of desmin or actin usually reflects the presence of heterologous rhabdomyoblastic differentiation (Triton tumour). Focal Keratin K8 and K18 positivity is quite common, but K7 and K19 are absent. Considering that synovial sarcoma can also be S100 protein positive, immunohistochemical results need to be interpreted with caution and molecular diagnostics are useful in the differential diagnosis.

Alveolar soft part sarcoma

This sarcoma has a female preponderance occurring in the first two decades of life but also in children. When the tumour occurs in infants and children it is often located in the region of the head and neck, especially the orbit and tongue.

The histologic features are distinctive. The immunohistochemical profile is non-specific with variable reactivity for Vimentin, Desmin and S100 protein. A non-balanced translocation, t(x;17), has been described. The differential diagnosis includes alveolar RMS, epithelioid, paraganglioma and adenocarcinoma.

Malignant rhabdoid tumour of soft tissues

This tumour, first described in the kidney, has also been reported in the central nervous system, soft tissues, skin and other sites. This disgnosis should only be made in tumours in which there is a predominant rhabdoid morphology and in which no other morphologic evidence of differentiation is seen. These tumours are more common in children. Congenital disseminated malignant rhabdoid tumour with cutaneous involvement and abnormalities of chromosome 22q11 has been reported in infants. The immunohistochemical profile is polyphenotypic with both mesenchymal and epithelial features characterised by reactivity for Vimentin, Cytokeratin, EMA, NSE, S100, CD99, CD34 and Synaptophysin. The hSNF5/INI 1 gene has been reported to be mutated in rhabdoid tumours.

Desmoplastic small round cell tumour (DSRCT)

This tumour primarily affects children and young adults, usually presenting with widespread abdominal involvement, frequently located in the retroperitoneum, pelvis, omentum and mesentery. It does occur in thoracic cavity and paratesticular sites.

The microscopic appearance is characteristic with nests of undifferentiated tumour cells surrounded by abundant fibrous stroma. The following features have been observed in some tumours:

- Central necrosis of large tumour nests.
- Cords of cells surrounded by dense fibrous stroma.
- Rhabdoid-like foci.
- Cells with signet ring-like appearance

Other unusual features include Homer-Wright-like rosettes, papillary areas, transitional carcinoma-like areas and spindle cell areas. Virtually all tumours stain for EMA and Cytokeratin (CK20, CK5 & 6 are negative) and Vimentin. Up to 90% of cases are positive for Desmin with a perinuclear dot-like pattern. Myogenin and MyoD1 are negative. CD99 and NB84a may be positive. WT1 is often expressed as strong nuclear positivity. SCDT is defined by a reciprocal translocation t(11;22)(p13;q12). Occasional cases that clinically and phenotypically appear to be SCDT show the Ewing's sarcoma phenotype Fli-1/EWS.

Congenital Infantile Fibrosarcoma (CIFS)

These tumours usually occur in the distal extremities and the head and neck, mostly diagnosed in the first year of life, some are congenital. The histologic appearance simulates adult-type fibrosarcoma, but the natural history is more like the fibromatosis, with a five-year survival of more than 90% and a recurrence rate of approximately 30%. Metastases are very rare.

These are spindle cell tumours, mitotically very active with interlacing cords, fascicles and even a herring-bone pattern. Collagen formation is common but some cases with a round cell component may have minimal collagen. Focal necrosis, haemangiopericytomatous pattern, focal extramedullary haematopoiesis and a patchy mononuclear inflammatory cell infiltrate have all been described. A chromosomal translocation t(12;15)(p13;q26) have been identified in these cases. Trisomies for chromosomes 8, 11, 17 and 20 are nearly as characteristic as the translocation. This genetic profile is similar to that described in congenital mesoblastic nephroma.

Fibroblastic-Myofibroblastic Proliferations of Childhood and Adolescence

These are an important group of lesions in childhood and adolescence. Diagnostically they can be challenging because of their histologic similarities.

Inflammatory Myofibroblastic Tumour (IMT)

This is a pseudosarcomatous lesion that occurs in the viscera and soft tissue of children and young adults. These lesions are lobular or multinodular with a hard cut surface. The tumours range from 2 to 20 cm. Histologically they are composed of spindle or stellate shaped cells in a myxoid or hyaline stroma with scattered inflammatory cells. Some are composed of spindle cells arranged in a more storiform or fascicular growth pattern. Mitotic figures are present but are not atypical. A prominent lymphoplasmacytic infiltrate is usually present. In some lesions there is a pronounced cytologic atypia with spindle cells having large nuclei and distinct nucleoli.

Immunophenotypes of these lesions include diffuse staining for vimentin, muscle actin, and focally for desmin and smooth muscle actin. There is focal cytokeratin positivity in about one third of

cases. CD68 is seen in 25% of cases. The lesions are always negative for myoglobin and S-100 protein. A number of intra-abdominal inflammatory tumours show immunohistochemical expression of ALK.

The differential diagnoses include nodular fasciitis, rhabdomyosarcoma and myxoid sarcoma. The more cellular variants of IMT simulate fibrohistiocytic neoplasms, fibromatosis and gastrointestinal stromal tumour.

Desmoid-Type Fibromatosis (Aggressive Fibromatosis)

Desmoid is subclassified by location into abdominal wall, extra-abdominal and mesenteric forms. These lesions vary greatly in size from a small nodule to bulky tumours. They can measure between 3 to 20 cm.

Microscopically they show longitudinally orientated fascicles of spindle fibroblasts and myofibroblasts in a collagenous stroma. This stroma may contain thick keloid-like collagen fibres. The nuclei are oval with delicate nucleoli. Mitotic activity is typically low. The lesions have a prominent, evenly spaced, vascular pattern with ectatic vessels. These tumours may be focally positive for smooth muscle actin and desmin.

The differential diagnoses include nodular fasciitis; this is usually an issue when assessing small biopsies. The lack of lymphohistioctytic infiltrate and the presence of gaping vessels support the diagnosis of desmoid.

The highly cellular lesions, especially those with mitotic activity, have to be separated from fibrosarcoma.

Leiomyosarcoma

These tumours very rarely occur in children; commonly in immuno-suppressed patients. Most of these tumours in immuno-competent children tend to be of low grade with good prognoses. They are spindle cell lesions with longitudinally orientated tumour cells, 'cigar-shaped' nuclei and eosinophilic cytoplasm. Some tumours have a myxoid stroma. Although focal pleomorphism is common, some cases show extensive pleomorphism. In some leiomyosarcomas there are foci of osteoclast giant cells and some tumours have cells with granular cytoplasm.

Immunohistochemically, they are positive for smooth muscle actin. Desmin positivity varies. Heavy caldesmon is smooth muscle specific. Some keratins (especially 8 & 18) and EMA are sometimes expressed in these tumours.

Ewing Sarcoma/PNET

These tumours are not being treated in these protocols. However, the differential diagnosis of these tumours includes numerous small round cell tumours. Within the context of soft tissue tumours, rhabdomyosarcoma, especially the alveolar subtype, desmoplastic small cell tumour, myxoid or mesenchymal chondrosarcoma, small cell variant (undifferentiated) synovial sarcoma and malignant rhabdoid tumour need to be considered.

3. IMMUNOHISTOCHEMISTRY

The following list of antibodies is useful when used in 'Panels' in the differential diagnosis of soft tissue sarcomas.

MARKERS

CD31	Angiosarcoma, Kaposi Sarcoma
CD34	Kaposi Sarcoma, fibroblastic and other tumours
Fli-1	Ewing's Sarcoma, Angiosarcoma
CD99	Ewing's Sarcoma, Synovial Sarcoma, Lymphoma
Smooth Muscle Actin	Smooth muscle and myofibroblastic tumours.
Common Muscle Actin HHF35	Smooth and skeletal muscle tumours and myofibroblastic tumours.
Sarcomerin	Skeletal muscle and RMS.
Desmin	Smooth and skeletal muscle tumours and some others.
Calponin	Smooth muscle, myofibroblasts, myoepithelial., Synovial sarcoma (often).
MyoD1	Rhabdomyosarcoma.
Myf 4	Rhabdomyosarcoma.
Synaptophysin	Neuroblastoma, Paraganglioma. Neuroendocrine carcinoma.
Chromogranin	Paraganglioma, Neuroendocrine carcinoma.
NF protein	Neuroblastoma, Paraganglioma, Merkel Cell Ca.
S100 protein	Melanocytic, Schwannomas, Chondroid, Langerhans cell.
CD56 (NCAM)	Neuroendocrine Ca., RMS, many other sarcomas.
HMB45	Melanoma, Clear Cell Sarcoma, Angiomyolipoma.
Melan A	Naevi, Melanoma, Angiomyolipoma
CD63	Melanoma, Alveolar Soft Part Sarcoma.

Lysozyme	Histiocytes, Myelomonocytic cells.
AAT	Histiocytes, many tumours of any lineage.
AACT	Histiocytes, many tumours of any lineage.
CD68	Histiocytes, Melanoma, Paraganglioma, Schwannoma, Granular cell tumour.
Keratins	Synovial and Epithelioid Sarcomas, Carcinomas, Chordoma, Metastatic Melanoma.
EMA	Synovial Sarcoma, Epithelial Sarcomas, Perineural tumours, and epithelial tumours in general.
WT protein	DSRCT, Mesothelioma, Ovarian Serous Carcinoma And other tumours.
ALK 1	Anaplastic lymphomas, Inflammatory myofibroblastic tumours.
CD10	Endometrial stromal sarcoma.
CD117 (C-Kit)	GI stromal tumours, Mast cell neoplasms, Ewing's Sarcoma, Neuroblastoma, Seminoma/Dysgerminoma, Clear Cell Sarcoma, Adenoid Cystic Carcinoma and some other carcinomas.
GFAP	Glial tumours, Schwannomas, Myoepithelial tumours.

4. COMMON TRANSLOCATIONS IN SOFT TISSUE SARCOMAS

Histological classification	*Translocated Chromosomes*	*Genes Fused*
ALVEOLAR RHABDOMYOSARCOMA	t(2;13)(q35;q14) t(1;13)p36;q14)	PAX3/FKHR PAX7/FKHR
EWING'S/PNET	t(11;22)(q24;q12) t(21;22)(q22;q12) t(17;22)(q12;q12) t(7;22)(p22;q12)	FLI1/EWS ERG/EWS E1AF/EWS ETV1/EWS
DSRCT	t(11;22)(p13;q12)	WT1/EWS
MYELOID LEUKAEMIA	t(16;21)	TLS/ERG
MYXOID LIPOSARCOMA	t(12;16)(q13;p11)	CHOP/TLS
MALIGNANT MELANOMA OF SOFT PARTS (CLEAR CELL SARCOMA)	t(12;22)(q13;q12)	ATF1/EWS
MYXOID CHONDROSARCOMA	t(9;22)(q22;q12) t(9;15)(q22;21)	CHN/EWS CHN/TFC12
CONGENITAL FIBROSARCOMA/CONGEN. MESOBLASTIC NEPHROMA	t(12;15)(p13;q25)	ETVG(TEL)/NTRK3
ALVEOLAR SOFT PART SARCOMA	t(X;17)(p11;q25)	TFE3/ASPL
SYNOVIAL SARCOMA	t(X;18)(p11;q11)	SYT/SSX1 SYT/SSX2 SYT/SSX4
INFLAMMATORY MYOFIBROBLASTIC TUMOUR	t(1;2)(q25;p23) t(2;19)(p23;q13)	TPM3/ALK ALK/TPM4
DERMATOFIBROSARCOMA PROTUBERANS	t(2;17)(p23;q23) t(17;22)(q22;q13)	ALK/CLTC COL1A1/PDGFB
ENDOMETRIAL STROMAL SARCOMA	t(7;17)(p15;q21)	JAZF1/JJAZ1

5. THE GRADING OF NRSTS

The grading of NRSTS represents one of the most debated and complex subjects concerning the information that the pathologist must give to the clinician.

The grade of malignancy usually describes the aggressiveness of the tumour and its natural history. It is determined by a combined assessment of histological features 1) degree of cellularity, 2) cellular pleomorphism or anaplasia, 3) mitotic activity, 4) degree of necrosis. Generally, low grade tumours usually have local aggressiveness but low tendency to metastatic spread. High grade tumours are more frequent and have a more invasive behaviour with high propensity to metastatise. Some histotypes (i.e. synovial sarcoma, alveolar sarcoma, angiosarcoma) should be considered as high grade independently from mitotic index, necrosis and cellularity.

Different grading systems (generally three-grade systems) have been defined over the years by paediatric and adult oncologists for predicting clinical course and prognosis, and defining a risk-adapted treatment. Unfortunately, a universally accepted grading system does not exist. The most used grading systems (POG System for paediatric sarcomas and FFCLCC System for adult sarcomas) suffer from many limitations due to their low reproducibility and the high rate of error. Furthermore recent advances in classification of some entities such as infantile hemangiopericytoma, now included in the group of myofibroma-myofibromatosis, are not taken into account in the POG classification.

The application of any grading system must take into account the following considerations:

- Grading should be used only in pre-treatment tumours
- Samples must be well preserved and representative of the whole lesion.. Tru-cut biopsies represent a limitation and can give only a "minimum" grade due to sampling.
- Grading must be applied only after a precise diagnosis of histotype. The grading cannot be used instead of a correct diagnosis of histotype. In fact for some histotypes the diagnosis *per se* identifies an high grade neoplasia and does not need further grading. Other sarcomas (such as Epithelioid sarcoma, Alveolar soft part sarcoma, Clear cell sarcoma, Angiosarcoma, extraskeletal myxoid chondrosarcoma) have a biological course not predictable by any morphological parameter evaluated by the classic grading systems.

For the purpose of this study both the POG and the FNCLCC grading systems will be evaluated.

►► **For patient stratification, the FNCLCC grading system will be used**.

POG (Pediatric Oncology Group) *(Parham et al. Modern Pathol 1995;8:705-710)*

3 grades based on histopathologic subtype, amount of necrosis, number of mitoses, and cellular pleomorphism

grade 1
- myxoid and well-differentiated liposarcoma
- well-differentiated or infantile (age < 4 yrs) fibrosarcoma
- well-differentiated or infantile (age < 4 yrs) hemangiopericytoma
- well-differentiated malignant peripheral nerve sheath tumour
- angiomatoid malignant fibrous histiocytoma
- deep seated dermatofibrosarcoma protuberans
- myxoid chondrosarcoma

grade 2
- soft tissue sarcomas in which:
  - <15% of the surface area shows necrosis
  - mitotic count < 5/10 high power fields using a 40x objective
  - nuclear atypia not marked
  - tumour not markedly cellular

grade 3
- pleomorphic or round cell liposarcoma
- mesenchymal chondrosarcoma
- extraskeletal osteogenic sarcoma
- malignant triton tumour
- alveolar soft part sarcoma
- any other sarcoma not in grade 1, with > 15% necrosis, or > 5 mitoses/10 HPF using a 40x

FNCLCC (French Federation of Cancer Centers Sarcoma Group)
(Guillou et al. J Clin Oncol 1997;15:350-362)

- **Differentiation**

1 – well-differentiated liposarcoma, well-differentiated fibrosarcoma, well-differentiated malignant schwannoma, well-differentiated leiomyosarcoma, well-differentiated chondrosarcoma

2 – myxoid liposarcoma, conventional fibrosarcoma, conventional malignant schwannoma, well-differentiated malignant hemangiopericytoma, myxoid malignant fibrous histiocytoma, pleomorphic malignant fibrous histiocytoma, conventional leiomyosarcoma, myxoid chondrosarcoma, conventional angiosarcoma

3 – round-cell liposarcoma, pleomorphic liposarcoma, dedifferentiated liposarcoma, poorly differentiated fibrosarcoma, poorly differentiated malignant schwannoma, epithelioid malignant schwannoma, malignant triton tumour, conventional malignant hemangiopericytoma, giant cell and inflammatory malignant fibrous histiocytoma, poorly differentiated/pleomorphic/epithelioid leiomyosarcoma, synovial sarcoma, rhabdomyosarcoma, mesenchimal chondrosarcoma, poorly differentiated/epithelioid angiosarcoma, extraskeletal osteosarcoma, Ewing's sarcoma/pPNET, alveolar soft tissue sarcoma, epithelioid sarcoma, malignant rhabdoid tumour, clear cell sarcoma, undifferentiated sarcoma

- **Mitotic index**

1 (0-9 mitoses per 10 HPF)
2 (10-19)
3 (>19)

- **Tumoural necrosis**

0 – no necrosis on any examined slides
1 <50% of necrosis
2 >50% of necrosis

grade 1 – score 2-3
grade 2 – score 4-5
grade 3 – score 6-8

6. HANDLING OF SPECIMENS

The type of surgical procedure influences the handling of the specimen and the extent of information that can be gained from its pathological examination.

Important **- Please note, specimens should be received fresh in the laboratory. It is important that the surgeon/oncologist liaises with the pathologist to ensure that fresh specimens can be received fresh in the laboratory.**

Biopsy

Open biopsy is recommended to ensure sufficient material is available for:

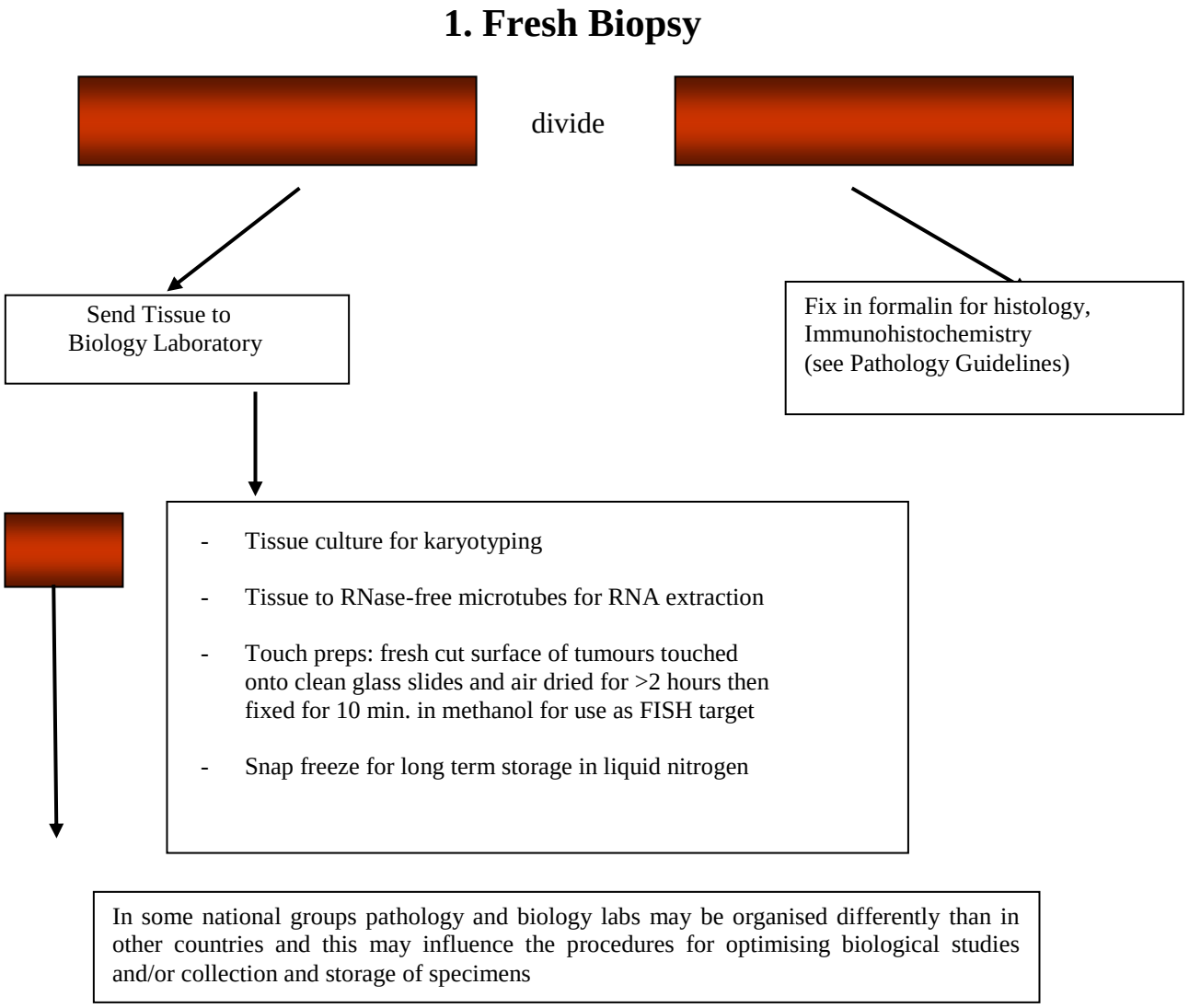
1. Diagnosis
2. Molecular characterisation/research (see schematic diagram)

Resected Specimens (read surgical guidelines for definition of primary resection - primary re-operation - secondary operation)

All primary and post-chemotherapy resection specimens need margins to be evaluated by the pathologist.

- Surface of specimen should be inked before incision.
- Specimen should be weighed and measured (in 3 dimensions).
- Orientation of specimen is important – this may need to be done with the surgeon. The distance of tumour from the minimum nearest resection margin is important. In resected specimens tumour depth e.g. dermal, subcutaneous, subfascial, intramuscular, needs to be specified macroscopically and microscopically.
- Ideally the specimen should be photographed, including the cut surface, and a block guide prepared.
- At least a block per centimetre of greatest tumour diameter needs to be sampled. However, it is strongly recommended that, where feasible, the entire specimen should be processed to ensure adequacy of excision, and in post-chemotherapy specimens to assess percentage of necrosis.
- The cut surface(s) should be examined and the pathologist should sample as above as well as taking blocks from areas which look macroscopically different in consistency or texture from other areas, in particular take note of nodularity and sample.
- Document macroscopic % of necrosis – sample areas of necrosis.
- The pathologist should assess what tissue has been kept for molecular diagnostics/research. This can be done in one of two ways, either A – do a frozen section from the cut surface to assess i) tumour is present and ii) tumour is not necrotic, or B – a paraffin section, identified as representative section of tissue sent for molecular diagnostics/research can be taken and assessed as per frozen section.
- Lymph nodes - please note – site of lymph nodes sampled should be documented as this is important in staging. All lymph nodes received by the pathologist should be examined. The entire lymph node or lymph nodes should be processed to ensure accurate assessment. Multiple levels need to be examined to exclude micro metastases.
- Molecular characterisation (see schematic diagram)

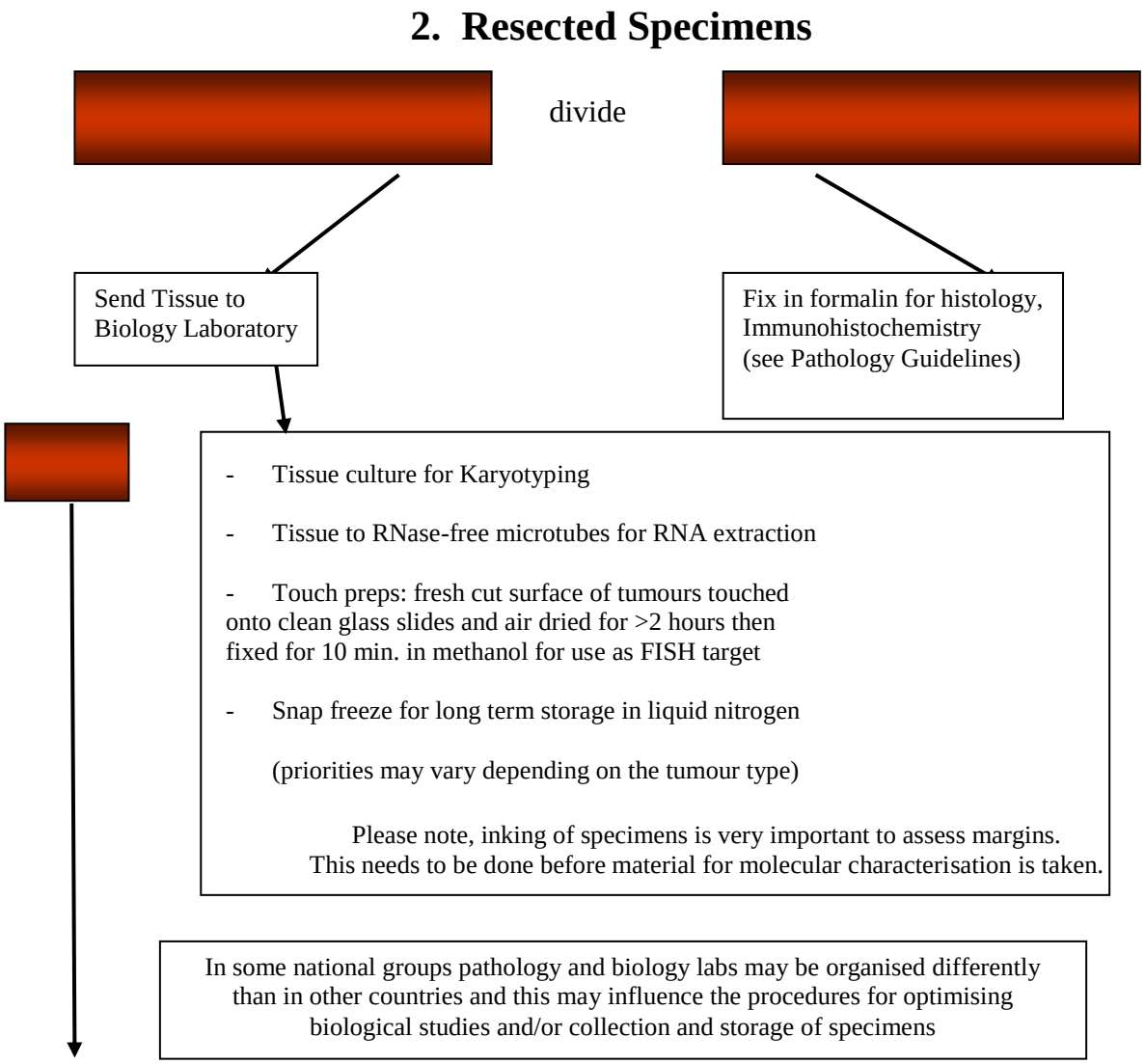
6.1. HANDLING OF SPECIMENS



NB: The pathologist needs to document what tissue has been sent for molecular diagnostic/research.
The pathologist should be informed by the oncologist if consent has been obtained for storage of material for research. We strongly recommend that each centre has a system set up whereby the pathologist is informed in writing that consent has been given. It is up to individual centres to ensure that this is taking place. We also strongly recommend that consent is obtained prospectively and not retrospectively.

In most cases the pathologists will receive biopsy material. It is important that such specimens are received fresh, promptly in the laboratory and handled only by pathologists who will decide on how the specimen can be divided. Please note treatment depends on good histological diagnosis and therefore this should not be compromised for molecular studies. This, however, is at the discretion of the local pathologists.

6.2. HANDLING OF SPECIMENS



NB: The pathologist needs to document what tissue has been sent for molecular diagnostic/research. See item 8 under handling of specimens.
The pathologist should be informed by the oncologist if consent has been obtained for storage of material for research. We <u>strongly recommend</u> that each centre has a system set up whereby the <u>pathologist is informed</u> <u>in writing</u> that consent has been given. It is up to individual centres to ensure that this is taking place. We also strongly recommend that consent is obtained <u>prospectively and not retrospectively</u>.

In resected specimens, inking of the surface, with photograph and documentation of blocks taken will be necessary. Please note treatment depends on good histological diagnosis and therefore this should not be compromised for molecular studies. This, however, is at the discretion of the local pathologists.

HANDLING OF SPECIMENS

3. AMPUTATION OR DISARTICULATION FOR SOFT TISSUE SARCOMAS

PROCEDURE INCLUDES:

Macroscopy

1. Review radiological investigations if available.
2. Measure and describe limb (include measurement between major joints).
3. Measure circumference at level of tumour.
4. Examine skin surface for presence of tumour.
5. Orientate the specimen and cut through the centre of the specimen coronally, saggitally or transversely to give the largest surface area.
6. Measure and describe the tumour with special reference to:
    - Size
    - Encapsulation
    - Colour
    - Consistency
    - Necrosis (estimate %)
    - Gross margins (measured in mm.). Note distance of tumour from the amputation margins.
      Assess involvement of the compartments i.e. muscle groups/fascia etc.
    - Satellite lesions
7. Photograph the cut specimens.
8. Cut perpendicular to original cut noting appearance and closest margins.

Blocks for Histology

1. Take blocks of vessels at amputation margin and sample any lymph nodes present.
2. Sample and record position of closetst margin (minimum of posterior, anterior, lateral and medial)
3. Sample tumour including necrotic areas (one block per cm. of tumour)
4. Sample skin to include biopsy tract.
5. Sample neurovascular tissues if present.

Wide Resections – Please note the above descriptions can also be used when dealing with wide resections. In these cases it is extremely important to assess margins macroscopically and microscopically.

7. THE PATHOLOGY REPORT

The following need to be included:

►Macroscopic

Specimen type

Biopsy – excision or trucut – please state
Primary resection
Primary re-operation
Secondary operation (post-chemotherapy)

Specimen site

Head/neck
Bladder/prostate
Genitourinary (not bladder/prostate)
Cranial
Extremity
Orbit
Parameningeal
Other- specify (include trunk, retroperitoneum etc.)
Not specified

Laterality (as appropriate)

Tumour size

Three dimensions – specify maximum diameter

►Microscopic

Histologic type

Example: Congenital infantile fibrosarcoma
Synovial sarcoma – biphasic
Synovial sarcoma – monophasic
Alveolar soft part sarcoma

Sarcoma, not otherwise specified (NOS). Please note this is not a diagnostic group. It indicates that a specific diagnosis cannot be made. This usually arises when the biopsy is very small, but the pathologist can exclude other tumours.

Necrosis

Absent
Present
Extent %

Mitotic rate

(x40 objective)
-/10 high power fields

Regional lymph nodes

None sampled
No regional lymph node metastases
Regional lymph node metastases – specify:
Site of lymph node
Number examined
Number involved

Margins

Cannot be assessed
No tumour at margins – please give distance of sarcoma to nearest margin in mm.
Margins involved by sarcoma – specify.

Note:
see the definitions R0, R1 and R2 surgery and the definition of margins given in the "Surgical section" (*> 1 cm of healthy tissue around the tumour in all directions (when the tissue is a muscle), > 1 mm of healthy tissue around the tumour when the tissue is periostium, vessel sheath, epineurium, muscular fascia)*.

Venous/lymphatic invasion

Present
Absent
Cannot be assessed

Grading of Soft Tissue Sarcoma

Use FNCLCC system

Molecular characterisation

Please note: if molecular characterisation has been undertaken, then this should either be included in the main body of the report or set out as a separate report. A copy of this report needs to be sent to the national coordinator together with the copy of the histology report and form.

Post-chemotherapy specimens

Same procedure as above. It is important to specift the following:
% of necrosis
% of fibrosis
% of viable tumour

8. MATERIAL TO BE SENT TO NATIONAL CO-ORDINATORS

1. In the case of **trucut biopsies**, both primary and post-chemotherapy, **1 H&E** and **15uss** (or the loan of the block).

2. In the case of **open biopsies/resected specimens**, including post-chemotherapy specimens – **1 H&E** from each block, and at least **20 uss** from representative block(s) (or the loan of the blocks).

3. The uss should be on coated slides to be used for immunohistochemistry.

4. It is important that material from primary biopsy/resection and post-chemotherapy biopsy/resection and biopsy/resection of metastases is sent for review by the local co-ordinator.

5. If in the case of a very small biopsy there is not sufficient material left in the block, please send **1 H&E** to be kept by the local co-ordinator and the original H&E and immunohistochemistry slides, which will be returned.

6. It is understandable that these requests create more work for the pathologist and laboratory staff. Therefore, it is possible to send blocks to the local co-ordinator. These will be returned.

7. The local pathologist report and the form need to be sent with the slides.

8. The national co-ordinators and panel of pathologists are offering real time review.

9. The slides/block and forms should be sent directly to the national co-ordinators.

NB: It is very important that we collect prospectively the results of the molecular diagnostics. Each oncology centre/pathology lab. should ensure that, if this cannot be carried out in their centre/lab., arrangements should be made with other laboratories to ensure that, whenever possible, molecular diagnostics are carried out.

In cases where there is a discrepancy between the local pathologist's evaluation and the molecular diagnostic result, then rapid pathology review is recommended. All results will be sent to the referring pathologist and in case of discrepancy cases will be discussed with the referring pathologist.

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E*p*SSG NRSTS 2005 protocol: Biological aspects

BIOLOGICAL CHARACTERIZATION OF PAEDIATRIC NON-RHABDOSARCOMA SOFT TISSUE SARCOMAS

General considerations.

The knowledge of biological phenomena involved in solid tumours is becoming increasingly relevant for the understanding of the behaviour of a variety of cancers. This, together with the availability of recent powerful technologies and new reagents for cellular and molecular biology studies, makes the field of sarcoma biology particularly attractive and challenging.

Recent molecular studies have contributed to an expanding list of genetic abnormalities in pAediatric solid tumours, including chromosomal translocations and inversions, amplification of proto onco-genes and gene-deregulation.

The group of malignancies known as "small round cell tumours" of childhood are still a diagnostic problem due to the relative lack of differentiation of these tumours, but other less frequent entities still represent a challenge both from the diagnostic and therapeutic perspectives, as well. Among them, tumours such as desmoplastic small round cell tumour (DSRCT), synovial sarcoma (SS) and congenital infantile fibrosarcoma (CIFS) are to be considered.

Cytogenetic studies of several childhood sarcomas have identified reciprocal chromosomal translocations which correlate with specific tumour types. Molecular cloning of the translocation breakpoints has identified fusions between genes located at the breakpoints of each partner chromosome that result in the expression of chimeric oncoproteins.

From a clinical perspective, some of the genetic abnormalities represent tumour associated markers that can be used to confirm the histological diagnosis or to assess biological characteristics that may have clinical impact. Furthermore, they can be used as tumour markers to detect minimal dissemination of disease with a much higher sensitivity than standard histopathological approaches.

Common molecular targets in paediatric sarcomas

Several RT-PCR protocols were recently established to specifically detect transcripts that can be used for the identification of paediatric sarcomas. Among others, the ETV6-NTRK3 chimeric transcript is found in congenital infantile fibrosarcoma (CIFS); EWS-WT1 in desmoplastic sarcoma (DSRCT) and SYT-SSX1 and SYT-SSX2 are characteristic of synovial sarcoma (SS).

This situation has some similarity to the genetic alterations of alveolar rhabdomyosarcoma and Ewing's sarcoma family tumours, where reciprocal translocations have been well characterized.

Moreover, new molecular markers may be identified in the future that could have clinical applications and may further improve our knowledge of soft tissue sarcomas of childhood.

The table below summarizes the most frequent genetic targets that are currently used in most laboratories for the characterization of paediatric sarcomas, excluding rhabdomyosarcoma and Ewing/PNET and their association to the specific histological subtype.

Tumour	Chromosomal translocation	Transcript
SS	t(X ;18)(q11;q11) t(X ;18)(q11;q11)	SSX1-SYT SSX2-SYT
CIFS	t(12;15)(p13;q25)	ETV6-NTRK3
DSRCT	t(11;22)(q13;q12)	EWS-WT1
Liposarcoma	t(12;16)(q13 ;p11)	TLS-CHOP
Clear cell sarcoma	t(12;22)(q13;q12)	EWS-ATF1
Extraskeletal mixoid chondrosarcoma	t(9 ;22)(q22;q12)	EWS-TEC
Dermatofibroma protuberans	t(17;22)(q22;q13)	COL1A1-PDGFB

Role of biological studies in paediatric sarcomas

The new clinical trials of the European paediatric Soft Tissue Sarcoma Study Group (E*p*SSG) represent a unique opportunity to conduct prospective clinical and biological studies in the context of uniform diagnostic and therapeutic strategies. Moreover, the relatively large patient accrual in reasonable time periods, would give biologists and clinicians the possibility of translating into the clinical setting any relevant findings that may emerge from collaborative studies.

Thus, a great effort is warranted by all the national participating groups and each clinical Institution in collecting biological samples to conduct selected and potentially relevant biological studies.

A Biology Subcommittee has been created in which representatives from each national groups should participate and collaborate both in identifying specific priorities and methods to make the collaboration most fruitful and translatable into clinical relevant information as well as in collecting biological samples for further studies.

Cytogenetics

Although characteristic genetic abnormalities have been reported in specific types of sarcomas, in some cases no specific genetic tumour marker can be identified. For this reason cytogenetic analysis should be performed in any solid tumour and results should be collected prospectively: this will allow us to learn about yet unknown genetic alterations that may be associated to specific tumours or subgroups of patients and to identify recurrent complex alterations that cannot be determined by molecular methods. Cytogenetic studies are only possible on fresh tumour tissue.

FISH

Fluorescent-in-situ hybridization is a rather recent technique that, making use of specific labeled DNA fragments, can detect genetic abnormalities both with regard to gene/chromosome structure and number. By this technique specific chromosomal translocations, including reciprocal translocations of the most common paediatric sarcomas, can be identified. Amplification or loss of genetic material can also be determined. Similarly to cytogenetics, fresh tumour tissue or cells are the optimal starting material for the assay.

Reverse transcriptase polymerase chain reaction (RT-PCR) for chimeric transcripts

Cytogenetic studies of childhood sarcomas have identified chromosomal translocations associated with specific tumour types. These genetic abnormalities give rise to fusion genes that are transcribed into specific chimeric RNA that can be revealed by RT-PCR. Chimeric transcripts may thus represent tumour associated markers that can be exploited as diagnostic tools.
In most instances, the prognostic implications of the presence or absence of specific reciprocal translocations are not known.

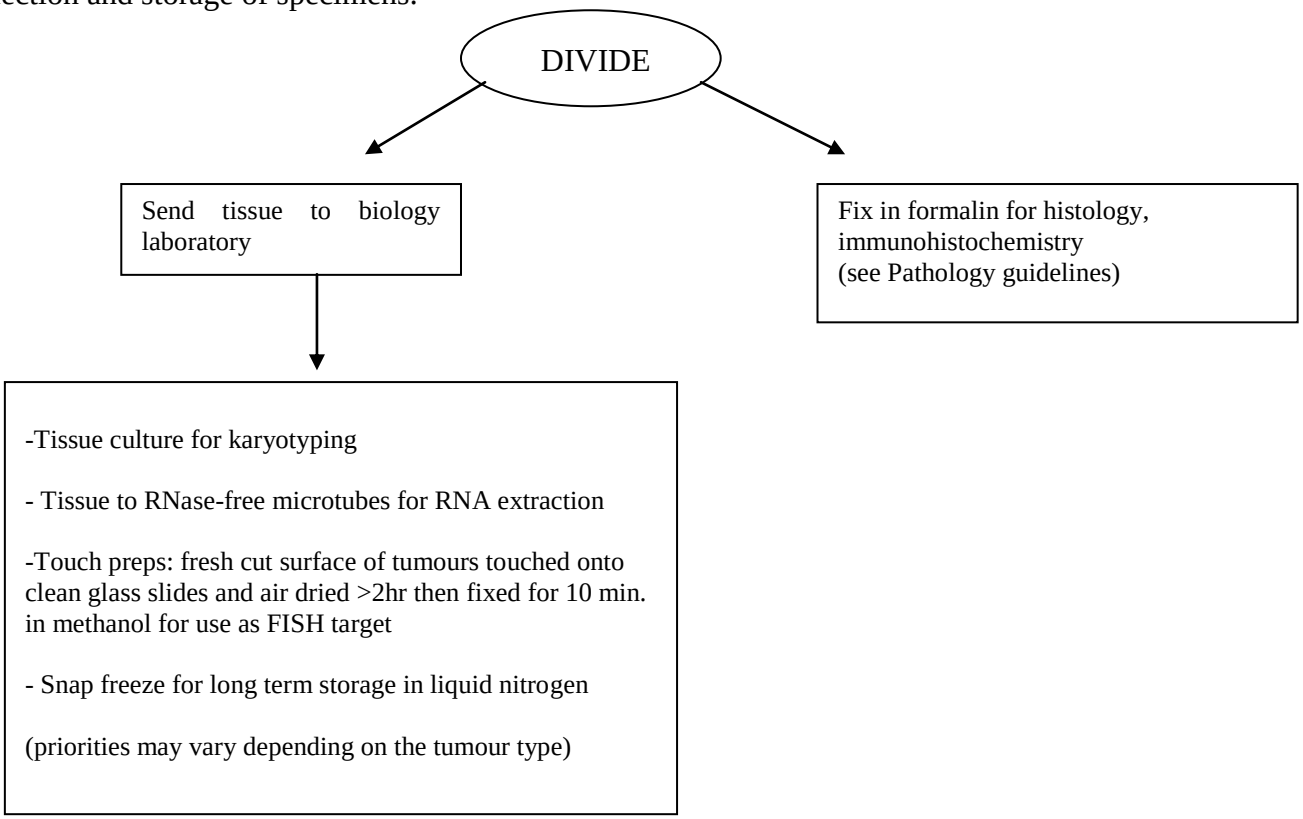
Storage of biological material for further analysis

Although we can plan studies on specific biological issue that would appear meaningful at present, there might be more important questions with clinical consequences that may become evident as our clinical and biological knowledge of the tumour progress. Furthermore, the availability of new technologies may render it possible to answer critical questions that are not approachable with the current scientific and technical resources.
For this reasons it is necessary that, whenever possible, biological specimens can be collected and stored appropriately for further studies as scientific priorities or feasibility become evident.
A clear example of this is the study of gene expression profile in tumours, by gene arrays, which is ongoing in many laboratories and that may indeed represent a significant improvement compared to previous approaches.

HANDLING OF SPECIMENS

FRESH OPEN BIOPSY OR TRU-CUT

Note: In some national groups pathology and biology laboratories may be organized differently than in other Countries and this may influence the procedures for optimizing biological studies and/or collection and storage of specimens.



Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any

serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
The subjects must be volunteers and informed participants in the research project.
The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be informed on legally competent persons.
When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Information sheet / Consent forms

The following text is a suggested form of information suitable for parents of children with NRSTS
Local Research Ethical Committees may demand differing levels of written information as a part of the process of obtaining informed consent. The E*p*SSG NRSTS 2005 protocol is an observational study and the provision of written consent is a matter for individual institutions to agree in the context of their local ethical approval policies.
It is also advisable to have the family consent to the storage of biological material for future studies according to the rules existing in different countries.

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A1 - INFORMATION SHEET FOR PARENTS

Your child has recently been diagnosed with a tumour included in the group of the so-called Non-Rhabdomyosarcoma Soft Tissue Sarcomas (NRSTS). This is a very heterogeneous group of tumours with different biology and clinical behaviour. These tumours can occur at any age, almost anywhere in the body. Usually, they are characterized by local aggressiveness, but sometimes they can provoke distant metastases. Their clinical behaviour is directly correlated to their grade of malignancy: generally, low-grade tumors usually may have local aggressiveness but low tendency to metastatic spread. High-grade tumors have a more invasive behaviour with higher propensity to metastasize (in particular at the lung). Other variables are important to predict the clinical outcome, particularly the tumour size and the extent to which the tumour can be removed by operation at the start of treatment.

The treatment of children with NRSTS is complex and necessitates multidisciplinary approach. Surgery is the mainstay of treatment, but in some cases tumour resection is not enough, because there is a high risk of local or metastatic relapse: therefore, adjuvant treatments as chemotherapy (anti-cancer drugs) and radiotherapy (x-ray treatment) are necessary. Moreover, in some cases the complete removal of the tumour is not possible and chemotherapy is administered in the view to shrink the tumour and make it resectable.
Many children with NRSTS can be cured but it is still necessary to collect further information about the treatment they have received, whether that is chemotherapy, surgery or radiotherapy to learn more about the best way of treating such patients in the future.

1. What is the purpose of this study?

The purpose of this study is to treat children in a systematic way according to an internationally agreed treatment protocol and to document their response to treatment in order to identify in a large number of patients, how their treatment can be optimised.

2. Why has my child been chosen?

Your child has been diagnosed with a NRSTS and fulfils the eligibility criteria for this study.

3. Does my child have to take part?

It's up to you and your child whether or not to take part. If you decide to take part you will be given these information sheets to keep and asked to sign a consent form. If you and your child

decide to take part, you are free to withdraw at any time without having to give a reason. Your doctor may wish to withdraw your child from the study if it is felt to be in their best interest. A decision to withdraw or not take part at all will not affect the standard of your child's care or the relationship with your child's doctor. You may take part in the clinical study without agreeing to have your child's tumour stored for a biological study (details to be given in an attached sheet).

4. What will happen to my child if we take part?

Your child will be treated according to the E*p*SSG protocol appropriate for your child's tumour depending on the extent to which the tumour has been (or can be) removed by operation, whether it has spread, how large it is and what histological grade of malignancy it has. All treatments have side effects. Your doctor will discuss these in detail with you. Surgery might cause physical, functional or aesthetic damages The commonest side effect of chemotherapy is a temporary poor functioning in the bone marrow. This caused an increased susceptibility to infection for the whole duration of treatment. You will be instructed what to do if your child has a fever or appears unwell during this time. This side effect is temporary and your child's ability to fight infection will return to normal by six months from the end of treatment. Your child may also need blood and platelets transfusions during the course of treatment. There are also some drug specific side effects, some of which can be permanent (e.g. kidney damage from ifosfamide, cardiotoxicity for doxorubicin) but the risk of these problems is low and your doctor will explain them in more detail. Moreover, there may be a possibility of infertility in later life. Radiotherapy may cause fibrosis, bone and soft tissues growth retardation, and other sequelae in relation to the site of the tumour and the age of your child. Second malignancies also might occur in patients treated with chemotherapy and in particular with radiotherapy, but the risk is very low. Your doctor will discuss your child's individual risk of these problems.

For all children with NRSTS we would like to store a small piece of tumour that is left over after making the diagnosis and/or at a further operation to remove the tumour after treatment. Also frozen and standard pathology wax blocks of tumour will be stored. These stored specimens will be used for scientific research to improve our understanding of NRSTS. Any research studies using your child's sample will only be undertaken once they have received full ethical approval.

5. Will there be any inconveniences?

We do not anticipate there will be any inconveniences over and above the normal treatment for NRSTS from taking part in this study.

6. What are the possible benefits of taking part?

Whether or not you decide to take part your child will receive the best possible medical care. By taking part in this study, we will learn about how best to treat it in the future. We hope to learn more about why some tumours do well and where for those who do less well to improve treatment for children with NRSTS in the future. We are asking your permission to keep records of your child's treatment.

7. What are the possible risks of taking part?

There are usually no extra risks involved in collecting data or samples for storage for research. We are asking your permission to collect detailed information about your child's treatment.

8. Will my child taking part in the study be kept confidential?

With your consent we will be informing your doctor about your child's participation in the study. Information on all patients entered into this study will be kept at the National Coordinator Data Center. Data including your child's initials, date of birth, their diagnosis and the extent of their tumour, details of the treatment, any side effects and tumour response, and whether tissues have

been stored will be recorded. Information relating to your child's treatment will then be forwarded electronically to an international database in Italy. No personally identifiable information will be released in this way. Only limited clinic information on your child diagnosis and response to treatment will be sent to the central tumour office, in accordance with normal standards of medical confidentiality and data protection.

9. What will happen to the results of the research study?
The results of this study will be published in a medical journal once the study has been completed and all patients who have been followed up for at least one year. Your child will not be identified in any publication.

10. Who is organising and funding the research?
This research is being organised by the European paediatric Soft Tissue Sarcoma Study Group. This group includes experts from a number of countries throughout Europe who have considerable experience in the treatment of this tumour.

11. What if I have any other concerns?
If you have any concerns or other questions about this study or the way it has been carried out you should contact your doctor or you may contact the hospital complaints department.

Thank you for taking the time to read this information sheet and for taking part in the study if you agree to do so.

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A2 - INFORMATION SHEET FOR OLDER PATIENTS

You have recently been diagnosed with a tumour called soft tissue sarcoma. This is a form of cancer that can occur almost anywhere in the body and of which there are many different types. The treatment you will need is influenced by several factors including the exact subtype of the tumour, its size and whether it can be removed by operation at the start of treatment.
Surgery is the mainstay of treatment, but in some cases tumour resection is not enough, and adjuvant treatments are necessary; anti-cancer drugs (chemotherapy) and/or x-ray treatment (radiotherapy) may be useful for cure you.
We would like to collect information about the treatment you receive, whether that is chemotherapy, surgery or radiotherapy to learn more about the best way of treating patients like you in the future.

1. What is the purpose of this study?
For many patients the purpose is to treat the tumour in a systematic way to according to a treatment protocol that has been agreed in many different countries. If the response to treatment is documented in a large number of patients, it is hoped that we will better understand how the treatment of soft tissue sarcomas can be improved.

2. Why have I been chosen?
You have a soft tissue sarcoma and are therefore eligible for this study.

3. Do I have to take part?

It is up to you whether or not you take part. If you decide to take part you will be given these information sheets to keep and asked to sign a consent form. You are free to withdraw from the study at any time without having to give a reason. Your doctor may also want to withdraw you from the study if it is felt to be in your best interest. A decision to withdraw or not take part at all will not effect the standard of your care or your relationship with your doctor and nurses.

4. What will happen to me if I take part?

You will be treated according to the protocol appropriate for your type of tumour, depending on the exact subtype of the tumour, how large it is, whether it has spread and whether it can be removed by operation.

All treatments have side effects, and your doctor will discuss these with you in details. All treatments have side effects. Your doctor will discuss these in detail with you. Surgery might cause physical, functional or aesthetic damages. The commonest side effects of chemotherapy are loss of hair and a temporary poor functioning in the bone marrow. This then reduces your ability to fight infection throughout your whole treatment. You will be told that if you have a temperature or you feel unwell that you must contact your doctor straight away. This is temporary side effect and once the treatment is finished your ability to fight infection will return to normal within 6 months. You may also need blood and platelet transfusions during the treatment because your bone marrow will not be making these properly. There are other specific side effects some of what can be permanent e.g. infertility or kidney damage from the ifosfamide but the risk of these problems is low and your doctor will explain them in more detail. You may also receive radiotherapy or further surgery depending on the size and place of your original tumour. The details of the surgery and radiotherapy will again be explained to you by the treating doctor.

For all people included in the protocol, we would like to store a small piece of the tumour that is left over after making the diagnosis and / or a further operation to remove the tumour. These stored specimens will be used for scientific research to improve our understanding of these neoplasms. Any research studies, using your sample will only be undertaken once they have received full ethical approval.

5. Will there be any inconveniences?

We do not anticipate any inconveniences over and above the normal treatment for soft tissue sarcomas from taking part in this study. We simply want to record the details of your treatment at a central database.

6. What are the possible benefits of taking part?

Whether or not you decide to take part, you will receive the possible medical care. By taking part in this study, we hope that we will learn more about how to best treat it in the future. We are asking your permission to keep your records although these will be anonymised outside this hospital.

7. What are the possible risks of taking part?

There are usually no risks involved in collecting data or samples for storage for research.

8. Will my taking part be kept confidential?

We will be letting your doctor know that you are taking part in this study with your consent and if you agree, your notes may be inspected by authorised professionals other than those directly involved in your care. Information on all patients entered into this study will be kept at the National Coordinator Data Center, where it is kept and anonymised. Information relating to your treatment will then be forward electronically to an International Database in Italy. No personally identifiable

information will be released in this way (i.e. it will all be anonymised). Only limited clinical information on your diagnosis and response to treatment will be sent to the Central Tumour Office, in accordance with normal standards of medical confidentiality and data protection.

9. What will happen to the results of the research study?
The results of this study will be published in a medical journal once the study has been completed and all patients who have been followed up for at least one year.

10. Who is organising and funding the research?
This research is being organised by the European paediatric Soft Tissue Sarcoma Study Group. This group includes experts from a number of countries throughout Europe who have considerable expertise in the treatment of this tumour.

11. What if I have any other concerns?
If you have any concerns or questions about this study or the way it has been carried out you should contact the investigator in your centre or you may contact the hospital complaints department.Thank you for taking the time to read this information sheet and for taking part in the study if you agree to do so.

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A3 - INFORMATION SHEET FOR YOUNGER PATIENTS

This information sheet can be given or read to children as appropriate

Dear Patient

You have a lump or tumour called a sarcoma. We do not know why it has happened to you but we do know ways of trying to make you better. You need an operation that aims to remove the tumour; some children with this disease sometimes need treatments as medicines called 'chemotherapy' or x-ray treatment called 'radiotherapy'.

We are trying to make the treatment for sarcoma better by lots of doctors in Europe working together to plan the best treatment for this tumour. We keep a register of all the children having treatment for sarcomas. Some of the information from your treatment will also be sent by a computer to Italy.

If you want to know about the details of treatment, you can ask your nurse, doctor or your mum or dad to explain it some more.