RMS 2005

RG_09-207

a protocol for non metastatic rhabdomyosarcoma

UK Chief Investigator:
Dr Meriel Jenney

MREC Number: 05/MRE04/13	**Approval date: 19th August 2005**
CTA Number: 21761/0228/001-0001 (Formerly 21275/0274)	**Approval date: 19th April 2004**
EUDRACT Number: 2005-000217-35	**UK start date: 1st May 2006**
Final Version	**January 2005**
Protocol Version: 5.0	**Date: 29th July 2015**
Substantial amendment-17	**MREC approval date: 7th October 2015**
MHRA	**Approval date: 9th November 2015**

UK Co-ordinating Centre
Children's Cancer Trials Team (CCTT)
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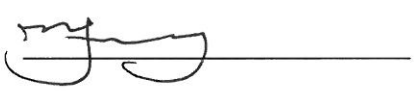
Study Title: RMS 2005 – A protocol for non-metastatic rhabdomyosarcoma (STS 2006 04)

Protocol approved by:

	Signature	**Date**
Chief Investigator		
Dr Meriel Jenney		31/7/15

UK SYNOPSIS

Full Title: RMS 2005 - a protocol for non metastatic rhabdomyosarcoma
Short Title: RMS 2005
(incorporates EpSSG-RMS-MET 2008: Treatment Arm for Metastatic Disease)

Protocol Number: RG_09-207	**Phase:** III	**Indication:** rhabdomyosarcoma

Chief Investigator (UK):
Dr Meriel Jenney
Children's Hospital for Wales, University Hospital, Heath Park, Cardiff, CF14 4XW

National / International: International	**Co-ordinating Data Centre:** EpSSG International Data Centre Padua, Italy	*Randomised non-blinded clinical trial*: High risk group only *Observational study*: other risk groups

Study Duration (Treatment plus follow-up):

Initial chemotherapy will be given over a period of 6 months. This will be followed by a further 6 months of maintenance chemotherapy for randomised patients in the high risk group and all patients in the very high risk group, or 12 months of maintenance chemotherapy for metastatic patients.

Therapeutic phase:
UK start date: 1st May 2006 **Expected completion date:** 31st December 2016
Follow-up: Minimum 3 years **Expected completion date:** June 2021

End of trial:
Enrolment of sufficient evaluable patients to answer the randomised question. Completion date is calculated as final treatment course of the last patient enrolled in the randomised arm of the protocol.

Study Design:

Randomised trial
Patients ≥ 6months and < 21 years diagnosed with non-metastatic rhabdomyosarcoma, stratified as High Risk according to the protocol criteria. There are two randomisations; the first involves the addition of doxorubicin to standard induction therapy, and the second involves the addition of vinorelbine and cyclophosphamide maintenance chemotherapy.

Observation study
Patients under 21 years diagnosed with rhabdomyosarcoma in the following risk stratifications: low risk, standard risk, very high risk, and metastatic patients.
Patients ≥ 21 years may be registered for observation at the clinician's discretion, but are not eligible for the randomised trial.

Patient Population:

Randomised trial: Patients with pathologically confirmed rhabdomyosarcoma in the high risk group with no evidence of metastatic disease and aged >6months - < 21 years.
Observation Study: patients under 21 years of age diagnosed with rhabdomyosarcoma who are not eligible for the randomised study.

Full Title: RMS 2005 - a protocol for non metastatic rhabdomyosarcoma
Short Title: RMS 2005
(incorporates EpSSG-RMS-MET 2008: Treatment Arm for Metastatic Disease)

Protocol Number: RG_09-207	**Phase:** III	**Indication:** rhabdomyosarcoma

Number of patients:
Randomised trial: an estimated 600 across Europe (125 in UK).
Observation study: target not given.

Diagnosis and main criteria for inclusion:

Observational study
Patients with pathologically confirmed rhabdomyosarcoma
Age 0 to < 21 years
Previously untreated except for primary surgery
Diagnostic material available for pathology review
Interval between diagnostic surgery and start of chemotherapy no longer than 8 weeks
No previous malignant tumours
No evidence of metastatic disease (except for those patients eligible for the metastatic arm of the observational study)
Available for long term follow up through the treatment centre
Written informed consent

Investigational study (randomised trial)
Eligible for the protocol and stratified to the High Risk Group
Age > 6 months (younger children are eligible for the protocol study treatment but they will not enter in the randomised trial)
Informed consent given for the randomised study.
Additional criterion for the second randomisation: patient in complete remission or with minimal abnormalities at the end of standard treatment.

Adults >21 years with RMS may be eligible for registration and standard treatment on study but not for randomisation.

IMPs:

Investigational medicinal products are administered in the randomised trial to High Risk patients. The same investigational medicinal products are also given to the Very High Risk patients in the Observation study:

- **Doxorubicin** (iv) given as part of IVADo therapy
- **Cyclophosphamide** (oral) given as maintenance therapy
- **Vinorelbine** (iv) given as maintenance therapy

Standard chemotherapy
All other chemotherapy drugs are given as standard treatment and are therefore considered to be Non-IMPs. NB: drugs given to metastatic patients are NIMPs.

Primary Objectives:

- To give a homogenous local and systemic treatment Europe-wide according to the risk of local and metastatic relapse in patients with rhabdomyosarcoma categorized in Low, Standard and Very High Risk Groups (observational study)
- To investigate the role of doxorubicin in induction chemotherapy, and to investigate the addition of vinorelbine and cyclophosphamide in the maintenance chemotherapy in patients with rhabdomyosarcoma in the High Risk Group (randomised trial)

Full Title: RMS 2005 - a protocol for non metastatic rhabdomyosarcoma
Short Title: RMS 2005
(incorporates EpSSG-RMS-MET 2008: Treatment Arm for Metastatic Disease)

Protocol Number: RG_09-207	**Phase:** III	**Indication:** rhabdomyosarcoma

Secondary objectives:

Low Risk goup: to evaluate standard VA therapy in risk stratified patients

Standard Risk group: to evaluate standard therapies in a variety of risk stratified patients

Very High Risk group: To evaluate outcome of more intensive therapy in an observational study.

Metastatic patients: to evaluate standard metastatic therapy

Endpoints / Criteria for evaluation:

Randomised trial
Primary: 3 year Event Free Survival (EFS)
Secondary: response to initial treatment (9^{th} week) and minimum 5 year overall survival (OS)

Special aspects:

- Central pathology review (national and international) to confirm patient eligibility
- There is a prospective biological study incorporated in to the trial
- Treatment of metastatic disease has been incorporated into this protocol as appendix 14

LIST OF AMENDMENTS

Protocol substantial Amendment 06 29th July 2015

Chapter/ Paragraph/ Page Number	Version 4.0, 17th June 2014	Version 5.0, 29thd July 2015
Front cover	Protocol version 4.0, 17th June 2014 Substantial amendment 14 MREC approval date 26th August 2014 MHRA approval date 11th September 2014 UK Coordinating Centre Tel: 0121 515 8578/ 8572	Protocol version 5.0, 29th July 2015 Substantial amendment 14 MREC approval date <insert date of approval> MHRA approval date <insert date of approval> UK Coordinating Centre Tel: 0121 414 7581
Page footers		Updated throughout
Page 1	Expected completion date: 31st December 2014 Follow-up Expected completion date: June 2019	Expected completion date: 31st December 2016 Follow-up Expected completion date: June 2021
Page 139 26 Adverse event reporting	The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the reference safety information (RSI) for doxorubicin, cyclophosphamide and vinorelbine (the Investigational Medicinal Products).	The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the reference safety information (RSI) for doxorubicin, cyclophosphamide and vinorelbine (the Investigational Medicinal Products) or the applicable Summary of Product Characteristics for ifosfamide, vincristine and actinomycin D and drugs given as second line therapy (NIMPS).
Page 139 26.1.2 Serious Adverse Events	Investigators should report AEs that meet the definition of an SAE (see Appendix 7 for definition) and are not excluded from the reporting process as described below.	Investigators should report all AEs that meet the definition of an SAE (see Appendix 7 for definition) unless the event is excluded from the reporting process as described below.
Page 139 26.1.2.1 Events that do not	Applicable to ALL risk groups **Applicable to Low, Standard**	Exclusions applicable to ALL risk groups **Exclusions applicable to Low,**

require reporting on a Serious Adverse Event Form	**or Metastatic risk groups**	**Standard or Metastatic risk groups and to High and Very High risk group patients NOT receiving IMPs**
Page 140 26.1.2.1 Events that do not require reporting on a Serious Adverse Event Form	**Applicable to High and Very High risk group:** The following events should be **reported on an Expected SAR Form** rather than an SAE Form: This section is only applicable to the **high** and **very high risk group** patients who experience **a SAR**. This section is **not** applicable to high and very high risk patients receiving **NIMPs**.	**For patients in the High and Very High risk groups receiving IMPs:** The following events should be **reported on an Expected SAR Form** rather than an SAE Form: This section is only applicable to **high** and **very high risk group** patients who experience **an expected SAR**. **i.e. the event is listed below and is causally related to an IMP**
Page 141 26.1.3 Reporting period	Details of all AEs (except those listed above) will be documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment.	Details of all AEs (except those listed above) will be documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment. SAEs which occur more than 30 days after the administration of the last treatment and which are judged to be at least possibly related to the trial treatment should be reported irrespective of how long after administration the reaction occurred

Protocol Substantial Amendment 05, 17th June 2014

Chapter/ Paragraph/ Page Number	**Version 3.0a, January 2013**	**Version 4.0, 17th June 2014**

Front cover	Protocol version 3.0a, 10th January 2013 Substantial amendment 12 MREC approval date 7th March 2013 MHRA approval date 25th March 2013	Protocol version 4.0, 17th June 2014 Substantial amendment 14 MREC approval date <insert date of approval> MHRA approval date <insert date of approval>
Page footers		Updated throughout
Page 1	Expected completion date: 30th June 2014 Follow-up Expected completion date: December 2018	Expected completion date: 31st December 2014 Follow-up Expected completion date: June 2019
Page 32	Contact details removed from v4.0: *Prof. Modesto Carli* Haematology/Oncology Division Department of Paediatric Via Giustiniani, 3 35128 Padova, Italy Tel +39 049 8213565 Fax +39 049 8211462 E-mail: modesto.carli@unipd.it	Contact details added to v4.0: *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
	Contact details removed from v4.0: *Dr. Odile Oberlin* Paediatric Oncology Institut Gustave Roussy Rue Camille Desmoulins 94805 Villejuif Cedex, France Tel +33-1-45 59 41 42 Fax +33-1-45 59 E-mail: Oberlin@igr.fr	Contact details added to v4.0: *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
Page 32		Addition of EpSSG Board members details: *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 paediatric 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.net

Page 34	(Contact details removed from v4.0) *Dr. Mark Gaze* University College London Hospital, 1st Floor Central, 250 Euston Road London, NW1 2PQ Fax: 020 7380 9321 Tel (Sec): 0845 155 5000 ext 9088 E-mail: mark.gaze@uclh.nhs.uk	(Contact details added to v4.0) *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
	(Contact details removed from v4.0) *Dr. Angelo Rosolen* Haematology/Oncology Division Department of Paediatric, Via Giustiniani, 3 - 35128 Padova, Italy Tel +39 049 8215678 Fax +39 049 8211462 E-mail: angelo.rosolen@unipd.it	(Contact details added to v4.0) *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
	(Contact details removed from v4.0) *Dr. Hervé Brisse* Institut Curie Service de Radiodiagnostic 26 rue d'Ulm 75005 Paris - France Tel 33 1 44 32 42 00 Fax 33 1 44 32 40 15 E-mail: herve.brisse@curie.net	(Contact details added to v4.0) *Dr. Kieran McHugh* Radiology Department, Great Ormond Street Hospital London WC1N 3JH, UK Tel 00442074059200 Fax 00442078298665 E-mail: kmchugh@gosh.nhs.uk
Page 36	*Ilaria Zanetti* 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: ilaria.zanetti@unipd.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

Pages 37 and 38		Addition of National Coordinator details: **Argentina :** *Adriana Rose* Hematology-Oncology Department Hospital de Pediatría SAMIC Prof. Dr. Juan P. Garrahan Pichincha Nº 1890 (CPA: C 1249 ABP) Ciudad Autónoma de Buenos Aires - República Argentina Teléfono: (54 - 11) 4308 – 4300 adri.rose@yahoo.com **Brazil :** *Sima Ferman* Instituto Nacional de Câncer Praça da Cruz Vermelha 23/5 andar Chefia de Clínica-Pediatria CEP20230130 Rio de Janeiro-Brazil 5521-25066527 5521-99826268 sferman@uol.com.br; sferman@inca.gov.br **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
Page 40		EpSSG RMS 2005 Independent data Monitoring committee: Dr Bruno de Bernadi's details have been removed
Page 169/ para 2	Sample size (no longer applicable, see page 166)	Sample size (no longer applicable, see page 170)
Page 169/ Para 3	Interim Analysis and stopping rules (no longer applicable, see page 166)	Interim Analysis and stopping rules (no longer applicable, see page 170)
Page 170/ Para 2	*Intensification question 2012* Therefore, the first interim analysis for the intensification question will be conducted after 85 events. The trial will be terminated after an interim analysis if the main question is answered.	*Intensification question 2012* Therefore, the first interim analysis for the intensification question will be conducted after 85 events. The trial will be terminated after an interim analysis if the main question is answered (see Addendum – page 218).

	Treatment according to the "observational study" (that includes low, standard and—very high risk strategy): *Patient Information Sheets (low, and standard risk)*	**Treatment according to the "observational study" (that includes low, standard, high and—very high risk strategy):** *Patient Information Sheets (low, standard and high risk)*
	Randomisation into high risk strategy	**Randomisation for high risk patients after initial treatment.**
	Consent forms • 1ST RANDOMISATION: STANDARD TREATMENT *or* STANDARD TREATMENT WITH ADDITIONAL DOXORUBICIN Parent/Child Young person aged 16+ • 2nd RANDOMISATION: STANDARD TREATMENT *or* STANDARD TREATMENT WITH ADDITIONAL MAINTENANCE CHEMOTHERAPY Parent/Child Young person aged 16+	***Consent forms*** RANDOMISATION: STANDARD TREATMENT *or* STANDARD TREATMENT WITH ADDITIONAL MAINTENANCE CHEMOTHERAPY
Page 218		**Addendum – Instructions for early first randomisation stop** An interim analysis has been undertaken and the DMC has advised that the first randomisation should be closed. New patients with localized Rhabdomyosarcoma, allocated to the High Risk group and eligible to the first randomisation, will be treated according to the standard chemotherapy (IVA) regimen. This decision will not influence the second randomization: maintenance vs observation and this randomisation will continue as planned

Protocol Non-Substantial Amendment 01 (CRCTU)

Chapter/ Paragraph/ Page Number	Version 3.0, January 2013	Version 3.0a, January 2013

Front cover	Protocol version 3.0, 10th January 2013	Protocol version 3.0a, 10th January 2013
Page footers		Updated throughout
Page 1	Expected completion date: April 2013 Follow-up Expected completion date: November 2017	Expected completion date: 30th June 2014 Follow-up Expected completion date: December 2018

Protocol Substantial Amendment 04, 10th January 2013

Chapter/ Paragraph/ Page Number	**Version 2.0, August 2010**	**Version 3.0, January 2013**
Front cover	Protocol version 2.0, 5th August 2010 Substantial amendment 03 MREC approval date 20th September 2010 MHRA approval date 28th September 2010	Protocol version 3.0, 10th January 2013 Substantial amendment 12 MREC approval date <insert date of approval> MHRA approval date <insert date of approval>
Page footers		Updated throughout
Page numbering		Updated throughout
Throughout	*Dr. Anna Kelsey* Royal Manchester Children's Hospital, Oxford Road Manchester, M13 9WL Tel +44 161 701 2247 Fax +44 161 701 2249 E-mail: anna.kelsey@cmft.nsh.uk E-mail: meriel.jenney@CardiffandVale.wales.nhs.uk	*Dr. Anna Kelsey* Department of Diagnostic Paediatric Histopathology, Royal Manchester Children's Hospital, 4th Floor Oxford Road Manchester, M13 9WL Tel +44 161 701 2247 Fax +44 161 701 2249 E-mail: anna.kelsey@cmft.nhs.uk E-mail: meriel.jenney@wales.nhs.uk
Page 1	Expected completion date: April 2012 Follow-up: Minimum 5 years	Expected completion date: April 2013 Follow-up: Minimum 3 years
Page 31	*Dr. Laura Cestari* 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: laura.cestari@ioveneto.it	*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

Page 35	*Dr. Guido Pastore* SCDU Pediatria ASO Maggiore della Carità Via Mazzini, 19 – Novara, Italy Tel +39 0321 3733790 Fax +39 0161 253504 E-mail: pastoreguido@tin.it	*Dr. Bruno De Bernardi* Department of Paediatric Hematology-Oncology "G. Gaslini" Children's Hospital Largo G. Gaslini, 5 – 16148 Genova Quarto Tel 010/5636694 Fax 010/5636714 E-mail: brunodebernardi@ospedale-gaslini.ge.it
Page 68	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%).	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%). Echocardiogram at baseline is only required for patient's stratified to either the high risk or very high risk group.
Page 134	Serious Adverse Event Reporting	Section re-written
Page 165/paragraph 2 Page 165/paragraph 3	Sample size Interim Analysis and stopping rules	Sample size (no longer applicable, see page 166) Interim Analysis and stopping rules (no longer applicable, see page 166)
Page 166/ paragraph		Sample size amendment (September 2012) – section amended Interim Analysis and stopping rules amendment (September 2012) – section amended
Page 184		Inserted a new Appendix, A.7. This Appendix contains the AE definitions. The subsquent Appendices were all re-numbered.
Page 195/paragraph 4 Page 195/paragraph 6	SMPU contact details updated from: St Mary's Pharmaceutical Unit Quadrant Centre Cardiff Business Park Llanishen Cardiff CF14 5RA manufacturer's (IMP) authorisation (Ref 18523)	St Mary's Pharmaceutical Unit 20 Field Way Cardiff CF14 4HY manufacturer's (IMP) authorisation (Ref 35929)

Page 197/paragraph 5	CRCTU (fax: 0121 414 3700 or 0121 414 7989	CRCTU (fax: 0121 414 3700 or 0121 414 9520
Page 198	ORDER FORM – Cyclophosphamide Oral Solution	Order form amended to include an option for selecting syringe size and 'Copy faxed to the consignee on dispatch: Y/N' removed

Protocotol Substantial Amendment 03, 5th August 2010

Chapter/ Paragraph/ Page Number	**Version 1.2 September 2008 (Substantial Amendment 02)**	**Version 2.0 August 2010**
Front cover	Study code STS 2006 04 CTA number 21275/0274 Protocol version 1.2, September 2008 Substantial amendment 02 MREC approval date 7th May 2009 MHRA approval date 11th May 2009 CCLG contact details	Study code RG_09-207 CTA number 21761/0228/001-0001 Protocol version 2.0, August 2010 Substantial amendment 03 MREC approval date 20th September 2010 MHRA approval date 28th September 2010 CRCTU contact details
Signature page	Prof Sue Ablett details deleted	
Throughout	CCLG	CRCTU
Throughout		Contact details for Dr Meriel Jenney, Dr Anna Kelsey and Dr Mark Gaze updated
Throughout		Page numbers updated throughout
Page footers		Updated throughout
Page 4		New section: List of Amendments August 2010
Page 13 and Page 132	Following sentence deleted : A specific document regarding safety has been issued (Standard Operative Procedures (SOPs) for managing Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) throughout the EpSSG RMS 2005 Trial). Investigators are requested to refer to this document for the management of safety aspects.	
Page 22- *Contents Page 192*	Information Sheets/Consent Forms (RMS 2005)	Overview of Information Sheets/Consent Forms (RMS 2005)
Page 22- *Contents Page 203*	Information Sheets/Consent Forms (RMS-MET 2005)	Overview of Information Sheets/Consent Forms (RMS-MET 2005)
Page 23		Addition of the following: NCRI (National Cancer Research Institute)

Page 23	CCLG - Children's Cancer and Leukaemia Group and UKCCSG – United Kingdom Children's Cancer Study Group	Sarcoma Clinical Study Group (formerly known as CCLG - Children's Cancer and Leukaemia Group and UKCCSG – United Kingdom Children's Cancer Study Group)
Page 132	CCLG Data Centre by fax on 0116 254 9504	CRCTU by fax on 0121 414 3700 or 0121 414 7989

Substantial Amendment 02, September 2008
(Incorporates Minor Amendment 01, 17 Sept 2008)

Chapter/ Paragraph/ Page Number	**Final version January 2005**	**Version 1.2 September 2008 (Substantial Amendment 02)**
Front cover		Updated
Page footers		Updated throughout
Throughout	randomization	randomisation
Throughout	tumor	tumour
Throughout	hospitilization	Hospitalisation
Page 1		New section: Signature page
Pages 2-4		New section: UK synopsis
Pages 5-16	1.1.1	New section: List of changes from Final Version January 2005
Pages 1-7	1.1.2	Contents updated
2	UKCCSG: United Kingdom Children's Cancer Study Group	**CCLG** - Children's Cancer and Leukaemia Group (former UKCCSG: United Kingdom Children's Cancer Study Group
4	Old version deleted	New version of Chapter 4 updated to reflect new EpSSG structures and personal details
5		Abbreviation list updated
6 Patients eligibility	Interval between diagnostic surgery and start of treatment no longer than 8 weeks	Interval between diagnostic surgery and start of chemotherapy no longer than 8 weeks

6		New text: Investigational Medicinal Products (IMPs) In the UK, the following drugs have been defined as IMPs for this trial: • **Doxorubicin** (iv) given as part of IVADo therapy • **Cyclophosphamide** (oral) given as maintenance therapy • **Vinorelbine** (iv) given as maintenance therapy Investigational medicinal products are administered in the randomised trial to High Risk patients. The same investigational medicinal products are also given to the Very High Risk patients in the Observation study. All other chemotherapy drugs are given as standard treatment and are therefore considered to be Non-IMPs. NB: drugs given to metastatic patients are NIMPs.
6.6	randomised within 6 weeks	randomised within 8 weeks
8.3.3	8.3.2	8.3.3
8.4.4	-	New text: Patients with Alveolar N1 tumour will be treated according to the very high risk arm.
11.1 Eligibility to the Protocol	Interval between diagnostic surgery and treatment no longer than 8 weeks.	Interval between diagnostic surgery and start of chemotherapy no longer than 8 weeks.
11.2.2 Second randomisation	Patients will be randomised within 6 weeks after the administration of the 9th block of chemotherapy using the RDE system (see randomisation procedure chapter 33.5)	Patients must be randomised within 8 weeks after the end of treatment. The end of treatment is defined as the last day of the 9th chemotherapy cycle. However: - if surgery is performed after the 9th chemotherapy cycle, the date of surgery will be considered; - if radiotherapy is administered after 9 cycles of chemotherapy, the date of the end of RT will be considered. Since maintenance CT should be started within 8 weeks from the last day of the 9th CT cycle, it would be better to start the maintenance CT during irradiation. (See randomisation procedure chapter 33.5)

12.4.1 Evaluation of lung lesions	Smaller solitary nodules (<0.5 cm) are questionable evidence of metastatic disease unless the radiologist is reasonable sure to consider them as metastatic lesions.	For EpSSG studies, the following patterns will be considered as metastatic pulmonary disease (assuming there is no other clear medical explanation for the 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 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".
15.2		New text: paratesticular
15.2		New text: (excluding undifferentiated sarcoma of the liver)
15.3	30 mg/m2	30 mg/m^2
15.4		New text: Patients must be randomised within 8 weeks after the end of treatment. The end of treatment is defined as the last day of the 9^{th} chemotherapy cycle. However: - if surgery is performed after the 9th chemotherapy cycle, the date of surgery will be considered; - if radiotherapy is administered after 9 cycles of chemotherapy, the date of the end of RT will be considered. Since maintenance CT should be started within 8 weeks from the last day of the 9^{th} CT cycle, it would be better to start the maintenance CT during irradiation.
15.4	Arm D: 6 courses Vinorelbine+ Cyclophospamide	Arm D: 6 courses Vinorelbine + Cyclophosphamide
15.4	**Randomization should be performed and (if allocated) treatment started within 6 weeks following the administration of 9th course of chemotherapy.**	**Randomisation should be performed and (if allocated) treatment started within 8 weeks following the end of treatment.**

15.4	**decision & randomisation within 6 weeks**	**decision & randomisation within 8 weeks**
15.4.1	N.B. Cyclophosphamide is only available in capsules of 50 mg, which cannot be cut in smaller capsules so the doses should be divided over more days. Capsules should be administered early in the day and followed by adequate fluid intake to minimize bladder toxicity.	N.B. Oral cyclophosphamide is only commercially available in the UK as 50mg sugar-coated tablets, which cannot be halved. If tablets are preferred, metronomic dosing can be used, i.e. cumulative weekly dose given over several days as required. For smaller doses or patients requiring a liquid formulation, an oral solution is available as an IMP supply (see Appendix 11). Cyclophosphamide should be administered early in the day and followed by adequate fluid intake to minimize bladder toxicity.
16.2.2	N.B. Cyclophosphamide is only available in capsules of 50 mg, which cannot be cut in smaller capsules so the doses should be divided over more days. Capsules should be administered early in the day and followed by adequate fluid intake to minimize bladder toxicity.	N.B. Oral cyclophosphamide is only commercially available in the UK as 50mg sugar-coated tablets, which cannot be halved. If tablets are preferred, metronomic dosing can be used, i.e. cumulative weekly dose given over several days as required. For smaller doses or patients requiring a liquid formulation, an oral solution is available as an IMP supply (see Appendix 11). Cyclophosphamide should be administered early in the day and followed by adequate fluid intake to minimize bladder toxicity.
18.2	If eligible, the child should be randomised within 6 weeks after the administration of the 9th block.	If eligible, the child should be randomised within 8 weeks after the end of treatment.
20.1.1 Topo – Carbo Regimen	Topotecan: 2 mg/m^2/day on day 1 to 3 (total dose 6 mg/m^2/course). Carboplatin: 250 mg/m^2/day on day 4 and 5 (total dose 500 mg/m^2/course). Cyclophosphamide: 1500 mg/m^2/day on day 1 and 2 (total dose 3000 mg/m^2/course). VP16: 100 mg/m^2/day on day 1 to 3 (total dose 300 mg/m^2/course).	Topotecan: 2 mg/m^2/day on day 1 to 3 (total dose 6 mg/m^2/course) *in 30 minutes.* Carboplatin: 250 mg/m^2/day, *in 1 hour,* on day 4 and 5 when given with topotecan, on day 1 and 2 when given with VP16 (total dose 500 mg/m^2/course). Cyclophosphamide: 1500 mg/m^2/day on day 1 and 2 (total dose 3000 mg/m^2/course*) in 4 hours.* VP16 (Etoposide): 100 mg/m^2/day on day 1 to 3 (total dose 300 mg/m^2/course) *in 2-4 hours.*

20.1.1 Doxo – Carbo Regimen	Doxorubicin: 60 mg/m^2/day on day 1 (total dose 60 mg/m^2/course, 10 mg/m^2/h). Carboplatin: 250 mg/m^2/day on day 1 and 2 (total dose 500 mg/m^2/course). Cyclophosphamide: 1500 mg/m^2/day on day 1 and 2 (total dose 3000 mg/m^2/course).	Doxorubicin: 60 mg/m^2/day on day 1 (total dose 60 mg/m^2/course) *1 to 6 hours according to institutional policies.* Carboplatin: 250 mg/m^2/day on day 1 and 2 (total dose 500 mg/m^2/course) *in 1 hour.* Cyclophosphamide: 1500 mg/m^2/day on day 1 and 2 (total dose 3000 mg/m^2/course) *in 4 hours.*
20.1.1 Response assessment		*Important note:* please remember that patients in CR after second line chemotherapy are still eligible to second randomisation
22.2		New text: **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.
22.9.1	Radiotherapy is always necessary in patients over 3 years and should be given at week 9 regardless of response to initial chemotherapy.	Radiotherapy is always necessary in patients over 3 years and should be given at week 13 regardless of response to initial chemotherapy.
24		New text: **Investigational Medicinal Products (IMPs)** In the UK, the following drugs have been defined as IMPs for this trial: • **Doxorubicin** (iv) given as part of IVADo therapy • **Cyclophosphamide** (oral) given as maintenance therapy • **Vinorelbine** (iv) given as maintenance therapy Investigational medicinal products are administered in the randomised trial to High Risk patients. The same investigational medicinal products are also given to the Very High Risk patients in the Observation study. All other chemotherapy drugs are given as standard treatment and are therefore considered to be Non-IMPs. NB: drugs given to metastatic patients are NIMPs.

24.3 Cyclophos-phamide	CPM: 25 mg/m^2 per os every day (no rest between cycles) Oral cyclophosphamide is only available in capsules of 50 mg which cannot be cut in smaller capsules so the doses should be divided over more days. For example, in the case of a patient with a body surface of 1.3 m^2, the daily dose should be 32.5 mg, corresponding to about 100 mg every 3 days: therefore one entire tablet (50 mg) for two consecutive days followed by one day off should be given. In the UK, unlicensed specials formulations of oral liquid CPM are currently available but these must not be used if CPM is being administered as an IMP (in accordance with current UK regulations). The UK Sponsor is in the process of sourcing a QP-released, IMP oral liquid formulation of CPM for use in this trial. A protocol amendment will be issued whenever this formulation is approved by the MHRA.	CPM: 25 mg/m^2 per os every day (no rest between cycles) Oral cyclophosphamide is only commercially available in the UK as 50 mg sugar coated tablets which cannot be halved If tablets are preferred, metronomic dosing can be used, i.e. cumulative weekly dose given over several days as required. For example, in the case of a patient with a body surface of 1.3 m^2, the daily dose should be 32.5 mg, corresponding to about 100 mg every 3 days: therefore one entire tablet (50 mg) for two consecutive days followed by one day off should be given. If smaller doses are required or the patient is unable to swallow tablets, the oral liquid IMP formulation may be provided. An IMP supply of cyclophosphamide 10mg/mL oral solution is available for UK trial patients (see Appendix 11). NB: unlicensed Specials formulations must not be used for IMP doses.
24.3 Cyclophos-phamide	It is advised to administer CPM tablets early in the day	It is advised to administer CPM early in the day
24.3 Vinorelbine	between 1.5 and 3 mg/dl	between 0.5 and 3 mg/mL *(Change required to meet DoH directive)*
24.4.1 Age ≤ 1 month	**Age ≤ 1 month** These patients are not eligible for the protocol and to the randomised study and …..	**Age ≤ 1 month** These patients are eligible for the protocol but they are not eligible for the randomised study and ……
24.4.1 Age > 1 month and ≤ 3 months	**Age > 1 months and ≤ 3 months** These patients are not eligible for the protocol and to the randomised study and should be initially treated with VA or IVA, according to the risk group, at doses calculated *by weight* without further reduction.	**Age > 1 months and ≤ 3 months** These patients are eligible for the protocol but they are not eligible for the randomised study and should be initially treated with VA or IVA, according to the risk group, at doses calculated *by weight* without further reduction (VA). Ifosfamide dose will be calculated *by weight and then reduced to 50%* .

24.4.1 Age > 3 months and ≤ 6 months	**Age > 3 months and ≤ 6 months** These patients are not eligible for the protocol and to the randomised study and the drug dose should be calculated *by weight* without further reduction.	**Age > 3 months and ≤ 6 months** These patients are eligible for the protocol but they are not eligible for the randomised study. Drug doses will be calculated *by weight* without further reduction. Doses are reported in Table 9.
24.4.1 Table 9 0 -≤ 1 month	months (x 3)	month (x3)
24.4.1 Table 9 1- 3 months		New text: (see note a)
24.4.1 Table 9 > 3 -≤ 6 months	VCR and ACT-D: drug dose calculated by body weight. The resulting dose is: - VCR 0.05 mg/kg/dose - ACT-D 0.05 mg/kg/dose IFO and Doxo: dose calculated by body weight and then reduced to 50%. The resulting dose is: - IFO 50 mg/kg/dose - Doxo: 0.5 mg/kg/dose	VCR, ACT-D, *IFO and Doxo*: drug dose calculated by body weight. The resulting dose is: - VCR 0.05 mg/kg/dose - ACT-D 0.05 mg/kg/dose - IFO 100 mg/kg/dose - Doxo: 1 mg/kg/dose
24.4.1 Table 9 > 6 - ≤ 12 months	VCR and ACT-D: drug dose calculated by body weight. The resulting dose is: - VCR 0.05 mg/kg/dose - ACT-D 0.05 mg/kg/dose IFO: 100mg/kg/dose by weight and then reduced to 50%. The resulting dose is: - IFO 50 mg/kg/dose Doxo: the dose is 0.75 mg/kg/dose	VCR, ACT-D, IFO and Doxo: drug dose calculated by body weight. The resulting dose is: - VCR 0.05 mg/kg/dose - ACT-D 0.05 mg/kg/dose - IFO 100 mg/kg/dose - Doxo: 1 mg/kg/dose
24.4.1 Table 9 Note a	if tolerated, drug dose	if tolerated, Ifosfamide dose
24.4.1 Table 9 Note b and c	b) IFO should not be given in children less than 3 months in the initial cycle(s), however it should be administered in the subsequent courses as the child grows up and providing the chemotherapy is well tolerated. c) Doxo	b) Doxo
24.4.1 Table 9 Note c	age	aged
26.2	"Expected" toxic events, even if they cause hospitalization, but are not life threatening, should not be regarded as a SAE and does not need to be reported with the SAE form.	"Expected" toxic events, even if they cause hospitalisation, but are not life threatening, should not be regarded as a SAE and do not need to be reported with the SAE form.

26.2	Moreover the Investigator must provide documentation of a serious adverse reaction in compliance with local laws. All serious adverse events, including cases of death, must also be communicated to the local Ethical Committee by the Investigator, according to regulations in force.	Moreover the Investigator must provide documentation of a serious adverse reaction in compliance with local laws. All SAEs occurring in patients registered by UK centres must also be reported to the CCLG Data Centre by fax on 0116 254 9504 (and copied to the Chief Investigator if the Data Centre is closed) immediately upon knowledge of the event, in accordance with standard CCLG procedure. All serious adverse events, including cases of death, must also be communicated to the local Ethical Committee by the Investigator, according to regulations in force.
29.1	Professor Vito Ninfo/Dr. Anna Kelsey – Co-Chairpersons; Dr. Rita Alaggio; Dr. Ivo Leuschner; Dr. Dominique Ranchere-Vince; Dr. Núriá Toran	Professor Vito Ninfo/Dr. Anna Kelsey – Co-Chairpersons; Dr. Rita Alaggio; Dr. Dominique Ranchere-Vince; Dr. Núriá Toran
29.1	Dr. A. Kelsey (UK); Dr. R. Alaggio/professor V. Ninfo (Italy); Dr. I. Leuschner (Germany); Dr. N. Toran Fuentes (Spain); Dr. D. Ranchere-Vince (France); Dr. J. Bras (Netherlands); Dr. Helena Barroca; Dr. Josephine Issakov**:**	Dr. A. Kelsey (UK); Dr. R. Alaggio/professor V. Ninfo (Italy); Dr. N. Toran Fuentes (Spain); Dr. D. Ranchere-Vince (France); Dr. J. Bras (Netherlands); Dr. Josephine Issakov (Israel) Updated contact details for Dr Issakov
29.4 i-iv	Rms	RMS
29.4 v RMS N.O.S	When subtyping is not possible, also on central review , a local decision has to be made with regard to patient management taking into consideration the clinical information. The risk Group will be therefore decided according to favourable or unfavourable characteristics: age, site and size of tumour and nodal involvement.	When subtyping is not possible, as a pragmatic decision and to avoid possible under-treatment of patients the risk group will be decided as per Alveolar RMS.
30	Appendix 11	Appendix 10
32.1 Design of the trial	Cyclofosfamide	Cyclophosphamide

33.3 Co-ordinating Centre	Dr. Gian Luca De Salvo Clinical Epidemiology Unit Regional Cancer Centre Via Gattamelata, 64 35128 Padova, Italy Tel: 0039-0498215704 Fax: 0039-0498215706 Email: cor.epiclin@unipd.it Website: www.corpadova.it	Dr. Gian Luca De Salvo International Data Centre Clinical Trials and Biostatistic Unit "Istituto Oncologico Veneto" Via Gattamelata, 64 35128 Padova – Italy Phone: 0039 – 049 – 8215704 Fax: 0039 – 049 – 8215706 **E-mail:** epssg@ioveneto.it **Web site**: https://epssg.cineca.org
33.5 Second randomisation	Patients must be randomised within 6 weeks after the administration of the 9th block of chemotherapy using the RDE system.	Patients achieving CR after second line treatment are still eligible to second randomisation. Patients must be randomised within 8 weeks after the end of treatment. The end of treatment is defined as the last day of the 9th chemotherapy cycle. However: - if surgery is performed after the 9th chemotherapy cycle, the date of surgery will be considered; - if radiotherapy is administered after 9 cycles of chemotherapy, the date of the end of RT will be considered. Since maintenance CT should be started within 8 weeks from the last day of the 9th CT cycle, it would be better to start the maintenance CT during irradiation.
33.5 Independent DMC		New text: (names are reported in the EpSSG Administrative organization section).
34.1	Appendix A.11	Appendix A.13
34.2	Appendix A.10	Appendix A.12
35 Appendices	Appendix	Appendices and list updated
A7 Toxicity	Nephrotoxicity garding : totak score see appendix A.9	Nephrotoxicity grading : total score see appendix A.9
A7 Toxicity	Siucidal ideation	Suicidal ideation
A10	UKCCSG	CCLG
A11 IMPs		New appendix: Investigational medicinal product (IMP) supplies and management

A12 Declaration of Helsinki	Full 1996 version included	• Renumbered (was A11) • Full declaration removed and replaced with new wording: The 2008 version of the Declaration of Helsinki can be downloaded from the World Medical Association (WMA) website: http://www.wma.net/e/policy/b3.htm
A13		• Renumbered (was A12) • List of information sheets/consent forms updated
A13	The text can be modified for use in discussions with older children/adolescents who may be giving their own consent. 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.	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.
A13		Patient and GP Information Sheets and Consent Forms revised and up-dated. New Patient Information Sheets for patients in the Very High Risk Group added.
A14		New Appendix: EpSSG-RMS-MET 2008: Treatment Arm for Metastatic Disease (metastatic protocol)
A15		New Appendix: Patient and GP Information Sheets and Consent Forms for the EpSSG-RMS-MET 2008 protocol

Contents

1. Protocol Sponsor

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

2. Protocol Co-ordination

This protocol is co-ordinated by the European paediatric Soft tissue sarcoma Study Group (in its abbreviated form E*p*SSG). This new collaborative structure has been founded by

- **The Co-operative Weichteilsarkom Studie (CWS)**
- **The AIEOP Soft Tissue Sarcoma Committee (AIEOP STSC)**
  (former ICG: Italian Cooperative Group for paediatric soft tissue sarcoma)
- **The SIOP Malignant Mesenchymal Tumour Committee (SIOP MMT)**

These Groups decided to join forces to design and implement a portfolio of pan-European studies addressed at children and adolescents affected by soft tissue sarcoma.

The three cooperative Groups act on behalf of the following Societies:
AIEOP - Associazione Italiana di Ematologia e Oncologia Pediatrica
BSPHO - Belgian Society of Paediatric Haematology Oncology
GPOH - *Germany, Austria*: Gesellschaft für pädiatrische Onkologie und Hämatologie
NOPHO *Denmark, Norway, Sweden* - Nordic Organisation of Paediatric Haematology and Oncology
SEOP - Sociedad Española de Oncologìa Pediátrica
SFCE - Société Française de lutte contre les Cancers de l'Enfant et de l'adolescent
NCRI (National Cancer Research Institute)
Sarcoma Clinical Study Group (formerly known as CCLG - Children's Cancer and Leukaemia Group and UKCCSG – United Kingdom Children's Cancer Study Group)
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 E*p*SSG RMS 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 E*p*SSG. 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 infrastructure. A state of emergency due to complications from the underlying disease or from its treatment can develop in every patient at any time. An experienced team with multidisciplinary competences should thus treat children with STS.

3. E*p*SSG Structure

Protocol Writing Group

EpSSG Chairmen

Prof. Joern Treuner (Chair, CWS)
Prof. Modesto Carli (Chair, AIEOP STSC)
Dr. Odile Oberlin (Co Chair, SIOP MMT Study Group)
Prof. Michael Stevens (Co Chair, SIOP MMT Study Group)

Committee for EpSSG RMS2005 Protocol

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Dr. Meriel Jenney (United Kingdom)
Dr. Bernada Kazanowska (Poland)
Prof. Ewa Koscielniak (Germany)
Dr. Soledad Gallego (Spain)
Dr. Catherine Rechnitzer (Denmark, on behalf of NOPHO)

Radiotherapy Panel

Dr. Andreas Schuck (Germany)

Surgical Panel

Prof. Helene Martelli (France)

Pathology Panel

Dr. Anna Kelsey (United Kingdom) and Prof. Vito Ninfo (Italy)

Biology Panel

Dr. Angelo Rosolen (Italy)

Radiology Panel

Hervé Brisse (France) and Kieran McHugh (United Kingdom)

Statistical & Data Management Panel

Dr. Gian Luca De Salvo (Italy)

Other collaborators:

Dr. Andrea Ferrari: maintenance treatment
Dr. Alberto Donfrancesco: second line treatment

4. Protocol E*p*SSG 2005 – Administrative organisation

The protocol is co-ordinated by a Trial Monitoring Committee under the supervision of E*p*SSG Board.The Committee will meet at least twice a year to monitor the progress of the study.
Protocol Panels will normally meet at the same time as the protocol Committee.
The structure of EpSSG is described in the document: "Structure and standard for EpSSG members".
The member of the different EpSSG Committee and Panels is reported in the document: "EpSSG Structure & Membership".

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The full list of the participants to the different Panels is provided in the *"EpSSG Structure & Membership list"* document

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Participating Centres

A list of participating centres broken down by country is provided in the *"EpSSG Structure & Membership list"* document.

4.1 SAFETY DESK

To deal with safety issues throughout the EpSSG RMS 2005 trial a safety desk has been instituted. A guide denominated "*Standard Operative Procedures for managing Serious Adverse Events (SAEs) and Suspect Unexpected Serious Adverse Reactions (SUSARs) throughout the EpSSG RMS 2005 Trial"* has been distributed to the EpSSG investigators.
In brief The EpSSG Safety Desk is responsible for the ongoing safety evaluation of the investigational medicinal products. The Safety Desk will monitor all communication regarding any findings that may adversely affect the health of subjects, have an impact on the conduct of the trial or induce the competent authority to withdraw authorisation to continue the trial in accordance with Directive 2001/20/EC.

Safety desk members

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E*p*SSG RMS 2005 INDEPENDENT DATA MONITORING COMMITTE

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5. Abbreviations

ACT-D	Actinomycin D
Adria	Adriamycin (doxorubicin)
aRMS	Alveolar Rhabdomyosarcoma
BM	Bone Marrow
Carbo	Carboplatin
CAV	Cyclophosphamide, Adriamycin, Vincristine
CRCTU	Cancer Research UK Clinical Trials Unit
CEVAIE	Carboplatin, Epirubicin, Vincristine, Actinomycin, Ifosfamide, Etoposide
CPM	Cyclophosphamide
CR	Complete Remission
CT	Chemotherapy
CTA	Clinical Trial Authorisation
CTC	Common Toxicity Criteria
CWS	Cooperative Weichteilsarkom Studie
DFS	Disease Free survival
Doxo	Doxorubicin
EFS	Event Free Survival
eRMS	Embryonal Rhabdomyosarcoma
EFS	Event Free Survival
E*p*SSG	the European paediatric Soft tissue Sarcoma Study Group
GCP	Good Clinical Practice
GU BP	Genito Urinary Bladder Prostate
GU non BP	Genito Urinary non Bladder Prostate
HN non PM	Head and Neck non Parameningeal
HN PM	Head and Neck Parameningeal
IDMC	International Data Monitoring Committee
IFO	Ifosfamide
IMP	Investigational Medicinal Product
IRS	Intergroup Rhabdomyosarcoma Study
IRSG	Intergroup Rhabdomyosarcoma Study Group
IVA	Ifosfamide, Vincristine, Actinomycin,

IVADo	Ifosfamide, Vincristine, Actinomycin, Doxorubicin
MMT	Malignant Mesenchymal Tumours
NOS	Not Otherwise Specified
ORR	Overall Response Rate
OS	Overall Survival
Per os	Oral
PFS	Progression free Survival
PNET	Peripheral Primitive NeuroEctodermal Tumour
PD	Progressive Disease
PR	Partial Response
QP	Qualified Person
RDE	Remote Data Entry
RMS	Rhabdomyosarcoma
RT	Radiotherapy
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SIOP	Société Internationale d'Oncologie Pédiatrique
SD	Stable Disease
STS	Soft Tissue Sarcoma
STSC	Italian Soft Tissue Sarcoma Committee
Topo	Topotecan
TNM	Tumour-Node-Metastasis
VA	Vincristine, Actinomycin
VAC	Vincristine, Actinomycin, Cyclophosphamide
VAIA	Vincristine, Actinomycin, Ifosfamide, Adriamycin (doxorubicin)
VAdrC	Vincristine, Adriamycin (doxorubicin) Cyclophosphamide,
VCR	Vincristine
VNL	Vinorelbine
VOD	Veno-Occlusive Disease

6. Summary

Three Cooperative Groups have been working in Europe on paediatric soft tissue sarcoma for the last twenty years: the SIOP MMT Committee, the CWS and the AIEOP STSC (former ICG). Cooperation has intensified over the last few years and has led to the foundation of the European paediatric Soft tissue sarcoma Study Group (E*p*SSG). This is the first E*p*SSG protocol and it addresses the treatment of children and young people presenting with non-metastatic rhabdomyosarcoma.
The protocol contains a randomised trial for "high risk patients" and observational studies for patients categorized in other risk groups.

Patients with metastatic rhabdomyosarcoma or other soft tissue sarcoma (non rhabdomyosarcoma) will be treated according to different protocols elaborated within the framework of E*p*SSG. These patients must be therefore registered in these protocols.

Objectives:
To give a homogenous local and systemic treatment Europe-wide according to the risk of local and metastatic relapse in patients categorized in Low, Standard and Very High Risk Groups (observational study)
To investigate the role of doxorubicin dose intensity and maintenance chemotherapy in patients included in the High Risk Group (randomised trial)

PATIENTS ELIGIBILITY

A) To the observational study
- Patients with pathologically confirmed rhabdomyosarcoma
- No evidence of metastatic disease
- Age 0 - < 21 years
- Previously untreated except for primary surgery
- No pre-existing illness preventing treatment
- No previous malignant tumours
- Interval between diagnostic surgery and start of chemotherapy no longer than 8 weeks
- Diagnostic material available for pathology review
- Available for long term follow up through the treatment centre
- Written informed consent for treatment available

B) To the investigational study (randomised trial)
- Eligible to the protocol
- Included in the High Risk Group
- Age > 6 months (younger children are eligible for the protocol study treatment but they will not enter in the randomised trial)
- Informed consent given for the randomised study

Adults with RMS (> 21 years) may be eligible for registration and treatment on study (according to institutional preference) but not for randomisation.

PATIENTS STRATIFICATION

Patients are subdivided according to the risk factors that have emerged from the analyses of previous European studies. A new stratification has been developed taking into account histology (alveolar vs. non alveolar RMS), post surgical stage (according to IRS grouping), tumour site and size, node involvement and patient age.
According to their risk profile four Groups have been identified: Low Risk, Standard Risk, High Risk and Very High Risk (see Table 1). Different objectives and treatment plans have been elaborated for each group.

1) Low Risk Group:

Stratification: favourable histology (non alveolar), IRS Group I, any site, N0, favourable age (< 10 years) and favourable tumour size (≤ 5 cm) - SUBGROUP A (see Table 1).
Objective: to further investigate whether low risk patients can be treated with Vincristine and Actinomycin D alone.
Surgery: no further surgery after initial complete resection.
Chemotherapy: Vincristine + Actinomycin D (VA) over 8 blocks (22 weeks).
Radiotherapy: not indicated in these patients.

2) Standard Risk Group

Stratification: this risk Group comprises 3 different sets of patients. All patients must have favourable histology and no evidence of nodal involvement. SUBGROUP B*:* IRS Group I, and unfavourable size or age; SUBGROUP C: IRS II or III and favourable site; SUBGROUP D*:* IRS II or III, unfavourable site but favourable size and age (see Table 1)
Objective: to evaluate whether a) the addition of a limited dose of ifosfamide may improve the results in SUBGROUP B; b) chemotherapy intensity may be reduced decreasing the cumulative dose of the alkylating agent ifosfamide (SUBGROUP C) or avoiding anthracycline (SUBGROUP D)
Surgery: no further surgery after initial resection in IRS groups I and II (but a primary re-excision should be considered in group II patients). In IRS group III patients delayed surgery should be considered after initial chemotherapy, if feasible. Delayed surgery in orbital RMS is not encouraged, however.
Chemotherapy: Ifosfamide + Vincristine + Actinomycin D (IVA) over 9 blocks. However ifosfamide will be withheld in Subgroup B and C after the initial 4 blocks.
Radiotherapy: Irradiation will be avoided when the tumour has been completely removed at diagnosis (Subgroup B). All other patients are to receive radiotherapy according to the radiotherapy guidelines with doses ranging between 36 Gy and 50.4 Gy depending on resection margins and response. Exceptions can be made in very young patients or in patients with tumours in particularly sensitive sites.

3) High Risk Group

Stratification: patients in IRS group II or III, with favourable pathology but unfavourable site and size or age (SUBGROUP E); patients in IRS Group I, II or III with favourable pathology, site, size and age but with nodal involvement (SUBGROUP F); all patients with unfavourable histology (SUBGROUP G) except alveolar N1 (see Table 1)
Objective: to improve the EFS of the whole group evaluating through a double randomisation 1) the value of adding doxorubicin in the initial part of the treatment and 2) the role of low dose maintenance chemotherapy.
Surgery: no further surgery after initial resection in IRS groups I and II (but a primary re-excision should be considered in group II patients). In group III patients delayed surgery should be considered after initial chemotherapy, if feasible.

Chemotherapy: IVA vs. IVADo (IVA + Doxorubicin) over the initial 4 blocks followed by 5 IVA blocks. All patients in complete remission will then be randomised to stop treatment or to continue with low dose maintenance therapy with a combination of cyclophosphamide and vinorelbine.
Radiotherapy: All patients are to receive radiotherapy according to the radiotherapy guidelines with doses ranging between 36 Gy and 50.4 Gy depending on histology, resection margins and response.

4) Very High Risk Group
Stratification: unfavourable histology (alveolar) and node involvement (N1), regardless of the other risk factors (see Table 1)
Objective: to improve the EFS by adding doxorubicin in the initial part of the treatment and low dose maintenance chemotherapy.
Surgery: no further surgery after initial resection in IRS groups I and II (but a primary re-excision should be considered in group II patients). In group III patients delayed surgery should be considered after initial chemotherapy, if feasible.
Chemotherapy: IVADo over the initial 4 blocks followed by 5 IVA blocks and low dose cyclophosphamide and vinorelbine.
Radiotherapy: patients are to receive radiotherapy according to the radiotherapy guidelines with doses ranging between 41.4 Gy and 50.4 Gy depending on resection margins and response.

INVESTIGATIONAL MEDICINAL PRODUCTS (IMPs)

In the UK, the following drugs have been defined as IMPs for this trial:

- **Doxorubicin** (iv) given as part of IVADo therapy
- **Cyclophosphamide** (oral) given as maintenance therapy
- **Vinorelbine** (iv) given as maintenance therapy

Investigational medicinal products are administered in the randomised trial to High Risk patients. The same investigational medicinal products are also given to the Very High Risk patients in the Observation study. All other chemotherapy drugs are given as standard treatment and are therefore considered to be Non-IMPs. NB: drugs given to metastatic patients are NIMPs.

PATHOLOGY AND BIOLOGY

The diagnosis of the patients registered into the protocol will be reviewed by the E*p*SSG Pathology Panel to confirm the diagnosis and the RMS subtype, as this is essential in the patient's management. Different pathology studies will be implemented to analyse the prognostic meaning of several features including cellular anaplasia and post chemotherapy maturation.
Tumour samples will also be analysed, using the RT-PCR technique, to specifically detect transcripts that can be used for the identification of paediatric sarcomas. Among others, PAX-FKHR transcripts that characterize alveolar rhabdomyosarcoma; EWS-FLI1 and EWS-ERG that are expressed in the Ewing's family of tumours; ETV6-NTRK3 in congenital infantile fibrosarcoma; EWS-WT1 in desmoplastic sarcoma, and SYT-SSX1 and SYT-SSX2 in synovial sarcoma.
Other transcripts such as MyoD1 and Myogenin will be used in the study of minimal bone-marrow infiltration. New molecular markers may be identified in the future that could have clinical applications.

STATISTICAL CONSIDERATIONS

This study is a prospective phase III international, multi-institutional, non-blinded double-randomised clinical trial.

Aims of the trial are to evaluate the addition of doxorubicin to the standard therapy with ifosfamide, vincristine and actinomycin (IVA) in paediatric patients with rhabdomyosarcoma in High Risk Group – *intensification question*, and the role of a maintenance therapy with vinorelbine and cyclophosphamide in the same category of patients who have achieved a complete remission with first line treatment – *maintenance question.*
The estimated number of patients to be included in the randomised trial is 600 and the expected accrual period of the trial is 5 years followed by a minimum follow up period of 3 years.

ORGANIZATION OF THE STUDY

The E*p*SSG is an inter-group structure, which is based on the already existing national and international organisations built with the efforts of the participants to CWS, STSC and SIOP MMT studies over many years.
The existing national coordinating centres, will continue their work ensuring pathology review, clinical advice and data quality control.
All clinical centres previously part of the SIOP, CWS or STSC 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.
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.

DATA MANAGEMENT AND ANALYSIS

The E*p*SSG RMS 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.
Results of the interim analysis shall be reported to the International Data Monitoring Committee (IDMC) as scheduled by the protocol. The IDMC may recommend early stopping, continuation or extension of the study to the Protocol Committee.

ETHICAL CONSIDERATIONS

The protocol will be submitted, before patients enrolment, to the Ethics Committee of each participating Centre for review and approval according to law in force .
The patient's and/or parent's written consent to participate in the study must be obtained after a full explanation has been given of the treatment options including the conventional and generally accepted methods of treatment and the manner of treatment allocation.
Consent for participation for data management and biology material handling will be also obtained.
All patients and/or their parents must give written consent to inclusion into the trial, data processing and – if applicable – to sending diagnostic material to reference institutions, which in all participating countries has to conform to the national data protection legislation.
The investigator agrees, by accepting the protocol, to adhere to the principles of Good Clinical Practice.

Table 1 - Risk Stratification for EpSSG non metastatic RMS study

Risk Group	Subgroups	Pathology	Post surgical Stage (IRS Group)	Site	Node Stage	Size & Age
Low Risk	**A**	Favourable	I	Any	N0	Favourable
Standard Risk	***B***	Favourable	I	Any	N0	Unfavourable
	C	Favourable	II, III	Favourable	N0	Any
	D	Favourable	II, III	Unfavourable	N0	Favourable
High Risk	***E***	Favourable	II, III	Unfavourable	N0	Unfavourable
	F	Favourable	II, III	Any	N1	Any
	G	Unfavourable*	I, II, III	Any	N0	Any
Very High Risk	***H***	Unfavourable	I, II, III	Any	N1	Any

- **Pathology:**

Favourable = all embryonal, spindle cells, botryoid RMS
Unfavourable = all alveolar RMS (including the solid-alveolar variant)

- **Post surgical stage** (according to the IRS grouping, see appendix A.2):

Group I = primary complete resection (R0);
Group II = microscopic residual (R1) or primary complete resection but N1;
Group III = macroscopic residual (R2);

- **Site:**

Favourable = orbit, GU non bladder prostate (i.e. paratesticular and vagina/uterus) and non PM head & neck
Unfavourable = all other sites (parameningeal, extremities, GU bladder-prostate and "other site")

- **Node stage** (According to the TNM classification, see appendix A1 and A.5):

N0 = no clinical or pathological node involvement
N1 = clinical or pathological nodal involvement

- **Size & Age:**

Favourable = Tumour size (maximum dimension) ≤5cm ***and*** Age <10 years
Unfavourable = all others (i.e. Size >5 cm ***or*** Age ≥10 years)

Notes:
- *for paratesticular alveolar RMS see paragraph 8.4.4.*
- *for patients with RMS N.O.S, Undifferentiated STS and Ectomesenchymoma see paragraph 29.4*
- *Children with ascites/pleural effusion or CSF positive for malignant cells should be enrolled in the protocol for metastatic RMS*

6.1 SUMMARY FOR ELIGIBILITY

Diagnosis of Rhabdomyosarcoma or other malignant mesenchymal tumours*

ELIGIBLE FOR REGISTRATION

A pathologically proven diagnosis of RMS
Age < 21 years
Previously untreated except initial surgery
No pre-existing illness preventing treatment
No previous malignant tumours

Diagnosed ≤ 8 weeks
Pathology available for central review
Available for follow up
Written consent for treatment available

YES

NO

Registration only

Evidence of Distant Metastases

NO

YES

Treat in EpSSG Stage IV Study

ELIGIBLE FOR RMS 2005 PROTOCOL

Low Risk Group	**Standard Risk Group**	**High Risk Group**	**Very High Risk Group**
Subgroup A: ♦ VA x8	*Subgroup B:* ♦ IVA + VA *Subgroup C:* ♦ IVA ±VA *Subgroup D:* ♦ IVA	*Subgroup E* *Subgroup F* *Subgroup G* *if* -Age > 6 months -Informed consent given **Randomised trial No. 1** *(IVA vs. IVADo)* *if* -In CR or with minimal anomalies at the end of treatment **Randomised trial No. 2** (stop treatment vs. maintenance)	*Subgroup H* ♦ IVADo + maintenance

** undifferentiated soft tissue sarcoma and ectomesenchymoma are included in this protocol*

6.2 TREATMENT SUMMARY: LOW RISK GROUP

Low Risk Group	**Localised non alveolar RMS, microscopically completely resected (IRS Group I), at all sites,** *and* **nodes negative** *and* **tumour size ≤ 5 cm** *and* **age < 10 years**

	V	V	V	V			V	V	V	V			V	V	V	V			V	V	V	V
Surgery	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

V = Vincristine 1.5 mg/m^2 (maximum single dose 2 mg) as a single intravenous injection.
A = Actinomycin D 1.5 mg/m^2 (maximum single dose 2 mg) as a single intravenous injection.

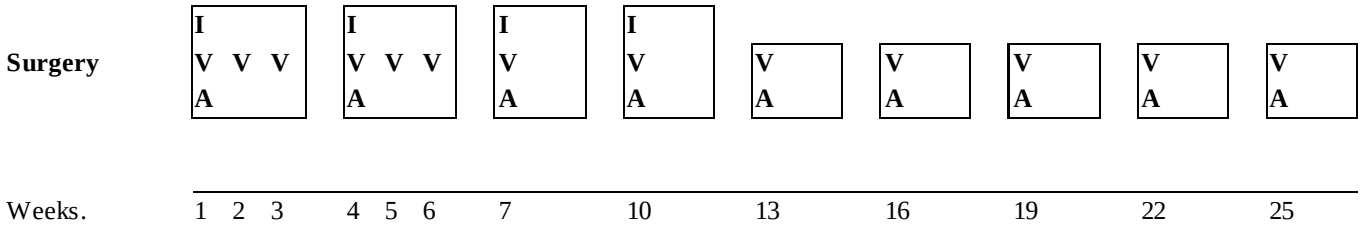
Cycles should not be started unless all these conditions are present: 2 x10^9/l WBC (or 1 x10^9/l neutrophils) + 80 x10^9/l platelets + absence of any relevant organ dysfunction.
Weekly vincristine should be administered irrespective of pancytopenia providing the child is in good condition.

For children ≤ 1 year (or ≤ 10 kg body weight) see first cycle doses will be calculated by body weight and increased in the following cycles if tolerated, see chapter 24.4.1.

For Low Risk Group treatment details: see chapter 13
For chemotherapy guidelines and dose modifications: see chapter 24.

6.3 TREATMENT SUMMARY: STANDARD RISK GROUP - SUBGROUP B

SUBGROUP B	**Localised non alveolar RMS, microscopically completely resected (IRS Group I), at all sites,** *and* **nodes negative** *and* **tumour size > 5 cm *or* age ≥ 10 years**



I Ifosfamide 3 g/m^2 is given as a 3 hour i.v. infusion daily, with Mesna (3 g/m^2) and hydration, on days 1 & 2 for each course of treatment. (Total IFO dose/course = 6 g/m^2).

V Vincristine 1.5 mg/m^2 (maximum single dose 2 mg) is given as a single i.v. injection on day 1 of each course and weekly, for total of seven consecutive doses, from week 1 to 7.

A Actinomycin D 1.5 mg/ m^2 (maximum single dose 2 mg) as a single i.v. injection on day 1 of each course.

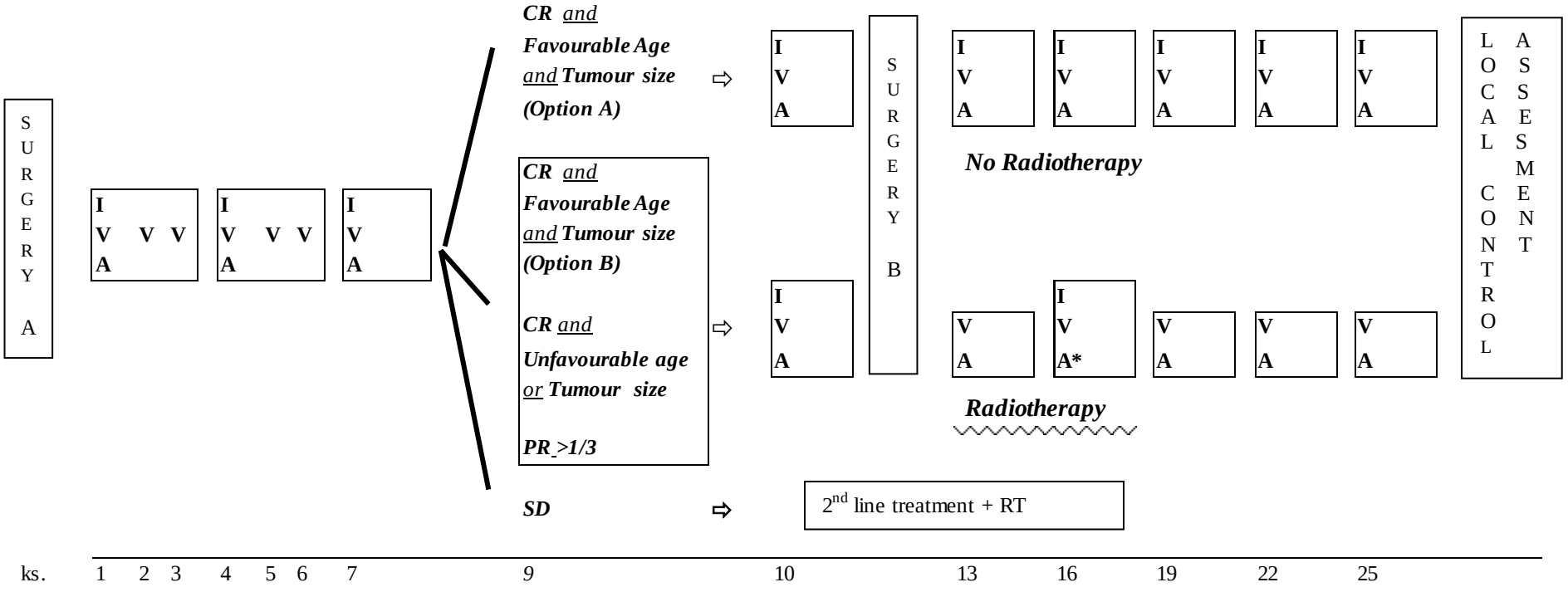
Interval between courses is 3 weeks and chemotherapy courses should not be started unless all these conditions are present: 2 x10^9/l WBC (or 1 x10^9/l neutrophils) + 80 x10^9/l platelets + absence of any relevant organ dysfunction.
Weekly vincristine should be administered irrespective of pancytopenia providing the child is in good condition.

For children ≤ 1 month VA only should be administered in the 1st cycle. For children ≤ 1 year (or ≤ 10 kg) specific precautions (doses calculated by body weight, reduced ifosfamide dose if age < 3 mos, …) must be applied, see chapter 24.4.1.

For *Standard Risk Group-Subgroup B* treatment details see chapter 6.3.
For chemotherapy guidelines and dose modifications: see chapter 24.

6.4 TREATMENT SUMMARY: STANDARD RISK GROUP – SUBGROUP C

SUBGROUP C	**non alveolar RMS, IRS Group II or III, localised in orbit, head and neck non PM or GU non bladder-prostate,** *and* **nodes negative** *and* **any size *or* age**



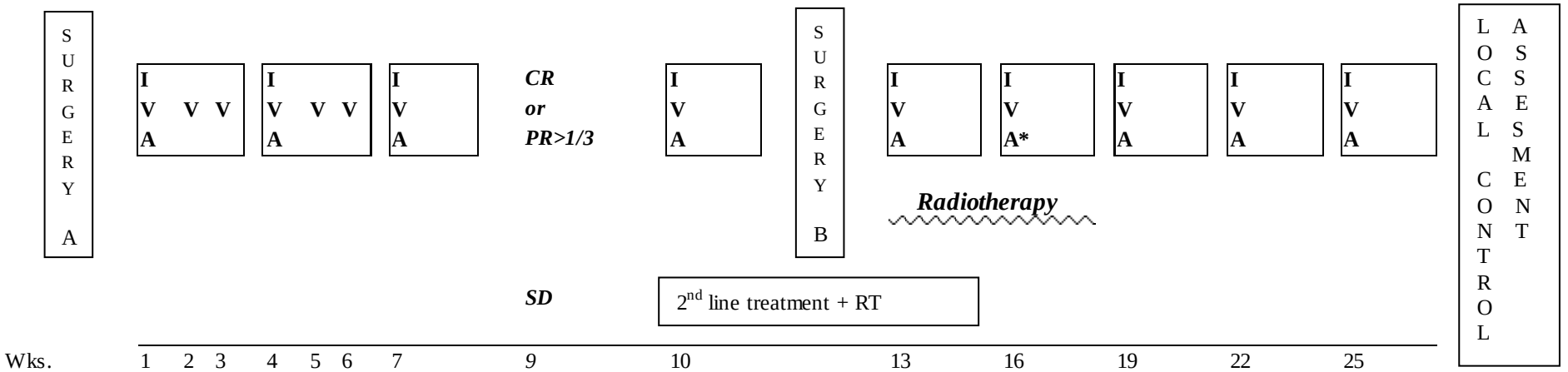
I Ifosfamide 3 g/m^2 is given as a 3 hour i.v. infusion daily, with Mesna (3 g/m^2) and hydration, on days 1 & 2 for each course of treatment. (Total IFO/course = 6 g/m^2).
V Vincristine 1.5 mg/m^2 (max. single dose 2 mg) is given as a single i.v. injection on day 1 of each course and weekly, for a total of 7 consecutive doses, from week 1 to 7.
A Actinomycin D 1.5 mg/ m^2 (maximum single dose 2 mg) as a single i.v. injection on day 1 of each course.
** Actinomycin may be given at the very beginning of RT (week 13) but is omitted during RT (week 16), see chapter23.11.*

Note: Patients with favourable age (< 10 years) and tumour ≤ 5 cm at diagnosis, who achieve the complete remission after the initial treatment (3 courses of IVA + surgery) have two options:

- **Option A:** patients will receive 9 courses of IVA without radiotherapy.
- **Option B:** patients will receive 9 courses of IVA without radiotherapy only if the CR has been obtained through a secondary operation (histologically CR). Otherwise they will be treated as patients in CR with unfavourable features. *NOTE: The German (CWS), the Italian (STSC) and the Spanish Group do recommend option B.*

6.5 TREATMENT SUMMARY: STANDARD RISK GROUP – SUBGROUP D

SUBGROUP D	**non alveolar RMS, IRS Group II or III, localised in parameningeal, extremities, GU bladder-prostate or "other sites"** *and* **nodes negative** *and* **tumour size ≤ 5 cm and age < 10 years**



I Ifosfamide 3 g/m^2 is given as a 3 hour i.v. infusion daily, with Mesna (3 g/m^2) and hydration, on days 1 & 2 for each course of treatment. (Total IFO dose/course = 6 g/m^2).

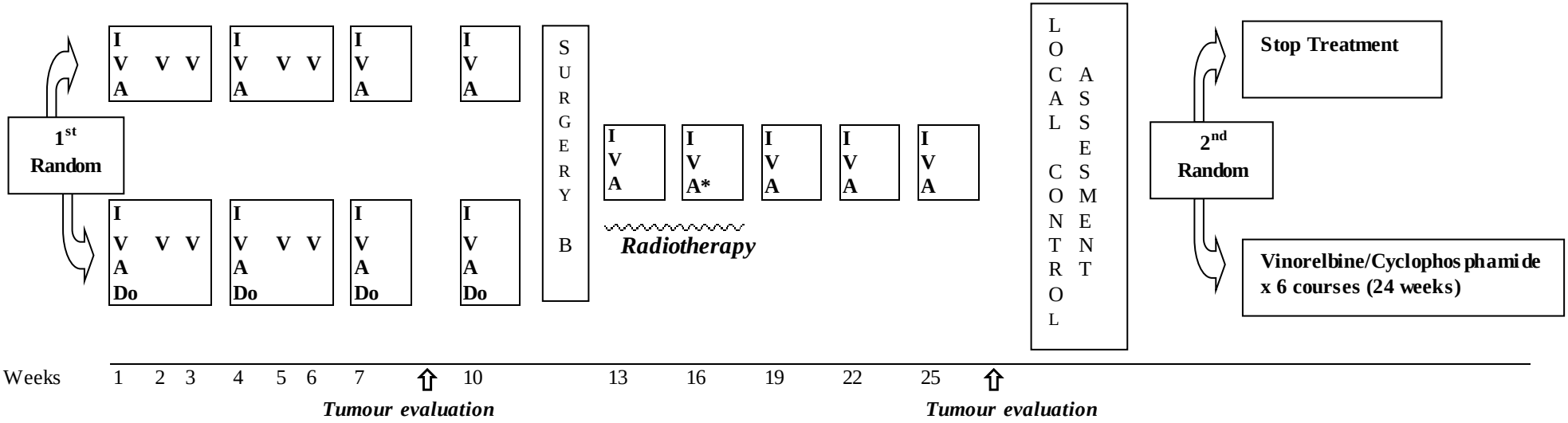
V Vincristine 1.5 mg/m^2 (max. single dose 2 mg) is given as a single i.v. injection on day 1 of each course and weekly, for a total of 7 consecutive doses, from week 1 to 7.

A Actinomycin D 1.5 mg/ m^2 (maximum single dose 2 mg) as a single i.v. injection on day 1 of each course.
* *Actinomycin may be given at the very beginning of RT (week 13) but is omitted during RT (week 16), see chapter 23.11.*

Interval between courses is 3 weeks and chemotherapy courses should not be started unless all these conditions are present: 2 x10^9/l WBC (or 1 x10^9/l/µl neutrophils) + 80 x10^9/l platelets + absence of any relevant organ dysfunction.
Weekly vincristine should be administered irrespective of pancytopenia providing the child is in good condition.
For children ≤ 3 months VA only should be administered in the 1st cycle. For children ≤ 1 year (or ≤ 10 kg) specific precautions (doses calculated by body weight, reduced ifosfamide dose if age < 3 mos, …) must be applied, see chapter 24.4.1.
For *Standard Risk Group - Subgroup D* treatment details see chapter 14.5.
See chapter 24 for chemotherapy guidelines and dose modifications.

6.6 TREATMENT SUMMARY: HIGH RISK GROUP

SUBGROUP E	**non alveolar RMS, IRS Group II or III, localised in parameningeal, extremities, GU bladder-prostate or "other sites" *and* nodes negative, *and* tumour size > 5 cm *or* unfavourable age ≥ 10 year**
SUBGROUP F	**non alveolar RMS, IRS Group I or II or III, any site *and* nodes positive, *and* any tumour size or age**
SUBGROUP G	**alveolar RMS, and any IRS Group I or II or III, and any site *and* nodes negative, *and* any tumour size or age**

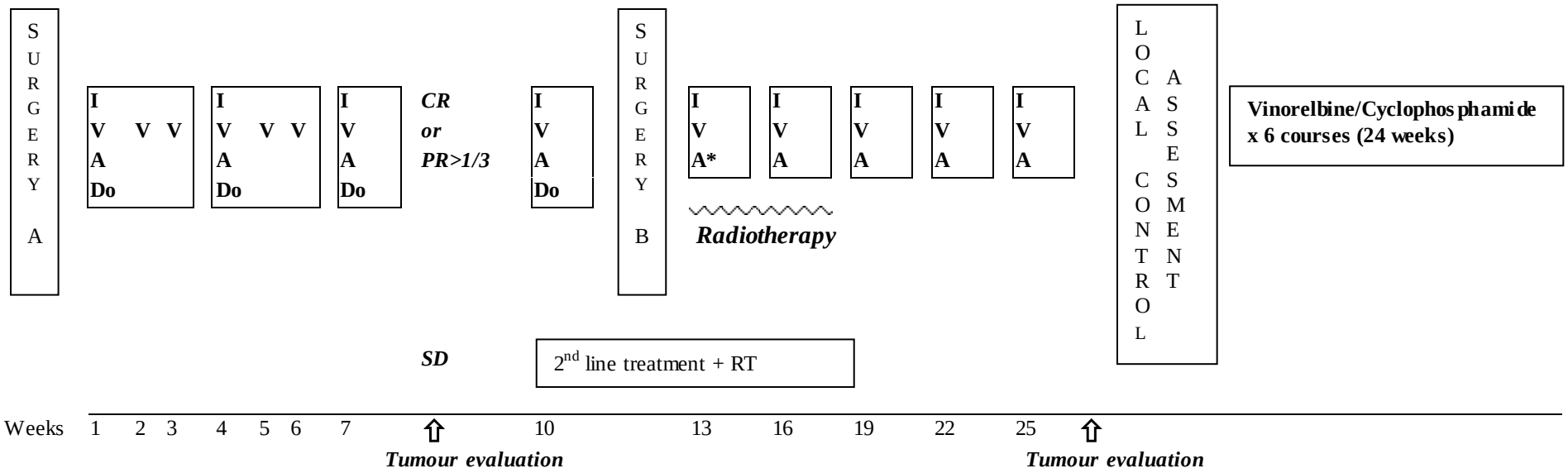


I Ifosfamide 3 g/m^2 is given as a 3 hour i.v. infusion daily, with Mesna (3 g/m^2) and hydration, on days 1 & 2 for each course of treatment. (Total IFO/course = 6 g/m^2).
V Vincristine 1.5 mg/m^2 (max. single dose=2 mg) is given as a single i.v. injection on day 1 of each course and weekly for a total of 7 consecutive doses, from week 1 to 7.
A Actinomycin D 1.5 mg/m^2 (maximum single dose = 2 mg) as a single i.v. injection on day 1 of each course of treatment.
** Actinomycin may be given at the very beginning of RT (week 13) but is omitted during RT (week 16), see chapter23.11.*
Do Doxorubicin 30 mg/m^2 given as a 4-hour i.v. infusion daily on days 1 & 2 for courses 1-4 of treatment (total dose per course = 60 mg/m^2).

First Randomisation: eligible patients must be randomised before chemotherapy treatment is started using the RDE system. *If the randomisation is refused or not applicable for whatever reason patients should be treated in Arm A (IVA).*
Second Randomisation: eligible patients should be randomised within 8 weeks following the administration of the 9th course of chemotherapy. *If the randomisation is refused or not applicable for whatever reason the standard treatment strategy is to stop treatment.*
Interval between courses is 3 weeks and chemotherapy courses should not be started unless all these conditions are present: 2 x10^9/l WBC (or 1 x10^9/l neutrophils) + 80 x10^9/l platelets + absence of any relevant organ dysfunction. Weekly vincristine should be administered irrespective of pancytopenia providing the child is in good condition.
For *High Risk Group* treatment details: see chapter 15.
For chemotherapy guidelines and dose modifications:see chapter 24.

6.7 TREATMENT SUMMARY: VERY HIGH RISK GROUP

SUBGROUP H	**alveolar RMS and nodes positive** (independently from any other variable such as tumour histology, site, size or patient age)



I Ifosfamide 3 g/m^2 is given as a 3 hour i.v. infusion daily, with Mesna (3 g/m^2) and hydration, on days 1 & 2 for each course of treatment. (Total IFO dose/course = 6 g/m^2).

V Vincristine 1.5 mg/m^2 (maximum single dose = 2 mg) is given as a single i.v. injection on day 1 of each course of IVA and weekly for a total of seven consecutive doses, until week 7. Weekly vincristine should be administered irrespective of pancytopenia providing the child is in good condition.

A Actinomycin D 1.5 mg/m^2 (maximum single dose = 2 mg) as a single i.v. injection on day 1 of each course of IVA.
** Actinomycin may be given at the very beginning of RT (week 13) but is omitted during RT (week 16), see chapter 23.11.*

Do Doxorubicin 30 mg/m^2 given as a 4-hour i.v. infusion daily on days 1 & 2 for courses 1-4 of treatment (total dose per course = 60 mg/m^2).

Interval between courses is 3 weeks and chemotherapy courses should not be started unless all these conditions are present: 2 x10^9/lWBC (or 1 x10^9/l neutrophils) + 80x10^9/l platelets + absence of any relevant organ dysfunction.
For *High Risk Group* treatment details: see chapter 16. For chemotherapy guidelines and dose modifications: see chapter 24

7. Background

The prognosis of children with localized rhabdomyosarcoma has improved dramatically since the introduction of co-ordinated multimodality treatment. Cure rates have improved from 25% in the early seventies, when combination chemotherapy was first implemented, to approximately 70% in more recent years.
A major role in developing new strategies has been carried by Cooperative Groups working in Europe and North America. They have optimised the treatment for children with RMS matching the complexity of treatment against known prognostic factors such as site, stage and pathological subtype.
In fact the role of radiotherapy, surgery and chemotherapy regimen in different risk groups has been explored in a series of multicentre clinical trials on both sides of the Atlantic.
This protocol has been derived from the evolving cooperation of European Groups, namely the SIOP Malignant Mesenchymal Tumours (MMT) Committee, the AIEOP Soft Tissue Sarcoma Committee (AIEOP STSC) (former ICG: Italian Cooperative Group for paediatric soft tissue sarcoma) and the German Co-operative Soft Tissues Sarcoma Group (CWS).
This collaboration will allow the recruitment of patients from all over Europe to the same protocol and thus be able to answer more rapidly some still unanswered questions regarding the treatment of children with soft tissue sarcomas.

7.1 RHABDOMYOSARCOMA

Rhabdomyosarcoma (RMS) is thought to arise from primitive mesenchymal cells committed to develop into striated muscles. It can be found virtually anywhere in the body, including those sites where striated muscles are not normally found. It is the commonest form of soft tissue sarcoma in children and young adults and accounts for approximately 4 - 5 % of all childhood malignancy with an annual incidence of 5.3 per million children under the age of 15. The peak incidence is seen early in childhood with a median age at diagnosis of about 5 years. Males are reported to be more frequently affected than females.
The aetiology is unknown. Genetic factors may play an important role as demonstrated by an association between RMS and familial cancer syndrome (Li Fraumeni), congenital anomalies (involving the genitourinary and central nervous system) and other genetic conditions, including neurofibromatosis type 1.

Depending on histological appearance two main forms of RMS have been distinguished: the embryonal (which accounts for approximately 80% of all RMS) and the alveolar subtypes (15 - 20% of RMS).
However it has been shown that some subtypes have an impact on survival. In 1995 pathologists from the different Cooperative Groups agreed a new classification which identified prognostically significant and reproducible subtypes [1]. Three main classes have been identified:
1) superior prognosis: including botryoid RMS and spindle cell or leiomyomatous RMS;
2) intermediate prognosis: represented by embryonal RMS;
3) poor prognosis: including alveolar RMS and its variant solid alveolar.
This classification system does not include the pleomorphic category, as this is very rarely observed in children.

Molecular biology studies have identified two characteristic chromosomal alterations in RMS: reciprocal chromosomal translocations t(2;13)(q 35; q14) or t(1;13)(p36;q14) in alveolar RMS [2] whilst genetic loss on chromosome 11p15.5 has been shown in embryonal RMS [3]

Different staging systems have been elaborated to classify RMS into categories from which treatment can be planned and prognosis predicted. The most widely used are the pre-treatment TNM staging and the postoperative IRS Grouping system (see appendix A.2). However with the evolution of treatment and trial results new, more complex, categorization has been used to better tailor the treatment to the risk of relapse.

Modern risk grouping attempts to take into account all the factors shown to be prognostically important. The most important are *Stage, Site and Histology*. They are also interdependent with, for instance, orbital tumours being almost exclusively of the embryonal subtype and limb tumours over represented amongst those with alveolar histology

The size of the tumour has a prognostic impact similar to that of other soft tissue sarcomas. More recently the patient's age at diagnosis has been recognised as a predictor of survival, with the older children ($\geq$ 10 years old) having the worse outcome [4].

7.2 TREATMENT STRATEGIES

A multimodality approach involving surgery, chemotherapy and radiotherapy is necessary in the treatment of children with RMS. The optimal timing and intensity of these three treatment modalities must be planned with regard to the prognostic factors and considering the late effects of treatment.

Local control is necessary to cure children with localized RMS and this may be achieved with surgery and/or radiotherapy. A conservative approach is recommended and tumour resection or irradiation is usually performed taking into account the activity of chemotherapy in reducing the tumour volume.

Different drug combinations proved to be effective against RMS. The most widely used regimens are: VAC (vincristine, actinomycin D, cyclophosphamide), VACA (VAC plus adriamycin alternating with actinomycin D), IVA (as VAC, but with ifosfamide replacing cyclophosphamide) and VAIA (IVA with adriamycin alternating with actinomycin D).

The multimodality approach according to different strategies and different chemotherapy regimens has been tested in several clinical trials run by the Cooperative Groups already named. Their results constitute the evidence for this protocol.

7.3 SIOP MMT STUDIES

The philosophy behind the SIOP studies has explored the use of more intensive primary chemotherapy in an attempt to reduce, where possible, the systematic use of definitive local therapy (surgery or radiotherapy). The objective has been to reduce the risk of important late functional or cosmetic sequelae, whilst maintaining satisfactory overall survival.

SIOP 75 and MMT 84

SIOP 75 was performed between 1975 and 1984 and compared treatment with a VAC based regimen given before or after definitive local therapy. Although there was no difference between the 2 arms (overall survival = 52%), the patients who received initial chemotherapy followed by local therapy achieved a similar survival with less aggressive local treatment and, predictably less important sequelae [5].

MMT 84 followed this by using the strategy of intensified initial chemotherapy (IVA, IFO 6 g/m^2/course, VCR and ACT-D) to try and reduce or avoid local therapy for patients who achieved complete remission (CR) with chemotherapy with or without conservative surgery. Patients achieving CR with chemotherapy +/- surgery did not receive radiotherapy or further extensive surgery. Those remaining in partial remission (PR) required definitive local therapy, or if not feasible, a trial of second line chemotherapy. Only patients over the age of 5 years with parameningeal tumours, and those aged >12 years with tumours at any site, received systematic radiotherapy.
The overall results of MMT 84 demonstrated a high CR rate (91%) in patients with localised disease. CR was achieved with chemotherapy alone in 48% patients. Overall survival at 5 years was 68% with an event free survival of 53% [6]. Only 34% patients received intensive local therapy.

MMT 89
The overall objectives of MMT 89 were to improve treatment outcome for children with non-metastatic RMS and to continue to reduce the systematic use of local therapy to reduce, where possible, the consequences of local therapy.
For standard and high risk patients, specific aims were a) to improve outcome by evaluating early tumour response and modifying chemotherapy in poor responders and b) to explore the value of an increased dose intensity of IFO (9 g/m^2/course compared to 6 g/m^2/course in MMT 84). Intensified chemotherapy using the multiagent (6 drug) combination was used for patients with high risk (stage III) disease and for young patients with parameningeal disease. Systematic radiotherapy again was avoided in patients who achieved CR with chemotherapy with or without surgery, except in children $\geq$3 years with parameningeal tumours.
In patients with a very good prognosis (completely resected disease at favourable sites) an attempt was made to further reduce the sequelae of treatment by avoiding the use of alkylating agents.
Complete remission was achieved in 93% of patients. Five-year overall and event free survival were 71% and 57%, respectively. Overall survival was not significantly better than that achieved in the previous MMT 84 study but 49% of survivors (33% of all patients) were cured with limited local therapy.
Other key findings were:

- In low stage disease (pT1) it was confirmed that duration and intensity of therapy can be reduced as there was no reduction in overall survival in patients treated with two drugs (VCR and ACT-D) for two cycles compared to historical controls treated in MMT 84 with three drug (additional IFO) over 6 cycles. However EFS was less satisfactory (67% vs. 85%).
- There was an improvement in survival for patients with regional lymph node (SIOP Stage III) disease treated with 6 drugs (including anthracyclines) in MMT 89, compared to those treated with IVA in MMT 84 (5 year OS 60% compared to 42%).

For younger patients ($\leq$3 years) with parameningeal disease, the results of MMT 89 demonstrate that the survival in these patients in whom radiotherapy was deferred was not significantly worse than others receiving systematic radiotherapy. However almost all those who survived ultimately received radiotherapy (only 3/27 patients were cured without radiotherapy). The question of whether a delay in the administration of radiotherapy is of long term benefit remains unanswered.

Issues of local control
It was to be expected that the strategy of determining local therapy based on initial chemotherapy response (as in MMT 84 and MMT 89) would result in higher local relapse rates compared to other treatment strategies. However, a secondary objective of the SIOP studies has been to determine whether patients initially treated with chemotherapy without local definitive therapy could be salvaged by local treatment and further chemotherapy at the time of relapse. Although certain subsets of patients appear to benefit from this strategy (e.g. those with orbital [7] or bladder prostate

tumours [8] this has not been true for all. It has become clear that following the analysis of mature data from MMT 89 when compared to equivalent data from the IRS III and IV studies, the modification of local treatment strategy for some groups of patients was necessary. Systematic radiotherapy is now recommended for all patients $\geq$3 years with alveolar tumours (excluding paratesticular), and, regardless of pathology, those with non-parameningeal head and neck and those over 10 years with limb primaries.

In summary IVA remains the therapy for standard and high risk patients within the MMT studies. The strategy of withholding systematic local therapy has been of benefit to certain subsets of patients, minimising the late effects of therapy whilst others clearly require more aggressive local treatment.

7.4 CWS STUDIES

The first multi-centre German STS study (CWS-81) was conducted under the auspices of the German Society of Paediatric Oncology (GPOH) between 1981 and 1986, the second CWS-86 between 1986-1990. The results of these studies have already been reported [9, 10]. The CWS-91 was conducted between 1991-1996 and CWS-96 between 1996-2002.

Chemotherapy
In the CWS-81 and -86 Studies, all patients received a four drug chemotherapy regimen comprising VCR, AMD, Doxo, and alkylating agent: CPM in the CWS-81 Study (VACA cycle) or IFO in the CWS-86 Study (VAIA cycle). This decision was based on data showing that IFO appeared to be a more effective agent in the treatment of some paediatric tumours. The replacement of CPM by IFO improved the response in patients with macroscopic residual tumour by increasing the proportion of patients with 2/3 or more tumour volume reduction. However, no clear benefit for the event-free and overall survival was seen.
Due to the lack of result improvement and a relatively high incidence of nephrotoxicity, a decision was made to reintroduce CPM in place of IFO in the CWS-91 study for better prognostic groups of patients. In the CWS-91 Study the chemotherapy was also intensified for poor prognostic patients by adding VP16 to VAIA combination (EVAIA cycle). The results did not show a definitive survival advantage, in particular there was no change in the local relapse rate.
The intensification of chemotherapy did not reduce the number of patients who required radiotherapy: the proportion of irradiated patients was similar in the three studies, CWS-81: 77%, CWS-86: 79% and CWS-91: 85%.

Local treatment
In the CWS-81 Study radiation was stratified according to the results of second look surgery at week 16-20, given only to patients who still had microscopic (40 Gy) or macroscopic (50 Gy) residual disease. In the CWS-86 Study radiation was given prior to second look surgery after one cycle of chemotherapy (7-10 weeks). The cumulative dose was stratified according to the degree of tumour volume reduction (32 Gy and 54.4 Gy) and given simultaneous to chemotherapy. In the CWS-91 Study radiation was stratified by tumour invasiveness (T) characteristic, the degree of tumour volume reduction and the results of second look surgery at week 10-13. Since 1986 the German STS studies (CWS) recommend an accelerated hyperfractionated irradiation (2x1,6 Gy daily). The prognosis improved dramatically in the CWS-86 and -91 Study in the group of patients who responded to chemotherapy and had been irradiated mainly prior to secondary surgery in comparison to the CWS-81 Study (EFS 69% vs.67% vs. 41%) .

It is noteworthy that 130 patients in the CWS-86 and -91 studies were irradiated with 32 Gy, the local control rate in this group was 73% and 77% respectively [11]. The comparable dose of 40 Gy conventionally fractionated was given to 25 children in the CWS 81 Study (local tumour control rate 48%).

It has been concluded that: 1) Tumour-volume reduction after preoperative chemotherapy combined with primary tumour size in patients with residual tumour can be used as a basis for risk adapted radiation. 2) Early (10-13 weeks), hyperfractionated, accelerated radiation given simultaneously to chemotherapy improved local tumour control in patients with a good response after preoperative chemotherapy. 3) The dose of 32 Gy when accelerated and hyperfractionated, given simultaneously to chemotherapy is adequate for local tumour control in patients showing a good response to preoperative chemotherapy. Whether the same principle can be applied to each histological entity cannot be answered on the basis of the CWS-Studies.

7.5 AIEOP STSC STUDIES

The Italian studies tried to identify patients with low risk characteristics for whom treatment could be reduced and those patients who needed a more intensive treatment.
Despite the variation in chemotherapy regimens between protocols, the treatment philosophy which dictated the therapeutic decisions was quite similar in the first (RMS 79) and second (RMS 88) Italian protocols. It was based on a) conservative surgery or biopsy at diagnosis; b) initial chemotherapy according to different regimen adopted; c) disease evaluation after an initial 3 to 4 courses of chemotherapy; d) second look surgery in case of residual disease, e) adjuvant chemotherapy following initial or delayed radical surgery, and f) radiotherapy in patients with persistent disease.
In RMS 79 protocol patients classified in Group I received 12 courses of alternating CAV (CPM, Adria, VCR) and VAC (VCR, ACT, CPM) over 11 courses. Group II and III patients received alternating CAV and VAC for a total of 12 courses. Patients with alveolar histology or primary tumour located in the extremities received 18 alternating courses of CAV/VAC. RT was avoided in Group I but delivered to a total dose of 40-45 Gy to Group II and III patients.
In the RMS 88 protocol chemotherapy was reduced to 22 weeks VCR and ACT-D in patients with embryonal histology in IRS group I.
In patients staged in IRS Group II or III chemotherapy intensity was increased in RMS 88 protocol compared to RMS 79 replacing cyclophosphamide with ifosfamide, increasing the ACT-D dose and using the VCR more intensively in the first part of treatment. The regimens used were VAIA and IVA. Radiotherapy doses did not vary substantially but it was administered according to the hyperfractionated and accelerated techniques in RMS 88 study.
In RMS 88 study the 5 years PFS resulted 82%, 72%, and 59% in patients in Group I , II, and III respectively. The overall 5-year PFS and OS were 65.6% and 74% respectively. This represents an improvement from RMS 79 (5 yrs PFS 53.5 and OS 64%). The patients who benefited more were those with the following characteristics: embryonal histology, parameningeal or other primary site, large and invasive tumours (size > 5 cm and T2), node negative [12].
More detailed analyses for subset of patients were carried out. A joint Italian/German study on paratesticular RMS confirmed the good outcome of patients with localized disease (5 years survival 94.6%). Major prognostic factors were tumour invasiveness, size, resectability as well as nodal involvement and age. This allowed the identification of subset of patients at low risk that could be treated with VA. Alveolar histology did not have an adverse impact on the patients outcome (5 year survival 93.3% vs. 88.1% in non alveolar RMS) [13].

In conclusion the Italian experience showed that it is possible to avoid the administration of anthracyclines and alkylating agents in patients with favourable characteristics and chemotherapy intensification improved the results in some subsets of high risk patients. Due to the improved results in RMS 88 an IFO-based regimen became the reference regimen in the Italian studies.

7.6 IRSG STUDIES

The IRS Group has concluded 4 consecutive studies (from IRS-I to IV) from 1972 to 1997. The IRS-V study is currently ongoing.
The 5-year survival improved significantly from 55% on the IRS I protocol, to 63% on the IRS-II and to more than 70% on the IRS-III and IV protocols. [14].
The initial studies used the IRS grouping system to stratify patients and treatment.
Early IRS trials showed that for patients in Group I VCR and ACT-D are enough and radiotherapy is not necessary [15]. More recent analysis showed a role of irradiation for patients with alveolar histology [16].
In Group II patients the VA regimen (VCR, ACT-D) with radiotherapy have been considered the standard treatment for non alveolar nonextremity RMS. The benefit of the addition of other drugs such as doxorubicin and cyclophosphamide is not clear due to the contradictory results noted in IRS-III trial [17].
In Group III patients the intensification of treatment increasing the cumulative drug dose and moving from standard VAC to pulsed VAC has improved the survival from 52% in IRS-I to 74% in IRS-III [15]. No clear benefit was evident with the addition of doxorubicin.

In more recent IRS trials other prognostic factors have been recognised and used to decide the treatment, in particular histology, tumour site and size.
In IRS-IV the 3 years survival was 86%. In this study patients were randomised to receive chemotherapy with VAC or VAI or VIE. No significant difference in outcome was noted and the VAC was elected as gold standard by the American investigators due to the lower cost and nephrotoxicity of cyclophosphamide [4].

7.7 RESULTS OF CWS/RMS 96 AND MMT 95 STUDIES

These studies represent the basis for the ongoing European collaboration. In fact a common stratification has been used (Table 2) and a similar randomised study has been run by the three Cooperative Groups. With the goal to explore the value of more intensive chemotherapy for RMS, the regimen used in the European Intergroup Stage IV Protocol (CEVAIE) was randomised against the standard treatment, i.e. VAIA in the German/Italian CWS/RMS 96 or IVA in the MMT 95 study. Differences in local treatment philosophy at that time precluded the possibility of planning a common study.

Table 2 - CWS/RMS 96 & MMT 95 Common Stratification

N-Status	Histology	Group	Site	pT-Status	Risk Group
N0	ERMS/RMS nos	I	Any	pT1	***LOW***
		I	Any	pT2	***STANDARD***
		II+III	ORB, HN, NBP	pT3a/b/c	
		II+III	PM, UG-BP, EXT, OTH	pT3a/b/c	***HIGH***
	ARMS, EES/PNET	Any	Any	Any	
N1	All				

In the CWS/STSC experience Low, Standard and High Risk Group showed good preliminary results: EFS 88%, 77% and 62% respectively and OS 97%, 95% and 78% respectively (see Figure 1 and 2).

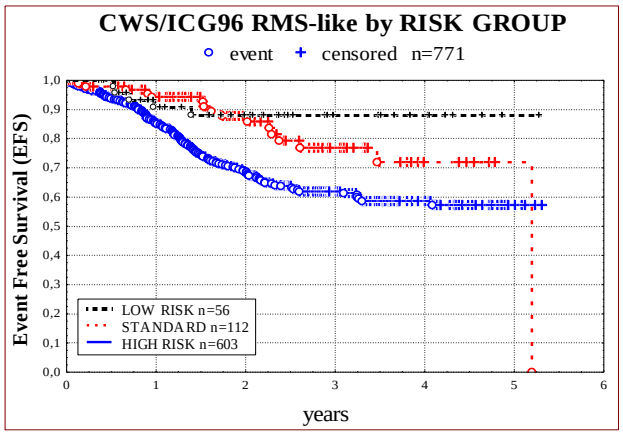


Figure 1: Event free survival according to risk group

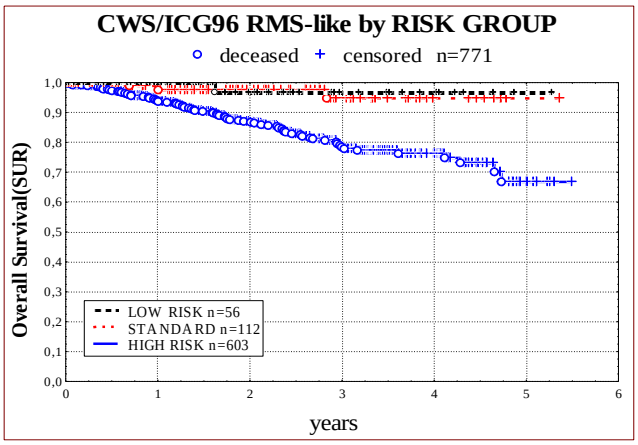


Figure 2: Overall survival according to risk group

Low Risk: patients were treated both in the SIOP MMT 95 and the CWS/RMS 96 study with Vincristine and Actinomycin D only. This treatment approach followed the Italian experience of the RMS 88 study in which 4 blocks of VA was used for the first time. The good results achieved with this low toxic regimen has led to its adoption in this protocol [13 18].

Standard risk: These patients have been treated with IVA (9 blocks over 25 weeks) both in MMT 95 and CWS/RM S96. This represented a treatment reduction for the CWS group that used anthracyclines in the previous protocol. The total length of therapy has also been reduced from 35 (CWS-81 and RMS 88) to 25 weeks.
In the CWS/STSC experience events in this group were mainly local. The main reason for the greater number of relapses has been attributed to the cautious administration of RT. Of the irradiated group within the standard risk group only 7% relapsed vs. 15% in the non-irradiated group even though the irradiated group have been negatively selected (prognostic risk factors poorer than in non-irradiated group).

High risk: In the CWS/RMS 96 protocol these patients were enrolled in a randomised trial with the aim to compare a 6-drug regimen (CEVAIE) with the "standard" 4-drug regimen VAIA. In the MMT 95 study CEVAIE was randomised against IVA.
Both studies failed to show a superior outcome for patients treated with CEVAIE (unpublished data).

7.8 CONCLUSIONS

The treatment of patients with RMS undergoes continuing evolution and should be adapted constantly as new evidence emerges from clinical trials. It is therefore not possible to define a true "standard treatment" for these patients. This evolving process has lead to the improved survival seen over the last decades and should continue in the future.

- A more accurate prognostic assessment at diagnosis is needed to ensure that those patients with a good prognosis are not over treated and to identify those with a poorer prognosis who require a more aggressive approach. Histology, staging (IRS grouping), node involvement tumour site and size and patient's age have been presently identified as major prognostic factors.

- A better selection of children that can be treated with less intensive treatment (VA alone $\pm$ radiotherapy) should be attempted to avoid acute and late sequelae of alkylating agents and anthracyclines.

- Chemotherapy regimens based on the VAC or IVA combinations appear equally effective and may be considered the "reference regimen" for most children with RMS. However a substantial proportion of children are not cured with such regimens and the search for new combinations must continue. The value of the addition of other drugs should be investigated in randomised trials.

- Local treatment is a fundamental part of RMS but the advantages and disadvantages of aggressive surgery and/or radiotherapy should be balanced against the late effects for young children.

- Conservative surgery is recommended, and experience should be gathered to select those children for whom surgery may be the only necessary local treatment.

- Although it is possible to cure about 30% of patients without radiotherapy, only a subgroup of them (i.e. embryonal tumour completely resected at diagnosis) can confidently be identified at diagnosis. Further efforts should be made to better define a favourable population in whom irradiation and its late effects can be avoided.

Increasing international collaboration should improve the treatment stratification and explore through well designed, randomised studies better treatment strategies for children with RMS.

8. Rationale for the E*p*SSG RMS 2005 protocol

8.1 RATIONALE FOR THE NEW E*p*SSG STRATIFICATION

An analysis carried out by the CWS group using the CWS/RMS 96 preliminary data and validated using the data of studies with longer follow up: the SIOP MMT 84 and 89, the German CWS-81 and 91 and the Italian RMS 79 and RMS 88 studies (see Table 4) identified as significant prognostic factors for localized RMS the following:

- HISTOLOGY (aRMS *vs.* eRMS)
- POST SURGICAL STATUS (AS DEFINED BY IRS GROUPING SYSTEM),
- TUMOUR SITE,
- NODE INVOLVEMENT (N0 ABSENT, N1 PRESENT),
- TUMOUR SIZE (> OR ≤ 5 CM)
- PATIENT'S AGE (UNFAVOURABLE IF ≥10 YEARS)

Combining these factors 8 subgroups of patients have been identified (see Table 3).

Table 3 – Patient Subgroups

Subgroup	**Pathology**	**IRS Group**	**Site**	**Node Stage**	**Tumour Size & Age**
A	eRMS	I	Any	N0	≤5 cm and <10 yr
B	eRMS	I	Any	N0	>5 cm or ≥10 yr
C	eRMS	II, III	Orbit; Head & Neck non PM GU non Bladder-Prostate	N0	Any
D	eRMS	II, III	Extremity; Parameningeal; Bladder-Prostate; Other sites	N0	≤5 cm and <10 yr)
E	eRMS	II, III	Extremity; Parameningeal; Bladder-Prostate; Other sites	N0	>5 cm or ≥10 yr
F	eRMS	I, II, III	Any	N1	Any
G	aRMS	I, II, III	Any	N0	Any
H	aRMS	I, II, III	Any	N1	Any

Table 4 - Results for each subgroup in the different European studies

	CWS/RMS 96		MMT 84 & 89		CWS81 & 91		RMS 79 &88	
Subgroups	**% of patients**	**3 yrs EFS**	**% of patients**	**5 yrs EFS**	**% of patients**	**5 yrs EFS**	**% of patients**	**5 yrs EFS**
A	7	93%	6	93%	8	88%	6	94%
B	6	73%	8	69%	27	72%	6	78%
C	18	81%	21	61%			18	72%
D	11	77%	10	61%			9	83%
E	27	59%	29	52%	57	59%	27	55%
F	10	43%	10	55%			8	51%
G	15	64%	12	28%			20	52%
H	6	25%	4	31%	7	36%	6	39%

Taking into consideration these results and their implications for treatment, 4 Risk Groups have been identified. (See Table 5)

Table 5 - Risk Group and predicted EFS and OS

Risk Group	Subgroup	Estimated % of patients	Estimated 3 yrs EFS
Low Risk	***A***	***6-8%***	***90%***
Standard Risk	***B***	***25-35%***	***70-80%***
	C		
	D		
High Risk	***E***	***55-60%***	***50-55%***
	F		
	G		
Very High Risk	***H***	***4-7%***	***30-40%***

8.2 RATIONALE FOR LOW RISK PATIENTS TREATMENT

This represents a very selected group of patients, accounting for 6 to 8% of the whole population of localized RMS, with an excellent outcome. Most of these patients are represented by children with paratesticular RMS.
Reducing the toxicity without jeopardizing the results is therefore the goal in this group of patients.
The VA chemotherapy adopted in the previous protocols RMS 88, CWS/RMS 96 and SIOP MMT 95 showed good results with event-free and overall survival above 80 and 90%, respectively [13].
The results achieved in MMT 89 with 12 of 41 stage I patients relapsing after only 2 blocks of VA suggest caution in further reducing the treatment in this subset of patients [18].
In conclusion VA x 22 weeks (8 VA blocks) represents a low-toxic, effective regimen for this group of patients and will be adopted in this protocol.

8.3 RATIONALE FOR STANDARD RISK PATIENTS TREATMENT

This group includes patients with a satisfactory prognosis for whom the goal is to reduce the treatment without compromising survival.
Three Subgroups of patients have been identified with similar outcome. However because their characteristics are quite different it has not been possible to design an identical treatment. Three treatment arms have been proposed, maintaining IVA as the regimen of reference.

8.3.1 Subgroup B: Treatment Arm SR-B

These patients are similar to the ones included in the Low Risk Group but tumour size or age are unfavourable. Most of these patients are represented by children with paratesticular RMS older than 10 years and/or with large tumour (> 5 cm).
There is increasing evidence from the European and USA experience that older children ($\geq$ 10 years) with low risk characteristics fare worse than their younger counterparts [13, 18]. In the IRS studies an increased risk of nodal relapse have been seen in Group I patients with paratesticular tumour and age $\geq$ 10 years. This prompted the IRSG colleagues to return to a surgical staging for older patients [4].
The European experience reported a lower rate of nodal involvement as laparotomy with nodal exploration is avoided, but caution has been recommended in reducing the treatment in such patients.
The Subgroup B has been created to upstage these patients and treat them with a limited dose of alkylating agents with the aim of reduce the risk of relapse and avoiding important toxicity.

8.3.2 Subgroup C: Treatment Arm SR-C

This group is mainly represented by orbital and head and neck non parameningeal RMS.
The Italian, German and North American experience is in favour of the use of systematic irradiation of these patients. The MMT studies have demonstrated, however, that some children can be treated with chemotherapy alone and eventually salvaged after relapse with irradiation [7].
In the more recent IRS IV study patients with orbital RMS in IRS Group I or II have been treated with VA and irradiation with an excellent outcome [4]. The same strategy is currently used for all orbital RMS in the ongoing IRS V study.
Therefore it seems possible in this subgroup *a)* to reduce the cumulative dose of alkylating agents compared with previous European protocols using radiotherapy and *b)* to try to select prospectively patients with favourable features that can avoid irradiation. These patients will be selected according to chemotherapy response (CR after the initial 3 blocks of IVA) and favourable tumour size and age.

8.3.3 Subgroup D: Treatment Arm SR-D

Patients with embryonal RMS, N0, favourable age and tumour size are included in this category. They are mainly represented by young children with small tumour arising in the extremities, parameningeal, bladder-prostate or other site areas.

An analysis of patients included in the high risk category according to CWS/RMS 96 and MMT 95 stratification showed that children with embryonal RMS, N0, favourable age and tumour size (see Table 4) have a prognosis comparable to patients treated in the standard risk group of CWS/RMS.

Consequently these patients have been included in the Subgroup D in this protocol and down staged to receive the treatment planned for the standard risk group.

These patients will continue to receive the IVA regimen as in the MMT 95 study but this represents a treatment reduction in comparison with the CWS/RMS 96 protocol where the VAIA regimen was used.

8.4 RATIONALE FOR HIGH RISK PATIENTS TREATMENT

Patients with large embryonal RMS localized in unfavourable sites, alveolar RMS, and N1 are included in this Group.

The different Subgroups included in this category share the same unsatisfactory prognosis and therefore the need for a more effective strategy.

This protocol will try to improve the outcome of these patients by implementing two novel strategies:

1) the intensification of initial chemotherapy adding anthracyclines to the standard IVA regimen
2) the adoption of a low dose maintenance treatment after 1st line chemotherapy.

8.4.1 Doxorubicin in RMS treatment

Doxorubicin (Doxo) is an effective drug in the treatment of RMS. However its role as part of a multidrug regimen is controversial. It is not clear whether adding Doxo to an established regimen such as VAC or IVA improves the survival of patients. This must be carefully considered as the toxicity profile of the drug may worsen the immunosuppression in the short term and cause cardiotoxicity in the long term.

An IRS phase II window in children with newly diagnosed metastatic rhabdomyosarcoma demonstrated the efficacy of IFO and Doxo with a 63% CR+PR rate at 12 weeks [19]. Furthermore the preliminary results of the window study with Doxo in high risk RMS in the SFCE experience (65% CR+PR) support the value of Doxo as an efficient drug in RMS (Bergeron C, unpublished data). Doxo is also considered an important drug in the treatment of other paediatric sarcomas such as osseous Ewing's and PNET [20]. Moreover a meta-analysis of several trials demonstrated that an induction treatment including Doxo in every course was better than a schema alternating Doxo with ACT-D [21].

Doxo is also one of the most effective drugs in the treatment of soft tissue sarcoma in adult patients [22].

Unfortunately different randomised trials performed by the IRS Group did not show a substantial difference in survival and progression free survival for patients with RMS treated with VAC or VAC plus anthracyclines. In IRS-I the addition of 5 VadrC course to VAC did not improve the results [23]. In IRS-II a similar comparison, but with higher cumulative doses of Doxo (480 mg/m^2) showed no improvement [24]. In IRS III further randomised comparison did not yield to different results. However it was noted that a more complex therapy including administration of Doxo and cisplatin appeared to have caused a significative improvement in some subgroups of patients i.e. IRS group I/II alveolar histology and special pelvic sites [17]

It should be noted that in IRSG studies the treatment scheme was based on the alternating administration of VAC and VadrC, consequently the intervals between Doxo containing courses were wide, reducing the anthracycline dose-intensity.
In conclusion Doxo seems a very effective drug against RMS, however its role as part of a multi-drug regimen remains to be established.

8.4.2 The IVADo Regimen

This regimen combines the Doxo with the standard combination IVA. This allows the intensification of the chemotherapy avoiding the need to alternate courses with and without the anthracyclines as has been done up to now. This combination has been tested in a pilot study conducted by the STSC in which 29 patients with metastatic STS have been treated with the IVADo regimen (G. Bisogno et al, Cancer in press). Toxicity was mainly haematological with grade 4 neutropenia encountered in 67% of evaluable cycles and 17 patients and 8 patients receiving blood and platelets, respectively. Major toxicity occurred in two patients: VOD and seizures. Grade 3-4 organ toxicity were constipation (9.7% of cycles), mucositis (6.5%) and peripheral neuropathy (6.5%). The median interval between courses was 23 days (range 19-51). Clinical complete response after three IVADo was evident in 5 patients, PR in 17, minor PR in 2, mixed response in 2. Stable tumour was evident in 2 children with desmoplastic small round cell tumour, whereas tumour progression was evident in a patient with malignant schwannoma.
These data are also supported by preliminary data from a window study for metastatic RMS run by the SFCE group in France where no unexpected toxicities were observed in the first 7 patients enrolled.
In conclusion the IVADo regimen has proved to be active against soft tissue sarcomas but, more importantly, it is feasible because no unacceptable toxicities have been reported.

8.4.3 Maintenance treatment in RMS

Chemotherapy regimens have been progressively intensified [15] improving the survival of patients with localised disease. However patients with unfavourable characteristics, such as unfavourable site or alveolar subtype, did not show major improvements [25] and any attempt to further increase the drug dose in metastatic RMS has not significantly changed the poor prognosis of these patients [26]. When complete remission has been achieved, minimal residual disease, resistant to high dose short-term treatment, remains an obstacle to major increases in cure rate.
It is, therefore, important to identify new approaches to improve the outcome for high-risk patients.
Low dose continuous chemotherapy has been used with some success [27] and new hypotheses on antitumour mechanism have been advanced [28]. This approach is also attractive if we consider the reduced toxicity of low dose treatment.
Although there is little experience in the treatment of soft tissue sarcoma promising results have been reported by the CWS group. They used standard chemotherapy in children with metastatic soft tissue sarcoma followed by high dose chemotherapy (thiotepa + cyclophosphamide and melphalan + etoposide) or an oral treatment with trofosfamide + idarubicine. The results in 62 patients are very promising with 3-year EFS above 50% for patients taking oral treatment (and EFS 20% after high dose). Since the comparison was not randomised a risk bias between the two groups must be taken into consideration. It seems though that oral maintenance therapy has a greater benefit for group IV patients than does high dose chemotherapy.

The duration of treatment should also be addressed. This has been progressively decreased over years without apparently impairing the results. In IRS-I chemotherapy was administered for 2 years. In the latest North American protocols most patients received one year of treatment.

In the SIOP studies the treatment duration for the majority of patient was 27 weeks.
In Italian protocols the treatment duration has been progressively reduced from 52-78 weeks in the first study to 22-37 weeks in the second and 25 in the third one. Also in the CWS studies the treatment duration have been reduced for most patients from 35 weeks in the early studies to 25 in the latest ones.

The drug doses administered in each cycle have been increased progressively in the most modern protocols and this may have hindered the benefit of a longer treatment. Up to now no studies have been performed to establish which is the optimal duration of treatment for RMS.

In this protocol we propose to investigate the role of low dose chemotherapy in patients with RMS.

On the basis of previous experience with RMS cyclophosphamide appears an interesting drug for the following reasons:
a) is active against RMS
b) has been successfully used at low dose (2.5 mg/kg/day for up to 2 years) in the initial IRS studies[23, 24].
c) it may be easily included in the current European protocols where different drugs are used during the initial intensive treatment.

The activity of vinorelbine in the treatment of heavily pre-treated patients with soft tissue sarcoma has recently been published [29]. A dose finding study has been performed by the STSC [30].
Therefore the combination of these two drugs is proposed to investigate the role of low dose chemotherapy in patients with rhabdomyosarcoma. Patients in complete remission at the end of standard treatment will be randomised to stop the therapy or to continue for 6 more months with the vinorelbine-cyclo regimen.

8.4.4 Alveolar Paratesticular tumours

Despite unfavourable pathology this very small group of patients showed a good outcome in previous European studies. In the CWS/STSC experience they represented 8% of all paratesticular RMS and the 5 year survival rate was 93% after IVA $\pm$ doxorubicin chemotherapy [31]. However 4 relapses occurred. Similar data come out from the SIOP experience.
According to these data patients with paratesticular alveolar RMS will be kept in the high risk group, according to the histology factor, however in consideration of the better outcome they will not be included in the randomised trial and will be treated with IVAx9 (avoiding anthracyclines).
Patients with Alveolar N1 tumour will be treated according to the very high risk arm.

8.5 RATIONALE FOR VERY HIGH RISK PATIENTS TREATMENT

In an attempt to better define patients at high risk of relapse, an analysis of the High risk arm of the CWS/RMS 96 has been made. The group of patients with alveolar RMS and nodal involvement had the poorest outcome, comparable to that of group IV patients. In CWS/RMS 96 the 3 years EFS was 28% and OS 29%.
Results in the SIOP experience were only partially better with 5-year EFS of 39%.
These patients consequently will be treated with the more intensive strategy outlined in this protocol comprising the IVADo regimen and the maintenance chemotherapy to improve the results in comparison with historical controls.

9. References

1. Newton WA, Jr., Gehan EA, Webber BL, et al. Classification of rhabdomyosarcomas and related sarcomas. Pathologic aspects and proposal for a new classification--an Intergroup Rhabdomyosarcoma Study. *Cancer* 1995;76:1073-1085.

2. Barr FG. Molecular genetics and pathogenesis of rhabdomyosarcoma. *J Pediatr Hematol Oncol* 1997;19:483-491.

3. Scrable H, Witte D, Shimada H, et al. Molecular differential pathology of rhabdomyosarcoma. *Genes Chromosomes Cancer* 1989;1:23-35.

4. Crist WM, Anderson JR, Meza JL, et al. Intergroup rhabdomyosarcoma study-IV: results for patients with nonmetastatic disease. *J Clin Oncol* 2001;19:3091-3102.

5. Flamant F, Rodary C, Voute PA, Otten J. Primary chemotherapy in the treatment of rhabdomyosarcoma in children: trial of the International Society of Pediatric Oncology (SIOP) preliminary results. *Radiother Oncol* 1985;3:227-236.

6. Flamant F, Rodary C, Rey A, et al. Treatment of non-metastatic rhabdomyosarcomas in childhood and adolescence. Results of the second study of the International Society of Paediatric Oncology MMT84. *Eur J Cancer* 1998;34:1050-1056.

7. Oberlin O, Rey A, Anderson J, et al. Treatment of orbital rhabdomyosarcoma: survival and late effects of treatment--results of an international workshop. *J Clin Oncol* 2001;19:197-204.

8. Anderson J, Raney RB, Carli M, al. e. International study of characteristics and outcome of patients with primary rhabdomyosarcoma of the bladder / prostate. *Med Pediatr Oncol* 2001;37:181.

9. Koscielniak E, Jurgens H, Winkler K, et al. Treatment of soft tissue sarcoma in childhood and adolescence. A report of the German Cooperative Soft Tissue Sarcoma Study. *Cancer* 1992;15:2557-2567.

10. Koscielniak E, Harms D, Henze G, et al. Results of treatment for soft tissue sarcoma in childhood and adolescence: a final report of the German Cooperative Soft Tissue Sarcoma Study CWS-86. *J Clin Oncol* 1999;17:3706-3719.

11. Koscielniak E, Schmidt B, Knietig R, al. e. Effectiviy of a 32 Gy radiation dose in children with rhabdomyosarcoma: Report of the German Cooperative Soft Tissue Sarcoma Studies (CWS). *Med Pediatr Oncol* 2001;37:186.

12. Carli M, Bisogno G, Cecchetto G, al. e. Childhood Rhabdomyosarcoma: Results of the Italian Cooperative study RMS88. *Medical and Pediatric Oncology* 1998;31:262.

13. Ferrari A, Bisogno G, Casanova M, et al. Paratesticular rhabdomyosarcoma: report from the Italian and German Cooperative Group. *J Clin Oncol* 2002;20:449-455.

14. Raney RB, Anderson JR, Barr FG, et al. Rhabdomyosarcoma and Undifferentiated Sarcoma in the First Two Decades of Life: A Selective Review of Intergroup Rhabdomyosarcoma Study Group Experience and Rationale for Intergroup Rhabdomyosarcoma Study V. *Am J Pediatr Hematol Oncol* 2001;23:215-220.

15. Pappo AS, Shapiro DN, Crist WM, Maurer HM. Biology and therapy of pediatric rhabdomyosarcoma. *J Clin Oncol* 1995;13:2123-2139.

16. Wolden SL, Anderson JR, Crist WM, et al. Indications for radiotherapy and chemotherapy after complete resection in rhabdomyosarcoma: A report from the Intergroup Rhabdomyosarcoma Studies I to III. *J Clin Oncol* 1999;17:3468-3475.

17. Crist W, Gehan EA, Ragab AH, et al. The Third Intergroup Rhabdomyosarcoma Study. *J Clin Oncol* 1995;13:610-630.

18. Stewart RJ, Martelli H, Oberlin O, et al. Treatment of children with nonmetastatic paratesticular rhabdomyosarcoma: results of the Malignant Mesenchymal Tumours studies (MMT 84 and MMT 89) of the International Society of Pediatric Oncology. *J Clin Oncol* 2003;21:793-798.

19. Sandler E, Lyden E, Ruymann F, et al. Efficacy of ifosfamide and doxorubicin given as a phase II "window" in children with newly diagnosed metastatic rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study Group. *Med Pediatr Oncol* 2001;37:442-448.

20. Rodriguez-Galindo C, Spunt SL, Pappo AS. Treatment of Ewing sarcoma family of tumors: current status and outlook for the future. *Med Pediatr Oncol* 2003;40:276-287.

21. Smith MA, Ungerleider RS, Horowitz ME, Simon R. Influence of doxorubicin dose intensity on response and outcome for patients with osteogenic sarcoma and Ewing's sarcoma. *J Natl Cancer Inst* 1991;83:1460-1470.

22. Spira AI, Ettinger DS. The use of chemotherapy in soft-tissue sarcomas. *Oncologist* 2002;7:348-359.

23. Maurer HM, Beltangady M, Gehan EA, et al. The Intergroup Rhabdomyosarcoma Study-I. A final report. *Cancer* 1988;61:209-220.

24. Maurer HM, Gehan EA, Beltangady M, et al. The Intergroup Rhabdomyosarcoma Study-II. *Cancer* 1993;71:1904-1922.

25. Baker KS, Anderson JR, Link MP, et al. Benefit of intensified therapy for patients with local or regional embryonal rhabdomyosarcoma: results from the Intergroup Rhabdomyosarcoma Study IV. *J Clin Oncol* 2000;18:2427-2434.

26. Carli M, Colombatti R, Oberlin O, et al. High-dose melphalan with autologous stem-cell rescue in metastatic rhabdomyosarcoma. *J Clin Oncol* 1999;17:2796-2803.

27. Kushner BH, Kramer K, Cheung NK. Oral etoposide for refractory and relapsed neuroblastoma. *J Clin Oncol* 1999;17:3221-3225.

28. Kamen BA, Rubin E, Aisner J, Glatstein E. High-time chemotherapy or high time for low dose. *J Clin Oncol* 2000;18:2935-2937.

29. Casanova M, Ferrari A, Spreafico F, et al. Vinorelbine in previously treated advanced childhood sarcomas: evidence of activity in rhabdomyosarcoma. *Cancer* 2002;94:3263-3268.

30. Casanova M, Ferrari A, Bisogno G, Merks JH, De Salvo GL, Meazza C, Tettoni, K, Provenzi M, Mazzarino I, Carli M. Vinorelbine and low-dose cyclophosphamide in the treatment of pediatric sarcomas: pilot study for the upcoming European Rhabdomyosarcoma Protocol. *Cancer*. 2004; 101:1664-71.

31. Ferrari A, Bisogno G, Casanova M, et al. Is alveolar histotype a prognostic factor in paratesticular rhabdomyosarcoma? The experience of Italian and German Soft Tissue Sarcoma Cooperative Group. *Pediatr Blood Cancer* 2004;42:134-138.

10. Study structure

This protocol includes:

- an observation study
for patients in the low, standard and very high risk groups.

- an investigational study (randomised trial)
for children within the high risk group

10.1 STRATIFICATION AND RISK GROUPS

Patients have been stratified in 8 Subgroups (A through H) that are subsequently grouped in 4 Risk Groups: low, standard, high and very high.

The prognostic factors considered are:

- **Pathology:**

Favourable = all embryonal, spindle cells, botryoid RMS
Unfavourable = all alveolar tumours (including the solid-alveolar variant)

- **Post surgical stage:**

according to the IRS grouping. Briefly
Group I = primary complete resection (equivalent to SIOP pT1);
Group II = microscopic residual (equivalent to SIOP pT3a) or primary complete resection but node involvement (N1);
Group III = macroscopic residual (equivalent to SIOP pT3b).
For more details on IRS grouping system see also appendix A.2.

- **Site:**

Favourable = orbit, GU non bladder prostate (i.e. paratesticular and vagina/uterus) and head & neck non PM
Unfavourable = all other sites (parameningeal, extremities, GU bladder-prostate and "other site")

- **Node stage**

According to the TNM classification
N0 = no clinical or pathological node involvement
N1 = clinical or pathological nodal involvement

- **Size & Age:**

Favourable = Tumour size (maximum dimension) $\leq$5 cm ***and*** Age < 10 years
Unfavourable = all others (i.e. Size >5 cm ***or*** Age $\geq$ 10 years)

Note: patients with malignant effusion (i.e. tumour cell in peritoneal or pleural fluid) or cells in the spinal fluid should be treated according to the protocol for metastatic RMS

Table 6 - Risk Stratification for EpSSG non metastatic RMS study

Risk Group	Subgroups	Pathology	Post surgical Stage (IRS Group)	Site	Node Stage	Size & Age
Low Risk	**A**	Favourable	I	Any	N0	Favourable
Standard Risk	***B***	Favourable	I	Any	N0	Unfavourable
	C	Favourable	II, III	Favourable	N0	Any
	D	Favourable	II, III	Un favourable	N0	Favourable
High Risk	***E***	Favourable	II, III	Unfavourable	N0	Unfavourable
	F	Favourable	II, III	Any	N1	Any
	G	Unfavourable*	I, II, III	Any	N0	Any
Very High Risk	***H***	Unfavourable	I, II, III	Any	N1	Any

** Note: for paratesticular alveolar RMS see paragraph 8.4.4..*

11. Patient eligibility

Participating centres are expected to register all patients with Rhabdomyosarcoma and other Soft tissue sarcomas.

There are two levels of eligibility for this protocol: according to the risk group patients may be eligible to be treated according to the observation study or to entry (high risk group) into the randomised trial (see summary chart chapter 11.3).
Centres are not allowed to enrol patients only in the trial or in the observation study.

11.1 ELIGIBILITY TO THE PROTOCOL (STUDY + TRIAL)

Patients with the following criteria are eligible for EpSSG RMS 2005 protocol:

- A pathologically proven diagnosis of Rhabdomyosarcoma.
- No evidence of metastatic lesions.
- Age less than 21 years (20 years and 364 days) of age.
- Previously untreated except for primary surgery.
- 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%). Echocardiogram at baseline is only required for patient's stratified to either the high risk or very high risk group.
- No previous malignant tumours.
- Interval between diagnostic surgery and start of chemotherapy no longer than 8 weeks.
- Diagnostic material available for pathology review.
- Available for long term follow up through the treatment centre.
- Written informed consent for treatment available.

Patients with a diagnosis of RMS not satisfying the above criteria will be registered, but not evaluated for the purpose of this study.

*Patients with **RMS N.O.S, Undifferentiated STS** and **Ectomesenchymoma** are eligible to RMS 2005 protocol: see paragraph 29.4*

Notes
- *patients with malignant effusion* (i.e. tumour cell in peritoneal or pleural fluid) or malignant cells in the spinal fluid should be treated according to the protocol for metastatic RMS.

- *Adults with RMS* (> 21 years) may be eligible for registration and treatment on study (according to institutional preference) but not for randomisation.

11.2 ELIGIBILITY TO THE RANDOMISED TRIALS

Patients eligible for the EpSSG RMS 2005 Protocol are also eligible for the randomised trials when the following criteria are satisfied:

11.2.1 First Randomisation

This randomisation will take place after the diagnostic surgery, before chemotherapy treatment is started using the Remote Data Entry (RDE) system (see randomisation procedure chapter 33.5).

Patients with the following criteria are eligible for EpSSG RMS 2005 randomised:

- stratification according to the High Risk Arm
- age > 6 months (and < 21 years)
- informed consent given for the randomised study

11.2.2 Second Randomisation

- stratification and treatment according to the High Risk Arm
- age > 6 months at the moment of randomisation (some infants, not eligible for the first randomisation, may be randomised here) and < 21 years at diagnosis (patients older than 21 years at the moment of second randomisation are eligible too)
- in complete remission or with minimal abnormalities* on imaging studies at the end of "standard " treatment (9 courses of chemotherapy ± surgery ± radiotherapy)

** It is intended that minimal radiological anomalies describe imaging studies in which there may be residual abnormalities, compatible with fibrosis and the responsible clinician would be ready to stop the treatment.*

Patients must be randomised within 8 weeks after the end of treatment.
The end of treatment is defined as the last day of the 9th chemotherapy cycle. However:

- if surgery is performed after the 9th chemotherapy cycle, the date of surgery will be considered;
- if radiotherapy is administered after 9 cycles of chemotherapy, the date of the end of RT will be considered. Since maintenance CT should be started within 8 weeks from the last day of the 9th CT cycle, it would be better to start the maintenance CT during irradiation. (See randomisation procedure chapter 33.5)

Note: the RDE system will guide the clinician to check the eligibility criteria and assign the risk group.

11.3 SUMMARY FOR ELIGIBILITY

Diagnosis of Rhabdomyosarcoma or other malignant mesenchymal tumours

ELIGIBLE FOR REGISTRATION

A pathologically proven diagnosis of RMS
Age < 21 years
Previously untreated except initial surgery
No pre-existing illness preventing treatment
No previous malignant tumours

Diagnosed ≤ 8 weeks
Pathology available for central review
Available for follow up
Written consent for treatment available

YES

NO

Registration only

Evidence of Distant Metastases

NO

YES

Treat in EpSSG Stage IV Study

ELIGIBLE FOR RMS 2005 PROTOCOL

Low Risk Group	**Standard Risk Group**	**High Risk Group**	**Very High Risk Group**
Subgroup A: ♦ VA x8	*Subgroup B:* ♦ IVA + VA *Subgroup C:* ♦ IVA ±VA *Subgroup D:* ♦ IVA	*Subgroup E* *Subgroup F* *Subgroup G* *if* -Age > 6 months -Informed consent given **Randomised trial No. 1** *(IVA vs IVADo)* if -In CR or with minimal anomalies at the end of treatment **Randomised trial No. 2** (stop treatment vs. maintenance)	*Subgroup H* ♦ IVADo + maintenance

12. 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.

12.1 DIAGNOSIS

This 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. On rare occasions diagnosis may be achieved by cytology of a malignant effusion or bone marrow aspirate. (See Surgical Guidelines about initial biopsy techniques and Pathology Guidelines for details about tissue handling and diagnostic pathology techniques)

12.2 CLINICAL ASSESSMENT

- Weight, Height and Body Surface Area
- Blood pressure, pulse
- Site and clinical extent of the tumour. *For site definition see Appendix A.4.*
- Regional lymph node involvement should be assessed and recorded in all cases, including biopsy if involvement is suspected but is clinically/radiologically uncertain - under these circumstances needle biopsy or fine needle aspirate cytology may be sufficient to confirm tumour infiltration.

12.3 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: at least one bone marrow aspirate and trephine should be performed. Patients with evidence of node or distant metastases and all those with alveolar primaries should have bilateral aspirates and trephines.
- CSF Examination for cytospin and cell count is required only for parameningeal tumours

- **Echocardiogram:** baseline assessment is required in all patients included in High and Very High risk groups.

Optional investigations:

- Pulmonary function test
- Hormonal status in patients with tumours close to endocrine organs (thyroid gland, adrenal gland, hypophysis etc).

Note: Semen storage should be considered in post-pubertal boys before commencing chemotherapy.

12.4 RADIOLOGICAL GUIDELINES

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, other than the chest, including head and neck tumours with possible skull base invasion [1-5].
MRI is mandatory for genito-urinary primaries and paraspinal tumours.
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)

See also Appendix A.6 for MRI and CT scanning technical recommendations.

- **CT scan or MRI** of the primary site (+ initial ultrasound if follow-up with ultrasound is possible).

  CT or MRI examination should be carried out with the use of contrast.
  The investigation will need to be performed (again) after surgical excision biopsy if significant volume has been resected.

Imaging of the primary site should include tumour volume measurement and examination of regional lymph nodes especially if not evaluable clinically or if clinically suspicious.

- **Chest CT scan:** the presence of lung metastases must be evaluated in all patients at diagnosis by CT scan *and* Postero-Anterior and Lateral **Chest X-Ray.**

  Intravenous-contrast enhancement is mandatory for limb or abdominal primaries (and ideally for other primaries).

- **Abdomen-pelvic CT scan** (during same acquisition as chest CT)

  For abdominal, pelvic primaries if MRI has not been performed. To assess the presence of abdominal lymphadenopathy in case of 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** (with plain X rays and / or MRI of any isolated abnormal site)

  Mandatory in all patients at diagnosis.

- **Craniospinal MRI**

  If intraspinal extension or suspected meningeal involvement.

Optional investigation:

- **PET-CT:** According to local availability and local protocols.

Special Notes

Paratesticular tumours must have evaluation of regional (para aortic) lymph nodes by CT/MRI and Ultrasound.

Limb tumours

- Lower limb tumours must have evaluation of pelvic lymph nodes by CT or MRI even if femoral nodes are clinically/radiologically (including ultrasound) normal.
- Upper and lower limb tumours must have surgical evaluation of axillary or inguinal nodes, respectively, even if nodes are clinically/radiologically normal. This applies for both alveolar and embryonal RMS.

Tumour dimensions should be recorded in 3 diameters choosing, as far as possible, the 3 maximum diameters (sagittal, coronal and axial)

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)

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

12.4.1 Evaluation of lung lesions

Chest CT scan at diagnosis is mandatory in all patients. 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 [6-8]. 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 it is the radiologist, expert in such problems, that gives the interpretation of lung lesions, in discussion with the oncologist. Similarly to what is recommended for other solid tumours (i.e. Ewing sarcoma), one pulmonary/pleural nodule of 1 cm, or lesions > 0.5 cm in more than one site, are considered evidence of pulmonary metastasis, as long as there is no other clear medical explanation for these lesions. For EpSSG studies, the following patterns will be considered as metastatic pulmonary disease (assuming there is no other clear medical explanation for the 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 smaller 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".

In such cases a biopsy may be performed but it is not recommended. In fact, these lesions may be considered as "evident micrometastasis" and because micrometastasis probably is present in every case of localized RMS the patients will be eligible for the protocol for localised RMS.

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

12.4.2 Evaluations of Lymph nodes

Defining lymph nodal spread of tumour is critical to staging [9], 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: see appendix A.5.

Evidence of nodal involvement beyond the regional lymph nodes must be interpreted as distant metastasis and the patient must be treated according to the protocol for metastatic RMS.
Examples:

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

12.5 REFERENCES – RADIOLOGY

1. McHugh K, Boothroyd AE. The role of radiology in childhood rhabdomyosarcoma. *Clin Radiol* 1999;54:2-10.

2. De Schepper AM, De Beuckeleer L, Vandevenne J, Somville J. Magnetic resonance imaging of soft tissue tumors. Eur Radiol 2000;10:213-223.

3. Kransdorf MJ, Murphey MD. Radiologic evaluation of soft-tissue masses: a current perspective. AJR Am J Roentgenol 2000;175:575-587.

4. Berquist TH, Dalinka MK, Alazraki N, et al. Soft tissue masses. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000;215 Suppl:255-259.

5. Tomura N, Hirano H, Sashi R, et al. Comparison of MR imaging and CT in discriminating tumor infiltration of bone and bone marrow in the skull base. Comput Med Imaging Graph 1998;22:41-51

6. Picci P, Vanel D, Briccoli A, et al. Computed tomography of pulmonary metastases from osteosarcoma: the less poor technique. A study of 51 patients with histological correlation. Ann Oncol 2001;12:1601-1604

7. Seo JB, Im JG, Goo JM, Chung MJ, Kim MY. Atypical pulmonary metastases: spectrum of radiologic findings. Radiographics 2001;21:403-417

8. Grampp S, Bankier AA, Zoubek A, et al. Spiral CT of the lung in children with malignant extra-thoracic tumors: distribution of benign vs malignant pulmonary nodules. Eur Radiol 2000;10:1318-1322.

9. Lawrence W, Jr., Hays DM, Heyn R, et al. Lymphatic metastases with childhood rhabdomyosarcoma. A report from the Intergroup Rhabdomyosarcoma Study. Cancer 1987;60:910-915.

13. Low Risk Group Study

13.1 OBJECTIVE

To further improve the outcome, trying to better select patients that can be treated with VA alone.

13.2 PATIENTS AND TREATMENT

All patients eligible for the protocol (see chapter 11) with the following characteristics:

SUBGROUP A:

Risk Group	Subgroups	Pathology	Post surgical Stage (IRS Group)	Site	Node Stage	Size & Age
Low Risk	**A**	Favourable	I	Any	N0	Favourable

Localised non alveolar RMS, microscopically completely resected (IRS Group I), at all sites,
and
nodes negative
and
tumour size ≤ 5 cm
and
age < 10 years

This group of patients must be selected with great accuracy as they receive limited chemotherapy. It is necessary, therefore, to be very careful about the adequacy of resection margins and to ensure that the case is discussed in detail with the surgeon and pathologist before agreeing allocation to Low Risk treatment.

Primary re-excision is justified if this can be done without important functional or cosmetic sequelae, and if there is a realistic prospect of achieving complete microscopic resection (see paragraph 22.4). If the primary re-excision confirms clear margins, whether or not there is residual tumour in the resected specimen, the patient will be classified in the Low Risk Group and treated accordingly. If there is any doubt whatsoever about the completeness of resection, the patient should be allocated and treated in the Standard Risk Group (Subgroup C or D).

Note: *patients with paratesticular disease in whom the initial surgical approach has been through the scrotum should receive hemiscrotectomy, otherwise they cannot be treated in this group and will be upstaged to standard risk – Subgroup B (see Surgical guidelines Chapter 22)*

Urgent pathology review is required for any patient eligible for Low Risk Group strategy in which a diagnosis of Embryonal RMS is made by the local pathologist.
Previous experience has shown a high concordance between centre diagnosis and central review in cases of alveolar RMS. The agreement is lower when the centre reaches a diagnosis of embryonal RMS.

13.3 LOW RISK GROUP TREATMENT DETAILS

The treatment consists of 8 courses of Vincristine and Actinomycin D (VA) separated by a 3-week rest period. Weekly vincristine will be administered between cycle 1 and 2, 3 and 4, 5 and 6, 7 and 8. The total duration of chemotherapy is 22 weeks.

	V	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

V = Vincristine 1.5 mg/m^2 (maximum single dose 2 mg) as a single intravenous injection.
A = Actinomycin D 1.5 mg/m^2 (maximum single dose 2 mg) as a single intravenous injection.

VA cycles should not be started unless all these condition are present: 2 x10^9/l WBC or 1 x10^9/l neutrophils + 80 x10^9/l platelets + absence of any relevant organ dysfunction.
Weekly vincristine should be administered irrespective of pancytopenia providing the child is in good conditions.

See chapter 24 for chemotherapy guidelines and dose modifications
For children $\leq$ 1 year (or $\leq$ 10 kg body weight) see chapter 24.4.1.

No further local treatment procedures are needed after the initial complete resection (except for primary re-excision when indicated, see chapter 22.4)

14. Standard Risk Group Study

14.1 OBJECTIVES

Subgroup B: to evaluate whether the outcome for older patients with favourable features may be improved /maintained by administering a treatment with limited intensity.

Subgroup C: to evaluate whether chemotherapy intensity for standard risk patients can be reduced, lowering the cumulative dose of Ifosfamide from 54 g/m² to 36 g/m².

Subgroup D: to evaluate whether the treatment can be reduced in a subgroup of patients with RMS arising in *unfavourable* site (parameningeal, other site) but with *favourable* site and age.

14.2 PATIENTS AND TREATMENT

Patients included in the subgroups B, C and D are part of the Standard Risk Group. The treatment varies in the different Subgroups.

Risk Group	Subgroups	Pathology	Post surgical Stage (IRS Group)	Site	Node Stage	Size & Age
Standard Risk	***B***	Favourable	I	Any	N0	Unfavourable
	C	Favourable	II, III	Favourable	N0	Any
	D	Favourable	II, III	Unfavourable	N0	Favourable

Urgent pathology review is required for any patient eligible for Standard Risk Group strategy in which a diagnosis of Embryonal RMS is made by the local pathologist.
Previous experience has shown a high concordance between centre diagnosis and central review in cases of alveolar RMS. The agreement is lower when the centre reaches a diagnosis of embryonal RMS.

14.3 SUBGROUP B

All patients eligible to the protocol (see chapter 11) with the following characteristics:

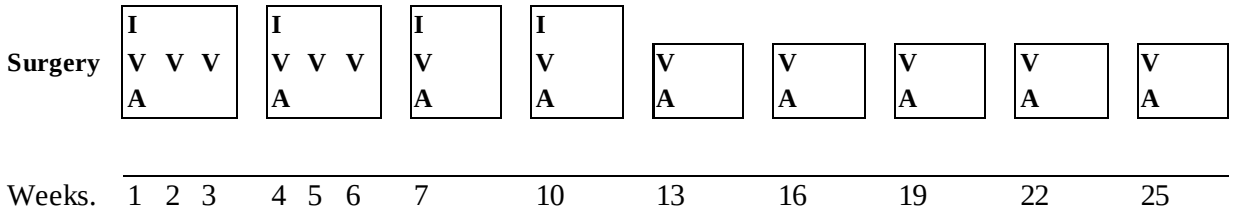
Localised non alveolar RMS, microscopically completely resected (IRS Group I), at all sites,
and
nodes negative
and
tumour size > 5 cm *or* age ≥ 10 years

Note: *patients with paratesticular RMS in whom the initial surgical approach was through the scrotum should be treated in this group if primary re-excision with hemiscrotectomy has not been performed, even if they have favourable characteristics.*

14.3.1 Subgroup B Treatment (ARM SR-B)

The treatment comprises of 4 cycles of Ifosfamide, Vincristine and Actinomycin D (IVA) followed by 5 courses of Vincristine and Actinomycin D (VA). The total duration of chemotherapy is 25 weeks.

These patients are in complete remission after initial surgery therefore they will not receive further local treatment (no RT or second look surgery).



I Ifosfamide 3 g/m^2 is given as a 3 hour intravenous infusion daily, with Mesna (3 g/m^2) and hydration, on days 1 & 2 for each course of treatment. (Total IFO dose/course = 6 g/m^2).

V Vincristine 1.5 mg/m^2 (maximum single dose 2 mg) is given as a single intravenous injection on day 1 of each course and weekly, for a total of seven consecutive doses, from week 1 to 7.

A Actinomycin D 1.5 mg/ m^2 (maximum single dose 2 mg) as a single intravenous injection on day 1 of each course of treatment.

Interval between courses is 3 weeks and chemotherapy courses should not be started unless all these conditions are present: 2 x10^9/l WBC or 1 x10^9/l neutrophils) + 80 x10^9/l platelets + absence of any relevant organ dysfunction.

See chapter 24 for chemotherapy guidelines and dose modifications
For children $\leq$ 1 year (or $\leq$ 10 kg body weight) see chapter 24.4.1.

Growth factors may be used at the physicians' discretion. It is suggested to use them in case of life-threatening neutropenic CTC grade III-IV infection, or treatment delay $\geq$ 1 week due to toxicity after previous cycles. For the use of growth factors see also chapter 27.2.

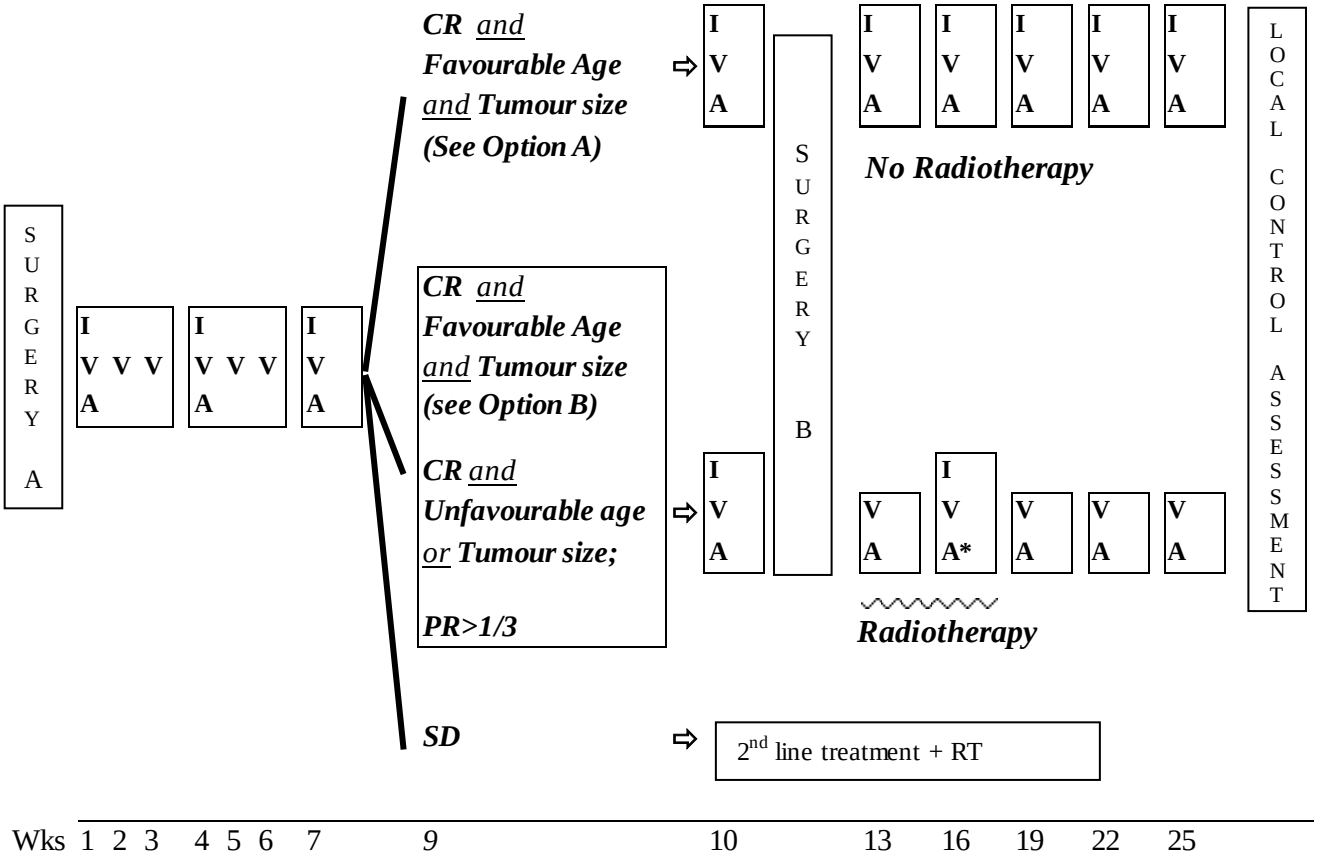
14.4 SUBGROUP C

All patients eligible for the protocol (see chapter 11) with the following characteristics:

non alveolar RMS, IRS Group II or III,
localised in orbit, head and neck non PM or GU non bladder-prostate,
and
nodes negative
and
any size *or* age

14.4.1 Subgroup C treatment (ARM SR-C)

The treatment comprises of 5 courses of Ifosfamide, Vincristine and Actinomycin (IVA) and 4 courses of Vincristine and Actinomycin (VA) ± Ifosfamide.
Local treatment will be administered at week 13.



I Ifosfamide 3 g/m^2 is given as a 3 hour intravenous infusion daily, with Mesna (3 g/m^2) and hydration, on days 1 & 2 for each course of treatment. (Total IFO dose/course = 6 g/m^2).

V Vincristine 1.5 mg/m^2 (max. single dose 2 mg) is given as a single intravenous injection on day 1 of each course and weekly, for a total of seven consecutive doses, from week 1 to 7.

A Actinomycin D 1.5 mg/m^2 (maximum single dose 2 mg) as a single intravenous injection on day 1 of each course of treatment.

** Actinomycin should be given at the very beginning of RT (week 13) but may be omitted during RT (week 16). Caution is needed in the administration of week 19 ACT-D. For more details see chapter 23.11.*

Interval between courses is 3 weeks and chemotherapy courses should not be started unless all these conditions are present: 2 $x10^9$/l WBC (or 1 $x10^9$/l neutrophils) + 80 $x10^9$/l platelets + absence of any relevant organ dysfunction.

See chapter 24 for chemotherapy guidelines and dose modifications
For children $\leq$ 1 year (or $\leq$ 10 kg body weight) see chapter 24.4.1.

Growth factors may be used at the physicians' discretion. It is suggested to use them in case of life-threatening neutropenic CTC grade III-IV infection, or treatment delay $\geq$ 1 week due to toxicity after previous cycles. For the use of growth factors see also chapter 27.2.

14.4.2 Assessment of tumour response and treatment decisions

- *1st assessment*: after the initial 3 cycles of chemotherapy (week 9) a full clinical and radiological assessment of the tumour response will be evaluated.

➲ At this time local control modality must be decided

a) Patients with favourable age (< 10 years) and tumour $\leq$ 5 cm at diagnosis, who achieve the complete remission after the initial treatment (3 courses of IVA $\pm$ surgery):
Please note that complete remission must be confirmed by central review
Two options are contemplated in this protocol:
- Option A: patients will receive 9 courses of IVA without radiotherapy.
- Option B: patients will receive 9 courses of IVA without radiotherapy if the CR has been obtained through a secondary operation (histological CR). Otherwise they will be treated as patients in CR with unfavourable features (radiotherapy plus VA chemotherapy).

NOTE: The German (CWS), the Italian (STSC) and the Spanish Group do recommend option B.

b) Patients in CR with unfavourable features (age $\geq$ 10 years and/or tumour size > 5 cm) or tumour volume reduction > 1/3 will continue the treatment they have been allocated at diagnosis.

c) Patients with stable disease (SD: tumour volume reduction < 1/3), will be eligible for 2nd line treatment (see chapter 20)

After the tumour response assessment one more chemotherapy cycle will be administered and in the meantime the appropriate local control modality will be planned and implemented at week 13.

Surgery: Where residual masses are demonstrated or in cases of doubt, surgical resection should be done (surgery B). However resection in this Subgroup may be difficult because of the anatomical sites.
Surgery for tumours localised in the head and neck may not be feasible and the final decision in these cases is left to the discretion of the individual Surgeon.
In orbital RMS a delayed surgery is discouraged and radiotherapy should be the preferred local treatment.

Secondary operations are not indicated if clinically and radiologically (CT and/or MRI) there is no visible tumour (see chapter 22.5).
Secondary operations should, as a rule, be conservative but demolitive operations may be appropriate in certain circumstances. "Debulking" is not recommended. Particular care must be taken to ascertain completeness of resection.
Week 13 chemotherapy (5^{th} cycle) and radiotherapy should begin after recovery from surgery B.
Surgery may be appropriate at the end of treatment in order to assess or achieve the local control after chemotherapy + radiotherapy. Mutilating surgery ("salvage surgery") could be considered in some cases.

Radiotherapy Patients in IRS Group II and III must be irradiated (unless in CR after the inital 3 cycles of chemotherapy and with favourable age and tumour size). Different doses will be delivered according to chemotherapy response and delayed surgery results (see Chapter 23 for details). Radiotherapy must be performed concomitantly with the 5^{th} cycle (week 13).
If Surgery B is not possible and radiotherapy is decided this must be delivered beginning at week 13. Guidelines for patients less than 3 years of age are given in chapter 23.12.

Adjustments to the chemotherapy schedule are necessary during radiotherapy in particular for the administration of actinomycin (see paragraph 23.11).

- *2^{nd} assessment* a second assessment of tumour response may be undertaken after 6-7 courses of chemotherapy (week 18)
  Any patient with progressive disease must proceed to 2^{nd} line treatment.

- *3^{rd} assessment:* a third assessment must be performed after 9 courses of chemotherapy (end of standard treatment).
  At this point surgery should be reconsidered (Local control assessment) in case of residual tumour.

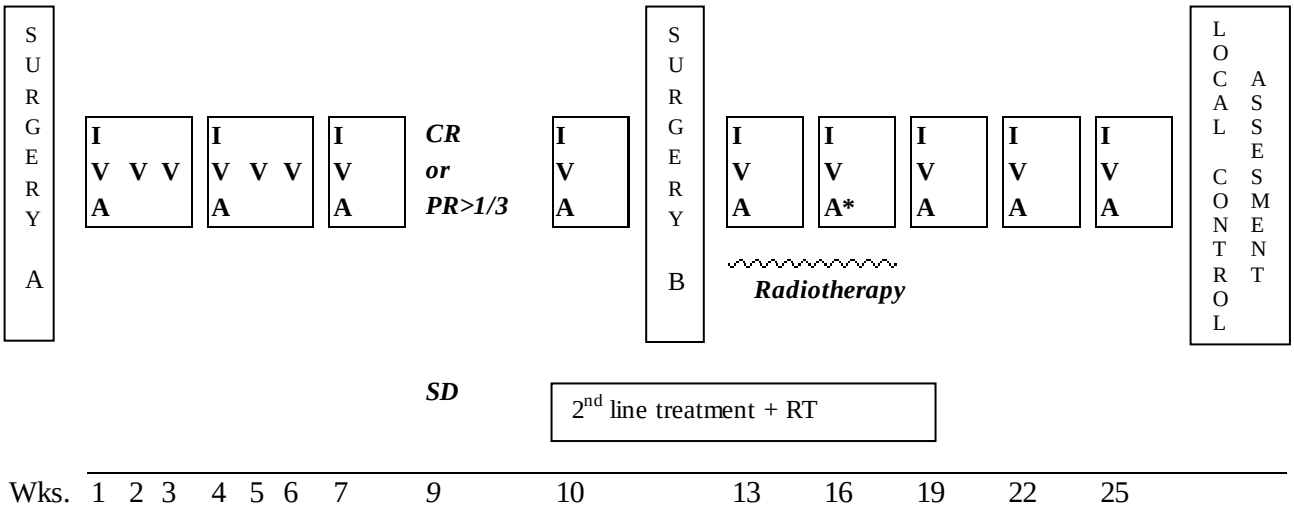
14.5 SUBGROUP D

All patients eligible to the protocol (see chapter 11) with the following characteristics:

Localised non alveolar RMS, IRS Group II or III,
arising in parameningeal, extremities, GU bladder-prostate or "other sites"
and
nodes negative
and
tumour size $\leq$ 5 cm and age < 10 years

14.5.1 Subgroup D Treatment (ARM SR-D)

The treatment comprises of 9 courses of Ifosfamide, Vincristine and Actinomycin (IVA). Local treatment (radiotherapy $\pm$ surgery) will be administered at week 13.



I Ifosfamide 3 g/m2 is given as a 3 hour intravenous infusion daily, with Mesna (3 g/m2) and hydration, on days 1 & 2 for each course of treatment. (Total IFO dose/course = 6 g/m2).

V Vincristine 1.5 mg/m^2 (maximum single dose 2 mg) is given as a single intravenous injection on day 1 of each course and weekly, for a total of seven consecutive doses, from week 1 to 7.

A Actinomycin D 1.5 mg/ m2 (maximum single dose 2 mg) as a single intravenous injection on day 1 of each course of treatment.

** Actinomycin should be given at the very beginning of RT (week 13) but may be omitted during RT (week 16). Caution is needed in the administration of week 19 ACT-D.*
For more details see chapter 23.11)

Interval between courses is 3 weeks and chemotherapy courses should not be started unless all these conditions are present: 2 x10^9/l WBC (or 1 x10^9/l neutrophils) + 80 x10^9/l platelets + absence of any relevant organ dysfunction.
Weekly vincristine should be administered irrespective of pancytopenia providing the child is in good condition.

See chapter 24 for chemotherapy guidelines and dose modifications
For children $\leq$ 1 year (or $\leq$ 10 kg body weight) see chapter 24.4.1.

Growth factors may be used at the physicians' discretion. It is suggested to use them in case of life-threatening neutropenic CTC grade III-IV infection, or treatment delay $\geq$ 1 week due to toxicity after previous cycles. For the use of growth factors see also chapter 27.2.

14.5.2 Assessment of Tumour response and treatment continuation

- *1st assessment*: after the initial 3 blocks of chemotherapy (week 9) a full clinical and radiological assessment of the tumour response will be evaluated.

➲ *At this time local control modality must be decided*

Patients in CR or tumour volume reduction > 1/3 will continue the treatment as detailed above.
Patients with stable disease (SD: tumour volume reduction $\leq$ 1/3), will be eligible for 2nd line treatment (see chapter 20)

After the tumour response assessment one more chemotherapy cycle will be administered and in the meantime the appropriate local control modality will be planned and implemented at week 13.

Surgery Secondary operations are not indicated if clinically and radiologically (CT and/or MRI) there is no visible tumour (see chapter 22.5). Where residual masses are demonstrated, or in cases of doubt, surgical verification is recommended.

Secondary operations (Surgery B) should, as a rule, be conservative but demolitive operations may be appropriate in certain circumstances. "Debulking" is not recommended. Particular care must be taken to ascertain completeness of resection.
Surgery may be appropriate at the end of treatment in order to assess the or to achieve the local control after chemotherapy + radiotherapy. Mutilating surgery ("salvage surgery") could be considered in some cases.

Radiotherapy Patients in IRS II and III must be irradiated. Different doses will be delivered according to chemotherapy response and delayed surgery results (see Chapter 23 for details). *Radiotherapy must be performed beginning at week 13.*
The local treatment modality in patients with parameningeal RMS must be radiotherapy.

Guidelines for patients less than 3 years of age are given in chapter 23.12.

Adjustments to the chemotherapy schedule are necessary during radiotherapy in particular for the administration of actinomycin (see paragraph 23.11).

- *2nd assessment* A second assessment of tumour response may be undertaken after 6-7 courses of chemotherapy (week 18)
  Any patient with progressive disease must proceed to 2nd line treatment.

- *3rd assessment:* A third assessment must be performed after 9 courses of chemotherapy (at the end of treatment).

15. High Risk Group Trial

15.1 OBJECTIVES

To improve the outcome of this group of patients investigating in a randomised way:

1. the value of early intensification with Doxorubicin comparing in the initial part of the treatment, a standard chemotherapy regimen IVA (Ifosfamide, Vincristine, Actinomycin D) with a novel combination with additional doxorubicin (IVADo)
2. the role of low dose "maintenance" chemotherapy with 6 months of cyclophosphamide and vinorelbine in the experimental arm

End points for both randomisations are:
a) primary: 3-year EFS
b) secondary: response to initial treatment (9^{th} week) and 5 yrs OS

15.2 PATIENTS AND TREATMENT

The following patients are eligible for E$_P$*SSG RMS 2005 randomised trial:*

- eligibility to E$_P$SSG RMS2005 protocol (see paragraph 11.1)
- stratification according to the High Risk Arm
- age > 6 months (and < 21 years)
- not paratesticular alveolar RMS
- informed consent given for the randomised study

The High risk group includes patients with different characteristics, however the treatment will be the same for the different Subgroups.

Risk Group	Subgroups	Pathology	Post surgical Stage (IRS Group)	Site	Node Stage	Size & Age
High Risk	***E***	Favourable	II, III	Unfavourable	N0	Unfavourable
	F	Favourable	I, II, III	Any	N1	Any
	G	Unfavourable*	I, II, III	Any	N0	Any

Note: For patients < 6 months see chapter 24.4.1 for chemotherapy modifications according to age.

SUBGROUP E

non alveolar RMS, IRS Group II or III, localised in parameningeal, extremities, GU bladder-prostate or "other sites"
and
nodes negative
and
tumour size > 5 cm *or* unfavourable age (≥ 10 year)

SUBGROUP F

non alveolar RMS, IRS Group I or II or III, any site
and
nodes positive
and
any tumour size or age

SUBGROUP G

alveolar RMS,
and
any IRS Group I or II or III, and any site
and
nodes negative
and
any tumour size or age

Notes*:*
The following groups of patients are included in the High Risk Group but they are not eligible to the randomised trial and should be treated according to Arm A, with 9 cycles of IVA
a) paratesticular alveolar RMS: See also chapter 8.4.4
b) patients with Undifferentiated soft tissue sarcoma (excluding undifferentiated sarcoma of the liver) or ectomesenchymoma. See chapter 29.4.

15.3 RANDOMISED TRIAL NO. 1 – *THE INTENSIFICATION QUESTION*

After the diagnosis of RMS has been established and written informed consent obtained eligible patients will be randomised to receive:

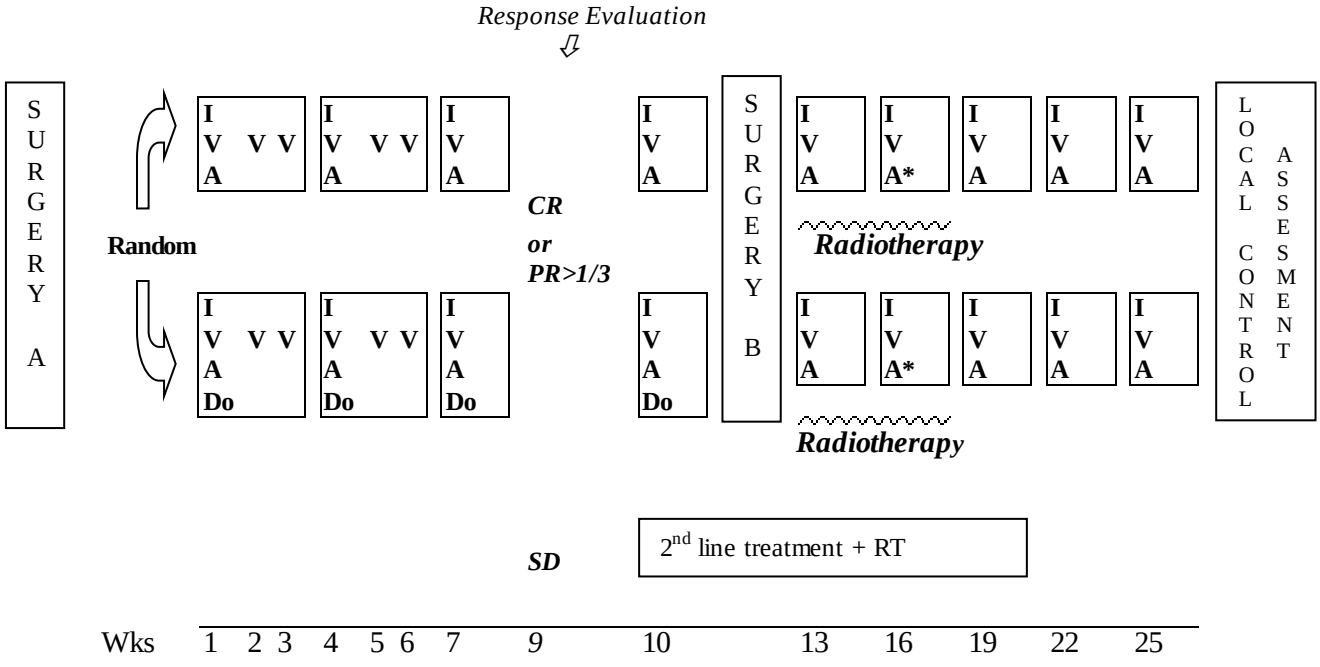
- **Arm A:** 4 courses of Ifosfamide, Vincristine and Actinomycin D (IVA)

or

- **Arm B:** 4 courses of IVA+ Doxorubicin (IVADo).

Eligible patients must be randomised before chemotherapy treatment is started using the RDE system.
For randomisation procedure see chapter 33.5.
If the randomisation is refused or not applicable for whatever reason patients should be treated in Arm A.

After the diagnostic surgery primary re-operation can be considered, before chemotherapy start, in selected cases (see paragraph 22.3).



I Ifosfamide 3 g/m^2 is given as a 3 hour intravenous infusion daily, with Mesna (3 g/m^2) and hydration, on days 1 & 2 for each course of treatment. (Total IFO dose/course = 6 g/m^2).

V Vincristine 1.5 mg/m^2 (maximum single dose 2 mg) is given as a single intravenous injection on day 1 of each course and weekly, for a total of seven consecutive doses, from week 1 to 7.

A Actinomycin D 1.5 mg/m^2 (maximum single dose 2 mg) as a single intravenous injection on day 1 of each course of treatment.

Do Doxorubicin 30 mg/m^2 given as a 4-hour intravenous infusion daily on days 1 & 2 for courses 1-4 of treatment (total dose per course = 60 mg/m^2).

** Actinomycin should be given at the very beginning of RT (week 13) but may be omitted during RT (week 16). Caution is needed in the administration of week 19 ACT-D. See chapter 23.11)*

Interval between courses is 3 weeks and chemotherapy courses should not be started unless all these conditions are present: 2 x10^9/l WBC or 1 x10^9/l neutrophils + 80 x10^9/l platelets + absence of any relevant organ dysfunction.

Weekly vincristine should be administered irrespective of pancytopenia providing the child is in good condition.

See chapter 24 for chemotherapy guidelines and dose modifications
For children $\leq$ 1 year (or $\leq$ 10 kg body weight) see chapter 24.4.1.

Growth factors may be used at the physicians' discretion. It is suggested to use them in case of life-threatening neutropenic CTC grade III-IV infection, or treatment delay $\geq$ 1 week due to toxicity after previous cycles. For the use of growth factors see also chapter 27.2.

15.3.1 Assessment of tumour response and treatment decisions

- *1st assessment*: after the initial 3 cycles of chemotherapy (week 9) a full clinical and radiological assessment of the tumour response will be evaluated.

➲ At this time local control modality must be decided

Patients in CR or tumour volume reduction > 1/3 will continue the treatment they have been allocated at diagnosis.
Patients with stable disease (SD: tumour volume reduction $\leq$ 1/3), will be eligible for 2nd line treatment (see chapter 20)

After the tumour response assessment, one more chemotherapy cycle (IVA or IVADo according to the treatment arm) will be administered and in the meantime the appropriate local control modality will be planned and implemented at week 13.

Surgery Where residual masses are demonstrated or in case of doubt, surgical resection should be done (surgery B), although there may be certain anatomical sites, particularly in the head and neck, where this may not be feasible and the final decision in these cases is left to the discretion of the individual Surgeon. Secondary operations are not indicated if clinically and radiologically (CT and/or MRI) there is no visible tumour (see chapter 22.5).
Secondary operations should, as a rule, be conservative but demolitive operations may be appropriate in certain circumstances. "Debulking" is not recommended.
Week 13 chemotherapy (5th cycle) should begin after recovery from surgery B, and radiotherapy should start with the fifth chemotherapy cycle.
Surgery may be appropriate at the end of treatment in order to assess the or to achieve the local control after chemotherapy + radiotherapy. Mutilating surgery ("salvage surgery") could be considered in some cases.

Radiotherapy Patients in IRS Group II and III must be irradiated. Different doses will be delivered according to chemotherapy response and delayed surgery results (see Chapter 23 for details). Radiotherapy must be performed concomitantly with the 5th cycle (week 13).
If Surgery B is not possible and radiotherapy is decided this must be delivered beginning at week 13, after the administration of the fourth cycle.
Guidelines for patients less than 3 years of age are given in chapter 23.12.

Adjustments to the chemotherapy schedule are necessary during radiotherapy in particular for the administration of actinomycin (see paragraph 23.11).

- *2nd assessment* a second assessment of tumour response may be undertaken after 6-7 courses of chemotherapy (week 18).
  Any patient with progressive disease must proceed to 2nd line treatment.
- *3rd assessment:* a third assessment must be performed after 9 courses of chemotherapy (end of standard treatment).
  Patients in CR or with evidence of minimal radiological anomalies are eligible for the second randomisation.
  At this point surgery should be reconsidered (Local control assessment) in case of residual tumour. Patients who achieve a CR after surgery are eligible for the second randomisation

15.4 RANDOMISED TRIAL NO. 2 - *THE MAINTENANCE QUESTION*

The following patients are eligible for second randomisation:

- eligibility to E*p*SSG RMS2005 protocol (see paragraph 11.1)
- stratification and treatment according to the High Risk Arm
- age > 6 months at the moment of randomisation (some infants, not eligible for the first randomisation, may be randomised here) and < 21 years at diagnosis (some patients may be older than 21 years at the moment of second randomisation)
- in complete remission or with minimal abnormalities* on imaging studies at the end of "standard " treatment (9 courses of chemotherapy ± surgery ± radiotherapy)
- absence of severe vincristine neuropathy (requiring discontinuation of vincristine treatment)

After the end of standard therapy, patients have received 9 blocks of chemotherapy similar to that administered in previous European protocols. Clinicians must be prepared to end the patient's treatment because the patient is in CR or minimal radiological anomalies are evident and they are reasonably suspected not to be disease (i.e. fibrosis). This frequently occurs in parameningeal RMS and the standard strategy is to stop treatment.

Following the 9th block of chemotherapy, surgery or a biopsy of what appears to be a possible residual tumour, may be performed. Patients are not eligible for the second randomisation if viable tumour is found and the clinician thinks that more chemotherapy would be appropriate.
If the clinician wants to give more chemotherapy after the initial 9 blocks this should NOT be vinorelbine/cyclophosphamide and these patients will not be eligible for randomisation.

Patients must be randomised within 8 weeks after the end of treatment.
The end of treatment is defined as the last day of the 9th chemotherapy cycle. However:
- if surgery is performed after the 9th chemotherapy cycle, the date of surgery will be considered;
- if radiotherapy is administered after 9 cycles of chemotherapy, the date of the end of RT will be considered. Since maintenance CT should be started within 8 weeks from the last day of the 9th CT cycle, it would be better to start the maintenance CT during irradiation.

Patients in CR will be randomised to:

- **Arm C:** stop treatment

or

- **Arm D:** 6 courses Vinorelbine + Cyclophosphamide

► **Randomisation should be performed and (if allocated) treatment started within 8 weeks following the end of treatment.**

N.B. If the first randomisation has been refused or not done for whatever reason patients are still eligible for the second randomisation if they satisfy the eligibility criteria

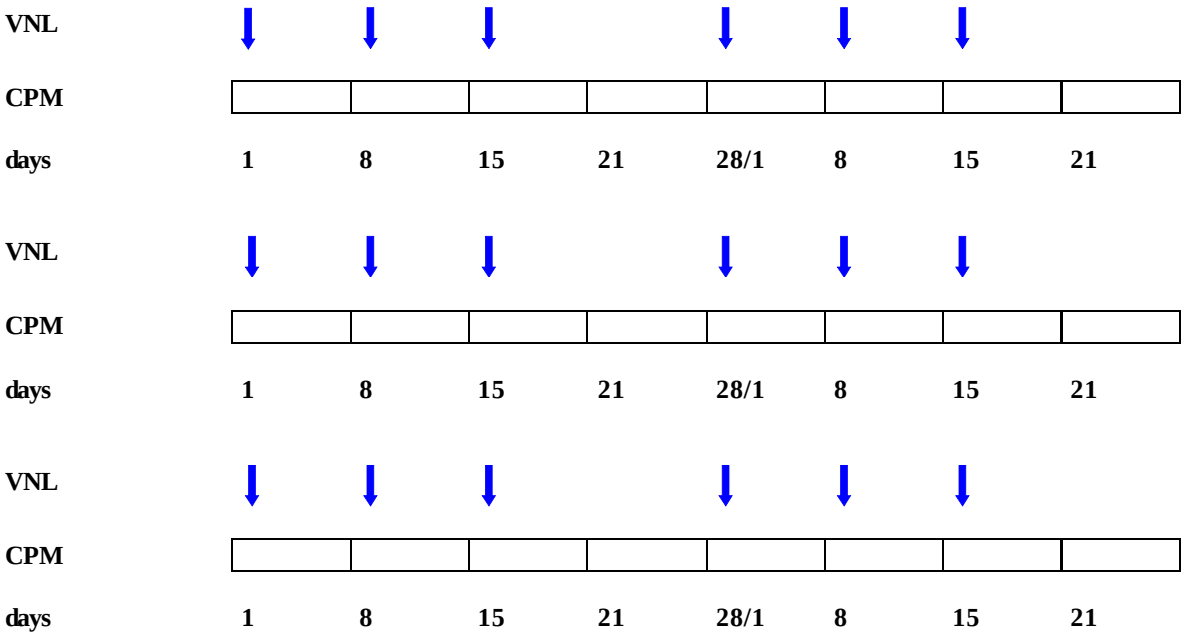
Stop treatment

9th CT block ⇦ **decision & randomisation within 8 weeks** ⇨ **Vinorelbine/Cyclophosphamide x 6 courses (24 weeks)**

Very important:

The standard treatment strategy is to stop treatment because the benefit of vinorelbine/cyclophospamide maintenance is not proven.
Consequently when randomisation is refused or thought by the responsible clinician not to be appropriate for the patient, no further treatment after the initial 9 blocks should be administered.

15.4.1 Vinorelbine / cyclophosphamide Maintenance schema



VNL: Vinorelbine 25 mg/m^2 i.v. over 5-10 minutes day 1,8,15 of each cycle
CPM: Cyclophosphamide 25 mg/m^2 per os every day (no rest between cycles)

This treatment is usually given on an outpatient basis.

N.B. Oral cyclophosphamide is only commercially available in the UK as 50mg sugar-coated tablets, which cannot be halved. If tablets are preferred, metronomic dosing can be used, i.e. cumulative weekly dose given over several days as required. For smaller doses or patients requiring a liquid formulation, an oral solution is available as an IMP supply (see Appendix 11).
Cyclophosphamide should be administered early in the day and followed by adequate fluid intake to minimize bladder toxicity.

For drug administration details see also paragraph 24.2 and 24.3.

16. Very High Risk Group Study

16.1 OBJECTIVE

To improve the results in this poor prognosis group of patients administering the more intensive treatment IVADo plus maintenance chemotherapy.

16.2 PATIENTS AND TREATMENT

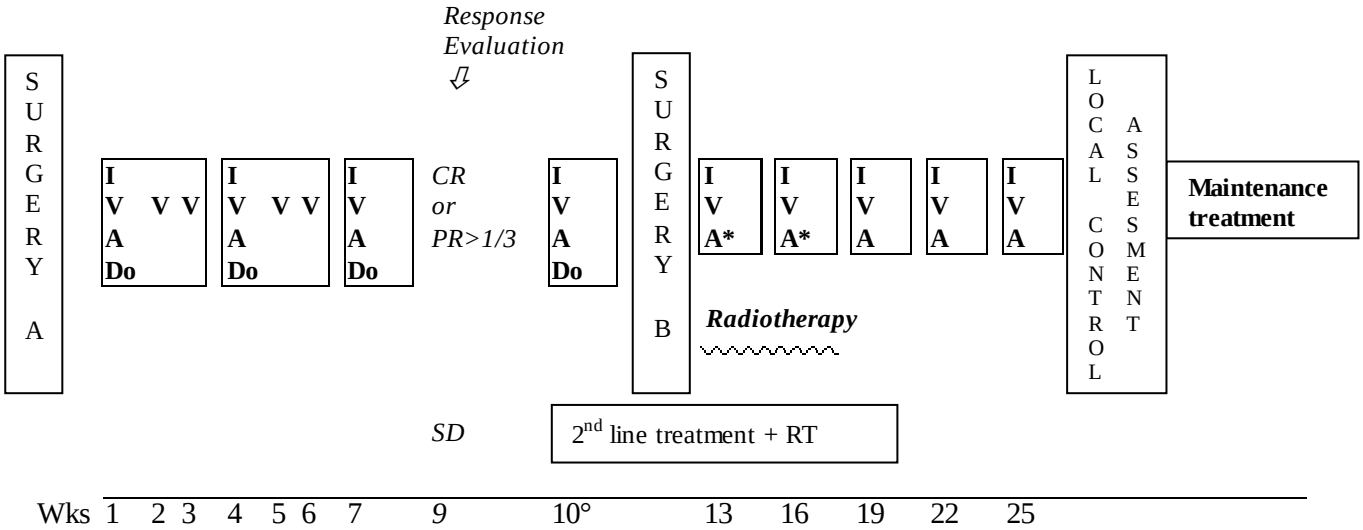
All patients eligible to the protocol (see paragraph 11.1) with the following characteristics:

Localised alveolar RMS
and
nodes positive

(independently from any other variable such as tumour site, size or patient age)

After the diagnostic surgery primary re-operation can be considered, before chemotherapy start, in selected cases (see paragraph 22.4).

16.2.1 Very high risk patients: Intensive Treatment



I Ifosfamide 3 g/m^2 is given as a 3 hour intravenous infusion daily, with Mesna (3 g/m^2) and hydration, on days 1 & 2 for each course of treatment. (Total IFO dose/course = 6 g/m^2).

V Vincristine 1.5 mg/m^2 (maximum single dose 2 mg) is given as a single intravenous injection on day 1 of each course and weekly, for a total of seven consecutive doses, from week 1 to 7.

A Actinomycin D 1.5 mg/m^2 (maximum single dose 2 mg) as a single intravenous injection on day 1 of each course of treatment.

Do Doxorubicin 30 mg/m^2 given as a 4-hour intravenous infusion daily on days 1 & 2 for courses 1-4 of treatment (total dose per course = 60 mg/m^2).

** Actinomycin should be given at the very beginning of RT (week 13) but may be omitted during RT (week 16). Caution is needed in the administration of week 19 ACT-D.*
For more details see chapter 23.11)

Interval between courses is 3 weeks and chemotherapy courses should not be started unless all these conditions are present: 2 x10^9/l WBC (or 1 x10^9/l neutrophils) + 80 x10^9/l platelets + absence of any relevant organ dysfunction.

For children $\leq$ 1 month VA only should be administered in the 1st cycle. For children $\leq$ 1 year (or $\leq$ 10 kg body weight) first cycle doses will be calculated by body weight and increased in the following cycles if tolerated. See chapter 24.4.1.

Growth factors may be used at the physicians' discretion. It is suggested to use them in case of life-threatening neutropenic CTC grade III-IV infection, or treatment delay $\geq$ 1 week due to toxicity after previous cycles.
For the use of growth factors see also chapter 27.2.

16.2.1.1 ASSESSMENT OF TUMOUR RESPONSE AND TREATMENT DECISIONS

- *1st assessment*: after the initial 3 cycles of chemotherapy (week 9) a full clinical and radiological assessment of the tumour response will be evaluated.

➲ At this time local control modality must be decided

Patients in CR or tumour volume reduction > 1/3 will continue the treatment they have been allocated at diagnosis.
Patients with stable disease (SD: tumour volume reduction $\leq$ 1/3), will be eligible for 2nd line treatment (see chapter 20).

After the tumour response assessment, one more chemotherapy cycle will be administered and in the meantime the appropriate local control modality will be planned and implemented at week 13.

Surgery Where residual masses are demonstrated or in case of doubt, surgical resection should be done (surgery B), although there may be certain anatomical sites, particularly in the head and neck, where this may not be feasible and the final decision in these cases is left to the discretion of the individual Surgeon. Secondary operations are not indicated if clinically and radiologically (CT and/or MRI) there is no visible tumour (see chapter 22.5).
Secondary operations should, as a rule, be conservative but demolitive operations may be appropriate in certain circumstances. "Debulking" is not recommended. Particular care must be taken to ascertain completeness of resection.
Radical lymph node dissections are not indicated and involved lymph nodes should be irradiated, whether resected or not. There are rare occasions when, if radiotherapy is contraindicated (e.g. age $\leq$ 3 years), a lymph node dissection may be considered as definitive local treatment.
Week 13 chemotherapy (5th cycle) should begin after recovery from surgery B, and radiotherapy should start with the fifth chemotherapy cycle.

Radiotherapy Patients in IRS Group II and III must have the primary tumour irradiated. Different doses will be delivered according to chemotherapy response and delayed surgery results (see Chapter 23 for details). Radiotherapy must be performed concomitantly with the 5th cycle (week 13).
If Surgery B is not possible and radiotherapy is decided this must be delivered beginning at week 13, after the administration of the fourth cycle.
Radiotherapy to the involved lymph node sites is performed independently of histology and surgical resection (see paragraph 23.5).
Guidelines for irradiation of patients less than 3 years of age are given in paragraph 23.12.
Adjustments to the chemotherapy schedule are necessary during radiotherapy in particular for the administration of doxorubicin and actinomycin (see paragraph 23.11).

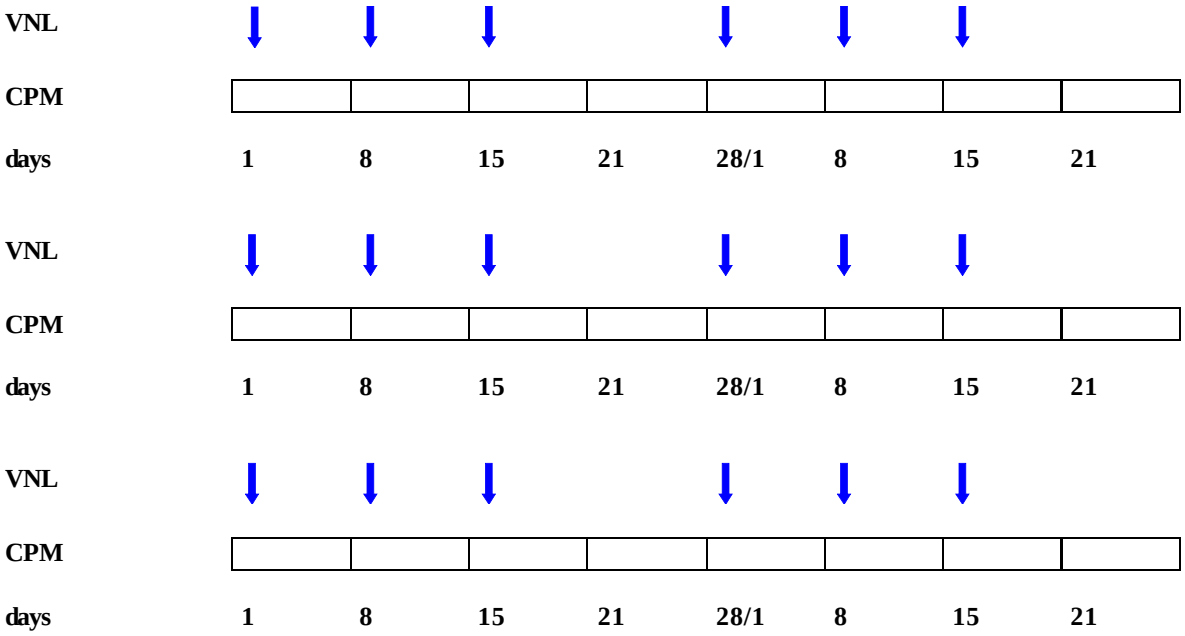
- *2nd assessment* a second assessment of tumour response may be undertaken after 6-7 courses of chemotherapy (week 18).
  Any patient with progressive disease must proceed to 2nd line treatment.

- *3rd assessment:* a third assessment must be performed after 9 courses of chemotherapy (end of standard treatment).

At this point surgery should be reconsidered (Local control assessment) in case of residual tumour.

16.2.2 Very High risk patients: Maintenance Treatment

Following the 9th block of chemotherapy, surgery or a biopsy of what appears to be a possible residual tumour may be performed. Patients may not continue with the maintenance treatment if viable tumour is found and the clinician thinks that more intensive chemotherapy would be appropriate. However in presence of limited quantity of viable tumour maintenance treatment should be adopted.



VNL: Vinorelbine 25 mg/m^2 i.v. over 5-10 minutes day 1,8,15 of each cycle
CPM: Cyclophosphamide 25 mg/m^2 per os every day (no rest between cycles)

This treatment is given on an outpatient basis.

N.B. Oral cyclophosphamide is only commercially available in the UK as 50mg sugar-coated tablets, which cannot be halved. If tablets are preferred, metronomic dosing can be used, i.e. cumulative weekly dose given over several days as required. For smaller doses or patients requiring a liquid formulation, an oral solution is available as an IMP supply (see Appendix 11). Cyclophosphamide should be administered early in the day and followed by adequate fluid intake to minimize bladder toxicity.

For drug administration details see also paragraph 24.2 and 24.3.

17. Specific Site treatment Information

17.1 PARAMENINGEAL SITE

Unfavourable site

MRI is recommended as radiological investigation.

CSF examination at diagnosis has to be performed.

Complete surgical resection is difficult and generally not possible.

An initial resection will not be accepted if permanent severe uncorrectable 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.

Radiotherapy is always necessary in patients over 3 year of age and should be given at week 13 regardless of response to initial chemotherapy.

Only after radiotherapy is a secondary resection acceptable. Secondary resections in PM site should only be performed in centres with experience in this field.

17.2 CSF POSITIVE

Patients with malignant cells in the spinal fluid will be treated in the protocol for metastatic tumours.

17.3 ORBIT

Favourable site if not bone involvement and not parameningeal site involvement. In case the orbital bone is perforated the tumour has to be classified as PM and the appropriate guidelines have to be applied.

Initial surgery should almost always include a biopsy only. Complete resection of an orbital tumour is rarely possible and most of the time associated with a loss or impairment of vision.

Local treatment: after 4 blocks of chemotherapy most orbital tumours will receive radiotherapy independently of resection status. The doses and target volume definitions will follow the general guidelines. The radiation of the entire orbit is not mandatory and is dependent on the initial tumour size and location. The decision for or against radiotherapy in patients with favourable characteristics (included in Subgroup C) and clinical complete remission following chemotherapy is made according to the recommendations described in chapter 14.4.2.

After chemotherapy + radiotherapy a secondary resection or a biopsy may be indicated in patients with residual tumour. Enucleation or exenteration are very rarely indicated in the course of first line treatment.

17.4 HEAD AND NECK

Favourable site

MRI is recommended as radiological investigation.

An initial complete resection may be achieved but in all cases where resectability is uncertain only a biopsy should be taken. Revision of suspicious lymph nodes should be performed but neck dissections are not indicated.

In some circumstances a major tumour resection with reconstruction may be considered after neoadjuvant chemotherapy. In Non-Responders or tumours that are locally persistent a mutilating approach may be indicated.

17.5 BLADDER/PROSTATE

Unfavourable site

MRI is recommended as radiological investigation

Cystoscopy should be done at diagnosis and during follow up.

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

In all other cases a biopsy has to be performed and secondary surgery will be planned after chemotherapy (see chapter 19). A conservative surgery of Bladder-Prostate RMS may be considered (partial cystectomy and/or partial prostatectomy) in conjunction with brachytherapy. If conservative treatment is not feasible, the choice of treatment is between radiotherapy and total cystectomy and/or total prostatectomy. The doses and target volume definitions will 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.

17.6 VAGINA / UTERUS

Favourable site

Examination under general anaesthesia may be required to define the local extent of tumour. Complete tumour resection at diagnosis is not recommended and only a biopsy should be performed. RMS of the vagina with favourable histology (embryonal RMS) will not receive local treatment (surgery or radiotherapy) if in clinical complete remission after chemotherapy. In case of residual tumour partial vaginectomy may be feasible, but brachytherapy is often preferable.

Patients with unfavourable histology (alveolar RMS) need to be treated with radiotherapy. Depending on the extent and infiltration of the disease these patients may be treated with afterloading techniques/brachytherapy. Individual planning and discussion with the respective reference centre is advised. Oophoropexy has to be considered in order to avoid irradiation of the ovary in all girls treated for pelvic tumours.

17.7 PARATESTICULAR

Favourable site

Paratesticular tumours should have scrotal ultrasound and must have evaluation of regional (paraaortic) lymph nodes by CT scan and ultrasound.

Complete tumour resection at diagnosis is possible but should be performed according to the recommendations (see chapter 22.3). Retroperitoneal lymphadenectomy or node sampling at diagnosis is not recommended unless there is uncertainty on imaging.

If the initial surgical approach was through the scrotum a primary re-operation should be done according to the recommendations (see chapter 22.4). When there is a doubt about a scrotal dissemination, hemiscrotectomy should be performed, if not the tumour will be upstaged.

Incompletely resected paratesticular RMS need radiotherapy (see chapter 23.4.11).

Paratesticular alveolar RMS will be kept in the high risk group, according to the histology, however in consideration of the better outcome they will not be included in the randomised trial and will be treated with IVAx9 (avoiding anthracyclines). Radiotherapy should not be performed if group I.

17.8 LIMBS

Unfavourable site

Particular attention is recommended to the initial evaluation of regional lymph nodes. Lower Limb tumours must have evaluation of pelvic lymph nodes by CT or MRI even if inguinal nodes are

clinically/sonographically normal. Even if the inguinal nodes are clinically/sonographically normal a surgical picking will be performed.
When the primary tumour can be completely resected, regional lymph nodes should be systematically biopsied during the same procedure, even if they are not clinically suspect.
At secondary operation, formal compartmental resection may be appropriate for some tumours but less "anatomical" resections may be better providing an adequate margin of normal tissue.
According to the protocol extremity tumours should be irradiated (see chapter 23). Tissue contaminated during surgery must be included in the irradiated field. After surgical procedures, all scars and drainage sites should be irradiated with a safety margin of 1-2 cm.

17.9 PATIENTS WITH PLEURAL EFFUSION OR ASCITES

In case of important effusion, examination of the fluid is mandatory (biological studies may be of help).
If malignant cells are found on morphology the patients will be treated according to the metastatic protocol.
If peritoneal or pleural nodules are evident on imaging the tumour will be considered as metastatic and treated accordingly.
In case of a small amount of fluid this may be „reactive" and sampling is not necessary, i.e. a tumour located below the diaphragm with limited ipsilateral pleural effusion, the patient will be treated in the E*p*SSG RMS 2005 protocol according to his risk profile.

18. Investigation during and at the end of treatment

18.1 EXAMINATIONS DURING THERAPY

18.1.2 Physical Examination

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

18.1.3 Laboratory Investigations

- Full blood count (including differential white cell count and platelets) before each course of chemotherapy (neutrophils $> 1 \times 10^9$/l and platelets $> 80 \times 10^9$/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:* in standard and high risk patients, 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)

18.1.4 Tumour Reassessment

Evaluation during treatment should be performed when possible **with the same techniques** as initially used.
If no signs of progression are present a formal tumour revaluation is advised

- *low risk patients:* at the end of treatment
- *standard risk patients:* after the initial 3 blocks of chemotherapy (with tumour response evaluation, see paragraph 19) and at the end of treatment
- *high risk patients:* after the initial 3 blocks of chemotherapy (with tumour response evaluation, see paragraph 19) and after 9 blocks of chemotherapy (at the time of randomisation decision, see paragraph 15.4). During maintenance treatment: after 3 and 6 months.
- *very high risk patients:* after the initial 3 blocks of chemotherapy (with tumour response evaluation, see paragraph 19), after 9 blocks of chemotherapy. During maintenance treatment: after 3 and 6 months.

MRI or CT remains necessary prior to surgery.

18.2 INVESTIGATIONS BEFORE RANDOMISATION

For the first randomisation, the investigations at diagnosis are sufficient.
For the second randomisation, CR should be achieved before randomisation, therefore a thorough tumour evaluation should be performed 2-3 weeks after the administration of the 9^{th} block of chemotherapy.
If eligible, the child should be randomised within 8 weeks after the end of treatment.

18.3 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, Chest x-ray, abdominal ultrasound.
- Echocardiogram if doxorubicin has been administered
- Other investigations if previously abnormal (CSF, hormonal status, ECG, PET) may be indicated but are not generally recommended.

19. Tumour response evaluation

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.
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. 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.
Very good partial response and minor partial response criteria are not recognised international criteria but have been added for this protocol.

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.

For the patients in standard and high risk group with evidence of macroscopical residues after initial surgery a formal reassessment of Tumour Response is undertaken *at week 9, after the initial 3 cycles of chemotherapy.*

Assessment must include a detailed clinical examination with external tumour measurements where relevant and radiology using comparable techniques to those used at diagnosis (MRI and/or CT scan).
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)

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

19.1 RESPONSE EVALUATION CRITERIA

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

Complete Response ***(CR)***	Complete disappearance of all visible disease
Very Good Partial Response ***(VGPR)***	Tumour volume reduction $\geq$ 90% but < 100%
Partial Response ***(PR$\geq$2/3)***	Tumour volume reduction $\geq$ 66% but < 89%
Minor Partial Response ***(PR<2/3)***	Tumour volume reduction > 33% but < 66%
Stable disease ***(SD)***	No criteria for PR or PD (< 33% tumour volume reduction)
Progressive Disease ***(PD)***	Any increase of more than 40% in volume (or > 25% in area) of any measurable lesion, or appearance of new lesions.

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

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.

20. Second line therapy

A poor response to initial chemotherapy appears correlated with a poor prognosis in RMS patients. Data from the CWS-81 and CWS-86 studies demonstrated a significantly worse prognosis for children with a poor response after the initial three blocks of chemotherapy.
Therefore the current management of patients with evidence of poor response after the initial chemotherapy phase includes the administration of drugs not previously administered and the implementation of local treatment measures (surgery and/or radiotherapy).
In this protocol, we suggest to treat such patients with alternative chemotherapy combinations along with surgery and radiotherapy. Chemotherapy regimen should be chosen taking into account chemotherapy previously administered and patient tolerance. We suggest different chemotherapy regimens that could be used by the responsible clinicians.

Local treatment must be considered at any time when an unsatisfying response to initial chemotherapy is evident.

When more chemotherapy treatment is thought appropriate by the responsible clinician before local control measures (surgery and/or radiotherapy) chemotherapy response evaluation will be possible.
A proper phase II study is not part of this protocol, however we ask centres to record the response to the regimen administered to collect more information.
Patients eligible to second line chemotherapy response evaluation may be for instance:
- young patients for whom local treatment is thought to be excessively toxic or not possible
- patients in good condition with stable tumour for whom a second chemotherapy test is retained appropriate
- patients for whom surgery or irradiation is not possible in a short time (i.e. within 6-8 wks)

20.1 SECOND LINE CHEMOTHERAPY

Drugs not administered during first line therapy should be used.
- Topotecan has been demonstrated to be active in paediatric malignancies including RMS. Carboplatin has been part of previously used regimens (CEVAIE) that proved to be effective against RMS. It has also been used alone in a window study conducted by the UKCCSG (unpublished data). A phase II trial has been performed at the Bambino Gesù Hospital in Rome showing the feasibility of the proposed regimen. The Topo-Carbo combination is also used as window treatment in the current CWS protocol for metastatic RMS.

- Doxorubicin may be used instead of Topotecan in patients if they have not received anthracyclines in the initial treatment.

After 2 cycles there will be a tumour response evaluation and decisions will be taken accordingly:

a) **Good response** (including CR, VGPR and PR): the initial chemotherapy will continue: *see second line treatment schema.*

b) **No response** (stable or progressive disease): local treatment must be evaluated and a new chemotherapy regimen may be considered.

20.1.1 Second line treatment schema

Topo - Carbo Regimen

	Topo Carbo	Topo Carbo	*Good Response*	Topo Cyclo	VP16 Carbo	Topo Cyclo	VP16 Carbo
weeks	1	4	⇧	7	10	13	16
		Tumour response evaluation					

Topotecan: 2 mg/m^2/day on day 1 to 3 (total dose 6 mg/m^2/course) *in 30 minutes*.
Carboplatin: 250 mg/m^2/day, *in 1 hour*, on day 4 and 5 when given with topotecan, on day 1 and 2 when given with VP16 (total dose 500 mg/m^2/course).
Cyclophosphamide: 1500 mg/m^2/day on day 1 and 2 (total dose 3000 mg/m^2/course) *in 4 hours.*
VP16 (Etoposide): 100 mg/m^2/day on day 1 to 3 (total dose 300 mg/m^2/course) *in 2-4 hours.*

Doxo – Carbo Regimen

	Doxo Carbo	Doxo Carbo	*Good Response*	Doxo Cyclo	Doxo Carbo	Doxo Cyclo	Doxo Carbo
weeks	1	4	⇧	7	10	13	16
		Tumour response evaluation					

Doxorubicin: 60 mg/m^2/day on day 1 (total dose 60 mg/m^2/course) *1 to 6 hours according to institutional policies.*
Carboplatin: 250 mg/m^2/day on day 1 and 2 (total dose 500 mg/m^2/course) *in 1 hour*.
Cyclophosphamide: 1500 mg/m^2/day on day 1 and 2 (total dose 3000 mg/m^2/course) *in 4 hours*.

Chemotherapy modulation
The interval between courses should be 21 days and the following chemotherapy course should not be started unless all these conditions are present:

- 2 x10^9/l WBC, or 1 x10^9/l neutrophils
- 80 x10^9/l platelets are reached.
- absence of any relevant organ dysfunction

Response assessment

This should be done according to the same recommendations and criteria adopted for the first line treatment (see paragraph 19.1). However the tumour volume after the initial two courses of second line chemotherapy must be compared to the tumour evaluated at week 9th and not at diagnosis.

***Important note*: please remember that patients in CR after second line chemotherapy are still eligible to second randomisation.**

21. Adequate Local Therapy Diagram

(for details see surgical and radiotherapy guidelines)

Upfront local therapy

Initial surgery is only recommended when not mutilating and when macroscopic and microscopic complete resection is possible; evaluate complete non-mutilating reexcision in Group II and III pts

In extremity sites : biopsy of axillary or inguinal lymph nodes

Initial chemotherapy according to risk groups

Restaging at week 9

Radiotherapy planning in pts. with alveolar RMS IRS group I and in all patients with IRS group II

Start of radiotherapy at week 13.

In high risk patients, the application of doxorubicin has to be completed.

Decision about further local therapy in pts. with IRS group III

Non-mutilating appropriate oncologic resection with negative margins possible ?

Yes

Resection should be performed*

POSTOPERATIVE RTX ACCORDING TO THE MARGIN STATUS	
R0	36 Gy in eRMS and CR or PR (>2/3) following induction chemotherapy 41.4 Gy in eRMS and less than PR(>2/3) 41.4 Gy in aRMS
R1	50.4 Gy
R2	50.4 Gy

No

PLANNING OF RTX STARTING AT WEEK 13
CR and eRMS: .....
PR, SD, PD, aRMS: .....
(exception: orbit, see radiotherapy guidelines)

*preoperative RT in selected patients who will receive reconstructive surgery

22. SURGICAL GUIDELINES

Local treatment is essential in non-metastatic RMS. It can be achieved by surgery, radiotherapy (external beam RT and/or brachytherapy) 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 response to neoadjuvant chemotherapy. Surgical planning should include all reconstructive procedures with optimal timing of possible additional radiotherapy.

22.1 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 *(= microscopically 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.

- *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*.

22.2 BIOPSY

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

Biopsy should be the initial surgical procedure in all patients except when primary excision with adequate margins is possible (rare except for paratesticular tumours).
Open biopsy is recommended and should be **incisional** although US or CT scan guided core needle (Tru-cut) biopsies 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 haematoma. 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:**
    - 18 or 16 Gauge needles (1.2 or 1.6 mm) should be used with 4 to 6 cores performed.
    - The biopsy track must always go directly to the tumour, through the muscle fibres 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 (see Pathology Guidelines).

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 on 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 that 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.

22.3 PRIMARY RESECTION (SURGERY A)

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.

A layer of healthy tissue between tumour and resection margins should exist. This layer of healthy tissue is defined as a **safety distance**. The metric definition of the safety distance (2-5 cm) cannot be used in paediatric tumour surgery. The kind of tumour growth has to be settled as well defined with pseudocapsule or locally infiltrating, and should be documented. This information is 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.

In practice, the only common situation when primary resection is appropriate is a paratesticular tumour.

"Debulking" procedures are not recommended.

Extensive, "mutilating" operations should never be considered at primary resection. "Mutilating" is defined as: leading to significant long term anatomical, functional or cosmetic impairment. Mutilating surgery are considered:

- orbital exenteration,
- major resection of the face
- pneumonectomy
- pelvic exenteration with definitive intestinal or urinary diversion
- total cystectomy
- total prostatectomy
- hysterectomy
- extremity amputation and major muscular resections leading to important functional impairment

22.4 PRIMARY RE-OPERATION (SURGERY A)

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 [1,2]. This applies particularly to trunk, limb and paratesticular tumours. The interval between initial surgical approach and chemotherapy, including primary reexcision should be as short as possible and should never 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.

22.5 SECONDARY OPERATION (SURGERY B)

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

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[3].

Where a residual mass is demonstrated or in doubtful cases, 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. Marginal resection (R1 resections) in sites where R0 resection is not possible may also be acceptable, provided that 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 after unsuccessful neo-adjuvant chemotherapy or radiotherapy or in patients under 3 years for whom external beam radiotherapy is not indicated.

"Debulking" procedures are not recommended.

22.6 LOCAL CONTROL ASSESSMENT

Surgery may be discussed at the end of treatment in order to assess or to achieve local control after chemotherapy + radiotherapy. Mutilating surgery ("salvage surgery") could be appropriate in some cases.

22.7 RECONSTRUCTIVE SURGERY AND LOCAL CONTROL

Reconstructive procedures have to be included early enough in the planning of the resection. It is desirable to have the histological evaluation before reconstructive surgery. In cases however where reconstructive vascular surgery or microvascular surgery is involved, this is mostly not possible. Therefore in some cases resection and reconstructive surgery have to be performed at the same time without histological confirmation of the status of the resection.

Pre or post operative irradiation has to be considered depending on the necessary reconstructive measures :

- Bone reconstruction (e.g. 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.

22.8 SURGERY OF THE 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 or true-cut biopsy may be useful to confirm nodal involvement but only if a conventional biopsy of the primary tumour has been obtained for diagnostic purposes.

In extremity sites, systematic biopsy of regional nodes (see definition in appendix A5) should be performed even if nodes are not palpable or enlarged on imaging. New techniques of sentinel node mapping (with blue dye and/or radioactive tracer) are recommended whenever feasible [4].

Radical lymph node dissections are generally not indicated and involved lymph nodes should be irradiated, as should enlarged nodes at relapse, whether resected or not. It should be remembered that the combination of radiation therapy and radical lymph node dissection should be absolutely avoided as it can induce severe lymph oedema.
There are rare occasions when, if radiotherapy is contraindicated (e.g. age < 3 years), a lymph node dissection may be considered as definitive local treatment.

22.9 SPECIFIC SITES

22.9.1 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 13 regardless of response to initial chemotherapy.
An initial resection will not be accepted if permanent severe uncorrectable 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 PM site should only be performed in centres with experience in this field.

22.9.2 Orbit

Biopsy is usually the only surgical procedure required for orbital tumours.
Secondary resections are not recommended. Enucleation or exenteration are very rarely indicated [5].
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.

22.9.3 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.
A combination of surgery and brachytherapy ("Amore" technique) is practised in some Centres [6].

22.9.4 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 dome 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 [7,8] or external beam radiotherapy.
Partial prostatectomy, without radiotherapy, carries a high risk of local relapse[9].
Where conservative treatment is not feasible, the treatment will include total cystectomy and/or total prostatectomy with or without post-operative radiotherapy.

22.9.5 Vagina

Partial vaginectomy may be feasible after chemotherapy but brachytherapy is often preferable after ovarian transposition [10].

22.9.6 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 uncertainty on imaging [11,12].

If the initial operation before referral was scrotal then primary re-operation should be done to excise the cord at the internal ring. Complementary hemiscrotectomy is not necessary [13,14] if the patient is upstaged, being treated according to the Subgroup B strategy (i.e. if in the Low Risk group the child will be upstaged). When there is a doubt about scrotal contamination, hemiscrotectomy should be performed.

22.9.7 Extremities

Particular attention is recommended initially in evaluating the regional lymph nodes. Upper and lower limb tumours must have surgical evaluation of axillary or inguinal nodes, respectively, even if nodes are clinically/radiologically normal. New techniques of sentinel node mapping (with blue dye and/or radioactive tracer) are recommended whenever feasible [4].

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, sciatic-popliteal, external/internal, median, ulnar and radial). These structures must not show tumour infiltration. Should doubt arise about a possible oedema 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, 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 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 these 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 that 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 oedema 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 radiation on growth and function.

22.9.8 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.

22.10 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.

22.11 MARKER CLIPS

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

22.12 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.

22.13 REFERENCES – SURGERY

1. Hays DM, Lawrence W Jr, Wharam M, Newton W Jr, Ruymann FB, Beltangady M, Maurer HM. Primary reexcision for patients with 'microscopic residual' tumor following initial excision of sarcomas of trunk and extremity sites. J Pediatr Surg. 1989 Jan;24(1):5-10.
2. Cecchetto G, Guglielmi M, Inserra A, Zanetti I, Dall'Igna P, Gigante C, Carli M; Italian Cooperative Group on Soft-tissue Sarcomas. Primary re-excision: the Italian experience in patients with localized soft-tissue sarcomas. Pediatr Surg Int 2001 Sep;17(7):532-534
3. Godzinski J, Flamant F, Rey A, Praquin MT, Martelli H. Value of postchemotherapy bioptical verification of complete clinical remission in previously incompletely resected (stage I and II pT3) malignant mesenchymal tumors in children: International Society of Pediatric Oncology 1984 Malignant Mesenchymal Tumors Study. Med Pediatr Oncol. 1994;22(1):22-26.
4. McMulkin HM, Yanchar NL, Fernandez CV, Giacomantonio C. Sentinel lymph node mapping and biopsy : a potentially valuable tool in the management of childhood extremity rhabdomyosarcoma. Pediatr Surg Int. 2003, Aug;19(6):453-6
5. Oberlin O, Rey A, Anderson J, Carli M, Raney RB, Treuner J, Stevens MC. Treatment of orbital rhabdomyosarcoma: survival and late effects of treatment -- results of an international workshop. J Clin Oncol. 2001 Jan 1;19(1):197-204.
6. Buwalda J, Schouwenburg PF, Blank LE, Merkx JH, Copper MP, Strackee SD, , Voute TA. Caron HN. A novel local treatment strategy for advanced stage head and neck rhabdomyosarcomas in children: results of the AMORE protocol. Eur J Cancer. 2003;39(11):1594-602
7. Haie-Meder C, Breton-Callu C, Oberlin O, Martelli H, Audry G, Valayer J, Habrand JL, Terrier-Lacombe MJ, Gerbaulet A. Brachytherapy in the treatment of vesicoprostatic rhabdomyosarcomas in children. Cancer Radiother. 2000 Nov;4 Suppl 1:145s-149s.
8. Martelli H, Haie-Meder C, Oberlin O. Conservative surgery + brachytherapy treatment in very young boys with bladder-prostate rhabdomyosarcoma: a single team experience. Med Pediatr Oncol, 2003, 41, 260
9. Audry G, Oberlin O, Capelli C, Martelli H, Godzinski J, Spicer R, Gruner M, Praquin MT, Corkeri J, Ransley PG, Van Unnick A, Quintana E, Stevens MCG. The role of conservative surgery in bladder-prostate rhabdomyosarcoma – an update of the SIOP experience. Med Pediatr Oncol. 1998;31(4):198 (abstract).
10. Martelli H, Oberlin O, Rey A, Godzinski J, Spicer RD, Bouvet N, Haie-Meder C, Terrier-Lacombe MJ, Sanchez de Toledo J, Spooner D, Sommelet D, Flamant F, Stevens MC. Conservative treatment for girls with nonmetastatic rhabdomyosarcoma of the genital tract: A report from the Study Committee of the International Society of Pediatric Oncology. J Clin Oncol. 1999 Jul;17(7):2117-2122.
11. Olive D, Flamant F, Zucker JM, Voute P, Brunat-Mentigny M, Otten J, Dutou L. Paraaortic lymphadenectomy is not necessary in the treatment of localized paratesticular rhabdomyosarcoma. Cancer. 1984 Oct 1;54(7):1283-1287.
12. Ferrari A, Bisogno G, Casanova M, Meazza C, Piva L, Cecchetto G, Zanetti I, Pilz T, Mattke A, Treuner J, Carli M. Paratesticular rhabdomyosarcoma: report from the Italian and German Cooperative Group. J Clin Oncol. 2002 Jan 15;20(2):449-455.
13. Dall'Igna P., Bisogno G., Ferrari A., Treuner J., Carli M., Zanetti I., Guglielmi M., Cecchetto G. Primary transcrotal excision for paratesticular RMS. Is hemiscrotectomy really mandatory? Cancer, 2003, 97, 1981-1984
14. Stewart RJ, Martelli H, Oberlin O, Rey A, Bouvet N, Spicer RD, Godzinski J, Stevens MC. Treatment of Children With Nonmetastatic Paratesticular Rhabdomyosarcoma: Results of the Malignant Mesenchymal Tumors Studies (MMT 84 and MMT 89) of the International Society of Pediatric Oncology. J Clin Oncol. 2003 Mar 1;21(5):793-798.

23. RADIOTHERAPY GUIDELINES

23.1 ROLE OF RADIOTHERAPY

Radiotherapy is an essential treatment for selected patients with rhabdomyosarcoma. This chapter gives guidelines about indications for radiotherapy, doses and target volume definitions. Here are some of the underlying data and the rationale for the recommendations shown.

IRS group I *(initial complete resection, no microscopic or macroscopic residual tumour, no lymph node involvement):*
Data from the IRS trials I, II and III have been published about the use of radiotherapy in patients with IRS group I tumours [1]**.** In the IRS-I trial, the use of radiotherapy was randomised, in IRS-II, no radiotherapy was recommended and in IRS-III, radiotherapy was indicated for patients with alveolar histology only. In the analysis of all 3 trials, there was a trend for increased failure free survival (not statistically significant) for patients with favourable histology who received radiotherapy, but the overall survival with or without radiotherapy was identical (about 95 % after 10 years). Failure free survival in the IRS trials I-III was significantly improved for patients with alveolar RMS who received radiotherapy. In IRS I and II, the overall survival for patients with alveolar RMS was also statistically significantly improved with radiotherapy (82 % vs. 52 % after 5 years). There was also a trend for improved overall survival in IRS-III (95 % vs. 86 %; p=0.23). The conclusion is that patients with alveolar RMS IRS group I benefit from radiotherapy, but not patients with favourable histology. This is also the policy in the current E*p*SSG radiotherapy guidelines.

IRS group II *(grossly resected tumour with microscopic residual disease or evidence of regional lymph node involvement):*
An analysis of radiotherapy in patients with IRS group II RMS and RMS-like tumours has been performed for patients treated in the CWS trials 81, 86, 91 and 96 [2]. Indications for radiotherapy differed amongst the trials, but there were favourable subgroups of patients that did not receive radiotherapy. Radiation doses ranged between 32 Gy and 54 Gy. There was a statistically significant difference in local control and event free survival in favour of patients treated with radiotherapy despite selection bias. Local control after 5 years was 83 % with and 65 % without radiotherapy ($p<0.004$), event free survival was 76 % with and 58 % without radiotherapy ($p<0.005$). There was a trend for improved survival in the radiation group (84 % vs. 77 %, n.s.). The improvement in local control and event free survival was independent of histology (favourable vs. unfavourable), tumour size, tumour site and age of the patient. Even patients with favourable histology and small primary tumours ($\leq$ 5 cm) benefited from the use of radiotherapy. When the patients of each single trial (CWS 81, 86, 91 or 96) were analyzed separately, the difference in local control and event free survival was not statistically significant any more. The difference in overall survival for the whole study population, although better in all analyzed subgroups who received radiotherapy, was statistically significant only for patients with unfavourable histology (80 % vs. 56 % after 10 years).
In order to avoid a high local failure rate, the use of radiotherapy in patients with IRS group II is therefore recommended. This is compulsory for the patients treated in the high risk group. Because there is no statistically significant difference in overall survival for standard risk patients with

favourable histology, radiotherapy can be omitted if considering the tumour site and age of the patient, radiotherapy is too toxic. The risk of a higher local relapse rate must then be discussed.

IRS group III *(initial incomplete resection with gross residual disease):*

Radiotherapy is the only available local therapy in patients who cannot receive a secondary complete resection. Patients with vaginal tumours and favourable histology are usually very young and local control is acceptable without radiotherapy in patients in complete remission after chemotherapy [3, 4]. In patients with IRS group III disease at other sites with clinical complete remission without the option of second surgery and favourable histology, radiation doses of 32 Gy using accelerated hyperfractionation have resulted in satisfactory local control in the CWS trials [5,6] ; with conventional fractionation, doses of 40 Gy or more have been reported to be sufficient to obtain local control [7] . For patients with alveolar RMS, a higher radiation dose has usually been given.
In the IRS IV trial, radiotherapy doses of 50.4 Gy in conventional fractionation were randomised against 59.4 Gy using hyperfractionation in patients with group III tumours [8]. The results with higher radiation doses were not improved, therefore 50 Gy is considered as sufficient for alveolar RMS independent of remission status and for embryonal RMS with residual disease following induction chemotherapy without an option for second surgery.
If delayed second surgery is possible and complete resection is achieved, patients still benefit from additional radiotherapy. In an analysis of the trials CWS 81, 86, 91 and 96, patients with RMS and RMS-like tumours who had IRS group III tumours with secondary complete resection (n=132) were evaluated. Indications for radiotherapy differed amongst the trials but radiotherapy was usually omitted in low risk patients. The calculated local control was 85 % for patients who did and 67 % for those who did not receive radiotherapy ($p<0.01$). EFS after 5 years was 77 % with and 58 % without radiotherapy ($p<0.02$). OS after 5 years with and without radiotherapy was 84 % and 79 % (n.s.). There was no difference in the incidence of systemic failures between the two groups. Patients with small as well as with large initial tumours profited from radiotherapy. The advantage for irradiated patients was seen in patients with favourable and unfavourable histology. The 5 year local control rate in patients without tumour cells in the resected specimen and no radiotherapy was 50 % compared with 89 % in those who did receive radiotherapy ($p<0.01$). Concerning patients with favourable histology and favourable site, overall survival is good following complete secondary resection even when postoperative radiotherapy is omitted, particularly in uro-genital non-bladder-prostate tumours. [3,4] Radiotherapy following second surgery is therefore usually indicated in this trial except for patients with favourable site and favourable histology (subgroup C). Moderate radiation doses are recommended (36 Gy or 41.4 Gy depending on histology). This is compulsary for the patients treated in the high risk group. Because there is no statistically significant difference in overall survival for standard risk patients with favorable histology, radiotherapy can be omitted if considering the tumour site and age of the patient, radiotherapy is too toxic. The risk of a higher local relapse rate must then be discussed.

23.2 EQUIPMENT

23.2.1 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.

23.2.2 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.

23.2.3 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 bean radiotherapy must take into account radiation-tolerance of adjacent tissue and should be calculated individually in each case.

23.3 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.

23.4 RADIATION DOSE FOR THE PRIMARY TUMOUR

The radiation dose is prescribed according to histology of the tumour, response and the IRS group (extent of initial resection). The doses are summarized in table 1. This section relates to children aged 3 years and older.

- IRS group I (initial complete resection, no microscopic or macroscopic residual tumour, no lymph node involvement):

Radiotherapy is only performed in patients with alveolar RMS. The dose is 41.4 Gy in 23 fractions.

Exceptions: see below

- IRS group IIa (grossly resected tumour with microscopic residual disease, no evidence of regional lymph node involvement), IIb and c (with regional lymph node involvement):

All patients receive radiotherapy independently of histology. The dose is 41.4 Gy in 23 fractions.

- IRS group III (initial incomplete resection with gross residual disease):

In all patients with gross residual disease and residual disease following initial chemotherapy, a secondary complete resection is recommended. Second surgery should only be anticipated when a macroscopically and microscopically complete resection is possible. In case of second surgery, radiotherapy is usually given following second surgery. In patients with reconstructive second surgery, radiotherapy before this procedure may be recommendable.

- *Favourable (embryonal) histology:*
  Patients in subgroup C with complete secondary resection may not receive postoperative radiotherapy (see option A).
  In all other patients, a dose of 36 Gy in 20 fractions is given following complete secondary resection and good clinical response at restaging following initial chemotherapy.

  A dose of 41.4 Gy in 23 fractions is given following complete secondary resection and poor clinical response at restaging following initial chemotherapy.

  In patients who receive radiotherapy *before* (expected) complete second surgery, the same doses according to response are applied.

  The dose is 41.4 Gy in 23 fractions when there is complete clinical remission following initial chemotherapy and no second surgery is performed.

  A dose of 50.4 Gy in 28 fractions is given following incomplete second surgery.

  A dose of 50.4 Gy in 28 fractions is given in patients with residual tumour following initial chemotherapy (partial remission, progressive disease) when no second surgery is performed.

  A boost of 5.4 Gy in 3 fractions may be given in large tumours with poor response to chemotherapy.

- *Unfavourable (alveolar) histology:*
  A dose of 41.4 Gy in 23 fractions is given following complete secondary resection.

In patients who receive radiotherapy *before* (expected) complete second surgery, the same dose is applied.

A dose of 50.4 Gy in 28 fractions is given following incomplete second surgery.

The dose is 50.4 Gy in 28 fractions when there is complete clinical remission following initial chemotherapy (no second surgery) and in patients with residual tumour following initial chemotherapy (partial remission, progressive disease) when no second surgery is performed. A boost of 5.4 Gy in 3 fractions may be given in large tumours with poor response to chemotherapy.

Radiotherapy of lymph nodes: see following chapter.

Exceptions:
a. *Vaginal tumour* site and embryonal histology: no radiotherapy is performed if a complete remission is achieved after the completion of chemotherapy. In patients without complete remission, brachytherapy can be considered.
b. *Orbital tumour* site: The decision for or against radiotherapy in patients with group II and group III embryonal RMS is made individually following full informed consent. (see chapter treatment guidelines for special sites:orbit). Patients with partial remission (more than 66 % tumour shrinkage) receive 45 Gy instead of 50.4 Gy.
c. *Patients $\leq$ 3 years* of age: see paragraph 23.12.

Important comment: The radiotherapy guidelines have to be followed strictly in all high risk patients. Furthermore they should be followed for patients treated in the standard risk group. As stated in the introduction of the radiotherapy chapter, event free survival is improved in patients with the use of radiotherapy in IRS groups II and III even when they had complete second surgery or are in complete clinical remission after initial chemotherapy. For patients in this situation presenting with favourable histology, despite differences in event free survival, there is no statistical difference in overall survival because of effective (but also aggressive) salvage treatment. Therefore, because of concerns of radiation-associated side effects, particularly in very young patients and/or vulnerable tumour sites, omission of radiotherapy may be justified in single patients who present with favourable histology and achieve clinical complete remission with chemotherapy and second surgery despite the higher risk of relapse. *This situation must be discussed with the reference centre and the patient/parents must be informed about the increased risk of local relapse.*

Table 7: **Radiation doses for the primary tumour according to histology and IRS - group for children age 3 years or older (RT: radiotherapy; F: fractions).**

IRS Group	**embryonal RMS**	**alveolar RMS**
I	no RT	41.4 Gy; 23 F
IIa, b and c	41.4 Gy; 23 F	41.4 Gy; 23 F
III followed by:		
- secondary complete resection	36 Gy; 20 F *(partial response)* 41.4 Gy; 23 *F (minor partial response, SD)* *Subgroup C: option A (no RT) or B (36 Gy)*	41.4 Gy; 23 F
- second look surgery but incomplete secondary resection	50.4 Gy; 28 F	50.4 Gy; 28 F
- clinical complete remission, no second look surgery	41.4 Gy; 23 F	50.4 Gy; 28 F
- partial remission, minor PR, SD, progressive disease, no second surgery	50.4 Gy; 28 F (+ Boost of 5.4 Gy; 3 F) orbit and PR (>2/3) 45 Gy; 25 F	50.4 Gy; 28 F (+ Boost of 5.4 Gy; 3 F)

23.4.1 Radiation in patients with stable or progressive disease at restaging

Patients who have stable or progressive disease at restaging at week 9 receive second line therapy. Patients in whom a secondary complete resection is possible will be treated with postoperative radiotherapy with 41.4 Gy, 23 F independently of histology. Patients with inoperable tumours or with incomplete second surgery will be treated with 50.4 Gy in 28 fractions and a boost of 5.4 Gy in 3 fractions at the discretion of the treating radiation oncologist.

23.5 RADIATION DOSE FOR INVOLVED REGIONAL LYMPH NODES

Radiotherapy to regional lymph nodes is only performed when there is clinical or pathological evidence of lymph node involvement. Radiotherapy is not performed when there is no evidence of lymph node involvement at diagnosis, either clinically or histologically. The risk of lymph node involvement in patients with embryonal RMS is very low, it is higher in patients with alveolar RMS. In the CWS trials 81-96, there were 184 patients with alveolar RMS without clinically involved lymph nodes at diagnosis. The incidence of loco-regional lymph node failure was 9 % overall. Analyzed according to tumour site, it was highest for extremity tumours (14 %;11 of 78 pts.). There was no difference in the incidence according to IRS group or according to age. Of the 17 lymph node relapses, only 7 were isolated relapses. Radiotherapy of clinically uninvolved regional lymph nodes seems therefore not justified.
Radiotherapy to the involved lymph node sites is performed independently of histology. In patients with clinical or pathological evidence of lymph node involvement, a radiation dose of 41.4 Gy is given when there are no enlarged lymph nodes following initial chemotherapy before the onset of radiotherapy. This dose is given also when a lymph node excision was performed initially. In patients with enlarged lymph nodes at the onset of radiotherapy, an additional boost of 9 Gy is applied.

Table 8: **Radiation dose for regional lymph node areas (RT: radiotherapy; F:fractions)**

Situation	**embryonal/alveolar RMS**
no clinical or pathological involvement of regional lymph nodes	no RT
clinically or pathologically positive lymph nodes; excised or in complete remission before RT	41.4 Gy; 23 F
positive lymph nodes, macroscopical residual disease before RT	41.4 Gy; 23 F + 9 Gy boost; 5 F

23.6 FRACTIONATION

Treatment is applied in conventional fractionation with 1.8 Gy per day. In patients with large abdominal or cranio-spinal fields, smaller fractions are used. In patients $\leq$ 3 years of age, smaller fractions may be used as well (1.6 Gy). The radiation dose is prescribed according to ICRU 50.

23.7 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 feasible from the irradiated volume..

23.8 TARGET VOLUME DEFINITION FOR PRIMARY TUMOUR

1. The target volume is chosen according to the initial tumour volume (gross tumour volume; GTV). The pretherapeutic T1 MR image with contrast is usually the optimal imaging study. Exceptions: intrathoracic or pelvic tumour bulk (see paragraph 23.14)
2. The clinical target volume (CTV) is defined as the GTV + 1 cm (exception limbs: 2 cm in longitudinal direction).
3. 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.
4. The planning target volume (PTV) is defined as the CTV + 1 cm (exception chest wall: 2 cm). orbit: whole orbit included in the PTV up to 36 Gy).
5. In patients receiving 50.4 Gy, the CTV and hence the PTV is reduced by 1 cm after 41.4 Gy. In patients with orbital tumours, the initial radiation of the whole orbit is reduced to the initial tumour extent + 1 cm after 36 Gy.
6. In patients receiving a boost after 50.4 Gy, the PTV for the boost is the residual tumour at the start of radiotherapy plus a margin of 1-2 cm.
7. 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) and orbit (entire orbit) for 41.4 Gy. Areas contaminated during surgery including scars and drainage sites must be included in the PTV. If 50.4 Gy need to be applied, the PTV is reduced by 1 cm after 41.4 Gy.

23.9 TARGET VOLUME DEFINITION FOR LYMPH NODES

The dose of 41.4 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. The boost is used for the enlarged lymph node(s) as it is defined in the CT or ultrasound examination before the onset of radiotherapy. An additional margin of 2 cm is to be used for the PTV of the boost.
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.

23.10 TIMING OF RADIOTHERAPY

In patients with IRS group III (macroscopical residual disease), the option for second look surgery must be checked before the onset of radiotherapy. In patients receiving no second surgery,

radiotherapy is performed at week 13. In high risk patients, the full dose of doxorubicin must have been given before the onset of radiotherapy.
After second look surgery, postoperative radiotherapy should be started within 21 days except when there are postoperative complications.
In patients who receive reconstructive surgery, radiotherapy before second look surgery may be beneficial. This must be discussed with the study centre. The interval between the end of radiotherapy and second surgery should be approximately 5 weeks. Surgery immediately following radiotherapy can result in higher operative morbidity.

23.11 SYNCHRONOUS CHEMOTHERAPY AND RADIOTHERAPY

Synchronous application of radiotherapy and chemotherapy with doxorubicin and actinomycin D should in general be avoided.
However irradiation will take from 5 to 6 weeks and it is important not to reduce excessively the cumulative dose of the drugs administered.
According to the protocol the whole dose of doxorubicin will be administered before start of radiotherapy.

Parallel application of radiotherapy and actinomycin D should be given:
- when extremity tumours are treated
- mucosae are not included in the irradiation field.
- at the very beginning of RT (week 13)

Actinomycin-D should be omitted at week 16 when the treatment fields include the trunk, abdomen, or the head and neck

Caution is needed in the administration of Actinomycin-D at week 19: in general if 2 weeks have passed from the end of irradiation Actinomycin-D should be given. In case of a shorter interval Actinomycin-D may be re administered when no toxicity is anticipated (in case of doubt reduce Actinomycin dose to 50%)

The omitted doses of actinomycin will not be administered later.

23.12 AGE ADAPTATION

23.12.1 Age > 1 and ≤ 3 years at the time of radiotherapy

Embryonal RMS: Radiotherapy will only be performed if there is residual disease at the end of chemotherapy.
Exception: parameningeal tumours will always receive radiotherapy even if in complete clinical remission after chemotherapy. The radiation dose should be given according to older patients. Depending on tumour size and site, this can result in unacceptable toxicity. In these special cases, a dose reduction can be performed. This should be discussed with the reference center.

Alveolar RMS:	Group I:	no radiotherapy
	Group II and III:	radiotherapy according to older patients (no dose reduction; exceptions as above)

Smaller fraction sizes can be used (1.5 or 1.6 Gy).

23.12.2 Age ≤ 1 year

An individual decision for or against radiotherapy must be made depending on tumour histology, tumour site, response to chemotherapy, extent of previous resections and options for second surgery. This should be discussed with the study centre.

23.13 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) spinal cord in pts. with residual spinal tumour (on MRI)	**41.4** Gy; 23 F **50** Gy; 28 F
optic nerve/optic chiasm	**45** Gy; 25 F

23.14 TREATMENT GUIDELINES FOR SPECIAL SITES

23.14.1 Parameningeal tumours

Surgery in parameningeal tumours is usually incomplete. Therefore second surgery should not be performed. Radiotherapy must be applied at week 13.

23.14.2 No skull base erosion/no cranial nerve palsy

The brain/meninges are NOT routinely irradiated. The CNS volume irradiated will be that included within the fields required to cover the primary volume, (e.g. nasopharynx/paraspinal situations) according to the general guidelines.

23.14.3 Skull base erosion/cranial nerve palsy/no intracerebral component

RMS with skull base erosion/cranial nerve palsy but no intracerebral components will be irradiated as follows:
The PTV will be that required to treat the primary tumour (initial tumour volume + 2 cm) and the skull base for the involved fossa only. Radiation fields must adequately cover the initial skull base erosion but there is no routine whole brain irradiation.

23.14.4 Skull base erosion/cranial nerve palsy/with intracranial component

The PTV for the intracranial extent of the tumour is defined according to the residual intracranial component at restaging before the onset of radiotherapy with an additional safety margin of 2 cm. It is not necessary to consider the full initial intracranial tumour extent. The amount of skull base included in the PTV is as defined above.

23.14.5 Disseminated meningeal disease or CSF positive cytology

These patients are treated in the protocol for metastatic disease.

23.14.6 Target volume definition in parameningeal RMS with positive lymph nodes

The PTV is according to the treatment guidelines for parameningeal site and to the treatment guidelines for nodal involvement.

23.14.7 Head and neck non-parameningeal

Radiotherapy is given according to the general radiation guidelines described above. Patients in subgroup C (favourable histology) may not receive radiotherapy when a secondary complete resection was performed.

23.14.8 Orbit

The decision for or against radiotherapy in patients with group II and group III embryonal RMS and clinical complete remission following induction chemotherapy is made individually following full informed consent. Patients in this treatment situation who receive radiotherapy have a lower risk of local relapse, an improved event free survival but experience radiation associated side effects. Patients in this treatment situation who do not receive radiotherapy have a higher risk of local relapse, less good event free survival but no radiation associated side effects in case there is no local relapse and increased toxicity due to salvage treatment including radiotherapy if a relapse occurs. Overall survival in both approaches is equivalent. This is due to effective salvage treatment[9]. The decision for or against radiotherapy is therefore a question of priorities of the treating physician and of the patient/parents. Two options are given in this protocol (see chapter 14.4)

When given, radiation of the entire orbit is performed up to 36 Gy, then the PTV is reduced to the initial tumour size and an additional margin of 1 cm, if possible sparing the lacrimal gland. Patients with favourable histology and clinical complete remission following induction chemotherapy receive 41.4 Gy, patients with partial response (>2/3) 45 Gy, patients with minor partial response, SD or PD receive 50.4 Gy.

23.14.9 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 lymphoedema. 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.
For lymph node positive extremity RMS see paragraphs 2.4 and 2.8.

23.14.10 Urogenital Bladder/Prostate 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). Depending on the extent and infiltration of the disease, patients with bladder/prostate tumours may be treated with afterloading techniques/brachytherapy. Individual planning and discussion with the respective reference centre is advised.

23.14.11 Urogenital Non-Bladder/Prostate Site

Patients in subgroup C (favourable histology) with complete secondary resection may not receive postoperative radiotherapy (see chapter 14.4).

Incompletely resected paratesticular RMS need to be irradiated. In order to avoid late sequelae all non mutilating surgical possibilities should be exhausted. In case radiotherapy is necessary (microscopically complete resection not possible), the dose according to the general guidelines should be given with a PTV margin of 2 cm around the initial tumour volume. The contralateral testicle should be positioned out of the treatment volume if possible (orchidopexy). Radiotherapy to lymph node sites is performed according to the general recommendations. When there is scrotal involvement, the infiltrated scrotal area must be treated with a PTV margin of 2 cm.

RMS of the vagina with favourable histology (embryonal RMS) do not receive radiotherapy if in clinical complete remission after chemotherapy. Patients with unfavourable histology (alveolar RMS) and patients who are not in complete clinical remission after chemotherapy need to be treated with radiotherapy. Depending on the extent and infiltration of the disease these patients may be treated with afterloading techniques/brachytherapy. Individual planning and discussion with the respective reference centre is advised. Oophoropexy has to be considered in order to avoid radiation doses at the ovary in all girls treated for pelvic tumours.

23.14.12 Abdomen

Intraperitoneal RMS or RMS of small and large bowel should be resected and only rarely irradiated. Abdominal structures most often prevent high radiation doses.

If radiotherapy to the abdomen is performed, the kidney and liver tolerance doses have to be respected (see paragraph 2.12). 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.

Whole abdominal radiotherapy is performed only when there is malignant ascites or gross tumour spillage during surgery. These patients will be treated in the protocol for metastatic RMS.

23.14.13 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 tissue expander.

Tumours with non-infiltrating extension into the preformed pelvic cavity often show a large intrapelvic mass which shrinks dramatically after chemotherapy. 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 chemotherapy at the beginning of radiotherapy and a 2 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.

23.14.14 Retroperitoneum

RMS of the retroperitoneum should be irradiated as outlined in the general radiotherapy guidelines and treatment planning should be CT-based. 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.

23.14.15 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 which shrinks dramatically after chemotherapy. 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 chemotherapy at the beginning of radiotherapy and a 2 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.

Radiotherapy of the hemithorax is performed only when there is malignant pleural effusion or gross tumour spillage during surgery. These patients will be treated in the protocol for metastatic RMS.

23.15 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.

23.16 REFERENCES – RADIOTHERAPY

1. Wolden S, J Anderson, W Crist et al.: Indications for radiotherapy and chemotherapy after complete resection in rhabdomyosarcoma: A report from the Intergroup Rhabdomyosarcoma Studies I to III. J Clinical Oncology 17 (11):3468-75; 1999

2. Schuck A, A Mattke, D Kunz et al.: IRS-Group II rhabdomyosarcoma and rhabdomyosarcoma-like tumors: Is radiotherapy necessary? JCO, 22(1):143-9; 2004

3. Arndt C, S Donaldson, J Anderson et al.: What constitutes optimal therapy for patients with rhabdomyosarcoma of the female genital tract? Cancer 91:2454-68; 2001

4. Martelli H, O Oberlin, A Rey et al.: Conservative treatment for girls with nonmetastatic rhabdomyosarcoma of the genital tract: A report from the study committee of the International Society of Pediatric Oncology. JCO 17:2117-2122; 1999.

5. Koscielniak E, B Schmidt, R Knietig et al.: Effectivity of a 32 Gy radiation dose in children with RMS: Report of the German Cooperative Soft Tissue Sarcoma Studies (CWS). Med Pediatr Oncol 37: 186; 2001.

6. Koscielniak E, M Morgan, J Treuner: Soft tissue sarcoma in children. Prognosis and management (review). Paediatr Drugs 4:21-28;2002.

7. Regine WF, J Fontanesi, P Kumar et al. Local tumor control in rhabdomyosarcoma following low-dose irradiation: comparison of group II and select group III patients. Int J Radiat Oncol Biol Phys. 31(3):485-91; 1995

8. Donaldson S, J Meza, JC Breneman et al.: Results from the IRS-IV randomized trial of hyperfractionated radiotherapy in children with rhabdomyosarcoma--a report from the IRSG. Int J Radiat Oncol Biol Phys. 51 (3):718-28; 2001.

9. Oberlin O, A Rey, J Anderson et al. Treatment of orbital rhabdomyosarcoma: survival and late effects of treatment-results of an international workshop. JCO 19:197-204;2001

24. Chemotherapy guidelines

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

Investigational Medicinal Products (IMPs)

In the UK, the following drugs have been defined as IMPs for this trial:

- **Doxorubicin** (iv) given as part of IVADo therapy
- **Cyclophosphamide** (oral) given as maintenance therapy
- **Vinorelbine** (iv) given as maintenance therapy

Investigational medicinal products are administered in the randomised trial to High Risk patients. The same investigational medicinal products are also given to the Very High Risk patients in the Observation study. All other chemotherapy drugs are given as standard treatment and are therefore considered to be Non-IMPs. NB: drugs given to metastatic patients are NIMPs.

24.1 CHEMOTHERAPY STARTING/ STOPPING RULES

The following chemotherapy courses should not be started unless all these conditions are present:

- 2 $x10^9$/l WBC, or 1 $x10^9$/l neutrophils
- 80 $x10^9$/l platelets are reached.
- absence of any relevant organ dysfunction (especially heart, kidney or liver)

24.2 GENERAL GUIDELINES

24.2.1 Drug modulation during IVADo treatment

Dose/time intensity is regarded to be an essential aspect of the IVADo strategy. In case of relevant (≥ CTC grade III) toxicity, actinomycin D (ACT-D) is the first drug to be reduced.
It is suggested, that in case of life-threatening neutropenic CTC grade III-IV infection, or treatment delay $\geq$ 1 week due to neutropenia-related toxicity the use of G-CSF with subsequent courses is recommended.
In case of severe mucositis or hepatotoxicity or treatment delay due to ACT-D related cause, ACT-D shall be reduced by 25% for the subsequent course.
If further episodes of treatment delay and/or severe mucositis/neutropenic infections should occur, the dose of actinomycin D should be further reduced or even omitted.
The dose of Doxorubicin should not be modified unless there is evidence of cardiac toxicity (see also paragraph 24.4.2)

24.2.2 Drug modulation in the Maintenance phase

In case of neutropenia (<1 x10^9/l neutrophils) and/or thrombocytopenia (< 80 x10^9a/l platelets) stop Cyclophosphamide administration until count recovery and consider withholding the third vinorelbine dose in the following course.

In case of further haematological toxicity, vinorelbine will be administered at 66% dose at day 1 and 8 (skip the third dose).

24.3 DRUGS INFORMATION AND MODE OF ADMINISTRATION

ACTINOMYCIN D (ACT)
Mechanism of action: inhibition of DNA synthesis

Side effects: gastrointestinal irritation (nausea, vomiting, diarrhoea, ulcerative stomatitis, gastroenteritis), hepatotoxicity (veno-occlusive disease, particularly in young children), bone marrow depression, alopecia, exanthema. It is a radiosensitizer and may enhance radiotherapy damage when given concomitantly.
Extravasation may cause severe local and regional ulceration.

Dose and mode of administration in this protocol:
ACT-D: 1,5 mg/m² iv. as bolus injection. Single doses should not exceed 2 mg.
The drug can be given by peripheral iv. cannula or central line with appropriate precautions against extravasation.

CYCLOPHOSPHAMIDE (CPM)
Mechanism of action: alkylating agent (CPM has to be activated by hepatic hydroxylation)

Side effects: bone marrow depression (nadir 8-14 days), haemorrhagic cystitis (Mesna uroprotection), gastrointestinal irritation (nausea, vomiting, diarrhoea, stomatitis), alopecia, dermatitis, infertility, immunosuppression. Rarely cardiotoxicity and SIADH have been reported.

Dose and mode of administration in this protocol:
CPM: 25 mg/m^2 per os every day (no rest between cycles)
Oral cyclophosphamide is only commercially available in the UK as 50 mg sugar coated tablets which cannot be halved. If tablets are preferred, metronomic dosing can be used, i.e. cumulative weekly dose given over several days as required.
For example, in the case of a patient with a body surface of 1.3 m^2, the daily dose should be 32.5 mg, corresponding to about 100 mg every 3 days: therefore one entire tablet (50 mg) for two consecutive days followed by one day off should be given.
If smaller doses are required or the patient is unable to swallow tablets, the oral liquid IMP formulation may be provided. An IMP supply of cyclophosphamide 10mg/mL oral solution is available for UK trial patients (see Appendix 11). NB: unlicensed Specials formulations must not be used for IMP doses.

It is advised to administer CPM early in the day to decrease the amount of drug remaining in the bladder overnight. During the treatment, an adequate fluid intake (at least 1 L/m^2) is recommended in order to minimize damage of transitional epithelium.

DOXORUBICIN (ADRIAMYCIN) (DOXO)
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.
Extravasation causes local ulceration.

Dose and mode of administration in this protocol:
Doxo: 30 mg/m^2 day 1 and 2 (60 mg/m^2 total) in 4 hour infusion.
Longer infusion does not seem cardioprotective and may increase the risk of mucositis, especially if Doxo is administered along with actinomycin.
The drug can be given by peripheral iv. cannula or central line with appropriate precautions against extravasation.

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

Side effects: haemorrhagic cystitis (Mesna uroprotection), nephrotoxicity (tubulopathy with glucosuria, aminoaciduria, loss of phosphate and Ca, full range of tubulopathies from subclinical changes to a full Fanconi 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:
IFO: 3 g/m^2 day 1 and 2 (6 gram total) as iv. infusion over 3 hours in each block.
Hyperhydration 3 L/m^2/day and Mesna 3 g/m^2 , day 1 and 2, are required until 12 hrs after completion of IFO .

VINCRISTINE (VCR)
Mechanism of action: mitotic inhibitor; block microtubule polymerization

Side effects: peripheral neuropathy (including constipation and/or paralytic ileus, ptosis, vocal cord paralysis, jaw pain, areflexy, paresthesia, muscular weakness, ataxia), central neurotoxicity (including hallucinations, convulsions, SIADH), arthralgia, myalgia, minimal bone marrow depression, alopecia.
Extravasation causes local ulceration.

Dose and mode of administration in this protocol:
VCR: 1,5 mg/ m^2 iv. as bolus injection day 1 of each cycle (weekly during the first 7 weeks).
Single doses should not exceed a maximum of 2 mg.
The drug should be given by peripheral iv. cannula or central line with appropriate precautions against extravasation.

VINORELBINE (VNL)
Mechanism of action: mitotic inhibitor; block microtubule polymerization

Side effects: myelosuppression, alopecia, mucositis, neurotoxicity. Vesicant.

Dose and mode of administration in this protocol:
VNL: 25 mg/m^2 i.v. day 1,8,15 of each cycle
The drug is given on an outpatient basis, diluted in isotonic solution to a concentration between 0.5 and 3 mg/mL and infused over 5 to 10 minutes into either a large central vein or a free-flowing infusion of 0.9% sodium chloride or 5% dextrose into a fixed peripheral venous infusion device. In patients who receive vinorelbine in a peripheral vein, the vein should be then flushed with a rapid infusion of at least 75 to 125 ml of normal saline solution to reduce the risk of chemical phlebitis.

24.4 DOSE MODIFICATIONS

24.4.1 Age and weight

Age ≤ 1 month
These patients are eligible for the protocol but they are not eligible for the randomised study and should be initially treated with VA at doses calculated *by weight* without further reduction.
Ifosfamide should be added when the child is > 1 months old.
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 > 1 months and ≤ 3 months
These patients are eligible for the protocol but they are not eligible for the randomised study and should be initially treated with VA or IVA, according to the risk group, at doses calculated *by weight* without further reduction (VA). Ifosfamide dose will be calculated *by weight and then reduced to 50%* .
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 ≤ 6 months
These patients are eligible for the protocol but they are not eligible for the randomised study. Drug doses will be calculated *by weight* without further reduction. Doses are reported in Table 9.

Age > 6 months and ≤ 12 months (or ≤ 10 kg body weight)
These children are eligible for the protocol and randomised study according to the risk stratification. Drug dose should be calculated *by weight* without further reduction.

Table 9 - Age and Drug dose calculation

Age	Eligibility	Drugs and dose calculation	Regimen
0 – ≤ 1 months	Not eligible to the randomised trial	Drug dose calculated by body weight. The resulting dose is: - VCR 0.05 mg/kg/dose - ACT-D 0.05 mg/kg/dose No IFO or Doxo administration. Add IFO when the child is > 1 months	VA only (to be modified when the child > 1 months)
1- 3 months (see note a)	Not eligible to the randomised trial	VCR and ACT-D: drug dose calculated by body weight. The resulting dose is: - VCR 0.05 mg/kg/dose - ACT-D 0.05 mg/kg/dose IFO: dose calculated by body weight and then reduced to 50%. The resulting dose is - IFO 50 mg/kg/dose No Doxo administration.	VA or IVA
> 3 - ≤ 6 months	Not eligible to the randomised trial	VCR, ACT-D, IFO and Doxo: drug dose calculated by body weight. The resulting dose is: - VCR 0.05 mg/kg/dose - ACT-D 0.05 mg/kg/dose - IFO 100 mg/kg/dose - Doxo: 1 mg/kg/dose	VA or IVA (IVADo only for very high risk group)
> 6 – ≤ 12 months > 6 months and/or ≤ 10 kg	Eligible to the randomised trial if in the high risk group	VCR, ACT-D, IFO and Doxo: drug dose calculated by body weight. The resulting dose is: - VCR 0.05 mg/kg/dose - ACT-D 0.05 mg/kg/dose - IFO 100 mg/kg/dose - Doxo: 1 mg/kg/dose	VA, IVA or IVADo (depending on risk group)
> 12 months and > 10 kg	Eligible to the randomised trial if in the high risk group	Full m² dose	VA, IVA or IVADo (depending on risk group)

Note:

a) if tolerated, Ifosfamide dose should be increased by 25-30% at each cycle to full dose by body weight.

b) Doxo should not be administered in children aged less than 3 months at diagnosis. Therefore they will be treated initially with VA and subsequently with IVA.

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 (observe maximum single dose 2 mg for VCR and ACT-D).
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.

24.4.2 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.
For neutropenia management during IVADo see chapter 24.2.1, for the Maintenance phase see Chapter 24.2.2. For the other cases if count recovery is delayed more than 5 days after the planned start of the next course of chemotherapy on more than one occasion, consider the use of growth factors (see) or dose reduction of all drugs in the subsequent course to 75% of previous dose (except vincristine).

BLADDER TOXICITY

Haemorrhagic cystitis with ifosfamide is rare if hydration and mesna are utilised appropriately. Microhaematuria usually can 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 CPM 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 (see Appendix A.10) and is more likely to occur with an increasing cumulative dose. If nephrotoxicity (tubular or glomerular toxicity > grade 2) occurs discontinue IFO and substitute CPM 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 tubular dysfunction is usually transient, and does not require dose modification.

CARDIOTOXICITY

In this protocol the total cumulative dose of doxorubicin is 240 mg/m^2, therefore lower than the threshold dose for late cardiotoxicity reported in most studies. However, careful monitoring for possible acute or late cardiotoxicity is recommended.
Significant deterioration in cardiac function is indicated by a shortening fraction (SF) <28%. In this event, temporarily withdraw Doxo.
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. In this event omit Doxo in the next course.
If the decrease is not persistently proven, i.e. if repeated investigations (after a week) cannot reproduce the dysfunction, Doxo can be recommenced (and the omitted dose of Doxo should be supplied instead of ACT with the first possible cycle).
If persistent deterioration of myocardial function occurs, e.g. persistent decrease in fractional shortening by an absolute value of 10 percentile points from previous tests or a persistent fractional shortening below 28%, consider further avoidance of Doxo and the patient should be referred to a cardiologist.

LIVER TOXICITY AND VOD

Liver dysfunction related to chemotherapy or abdomen irradiation may occur. Patients with signs of liver dysfunction should be monitored carefully.
A particular type of hepatic toxicity is represented by the veno-occlusive disease (VOD). VOD appears related to the administration of different drugs and ACT-D in particular. No specific predisposing factor has been found to identify the patient at risk. A prior persistent or slow recovery of thrombocytopenia may be an indicator of VOD.
In case of VOD actinomycin D should not be given until the main abnormalities have returned to normal and half the dose should be given for the first following course. If tolerated ACT-D dose may be increased progressively in the following cycles.
If the symptoms reappear during ACT-D treatment, this drug should be withdrawn permanently.

VOD of any grade is considered a serious adverse event and must be reported immediately (see chapter 26) using the RDE system

Criteria for diagnosis and grading of VOD are reported in appendix A.9.

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 mgs) 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 IFO and substitute with cyclophosphamide 1500 mg/ m^2 per cycles.

Peripheral neurotoxicity from vincristine is a common but usually mild side effect. If grade 3-4 peripheral neurotoxicity occurs (intolerable paresthesia, marked motor loss, paralysis or paralytic ileus) one or two injections of vincristine should be omitted and restarted at a 50% dose.
Laxatives should be prescribed when weekly vincristine is given and thereafter if needed to prevent constipation.

25. Toxicity Monitoring

Patients having adverse events will be monitored with relevant clinical assessments and laboratory tests as determined by the Investigator. All adverse events must be followed to satisfactory resolution or stabilisation of the event(s).

Any action taken and follow-up results must be recorded either on the appropriate page of the Case Report Form, as well as in the subject's source documentation. Follow-up laboratory results should be filled with the subject's source documentation.

For all adverse events that require the subject to be withdrawn from the study, relevant clinical assessment and laboratory tests will be repeated on at least a weekly basis (if possible), until final resolution or stabilisation of the event(s).

26. Adverse Event Reporting

The collection and reporting of Adverse Events (AEs) will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments. Definitions of different types of AE are listed below. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the reference safety information (RSI) for doxorubicin, cyclophosphamide and vinorelbine (the Investigational Medicinal Products) or the applicable Summary of Product Characteristics for ifosfamide, vincristine and actinomycin D and drugs given as second line therapy (NIMPS).

26.1 REPORTING REQUIREMENTS

26.1.1 Adverse Events

All medical occurrences which meet the definition of an AE (see Appendix 7 for definition) should be reported. Please note this includes abnormal laboratory findings.

26.1.2 Serious Adverse Events

Investigators should report all AEs that meet the definition of an SAE (see Appendix 7 for definition) unless the event is excluded from the reporting process as described below.

26.1.2.1 Events that do not require reporting on a Serious Adverse Event Form

Exclusions applicable to ALL risk groups:

The following events should not be reported on an SAE Form:

- Hospitalisations for:
  - Protocol defined treatment
  - Pre-planned elective procedures unless the condition worsens
  - Treatment for progression of the patient's cancer
- Progression or death as a result of the patient's cancer, as this information is captured elsewhere on the Case Report Form

Exclusions applicable to Low, Standard or Metastatic risk groups and to High and Very High risk group patients NOT receiving IMPs:

The following events should not be reported on an SAE Form, these events should be captured on the Chemotherapy Summary CRF:

- Any event that is consistent with the applicable (compendium of) Summary of Product Characteristics which does not meet the definition of fatal or life threatening. A fatal or life threatening event must be reported using an SAE Form

For patients in the High and Very High risk groups receiving IMPs:

The following events should be **reported on an Expected SAR Form** rather than an SAE Form:

This section is only applicable to **high** and **very high risk group** patients who experience **an expected SAR**. **i.e. the event is listed below and is causally related to an IMP**

The following events should be reported via the Expected SAR Form unless they prove to be life threatening or fatal, in which case they should be reported via the SAE Form:

- Admissions to control symptoms of nausea and vomiting
- Admissions for supportive treatment during an episode of myelosuppression (including febrile neutropenia without septic shock, blood or platelets transfusions) unless this proves fatal or requires admission to a high dependency or intensive care facility
- Admissions for mucositis
- Admissions for constipation
- Admissions for haematuria
- Admissions for significant weight loss +/- nasogastric feeding

SAR Forms should be completed and returned in the post as soon as possible.

26.1.2.2 Monitoring pregnancies for potential Serious Adverse Events

It is important to monitor the outcome of pregnancies of patients in order to provide SAE data on congenital anomalies or birth defects.
In the event that a patient or their partner becomes pregnant during the SAE reporting period please complete a Pregnancy Notification Form (providing the patient's details) and return to the Trials Office as soon as possible. The patient should be given a Release of Medical Information Form or the patient should be asked to give this to their partner. If the patient/partner is happy to provide information on the outcome of their pregnancy they should sign the Release of Medical Information Form. Once consent has been obtained provide details of the outcome of the pregnancy on a follow-up Pregnancy Notification Form and if necessary also complete an SAE Form.

26.1.3 Reporting period

Details of all AEs (except those listed above) will be documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment. SAEs which occur more than 30 days after the administration of the last treatment and which are judged to be at least possibly related to the trial treatment should be reported irrespective of how long after administration the reaction occurred.

26.2 Reporting Procedure for the Participating Site

26.2.1 Adverse Events

AEs experienced during treatment should be recorded on the appropriate Chemotherapy Summary or Toxicity Form. AEs will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

26.2.2 Serious Adverse Events

For more detailed instructions on SAE reporting refer to the SAE Form Completion Guidelines contained in the Investigator Site File (ISF).
AEs defined as serious and which require reporting as an SAE (excluding events listed in Section 26.1.2.1 above) should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality of the AE which should be documented using the CTCAE version 3.0.
On becoming aware that a patient has experienced an SAE, the Investigator (or delegate) must complete, date and sign a CRCTU SAE Form. The form should be faxed together with a SAE Fax Cover Sheet to the Trials Office using one of the numbers listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, fax the SAE Form with an SAE Fax Cover Sheet to:

0121 414 3700 or 0121 414 9520

On receipt the Trials Office will allocate each SAE a unique reference number. This number will be transcribed onto the SAE Fax Cover Sheet which will then be faxed back to the site as proof of receipt. If confirmation of receipt is not received within 1 working day please contact the Trials Office. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Fax Cover Sheet completed by the Trials Office should be filed with the SAE Form in the Investigator Site File.
For SAE Forms completed by someone other than the Investigator the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality assessments. The form should then be returned to the Trials Office in the post and a copy kept in the Investigator Site File.
Investigators should also report SAEs to their own Trust in accordance with local practice.

26.2.3 Provision of follow-up information

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

26.2.4 Reporting Procedure by the Trials Office

On receipt of an SAE Form seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The Clinical Coordinator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the reference safety information, it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR)).

26.2.5 Reporting to the International Collaborators and the EpSSG Co-ordinating Centre

Immediately following categorisation of an SAE the Trials Office will enter the SAE data onto the trial Remote Data Entry System for inclusion in the international data set.

26.2.6 Reporting to the Competent Authority and main Research Ethics Committee

26.2.6.1 Suspected Unexpected Serious Adverse Reactions

The Trials Office will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA) and main Research Ethics Committee (REC) within 7 days. Detailed follow-up information will be provided within an additional 8 days.
All other events categorised as SUSARs will be reported within 15 days.

26.2.6.2 Serious Adverse Reactions

The Trials Office will report details of all SARs (including SUSARs) to the MHRA and main REC annually from the date of the Clinical Trial Authorisation, in the form of a Development Update Safety Report.

26.2.6.3 Adverse Events

Details of all AEs will be reported to the MHRA on request.

26.2.6.4 Other safety issues identified during the course of the trial

The MHRA and main REC will be notified immediately if a significant safety issue is identified during the course of the trial.

26.2.7 Informing Investigators of SUSARS

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the Investigator Site File.

26.2.8 Independent Data Monitoring Committee

The Independent Data Monitoring Committee will review all SAEs.

27. Supportive Care

The treatment of patients with RMS requires 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.

27.1 HEMATOLOGICAL TOXICITY

- Anaemia 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 $x10^9$/l or in hemorrhagic patients with thrombocytopenia.

27.2 USE OF GROWTH FACTORS (G-CSF)

Primary prophylaxis with G-CSF is not required for the chemotherapeutical regimen outlined in E*p*SSG RMS 2005.
During IVADo treatment, in case of life-threatening neutropenic infection, or treatment delay $\geq$ 1 week due to neutropenia, the use of G-CSF (lenograstim 150 $\mu g/m^2$/day) with subsequent courses is recommended (see also chapter 24.2.1).
In other cases if infection complications (neutropenic fever) or prolonged neutropenia develops administration of growth factors will be considered according to Centre guidelines.
G-CSF should be continued until WBC > 1 $x10^9$/l for 3 consecutive days.

27.3 NAUSEA AND VOMITING

These symptoms are expected with all drug combinations of E*p*SSG RMS2005 except single dose vincristine. Antiemetic therapy according to the institutional policy should be given with each major block of therapy.

27.4 INFECTIONS

Neutropenic Fever

Episodes of neutropenic infection are likely to occur after EpSSG RMS2005 cycles of 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 treated in the standard, high and very high risk arm may receive cotrimoxazole according to the centre guidelines. 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.

27.5 CONSTIPATION

Approximately 10% of patients suffered from grade 3-4 constipation during the IVADo pilot study. Laxatives should be prescribed when weekly vincristine is given and thereafter if needed to prevent constipation.

27.6 CENTRAL LINE

The use of central lines is recommended (apart from patients treated in the low risk regimen).

28. Follow up recommendations

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

28.1 TUMOUR RELAPSE SURVEILLANCE

	1st year	2nd year	3rd year	4th and 5th year
Clinical examination	Every 3 months	Every 4 months	Every 4 months	Every 12 months
Ultrasound ± CT scan or MRI of the primary tumour site				
Chest x-ray				

Bone marrow aspiration and bone scintigraphy should be performed in case of clinical suspicion

28.2 LATE EFFECTS SURVEILLANCE

1. General studies for all patients

a. 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 evaluated for thyroid and pituitary function.

b. Annual blood pressure measurement.

c. Annual Tanner Staging for girls and boys till maturity. If there is delayed appearance of secondary sexual maturation, the patient warrants evaluation of gonadal hormone values, i.e., at 12-14 years for girls (FSH, LH and estradiol) and boys (FSH, LH and testosterone).

d. 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.

e. Record the onset of menses in girls and regularity of periods. Because of local radiotherapy or alkylating agents therapy, ovarian failure may occur in some patients.

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

2. Studies in children receiving specific chemotherapeutic agents.

a. Doxorubicin. If cardiac toxicity occurred while on therapy (decreased ejection fraction on MUGA scan or decreased shortening fraction on Echocardiogram), annual evaluation of cardiac function should be made for at least 5 years. Histories should include reference to exercise tolerance or shortness of breath.

b. Cyclophosphamide, Ifosfamide. 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.
In girls, evidence of ovarian dysfunction should be investigated by getting values for FSH, LH and estradiol.
If hemorrhagic cystitis occurred while on therapy, urinary should be followed till clear for 2 years. Bladder function can best be assessed by voiding cysto- urethrograms.

3. Studies for specific primary sites

A. HEAD/NECK

1**) Annual growth measurements** plotted on standard growth curves for all patients (see 1.a.).

2) **Annual ophthalmologic exam** by an ophthalmologist if eye was in radiotherapy field.

3) **Annual dental exam** if maxillary/mandibular sites were in radiotherapy field.

4) **Auditory examination every year** if the ears were in the irradiated field.

6) **Thyroid function** (TSH, T3, T4) must be verified every 2 years in case of irradiation on the neck.

B. TRUNK

1) 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.).
2) Studies appropriate to investigate problems fol1owing **abdominal/pelvic irradiation** which may include bowel obstruction, chronic diarrhoea, inadequate absorption, recta1 stenosis, and sphincter problems.

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

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

5) If radiotherapy was given to primary tumours of the chest or to pulmonary metastases consider the risk of breast cancer and give screening advice (self palpation, mammography).

C. G-U SITES

1) **Children without a bladder** and with various types of urinary diversion should have kidney function evaluated with imaging studies every 1-2 years for hydronephrosis, evidence of pyelonephritis and rena1 function. Contrast studies of ilea1 loops may be necessary to detect kinking, stenosis or reflux of the ureters.

2) Girls with **uterine or vaginal tumours** should be followed for sexual maturation and ovarian failure as in l.b., 1.e. and 2.b. Vaginal examination under anaesthesia until 5 years follow-up and after depending on the treatment received.

3) Boys treated for bladder, prostate or paratesticular primaries should be followed as in l.b. and c. and 2.b.

4) If radiotherapy was given to the bladder, the volume and function should be assessed by voiding cysto-urethrograms or other imaging studies if indicated.

5) History in teen-age boys should include questions of normal **ejaculatory function**, particularly in patients with bladder/prostate or paratesticular primaries.

6) Semen analysis as described in l.b.

D. EXTREMITY SITES

1) If radiotherapy was given, appropriate **bilateral limb length measurements** should be done annually.

2) 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 (see SAE report, section 26.2).

29. Pathology guidelines

29.1 E*p*SSG PATHOLOGY PANEL

Professor Vito Ninfo/Dr. Anna Kelsey – Co-Chairpersons

Dr. Rita Alaggio

Dr. Dominique Ranchere-Vince

Dr. Núria Torán

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29.2 GENERAL REMARKS

Pathology Protocol

All rhabdomyosarcomas diagnosed up to the age of 21 years should be registered.

Role of the pathologist in a participating centre:

The local pathologist has an essential role in both the clinical trial and the prospective study.

1. The diagnosis and sub-typing of rhabdomyosarcoma is made by the local pathologist.

2. Patient stratification is dependent on a number of factors but the diagnosis and subtyping is critical to the management of the patient.

3. Material needs to be sent to the national coordinators as soon as possible following the biopsy or resection.

4. The local pathologist needs to liaise with the molecular biology laboratories so that appropriate molecular characterisations are carried out; it is important for the study that molecular studies are carried out on all rhabdomyosarcomas.

5. The local pathologist needs to be involved in/coordinate tissue banking.

THE NATIONAL COORDINATORS AND THE EpSSG PANEL OF PATHOLOGISTS ARE WILLING TO OFFER REAL TIME REVIEW OF ALL SOFT TISSUE SARCOMAS. THE SUBTYPING OF RHABDOMYOSARCOMA IS IMPORTANT IN PLANNING MANAGEMENT AND RANDOMISATION.

SLIDES, BLOCKS AND FORMS SHOULD BE SENT DIRECTLY TO THE NATIONAL COORDINATORS AS SOON AS POSSIBLE TO AVOID DELAYS. THE REVIEW DIAGNOSIS WILL BE COMMUNICATED DIRECTLY TO THE REFERRING PATHOLOGIST.

29.3 CLASSIFICATION AND DIAGNOSIS OF RHABDOMYOSARCOMA

This is not meant to be a comprehensive review. For full description refer to:

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 sarcomas constitute approximately 7% of malignant tumours in children, 15 years old or less at diagnosis. For the morphologic-based classification refer to WHO Histologic Typing of Soft Tissue Tumours.

29.4 RHABDOMYOSARCOMA

RMS is the most common STS in children, accounting for up to 60% of soft tissue tumours (data from Manchester Children's Tumour Registry) with an overall survival exceeding 65%. The clinicopathologic classification proposed by the Intergroup Rhabdomyosarcoma Study is currently used:

1. Superior Prognosis
   - A. Botryoid Embryonal RMS
   - B. Spindle cell RMS
2. Intermediate Prognosis
   - Embryonal RMS
3. Poor Prognosis
   - Alveolar RMS including
   - Solid Variant RMS

Embryonal rhabdomyosarcoma and its subtypes, botryoid and spindle cell, occur most often in the head and neck region, genitourinary tract and body cavities, and they have an intermediate to highly favourable prognosis. Alveolar rhabdomyosarcoma, including the solid variant, has a predilection for the extremities and a poor prognosis. Prognosis is determined by histological classification, stage and risk group, age and site of origin.

i. Botryoid Embryonal RMS

This tumour is characterised macroscopically by its polypoid (grape-like) growth. Most are found in mucosa-lined hollow regions such as the nasal cavity, vagina and urinary bladder.

The consensus criterion for the diagnosis of Botryoid Embryonal RMS is the demonstration of a **cambium layer** beneath an **intact epithelium**, in at least one microscopic field – irrespective of the gross description, and therefore supersedes the gross demonstration of a 'grape-like' tumour. The degree of differentiation of rhabdomyoblasts may vary from slight to well differentiated

ii. Spindle-Cell RMS

Spindle cell RMS is a rare subtype of RMS accounting for approximately 4.4% of RMS (data from the German-Italian Cooperative STS Study Group). This tumour is commonly seen in the paratesticular region, followed by the head and neck region, but can occur in other sites. Grossly the tumour is firm and well circumscribed but not encapsulated. The cut surface shows a nodular pattern often with a whorled appearance. Histologically the tumour is composed almost exclusively of spindle cells with cigar-shaped nuclei and prominent nucleoli. At least 80% of the tumour should consist of spindle cells for a tumour to warrant a diagnosis of spindle cell RMS. Some tumours are rich in collagen and have a storiform or whorled pattern, whereas the more cellular and collagen-poor tumours have a fascicular pattern.

Please note this diagnosis should not be made on a trucut biopsy as the sample may not be representative.

iii. Embryonal RMS

Embryonal RMS form poorly circumscribed, fleshy, pale masses that may show areas of haemorrhage, necrosis and even cyst formation.

These tumours have a variable pattern ranging from poorly differentiated tumours to well differentiated neoplasms. There are a number of features common to all these tumours:

a. a myxoid stroma
b. a mixture of small cells with hyperchromatin-rich or spindle shaped cells and other cells showing variable degrees of rhabdomyoblastic differentiation.
c. Variable degree of cellularity with dense areas usually around vessels alternating with loose hypocellular myxoid areas.

Note – foci of immature cartilage can be seen in some Embryonal RMS

Two differential diagnoses that can cause problems:

Fetal Rhabdomyoma
Pseudosarcomatous Myofibroblastic Tumour

iv. Alveolar RMS

Alveolar RMS is a rapidly growing, soft-tissue tumour with a fleshy, grey tan appearance. ARMS displays a nesting alveolar or solid pattern of cells in a fibrous stroma. The cells have monotonous, round to oval nuclei and inconspicuous nucleoli, but some can have prominent nucleoli. Multi-nucleated tumour cells with eosinophilic cytoplasm and nuclei arranged in a 'wreath-like' fashion are seen in the alveolar structures and can be helpful in the diagnosis of alveolar RMS especially in small biopsies.

The characteristic "alveolar" pattern is well recognised. In MMT'95 the diagnosis of Alveolar RMS was made even if the tumour shows **focal** alveolar **histology**. However, there still remains a degree of discordance in the diagnosis and definition of Solid Variant Alveolar RMS. At present there does not appear to be a different prognosis for Solid versus Classic Alveolar RMS.

Definition of Solid Variant RMS:

A poorly differentiated, cellular tumour composed of sheets of cells with no fibrous septa or may have thin, fibrous septa or fibrovascular septa running through the tumour, but lacking well defined alveolar spaces. Reticulin staining can be helpful in highlighting this sub-type.

Some alveolar RMS present with bone marrow infiltration and the only material available for diagnosis is a trephine biopsy. The same criteria for making the diagnosis apply.

v. RMS N.O.S. – subtype cannot be determined.

Please note, RMS N.O.S. (not otherwise specified) is not a subtype; it indicates that a diagnosis of RMS can be made but no further subtyping is possible. This usually arises when the biopsy is very small, sometimes with crushing artifact; it is only possible for the histopathologist to make a diagnosis of RMS. When clinically feasible, a re-biopsy is indicated to ensure subtyping and molecular characterization.

When subtyping is not possible, as a pragmatic decision and to avoid possible under-treatment of patients, the risk group will be decided as per Alveolar RMS.

vi. Undifferentiated Soft tissue sarcoma

These are a rare group of tumours associated with a poor prognosis similar to alveolar rhabdomyosarcoma.
The histologic appearance is that of a high grade, cellular tumour with no specific differentiation by light microscopy, immunohistochemistry or electron microscopy. They usually express Vimentin.
Patients with undifferentiated soft tissue sarcoma will be treated according to this protocol with the same strategy as unfavourable RMS. These patients are not elegible to the randomised trial and will receive chemotherapy according to Arm A (9 cycles of IVA) if categorized in the High Risk Group.

Be aware that undifferentiated (embryonal) sarcoma of the liver is not part of this entity.

vii. Ectomesenchymoma

These are rare tumours occurring most commonly in young male patients, Histologically this tumour combines a rhabdomyosarcoma (embryonal, spindle cell or alveolar) with variable neurons or neuroblasts. Immunohistochemistry is important as the neural component may be focal and scarce. Positive immunostaining with S100, Synaptophysin, Neurofilament, Glial Fibrillary Acidic Protein or Protein Gene Product 9.5 is seen.
Patients with ectomesenchymoma will be treated according to this protocol with the same strategy as unfavourable RMS. These patients are not elegible to the randomised trial and will receive chemotherapy according to Arm A (9 cycles of IVA) if categorized in the High Risk Group.

29.5 IMMUNOHISTOCHEMISTRY

It is recommended that a panel of antibodies be used for the diagnosis of RMS:

- Vimentin	- Cam5.2	- CD3
- Desmin	- S100	- CD79a
- Sarcomeric Actin	- EMA	- Mic2**
- MYF4 or MyoD1 *	- LCA (CD45)	- Fli-1

* MYF4 or MyoD1: Nuclear positivity. % of tumour cells positive is higher in Alveolar>Embryonal
**Mic2: Although some RMSs demonstrate immunopositivity to Mic2, it is often weakly granular and intra-cytoplasmic, as opposed to the distinct plasma membrane staining seen in extra-osseous Ewing's/peripheral primitive neuroectodermal tumour. Mic2 immunostain should always be done as part of a panel of antibodies that includes specific myogenic markers.

Immunostaining with monoclonal antibodies against the intranuclear myogenic transcription factors Myogenin (MYF4)) and MyoD1 is recommended for all RMS subtypes. These are excellent markers showing high sensitivity and specificity. Myogenin seems to give more consistent results.
Also note that a small % of RMS can show focal positivity with Cam5.2 (cytokeratin).

29.6 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 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 full definition)

Primary resection: example orchidectomy for paratesticular tumours.

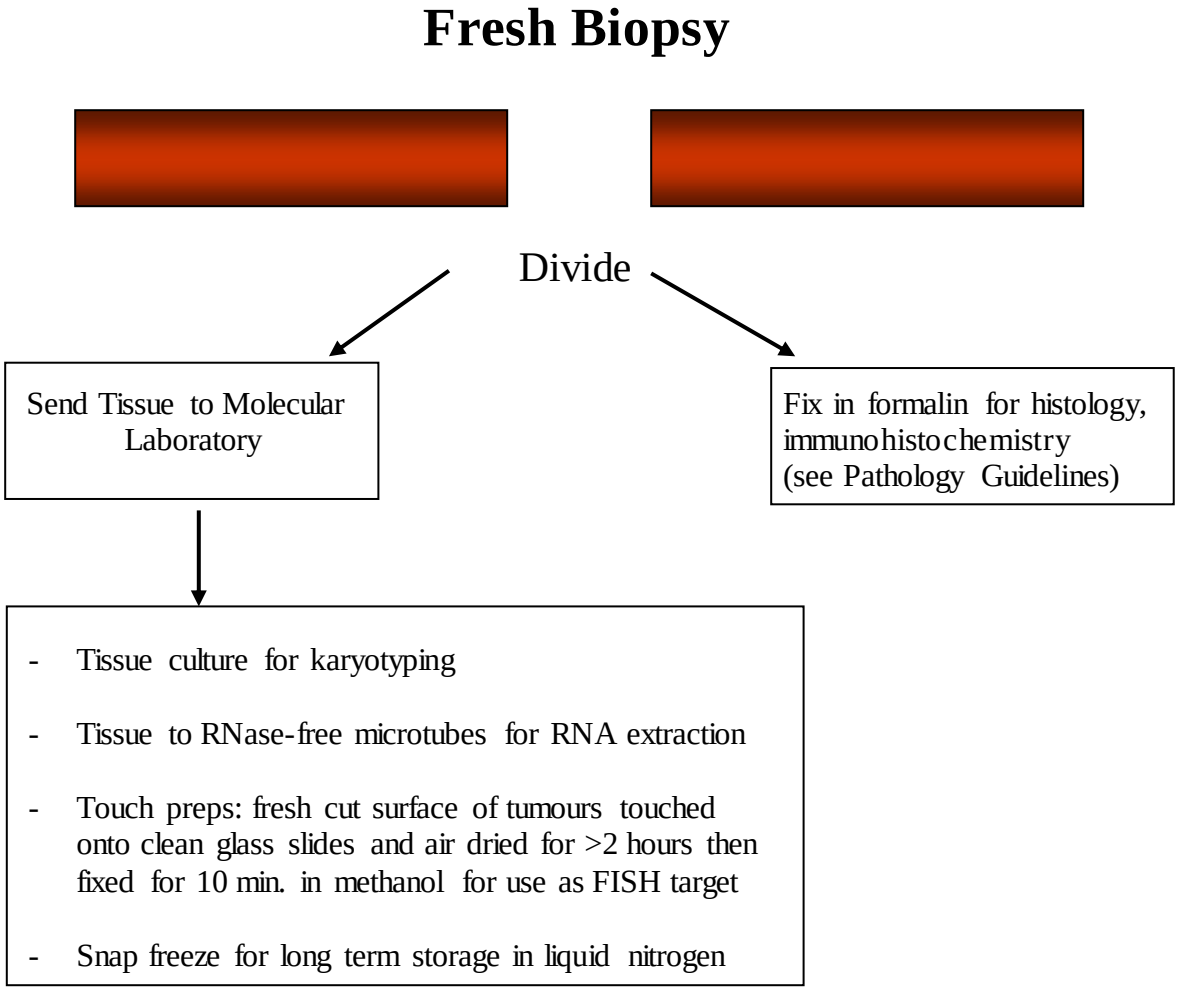
Primary re-operation: to achieve resection in patients with microscopic disease before other therapy.

Secondary operation (post chemotherapy): to achieve complete resection of a residual mass after chemotherapy e.g. bladder/prostate.

All primary and post-chemotherapy resection specimens need margins to be evaluated by the pathologist.

1. Surface of specimen should be inked before incision.
2. Specimen should be weighed and measured (in 3 dimensions).
3. 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.
4. Ideally the specimen should be photographed, including the cut surface, and a block guide prepared.
5. 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 for accurate sub-typing of the RMS, for example in mixed embryonal/alveolar RMS.
6. 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.
7. Document macroscopic % of necrosis – sample areas of necrosis.
8. 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.
9. 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.
10. Molecular characterisation (see schematic diagram).

29.6.1 Biopsy



NB: When handling small biopsies it may be important to prioritise type of biological study to be undertaken. Although we would recommend taking material for RTPCR and FISH, the pathologist should liaise with the molecular laboratory that the material is being sent to.

In some national group's pathology and biology labs 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

NB: The pathologist needs to document what tissue has been sent for molecular characterization/research. The pathologist should be informed by the oncologist if consent has been obtained for storage of material for research. **It is 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 centers to ensure that this is taking place. It is also strongly recommended 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 and 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.

29.6.2 Resected Specimens

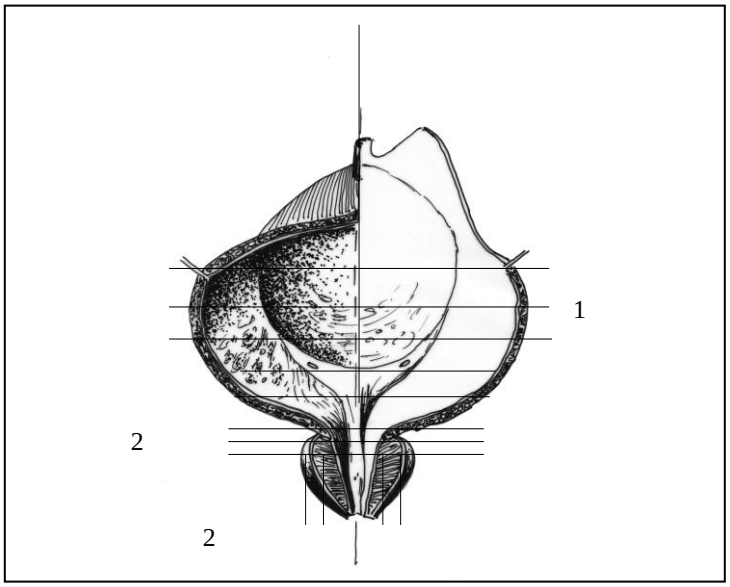
- The surface of the specimens should be inked before opening/bisecting.

- Tumour for molecular characterization/research/storage should be taken ensuring that the margins are not affected by this procedure.

- Same protocol should be followed as for open biopsy.

- In resected specimens, photographs and documentation of blocks taken (block guide) is necessary. The following are examples:

Fig. 1 Bladder/prostate



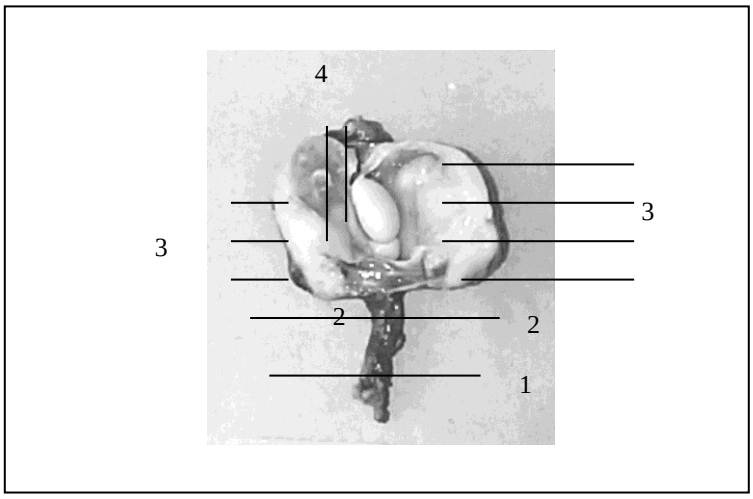
Procedure:

- Paint the whole external surface of bladder and prostate, if present, with India ink.
- Follow your preferred procedure to open the bladder; we recommend to open it through the anterior wall with a Y-shaped cut.
- Fix overnight in formalin.

Sampling:

1. Tumour: include most of it.
2. Bladder neck and prostate: include all with cuts as shown in figure 1.
3. Bladder wall: anterior and posterior wall, at least two sections each, if not involved by tumour.
4. Urethral orifices.
5. Perivisceral lymph nodes, if present.
6. Any abnormal area.

Fig. 2 Orchidectomy for paratesticular RMS



Procedure:

1. Ink surface of specimen.
2. Cut specimen sagitally while it is in the fresh state and put in formalin.
3. Take photographs of specimen and use for block guide.

Description:

Weight and dimension of tumour.
Extent of tumour involvement.
Length of spermatic cord.
Features of tumour, in particular presence of nodularity, haemorrhage and necrosis.

Sections for histology:

1. Spermatic cord and surrounding soft tissue at time of resection - one cross section.
2. Spermatic cord and surrounding soft tissue at about 1 cm from testicle - one cross section.
3. Tumour – at least one section for each centimeter. The sections should include the tunica albuginea. Always take sections from hemorrhagic and necrotic areas of tumour as well as from solid or fleshy areas. In addition, any nodules or vague nodularity should be sampled. Each block should be identified separately and linked to photograph.
4. Uninvolved testicle – at least two sections.
5. Epididymis – one section, if identified.

29.6.3 Bone Marrow Trephine Biopsy

1. Should be fixed in buffered formalin and decalcified according to the laboratory protocol.

2. Multiple levels (H&E stain) should be examined to exclude metastatic RMS. Reticulin stain is helpful in highlighting small foci of tumour.

3. It is also important that when cutting levels intermediate sections are kept for immunostaining to avoid cutting out of micrometastases.

4. Routinely stain for Desmin, MYF4 and MyoD1.

5. Please note: in cases where bone marrow aspirates/peripheral blood is sent for the detection of MRD, then the corresponding trephine biopsy needs to be sent for central review.

29.7 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:

Embryonal – botryoid
Embryonal – spindle cell
Embryonal – not otherwise specified
Alveolar - classic
Alveolar – solid variant
Mixed alveolar /embryonal

Rhabdomyosarcoma NOS – subtype cannot be determined.
Please note, RMS – NOS is not a subtype; it indicates that a diagnosis of RMS can be made but no further subtyping is possible. This usually arises when the biopsy is very small, sometimes with crushing artifact, it is only possible for the histopathologist to make a diagnosis of RMS. When clinically feasible, a re-biopsy is indicated to ensure subtyping and molecular characterization.

Anaplasia:

Absent
Focal
Diffuse
Indeterminate

Necrosis:

Absent
Present
Extent %

Mitotic rate:

(x 40 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.

Venous/lymphatic invasion:

Present
Absent
Cannot be assessed

Molecular characterization:
Please note: if molecular characterization 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 specify the following:

- % of necrosis
- % of fibrosis
- presence of rhabdomyoblasts - % of tumour cells
- Presence of anaplasia

29.8 MATERIAL TO BE SENT TO NATIONAL COORDINATORS.

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). In the case of specimens in which there are focal areas of alveolar histology it is important that H&E and uss from these areas are sent to the local co-coordinator.

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. If bone marrow aspirate/peripheral blood is sent for the detection of Minimal Residual Disease (MRD), then the corresponding trephine biopsy (H&E + 5 uss) needs to be sent for central review.

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 coordinator 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 coordinator. These will be returned.

7. The local pathologist report and the form need to be sent with the slides.

8. The histological subtyping of RMS is important for patient stratification and management. The national coordinators and EpSSG panel of pathologists are offering real time review.

9. The slides/block and forms should be sent directly to the national coordinators.

NB: It is very important that the results of the molecular characterisation are collected prospectively. 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.

29.9 PATHOLOGY STUDIES

Anaplastic RMS

A recent study[5] based on IRS I-III patients, looking at the significance of anaplasia, showed that the presence of diffuse anaplasia was of prognostic significance.

Definition of Anaplasia:
The presence of anaplasia needs to be documented. Anaplasia is diagnosed if RMS (both embryonal and alveolar) contains cells with large, lobulated hyperchromatic nuclei (at least 3 times the size of neighbouring nuclei) and atypical (multipolar) mitoses. Furthermore, it is important to document whether these cells are focal or diffuse.

Current study: - The presence of anaplasia will not be used for stratification of patients. However, in this study we will be prospectively assessing the incidence of anaplasia as well as the distribution of the anaplastic cells in both biopsies and resected specimens.

Presence of maturation

In MMT'95, the presence of maturation was defined as the presence of 10% or more of tumour cells showing rhabdomyoblastic differentiation on haematoxylin and eosin stained sections. We will continue to assess the presence of maturation prospectively in E*p*SSG RMS2005.

Tissue Microarrays

As part of the collection of biological specimens, it is intended that the pathology coordinators for this European study of rhabdomyosarcomas also coordinate collection of blocks for the preparation of tissue microarrays. This will only be undertaken if:

1. there is consent for research
2. consent from the local pathologists
3. process does not compromise any future diagnostic process.

The national pathology coordinators will supervise the process.

29.10 REFERENCES - PATHOLOGY

1. Newton WA Jr, Gehan EA, Webber BL, et.al. Classification of rhabdomyosarcomas and related sarcomas. Pathologic aspects and proposal for a new classification – an Intergroup Rhabdomyosarcoma Study. Cancer 1995;76:1073-85.
2. Qualman SJ, Coffin CM, Newton WA, et.al. Intergroup Rhabdomyosarcoma Study: update for pathologists. Pediatr.Dev.Pathol. 1998;1:550-61.
3. Cavazzana AO, Schmidt D, Ninfo V et al. Spindle cell rhabdomyosarcoma. Am.J.Surg.Pathol.16:229, 1992.
4. Leuschner I, Newton WA Jr, Schmidt D, et.al. Spindle cell variants of embryonal rhabdomyosarcoma in the paratesticular region, a report of the Intergroup Rhabdomyosarcoma Study. Am.J.Surg.Pathol. 1993;17:221-230.
5. Kodet R, Newton WA Jr, Hamoudi A, Asmar L, Jacobs DL, Maurer H. Childhood rhabdomyosarcoma with anaplastic (pleomorphic) features, a report of the Intergroup Rhabdomyosarcoma Study. Am.J.Surg.Pathol. 1993;17:443-453.
6. Coffin C. The new international rhabdomyosarcoma classification, its progenitors and considerations beyond morphology. Adv.Anat.Pathol.1997;4:1-16.

30. Biological aspects

(see paragraph 29.6.1 for tissue handling)

For UK Guidelines for molecular cytogenetic analysis and quality assurance, please see Appendix A.11.

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 in these tumours. Traditionally included in this group is the alveolar (aRMS) and embryonal (eRMS) rhabdomyosarcoma and the Ewing's sarcoma family, including PNET. Other entities also entering this differential diagnosis include intra-abdominal desmoplastic small round cell tumour (DSRCT) and, among fibrous or spindle cell malignancies, synovial sarcoma (SS) and congenital infantile fibrosarcoma (CIFS).

Cytogenetic studies of several childhood sarcomas have identified reciprocal chromosomal translocations which correlate with specific tumour types. Molecular cloning of the translocation breakpoints have identified fusions between genes located at the breakpoints of each partner chromosome and which 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, PAX-FKHR transcripts characterize alveolar rhabdomyosarcoma; EWS-FLI1 and EWS-ERG are expressed in the Ewing's family of tumours; ETV6-NTRK3 in congenital infantile fibrosarcoma; EWS-WT1 in desmoplastic sarcoma, whereas SYT-SSX1 and SYT-SSX2 are found in synovial sarcoma.

Other transcripts may be useful in the detection of tumour cells: MyoD1 and Myogenin transcripts are present in the vast majority of RMS, independently of the histological subtype, and they can be used in the study of minimal bone-marrow (BM) infiltration. New molecular markers may be identified in the future that could have clinical applications

Role of biological studies in paediatric sarcomas

The new clinical trials of the European paediatric Soft tissue sarcoma Study Group (E*p*SSG) represent an 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 Panel 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 hybridisation is a rather recent technique that, making use of specific labelled 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 for chimeric transcripts

Cytogenetic studies of childhood sarcomas have identified chromosomal translocations which are correlated with specific tumour types. These genetic abnormalities give rise to fusion genes that are transcribed into specific chimeric RNA that can be revealed by Reverse transcriptase polymerase chain reaction (RT-PCR). Often chimeric transcripts represent tumour associated markers that can be used as a diagnostic tool. Identical fusion transcripts can be found in specific subgroups of tumours with the similar histologic appearance or, alternatively, identical tumours can harbour different chimeric genes. The prognostic implications of the presence or absence of specific reciprocal translocations are not known.
In addition, not only the presence of genetic abnormalities may be of relevance for the biology of a cell, but the level of expression may be important as well. Quantitative PCR (Real-time PCR) is a technique that allows not only the identification of specific genetic characteristics, but also can determine their level of expression.

Other molecular markers of disease

Tumour cells may possess entirely new genetic markers, such as fusion genes, but they may also express genes that are silent in normal cells. Moreover, genes may represent a tool to identify lineage specific characteristics that may be relevant to identify tumour cells in the context of cells of different origin/lineage. From this viewpoint the expression of that specific gene represents a tumour marker. This is the case for MyoD1 and Myogenin which are expressed in cells of skeletal muscle lineage.

30.1 BIOLOGICAL CHARACTERISATION OF RHABDOMYOSARCOMA

Among the soft tissue sarcomas of childhood, RMS represents one of the best characterised malignancies from the biological point of view. Although the progress in this field has elucidated relevant biological features and mechanisms in RMS, not many results have been achieved in terms of biological research that can potentially be translated into the clinical setting. This is the case for the group of RMS as a whole, but also for selected subgroups of this disease, such as the aRMS which are still characterised by a poor prognosis.
In particular, despite some reports in the literature suggesting that aRMS may differ biologically and prognostically, based on the presence or absence of the reciprocal chromosomal translocation t(2;13)(q35;q14) or its rarer variant t(1;13)(p36;q14), there is a lack of prospective studies conducted in the context of homogeneous treatment protocols that may give a clear insight in this issue. Furthermore, although RMS, specially aRMS, have a proneness to metastasise or are metastatic at diagnosis, very little information is available on the prevalence and potential clinical impact of circulating tumour cells at diagnosis or of microdissemination of rhabdomyoblasts to the bone marrow.
These and other reasons suggested to us the need to strongly pursue few and well defined translational biological studies, in an attempt to optimise the diagnostic and therapeutic approach to children with RMS.
Below are some of the major objectives that have been discussed and are to be implemented in a prospective biological study of RMS patients enrolled in this study. Any medical professional involved in the care of children with solid tumours should make every effort to achieve the biological specimen collection in order for the nations' laboratories to ensure that all tumours banked are well characterised. We are convinced (based on previous experience) that this goal is achievable, but only if we can establish a strong and coordinated interaction among oncologists, pathologists, surgeons and biologists who, at different points in time are involved in the management of these patients.

For UK Guidelines for molecular cytogenetic analysis and quality assurance, please see Appendix A.11.

30.1.1 Aims of the Study

As it might be clear from the general introduction on the biological studies in paediatric STS and from the more specific considerations on RMS, within this E*p*SSG protocol for the diagnosis and treatment of RMS, we selected the following studies/activities to be conducted prospectively:

- Expression of tumour associated molecular markers
- Analysis of specific ARMS chromosomal translocations
- Prevalence and kinetics of minimal disseminated disease
- Cytogenetics and FISH
- Collection of biological specimens for further analysis

This may appear rather limited in terms of goals to be achieved within the current clinical trial, but the aim has been to keep the approach as simple as possible, with the further aim of setting the basis for more ambitious biological studies for the next generation of collaborative trials.

30.1.2 Expression of tumour associated molecular markers.

We and others have suggested that selected markers, including *MyoD1* and *Myogenin*, are expressed by virtually all RMS. Although both markers can be determined at the protein level, there are some technical draw-backs that make the interpretation of immunohistochemical analysis rather difficult (and this is the case of MyoD1, especially). MyoD1 and Myogenin expression can be studied at the RNA level as well as by reverse transcriptase polymerase reaction (RT-PCR). We and others have observed that, at least 95% of RMS are positive for MyoD1 and Myogenin transcript. Expression of MyoD1 and Myogenin will be studied in each suspect RMS, independently from its histological subtype.

30.1.3 Analysis of Alveolar RMS specific chromosomal translocations.

Several reports have described the reciprocal chromosomal translocations t(2;13)(q35;q14) or the less frequent t(1;13)(p36;q14) in aRMS. They give rise to the chimeric genes PAX3-FKHR and PAX7-FKHR, respectively, whose products possess transcriptional activity and are involved in the tumourigenesis of aRMS. Recent data suggests that, the translocation is not only characteristic of aRMS subtype, but may have prognostic significance. Although it needs to be further confirmed in a large prospective study and multivariate analysis, the presence of t(2;13) may be associated to a worse prognosis compared to the negative aRMS, whereas the t(1;13) positive aRMS might possess an intermediate outcome.

The translocations will be determined by RT-PCR, but whenever possible also by FISH analysis, and molecular findings would be compared to the standard cytogenetics results.

30.1.4 Prevalence and response kinetics of minimal disseminated disease.

One of the aims of the biological studies in this protocol would be the assessment of the prevalence of minimal disseminated disease (MDD) and the response kinetics of BM tumour infiltration during treatment.

Based on previous experience and in an attempt to study MDD in aRMS, as well as in eRMS, we elected MyoD1 and Myogenin as tumour associated markers that, if expressed in the tumour biopsy, should be evaluated in the BM and peripheral blood of each patient with RMS. At present we have concluded a pilot analysis of MyoD1 and Myogenin expression by RT-PCR and have established a method for the quantitative analysis of MDD by Real Time PCR.

This study will be extended to as many patients as possible, through the optimisation of specific protocols to this aim. Although the study of PAX-FKHR chimeric transcripts (by RT-PCR), in our preliminary experience, may be less sensitive than MyoD1, in case of positivity of a RMS for these genetic markers, they should also be assessed in the BM by RT-PCR.

Identical studies would be conducted on peripheral blood.

30.1.5 Cytogenetics and FISH.

Cytogenetics and FISH analysis are important assessments that should be performed in any malignancy. While FISH analysis would be possible in the great majority of the cases (on touch preps - see "handling of specimens" flow chart), cytogenetics needs a larger amount of "very good quality" viable tumour cells and might be more difficult to accomplish. *Every* effort though should be made to perform standard cytogenetics studies.

30.1.6 Collection of biological specimens for further analysis.

Willingly, a limited number of biological studies have been selected that realistically can and should be accomplished in a prospective manner during the course of this E*p*SSG-collaborative trial. Nevertheless, the biological characterisation of paediatric RMS should be conducted more extensively and in greater depth. To this goal it is of foremost importance that tumour tissue and other biological specimens be collected and stored appropriately to make them available for future research. As an example, each participating Group and each single Institution should be aware that tumour genetic profiling by oligo or cDNA microarrays, is already pursued in selected Centres and will very likely become a more readily available and affordable technology for the biological studies of RMS. This though would imply that tumour tissue should be collected, carefully characterised and stored for this aim. Similarly, studies on the expression profile of proteins might be accomplished by the combination of different techniques as part of the proteomic approach. Lastly, the availability of serum from patients with RMS might allow future studies of soluble tumour related molecules that may be used as markers of disease, possibly related to prognosis.

Table 10 - Summary of sample collection for minimal disseminated and minimal residual disease studies

	Fresh tumour in medium	Bone marrow in NaCitrate 3 ml	Blood in NaCitrate 5-7 ml	Serum 2-3 ml
Diagnosis°	X*	X	X	X
Before cycle II		X**	X**	X**
Assessment of tumour response (after the initial three cycles of CT°°)		X**	X**	X**
In case of delayed surgery	X*	X**	X**	X**
End of treatment		X**	X**	X**

° Whenever possible, bone marrow aspirate and peripheral blood should be obtained prior to the initiation of any surgical approach to any tumour mass (to prevent a possible tumour cell dissemination caused by surgery)

*Fresh tumour tissue must be received in the laboratory at latest within 24 hours from surgery: viable cells are needed for cytogenetic analysis.

** Except at diagnosis any other BM or blood/serum examination should be performed only if positive at the previous assay or in case of a suspected relapse or based on other clinical conditions

BM, peripheral blood and serum should also be obtained in case of relapse in a patient with positive molecular markers (MyoD1, myogenin, PAX-FKHR transcripts). MDD should also be determined in case a relapsed patient would enter an intensified treatment program with autologous peripheral blood stem cell (PBSC) rescue. In this case an aliquot of PBSC harvest should also be tested.

Details on methods, protocols and technical questions will be discussed and decided within the Biological Committee of the Trial. Standards and quality controls for the biological studies will be set.

It is strongly recommend that biological studies be conducted in a single laboratory for each participating National Group.

31. Diagnostic problems

31.1 BONE MARROW INFILTRATION ON MOLECULAR BIOLOGY ONLY

Morphology: Bone marrow negative for RMS infiltration
Molecular biology: positive for RMS markers
The tumour should be considered as a localised RMS and treated accordingly, provided there are not signs of distant lesions in other organs.
In such cases it is strongly requested:
a) to send BM slides for urgent central review
b) to perform follow up bone marrow aspirate as summarised in table 10.

31.2 ALVEOLAR TRANSLOCATIONS FOUND IN EMBRYONAL RMS

Morphology: embryonal RMS
Molecular biology: positive for t(1;13) or (2;13) translocation.
The presence of a t(2;13) or t(1;13) translocation is strongly correlated with alveolar RMS. In a case where the local pathologist has made a diagnosis of embryonal RMS, but a translocation is identified, rapid central review of the case is mandatory. If the diagnosis of embryonal RMS is confirmed on central review, a local decision has to be made with regard to patient management taking into consideration the possibility of sampling issues in mixed tumours and clinical information (i.e. age and site of tumour). Moreover, it may also be appropriate that the molecular characterization be repeated. In these cases molecular characterization should also be undertaken in post-chemotherapy specimens if viable tumour is present.

As general recommendations these patients should be treated as alveolar RMS.

In such cases it is strongly requested:
a) to ask the local pathologist to carefully review the tumour material
b) to send slides for urgent central review
c) to register the case appropriately (a special items for such cases will be prepared in the database)

32. Statistical considerations and analysis

32.1 RANDOMISED TRIAL – PATIENTS IN HIGH RISK GROUP

Design of the trial

This study is a prospective phase III international, multi-institutional, non blinded double-randomised clinical trial.
The aims of the trial are to evaluate the addition of Doxorubicin to the standard therapy with Ifosfamide, Vincristine and Actinomycin (IVA) in paediatric patients with rhabdomyosarcoma in high risk group, as defined in chapter a 15 – *intensification question*, and the role of a maintenance therapy with Vinorelbine and Cyclophosphamide in the same category of patients who have achieved a complete remission at the end of first line treatment – *maintenance question*.
The expected accrual period is 5 years followed by a minimum follow up period of 3 years.
First and second randomisation are provided centrally, by a computer-based service (supplied by CINECA, Casalecchio ITALY) that is accessible via Internet, for all countries and Institutions. Access to the randomisation system is managed according to specific policies adopted by each country (both direct local site and mediated by national data centre access are possible). All eligibility criteria (see chapter 15) and requirements for randomisation have to be fulfilled prior to the randomisation process.
Randomisation is stratified according to participating country and risk subgroup (E, F and G). To reduce possible imbalances in the number of treatment assignments, a randomised blocked design will be used.

End points

Intensification question

1. Primary end point for the intensification question is event free survival, measured as time from date of first randomisation 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 and switch for a second line chemotherapy in patients without good response. Patients without an event at the end of the study or lost to follow up will be censored at the date of last observation.
2. Secondary end points are:

- Overall survival, measured as time from date of first randomisation 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.
- Progression free survival, measured as time from date of first randomisation up to tumour progression. Patients without a progression 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 19.
- toxicity according to NCI-CTC version 3 (see appendix A.7)

Maintenance question

1. Primary end point for the maintenance question is disease free survival, measured as time from date of second randomisation up to relapse or death. Patients still alive and without relapse at the end of the study or lost to follow up will be censored at the date of last observation.
2. Secondary end points are:

- overall survival, measured as time from date of second randomisation 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.
- toxicity according to NCI-CTC version 3 (see appendix A7)

Population Analysis

All efficacy analysis will be carried out according to the intention to treat principle. It foresees that all randomised subjects, whether or not they received any study medication, will be analysed in the arm to which they were assigned.
Patients will also be analysed according to the treatment they actually received only for explorative purposes. 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.

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 (≤1 year, 1-10 years, ≥10 years)
    - Gender
2. Prognostic Factors
    - Pathology (favourable, unfavourable)
    - Post-surgical stage (IRS group)
    - Site of disease
    - Node stage
    - Size of the tumour (maximum diameter ≤ or > 5 cm)

Description of treatment exposure

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 IVA regimen will be summarised using descriptive statistics (median, range).

Survival Analysis

Event Free Survival, Disease Free Survival, Progression Free Survival and Overall Survival in the two treatment arms (standard vs intensification and maintenance vs. control, respectively) 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 on a significance level of 5%. Summary statistics (3-yr and 5-yr, EFS, DFS, PFS and OS) will be reported together with their 95% confidence interval.
In addition, the Cox regression model will be used to adjust the treatment comparison for possible prognostic factors, whenever all assumptions will be satisfied.

The p-value corresponding to the secondary questions will be regarded as explorative.

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 category and grade (all grades, grade 3 and grade 4) for the worst grade documented. Tables will be generated on a per cycle and an overall basis. All comparisons will be performed using two-sided chi squared test on a significance level of 5%. Adjustments for multiplicity will not be made.

Sample size (no longer applicable, see page 170)

~~On the basis of the accrual of the latest studies carried out by SIOP and ICG-CWS (MMT-95 and RMS-CWS-96) a minimum enrolment rate of 100-125 patients per year may be expected. Taking into account previous experience and that new therapeutic strategies may not be available in the near future, the accrual period could be prolonged for at least five years, so that the dimension of the study will be 600 patients roughly.~~

~~The 3-years EFS in the high risk group treated with the IVA regimen should be approximately 50%. The minimal difference that the study should be able to detect is an absolute increase in 3-yrs EFS from 50% to 60%, corresponding to a 26.3% relative reduction in event rates in the IVADo regimen (HR=0.737). In order to detect a difference of this magnitude, under the assumption of exponential distributed EFS, with an 80% power at the 5% significance level (2-sided), 343 events must be observed, and approximately 119 patients per year will have to be enrolled for 5 years, and followed for about 3 more years, taking into account a drop-out rate of 5%.~~

~~Assuming an 80% of complete remission rate at the end of first period of treatment, 15% of refusal to second randomisation and 5% drop out rate during the recruitment period, 388 patients roughly will be available for maintenance comparison. This sample size allows to detect an absolute increase in 3-yr DFS from 55% to 67% corresponding to a relative reduction in relapse rate of 33% in the maintenance arm with 80% power and alpha 5% (two sided test). The patients, after the enrolment period of 5 years, should be followed for further 3 years until 200 relapses have occurred.~~

~~The sample sizes for the intensification and maintenance questions were calculated for a one-step design with nQuery Advisor 5.0 and adapted to a three-step group sequential design (two interim analyses plus the final analysis) (Jennison C., Turnbull BW. Group sequential methods with applications to clinical trials. Chapman & Hall / CRC (2000))~~

Interim Analysis and stopping rules (no longer applicable, see page 170)

~~Two formal interim analyses will be performed after 1/3 and 2/3 the expected events occurred, unless the trial is stopped before to reject the hypothesis of no treatment difference.~~

~~*Intensification question*~~

~~With an accrual period of 5 years, a minimum follow up period of 3 years, an accrual rate of 119 patients per year, a 3-year EFS of 50% for the IVA regimen and 60% for the IVADo regimen, and a drop-out rate of 5%, a total number of 343 events is expected. Therefore, the first interim analysis for the intensification question will be conducted after 114 events and the second after 229 events. The trial will be terminated after an interim analysis if the main question is answered.~~

~~The O'Brien & Fleming stopping boundaries will be used to monitor the study.~~

~~*Maintenance question*~~
~~To answer the maintenance question, a total number of 200 relapses is needed. Therefore, the first interim analysis will be performed after 67 relapses and the second after 133 relapses. The trial will be terminated after an interim analysis if the hypothesis of no treatment difference is rejected. The O'Brien & Fleming stopping boundaries will be used to monitor the study.~~

Sample size amendment (September 2012)

The EpSSG RMS 2005 randomised trial planned to randomise about 600 patients in 6 years thus, considering that the study started in 2006, it should have been closed by the end of 2011. Six years from the start of the study, the randomisation rate of about 60 patients per year (364 randomised patients at the end of 2011), as well as clinical, ethical and administrative considerations, have induced the Independent Data Monitoring Committee to suggest prolonging the accrual period until 2013. The Trial Management Committee approved the amendment of the sample size during the 2012 EpSSG spring meeting.
With a total sample size of about 500 patients, the minimal difference that the study will be able to detect, with an 80% power, is about a 35% relative reduction in event rates in the IVADo regimen (HR=0.65), compared to the standard IVA regimen. In order to detect a difference of this magnitude, under the assumption of exponential distributed EFS, at the 5% significance level (2-sided), 169 events must be observed. The enrolment of about 500 patients over 8 years with a further follow-up period of 2 years should generate the required total number of events.
Since about 60% of patients randomised at first randomisation have been randomised at the second randomisation, a sample size of about 300 patients will be available for the comparison maintenance versus no maintenance. This sample size will allow a detection of a relative reduction in the relapse rate of 50% in the maintenance arm, with an 80% power testing at the 5% significance level (2-sided). Final analysis will be performed when 65 relapses have occurred.
The sample sizes for the intensification and maintenance questions were calculated for a one-step design with nQuery Advisor 6.0 and adapted to a two-step group sequential design (one interim analyses plus the final analysis) (Jennison C., Turnbull BW. Group sequential methods with applications to clinical trials. Chapman & Hall / CRC (2000))

Interim Analysis and stopping rules amendment (September 2012)

One formal interim analysis will be performed after half the expected events occurred.
Intensification question 2012
Therefore, the first interim analysis for the intensification question will be conducted after 85 events. The trial will be terminated after an interim analysis if the main question is answered (see Addendum – page 218).
The O'Brien & Fleming stopping boundaries will be used to monitor the study.
Maintenance question 2012
To answer the maintenance question, a total number of 65 relapses is needed. Therefore, the first interim analysis will be performed after 33 relapses. The trial will be terminated after the interim analysis if the hypothesis of no treatment difference is rejected. The O'Brien & Fleming stopping boundaries will be used to monitor the study.

33. 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, STSC 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.

33.1 PARTICIPATING CENTRES

All clinical centres previously part of the SIOP, CWS or STSC 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.

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 approval for the study from their local Research Ethical Committee
- obtain patient's/parents' written consent to inclusion into the randomised trial (if applicable), data processing and sending diagnostic material to reference institution
- register all patients with non-metastatic Rhabdomyosarcoma
- randomise all eligible patients for the duration of their participation in the study
- submit in a timely and accurate manner 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

33.2 CO-OPERATIVE GROUPS 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.

33.3 E*p*SSG 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

E*p*SSG Co-ordinating Centre contact details:

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33.4 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 if required by each Co-ordinating Centre.

Any amendments to the protocol must be agreed by all the participating 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 latest version of 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.

33.5 DATA MANAGEMENT

Data flow

The E*p*SSG RMS 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.
Centers may enter directly the data into the electronic data base via Internet or may use the traditional paper based flow of data within their Co-ordinating Centre.
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.

Patient Registration procedure

Patients with a diagnosis of localised RMS 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.

Randomisation procedure

First randomisation:
Every patient with a diagnosis of localised RMS who fulfils the trial eligibility criteria must be randomised before treatment is started using the RDE system.

Second randomisation
Patients eligible to the first randomisation will also be eligible to the second randomisation if in CR after the completion of standard treatment (i.e. 9 cycles of chemotherapy+ surgery/radiotherapy).
Patients not eligible for the first randomisation because younger than 6 months at diagnosis are eligible to the second randomisation if older than 6 months at the end of standard treatment.
Patients achieving CR after second line treatment are still eligible to second randomisation.
Patients must be randomised within 8 weeks after the end of treatment.
The end of treatment is defined as the last day of the 9th chemotherapy cycle. However:

- if surgery is performed after the 9th chemotherapy cycle, the date of surgery will be considered;
- if radiotherapy is administered after 9 cycles of chemotherapy, the date of the end of RT will be considered. Since maintenance CT should be started within 8 weeks from the last day of the 9th CT cycle, it would be better to start the maintenance CT during irradiation.

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 randomise the patient using the RDE system and will communicate the randomisation results to the treating Centre.

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 access, despite geographical location.
The Co-ordinating Centre of each group, for example, could have access to all data from its Clinical Centres; instead the principal 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 Protocol Committee shall meet as appropriate to consider patient accrual, eligibility, treatment allocation and outcome and ensure a smooth conduct of the study.
Results of the interim analysis shall be reported to the International Data Monitoring Committee (IDMC) as scheduled by the protocol. The IDMC may recommend early stopping, continuation or extension of the study to the international study committee.

Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) composed of 3 international experts will be designated to monitor the progress of the study from an ethical and scientific point of view (names are reported in the EpSSG Administative organisation section).

The role of IDMC will be:

- to review the patient accrual and to be involved with all interim analysis according to the statistical plan. These interim analyses will remain confidential. On the basis of these analyses, the IDMC will recommend whether the study can continue, whether it has to be extended or changed or terminated prematurely.
- to monitor toxicity of all treatments but especially toxicity of the experimental arms and serious adverse events. Every 6 months a report of toxicity will be prepared by the E*p*SSG Co-ordinating centre and circulated among the participating national groups and to the IDMC. The IDMC will review these interim toxicity data and any relevant information will be forwarded to each co-operative group. Problems and patterns of major toxicity shall be analysed to prevent major toxicity endangering the conduct of the study.
- to examine other pertinent trials. The IDMC will review reports of related studies performed by other groups or organisations to determine whether such information materially affects the aims or preliminary findings of the trial. In case that interim analyses or the results of other studies imply that the study questions have been answered, the IDMC has to decide in conjunction with the Protocol Committee about the continuation of the current study.
- to review any major modification to the study proposed by the Protocol Committee prior to its implementation.

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.

33.6 INSURANCE

The study should be covered by a specific insurance against damage ensuing from the organisation of the trial, if requirements are stated in the national laws.
These aspects will be dealt with on a country basis.

33.7 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**.**

33.8 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 Protocol EpSSG RMS2005, in part or in total.
Similarly each Cooperative Group forming the E*p*SSG agrees that the results of the Protocol RMS2005 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 Protocol RMS 2005 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 Protocol 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.

34. Ethical issues

The protocol will be submitted, before patients enrolment, to the Ethics Committee of each participating Centre for review and approval according to in force law.

34.1 INFORMED CONSENT

The patient's and/or parent's written consent to participate in the study must be obtained after a full explanation has been given of the treatment options including the conventional and generally accepted methods of treatment and the manner of treatment allocation.

If the patient is a minor, the treatment must be explained to and consent received from his/her guardian. Additionally the child should receive an explanation as to his/her means of understanding and should give consent as well, if he/she is able to do so. 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 without giving reasons must be respected.

Consent for participation in the study, for data management and biology material handling will be also obtained.

The patient must remain free to withdraw at any time from the study and the protocol treatment or to withdraw his/her data from the study without giving reasons and without prejudicing his/her further treatment.

All patients and/or their parents must give written consent to inclusion into the trial, data processing and – if applicable – to sending diagnostic material to reference institutions, which in all participating countries has to conform to the national data protection legislation.

Examples of Information sheet/Consent Form are provided in Appendix A.13.

Administrative documents, consent forms and copies of the study documentation of a study patient have to be kept according to set archival terms.

34.2 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 A12.

34.3 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.

35. Appendices

- A1.TNM Classification and Grouping
- A2. IRS Grouping
- A3. pTNM and Grouping System
- A4. Definition of sites
- A5. Regional lymph Nodes definition
- A6. Radiology guidelines
- A7. Definition of Adverse Events
- A8. Toxicity grading
- A9. Veno-Occlusive Disease of the liver - Grading
- A10. Nephrotoxicity Grading
- A11. Guidelines for molecular cytogenetic analysis and quality assurance of rhabdomyosarcoma for patients entered onto EpSSG study
- A.12. Investigational Medicinal Product (IMP) Supplies and Management
- A13. Declaration of Helsinki
- A14.Overview of Parent/Patient/GP Information sheets and Consent Forms
- A15. EpSSG-RMS-MET 2008: Treatment Arm for Metastatic Disease
- A16. Overview of Information Sheets/Consent forms (RMS-MET 2008)

A.1 TNM CLASSIFICATION

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 lymph nodes

M1: Evidence of distant metastasis or involvement of non-regional lymph nodes

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 non-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

A.2 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 (which 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 microscopic 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 onset
(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 favourable 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.

A.3 IRS AND pTNM GROUPING SYSTEM

IRS 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 Lymph nodes not affected Lymph nodes affected but removed	pT3a
III	Macroscopic complete resection but microscopic residuals and lymph nodes affected and not removed	pT3a
	Macroscopic residuals after resection or biopsy With malignant effusion	pT3b pT3c
IV	Metastasis present or non-regional lymph nodes involved	pT4

A.4 DEFINITION OF SITES

To define the site of origin may be difficult in some cases of RMS. 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 acknowledge 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 Para nasal Sinuses
The three Para nasal 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 treatment 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 Para nasal sinus is unclear, the site selected should be Para nasal 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/Pterygopalatinand 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 (excluding parotid tumours with facial nerve palsy)
- 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 try 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 wrong because the tumours arise from paratesticular structures and may invade the testis.

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 (corpus or cervix) 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 toes to the ankle

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

7. Thigh
Refers to 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:

1. 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 trachea, heart or nearby areas.

c) Lung:
includes tumours arising form the lung parenchyma, bronchus and visceral pleura

d) Breast

e) Diaphragm

2. Abdomen

a) 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.

b) Liver
True liver rhabdomyosarcoma are less frequent than bile duct tumours.

c) 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.

d) Pancreas

e) Bowel

f) 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.

g) Retroperitoneum

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.

3. 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.

4. 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.

5. Perianal

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

6. Perineum

This should include the site which appear between the anus and the scrotum in males and 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 perianal sites.

A.5 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 (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 interested)
Vagina: iliac nodes (external, internal and common chains; notes 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)

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 metastatic disease 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 controlateral involved lymph nodes (except in the head and neck).

A.6 MRI AND CT SCAN TECHNICAL RECOMMENDATIONS

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).
- 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

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.

A.7 DEFINTION OF ADVERSE EVENTS

Adverse Event
Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Comment:
An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

Adverse Reaction
All untoward and unintended responses to an IMP related to any dose administered.
Comment:
An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event
Any untoward medical occurrence or effect that at any dose:

- Results in death (excluding disease related death)
- Is life-threatening*
- Requires hospitalisation** or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Or is otherwise considered medically significant by the Investigator*** including:
    - Second malignancies
    - Unexpected grade IV toxicities
    - Other

Comments:
The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.
* Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.
*** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

Serious Adverse Reaction
An Adverse Reaction which also meets the definition of a Serious Adverse Event.

Suspected Unexpected Serious Adverse Reaction
A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information.
A SUSAR should meet the definition of an AR, UAR and SAR.

Unexpected Adverse Reaction
An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product).
When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.

A.8 TOXICITY GRADING

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

ALLERGY/IMMUNOLOGY

Adverse Event	1	2	3	4
Allergic reaction/ hypersensitivity (including drug fever)	transient flushing or rash; drug fever < 38°C (<100.4°F))	Rash; flushing; urticaria, dyspnea; drug fever ≥ 38°C (≥100.4°F),	Symptomatic bronchospasm, with or without urticaria parenteral medication(s) idicated; allergy-related edema/angioedema; hypotension	anaphylaxis

REMARK: Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever).

AUDITORY/EAR

Hearing: patients without baseline audiogram and not enrolled in a monitoring program	-	Hearing loss not requiring hearing aid or intervention (i.e., not interfering with ADL)	Hearing loss requiring hearing aid or intervention (i.e., interfering with ADL)	Profound bilateral hearing loss (>90 dB)

BLOOD/BONE MARROW

Haemoglobin	< LLN - 10.0 g/dl < LLN – 6.2 mmol/L < LLN – 100 g//L	<10.0 – 8.0 g/dL <6.2 – 4.9 mmol/L <100 – 80 g/L	<8.0 – 6.5 g/dL <4.9 – 4.0 mmol/L <80 – 65 g/L	< 6.5 g/dl <4.0 mmol/L <65 g/L
Leukocytes (total WBC)	< LLN - 3.0 x 10^9/L < LLN - 3000/mm^3	<3.0 - 2.0 x 10^9/L <3000 - 2000/mm^3	<2.0 - 1.0 x 10^9/L <2000 - 1000/mm^3	< 1.0 x 10^9/L < 1000/mm^3
Neutrophils/granulocytes (ANC/AGC)	<1.5 – 1.5 x 10^9/L <1500/mm^3	<1.5 - 1.0 x 10^9/L <1500 - 1000/mm^3	<1.0 – 0.5 x 10^9/L <1000 - 500/mm^3	< 0.5 x 10^9/L < 500/mm^3
Platelets	< LLN - 75.0 x 10^9/L < LLN – 75.000/mm^3	<75.0 - 50.0 x 10^9/L <75.000 – 50.000/mm^3	<50.0 - 25.0 x 10^9/L <50.000 – 25.000/mm^3	< 25.0 x 10^9/L < 25.000/mm^3

CARDIAC ARRHYTHMIA

Conduction abnormality/ atrioventricular heart block	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Incompletely controlled medically or controlled with device (e.g., pacemaker)	Life – threatening (e.g., arrhytmia associated with CHF, hypotension, syncope, shock)
Prolonged QTc interval	QTc>0.45 – 0.47 second	QTc >0.47 - 0.50 second; ≥0.06 second above baseline	QTc >0.50 second	QTc >0.50 second; life-threatening sings or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes
Supraventicular and nodal arrhythmia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Ventricular arrhythmia	Asymptomatic, no intervention indicated	Non-urgent medical intervention indicated	Asymptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)

CARDIAC GENERAL

Cardiac Ischemia/infarction	Asymptomatic arterial narrowing without ischemia	Asymptomatic and testing suggesting ischemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction
Cardiopulmonary arrest,	-	-	-	
Hypertension	Asymptomatic, transient (<24 hrs) BP increase >ULN; intervention not indicated	Recurrent or persistent (>24 hrs) BP >ULN; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously	Life-threatening consequences (e.g. hypertensive crisis)

REMARK: Use age and gender-appropriate normal values >95th percentile ULN for pediatric patients

Hypotension ALSO CONSIDER: Syncope (fainting)	intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (≥24 hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g., acidemia; impairment of vital organ function)
Left ventricular diastolic dysfunction	Asymptomatic diagnostic finding; intervention not indicated	Asymptomatic, intervention indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled; intervention such as ventricular assist device or heart transplant indicated
Left ventricular Systolic dysfunction	Asymptomatic , resting ejection fraction (EF) <60-50%; shortening fraction (SF) <30 – 24%	Asymptomatic, resting EF <50 – 40% SF <24 – 15%	Symptomatic CHF responsive to intervention; EF <40 – 20% SF <24 – 15%	Refractory CHF or poorly controlled;<20%; intervention such as ventricular assist device , ventricular reduction surgery, or heart transplant indicated

COAGULATION

Adverse Event	1	2	3	4
DIC (disseminated intravascular coagulation)	__	Laboratory findings with no bleeding	Laboratory findings and bleeding	Laboratory findings, life-threatening or disabling consequences (e.g., CNS haemorrhage, organ damage, or hemodynamically significant blood loss)

REMARK: DIC (disseminated intravascular coagulation) must have increased fibrin split products or D-dimer

CONSTITUTIONAL SYMPTOMS

Fatigue (asthenia, lethargy, malaise)	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling
Weight gain	5-<10% of baseline	10 - <20% of baseline	≥20% of baseline	__

REMARK: Oedema, depending on aetiology, is graded in the CARDIAC GENERAL or LYMPHATICS CATEGORIES.
ALSO CONSIDER: Ascites (non-malignant); Pleural effusion (non-malignant).

Weight loss	5 to <10% from baseline; intervention not indicated	10 - <20% from baseline; nutritional support indicated	≥20% from baseline; tube feeding or TPN indicated	__

DERMATOLOGY/SKIN

Burn	Minimal symptoms; Intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences

REMARK: Burn refers to all burns including radiation, chemical, etc.

Injection site reaction/extravasation changes	Pain; itching; erythema	Pain or swelling, with inflammation or phlebitis	Ulceration or necrosis that is severe; operative intervention indicated	__

ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever); Ulceration

Rash/desquamation	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vescicular eruption; desquamation covering ≥50% BSA	Generalized exfoliative, uklcerative, or bullous dermatits.

REMARK: Rash/desquamation may be used for GVHD.

Rash: dermatitis associated with radiation -	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate oedema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site
Ulceration	__	Superficial ulceration <2 cm size; local wound care; medical intervention indicated	Ulceration ≥2 cm size; operative debridement, primary closure or other invasive intervention indicated (e.g., hyperbaric oxygen)	Life-threatening consequences; major invasive intervention indicated (e.g., complete resection, tissue reconstruction, flap, or grafting)
Urticaria (hives, welts, wheals)	Intervention not indicated	Intervention indicated for <24 hrs	Intervention indicated for≥24 hrs	__

ALSO CONSIDER: Allergic reaction/hypersensitivity (including drug fever).

ENDOCRINE

Neuroendocrine: ADH secretion abnormatity (e.g., SIADH or low ADH)	Asymptomatic	Symptomatic, not interfering with ADL; intervention indicated	Symptoms interfering with ADL	Life-threatening consequences

GASTROINTESTINAL

NAVIGATION NOTE: Abdominal pain or cramping is graded as pain-*Select* in the PAIN CATEGORY.

Anorexia	loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated	Life-threatening consequences
Ascites (non-malignant)	Symptomatic, medical intervention indicated	Symptomatic, invasive procedure indicated	Life-threatening consequences	

REMARK: Ascites (non-malignant)refers to documented non-malignant ascites or unknown aetiology, but unlikely malignant, and inclused chylous ascites.

Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis, toxic megacolon)
Constipation	requiring stool softener or dietary modification	Requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon

ALSO CONSIDER:Ileus, GI (functional obstruction of bowel, i.e., neurocostipation);

Adverse Event	1	2	3	4
Diarrhoea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4-6 stools per day over baseline; IV fluids indicated <24 hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalisation; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)

REMARK: Diarrhoea includes diarrhoea of small bowel or colonic origin, and/or ostomy diarrhoea.

Enteritis (inflammation of the small bowel)	Asymptomatic, pathologic or radiographic findings only	Abdominal pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits with ileus; peritoneal sings	Life-threatening consequences (e.g.., perforation, bleeding, ischemia, necrosis)

Esophagitis	Asymptomatic pathologic, radiographic, or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥ 24 hrs	Life-threatening consequences

REMARK: Esophagitis includes reflux esophagitis.

Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	Asymptomatic, radiographic findings only	Symptomatic; altered GI function (e.g., altered dietary habits); IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; IV fluids, tube feeding, or TPN indicated ≥ 24 hrs	Life-threatening consequences

REMARK: Ileus, GI is to be used for altered upper or lower GI function (e.g., delayed gastric or colonic emptying).

Mucositis/Stomatitis (clinical exam)	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated < 24 hrs.	Inadequate oral caloric or fluid intake; IV fluids, tube feedings or TPN indicated > 24 hrs.	Life-threatening consequences
Vomiting	1 episode in 24 hrs	2-5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences

Gastrointestinal-Other (Specify__)	Mild	Moderate	Severe	Life-threatening; disabling

HEMORRHAGE/BLEEDING

Hematoma	Minimal symptoms, invasive intervention not indicated	Minimal invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life- threatening consequences; major urgent intervention indicated

REMARK: Hematoma refers to extravasation at wound or operative site or secondary to other intervention. Transfusion implies pRBC.

Haemorrhage/bleeding associated with surgery, intra-operative or postoperative	__	__	Requiring transfusion of 2 units non-autologous (10cc/Kg for pediatrics) pRBCs beyond protocol specification; postoperative interventional rediology, endoscopic, or operative intervention indicated	Life-threatening consequences

REMARK: Postoperative period is defined as ≤72 hrs after surgery. Verify protocol-specific acceptable guidelines regarding pRBC transfusion.
ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PPT (Partial Thromboplastin Time).

Hemorrhage, CNS	Asymptomatic, radiographic findings only	Medical intervention indicated	Ventriculostomy, ICP monitoring, intraventicular thombolysis, or operative intervention indicated	Life-threatening consequences; neurologic deficit or disability

ALSO CONSIDER: Fibrinogen; INR (International Normalized Ratio of prothrombin time); Platelets; PPT (Partial Thromboplastin Time).

Haemorrhage, GI	Mild, intervention (other than iron supplements) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding indicated)	Life-threatening consequences; major urgent intervention indicated

REMARK: Transfusion implies pRBC.

Haemorrhage/Bleeding –Other (Specify__)	Mild without transfusion	__	Catastrophic bleeding, requiring major non-elective intervention	

HEPATOBILIARY/PANCREAS

Liver dysfunction/failure (clinical)	__	Jaundice	Asterixis	Encephalopathy or coma

REMARK: Jaundice is not an AE, but occurs when the liver is not working properly or when a bile duct is blocked. It is graded as a result of liver dysfunction/failure or elevated bilirubin.

Pancreatitis	Asymptomatic, enzyme elevation and/or radiographic findings	Symptomatic, medical intervention indicated	Interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., circulatory failure, haemorrhage, sepsis

INFECTION

Adverse Event	1	2	3	4
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 1.0^9/L fever ≥ 38.5°)	__	__	Present	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)

ALSO CONSIDER: Neutrophilis/granulocytes (ANC/AGC).

Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophilis (ANC <1.0 x 1.0^9/L)	__	Localized, local interventio indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)
Infection with normal ANC or Grade 1 or 2 neutrophilis	__	Localized, local intervention indicated	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated	Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)
Infection – Other (Specify, __)	Mild	Moderate	Severe	Life – Threatening; disabling

METABOLIC/LABORATORY

ALT; SGPT (serum glutamic oxaloacetic)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
AST, SGOT (serum glutamic oxaloacetic transaminase) (ANC < 1.0 x 10^9/L)	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN

REMARK: jaundice is not an AE, but may be a manifestation of liver dysfunction/failure or elevated bilirubin. If jaundice is associated with elevated bilirubin, grade bilirubin.

Calcium, serum-low (hypocalcaemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L 35.1.1 lionized calcium: <LLN – 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L lionized calcium: <1.0 – 0.9 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L lionized calcium: <0.9 – 0.8 mmol/L	<6.0 mg/dL <1.5 mmol/L lionized calcium: <0.8 mmol/L

REMARK: Calcium can be falsely low if hypoalbuminemia is present. Serum albumin <4.0 g/dL, hypocalcaemia is reported after the following corrective calculation has been performed: Corrected Calcium (mg/dL)= Total calcium (mg/dL) – 0.8 [Albumin (g/dL) - 4][4]. Alternatively, direct measurement of ionized calcium is the definitive method to diagnose metabolically relevant alterations in serum calcium.

Calcium, serum-high (hypocalcaemia)	>LLN – 11.5 mg/dL >LLN – 2.9 mmol/L lionized calcium: >LLN – 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L lionized calcium: >1.5 – 1.6 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L lionized calcium: >1.6 – 1.8 mmol/L	>13.5 mg/dL >3.4 mmol/L lionized calcium: >1.8 mmol/L

NEPHROTOXICITY

Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6.0 x ULN	>6.0 x ULN

REMARK: Adjust to age-appropriate levels for pediatric patients.
ALSO CONSIDER: Glomerular filtration rate.

Glomerular filtration rate	<75 – 50% LLN	<50 – 25% LLN	<25%LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated

ALSO CONSIDER: Creatinine.

Proteinuria	1+ or 0.15 – 1.0 g/24 hrs	2+ to 3+ or >1.0 – 3.5 g/24 hrs	4+ or >3.5 g/24 hrs	Nefrotic syndrome

Nephrotoxicity grading : total score see appendix A.10

NEUROLOGY

Ataxia (incoordination)	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; mechanical assistance indicated	Disabling

REMARK: Ataxia (incoordination) refers to the consequence of medical or operative intervention.

CNS cerebrovascular ischemia	__	Asymptomatic, radiographic findings only	Transient ischemic event or attack (TIA) ≥24 hrs duration	Cerebral vascular accident (CVA, stroke), neurologic deficit >24 hrs

Adverse Event	1	2	3	4
Cognitive disturbance	Mild cognitive disability; not interfering with work/school//life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independed living; specialized resources on part-time basis indicated	Severe cognitive disability, significant impairment of work/school/life performance	Unable to perform ADL; full-time specialized resources or institutionalization indicated
Confusion	Transient confusion, disorientation, or attention deficit	Confusion, disorientation, or attention deficit interfering with function, but not interfering with ADL.	Confusion or delirium interfering with ADL	Harmful to other or self; hospitalisation indicated
Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADL	Interfering with ADL	Disabiling

REMARK: Dizziness includes diequilibrium, light-headedness, and vertigo.

Encephalopathy	__	Mild simgs or symptoms; not interfering with ADL	Sings or symptoms interfering with ADL; hospitalisation indicated	Life-threatening; disabiling

ALSO CONSIDER: Cognitive disturbance; Confusion; dizziness; Memory impairment; Mental status; Mood alteration – *Select* Psychosis (hallucinations/delusions)

Extrapyramidal/involuntary movement/ restlessness	Mild involuntary movements not interfering with function	Moderate involuntary movements interfering with function, but not interfering with ADL	Severe involuntary mevements or torticollis interfering with ADL	Disabiling
Mood alteration -*Select* -Agitation -Anxiety -Depression -Euphoria	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated	Severe mood alteration interfering with ADL	Suicidal ideation; danger to self or other
Neuropathy: Cranial -Select -CN I Smell -CN II Vision -CN III Pupil, upper eyelid, extra ocular movements CN IV Downward, inward movement of eye CN V Motor-jaw muscles; Sensory-facial CN VI Lateral deavition of eye CN VII Motor-face; Sensory-taste CN VIII Hearning and balance CN IX Motor-pharynx; Sensory-ear, pharjnx, larynx CN X Motor-palate; pharynx, larynx CN XI Motor-sternomastoid and trapezius CN XII Motor-tongue	Asymptomatic, detected on exam/testing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabiling
Psychosis (hallucinations/delusion)	__	Transient episode	Interfering with ADL; medication, supervision or restraints indicated	Harmful to other or self; life-threatening consequences
Seizure	__	One brief generalized seizure; seizure (s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)
Somnolence/depressed Level of consciousness	__	Somnolence or sedation interfering with function, but not interfering with ADL	Obtundation or stupor; difficult to arouse; interfering with ADL	Coma
Neurology-Other (Specify__)	Mild	Moderate	Severe	Life-Threatening; disabling

PAIN

Pain-Other (Specify__)	Mild pain not interfering with function	Moderate pain; pain or analogesics interfering with function, but not interfering ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling

PULMONARY/UPPER RESPIRATORY

Adult respiratory Distress Syndrome (ARDS)	__	__	Present, intubation not indicated	Present, intubation indicated
Pleural effusion (non-malignant)	Asymptomatic	Symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated	Symptomatic and supplemental oxygen, >2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated	Life-threatening (e.g, causing hemodynamic instability or ventilatory support indicated)

OCULAR

Ocular/Visual-Other (Specify, _____)	mild	Moderate	severe	unilateral or bilateral loss of vision (blindness)

A.9 VENO-OCCLUSIVE DISEASE OF THE LIVER - GRADING

VOD appears related to the administration of actinomycin among different drugs. No specific predisposing factor has been found to identify the patient at risk. A prior persistent or slow recovery of thrombocytopenia may be an indicator of VOD.

We considered hepatic toxicity as compatible with the clinical diagnosis of VOD when no other causes of liver disease were identified and at least 2 of the following features are present:
a) jaundice
b) hepatomegaly ($\geq$ 2 cm below the costal margin) and/or right upper quadrant pain,
c) ascites and/or sudden weight gain (> 2% of baseline body weight) due to fluid retention.

Doppler study of the liver may document retrograde portal venous flow.

Grading Criteria for VOD.

Mild VOD:
Total bilirubin $\leq$ 6 mg/dL
Weight gain of $\leq$ 5% of baseline of noncardiac origin
Reversible hepatic dysfunction

Moderate VOD:
Total bilirubin > 6 mg/dL and < 20 mg/dL
Weight gain > 5% of baseline of noncardiac origin
Clinical or image documented ascites
Reversible hepatic dysfunction

Severe VOD:
Total bilirubin > 20mg/dL and/or
Ascites compromising respiratory function and/or
Renal deterioration and/or
Hepatic encephalopathy which may not be reversible

Therapy modifications:
In case of VOD actinomycin should not be given until the main abnormalities have returned to normal and half the dose should be given for the first following course. If tolerated actinomycin dose may be increase progressively in the following cycles.
If the symptoms reappear during actinomycin treatment, this drug should be withdrawn permanently.

VOD is considered a Serious Adverse Event and must be reported within 24 hours of knowledge of the event (see chapter 26) using the RDE system.

A.10 NEPHROTOXICITY GRADING

Table 11 - 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 severe 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 hyperparathyroidism with subperiostal erosion) or with both.

HCMA: Hyperchloremic Metabolic Acidosis: Defined by biochemistry (moderate or severe metabolic 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. Kussmaul respiration)

NDI: Nephrogenic Diabetes Insipidus: Defined by clinical symptoms/signs (polyuria, polydipsia, dehydration) with or without biochemistry (moderate or severe hypernatremia < 150 mmol/l) with lack of response to DDAVP (a normal response is defined as a urine osmolality ≥ 800 mOsm/kg).

Table 12 - 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

A.11 GUIDELINES FOR MOLECULAR CYTOGENETIC ANALYSIS AND QUALITY ASSURANCE OF RHABDOMYOSARCOMA FOR PATIENTS ENTERED ONTO EPSSG STUDY

Introduction

These guidelines have been produced on behalf of the CCLG soft tissue sarcoma working group. The aim of the guidelines is to facilitate high quality molecular cytogenetic analysis of patients entered into the study. High quality molecular cytogenetic data has two immediate benefits; aiding in accurate diagnosis, and allowing high quality research of clinico-pathological correlates of molecular alterations in patients enrolled in the study.

The results of an audit into current practice in UK labs performed in 2005 indicated that most UK centres are already performing molecular analysis to a high standard in accredited diagnostic laboratories. These guidelines encourage individual laboratories to continue to perform diagnostic testing on their own patients with simple agreed minimal standards.

General principles

- Molecular cytogenetic testing is an increasingly important component of the diagnostic work up of paediatric soft tissue tumours.
- Classical cytogenetics may be an aid to diagnosis, but it also an important component of basic research.
- Molecular cytogenetic analysis of paediatric soft tissue tumours should be performed to high standards in accredited diagnostic laboratories.
- Close liason between clinicians, pathologists, cytogeneticists and molecular biologists both facilitates the diagnostic process and identifies important research issues.
- Final diagnosis, especially of difficult soft tissue tumours, results from an understanding of the whole picture including clinical features, morphology, immunohistochemistry and molecular cytogenetics. At the time when primary diagnostic procedures are performed the information available from imaging is often unable to provide a high degree of differential diagnostic probability. Therefore molecular testing may be performed as an initial screen or following the histopathological diagnosis depending on local preferences. However for rhabdomyosarcomas, the trial recommends that all patients should have the FKHR fusions determined irrespective of histological subtype.
- FISH should be performed using commercially available probes that have been validated for the gene fusion being tested (see appendix).
- If there is a limitation on tumour availablity then priority should be given to diagnostic detection of FKHR fusions by FISH or RT-PCR over routine cytogenetic analysis.

Protocol

FKHR fusion gene status can be determined by interphase FISH or RT-PCR. Ideally, both techniques should be performed to confirm results or identify rare cases with discrepancy due to rare fusions, but operationally this in not always possible.

Classical cytogentics is to be encouraged on all patients and may be useful in confirming a diagnosis but should not be relied upon as a diagnostic tool for the presence or absence of a FKHR fusion.

Determination of tumour cell content

It is essential to confirm that the sample being analysed by FISH or RT-PCR is representative of tumour. This can be achieved in a number of ways:

- H and E stain of a touch imprint of the frozen sample to be analysed by interphase FISH of touch imprints, or RT-PCR.

- H and E stain of fresh tissue imprint prior to its analysis by RT-PCR, Interphase FISH of the fresh touch imprint, or by interphase FISH of the resulting disaggregated tumour.

- Analysis of H and E stain of adjacent section from a paraffin block when this is the material that is being analysed by interphase FISH or RT-PCR.

Bone marrow samples

Infiltrated bone marrow can be a very valuable source of large numbers of tumour cells for diagnostic purposes. Until advised otherwise, bone marrow aspirates taken at presentation from suspected rhabdomyosarcoma patients should be processed on the assumption that tumour cells are present (including storage of cells for possible mRNA extraction). Once cells have been harvested, it is recommended to obtain an estimate of percentage tumour cell infiltration before proceeding with cytogenetic, FISH or RT-PCR analysis.

FISH protocol

FISH can be performed on fresh tissue imprints, frozen sample imprints, disaggregated cells or sections from paraffin blocks. The choice is dependent on local laboratory preferences but there must be experience of the technique in the laboratory, a written protocol for the technique, and all appropriate controls included as indicated below:

FISH should be performed in accordance with ACC guidelines (FISH scoring in oncology available at http://www.cytogenetics.org.uk/info/fish_oncology.pdf. An initial screen with probes that detect disruption at 13q14 can be performed. If there is disruption then the nature of the partner gene must be determined. This can be achieved by FISH using probes for the PAX3 and PAX7 partner genes, or by RT-PCR (see below).

For FISH analyses a minimum of 100 nuclei should be scored. Several representative digital images of findings should be archived.

RT-PCR protocols

RT-PCR assays for PAX3-FKHR and PAX7-FKHR fusions should be performed using the following principles;

- There must be experience of the technique in the laboratory, a written protocol for the technique and all appropriate controls included as indicated below.
- An H and E assessment of the piece of frozen tissue used for making RNA should be performed to ensure tumour content (see above).
- Tests should be performed at least in duplicate with seprately prepared RNA or cDNA samples.
- Negative control samples should include a no RNA control taken through the cDNA synthesis step.
- Positive controls should be tumour or cell line RNA stored in batches.
- The RNA integrity control should be a ubiquitously expressed gene that is expressed at similar levels as the fusion gene, and the PCR reaction for which is at a similar efficiency.
- Validation of the identity of PCR products must be in place and can be determined in one of four ways
    - Hybridisation of a probe recognising an internal sequence in the PCR product
    - Sequencing of PCR product
    - The inclusion of more than one primer pair with different respective product sizes in the assay, and both products being appropriate sizes
    - Quantitative real time PCR using internal probes for the amplified sequence (eg Taqman probes)

External Quality Control

External quality control (EQA) complements the Internal Quality Control (IQC) procedures that laboratories use to monitor within- and between-analytical run variability. For the most part EQA provides affirmation that the laboratory is providing a quality diagnostic service.
In addition, EQA has an educational element to it, as both general and individual feedback is given in the summary reports. Laboratories should participate annually in recognised EQA programmes that are appropriate to their full repertoire of analyses.

It is recognized that both FISH and RT-PCR techniques are used in the diagnosis of paediatric sarcoma. UK NEQAS for Clinical Cytogenetics will co-ordinate a pilot EQA in paediatric tumours. The first pilot will involve FISH but the possibility of an RT-PCR pilot EQA is also being discussed and will be explored further in the near future.

The aim of the pilot EQA is to be educational and it is possible that the pilot will reveal different approaches to analysis or interpretation of the same case. The pilot EQA will be available late August and more information will be sent nearer the time. In the meantime laboratories are encouraged to collaborate with each other on the different approaches to internal quality control so that robust quality procedures are undertaken routinely across the UK.

Appendix: Commercial FISH probes

Vysis / Abbott Molecular Diagnostics
LSI FKHR (13q14) dual colour break-apart probe

www.vysis.com

Zytolight RMS I dual colour fusion probe for t(2;13)

Zytolight RMS II dual colour fusion probe for t(1;13)

www.zytovision.com

A.12 INVESTIGATIONAL MEDICINAL PRODUCT (IMP) SUPPLIES AND MANAGEMENT

See section 24 for Investigational Medicinal Products (IMPs) for this protocol

Commercial supplies of licensed drugs taken from routine pharmacy stock may be used in this trial whenever appropriate and in accordance with the Clinical Trial Authorisation (CTA). However, if the licensed cyclophosphamide 50mg tablet formulation is not appropriate for the patient and an IMP formulation is required, a QP-certified cyclophosphamide 10mg/mL oral solution is available for use in this trial.

Cyclophosphamide 10mg/mL oral solution is manufactured and supplied by St Mary's NHS Pharmaceutical Manufacturing Unit (SMPU) for use as an IMP.

SMPU contact details: St Mary's Pharmaceutical Unit
20 Field Way
Cardiff
CF14 4HY

Tel 02920 748120 Fax 02920 748130

1. Packaging and labelling

Cyclophosphamide 10mg/mL oral solution (volume = 90mL) will be supplied in an amber glass bottle with child-resistant closure and tamper evident seal. Each bottle will be fitted with a stopper to allow the attachment of an oral syringe for dose measurement. The drug formulation contains cyclophosphamide in an aqueous preservative solution.

The product is manufactured, packaged and labelled under GMP conditions by the holder of a manufacturer's (IMP) authorisation (Ref: 35929). Each batch is checked and certified by a Qualified Person (QP) before distribution to authorised CRCTU trial sites. A copy of the QP declaration will be sent with each order of clinical trial material.

St Mary's Pharmaceutical Unit will label each bottle of cyclophosphamide 10mg/mL oral solution with the protocol code (EPSSG RMS 2005), EudraCT number, Sponsor's name, description of contents of the bottle, batch number, expiry, storage conditions, and the regulatory caution statement: "For Clinical Trial Use Only".

2. Drug Distribution Procedures

The Principal Investigator will maintain ultimate responsibility for the study drug at the Trial Site. The Site Pharmacist will manage the study drug including ordering, receipt, storage, accountability, record keeping and proper destruction of returned or unused IMP. Close communication is vital between the Investigator/Data Manager responsible for randomising patients and the Site Pharmacist.

- It is the responsibility of the Investigator/Data Manager to inform the Site Pharmacist of the patient's randomisation, ensuring adequate time is available to obtain supplies.
- If required for the patient, it is the responsibility of the Site Pharmacist to place an order for clinical trial material using the trial-specific Clinical Trial Material Request Form provided to sites and available from the CRCTU and fax directly to SMPU.

- The clinical trial material will be sent directly to the Site Pharmacy marked for the attention of the Pharmacist indicated on the Clinical Trial Material Request Form by the Pharmacist completing the order.
- Prior to the initial dispatch of clinical trial material, SMPU will verify the Trial Site name and Site Pharmacist information against the information supplied by CRCTU.
- The Site Pharmacist should order approximately 2 months supply of the clinical trial material per order, or as appropriate if additional orders are required to accommodate breakages / dose changes etc.

Distribution Timelines

- Clinical trial material will be manufactured upon receipt of a valid order.
- The maximum turn-around time from receipt of a valid order to delivery of the trial material to the Trial Site will be **seven calendar days**, unless a later date is specified on the order.
- Distribution to sites will be for delivery Monday to Friday, via Priority or Priority Overnight Delivery according to location of Trial Site. Due to cold-chain storage requirements, deliveries will not ordinarily arrive at Trial Sites on Saturdays unless explicitly agreed between the Trial Site and SMPU.
- If the order does not arrive as scheduled, contact SMPU (tel: 02920 748120).

Clinical Trial Material Acceptance

- Upon receipt of the clinical trial material, the pharmacist or designee must verify via the Packing Invoice that the material was received as stated.
- If the material was received as stated, the pharmacist or designee must note this on the form, then print, sign and date the form.
- The completed Packing Invoice must be faxed back to SMPU within 48 hours
- File the original Packing Invoice in the pharmacy trial file.

If there is a discrepancy with the material (i.e. broken bottles, incorrect quantity, etc.) SMPU should be contacted immediately for advice on replacement stocks. Note any discrepancies and agreed actions in the comments section on the Packing Invoice and fax to SMPU. If damaged supplies are received, retain all packing materials and damaged stock (if safe to do so), pending further investigation and/or advice from the Clinical Trials Pharmacist at SMPU.

3. Study Drug Storage and Accountability

ALL CLINICAL TRIAL MATERIAL SHOULD BE STORED SECURELY UNDER MONITORED REFRIGERATED STORAGE CONDITIONS.

- Cyclophosphamide 10mg/mL oral solution must be carefully and securely stored at the trial site, separately from other drugs, and at a monitored refrigerated storage temperature of between 2°C and 8°C.
- All temperature deviations should be documented appropriately and reported to the Clinical Trials Pharmacist at SMPU.
- Clinical trial material may not be used for any purpose other than this clinical study.
- It must be ensured that the study drug is not used beyond the expiry date indicated. It is the responsibility of the Site Pharmacist or designee to ensure the storage conditions and expiry date of the product are clearly indicated when the study drug is dispensed to patients.

Study Drug Dispensing

It is the responsibility of the Site Pharmacist or designee to dispense the study drug to patients in accordance with current Medicines and Clinical Trials Regulations.

Drug Accountability

The Principal Investigator is responsible for investigational product accountability at the Trial Site. The Investigator should ensure appropriate and complete accountability records are maintained by the Site Pharmacy of all study drug received, dispensed and destroyed at the Trial Site. A template Drug Accountability Log can be requested from the CRCTU for this purpose. Trial sites may use their own in-house accountability systems provided the following minimum data are recorded:

1. Date of receipt, dispensing or destruction
2. Patient initials
3. Patient trial number
4. Quantity received or dispensed or destroyed or returned
5. Batch number
6. Recorder's initials
7. Inventory balance
8. Any discrepancies noted e.g. broken bottles
9. Final reconciliation by Site Pharmacist (signature and date)

Upon completion or termination of the study, the Site Pharmacist or designee will destroy all unused study drug at the site as per the institutional SOP for the destruction of Investigational Medicinal Products. Study material returned by patients during the study should also be recorded and destroyed according to institutional SOP. Documentation of all destructions must be made on the drug accountability log.

At study close, the Site Pharmacist will fax a copy of the completed and reconciled accountability log(s) to CRCTU (fax: 0121 414 3700 or 0121 414 9520) and archive the original accountability documents in the Pharmacy Trial File, or otherwise in accordance with local Trial Documentation SOPs.

ORDER FORM – Cyclophosphamide Oral Solution

Investigational Medicinal Product Order Form **Cyclophosphamide Oral Solution 10mg/ml for EPSSG RMS 2005** **EudraCT Number: 2005-000217-35**	
Please supply the following medication	
Description: *90ml bottle cyclophosphamide 10mg/ml oral solution* **Number of bottles required:** **Syringe size required (please tick): 1 ml ☐ 3 ml ☐ not required ☐** **Site Regulatory Approval in place: Y / N**	
Centre Name:	
Principal Investigator:	
Date Required:	
Delivery Contact: (Consignee) **Refrigerated Delivery**	Name: Tel: Fax:
Delivery Address:	
Requested by: **NB** Signature confirms that all regulatory approvals for the investigator site requested are in place and that shipment may proceed.	Signature / Date: Print Name: Authority: Tel: Fax:
Please fax to 029 2074 8130 for the attention of the Clinical Trials Team	
Dispatch Details: St Mary's Pharmaceutical Unit	
Materials dispatched as requested above: Y / N	
Number of bottles shipped:	
Courier used: *Polar speed*	
Dispatched by: (initials & date)	
Checked by: (initials & date)	
Date shipped:	
Consignee: Acknowledgement of Receipt	
NB Package must be opened and contents checked on receipt Supplies received complete and in good condition: Y / N (if no comments) **Ensure that drug supplies are refrigerated between 2°C and 8°C**	
Consignee: (signature & date)	
Please fax completed form to the Clinical Trials team, SMPU, 029 2074 8130	

A.13 DECLARATION OF HELSINKI

The latest version of the Declaration of Helsinki can be downloaded from the World Medical Association (WMA) website:

http://www.wma.net/e/policy/b3.htm

A.14 OVERVIEW OF INFORMATION SHEETS / CONSENT FORMS (RMS 2005)

Treatment according to the "observational study" (that includes low, standard, high and very high risk strategy):

Patient Information Sheets (low, standard and high risk)
INFORMATION SHEET FOR PARENTS
INFORMATION SHEET FOR PATIENTS (16+)
INFORMATION SHEET FOR PATIENTS (14-15)
INFORMATION SHEET FOR PATIENTS (8-14)
INFORMATION SHEET FOR PATIENTS (under 8)

Patient Information Sheets (very high risk only)
INFORMATION SHEET FOR PARENTS
INFORMATION SHEET FOR PATIENTS (16+)
INFORMATION SHEET FOR PATIENTS (14-15)
INFORMATION SHEET FOR PATIENTS (8-14)
INFORMATION SHEET FOR PATIENTS (under 8)

GP INFORMATION SHEET

Consent forms
Parent/Child
Young person aged 16+

Randomisation for high risk patients after initial treatment.
ADDITIONAL INFORMATION SHEET FOR PARENTS OF PATIENTS WITH HIGH RISK TUMOURS
ADDITIONAL INFORMATION SHEET FOR PATIENTS WITH HIGH RISK TUMOURS (16+)
INFORMATION SHEET FOR PATIENTS (14-15)
INFORMATION SHEET FOR PATIENTS (8-14)
INFORMATION SHEET FOR PATIENTS (under 8)
GP INFORMATION SHEET
Consent forms
RANDOMISATION: STANDARD TREATMENT *or* STANDARD TREATMENT WITH ADDITIONAL MAINTENANCE CHEMOTHERAPY
Parent/Child
Young person aged 16+

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.

A.15 E*p*SSG-RMS-MET 2008: Treatment Arm for Metastatic Disease

1. BACKGROUND

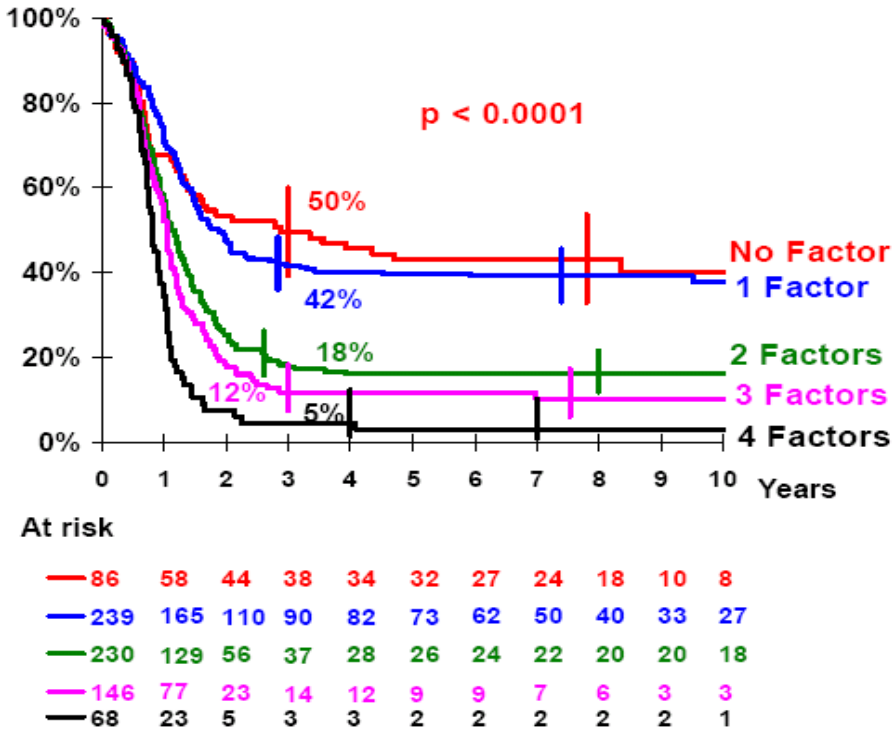
Although major accomplishments have been achieved during the last three decades for localized RMS (overall survival at 5 years is now 70%), overall survival of patients with metastatic RMS remains very poor. Despite impressive response rates observed with induction chemotherapy in various regimens [1-3], these tumors are difficult to cure, and the long-term event-free survival (EFS) of all series is below 30%, even after high dose chemotherapy with hematopoietic stem cell rescue [4,5].

Prognostic factors of clinical outcome of metastatic RMS have been investigated in several studies [4-7]. A recent pooled analysis of data from European and American studies since 1984 showed that the event-free survival of 788 patients with metastatic rhabdomyosarcoma reached a plateau of 27% at 3 years [8]. The univariate analysis showed that event-free survival (EFS) was correlated with several independent risk factors, among them being:

- Age
- Histology
- Site of the primary tumor
- Number of metastatic sites
- Presence/absence of bone or bone marrow involvement

The presence or absence of these prognostic factors defines the high risk group, as compared to the low risk group with a significant difference in outcome. The three-year EFS of patients who had none or one risk factor was 58% or 40%, respectively, whereas it was 22% or less for patients who had two or more risk factors (see Figure 1) [8]

Figure 1: Event-free survival of patients according to number of unfavourable prognostic factors



The standard chemotherapy for high risk RMS remains combination therapy with an alkylating agent (cyclophosphamide or ifosfamide), vincristine and actinomycin D. However, results for metastatic disease treated in this way are disappointingly poor. Clinical trials have demonstrated the efficacy of individual drugs such as ifosfamide and cisplatin in the classical phase II setting and others such as melphalan, topotecan, irinotecan and doxorubicin [9-16] in the phase II window setting, but the value of adding other drugs to the standard combination regimen has not been fully demonstrated in terms of survival benefit for children with localized or metastatic rhabdomyosarcoma [14,16]. Previous European studies in stage IV RMS often used the combination of 6 drugs for induction treatment in stage IV RMS [4,17-19]. For reasons described in chapter 8.4 (Rationale for high risk patients) the currently ongoing E*p*SSG study in localized RMS addresses the question of the value of dose intense doxorubicin combined with the standard combination IVA (IVADo).

Poor outcomes with standard or 6-drug chemotherapy in metastatic patients, combined with a very high response rate (65%) to single agent doxorubicin in a phase II window setting mean that in Europe, the current recommended standard therapy for stage IV RMS includes induction chemotherapy with IVADo [20].In this protocol we will offer metastatic patients IVADo/IVA as standard induction treatment and assess response to and outcome of this standard therapy.

The vinorelbine-cyclophosphamide combination, which will be used during maintenance therapy, has shown activity in soft-tissue sarcoma in a pilot study (ORR 38% in recurrent or progressive RMS) [21] and is currently being evaluated in the phase II setting in relapsed rhabdomyosarcoma, Ewing's sarcoma, neuroblastoma, and medulloblastoma with an encouraging response rate in relapsing RMS. The efficacy of the maintenance regimen and its possibility for long-term treatment are conducive to the use of this combination for one year after the nine IVADo/IVA cycles of induction therapy in this patient population who are at high risk of early relapse.

The CWS group showed promising results with maintenance treatment in stage IV RMS [17]. They used standard chemotherapy in children with metastatic soft tissue sarcoma followed by high dose chemotherapy (thiotepa + cyclophosphamide and melphalan + etoposide) or an oral treatment with trofosfamide + idarubicine. The results in 62 patients are very promising with 3-year EFS above 50% for patients taking oral treatment (and EFS 20% after high dose). Since the comparison was not randomised, a risk bias between the two groups must be taken into consideration. It seems though that oral maintenance therapy might have a greater benefit for group IV patients than does high dose chemotherapy.

The duration of treatment for RMS has been progressively decreased over the years without apparently impairing the results. However, in view of persistently poor outcome, stage IV disease patients might benefit from a longer duration of treatment. Although in the European Intergroup Studies [4] 73% of patients achieved complete remission with the combination of intense induction treatment and local therapy, many patients suffered from relapse (5-year EFS 20%). A longer duration of maintenance treatment might be effective in treating minimal residual disease especially in the metastatic patient group. European guidelines now recommend maintenance treatment with vinorelbine and cyclophosphamide for a duration of 1 year in metastatic RMS; in this study we will assess the efficacy of IVADo/IVA in combination with prolonged maintenance chemotherapy.

1. Pappo A, Lyden E, Breneman J, et al. Up-front window trial of topotecan in previously untreated children and adolescents with metastatic rhabdomyosarcoma: an intergroup rhabdomyosarcoma study. J Clin Oncol 2001;19: 213-219.

2. Pappo A, Lyden E, Breitfeld P, ey al. Vincristine and irinotecan: A highly active combination in metastatic rhabdomyosarcoma. A report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group (STSCOG). J Clin Oncol 2005;23: 8509 (abstract).

3. Lager J, Lyden E, Anderson J, et al. Pooled analysis of phase II window studies in children with contemporary high-risk metastatic rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. J Clin Oncol 2006;24: 3415-3422.

4. Carli M, Colombatti R, Oberlin O, et al. European Intergroup Studies (MMT4-89 and MMT4-91) on Childhood Metastatic Rhabdomyosarcoma: Final Results and Analysis of Prognostic Factors. J Clin Oncol 2004;22: 4787-4794.

5. Koscielniak E, Rodary C, Flamant F, et al. Metastatic rhabdomyosarcoma and histologically similar tumors in childhood: a retrospective European multi-center analysis. Med Pediatr Oncol 1992;20: 209-214.

6. Anderson J, Ruby E, Lin M, et al. Identification of a favorable subset of patients (pts) with metastatic (MET) rhabdomyosarcoma (RMS): A report from the Intergroup Rhabdomyosarcoma Study Group (IRSG). Proc Am Soc Clin Oncol 1997;16: 1836 (abstract).

7. Breneman J, Lyden E, Pappo A, et al. Prognostic Factors and Clinical Outcomes in Children and Adolescents With Metastatic Rhabdomyosarcoma - A Report From the Intergroup Rhabdomyosarcoma Study IV. J Clin Oncol 2003;21: 78-84.

8. Prognostic Factors in Metastatic Rhabdomyosarcomas. The results of a pooled analyze from US and European cooperative groups. Odile Oberlin, Annie Rey, Elizabeth Lyden, Gianni Bisogno, Michael Stevens, William Meyer, Modesto Carli, James Anderson. Submitted to J Clin Oncol.

9. Hays DM. Rhabdomyosarcoma. Clin Orthop Relat Res. 1993; 289:36-49.

10. Rodriguez-Galindo C, Crews KR, Stewart CF, Furman W, Panetta JC, Daw NC, Cain A, Tan M, Houghton PH, Santana VM. Phase I study of the combination of topotecan and irinotecan in children with refractory solid tumors. Cancer Chemother Pharmacol. 2006; 57(1): 15-24.

11. Walterhouse DO, Lyden ER, Breitfeld PP, Qualman SJ, Wharam MD, Meyer WH. Efficacy of topotecan and cyclophosphamide given in a phase II window trial in children with newly diagnosed metastatic rhabdomyosarcoma: a Children's Oncology Group study. J Clin Oncol. 2004; 22(8): 1398-403.

12. Raney RB, Anderson JR, Barr FG, Donaldson SS, Pappo AS, Qualman SJ, Wiener ES, Maurer HM, Crist WM. Rhabdomyosarcoma and undifferentiated sarcoma in the first two decades of life: a selective review of intergroup rhabdomyosarcoma study group experience and rationale for Intergroup Rhabdomyosarcoma Study V. J Pediatr Hematol Oncol. 2001; 23(4): 215-20.

13. Pappo AS, Lyden E, Breneman J, Wiener E, Teot L, Meza J, Crist W, Vietti T. Up-front window trial of topotecan in previously untreated children and adolescents with metastatic rhabdomyosarcoma: an intergroup rhabdomyosarcoma study. J Clin Oncol. 2001; 19(1): 213-9.

14. Stevens M, Rey A, Bouvet N, et al. SIOP MMT 95: Intensified (6 drug) versus standard (IVA) chemotherapy for high risk non metastatic rhabdomyosarcoma (RMS). J Clin Oncol 2004;22(14S): 8515 (abstract).

15. Crist W, Gehan E, Ragab A, et al. The Third Intergroup Rhabdomyosarcoma Study. J Clin Oncol 1995;13:610-630.

16. Bergeron C, Thiesse P, Rey A, et al. Revisiting the role of doxorubicin in the treatment of rhabdomyosarcoma: an up-front window study in newly diagnosed children with high-risk metastatic disease. Eur J Cancer. 2008 Feb;44 (3):427-31.

17. T. Klingebiel et al, SIOP XXXV Annual Conference-Abstracts, MPO, Volume 41, Issue 4, page 278 (O.085), 2003.

18. H. McDowell et al, SIOP XXXVII Annual Conference-Abstracts, PBC, Volume 45, Issue 4, page 411 (O.110), 2005.

19. G. Bisogno et al., SIOP XXXV Annual Conference-Abstracts, MPO, Volume 41, Issue 4, page 278 (O.086), 2003.

20. Metastatic rhabdomyosarcoma (RMS) – interim treatment recommendations 16/06/2008 - Version 2.0. www.ukccsg.org/members/wg/treatment_guidelines/index.php?doc_wg=33

21. Casanova M, Ferrari A, Bisogo G, et al. Vinorelbine and low-dose cyclophosphamide in the treatment of pediatric sarcomas: pilot study for the upcoming European Rhabdomyosarcoma Protocol. Cancer 2004;101(7): 1664-1671.

2. OBJECTIVE

To improve the results in this poor prognosis group of patients by administering the more intensive treatment IVADo plus 1 year of maintenance chemotherapy.

3. PATIENTS AND TREATMENT

Patients with the following criteria are eligible for the EpSSG-RMS-2005 protocol for Metastatic disease:

- A pathologically proven diagnosis of Rhabdomyosarcoma.
- Evidence of metastatic lesions, i.e. presence of any distant lesion other than regional lymph node involvement, e.g. bone or bone marrow disease, lung metastases, liver metastases, distant lymph node involvement (for definitions see Appendix 5), or patients with malignant effusion (i.e. tumour cell in peritoneal or pleural fluid) or malignant cells in the spinal fluid).
- Age less than 21 years (20 years and 364 days) of age.
- Previously untreated except for primary surgery.
- 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%).
- No previous malignant tumours.
- Interval between diagnostic surgery and start of chemotherapy no longer than 8 weeks.
- Diagnostic material available for pathology review.
- Available for long term follow up through the treatment centre.
- Written informed consent for treatment available.

Patients with a diagnosis of RMS not satisfying the above criteria will be registered, but not evaluated for the purpose of this study.

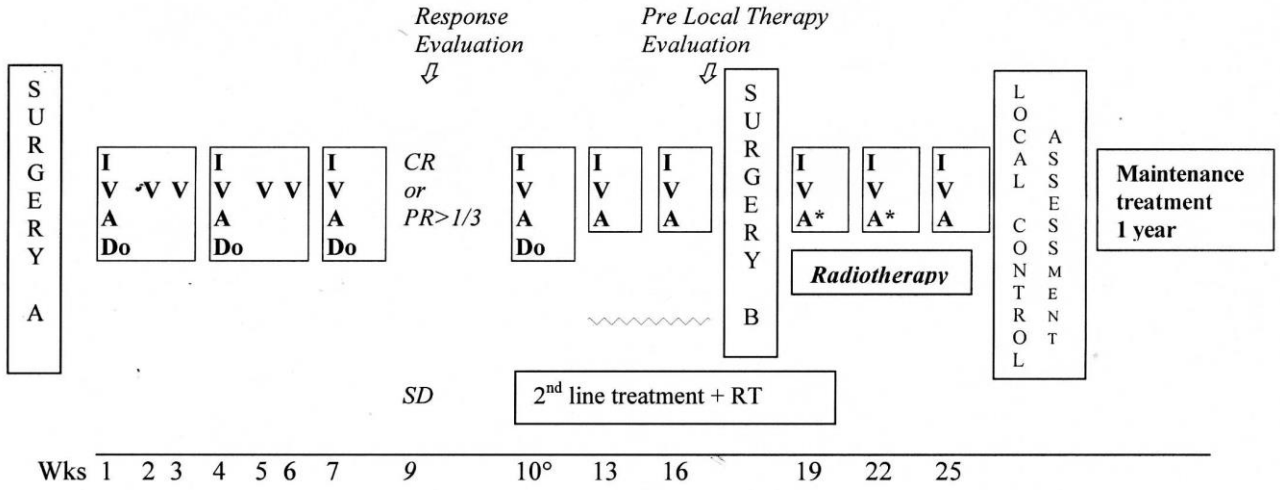
Patients with RMS N.O.S, Undifferentiated STS and Ectomesenchymoma are eligible for EpSSG-RMS-2005 protocol: see paragraph 29.4.

Notes
- Adults with RMS (> 21 years) may be eligible for registration and treatment on study (according to institutional preference)
After the diagnostic surgery primary re-operation can be considered, before chemotherapy starts, in selected cases (see paragraph 22.4).

Risk Groups

All patients with metastatic RMS (as defined in the inclusion criteria) are eligible for the EpSSG-RMS-2005 metastatic study. This includes the high risk and standard risk subgroups of metastatic RMS. However, other treatment options may be available within the framework of national or international studies, especially for high risk patients. It is strongly recommended that each patient should be discussed with the national study centre in order to be aware of any other relevant studies.

Metastatic patients: Intensive Treatment



I Ifosfamide 3 g/m^2 is given as a 3 hour intravenous infusion daily, with Mesna (3 g/m^2) and hydration, on days 1 & 2 for each course of treatment. (Total IFO dose/course = 6 g/m^2).

V Vincristine 1.5 mg/m^2 (maximum single dose 2 mg) is given as a single intravenous injection on day 1 of each course and weekly, for a total of seven consecutive doses, from week 1 to 7.

A Actinomycin D 1.5 mg/m^2 (maximum single dose 2 mg) as a single intravenous injection on day 1 of each course of treatment.

Do Doxorubicin 30 mg/m^2 given as a 4-hour intravenous infusion daily on days 1 & 2 for courses 1-4 of treatment (total dose per course = 60 mg/m^2).

** Actinomycin should be given at the very beginning of RT (week 19) but may be omitted during RT (week 22). Caution is needed in the administration of week 25 ACT-D.*
For more details see chapter 23.11)

Interval between courses is 3 weeks and chemotherapy courses should not be started unless all these conditions are present: 2 x10^9/l WBC (or 1 x10^9/l neutrophils) + 80 x10^9/l platelets + absence of any relevant organ dysfunction.

For children $\leq$ 1 month VA only should be administered in the 1st cycle. For children $\leq$ 1 year (or $\leq$10 kg body weight) first cycle doses will be calculated by body weight and increased in the following cycles if tolerated. See chapter 24.4.1.

Growth factors may be used at the physicians' discretion. It is suggested to use them in case of life-threatening neutropenic CTC grade III-IV infection, or treatment delay $\geq$ 1 week due to toxicity after previous cycles.
For the use of growth factors see also chapter 27.2.

4. ASSESSMENT OF TUMOUR RESPONSE AND TREATMENT DECISIONS

- *1st assessment*: after the initial 3 cycles of chemotherapy (week 9) a full clinical and radiological assessment of the tumour response will be evaluated.

  Patients in CR or tumour volume reduction > 1/3 will continue the treatment they have been allocated at diagnosis.
  Patients with stable disease (SD: tumour volume reduction $\leq$ 1/3), will be eligible for 2nd line treatment (see chapter 20).

- *2nd assessment*: after 6 cycles of chemotherapy (week 18) a full clinical and radiological assessment of all tumour sites will be performed to plan local treatment. Any patient with progressive disease must proceed to 2nd line treatment.

➲ At this time local control modality must be decided

Surgery
In patients with metastatic disease surgery should be performed after cycle 6, i.e. around week 19.

Where residual masses are demonstrated or in case of doubt, surgical resection should be done (surgery B), although there may be certain anatomical sites, particularly in the head and neck, where this may not be feasible and the final decision in these cases is left to the discretion of the individual surgeon. Secondary operations are not indicated if clinically and radiologically (CT and/or MRI) there is no visible tumour (see chapter 22.5).
Secondary operations should, as a rule, be conservative but demolitive operations may be appropriate in certain circumstances. "Debulking" is not recommended. Particular care must be taken to ascertain completeness of resection.
Radical lymph node dissections are not indicated and involved lymph nodes should be irradiated, whether resected or not. There are rare occasions when, if radiotherapy is contraindicated (e.g. age $\leq$ 3 years), a lymph node dissection may be considered as definitive local treatment.
Week 19 chemotherapy (7th cycle) should begin after recovery from surgery B, and radiotherapy should start with the 7th chemotherapy cycle.

For general surgical guidelines see Chapter 22.

Radiotherapy
Patients in local IRS Group II and III must have the primary tumour irradiated. Different doses will be delivered according to chemotherapy response and delayed surgery results (see Chapter 23 for details). Radiotherapy must be performed concomitantly with the 7th cycle (week 19).
If Surgery B is not possible and radiotherapy is decided, this must be delivered beginning at week 19, after the administration of the 6th cycle.
Radiotherapy to the involved lymph node sites should be performed independently of histology, response to therapy, and surgical resection (see paragraph 23.5) .

Radiotherapy should also be given to all sites of metastatic disease, if feasible, regardless of response to therapy. Discretion by the treating clinician, with advice from the study's radiotherapy coordinator, if required, will be needed when multiple metastatic sites are present.

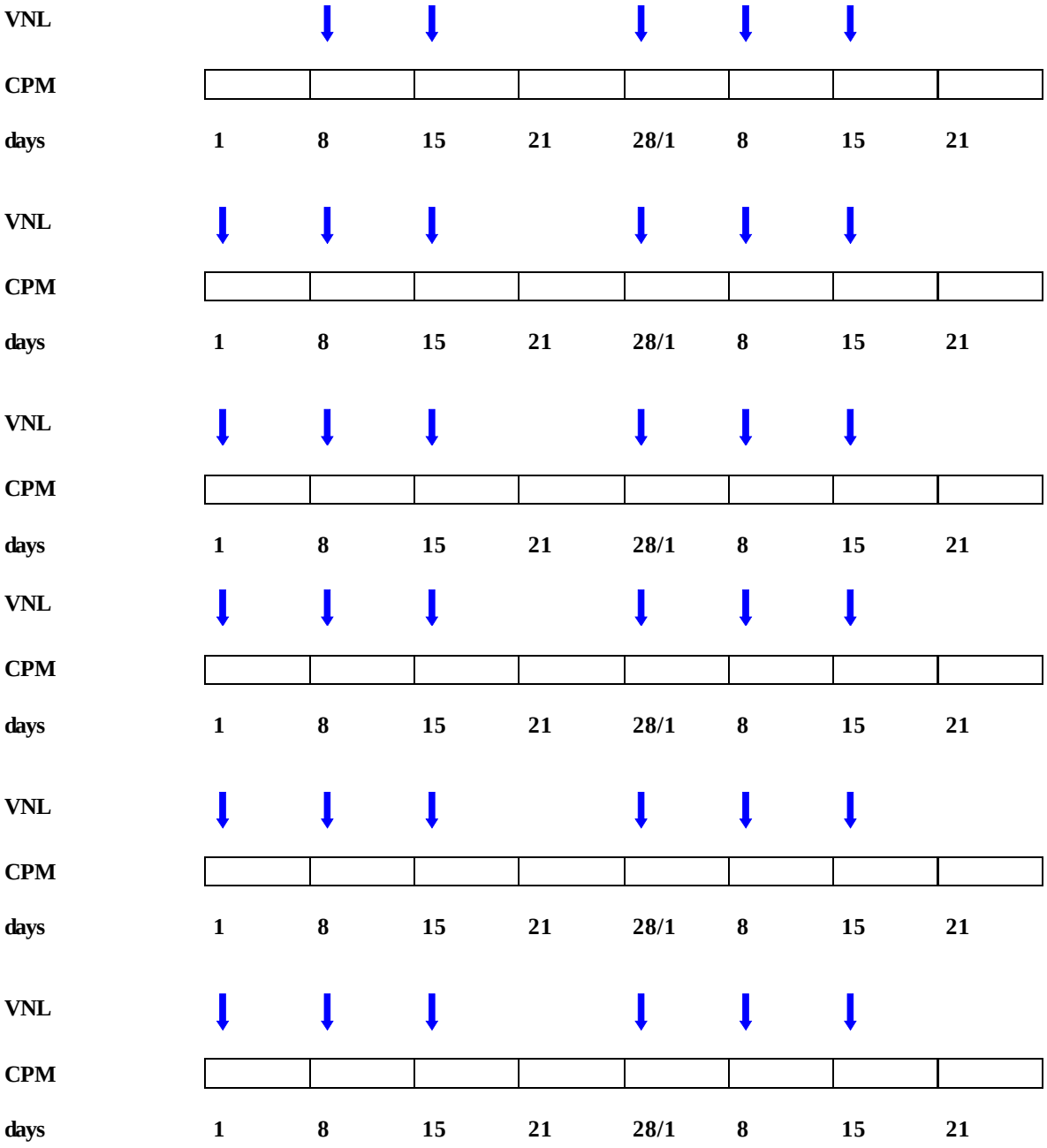
For general guidelines concerning radiotherapy see Chapter 23.
Radiation doses for distant metastases:

The number and localization of metastatic sites can be very variable, and the doses given here are a guide only. Patients have to be considered individually within the local multidisciplinary team, and if necessary discussed with the study's radiotherapy coordinator. In each case, consideration has to be given to the age of the patient, the normal tissues involved, the volume of disease and any medical co-morbidity. Surgery for metastatic disease also needs to be considered as adjunctive treatment. Treatment to distant metastatic sites will normally be given at the same time as primary and nodal radiotherapy.
For one or more lung metastases, whole lung radiotherapy is given. The usual dose will be 15 Gy in ten fractions with lung correction.
For bone metastases, and metastases at other sites, 30 Gy in up to 20 fractions depending on site, age and volume will usually be given.
In rare circumstances of very limited metastatic disease, where small volumes could safely be treated at higher doses of 40-50 Gy, this may be considered. Such exceptional cases should be discussed with the study's radiotherapy coordinator.
As these are all aggressive tumours, radiotherapy should also be considered in children less than 3 years of age, unless unacceptable sequellae are anticipated. General guidelines for irradiation of patients less than 3 years of age are given in paragraph 23.12.
Adjustments to the chemotherapy schedule are necessary during radiotherapy in particular for the administration of doxorubicin and actinomycin (see paragraph 23.11).

- *3rd assessment:* a third assessment must be performed after 9 courses of chemotherapy (end of standard treatment).
  At this point surgery should be reconsidered (Local control assessment) in case of residual tumour.

Metastatic patients: Maintenance Treatment

Following the 9th block of chemotherapy, surgery or a biopsy of what appears to be a possible residual tumour may be performed. Patients may not continue with the maintenance treatment if viable tumour is found and the clinician thinks that more intensive chemotherapy would be appropriate. However in presence of limited quantity of viable tumour maintenance treatment should be adopted.



VNL: Vinorelbine 25 mg/m^2 i.v. over 5-10 minutes day 1,8,15 of each cycle
CPM: Cyclophosphamide 25 mg/m^2 per os every day (no rest between cycles)

This treatment is given on an outpatient basis.

N.B. Oral cyclophosphamide is only licensed in the UK as 50mg sugar-coated tablets which cannot be halved. If tablets are preferred, metronomic dosing can be used, i.e. cumulative weekly dose given over several days as required. For smaller doses or patients requiring a liquid formulation, oral solution formulations may also be purchased. NB: Cyclophosphamide is not an IMP for the metastatic group of patients.

Cyclophosphamide should be administered early in the day and followed by adequate fluid intake to minimize bladder toxicity.

For drug administration details see also paragraph 24.2 and 24.3.

A.16 OVERVIEW OF INFORMATION SHEETS / CONSENT FORMS (RMS–MET 2008)

INFORMATION SHEET FOR PARENTS
INFORMATION SHEET FOR PATIENTS (16+)
INFORMATION SHEET FOR PATIENTS (14-15)
INFORMATION SHEET FOR PATIENTS (8-14)
INFORMATION SHEET FOR PATIENTS (under 8)
GP INFORMATION SHEET

Consent forms
Parent/Child
Young person aged 16+

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.

Addendum – Instructions for early first randomisation stop

An interim analysis has been undertaken and the DMC has advised that the first randomisation should be closed. New patients with localized Rhabdomyosarcoma, allocated to the High Risk group and eligible to the first randomisation, will be treated according to the standard chemotherapy (IVA) regimen. This decision will not influence the second randomization: maintenance vs observation and this randomisation will continue as planned.