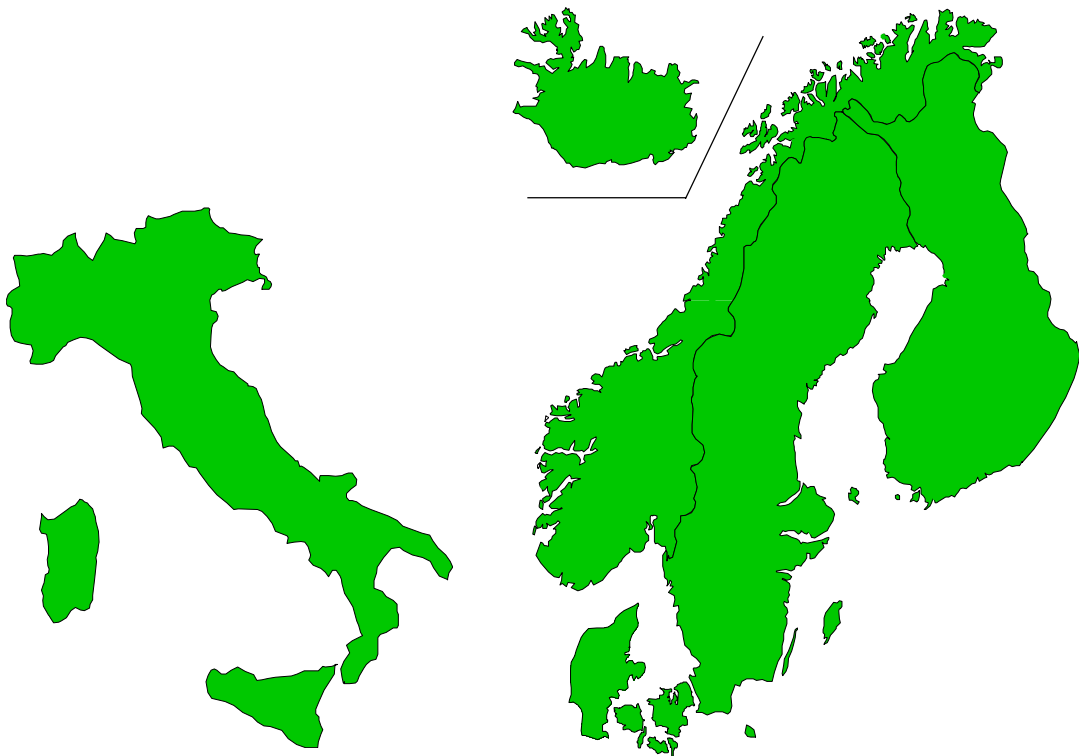


**Italian Sarcoma Group
Bologna, Italy**

**Scandinavian Sarcoma Group and
Oncologic Center, Lund, Sweden**

ISG/SSG IV

**An Italian – Scandinavian
treatment protocol for
high-risk Ewing's family tumors**



Version för Internet

Italian Sarcoma Group
Scandinavian Sarcoma Group
Bologna, Italy,
Oncologic Center, Lund, Sweden,

An Italian–Scandinavian treatment protocol for high–risk Ewing's family tumors

The ISG/SSG IV trial is an Italian–Scandinavian joint, multicenter, and prospective study for the evaluation of combination chemotherapy, surgery, radiotherapy and/or high-dose chemotherapy in patients with high-risk Ewing's family tumors. The study is not randomized and is open to specialized cancer center in the ISG/SSG network, which fulfills all the protocol criteria and complies with the other requirements for inclusion in the study.

All patients with high-risk Ewing's family tumors, treated according to this program, must be reported to the Scandinavian Sarcoma Group secretariat.

Prepared by the Joint Working Committee for the Italian and Scandinavian Sarcoma Groups.

PREFACE

The Scandinavian countries (Denmark, Finland, Iceland, Norway and Sweden) have a total population of about 24 million. They possess have similar social structures, a modern medical service, covering all inhabitants, and an effective registration system for all cancer patients. This serves as a good basis for cooperation. Accordingly, the Scandinavian Sarcoma Group was founded in 1979. Its aim was to improve the prognosis for sarcoma patients in the area. Its work has improved the organization of treatment for sarcoma. Guidelines for diagnosis, pathology, and treatment have been drawn up which are now generally accepted by tumor centers in Scandinavia.

Italy has a population of about 57 million. National protocols for Ewing's tumors have been in progress since 1978, in a special project granted by the Italian National Council of Research. The Italian Sarcoma Group was established 1997 to organize collaboration in research and treatment of sarcomas; it comprises more than 200 members from more than 50 centers.

The present ISG/SSG IV protocol replaces the SSG IX protocol for standard-risk patients. It is based on experience from the SSG IV/IX protocols and three neoadjuvant studies (REN 1–3) from the Rizzoli Institute and from recent international literature.

A working group consisting of 75 members of ISG and SSG have completed the present protocol during 2 years. The following members participated:

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Printing and distribution of the final protocol will be arranged by the Oncologic Center in Lund.

The ISG/SSG IV protocol will be activated as of June 1, 1999

Bologna, Lund, May 31, 1999

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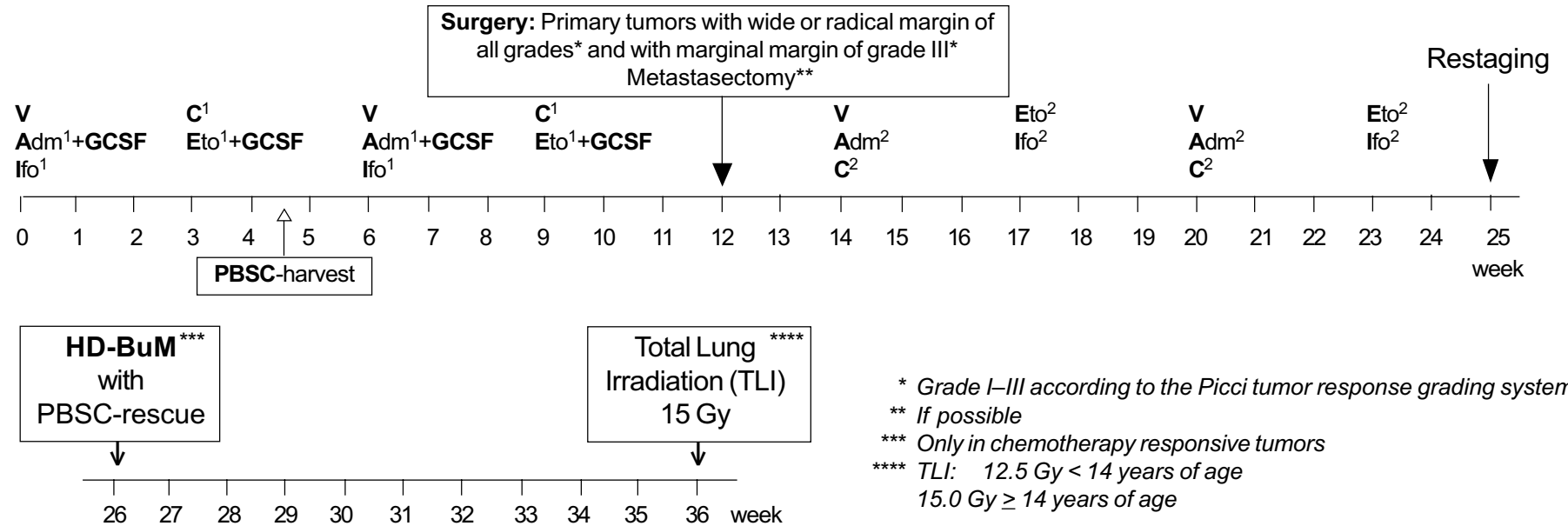
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Ewing's family tumors ISG/SSG IV

Metastatic at diagnosis

High-risk: Solitary lung metastasis >0.5 cm
Multiple lung and/or pleural metastasis(es)
Only one bone metastasis

1. Pre- and postoperative chemotherapy combined with surgery only and HD-BuM and TLI



<p>V: Vincristine 2 mg/m² (max 2 mg) i.v. push.</p> <p>Adm¹(in VAdm¹Ifo¹): Adriamycin (Doxorubicin) 45 mg/m²/day as 4 hours (2 days) i.v. inf. Total dose Doxorubicin = 90 mg/m² for 2 days</p> <p>Ifo¹(in VAdm¹Ifo¹): Ifosfamide 3000 mg/m²/day in 3 days as 2,5 hours continuous i.v. infusion (total dose 9000 mg/m² in 3 days).</p> <p>C¹ (in C¹Eto¹): Cyclophosphamide 4000 mg/m² as 3hours continuous i.v. inf.</p> <p>Eto¹ (in C¹Eto¹): Etoposide 200 mg/m²/day as 2 hours (3 days) i.v. infusion (total of 600 mg/m² Etoposide in 3 days).</p> <p>Adm²(in VAdm²C²): Adriamycin (Doxorubicin) 40 mg/m²/day as 4 hours (2 days) i.v. infusion. Total dose Doxorubicin = 80 mg/m² in 2 days</p>	<p>C² (in VAdm²C²): Cyclophosphamide 1200 mg/m² as 30 min continuous i.v. infusion.</p> <p>Eto² (in Eto²Ifo²): Etoposide 100 mg/m²/day in 3 days, day 1,3 and5 as 2 hours i.v. infusion.</p> <p>Ifo²(in Eto²Ifo²): Ifosfamide 1800 mg/m²/ day in 5 days as 21-24 hours continuous i.v. infusion (total dose of Ifosfamide 9000 mg/m² in 5 days).</p> <p>HD-BuM +PBSC: Busulfan 1 mg/kg p.o. x 4/day for 4 days Melphalan 140 mg/m² i.v. as 60 minutes i.v. infusion Peripher Blood Stem Cell rescue at 48 hours after termination of chemotherapy.</p>
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Ewing's family tumors ISG/SSG IV

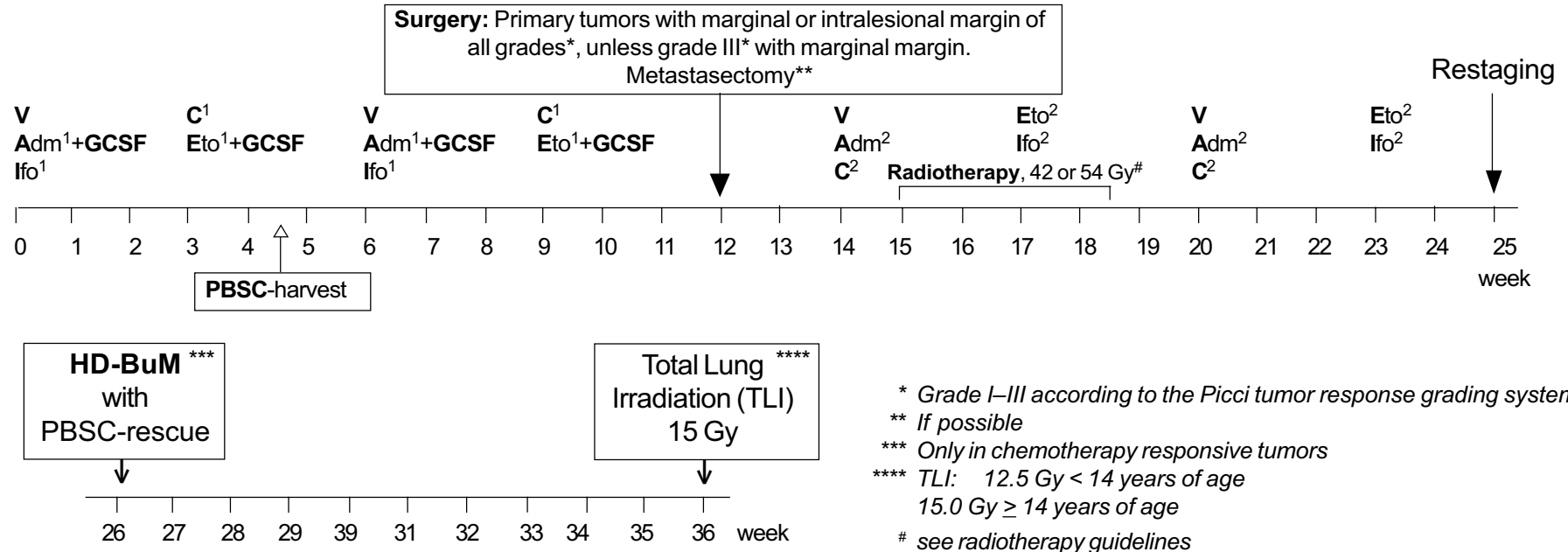
Metastatic at diagnosis

High-risk: Solitary lung metastasis >0.5 cm

Multiple lung and/or pleural metastasis(es)

Only one bone metastasis

2. Pre- and postoperative chemotherapy combined with radiotherapy, HD-BuM and TLI



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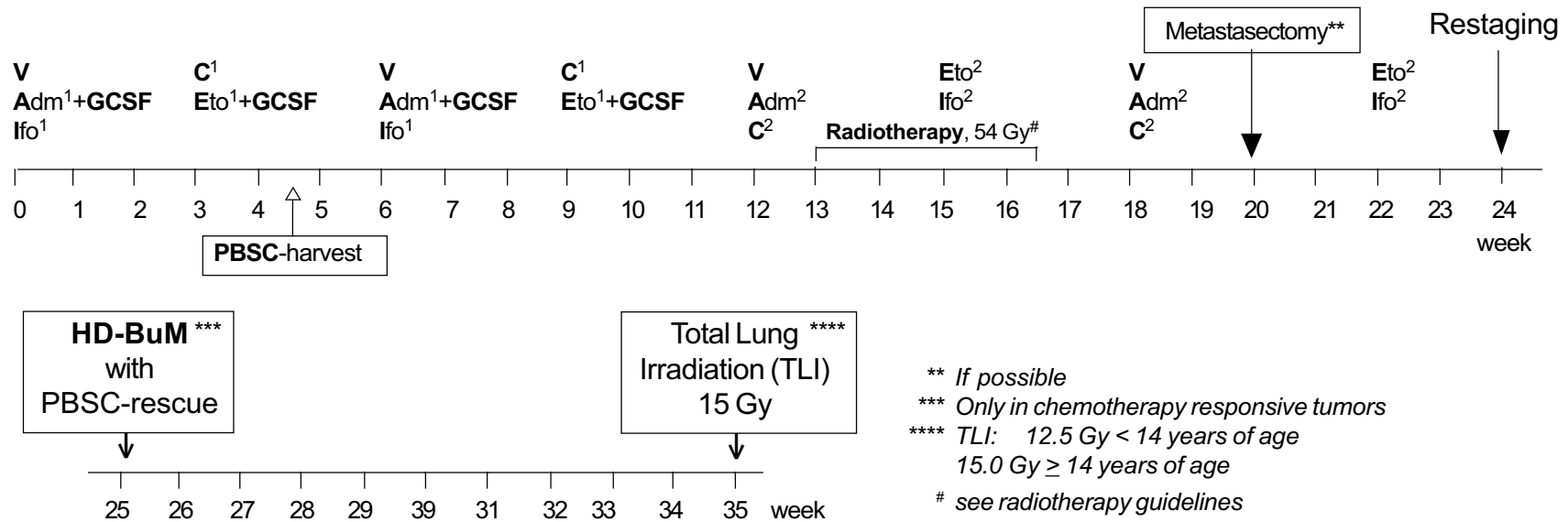
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Ewing's family tumors ISG/SSG IV

Metastatic at diagnosis

High-risk: Solitary lung metastasis >0.5 cm
Multiple lung and/or pleural metastasis(es)
Only one bone metastasis

3. Chemotherapy combined with radiotherapy only and HD-BuM and TLI



** If possible
 *** Only in chemotherapy responsive tumors
 **** TLI: 12.5 Gy < 14 years of age
 15.0 Gy ≥ 14 years of age
 # see radiotherapy guidelines

V:	Vincristine 2 mg/m ² (max 2 mg) i.v. push.	C² (in VAdm²C²):	Cyclophosphamide 1200 mg/m ² as 30 min continuous i.v. infusion.
Adm¹ (in VAdm¹Ifo¹):	Adriamycin (Doxorubicin) 45 mg/m ² /day as 4 hours (2 days) i.v. inf. Total dose Doxorubicin = 90 mg/m ² for 2 days	Eto² (in Eto²Ifo²):	Etoposide 100 mg/m ² /day in 3 days, day 1,3 and5 as 2 hours i.v. infusion.
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2. INTRODUCTION

Several groups have incorporated intensive chemotherapy or TBI in the strategy to improve the results in high-risk Ewing's sarcoma (Burdach, 1993, Marcus, 1988, Pession, 1996, Horowitz, 1993, Valteau-Couanet, 1996). The number of patients is small, and the patient populations are heterogeneous. Most patients have received high-doses of chemotherapy or TBI as a consolidation treatment. They have been given chemotherapy alone or in combination with TBI or TBI alone. Patients with metastatic disease (either at diagnosis or following first CR), and patients at high-risk, as defined by the individual group tumors, without metastases at presentation, have been included. The source of stem cells has been autologous in most cases, and recently blood-derived stem cells have almost completely replaced bone marrow-derived stem cells. Most of the results reported in these studies have been only preliminary.

To clarify the role of the various treatments given, and the heterogeneity of the patient population, the EBMT has reviewed patients reported to the EBMT register (Ladenstein, 1995).

Metastatic disease

Group	Patients	OS	DFS	Reference
ICESS	CR1 or CR2	4 (10) years, 39% (10%)	not given	Paulussen, 1996
EBMT	CR1	not given	5 years, 21%	Ladenstein, 1995
NCI	CR1 or CR2	6 years, 29 %	6 years, 19%	Horowitz, 1993

High-risk disease without metastases

Group	Patients	OS	DFS	Reference
NCI	CR	6 years, 46%	6 years, 41%	Horowitz, 1993
EBMT	local recurrence, CR	not given	5 years, 32%	Ladenstein, 1995
Florida	primary high risk	5 years, 75%	5 years, 62%	Marcus, 1988

The CESS material was compared to matched controls in the same group. The relapse-free survival was 45% among patients treated with intensified treatments requiring stem cell support, compared to 2% among historical controls (Burdach, 1993).

Therapeutic modality

TBI ± high-dose chemotherapy + stem cell transplantation

Group	Regimen	Reference
NCI	4 Gy × 2 days	Horowitz, 1993
Florida	4 Gy × 2 days	Marcus, 1988
ICESS	1.5 Gy × 2/day × 4 days + HD-CT	Burdach, 1993

In the review by EBMT, EFS was significantly lower in patients who received regimens including TBI than in those treated with high-dose chemotherapy alone (Ladenstein, 1995).

Chemotherapy agents

Group	HD regimen	Reference
Italy	Busulfan + VP 16 + Tiothepa	Pession, 1996
France	Busulfan + L-PAM	Valteau-Couanet, 1996
ICESS	L-PAM + VP 16 + CARBO (+TBI)	Burdach, 1993

L-PAM is the most widely used agent in HD regimens for Ewing's sarcoma. Efficacy has been shown in patients with measurable disease (Hartmann, 1991). More recently, Busulfan has also been introduced, either alone or in combination. This drug has also been found effective in patients with measurable disease (Hartmann, 1991, Khalil, 1995, Ghalie, 1994). In the review by EBMT, the Busulfan + L-PAM combination was superior to L-PAM alone. Patients who had received less intensive induction chemotherapy also fared better (Ladenstein, 1995).

Other drugs used are those that can be significantly dose-escalated. Preference is also given to drugs not used during the induction therapy.

3. AIMS AND GENERAL PROTOCOL DESIGN

(for treatment outline see pp. 11–13)

1. Evaluation of event-free survival in patients with high-risk EWS or PNET treated with a multi-modal protocol, characterized by:
 - High-intensity dose of chemotherapy and radiotherapy (hyperfractionated and accelerated radiotherapy)
 - An induction phase, using all five drugs active in Ewing's family tumors: Ifosfamide (Ifo), Etoposide (Eto), Vincristine (V), Adriamycin (Adm), Cyclophosphamide (C)
 - Patients will receive high-doses of Busulfan (Bu) and Melphalan (M) with reinfusion of peripheral blood stem cells (PBSC), followed by total lung irradiation (TLI)
2. Evaluation of the percentage of patients with a good histological response (p. 39), after induction chemotherapy with 5 drugs (V, Adm, C, Ifo, Eto) followed by surgery
3. Evaluation of the percentage of patients with good radiological response (p. 37), after induction chemotherapy with 5 drugs (V, Adm, C, Ifo, Eto)
4. Correlation between the radiological response and prognosis
5. Correlation between the histological and radiological responses to prognosis
6. Evaluation of the prognostic significance of: age at diagnosis, diagnosis (EWS, PNET), tumor location, tumor volume, and dose intensity of the chemotherapy received
7. Study the biological characteristics of EWS: immunohistochemical, cytogenetic, with their clinical correlations
8. We estimate to include approximately 20 patients/year in this protocol

4. TREATMENT STRATEGY AND RATIONALE

Induction chemotherapy

In view of the importance of the histological and/or radiological response to induction chemotherapy, compared to previous Italian and Scandinavian studies, this protocol intensify the chemotherapy by using all 5 of the most active drugs (Vincristine, Adriamycin, Cyclophosphamide, Ifosfamide, Etoposide) in the treatment of EWS/PNET.

Local treatment

It is universally accepted that local treatment is important for cure. The strategy for local control should be decided only in centers which have documented multidisciplinary experience.

General guidelines to be followed are here reported:

1. Surgery with wide margins is the treatment of choice. Surgery should be planned for beginning of week 11, when neutrophils $>1.0 \times 10^9/l$ and platelets count $>100 \times 10^9/l$. If surgery is not feasible, radiation therapy should be started at the beginning of week 11.
2. Should surgery unexpectedly prove to have inadequate margins (intralesional, marginal or contaminated) with poor preoperative chemotherapy response, it should be followed by radiotherapy, in full doses of 54 Gy.
3. Radiotherapy alone is reserved for tumors which because of site or dimensions exclude in advance any possibility for surgery with adequate margins.

Based on the previous experience of both Groups (ISG and SSG), radiation therapy will be given with hyperfractionated and accelerated modalities (p. 45).

For the Italian Sarcoma Group, these centers are:

Bologna:

Surgeon: Prof. M. Mercuri

Radiotherapist: Prof. E. Barbieri

Oncologist: Dr. G. Bacci

Milan:

Surgeon: Dr. S. Mapelli

Radiotherapist: Dr. F. Lombardi

Oncologist: Dr. F. Fossati Bellani

Firenze:

Surgeon: Dr. R. Capanna

Radiotherapist: Prof. P. Olmi

Oncologist: Prof. G. Bernini

For the Scandinavian Sarcoma Group there are 6 centers:

Bergen:

Surgeon: Dr. C. Trovik

Oncologist/radiotherapists: Dr. O. Monge, Dr. J. Helgestad

Oslo:

Surgeon: Dr. G. Follerås

Oncologist/radiotherapist: Dr. G. Saeter

Gothenburg:

Surgeon: Dr. B. Gunterberg

Oncologist/radiotherapists: Dr. K. Engström, Dr. I. Marky

Lund:

Surgeon: Dr. A. Rydholm, Dr. P. Gustafson

Oncologists/radiotherapists: Dr. T.A. Alvegård, Dr. T. Wiebe

Stockholm:

Surgeon: Dr. O. Brosjö

Oncologists/radiotherapists: Dr. H. Strander, Dr. O. Björk

Helsinki:

Surgeon: Dr. A. Kivioja

Oncologist/radiotherapist: Dr. T. Wiklund

Evaluation of response

All patients must be evaluated before and after induction chemotherapy with comparable CT and/or MRI.

Evaluation of the histological tumor response must be centralized in the referral centers mentioned above.

On the basis of these criteria, patients will be divided into two categories: *good responders* (tumor response grades II and III) and *poor responders* (tumor response grade I).

Local treatment based on histological tumor response

Surgery alone	<i>Histological good responders</i> Tumor-response grades II and III and wide or radical margin, grade III and marginal margin	<i>Histological poor responders</i> Tumor-response grade I and wide or radical margin
Surgery with radiotherapy	Tumor response grade II and marginal or intralesional margin, grade III and intralesional margin	Grade I and marginal or intralesional margin
Radiotherapy alone	<i>Radiological good responders</i> In nonoperable patients with complete disappearance of the soft tissue component and complete ossification.	<i>Radiological poor responders</i> In inoperable patients with incomplete disappearance of the soft tissue component and incomplete ossification

Maintenance chemotherapy

Since most patients (at least 70%) will undergo surgery as local treatment, and about 3 weeks are required to evaluate the specimen, all patients (irrespective of response) will receive VAdm²C² as the first cycle of maintenance. Patients treated with radiation therapy will also receive the same VAdm²C² cycle.

After this VAdm²C² cycle, all patients will receive Eto²Ifo², VAdm²C², Eto²Ifo² followed by high-dose chemotherapy treatment with Busulfan (Bu) and Melphalan (M) with subsequent PBSC rescue. Only patients with chemotherapy response tumors (PR or CR) after restaging with CT of the lungs will be treated with high-dose chemotherapy. Total lung irradiation is given 10 weeks after high-dose chemotherapy.

5. ORGANIZATION

Address of main study secretariat:

Evy Nilsson, Ingrid Dahlberg and Dr. Thor Alvegaard, Regional Tumor Register, University Hospital of Lund, SE-221 85 Lund, Sweden

Tel. +46-46-177555

Fax. +46-46-188143

A register of ISG patients will be kept at Istituto Ortopedico Rizzoli, Via Pupilli 1, IT-40136 Bologna, Italy. All the Italian patients will be registered in the ISG register and its data will be sent to the main study secretariat in Sweden.

Tel. +39-051-6366829 (Dr. Bacci), +39-051-6366759 (Dr. Picci)

Fax. +39-051-6366277 (Dr. Bacci), +39-051-584422 (Dr. Picci)

6. PUBLICATION

Both the ISG and SSG groups will have access to the entire database and individual institutions are free to publish their own data. However, one main purpose is to publish the ISG and SSG patient materials together. In this process, the list of authors will be worked out in collaboration between the principal investigators of the ISG and the SSG publication committee.

7. ISG/SSG IV "RESOURCE GROUP"

When performing a multicenter study with multimodality treatment and multiagent chemotherapy, unforeseen situations and complications may occur which may not be sufficiently covered in the protocol. To minimize protocol violations and ensure uniform handling of such situations, the ISG/SSG IV working group has formed a "Resource Group", whose task will be to help the local clinician to solve such problems, which include toxicity/safety, clinical suspicion of tumor progression during preoperative chemotherapy, etc.

In this event, the clinician should contact a member of the resource group from his own country who will assist him. Written documentation regarding the problem's nature and solution should be sent to the clinician in question, to all members of the resource group and should be included in the patient's file at the study secretariat.

Members of the Resource Group and Principal Investigators in the ISG/SSG IV study

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8. ASSOCIATED RESEARCH PROJECTS

A research protocol is under preparation and will be activated autumn 1999. Please preserve fresh frozen tumor material at the time at diagnosis, PBSC harvest and suspected relapse. Please follow the guidelines for analysis of genetic changes in musculoskeletal tumors, second edition, Lund, 1997 (SSG secretariat, Lund, Sweden). Bone marrow aspirates (1 ml samples into EDTA, from at least two sites) to be taken from the iliac crest at time at diagnosis, PBSC harvest and suspected relapse.

9. ETHICAL CONSIDERATIONS

1. ISG/SSG IV is a non-randomized phase II study based on experience from ISG, SSG and the medical literature.
2. Before treatment, the patients (and/or parents) will be informed about the nature of the disease, the treatment plan and the effects and side-effects, according to standard procedures in each country.
3. The effects and side-effects of the treatment will be recorded and reported in the international literature.
4. The physician responsible for the individual patient may deviate from the protocol or may terminate treatment for various medical reasons, on medical indications. The ISG and SSG provide a "Resource Group" of specialists to assist in such situations.

10. CRITERIA FOR ELIGIBILITY

1. Histologically proven Ewing's sarcoma or PNET
2. Diagnosis must be made by open biopsy, needle core biopsy or fine-needle aspiration (FNA) biopsy
3. Age ≤ 40 years
4. No previous treatment for EWS or PNET
5. Patient with one lung lesion ≥ 0.5 cm, multiple or pleural metastasis(es), and/or only one bone metastasis
6. Normal hepatic and renal function
7. White blood count $\geq 3.0 \times 10^9/l$ and platelets $\geq 100 \times 10^9/l$
8. Chemotherapy must be started within four weeks of the histological diagnosis
9. Patient registration form must be accompanied by representative histology slides (for verification of diagnosis) and CT images of the primary tumor (for estimation of tumor volume)
10. A completed Institution Commitment Form (Appendix 1) from each individual patient must be submitted to the secretariat (see p. 18)
11. The patient must be informed about the nature of the disease and of the effects and side-effects of the treatment, in accordance with the standard procedure in each country

11. CRITERIA FOR EXCLUSION

(Patients treated with the present protocol, but not eligible for the study can be registered in the study secretariats)

1. **”Standard risk patients”** – nonmetastatic Ewing's family tumors according to the ISG/SSG III protocol
2. **Very high risk patients** with multiple bone metastases or morphologic evidence of bone marrow and/or visceral involvement
3. Previous malignancy other than basal cell carcinoma of the skin and in situ/non-invasive carcinoma of the skin or cervix
4. Medical contraindications to the cytostatic agents and dose levels in question
5. Planned chemotherapy and/or follow-up not feasible
6. Major psychological and psychiatric diseases
7. Patient's refusal to participate in the treatment program
8. Missing patient/parents/tutor consent to treatment according to national guidelines
9. Local treatment decided without consulting of the referral centers (see 4.2, p. 16)

(PCR diagnosed EWS-FLI fusion on needle biopsy from the iliac crest will be studied retrospectively).

12. PRETREATMENT INVESTIGATIONS

(see also flow-sheet in Appendix 1, p. 34)

Mandatory requirements:

1. Complete medical history and physical examination (including date and nature of first symptoms, especially pain, fever and body height, weight and surface area).
2. Open surgical biopsy, needle core biopsy, or fine-needle aspiration (FNA), (representative slides should be sent to the study secretariat on registration).
The diagnosis should be confirmed by two pathologists.
3. Determination with RT-PCR of the gene fusion products.
4. Needle aspiration from both iliac crests and bone marrow biopsy from at least one side. For pelvic lesions, only from the contralateral side.
5. Laboratory studies:
 - a. Complete blood count (hemoglobin, white blood counts with differential, thrombocytes)
 - b. Sedimentation rate (ER) serum creatinine, GFR estimation using the method of the individual institution, ALP, LDH, total bilirubin and liver transaminases
 - c. Serum Na, K, and Mg
6. Hepatitis serology A, B, C

7. Radiological and scintigraphic studies:
 - a. A-P and lateral conventional X-rays of the entire involved bone (copies should be sent to the study secretariat on registration)
 - b. CT and MRI scan of the entire involved bone (copies of CTs should be sent to the study secretariat on registration for tumor volume determination)
 - c. A-P and lateral chest X-rays
 - d. CT scan of the chest
 - e. Total bone scan, preferably with dynamic study of the primary tumor area
 - f. CT scan of the abdomen (patients with lesions not involving the abdominal cavity)
 - g. Ultrasound of the abdomen
8. Electrocardiogram (ECG)
9. Cardiac ultrasound, with estimation of left ventricular ejection fraction (LVEF), before first course of Adriamycin treatment.

Recommended investigations (optional):

1. Positron Emission Tomography (PET)
2. Angiography of the involved limb
3. Dynamic cardiac scintigraphy
4. Urinary alfa1-microglobulin/urinary creatinine, tubular reabsorption of phosphate, fractional excretion of glucose
5. Sperm count. It is recommended that a sperm count be performed in all patients where feasible, and that these patients be offered sperm banking prior to chemotherapy.

13. REEVALUATION BEFORE SURGERY

Mandatory investigations:

1. Complete physical examination
2. Laboratory studies:
 - a. Complete blood count (hemoglobin, white blood counts with differential count, thrombocytes)
 - b. Serum creatinine, GFR estimation, ALP, LDH, total bilirubin and liver transaminases
 - c. Serum Na, K, and Mg
3. Radiological studies:
 - a. A-P and lateral conventional X-rays of the entire involved bone
 - b. CT and MRI scan of the entire involved bone
 - c. A-P and lateral chest X-rays
 - d. CT scan of the chest
4. Electrocardiogram

Recommended investigations (optional):

- 1 Total bone scan, preferably with dynamic study of the primary tumor area

14. INVESTIGATIONS AT END OF TREATMENT

Mandatory investigations:

1. Complete physical examination
2. Laboratory studies:
 - a. Complete blood count (hemoglobin, white blood counts with differential, thrombocytes)
 - b. Serum creatinine, GFR estimation, ALP, LDH, total bilirubin and liver transaminases
 - c. Serum Na, K, and Mg
3. Radiological studies:
 - a. A-P and lateral chest X-rays
 - b. A-P and lateral conventional X-rays of the entire involved bone
 - c. CT and MRI scan of the entire involved bone (not in cases where reconstructive surgery was performed)
4. Cardiac ultrasound, with estimation of left ventricular ejection fraction
5. Hepatitis serology A, B, C

Recommended investigations (optional):

1. Sperm count in patients with sufficient sexual maturation

15. RESPONSE CRITERIA

1. *Complete remission (CR)*: complete disappearance of all visible disease for at least 4 weeks. Bone marrow must be free of tumor cells.
2. *Very good partial response (VGPR)*: >2/3 reduction of tumor volume in every lesion (primary tumor and metastasis) with bone marrow free of disease.
3. *Partial response (PR)*: ≥50% reduction in the sum of areas of all lesions (primary tumor and metastases) calculated as the product of the two largest perpendicular diameters with bone marrow free of disease.
4. *Stable disease (SD)*: <50% reduction of increase <25% in the sum of areas of all lesions calculated as the product of the two largest perpendicular diameters, for at least 4 weeks. No new lesions.
5. *Progressive disease (PD)*: Any increase of more than 25% reduction in the sum of areas of all lesions, calculated as the product of the two largest perpendicular diameters or appearance of new lesion(s).

16. FOLLOW-UP AFTER END OF TREATMENT

(see also flow-sheet in Appendix 1, p. 34)

Patients should be followed at 3-month intervals for 3 years, at 4-month intervals during the 4th and 5th years, and then at 6-month intervals until 10 years after treatment.

Mandatory investigations at follow-up:

1. Complete physical examination
2. A-P and lateral chest X-rays and CT scan of the chest at each visit
3. Blood count (hemoglobin, white blood counts, trombocytes), transaminases, ALP, LDH and serum creatinine at each visit
4. Serum creatinine, GFR estimation at 4-month interval during the first year, at 6-month intervals during the second and third years and then yearly
5. Cardiac ultrasound with estimation of left ventricular ejection fraction at 6 months, 12 months and then at 3-year intervals
6. Bone scan and plain X-rays on clinical suspicion of bone metastases; if inconclusive, supplement with CT and/or MRI

Recommended investigations (optional):

1. Sperm count 3 years after treatment in patients with sufficient sexual maturation.

17. TREATMENT GROUPS

Treatment group 1

Pre- and postoperative chemotherapy combined with surgery only and HD-BuM and TLI:

In this group are patients included with primary tumors with wide or radical margin of all grades and grade III with marginal margin.

Treatment group 2

Pre- and postoperative chemotherapy combined with radiotherapy, HD-BuM and TLI:

In this group are patients included with primary tumors with marginal or intralesional margin of all grades, unless grade III with marginal margin.

Treatment group 3

Chemotherapy combined with radiotherapy only and HD-BuM and TLI.

18. ADMINISTRATION OF CHEMOTHERAPY

(See chemotherapy flow-sheets on pp. 11–13)

NOTE: All infusion volumes are specified per m² of body surface area to facilitate necessary adjustments for children.

1. VAdm¹Ifo¹ cycle (Vincristine, Adriamycin¹, Ifosfamide¹)

This combination is given to all three groups of patients on weeks 0 and 6.

Blood check-ups before starting VAdm¹Ifo¹-cycle: Hemoglobin, white blood counts, neutrophils, platelets, albumin, liver enzymes, bilirubin, Na, K, Ca, creatinine, Uristix for hematuria

Daily: Hemoglobin, white blood counts, platelets, Uristix, creatinine, GFR, Na, K, Ca, GOT and GPT (=ASAT, ALAT)

Basal solution: 5% glucose with 40 mmol NaHCO₃/l + 20 mmol KCl/l

Day 1

Timing	Drug	Infusion modalities
0	Vincristine	2.0 mg/m ² (max 2 mg) i.v. push
0–0.5 h	Mesna*	400 mg/m ² in 250 ml saline solution, in 30 minutes
0.5–3 h	Ifosfamide	3 000 mg/m ² i.v. in 250 ml 5% glucose, in 150 minutes
3h–12 h	Mesna*	3 000 mg/m ² in basal solution 1 500 ml/m ² , in 9 hours
12h–16 h	Adriamycin	45 mg/m ² /day i.v. in 1 000 ml 5% glucose in 4-hour continuous infusion

Day 2

0–0.5 h	Mesna	400 mg/m ² in 250 ml saline solution, in 30 minutes
0.5–3 h	Ifosfamide	3 000 mg/m ² in 250 ml 5% glucose, in 150 minutes
3–12 h	Mesna	3 000 mg/m ² in basal solution 1 500 ml/m ² , in 9 hours
12–16 h	Adriamycin	45 mg/m ² /day i.v. in 1 000 ml 5% glucose in 4 hours continuous infusion

Day 3

0–0.5 h	Mesna	400 mg/m ² in 250 ml saline solution, in 30 minutes
0.5–3 h	Ifosfamide	3 000 mg/m ² in 250 ml 5% glucose, in 150 minutes
3–24 h	Mesna	3 000 mg/m ² in basal solution 3 000 ml/m ² , in 21 hours

VAdm¹Ifo¹ courses are started if:

Neutrophil count >1.0 × 10⁹/l platelet count >100 × 10⁹/l, bilirubin <1.5 mg/dl (=20 mmol/l), and transaminases <5 times higher than the normal range. No severe signs or symptoms of Vincristine-induced neuropathy should be present.

In case of low blood counts or high serum bilirubin and transaminase values, recheck every other day.

In case of severe signs or symptoms of Vincristine-induced neuropathy, Vincristine is omitted.

When the cumulative dose of Adriamycin reaches 320 mg/m², an echocardiogram must be taken. In case of >10% reduction of LVET, compared to the baseline value, the last cycle with Adriamycin should be omitted.

When radiation therapy involves the heart with doses >20 Gy, the last cycle of Adriamycin is omitted, regardless of the LVET calculated.

2. C¹Eto¹ (Cyclophosphamide¹ and Etoposide¹)

This combination is given to all three groups of patients weeks 3 and 9.

Blood check-ups before starting C¹Eto¹: Hemoglobin, white blood counts, neutrophils, platelets, albumin, liver enzymes, including bilirubin, Na, K, Ca, creatinine, Uristix for hematuria

Daily: Hemoglobin, white blood counts, platelets, venous acid/base (or serum bicarbonate), Uristix, creatinine, Na, K, Ca, Mg, GOT and GPT (=ASAT, ALAT), Uristix for hematuria

Uristix for hematuria is repeated 6 and 24 hours after Cyclophosphamide infusion

Basal solution: 5% glucose with 40 mmol NaHCO₃/l + 20 mmol KCl/l

Day 1

Timing	Drug	Infusion modalities
0–3 h	Cyclophosphamide	Cyclophosphamide in a dose of 4 000 mg/ m ² is given as a 3 hour continuous intravenous infusion, together with Mesna in the same dose (4 000 mg/m ²). Cyclophosphamide and Mesna are dissolved in 500 ml 5% glucose.
3–24 h	Posthydration	3 000 ml/ m ² for 21 hours. Use basal solution.

Days 2–3–4

0–2 h	Etoposide	Etoposide in a dose of 200 mg/ m ² /day is given as a continuous infusion over 2 hour for 3 days (total dose 600 mg/m ² /3 days). Etoposide is dissolved in 500 ml/m ² of 0.9% NaCl. Start the infusion when the posthydration after Cyclophosphamide is completed.
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C¹Eto¹ courses are started if :

neutrophil count >1.0 × 10⁹/l and platelet count >100 × 10⁹/l.

In case of low blood counts, recheck every other days.

If Uristix is positive or macroscopic hematuria develops during the chemotherapy cycle, the 24-hour dose of Mesna must be doubled and administered in a continuous infusion in 2 000 ml/m²/24 hours 5% glucose for 48 hours after the development of hematuria.

Should hematuria reappear during the following cycle, contact the protocol coordinators.

3. VAdm²C² cycle (Vincristine, Adriamycin², Cyclophosphamide²)

This combination is given to all patients on weeks 13 and 19 in groups 1 and 2 and in patients in group 3 on weeks 12 and 18.

Blood check-ups before starting VAdm²C²-cycle: Hemoglobin, white blood counts, neutrophils, platelets, albumin, liver enzymes, bilirubin, Na, K, Ca, creatinine, Uristix for hematuria

Daily: Hemoglobin, white blood counts, platelets, Uristix, creatinine, Na, K, Ca, GOT and GPT (=ASAT, ALAT)

Uristix for hematuria is repeated 6 and 24 hours after Cyclophosphamide infusion

Basal solution: 5% glucose with 40 mmol NaHCO₃/l + 20 mmol KCl/l

Day 1

Timing	Drug	Infusion modalities
0	Vincristine	1.5 mg/m ² (max 2 mg) i.v. push
0–0.5 h	Mesna*	400 mg/m ² in 250 ml saline solution, for 30 minutes
0.5–1 h	Cyclophosphamide	1 200 mg/m ² i.v. in 250 ml 5% glucose (100 ml in children), for 30 minutes
1h–9 h	Mesna*	1 200 mg/ m ² in basal solution 1 500 ml/ m ² for 8 hours
9h–13 h	Adriamycin	40 mg/m ² i.v. in 1 000 ml 5% glucose in 4-hour infusion

Mesna* Variation is possible, based on local experience

Day 2

9–13 h	Adriamycin	40 mg/m ² i.v. in 1 000 ml 5% glucose in 4-hour continuous infusion. Total dose of Doxorubicin = 80 mg/m ² for 2 days
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Before Vincristine (day 8), check white blood cell counts, neutrophils, platelets, and hemoglobin

VAdm²C² courses are started if:

Neutrophil count >1.0 x 10⁹/l, platelet count >100 x 10⁹/l,

bilirubin <1.5 mg/dl (=20 mmol/l), and transaminases <5 times higher than the normal range.

No severe signs or symptoms of Vincristine-induced neuropathy should be present.

In case of low blood counts or high serum bilirubin and transaminase levels, recheck every other day.

If severe signs or symptoms of Vincristine-induced neuropathy, omit Vincristine.

When the cumulative dose of Adriamycin reaches 320 mg/m², an echocardiogram must be taken. In case of >10% reduction of LVET, compared to the baseline value, the last cycle with Adriamycin should be omitted.

When radiation therapy involves the heart with doses >20 Gy the last cycle of Adriamycin is omitted regardless the calculated LVET.

4. Eto²Ifo² cycle (Etoposide², Ifosfamide²)

This combination is given to all patients in groups 1 and 2 on weeks 16 and 22 and in patients in group 3 on weeks 15 and 22.

Blood check-ups before starting Ifosfamide: Hemoglobin, white blood counts, neutrophil, platelets, albumin, liver enzymes, including bilirubin, Na, K, Ca, creatinine, GFR, Uristix for hematuria.

Daily: Hemoglobin, white blood counts, platelets, venous acid/base (or serum bicarbonate), Uristix, creatinine, Na, K, Ca, Mg, GOT and GPT (=ASAT, ALAT), Uristix for hematuria.

Basal solution: 5% glucose with 40 mmol NaHCO₃/l + 20 mmol KCl/l.

Day 1

Timing	Drug	Infusion modalities
0–2 h	Etoposide	100 mg/m ² i.v. in 2 hours in saline solution 400 ml/m²
2–4 h	Prehydration and alkalization	Infuse 500 ml/m ² of basal solution
4–24 h	Ifosfamide*/Mesna	Ifo/Mesna in basal solution for 20 hours

Day 2

0–24 h	Ifosfamide*/Mesna	Ifo/Mesna in basal solution for 24 hours
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Day 3

0–2 h	Etoposide	100 mg/m ² i.v. for 1 hour in saline solution 400 ml/m²
2–24 h	Ifosfamide*/Mesna	Ifo/Mesna in basal solution for 22 hours

Day 4

0–24 h	Ifosfamide*/Mesna	Ifo/Mesna in basal solution for 24 hours
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Day 5

0–2 h	Etoposide	100 mg/m ² i.v. for 2 hours in saline solution 400 ml/m²
2–24 h	Ifosfamide*/Mesna	Ifo/Mesna in basal solution for 22 hours

Eto²Ifo² courses are started if:

neutrophil count >1.0 × 10⁹/l platelet count >100 × 10⁹/l,
kidney function, expressed as serum creatinine, and creatinine clearance or GFR are within normal range.
(creatinine clearance or GFR >60 ml/min/1.73)

In case of low blood counts, recheck every other day.

- Prehydration and alkalization: Infuse 500 ml/m² over a 2-hour period.
- Dose:* The dose of Ifosfamide is 1 800 mg/m²/21–24 hours and the dose of Mesna is also 1 800 mg/m²/21–24 hours, each for 5 consecutive days, giving a total dose of both Ifosfamide and Mesna of 9 000 mg/m²/5 days each.
- Ifosfamide*/Mesna infusion:* Ifosfamide and Mesna are infused i.v. in 2 000 ml/m²/24 hours of basal solution. *Can be given in two hours infusion according to local hospital routine.

- d. *PostIfosfamide alkalinization and Mesna administration:* Following the Ifosfamide/Mesna infusion on day 5: give Mesna 750 mg/m² in 1 000/ ml/m² basal solution in 8 hours. Alternatively, give Mesna 250 mg/m² i.v. and NaHCO₃, 500 or 1 000 mg orally 4 and 8 hours after the Ifosfamide-Mesna infusion.
- e. *Diuresis:* If <400 ml/m² in 6 hours, give furosemide 0.5–1.0 mg/kg. The maximum dose of furosemide is 20 mg. Check for hematuria every 24 hours. If ++ or more for blood, Ifosfamide should be withheld and normal saline should be infused i.v., until the urine clears. The Ifosfamide infusion should then be started again.

NOTE: Uristix may be falsely negative or positive during treatment with Ifosfamide.

- f. *Additional alkalinization:* If urine pH <7 or venous acid/base indicates metabolic acidosis (serum bicarbonate <21 mmol/l), give 2 mmol NaHCO₃/kg intravenously for 30 minutes.
- g. *Treatment and prophylaxis of Ifosfamide-induced CNS toxicity:* The cause of Ifosfamide-induced acute encephalopathy is unknown. It may be dose-dependent and aggravated by metabolic acidosis. The condition is reversible. The commonest symptom of mild CNS toxicity is undue somnolence, which usually does not require specific measures other than to keep the serum bicarbonate levels >21 mmol/l. The Ifosfamide infusion should not be interrupted. *Severe encephalopathy* is recognized by disorientation, visual and cognitive disturbances, undue fear, nightmares, hallucinations or even convulsions. The symptoms usually start insidiously and slowly increase. The Ifosfamide infusion should be stopped and treatment instituted with methylene blue 50 mg i. v. every 8 hours (in children below 25 kg of body weight, the dose is reduced to 25 mg every 8 hours). The symptoms generally disappear quickly and 2–3 methylene blue infusions usually suffice. This Ifo course should not be restarted.

In subsequent Ifo courses, prophylactic treatment with oral methylene blue 50 mg 3 × daily should be given when starting Ifosfamide. This will usually prevent further CNS toxicity, as noted in patients at the Norwegian Radium Hospital and at Sahlgrenska Hospital, Gothenburg.

Methylene blue is a non-toxic agent. Its exact mechanism of action in this context is not precisely known.

NOTE: Methylene blue is not routinely available in hospital pharmacies and must be purchased in advance in institutions giving Ifo treatment!

Uristix for hematuria is repeated every 24 hours.

In case of low blood counts, recheck every other days.

In case of severe signs or symptoms of Vincristine-induced neuropathy, Vincristine is omitted.

After an Ifosfamide cumulative dose of 45 000 mg/ m² additional investigations are required to assess the tubular function before administration of each Eto/Ifo cycle: Urinary α1 microglobulin/Urinary creatinine, tubular reabsorption of phosphate, fractional excretion of glucose, and GFR.

If uristix is positive or macroscopic hematuria appears during the chemotherapy cycle the 24-hour dose of Mesna must be doubled and administered in continuous infusion in glucose 5% 2 000 ml/m²/ 24 hours to be continued for 48 hours after the appearance of hematuria. Check with echography and urine culture. Suspend Ifosfamide infusion.

Should hematuria reappear during the following cycle, contact the protocol coordinator.

In case of disorientation, visual and cognitive disturbances, undue fear, nightmares, hallucinations or even convulsions, the Ifosfamide infusion should be stopped and treatment instituted with methylene blue 50 mg i.v. every 8 hours (in children below 25 kg of body weight, the dose is reduced to 25 mg). Check the serum bicarbonate: in case of serum bicarbonate <21 mmol/l, give 2 mEq NaCO₃/kg

intravenously during 30 minutes. In subsequent Ifosfamide courses, prophylactic treatment with oral methylene blue 50 mg x 3 daily should be given when starting Ifosfamide.

In case of mild CNS toxicity, usually somnolence, the Ifosfamide infusion should not be interrupted. Check the serum bicarbonate level: in case of serum bicarbonate <21 mmol/l, give 2 mEq NaCO₃/kg intravenously for 30 minutes

5. High-dose chemotherapy and peripheral stem cell transplantation

This combination is given to all patients on week 25.

Day	Time	Drug
-7		Sodium Valproate: 12 hours before the first dose of Busulfan until day -3. First dose 20 mg/kg and subsequent doses 10 mg/kg × 2/day Allopurinol 300 mg/m ² /day p.o. divided into 4 doses days -8 to -1
-7		Granisetron to day -1
-6	0	Hydration: 5% glucose + 40 mmol/l NaHCO ₃ + 20 mmol KCl/l 2 000 ml/ m ² /day during HDCT (-7 to 0)
-6	0-6-12-18h	Busulfan 1 mg/kg × 4 times daily p.o.
-5	0-6-12-18h	Busulfan 1 mg/kg × 4 times daily p.o.
-4	0-6-12-18h	Busulfan 1 mg/kg × 4 times daily p.o.
-6	0-6-12-18h	Busulfan 1 mg/kg × 4 times daily p.o.
-2		Melphalan 140 mg/ m ² i.v. infusion during 1 hour Furosemide 1 mg/kg i.v. push 1 hour after Melphalan
-1		Rest
0	45 minutes before re-infusion	6-Methylprednisolone: 1 mg/kg i.v. in 30 minutes
0	15 minutes before re-infusion	Chlor pheniramine: 0.2 mg/kg i.v. push
0		Reinfusion of PBSC

NOTE: when giving Busulfan monitor the pharmacokinetics!

Premedication before reinfusion of PBSC preparation should also be done in accordance with local routines.

Minimum CD34+ required for HDCT: 2.5 × 10⁶/kg

19. GENERAL CONSIDERATIONS

Guidelines for G-CSF

The administration of G-CSF is mandatory after all 4 induction chemotherapy cycles (i.g. VAdm¹Ifo¹, C¹Eto¹, VAdm¹Ifo¹, C¹Eto¹), starting 48 hours after end of chemotherapy up to a number of $2.0 \times 10^9/l$ neutrophils. It takes usually 6–8 days.

If G-CSF is given during the maintenance chemotherapy period after VAdm²Ifo², Eto²Ifo², VAdm²C² cycles, because of neutropenic fever, it must be discontinued at least 24 hours before starting the next course of chemotherapy and it should be stopped if the total white blood count exceeds $10.0 \times 10^9/l$.

It is administered as a subcutaneous injection once daily. The dose for children is 5 µg/kg. Adults are given 300 µg, if the body weight is <80 kg, and 480 µg, if the body weight is >80 kg.

The administration of G-CSF is mandatory when the previous course is followed by white blood count $<1.0 \times 10^9/l$ or neutropenic fever (temp. >38.5 °C and neutrophil count $<0.5 \times 10^9/l$).

After C¹Eto¹ G-CSF must be given in a higher dose because of the following PBSC harvest. The dose for children should be 10 µg/kg body weight. For adults should be given 600 µg if the body weight is <80 kg and 900 µg if the body weight is >80 kg.

SSG institutions is obliged to use "Neupogen Amgen/Roche".

Indications for red blood cell and platelet transfusions

The decision to give red blood cell and platelet transfusions is left to the center that is treating the patient.

As a general guideline, transfusion is recommended when the values of the red blood cells are Hemoglobin <80g/L.

Platelet transfusion is indicated when petechiae or signs of bleeding are present whatever the platelet count. If petechiae or bleeding is not present, platelet transfusion is recommended when the values are $<10.0 \times 10^9/L$.

Antiemetic therapy

Is left to local experience.

Local surgical treatment of the disease

Surgery should be planned for beginning of week 11, with neutrophil values of $>1\ 000/mm^3$ and platelets $>100\ 000/mm^3$.

If surgery is not feasible, radiation therapy should be started at the beginning of week 11.

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Appendix 1

NOTE: Follow-up after treatment. Patients should be followed at 3-month intervals for 3 years, at 4-month intervals during the 4th and 5th years, and then at 6-month intervals until 10 years after treatment.

EWS family tumors ISG/SSG IV

INVESTIGATION AND FOLLOW-UP FLOW-SHEET

	Pre-treatment	Pre-surgery	End of treatment	Every follow-up	Other (see comments)	Comments
Physical examination	X	X	X	X		
Std. blood sample ¹	X	X	X	X		
S-creatinine	X	X	X	X		
GFR	X	X	X		X	
Hepatitis serology	X		X			
X-rays of involved bone	X	X		X		
CT and MRI of involved bone	X	X	X			↑ and in inoperable patients before radiotherapy for tumor's radiological response
Chest X-ray	X	X	X	X		
CT of chest	X	X	X	X		
Spirometry	X		X		(X)	(at 6 month and then every 3 years after treatment)
Bone scan	X	(X)	(X)		X	If bone metastases are suspected
ECG	X	X	(X)		(X)	(every 3 years after treatment)
Cardiac ultrasound/LVEF ²	X		X		X	at 3 months, 6 months and then every 3 years after treatment
Bone marrow biopsy and -aspiration	X					
Sperm count	(X)		(X)		(X)	(3 years after treatment)

X = mandatory, (X) = recommended

1. Includes: Hemoglobin, white blood counts with differential, thrombocytes, creatinine, ALP, LDH, total bilirubin, transaminases, Na, K, Mg

2. Left ventricular ejection fraction

Appendix 2

METHOD OF DETERMINE TUMOR VOLUME

Tumor volume is determined on CT scan, by evaluating the 3 maximum tumor diameters and globally calculating the tumor component in the soft tissues and bone.

It is of utmost importance that tumor dimensions be measured during CT scan, because this reduces the possibility of error. Furthermore, the axial diffusion of the tumor i.e. the extreme proximal and distal ends, is visible in these projections. Tumors can be evaluated as ellipsoid or cylindrical.

The following tumors should be calculated as an ellipsoid:

- tumors with a visible soft tissue component (>0.5 cm/side)
- extremity tumors involving a condyle

Three maximum tumor diameters are measured: height (a), width (b), and depth (c). The volume is calculated by the following formulas:

Formula 1

$$V = 4/3 \pi \times a/2 \times b/2 \times c/2$$

$$V = a \times b \times c \times 0.52$$

In cylindrical or diaphyseal tumors with or without (<0.5 cm/side) considerable involvement of the soft tissues, a modified formula for cylindrical volume is used instead:

Formula 2

$$V = 2 \pi \times a/2 \times b/2 \times c/2$$

$$V = a \times b \times c \times 0.785$$

a, b, c, are the maximum diameters for height (a), width (b) and depth (c).

In unclear cases (soft tissue component about 0.5 cm/side, formula 2, is used to calculate the volume.

Appendix 3

EVALUATION OF RADIOLOGICAL RESPONSE

Background

Systemic neo-adjuvant chemotherapy has dramatically increased the survival rate of patients with Ewing's sarcoma. Response to induction chemotherapy is one of the most reliable predictors of outcome.

Histopathological examination of the entire specimen should be done in all patients in whom a wide tumor resection has become possible after induction chemotherapy. In cases showing a poor histological response, assessed by the amount of necrosis and remaining viable-appearing tumor, postoperative chemotherapy must be intensified. When tumors are found in a skeletal location, where wide resection is impossible, radiation therapy is given. Since no surgical specimen is available for histopathological examination, the response can only be evaluated by imaging alone.

Better imaging methods are needed to detect patients with a poor prognosis so that more adequate additional treatment can be given. Radiographic changes during initial chemotherapy loosely correlation with histological grades, but CT is of value in following evolution of the tumor. However, neither method safely predicts the response. MRI is generally accepted as the best imaging method to monitor the effect of chemotherapy, but the findings are nonspecific. Thus high SI areas on T2-weighted images may reflect solid viable tumor, complete necrosis, loose vascular tissue or predominantly necrotic areas containing scattered residual tumor cells. Dynamic contrast-enhanced MRI may help to detect the most viable parts of the tumor, but the results are not uniform with different magnet strengths and imaging parameters, and differentiation between responsive and non-responsive tumors is unreliable.

Our objective was to find a parameter predictive of outcome and simple enough to be reproducible in a multicenter setting, yet reliable enough to serve as a basis for risk stratification, allowing intensified maintenance chemotherapy for patients with a poorer prognosis.

The presence and size of a soft tissue component on CT and/or MR images was chosen as the principal factor of interest. In a joint ISG/SSG study, the pre- and postchemotherapy images in 16 Norwegian and 47 Italian Ewing's sarcoma patients were reviewed. In the years 1985–1996, all patients were treated in accordance with protocols in use at the time and had surgery as local treatment. 55 patients had a soft tissue mass at diagnosis and were included in the study. Total disappearance or complete ossification of the soft tissue component was considered a good radiological response, while a persistent soft tissue mass, whatever the size, was considered a poor one. The radiological response was correlated with the histological response and survival.

22 patients (40%) had a good radiological response and 28 patients (51%) had a good histological one. 18 patients (33%) had a good radiological and histological response and they have all remained continuously disease-free. 23 patients (42%) showed a poor response both radiologically and histologically and 17 of them died. Total concordance of the radiological/histological response was 41 of 55 (75%). 10 patients with a poor radiological response had a good histological response (18%), 4 of them died. 4 patients with a good radiological response had a poor histological response (7%), 1 of them is dead. Interestingly, a good radiological response predicted the outcome in 3 of these 4 patients. In total, 21 of the 22 patients with a good radiological response (95%) are alive without disease, as opposed to 12 of the 33 patients with a poor radiological response (36%). 24 of the 28 patients with a good histological response are alive (86%), 9 of the 27 patients with a poor histological response (33%). The 8 additional patients who were excluded because they had only intraosseous tumors are all alive without disease, supporting the hypothesis that the presence of a soft tissue component is a predictor of outcome.

Method for evaluating the radiological response

On the basis of the above results, the Protocol Committee of ISG/SSG III decided to include this criterion (complete disappearance or complete ossification of the soft tissue component during induction chemotherapy) for selecting the subsequent chemotherapy of patients to be given radiotherapy as definitive local treatment. Patients with a persistent soft tissue mass are considered poor responders who should receive high-dose treatment with stem cell support.

CT and/or MR images should be obtained before starting chemotherapy and after induction chemotherapy. MRI provides better soft tissue contrast and should be preferred. CT requires contrast-enhanced images with a soft tissue window setting. It is essential to have comparable images with identical imaging planes. The prechemotherapy images should be available for the radiologist who performs the control examination, to ensure conformity. The following measurements of soft tissue tumor should be made: maximum tumor length or craniocaudal extension (coronal or sagittal MR or calculation of transverse CT-images) and two perpendicular diameters in the transverse plane (if the soft tissue component completely encircles the bone, this measurement includes the bone). Finally, the maximum extramedullary tumor thickness should be measured perpendicular to the bone at the point where the soft tissue mass is most prominent.

MRI. Soft tissue tumor will appear as tissue with low T1-signal comparable to muscle, medium to high T2-signal, and enhancement after i.v. gadolinium injection. Tumor may push the surrounding muscles away from the bone or invade them, but in most cases the outer contour of the tumor is relatively smooth. This helps to distinguish tumor from edema, which is usually more diffuse and leaves intact fat planes evident on T1-weighted, non-enhanced transverse images. The T2-signal of edema tends to be higher than the signal of tumor tissue, especially with fast spin echo techniques.

Complete disappearance of the soft tissue component means no remaining abnormal solid soft tissue outside the cortex.

Complete ossification means incorporation of the former soft tissue tumor into the pre-existing cortex, with a signal identical to cortical bone, or a complete bony outer shell surrounding tissue with a signal identical to fatty marrow (high SI -T1-T2, loss of signal with fat suppression techniques such as STIR).

CT. Soft tissue tumor has attenuation values close to normal muscle and enhances with iodinated contrast medium.

Complete disappearance means no remaining contrast-enhancing solid tissue outside the cortex.

Complete ossification means incorporation of the former soft tissue into the preexisting cortex, or a complete neocortex surrounding tissue with attenuation as fat. If the distinction between fatty marrow and other soft tissue is uncertain, MR must be performed or else persistent soft tissue tumor cannot be excluded.

Appendix 4

GUIDELINES FOR MORPHOLOGY

Diagnosis

Biopsy method. The best material for diagnosis is obtained from open surgical, needle core or fine-needle aspiration biopsy (FNA). Needle biopsy may be used on the soft tissue component of the tumor, but should be avoided in the intraosseous part of tumors. Fresh operative specimens should be sent immediately to the Department of Pathology. *Fresh tumor tissue* should be saved for ancillary diagnostic investigations, such as electron microscopic examination and genetic analyses (karyotyping, FISH and/or RT-PCR). Imprints (touch preparations) from surgical or coarse biopsies should also be made for cytological examination.

Diagnosis. The diagnosis (cytological or histopathological) should be based on the examination of routinely stained material (FNA or histological sections + imprint) supplemented by ancillary diagnostic methods. Imprints and FNAs shall be stained with Hematoxylin and Eosin (H&E) or Papanicolaou (Pap) and May-Grünwald-Giemsa (MGG). MGG allows detailed study of cytoplasmic features but H&E or Pap are better for the examination of nuclear structures.

Ancillary diagnostics. Immunohistochemistry. The following antibodies are the minimum required: CD99 (MIC² antigen; note that a positive staining reaction has been reported in synovial sarcoma, myelosarcoma, precursor lymphoma, Burkitt's lymphoma, alveolar rhabdomyosarcoma and thymocytes in thymoma), Vimentin, Desmin, CD45 (leucocyte common antigen), NSE, Neurofilament, Chromogranin, Synaptophysin, S-100 protein. Pan B-cell antibodies, pan T-cell antibodies. Tdt (terminal deoxynucleotidyl transferase) and MPO (myeloperoxidase) in tumors suspected of precursor lymphoma, Burkitt's lymphoma and myelosarcoma.

Electron microscopy. A small sample is immediately fixed in 2% glutaraldehyde. If electron microscopic examination is not routinely performed at the local pathology department, the sample should be sent to another department with that facility.

Cytogenetic analyses. Tissue sample (and fine-needle aspirate) may be used. Samples should be sent to a genetic laboratory (see Analysis of Genetic Changes in Musculoskeletal Tumors, 2nd edition, Lund 1997, pp. 1–22).

The final diagnosis. This diagnosis can be based on examination of routinely stained material + the following combinations:

- a. Cytogenetic analysis [t(11;22)] + electron microscopic examination
- b. Electron microscopic examination + immunohistochemical CD99 positivity
- c. Immunohistochemical examinations, using the entire antibody panel outlined above.

Since the tumor may be partly necrotic and an ancillary method may fail, it is important to save material, as indicated above.

These guidelines are based on our experience in the reevaluation of SSG IV and IX and on the following articles:

Llombart-Bosch A, et al. Histology, immunohistochemistry, and electron microscopy of small round cell tumors of bone. *Diagnostic Pathology*, 1996; 13: 153–170.

Meis-Kindblom J M, et al. Differential diagnosis of small round cell tumors. *Seminars in Diagnostic Pathology*, 1996; 13: 213–241.

Two independent pathologists/cytologists with experience of diagnosing Ewing's family tumors should confirm the findings in every case.

Macroscopic evaluation of the surgical specimen.

Macroscopic examination. Ideally the surgeon and the pathologist should examine the specimen together or at least discuss the problems that may arise regarding orientation of the specimen and resection margins. Copies of radiographic studies and drawings should be submitted with the specimen, whenever possible. The size of the tumor is measured in three dimensions. The closest margin of resection should be measured and the type of tissue recorded. Photographic documentation of all tumors is recommended.

Histopathological examination. At least as many sections as the largest tumor dimension should be examined, e.g., no less than 6 sections of a 6 cm tumor should be taken. Experience shows that the following sites are especially important to inspect:

1. Areas of hemorrhage
2. Subperiosteal reactive new bone areas
3. The medullary canal
4. The soft tissue extension of the tumor

In the reevaluation of SSG IX it was found that the intraosseous part of the tumor may be totally necrotic (Grade III Picci), while the soft tissue extension may show viable tumor corresponding to Grade I Picci. It is thus important to have thorough sampling and documentation of the response grading in various sites of the specimen. A schematic drawing is very valuable.

Guidelines for histological response grading of Ewing's family tumors

Based on the findings from Rizzoli and a reevaluation of Ewing's sarcoma protocol SSG IX, it is strongly recommended that the histological response grading after multidrug chemotherapy be based on the grading system proposed by P. Picci and coworkers instead of on the Huvos grading system. In our experience the Picci system is more informative and easier to use. Moreover, all institutions in a collaborative study should employ the same grading system.

The Picci 3-grade system is based on microscopic evaluation of the amount of remaining viable tumor after chemotherapy.

Picci grading system

Grade I The chemotherapy response when the surgical specimen contains at least one "macroscopic" nodule of viable tumor. A "macroscopic" nodule is defined as an individual nodule larger than one 10X objective magnification field or scattered nodules that individually are smaller than one 10X field, but the total areas of these nodules exceed one 10X field (Fig. 1).

Grade II The chemotherapy response when the surgical specimen contains **viable** tumor; the summation of all areas is less than one 10x field (Fig. 2).

Grade III The chemotherapy response when **no viable** tumor can be identified in the surgical specimen (Fig. 3).

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TUMOR RESPONSE GRADE

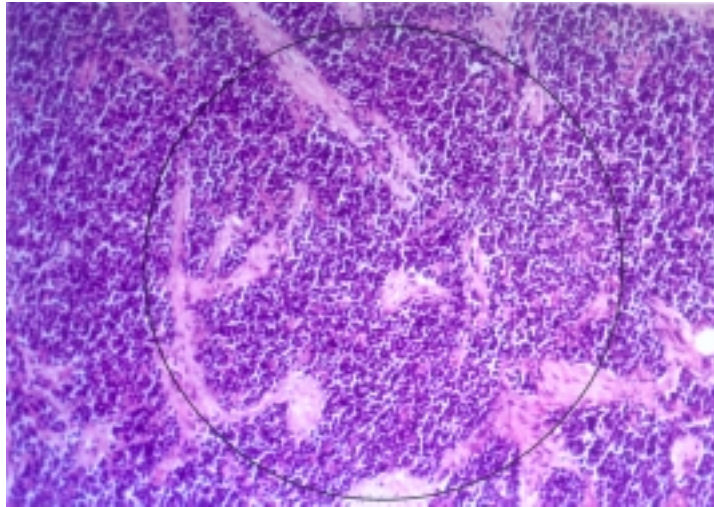


Fig. 1

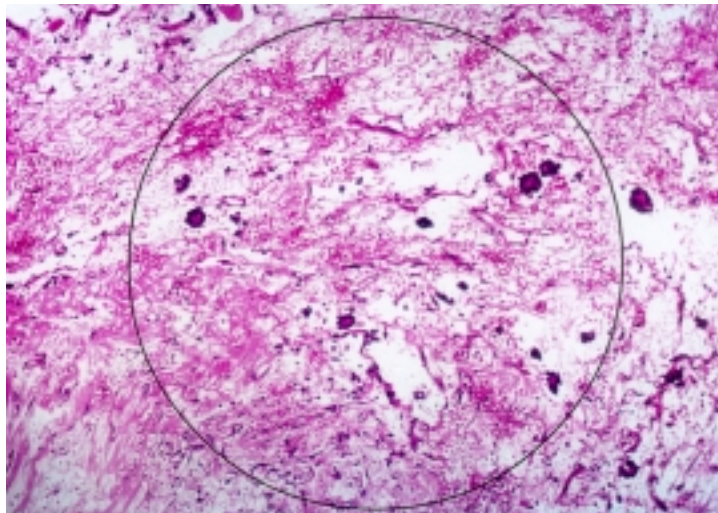


Fig. 2

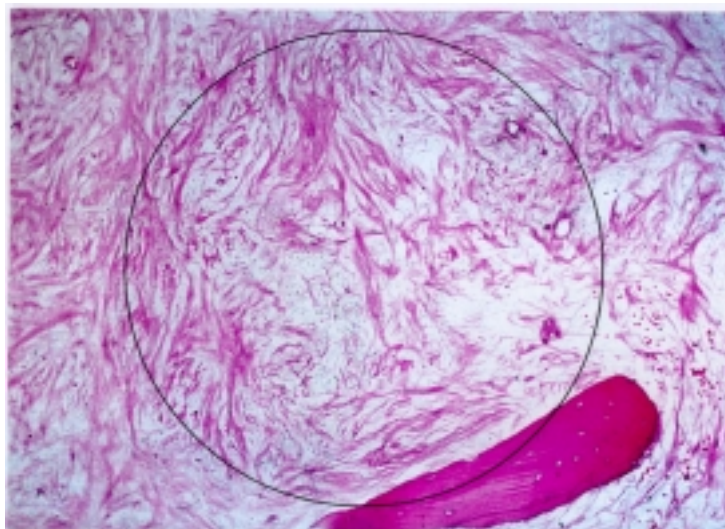


Fig. 3

Appendix 5

GUIDELINES FOR ORTHOPEDIC SURGERY

Biopsy

All bioptic procedures (incisional biopsy, needle biopsy, and fine-needle aspiration) are accepted, provided that adequate material is collected for diagnosis and additional cytological and biological investigations.

Incisional biopsy. The incision must be small, longitudinal and excisable during final surgery. To avoid dissemination of tumor cells, the bioptic tract must pass through muscular fibers. Avoid contamination of nerves and blood vessels and muscle interstices. After tissue sampling, close the tumor pseudocapsula and fascia without drainage.

Needle biopsy. The advantages of this method are that it is less traumatizing and it significantly reduces the risk of bleeding and dissemination of tumor cells. The disadvantages are the paucity of material obtained and the difficulty of performing the biopsy in representative areas. CT-guided needle biopsies can be done to visualize the area where the needle should enter. Tru-cut biopsy is of limited value. It can be performed for localized lesions in easily accessible anatomic sites, when there is no risk of harming nerves and blood vessels.

Fine-needle aspiration biopsy. This procedure should be done only in centers with adequate expertise for both the diagnosis and the cytological investigations required by this protocol.

Surgery

Surgical treatment, performed within 2–3 weeks after preoperative chemotherapy, is indicated when the lesion can be removed with adequate margins.

A local excision can be done in the following sites:

1. Bones that do not require reconstruction after resection (clavicle, rib, scapula, some parts of the pelvis (iliac wing, anterior pelvic arch), distal sacrum, proximal radius, distal ulna, and fibula)
2. Pelvis and long bones that require reconstruction (humerus, distal radius, proximal ulna, femur, and tibia).

The following reconstruction techniques may be used: special HMRS (Howmedica Modular Resection System) prostheses for the upper and lower limbs and MRS (Modular Rotatory Shoulder), IOR for the upper limb; custom-made prostheses; metatarsal pro-metacarpal, radius pro-ulna; plate plus cement; Küntscher rod plus cement; Küntscher rod plus grafts-arthrodesis, massive grafts osteoarticular, diaphyseal, composite grafts vascularized fibula, rotation plasty.

Ablative surgery can be performed in the following cases:

1. When the functional deficit caused by radiation therapy would be greater than that after amputation (children under 8 years of age whose lesion involves a major growth cartilage and where radiation would cause a severe limb length discrepancy)
2. In patients with a pathologic fracture

Rotation plasty can be done in patients under 10 years of age with lesions of the proximal and distal femur.

Evaluation of surgical margin

Enneking's method should be used to describe the surgical margin:

1. Intralesional margin: the tumor is opened or transected during surgery
2. Marginal margin: the closest margin is outside the tumor, but near the tumor and through the reactive zone
3. Wide margin: there is a cuff of healthy tissue surrounds the specimen, covering the reactive zone around the tumor
4. Radical margin: the whole tumor-bearing compartment is removed.

Appendix 6

GUIDELINES FOR THE RESECTION OF METASTASES

In patients with *lung metastases at diagnosis*, surgical removal of the primary tumor and the metastases should preferably be performed at the same time, i.e., in the same surgical session with the orthopedic procedure preceding unilateral thoracotomy, bilateral thoracotomy, or sternotomy. The Rizzoli Institute has considerable experience in performing such contemporary procedures, and has not reported any unacceptable complications. However, the policies of individual institutions may differ and removal of the primary tumor and the metastases in the same surgical session may not be feasible in all centers.

Thus, the minimum requirement is that *all surgery should be performed in two weeks*. Chemotherapy should preferably be resumed within 10–14 days of the last surgical procedure.

Surgical methods

For lung surgery, the choice of sternotomy or lateral thoracotomy is left to the thoracic surgeon. It should be stressed that in the case of unilateral metastases on CT scan, it is recommended that the contralateral side also be explored surgically, since occult metastases have been reported in up to 30% of the patients. Both lungs should preferably be explored at the same time, but no later than within one week. In cases where lung metastases go into complete remission on CT scan during preoperative chemotherapy, surgical exploration of the lung should nevertheless be performed because foci of viable tumor may still be found and removed.

When operable and curative treatment is feasible, *extrapulmonary (usually skeletal) metastases* should be removed with a wide margin, although a marginal procedure may also be acceptable.

It is not possible to define the exact criteria for when curative treatment or palliative treatment should be given. This evaluation largely depends on the resectability of the metastatic lesions or, in some cases, the possibility of reclassification as to resectability, following a good chemotherapy effect.

Contact the Resource Group if in doubt.

Appendix 7**GUIDELINES FOR RADIOTHERAPY**

(See treatment flow-sheet pp. 11–13)

Radiobiological aspects

Radiotherapy in this protocol will be given in an hyperfractionated-accelerated schedule in order to shorten treatment time, to facilitate the superimposition of chemotherapy and radiotherapy, and in the attempt to reduce long-term sequelae while maintaining the same therapeutic effect as compared with conventional fractionation. The appropriate total and single fraction doses to be given with an hyperfractionated-accelerated regimen were calculated according to the linearquadratic equation as modified by Dale (1) that take into account for the timedependent tumor repopulation factor. The extrapolated response dose (ERD) for tumor (ERD T) and late effect (ERD L) were calculated with an alfa/beta ratio equal to 10 Gy for tumor and equal to 3 Gy for late sequelae. In the following table, the ERD T and ERD LE of a conventional fractionation schedule at standard dose level are compared with those of the selected hyperfractionated–accelerated regimen:

	ERD T	ERD LE
1.8 Gy/day = 50.4 Gy	36.0	80.6
1.8 Gy/day = 59.4 Gy	42.4	95.0
1.5 Gy × 2 days = 42 Gy	36.9	63.0
1.5 Gy × 2 days = 54 Gy	47.0	81.0

With the hyperfractionated-accelerated regimen at the selected total dose levels (42 Gy and 54 Gy) there should be a potential therapeutic advantage in terms of reduction of frequency of late effects between 15% and 20% as compared with the conventional one, while the therapeutic efficacy in terms of tumor control should be equal or slightly increased.

General guidelines

The radiotherapist/oncologist should participate in the initial planning of treatment of each new patient with Ewing's family tumor. The radiotherapist/oncologist is on the team that decides about local treatment in the referral centers.

These guidelines should be followed meticulously in cases of nonmetastatic Ewing's family tumors.

Radiotherapy is indicated:

1. After marginal surgery showing viable tumor in the surgical specimen, Picci tumor response grades I and II
2. After intralesional surgery
3. In nonoperable Ewing's sarcoma
4. For metastatic lesions

Radiotherapy is not indicated after a radical or wide operation, or a marginal resection, if the surgical specimen shows no viable tumor cells, Picci tumor response grade III.

Target volume. Radiation dose and technique

The target absorbed dose is specified in the center of the tumor volume, if present, or else at a point considered to best represent the entire target volume. Such a point is usually found at the intersection of central axes of beams, or midway between the entrance points on the central axes of two opposing beams (5). The location of the specification point should be clearly stated. The target volume refers to the TC/MR, carried out at the time of diagnosis. The treatment fields are reduced when a total dose of 42 Gy has been given.

The variation of the dose within the target volume should be kept to a minimum and preferably not exceed $\pm 5\%$ of the dose at the specification point (= target-absorbed dose). *The treatment is given in an accelerated hyperfractionated fashion, with two daily fractions of 1.5 Gy each, at an interval of no less than 6 hours.* Radiotherapy is started on the 6 day after VAdmC and CEto. This is most practically achieved by starting chemotherapy on a Monday. Radiotherapy is given between chemotherapy phases. Chemotherapy should proceed according to the schedule, without extra pauses for radiotherapy, unless excessive toxicity is seen. Radiotherapy is given in one course. It is continued to a total dose of 42 or 54 Gy depending on how radical the surgery is and the pathologic findings of the surgical specimen.

Total dose according to tumor response and/or surgical margin

1. Pre- and postoperative chemotherapy (local treatment – surgery alone) with wide or radical surgical margin

2. Pre- and postoperative chemotherapy combined with postoperative radiotherapy

2.1 *Histological good responders*: Histological grade II with marginal or intralesional margin with histological grade III.

Postoperative radiotherapy in weeks 14–17; total radiation dose 42 Gy, 1.5 Gy twice daily, 5 days a week/28 fractions

2.2 *Histological poor responders*: Histological grade I with marginal or intralesional margin

Maintenance: Postoperative radiotherapy in weeks 18–21; total radiation dose 42 Gy with a boost of 12 Gy in case of micro-macroscopical residual disease, 1.5 Gy twice daily, 5 days a week/28 or 36 fractions. (These patients also receive highdose chemotherapy!)

3. Chemotherapy combined with radiotherapy (without surgery)

3.1 *Radiological good responders*: Radiological complete disappearance of soft tissue mass and ossification

Induction: No radiotherapy

Maintenance: Postinduction chemotherapy radiotherapy in weeks 13–16; total radiation dose 54 Gy, 1.5 Gy twice daily, 5 days a week/36 fractions

3.2 *Radiological poor responders*: Radiological incomplete disappearance of soft tissue mass and ossification

Induction: No radiotherapy

Maintenance: Postinduction chemotherapy radiotherapy in weeks 17–20; total radiation dose 54 Gy, 1.5 Gy twice daily, 5 days a week/36 fractions

Target volume (see 2.1, 2.2, 3.1, 3.2 above)

Target volume I: Clinically and radiographically evident tumor at start of radiotherapy, with a margin of 2 cm

Target volume II: The original tumor volume has at least 2–5 cm of margin, with the following exceptions:

- if the tumor is adjacent to the epiphysis, the opposite epiphysis must not be included
- if the tumor is in the middle of the bone, both epiphyses must be excluded

Dose, target I 54 Gy/36 fractions

Dose, target II 42 Gy/28 fractions

If a Ewing's family tumor is located in the spine, the medulla spinalis is included in the treatment volume.

The target volume includes manifest tumor, with a margin of two vertebrae above and below this.
Dose: 42 Gy/28 fractions

Technique

Treatment should be given with high-energy radiation, photons or electrons. Planning of the individual dose is recommended to optimize treatment using, for example, multiple beams with secondary field-shaping, individual filters, wedges, etc. Computerizing the planning, using a map of isodose distribution on at least 3 slices is required: one central (reference plane) and two between the central and peripheral planes.

Precise of the positioning patient during treatment may require the use of immobilization devices. Whenever possible, some portion of the circumference of an extremity should be excluded from the treatment volume, to reduce the risk of peripheral edema.

Radiation therapy for bone metastasis

A bone metastasis if not surgically removed, is treated at the same time as the primary tumor with 2 cm margin, using the same modality as in treatment of the primary lesion, up to 54 Gy. If a bone metastasis is surgically removed, radiotherapy guidelines (indications, total dose, fractionation, target volume) are the same as for the primary lesion.

Lung irradiation

Radiotherapy of the lung must be done after complete recovery from the toxicity of high-dose chemotherapy, about 60 days after the high-dose Busulfan-Mephalan treatment. Patients in complete remission will receive a total dose of 15 Gy, divided in 10 daily fractions of 1.5 Gy.

Radiotherapy for lung metastasis(es) has to be performed 60–90 after the high-dose treatment. In patients with persistent lung nodules, supplemental lung surgery can be considered. Lung metastasis(es) not in complete remission can be given up to 25.2 Gy \times 14 once daily fraction, if the treatment volume is smaller than 25% of the total lung volume.

Spirometry must be done before Busulfan treatment, before total lung irradiation and thereafter every 6 months for the first 3 years, and then yearly.

References

1. Dale R.G.: Time-dependant tumor repopulation factors in linear – quadratic equations. Implications for treatment strategies. *Radiotherapy and Oncology* 1989; 15: 371–82.
2. Dunst J., Jurgens H., Sauer R., Pape R., Paulussen M., Winkelmann W., Rube C: Radiation therapy in Ewing's sarcoma: an update of the CESS 86 trial. *Int J Radiation Oncology Biol Phys* 1995; 32(4): 919–30.
3. Turesson I, Thames H D. Repair capacity and kinetics of human skin during fractionated radiotherapy: erythema, desquamation, and teleangiectasia after 3 and 4 years' follow-up. *Radiotherapy and Oncology* 1989; 15: 169–88.
4. Turesson I, Notter G. Accelerated versus conventional fractionation. The degree of incomplete repair in human skin with a four-hour fraction interval studied after postmastectomy irradiation. *Acta Oncologica* 1988; 27: 169–79.
5. ICRU report 50. International commission on radiation units and measurements. Washington 1993.
All radiotherapists who give radiotherapy to patients with Ewing's sarcoma are advised to study the following article:
6. Cassady J R. Ewing's sarcoma – the place of radiation therapy. In Jaffe N (ed): *Bone tumors in children*. Littleton, MA, PSG, publisher, 1979.

Appendix 8

SUBMISSION OF FORMS

FORM	CONTENTS	REPORTING
Institution's commitment Form 1		Completed by responsible principal investigator
Registration Form 2	Patient data, date of biopsy, localization of tumor, date when chemotherapy was started	Completed by pediatrician or oncologist
Pathology report I Form 3	Primary diagnostic procedure	Completed by pathologist
On-study Form 4	Patient data, primary tumor status, type of surgery	Completed by pediatrician or oncologist, at latest 4 weeks after surgery
Pathology report II Form 5	Final diagnosis, response of primary tumor and metastatic disease	Completed by pathologists
Chemotherapy flow-sheet Form 6A Form 6B	Details about each preoperative or preradiation therapy cycle, patient data, date, dose of chemotherapy and toxicity data	Completed by pediatrician or oncologist
Chemotherapy flow-sheet Form 7A Form 7B	Details about postoperative or postradiation chemotherapy and toxicity data	Completed by pediatrician or oncologist
Chemotherapy flow-sheet Form 8A Form 8B	Details about high-dose chemotherapy with Busulfan, Melphalan with PBSC rescue and toxicity data	Completed by pediatrician or oncologist
Radiotherapy flow-sheet Form 9	Details about radiotherapy	Completed by radiotherapist
Follow-up Form 10	Clinical evaluation of patients from time of diagnosis	Completed by examining physician at each follow-up visit

NOTE: The following forms are sent to the SSG secretariat:

- I. Forms 1, 2 and 3 together with anteroposterior and lateral X-rays of the primary tumor. Bone and histological slides of the primary tumor are sent *1 week after starting chemotherapy*.
- II. Forms 4, 5, 6A and 6B are sent *4 weeks after preoperative (or preradiotherapy) chemotherapy*.
- III. Forms 7A, 7B, are sent *4 weeks after postoperative (or postradiotherapy) chemotherapy*.
- IV. Forms 8A and 8B are sent *4 weeks after high-dose Busulfan and Melphalan*.
- V. Form 9 is sent *shortly after radiotherapy*.
- VI. Form 10 is sent *immediately after end of treatment and each follow-up visit*.

Ewing's sarcoma family tumors ISG/SSG IV
INSTITUTION'S COMMITMENT FORM 1

Name (first & family name)
Date of birth (day, month, year)

Send to:
SSG secretariat
Regional Tumor Registry
Lund University Hospital
SE-221 85 LUND
Sweden

Department: Hospital:
City: Country:

This form is a prerequisite for patient eligibility in ISG/SSG IV and should be completed and sent to the secretariat, together with the following:

1. CT scan of the primary tumor involved bone.
2. Representative histological slides of the primary tumor.

The above named institution and department(s) commit themselves to participate in the clinical ISG/SSG IV study and will comply with the scheduled investigations, treatment and follow-up. The institution has the competence and resources to comply with the entire ISG/SSG IV protocol, including PBSC harvest and storage, and high-dose treatment with PBSC support.

Yes No

.....
day month year

.....
Name and signature of the responsible principal investigator

Ewing's sarcoma family tumors ISG/SSG IV
REGISTRATION FORM 2

Name (first & family name)
Date of birth (day, month, year)

Send this form one week after start of chemotherapy to:

SSG secretariat
Regional Tumor Registry
Lund University Hospital
SE-221 85 LUND
Sweden

Hospital and department

Date Day Month Year

Physician

- Enclosed are:**
1. CT of the primary tumor involved bone
 2. Histological representative slides of diagnostic material
 3. Institution commitment form

Date of biopsy Day Month Year

Tumor site:

Ewing's sarcoma Atypical Ewing's sarcoma PNET

Other, specify;.....

Start of chemotherapy Day Month Year

Ewing's sarcoma family tumors ISG/SSG IV
PATHOLOGY REPORT I FORM 3

Name (first & family name)
Date of birth (day, month, year)

Send to:
SSG secretariat
Regional Tumor Registry
Lund University Hospital
S-221 85 LUND
Sweden

Department: Hospital:

City: Country:

Pathologist: Sign.:

Biopsy number:

Diagnosis

Initial diagnosis, date: day month year based on:

- Open biopsy
- Core biopsy
- Fine needle aspiration biopsy

Additional methods used in diagnostics, specify:

- Ewing's sarcoma Atypical Ewing's sarcoma PNET

Other, specify.....

Ewing's sarcoma family tumors ISG/SSG IV
ON-STUDY FORM 4

Name (first & family name)
 Date of birth (day, month, year)

Submit this form to:
 SSG secretariat
 Regional Tumor Registry
 Lund University Hospital
 SE-221 85 LUND
 Sweden

Hospital and department

Physician Date Day Month Year

PATIENT DATA

Age | | | years Sex: male female

Duration of symptoms, month | | | (Time interval from first symptom to pathologic confirmation of diagnosis)

Soft tissue involvement: no yes
 Fatigue no yes Weightloss (10 % in 6 months) no yes Fever no yes

Site:

INVESTIGATIONS PRIOR TO TREATMENT

Plane x-ray: performed not performed
 CT of involved bone: performed not performed
 MRI of involved bone: performed not performed
 Bone scan: solitary lesion multiple lesions not performed
 Chest x-ray: normal prob benign prob malign not performed
 CT of lung: normal prob benign prob malign not performed
 Alkaline phosphatase | | | | specify units LDH | | | | specify units

CHEMOTHERAPY

Cycle 1 completed <input type="checkbox"/> yes <input type="checkbox"/> no Date Day Month Year	Cycle 2 completed <input type="checkbox"/> yes <input type="checkbox"/> no Date Day Month Year
Cycle 3 completed <input type="checkbox"/> yes <input type="checkbox"/> no Date Day Month Year	Cycle 4 completed <input type="checkbox"/> yes <input type="checkbox"/> no Date Day Month Year

SURGERY

Resection Amputation No surgery Date Day Month Year

TYPE OF RECONSTRUCTION

None Allograft Vascularized graft Endoprosthesis
 Other, specify;

Ewing's sarcoma family tumors ISG/SSG IV
PATHOLOGY REPORT II FORM 5

Name (first & family name)
Date of birth (day, month, year)

Final report including photograph
(Polaroid picture or slide)

Send to: SSG secretariat
Regional Tumor Registry
Lund University Hospital
S-221 85 LUND,
Sweden

Department: Hospital:

City: Country:

Pathologist: Sign.:

Number of specimen: Date:
day month year

Primary tumor

Macroscopy
Tumor localization:

Tumor size (three dimensions) : cm × cm × cm

Margins: intralesional marginal wide radical

Microscopy
Final diagnosis

Ewing's sarcoma
 Atypical Ewing's sarcoma
 PNET
 Other, specify

Chemotherapy response:
Poor response
 Grade I
Good response
 Grade II
 Grade III

Number of blocks: Whole tumor section available: Yes No

Metastatic disease

Metastase(s) localization:

Metastase(s) size: cm × cm

Margins: intralesional marginal wide

Chemotherapy response:
Poor response: Grade I Good response: Grade II Grade III

Comments:
.....

Sending institution (if not same as above):

Ewing's sarcoma family tumors ISG/SSG IV
CHEMOTHERAPY FLOW-SHEET FORM 6A

Name (first & family name)
 Date of birth (day, month, year)

Submit this form to:
 SSG secretariat
 Regional Tumor Registry
 Lund University Hospital
 SE-221 85 LUND
 Sweden

Hospital and department

Physician

Date Day Month Year

Preoperative or preradiation chemotherapy

Year: _____

Ifosfamide

Weight: _____ kg

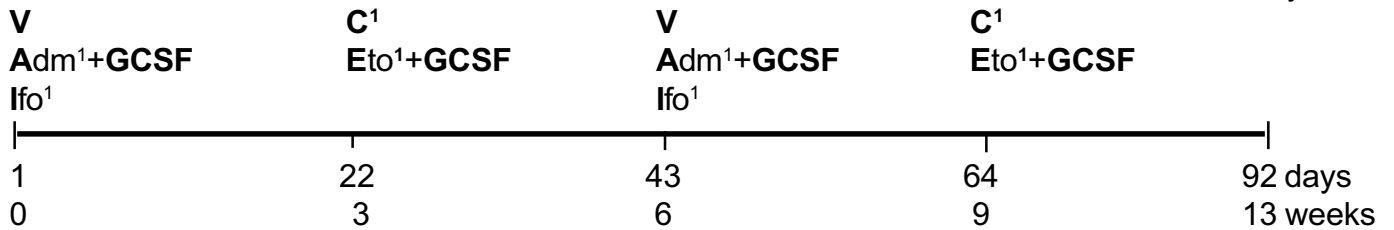
Short-time infusion no yes

Height: _____ cm

Long-time infusion no yes

Body surface: _____ m²

Start of new cycle



	Start	Nadir	Start	Nadir	Start	Nadir	Start	Nadir
Date, D/M/Y/..../....	/..../....	/..../....	/..../....	
Hb								
WBC								
Tromb								
Given doses								
V mg								
Adm¹ mg								
Ifo¹ mg								
C¹ mg								
Eto¹ mg								

V: Vincristine 2 mg/m² (max 2 mg) i.v. push.

Adm¹(in VAdm¹Ifo¹): Adriamycin (Doxorubicin) 45 mg/m²/day as 4 hours (2 days) i.v. inf.
 Total dose Doxorubicin = 90 mg/m² for 2 days

Ifo¹(in VAdm¹Ifo¹): Ifosfamide 3000 mg/m²/day in 3 days as 2,5 hours continuous i.v. infusion
 (total dose 9000 mg/m² in 3 days).

C¹ (in C¹Eto¹): Cyclophosphamide 4000 mg/m² as 3hours continuous i.v. inf.

Eto¹ (in C¹Eto¹): Etoposide 200 mg/m²/day as 2 hours (3 days) i.v. infusion
 (total of 600 mg/m² Etoposide in 3 days).

Submit this form together with Form 6A to:
 SSG secretariat
 Regional Tumor Registry
 Lund University Hospital
 SE-221 85 LUND
 Sweden

Preoperative or preradiation chemotherapy

	VAdm ¹ Ifo ¹	C ¹ Eto ¹	VAdm ¹ Ifo ¹	C ¹ Eto ¹
Date	Day/Month/Year/...../.....	Day/Month/Year/...../.....	Day/Month/Year/...../.....	Day/Month/Year/...../.....
Delay	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
Reduction	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
Transaminase*	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Creatinine*	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Stomatitis*	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Hematuria*	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Low Bicarb.	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
Fever	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
Hospitalization	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
Transfusion Erythrocyt	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
Transfusion Platelets	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
G-CSF	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
Cardiotoxicity	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no

* According to NCIC CTG Expanded common toxicity criteria

Toxicity grade	0	1	2	3	4
Transaminase	normal	≤2.5xN	2.6–5.0xN	5.1–20.0xN	>20.0xN
Creatinine	normal	<1.5xN	1.5–3.0xN	3.1–6.0xN	>6.0xN
Stomatitis	none	painless ulcers, erythema, or mild soreness	painful erythema, edema, or ulcers but can eat	painful erythema, edema, or ulcers, and cannot eat dehydration	mucosal necrosis and/or req parenteral or enteral support,
Hematuria	none	micro only	gross, no clots	gross –clots	req transfusion

Ewing's sarcoma family tumors ISG/SSG IV
CHEMOTHERAPY FLOW-SHEET FORM 7A

Name (first & family name)
 Date of birth (day, month, year)

Submit this form to:
 SSG secretariat
 Regional Tumor Registry
 Lund University Hospital
 SE-221 85 LUND
 Sweden

Hospital and department

Physician

Date Day Month Year

Postoperative or postradiation chemotherapy

Year: _____

Ifosfamide

Weight: _____ kg

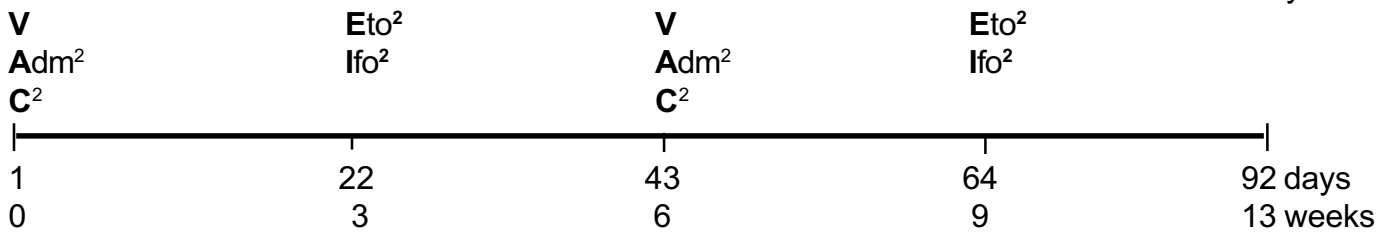
Short-time infusion no yes

Height: _____ cm

Long-time infusion no yes

Body surface: _____ m²

Start of new cycle



	Start	Nadir	Start	Nadir	Start	Nadir	Start	Nadir
Date, D/M/Y/..../....	/..../....	/..../....	/..../....	
Hb								
WBC								
Tromb								
Given doses								
V mg								
Adm² mg								
C² mg								
Eto² mg								
Ifo² mg								

- V:** Vincristine 2 mg/m² (max 2 mg) i.v. push.
- Adm²(in VAdm²C²):** Adriamycin (Doxorubicin) 40 mg/m²/day as 4 hours (2 days) i.v. infusion.
Total dose Doxorubicin = 80 mg/m² in 2 days
- C² (in VAdm²C²):** Cyclophosphamide 1200 mg/m² as 30 min continuous i.v. infusion.
- Eto² (in Eto²Ifo²):** Etoposide 100 mg/m²/day in 3 days, day 1,3 and 5 as 2 hours i.v. infusion.
- Ifo²(in Eto²Ifo²):** Ifosfamide 1800 mg/m²/ day in 5 days as 21–24 hours continuous i.v. infusion (total dose of Ifosfamide 9000 mg/m² in 5 days).

Submit this form together with Form 6A to:
 SSG secretariat
 Regional Tumor Registry
 Lund University Hospital
 SE-221 85 LUND
 Sweden

Postoperative or postradiation chemotherapy

	VAdm ² C ²	Eto ² Ifo ²	VAdm ² C ²	Eto ² Ifo ²
Date	Day/Month/Year/...../.....	Day/Month/Year/...../.....	Day/Month/Year/...../.....	Day/Month/Year/...../.....
Delay	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
Reduction	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
Transaminase*	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Creatinine*	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Stomatitis*	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Hematuria*	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Low Bicarb.	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
Fever	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
Hospitalization	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
Transfusion Erythrocyt	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
Transfusion Platelets	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
G-CSF	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
Cardiotoxicity	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no

* According to NCIC CTG Expanded common toxicity criteria

Toxicity grade	0	1	2	3	4
Transaminase	normal	≤2.5xN	2.6–5.0xN	5.1–20.0xN	>20.0xN
Creatinine	normal	<1.5xN	1.5–3.0xN	3.1–6.0xN	>6.0xN
Stomatitis	none	painless ulcers, erythema, or mild soreness	painful erythema, edema, or ulcers but can eat	painful erythema, edema, or ulcers, and cannot eat dehydration	mucosal necrosis and/or req parenteral or enteral support,
Hematuria	none	micro only	gross, no clots	gross –clots	req transfusion

Ewing's sarcoma family tumors ISG/SSG IV
CHEMOTHERAPY FLOW-SHEET FORM 8A

Name (first & family name)
 Date of birth (day, month, year)

Submit this form to:
 SSG secretariat
 Regional Tumor Registry
 Lund University Hospital
 SE-221 85 LUND
 Sweden

Hospital and department

Physician _____ Date Day _____ Month _____ Year _____

High-dose Busulfan and Melphalan with PBSC rescue

Year: _____

Weight: _____ kg

Height: _____ cm

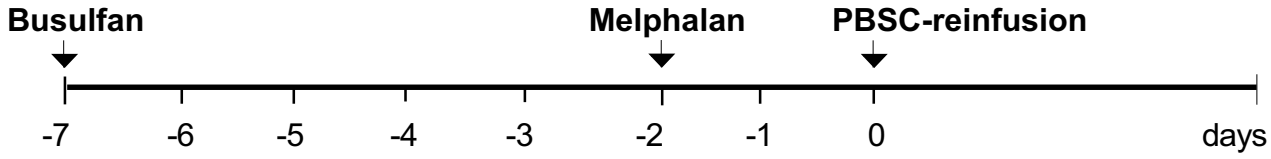
Body surface: _____ m²

Dates for harvest after C², Eto²: Day _____ Month _____ Year _____

PBSC yield: _____ x 10⁶ CD34 cells/kg

Date for reinfusion of PBSC Day _____ Month _____ Year _____

Number of PBSC infused _____ x 10⁶ CD34 cells/kg



	Start	Start	Nadir	Leukocytes >1.5 Platelets ≥50.000
Date, D/M/Y/...../...../...../.....		
Hb				
Wbc				
Tromb				
Given doses				
Busulfan mg				
Melphalan mg				

HD-BuM +PBSC: Busulfan 1 mg/kg p.o. x 4/day for 4 days
 Melphalan 140 mg/m² i.v. as 60 minutes i.v. infusion
 Peripher Blood Stem Cell rescue at 48 hours after termination of chemotherapy.

Submit this form together with Form 6A to:
 SSG secretariat
 Regional Tumor Registry
 Lund University Hospital
 SE-221 85 LUND
 Sweden

High-dose Busulfan and Melphalan with PBSC rescue

	Bu	M
Date	Day/Month/Year/...../.....	Day/Month/Year/...../.....
Delay	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
Reduction	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
Transaminase*	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Creatinine*	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Stomatitis*	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Hematuria*	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 4 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Low Bicarb.	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
Fever	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
Hospitalization	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
Transfusion Erythrocyt	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
Transfusion Platelets	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
G-CSF	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no
Cardiotoxicity	<input type="checkbox"/> yes <input type="checkbox"/> no	<input type="checkbox"/> yes <input type="checkbox"/> no

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Creatinine	normal	<1.5xN	1.5–3.0xN	3.1–6.0xN	>6.0xN
Stomatitis	none	painless ulcers, erythema, or mild soreness	painful erythema, edema, or ulcers but can eat	painful erythema, edema, or ulcers, and cannot eat dehydration	mucosal necrosis and/or req parenteral or enteral support,
Hematuria	none	micro only	gross, no clots	gross –clots	req transfusion

Ewing's sarcoma family tumors ISG/SSG IV
Radiation therapy FORM 9

Name (first & family name)
 Date of birth (day, month, year)

Submit this form to:
 SSG secretariat
 Regional Tumor Registry
 Lund University Hospital
 SE-221 85 LUND
 Sweden

Hospital and department Date Day Month Year

Physician

Start of treatment, date Day Month Year
 End of treatment, date Day Month Year

Target absorbed dose(s)

	Target 1, specify;	Target 2, specify;
Radiation quality:		
Specified target dose	□□□, □□ Gy	□□□, □□ Gy
Number of fractions	□□□	□□□
Number of days	□□□	□□□

Dose to clinical organs

Spinal cord	□□□, □□ Gy
Heart	□□□, □□ Gy
Liver	□□□, □□ Gy
Lung	□□□, □□ Gy
Kidney	□□□, □□ Gy

Acute toxicity

Specify;

Dose modification

Dose modification factors
 no yes, specify;

Deviation from plan

no yes, specify;

Ewing's sarcoma family tumors ISG/SSG IV
FOLLOW-UP FORM 10

Name (first & family name)
 Date of birth (day, month, year)

Submit this form to:
 SSG secretariat
 Regional Tumor Registry
 Lund University Hospital
 SE-221 85 LUND
 Sweden

Hospital and department Date

Day	Month	Year

Physician

CLINICAL EVALUATION

Date of evaluation	<table border="1" style="display: inline-table; border-collapse: collapse;"><tr><td style="width: 20px;">Day</td></tr><tr><td> </td></tr></table>	Day		<table border="1" style="display: inline-table; border-collapse: collapse;"><tr><td style="width: 20px;">Month</td></tr><tr><td> </td></tr></table>	Month		<table border="1" style="display: inline-table; border-collapse: collapse;"><tr><td style="width: 20px;">Year</td></tr><tr><td> </td></tr></table>	Year		
Day										
Month										
Year										
Physical exam	<input type="checkbox"/>	no	<input type="checkbox"/>	yes						
Chest x-ray	<input type="checkbox"/>	no	<input type="checkbox"/>	yes						
CT of chest	<input type="checkbox"/>	no	<input type="checkbox"/>	yes						
X-ray of the primary tumor site	<input type="checkbox"/>	no	<input type="checkbox"/>	yes						
CT of the primary tumor site	<input type="checkbox"/>	no	<input type="checkbox"/>	yes						
MRI of the tumor site	<input type="checkbox"/>	no	<input type="checkbox"/>	yes						
Bone scan	<input type="checkbox"/>	no	<input type="checkbox"/>	yes						
Alkaline phosphatase	<table border="1" style="display: inline-table; border-collapse: collapse;"><tr><td style="width: 20px;"> </td><td style="width: 20px;"> </td><td style="width: 20px;"> </td></tr></table>				specify units	LDH	<table border="1" style="display: inline-table; border-collapse: collapse;"><tr><td style="width: 20px;"> </td><td style="width: 20px;"> </td><td style="width: 20px;"> </td></tr></table> specify units			

STATUS

Tumor status										
<input type="checkbox"/> No evidence of disease	<input type="checkbox"/> Local recurrence	<input type="checkbox"/> Distant metastasis								
<input type="checkbox"/> Death	Date	<table border="1" style="display: inline-table; border-collapse: collapse;"><tr><td style="width: 20px;">Day</td></tr><tr><td> </td></tr></table>	Day		<table border="1" style="display: inline-table; border-collapse: collapse;"><tr><td style="width: 20px;">Month</td></tr><tr><td> </td></tr></table>	Month		<table border="1" style="display: inline-table; border-collapse: collapse;"><tr><td style="width: 20px;">Year</td></tr><tr><td> </td></tr></table>	Year	
Day										
Month										
Year										
		Autopsy <input type="checkbox"/> no <input type="checkbox"/> yes								
<input type="checkbox"/> Died from Ewing's sarcoma	<input type="checkbox"/> Died with Ewing's sarcoma from other cause									
<input type="checkbox"/> Died from treatment related complications	<input type="checkbox"/> Died NED from other causes, specify;									

IN CASE OF DISTANT METASTASE(S)

Lung	<input type="checkbox"/> no	<input type="checkbox"/> yes	<input type="checkbox"/> unilateral	<input type="checkbox"/> bilateral		
Liver	<input type="checkbox"/> no	<input type="checkbox"/> yes	Number of metastases	<table border="1" style="display: inline-table; border-collapse: collapse;"><tr><td style="width: 20px;"> </td><td style="width: 20px;"> </td></tr></table>		
Bone	<input type="checkbox"/> no	<input type="checkbox"/> yes	Number of metastases	<table border="1" style="display: inline-table; border-collapse: collapse;"><tr><td style="width: 20px;"> </td><td style="width: 20px;"> </td></tr></table>		
<input type="checkbox"/> Other, specify;.....						

TREATMENT FOR RELAPSE

<input type="checkbox"/> Curative intent	<input type="checkbox"/> Palliative intent
Treatment plan:	<input type="checkbox"/> chemotherapy <input type="checkbox"/> surgery <input type="checkbox"/> other, specify;