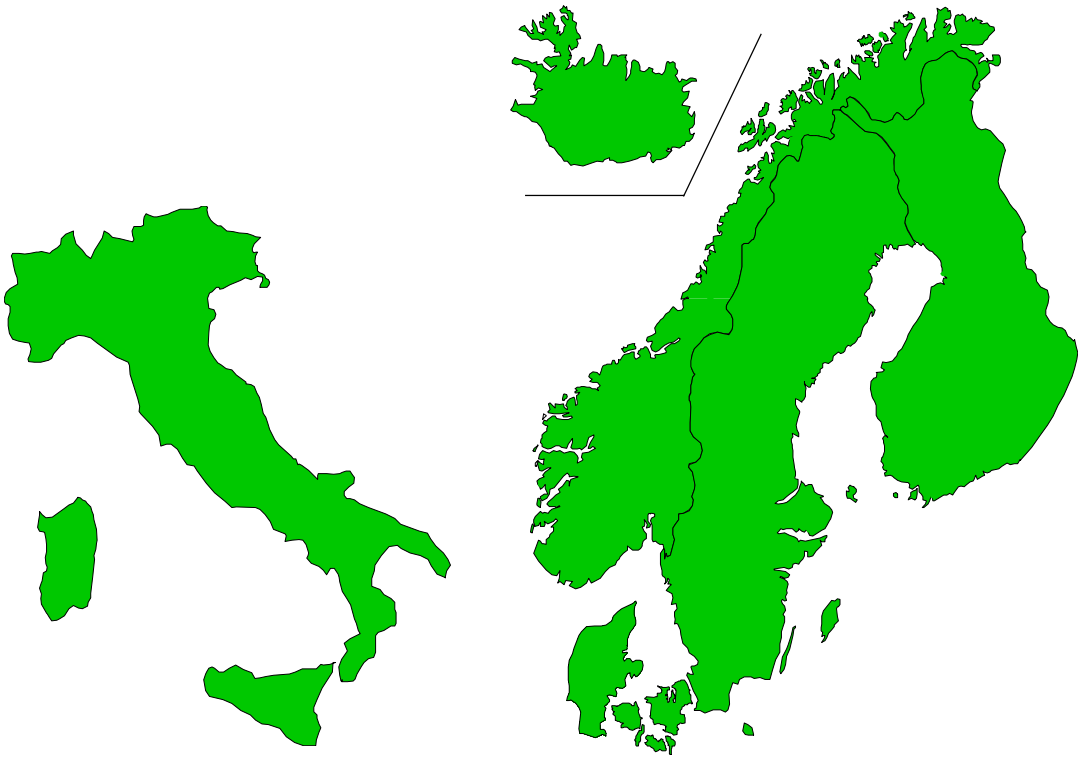
Italian Sarcoma Group
Bologna, Italy

Scandinavian Sarcoma Group and
Oncologic Center, Lund, Sweden

ISG/SSG III

An Italian – Scandinavian treatment protocol for nonmetastatic Ewing´s family tumors



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

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

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

All patients with nonmetastatic 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 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. The Scandinavian Sarcoma Group was founded in 1979. The aim of the Group was to improve the prognosis of sarcoma patients in this region. Its work has improved the organization of treatment for sarcoma. Guidelines for diagnosis, pathology, and treatment have been drawn, 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 use since 1978 in a special project financed by the Italian National Council of Research. The Italian Sarcoma Group was founded in 1997 to formalize the collaboration for research and treatment in the field of sarcomas – it comprises more than 200 members from over 50 centers.

The present ISG/SSG III protocol replaces the SSG IX and SE91 protocols. It is based on experience using the SSG IV/IX protocols and three neoadjuvant studies conducted in Italy and from recent international literature.

A working group, consisting of 75 members of ISG and SSG, 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 III protocol will be activated as of June 1, 1999

Bologna, Lund, May 31, 1999

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Ewing´s family tumors ISG/SSG III

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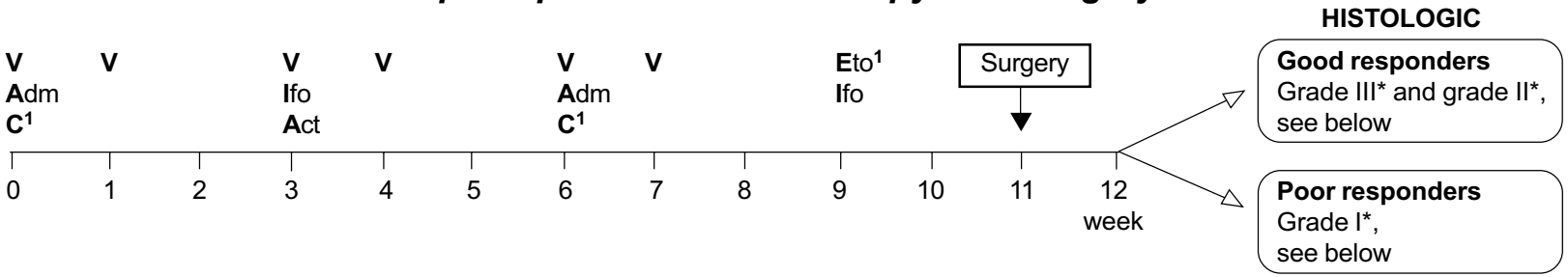
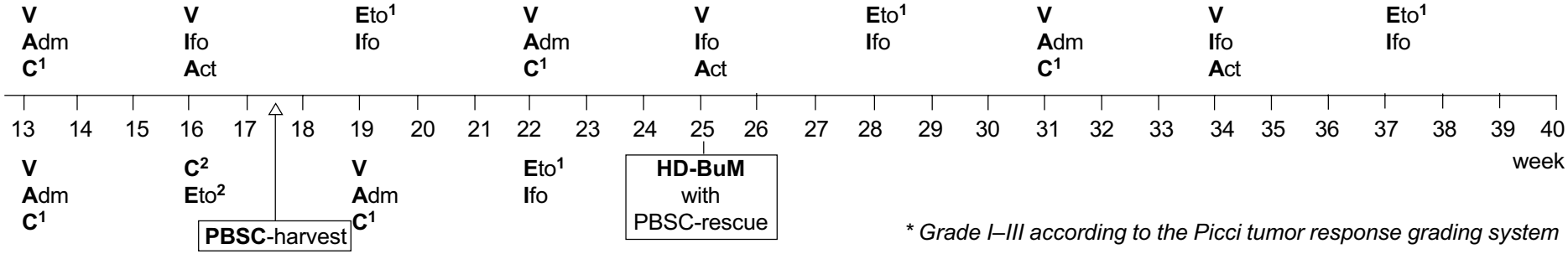
1. Pre- and postoperative chemotherapy with surgery alone



Good responders: grade III* and grade II* with wide or radical margin and grade III with marginal margin



** Grade I–III according to the Picci tumor response grading system*

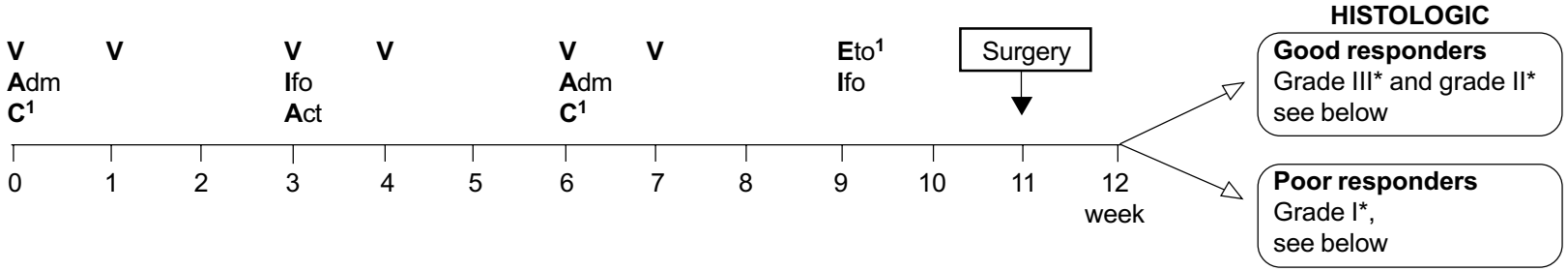
Poor responders: grade I* with wide or radical margin

V:	Vincristine 1.5 mg/m² (max 2 mg) i.v. push
Adm(in**VA**dm**C**[1]):	Adriamycin (Doxorubicin) 40 mg/m²/day as 4 hours (2 days) i.v. inf. Total dose of Doxorubicin = 80 mg/m² in 2 days
C[1] (in **VA**dm**C**[1]):	Cyclophosphamide 1200 mg/m² i.v. as 30 minutes i.v. inf.
Ifo (in **VI**fo**A**ct and **E**to[1]**I**fo):	Ifosfamide 3000 mg/m²/ 21–24 hour as 72 hours (3 days) continuous i.v. infusion (total dose 9000 mg/m²)
Act (in**VI**fo**A**ct):	Actinomycin-D 1.5 mg/m² (max 2 mg) i.v. push
Eto[1] (in **E**to[1]**I**fo):	Etoposide 150 mg/m²/day in 3 days as 2 hours i.v. inf. Total dose of Etoposide = 450 mg/m² in 3 days
C[2] (in **C**[2]**E**to[2]):	Cyclophosphamide 4000 mg/m² i.v. as 3 hours i.v.inf.
Eto[2] (in **C**[2]**E**to[2]):	Etoposide 200 mg/m²/day as 2 hours (3 days) i.v. inf. Total dose of Etoposide = 600 mg/m² in 3 days
HD-BuM +PBSC:	Busulfan 1 mg/kg p.o. x 4/day for 4 days Melphalan 140 mg/m² i.v. as 60 minutes continuous i.v. inf. Peripher Blood Stem Cell rescue at 48 hours after termination of chemotherapy

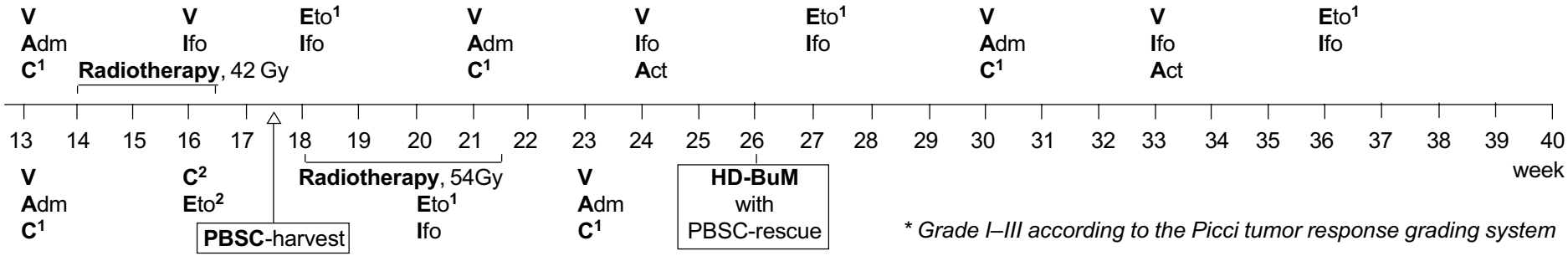
Ewing´s family tumors ISG/SSG III

Nonmetastatic at diagnosis
Standard risk – localized

2. Pre- and postoperative chemotherapy combined with postoperative radiotherapy



Good responders: grade III* with intralesional margin, grade II* with marginal or intralesional margin



** Grade I–III according to the Picci tumor response grading system*

Poor responders: grade I* with marginal or intralesional margin

V:	Vincristine 1.5 mg/m² (max 2 mg) i.v. push
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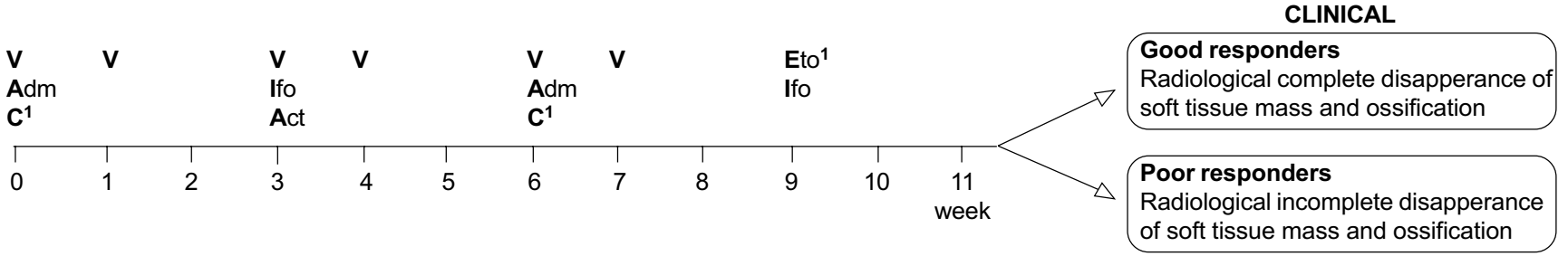
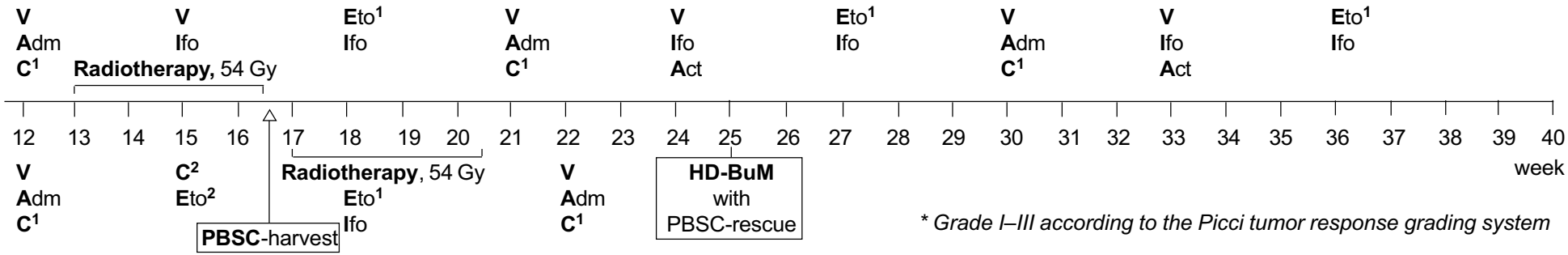
Ewing´s family tumors ISG/SSG III

Nonmetastatic at diagnosis
Standard risk – localized

3. Chemotherapy combined with radiotherapy (without surgery)



Good responders: clinical



Poor responders: clinical

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2. INTRODUCTION

Ewing's sarcoma, peripheral neuroectodermal tumor (PNET) and Askin's tumor belong to the "Ewing's tumor family" (ET), a group of neoplasms of neural origin, histologically and cytogenetically indistinguishable from one another. The clinical behaviors of these tumors are similar and the therapeutic approach follows the same basic principles (Miser 1987, JCO; Verril 1997 JCO). A specific cytogenetic marker of these neoplasms is the t(11;22) (q24;q12) reciprocal translocation which results in the fusion of the FLI-I gene, located on chromosome band 11q24, with the EWS gene, on chromosome band 22q12. Up to 18 possible types of EWS-FLI 1 fusion transcripts have been described, and the presence of type 1 EWS-FLI 1 fusion seems to define a clinically favorable subset of EWS/PNET (de Alava 1998 JCO).

Previous studies

The results obtained in 252 patients with nonmetastatic EWS/PNET, treated with chemotherapy at the Rizzoli Institute between 1972–1988 have recently been updated (Bacci 1998 Oncol Rep). They found that 40% of the patients with a median follow-up of 14 years have been continuously free of disease. Tumor site, tumor volume, LDH level at presentation and type of local treatment were significant prognostic factors for survival.

The chemotherapy regimen also significantly influenced the prognosis: the outcome using the 3-drug regimen Vincristine, Adriamycin and Cyclophosphamide was significantly worse than that of the 4-drug regimen with Vincristine, Adriamycin, Actinomycin-D and Cyclophosphamide (VAdmCA). The VACA regimen gave similar results, whether employed in an adjuvant or a neoadjuvant setting.

In 1998, Nilbert et al. reported the long-term follow-up of the first cooperative Scandinavian Sarcoma Group study (SSG IV) of Ewing's sarcoma of bone. It was based on 52 patients treated between 1984 and 1990. The combined treatment included Vincristine, Methotrexate, Doxorubicin, Cyclophosphamide, Bleomycin and Actinomycin. Local tumor relapse developed in 10 patients and in all but 1 patient was accompanied by metastatic disease. 5 patients had metastases at diagnosis and distant metastases developed after primary treatment in 27 patients after a median of 14 months. The 20 surviving patients had a median follow-up time of 10 years. At 5 years, the overall survival was 46% and the disease-free survival 43%. Late tumor relapses occurred in 4 patients, which reduced the 10-year tumor-related survival to 41% and the metastasis-free survival to 38%. Histopathological tumor response correlated with survival, the 5-year metastasis-free survival rates being 73% in the good responders and 35% in the poor responders.

In the first study by the French Society of Pediatric Oncology (Oberlin 1985, Eur J Cancer), the VACA regimen gave a 5-year DFS of 51%. In the first Intergroup Ewing's sarcoma study (Nesbit 1990, JCO), patients treated with the VACA regimen had a 5-year DFS of 60%, which was significantly higher than that obtained in patients who received only Vincristine, Actinomycin-D, Cyclophosphamide. The CESS-81 study (Dunst 1990, Cancer) using the VACA regimen had a 3-year relapse-free survival of 55%. In all these studies, the central location of the tumor and/or of a tumor volume >100 ml were negative prognostic factors.

More recent experiences

The VACA regimen can be considered the standard treatment for Ewing's sarcoma, but other drugs such as Ifosfamide (Ifo) and Etoposide (Eto) have given a high response rate in metastatic and localized EWS (Miser 1987 JCO, Meyer 1992, JCO). They were therefore used in an attempt to improve prognosis, but their role is still debated: can or should Ifosfamide be substituted for Cyclophosphamide or should Ifosfamide be given in addition to Cyclophosphamide, since no cross resistance has been found?

The CESS-86 study (Dunst 1990, Cancer) reported a 3-year relapse-free survival rate of 62%. In this protocol, standard-risk patients (those with a tumor volume <100 ml or a tumor location other than central) were treated with the VACA regimen. The other patients, classified as high-risk patients, were treated with the VAIA regimen, where Ifosfamide was given instead of Cyclophosphamide. No differences in prognosis were observed between the two groups.

The CCG POG study randomized patients to receive the VACA regimen or the VACA plus Eto/Ifo. Some advantages were reported in patients treated with the latter chemotherapy regimen (Grier 1994, ASCO). They were mainly due to an improved prognosis of EWS not involving the extremities and in patients under 14 years of age. In a second study by the French Society of Pediatric Oncology (Oberlin 1992, JCO) using the VAIA regimen, however, a 5-year DFS of 52% was achieved which was the same as the outcome of the first study with the VACA regimen. In this case, Ifosfamide was given instead of Cyclophosphamide.

Italian experience (Bacci 1998, Cancer) shows that the addition of Ifosfamide/Etoposide, given only in the maintenance phase, to the VACA regimen did not improve the disease-free survival, when compared with the first neoadjuvant chemotherapy study, using the VACA regimen. When the data were analyzed according to the tumor site, no differences were detected between the prognosis of central and extremity locations were observed.

The preliminary results (Rosito 1997, SIOP) of the third Italian neoadjuvant chemotherapy study (CNR SE-91) seem very encouraging i.e., Ifosfamide was started in the induction phase, added to the VACA regimen, while Etoposide was started in the maintenance phase, combined with Ifosfamide. With a median follow-up of 31 months, the 4-year event-free survival rate is 78%, with no differences according to tumor site (central or extremity), serum LDH values (normal vs. high), age (<14 years vs. >14 years), type of local treatment (surgery alone vs. surgery + radiation therapy vs. radiotherapy alone). A trend towards a better prognosis, but not significant, was reported in patients whose tumor size was <100 ml. The only significant prognostic factor was the histological response to the induction chemotherapy with a significant advantage in patients with a good histological response (no viable tumor cells or only small foci of tumor cells) than those with a poor response (macrofoci of viable tumor cells). The new chemotherapy regimens seem thus overcome the negative effect of two factors on prognosis, i.e., the central location of the tumor and tumor volume, which in the past were considered of ominous significance.

In 1990, the Scandinavian Sarcoma Group introduced a second protocol for the treatment of patients with Ewing's sarcoma (SSG IX). This protocol consisted of four chemotherapy cycles, each including two cycles Vincristine, Adriamycin, and Ifosfamide (VAI) alternating with one cycle of Cisplatin, Adriamycin, and Ifosfamide (PAI) at 3 week intervals (Elomaa et al. 1996). The total treatment time was 35 weeks. Local therapy was given in week 9. Inoperable or non radically operated patients received accelerated hyperfractionated radiotherapy 1.5 Gy twice daily between chemotherapy cycles to a total dose of 42 or 60 Gy, depending on the surgical radicality and tumor site. After 5 years, recurrences developed in 10% of the patients. Distant metastases developed in 33% of M0-patients. The overall survival rate of M0-patients was 70%

and the disease-free survival rate 58%. Patients with a localized extremity tumor had a survival rate of 90%. Patients with a good tumor response (Huvos III–IV) to chemotherapy had a better survival rate than those with a poor response (grades I–II) (P<0.003). Furthermore, metastases at the time of diagnosis, localized extremity tumor and surgical margins influenced the outcome, whereas age, sex and tumor size did not.

With the use of neoadjuvant treatments in localized EWS/PNET, a new prognostic factor must be considered: the histological response to induction chemotherapy. Recently (Picci 1993, 1997, JCO), 118 patients having EWS sarcoma treated with neoadjuvant chemotherapy and surgical resection of the tumor were evaluated to test the prognostic significance of the histological response. Patients with a poor histological response e.g., macrofoci of viable cells had a much poorer prognosis than those with a good or complete histological response. The prognostic significance of the histological response in EWS/PNET was also reported by the FPSO, CESS, SSG and Dutch.

Thus in localized EWS/PNET, as in osteosarcoma, histological response to primary chemotherapy must be included among the main prognostic factors.

Not all patients undergo surgery for local treatment, therefore a different evaluation system must be used for patients treated with radiation therapy. A retrospective evaluation of CT and/or MRI, pre- and postinduction chemotherapy, of 55 patients treated in Italy and Scandinavia with the surgical specimen evaluable for correlation, revealed that the total disappearance of the soft tissue component of the tumor is closely related to the histological response and event-free survival. Of the 22 patients who showed a total disappearance of the soft tissue mass 18 (82%) had a good histological response, while of the 33 cases who did not have a good radiological response, good histological responses occurred in 10 (30%). Regarding prognosis, 21 of the 22 patients (95%) with a good radiographic response continued to be disease–free as compared to 12 of the 33 with a poor radiographic response (36%) with the minimum follow-up time of three years.

A new chemotherapy protocol for localized EWS/PNET must aim at increasing the rate of good chemotherapy response, while new therapeutic approaches are needed to improve the prognosis in patients with poor response.

The worst prognosis in EWS sarcoma is related to the presence of metastasis(es) at presentation. In such patients, high-dose treatment with bone marrow transplant or stem cell rescue is justified.

The results of treatment are not encouraging and sometimes contradictory. For example, the French Society of Pediatric Oncology (EMSOS meeting 1997) reported an advantage of high-doses for patients with metastases while the EICESS recently reported (Paulussen et al. Ann Oncol 1998; 9:275–281) no advantages of megatherapy, except in a subset of patients with bone and lung metastases.

The Italian data are based on the previous High Risk Ewing's Sarcoma protocol which went into effect in 1993 (EWHR 1993). This protocol included an induction phase with Hyper-Vincristine-Adriamycin-Cyclophosphamide (HyperVAdmC) and Cyclophosphamide/ Etoposide (CEto) – also as the mobilizing cycle, local treatment, maintenance phase with Vincristine-Adriamycin-Cyclophosphamide (VAdmC) and Ifosfamide/Etoposide (IfoEto) followed by a high-dose regimen including Busulfan, Thiotepa and Etoposide, with PBSC rescue. Of the 54 patients with metastases who entered the protocol, 47 reached the high-dose regimen. After a median follow-up of 28 months (13–57mos), 19 patients continue to be disease-free (35%). In patients with lung metastases only (27 cases), or a single-bone metasta-

sis (5 cases), the disease-free survival rate is 53%, but 9% in 22 patients with multiple-bone metastases, whether or not associated with lung metastases. The results in adult patients only were reported at the 1997 ASCO meeting (Tienghi A et al. ASCO 1997, abstract 1792, p 498a) and they were encouraging, considering that these patients had a very poor prognosis when treated with standard chemotherapy.

Regarding local treatment, an aggressive surgical approach, combined with hyperfractioned accelerated radiotherapy, when feasible, has resulted in good local control in recent studies (5% in the last Italian study (EWHR, 1993) and 5% in the last Scandinavian study (SSG IX, 1991)).

3. AIMS AND GENERAL PROTOCOL DESIGN

(for treatment outline see pp. 10–12)

1. Evaluation of event-free survival in patients having localized EWS or PNET treated with a multimodal protocol, characterized by:
   a. An *induction phase* using all 6 drugs active in Ewing's family tumors: Ifosfamide (Ifo), Etoposide (Eto), Vincristine (V), Actinomycin-D (Act), Adriamycin (Adm), Cyclophosphamide (C)
   b. *Local treatment* consistent of surgery or surgery combined with radiotherapy and radiotherapy alone (hyperfractioned and accelerated radiotherapy)
   c. A different treatment in the *maintenance phase*, based on tumor response to induction chemotherapy. Patients showing a poor response will receive high-doses of Busulfan (Bu) and Melphalan (M), with reinfusion of peripheral blood stem cells (PBSC)
2. Evaluation of the percentage of patients with a good radiological response after induction chemotherapy with 6 drugs (V, Adm, Act, C, Ifo, Eto)
3. Evaluation of the percentage of patients with a good histological response after induction chemotherapy using 6 drugs (V, Adm, Act, C, Ifo, Eto), followed by surgery
4. Correlation between the radiological response and prognosis
5. Correlation between the histological and radiological responses and the prognosis
6. Evaluation of the prognostic significance of: age at diagnosis, histotypes (EWS, PNET), tumor location, tumor volume, dose intensity of the chemotherapy received and type of local treatment
7. Study the biological characteristics of EWS , PNET: immunohistochemical, cytogenetic, with their clinical correlations
8. We estimate to include approximately 50 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 chemotherapy by using all 6 of the most active drugs (Vincristine, Adriamycin, Actinomycin-D, 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 treatment should be decided only in centers which have documented their 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 $\geq 1 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L.
   If surgery is not feasible, radiation therapy should be started at the beginning of week 13.
2. Should surgery unexpectedly prove to have inadequate margins (intralesional or marginal) with good or poor preoperative chemotherapy response, it must be followed by radiotherapy, in full doses of 42 or 54 Gy.
3. Radiotherapy alone is reserved for tumors which, because of site or dimensions, exclude in advance the possibility of surgery with adequate margins.

Based on previous experience in both Groups (ISG and SSG), radiation therapy will be given, with hyperfractioned and accelerated modalities (p. 53).

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

Ravenna:
Radiotherapist: Dr. E. Emillani

Torino:
Radiotherapist: Dr. U. Ricardi
For the Scandinavian Sarcoma Group there are 6 centers:

Bergen:
Surgeon: Dr. C. Trovik
Oncologist/radiotherapist: Dr. O. Monge, Dr. J. Helgestad

Oslo:
Surgeon: Dr. G. Follerås
Oncologist/radiotherapist: Dr. G. Saeter

Gothenburg:
Surgeon: Dr. B. Gunterberg
Oncologist/radiotherapist: 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. Y. Wahlqvist, Dr. O. Björk

Helsinki:
Surgeon: Dr. A. Kivioja
Oncologist/radiotherapist: Dr. T. Wiklund

Evaluation of response

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

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

For patients undergoing surgery (without preoperative radiation therapy) as local treatment, further chemotherapy will be determined by the histological response (p. 48).

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

For patients receiving radiotherapy alone or radiotherapy followed by surgery as local treatment, the response to radiological treatment (p. 45) will determine further chemotherapy. Radiological good responders are defined as complete disappearance of the soft tissue component and complete ossification. Radiological poor responders are defined as incomplete disappearance of the soft tissue component and incomplete ossification.

Local treatment based on tumor response

Surgery alone	*Histological good responders* Tumor-response grades II and III and wide or radical margin, grade III and marginal margin	*Histological poor responders* 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	*Radiological good responders* In nonoperable patients with complete dissappearance of the soft tissue component and complete ossification	*Radiological poor responders* In inoperable patients with incomplete disappearance of the soft tissue component and incomplete osification

Maintenance chemotherapy

Since most patients (at least 70%) undergo surgery as local treatment, and about 3 weeks are required to evaluate the specimen, all patients (irrespective of response) should be given VAdmC[1] as the first cycle of maintenance. Similarly, patients treated with radiation therapy should also be given the same VAdmC[1] cycle.

After this VAdmC[1] cycle, patients should be divided into 2 groups depending on their response to induction treatment:

- Good responders: These patients are continued on standard chemotherapy, using the same 6 drugs and modalities as in the induction treatment.
- Poor responders: These patients are switched to a different treatment, including one mobilizing cycle with C[2]Eto[2], followed by peripheral blood stem cell (PBSC) harvest, by further Eto[1]Ifo and VAdmC[1], and high-dose chemotherapy treatment using Busulfan (Bu) and Melphalan (M), with subsequent PBSC rescue.

5. ORGANIZATION

Address of main study secretariat:

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

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A register of ISG patients will be kept at Istituto Ortopedico Rizzoli, Via Pupilli 1, IT-40136 Bologna, Italy. All Italian patients will be in the ISG register and its data 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 aim 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 III ”RESOURCE GROUP”

When running a multicenter study with multimodality treatment and multiagent chemotherapy, unforeseen situations and complications may occur which are not sufficiently covered in the protocol. To minimize protocol violations and ensure uniform handling of such situations, the ISG/SSG III working group has formed a ”*Resource Group”*, 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. 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 III 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 III is a non-randomized phase II study, based on experience from ISG, SSG and the medical literature.
2. Before the 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 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 $\leq$40 years
4. No previous treatment for EWS or PNET
5. Patient with one lung lesion less than 0.5 cm
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 4 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 about each individual patient must be submitted to the secretariat (see p. 57).
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 registrered in the study secretariats.)

1. Previous malignancy other than basal cell carcinoma of the skin and in situ/non-invasive carcinoma of the skin or cervix
2. Medical contraindications to the cytostatic agents and dose levels in question
3. Planned chemotherapy and/or follow-up not feasible

4. Major psychological or psychiatric diseases
5. Patient's refusal to participate in the treatment program
6. Missing patient/parents/tutor consent to treatment according to national guidelines
7. Local treatment decided without obtaining the opinion of referral centers (see 4.2, p. 18)
8. Metastatic disease. This includes solitary lung lesions >0.5 cm and smaller solitary lung lesions that are histologically verified. These patients will be treated according to the ISG/SSG IV protocol.

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

Patients with morphologic evidence of tumor cells in the bone marrow biopsy are considered metastatic.

Patients with tumor cells in the regional lymphnodes documented by biopsy, with pleural effusion and/or ascites from cancer or with neoplastic cells in the liquor are considered metastatic.)

12. PRETREATMENT INVESTIGATIONS

(see also flow-sheet in Appendix 1, p. 43)

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 of the gene fusion products with RT-PCR.
4. Needle aspiration from both iliac crests and bone marrow biopsy at least from 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 methodology 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
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. CT scan of the abdomen (patients with lesions not involving the abdominal cavity)
4. Ultrasound of the abdomen
5. Dynamic cardiac scintigraphy
6. Urinary alfa1-microglobulin/urinary creatinine, tubular reabsorption of phosphate, fractional excretion of glucose
7. Sperm count. It is recommended that a sperm count is performed in all patients where feasible, and that these patients are offered sperm banking prior to chemotherapy.

13. REEVALUATION BEFORE SURGERY OR RADIOTHERAPY

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
4. Electrocardiogram

Recommended investigations (optional):

1. CT scan of the chest in patients with localized disease at diagnosis
2. Total bone scan, preferably with dynamic study of the primary tumor area

14. INVESTIGATIONS AT THE 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. CT scan of the chest
2. Sperm count in patients with sufficient sexual maturation

15. FOLLOW-UP AFTER END OF TREATMENT

(see also flow-sheet in Appendix 1, p. 43)

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 at each visit. The CT scan of the chest is optional as routine, but it must always be done if chest X-ray shows metastases or is inconclusive
3. Blood count (hemoglobin, white blood counts, thrombocytes), transaminases, ALP, LDH and serum creatinine at each visit
4. Serum creatinine, GFR estimation at 6-month intervals during the first year, 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 the treatment in patients with sufficient sexual maturation.

16. ADMINISTRATION OF CHEMOTHERAPY

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

NOTE: All infusion volumes are specified per m^2 of body surface area to facilitate necessary adjustments for children.

1. VAdmC[1]cycle (Vincristine, Adriamycin, Cyclophosphamide)

1. Pre- and postoperative chemotherapy (local treatment – surgery alone)

Good responders: Histological grades III and II with wide or radical margin, grade III with marginal margin
Induction: weeks 0, 6
Maintenance: weeks 13, 22, 31

Poor responders: Histological grade I with wide or radical margin
Induction: weeks 0, 6
Maintenance: weeks 13, 19

Pre- and postoperative chemotherapy combined with postoperative radiotherapy

Good responders: Histological grade II with marginal or intralesional margin, grade III with intralesional margin
Induction: weeks 0, 6
Maintenance: weeks 13, 21, 30

Poor responders: Histological grade I with marginal or contaminated or intralesional margin
Induction: weeks 0, 6
Maintenance: weeks 13, 23

3. Chemotherapy combined with radiotherapy (without surgery)

Good responders: Clinical, radiological complete disappearance of soft tissue mass and complete ossification
Induction: weeks 0, 6
Maintenance: weeks 12, 21, 30

Poor responders: Clinical, radiological incomplete disappearance of soft tissue mass and complete ossification
Induction: weeks 0, 6
Maintenance: weeks 12, 22

Blood check-ups before starting VAdmC[1]-cycle: Hemoglobin, white blood counts, neutrophils, platelets, albumin, liver enzymes, bilirubin, Na, K, Ca, creatinine

Basal solution: 5% glucose with 40 mmol $NaHCO_3$/L + 20 mmol KCl/L

Day 1

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

Mesna* Variation is possible, based on local experience

Before Vincristine (day 8), check white blood cell counts, neutrophils, platelets, and hemoglobin.

Day 2

Timing	**Drug**	**Infusion modalities**
9–13h	Adriamycin	40 mg/m^2 i.v. in 1000 ml 5% glucose in 4-hour continuous infusion

Day 8**

Timing	**Drug**	**Infusion modalities**
0	Vincristine	1.5 mg/ m^2 (max 2 mg) i.v. push

**Only in the induction phase, i.e., cycles of weeks 0 and 6

VAdmC[1] courses are started if:

Neutrophil count >1.0 × 10^9/L platelet count >100 × 10^9/L,

bilirubin is <1.5 mg/dl (=20 mmol/L), and transaminases <5 times the higher levels in the normal range.

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

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

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

After a cumulative dose of 320 mg/m^2 Adriamycin, an echocardiogram must be performed. In case of >10% reduction of LVET compared to the baseline value, the last cycle with Adriamycin should be omitted (Steinherz 1992, Pediatrics).

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

2. VIfoAct cycle (Vincristine, Ifosfamide, Actinomycin-D)

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

Good responders: Histological grades III and II with wide or radical margin, grade III with marginal margin
Induction: week 3
Maintenance: weeks 16, 25, 34

Poor responders: Histological grade I with wide or radical margin
Induction: week 3
Maintenance: 0

2. Pre- and postoperative chemotherapy combined with postoperative radiotherapy

Good responders: Histological grade II with marginal or intralesional margin, grade III with intralesional margin
Induction: week 3
Maintenance: weeks 16, 25, 34 (Actinomycin-D is omitted week 16)

Poor responders: Histological grade I with marginal or intralesional margin
Induction: week 3
Maintenance: 0

3. Chemotherapy combined with radiotherapy (without surgery)

Good responders: Clinical, radiological complete disappearance of soft tissue mass and ossification
Induction: week 3
Maintenance: weeks 15, 24, 33 (Actinomycin-D is omitted week 15)

Poor responders: Clinical, radiological incomplete disappearance of soft tissue mass and complete ossification
Induction: week 3
Maintenance: 0

Blood check-ups before starting **VIfoAct-cycle**: Hemoglobin, white blood counts, neutrophils, platelets, albumin, liver enzymes, 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, GOT and GPT (=ASAT, ALAT)
Basal solution: 5% glucose with 40 mmol $NaHCO_3$/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	Actinomycin-D	1.5 mg/ m^2 (max 2 mg) i.v. push (omitted in weeks 15 and 16 in group 2 and 3)
0–2h	Prehydration and alkalinization	Infuse 500 ml/m^2 of basal solution
2–24h	Ifosfamide*/Mesna	Ifo/Mesna in basal solution in 22 hours

Day 2

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

Day 3

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

a. Prehydration and alkalinization: Infuse 500 ml/m^2 over a 2-hour period.

b. *Dose:* The doses of Ifosfamide and of Mesna are 3 000 mg/m^2/22–24 hours, each for 3 consecutive days, giving a total dose of both Ifosfamide and Mesna of 9 000 mg/m^2/3 days.

c. *Ifosfamide*/Mesna infusion:* Ifosfamide and Mesna are infused i.v. in 2 000 ml/m^2/24 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 3: Mesna 1 500 mg/m^2 in 1 000/ ml/m^2 basal solution in 8 hours. Alternatively, Mesna 500 mg/m^2 i.v. and $NaHCO_3$, 500 or 1 000 mg may be given orally 4 and 8 hours after the Ifosfamide-Mesna infusion.

e. *Diuresis:* If <400 ml/m^2 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 $NaHCO_3$/kg intravenously during 30 minutes.

g. *Treatment and prophylaxis for Ifosfamide-induced CNS toxicity:* The cause of Ifosfamide-induced acute encephalopathy is unknown. It may be dose-dependent and may be aggravated by metabolic acidosis. This 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 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 entirely understood.

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

Uristix for hematuria should be repeated every 24 hours.

Before giving Vincristine (day 8), check white blood cell counts, neutrophils, platelets, and hemoglobin.

Day 8**

Timing	**Drug**	**Infusion modalities**
0	Vincristine	1.5 mg/ m^2 (max 2 mg) i.v. push

**Only in the induction phase, i.e., cycles of weeks 0 and 6

VIfoAct courses are started if :

Neutrophil count >1.0 × 10^9/L, platelet count >100 × 10^9/L,

kidney function, expressed as serum creatinine, and creatinine clearance are within normal range (creatinine clearance or GFR >60 ml/min/1.73).

No severe signs or symptoms of Vincristine-induced neuropathy have been reported.

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

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

After a cumulative dose of 45 000 mg/m^2 Ifosfamide, additional investigations should be done to assess the tubular function before administration of each VIfoAct cycle: urinary α1 microglobulin/urinary creatinine, tubular reabsorption of phosphate, fractional excretion of glucose, and GFR.

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 5% 2 000 ml/m^2/24 hours, to be continued for 48 hours after the appearance of hematuria. Check with echography and urine culture. Stop the Ifosfamide infusion.

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

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 $NaCO_3$/kg intravenously for 30 minutes. In subsequent Ifosfamide courses, prophylactic treatment with oral methylene blue 50 mg × 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 $NaCO_3$/kg intravenously in 30 minutes.

3. Eto[1]Ifo cycle (Etoposide, Ifosfamide)

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

Good responders: Histological grades III and II with wide or radical margin, grade III with marginal margin

Induction: week 9
Maintenance: weeks 19, 28, 37

Poor responders: Histological grade I with wide or radical margin
Induction: week 9
Maintenance: week 22

2. Pre- and postoperative chemotherapy combined with postoperative radiotherapy

Good responders: Histological grade II with marginal or intralesional margin, grade III with intralesional margin
Induction: week 9
Maintenance: weeks 19, 28, 37

Poor responders: Histological grade I with marginal or intralesional margin
Induction: week 9
Maintenance: week 20

3. Chemotherapy combined with radiotherapy (without surgery)

Good responders: Clinical, radiological complete disappearance of soft tissue mass and complete ossification
Induction: week 9
Maintenance: weeks 18, 27, 36

Poor responders: Clinical, radiological incomplete disappearance of soft tissue mass and ossification
Induction: week 9
Maintenance: week 19

Blood check-ups before starting Ifosfamide: Hemoglobin, white blood counts, neutrophil, platelets, 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.

Basal solution: 5% glucose with 40 mmol $NaHCO_3$/L + 20 mmol KCl/L.

Day 1

Timing	**Drug**	**Infusion modalities**
0–2h	Etoposide	***150 mg/m² i.v. in 2 hours in saline solution 400 ml/m²***
2–4h	Prehydration and alkalinization	Infuse 500 ml/m² of basal solution
4–24h	Ifosfamide*/Mesna	Ifo/Mesna in basal solution for 20 hours

Day 2

0–2h	Etoposide	150 mg/ m^2 i.v. in 2 hours in saline solution ***400 ml/m²***
2–24h	Ifosfamide*/Mesna	Ifo/Mesna in basal solution for 22 hours

Day 3

Timing	**Drug**	**Infusion modalities**
0–2h	Etoposide	150 mg/ m^2 i.v. for 2 hours in saline solution ***400 ml/m²***
2–24h	Ifosfamide*/Mesna	Ifo/Mesna in basal solution for 22 hours

Eto[1]Ifo courses are started if:

neutrophil count >1.0 × 10^9/L platelet count >100 × 10^9/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.

a. Prehydration and alkalinization: Infuse 500 ml/m^2 over a 2-hour period.

b. *Dose:* The dose of Ifosfamide is 3 000 mg/m^2/21–23 hours and the dose of Mesna is also 3 000 mg/m^2/21–24 hours, each for 3 consecutive days, giving a total dose of both Ifosfamide and Mesna of 9 000 mg/m^2/3 days each.

c. *Ifosfamide*/Mesna infusion:* Ifosfamide and Mesna are infused i.v. in 2 000 ml/m^2/24 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 3: give Mesna 1 500 mg/m^2 in 1 000/ ml/m^2 basal solution in 8 hours. Alternatively, give Mesna 500 mg/m^2 i.v. and $NaHCO_3$, 500 or 1 000 mg orally 4 and 8 hours after the Ifosfamide–Mesna infusion.

e. *Diuresis:* If <400 ml/m^2 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 $NaHCO_3$/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/ m^2 additional investigations are required to assess the tubular function before administration of each Eto[1]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/m^2/24 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 $NaCO_3$/kg intravenously during 30 minutes. In subsequent Ifosfamide courses, prophylactic treatment with oral methylene blue 50 mg × 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 $NaCO_3$/kg intravenously for 30 minutes.

4. C^2Eto^2 cycle (Cyclophosphamide, Etoposide)–Mobilizing cycle

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

Good responders: Histological grades III and II with wide margin, grade III with marginal margin
Induction: 0
Maintenance: 0

Poor responders: Histological grade I with wide margin
Induction: 0
Maintenance: week 16

2. Pre- and postoperative chemotherapy combined with postoperative radiotherapy

Good responders: Histological grade II with marginal or intralesional margin, grade III with intralesional margin
Induction: 0
Maintenance: 0

Poor responders: Histological grade I marginal or intralesional margin
Induction: 0
Maintenance: week 16

3. Chemotherapy combined with radiotherapy (without surgery)

Good responders: Clinical, radiological complete disappearance of soft tissue mass and ossification
Induction: 0
Maintenance: 0

Poor responders: Clinical, radiological incomplete disappearance of soft tissue mass and ossification
Induction 0
Maintenance: week 15

G-CSF administration and PBSC harvest: G-CSF administration is started 24 hours after chemotherapy in a dose of 10 µg/kg/day.

The mobilization of CD34+ cells in peripheral blood is monitored and CD34+ cells are harvested according to local routines.

If the yield is insufficient ($<2.5 \times 10^6$ CD34+ cells/kg), consider a second collection before megatherapy (after the $VAdmC^1$ cycle).

Investigations before starting C^2Eto^2

Blood check-ups: White blood cell counts, neutrophils, platelets, hemoglobin, liver enzymes, bilirubin, serum creatinine, Na, K, Mg, Ca, P

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

Day 1

Timing	**Drug**	**Infusion modalities**
0–3h	Cyclophosphamide	Cyclophosphamide in a dose of 4 000 mg/ m^2 is given as a 3-hour continuous intravenous infu sion, together with Mesna in the same dose (4 000 mg/ m^2). Cyclophosphamide and Mesna are dissolved in 500 ml 5% glucose.
3–24h	Posthydration	3 000 ml/ m^2 for 21 hours. Use 5% glucose with 40 mEq$NaHCO_3$/L and 20 mEq K/L.

Days 2–3–4

0–2h	Etoposide	Etoposide in a dose of 200 mg/ m^2/2 hours is gi ven as a continuous infusion over 2 hours (total dose 600 mg/m^2/3 days). Etoposide is dissolved in ***500 ml/m^2***/2 hours of 0.9% NaCl. Start the in fusion when the posthydration after Cyclophosphamide is completed.

C^2Eto^2 courses are started if :

neutrophil count >1.0 × 10^9/L and platelet count >100 × 10^9/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/m^2/24 hours 5% glucose for 48 hours after the development of hematuria.
Should hematuria reappear during the following cycle, contact the protocol coordinators.

5. High-dose chemotherapy and peripheral stem cell transplantation

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

Good responders: Histological grades III and II with wide or radical margin, grade III with marginal margin
Maintenance: 0

Poor responders: Histological grade I with wide or radical margin
Maintenance: week 25

2. Pre- and postoperative chemotherapy combined with postoperative radiotherapy

Good responders: Histological grade II with marginal or intralesional margin, grade III with intralesional margin
Maintenance: 0

Poor responders: Histological grade I with marginal or intralesional margin
Maintenance: week 26

3. Chemotherapy combined with radiotherapy (without surgery)

Good responders: Clinical, radiological complete disappearance of soft tissue mass and ossification
Maintenance: 0

Poor responders: Clinical, radiological incomplete disappearance of soft tissue mass and ossification
Maintenance: 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.
–3	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	Clorfeniramina: 0.2 mg/kg i.v. push
0		Reinfusion of PBSC

NOTE: When giving Busulfan the pharmacokinetics should be monitored!

Premedication before reinfusion of PBSC preparation can also be done according to local routines.

The minimum CD34+ required for HDCT is 2.5 × 10^6/kg

17. GENERAL CONSIDERATIONS

Guidelines for G-CSF

If G-CSF is used after VAdmC[1], VIfoAct, Eto[2]/Ifo[2] cycles, due to neutropenic fever, it must be stopped at least 24 hours before starting the next course of chemotherapy and when the total white blood count exceeds 10.0 x 10^9/l.

G-CSF 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 × 10^9/l or neutropenic fever (temp. >38.5 °C and neutrophil count <0.5 × 10^9/L).

After C[2]Eto[2], 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.

The Scandinavian Sarcoma Group institutions are obliged to use "Neupogen Amgen/Roche"

Indications for red blood cell and platelet transfusions

The decision when to give red blood cell and platelet transfusions is left up 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 petecchiae or signs of bleeding are seen, despite the platelet values. If petecchiae or bleeding is not present, platelet transfusion is recommended when values <10.0 × 10^9/L.

Antiemetic therapy

In accordance with local experience.

Local treatment of the disease

Surgery should be planned for beginning of week 11, when neutrophils >1 000/mmc and platelets >100 000/mmc.

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

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Appendix 1

EWS family tumors ISG/SSG III

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 end of treatment

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/or MRI of involved bone	X	X ↑ and in inoperable patients before radiotherapy for determination for tumor's radiological response	X			
Chest X-ray	X	X	X	X		
CT of chest	X	(X)	(X)	(X)	X	If lung metastases are suspected on chest X-ray
Bone scan	X	(X)	(X)		X	If bone metastases are suspected
ECG	X	X	(X)		(X)	(every 3 years after treatment)
Cardiac ultra-sound/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 TO 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 (>0.5cm/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

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

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

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

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

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

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 show a poor 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 measurments 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 appears 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 preexisting 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-Grüünwald-Giemsa (MGG). MGG allows detailed study of cytoplasmic features but H&E or Pap are better for the examination of nuclear structures.

Ancillary diagnostics. *Immunohistocytochemistry.* The following antibodies are the minimum required: CD99 (MIC^2 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, 2^{nd} edition, Lund 1997, pp. 2–23).

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 + immunohistocytochemical CD99 positivity

c. Immunohistocytochemical 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 sound 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 examinations 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 intraosseuos 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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Åkerman M, Stenwig E. A critical re-examination of Ewing's sarcoma trial SSG IX-primary diagnosis and histological response grading. Acta Orthop Scand 1998; (Suppl. 282): 32.

TUMOR RESPONSE GRADE

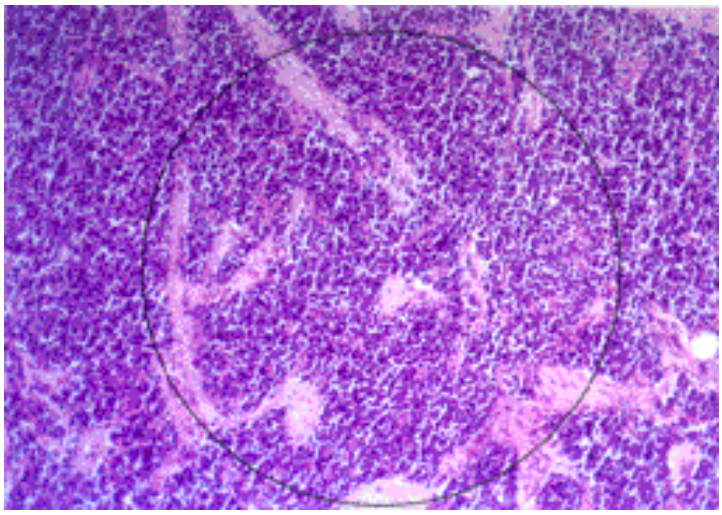

Fig. 1

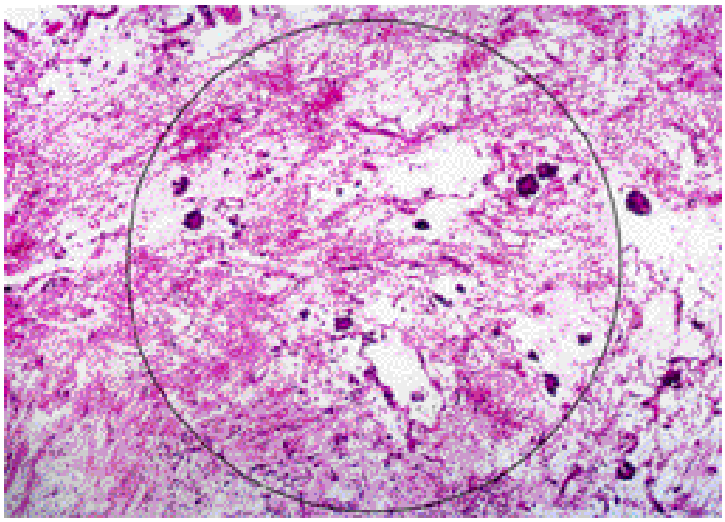

Fig. 2

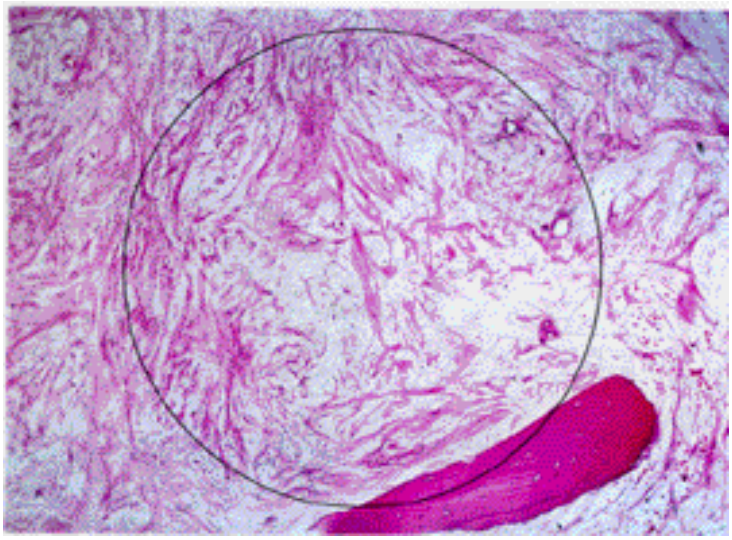

Fig. 3

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 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 LE) were calculated with an alfa/beta ratio equal to 10 Gy for tumor and equal to 3 Gy for late sequealae. 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 advatange in terms of reduction of frequencyof 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 in 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

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 CT/MRI, 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 ± 5 % of the dose at the specification point (= target–absorbed dose). *The treatment is given in an accelerated hyperfractioned fashion, with two daily fractions of 1.5 Gy each, at an interval of no less than 6 hours.* Radiotherapy is started on the 7th day after VAdmC^{1} and on the 14th day after C^{2}Eto^{2}. 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

1.1 Histological good responders: Histological grades II and III with wide or radical margin, grade III with marginal margin

Induction: No radiotherapy
Maintenance: No radiotherapy

1.2 Histological poor responders: Histological grade I with wide or radical margin

Induction: No radiotherapy
Maintenance: No radiotherapy

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

Induction: No radiotherapy
Maintenance: 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. See 2.2.

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: The original tumor volume with a margin of 3 cm 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 42 Gy/28 fractions

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

Dose, target II 54 Gy/36 fractions

Tumors that expand in preformed cavities (i.e. pelvis or thorax) usually do not infiltrate organs and the soft tissue componet responds well to chemotherapy. For these tumors the target volume may be planned based on the residual soft tissue mass after chemotherapy with a margin of 2 cm, while the initial extent of bone and soft tissue infiltration must be included in the treatment volume (2,3).

Dose to critical organs

The dose to kidney, heart, liver, lung, and spinal cord shall be calculated. Doses to the critical organs should not exceed the maximum values listed below:

spinal cord	45 Gy
heart	30 Gy to more than 50% of its volume
liver	30 Gy to more than 50% of its volume
lung	20 Gy to the whole lung
kidney	14 Gy to the whole kidney

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.

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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 7

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 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 good responders chemotherapy and toxicity data	Completed by pediatrician or oncologist
Chemotherapy flow-sheet **Form 8A** **Form 8B**	Details about postoperative or postradiation poor responders chemotherapy and toxicity data	Completed by pediatrician or oncologist
Chemotherapy flow-sheet **Form 9A** **Form 9B**	Details about high-dose chemotherapy with Busulfan, Melphalan and toxicity data	Completed by pediatrician or oncologist
Radiotherapy flow-sheet **Form 10**	Details about radiotherapy	Completed by radiotherapist
Follow-up **Form 11**	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
II. histological slides of the primary tumor are sent *1 week after starting chemotherapy.*
III. Forms 4, 5, 6A and 6B are sent *4 weeks after preoperative (preradiotherapy) chemotherapy*.
IV. Forms 7A, 7B, 8A and 8B are sent *4 weeks after postoperative (postradiotherapy) chemotherapy*.
V. Forms 9A and 9B are sent *4 weeks after high-dose Busulfan and Melphalan.*
VI. Form 10 is sent *shortly after end of radiotherapy*.
VII. Form 11 is sent *immediately after end of treatment and each follow-up visit*.

Ewing´s sarcoma family tumors ISG/SSG III

INSTITUTION´S COMMITMENT FORM 1

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

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

Department: ..... Hospital: .....

City: ..... Country: .....

This form is a prerequisite for patient eligibility in ISG/SSG III 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 III 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 III 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 III

REGISTRATION **FORM 2**

Send this form one week after start
of chemotherapy to:
SSG secretariat
Regional Tumor Registry
Lund University Hospital
SE-221 85 LUND
Sweden

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

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

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Ewing´s sarcoma family tumors ISG/SSG III

PATHOLOGY REPORT I **FORM 3**

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

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

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 III

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		Weightloss (10 % in 6 months)		Fever	
☐ no	☐ yes	☐ no	☐ yes	☐ 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
☐ yes ☐ no Date Day Month Year

Cycle 2 completed
☐ yes ☐ no Date Day Month Year

Cycle 3 completed
☐ yes ☐ no Date Day Month Year

Cycle 4 completed
☐ yes ☐ no Date Day Month Year

Surgery

☐ Resection ☐ Amputation ☐ No surgery Date Day Month Year

Type of reconstruction

☐ None ☐ Allograft ☐ Vascularized graft ☐ Endoprothesis

☐ Other, specify; .....

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Ewing´s sarcoma family tumors ISG/SSG III

PATHOLOGY REPORT II **FORM 5**

Final report including photograph
(Polaroid picture or slide)

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

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

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

Sending institution (if not same as above): .....

Ewing's sarcoma family tumors ISG/SSG III
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: _____

Weight: _____ kg

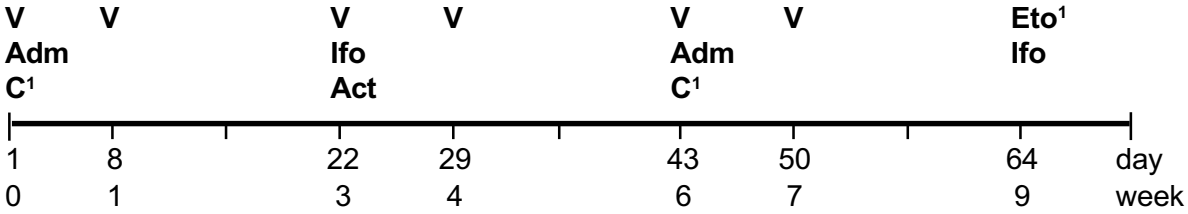
Height: _____ cm

Body surface: _____ m^2

Ifosfamide

Short-time infusion ☐ no ☐ yes

Long-time infusion ☐ no ☐ yes



	Start	Nadir	Start	Nadir	Start	Nadir	Start	Nadir
Date, D/M/Y	.... /.... /....		.... /.... /....		.... /.... /....		.... /.... /....	
Hb								
WBC								
Tromb								
Given doses								
V mg								
Adm mg								
C^1 mg								
Ifo mg								
Act mg								
Eto^1 mg								

V: Vincristine 1.5 mg/m^2 (max 2 mg) i.v. push

Adm(in**VA**dm**C**[1]): Adriamycin (Doxorubicin) 40 mg/m^2/day as 4 hours (2 days) i.v. inf.
Total dose of Doxorubicin = 80 mg/m^2 in 2 days

C[1] (in **VA**dm**C**[1]): Cyclophosphamide 1200 mg/m^2 i.v. as 30 minutes i.v. inf.

Ifo (in **VI**fo**A**ct and **E**to[1]**I**fo): Ifosfamide 3000 mg/m^2/ 21–24 hour as 72 hours (3 days) continuous i.v. infusion (total dose 9000 mg/m^2)

Act (in**VI**fo**A**ct): Actinomycin-D 1.5 mg/m^2 (max 2 mg) i.v. push

Eto[1] (in **E**to[1]**I**fo): Etoposide 150 mg/m^2/day in 3 days as 2 hours i.v. inf.
Total dose of Etoposide = 450 mg/m^2 in 3 days

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Ewing's sarcoma family tumors ISG/SSG III
Chemotherapy toxicity flow-sheet FORM 6B

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

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

Preoperative or preradiation chemotherapy

	VAdm**C**[1]	**VI**fo**A**ct	**VA**dm**C**[1]	**E**to[1]**I**fo
Date	Day /Month /Year ...../ ...../	Day /Month /Year ...../ ...../	Day /Month /Year ...../ ...../	Day /Month /Year ...../ ...../ .....
Delay	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
Reduction	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
Transaminase*	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐
Creatinine*	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐
Stomatitis*	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐
Hematuria*	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐
Low Bicarb.	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
Fever	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
Hospitalization	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
Transfusion Erytrocyt	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
Transfusion Platelets	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
G-CSF	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
Cardiotoxicity	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no

*** According to NCIC CTG Expanded common toxicity criteria**

Toxicity grade	**0**	**1**	**2**	**3**	**4**
Transaminase	normal	≤2.5 x N	2.6–5.0 x N	5.1–20.0 x N	>20.0 x N
Creatinine	normal	<1.5 x N	1.5–3.0 x N	3.1–6.0 x N	>6.0 x N
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 III
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
Good responders

Year: _____

Weight: _____ kg

Height: _____ cm

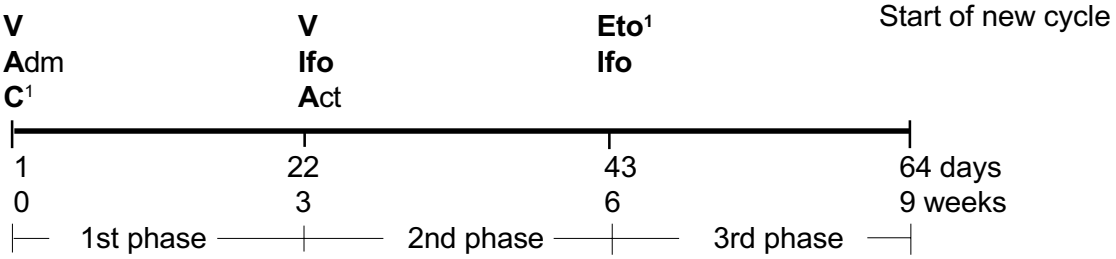
Body surface: _____ m^2

Cycle No: _____

Ifosfamide

Short-time infusion ☐ no ☐ yes

Long-time infusion ☐ no ☐ yes



	Start	Nadir	Start	Nadir	Start	Nadir
Date, D/M/Y	..... /..... /.....		..... /..... /.....		..... /..... /.....	
Hb						
WBC						
Tromb						
Given doses						
V mg						
Adm mg						
C1 mg						
Ifo mg						
Act mg						
Eto1 mg						

V: Vincristine 1.5 mg/m^2 (max 2 mg) i.v. push

Adm(in**VA**dm**C**1): Adriamycin (Doxorubicin) 40 mg/m^2/day as 4 hours (2 days) i.v. inf.
Total dose of Doxorubicin = 80 mg/m^2 in 2 days

C1 (in **VA**dm**C**1): Cyclophosphamide 1200 mg/m^2 i.v. as 30 minutes i.v. inf.

Ifo (in **VI**fo**A**ct and **E**to1**I**fo): Ifosfamide 3000 mg/m^2/ 21–24 hour as 72 hours (3 days) continuous i.v. infusion (total dose 9000 mg/m^2)

Act (in**VI**fo**A**ct): Actinomycin-D 1.5 mg/m^2 (max 2 mg) i.v. push

Eto1 (in **E**to1**I**fo): Etoposide 150 mg/m^2/day in 3 days as 2 hours i.v. inf.
Total dose of Etoposide = 450 mg/m^2 in 3 days

Ewing's sarcoma family tumors ISG/SSG III
Chemotherapy toxicity flow-sheet FORM 7B

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

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

Postoperative cycle No. .....

Postoperative or postradiation chemotherapy
Good responders

	VAdm**C**[1]	**VI**fo**A**ct	**E**to[1]**I**fo
Date	Day /Month /Year ...../ ...../	Day /Month /Year ...../ ...../	Day /Month /Year ...../ ...../ .....
Delay	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
Reduction	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
Transaminase*	0 1 2 3 4 ☐ ☐ ☐ ☐ ☐	0 1 2 3 4 ☐ ☐ ☐ ☐ ☐	0 1 2 3 4 ☐ ☐ ☐ ☐ ☐
Creatinine*	0 1 2 3 4 ☐ ☐ ☐ ☐ ☐	0 1 2 3 4 ☐ ☐ ☐ ☐ ☐	0 1 2 3 4 ☐ ☐ ☐ ☐ ☐
Stomatitis*	0 1 2 3 4 ☐ ☐ ☐ ☐ ☐	0 1 2 3 4 ☐ ☐ ☐ ☐ ☐	0 1 2 3 4 ☐ ☐ ☐ ☐ ☐
Hematuria*	0 1 2 3 4 ☐ ☐ ☐ ☐ ☐	0 1 2 3 4 ☐ ☐ ☐ ☐ ☐	0 1 2 3 4 ☐ ☐ ☐ ☐ ☐
Low Bicarb.	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
Fever	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
Hospitalization	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
Transfusion Erytrocyt	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
Transfusion Platelets	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
G-CSF	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
Cardiotoxicity	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no

*** According to NCIC CTG Expanded common toxicity criteria**

Toxicity grade	**0**	**1**	**2**	**3**	**4**
Transaminase	normal	≤2.5 x N	2.6–5.0 x N	5.1–20.0 x N	>20.0 x N
Creatinine	normal	<1.5 x N	1.5–3.0 x N	3.1–6.0 x N	>6.0 x N
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 III
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

Postoperative or postradiation chemotherapy
Poor responders

Year: _____

Weight: _____ kg

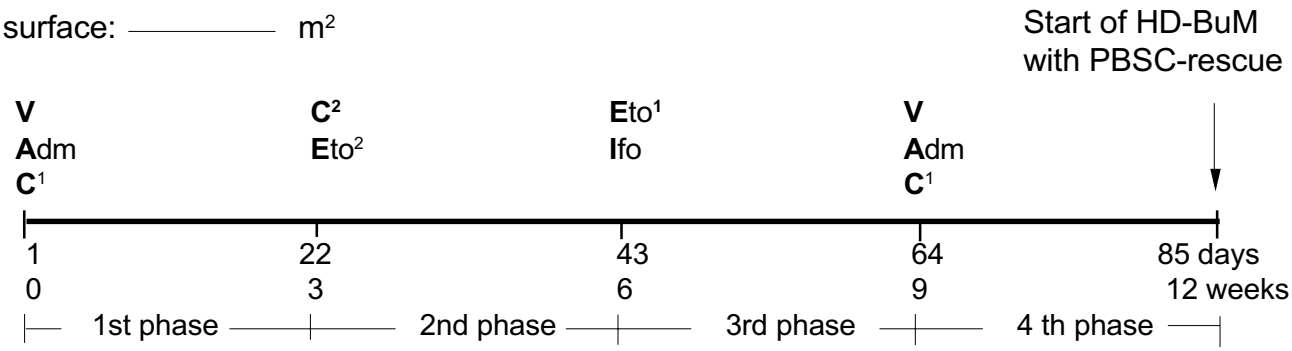
Height: _____ cm

Body surface: _____ m^2

Ifosfamide

Short-time infusion ☐ no ☐ yes

Long-time infusion ☐ no ☐ yes



	Start	Nadir	Start	Nadir	Start	Nadir	Start	Nadir
Date, D/M/Y	... /.... /....		.... /.... /....		.... /.... /....		.... /.... /....	
Hb								
WBC								
Tromb								
Given doses								
V mg								
Adm mg								
C^1 mg								
C^2 mg								
Eto^2 mg								
Eto^1 mg								
Ifo mg								

V: Vincristine 1.5 mg/m^2 (max 2 mg) i.v. push

Adm(in**VA**dm**C**^{1}): Adriamycin (Doxorubicin) 40 mg/m^2/day as 4 hours (2 days) i.v. inf.
Total dose of Doxorubicin = 80 mg/m^2 in 2 days

C^1 (in **VA**dm**C**^{1}): Cyclophosphamide 1200 mg/m^2 i.v. as 30 minutes i.v. inf.

C^2 (in **C**^{2}**E**to^2): Cyclophosphamide 4000 mg/m^2 i.v. as 3 hours i.v.inf.

Ifo (in **VI**fo**A**ct and **E**to^1**I**fo): Ifosfamide 3000 mg/m^2/ 21–24 hour as 72 hours (3 days) continuous i.v. infusion
(total dose 9000 mg/m^2)

Eto^1 (in **E**to^1**I**fo): Etoposide 150 mg/m^2/day in 3 days as 2 hours i.v. inf. Total dose of Etoposide = 450 mg/m^2 in 3 days

Eto^2 (in **C**^{2}**E**to^2): Etoposide 200 mg/m^2/day as 2 hours (3 days) i.v. inf. Total dose of Etoposide = 600 mg/m^2 in 3 days

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Ewing's sarcoma family tumors ISG/SSG III
Chemotherapy toxicity flow-sheet FORM 8B

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

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

Postoperative or postradiation chemotherapy
Poor responders

	VAdm**C**[1]	**C**[2]**E**to[2]	**E**to[1]**I**fo	**VA**dm**C**[1]
Date	Day /Month /Year ...../ ...../	Day /Month /Year ...../ ...../	Day /Month /Year ...../ ...../	Day /Month /Year ...../ ...../ .....
Delay	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
Reduction	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
Transaminase*	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐
Creatinine*	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐
Stomatitis*	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐
Hematuria*	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐	0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐
Low Bicarb.	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
Fever	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
Hospitalization	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
Transfusion Erytrocyt	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
Transfusion Platelets	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
G-CSF	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
Cardiotoxicity	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no

*** According to NCIC CTG Expanded common toxicity criteria**

Toxicity grade	**0**	**1**	**2**	**3**	**4**
Transaminase	normal	≤2.5 x N	2.6–5.0 x N	5.1–20.0 x N	>20.0 x N
Creatinine	normal	<1.5 x N	1.5–3.0 x N	3.1–6.0 x N	>6.0 x N
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 III
CHEMOTHERAPY FLOW-SHEET FORM 9A

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

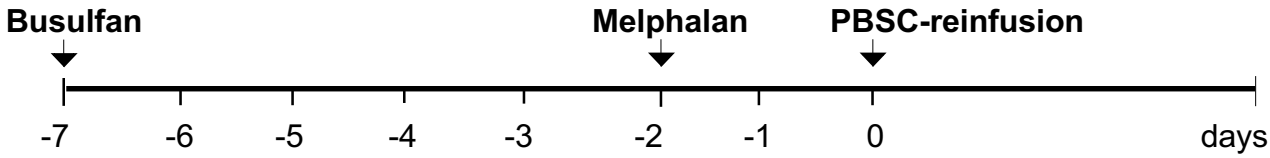
Body surface: _____ m^2

Dates for harvest after C^2, Eto^2: Day Month Year

PBSC yield: ___ x 10^6 CD34 cells/kg

Date for reinfusion of PBSC Day Month Year

Number of PBSC infused ___ x 10^6 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/m^2 i.v. as 60 minutes continuous i.v. inf.
Peripher Blood Stem Cell rescue at 48 hours after termination of chemotherapy

99 05 MM

Ewing's sarcoma family tumors ISG/SSG III
Chemotherapy toxicity flow-sheet FORM 9B

Submit this form together with Form 9A to:
SSG secretariat
Regional Tumor Registry
Lund University Hospital
SE-221 85 LUND
Sweden

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

High-dose Busulfan and Melphalan with PBSC rescue

	Bu	M
Date	Day /Month /Year ...../ ...../	Day /Month /Year ...../ ...../ .....
Delay	☐ yes ☐ no	☐ yes ☐ no
Reduction	☐ yes ☐ no	☐ yes ☐ no
Transaminase*	0 1 2 3 4 ☐ ☐ ☐ ☐ ☐	0 1 2 3 4 ☐ ☐ ☐ ☐ ☐
Creatinine*	0 1 2 3 4 ☐ ☐ ☐ ☐ ☐	0 1 2 3 4 ☐ ☐ ☐ ☐ ☐
Stomatitis*	0 1 2 3 4 ☐ ☐ ☐ ☐ ☐	0 1 2 3 4 ☐ ☐ ☐ ☐ ☐
Hematuria*	0 1 2 3 4 ☐ ☐ ☐ ☐ ☐	0 1 2 3 4 ☐ ☐ ☐ ☐ ☐
Low Bicarb.	☐ yes ☐ no	☐ yes ☐ no
Fever	☐ yes ☐ no	☐ yes ☐ no
Hospitalization	☐ yes ☐ no	☐ yes ☐ no
Transfusion Erytrocyt	☐ yes ☐ no	☐ yes ☐ no
Transfusion Platelets	☐ yes ☐ no	☐ yes ☐ no
G-CSF	☐ yes ☐ no	☐ yes ☐ no
Cardiotoxicity	☐ yes ☐ no	☐ yes ☐ no

*** According to NCIC CTG Expanded common toxicity criteria**

Toxicity grade	0	1	2	3	4
Transaminase	normal	≤2.5 x N	2.6–5.0 x N	5.1–20.0 x N	>20.0 x N
Creatinine	normal	<1.5 x N	1.5–3.0 x N	3.1–6.0 x N	>6.0 x N
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 III
Radiation therapy **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

Start of treatment, date Day Month Year

End of treatment, date

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; .....

99 05 MM

Ewing's sarcoma family tumors ISG/SSG III
FOLLOW-UP **FORM 11**

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	Day Month Year		
Physical exam	☐ no	☐ yes	
Chest x-ray	☐ no	☐ yes	
CT of chest	☐ no	☐ yes	
X-ray of the primary tumor site	☐ no	☐ yes	
CT of the primary tumor site	☐ no	☐ yes	
MRI of the tumor site	☐ no	☐ yes	
Bone scan	☐ no	☐ yes	
Alkaline phosphatase	specify units	LDH	specify units

Status

Tumor status
☐ No evidence of disease ☐ Local recurrence ☐ Distant metastasis

☐ Death Date Day Month Year Autopsy ☐ no ☐ yes

☐ Died from Ewing´s sarcoma ☐ Died with Ewing´s sarcoma from other cause

☐ Died from treatment related complications ☐ Died NED from other causes, specify; .....

In case of distant metastase(s)

Lung	☐ no	☐ yes	☐ unilateral	☐ bilateral
Liver	☐ no	☐ yes	Number of metastases	
Bone	☐ no	☐ yes	Number of metastases	
☐ Other, specify;.....				

Treatment for relapse

☐ Curative intent ☐ Palliative intent

Treatment plan: ☐ chemotherapy ☐ surgery ☐ other, specify; .....

99 05 MM