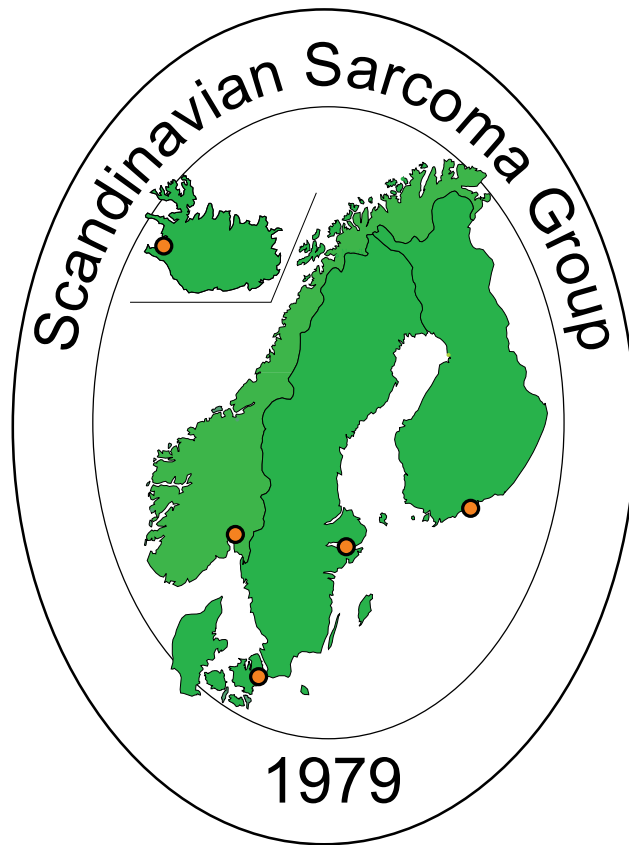


Scandinavian Sarcoma Group and
Oncologic Center, Lund, Sweden

SSG XIII

**A Scandinavian Sarcoma Group Treatment Protocol
for Adult Patients with High-Risk Soft Tissue Sarcoma
of the Extremities and Trunk Wall**



Date of activation July 1, 1998

Scandinavian Sarcoma Group and
Oncologic Center, Lund, Sweden

A Scandinavian Sarcoma Group treatment protocol for adult patients with high-risk soft tissue sarcoma of the extremities and trunk wall

Trial SSG XIII is a Scandinavian Sarcoma Group multicenter, prospective study for evaluation of surgery, radiation therapy and adjuvant combination chemotherapy for adults with high-risk soft tissue sarcoma of the extremities and trunk wall. The study is not randomized and it is open to any specialized cancer center that is part of the SSG network, and that fulfills all the protocol criteria.

All patients with soft tissue sarcoma treated according to this program must be reported to the Scandinavian Sarcoma Group secretariat.

Prepared by the Working Committee of the Scandinavian Sarcoma Group

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 base for cooperation. Accordingly, the Scandinavian Sarcoma Group (SSG) was founded in 1979. The aim of the Group was to improve the prognosis for sarcoma patients in the area. Guidelines for diagnosis, pathology, and treatment have been drawn which are now generally accepted by sarcoma centers in Scandinavia.

Our first randomized adjuvant chemotherapy trial for high-grade soft tissue sarcoma was done during 1981–1986 (2). A total of 240 patients were included also in the large meta-analysis, where adjuvant chemotherapy improved metastasis-free survival and local tumor control.

The present SSG XIII protocol will be the second, chemotherapy study of soft tissue sarcoma and this time a non-randomized adjuvant chemotherapy trial for a subgroup of patients with high-risk to develop metastasis (3).

The following members have participated in the protocol design:

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

The SSG XIII will be activated as of July 1, 1998.

Lund June 30, 1998

Organization of the Scandinavian Sarcoma Group

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Past and present protocols chairmen

Protocols	Oncology	Surgery	Pathology	Radiotherapy
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<i>Ewing's sarcoma:</i> SSG IV, SSG IX	I. Elomaa, Helsinki T. Wiklund, Helsinki T. Wiebe, Lund	O. Brosjö, Stockholm	M. Åkerman, Lund A.E. Stenwig, Oslo	C. Blomqvist, Helsinki
<i>Localized soft tissue sarcoma:</i> SSG I, XIII	T.A. Alvegård, Lund I. Turesson, Uppsala G. Saeter, Oslo C. Blomqvist, Helsinki	A. Rydholm, Lund P. Gustafson, Lund G. Follerås, Oslo	L. Angervall, Gothenburg N.O. Berg, Lund L.G. Kindblom, Gothenburg H. Willén, Lund	C. Blomqvist, Helsinki I. Turesson, Uppsala
<i>Advanced soft tissue sarcoma:</i> SSG X, SSG XII	T.A. Alvegård, Lund G. Sæter, Oslo C. Blomqvist, Helsinki	J. Høie, Oslo	A.E. Stenwig, Oslo H. Willén, Lund	C. Blomqvist, Helsinki I. Turesson, Uppsala
<i>SSG Central Registry:</i> SSG VII	T.A. Alvegård, Lund G. Saeter Oslo	H. Bauer, Stockholm P. Gustafson, Lund	L.G. Kindblom, Gothenburg M. Åkerman, Lund	C. Blomqvist, Helsinki I. Turesson, Uppsala

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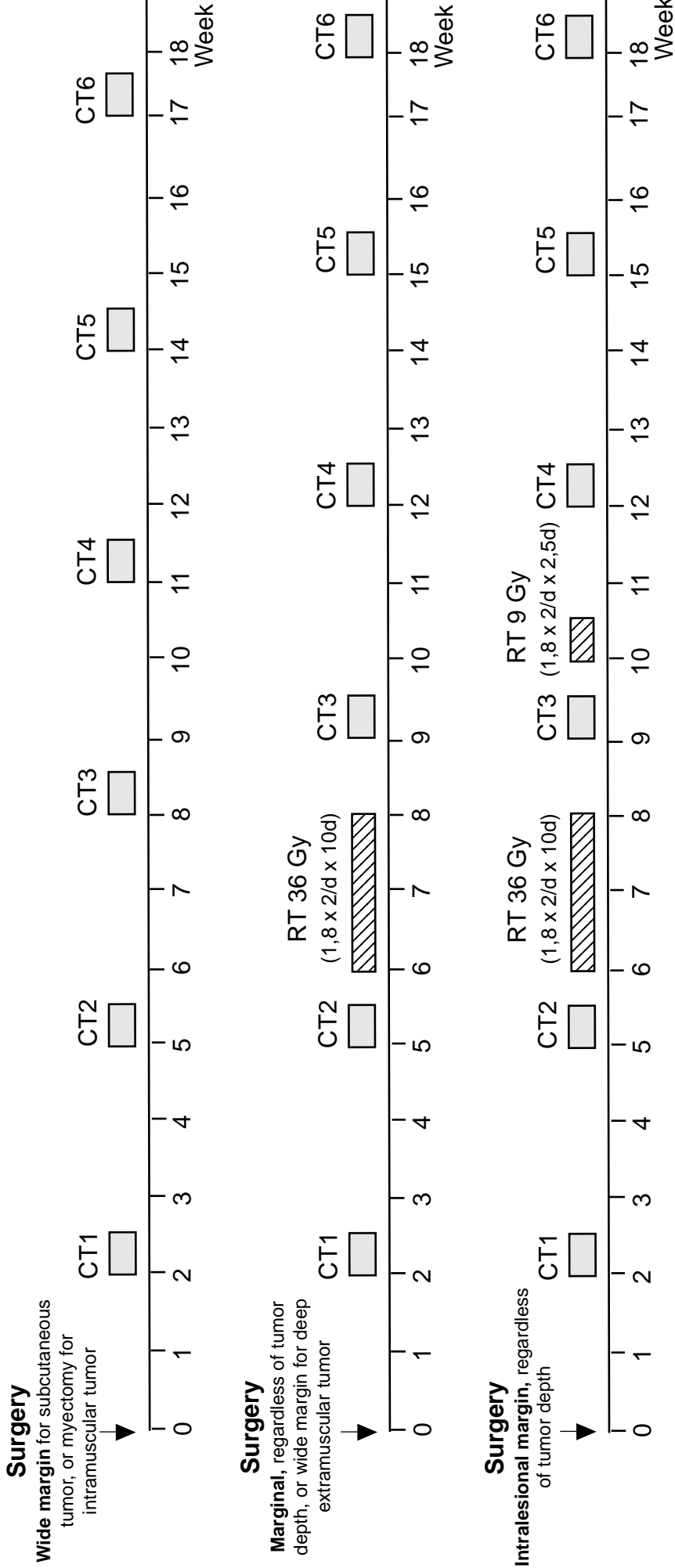
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Soft tissue sarcoma (STS) SSG XIII

1. Treatment Schedule

Adjuvant treatment for adult high-risk STS in extremities and trunk wall



CT regimen

Doxorubicin: 50 mg/m² as 4 hours infusion

Ifosfamide: 5 g/m² as 24 hours infusion

Mesna: According to protocol

Dose levels

CT1 Baseline

CT2-6 If CT1 WBC nadir >1.0 x 10⁹/l and Trombocytes nadir >90 x 10⁹/l escalate both drugs by 20%

If necessary, use G-CSF (Filgrastim) to maintain dose level

If CT1 WBC nadir <0.5 x 10⁹/l or Trombocytes nadir <40 x 10⁹/l reduce both drugs by 20%

2. Introduction

Soft tissue sarcoma (STS) in adults is associated with a relatively high rate of mortality. About 80% of the patients have highly malignant tumors. Even with optimal local treatment, more than 50% of patients with high-grade malignancies die because of metastases.

To improve relapse-free and overall survival, adjuvant chemotherapy has been evaluated in about twenty prospective, randomized studies. Quite a few of them showed a real improvement in relapse-free survival but not concerning overall survival. However, in the majority of studies the chemotherapy arm tended to do slightly better than the control arm.

The possible benefit of adjuvant chemotherapy found in these relatively small studies was confirmed in a recent quantitative meta-analysis (3). This was based on updated individual patient data from 14 trials and totally 1568 patients, using doxorubicin-based chemotherapy. The material represented 98% of patients from all known randomized trials. This analysis provided evidence that adjuvant chemotherapy significantly improved the local recurrence-free and distant recurrence-free interval and overall recurrence-free survival: the 10-year results improved from 75 to 81%, 60 to 70% and 45 to 55% respectively, when doxorubicin as a single drug or in combination with other drugs was added. There was a trend toward improved overall survival from 50 to 54% at 10 years ($p=0.12$).

This reevaluation of the effect of adjuvant chemotherapy in STS illustrates the problem in dealing with a very heterogeneous group of tumors. The rarity and complexity of soft tissue sarcoma has meant that accruing sufficient numbers of patients into trials has been, and continues to be, a problem. However, the evidence of benefit of adjuvant chemotherapy in STS from this meta-analysis is so robust that it could be recommended to high-risk patients outside the context of a clinical trial.

Clearly, all patients with STS does not need adjuvant chemotherapy. Therefore, prognostic factors to identify those patients who need adjuvant therapy must be applied in a selection process. Although its somewhat subjective nature, the malignancy grade shown to be the most consistent prognostic factor. However, recently a thorough mapping of prognostic factors in STS has been presented by Gustafson (4). It was found that tumor size, microscopic tumor necrosis and vascular invasion were strong prognostic factors.

A prognostication system based on these factors has been described, and recently also tested for reproducibility. This system gives good separation between the groups, and the reproducibility is over 80%.

In this protocol adjuvant chemotherapy will be recommended to a well-defined subgroup of patients with STS with poor prognosis on the basis of this new knowledge.

3. Aims and General Protocol Design

(for treatment outline see p. 8)

To determine whether adjuvant chemotherapy, added to optimal local treatment, in a well-defined subgroup of patients with STS and high-risk for distant metastases, improves overall survival.

SSG XIII is a comprehensive prospective Phase II study for high-risk soft tissue sarcoma of the extremities and trunk wall. It is an adjuvant combination chemotherapy protocol directed towards an optimal choice of chemotherapeutic agents (doxorubicin, ifosfamide). Based on previous experience within SSG as well as the experience reported in the literature, the protocol aims at the best results possible with modern chemotherapy in high-risk soft tissue sarcoma.

The principle aims of the study are:

1. To determine whether adjuvant chemotherapy, added to optimal local treatment, in a well defined subgroup of patients with soft tissue sarcoma and high-risk for distant metastases, improves the 5 and 10 years metastasis free survival from 40% and 32% to 70% and 60% respectively.
2. To increase the overall survival from approximately 50% to 70%.
3. To determine the morbidity of this treatment.

4. Organization

The main study secretariat is located in Sweden:

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5. Publication

The SSG group will have access to the entire data base, and individual institutions are free to publish their own data. However, a main purpose is to publish the SSG patient material jointly. In this process, the list of authors will be worked out in a collaboration between the principal investigators of SSG and the SSG publication committee.

6. Ethical Considerations

SSG XIII is a non-randomized phase II study based on SSG experience and reports in recent medical literature.

Before the start of treatment, the patients will be informed about the nature of the disease, the treatment plan and the expected benefit and side-effects, according to standard procedures in each country.

The benefit and side-effects of the treatment will be recorded and reported in the international literature.

The physician responsible for the individual patient may deviate from the protocol or may terminate treatment for various medical reasons on medical indications.

7. Definition of High-Risk Group

Tumors of malignancy grades III and IV and at least two of the following factors: tumor size >8cm, macroscopic and/or microscopic tumor necrosis or vascular invasion.

Tumor defined in this way constitutes about one third of all STS of the locomotor system. The 5 and 10 year metastasis-free survival rate for patients with such tumors is expected to 40% and 32%, respectively, in the absence of adjuvant treatment. About 55% of all patients with STS of the locomotor system who will develop metastases, will be classified in this high-risk group.

8. Definition of the Low-Risk Group

Tumors of malignancy grade III and IV and none or only one of the following factors: tumor size >8 cm, macroscopic and/or microscopic tumor necrosis or vascular invasion.

Tumors of malignancy grade I and II.

9. Eligibility Criteria

1. Age ≥ 18 years and ≤ 70 years.
2. Performance status 0 or 1 (WHO).
3. Adequate hematologic, hepatic and renal functions.
4. Extremity or trunk wall localization.
5. Subcutaneous or deep-seated tumor.
6. All histotypes except those listed below.
7. High-risk criteria as defined above.

10. Exclusion Criteria

1. Age < 18 years and > 70 years.
2. Performance status ≥ 2 (WHO).
3. Inadequate hematologic, hepatic and renal functions, or other severe medical illness.
4. Second primary cancer.
5. Histotype: X-skeletal Ewing sarcoma, PNET, -osteosarcoma and -chondrosarcoma, malignant mesenchymoma, clear cell sarcoma, alveolar soft part sarcoma, epithelioid sarcoma, rhabdomyosarcoma, Kaposi sarcoma.
6. Low-risk criteria as defined above.

11. Pretreatment Investigations

(also see flow-sheet in Appendix 1, p. 19)

Mandatory requirements:

1. Complete medical history and physical examination (including date and nature of first symptoms and body height, weight and surface area).
2. The surgical specimen, surgical or large coarse needle biopsy (representative slides should be sent to the study secretariat upon registration) should be evaluated by two pathologists concerning diagnosis and risk factors.
3. Laboratory studies:
 - a. Complete blood count (hemoglobin, white blood counts with differential, trombocytes).
 - b. Serum creatinine, creatinine-clearance, ALP, total bilirubin and liver transaminases.
4. Radiological and scintigraphic studies pre- and/or postoperatively.
 - a. A–P and lateral conventional x-ray of the entire involved extremity or trunk wall.
 - b. CT and/or MRI scan of the entire involvement extremity.
 - c. A–P and lateral chest x-rays.
 - d. CT scan of the chest.
5. Electrocardiogram (ECG).
6. Cardiac ultrasound, with estimation of left ventricular ejection fraction (LVEF), before first course of adriamycin treatment.

Recommended investigations (optional):

1. Sperm count. It is recommended that a sperm count is performed in young patients where it is feasible, and that these patients are offered sperm banking prior to chemotherapy.

12. Investigation During Treatment and Follow-up

(see also flow-sheet in Appendix 1, p. 19)

Mandatory investigations at follow-up

1. Complete physical examination before each cycle and at each follow-up visit.
2. A–P lateral chest x-rays at the end of treatment and at each visit. The CT scan of the chest is optional, but it should be performed if chest x-ray shows metastasis or is inconclusive.
3. Blood count (hemoglobin, white blood counts, trombocytes), transaminases, ALP, and serum creatinine at each visit.
4. Cardiac ultrasound with estimation of left ventricular ejection fraction at the end of treatment and at 6 months, 12 months and then at 3 year intervals.

Recommended investigations (optional):

1. Sperm count at the end and 3 years after the end of treatment in young patients.

During the treatment the patient should be investigated and scored for acute radiation morbidity once a week. After therapy patients will be evaluated concerning tumor status and late radiation morbidity each three months in the first and second year, the third and fourth year each half a year and then yearly up to 10 years.

Scoring of radiotherapy side effect

Acute skin reactions

Score 0	none
Score 1	minimal erythema
Score 2	moderate erythema
Score 3	brisk erythema
Score 4	spotted moist desquamation
Score 5	confluent moist desquamation

Late effects

Score 0	none
Score 1	minimal fibrosis or induration
Score 2	distinct fibrosis or induration
Score 3	very marked fibrosis or induration
Score 4	reduced function due to fibrosis or induration
Score 5	necrosis

13. Treatment Protocol

After surgery, adjuvant radiotherapy and/or chemotherapy is given depending on both the quality of the surgical margin and the grading of the tumor. Adjuvant radiotherapy shall be given to all patients operated upon with intralesional or marginal margins since these margins have high local recurrence rates. Also, deep extramuscular tumors operated with wide margin should receive radiotherapy. Adjuvant chemotherapy should be given to all patients with a high-risk tumor, regardless of surgical margin

13.1 Patient category I.

Patients operated upon with wide margins for a subcutaneous tumor or patients operated upon with myectomy for an intramuscular tumor.

13.1.1 *Low-risk* (see p. 11)

- no further treatment

13.1.2 *High-risk* (see p. 11)

- adjuvant chemotherapy, 6 cycles

13.2 Patients category II.

Patients operated upon with marginal margins regardless of tumor depth, or patients operated upon with wide margin for a deep extramuscular tumor.

13.2.1 *Low-risk* (see p. 11)

- radiotherapy, 5×2.0 Gy/week, total dose of 50 Gy

13.2.2 *High-risk* (see p. 11)

- Chemotherapy, 2 cycles, followed by
- radiotherapy, $2 \times 1,8$ Gy/day $\times 10$ days, i.e. a total dose of 36 Gy, followed by
- chemotherapy, 4 cycles

13.3 Patients category III.

Patients operated upon with intralesional margins, regardless of tumor depth.

13.3.1 *Low-risk* (see p. 11)

- radiotherapy 5×2.0 Gy/week, total dose of 50 Gy + boost dose of 10 Gy in 5 fractions

13.3.2 *High-risk* (see p. 11)

- chemotherapy, 2 cycles, followed by
- radiotherapy, 2×1.8 Gy/day $\times 10$ days, i.e. a total dose of 36 Gy, followed by
- chemotherapy, 1 cycle, followed by
- radiotherapy, 2×1.8 Gy/day $\times 2.5$ days, i.e. a boost dose of 9 Gy in 5 fractions followed by
- chemotherapy, 3 cycles

14. Radiobiological Considerations

Over the last 10 years evidence has been gained both from experimental and clinical studies, that accelerated proliferation of surviving cells during prolonged treatment times or rest periods in the treatment might significantly decrease the probability of local cure. Regrowth of subclinical disease or within the primary tumor might also decrease the curability potential by multimodal treatment because of long time periods, often due to logistical reasons, between surgery, radiotherapy and chemotherapy.

Therefore, in general, we should aim at shortening the overall treatment time as much as possible without compromising wound healing and tolerance of acute radiation side effects.

14.1 Fractionation schedules and dose levels

In order to shorten the overall treatment period, the fractionation schedule proposed in this protocol is 2×1.8 Gy/day, with 6 hours interval between the two daily fractions, and 5 treatment days per week. The rationale behind this proposal is that, for the same number of fractions, 2×1.8 Gy/day \times 5/week is equivalent to 5×2.0 Gy/week concerning **late effects**, i.e. 25 fractions using 1×2.0 Gy/day is equivalent to 25 fractions using 2×1.8 Gy/day.

The reduction of 10% in dose per fraction is necessary because of less repair of sublethal damage within 6 hours compared to 24 hours interval between fractions in various late reacting tissues (1, 5, 6). However, unexpectedly, this dose reduction is not necessary for **acute effects** in skin, such as erythema, moist desquamation and basal cell killing (7), i.e. 25 fractions with 1×2.0 Gy/day results in significantly more pronounced acute skin damage than 25 fractions with 2×1.8 Gy/day.

14.2 Combination of adjuvant chemotherapy and radiotherapy

When radiotherapy is combined with doxorubicin and ifosfamide dose-modifying effects are to be expected both for acute and late tissue reactions. However, there is a lack of any reliable clinical information of the size of this effect when radiotherapy is tightly interfoliated with chemotherapy, as is recommended in this protocol. A dose modifying factor of 1.15 was assumed both for acute and late tissue reactions in the present protocol (8).

In summary, the dose levels proposed for the combined treatment, adjuvant chemotherapy and radiotherapy, are 36 Gy for marginal surgery and also for wide margins in deep seated tumors and 45 Gy for intralesional resections. The late morbidity, which is of major concern, is estimated, as accurate as possible, to be equivalent to the conventional doses of 50 and 60 Gy, respectively, for radiotherapy alone. However, the acute morbidity of this combined modality is expected to be some what less than after the conventional postoperative radiotherapy.

Radiation therapy is given one week apart from chemotherapy according to treatment schedule (p. 8).

15. Target Volume and Technique

The target volume should include all anatomical regions at risk for tumor cell dissemination. In extremity tumors, the target volume should encompass the whole affected compartment(s) in the transverse direction and the surgical and drainage scars in the longitudinal direction with a margin of at least 5 cm. The boost should encompass the tumor bed (and operative area if feasible) with a 2 cm margin.

In extremity tumors the limb should be immobilized in a custom made cast in order to ensure the reproducibility of the field set-up. Individual dose planning should be used. It is recommended that the target volume are worked out in collaboration with the surgeon.

16. Chemotherapy Regimen

For SSG institutions, chemotherapy will consist of:

- Doxorubicin 50 mg/m² 4-hour infusion, day 1
- Ifosfamide 5 g/m² 24-hour infusion, day 1
- If necessary G-CSF (Filgrastim) 1.0 ml (0.3 mg) s.c./daily day 3–13. The first G-CSF injection should be given at least 24 hours after the cessation of chemotherapy
- Cycles to be repeated every 21 days

16.1 Drug formulation and administration

Doxorubicin is available in vials of 10 mg and 50 mg. It should be dissolved in sterile water at a concentration of 5 mg/ml and can be further diluted in normal saline and given as a intravenous infusion.

Ifosfamide is available in vials of 500 mg, 1 g and 2 g. It should be dissolved in sterile water at concentration of 1 g/12,5 ml. The total dose should be further dissolved in 3 liters NaCl 0.9% with mesna 2.5 g/m² and infused intravenously over 24 hours. A diuresis should be established before treatment using 1 liter NaCl 0.9% over 2 hours. Mesna 1.25 g/m² should be given by iv bolus immediately before starting the ifosfamide/mesna infusion. Following the ifosfamide/mesna infusion, 2 liters NaCl 0.9% containing 1.25 g/m² mesna should be infused over 12 hours.

16.2 Dose modifications for hematological toxicity

At start of next treatment

WBC × 10 ⁹ /l	Platelets × 10 ⁹ /l	Drug dose
≥3.0	≥100	100%
<3.0	<100	delay one week until recovery

16.3 Dose modification based on nadir values

If CT1 WBC nadir <0.5 × 10⁹/l and platelets <40 × 10⁹/l or neutropenic fever reduce both doxorubicin and ifosfamide by 20%.

16.4 Dose escalation

Chemotherapy course (CT1): Baseline

Chemotherapy course (CT2-6): If CT1 WBC nadir >1.0 × 10⁹/l and platelets nadir >90 × 10⁹/l escalate both doxorubicin and ifosfamide by 20%.

If necessary, use G-GSF (Filgrastim) to maintain dose level.

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Appendix 1

Soft Tissue Sarcoma XIII

Localized high-risk

Investigation and follow-up flow sheet

NOTE: Follow-up after end of treatment. Patients should be followed at 3 month intervals for 2 years, at 6 month intervals during the 3rd and 4th years, and then at one year interval until 10 years after end of treatment.

	Pre-treatment	During* treatment	End of treatment	Every follow-up	Other, comments
Physical examination	×	×	×	×	
Std. blood sample ¹	×	×	×	×	
S-creatinine,	×	×	×	×	
X-rays of involved tumor site	×	×		×	
CT and/or MRI of involved tumor site	×	(×)			
Chest x-ray	×	(×)	×	×	
CT of chest	×	(×)	(×)	(×)	× On suspicion of lung metastases on chest x-ray
ECG	×	(×)	(×)		(×)(every 3 years after treatment)
Cardiac ultra-sound/LVEF ²	×		×		× at 3 months, 6 months and then every 3 years after treatment
Sperm count	(×)		(×)		(×)(3 years after treatment)

× = mandatory (×) = recommended

* After each chemotherapy cycle

1. Includes: hemoglobin, white blood counts with differential, trombocytes, creatinine, ALP, LDH, total bilirubin, transaminases
2. Left ventricular ejection fraction

Submission of forms

Form	Contents	Reporting
Form 1 Registration	Patient data, date of biopsy, date of surgery, localization of tumor, histologic diagnosis, risk factors, date of start of chemotherapy	Completed by oncologist
Form 2 Pathology review for sarcomas	Primary diagnostic procedure	Completed by pathologists and surgeon
Form 3 On-study	Patient data, investigation prior to treatment, chemotherapy details	Completed by oncologist latest four weeks after last 6 th chemotherapy cycle
Form 4A Chemotherapy flow-sheet Form 4B Chemotherapy toxicity flow-sheet	Details of each postoperative chemotherapy cycle, patient data, date and dose of chemotherapy and toxicity data	Completed by oncologist
Form 5 Radiation therapy flow-sheet	Details of radiation therapy, side effects	Completed by oncologist
Form 6 Follow-up	Clinical evaluation of patients from time of diagnosis	Completed by a examining physician at each follow-up visit

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

- I. Form 1 and 2 together with histological slides of the primary tumor are sent *one week after start of chemotherapy*.
- II. Form 3, 4A and 4B are sent *3 weeks after end of completed postoperative chemotherapy*.
- III. Form 5 are sent *3 weeks after completed postoperative radiation therapy*.
- IV. Form 6 are sent *immediately after end to follow-up visit*.

Soft Tissue Sarcoma SSG XIII (localized high-risk)
REGISTRATION FORM 1

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

Send this form one week after start of chemotherapy to:

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

Hospital and department

Date Day Month Year

Physician

- Enclosed are:** 1. SSG Pathology review for sarcomas form 2
 2. Histological representative slides of diagnostic material

Date of biopsy Day Month Year Date of surgery Day Month Year

Tumor site:

Histological diagnosis, specify;

Risk factors

Tumor size: | | | cm

Necrosis no yes

Tumour grade I II III IV

Vascular invasion no yes

Number of risk factors | |

Start of chemotherapy Day Month Year

Soft Tissue Sarcoma SSG XIII (localized high-risk)
Pathology Review for Sarcomas FORM 2

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

Send this form one week after start of chemotherapy to:

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

Hospital and department

Date Day Month Year

Preop treatment			
History	<input type="checkbox"/> None	<input type="checkbox"/> Chemotherapy	<input type="checkbox"/> RT <input type="checkbox"/> Both
Type of tumor:	<input type="checkbox"/> Bone sarcoma	<input type="checkbox"/> Soft tissue sarcoma	
Current specimen:	<input type="checkbox"/> Primary tumor	<input type="checkbox"/> Reexcision	<input type="checkbox"/> Local recurrence <input type="checkbox"/> Metastasis
Previous diagnoses (cytologic and histologic) with their accession numbers:			

Accession number	Tumor site	Size x x cm
Depth:		
<input type="checkbox"/> Cutaneous	<input type="checkbox"/> Subcutaneous	<input type="checkbox"/> Deep fascia
<input type="checkbox"/> Intramuscular/	<input type="checkbox"/> Extramuscular/	<input type="checkbox"/> Bone/periosteum
<input type="checkbox"/> intraosseus	<input type="checkbox"/> extraosseus	<input type="checkbox"/> involvement
Macroscopic description of tumor		
Histological diagnosis		
Tumor grade: <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV <input type="checkbox"/> not applied		
Necrosis:		
Macroscopic	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Unknown
Microscopic	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Can't assess
% Necrosis:	<input type="checkbox"/> <25% <input type="checkbox"/> 25-50%	<input type="checkbox"/> > 50-95% <input type="checkbox"/> >95-99% <input type="checkbox"/> 100% <input type="checkbox"/> Can't assess
Largest extension mm		
Vascular invasion:		
<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Can't assess		
Assessment of surgical resection margin:		
<input type="checkbox"/> Surgeon alone	<input type="checkbox"/> Pathologist alone	<input type="checkbox"/> Both
<input type="checkbox"/> Intralesional	<input type="checkbox"/> Marginal	<input type="checkbox"/> Wide <input type="checkbox"/> Myectomy <input type="checkbox"/> Compartmental
Thickness and type of tissue at biologically poorest margin for wide excisions:		
Thickness mm	<input type="checkbox"/> Fat	<input type="checkbox"/> Loose areolar tissue <input type="checkbox"/> Muscle <input type="checkbox"/> Bone <input type="checkbox"/> Fascia

Mitotic rate: <input type="checkbox"/> Low $\leq 2/10$ hpf <input type="checkbox"/> Mod 3-9/10hpf <input type="checkbox"/> High $\geq 10/10$ hpf	Ki67 immunostains %
Predominant tumor surrounding/tissue interface: <input type="checkbox"/> Pushing <input type="checkbox"/> Infiltrative	
Focally infiltrative interface: <input type="checkbox"/> Yes <input type="checkbox"/> No	
Immunostains performed: <input type="checkbox"/> No <input type="checkbox"/> Yes, + stains <input type="checkbox"/> Yes, - stains	
EM performed: <input type="checkbox"/> Yes <input type="checkbox"/> No Findings:	
Cytogenetics/FISH/RT-PCR: <input type="checkbox"/> Yes <input type="checkbox"/> No Results:	
Frozen material: <input type="checkbox"/> Yes <input type="checkbox"/> No	DNA cytometry <input type="checkbox"/> Yes <input type="checkbox"/> No

Responsible Pathologist's name

Guidelines

1. Depth

Cutaneous: The tumor originates in the skin and may extend into the subcutaneous tissue.

Subcutaneous: The tumor lies in the fatty tissue between the skin and the deep fascia. If it penetrates the deep fascia it should be categorized as deep.

Deep fascia: The fascia that divides the subcutaneous compartment from the muscular compartment.

Intramuscular/intraosseous: The tumor is located beneath the deep fascia, originates in a muscle/bone, and is surrounded by muscle fascia/periosteum which is not engaged by the tumor.

Extramuscular/extraosseous: The tumor is located beneath the deep fascia, can lie between muscles or penetrates the boundaries of the muscle/bone.

Bone/periosteum involvement: Yes/no, should be filled in for STS.

2. Assessment of surgical resection margin

Intralesional margin: The tumor is opened or transected during the operation.

Marginal margin: The closest margin is outside the tumor, but near the tumor and through the reactive zone.

Wide margin: There is a cuff of healthy tissue around the specimen, covering the reactive zone all around the tumor.

Myectomy: A strictly intramuscular tumor is removed by excision of the entire muscle.

Compartmental margin: The whole tumor-bearing compartment is removed en bloc.

Wide contaminated margin is not used in SSG.

Thickness of tissue at biologically poorest margin:

The most interesting margin is the poorest margin, that is the part of the specimen where the tissue coverage is poorest (qualitatively and quantitatively). In that area you should register the type of tissue (e.g. fat, connective tissue) and the thickness (mms) of tissues covering the tumor.

3. Grading

A four-tiered grading system should be used whenever possible. For many soft tissue sarcomas the grade is understood or implicit in the diagnosis. For instance, atypical fibroxanthoma of skin, dermatofibrosarcoma protuberans and well differentiated liposarcoma are all grade 1 sarcomas. Typical examples of grade 2 sarcomas include myxoid liposarcoma and many subcutaneous myxofibrosarcomas. For high grade sarcomas (grades 3 and 4) the grade is partly based upon histogenetic diagnosis and partly upon the morphologic features, including cellularity, degree of differentiation, cellular pleomorphism, mitotic activity and necrosis. Examples of grade 4 sarcomas include round cell liposarcoma and pleomorphic liposarcoma.

4. Necrosis

Microscopic tumor necrosis is defined as the presence of amorphous cellular debris, usually associated with a neutrophil polymorphonuclear cell response. Dead cells generally are arranged in sheets, often with ghost nuclear outlines. Individual cell death, apoptotic bodies, areas of hyalinosis or edema, areas of fibrinous exudate lacking tumor cells, and areas of acellular fibrosis are not accepted within the definition of necrosis.

5. Vascular invasion

Vascular invasion can be seen within the tumor or in the adjacent tissues and is defined as the presence of tumor within any space having an endothelial lining. Such tumor either has to be adherent to the luminal aspect of the vessel wall or, if free-floating, has to be associated with adherent fibrin, red blood cells, or leucocytes. If the tumor is covered by an intact layer of endothelium, if the involved space has no discernible endothelial lining or if the tumor invades the vessel wall (but not the lumen) then this is not accepted within the definition of vascular invasion.

Bone and soft tissue tumors

Guidelines for handling of surgical specimens and histopathological diagnosis

- 1. *Fresh (unfixed) surgical specimens*** should be submitted immediately after removal to the Department of Pathology. The specimen should be handled immediately upon arrival for optimal fixation of samples for electron microscopy and deep-freezing (at least –80°). When there is a reason to believe (based on previous FNA, surgical biopsy or clinical and/or radiological features) that the sarcoma may have a characteristic cytogenetic abnormality (e.g. myxoid-round cell liposarcoma, synovial sarcoma, hemangiopericytoma, extraskeletal myxoid chondrosarcoma, clear cell sarcoma, alveolar rhabdomyosarcoma, extraskeletal Ewing’s sarcoma/PNET, desmoplastic small round cell tumor) samples should be processed for cytogenetic analyses (karyotyping, FISH-analysis or RT-PCR). Imprints (touch preparations) of samples that are deep-frozen or saved for special analyses are recommended to certify that representative sarcoma tissue has been saved.
- 2. *Macroscopic examination.*** Ideally the surgeon and the pathologist should examine the specimen together or at least communicate about problems that may arise regarding orientation of the specimen and resection margins. Copies of radiographic studies and drawings should be submitted with the specimen whenever possible. The tumor size is measured in three dimensions. The type of surrounding tissues and the percentage of macroscopic necrosis (based on tumor volume) and hemorrhage should also be stated. The closest margin of resection should be measured and it’s type of tissue recorded. Photographic documentation of all tumors is recommended.
- 3. *Histopathological examination.*** At least as many sections as the largest tumor dimension should be examined, e.g. at least 6 sections of a 6 cm tumor should be taken. Sections of the tumor interface with surrounding tissues as well as macroscopically divergent areas (including necrotic and hemorrhagic areas) should be sampled. Vascular invasion is seen best in the tumor periphery. Large sections (storsnitt) are excellent for the examination of tumor heterogeneity, relationship of the tumor to surrounding tissues and the presence of vascular invasion.
- 4. *Microscopic examination.*** In every case information on necrosis, vascular invasion, pattern of tumor interface, and type of tissue infiltrated as well as on mitotic activity (mitoses/HPF, 40 x objective) should be recorded. Immunostains for proliferative activity with Ki67 (MIB1) are recommended. Sarcomas should be graded on a four-tiered scale and standardized diagnoses used.
- 5. *Standardized protocol.*** As a supplement to the routine histopathologic report, a standardized protocol, which includes the most important macroscopic and microscopic information, should be filled out in every sarcoma (see enclosure).

“Second opinion“ diagnoses are strongly recommended.

Soft Tissue Sarcoma SSG XIII (localized high-risk)
ON-STUDY FORM 3

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

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

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)

Investigations prior to treatment

Plane x-ray: performed not performed

CT of involved tumor site: performed not performed

MRI of involved tumor site: 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

Chemotherapy

			Day	Month	Year
Cycle 1 completed	<input type="checkbox"/> no	<input type="checkbox"/> yes	Date		
Cycle 2 completed	<input type="checkbox"/> no	<input type="checkbox"/> yes			
Cycle 3 completed	<input type="checkbox"/> no	<input type="checkbox"/> yes			
Cycle 4 completed	<input type="checkbox"/> no	<input type="checkbox"/> yes			
Cycle 5 completed	<input type="checkbox"/> no	<input type="checkbox"/> yes			
Cycle 6 completed	<input type="checkbox"/> yno	<input type="checkbox"/> yes			

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

Hospital and department

Physician

Date Day Month Year

Chemotherapy

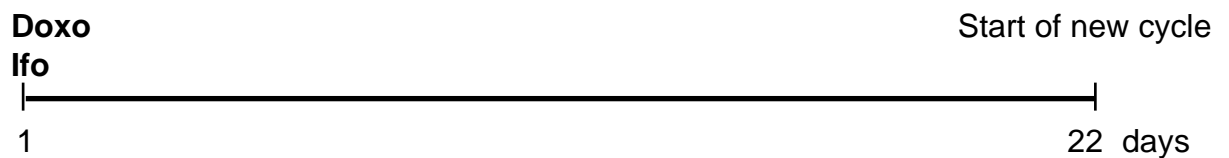
Year: _____

Weight: _____ kg

Height: _____ cm

Body surface: _____ m²

Cycle No: _____



	Start	Nadir
Date, D/M/Y		
WBC		
Tromb		
Hb		
Given doses		
Doxo mg		
Ifo mg		

Doxo = Doxorubicine 50 mg/m²

Ifo = Ifosfamide 5000 mg/m²

Mesna, according to protocoll

Soft Tissue Sarcoma SSG XIII (localized high-risk)
Chemotherapy toxicity flow-sheet FORM 4B

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

Submit this form together with Form 6A to:

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

Chemotherapy

Cycle No.

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

* According to NCIC CTG Expanded common toxicity criteria

Toxicity grade	1	2	3	4
Transaminase	$\leq 2.5 \times N$	$2.6-5.0 \times N$	$5.1-20.0 \times N$	$>20.0 \times N$
Creatinine	$<1.5 \times N$	$1.5-3.0 \times N$	$3.1-6.0 \times N$	$>6.0 \times N$
Stomatitis	painless ulcers, erythema, or mild soreness	painful erythema, edema, or ulcers but can eat	painful erythema, edema, or ulcers, and cannot eat	mucosal necrosis and/or req parenteral or enteral support, dehydration
Hematuria	micro only	gross, no clots	gross -clots	req transfusion

Soft Tissue Sarcoma SSG XIII (localized high-risk)
RADIOTHERAPY SUMMARY FORM 5

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

Send this form one week after start of chemotherapy to:

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

Hospital and department

Date

Day	Month	Year

Physician

Radiation therapy

Start after chemotherapy course No.

Start after chemotherapy course No.

Other, specify (ex preop-RT);

Target absorbed dose(s)

	Target 1, specify;	Target 2, specify;
Radiation quality		
Specified target dose		
Number of fractions		
Number of days		
Number of series		

Dose modification

Dose modification factors no yes, specify;

Deviation from plan

no yes, specify;

Scoring of radiotherapy acute side effect

- Score 0 none
- Score 1 minimal erythema
- Score 2 moderate erythema
- Score 3 brisk erythema
- Score 4 spotted moist desquamation
- Score 5 confluent moist desquamation

Soft Tissue Sarcoma SSG XIII (localized high-risk)
FOLLOW-UP FORM 6

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

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

Hospital and department

Date Day Month Year

Physician

Clinical evaluation

Date of evaluation	Day	Month	Year	
Physical exam	<input type="checkbox"/>	no	<input type="checkbox"/>	yes
Chest x-ray	<input type="checkbox"/>	no	<input type="checkbox"/>	yes
CT of chest	<input type="checkbox"/>	no	<input type="checkbox"/>	yes
X-ray of the primary tumor site	<input type="checkbox"/>	no	<input type="checkbox"/>	yes
Bone scan	<input type="checkbox"/>	no	<input type="checkbox"/>	yes

Tumor status

No evidence of disease Local recurrence

Late effects

Score 0 none
 Score 1 minimal fibrosis or induration
 Score 2 distinct fibrosis or induration
 Score 3 very marked fibrosis or induration
 Score 4 reduced function due to fibrosis or induration
 Score 5 necrosis

New metastasis

Lung no yes Date Day Month Year

Bone no yes Date

Other, specify;

Deceased

Death Date Day Month Year Autopsy no yes

Died from osteosarcoma Died with osteosarcoma from other cause

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

Treatment for relapse

Curative intent Palliative intent

Treatment plan: chemotherapy surgery other, specify;

III. Addendum

Preoperative Radiotherapy

Preoperative radiotherapy might have an indication under certain circumstances and is considered to be superior to postoperative radiotherapy by several experienced clinicians. However, there are still no strict scientific basis showing a benefit of preoperative compared to postoperative radiotherapy. The main disadvantage with preoperative radiotherapy, for the aim with this treatment program, is that preoperative radiotherapy will disable a strict classification of the patients into the high and the low risk category for distant metastases. However, two of the three risk factors: size and macroscopic necrosis may be evaluated from CT and/or MRI. The conventional preoperative treatment is given with 5×2.0 Gy/week and total doses in the range of 44 to 50 Gy. Surgery is performed about 3 weeks after completion of radiotherapy when the acute radiation effects have subsided. The main advantage with this strategy is that the tumor may shrink significantly over this long period and therefore is easier to remove. However, the long preoperative delay may reduce the probability of tumor curability.

In order to reduce the overall treatment time of the whole combined modality (see page 15), *the dose schedule proposed in this protocol* for preoperative radiotherapy is 2×1.8 Gy/day with 6 hrs interval between the two daily fractions, and a total dose of 45 Gy in 2.5 weeks. *The surgery should be done within a few days after finishing radiotherapy* in order to avoid interference with the maximum acute skin reaction about 3 weeks later (the peak skin reaction will appear at 5 to 6 weeks after commencement of radiotherapy). Further, as discussed above, this schedule results in significantly less pronounced acute skin reactions than the conventional dose of 50 Gy in 25 fractions over 5 weeks. The late effects will be the same for both schedules (5, 7).

The main advantage with this accelerated radiotherapy schedule is that the overall time period for preoperative radiotherapy and surgery is reduced from about 8 weeks to about 3 weeks. One may consider as a disadvantage that any significant tumor shrinkage is not expected to be observed over this short treatment period. However, the resection margins should have been decided upon already before the preoperative radiotherapy, and should not be changed even if there is a reduction of tumor size because of the preoperative treatment.

Treatment of high-risk patients

High-risk patients as defined on page 11, who fulfill the inclusion criteria (page 11) should receive adjuvant chemotherapy for 6 cycles according to page 16 in the protocol.

Amendment. December 2003

Pegylated filgrastim is available.

Therapeutic indication posology and method of administration is described below:

Therapeutic indications

Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients above the age of 18 years treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

Posology and method of administration

One 6 mg dose (a single pre-filled syringe) of Neulasta is recommended for each chemotherapy cycle, administered as a subcutaneous injection approximately 24 hours following cytotoxic chemotherapy. There are insufficient data to recommend the use of Neulasta in children and adolescents under 18 years of age.

Neulasta therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.