Tumorzentrum München an den Medizinischen Fakultäten der **Ludwigs-Maximilians-Universität** und der **Technischen Universität München**

EORTC 62961/ESHO RHT-95

RANDOMIZED STUDY COMPARING NEOADJUVANT CHEMOTHERAPY ETOPOSIDE + IFOSFAMIDE + ADRIAMYCIN (EIA) COMBINED WITH REGIONAL HYPERTHERMIA (RHT) VERSUS NEOADJUVANT CHEMOTHERAPY ALONE IN THE TREATMENT OF HIGH-RISK SOFT TISSUE SARCOMAS IN ADULTS

AN INTERGROUP STUDY WITH THE EUROPEAN SOCIETY FOR HYPERTHERMIC ONCOLOGY

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Find more Information at:

- Tumorzentrum München
- Tumorregister München
- www.krebsinfo.de
- www.mammakarzinom.de
- www.sb-online.de
- www.uni-duesseldorf.de/WWW/AWMF

- **Appendix 2: Radiotherapy**
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DOCUMENTATION FORMS

All documentation forms are filed separately and
are available upon request from the study co-ordinator.

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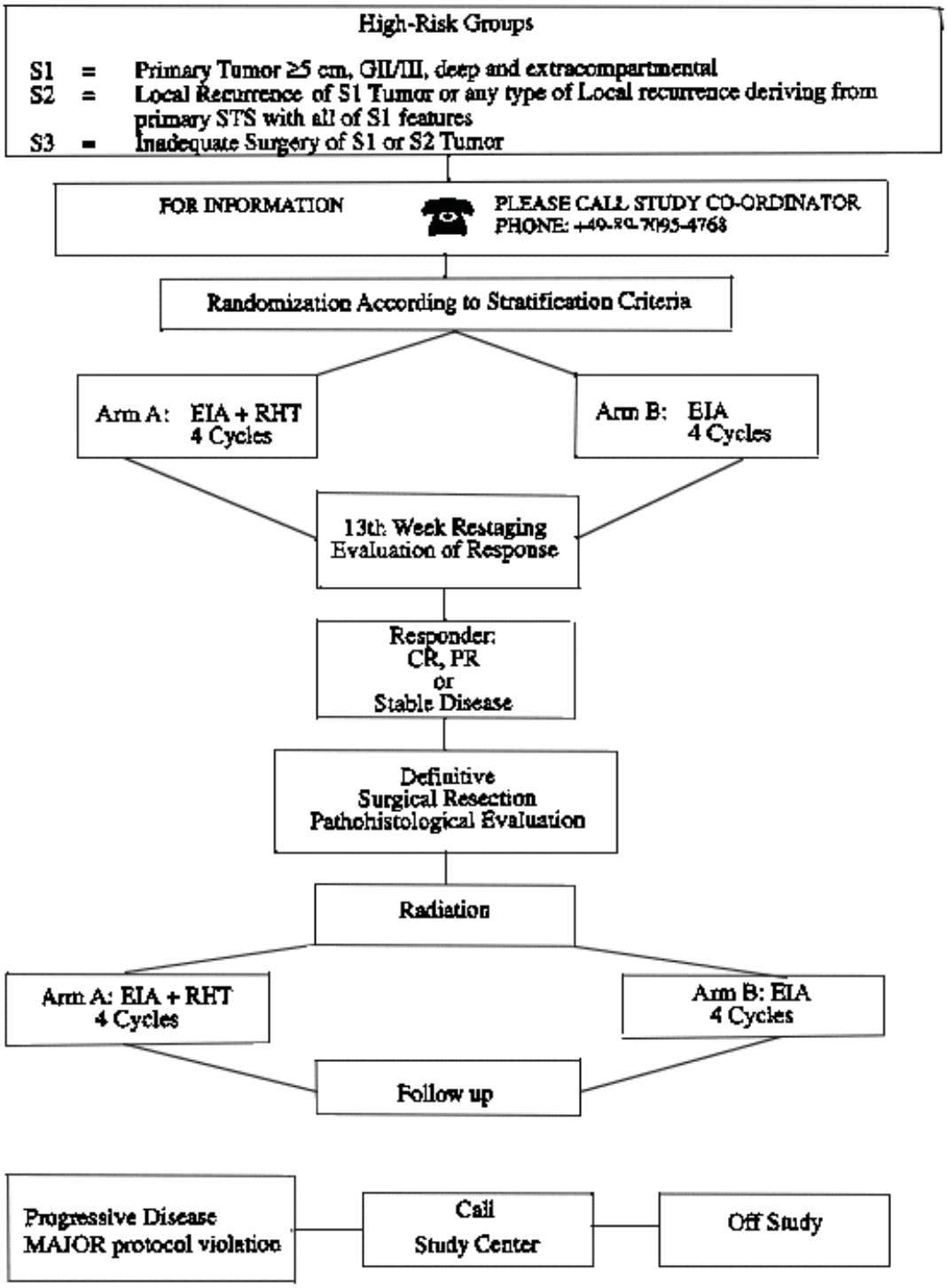
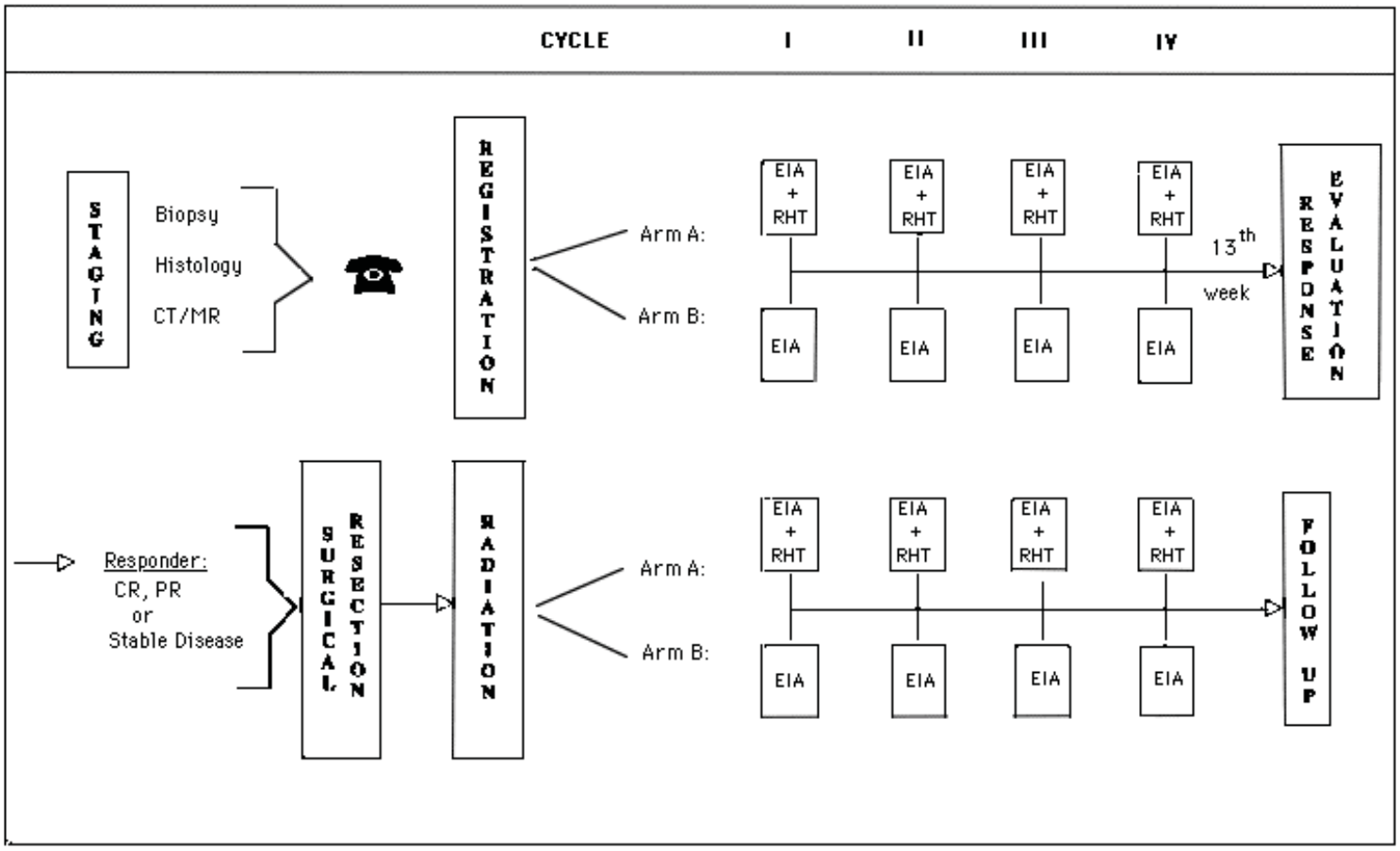
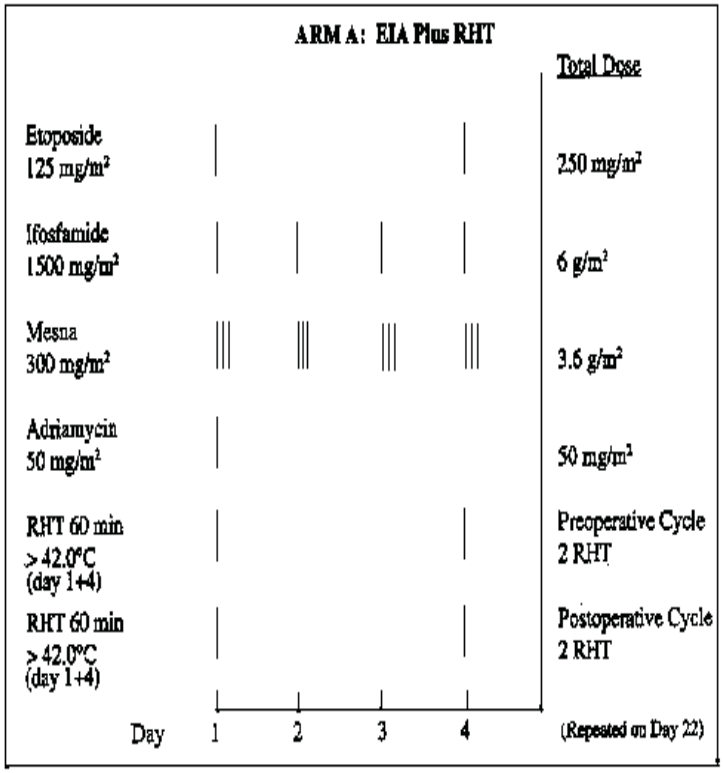
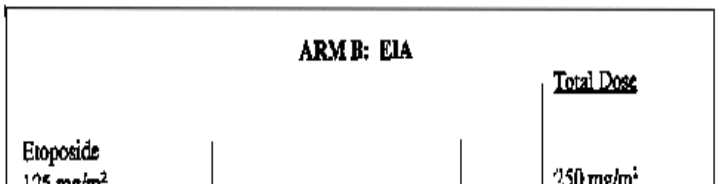
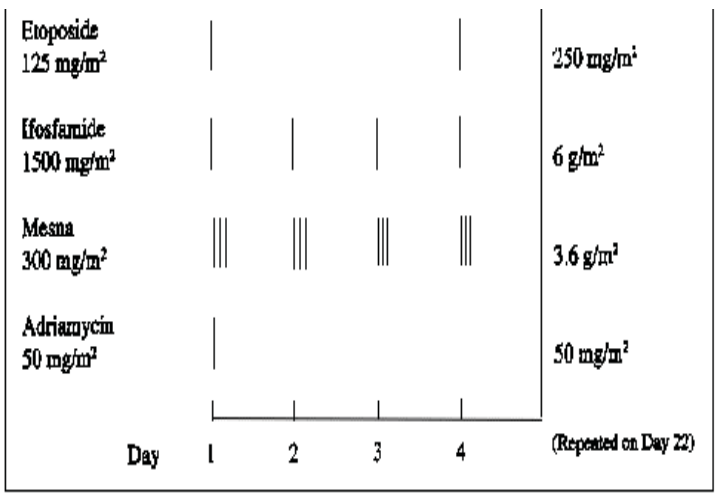
EORTC 62961/ESHO RHT-95: High-Risk Soft Tissue Sarcoma Study




CYCLE I II III IV
STAGING
Biopsy
Histology
CT/MR
REGISTRATION
Arm A:
Arm B:
EIA + RHT
EIA
13th week
RESPONSE EVALUATION
Responder:
CR, PR
or
Stable Disease
SURGICAL RESECTION
RADIATION
FOLLOW UP


ARM A: EIA Plus RHT
Total Dose
Etoposide 125 mg/m²
250 mg/m²
Ifosfamide 1500 mg/m²
6 g/m²
Mesna 300 mg/m²
3.6 g/m²
Adriamycin 50 mg/m²
50 mg/m²
RHT 60 min > 42.0°C (day 1+4)
Preoperative Cycle 2 RHT
RHT 60 min > 42.0°C (day 1+4)
Postoperative Cycle 2 RHT
Day 1 2 3 4
(Repeated on Day 22)


ARM B: EIA
Total Dose
Etoposide



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1. BACKGROUND AND INTRODUCTION

Soft tissue sarcomas are uncommon malignant tumors of mesenchymal origin, comprising about 1% of malignancies. High-grade soft tissue sarcomas, like many other solid tumors, present a dual management problem: local control and prevention of distant metastases. In the last decade the current standard of either limb-sparing surgery plus radiation therapy for microscopic residual disease or radical resection (often amputation) has largely improved local control rates for extremity lesions (**1,2**). However, the anatomic location and invasiveness of sarcomas (e.g. retroperitoneal) most often prevents resection with adequate margins (**3**), and the toxicity of radiotherapy limits the use of potentially therapeutic doses.

In addition, patients with large, high-grade sarcoma or recurrent local disease are at high risk for developing metastases. Despite multimodality management for this disease, currently 40-60% of all patients die within 5 years (**4**).

By a large analysis on 423 patients from the Memorial Sloan-Kettering Cancer Center (MSKCC) unfavourable characteristics for localized soft tissue sarcomas of the extremity have been defined as major prognostic factors for the rates of distant metastases and tumor mortality (**5**):

size (≥ 5 cm), high-grade, and deep location.

Results of the Cox model analysis for both rates are nearly identical showing that once these three factors were selected, tests to include additional risk factors (e.g. proximal site, unfavourable histological subtype, microscopic positive surgical margin, larger size (>= 6 cm) were not significant. Patients with tumors at presentation that are ≥ 5 cm, high-grade and deep have estimated 50% probabilities of developing distant metastases by 17.6 months and of dying of tumor mortality by 33.4 months. In addition, local recurrence seems only to have a direct impact on the rate of distant metastases among patients who presented with less unfavourable risk factors (**6,7,8**). Although with each local recurrence there is an increasing chance that the tumor would transform from low to high-grade, penetrate beyond the fascia (= deep), or become large (≥ 5 cm), once the patient acquired all three of the unfavourable characteristics as mentioned above local recurrence itself would no longer have an effect (5).

The overall 5-year survival rate for high-risk patients with retroperitoneal sarcoma is in the range of 15-35% (**9,10**). A retrospective analysis on 114 patients showed that high-risk tumors (≥ 5cm, high-grade and deep) were associated with only 20-months median survival compared to 80 months for low-risk tumors (**11**).

In conclusion, a high-risk group of patients with soft tissue sarcomas can be clearly defined at the time of first presentation.

n regard to most appropriate chemotherapeutic agents the two drugs with highest single agent activity

in this disease are doxorubicin (average response rate 24%, range 16-41%) and ifosfamide (average response rate 28%, range 18-38%) (**12**). Combination chemotherapy has achieved response rates of 25-40% in advanced soft tissue sarcoma (**13**). Randomized trials of adjuvant chemotherapy in soft tissue sarcoma after complete resection have been undertaken using doxorubicin alone and doxorubicin containing combinations. In both, extremity and abdominal tumors, no clear advantage has been shown for chemotherapy over no-adjuvant treatment (4). Many studies - although showing no survival benefit - have shown improved local control and a delay in the development of metastases. Furthermore, a recent meta-analysis including the data from all randomized adjuvant chemotherapy studies has shown a small but significant survival advantage for patients receiving chemotherapy (**14**).

Neoadjuvant chemotherapy is intended to induce tumor regression and eradicate distant micrometastases before locally curative treatment. Several phase-II studies of neoadjuvant chemotherapy have been carried out in patients with bulky soft tissue sarcomas according to risk factors (tumor size, grade, inadequate surgery, local recurrence) (**15,16,17**). It appeared that patients may benefit from chemotherapy because in some of these studies formerly inoperable patients were rendered operable. Also tumor response to preoperative chemotherapy provided prognostic information and identified a sub-group of patients most likely to benefit from neoadjuvant chemotherapy (**18**).

The combination of anticancer drugs with hyperthermia has become a new clinical strategy in the treatment of high-risk soft tissue sarcomas (**19**). The rationale for thermochemotherapy (40-44°C) rests on the assumption that heat exposure increases tumor-cell kill by direct thermal cytotoxicity and causes thermal chemosensitization within different areas of the tumor. The application of regional hyperthermia (RHT) with external annular phased array applicators (60-180 MHz) results in a selective temperature elevation in the tumor and in the immediate adjacent tissue. Temperature is measured invasively by catheters placed within the tumor by surgical procedures. Special thermistors are inserted into these catheters during the RHT-treatment cycles (**20**). Besides direct cytotoxic effects of hyperthermia in less perfused areas (temperature $\geq$ 42.5°C), a synergistic effect (temperature range: 40°-44°C) is observed in combination with simultaneously given systemic chemotherapy (**21**).

In clinical pilot studies with the BSD system (BSD Medical Corporation, Utah), the technical feasibility especially in abdominal and pelvic sites as well as in extremities with clinically relevant temperatures has been shown (**22,23,24,25**). The complication rate and incidence of more severe side effects were acceptable and not regarded as significant.

In 1986, the Klinikum Großhadern Medical Center (KGMC) initiated a phase II study for locally advanced sarcomas (92% of the patients pretreated) supported by the Deutsche Krebshilfe combining second-line chemotherapy (ifosfamide plus etoposide) with a regional hyperthermia (>80% pelvic sites) in repeated cycles (2 RHT/Cycle) **(26)**. The objective local response rate including 40 patients (interim analysis after 3 years) was 37% separating responders and non-responders by the achieved temperatures within the tumors (T_{20}, T_{50}, T_{90} parameters) in a statistically highly significant order ($P < .005$). In patients pretreated with ifosfamide local tumor control following the combined application of etoposide plus ifosfamide with regional hyperthermia could be observed (**26**). These results could be confirmed with 61 evaluable patients (objective response rate 34%). The mean observation time of the tumor control for responders (n=21) was 16.3 months (**27**).

Because of the promising results of the RHT-86 study and the acceptable (<5%) severe complication rate (e.g. burns, septic shock) the RHT-91 study for high-risk patients (grade II or III, size >8cm) with soft tissue sarcoma combining RHT with preoperative systemic chemotherapy was initiated. In this protocol the application of etoposide (250mg/m^2) plus ifosfamide (5g/m^2) plus adriamycin (=doxorubicin) (50mg/m^2) was combined with 2 RHT-treatments per cycle and given in repeated cycles every three weeks. The potential of etoposide to increase the effects of alkylating agents under heat conditions has previously been reported (**28,29**) and also the more recent experience of the Scandinavian Sarcoma Group using ifosfamide combined with etoposide alone shows the high activity of this regimen (**30**).

The EIA regimen combines conventional doses of the most active single agents (doxorubicin and ifosfamide) in soft tissue sarcomas, with etoposide being added prior to regional hyperthermia on day 1 and 4. First data obtained from the pilot study (**31**) were encouraging in regard to both the rate of patient accrual at the KGMC and the feasibility of this new treatment modality. Combination of systemic EIA chemotherapy with regional hyperthermia showed also to be effective allowing an adequate, conservative surgical approach after 4 EIA/RHT cycles in patients for whom radical resection without mutilation (e.g. hemipelvectomy, amputation) was formerly considered impossible (**32**).

In a more recent up-dated report (**33**) the results of the RHT-91 study including 59 protocol patients have been presented. By the cut-off date for this analysis 49 patients had undergone surgery after receiving 2 to 5 cycles (mean: 3.6) of EIA chemotherapy combined with RHT. 40 tumors could be resected without amputation, while 9 could not. In 59 evaluable patients, the clinical response rate was 42%. In 6 patients a pathological complete response (PCR) was found at the time of surgery. Best response was obtained by strategy of the RHT-91 study in 37 patients showing no evidence of disease (NED) with a median observation time of 34 months.

Overall survival and distant disease free survival of all protocol patients was 50% and 40%, respectively (median observation time 34 months). From the overall experience of more than 2000 RHT treatments performed in locally advanced, soft tissue sarcomas showing efficacy of combined chemotherapy with RHT a prospective, randomized trial is warranted to prove the benefit of adding hyperthermia to EIA chemotherapy alone in regard to tumor control and long-term survival.

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2. OBJECTIVES

2.1. Clinical Investigation

The prospective, randomized EORTC 62961/ESHO RHT-95 study for high-risk soft tissue sarcomas has the following aims:

a) To determine whether preoperative chemotherapy using Etoposide, Ifosfamide and Adriamycin (=EIA) combined with Regional Hyperthermia (RHT) compared with EIA chemotherapy given alone in addition to optimum local treatment followed by adjuvant chemotherapy (± RHT) will result in a significantly better tumor response, local disease control, overall survival, and relapse-free survival in three defined high-risk groups of patients.

b) The determination of acute complication rate and late toxicity in both treatment arms.

c) The determination of acute complication rate and late toxicity in both treatment arms.

2.2. Biological Studies

Parallel to the clinical investigation biological studies will be undertaken according to protocols of the study co-ordinator (optional):

a) To determine whether depletion of glutathione (GSH) in peripheral blood lymphocytes (PBL) can be measured at the end (day 4) of each cycle of EIA chemotherapy either combined with RHT or given alone. Recent results indicate ifosfamide induced GSH depletion in PBL monitoring drug sensitivity of tumors **(34, 35, 36, 37).**

b) The determination of changes in T-cell fractions (e.g. CD8+; CD4+; gamma/delta T-lymphocytes) or NK cells (CD16+; CD56+) in PBL of patients treated in arm A or arm B. There is evidence that heat shock proteins (hsp) induced in tumor cells under stress conditions (i. e. hyperthermia) elicit specific T-cell immune response **(38,39,40,41,42)**.

c) Comparative analysis of different hsp (e.g. hsp27, hsp70) in biological material (e.g. PBL, tumor tissue) of patients in both treatment arms. Such analysis might be useful as marker for stress induced heat shock response **(43).**

Additional informed consent of patients will be required to use biological material for such studies (see also 3.1.8.).

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3. SELECTION OF PATIENTS

Patients with histologically proven soft tissue sarcoma who meet the criteria for eligibility are **Protocol**-patients.

3.1. Criteria for Eligibility

3.1.1. Histology

Patients with the following histological subtypes of tumors showing grade II or III can enter the EORTC 62961/ESHO RHT-95 study:

- Malignant fibrous histiocytoma (MFH)
- Liposarcoma (round cell and pleomorphic)
- Leiomyosarcoma
- Fibrosarcoma
- Rhabdomyosarcoma
- Synovialsarcoma
- Malignant paraganglioma
- Neurofibrosarcoma (Malignant schwannoma)
- Extraskeletal Ewing's sarcoma
- Extraskeletal osteosarcoma
- Malignant peripheral neuroectodermal tumors (MPNET)
- Mesenchymal chondrosarcoma
- Angiosarcoma
- Miscellaneous sarcoma
- Unclassified sarcoma

The following entities are excluded (ineligible):

- Stroma cell sarcoma (endometrium)
- Osteosarcoma
- Ewing's sarcoma (children younger than 18 years)
- Embryonal rhabdomyosarcoma (children younger than 18 years)
- Chondrosarcoma (not mesenchymal)
- Kaposi sarcoma
- Malignant mesothelioma
- Dermatofibrosarcoma

- Chordoma

3.1.2. Description of Risk Criteria

Only patients with the following risk criteria are to be included:

a. Grade of Tumor:

Patients with included histology of **grade II** or **grade III** are eligible for the EORTC 62961/ESHO RHT-95 study. The histologic criteria for grading is based on the following score (**44**).

[A]: Tumor differentiation (score 1-3)
[B]: Mitosis count (score 1-3)
[C]: Tumour necrosis (score 0-2)

Score = sum of A + B + C
Grade II = 4,5 Grade III = 6, 7, 8

The Pathological Data (see Documentation Forms) has to be completed in by the local reference pathologist and must be sent to the respective Data Center at the time of registration.

b. Size of the Tumor:

Tumor ≥ 5 cm
The largest perpendicular diameter of the individual lesions should be measured by CT/MR imaging.

c. Depth of the Tumor:

Tumors that are not superficial to the initial fascia are defined to be **deep**.

This definition of tumor depth has been suggested to be an important factor (**5**).

d. Compartmental Category of the Tumor:

Tumors must extend into an adjacent compartment or be not confined strictly within one compartment and therefore classified as extracompartmental.

(For definition of extracompartmental sites at extremities, girdles and trunk see Appendix 1: Surgery).

e. Local Recurrence:

Patients with a recurrent tumor are eligible, if treated before by surgery, or if the recurrent lesion is in part outside of a previously irradiated area. Locally recurrent lesion is defined to appear after at least 2 months of disease-free postoperative follow-up. If the growth appears within a shorter interval it is considered as persistent disease.

f. Inadequate Surgery:

Patients with inadequate excision (e.g. intralesional, marginal) ≤ 8 weeks earlier for whom further surgery is necessary are eligible. (For definition of adequacy of surgery and of surgical margins see Appendix 1: Surgery).

For lesions removed at another hospital for which no evaluable clinical or imaging parameter exists, a reappraisal of the primary lesion and previous operation must be carefully performed: eligible cases are those sufficiently documented.

3.1.3. High-Risk Groups

The patients must belong to one of the high-risk groups:

S1 = Primary Tumor
Size ≥ 5cm
and
Grade II or Grade III
and
deep
and
extracompartmental

S2 = Local Recurrence
of S1 Tumor or any type of Local Recurrence deriving from primary STS with all of the S1 features

S3 = Inadequate Surgery
of S1 or S2 tumors

3.1.4. Age

Patients aged from 18 to 70 years

3.1.5. Performance

Performance status of 0, 1, or 2 (WHO scale) or Karnofsky index 60- 100% is required (see Appendix 5: Performance Status).

3.1.6. Site

Patients with tumors sited in extremities (=**E**), or in the, pelvis, trunk and abdomen (=**NE**).

In some anatomical sites (e.g. head and neck) technical application of RHT might not be feasible and should be checked before by the local investigator.

3.1.7. Haematologic, Hepatic and Renal Function

The patients must have an adequate haematologic, hepatic and renal function:

WBC	$\geq$	3.5 x 10^9/l
Platelets	$\geq$	100x 10^9/l
Bilirubin	<	1.25 x N (N = upper limit of normal range, [SI-Norm] = 17,0 µmol/L)
Creatinine Clearance	>	60 ml/min (e.g. Cockroft formula)

3.1.8. Consent

Patients must give informed consent according to national regulations. Those unable to give informed consent or comply with treatment are excluded (see Appendix 4: Human Consent). All relevant information has to be given in their patients' native language at the participating institutions.

3.1.9. Registration and Randomization

Patients must be randomized and should start treatment (**arm A or arm B**) within 8 weeks following staging procedures but at least within 3 weeks following registration (see Documentation Forms)**.**

3.2. Exclusion Criteria

- Patients with distant metastases (except regional lymph node involvement) after staging including thoracic CT scan.
- Prior or concurrent primary malignancies (except adequately treated basal cell carcinoma of the skin or in situ carcinoma of the cervix).
- Previous chemotherapy.
- Previous mutilative surgery (e.g. amputation, external hemipelvectomy).
- Patients with bleeding disorders, severe hepatic dysfunction and documented existing cardiac failure (e.g. myocardial infarction within 6 months before protocol entry).
- Manifest heart failure or other severe disease (class III or IV/NYHA classification).
- Left Ventricular Ejection Fraction (LVEF) more than 10% below the nominal limit of the institution (e.g. < 45%).
- Patients with chronic renal failure.
- Patients with severe cerebrovascular disease.
- Very obese patients.
- Technical impossibility to heat the tumor.
- Patients with metallic implants relevant to the RHT-field:

  pacemakers

  orthopedic/surgical rods and plates of dimensions > 1000/frequency MHz
  [e.g. > 10 cm at 100 MHz]

  (Note that any metal implant will modify the heating pattern and cause increased local heating near metal surfaces not parallel to the current flow.)

- Pregnancy.
- Nursing mother.

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4. TRIAL DESIGN

(for summary see flow chart)

4.1. Stratification

Patients will be stratified at the time of randomization according to the high-risk groups (defined in 3.1.3: S1, S2, or S3) to the site (extremity = E versus not-extremity e. g. pelvis, trunk, abdomen = NE).

4.2. Preoperative Chemotherapy

Eligible patients will be randomized to receive either:

arm A: Preoperative EIA chemotherapy for 12 weeks (4 cycles) combined with two fractions of regional Hyperthermia (2 RHT per cycle, day 1 and day 4)

or

arm B: Preoperative EIA chemotherapy for 12 weeks (4 cycles) alone

In case of tumor progression (for definition see 8.1.4.) patients will be considered for immediate surgery. The choice of 4 cycles is based upon the fact that best response rate has been observed after 4 cycles combined with RHT in the previous RHT-91 study. The risk of local progressive disease for patients treated either with neoadjuvant chemotherapy alone or with the combined regimen is relatively low (**18, 32**). Of comparable not pretreated patients in the RHT-91 study, the observed early progression rate during the time of neoadjuvant chemotherapy was about 10%.

4.3. Definitive Surgery

Patients of both treatment arms (arm A and arm B) should undergo definitive surgery in 4-6 weeks after the end of the preoperative neoadjuvant chemotherapy regimen. In case of previous inadequate surgery (S3-group) reoperation - if possible - is indicated. Patients showing No Change (stable disease) after 4 cycles EIA +/- RHT (arm A or arm B) with non-resectable tumors should undergo incisional biopsy for evaluation of pathological response. (The guidelines for surgery are given in Appendix 1: Surgery).

4.4. Radiotherapy

Immediately after receiving definitive surgery or (preferable) before surgery the surgeon and radiotherapist should jointly assess the indications for routine radiotherapy. Most patients will require radiotherapy. Patients showing No Change (stable disease) and no pathological response with non-resectable tumors should undergo radiotherapy, if possible. (Guidelines for radiotherapy are given in 5.4. and Appendix 2: Radiotherapy).

4.5. Postoperative Chemotherapy

Following adequate surgery and radiation the randomized patients of both arms A and B then will receive:

arm A: Postoperative EIA chemotherapy for 12 weeks (4 cycles) combined with two fractions of regional Hyperthermia (2 RHT per cycle, day 1 and 4)

or

arm B: Postoperative EIA chemotherapy for 12 weeks (4 cycles) alone

Patients with non-resectable tumors showing no progression (PD) will receive postoperative chemotherapy +/- RHT according to initial randomization.

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5. THERAPEUTIC REGIMEN

5.1. Chemotherapy

5.1.1. EIA-Cycle

Etoposide + **I**fosfamide + **A**driamycin = **EIA**

Etoposide (total dose: 250mg/m$^{2)}$.	125 mg/m^2 x 30 min i.v. infusion, day 1. + 4
Ifosfamide (total dose: 6g/m^2)	1500 mg/m^2 x 60 min i.v. infusion, day 1-4 with mesna (see below)
Adriamycin (total dose: 50mg/m^2)	50 mg/m^2 x 5 min (Bolus) or x 30 min i.v. infusion, day 1

The first cycle can be started if:

WBC count is ≥ 3.5 x 10^9/l

or absolute neutrophil count (ANC) is ≥ 2 x 10^9/l

and platelets are >= 100 x 10^9/l

The second cycle should start on day 22 (see also 5.1.3.)

5.1.2. Drug Formulation and Administration

Etoposide (VP-16) is available in vials of 100 mg. It should be dissolved in sterile water at a concentration of 5 mg/ml and can be further diluted in 0.9 % NaCl. Etoposide is given as 30 min i.v. infusion.

Ifosfamide is available in vials of 500 mg, 1g, and 2g. It should be dissolved in sterile water at a concentration of 1g/12.5 ml. The total dose should be dissolved in 5% dextrose saline. Ifosfamide is given as 60 min
i.v. infusion.

Mesna (= Uromitexan^R) 300 mg/m^2 should be given by i.v. bolus immediately before starting the

ifosfamide infusion. At 4 hours and 8 hours after the beginning of the ifosfamide infusion bolus i.v. injection of mesna
(300 mg/m^2) should be repeated.

Adriamycin (= 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 0.9% NaCl. Adriamycin is given as bolus (5 min) or 30 min i.v.infusion.

5.1.3. Dose Modification

According to the guidelines given in Table 1 dose modification and G-CSF support should be performed if at the time of the scheduled EIA cycle white blood count (WBC) and/or absolute granulocytes (ANC) show grade 1, 2 or 3 toxicity.

Independently platelet recovery must be

$\geq$ 75.000 10^9/l

to start EIA chemotherapy.

If treatment has to be postponed for more than 3 weeks, the patient should proceed to the next step of the protocol.

Table 1:

Toxicity	WBC (x 10^9/l)	ANC (x 10^9/l)	Dose
Grade 1	3.0-3.9	1.5-1.9	100%
Grade 2	2.0 - 2.9	1.0 - 1.4	100% + G-CSF
Grade 3	1.0 - 1.9	0.5 - 0.9	Delay until grade 2 recovery

(* see 5.1.4. G-CSF)

5.1.4. G-CSF

In order to avoid further treatment delay or dose reductions in subsequent cycles of the EIA regimen and also to reduce the risk of neutropenic infections, patients should receive rh G-CSF starting 24 h after completing

EIA chemotherapy.

It should be noted that in the RHT-91 study the observed rate of such unfavourable events (in comparison to the previous RHT-86 study) became remarkably reduced (<10% versus 18%) since G-CSF (e. g. Filgrastim) support was added. (For administration of rh G-CSF see Appendix 6).

The application of rh G-CSF is indicated for:

If the patient experienced one of the above mentioned complications in the previous course of the EIA chemotherapy, G-CSF should be used in the following EIA-cycles 24 h after completing EIA chemotherapy (secondary prophylaxis) to protect against new episodes of febrile neutropenia or chemotherapy dose-modifications in subsequent cycles.

- Nadir [x 10^9/l] — WBC < 1.0, ANC < 0.5
- Nadir [x 10^9/l] — WBC < 1.5, ANC < .75, <u>plus</u> signs of neutropenic infection and/or fever
- Grade 2 — WBC or ANC toxicity (see Table 1) at the time of retreatment. In this case 100 % of dose will be given as indicated, but combined with rh G-CSF starting 24 h after completing EIA chemotherapy.

Neupogen should be discontinued after reaching leucocyte counts of 10.000/µl or if the leucocyte counts exceed 2.000/µl on 2 - 3 subsequent days, following the expected chemotherapy-induced neutrophil nadir.

5.1.5. <u>Other Supportive Treatment Modalities</u>

The patients should receive continuous infusion (5% dextrose/isotonic saline) via peripheral or central venous catheter (4l / 24h) started 12 hours prior to chemotherapy and continued for 12 hours after the end of each EIA cycle.

A careful record of fluid input and output should be kept. If diuresis falls below 400 ml/m^2 per 6 hours furosemide 20-40 mg IV should be given.

- The patients should receive standard antiemetics (e.g. ondansetron, alizaprid).

- If signs of systemic infection (fever, sepsis) occur, systemic application of standard antibiotics (e.g. cefotaxim or piperacillin combined with tobramycin) is required.

  In general, routine medical treatments, analgesics and antiemetics may be given according to local protocols.
- No investigational drugs are permitted

5.1.6. Drug Toxicity

Beside bone marrow toxicity known for each component of the EIA regimen renal failure, haematuria, and reversible encephalopathy have been reported with higher doses of ifosfamide. Therefore renal function should be carefully monitored especially in later courses.

The EIA regimen should not be initiated if the creatinine clearance is below 60ml/min.

Patients more likely to develop encephalopathy are those with low serum albumin and high serum creatinine. Special care with hydration and mesna therapy should be taken if there have been rises in serum creatinine in previous courses.

- Cardiac toxicity with adriamycin (= doxorubicin) has been reported in adults especially at total doses $\geq$ 550mg/m^2. Left Ventricular Ejection Fraction (LVEF) should be monitored prior to treatment, before definitive surgery, and at the end of the protocol.

- G-CSF toxicity at the doses used in the study should be minimal. Occasional mild skin rashes, arthralgia, bone pain and headaches have been seen in the previous RHT-91 study. These side-effects were usually controlled with mild analgetics (paracetamol).

5.2. Regional Hyperthermia (RHT)

5.2.1. Hyperthermia System

Regional hyperthermia may be produced by any device shown to be appropriate (see Appendix 3). For heating of deep-seated malignancies with the BSD-2000 (BSD Medical Corporation, Salt Lake City, Utah) system, a concentric array of high frequency electro-magnetic applicators (e.g. "Annular Phased Array") is used. Frequency is ranging from 60 to 180 MHz and forward power ranging from 0 to 2000 Watts. Phase and amplitude steering is permitted in order to focus the heating field also to more excentric tumors. The operational details including patient positioning and the coupling at the body surface by means of the water bolus system have been described (**25**). The choice of the ring applicators Sigma-60 (adults) and Sigma-40 (children) depends on tumor location and body geometry. According to the BSD system set up patients are positioned with their longitudinal axis parallel to the

center axis of the ring applicators. For the treatment of extremities an additional applicator (Sigma-30) is available. The dimensions of the different ring apertures allow that an electric field is generated preferentially in the body center which originates from the single components of the ring applicators. Targeted energy absorption and reduced heat convection in parts of the tumor tissue allow the preferential heating in deep areas of the body.

By definition, the effective treatment time of 60 minutes is calculated from the time when the temperature of ≥ 42.0°C at any location in the tumor tissue is achieved. In the initial phase (heating-up time) of the RHT treatment (30 minutes) the power increase of the high-frequency generators is adapted to the corresponding increase of the measured temperatures in the tumor and the normal tissue. If the temperature exceeds 43.0°C in the adjacent normal tissue, the technical parameters should be changed, otherwise the applied power is switched off or reduced until acceptable temperatures are reached. If the hyperthermia catheters have been shown centrally located in the tumor or in parts of the tumor with necrosis or low perfusion, higher tumor temperatures might be accepted, if the patient has no complaints.

Systemic temperature must be measured regularly during hyperthermia and special attention must be taken at temperatures above 38.5 °C. Cooling procedures (5.2.5) and measurements to maintain the blood or central venous pressure should be initiated. Besides the objective criteria determined by temperature measurements the treatment will be discontinued if the patient complains about severe subjective symptoms (e.g. pressure, pain) - especially in the initial heating up period. The treatment is only continued if the cause for these symptoms can be eliminated by changing the HF-field or new positioning of the patient. Bladder cooling by patients with tumors in abdomen, pelvis or thighs is indicated (see 5.2.5).

In RHT-treatments unable to achieve an intratumoral temperature ≥ 42°C during the heating-up time (30 minutes) power supply is continued for another 60 minutes (= effective treatment time) in order to increase the tumor temperature to the target level as close as possible.

5.2.2. Thermometry

Depending on the size and location of the tumor at least two closed-end teflon catheters (e.g. Fa. Angiomed, Karlsruhe, Germany) are placed into the tumor tissue and the surrounded normal tissue either intraoperatively or percutaneously for invasive temperature measurement (strictly required only for preoperative hyperthermia treatments). The postoperative hyperthermia treatment can be performed without catheters.

When placed intraoperatively by the surgeon, the catheters should be located into different parts of the tumor (S1/S2) or tumor bed (S3) for hyperthermia treatments after an exploratory laparotomy. The catheters should be fixed in a way, so that they can be removed externally later on. The surgeon should avoid to restrict the lumen of the catheter or to crack the catheter itself. The surgical report should include a topographic- anatomical description of the location of the catheter, allowing the identification of different catheters which are marked in different colors.

When placed percutaneously, preplanning is done after prior topographic and anatomic orientation on the basis of CT/MR imaging. For painless implantation local anaesthesia is required. Positioning of the catheters into the tumor(S3) for hyperthermia treatments and the normal tissue has to meet the guidelines mentioned above. The catheters should be fixed at the point of skin exit with non-absorbable suture material.

Into the intraoperatively or percutaneously implanted catheters a flexible guide wire should then be inserted to prevent the catheters from cracking. The catheter location and the spatial relation of the catheters to the tumor or tumor bed and the normal tissue has to be documented by CT/MR and X-ray radiograph before starting the hyperthermia treatment. In order to avoid artefacts, removal of the flexible guide wire is necessary before any imaging procedure.

Temperatures are measured with calibrated Bowman thermistors which allow an accurate temperature display ($\pm 0.1^{o}C$) without interference with the high-frequency field (**20**). The temperatures are measured at the top of the thermistors. Single Bowman thermistors are inserted into the lumen of each catheter at the time of RHT and their ends are connected to the automatic transportation system of the BSD equipment. Thereby the location of all temperature probes in the catheters can be changed simultaneously. The temperatures can be measured along the catheter axis at fixed intervals (0.5 or 1.0 cm) during the RHT treatment (**45**). This mapping procedure is repeated every five minutes in order to monitor the temporal changes of this temperature distribution in the tumor tissue and in the adjacent normal tissue during the treatment. Immediately prior to each RHT treatment additional catheters are inserted (e.g. into the rectum and bladder) to allow continuous temperature measurement in these organs. Skin temperatures should be monitored at different areas within the field of the applicator. The systemic temperature can be intermittently measured within an intra-oral probe.

5.2.3. Thermal Dosimetric Analysis

Because of the nonuniformity of heating typically produced in tumors treated with regional hyperthermia, methods of consistently characterizing nonuniform temperature distributions have been developed so that descriptors of the temperature distribution can be used in appropriate statistical analysis to be related to outcome of therapy. For deep seated tumors most recent reports made use of the frequency distribution of temperatures within the tumor and related descriptors of the distribution such as T_{90} (temperature exceeded by 90% of the temperatures measured throughout a treatment within tumor), T_{50} (temperature exceeded by 50% of the temperatures measured throughout a treatment within tumor), and T_{20} (temperature exceeded by 20% of the temperatures measured throughout a treatment within tumor). In patient populations consisting of patients with moderate to high grade soft tissue sarcoma, the cumulative minutes of treatment for specific T_{50} and T_{90} temperatures were good predictors of the extent of necrosis in the corresponding specimen (**46**). The frequency distribution descriptors correlated more strongly with outcome than did minimum temperature. Similarly, in patients with superficial tumors, cumulative duration of treatment for specific T_{90} temperatures was a statistically significant correlate with complete response rate whereas minimum temperature was not (**47**).

To extend the preceding concepts of thermal dosimetry one can utilize a thermal isoeffective dose formula (**48**) and convert the time/temperature records of treatment into equivalent minutes for T_{90} equals 40.5°C, for T_{50} equals 41.5°C, and T_{20} equals 42.5°C in patients with soft tissue sarcomas. This analysis will allow to determine the outcome of treatment to treatment temperature, time, and thermal isoeffective dose. Therefore, the T_{90}, T_{50} and T_{20} parameters for each RHT treatment as well as the cumulative minutes for specific T_{90}, T_{50} and T_{20} temperatures of all RHT treatments will be calculated. (Please contact the EORTC 62961/ESHO RHT-95 study co-ordinator for further information).

5.2.4. EIA Chemotherapy Cycle plus RHT

Immediately prior to the heating-up period

etoposide (VP-16) followed by **adriamycin** (= doxorubicin) (**day 1**)

are infused as indicated in 5.1.1.

(There is no difference between total dose and dose modifications of EIA-chemotherapy in treatment arm A and B respectively).

Then the heating-up period (30 min) should be initiated.

The infusion of ifosfamide (day 1 or day 4) is started and mesna is administered by i.v. bolus injection as soon as tumor temperature of ≥ 41.5°C is reached. If tumor temperatures ≥ 41.5°C are not achievable or not measurable in the tumor tissue at the end of the 30 min heating-up period, the ifosfamide infusion and the i.v. bolus injection of mesna is started and a total treatment time (60 min) of RHT is given.

5.2.5. Additional Support

For recommendations of dose modification (5.2.3), G-CSF support (5.2.4.), and other supportive treatment (5.2.5), see sections as indicated.

In addition, immediately prior during and after the RHT treatment heart rate, blood pressure, or CVP (= central venous pressure) should be monitored at repeated times. In case of systemic vasodilatation (increase of heart rate, drop in blood pressure) at the time the tumor reaches the target temperature, volume deficiency should be compensated by increasing the infusion rate (CVP-control).

If patients start to sweat, cooling procedures should be applied (bolus cooling, icebags, cold blankets) especially in the head and neck area. Bladder cooling can be provided by repeated instillation of cold water to keep the measured bladder temperature at an acceptable level (e.g. 38°C). Mild sedation and

analgesics can be applied according to local protocols. Special care has to be given to the cutaneous entry of each catheter by daily inspection (e.g. signs of local infection, check-up for bacterial contamination).

5.3. Surgery

Surgery should be performed 4 - 6 weeks after the 4^{th} cycle of EIA/RHT or EIA neoadjuvant chemotherapy.

In case of early progression of tumor (for definition see 8.1.4.), patients will be considered for immediate surgery.

Surgery should be curative in intent, removing all macroscopic disease. Wide excision (including an involved fascia or at least 2 cm of healthy tissue around the tumor measurement made on unfixed tissue) is required. Marginal resection (i. e. disease-free margin of less than 1 cm) is only acceptable if the patient will receive later on postoperative radiotherapy. If the considered operation is argued to be intralesional (macroscopic disease left behind), the surgical procedure in the case of extremity or pelvic lesions should be exarticulation or hemipelvectomy, unless the patient refuses or extended surgery is contraindicated for medical reasons.

It is recommendable to implant hyperthermia catheters in the tumor bed for the postoperative hyperthermia treatment, but it is not strictly required.

Surgery at an outside hospital should be performed following the guidelines of the participating center (guidelines for surgery see Appendix 1).

5.4. Radiotherapy

Routine radiotherapy will commence within 4 and 6 weeks following definitive surgery.

Radiotherapy following previous surgery is indicated if:

- The resection is microscopically or macroscopically incomplete.
- Following R0 resection after for previously incomplete or otherwise inadequate surgery.

- In case of inadequate surgery.

- In case of mutual agreement by surgeon and radiation oncologist for other reasons, e.g. surgical difficulty.

Radiotherapy is not indicated after primary R0 (neither microscopic nor macroscopic tumor rest) resection.
(Guidelines for radiotherapy see Appendix 2).

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6. REQUIRED CLINICAL EVALUATIONS AND LABORATORY TESTS

6.1. At Study Entry:

- Medical History
- Physical examination (height, weight)
- Performance status
- Measurement of the tumor (e.g. circumference)
- Full blood count
- Blood chemistry (AP, SGOT, LDH, γ-GT, Bilirubin, Coagulation test Creatinine, serum albumin)
- Creatinine clearance (e.g. Cockroft formula)
  or J-Hippuran clearance
- ECG
- Cardiac ejection fraction (any appropriate technique)
- CT scan of the lungs
- CT-scan (i.v. contrast medium) of the tumor area of interest
  (8 mm; measurement of the maximum of tumor dimensions: x, y, z)
  or
  MR-imaging (Gd-contrast)
- Bone scan
- Randomization/Eligibility Form (EORTC- and ESHO- Members)

6.2. During Neoadjuvant or Adjuvant Chemotherapy

Before each cycle:

- Physical examination
- Blood count + Na, K
- Bilirubin
- LDH, AP, other markers if initially pathological
- Creatinine, + clearance
- CT scan for catheter placement control)

6.3. After Completion of Neoadjuvant or Adjuvant Chemotherapy

a) Before definitive surgery (13th week)

b) Before radiation

c) at end of the study protocol

- Physical examination
- Full blood count + Na, K
- Blood chemistry (AP, SGOT, LDH, Coagulation, ɣ-GT, other markers if initially pathological)
- Creatinine, + clearance
- ECG
- Chest X-ray
- CT scan of the lungs
- CT scan (i.v. contrast medium) of the tumor area of interest
  (8 mm; measurement of the maximum of tumor dimension: x, y, z)
  or
  MR imaging (Gd-contrast)

SUMMARY TABELE

	At Study Entry	During Neoadjuvant or Adjuvant Chemotherapy Before each cycle	After Completion of Neoadjuvant or Adjuvant Chemotherapy
Medical History	x		
Physical examination	x	x	x
Performance status	x	x	x
Haematology*	x	x	x
Blood chemistry	x	x	x
Creatinine clearance or J-Hippuran clearance	x	x	x
ECG	x		x
Cardiac ejection fraction	x		x
CT-scan of the lungs	x		x
CT-scan (i.v. contrast) of the tumor or MR-imaging (Gd-contrast)	x		x
Bone scan	x		
Randomization/Eligibility Form	x		

*haematology includes white blood count and differential, platelets cout, haemoglobin count

6.4. During Radiotherapy

- Blood count every week

6.5. Follow-Up

All patients will be reviewed at the following intervals by the local investigator (see Table 2)

Table 2

Year after Completion of EORTC 62961/ESHO RHT-95			
	First	Second/Third	Fourth/Fifth
Chest X-ray	every 3 months	every 4 months	every 6 months
CT or MRI of the area of interest	every 3 months	every 4 months	every 6 months
Blood count, LDH, AP, others if initially pathological	every 3 months	every 4 months	every 6 months

Follow-up forms at the given intervals must be sent to the respective Data Center (see Documentation forms).

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7. THERAPY FOR PROGRESSIVE DISEASE

Although there is no strict regimen for the disease of non-responders with progressive disease, the following recommendations might be helpful for further decisions about the treatment procedure.

7.1. Progression or Relapse of Local Disease

In case of early progression of local disease (see 8.1.4.) or local relapse patients should be considered for immediate surgery. For non-resectable patients radiotherapy should be assessed (for second-line chemotherapy see 7.2.).

7.2. Metastatic Disease

For non-responders or in case of metastatic disease the use of high-dose infosfamide should be considered as second-line chemotherapy. There is clinical evidence that patients responding to this regimen have been previously resistant or refractory to standard dose of ifosfamide combined chemotherapy. A total ifosfamide dose of 12 g/m^2 should be administered over 3 days as continuous i.v. infusion repeated every 28 days. (For G-CSF support see 5.1.4.).

Detailed information about the high-dose infosfamide regimen can be obtained from the study co-ordinator.

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Tumorzentrum München, (1-November-1997)

8. EVALUATION OF RESPONSE

8.1. Response by Site

Target lesions are measured in their two largest perpendicular diameters. Their area is conventionally calculated as the product of these diameters. In case of more than one individual lesion the total tumor size is calculated as the sum of all calculated target lesions in this site.

Response by site is defined as follows:

8.1.1. Complete Response (CR):

Complete disappearance of all known manifestations of disease, determined by two observations not less than 4 weeks apart.

8.1.2. Partial Response (PR):

A 50% or more decrease of the product of the two largest perpendicular diameters (relatively to the initial product), determined by two observations not less than 4 weeks apart. In addition, there can be no appearance of new lesions, or progression of any lesion.

8.1.3 Stable Disease (SD):

Neither a complete or partial response, nor a progression has been demonstrated, at least 4 weeks after start. Minor response showing more than 25% but less than 50% tumor regression is also defined as stable disease.

8.1.4. Progressive Disease (PD):

A 25% or more increase in the product of one or more measurable lesions (relatively to the smallest size measured since treatment start), or the appearance of new lesions.

8.2. Result of Definitive Surgery

The final evaluation of definitive surgery is dependent upon:

- Resection margins marked at the time of surgery.
- The exact description of surgical margin considered within the surgical report (for definition of surgical margins see Appendix 1).
- Tumor left intact.
- The pathohistological examination of the resected specimen (for definition of adequacy of resection see Appendix 1).

Based upon these informations the results of definitive surgery will be supplemented by the "Residual Tumor (R) Classification". It reflects the effects of the therapy given, influences therapeutic procedures, and is a strong predictor of prognosis.

8.2.1. R0-Resection:

No residual tumor (meaning thus neither microscopic nor macroscopic).
Macroscopically complete removal by non-contaminated operation with wide or radical margin.

8.2.2. R1-Resection:

Microscopic residual tumor.
Macroscopically complete removal of gross disease but resection margin contains microscopic evidence of disease or disease-free margin is less than 1 cm (fixed) or 2 cm (vital).

8.2.3. R2-Resection:

Macroscopic residual tumor.
When macroscopic tumor - even if only minimal - is left in situ.

8.2.4. RX-Resection:

Presence of residual tumor cannot be assessed.

8.3. Pathohistologic Result

Beside assessment of the adequacy of resection the pathohistologic examination of the resected

specimen has also the objective to determine the response to the preoperative regimen given in both treatment arms.

8.3.1. Pathohistological Complete Response (pCR):

No evidence of typical malignant cells within representative tumor slices.

8.3.2. Favourable Histological Response (FHR) or Minor Histological Response (MHR):

≥ 75% (FHR) or less than 75% but ≥ 25% (MHR) of the tumor tissue within representative tumor cuts show histological signs of regression (e.g. larger necrosis, fibrosis) in comparison with the initial histological assessment of the tumor biopsy.

8.3.3. Pathohistological No Response (NR):

Less the 25% of the tumor tissue within representative tumor cuts show histological signs of regression (e.g.
larger necrosis, fibrosis) in comparison with the initial histological assessment of the tumor biopsy.

8.4. Overall Response

The overall response is evaluated at each assessment of the disease. If progressive disease exists in any lesion, or when a new lesion appears, then the overall result will be progressive disease (PD). Progression in non-measurable lesions leading to deterioration of the patient due to tumor bulk should be taken to indicate disease progression, regardless of what happens in measurable disease.

8.4.1. Best Overall Response:

Best overall response is the best response designation recorded from the start of treatment until disease progression. For example, no evidence of disease (NED) or pathohistological complete response (pCR) can be assessed after surgical resection.

8.4.2. Toxic Death:

Death occurring during the chemotherapeutic phase (including 4 weeks after its end) and due to drug toxicity. These patients additionally should be reported according to their best overall response status.

8.4.3. Death from Malignant Disease:

Death occurring during the chemotherapeutic phase (including 4 weeks after its end) and due to malignant disease. These patients additionally should be reported according to their best overall response status.

8.5. Patients without Assessment of Response

8.5.1. Early Death:

Death within 6 weeks (after commencing chemotherapy) without severe toxicity (not being assessable concerning response).

8.5.2. Toxicity Related Early Death:

Death occurring within 6 weeks after commencing chemotherapy due to signs of toxicity.

8.5.3. Malignancy Related Early Death

Death occurring within 6 weeks after commencing chemotherapy due to soft tissue sarcoma and without signs of toxicity. These patients will be assessed as nonresponders with progressive disease (PD).

8.5.4. Other Causes of Early Death:

Death occurring within 6 weeks after commencing chemotherapy due to a non-medical reason and not related to the malignant disease (i.e. for example a traffic accident or others).

- Patients stopping (or changing) treatment with an unconfirmed response, or only short stabilisation are considered as inevaluable, unless the response or stabilisation is further confirmed in the absence of any treatment.

- If the disease is not reevaluated for any reasons (lost to follow-up, patient refusing further examinations), the cases are considered as progressive disease. The reason for not reevaluating must be reported.

8.6. Duration of Response

8.6.1. Complete Response:

The period of complete response lasts from the date the treatment was initiated until the date on which progressive disease is first noted.

Comment: The WHO definition of complete response states that the CR only lasts from the date the complete response is first recorded until progression first noted. This has led to major confusion in reporting durations of CR's. Besides the duration of a CR can with the WHO definitions be shorter than the duration of a PR measured from the start of the treatment, an illogic effect.

8.6.2. Partial Response:

The period of partial response lasts from the first day of treatment to the date of first observation of progression.

8.6.3. Time to Progression (TTP):

The time to tumor progression lasts from the first day of treatment to the date of the first observation of progressive disease. Progression is defined in relation to the best response obtained.

8.6.4. Local Progression-free Survival (Main Objective):

The local progression free survival lasts from the date of randomization to the date of tumor relapse or progression of persistent disease.

8.7. Disease-free Interval

The disease-free interval lasts from the date of adequate surgery to the date of first observation of tumor recurrence. Patients will be analyzed according to the site of the recurrence (local, regional,

distant).

8.8. Duration of Survival

Survival will be dated from the date of randomization until death or last information. All randomized patients must be followed-up for survival.

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9. STATISTICAL CONSIDERATIONS

Sample Size Estimation:
The main endpoint of the EORTC 62961/ESHO RHT-95 study is "local progression-free survival" (LPFS). A LPFS rate of 30 % at 4 years (Median LPFS 30 months) is assumed in the control group (treatment arm B). In the hyperthermia-treated group (treatment arm A) a LPFS rate of 45 % at 4 years will be expected (median LPFS 43 months).To detect the expected difference (15% or 1.6 years) with type I error alpha = 0.05 and power of statistical test = 0.8 and drop-out rate of 10% using a two-sided logrank test, about 170 patients are required in each treatment arm. All patients should be recruited within 3.5 years. A follow-up period at 4 years is planned. The final analysis will be performed when a total of 146 distant failures will have been recorded (50).

Interim Analysis:
The main aim of the interim analysis is to detect a possible early effect according to the main efficacy parameter. With respect to this trial it means: the detection of an early significant difference between the survival curves of the randomised groups.

Three interim analyses and one final analysis are planned. The probability for a type I error (alpha) will be adjusted according to group sequential methods (49) in order not to exceed an overall alpha of 5 %.

The corrected alpha levels for the test at each interim analysis and the final analysis are:

No. of Interim Analysis	**Years after Study Begin**	**Test Statistics**	**Adjusted alpha-level**
1	1.5	4.0486	**0.00005**
2	2.5	2.86279	**0.0042**
3	3.5 Final Analysis	2.35889	**0.01942**
4	5.0 End of Study	2.02430	**0.04294**

Statistical Analysis

Descriptive Analyses:
All data will be analysed using descriptive methods and graphical techniques. For discrete data

frequency distributions will be calculated. Continuous data will be summarized by mean, standard deviation, median, minimum and maximum.

Inferential Analyses:
Baseline variables (possible prognostic factors) will be compared in order to determine whether the randomization has provided homogeneous treatment groups. These comparisons will be made using a test depending on the distribution of the continuous variable (for normally distributed data t-test and Wilcoxon-test otherwise). For comparison of discrete variables the X^2-test will be used (alternatively exact-Fisher-test).

For the analysis of LPFS time and overall survival time the Kaplan-Meier method will be used. The difference between survival curves will be tested using the logrank test.

For the multivariate analyses of survival time and all other right censored outcome variables the proportional hazards Cox's model will be computed. For the dichotomous outcome variables logistic models will be fitted and for continuous normally distributed parameter the analyses of variance (ANOVA) will be done. All these analyses are of an exploratory nature.

Analyses of Adverse Drug Reactions
All data concerning adverse drug reactions, either discrete or continuous (lab values), will be analysed in detail. The data will be described by the type of adverse events, time of their occurrence, severity and outcome.

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10. ADVERSE DRUG REACTIONS

ADR-Monitoring:
In long-term clinical trials the monitoring of adverse drug reactions (ADR) is an important part of the trial concept to ensure the safety of the patients (see European Guideline for Good Clinical Practice GCP).

The results of regular continuous monitoring will be presented at the annual meeting of the study group. If more than 20 % of severe side effects (WHO-grade 3/4) or unexpected events occur in one of the treatment groups the Protocol Review Committee (PRC) will be informed immediately and the continuation of the trial will be discussed.

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11. REGISTRATION AND RANDOMIZATION OF PATIENTS

All eligible patients must give their consent and be randomized:

- for EORTC-Members at the EORTC Data Center

  by phone (tel. +32-2-774 16 00), through the EuroCODE network (direct line: +32-2-772 04 26/X25 network: 206-2 210 142 or through Internet (telnet to ecvax.eortc.be or http://www.eortc.be).

- for ESHO-Members at the BZT in Munich

  by fax (fax +49-89-544 202-14).

Page 1 and page 2 of he randomization/eligibility form (Form No. 0) will be filled in before calling the data
center or loging into the network. All questions will be interactively asked during the registration procedure. Therapy will be allocated to patients using a dynamic randomization scheme, with center, risk group and tumor site (E vs NE) as stratification criteria. The randomization form must be signed by the responsible investigator after treatment allocation, and faxed back to the respective Data Center.

If you randomize by fax, fill in page 1, page 2 and the head of page 3 of Form No. 0 and send all three pages to the respective Data Center. The Data Center will fax page 3 to you with the allocated randomized treatment

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12. ETHICAL CONSIDERATIONS

12.1 Patient Protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration
of Helsinki (Tokyo 1975, Venice 1983, and Hong Kong 1989, amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol has been written, and the study will be conducted according to the guidelines for Good Clinical Practice issued by the European Union. The protocol will be approved by the Local, Regional or National Ethics Review Boards.

12.2 Subject Identification

The name of the patient will not be recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, patients initials (first name, name, maximum of 4 letters), date of birth and local chart number (if available) will be also reported on the case report forms.

12.3 Informed Consent

All patients will be informed of the aims of the study, the possible adverse experiences, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation.

The informed consent must be obtained for the application of all protocol treatments. The special requirements for the application of regional hyperthermia are outlined and given as an appendix to this protocol.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not have any consequences for the patient subsequent care.

Documented informed consent must be obtained for all patients included in the study, before they are registered and randomized at the Data Center. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must be conform to the EEC

guidelines on Good Clinical Practice. This implies that "Consent must be documented either by the subject's dated signature or by the signature of an independent witness who records the subject's assistant".

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13. INVESTIGATOR COMMITMENT STATEMENT

Investigators will only be authorized to register patients in this trial when they have returned to the Study
Co-ordinator:

- a commitment statement, indicating that they will fully comply with the protocol, and including an estimation of their accrual
- a copy of the letter of acceptance of the protocol by their Local Ethical Committee.

The filled in STUDY ACKNOWLEDGEMENT must be sent to the Study Co-ordinator. The new investigator will be enabled to randomize patients in the trial. Randomization/Eligibility Forms from centers not authorized by the Study Co-ordinator will not be accepted.

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14. ADMINISTRATIVE RESPONSIBILITIES

14.1. Central Pathology Review

- ESHO-Members

For all patients entered into the EORTC 62961/ESHO RHT-95 study, 8 unstained slides with the paraffin block(s), if available, plus a copy of the Local Pathology report (see Form 1 of Documentation Forms) must be sent to one of the members of the Pathology Review Committee. The local pathologist, as principal investigator, will be informed about the results of the review of the committee.

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- EORTC-Members

All slides will be externally reviewed, according to the standard procedure of the group. Three forms will be used for this purpose and completed by the clinical investigator (the clinican who has registered the patient in the trial):

Form A: Patient information transmitted to the local pathologist
Form B: Patient clinical data transmitted to the reference pathologist
Form C: Review form to be handled partly by the clinical investigator and partly by the reference

1. The clinical investigator sends:

Form A (completed) to the local pathologist with a copy to:

the reference pathologist
the chairman of the PSC (Prof. Oosterhuis)
the Data Center

Form B (completed) and Form C (upper part completed) to the reference pathologis

2. The local pathologist sends to the reference pathologist:

8 unstained slides (suitable for immunohistochemistry) or 1 or 2 blocks
EM photographs (if necessary)
his own report (including gross morphology, note necrosis)

3. The reference pathologist (list hereunder) sends:

Form C (completed) to the Data Center with a copy to

the clinical investigator
he chairman of the PSC (Prof. Oosterhuis)
the local pathologist

retains 8 slides for his own file

returns the rest of the material to the local pathologist

For	the reference pathologist is	For	the reference pathologist is
Benelux S. Arabia Greece	Prof. J. W. Oosterhuis (PSC Chairman) Dr. Daniel den Hoed Center Groene Hilledijk 301 3075 EA Roterdam - The Netherlands	Denmark Germany Poland Czech Republ.	Dr. S. Daugaard Dept. of Pathology Teilum-Building Frederik 5's Vej 11 2100 Copenhagen - Denmark
U.K. Canada	Dr. M. Harris Dept. of Pathology Christie Hospital Wilmslow Road Manchester M20 9BX - United Kingdom	France	Dr. F. Collin Service d'anatomie patholog. Cent. Georges-François Leclerce 1, rue du Pr. Marion 21034 Dijon Cedex - France
Spain	Dr. T. G. Miralles Dept. of Pathology Hospital General de Asturias Julian Claveria S/N 33006 Oviedo - Spain	Italy Austria	Dr. S. Pilotti Dept. of Pathology Istituto Nazionale dei Tumori Via Venezian 1 20133 Milano - Italy

14.2. Study Co-ordinator

Prof. Dr. R. Issels

Klinikum Großhadern
Medizinische Klinik III
Marchioninistr. 15
D-81377 Munich
Germany

Phone: +49-89-7095-4768
Fax: +49-89-7095-4776

The Study Co-ordinator is responsible for the protocol (in cooperation with the Data Centers), reviewing all case report forms and documenting his/her review on evaluation forms, discussing the contents of the reports with the Data Manager and/or the Statistician, and publishing the study results.

14.3. Data Center

All investigators send their original Documentation Forms to one of the following Data Centers.

- FOR EORTC-Members:

Ms. Martine van Glabbeke
Assistant Director
EORTC Data Center
Avenue E. Mounier 83 Bte 11
1200 Brussels
Belgium

Fax: +32-2-7723545

- For ESHO-Members:

Biometrisches Zentrum für Therapiestudien (BZT)
Pettenkoferstr. 35
D-80336 Munich
Germany

Fax:: +49-89-544202-14

The EORTC Data Center will transfer all documentation forms to the BZT Data Center. The BZT Data Center will be responsible for reviewing the protocol, collecting documentation forms, controlling the quality of the reported data, and generating reports and analyses, in cooperation with the Study Co-ordinator.

All methodological questions should be addressed to the BZT Data Center.

STATISTICIAN:

Prof. Dr. D. Hölzel
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DATA MANAGER:

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Biometrisches Zentrum für Therapiestudien (BZT)
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Germany

Phone: +49-89-544202-0
Fax: +49-89-544202-14

14.4. Control of Data Consistency

Data will be entered in the database of the Data Center by a GCP/GMP conform procedure. Forms will be checked and coded manually and queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager to be entered in the master database. Inconsistent forms will be kept 'on-hold' until resolution of the inconsistencies. All entered data will be checked independently by a third person and inconsistencies will be removed by an audit trial controlled update procedere.

14.5. Documentation Forms and Schedule for Completion

Data will be reported on the Documentation Forms of the EORTC 62961/ESHO RHT-95 Study.

- EORTC-Members
  send the Documentation Forms to:

  Ms. Martine van Glabbeke
  Assistant Director
  EORTC Data Center
  Avenue E. Mounier 83 Bte 11
  1200 Brussels
  Belgium

- ESHO-Members
  send the Documentation Forms to:

  Biometrisches Zentrum für
  Therapiestudien (BZT)
  Pettenkoferstr. 35
  D-80336 Munich
  Germany

Documentation Forms must be completed according to the following schedule, and sent to the respective Data Center.

A. Before the Treatment Starts

- the patient must be registered and randomized at the respective Data Center
  (see REGISTRATION AND RANDOMIZATION OF PATIENTS)

- the following set of forms has to be returned to the respective Data Center:

  the Randomization/Eligibility Form (Form No. 0)

  the Baseline Characteristics Form (Form No. 1)

B. After Preoperative Chemotherapy ± RHT

Each cycle of therapy needs to be documented separately (see Form No. 2). At the end of 4 cycles the Preoperative Chemotherapy Form (Form No. 2) and the Preoperative Hyperthermia Form (Form No. 3, only arm A) have to be sent to the respective Data Center.

C. After Definitive Surgical Resection

All objective responses according to the reports of surgery and pathologist must be documented.

- the Evaluation of Response to Preoperative Regimen And Surgical Form (Form No. 4) should be sent to the respective Data Center.

D. After Radiotherapy Treatment

- a Radiotherapy Form (Form No. 5) must be completed through the radiotherapist or the investigator according to the report of the radiotherapist and has to be returned to the respective Data Center.

E. After Postoperative Chemotherapy ± RHT

- Each cycle of therapy needs to be documented separately (see Form No. 6). At the end of 4 cycles the Preoperative Chemotherapy Form (Form No. 6) and the Postoperative Hyperthermia Form (Form No. 7, only arm A) have to be sent to the respective Data Center.

F. Follow-up after Completion of Protocol Treatment

- a Follow-up Form (Form No. 8) has to be returned to the respective Data Center.

This form is sent every 3 months during the first year, every 4 months during the second and third years, every 6 months during the fourth and fifth years, thereafter every year and as long as the patient is not progressive.

It is sent to the respective Data Center.

ALL FORMS MUST BE DATED AND SIGNED BY THE RESPONSIBLE INVESTIGATOR.

G. For Patient Going off-Study

in case of death, patient is lost to follow-up, relapse, progression, metastasis formation, MAJOR protocol violation or regular end of study

- a Summary Form (Form No. 9) has to be returned to the respective Data Center.

H. Upon Occurrence of Metastases, Relapse or Progression

in case of relapse or metastases after surgery (R0) or progression before or after (R1 or R2) surgery

- a Progression Report Form (Form No. 10) has to be returned to the respective Data Center.

  This form is sent every year after the described occurrence.

I. Upon Occurrence of a Serious Adverse Event

- all serious adverse events must be reported within 48 hours to the respective Data Center and the Study Co-ordinator by phone or fax using the respective form (Form No. 2, 3, 5, 6 or 7) according to the therapy where the adverse event has occurred.

14.6 Data Flow

The Documentation Forms must be completed and signed by the investigator as soon as the requested information is available, according to the above described schedule. It is the responsibility of the investigator to check that original Documentation Forms are sent to the Data Center and that they are filled in completely and correctly.

The original must be immediately returned to the respective Data Center, and a copy must be kept by the investigator.

The BZT Data Center will perform extensive consistency checks on the Documentation and issue Query Forms (for ESHO- and EORTC- Members) in case of inconsistent data. Those Query Forms must be immediately answered and signed by the investigator. The original must be returned to the BZT Data Center, and a copy must be appended to the invesigator's copy of the Documentaton Forms.

If modifications have to be brought to a Documentation Form after the original copy has been returned to the BZT Data Center, this should be recorded on a Query Form following the same procedure as those issued by the Data Center.

The investigator's copy of the Documentation Forms may not be modified unless modifications are reported.

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15. TRIAL SPONSORSHIP

The legal sponsor of the study is:

ESHO (EUROPEAN SOCIETY FOR HYPERTHERMIC ONCOLOGY).

The chairman of the ESHO Clinical-Committee is:

Prof. Dr. Jens Overgaard
Danish Cancer Society
Department of Experimental Clinical Oncology
Radiumstationen
Nørrebrogade 44
DK-8000 Aarhus C
Denmark

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16. PUBLICATION POLICY

The final publication of the trial results will be written by the Study Co-ordinator on the basis of the statistical analysis performed at the BZT Data Center. A draft manuscript will be completed no later than 6 months after the last patient has discontinued therapy. After revision by the co-authors and the sponsor, this manuscript will be sent to a major scientific journal.

Authors of the manuscript will include the Study Co-ordinator, the investigators who have included more than 5 % of the eligible patients in the trial (by order of inclusion), the reference pathologist (if a central pathology review has been performed), and the Data Center manager and statistician in charge of the trial. ESHO will be referenced as the legal sponsor of the study.

Interim presentations of the study will include demographic data, overall results and prognostic factor analysis, but no comparison between randomized treatment arms may be made publicly available before the recruitment is discontinued and all responses have been externally reviewed

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17. INSURANCE AND LIABILITY

All patients who are taking part in this clinical trial are sufficiently insured against any injury caused by the trial.

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APPENDIX 1: SURGERY

According to the surgical staging system for musculoskeletal sarcomas by Enneking (**51**) and to the risk-adapted treatment procedures for compartmental versus extracompartmental tumors as proposed by Azzarelli (**52**), the following surgical guidelines and definitions are of importance:

1. SURGICAL REQUIREMENTS

Definitive surgery of the primary or recurrent tumor 4-6 weeks after the FOURTH preoperative cycle should be curative in intent, either by removal of all macroscopic disease surrounded by a cuff of normal tissue. Patients with marginal or microscopic non-radical resections will receive postoperative radiotherapy plus an eventual booster dose (or brachytherapy, or intra-operative RT) to the area at major risk of recurrence. In the case of extremity lesions if the operation is intralesional (macroscopic disease left behind) the final operation should be exarticulation, unless the patient refuses or exarticulation is contraindicated for medical reasons.

2. ADEQUACY OF LOCAL TREATMENT

Local surgery is regarded as adequate only when the definitive operation is non-contaminated and surgical clearance margins are wide or radical (**51**). It is of importance that the whole tumor/normal tissue along the axis of the implanted catheters is en bloc resected at the time of definitive surgery.

Local treatment is accepted as adequate if marginal resection or minimal contamination is later followed by radiation therapy. When a bone or major vessel lies close to the tumor the periosteum or adventitia must be stripped in the affected area. If the resection margins are adequate, the resection is called "radical". Where the resection margins are not adequate but macroscopically complete the resection is called "marginal". If the resection margin contains microscopic evidence of disease, the resection is called marginal microscopic non-radical resection. When there is macroscopic evidence of disease the resection is called "intralesional".

3. DEFINITIONS OF SURGICAL MARGINS

The operation is considered:

Intralesional - when macroscopic tumor, even if only minimal, is left in situ.

Marginal - when the tumor pseudocapsule is visible or there are minimal clearance margins (<1cm without any fascia), in any part of the surgical specimen, but no evidence of residual macroscopic tumor. It would be preferable if the pathologist examines the specimen together with the surgeon to ensure correct orientation of the original position of muscles which may later retract suggesting only marginal clearance in cases with adequate surgical clearance margins.

Wide - when the lesion is entirely surrounded by a cuff of normal tissue (at least 3 cm longitudinally and 1 cm laterally according to the line of muscles and fascia).

Radical - the entire lodge which includes the lesions is completely removed, delimited by uninvolved deep fascia. If the lesion is very close to or infiltrates the delimiting fascia the specimen must include part of the adjacent muscle lodge. The periosteum, adventitia and perineurium are considered delimiting fascia. If these fasciae are also infiltrated the operation should include bone, nerve or vascular resections with prosthetic replacement if needed.

Contaminated - if during the operation rupture of the tumor pseudocapsule occurs and tumor fragments spread over the surgical area. In this case the rupture must be controlled, the operative field repeatedly washed and the margin of operation enlarged. Contamination should be reported in the description of the operation.

4. DEFINITION OF SITES AND COMPARTMENTS

Note that in addition to the other defined high-risk factors **only extracompartmental tumors are eligible** for the EORTC 62961/ESHO RHT-95 study (see 3.1.3.). Tumors within extracompartmental sites but also tumors at any site which extend into an adjacent compartment or are not confined strictly within one compartment are classified as extracompartmental. The extension of primary tumors (extracompartmental or compartmental) has to be defined by the radiologist according to the following criteria.

EXTREMITIES (main muscle in brackets)

Lower Limb

Compartmental sites:	Posterior compartment of the thigh (biceps)
	Medial compartment of the thigh (adductors)
	Anterior compartment of the thigh (quadriceps)
	Anterolateral compartment of the lower leg (anterior tibial and peroneal)
	Posterior compartment of the lower leg (soleus and gastrocnemius)
	Rays of the foot
Extracompartmental sites:	Femoral triangle and Hunter's canal
	Popliteal fossa
	Soft parts close to the knee
	Ankle
	Mid and posterior foot

Upper Limb

Compartmental sites:	Posterior compartment of the arm (triceps)
	Anterior compartment of the arm (biceps)
	Anterior compartment of the forearm (pronator and flexors)
	Posterior compartment of the forearm (brachioradialis and extensors)
	Rays of the hand
Extracompartmental sites:	Neurovascular bundle of the arm
	Soft parts close to the elbow
	Wrist
	Carpal area

GIRDLES

Pelvic Girdle

Compartmental sites:	Buttock (gluteus)
Extracompartmental sites:	Groin Soft parts close to the hip

Scapular Girdle

Compartmental sites:	Pectoralis Periscapular region
Extracompartmental sites:	Axilla Soft parts close to the shoulder Periclavicular region

TRUNK

Extracompartmental sites:	Thoracic wall Abdominal wall Paraspinal muscles Intrapelvic area and retroperitoneum Head and neck

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APPENDIX 2: RADIOTHERAPY

All patients with soft tissue sarcomas treated with the preoperative regimen should be jointly assessed by the surgeon and radiotherapist, to consider radiation therapy.

1. TIMING OF RADIOTHERAPY

Radiotherapy should start within 4 and 6 weeks after definitive surgery (see flow chart).

2. RADIOTHERAPY GUIDELINES

2.1. General

Radiotherapy should be applied with megavoltage equipment. Dose specification and prescription should be in accordance with ICRU report 50; the dose within the planning target volume (PTV) should be between 95 % and 107 % of the prescribed dose. In case of multiple field treatment plans each field should be treated each day.

2.2. Planning Target Volume (PTV):

The planning target volume of elective irradiation should contain the whole compartment or compartments in which the original tumor was located, or at least the original tumor area with a margin of 5 cm in longitudinal direction and margin of 2 cm in other directions. The operation scar(s) and drain sites should be included in the planning target volume. (The addition of bolus over the scar is optional).

The planning target volume of the boost treatment should contain the original tumor area with a margin of 2 cm in all directions.

Organs at risk within the radiation fields should be documented. In limb sarcomas it is recommended

to avoid irradiation of the whole circumference of the extremity and if possible to avoid irradiation of the major nerves and vessels.

2.3. Treatment Technique:

CT planning should be performed.

All means to improve dose homogeneity within the planning target area and to avoid irradiation of organs at risk, such as multiple field techniques, wedge filters, tissue compensators etc. are highly recommended.

2.4. Radiation Dose and Fractionation

For patients with postoperative radiation either conventional fractionation or hyperfractionated accelerated split course radiotherapy will be applied. Centers may opt for one or the other for all patients treated at the center. The center policy will be decided prior to the entry of their first patient.

2.4.1. Conventional Fractionation

In conventional fractionation daily fractions of 1.8 - 2.0 Gy are administered 5 days per week. The minimal dose for complete (radical) microscopic (R0) excision would be 45 Gy (with an optional further boost to a total of
55-60 Gy). If there was an incomplete or marginal excision (R1), then a higher dose (50 Gy + boost 10-15 Gy) is mandatory. If the patient has residual post-operative macroscopic disease which cannot be resected for other reasons at least 60 Gy + boost 10 Gy should be given. The recommended doses have to be adjusted to the individual situation of the patient and to the neighbourhood of radiosensitive tissues and are to the discretion of the responsible radiotherapist.

2.4.2. Hyperfractionated Accelerated Split Course Radiotherapy

Patients are to receive single fractions of 1.6 Gy twice a day at an interval of at least 6 hours (10 fractions per week =16 Gy). Radiotherapy is applied in two courses. The first course starts on Monday and ends up on Friday next week with a total of 20 fractions and a total dose of 32 Gy. After a split of 9 - 11 days, irradiation is continued. Patients with adequate surgery (R0 resection by wide excision or compartmental resection) will receive another 10 fractions and a dose of 16 Gy (total dose 48 Gy). Patients with marginal resection (R1, microscopic disease) or with macroscopic tumor left in situ (R2-resection) which cannot be resected by other reasons may receive a boost of 8 Gy (total dose 56 Gy). The recommended doses have to be adjusted to the individual situation of the patient and to the neighbourhood of radiosensitive tissues and are to the discretion of the responsible radiotherapist.

2.5. Documentation

The following documents should be kept, and will be required fo a review of radiotherapy practice:

- Simulator planning films and plans.
- Isodose plots of at least the central transverse plane of planning.
- At least one portal image.
- Radiotherapy treatment sheet and summary and plan.

3. RADIOTHERAPY REACTION

Acute side effects as well as late effects will be recorded along routine guidelines and according to local
protocols (see Radiotherapy Form). After combined surgery and irradiation of tissue sarcoma of the extremities longterm physiotherapy to avoid contractures is recommended.

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APPENDIX 3: HYPERTHERMIA

1. QUALITY ASSURANCE

The clinical results obtained through implementation of this protocol will be of maximum value if all patients treated in arm A received equivalent thermotherapy. Accordingly, a primary goal of hyperthermia quality assurance is to facilitate the production of temperatures in tumor and normal tissues that are reproducible from treatment to treatment and are in satisfactory compliance with protocol treatment specifications. A second goal, of comparable importance, is to evaluate the thermal characteristics of treatments administered to protocol patients to determine if protocol requirements are being satisfactorily met.

The postoperative hyperthermia treatments can be performed without tumor bed catheters using the technical parameters of the preoperative hyperthermia treatments. The maximum applied power should not exceed that of the preoperative treatments.

The objectives of the quality assurance procedures are:

- To assure that the system is functioning as expected
- To assure that the phase and amplitude balance is correct

The simplest procedure uses only a LED or Lamp phantom. The phantom is placed inside the system and channels are tested one by one. This assures that the channels are functioning and that they are where you expect them to be (e.g. one is up, two is down...). Continue by adjusting the channels pair by pair. This checks the balance between opposite antenna pairs. Finally, test the focusing with all channels active. One can have a fixed set of configurations, e.g. focus (0,0), (5,0), (-5,0), (0,5), (0,-5). This test should not be run in treatment mode on the BSD-2000. In treatment mode there is a control loop to adjust power.

In the cases where the treatment is based only on measurements with an invasive E-field probe, the procedure above is adequate. If, however, the treatment is based on some sort of pre-planning, the system is expected to give correct phase and amplitude balance. If we trust the system, the test above is adequate. If we do not trust the system, additional test are needed to provide us with information regarding the proper adjustment of phase and amplitude in order to realize the desired/pre-planned treatment configuration. These can be made by use of network analyzers (expensive) or vector voltmeters (less expensive) and a phantom. Using this equipment, a procedure can be specified to test the different components of the system. By performing these extra test information will be gained regarding the true phase and amplitude balance in the system. This can also help in correcting skew

focusing, which has been reported by some institutions.

2. THERMOMETRY AND E-FIELD MEASUREMENTS

All temperatures will be measured by sensors calibrated with an NBS traceable standard. High resistant lead or fiberoptic type sensors are permissible if calibration determines their inaccuracy to be < 0.1.ºC. Single sensors will be "mapped" automatically within the entire thermometry catheter length in tissue during each hyperthermia session if technically feasible. As an alternative, multisensor thermometry may be used in a stationary or mapped mode. Systemic temperatures must be determined by intermittent (at least every 10 minutes) oral or rectal measurement, depending on the treatment site, (rectal temperature is not representative of systemic temperature during pelvic treatments). The temperature of the circulating coupling medium (bolus) should also be recorded.

If E-field measurements are used for treatment optimization a minimum of 4 averaging multiple dipole E-field sensors might be placed on the patient's surface in longitudinal direction such that the sensor is longitudinally centered within the device. In addition, "scanning" of a single E-field sensor can be performed within one or more of the thermometry catheters. Phase and amplitude steering should be tested at low levels of forward power (<250W) to attempt to maximize the ratio of E-field strengths detected in the tumor to normal tissue. Alternatively to E-field measurements, hyperthermia computed dose-planning according to the instituion's practice can be utilized.

3. POSITIONING OF PATIENT

At present, the devices most often employed for heating of deep-seated malignancies are concentric arrays of high frequency electromagnetic applicators (e.g. Sigma 60 of BSD Medical Corporation). However, heating may be produced by any device deemed appropriate to the task; e.g. capacitive plates, coaxial induction coils, scanned, focused ultrasound, multibeam ultrasound, etc.).

Whatever the approach, the positioning of the patient relative to the heating device should be guided by the CT scan or diagnostic x-ray films that clearly indicate the tumor margins and their relation to identificable points on the patient's surface.

For a given device or technique, dimensions of the useful heating fields in directions perpendicular to the axis of penetration should be estimated from published or measured in-house SAR or temperature distributions in appropriate phantoms. In general, maximal tumor coverage will be obtained if the patient is positioned with respect to the heating device so that as much of the tumor as possible lies between the 50% iso-SAR points along the respective directions. In coupling the Annular Phased Array(e. g. Sigma 60) it is important that air spaces between applicator and patient surface be minimized and - if possible - eliminated. Once the patient is in position within (or relative to) the applicator, "fine tuning" of patient-applicator position can be carried out through measurement of electric field intensities at several critical points on the patient surface. The E-Field sensors are placed at anterior-center, posterior-center, left-lateral and right-lateral positions on the skin of the pelvis, abdomen or limb. Measurements of surface electric fields (shown as normalized percanges outside the

ellipse) at low power levels (100-200 watts) can guide adjustments of the patient position within the ring, and reduce the severity of hot spots produced in skin and subcutaneous tissues during thermotherapy. Such adjustments can also lead to improved tumor heating.

4. DESCRIPTION OF TREATMENT SET- UP

For satisfactory description and evaluation of the treatment, details of the locations of both heating devices and thermometry probes relative to tumor and normal tissue must be recorded. A diagram of the treatment set-up should be prepared prior to beginning the initial treatment. The diagram must include the anatomic location of the treatment site and the location and extent of the tumor (tumor dimensions should be given). The physical borders of the heating device employed must be marked on the diagram, so as to clearly indicate the position of the applicators relative to the tumor volume. The locations of thermometry probes (or catheters) within the tumor and normal tissues should be clearly indicated on the diagram. Given the critical importance of this information, verification of indicated thermometer track locations should be provided. Prior to the initial treatment of the patient, a set of CT scans should be obtained that display clearly the catheter tracks.

5. MONITORING DURING TREATMENT

The power supplied to the heating applicators at the onset of the steady state phase of thermotherapy must be measured. Both forward and reflected power should be recorded, and the net power computed.

Hyperthermia produced by electromagnetic heating devices (e.g. Sigma 60), leakage intensities (mw/cm2) at critical points on the patient (e.g. eyes) and near the operator should be measured and recorded at the onset of the steady state phase of thermotherapy. The locations associated with the recorded leakage levels must be identified.

If the skin is actively cooled, the method used should be recorded.

Patient anxiety and general discomfort must be recorded, along with comments on possible causes and steps taken to reduce the existence of patient pain. The location, severity and duration of such pain, as well as its possible causes and steps taken for its alleviation must be indicated.

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APPENDIX 4:	HUMAN CONSENT FOR REGIONAL HYPERTHERMIA

ADMINISTRATION OF REGIONAL HYPERTHERMIA COMBINED WITH CHEMOTHERAPY

Deep regional hyperthermia (RHT) will be given as part of the EORTC 62961/ESHO RHT-95 study designed to evaluate success of either chemotherapy combined with RHT or chemotherapy alone on high-risk sarcomas. Deep heat will be delivered by external RF/microwave energy directed into the tumor by the BSD-2000 System using a cylindrical applicator which will surround the treatment region, and will be given in conjunction with systemic chemotherapy.

Deep heat involves heating of the tumor to an average temperature of about 108^{o}F (42^{o}C; range: 40^{o}-44^{o}C) by directing energy to the tumor and maintaining the temperature for approximately 60 minutes.

The hyperthermia machine is computer operated and is installed in a electromagnetic shielded room sectioned from the computer. (The shielded room prevents the energy from leaving the room.) A physician, technician or a nurse will be watching you from outside or inside the treatment room and can talk to you throughout the treatment. Vital signs will be monitored and your blood pressure and pulse rate will be taken frequently throughout the treatment.

PATIENT AUTHORIZATION

I hereby authorize Dr._____ and/or his assistants to perform upon me the following procedures in connection with the EORTC 62961/ESHO RHT-95 study. I understand that the following may be done:

a) Depending on the location of my tumor(s), prior to treatment, plastic catheters will be inserted into the tumor itself and into surrounding normal tissue, either requiring general or local anesthesia. These catheters will be stitched or otherwise secured in place to be used for temperature measurement during each treatment throughout my therapy.

b) Before the treatment, a temperature probe will be inserted into each of the catheters in the tumor and into surrounding tissue. During the treatment, these probes will constantly measure tissue temperature to provide the best control during the treatment. It might be possible in the future to perform RHT treatments based upon equivalent control parameters (e.g. E-field, blood flow, MRI parameters) without invasive probes.

c) A flexible rubber tube will be placed in my bladder through which urine will be drained into a bag.

POTENTIAL BENEFITS

I understand that the possible benefits associated with the procedures described above include tumor shrinkage or disappearance, relief of symptoms, and/or an improved quality of life. I acknowledge that no guarantee or assurance has been made to me regarding the clinical outcome, since results cannot be foreseen. Although the EORTC 62961/ESHO RHT-95 concept has the potential to cure the disease, it may be of no benefit to me and may have injurious effects.

I understand there is no guarantee that the tumor will decrease in size or be cured. The physician(s) will take every precaution consistent with good medical practice to ensure that my treatment with this program may prove to be a benefit to me and to the advancement of medical knowledge.

SIDE EFFECTS

I understand that certain hazards and discomfort might be associated with the procedures described above. These include: pain, burns/blisters, ulceration, muscle necrosis, and infection. Additional side effects such as nausea, fever and temporary nerve impairment have been observed in some deep hyperthermia treatment. Other side effects may include redness, tenderness or even small blisters on the skin that is located directly in the machine.

Although large clinical experience exists from the results of the RHT-91 study regarding the effect of hyperthermia and chemotherapy in combination on soft tissue sarcomas, the possibility of unforeseen side effects may occur.

Although only few cases of serious damage (< 5%) to the normal organs have been observed in these studies, it is possible that some damage to normal tissues occurs.

It is not expected that hyperthermia will alter the side effects of chemotherapy with the exception of the possibility of enhanced normal tissue reaction in the vicinity of the heated area: Should any of the above side effects appear, my physician(s) have assured me that they will take adequate steps to reduce or eliminate these effects by all necessary means. There can be no assurance that such effects can be reduced or eliminated.

Anesthesia: I also understand that regional anesthesia with hyperthermia will only be used under controlled conditions. Pain-killers or tranquilizers can be routinely used in my treatments as long as they do not significantly decrease my awareness of pain sensation in treatment area.

CONFIDENTIALITY

I agree to allow my name, medical records, and pathologic materials to be available to members of the medical staff and to other authorized individuals in order to evaluate the results of this treatment. All precautions necessary to maintain the confidentiality of medical records will be taken. I understand that the confidentiality of my records will be maintained in accordance with applicable state and federal laws.

QUESTIONS

I understand the local investigator is willing to answer any inquiries that I may have concerning the procedure described herein. All the inquiries I have at this time have been answered.

I understand that my participation is voluntary and that I may refuse to participate and/or withdraw my consent and discontinue participation in the project.

I also understand that the physician can terminate my participation without my consent at any time in the event of physical injury or other condition which makes further treatment an unnecessary risk in the medical opinion of my physician.

PHYSICAL INJURY

I have been informed that in the event of physical injury resulting from this research procedure immediate first aid treatment will be provided. Financial compensation is not available for this treatment nor in the event of physical injury.

AGREEMENT

The physician(s) involved in this treatment is

_____

He/she may be contacted by telephone at_____ if have any questions regarding my treatment.

I have discussed the above mentioned material with my physician(s) and they have answered my questions concerning the treatment program and other methods available for treatment of my disease.

I have reviewed the foregoing statements and understand them. I understand that I am not required to enter this treatment program and that if I agree to participate it will be a voluntary decision. I know how to contact my physician and his/her staff regarding any questions or problems.

I am of sound mind and clearly understand the potential risks involved in the use of hyperthermia combined with chemotherapy and hyperthermia equipment.

I have received a copy of this informed consent which I have read and understood. I hereby consent to the performance of the described procedures on me.

PATIENT_____ DATE___/___/_____

NOTE: If there is anything in the foregoing material you do not understand, ask the doctor to explain it before you sign.

PHYSICIAN'S STATEMENT

I have provided a verbal explanation of the treatment program outlined herein, along with a copy of this consent form. I have encouraged the patient to request additional information and have discussed possible alternative forms of treatment.

PHYSICIAN_____

Emergency telephone number _____

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APPENDIX 5: PERFORMANCE STATUS

WHO-SCALE [Grade]	KARNOFSKY-SCALE [%]
0 Able to carry out all normal activity without restriction.	100 Normal; no complaints
1 Restricted in physically strenuous activity by ambulatory and able to carry out light work.	90 Able to carry on normal activities; minor signs or symptoms of disease 80 Normal activity with effort.
2 Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50 % of waking hours.	70 Cares for self. Able to carry on normal activity or to do active work. 60 Ambulatory. Requires some assistance in activities of daily living and self-care.
3 Capable of only limited self-care; confined to bed or chair more than 50 % of waking hours.	50 Requires considerable assistance of frequent medical care. 40 Disabled; requires special care and assistance.
4 Completely disabled; cannot carry on any self-care: totally confined to bed or chair.	30 Severely disabled; hospitalization indicated though death not imminent. 20 Very sick; hospitalization and active supportive treatment. 10 Moribund. 0 Dead.

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APPENDIX 6: G-CSF (Neupogen^{R} = Filgrastim)

PRODUCTION:

Granulocyte colony-stimulating factor (e. g. filgrastim, Neupogen ^{R}) is produced using genetic engineering techniques, by means of which the human gene sequence is incorporated into the genome of E.coli bacteria. The gene product thus produced is identical to human G-CSF, except for its N-terminal methionine residue and its lack of glycosylation (174 AA, MW 18,800 daltons).

ACTION:

After binding to specific surface markers on granulocyte precursor cells, filgrastim induces the differentiation, maturation and proliferation of neutrophil granulocytes. The duration and severity of chemotherapy-induced neutropenia are thus reduced and the risk of infectious complications is lowered. The number of days spent in hospital and the use of antibiotics were significantly reduced by filgrastim.

PHARMACOLOGICAL EFFECTS:

Following intravenous or subcutaneous administration of filgrastim, the differential blood count shows a transient shift to the left of granulopoiesis up to the level of myeloblasts and promyelocytes. In addition, a slight dose-dependent increase in monocyte and lymphocyte counts was observed. This, however, did not lead to deviations from normal ranges in the differential blood count. All the modifications described above reverse on cessation of treatment.

PHARMACOKINETICS:

There is a positive linear correlation between doses administered and serum concentrations measured. The elimination half life is 3.5 hours. Continuous administration for a period of 2 weeks (when a steady state in the serum is reached) did not lead to an accumulation of the drug.

SIDE EFFECTS:

The only side effect observed relatively regularly was bone pain, which was experienced by approximately 25% of all patients treated. In most cases this can be controlled adequately by non-steroid analgesics. In rare cases hair loss, diarrhoea, mucositis, fever, headache, coughs, chest pains, weakness and constipation are observed. These symptoms, however, are indistinguishable from chemotherapy-induced side effects.

In very rare cases (< 2%) treatment with filgrastim causes an excessive increase in leukocyte counts up to values of 100,000 cells per mm^3. However, patients in whom such elevated leukocyte counts were observed suffered no negative clinical effects.

No life-threatening incidences directly associated with filgrastim have so far been reported.

CONTRAINDICATIONS:

Since filgrastim is a protein produced from E.coli bacteria using genetic engineering techniques, it should not be administered to patients with established allergies to protein substances derived from this strain of bacteria.

Pregnant and lactating women should only be treated with filgrastim in vital cases since current knowledge regarding embryotoxicity and the consequences of filgrastim uptake by infants via breast milk is limited.

ADMINISTRATION AND DOSE:

As part of the EORTC 62961/RHT-95 study, treatment with filgrastim is commenced on the day following administration of the last dose of chemotherapeutic agents in compliance with the indication guidelines (see 5.1.4 G-CSF support).

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APPENDIX 7: COMMON TOXICITY CRITERIA (CTC) SCALE

	Grade				
TOXICITY	**0**	**1**	**2**	**3**	**4**
Haematology					
WBC ($x10^3/\mu l$)	≥ 4.0	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	< 1.0
Platelets ($x10^3/\mu l$)	WNL	75.0 - normal	50.0 - 74.9	25.0 - 49.9	< 25.0
Haemoglobin (g/dl)	WNL	10.0 - normal	8.0 - 9.9	6.5 - 7.9	< 6.5
Granulocytes/ Bands ($x10^3/\mu l$)	≥ 2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
Lymphocytes ($x10^3/\mu l$)	≥ 2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5

Haemorrhage	none	mild, no	gross, 1 - 2 units transfusion per episode	gross, 3 - 4 units transfusion per episode	massive, > 4 units transfusion per episode
Coagulation					
Fibrinogen	WNL	0.99 - 0.75 x N	0.74 - 0.50 x N	0.49 - 0.25 x N	< 0.25 x N
Prothrombin time (Quick)	WNL	1.01 - 1.25 x N	1.26 - 1.50 x N	1.51 - 2.00 x N	> 2.00 x N
Partial thrombo-plastin time	WNL	1.01 - 1.66 x N	1.67 - 2.33 x N	2.34 - 3.00 x N	> 3.00 x N
Metabolic					
Hyperglycaemia (mg/dl)	< 116	116 - 160	161 - 250	251 - 500	> 500 or ketoacidosis
Hypoglycaemia (mg/dl)	> 64	55 - 64	40 - 54	30 - 39	< 30
Amylase	WNL	< 1.5 x N	1.5 - 2.0 x N	2.1 - 5.0 N	> 5.0 x N
Hypercalcaemia (mg/dl)	< 10.6	10.6 - 11.5	11.6 - 12.5	12.6 - 13.4	≥ 13.5
Hypocalcaemia (mg/dl)	> 8.4	8.4 - 7.8	7.7 - 7.0	6.9 - 6.1	≤ 6.0
Hypomagnesaemia (mg/dl)	> 1.4	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	≤ 0.5

Gastrointestinal					
Nausea	none	able to eat reasonable intake	intake significantly decreased but can eat	no significant intake	—
Vomiting	none	1 episode in 24 hrs	2 - 5 episodes in 24 hrs	6 - 10 episodes in 24 hrs	> 10 episodes in 24 hrs or requiring parenteral support
Diarrhoea	none	increase of 2 - 3 stools / day over pre-Rx	increase of 4 - 6 stools / day, or nocturnal stools, or moderate cramping	increase of 7 - 9 stools / day, or incontinence, or severe cramping	increase of > 10 stools / day or grossly bloody diarrhoea, or need for parenteral support
Stomatitis	none	painless ulcers, erythema, or mild soreness	painful erythema, oedema, or ulcers but can eat solids	painful erythema, oedema, or ulcers and cannot eat solids	requires parenteral or enteral support for alimentation
Liver					
Bilirubin (N = 17 μmol/L)	WNL	-----	< 1.5 x N	1.5 - 3.0 x N	> 3.0 x N
Transaminase (SGOT, SGPT)	WNL	≤ 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
Alk Phos or 5 nucleotidase	WNL	< 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N

Liver-clinical	No change from baseline	-----	-----	precoma	hepatic coma
Kidney, bladder					
Creatinine	WNL	< 1.5 x N	1.5 - 3.0 x N	3.1 - 6.0 x N	> 6.0 x N
Proteinuria	No change	1 (+) or < 0.3 g% or 3 g/L	2 - 3 (+) or 0.3 - 1.0 g% or 3 - 10 g/L	4 (+) or > 1.0 g% or > 10g/L	nephrotic syndrome
Haematuria	Negative	microscopic only	gross, no clots no Rx needed	gross and clots bladder irrigation	requires transfusion or cystectomy
Weight gain/ loss	< 5.0 %	5.0 - 9.9 %	10.0 - 19.9 %	≥ 20.0 %	-----
Pulmonary	none or no change	asymptomatic, with abnormality in PFTs	dyspnoea on significant exertion	dyspnoea at normal level of activity	dyspnoea at rest
Cardiac					
Cardiac arrhythmias	none	asymptomatic, transient, requiring no therapy	recurrent or persistent, no therapy required	requires treatment	requires monitoring; or hypotension, or ventricular tachycardia or fibrillation

Cardiac function	none	asymptomatic, decline of resting ejection fraction by less than 20 % of baseline value	asymptomatic, decline of resting ejection fraction by more than 20 % of baseline value	mild CHF, responsive to therapy	severe of refractory CHF
Cardiac ischaemia	none	non-specific T-wave flattening	asymptomatic, ST and T wave changes suggesting ischaemia	angina without evidence of infraction	acute myocardial infarction
Cardiac-pericardial	none	asymptomatic effusion, no itervention required	pericarditis (rub, chest pain, ECG changes)	symptomatic effusion; drainage required	tamponade; drainage urgently required
Hypertension	none or no change	asymptomatic, transient increase by greater than 20 mm Hg (D) or to > 150 / 100 if previously WNL. No treatment required.	recurrent or persistent increase by greater than 20 mm HG (D) or to > 150 / 100 if previously WNL. No treatment required.	requires therapy	hypertensive crisis
Hypotension	none or no change	changes requiring no therapy (incl-uding transient orthostatic hypo-tension)	requires fluid replacement or other therapy but not hospitalisation	requires therapy and hospitalisation; resolves within 48 hours of stopping the agent	requires therapy and hospitalis-ation for > 48 hrs after stopping the agent

Neurologic

Neuro: sensory	none or no change	mild paraesthesias; loss of deep tendon reflexes	mild or moderate objective sensory loss moderate paraesthesias	severe objective sensory loss or paraesthesias that interfere with function	-----
Neuro: motor	none or no change	subjective weak-ness; no objective findings	mild objective weakness without significant impair-ment of function	objektive weak-ness with impairment of function	paralysis
Neuro: cortical	none	mild somnolence or agitation	moderate somnolence or agitation	severe somnolence, (>50 % waking hours), agitation, confusion, disorientation or hallucinations	coma, seizures, toxic psychosis
Neuro: cerebellar	none	slight incoordination, dysdiadochokinesia	intention tremor, dysmetria, slurred speech, nystagmus	locomotor ataxia	cerebellar necrosis
Neuro: mood	no change	mild anxiety or depression	moderate anxiety or depression	severe anxiety or depression	suicidal ideation
Neuro: headache	none	mild	moderate or severe but transient	unrelenting and severe	-----
Neuro: constipation	none or no change	mild	moderate	severe	ileus > 96 hrs

Neuro: hearing	none or no change	asymptomatic, hearing loss on audiometry only	tinnitus	hearing loss interfering with function but correctable with hearing aid	deafness not correctable
Neuro: vision	none or no change	-----	-----	symptomatic subtotal loss of vision	blindness
Pain	none	mild	moderate	severe	reg. narcotics
Skin	none or no change	scattered macular ot papular eruption or erythema that is asymptomatic	scattered macular or papular eruption or erythema with pruritus or other associated symptoms	generalised symptomatic macular, papular or vesicular eruption	exfoliative dermatitis or ulcerating dermatitis
Alopecia	no loss	mild hair loss	pronounced or total hair loss	-----	-----
Allergy	none	transient rash, drug fever < 38^{o}C (100.4^{o}F)	urticaria, drug fever ≥ 38^{o}C (100.4^{o}F), mild bronchospasm	serum sickness, bronchospasm requiring parenteral medication	anaphylaxis
Local	none	pain	pain and swelling with inflammation or phlebitis	ulceration	plastic surgery indicated

Fever of unknown origin	none	37.1 - 38.0º C 98.7º - 100.4º F	38.1 - 40.0ºC 100.5 - 104ºF	> 40.0ºC > 104.0ºF for less than 24hrs	> 40.0ºC (>104ºF) for more than 24 hrs or accompanied by hypotension
Infection	none	mild	moderate	severe	life-threatening

WNL = Within normal limits

Additional events

Asthenia	analogous to Karnofsky index (WHO grading)
Chills	analogous to fever
Peripheral oedema	analogous to weight gain
Anorexia	analogous to weight loss

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APPENDIX 8: PARTICIPATING EUROPEAN RHT-CENTERS

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