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Neoadjuvant chemotherapy combined with regional hyperthermia (RHT) for locally advanced primary or recurrent high-risk adult soft-tissue sarcomas (STS) of adults: long-term results of a phase II study☆

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Abstract

In this phase II study, activity and safety of neoadjuvant regional hyperthermia (RHT) combined with chemotherapy was investigated in 59 patients with primary advanced or recurrent high-risk soft-tissue sarcoma (STS). Patients received four EIA cycles consisting of etoposide, ifosfamide and doxorubicin combined with RHT followed by surgical resection and adjuvant treatment. The overall objective response (OR) rate was 17%, with one complete (2%) and eight partial (15%) responses. In addition, 13 minor reponses (25%) were seen. At time of surgery, complete necrosis (pCR) occurred in 6 patients and >75% necrosis (favourable histological response (FHR)) in 12 patients. At the completion of protocol treatment, 36 patients were rendered disease-free which was significantly associated with the initial radiographic and/or pathological tumour response ($P=0.004$). Treatment-related toxicity was acceptable overall. At a medium follow-up of 82 months, local treatment failure occurred in 33 patients, median overall survival (OS) was 52 months, and the 5-year survival rate was 49% (95% confidence interval (CI): 36–61%). OS which did not differ for extremity versus non-extremity STS ($P=0.21$) was better for patients responding to EIA combined with RHT ($P<0.01$).

Keywords: Soft tissue sarcoma; High risk; Hyperthermia; Neoadjuvant; Chemotherapy; Recurrence; Survival

1. Introduction

Soft-tissue sarcomas (STS) represent a heterogeneous group of relatively rare malignancies with a wide spectrum in terms of histological type and prognosis [1]. In the last decade, the use of limb-sparing surgery and postoperative irradiation has become standard practice in the management of resectable extremity STS with 5-year rates of local control similar to those reported with radical resection or amputation [2–4]. However, the anatomical location (e.g. retroperitoneal) and invasiveness of STS often prevents resection with adequate margins [5], and the toxicity of radiotherapy limits the use of potentially therapeutic doses with a negative impact on local control [6,7].

In addition, patients with large (size >5 cm), high-grade and deep STS remain at increased risk for distant metastases and tumour-related mortality [8,9], despite local control. There is also strong evidence that the occurrence of local relapse in high-risk patients has an unfavourable impact upon subsequent survival [10,11]. For high-risk patients with retroperitoneal STS, the overall 5-year survival rate is in the range of 15–35%

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[12,13]. A retrospective analysis showed that high-risk tumours were associated with only 20-month median survival compared with 80 months for low-risk tumours [14].

Neoadjuvant chemotherapy is intended to induce local tumour regression and eradicate systemic distant micrometastases before local treatment. Only a few phase-II studies of neoadjuvant chemotherapy have been carried out in patients with bulky STS according to risk factors [15–17]. Within the last decade, hyperthermia in addition to radiation and/or chemotherapy has been tested in different tumour entities showing benefit in terms of tumour response, local control and survival [18,19].

In 1986, at the Klinikum Grosshadern Medical Center (KGMC) we initiated a phase I/II study for patients with advanced chemoresistant sarcomas combining second-line chemotherapy (ifosfamide plus etoposide) with regional hyperthermia (RHT) [20]. Radiographic and/or pathological response rate of different types of sarcomas was within the range of 30–35% and associated with high temperatures as measured within the tumours [20,21]. In February 1991, a consecutive study designed for patients, that were not pretreated with chemotherapy, with local advanced high-risk STS of extremity and non-extremity tumours was initiated (RHT-91 protocol) combining RHT with neoadjuvant systemic chemotherapy (EIA) [22]. Here, we report on 59 patients treated within the RHT-91 protocol with respect to radiographic and/or pathological response rates, surgical results, control of disease and survival parameters.

2. Patients and methods

2.1. Eligibility, patient characteristics and study design

Patients were required to have histologically-confirmed STS without evidence of distant disease. With regard to high-risk criteria, only progressively growing tumours of grade II or III, tumour size >8 cm and extracompartmental extension were eligible. Patients were required to have Karnofsky performance status of $\geqslant 60\%$, normal haematological, renal and hepatic function. Patients with persistent or recurrent high-risk STS after previous attempts of resection with or without radiotherapy were eligible. Written informed consent was required of all patients.

The RHT-91 protocol was designed as a monocentric, non-randomised controlled single arm phase II study with overall survival and objective response as the primary end-points. Because of the heterogenous patient population including non-extremity and extremity high risk-STS, sample size estimation for each subgroup was performed for the improvement in median survival from 20 months (historical control 14 months) to 49 months. In the case of 3.5 years recruitment period and 5-year follow-up, the required number of patients was estimated to be 25 ($\alpha = 5\%$; $\beta = 20\%$).

2.2. Staging, treatment and response evaluation

Before initiation of the protocol treatment, all patients in addition to physical examination underwent chest X-ray, computed tomographic (CT) scan of the chest and upper abdomen. Determination of tumour size were determined by contrast-enhanced CT scan and/or magnetic resonance imaging (MRI). From all patients, initial biopsy specimens were taken from the tumours for histopathological evaluation. Restaging after neoadjuvant thermochemotherapy included chest X-ray, and CT scan of chest and upper abdomen.

2.2.1. Treatment programme

For preoperative chemotherapy, patients were treated with the concurrent EIA regimen and RHT every 3 weeks. The systemic chemotherapy of each cycle consisted of doxorubicin (adriamycin) 50 mg/m^2 on day 1, etoposide 125 mg/m^2 on days 1 and 4, and ifosfamide 1250 mg/m^2 for 60 min on days 1–4. On days 1 and 4, this EIA regimen was combined with RHT as previously described in Refs. [20–22]. A total of four neoadjuvant EIA courses combined with RHT were given before assessment of the tumour response.

RHT was applied using the BSD 2000 system, which is an electromagnetic deep regional-heating device (BSD Medical Corporation, Salt Lake City, UT, USA) [23]. The treatment objective was the achievement of a maximum tumour temperature (T_{max}) of $\geqslant 42^{\circ}$C for a period of 60 min. Detailed description of the thermometry to obtain sufficient information about intratumoral temperature (T) gradients and T distributions in the RHT treatment field has been previously published [20]. All patients were hospitalised during the thermochemotherapy cycles for an average time of 8 days (range 6–12 days).

After preoperative treatment, patients were restaged (week 12) and those who were judged to be resectable underwent surgery (week 14). Resectability was defined to be adequate when wide or radical surgical margins without mutilation were deemed to be feasible.

After surgery, patients with signs of clinical and/or pathological response and without progressive disease were considered to receive four more cycles of chemotherapy consisting of etoposide (150 mg/m^2 on day 1–5) and ifosfamide (1500 mg/m^2 on days 1–5) combined with RHT on days 1 and 5, repeated every 4 weeks. Non-pre-irradiated patients with positive surgical margins or residual macroscopic disease were selected for external beam radiotherapy using mega-voltage equipment. Radiation was delivered to treatment fields that

included the tumour bed/scar with an approximately 5 cm margin. Radiotherapy attempted to give adequate total doses (range 55–65 Gy) in daily fractions (1.8–2.0 Gy). The total dose homogeneity to the boost volume was planned for ±5%.

2.2.2. Treatment evaluation

Toxicity was evaluated after each RHT combined chemotherapy cycle by medical history, clinical examination, laboratory tests according to World Health Organization (WHO) criteria [24].

Radiographic and pathological responses were defined by the following response criteria. Complete response (CR) was defined as the complete disappearance of all measurable or assessable disease on the post-treatment imaging study. Partial response (PR) was defined as ⩾50% reduction in the sum of the products of the perpendicular diameters of the primary lesion with no evidence of secondary lesions; minor regression (MR) was defined as 25–49% decrease in tumour size; stable disease (SD) was defined as no significant change (<25% increase or decrease) of tumour size; progressive disease (PD) was defined as an increase in the measured lesion by ⩾25% that was more than the size present at the time of entry onto the study. Pathological CR (pCR) was defined as the absence of residual viable tumour in the serial sectioned specimen after complete surgical resection. Favourable histological response (FHR) was defined as greater than 75% pathohistological necrosis, but residual viable tumour as previously described in Ref. [20].

By definition, patients were classed as NED at the time of surgery in cases of R0/R1 resection. Patients undergoing R2 resection were classified as non-NED.

For evaluation of the feasibility of RHT, time-averaged temperatures were calculated for each RHT at each monitored site. These temperatures were averaged over all RHT treatments to yield an average minimum (T_{min}) and maximum (T_{max}) temperature for an individual patient. In addition, the time-averaged temperatures achieved in 20, 50 and 90% of all measured tumour sites were determined from each RHT treatment. These values (°C) from all RHT treatments of each patient were expressed as T_{20}, T_{50} and T_{90} respectively [20].

2.3. Statistics

Statistical association of response (either radiographic or pathological) with remaining disease status was performed using the Chi square test according to Pearson. The time from start to therapy to local treatment failures and distant recurrences or death were estimated according to the method of Kaplan and Meier [25]. The 95% confidence intervals (CIs) of the Kaplan–Meier estimates were calculated with Greenwood's variances [26]. The end-points for actuarial analysis were local failure-free survival (LFFS), distant recurrence (metastasis)-free survival (DMFS), event-free survival (EFS) and overall survival (OS). The comparison of survival parameters in responding versus non-responding patients was performed by using the log-rank test [27]. A P value ⩽0.05 was considered to be statistically significant.

3. Results

3.1. Patient characteristics

Between February 1991 and October 1994, 59 eligible patients were treated according to the RHT-91 study protocol, patient characteristics are listed in Table 1. The patients entered the trial either with primary tumours of size >8 cm and/or extracompartmental location (31 patients) or with local regional recurrence of tumours bearing these characteristics (28 patients). In 31 non-extremity STS, tumours were located in the trunk (8 patients) or within the abdomen and pelvis (23 patients). Of the 28 patients with STS of the extremity, the tumours were located at the proximal part of the limb in the majority of cases. There were 31 men and 28 women with a median age of 50 years (range 21–77 years). Patients' history revealed that previous attempts of surgical resections alone (23 patients) or surgical resection followed by radiation (15 patients) have been performed.

All tumours were progressively growing, deep-seated and, in most cases, infiltrating the adjacent tissue (e.g.

Table 1
Patient characteristics

Characteristics	Eligible patients ($n=59$) n (%)
Median Karnofsky status	90% (range: 60–100%)
Sex	
Male	31 (53)
Female	28 (47)
Age at entry (years)	
20–40	16 (27)
>40–65	36 (61)
>65	7 (12)
Disease status	
Primary	31 (53)
Local recurrence	28 (47)
Non-extremity tumours	
Trunk	8 (14)
Abdomen	5 (8)
Pelvis	18 (31)
Extremity tumours	28 (47)
Prior treatment	
Surgery alone	23 (39)
Surgery plus radiation	15 (25)
None	21 (36)

Table 2
Histological diagnoses and grades ($n=59$)

Cell type	Grade		
	II ($n=28$)	III ($n=31$)	n (%)
Liposarcoma	9	5	14 (24)
Malignant fibrous histiocytoma	4	9	13 (22)
Leiomyosarcoma	6	4	10 (17)
Schwannoma	3	3	6 (10)
Synovial sarcoma	1	2	3 (5)
Rhabdomyosarcoma	0	3	3 (5)
Extraskeletal Ewing's sarcoma	1	1	2 (3)
Undifferentiated sarcoma	1	3	4 (7)
Others	3	1	4 (7)

bone, vessels, nerves) by diagnostic imaging. The median ellipsoidal tumour volume was 300 cc indicating the extensive local stage (71% of the primary tumour diameters were $\geqslant 8$ cm) of the lesions. Pathological features of cell type and grading of tumours are given in Table 2.

3.2. Feasibility and toxicity

The treatment characteristics of pre- and postoperative chemotherapy combined with RHT for all patients are listed in Table 3.

52 patients (88%) received the prescribed number of preoperative EIA chemotherapy cycles combined with RHT. These include eight patients who continued to receive one more cycle because of a delay in planning of surgery. The median number of EIA cycles administered was four (range, 2–5) combined with eight RHT treatments (range, 4–10). Therapy was stopped because of tumour progression in one patient and because of toxicity or refusal in 6 patients. Of the 39 patients who received the postoperative EI chemotherapy, 29 patients (74%) received four cycles combined with RHT. Reasons for discontinuation included early progression in 2, toxicity in 1 and refusal in another 3 patients. Another 4 patients received the EI regimen postoperatively without RHT because of the technical inability to heat. The median number of EI cycles administered was four (range, 1–4) combined with five RHT treatments (range, 2–8).

Among the 20 patients who did not receive the postoperative protocol treatment, 7 showed tumour progression, 4 received immediate radiation without further completion of postoperative chemotherapy and another nine refused further treatment.

Based upon a total of 658 RHT treatments, average maximum temperature (T_{max}) measured within the tumours was 42.5°C (95% confidence interval (CI), 42.2–42.7°C) and the median time-averaged temperatures achieved in 20, 50 and 90% of all the measured tumour sites were 41.4°C (T_{20}) (95% CI: 41.0–41.5°C), 40.6°C (T_{50}) (95% CI: 40.4–40.8°C), and 39.8°C (T_{90}) (95% CI: 39.4–39.9°C), respectively.

Side-effects of RHT combined chemotherapy for all 59 patients are summarised in Table 4. The percentage of patients (%) experiencing each grade of toxicity is shown according to WHO criteria. Haematological toxicity mainly consisted of leucopenia and to a lesser extent thrombocytopenia. In 49 of 59 patients, the maximum level of leucopenia was grade 3 (61%) or grade 4 (22%). The median absolute neutrophil count nadir was 2000 μl (range 650–6300/μl). A platelet count less than 50 000/μl was only observed in 5 patients (8%). Alopecia and nausea/vomiting were the most frequent non-haematological side-effects. Moderate pain combined with local discomfort occurred often during the initial heating-up period. Clinical signs of grade 1-2 neurotoxicity with headache, somnolence or disorientation were observed in 18 patients (31%). 2 patients experienced severe ifosfamide-induced central nervous system (CNS)-toxicity (1, grade 3 and 1 grade 4), but recovered within 24 h. Fever or infection usually occurring during neutropenic episodes was noted in approxi-

Table 3
Application of preoperative (EIA) and postoperative (EI) chemotherapy combined with RHT

Received cycle	No of patients
Preoperative EIA + RHT	$n=59$
1	–
2	2
3	5
4	44
>4	8
Postoperative EI + RHT	($n=39$)
1	5
2	2
3	3
4	29
>4	–

RHT, regional hyperthermia.

Table 4
Maximal toxicity during neoadjuvant chemotherapy combined with RHT ($n=59$)[a]

Toxicity (WHO grade)	I	II	III	IV
Leucopenia	2	13	61	22
Thrombocytopenia	48	2	8	0
Nausea/vomiting	39	42	2	0
Alopecia	10	34	56	0
Infection	20	4	8	2
Renal toxicity	2	0	0	2
Neurotoxicity	15	17	2	2
Cardiac toxicity	13	12	0	0
Pain within the applicator	8	66	14	0
Skin burn	0	7	12	0
Fever	12	24	0	0

WHO, World Health Organization; RHT, regional hyperthermia.
[a] The percentage of patients (%) experiencing each grade of toxicity.

mately one-third of the patients. In seven cases, bacterial contamination of thermometry catheters with signs of local infection occurred and therefore the catheters were withdrawn. 2 of these patients had documented sepsis which required aggressive antibiotic therapy. Skin burns (19%) after RHT treatments consisted of severe erythema (7 patients) and blisters (4 patients).

3.3. Response to treatment and surgery results

In 52 patients evaluable for radiographic response (88%), the objective response (CR + PR) rate was 17% including one complete response (CR), eight partial responses (PR). In addition, minor regression (MR) was seen in 13 patients (25%). 17 patients (33%) showed stable disease (SD) and 13 patients (25%) showed progressive disease (PD).

Of the 59 patients, 49 underwent surgery (83%) and mutilative surgery (eight amputations of the limb, one hemipelvectomy) was required for 9 patients (15%). Among the 49 resected patients, 37 (76%) were rendered NED (no evidence of disease) (R0/R1 resection) and 12 (24%) were non-NED (R2 resection) at the time of surgery. 10 patients (17%) did not undergo surgery. Reasons included early progression (PD) in 3 patients who refused further mutilative surgery and complete response (CR) in 1 patient. In the other 6 patients, the attending surgeon felt a definite adequate resection could not be accomplished despite the tumour response (1 PR, 2 MR) seen in 3 of these patients.

Extensive histopathological examination for response after surgery was performed in 43 resected tissue specimens. In 6 cases, the limited amount or altered quality of the resected specimens were considered not to be evaluable for pathological response. Absence of typical malignant cells (pCR) was found in 6 patients (14%). Radiographic response of 5 of these patients prior to surgery (1 not assessable) included 4 responders (3 PR, 1 MR) and 1 patient with stable disease (1 SD). In another 12 patients (28%) a FHR was found. The association of the initial radiographic response and the pathological response at the time of surgery is listed in Table 5a, b, respectively.

Postoperative radiotherapy was received by 21 patients with positive surgical margins (R1) or residual gross disease (R2), including 11 patients who had entered the protocol with primary STS. The remaining patients did not receive radiotherapy treatment because of previous radiotherapy, early progression of disease, or limitations in the use of an adequate dose.

At the end of the entire neoadjuvant treatment regimen, 36 patients (61%) had no measurable tumour as assessed radiographically. Persistent or progressive disease was documented in 23 patients (39%). A significant association between the remaining disease status and response to protocol treatment (radiographic and/or pathological) became apparent in these two groups of patients ($P = 0.004$; Pearson Chi square).

3.4. Relapse and survival

Within the group of 36 patients who were rendered disease-free, 19 developed local recurrences (32%). 12 had positive microscopic surgical margins after comple-

Table 5

	Type of surgery							Total *n* (%)
	Conservative resection ($n = 40$)			Amputation ($n = 9$)			None ($n = 10$)	
	R0	R1	R2	R0	R1	R2		
(a) Radiographic response and type of surgery								
Complete response (CR)	–	–	–	–	–	–	1	1 (2)
Partial response (PR)	3	2	–	–	2	–	1	86 (14)
Minor response (MR)	4	4	2	–	–	1	2	13 (22)
Stable disease (SD)	1	7	4	5	–	–	–	17 (29)
Disease progression (PD)	–	4	5	1	–	–	3	13 (22)
Not assessable	–	4	–	–	–	–	3	7 (12)
Total								
n	8	12	11	6	2	1	10	59
(b) Pathological response evaluation after surgery								
Complete necrosis	3	2	–	1	–	–	–	6 (10)
FHR	2	5	2	2	1	–	–	12 (20)
NR	3	10	7	3	1	1	–	25 (42)
n.e.	–	4	2	–	–	–	10	16 (27)
Total								
n	8	21	11	6	2	1	10	59
%	20	53	28	67	22	11		

FHR, favourable histological response (> 75% necrosis); NR, no histological response (⩽75% necrosis); n.e., not evaluated.

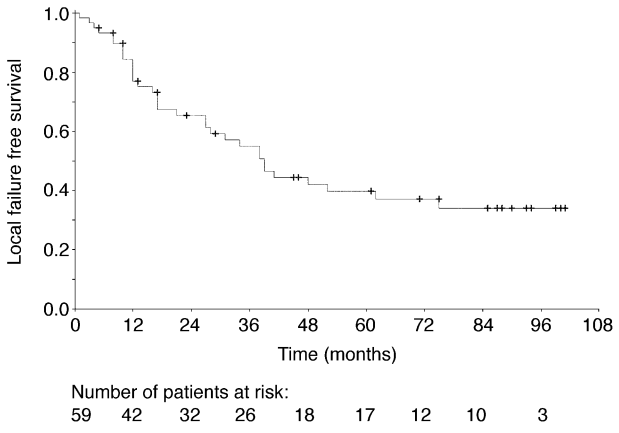

Fig. 1. Local failure-free survival (LFFS) for the entire cohort of 59 patients.

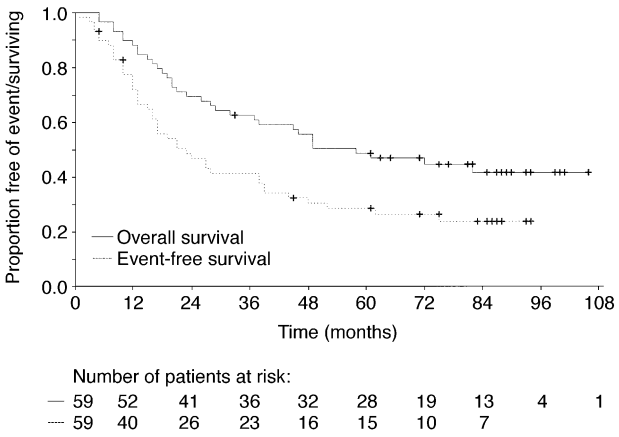

Fig. 3. Overall survival (OS) (solid line) and event-free survival (EFS) (dashed line) in the entire cohort of 59 patients.

tion of protocol treatment. Among the patients who developed local recurrences, 10 had entered the protocol as patients with previous locoregional failure and five of them had already received external-beam radiation as part of their initial local treatment. The median time to local recurrence was 39 months (range: 1–101 months).

Among 23 patients with persistent disease, local progression occurred in 14 patients (24%). 9 of them had entered the protocol as patients with recurrent STS. For this group of patients, who were never rendered free of disease by the protocol treatment, the median time to local progression was only 13 months (range: 4–90 months).

For the entire cohort of 59 patients at median follow-up time of 82 months (range: 61–106 months), the 5-year actuarial rates of local failure-free survival (LFFS) was 40% (95% CI: 26–54%) (Fig. 1).

27 patients (46%) developed distant disease, with a median time to metastases of 60 months (range: 1–106 months) corresponding to a 5-year actuarial DMFS rate of 50% (95% CI: 37–64%; Fig. 2).

42 patients (71%) developed either local or distant disease recurrence during the follow-up period. The 5-year actuarial EFS rate was 29% (95% CI: 17–40%; Fig. 3). At present, 26 patients (44%) are alive.

The median survival was 52 months (range: 5–106 months) and the 5-year actuarial OS rate was 49% (95% CI: 36–61%; Fig. 3).

Comparison of OS rates in responding (radiographic CRs + PRs + MRs + pathological pCRs + FHRs) patients versus non-responders (Fig. 4) showed statistically significant difference ($P < 0.01$).

The 5-year actuarial OS rate for high risk-STS patients with non-extremity tumours ($n = 31$) (e.g. abdominal, pelvis, trunk) was 45% (95% CI: 28–63%) and for patients with extremity tumours ($n = 28$) 53% (95% CI: 34–71%; $P = 0.21$; Fig. 5). The median survival was 41.5 months (95% CI: 24–77 months; range: 5–106 months) in the non-extremity group, whereas in the extremity group the median survival time has not yet been reached.

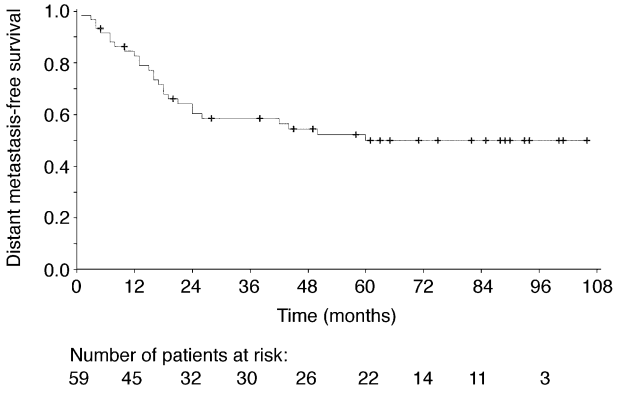

Fig. 2. Distant metastases-free survival (DMFS) in the entire cohort of 59 patients.

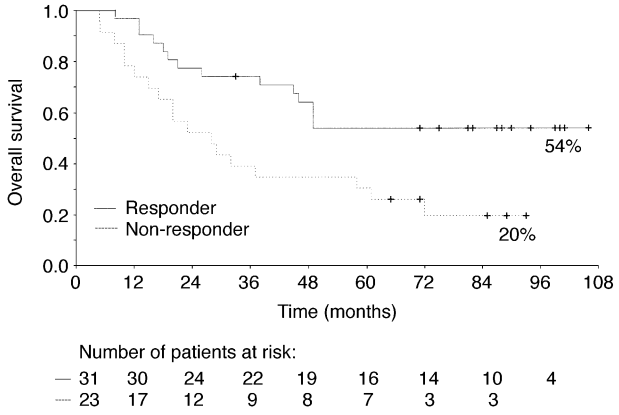

Fig. 4. Overall survival (OS) in patients with evidence of radiographic and/or pathological response complete responders (CRs) + partial responders (PRs) + minor responders (MRs) and/or pathological complete responders (pCRs) + favouarable histological responders (FHRs) ($n = 31$; solid line) versus non-responding patients ($n = 23$; dashed line). $P < 0.01$.

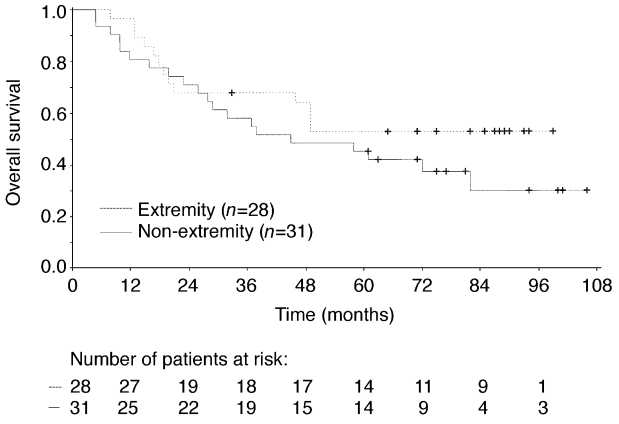

Fig. 5. Overall survival in patients with non-extremity soft tissue sarcomas (STS) (solid line) versus extremity STS (dashed line). $P = 0.21$.

4. Discussion

This study is unique in that the application of RHT combined with systemic chemotherapy as part of a multimodality therapy has been prospectively performed for a defined cohort of high-risk STS patients. Most of these patients showed more than one of the independent high-risk criteria at the time of entering the protocol (e.g. tumour size >8 cm, extracompartimental extension, high-grade). In addition, approximately half of our patients (47%) already had local recurrences. This is known to be a poor prognostic factor because of its strong association with the development of subsequent metastases and tumour mortality [11]. Important to note is the inclusion of retroperitoneal STS within the abdominal region or extension to the pelvic floor. These tumours are particularly difficult to manage because of their close proximity to vital structures in the abdominal cavity and adjacent structures. A comprehensive analysis has documented that complete surgical resection at the time of primary presentation is likely to afford the only chance for long-term survival [13]. Taking into account the eligibility criteria based on a careful risk assessment, the large extent of the tumour, and the unlikelihood of achieving complete gross resection, we considered this population of STS patients to represent appropriate candidates for whom an investigational treatment is justified.

With regard to the feasibility of delivering RHT in deep-seated, large STS, in all of our patients the treatment objective of adequate hyperthermia could be achieved. According to previous reports of several other institutions [23,28] and our own experience [20,21], controlling the phase and amplitude of the individual radiating applicators has enabled deep-heating to be delivered more uniformly to sarcomas and other primary tumours such as ovarian, cervical, bladder, and rectal cancer [23,29–31]. The intratumoral temperatures (T_s) and/or given fraction of the monitored sites exceeding an index T of STS tumours were quite similar to the results of more recent reports using the same heating device for the treatment of other tumours [32]. With regard to toxicity, serious RHT-related toxicity or an increase in chemotherapy-related side-effects were not observed, and the complication rate was acceptable.

Several previous reports have outlined long-term results of preoperative chemotherapy, but exclusively for high-grade extremity sarcomas [16,17,33]. From the M.D. Anderson Cancer Center, two consecutive reports became available with a retrospective analysis of their experience using preoperative chemotherapy alone for large extremity STS over two different time-frames. The first analysis by Pezzi and colleagues [16] on 46 patients treated between 1979 and 1985 showed that radiographic tumour response including minor responses to preoperative doxorubicin-based therapy provides strong prognostic information and identifies a subgroup of patients who are most likely to benefit. This contrasts with the more recent report by Pisters and colleagues from the same institution with the retrospective analysis of a larger cohort of 76 patients treated between 1986 and 1990 who received a median of three preoperative cycles of doxorubicin and dacarbazine (ADIC), cyclophosphamide and ADIC (CYADIC), or other doxorubicin-based regimens [17]. All patients in this cohort had AICC stage III B extremity STS (grade 3/4, T2 NO M0) and the majority of patients (91%) presented with localised primary sarcomas. Based on radiographic responses to preoperative chemotherapy, a 27% overall objective major response rate (6 CR plus 13 PR) was seen and at a median follow-up time of 85 months, responding patients appeared to have survival rates that were similar to those of the patients who did not respond to preoperative chemotherapy. In addition, a careful reanalysis to evaluate the different definitions of responses in the two studies has been performed, the variable definition of response did not appear to be a sufficient explanation [17]. In a small series of high-risk patients treated at the Memorial Sloan Kettering Cancer Center with two cycles of CYADIC, the preoperatively objective response rate was only 3% and the event-free outcome was not different from their previous experience with no chemotherapy or postoperative doxorubicin-based therapy [33].

Although the rate of objective response (CR + PR) in the present study was moderate (17%) and inferior compared with 24 and 27% response rates in the two previous studies from the M.D. Anderson Cancer Center [16,17], the rate of response defined as any degree of radiographic response (CR plus PR plus MR) was 42% (22 of 52 assessable patients). This agrees with the above-mentioned first report using the same broader definition of response [16]. There was a quite similar 40% overall response rate for patients treated with a mean of four cycles of CYADIC. Accurate measure-

ment of tumour shrinkage to determine response after RHT combined treatment modalities (e.g. with radiation or chemotherapy) is sometimes unreliable or underestimates the treatment effects because of the well-known effects creating tissue-oedema and coagulation necrosis within the field of the heat-treated tumour [34].

Therefore, it was not unexpected to see pathological responses such as pCR or FHR after the combined modality treatment in patients with radiographically no change (NC). As shown in Table 6, there was significant, but not complete concordance between radiographic response and PCRs. For example, 7 out of 16 evaluable patients with radiographic NC (<25% increase or decrease of tumour size) showed pathological responses (1 pCR + 6 FHRs). In addition, 5 out of 11 evaluable patients with only MR (25–49% decrease of tumour size) had a PCR or FHR (1 pCR + 4 FHRs). We conclude from these results that, in addition to the radiographic response evaluation (including MR), the pathological response criteria (pCRs + FHRs) should be taken into account to identify patients, with thermochemotherapy-sensitive STS. This avoids the exclusion of patients, with no evidence of an objective radiographic response (CRs + PRs), as 'nonresponders' from further treatment within the neoadjuvant protocol when these patients might in fact show complete or >75% necrosis of their tumours.

Resectability either by limb-sparing surgery or amputation is usually required as an eligibility criterion to enter individual protocols of preoperative chemotherapy for high-risk extremity STS. For instance, in the report by Pisters and colleagues, limb-sparing surgery was performed independent of tumour response in 91% (69 of 76 patients), and the amputation rate was 9% (7 patients). Obviously all patients achieved NED (R0/R1) and the majority of patients had microscopically negative (R0) surgical margins (68%) [17]. In this context, it is interesting to note that in the first report by Pezzi, limb-preserving resections were possible in only 69% (31 of 45 patients) and amputation was required in 31% (14 patients) [16]. The quite similar treatment outcome of high risk-STS at different sites (extremity versus non-extremity) might reflect the more proximal extension of the advanced stage of locoregional disease in our series of patients. Any retrospective comparison of previous trials is influenced by patterns of referral, no consistent inclusion of extracompartimental tumours, the different types of chemotherapy regimens, and variations in locoregional management. The definitive assessment on the efficacy of neoadjuvant combined treatment modality will require randomised prospective trials. The European Organization for Research and Treatment of Cancer (EORTC) has completed such a study involving 150 patients comparing preoperative doxorubicin (50 mg/m^2) plus ifosfamide (5 g/m^2) chemotherapy for high-risk, resectable STS, but survival outcome has not yet been reported. Patients in the control group proceeded to immediate surgery and postoperative radiotherapy.

Based upon dose–response data for anthracyclines (e.g. doxorubicin, epirubicin) and ifosfamide suggesting maximum therapeutic efficacy at higher doses in metastatic disease [35,36], preliminary results showed that aggressive dose-intensive regimens for primary STS of the extremities might be more active with overall response rates of 60–70% [37]. However, results of randomised studies testing the benefit of such intensified preoperative regimens compared with conventional dose chemotherapy are also not available. In the present study, since all the patients received RHT in combination with conventional dose chemotherapy, it is not possible to evaluate to what extent the addition of RHT had contributed to the improved therapeutic outcome in the responding patients. Therefore, a randomised multicentric phase III Intergroup study (EORTC protocol 62961/ESHO RHT 95) is ongoing comparing neoadjuvant EIA chemotherapy with or without RHT in order to determine the impact of RHT on local tumour control and long-term survival.

Table 6
Radiographic and pathological response to preoperative chemotherapy combined with regional hyperthermia

Radiographic response	No of patients				Total *n* (%)
	Pathological response				
	Complete necrosis (pCR)	>75% necrosis (FHR)	⩽75% necrosis (NR)	Not evaluated	
Complete response (CR)	–	–	–	1	1 (2)
Partial response (PR)	3	1	3	1	8 (15)
Minor response (MR)	1	4	6	2	13 (25)
Stable disease (SD)	1	6	9	1	17 (33)
Disease progression (DP)	–	1	6	6	13 (25)
Not assessable	1	–	1	5	7
Total					
n	6	12	25	16	59
%	10	20	43	27	

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References

1. Enzinger FM, Weiss SW. *Soft Tissue Tumors*. St. Louis, MO, CV Mosby, 1988.
2. Harrison LB, Franzese F, Gaynor JJ, Brennan MF. Long-term results of a prospective randomized trial of adjuvant brachytherapy in the management of completely resected soft tissue sarcomas of the extremity and superficial trunk. *Int J Radiat Oncol Biol Phys* 1993, **27**, 259–265.
3. Pisters PWT, Harrison LB, Leung DHY, Woodruff JM, Casper ES, Breannan MF. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. *J Clin Oncol* 1996, **14**, 859–868.
4. Yang JC, Chang AE, Baker AR, *et al*. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *J Clin Oncol* 1998, **16**, 197–203.
5. Alvarenga JC, Ball ABS, Fisher C, Fryatt I, Jones L, Thomas JM. Limitations of surgery in the treatment of sarcoma. *Br J Surg* 1991, **78**, 912–916.
6. Mundt AJ, Awan A, Sibley GS, *et al*. Conservative surgery and adjuvant radiation therapy in the management of adult soft tissue sarcoma of the extremities: clinical and radiobiological results. *Int J Radiat Oncol Biol Phys* 1995, **32**, 977–985.
7. Fein DA, Lee WR, Lanciano RM, *et al*. Management of extremity soft tissue sarcomas with limb-sparing surgery and postoperative irradiation: do total dose, overall treatment time, and the surgery-radiotherapy interval impact on local control? *Int J Rad Oncol Biol Phys* 1995, **32**, 969–976.
8. Gaynor JJ, Tan CC, Casper ES, *et al*. Refinement of clinicopathologic staging for localized soft tissue sarcoma of the extremity: a study of 423 adults. *J Clin Oncol* 1992, **10**, 1317–1329.
9. Coindre JM, Terrier P, Bui NB, *et al*. Prognostic factor in adult patients with locally controlled soft tissue sarcoma: a study of 546 patients from the French Federation of Cancer Centers Sarcoma Group. *J Clin Oncol* 1996, **14**, 869–877.
10. Singer S, Coson JM, Gonin R, Labow B, Eberlein IJ. Prognostic factors predictive of survival and local recurrence for extremity soft tissue sarcoma. *Ann Surg* 1994, **219**, 165–173.
11. Lewis JJ, Leung D, Heslin M, Woodruff JM, Brennan MF. Association of local recurrence with subsequent survival in extremity soft tissue sarcoma. *J Clin Oncol* 1997, **15**, 646–652.
12. Bevilacqua RG, Rogatko A, Hajdu SI, Brennan MF. Prognostic factors in primary retroperitoneal soft-tissue sarcomas. *Arch Surg* 1991, **126**, 328–334.
13. Heslin MJ, Lewis JJ, Nadler E, *et al*. Prognostic factors associated with long-term survival for retroperitoneal sarcoma: implications for management. *J Clin Oncol* 1997, **15**, 2832–2839.
14. Jaques DP, Coit DG, Hajdu SI, Brennan MF. Management of primary and recurrent soft-tissue sarcoma of the retroperitoneum. *Ann Surg* 1990, **212**, 51–59.
15. Rouëssé JG, Friedman S, Sevin DM, *et al*. Preoperative induction chemotherapy in the treatment of locally advanced soft tissue sarcomas. *Cancer* 1987, **60**, 296–300.
16. Pezzi CM, Pollock RE, Evans HL, *et al*. Preoperative chemotherapy for soft-tissue sarcomas of the extremities. *Ann Surg* 1990, **211**, 476–481.
17. Pisters PWT, Patel SR, Varma DGK, *et al*. Preoperative chemotherapy for stage IIIB extremity soft tissue sarcoma: long-term results from a single institution. *J Clin Oncol* 1997, **15**, 3481–3487.
18. Falk M, Issels R. Hyperthermia in oncology. *Int J Hyperthermia* 2001, **17**, 1–18.
19. Issels R. Hyperthermia combined with chemotherapy — biological rationale, clinical application and treatment results. *Onkologie* 1999, **22**, 374–381.
20. Issels RD, Prenninger SW, Nagele A, *et al*. Ifosfamide plus etoposide combined with regional hyperthermia in patients with locally advanced sarcomas: a phase II study. *J Clin Oncol* 1990, **8**, 1818–1829.
21. Issels RD, Mittermüller J, Gerl A, *et al*. Improvement of local control by regional hyperthermia combined with systemic chemotherapy (ifosfamide plus etoposide) in advanced sarcomas: updated report on 65 patients. *J Cancer Res Clin Oncol* 1991, **117**(Suppl. IV), S141–S147.
22. Issels RD, Bosse D, Abdel-Rahman S, *et al*. Preoperative systemic etoposide/ifosfamide/doxorubicin chemotherapy combined with regional hyperthermia in high-risk sarcoma: a pilot study. *Cancer Chemother Pharmacol* 1993, **31**(Suppl. 2), S233–S237.
23. van der Zee J, Gonzalez Gonzalez D, van Rhoon GC, van Dijk JD, van Putten WL, Hart AA. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumors: a prospective, randomised, multicentre trial. *Lancet* 2000, **355**, 1119–1125.
24. World Health Organization. *WHO Handbook for Reporting Results of Cancer Treatment* (WHO Offset Publication No 48). Geneva, Switzerland, WHO, 1979.
25. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
26. Greenwood M. The natural duration of cancer. In *Reports on Public Health and Medical Subjects*, vol. 33. London, UK, Her Majesty's Stationary Office, 1926, 1–26.
27. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. *J Clin Oncol* 1983, **1**, 710–719.
28. Leopold KA, Harrelson J, Prosnitz L, Samulski TV, Dewhirst MW, Oleson JR. Preoperative hyperthermia and radiation of soft tissue sarcomas: advantage of two vs one hyperthermia treatments per week. *Int J Radiat Oncol Biol Phys* 1989, **16**, 107–115.
29. Formenti SC, Shrivastava PN, Sapozink M, *et al*. Abdominopelvic hyperthermia and intraperitoneal carboplatin in epithelial ovarian cancer: feasibility, tolerance and pharmacology. *Int J Rad Oncol Biol Phys* 1996, **35**, 993–1001.
30. Rietbroek RC, Schilthuis MS, Bakker PJM, *et al*. Phase II trial of weekly locoregional hyperthermia and cisplatin in patients with a previously irradiated recurrent carcinoma of the uterine cervix. *Cancer* 1997, **79**, 935–948.
31. Rau B, Wust P, Löffel J, *et al*. Preoperative hyperthermia combined with radiochemotherapy in locally advanced rectal cancer. A phase II clinical trial. *Ann Surg* 1998, **227**, 380–389.
32. Wust P, Gellermann J, Harder C, *et al*. Rationale for using invasive thermometry for regional hyperthermia of pelvic tumors. *Int J Radiat Oncol Biol Phys* 1998, **41**, 1129–1137.
33. Casper ES, Gaynor JJ, Harrison LB, Panicek DM, Hajdu S, Brennan MF. Preoperative and postoperative adjuvant combination chemotherapy for adults with high grade soft tissue sarcoma. *Cancer* 1994, **73**, 1644–1651.
34. Takeshita N, Tanaka Y, Matsuda T. Evaluation of CT images, tumour response and prognosis after thermoradiotherapy for deep-seated tumours. *Int J Hyperthermia* 1993, **9**, 1–17.
35. Reichardt P, Tilgner J, Hohenberger P, Dorken B. Dose-intensive chemotherapy with ifosfamide, epirubicin, and filgrastim for

adult patients with metastatic or locally advanced soft tissue sarcoma: a phase II study. *J Clin Oncol* 1998, **16**, 1438–1443.

36. Le Cesne A, Antoine E, Spielmann M, *et al*. High-dose ifosfamide: circumvention of resistance to standard-dose ifosfamide in advanced soft tissue sarcomas. *J Clin Oncol* 1995, **13**, 1600–1608.
37. Patel SR, Vadhan-Raj S, Burgess MA, *et al*. Results of two consecutive trials of dose-intensive chemotherapy with doxorubicin and ifosfamide is highly active in patients with soft tissue sarocmas. *Am J Clin Oncol* 1998, **21**, 317–321.