Int. J. Hyperthermia, March 2010; 26(2): 127–135

Thermochemotherapy in patients with extremity high-risk soft tissue sarcomas (HR-STS)

M. SCHLEMMER[1], C. M. WENDTNER[1], L. LINDNER[1], S. ABDEL-RAHMAN[1], W. HIDDEMANN[1], & R. D. ISSELS[1,2]

[1]*Department of Internal Medicine III, Klinikum Grosshadern Medical Centre, Ludwig-Maximilians-University-Munich, Germany and* [2]*GSF-National Research Centre for Environment and Health, Institute of Molecular Immunology, Munich, Germany*

(Received 7 December 2008; Revised 11 September 2009; Accepted 13 September 2009)

Abstract

Purpose: We report data from phase II trials examining the efficacy of multimodality treatment with neoadjuvant chemotherapy, hyperthermia, surgery, radiation and postoperative thermochemotherapy in adult patients with high-risk sarcomas of the extremities.

Patients and methods: From 1991 to 2001 47 patients with high risk soft tissue sarcoma of the extremities were prospectively treated in two clinical trials with a treatment plan of four cycles of etoposide, ifosfamide and doxorubicin combined with regional hyperthermia followed by surgery, radiation and adjuvant chemotherapy.

Results: Objective response rate assessable in 39 patients was 21% (one complete and seven partial responses). A favourable histological response (>75% tumour necrosis) was observed in 34% of the 35 evaluable patients who had surgical resection. Median overall survival (OS) was 105 months. The five-year probability of local failure-free survival (LFFS), distant disease-free survival (DDFS), event-free survival (EFS) and OS were 48%, 55%, 35% and 57%, respectively. There were no significant differences between responders and non-responders of minimum temperatures (Tmin) and time-averaged temperatures achieved in 50% (T_{50}) and 90% (T_{90}) at all measured tumour sites. Response to this neoadjuvant regimen predicted for prolonged LFFS ($p = 0.0123$), but not for OS ($p = 0.2$). Limb preservation was achieved in 37 patients (79%) and did not result in inferior DDFS (52% versus 50%) or OS (61% versus 50%) at five years ($p = 0.8$) in comparison to patients who underwent amputation.

Conclusion: Response to combined modality treatment with RHT and neoadjuvant chemotherapy was predictive for an improved LFFS and led to limb preservation in 79% of patients with extremity sarcomas.

Keywords: *extremity sarcoma, hyperthermia, chemotherapy, multimodality*

Introduction

In the last 25 years the treatment of patients with extremity sarcomas has shifted from amputation to limb-sparing surgery. After complete resection of a localised tumour, adjuvant radiotherapy maintains low rates of local relapses [1]. Margins after surgical resection are an independent predictive factor for local relapse free survival for patients with extremity sarcoma [2, 3]. Multimodality treatment, including neoadjuvant chemotherapy and postoperative chemotherapy, is the standard treatment for patients with osteosarcomas and Ewing sarcomas. However, such therapy is not a standard of care for patients with soft tissue sarcomas of the extremities [4], who benefit much less, if at all, from adjuvant chemotherapy. Investigational techniques have been developed for patients with inoperable extremity sarcomas, such as isolated limb perfusion with tumour necrosis factor-alpha and melphalan to improve resectability, but long-term survival rates remain low due to systemic relapse [5].

Correspondence: Marcus Schlemmer, MD, Medizinische Klinik III, Klinikum Grosshadern, Marchioninistrasse 15, D-81377 München, Germany. Tel: +49 89 7095 4768. Fax: +49 89 7095 4776. E-mail: Marcus.Schlemmer@med.uni-muenchen.de

ISSN 0265–6736 print/ISSN 1464–5157 online
DOI: 10.3109/02656730903335995

In comparison to soft tissue sarcomas at other sites, e.g. retroperitoneum, extremities sarcomas have a better prognosis, but retrospective analysis of survival did not reveal a survival advantage in the evolving therapies of the last 20 years [6]. Therefore, strategies to enhance the efficacy of local therapy in combination with systemic modalities are needed. Local control is usually accomplished by surgical resection followed by radiation, although complete resection remains elusive in many cases. Regional hyperthermia combined with conventional chemotherapy has been integrated in multimodality treatment strategies for various tumours [7]. Recent results indicate that heat shock proteins, induced in tumour cells under hyperthermic stress, are able to elicit specific T-cell and natural-killer-cell immune responses, in addition to the direct toxic effect of heat upon the tumour cells. RHT was shown to be feasible and efficacious in previous phase II studies, including patients with locally advanced soft tissue retroperitoneal sarcomas, who received ifosfamide-based chemotherapy combined with RHT [8–11]. The objective of this analysis is to determine the efficacy in terms of response rate and survival parameters for patients with HR-STS of the extremities after neoadjuvant thermochemotherapy performed in two separate studies at our institution.

Patients and methods

Patient eligibility

Patients were required to have histologically confirmed soft tissue sarcomas without manifestation of distant disease. Furthermore, patients had to fulfil high-risk criteria: tumours with grade 2 or grade 3 histology, size $\geq$5 cm, and extracompartmental and deep extension. Patients had to have a good performance status (World Health Organization grade 0 to 2) and normal organ function. Patients with primary soft tissue sarcomas (S1 group), as well as with locally recurrent disease (S2 group) or marginally resected sarcomas (S3 group, $<$10 mm margin), were eligible. Previous chemotherapy was an exclusion criterion. Only patients with proximal and distal extremity sarcomas were included in this study. The ethics committee of the Ludwig-Maximilians-University, Munich, Germany, approved the study protocols. Written informed consent was obtained from all patients enrolled onto this study.

Staging procedures and treatment program

Before the start of protocol treatment and after completion of neoadjuvant therapy, staging involved computed tomography scan of the chest and abdomen/pelvis. Tumour size was determined by contrast-enhanced computed tomography scans, magnetic resonance imaging, or both. Neoadjuvant protocol treatment in both studies consisted of etoposide, ifosfamide, and doxorubicin (EIA) chemotherapy and regional hyperthermia (RHT). Chemotherapy consisted of doxorubicin 50 mg/m^2 day 1, etoposide 125 mg/m^2 days 1 and 4, and ifosfamide 1,500 mg/m^2 days 1 to 4. EIA chemotherapy was combined with regional hyperthermia (days 1 and 4). Patients without progressive disease after neoadjuvant therapy were eligible for postoperative treatment comprising four cycles of EI chemotherapy with RHT (RHT-91) or four cycles of EIA chemotherapy without RHT (RHT-95) [9, 10]. Patients who were not previously irradiated received external-beam radiotherapy using mega-voltage equipment (Figure 1). Radiation was applied to treatment fields and consisted of a total dose in the range of 45 to 65 Gy in daily fractions (1.8 to 2 Gy).

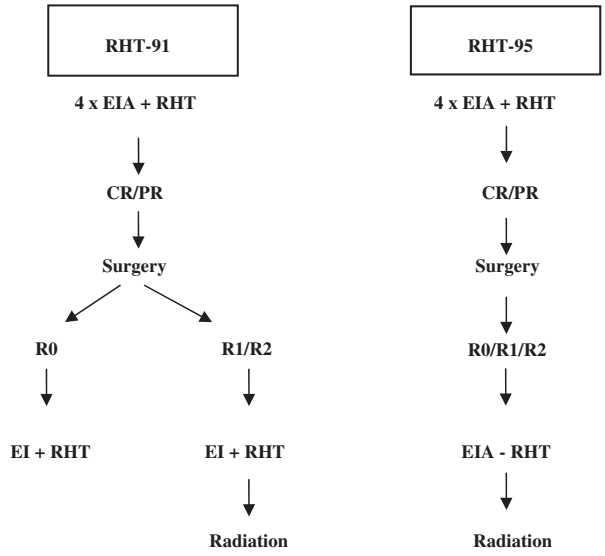

Figure 1. Treatment plans RHT-91 and RHT-95. EIA, Etoposide, ifosfamide, adriamycin; RHT, Regional hyperthermia; CR, complete response; PR, partial response.

Thermochemotherapy was repeated on day 22, and a total of four courses of neoadjuvant treatment were given. A BSD 2000 system was used to administer the hyperthermia, an electromagnetic deep regional-heating device (BSD Medical, Salt Lake City, UT) [12]. After completion of neoadjuvant therapy, patients underwent a restaging procedure with evaluation of response, and tumours were resected if possible.

Hyperthermia method

All patients in this study were treated with the BSD-2000 system. The choice of the ring applicators Sigma-60 (proximal lesions) and Sigma-30

(distal lesions) depended on tumour location and body geometry. Both applicators consisted of an Annular Phased Array with 8 dipole antennas, which provided 2D steering. Frequency ranged from 70 to 180 MHz and forward power ranged from 0 to 1200 W. The effective treatment time of 60 minutes was calculated from the time when the temperature of $\geq 42^{\circ}$C at any location in the tumour tissue was achieved. In the initial phase (heating-up time) of the RHT treatment (30 min) the power increase of the high-frequency generators was adapted to the corresponding increase of the measured temperatures in the tumour and the normal tissue.

Depending on size and location of the tumour at least one closed-end Teflon catheter (Angiomed, Karlsruhe) was placed into the tumour tissue and the surrounding normal tissue for invasive temperature measurement. The catheters for hyperthermia treatments were placed into the tumour with CT-control in the case of the S1-/S2-group or into the tumour bed in the case of marginal resection (S3).

Temperature was measured at the top of the single Bowman thermistors which allowed an accurate temperature display ($\pm 0.1^{\circ}$C). The temperature was measured at fixed intervals (1 cm) during the hyperthermia treatment by at least 19 fixed points along the catheters in the tumour, tumour bed and surrounding tissue. This mapping procedure was repeated every 6–7 min to achieve a temperature distribution in the tumour tissue and in the adjacent normal tissue during the treatment. Additional catheters were inserted (e.g. into the rectum and bladder) in case of proximal lesions to allow continuous temperature measurement in these organs. Skin temperatures were monitored at different areas within the field of the applicator.

For deep-seated tumours most recent reports made use of the frequency distribution of temperatures within the tumour and related descriptors of the distribution such as T_{90} (temperature exceeded by 90% of the temperatures measured throughout a treatment within the tumour), T_{50} (temperature exceeded by 50% of the temperatures measured throughout a treatment within the tumour), and T_{20} (temperature exceeded by 20% of the temperatures measured throughout a treatment within the tumour). Mean temperatures are shown in Table VII.

Treatment evaluation

Toxicity was evaluated after each treatment cycle according to National Cancer Institute Common Toxicity Criteria version 2.0 [13]. After completion of neoadjuvant therapy, radiographic and pathologic responses were documented. Radiologic response was determined by WHO criteria. Pathologic complete response (pCR) was defined as the absence of residual viable tumour cells in serial sectioned specimen after complete surgical resection. Favourable histologic response (FHR) was assessed if more than 75% tumour necrosis but residual viable tumour was documented.

Table I. Patient characteristics.

Characteristic	No. of patients	%
Gender		
Male	31	66
Female	16	34
Age at entry		
19–40 years	15	32
>40–65 years	28	60
>65 years	4	8
Disease status		
S1	23	48
S2	16	35
S3	8	17
Prior treatment		
Surgery alone	12	26
Surgery plus radiation	12	26
Radiation alone	0	0
None	23	48

S1, primary sarcoma; S2, relapsed sarcoma; S3, marginally resected sarcoma.

Feasibility of regional hyperthermia (RHT) was assessed by calculating time-averaged temperatures for each regional hyperthermia at each monitored site. Temperatures were averaged over all RHT treatments to yield an average minimum (T_{min}) and maximum (T_{max}) temperature for an individual patient. Time averaged temperatures achieved in 20% (T_{20}), 50% (T_{50}), and 90% (T_{90}) of all measured tumour sites were documented during each RHT treatment [8].

Statistics

Statistical association of response with remaining disease status was performed using the X^2 test according to Pearson. In the case of continuous parameters such as tumour volume or heat induction, a statistical association was determined using the *T*-test or the Mann-Whitney *U* test [14]. The time from start of therapy to local treatment failures and distant recurrences or death were estimated according to the method of Kaplan and Meier [15]. The 95% confidence intervals (CIs) of the Kaplan-Meier estimates were calculated with Greenwood's variances [16]. The endpoints for our analyses were local failure-free survival (LFFS), distant disease-free survival, event-free survival, and OS. The comparison of survival parameters in responding versus non-responding patients was performed using the log-rank test [17]. For all tests, $P \leq 0.05$ was considered to be statistically significant. The RHT-91 and RHT-95

protocols were each designed as a monocentric, non-randomised, controlled, single arm phase II study with objective response and overall survival as end points.

Results

Patient characteristics

Between February 1991 and June 1997, 47 patients with primary (S1-group), relapsed (S2-group), or marginally resected (S3-group) locally advanced sarcomas of the extremities were registered to the two clinical studies. The study population consisted of 31 male and 16 female patients with a median age of 47 years (range, 20 to 78 years) and a median WHO-performance status of 1. Twenty-four patients entered the protocol after previous surgical and/or radiotherapeutic interventions, whereas 23 patients never had treatment for the sarcoma before (Table I). The feasibility of an adequate R0-resection was excluded for every patient before inclusion in this study. After four cycles of thermochemotherapy 42 patients showed no evidence of disease (NED) due to neoadjuvant therapy and surgery. Based on all patients ($n=47$), the median ellipsoidal tumour volume was 271 cm^3 (Q1: 16 cm^3 Q3: 566 cm^3). Excluding all patients with only microscopic disease at entry of study (S3 category), the median tumour volume was calculated with 392 cm^3.

The most common histologic subtypes were malignant fibrous histiocytomas/high grade pleomorphic undifferentiated sarcoma ($n=10$), liposarcomas ($n=9$), nerve sheath tumours ($n=6$), and leiomyosarcomas ($n=5$). Of the 47 patients in the study, 21 had moderately differentiated (grade 2) sarcomas, and 26 patients had poorly differentiated (grade 3) sarcomas (Table II).

Table II. Histologic diagnosis and grades.

Cell type	No. of patients		Total no. of patients	%
	Grade 2	Grade 3		
Malignant fibrous histiocytoma	4	6	10	21
Liposarcoma	6	3	9	19
Malignant peripheral nerve sheath tumour/malignant schwannoma	4	2	6	13
Leiomyosarcoma	2	3	5	11
Synovial sarcoma	2	2	4	8
Rhabdomyosarcoma	0	3	3	6
Extra-skeletal Ewing sarcoma	2	1	3	6
Angiosarcoma	0	2	2	4
Unclassified sarcoma	0	2	2	4
Fibrosarcoma	0	1	1	2
Tenosynovial giant cell tumour	0	1	1	2
Clear-cell sarcoma	1	0	1	2

Table III. Number of treatment cycles.

No. of cycles	No. of patients		
	EIA + RHT pre-op	EI + RHT post-op (RHT 91)	EIA post-op (RHT 95)
0	0	10	8
1	1	1	0
2	1	1	1
3	3	2	0
4	37	14	10
>4	5	0	0
Total	47	28	19

E, etoposide; I, ifosfamide; A, adriamycin; RHT, regional hyperthermia.

Feasibility and toxicity

Of all patients, 37 (79%) received the prescribed number of preoperative four chemotherapy cycles combined with RHT. Five patients received one additional cycle. The median number of cycles administered was four (range, one to five cycles) combined with median eight RHT treatments (range, two to 16 treatments). Postoperative chemotherapy was not given to 18 patients because of disease progression or refusal of further therapy. Of the 29 patients who were started on post-operative chemotherapy, 24 patients (83%) received the intended four cycles (Table III).

During the neoadjuvant treatment, non-haematological toxicity was mainly mild; very severe (grade 4) side effects were not observed with this regimen. Three patients experienced grade 3 pain, one patient experienced grade 3 nausea and vomiting. The most frequent side effects were alopecia, which was observed for 29 patients, nausea or vomiting in 24 patients and treatment-related pain, which were seen in 19 patients. Infections were documented in five patients. Haematological side effects were mild to moderate. Leukopenia grade 3 in 18 patients and grade 4 in seven patients was observed. Two patients experienced thrombocytopenia grade 3 during neoadjuvant thermochemotherapy. One patient suffered from pain as a severe (grade 3) hyperthermia-associated side effect. Pain within the applicator (caused by water bolus pressure of the cooling system) was observed in a milder form in three patients. Mild to severe skin burns manifesting as blisters, were observed in two patients (Table IV).

Response to treatment and surgery results

Of 47 patients, 39 were assessable for response being evaluated after completion of neoadjuvant

Table IV. Maximum toxicity during neoadjuvant thermochemotherapy.

	No. of patients with CTC grade toxicity				
Toxicity	0	1	2	3	4
Leukopenia	1	1	4	18	7
Thrombocytopenia	14	12	2	2	0
Nausea/vomiting	6	15	8	1	0
Alopecia	1	0	29	0	0
Infection	25	4	1	0	0
Renal toxicity	28	2	0	0	0
Neurotoxicity	25	4	1	0	0
Cardiac toxicity	26	3	1	0	0
Pain	11	4	12	3	0
FUO	22	5	3	0	0

Note: Other side effects related to neoadjuvant chemotherapy were: chills, diarrhoea, headache, mucositis, digestive problems, oedema, neuropathy, pruritus, stomatitis, obstipation, asthenia, fatigue. Other side effects related to hyperthermia treatment: Hot flushes. CTC, common toxicity criteria; FUO, fever of unknown origin.

Table V. Radiographic response to preoperative thermochemotherapy ($n = 39$).

Radiographic response	No. of patients	%
CR	1	3
PR	7	18
MR	8	20
SD	14	36
PD	9	23
NE*	8	
Total	47	100

CR, complete response; PR, partial response; MR, minor response; SD, stable disease; PD, progressive disease; NE, not assessed.

thermochemotherapy. Previously R1-resected patients (S3 group) could only be evaluated in the case of disease progression. The overall objective response rate was 21%, and consisted of one complete response (CR) and seven partial responses (PR). Including minor responses (MR; $n = 8$), the radiographic response rate was 41% (Table V). Minor response in the protocol was defined as a 25% decrease or more of the products of the two largest perpendicular diameters.

** R1 resection*

Among patients with a measurable tumour volume at the start of treatment, there was no significant association between response and median tumour volume (Mann-Whitney U test, $P = 0.35$). Dividing the tumour volume in two classes with the median (271 cm^3) as cut point, there was no significant association observed between response and tumour volume (χ^2 test, $P = 0.39$). Of the 47 patients, 35 (74%) underwent surgery after completion of

Table VI. Radiographic and pathologic response to preoperative thermochemotherapy.

	No. of pathologic response						
Radiographic response	pCR	FHR	MHR	NR	No OP	Total	%
CR	0	0	0	0	1	1	2
PR	0	1	0	4	2	7	15
MR	0	2	0	5	1	8	17
SD	1	6	1	6	0	14	30
PD	0	2	2	4	1	9	20
NE	0	0	0	1	7	8	16
Total	1	11	3	20	12	47	
%	2	24	7	42	25		100

CR, complete response; PR, partial response; MR, minor response; SD, stable disease; PD, progressive disease; NE, not assessed; pCR, pathological complete response; FHR, favourable histological response; MHR, minor histological response; NR, no response.

Table VII. Comparison of preoperative temperatures for responders and non-responders.

	Responder			Non-responder			
Temp.	Mean	Median	Q3-Q1	Mean	Median	Q3-Q1	P
T_{Max}	42.66	42.68	1.7	42.92	42.85	0.74	0.4
T_{Min}	38.3	38.5	1.3	38.45	38.42	0.75	0.12
T_{90}	39.48	39.8	1.4	39.7	39.6	1.01	0.9
T_{50}	40.18	40.5	1.6	40.81	40.7	0.67	0.49
T_{20}	40.9	41.22	1.69	40.89	41.5	1.0	0.16

neoadjuvant thermochemotherapy. In the resected tissue, pCR was detectable in one patient (2%). The radiographic response of this patient showed stable disease. Favourable histologic response (FHR) was documented in 11 patients and was associated with one PR, two MR, six SD and two progression diseases as radiographic results. In summary, 12 of 35 assessable patients showed a favourable pathologic response in their resected tumour, resulting in a pathologic response rate of 34% (Table VI).

Comparison of pre-operative intratumoural temperatures for responders (CR, PR, MR, pCR, FHR, MHR) and non-responders was performed for 40 assessable patients. The median T_{max} achieved in tumours of responders and non-responders showed no statistically significant difference (Median 42.7°C, IR 1.7° versus Median 42.9°C, IR 0.7°; $P = 0.40$) as well as no significant differences were observed for T_{min} ($P = 0.12$), T_{20} ($P = 0.0.16$), T_{50} ($P = 0.49$) and T_{90} ($P = 0.90$ Mann-Whitney U test) (Table VII).

No association was observed between heat induction and tumour histology (T_{max} $P = 0.11$; T_{min} $P = 0.50$; T_{20} $P = 0.68$; T_{50} $P = 0.86$; T_{90} $P = 0.58$ (Kruskal-Wallis test)). Furthermore no association was seen between temperature and tumour grading (T_{max} $P = 0.45$, T_{min} $P = 0.24$ (T-Test); T_{20} $P = 0.64$,

T_{50} $P=0.84$, T_{90} $P=0.97$ (Mann-Whitney U test)) and between grading and response to neoadjuvant therapy ($P=0.21$ χ^2 test). To analyse the association between tumour volume and heat induction, we divided the tumour volume into two classes, with the median (271 cm^3) as cut point. No significant levels were achieved for all the temperature parameters.

After completion of surgery, 29 patients received adjuvant chemotherapy, and 19 of them completed therapy with external-beam radiation as consolidation for local tumour control. At the end of entire protocol treatment, 34 patients (72%) were free of tumour. A significant association between the remaining disease status and response to protocol treatment was not observed for these two groups of patients ($P=0.76$).

Relapse and survival

After a median follow-up time for censored patients of 108 months, 19 patients showed local recurrence, and five patients presented with local progression of persistent disease. The median time to any local relapse or progression for the entire study population was 43 months. The five-year local-failure-free rate estimated according to Kaplan-Meier was 48% (95% CI, 31% to 62%) (Figure 2).

Local-failure-free survival did not differ between the 18 patients without postoperative chemotherapy compared with the 28 patients receiving adjuvant chemotherapy ($P=0.0836$).

Distant disease was documented in 21 patients (45%). The five-year distant metastasis-free survival rate was 55% (95% CI, 40% to 69%) (Figure 3).

Thirty-two patients (68%) developed local and/or distant disease recurrence during the follow-up period. The five-year event-free survival rate was 35% (95% CI, 20% to 47%), and the median event-free-survival time was 17 months (Figure 4).

At present, 22 patients (47%) are alive. The five-year estimated overall survival rate was 57% (95% CI, 43% to 71%), with a median overall survival of 105 months (Figure 5).

Probability of overall survival was not significant higher for patients receiving post-operative chemotherapy compared to those who did not (105 month versus 76 month $P=0.59$).

To analyse the association between tumour volume and local-failure-free survival and overall survival, respectively, the tumour volume was divided by using the median as cut point. Excluding all patients with only microscopic disease at entry of the study, and based on the median tumour volume (392.45 cm^3) as the cut point, there was no significant association between tumour volume and local-failure-free survival ($P=0.443$) and overall survival ($P=0.173$).

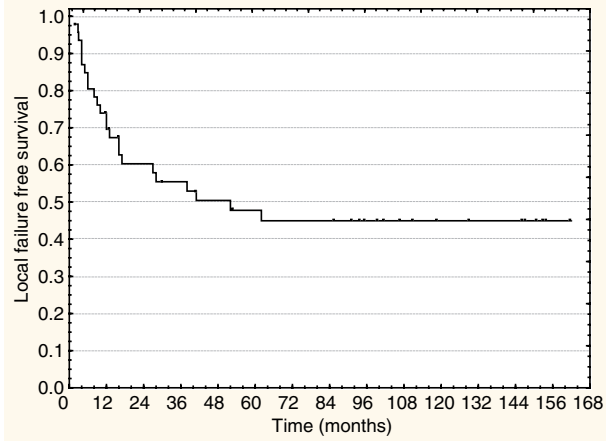

Figure 2. LFFS in the entire cohort of 47 patients.

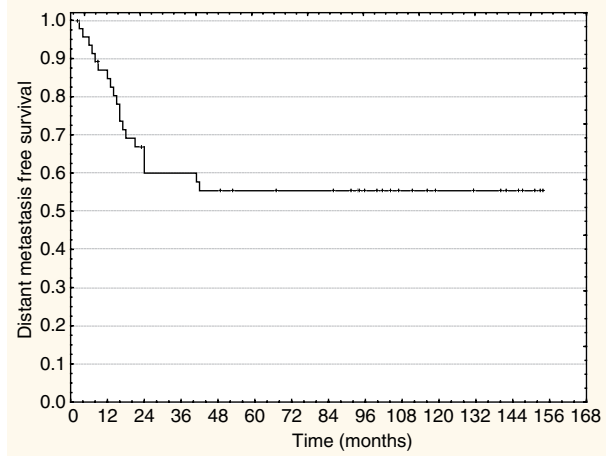

Figure 3. Distant metastasis-free survival in the entire cohort of 47 patients.

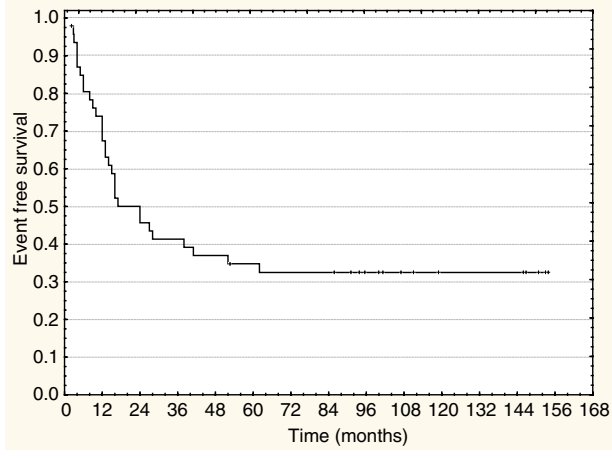

Figure 4. Event-free survival in the entire cohort of 47 patients.

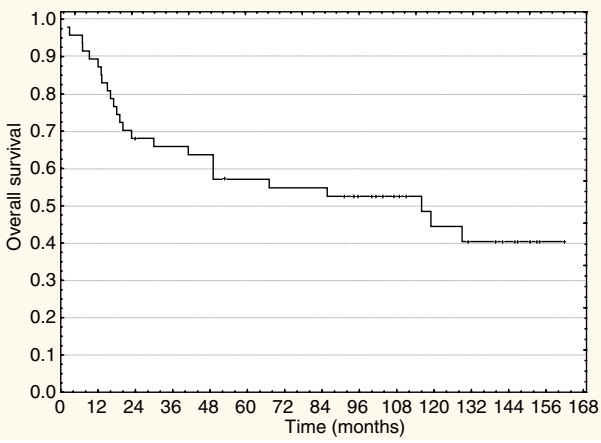

Figure 5. Overall survival in the entire cohort of 47 patients.

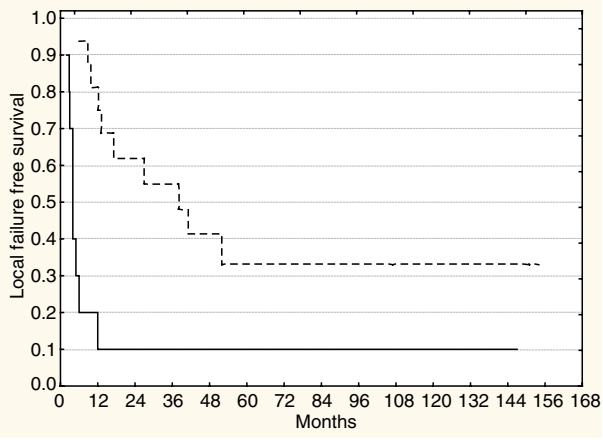

Figure 6. Local-failure-free survival responder versus non-responder.

Using the same statistical tests on the basis of all study patients ($n=42$), no significant association between tumour volume and overall survival was observed ($P=0.066$). A significant correlation was also not calculated between median tumour volume and local-failure-free survival ($P=0.0992$).

Probability of LFFS showed significant differences ($P=0.0123$) between responding (CR, PR, MR) and non-responding patients (PD); five-year LFFS rate was 33% (95% CI, 9% to 57%) for responders versus 0% for non-responders ($P=0.114$). Median LFFS time was four months for non-responders and 35 months for responders (Figure 6).

Comparison of estimated overall survival rates at five-year follow-up in responding patients 48%; (95% CI, 23% to 73%) versus non-responders 33% (95% CI, 3% to 63%) showed no statistical difference with respect to a superior survival for responders ($P=0.2$) (Figure 7).

Median overall survival time for responders was 49 months, the median overall survival time for patients not responding to neoadjuvant treatment was 12 months.

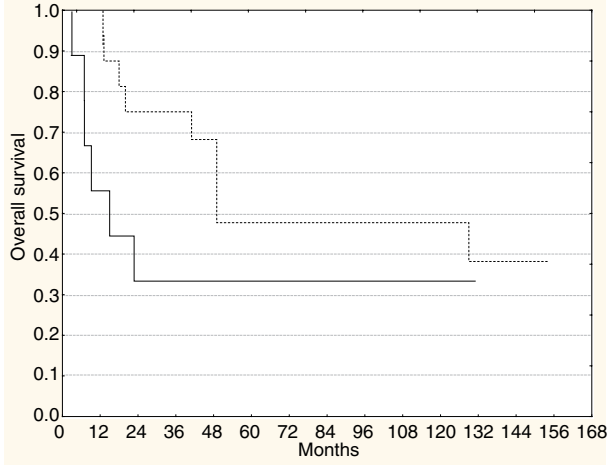

Figure 7. Overall survival responder versus non-responder.

Discussion

Neoadjuvant chemotherapy has been proven to prolong survival in patients with osteogenic and Ewing sarcomas [18, 19]. Whether there is a comparable effect for patients with high-grade soft tissue sarcomas of the extremities has never been proven by a large randomised trial [20]. Patients with soft tissue sarcomas of the extremities die of metastatic disease and generally not due to local progression. Whether local control can modify the risk of metastatic disease is not clear.

Conflicting data with regard to neoadjuvant treatment have been presented in the literature [21]. Patients in this trial were treated in a multimodality setting combining chemotherapy with regional hyperthermia, surgery and radiation. It is important to note that only patients who had tumours that were not completely resectable could be included into our study, thus a group of patients with a high risk of both local progression and systemic metastatic disease. This is in contrast to other neoadjuvant trials only including patients with tumours that are judged to be resectable [22]. In addition, these patients had primary tumours with multiple high risk features, including >5 cm, grade 2/3, and an extracompartmental and deep location, all adverse prognostic factors for local and distance recurrence and death from disease [23].

In our trial 35 patients, 74%, underwent surgery after completion of neoadjuvant chemotherapy. The favourable pathological response rate in our trial (as defined above) was 34%. Treatment-induced pathological necrosis is an independent predictor of local recurrence and overall survival in patients with

high-grade soft tissue sarcomas [24, 25]. The median overall survival time in our trial was 105 months and 19 patients showed a local relapse. As 20% relapse occur after five years of treatment, data from other trials with shorter follow-up periods have to be interpreted with caution [26]. The median time to local progression was 43 months resulting in a local-failure-free survival of 48%.

Furthermore, neoadjuvant thermochemotherapy in our trial achieved limb preservation in 79%. Whether avoiding amputation has a negative impact on distant-disease-free-survival or overall survival is controversial [6]. Our data support the contention that avoiding amputation does not jeopardise survival. Distant-disease-free survival and overall survival were the same in those with surgical resection of the primary tumour site versus amputation (52% versus 50% and 61% versus 50% respectively).

Adjuvant chemotherapy is not a widely recognised standard of care for patients with soft-tissue sarcomas that typically occur in adults. The post-operative adjuvant therapy for patients with extremity sarcomas published by the Italian cooperative sarcoma group with five cycles of epirubicin and ifosfamide showed an advantage for the treated patients with a median disease free survival of 48 months and an improvement in overall survival of 69% at four years. Patients who did not receive adjuvant chemotherapy showed a median disease-free survival of 16 months, however, this is an inferior outcome compared to historical data [27]. Furthermore, the distant or local recurrence rate for both patients who received and did not receive chemotherapy was similar at four years (44% versus 45%). The European Organization for Research and Treatment of Cancer recently reported data from trial 62931 randomising patients after surgery to treatment with doxorubicin and ifosfamide versus observation. This trial failed to show a survival advantage for patients being treated with chemotherapy in the adjuvant setting [28].

In sum, the multimodality treatment in our trial revealed that response to neoadjuvant thermochemotherapy predicts long term local-failure-free survival for patients with high-risk extremity sarcomas. In patients with high-risk soft tissue sarcomas of the extremity, phase III trials are required comparing chemotherapy alone versus thermochemotherapy to identify the role of neoadjuvant thermochemotherapy in this patient population.

Acknowledgements

We thank the following colleagues for their contribution: H.-R. Dürr, M. Reiser, R. Wilkowski, C. Salat, C. Adalin and A. Teuschl. This study was supported, in part, by the Deutsche Krebshilfe (M99/94/Wi II).

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Scaife CL, Pisters PW. Combined-modality treatment of localized soft tissue sarcomas of the extremities. Surg Oncol Clin N Am 2003;12:355–368.
2. McKee MD, Liu DF, Brooks JJ, Gibbs JF, Driscoll DL, Kraybill WG. The prognostic significance of margin width for extremity and trunk sarcoma. J Surg Oncol 2004;85:68–76.
3. Sojadinovic A, Leung DH, Hoos A, Jaques DP, Lewis JJ, Brennan MF. Analysis of the prognostic significance of microscopic margins in 2084 localized primary adult soft tissue sarcomas. Ann Surg 2002;235:424–434.
4. Bielack SS, Machatschek JN, Flege S, Jurgens H. Delaying surgery with chemotherapy for osteosarcoma of the extremities. Expert Opin Pharmacother 2004;5:1243–1256.
5. Noorda EM, Vrouenraets BC, Nieweg OE, van Coevorden F, van Slooten GW, Kroon BB. Isolated limb perfusion with tumor necrosis factor-alpha and melphalan for patients with unresectable soft tissue sarcoma of the extremities. Cancer. 2003;98:1483–1490.
6. Weitz J, Antonescu CR, Brennan MF. Localized extremity soft tissue sarcoma: Improved knowledge with unchanged survival over time. J Clin Oncol 2003;21:2719–2725.
7. Falk MH, Issels RD. Hyperthermia in oncology. Int J Hyperthermia 2001;17:1–18.
8. Issels RD, Prenninger SW, Nagele A, Boehm E, Sauer H, Jauch KW, Denecke H, Berger H, Peter K, Wilmanns W. Ifosfamide plus etoposide combined with regional hyperthermia in patients with locally advanced sarcomas: A phase II study. J Clin Oncol 1990;8:1818–1829.
9. Issels RD, Abdel-Rahman S, Wendtner C, Falk MH, Kurze V, Sauer H, Aydemir U, Hiddemann W. Neoadjuvant chemotherapy combined with regional hyperthermia for locally advanced primary or recurrent high-risk soft tissue sarcomas of adults: Follow-up report of a phase II study. Eur J Cancer 2001;37:1599–1608.
10. Wendtner C-M, Abdel-Rahman S, Baumert J, Falk MH, Krych M, Santl M, Hiddemann W, Issels RD. Treatment of primary, recurrent or inadequately resected high-risk soft tissue sarcomas (HR-STS) of adults: Results of a phase II pilot study (RHT-95) of neoadjuvant chemotherapy combined with regional hyperthermia. Eur J Cancer 2001;37:1609–1616.
11. Wendtner CM, Abdel-Rahman S, Krych M, Baumert J, Lindner LH, Baur A, Hiddemann W, Issels RD. Response to neoadjuvant chemotherapy combined with regional hyperthermia predicts long-term survival for adult patients with retroperitoneal and visceral high-risk soft tissue sarcomas. J Clin Oncol 2002;20:3156–3164.
12. Van der Zee J, González González 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 – Dutch Deep Hyperthermia Group. Lancet 2000;355:1119–1125.
13. Trotti A, Byhardt R, Stetz J, Gwede C, Corn B, Fu K, Gunderson L, McCormick B, Morrisintegral M, Rich T, Shipley W, Curran W. Common toxicity criteria version 2.0: An improved reference for grading the acute effects of cancer

treatment – Impact on radiotherapy. Int J Radiat Oncol Biol Phys 2000;47:13–47.
14. Mann HB, Whitney DR. On a test of whether one of 2 random variables is stochastically larger than the other. Ann Math Stat 1947;18:50–61.
15. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–481.
16. Greenwood M. The natural duration of cancer: Reports on public health and medical subjects. Vol. 33. London: Her Majestys Stationery Office; 1926. pp 1–26.
17. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. J Clin Oncol 1983;1:710–719.
18. Lindner NJ, Scarborough MT, Spanier SS, Enneking WF. Local host response in osteosarcoma after chemotherapy referred to radiographs, CT, tumor necrosis and patient survival. J Cancer Res Clin Oncol 1998;124:575–580.
19. Picci P, Böhling T, Bacci G, Ferrari S, Sangiorgi L, Mercuri M, Ruggieri P, Manfrini M, Ferraro A, Casadei R, et al. Chemotherapy-induced tumor necrosis as a prognostic factor in localized Ewing's sarcoma of the extremities. J Clin Oncol 1997;15:1553–1559.
20. Pisters PW. Chemoradiation treatment strategies for localized sarcoma: Conventional and investigational approaches. Sem Surg Oncol 1999;17:66–71.
21. Pisters PW, Leung DH, Woodruff J, Shi W, Brennan MF. Analysis of prognostic factors in 1041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol 1996;14:1679–1689.
22. Pezzi CM, Pollock RE, Evans HL, Lorigan JG, Pezzi TA, Benjamin RS, Romsdahl MM. Preoperative chemotherapy for soft-tissue sarcomas of the extremeties. Ann Surg 1990;211:476–481.
23. Kattan MW, Leung DH, Brennan MF. Postoperative nomogram for 12-year sarcoma specific death. J Clin Oncol 2002;20:791–796.
24. Eilber FC, Rosen G, Eckhardt J, Forscher C, Nelson SD, Selch M, Dorey F, Eilber FR. Treatment-induced pathologic necrosis: A predictor of local recurrence and survival in patients receiving neoadjuvant therapy for high-grade extremity soft tissue sarcomas. J Clin Oncol 2001;19:3203–3209.
25. DeLaney T, Spiro IJ, Suit HD, Gebhardt MC, Hornicek FJ, Mankin HJ, Rosenberg AL, Rosenthal DI, Miryousefi F, Ancukiewicz M, et al. Neoadjuvant chemotherapy and radiotherapy for large extremity soft tissue sarcomas. Int J Rad Oncol Biol Phys 2003;56:1117–1127.
26. Lewis J, Leung D, Casper E, Woodruff J, Hajdu SI, Brennan MF. Multifactorial analysis of long term follow-up (more than 5 years) of primary extremity sarcoma. Arch Surg 1999;134:190–194.
27. Frustaci S, Gherlinzoni F, DePaoli A, Bonetti M, Azzarelli A, Comandone A, Olmi P, Buonadonna A, Pignatti G, Barbieri E, et al. Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: Results of the Italian Cooperative trial. J Clin Oncol 2001;19:1238–1247.
28. Woll PJ, van Glabbeke M, Hohenberger H, Le Cesne A, Gronchi A, Hoekstra HJ, Radford JA, van Coevorden F, Blay J. Adjuvant chemotherapy with doxorubicin and ifosfamide in resected soft tissue sarcoma: Interim analysis of a randomised phase III trial. ASCO Annual Proceedings 2007;25:10008.