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Treatment of primary, recurrent or inadequately resected high-risk soft-tissue sarcomas (STS) of adults: results of a phase II pilot study (RHT-95) of neoadjuvant chemotherapy combined with regional hyperthermia☆

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Abstract

The efficacy of thermochemotherapy in adult patients with primary, recurrent or inadequately resected non-metastatic high-risk soft-tissue sarcomas (STS) was assessed. 54 patients were prospectively treated with four cycles of etoposide, ifosfamide and doxorubicin (EIA) combined with regional hyperthermia (RHT) followed by surgery, another four cycles of EIA without RHT and external beam radiation. The objective response rate was 16% and at a median follow-up time of 57 months, the 4-year estimated rates of local failure-free survival (LFFS), distant metastasis-free survival (DMFS), event-free survival (EFS) and overall survival (OS) were 59% (95% confidence interval (CI) 45–73%), 59% (95% CI 44–73%), 26% (95% CI 14–38%) and 40% (95% CI 27–53%), respectively. OS was in favour of patients responding to neoadjuvant treatment ($P=0.073$). In comparison to a preceding phase II study including pre- and postsurgical thermochemotherapy (RHT-91), at a 4-year follow-up the RHT-95 study cohort showed an inferior LFFS rate ($P=0.027$), but this did not affect DMFS ($P=0.558$) or OS ($P=0.126$). Hence, postsurgical thermochemotherapy seems critical for local tumour control without affecting survival.

Keywords: Soft-tissue sarcoma; High risk; Thermochemotherapy; Regional hyperthermia (RHT); Local failure-free survival; Overall survival

1. Introduction

Prognosis of patients with soft-tissue sarcomas (STS) of high-grade histology, large size ($\geqslant 5$ cm) and deep localisation is unfavourable according to a large analysis of the Memorial Sloan-Kettering Cancer Center (MSKCC) with a median overall survival (OS) of only 33 months [1]. Patients with high-grade tumours of the retroperitoneum were reported to have an even worse prognosis with a median OS of only 20 months and a 5-year OS rate between 15 and 35% [2,3]. Neoadjuvant treatment strategies seem attractive in order to identify a subgroup of patients who might be chemoresponsive for further postoperative systemic therapy [4]. While early trials including doxorubicin-based preoperative regimens showed a long-term benefit for responding patients, this could not be confirmed in later studies [5,6]. Furthermore, the role of postsurgical adjuvant chemotherapy remains to be defined: while most trials did not show any survival benefit, but only improved local tumour control and delay in formation of distant disease, recent meta-analysis revealed a trend for a survival advantage for those patients receiving chemotherapy [7–9].

The rationale for the combination of cytotoxic drugs with hyperthermia, i.e. thermochemotherapy, in the treatment of high risk-STS is based on experimental

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evidence that heat exposure increases the killing of tumour cells by direct thermal cytotoxicity and is able to sensitise perfused tumour tissue towards chemotherapy in a synergistic manner [10]. In addition, recent results indicate that heat shock proteins (hsp) induced in tumour cells under hyperthermic stress are able to elicit specific T-cell immune responses [11–13]. Hyperthermia in combination with radiotherapy as neoadjuvant treatment for high risk-STS patients was already shown to impact positively on local tumour control, while it did not appear to influence the rate of distant metastases or survival [14]. Hyperthermic isolated limb perfusion in combination with tumour necrosis factor (TNF) and melphalan or doxorubicin was proven to be efficious for locally advanced STS of the extremities [15,16]. With regard to regional hyperthermia (RHT), clinical efficacy was shown in a former phase II study (RHT-86) including pretreated patients with locally advanced STS who received ifosfamide-based chemotherapy combined with RHT [17]. In another phase II study (RHT-91) consisting of neoadjuvant chemotherapy combined with RHT, high risk-STS patients responding to neoadjuvant therapy showed a favourable overall survival [18]. In the study presented here (RHT-95), patients who were previously resected with microscopic or macroscopic tumour left after surgery were also eligible for the protocol treatment. Furthermore, the RHT-95 protocol included only neoadjuvant thermochemotherapy, while RHT was not given during postsurgical chemotherapy. The objectives of this review were to determine response rates and survival parameters in the RHT-95 study cohort and to compare the results with the preceding RHT-91 study.

2. Patients and methods

2.1. Patients' eligibility

Patients included in the RHT-95 study were required to have histologically-confirmed STS without manifestation of distant disease. Furthermore, patients had to fulfil high-risk criteria, i.e. only tumours with grade II or III histology, size $\geqslant 5$ cm, extracompartmental and deep extension were eligible. Patients with primary STS, as well as with recurrent or inadequately-resected tumours, with or without attempts of radiotherapy, were eligible, previous chemotherapy was an exclusion criteria. Written informed consent was obtained from all patients included in this study.

2.2. Staging procedures

Initial staging of all patients was required before starting the protocol treatment and comprised of physical examination, chest X-ray, computed tomography (CT) scan of chest and abdomen/pelvis and bone scan. Tumour size was determined by contrast-enhanced CT scan and/or magnetic resonance imaging (MRI) and defined as the maximum dimension obtained by assessment of the lesions using cross-sectional imaging. After completion of neoadjuvant thermochemotherapy, patients received chest X-ray, CT scan of chest and abdomen/pelvis and cross-sectional imaging of the tumour site as performed before the initiation of therapy.

2.3. Treatment programme

The neoadjuvant protocol treatment comprised EIA (etoposide/ifosfamide/doxorubicin) chemotherapy and RHT. Chemotherapy consisted of doxorubicin 50 mg/m^2 on day 1, etoposide 125 mg/m^2 on days 1 and 4, and ifosfamide 1500 mg/m^2 over 60 min on days 1–4. On days 1 and 4, EIA chemotherapy was combined with RHT as previously described in Ref. [18]. Thermochemotherapy was repeated every 3 weeks, a total of four courses of neoadjuvant treatment were given before assessment of tumour response. For RHT, the BSD 2000 system was used which is an electromagnetic deep regional-heating device (BSD Medical Corporation, Salt Lake City, UT, USA). Technical details of this system have been extensively described previously in Ref. [19].

After completion of neoadjuvant therapy, patients underwent a restaging procedure with evaluation of response (week 12–13) and tumours were resected if possible (week 14). A wide excision with preservation of function was primarily attempted during surgery. Patients without progressive disease after neoadjuvant therapy were eligible for post-operative protocol treatment comprising of four cycles of EIA chemotherapy without RHT. All patients who were not pre-irradiated received external beam radiotherapy using mega-voltage equipment irrespective of the resection status. Radiation was applied to treatment fields that included the tumour bed with a 5 cm safety margin and consisted of a total dose in the range of 55–65 Gy in daily fractions (1.8–2.0 Gy).

2.4. Treatment evaluation

Toxicity was evaluated after each treatment cycle according to the common toxicity criteria (CTC) [20]. After completion of neoadjuvant therapy, radiographic and pathological responses were defined as previously described in Ref. [18].

Feasibility of RHT was assessed by calculating time-averaged temperatures for each RHT 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, 50 and

90% of all measured tumour sites were determined during each RHT treatment and values from all RHT treatments of each patient were documented as T_{20}, T_{50} and T_{90}, respectively [17].

Rates of recurrence or progression of disease or death were estimated according to the method of Kaplan–Meier, with the time of recurrence or local progression of persistent disease defined as local treatment failure from the date of initiation of neoadjuvant thermochemotherapy. The 95% confidence intervals (CIs) of the Kaplan–Meier estimates were based on their variance estimates according to Greenwood's formula [21]. The endpoints for analysis were local failure-free survival (LFFS), distant metastasis-free survival (DMFS), event-free survival (EFS) and overall survival (OS). Comparison of survival parameters within the different stratification arms (S1, S2, S3), between responding vs. non-responding patients, as well as between RHT-91 and RHT-95 study protocol patients, was performed using the log-rank test [22]. A P value $\leqslant 0.05$ was considered to be statistically significant.

3. Results

3.1. Patients' characteristics

Between November 1994 and July 1997, a total of 54 patients with locally advanced high-risk sarcomas were enrolled on the RHT-95 study protocol, patients' characteristics are listed in Table 1. The study population consisted of 33 male and 21 female patients with a median age of 43 years (range 18–75 years) and a median performance status (World Health Organization (WHO)) of 1. The patients entered the trial either with non-resectable primary high risk-STS (S1) or with local recurrence of those tumours (S2). In addition, patients with inadequately (R1/R2) resected high risk-STS entered this trial and only patients with surgery within 8 weeks before study entry were included (S3). The majority of patients, i.e. 36 of 54, entered the protocol after prior surgical and/or radiotherapeutic interventions, 18 patients had never had previous treatment for their high risk-STS. The feasibility of an adequate R0-resection was excluded for every patient before inclusion in this study. The median ellipsoidal tumour volume was 240 cc indicating the extensive local stage of most lesions.

Pathological features including histology and tumour grading are given for all patients entering the trial in Table 2. The most common histological subtypes were liposarcomas ($n=12$), leiomyosarcomas ($n=11$) and malignant fibrous histiocytomas ($n=9$). Of the 54 patients in the study, 33 showed manifestation of a moderately differentiated (grade II) and 21 of a poorly differentiated (grade III) sarcoma.

Table 1
Patients' characteristics ($n=54$)

Characteristics	n (%)
Sex	
Male	33 (61)
Female	21 (39)
Age at entry (years)	
20–40	22 (41)
>40–65	29 (54)
>65	3 (5)
Performance status at entry	
WHO 0	15 (28)
WHO 1	33 (61)
WHO 2	6 (11)
Disease status	
S1	19 (35)
S2	9 (17)
S3	26 (48)
Site of tumour	
Trunk	7 (13)
Abdomen/Pelvis	28 (52)
Extremity	19 (35)
Prior treatment	
Surgery and/or radiation	36 (67)
None	18 (33)

WHO, World Health Organization.

3.2. Feasibility and toxicity

The treatment characteristics of pre- and postoperative chemotherapy, as well as RHT, for all patients in the RHT-95 study are given in Table 3. 45 patients (83%) received the prescribed number of preoperative EIA chemotherapy cycles combined with RHT. Postoperative protocol treatment was not given to 27 patients due to disease progression or refusal of further therapy. Of the 27 patients who were started on postoperative EIA chemotherapy, 20 patients (74%) received the intended four cycles.

Based upon a total of 400 RHT treatments, average maximum temperature (T_{max}) measured within the tumours was 42.2°C (95% CI: 41.5–42.4°C) and the

Table 2
Histological diagnoses and grades ($n=54$)

Cell type	Grade II	Grade III	Total (%)
Liposarcoma	9 (17)	3 (6)	12 (22)
Leiomyosarcoma	5 (9)	6 (11)	11 (20)
Malignant fibrous histiocytoma	8 (15)	1 (2)	9 (17)
Malignant schwannoma	3 (6)	2 (4)	5 (9)
Angiosarcoma	1 (2)	2 (4)	3 (6)
Synovial sarcoma	1 (2)	1 (2)	2 (4)
Rhabdomyosarcoma	0 (0)	2 (4)	2 (4)
Extraskeletal Ewing's sarcoma	1 (2)	1 (2)	2 (4)
Others	5 (9)	3 (6)	8 (15)

Table 3
Number of treatment cycles

Cycles	EIA (pre-op)	RHT (pre-op)	EIA (post-op)
0	–	–	27
1	1	3	1
2	1	3	2
3	3	3	3
4	49	45	20
>4	–	–	1

RHT, regional hyperthermia; EIA, etoposide, ifosfamide, doxorubicin; post-op, post-operatively; pre-op, pre-operatively.

median time-averaged temperatures achieved in 20, 50 and 90% of all measured tumour sites were 40.8°C (T_{20}) (95% CI: 38.9–44.9°C), 40.0°C (T_{50}) (95% CI: 39.1–42.0°C), and 39.3°C (T_{90}) (95% CI: 38.8–39.7°C), respectively. The technical quality of heating as assessed for 41 patients was as follows: in 15 patients (37%) T_{max} was $\geqslant$42.5°C, in 12 patients (29%) $\geqslant$41.5°C and $<$42.5°C, in 8 patients (20%) $\geqslant$40.5°C and $<$41.5°C and in 6 patients (15%) only temperatures $<$40.5°C were detected.

Side-effects associated with neoadjuvant chemotherapy are given for all 54 patients in Table 4a, shown as maximal toxicity occurring over all cycles. During the preoperative treatment segment, chemotherapy-associated non-haematological side effects were mainly mild (grades I–II), severe non-haematological side effects were noticed in less than 10% of patients. One patient suffered from a lethal fungal infection (grade IV) and 1 patient experienced grade IV toxicity with sensory defects. Haematological toxicity was significant in terms of leucopenia which occurred in approximately 89% of patients during the treatment courses (grade III: 52%; grade IV: 37%). Granulocyte-colony stimulating factor (G-CSF) support was given to 26 patients (48%) at least once during the pre-operative cycles. Severe thrombocytopenia (grade III) was observed only in 3 patients (6%). 15 patients (28%) required at least once dose reduction, among 21 patients (39%) at least once treatment delay was registered. For the 27 patients receiving the postoperative protocol treatment, besides nausea, very few severe non-haematological toxicities were documented: one grade III infection due to a cholecystitis and one grade IV neurotoxicity with sensory loss. Severe leucopenia (grade III: 18%; grade IV: 73%) occurred in almost every patient, while severe thrombocytopenia was observed in only a minority of patients (grade III: 0%; grade IV: 9%) (data not shown).

Table 4

(a) Maximal toxicity during neoadjuvant chemotherapy with RHT

Toxicity (CTC grade)	0	I	II	III	IV
Leucopenia	–	–	6	28	20
Thrombocytopenia	16	30	5	3	–
Nausea	8	29	15	2	–
Vomiting	28	15	11	–	–
Alopecia	–	1	53	–	–
Infection	46	5	2	–	1
Renal toxicity	51	3	–	–	–
Neurotoxicity	42	8	3	–	1
Cardiac toxicity	45	7	2	–	–
FUO	43	7	4	–	–

(b) Acute reactions related to hyperthermia

Side-effects	none	mild to moderate	severe
Skin burn	48	6	–
Subcutaneous tissue necrosis	51	3	–
Muscle necrosis	47	6	1
Pain within the applicator	44	9	1
Bolus pressure	40	9	5
Localized infection	54	–	–

RHT, regional hyperthermia; CTC, common toxicity criteria; FUO, fever of unknown origin.

Severe side-effects specifically associated with RHT were bolus pressure in 5 patients (9%), pain within the applicator in 1 patient (2%) and muscle necrosis in another patient (2%) (Table 4b). Mild pain occurred often during the initial heating-up period and could be controlled by changes in the positioning of the patient or changes of the phase- and amplitude-controlled power output of the RHT system. Skin burns consisted only of erythema in the heating field, no blisters or ulcers were observed. All together, treatment was well tolerated in 39 patients (72%) and fairly well in 13 patients (24%), respectively.

3.3. Response to treatment and surgical results

Response was evaluated after completion of neoadjuvant EIA chemotherapy combined with RHT, i.e. before surgical resection. 32 of 54 patients were assessable for response, since previously R1-resected patients (S3 category with microscopic disease) could only be evaluated in cases of disease progression. The overall objective response rate was 16% consisting of five partial responses (PR). Including the four minor responses (MR) in the assessment, the radiographic response rate was 28%. Disease could be stabilised in 10 patients (SD) (31%), 13 patients (41%) completed neoadjuvant therapy with progressive disease (PD) (Table 5).

Table 5
Radiographic response to preoperative chemotherapy combined with RHT

Radiographic response	No of patients (%)
Complete response (CR)	–
Partial response (PR)	5 (16)
Minor response (MR)	4 (12)
Stable disease (SD)	10 (31)
Disease progression (PD)	13 (41)
Not assessable (NA)	22 (41)

RHT, regional hyperthermia.

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

Radiographic response	Pathological response				
	pCR	FHR	NR	n.e.	*n*
Complete response (CR)	–	–	–	–	–
Partial response (PR)	2	–	2	1	5
Minor response (MR)	1	1	1	1	4
Stable disease (SD)	–	2	7	1	10
Partial disease (PD)	–	1	6	6	13
Not evaluable (n.e.)	–	–	–	22	22
Total	3	4	16	31	54

pCR, complete necrosis; FHR, favourable histopathological response, >75% necrosis; NR, no histopathological response, <75% necrosis; n.e., not evaluable.

25 of the 54 study patients (46%) underwent surgery after completion of neoadjuvant thermochemotherapy. Conservative resections were performed in 23 patients, while mutilative surgery was necessary for 2 patients (8%). For 25 patients, surgical resection was not necessary (S3 patients with microscopic disease) or possible. Complete tumour resection (R0) or marginal resection (R1) by non-mutilative methods was possible in 9 and 10 patients, respectively.

In the resected tissue of 23 evaluable patients, a pathological complete response (pCR) with the absence of typical malignant cells was found in 3 patients (13%). The clinical response of these patients to the preoperative protocol treatment included 2PRs and 1MR. A favourable histopathological response (FHR) defined by more than 75% necrosis in the resected tumour tissue was documented in 4 patients and was associated with 1MR, 2SDs and 1PD as clinical responses. Including these 3 patients, who were documented to have a pathological response in their resected tumour without clinical signs of response, results in a total response rate of 37.5% (12 of 32 evaluable patients). The relationship between radiographic and pathohistological responses for all evaluable patients is listed in Table 6.

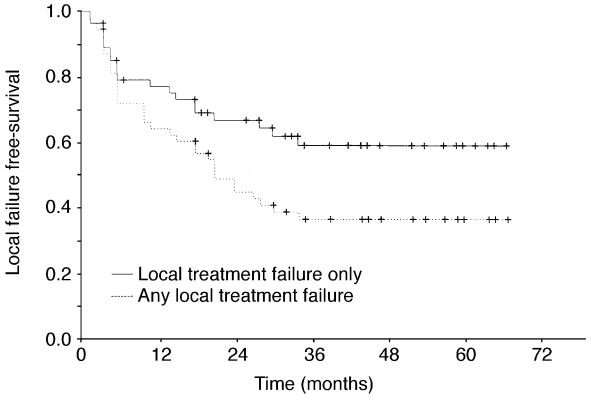

Fig. 1. Local failure-free survival (LFFS) in patients with local treatment failure only ($n=20$; solid line) or any local treatment failure ($n=34$; dashed line).

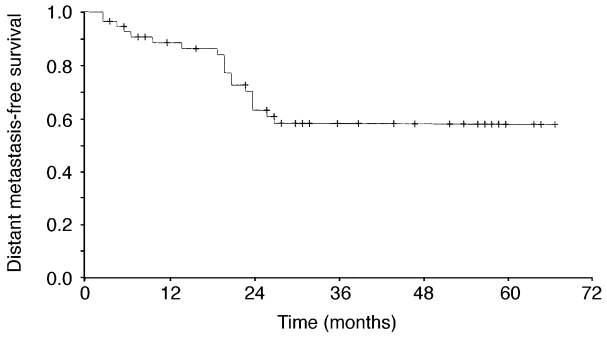

Fig. 2. Distant metastasis-free survival (DMFS) in the entire cohort of 54 patients.

3.4. Relapse and survival

After a median follow-up time of 57 months (95% CI: 50.2–58.8 months), 13 patients showed local recurrence and 20 patients presented with local progression of persistent disease. The median time to local relapse or progression for the entire study population was 21 months (range: 2–67).

The 4-year rate estimated according to Kaplan–Meier of local-failure free survival (LFFS) was 59% (95% CI: 45–73%). With regard to any local failure (including patients with combined local and distant failure) the 4-year LFFS rate was 36% (95% CI: 23–50%) (Fig. 1). There was no significant difference in the 4-year LFFS rate for patients with tumours located at the extremity (77%; 95% CI: 57–97%) versus patients with tumours at non-extremity sites (50%; 95% CI: 32–68%) ($P=0.148$).

Distant disease was documented in 19 patients (35%), while the median time to formation of metastases was 40 months (range: 3–67). The 4-year actuarial distant-metastasis-free-survival (DMFS) rate was 59% (95% CI: 44–73%) (Fig. 2).

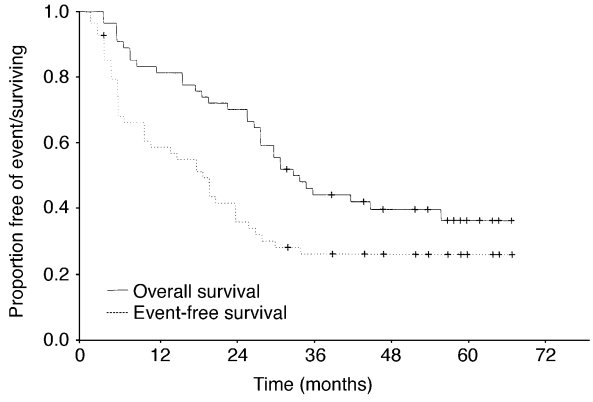

Fig. 3. Overall survival (OS) (solid line) and event-free survival (EFS) (dashed line) in the entire cohort of 54 patients.

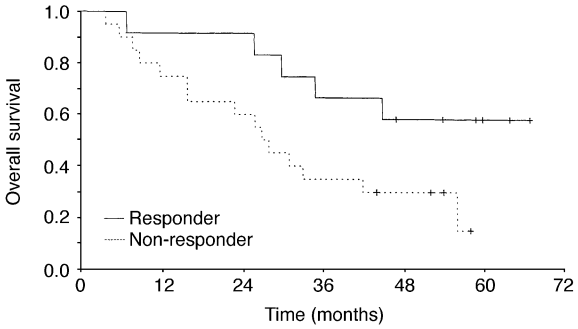

Fig. 4. Overall survival in patients with evidence of radiographic and/or pathological response (complete response (CR), partial response (PR), minor response (MR); complete necrosis (pCR), favourable histopathological response (FHR)) ($n=12$; solid line) versus non-responding patients ($n=20$; dashed line). $P=0.073$.

39 patients (72%) developed local and/or distant disease recurrence during the follow-up period. The 4-year actuarial EFS rate was 26% (95% CI: 14–38%), the median EFS time was 19 months (range: 2–67) (Fig. 3). At present, 21 patients (39%) are alive. The 4-year estimated overall survival (OS) rate was 40% (95% CI: 27–53%) with a median OS time of 33 months (range: 4–67) (Fig. 3). Patients with tumours located at the extremity had a favourable OS rate at 4-year (63%; 95% CI: 41–85%) in comparison to patients with tumours at non-extremity sites (28%; 95% CI: 13–43%) ($P=0.047$).

Comparison of the OS rates at 4-year follow-up in responding (radiographic and/or pathological) patients (58%; 95% CI: 30–86%) versus non-responders (30%; 95% CI: 10–50%) showed a trend for better survival for the responders ($P=0.073$) (Fig. 4).

Comparison of the newly introduced group of S3 patients with patients of the S1 and S2 group did not reveal any statistically significant differences with regard to OS ($P=0.919$), LFFS ($P=0.455$) and DMFS ($P=0.733$) at a 4-year follow-up. Patients with S3 tumours had an OS rate of 37% (95% CI: 18–56%) with a median OS time of 34 months (range: 6–67) in comparison to patients belonging to the S1/S2 category with an OS rate of 43% (95% CI: 24–61%) with a median OS time of 30 months (range: 4–60). The LFFS rate was 56% (95% CI: 36–76%) for S1/S2 patients and 63% (95% CI: 43–82%) for S3 patients. Including patients with any local failure, LFFS rates for both categories did not differ in a significant manner (S1/S2: 37% (95% CI: 19–55%) with median LFFS time of 17 months (range: 2–67); S3: 35% (95% CI: 16–54%) with median LFFS time of 23 months; range: 2–67) ($P=0.612$). With respect to DMFS, S1/S2 patients had the same outcome as patients having been inadequately resected (S3) before the protocol treatment (60%, 95% CI: 39–80% versus 57%, 95% CI: 37–77%).

At a 4-year follow-up, comparison of survival parameters between the present study, which included only presurgical thermochemotherapy, and the preceding RHT-91 protocol, which prescribed pre- and post-surgical thermochemotherapy in the protocol, revealed a significantly inferior LFFS rate in the RHT-95 study cohort ($P=0.027$) (Fig. 5a). Nevertheless, there was no

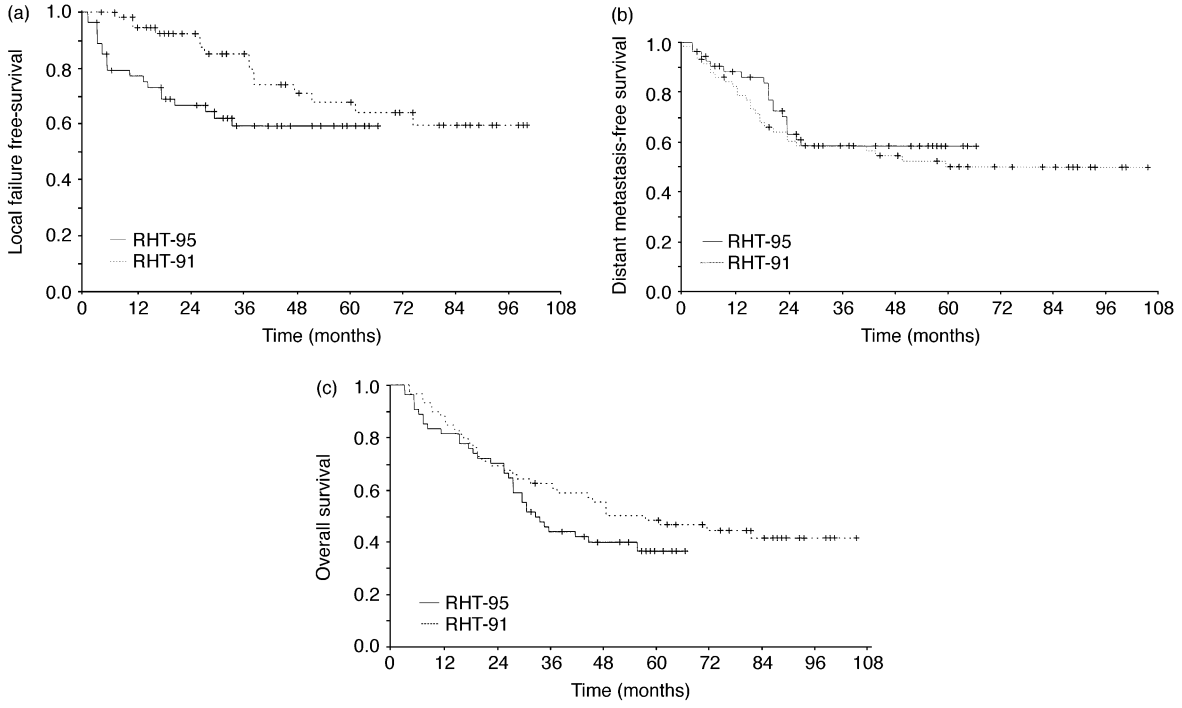

Fig. 5. Comparison of the regional hyperthermia (RHT)-91 ($n=59$; dashed line) versus RHT-95 ($n=54$; solid line) study cohort at a 4-year follow-up with respect to: (a) local failure-free survival ($P=0.027$); (b) distant metastasis-free survival ($P=0.558$); (c) overall survival ($P=0.126$).

difference between both studies with regard to DMFS ($P = 0.558$) (Fig. 5b) or OS ($P = 0.126$) (Fig. 5c).

4. Discussion

In this prospective trial, neoadjuvant thermochemotherapy for patients with high risk-STS was feasible since more than 80% of patients received the prescribed number of preoperative EIA cycles combined with RHT. The neoadjuvant therapy was well-tolerated with mostly mild non-haematological toxicities occuring. As expected, leucopenia was the most frequent haematological side-effect, but was controlled without leading to a substantial proportion of lethal infections. Hyperthermia itself was tolerated in the majority of patients. Finally, neoadjuvant thermochemotherapy did not lead to an increased postoperative morbidity in patients with high risk-STS as has also been shown for chemotherapy alone in a retrospective review of the M.D. Anderson Cancer Center [23].

At study entry, a proportion of patients (52%) presented with tumours located at retroperitoneal or visceral sites that are known to have a poorer prognosis than extremity lesions [24]. Furthermore, 9 of 54 patients (17%) had recurrent disease at presentation being an independent risk factor for local recurrence [25]. The median OS for all patients within the RHT-95 study including those who presented with these additional risk factors was 33 months and is similar to the survival time reported for patients treated at the MSKCC with a more favourable STS of the extremity [1].

In this study, response to neoadjuvant therapy for high risk-STS was shown to have prognostic significance confirming the early results by Pezzi and colleagues who showed a benefit in survival for responders to neoadjuvant chemotherapy [4]. Thus, survival of high risk-STS patients could be estimated after evaluation of response to neoadjuvant thermochemotherapy. In the RHT-95 study almost half of the patients being enrolled on protocol were previously resected with microscopic or macroscopic tumour left *in situ*. Interestingly, the rates of local disease recurrence, formation of distant metastases and overall survival did not differ in comparison to patients presenting with primary or recurrent tumours. This argues that a multimodality approach can rescue these patients rendering a substantial portion into a durable disease-free status.

One important finding in this study was the fact that local tumour control was significantly worse in comparison to a preceding phase II study (RHT-91) with almost the same protocol treatment, but with the difference that postsurgical thermochemotherapy instead of chemotherapy alone was included in the RHT-91 study. Critical is the observation that inferior local tumour control, as seen in the RHT-95 study, does not translate into an increase in distant metastases formation or in a worse overall survival. One significant risk factor for local recurrences are inadequate surgical margins [26]. After completion of neoadjuvant thermochemotherapy, 10 patients were conservatively resected with microscopically positive margins in the RHT-95 study, while in the RHT-91 study this proportion was much higher (21 R1-). Thus, the inferior LFFS rate in the RHT-95 is not due to a higher proportion of patients with positive margins. Furthermore, the lower LFFS rate in the RHT-95 is not attributed to a higher proportion of patients with tumour at high-risk anatomic sites, i.e. retroperitoneal or visceral (RHT-95: 52% versus RHT-91: 51%). Moreover, despite a higher number of patients with non-extremity high risk-STS in the RHT-95 study (RHT-95: 65% versus RHT-91: 53%), comparison of LFFS for non-extremity STS patients at a 4-year follow-up revealed no statistically significant difference (data not shown), thus arguing against a worse selection of patients with unfavourable tumour sites in the RHT-95 study cohort.

With regard to the technical quality of hyperthermia, adequate temperatures defined as maximum tumour temperatures (T_{max}) of greater than 42.0°C were achieved in both studies. This is important to note since a strong correlation was found between temperatures within the tumours and response to treatment [17]. Comparing the maximal temperatures in both studies, there was almost no difference (T_{max}: 42.5 (RHT-91) versus 42.2°C (RHT-95)). Time-averaged temperatures were only slightly lower in the RHT-95 study cohort. While there is no apparent difference in the quality of presurgical hyperthermia, the application of hyperthermia after surgical resection within the RHT-91 study protocol could be critical. It is well-described that hyperthermia with temperatures (T_{50}) below 44°C results in improved perfusion and oxygenation which is especially important in scar tissue after surgery [27,28]. Furthermore, it was shown that the oxygenation status influences local tumour control as the fastest proliferating tumour cells were found in the poorest oxygenated soft tissue sarcomas [29]. Thus, postsurgical hyperthermia could result in better oxygenation of scar tissue and thus leads to eradication of microscopic tumour residues. Important is the observation that the better local tumour control in the RHT-91 study does not affect the survival of patients. Similar results were obtained with adjuvant brachytherapy which also leads to better oxygenation of the tumour tissue: in STS patients reduction in local recurrence was not associated with a significant reduction in distant metastasis or improvement in disease-specific survival [30]. Finally, the results of the ongoing randomised multicentric phase III Intergroup study (European Organization for Research and Treatment of Cancer (EORTC) 62961/European Society for Hyperthermic Oncology (ESHO) RHT-95) which

includes both pre- and postsurgical hyperthermia combined with EIA chemotherapy in the experimental treatment arm will help to define the impact of hyperthermia on local tumour control and survival.

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