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ORIGINAL ARTICLE

Adjuvant therapy for resectable high-risk soft tissue sarcoma: feasibility and efficacy of a sandwich chemoradiotherapy strategy

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Abstract
Purpose Radical definitive surgery is the only curative treatment approach in resectable soft tissue sarcoma. Despite complete resection, patients with grade 2 and 3 soft tissue sarcoma are at high risk of local or distant recurrence. Local and systemic adjuvant treatment includes radiotherapy and chemotherapy, but the optimal scheduling is not known.

Methods In this phase II clinical trial, we combined surgery with adjuvant chemotherapy and radiotherapy in a novel trimodality treatment sequence. Two to 6 weeks after surgery, patients received 2 cycles of chemotherapy containing doxorubicin and ifosfamide, then 50.4 Gy of percutaneous radiotherapy followed by additional 2 cycles of chemotherapy.

Results Chemotherapy and radiotherapy-related toxicity was generally mild, without treatment delays in the majority of patients. After a median follow-up of 57 months, 81.5% of patients are alive in complete remission.

Conclusions The sandwich chemoradiation protocol proved to be feasible with manageable toxicity. The patient outcome compared favorably with other adjuvant trials in preventing relapse, particularly distant relapse which is predictive of poor outcome. This multidisciplinary approach warrants further investigation in a larger randomized trial.

Keywords Soft tissue sarcoma · Adjuvant · Multidisciplinary · Chemoradiotherapy

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Introduction

Soft tissue sarcomas (STS) are derived from mesenchymal tissue and are rare tumors, representing only around 1% of all tumors in adults [1]. Most STS originate from the lower extremity, groin or buttock (46%), the upper extremity (13%), followed by the trunk (18%), the retroperitoneum (13%) and the head and neck region (9%) [2]. STS are derived from mesenchymal tissue and their histological heterogeneity is due to their ability to differentiate toward smooth muscle, striated skeletal muscle, adipose and fibrous tissue. While the histological subtype is of some prognostic importance, the long-term prognosis is largely

determined by histological grading, the surgical resection margin and the initial tumor size (larger than 5 cm). Also, STS of the extremities and body wall have a better prognosis than retroperitoneal STS. These prognostic criteria of STS are summarized in the UICC classification [3].

The wide array of histological subtypes and the relative rarity of sarcomas contribute to the difficulty in understanding the biological behavior and patterns in response to treatment. In addition to their potential for locally destructive growth, STS have a significant risk of distant metastases. A multidisciplinary team approach in specialized centers with expertise in orthopedic, surgical, radiation and medical oncology is of paramount importance for optimal treatment of STS. Surgical resection is the only potentially curative therapy for STS regardless of their site of origin, while STS of the extremities are more often amenable to complete tumor excision.

The benefit of adjuvant chemotherapy in adult STS is controversial. While no clear benefit has been shown for adjuvant chemotherapy in patients with retroperitoneal or uterine sarcomas, a survival benefit for adjuvant doxorubicin-based regimens has been suggested in some but not all trials involving patients with STS of the extremities. A landmark quantitative meta-analysis of 14 large trials with 1,568 patients with localized resectable STS randomized to receive either no adjuvant treatment or adjuvant doxorubicin-based chemotherapy has found several benefits in the latter group [4]. This included a significantly longer local, distant and overall recurrence-free interval at 10 years. Although there was a tendency of tumors larger than 5 cm to profit most from adjuvant chemotherapy, the relative effect of chemotherapy did not significantly differ with respect to overall survival and recurrence-free interval in smaller and larger tumors [4]. A significant survival benefit of adjuvant chemotherapy was found among patients with extremity STS, in whom the hazard ratio was 0.80 ($P = 0.029$), equivalent to a 7% absolute benefit at 10 years [4]. This meta-analysis was recently updated, and included 18 randomized clinical trials with 1,953 patients. While this analysis confirmed many of the previous observations, it also included more recent trials using combinations of doxorubicin and ifosfamide and showed that this combination (but not doxorubicin alone) was associated with a statistically significant overall survival benefit (OR 0.56, 95% CI 0.36–0.85) and an absolute risk reduction of 11% [5].

Given the meta-analysis data supporting adjuvant chemotherapy in the treatment of STS, we decided to examine the feasibility and toxicity of an improved chemoradiotherapy protocol at our institution. The chemotherapy consisted of doxorubicin and ifosfamide, as these two cytotoxic drugs remain the two most active compounds in STS. With the aim of improving local and—most importantly—distant tumor control we combined surgery with adjuvant systemic chemotherapy and local radiotherapy in a novel trimodality treatment sequence for the treatment of patients with UICC stage II and III STS.

Patients and methods

Staging and study design

After a positive biopsy for sarcoma, patients with STS referred to our university hospital were evaluated for participation in this prospective phase II clinical trial. All patients underwent complete staging, which included computer tomography (CT) scan of the chest and abdomen, as well as a 3-phase bone scan and positron emission tomography (PET) scan. Additionally, all patients underwent pulmonary function testing, echocardiographic examination and electrocardiographic evaluation under physical stress. Male patients were offered the possibility to cryopreserve sperm. The patients who satisfied all the selection criteria were invited to participate in the trial.

The informed consent was obtained from patients after extensive information was given about the nature and extent of disease, available treatment options, effects and side effects of treatment and data management for scientific evaluation. The study protocol was approved by the local ethics committee.

Inclusion and exclusion criteria

Inclusion criteria were as follows: 1. histologically documented STS of all histological subtypes classified as G2 and G3 grading; [6] 2. complete tumor excision (R0) performed or planned; 3. UICC stage II or III; 4. Age $\geq$18 and $\leq$65 years; 5. Karnofsky score $\geq$70; 6. sufficient liver function (bilirubin $\leq$1.5 mg/dl); 7. sufficient kidney function (serum creatinine $<$1.5 mg/dl, creatinine clearance $>$30 ml/min); sufficient bone marrow function (leukocytes $>$4,000/μl, thombocytes $>$100,000/μl); and written informed consent to participate in this study.

Exclusion criteria were (1) distant metastases or lymph node involvement; (2) concurrent malignancy with the exception of carcinoma in situ and non-melanomous skin cancer (3) severe infection at treatment start; (4) pregnancy or breast feeding; (5) severe psychological or psychiatric disorder; (6) history of heart disease, including history of myocardial infarction, unstable angina (angina symptoms at rest) or new-onset-angina, congestive heart failure NYHA III or IV, cardiomyopathy or any other disease leading to left-ventricular insufficiency or cardiac ventricular arrthythmias requiring anti-arrythmic therapy; (7) arterial occlusive disease grade III and IV; (8) severe

uncontrolled hypertension, despite optimal medical management; (9) severe uncontrolled diabetes mellitus, despite optimal medical management.

Surgery

Preoperative biopsy was performed by open biopsy, and in rare cases by fine needle aspiration. After the initial staging and inclusion to the study, definitive surgery was performed with the intention of complete en bloc tumor resection (R0).

Patients with locally advanced STS in close proximity to neuro-vascular bundles and bone underwent intraoperative brachytherapy with 16–20 Gy (flap radiotherapy). The decision for intraoperative brachytherapy was made after interdisciplinary discussion.

Chemotherapy

After completed wound healing (around 1–2 weeks post-surgery), the first two cycles of chemotherapy were administered. Chemotherapy contained doxorubicin (75 mg/m^2 i.v. over 1 h on day 1) followed by ifosfamide (5 g/m^2 i.v. over 24 h starting on day 1). IV fluids were adequately administered. Granisetron and dexamethasone were applied on chemotherapy days to prevent nausea and vomiting.

Radiotherapy

Intraoperative brachytherapy was performed as described above. "Sandwiched" between chemotherapy cycles 2 and 3 (Fig. 1), patients underwent percutaneous radiation therapy. A total dose of 50.4 Gy fractionated in 5 × 1.8–2 Gy/week were applied onto the operative field. The radiation field was reduced to the initial tumor bed and a boost was applied to a cumulative dose of 60 Gy.

Toxicity and follow-up

Before adjuvant chemoradiation, baseline characteristics were evaluated. During chemotherapy, weekly clinical evaluation as well as blood counts and biochemistry measurements were recorded according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Before, during and after radiotherapy, we recorded radiation-induced acute toxicity (RTOG grade). Regular follow-up visits or telephone interviews were performed.

Statistical methods

The primary endpoint of this study was overall recurrence-free interval (RFI) at 2 years and at 5 years. Overall RFI was defined as the time between surgery and recurrence of disease at the local site or a distant site, whatever occurred first. Secondary endpoints were treatment-related morbidity and death. Further endpoints were the patterns of recurrence (local, distal), 5 years overall survival and the rate of complete surgical resections (R0).

The local recurrence-free interval (RFI) was defined as the time between surgery and recurrence of disease at the local site. Distant RFI was defined as the time between surgery and recurrence of disease at a distant (metastatic) site. The overall survival (OS) was defined as the time between surgery and death. A separate analysis was performed for all patients ($n = 27$) as well as for those with STS of the extremities only ($n = 25$).

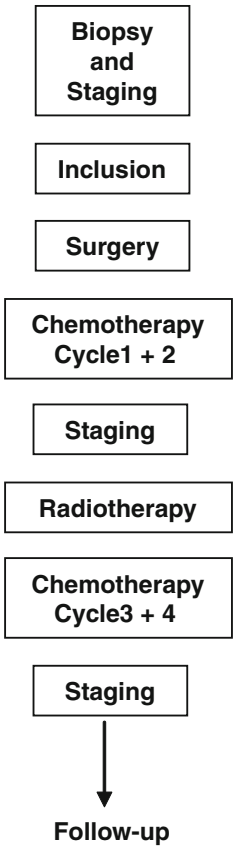

Fig. 1 Flow chart of the study design. Schematic depiction of the trimodality treatment sequence

Results

Inclusion

Between August 1997 and January 2004, twenty-seven patients entered this study at our institution and were regularly followed (see Flow chart, Fig. 1). Baseline characteristics are presented in Table 1. All but two patients presented with STS of the extremities. These represented a wide array of histologies, with the majority being synovial sarcomas and malignant fibrous histiocytoma. Most

Table 1 Baseline characteristics

Included patients	27
Age (years)	
Median (range)	34 (21–61)
Gender	
Female (%)	16 (59)
Male (%)	11 (41)
Disease site	
Extremity (%)	25 (92.6)
Retroperitoneum (%)	1 (3.7)
Neck (%)	1 (3.7)
Histology	
Synovial sarcoma	8
Malignant fibrous histiocytoma	8
Leiomyosarcoma	2
Liposarcoma	2
Other	7
Grade	
G2 (%)	7 (25.9)
G3 (%)	20 (74.1)
UICC Stage	
II (%)	7 (25.9)
III (%)	20 (74.1)
Tumor size	
<5 cm (%)	10 (37)
5–10 cm (%)	9 (33.3)
>10 cm (%)	8 (29.6)
Extent of resection	
Clear (R0)	26 (96.3)
Marginal involved (R1)	1 (3.7)

Table 2 Treatment regimen and adherence to protocol

Chemotherapy, *n* (%)	27 (100)
Cumulative ifosfamide dose	
Mean (standard deviation), g	35.3 (6.0)
Mean ifosfamide dose per cycle, g/m^2	4.96
Cumulative doxorubicin dose	
Mean (standard deviation), mg	536 (83)
Mean doxorubicin dose per cycle, mg/m^2	75.3
Intraoperative flap radiotherapy, *n* (%)	4 (14.8)
Radiotherapy, *n* (%)	27 (100)
Boost radiotherapy, *n* (%)	11 (40.7)
Mean dose (standard deviation), Gy	10,0 (2.4)
Total radiotherapy dose	
Mean dose (standard deviation), Gy	58,4 (5.5)
Adherence to protocol	
Yes	25
No	2
Reasons for non-adherence:	
Recurrent disease during treatment	1
Infection	1
Time from surgery to start of cycle 1 of chemotherapy	
Median (range), days	30 (13–64)
Time from cycle 1 of chemotherapy to start of radiotherapy	
Median (range), days	48 (30–123)
Time from start of radiotherapy to start of cycle 3 of chemotherapy	
Median (range), days	58.5 (45–95)
Time from surgery to last chemotherapy (cycle 4)	
Median (range), days	170 (123–242)
Follow-up, *n* (%)	24 (89)
Median follow-up (range), months	57 (32–117)
Loss to Follow-up, *n* (%)	3 (11)

patients had high-risk STS with aggressive G3 tumors (20 out of 27) and UICC stage III (20/27).

Surgery

All patients underwent radical definitive surgery. One patient with retroperitoneal STS was considered R0 by histological analysis, but later had a recurrence of disease at the initial tumor site. One patient with STS located at the neck also underwent a planned radical surgery. However, detailed histopathological analysis revealed involvement of the resection margins and the patient had a recurrence 15 months after surgery (i.e., 11 months after end of chemotherapy). Of the 25 patients with STS of the extremities all underwent limb-sparing surgery and none required amputation.

Adherence to protocol and feasibility

The cumulative ifosfamide and doxorubicin doses are shown in Table 2. When calculated per cycle, the mean administered ifosfamide and doxorubin doses are close to the per-protocol doses of 5 g/m^2 and 75 mg/m^2, respectively. One patient received only cycles 1 and 2 of chemotherapy and was withdrawn from further chemotherapy due to repeated infections. Radiotherapy was applied as per protocol in all patients.

We analyzed the time (in days) between individual treatment modalities (Fig. 1), as these time frames allow to assess the feasibility of the treatment concept. The median time between surgery, chemotherapy start (cycle 1), radiotherapy and chemotherapy continuation (cycle 3) is presented in Table 2. As expected the time between modalities varied from patient to patient, with a median duration within the expected range (Table 2).

Chemotherapy and toxicity

Weekly blood counts and biochemistry analysis during the chemotherapy phase revealed that most patients had only

Table 3 Treatment-related toxicities

Included patients, *n* (%)	27 (100)
Hematological, CTC grade	
Anemia (hemoglobin)	
Grade 1, *n* (%)	4 (14.8)
Grade 2, *n* (%)	13 (48.1)
Grade 3, *n* (%)	1 (3.7)
Leukopenia	
Grade 1, *n* (%)	8 (29.6)
Grade 2, *n* (%)	5 (18.5)
Grade 3, *n* (%)	1 (3.7)
Grade 4, *n* (%)	1 (3.7)
Thrombocytopenia	
Grade 1, *n* (%)	1 (3.7)
Nausea and vomiting, CTC grade	
Grade 1, *n* (%)	3 (11.1)
Grade 2, *n* (%)	11 (40.7)
Grade 3, *n* (%)	1 (3.7)
Radiation-related acute toxicity, RTOG grade	
Skin	
Grade 1, *n* (%)	9 (33.3)
Grade 2, *n* (%)	11 (40.7)
Joint, grade 2, *n* (%)	1 (3.7)
Bone, grade 2, *n* (%)	1 (3.7)

minor or moderate hematological toxicity, with the exception of one patient who had grade 3 anemia and thrombocytopenia, as well as an episode of grade 4 neutropenia. One patient only received cycle 1 and 2 of chemotherapy because of repeated infections. Despite antiemetic therapy, 40% of patients experienced grade 2 nausea and vomiting, with one patient showing grade 3 nausea and vomiting (Table 3).

The administered mean dose of ifosfamide and of doxorubicin did not differ significantly from the per-protocol dose, indicating that chemotherapy-related toxicity did not require dose reductions. One patient was diagnosed with stomach cancer 7 years after diagnosis and adjuvant chemoradiation.

Furthermore, the feasibility analysis included measurements of time between surgery, chemotherapy start, radiotherapy, chemotherapy continuation as these time frames allow to judge how stringently the treatment plan can be applied.

Radiotherapy and toxicity

After radiotherapy and follow-up, patients were examined and interviewed for radiation-related acute toxicity of the skin, joint and bone (Table 3). The most frequent observed was toxicity of the skin, while one patient had grade 2 joint toxicity and one patient had grade 2 bone toxicity. No chronic radiation-related toxicity was recorded.

Outcome

After a mean follow-up of 57 months (range 32–117 months) and a loss to follow-up of 11% (3/27), the data was analyzed for local, distant and overall recurrence-free interval as well as overall survival for all patients as well as those with STS of the extremities (25/27). The 2- and 5-year local recurrence-free interval (RFI) was 88.9 and 84.8%, respectively, while the local RFI of STS of the extremities was 96 and 91.6%, respectively. The 2- and 5-year distant RFI was 85.2 and 80.7%, respectively, while distant RFI of STS of the extremities was 84.0 and 79.3%, respectively. The 2- and 5-year overall RFI was 74.1 and 65.9%, respectively, while overall RFI of STS of the extremities was 80 and 71.3%, respectively. The Kaplan–Meyer curves for local, distant and overall RFI are presented in Fig. 2.

By intent-to treat analysis, the overall survival (OS) at 2 years was 92.6% and at 5 years was 80%, while the OS for STS of the extremities at 2 and 5 years was 92 and 82.8%, respectively. The Kaplan–Meyer curves for OS and OS for STS of the extremities are presented in Fig. 3.

One patient was diagnosed with stomach cancer 7 years after STS and adjuvant chemoradiation. No other additional malignancies have been observed so far.

Discussion

Radical surgical resection is the only potentially curative therapy in STS. However, despite advances in the surgical management, a significant number of patients experience a relapse of disease. For this reason, several clinical trials have investigated the impact of adjuvant therapy to reduce the risk of both local and distant relapse risk.

Adjuvant radiation therapy is generally recommended for better local disease control and prevention of local recurrence for patients with high-grade resected STS of the extremities, retroperitoneum, trunk or head and neck region. However, a significant survival benefit has not been demonstrated. While local recurrence can potentially be rescued to achieve a 2nd complete remission, treatment options for patients with recurrence at distant sites are often merely palliative.

In order to prevent relapse at distant sites, numerous clinical trials have been undertaken in the past 30 years. Randomized clinical trials until the mid-1990s compared doxorubicin monotherapy (or in combination with dacarbazine) versus surgery alone, with the majority showing no

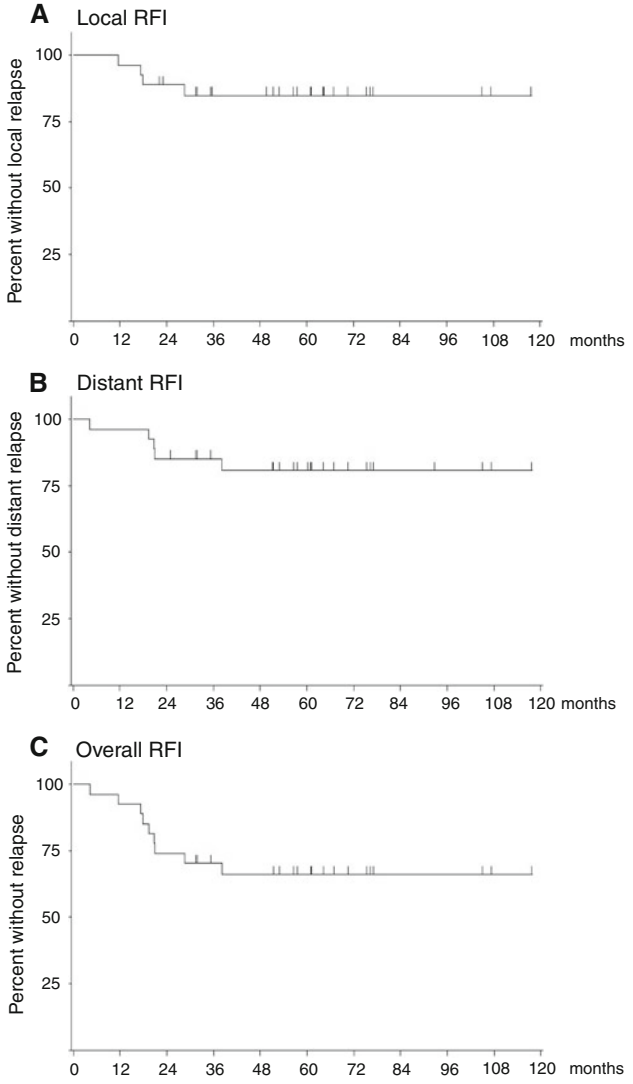

Fig. 2 Recurrence-free interval (RFI). **a** Local RFI. **b** Distant RFI. **c** Overall RFI. Data shown for all patients ($n = 27$)

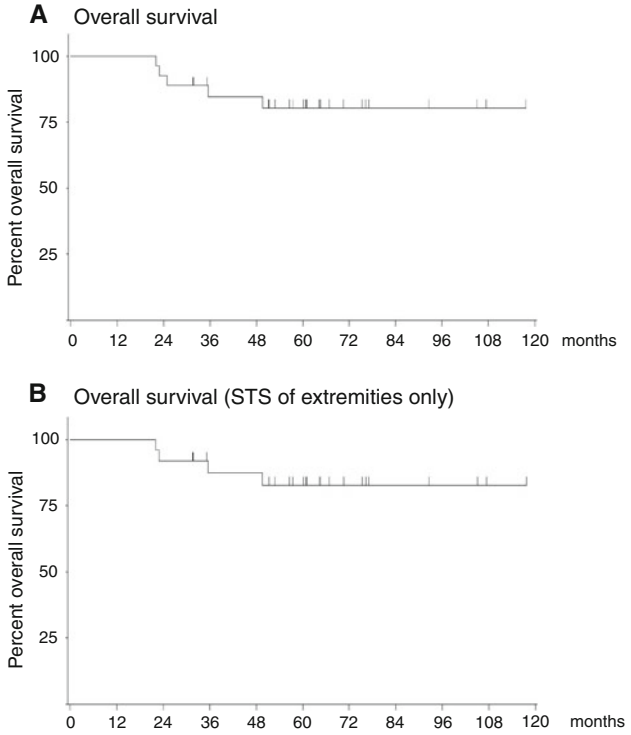

Fig. 3 Overall survival. **a** Overall survival of all patients ($n = 27$). **b** Overall survival of patients with STS of the extremities ($n = 25$)

difference in outcome in the treated groups (reviewed in [7]). However, a quantitative meta-analysis of over 1,500 patients from 14 randomized trials found a significant improvement of the relapse-free survival in patients with STS with doxorubicin-based chemotherapy but failed to demonstrate a significant difference in the overall survival [4]. Data from a large cohort analysis suggests that clinical benefits of doxorubicin-based adjuvant chemotherapy is not sustained beyond 1 year [8]. Later clinical trials have added ifosfamide to increase efficacy of anthracyclin-based chemotherapies in the adjuvant setting of resected STS, with evidence of a survival benefit [9–11]. In contrast, preliminary data (presented at ASCO 2007) from a large randomized EORTC trial [12] as well as a pooled analysis from two EORTC trials presented at ASCO 2008 [13] failed to show a survival advantage in the chemotherapy groups, but the final results have not yet been reported.

Finally, a recent updated meta-analysis (covering 1,953 patients from 18 trials) confirmed the findings of the 1997 meta-analysis [4] and found an important survival benefit in patients that received adjuvant doxorubicin in combination ifosfamide [5]. Specifically, the odds ratios (OR) for local recurrence was 0.73 (95% confidence interval [CI] 0.56–0.94; $P = 0.02$) in favor of chemotherapy. For distant and overall recurrence, the OR was 0.67 (95% CI 0.56–0.82; $P = 0.0001$) in favor of chemotherapy. In terms of survival, doxorubicin alone had an OR of 0.84 (95% CI, 0.68–1.03; $P = 0.09$), which was not statistically significant. However, the OR for doxorubicin combined with ifosfamide was 0.56 (95% CI, 0.36–0.85; $P = 0.01$) in favor of chemotherapy [5]. The absolute risk reduction for doxorubicin in combination with ifosfamide was 11% (30% vs. 41% risk of death) [5]. Because this modest survival advantage in favor of adjuvant chemotherapy has to be weighed against potential toxicity, ESMO guidelines [14] as well as NCCN guidelines (Version I. 2011, available at www.nccn.org) recommend adjuvant chemotherapy as part of a shared decision-making on an individual patient basis.

Importantly, the optimal scheduling of adjuvant chemotherapy and radiation has not been established. With the aim to particularly reduce the risk of distant recurrence while preventing local relapse, we undertook a phase II trial with adjuvant chemotherapy administered shortly after

surgery and radiation therapy "sandwiched" between chemotherapy cycles 2 and 3, and we evaluated feasibility, toxicity and efficacy. This sequence of treatment modalities has not been previously reported. For chemotherapy, we chose a combination of doxorubicin and ifosfamide, as these remain the two most active cytotoxic drugs in STS.

Baseline characteristics (Table 1) were essentially similar to those from other adjuvant trials [4, 5, 9]. Further analysis showed that this treatment sequence was feasible with manageable toxicity. The acute chemotherapy-related toxicity was mostly transient hemato-toxicity, and was found to be of similar extent when compared to other adjuvant trials [9]. As one patient was diagnosed with stomach cancer 7 years after diagnosis of STS it can be speculated whether this is a secondary malignancy following chemoradiation. With a median follow-up of almost 5 years no other long-term toxicity was observed, although it may be too early to observe secondary malignancies.

In the 1997, meta-analysis almost all recurrences occurred within the first 5 years, with hardly any recurrences occurring thereafter [4]. The local RFI at 5 years in our trial (84.8%) was very comparable to the data reported from the meta-analysis at 10 years (81%). In contrast, distant and overall recurrence was 80.7 and 71.3% in our trial, compared to 79 and 55% in the meta-analysis [4]. Besides potential differences in the risk profile of the studied patient population, the addition of ifosfamide to doxorubicin may explain the improved overall RFI observed in our trial. When comparing our data to the results from the Italian Randomized Cooperative Trial [9], the overall disease-free survival was only 50% at 4 years in the chemotherapy arm. Furthermore, at the time of publication, the curves had not reached a plateau [9]. As the level of distant metastases was equal in both the observation and the chemotherapy arm, it remained unclear in the Italian trial as how to interpret the significant differences between chemotherapy and observation arm [9].

The recurrence of disease in our trial was either local or distal and occurred within 3 years of diagnosis; simultaneous local and distant recurrence was not observed in any of the patients of this trial. Importantly, 3 of 4 local recurrences were resectable and patients are in continued 2nd complete remission (Table 4). In contrast, 4 of 5 patients with distant recurrences died due to progressive disease, underscoring the need for effective adjuvant treatment in prevention of distant recurrence.

The multidisciplinary team approach of our trial demonstrated that the trimodality treatment was feasible with acceptable toxicity. Given the limited number of patients in this non-randomized trial, the presented efficacy data should be cautiously interpreted but appears to provide a favorable long-term survival with low distant recurrence of disease. Importantly, our trial included patients with tumors <5 cm in size, which may have contributed to the excellent long-term survival. Today, most protocols recommend adjuvant chemotherapy only for patients with large (>8 cm) high-grade resected STS. Larger randomized phase III trials are clearly warranted to assess the value of adjuvant anthracyclines/ifosfamide and "sandwiched" radiation schedules in STS. Furthermore, issues of quality of life, fertility and measurements of long-term toxicity including secondary malignancies remain to be answered.

Table 4 Outcome

Included patients, *n* (%)	27 (100)
First complete remission, *n* (%)	18 (66.7)
Recurrent disease, *n* (%)	9 (33.3)
Dead, *n* (%)	5 (18.5)
After local recurrence, *n* (%)	1 (3.7) *
After distant recurrence, *n* (%)	4 (14.8)
Second complete remission, *n* (%)	4 (14.8)
After local recurrence, *n* (%)	3 (11)
After distant recurrence, *n* (%)	1 (3.7)
Alive with recurrence, *n* (%)	0 (0)

* Patient with STS of the trunk

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