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Original Research

Adjuvant chemotherapy and postoperative radiotherapy in high-risk soft tissue sarcoma patients defined by biological risk factors—A Scandinavian Sarcoma Group study (SSG XX)☆

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Soft tissue sarcoma;
Adjuvant treatment;
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Vascular invasion;
Growth pattern;
Tumour size;
Necrosis;
Survival

Abstract ***Purpose:*** To investigate the outcome following adjuvant doxorubicin and ifosfamide in a prospective non-randomised study based on a soft tissue sarcoma (STS) patient subgroup defined by specific morphological characteristics previously shown to be at a high-risk of metastatic relapse. The expected 5-year cumulative incidence of metastases in patients with this risk profile has previously been reported to be about 50% without adjuvant chemotherapy.

Methods: High-risk STS was defined as high-grade morphology (according to the Fédération Nationale des Centres de Lutte Contre le Cancer [FNCLCC] grade II–III) and either vascular invasion or at least two of the following criteria: tumour size ≥8.0 cm, infiltrative growth and necrosis. Six cycles of doxorubicin (60 mg/m^2) and ifosfamide (6 g/m^2) were given. Postoperative accelerated radiotherapy was applied and scheduled between cycles 3 and 4.

Results: For the 150 eligible patients, median follow-up time for metastases-free survival was 3.9 years (range 0.2–8.7). Five-year metastases-free survival (MFS) was 70.4% (95% confidence interval [CI]: 63.1–78.4) with a local recurrence rate of 14.0% (95% CI: 7.8–20.2). For overall survival (OS), the median follow-up time was 4.4 years (range: 0.2–8.7). The five-year OS was 76.1% (95% CI: 68.8–84.2). Tumour size, deep location and reduced dose intensity (<80%) had a negative impact on survival. Toxicity was moderate with no treatment-related death.

Conclusions: A benefit of adjuvant chemotherapy, compared to similar historical control groups, was demonstrated in STS patients with defined poor prognostic factors. Vascular invasion, tumour size, growth pattern and necrosis may identify patients in need of adjuvant chemotherapy.

1. Introduction

Adjuvant chemotherapy is not a standard treatment for soft tissue sarcoma (STS), and clinical practice guidelines are vague in their recommendations in this regard [1,2]. Furthermore, in STS, there is no consensus on which prognostic factors that may identify patients benefiting from adjuvant chemotherapy.

Outcomes of the former adjuvant protocol from the Scandinavian Sarcoma Group (SSG) conducted in high-risk STS, SSG XIII, showed that 5-year metastases-free (MFS) and overall survival (OS) were 59% and 68%, respectively [3]. In that study, classification of a high-risk STS was based on tumour size, vascular invasion and tumour necrosis [4–6]. In the current phase II non-randomised study (SSG XX), peripheral tumour growth was added as a risk factor [7]. The key inclusion criteria were either vascular invasion or presence of at least two of the three risk factors: size ≥8.0 cm, infiltrating peripheral growth pattern and necrosis. High-risk STS, as defined by this system (SING), had a five-year cumulative incidence of metastases of 0.51 (95% confidence interval [CI]: 0.41–0.60) as shown by Engellau *et al.* [7,8]. In SSG XIII, low chemotherapy dose intensity had a negative impact effect on both MFS and OS [3]. In SSG XX, the doses of doxorubicin and ifosfamide were increased by 20%. This publication reports data on MFS and OS with a focus on the impact of chemotherapy.

2. Methods

2.1. Criteria for inclusion

The main eligibility criteria were ages ≥18 to ≤75 years, World Health Organization (WHO) performance status ≤ 1, high-risk primary STS located in the extremities or trunk wall and surgery with an R0 or R1 excision. High-risk tumours were defined as high-grade (grade III or IV on a 4-grade scale) with risk factors as previously described, all defined microscopically by the pathologist on the surgical specimen [9].

The SSG Pathology Reference Group reviewed the morphology in all cases, according to WHO classification and malignancy grade with the FNCLCC system [10–12]. Vascular invasion and infiltrative peripheral tumour growth pattern were also reviewed. The tumour size was measured by the local pathologist. Tumour depth was defined in relation to the deep fascia.

The following histotypes were excluded: extraskeletal osteosarcoma and chondrosarcoma, Ewing's sarcoma, rhabdomyosarcoma, Kaposi sarcoma, clear cell sarcoma, alveolar soft part sarcoma, epithelioid sarcoma and radiation-induced sarcoma.

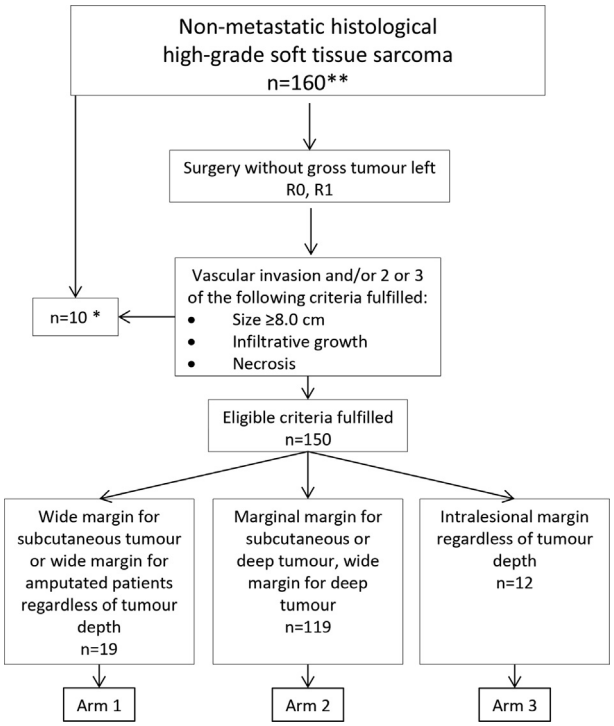

Fig. 1. **Study population**. * Three patients did not have STS, two had low-grade STS, one had a recurrent STS and one had heart disease and could not have chemotherapy. In three patients, the microscopic eligibility criteria were not fulfilled.**According to the primary pathology report. The 150 eligible patients were allocated to treatment arm 1, arm 2 or arm 3, depending on tumour depth and pathological/surgical margins.

The patients were allocated into three treatment groups depending on tumour depth and pathological/surgical margins: arm 1, arm 2 and arm 3 (Fig. 1). Investigations before, during treatment and in follow-up visits are presented in Appendix A. The full protocol is available on the SSG website [13]. The SSG XX protocol also had a separate arm devoted to few patients with locally advanced STS considered to have an obvious risk for intralesional surgery. They were given both preoperative chemotherapy and radiotherapy, but outcomes are beyond the scope of the current article and will be reported separately.

2.2. Treatment

All patients underwent surgery at a sarcoma centre. If the primary surgery was open biopsy only or intralesional surgery, the patient was considered for a second operation at a sarcoma centre aiming for at least a marginal margin. The classification of margins, according to the SSG guidelines (SSG VII: 4), was determined by the surgeon and pathologist at the sarcoma centre [13].

An outline of the chemotherapy and radiotherapy regimen is presented in Fig. 2. Doxorubicin 60 mg/m^2 and ifosfamide 6 g/m^2 were given in six cycles with a 3-week interval for patients <70 years of age and with doses of 50/5 from age 70 years and ≤75 years. Details of chemotherapy and granulocyte colony-stimulating factor (G-CSF) are provided in Appendix B. Accelerated and hyperfractionated radiotherapy was given in arm 2 and arm 3 (1.8 Gy twice daily to 36 Gy/45 Gy), depending on margin status (Fig. 2).

2.3. End-points

The primary end-point was MFS, calculated from the date of final surgery until the first of the events,

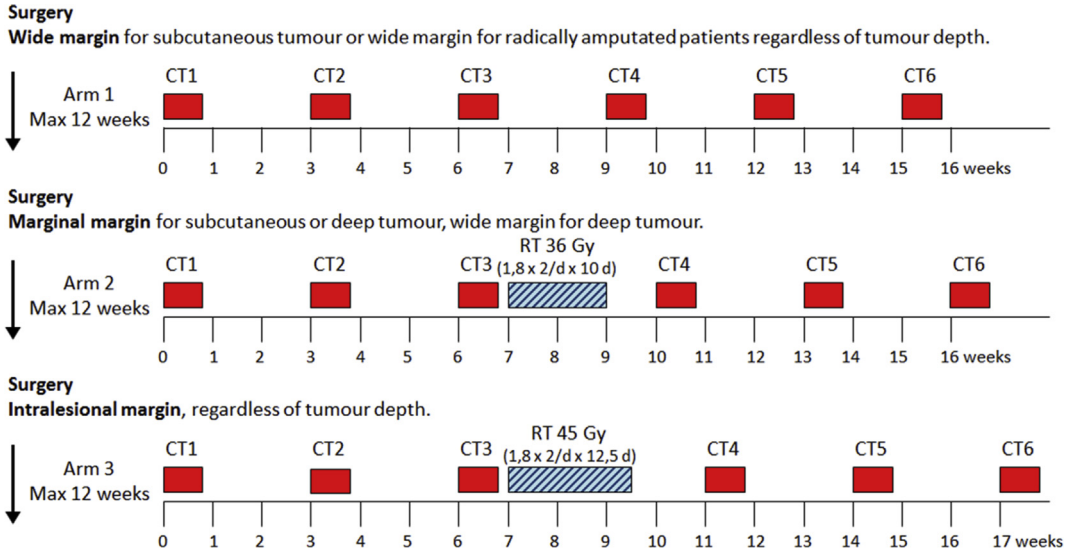

Fig. 2. **Treatment schedule**. Chemotherapy (CT): ≥18 and <70 years of age. Day 1: doxorubicin 60 mg/m^2, 4-h infusion (IV); day 1, 2 and 3: ifosfamide 2 g/m^2/day as 2-h infusion, dose per cycle 6 g/m^2 (with an equal dose of 2-mercaptoethane sulfonate sodium [MESNA]). ≥70 and ≤75 years: doxorubicin 50 mg/m^2 and ifosfamide 5 g/m^2 (given as above). Granulocyte colony-stimulating factor was given routinely after each cycle (Appendix B).

metastases or death of any cause. OS was a secondary end-point, defined as the time from final surgery until death of any cause. The secondary end-points also included local recurrence defined as the time from final surgery to local relapse, considering death as a competing event, and the proportions of wide, marginal and intralesional histopathological margins after final surgery. The occurrence of second malignancies is reported in the current publication.

2.4. Statistical analyses

Descriptive analyses were used. In total, 150 eligible patients were included in the analyses. Analyses of treatment end-points and chemotherapy toxicity were performed on all patients who had started chemotherapy.

Survival was estimated with Kaplan-Meier survival curves and differences tested for by the log rank test. Cox regression analyses, both univariate and multivariate, were used to study sizes of relative risks.

Factors reported to have a prognostic effect on survival in published studies, in addition to sex, were included. When performing the univariate and multivariate analyses, we chose 10 cm as the cut-off value for tumour size because most of the tumours were ≥8 cm (in 92 patients) and that value being an eligibility criterion. To choose a somewhat larger cut-off, we had a better chance to evaluate the importance of size, as a continuous variable.

A p-value of <0.05 was considered statistically significant. The software used for statistical analyses was the R statistical package, version 3.4.3 [14].

Patients with no events were censored either at the last date of follow-up or at the pre-specified date of the end of study (30th June, 2016, 2 years after the last patient enrolment). Dose intensity was calculated using the method reported in our previous protocol [3,15].

2.5. Ethical considerations

Written informed consent was obtained from all patients. The study was approved by ethical committees and legal authorities in Norway and Sweden.

3. Results

3.1. Patients

The patients were enrolled from June 2007 until June 2014. A total of 160 patients were registered (Fig. 1). Following review, 150 patients fulfilled the inclusion criteria and were included in the three treatment arms (arm 1, arm 2 and arm 3) according to the tumour depth and resection margins. The patients, tumour characteristics and histological subtypes are shown in Table 1.

Table 1
Demographics and tumour characteristics of eligible patients.

Characteristics	Numbers (%)
Age at diagnoses (Y)	
Median	59
Range	18–75
Gender	
Male	80 (53%)
Female	70 (47%)
Tumour site	
Lower extremity (including gluteal and groin)	115 (77%)
Upper extremity (including shoulder)	22 (15%)
Trunk wall	13 (9%)
Location	
Subcutaneous	26 (17%)
Deep	124 (83%)
Tumour size (cm)	
Median	9.0
Range	6.6–12.0
Malignancy grade[a]	
II	61 (40%)
III	89 (60%)
Histopathological subtype	
Undifferentiated pleomorphic sarcoma (UPS)	52 (35%)
Liposarcoma	18 (12%)
Pleomorphic	10
Myxoid cell	5
Dedifferentiated	3
Leiomyosarcoma	19 (13%)
Synovial sarcoma	12 (8%)
Malignant peripheral nerve sheath tumour	10 (7%)
Myxofibrosarcoma	39 (26%)
Microscopy	
Necrosis in specimen	136 (91%)
Vascular invasion present	22 (15%)
Infiltrative growth pattern present	147 (98%)

[a] According to FNCLCC grading system.

3.2. Metastases-free survival (MFS)

The analyses presented are based on the follow-up data up to 2 years after the last patient enrolment, at which time the data base was locked according to the *a priori* analysis plan.

Median follow-up of patients in the analyses of the primary end-point (metastases-free survival) was 3.9 years (range 0.2–8.7) and for the secondary end-point (OS) 4.4 years (range 0.2–8.7).

Thirty-eight patients (25%) developed metastases with the first site of metastasis in the lung for 28, in bone for three, in other anatomical sites for seven patients.

The estimated MFS rate at 5 years for all 150 patients was 70.4% (95% CI: 63.1–78.4) (Fig. 3). Univariate and subsequent multivariate analyses showed that only tumour size, depth and dose intensity of chemotherapy were significantly associated with MFS (Table 2).

Age, tumour localisation and sex did not influence the development of metastases.

By also including the risk factors (vascular invasion and necrosis) in the eligibility algorithm, the outcome

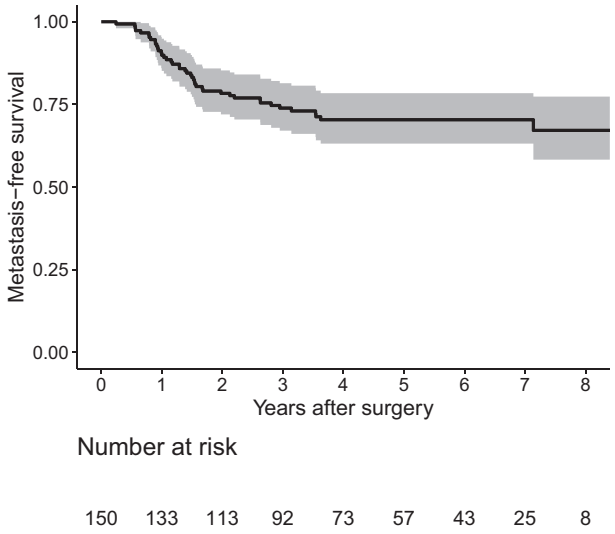

Fig. 3. Metastases-free survival (Kaplan-Meier Curve; % with 95% CI = confidence interval) of 150 high-risk soft tissue sarcoma patients with a median follow-up 3.9 years.

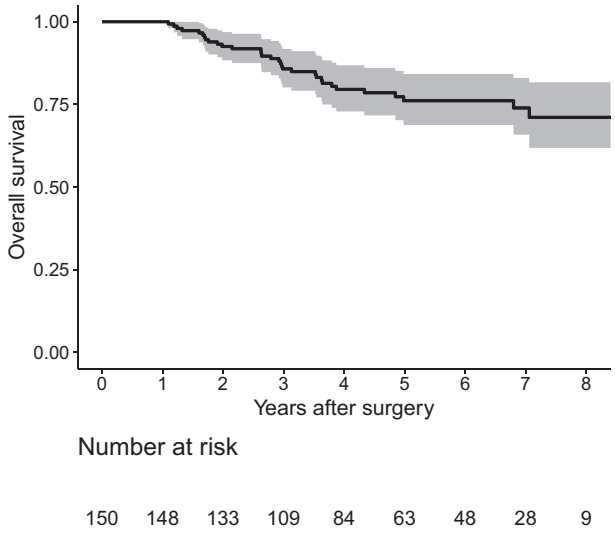

Fig. 4. Overall survival (Kaplan-Meier Curve; % with 95% CI = confidence interval) of 150 high-risk STS patients with a median follow-up 4.4 years.

of the multivariate analyses did not change. Infiltrative growth pattern was present in 147 of 150 patients and pushing growth only in three patients and could not be analysed in this subset of high-risk STS patients.

No significant difference in MFS was observed between histological subtypes (p = 0.110).

3.3. Local recurrence rate

The estimated local recurrence rate at 5 years for all 150 patients was 14.0% (95% CI: 7.8–20.2). Details of radiotherapy are beyond the scope of this publication and will be published later with focus on radiotherapy quality assurance, in-field versus outside portals location of recurrences, as well as the magnitude of late effects.

3.4. Overall survival (OS)

The estimated OS at 5 years for all 150 patients was 76.1% (95% CI: 68.8–84.2; Fig. 4).

Thirty-one patients died during follow-up, one from cardiac arrest (25 months after last chemotherapy cycle) and the remaining due to sarcoma.

In the univariate analysis for OS, tumour size and depth were of statistical significance, but in the subsequent multivariate analysis, only tumour depth retained borderline significance (Table 3).

3.5. Chemotherapy cycles and dose intensity

In total, 136 patients received all six cycles of chemotherapy, but not all with both drugs, and 144 got three or more cycles. Twenty-three patients did not receive one or more of chemotherapy cycles 2–6 with

Table 2
Potential prognostic factors for metastases-free survival.

Cox analysis of metastasis-free survival						
Factor		n	RR (univariate)	p-value (univariate)	RR (multivariate)	p-value (multivariate)
Age	<70 y	130	1	–	1	–
	≥70 y	20	0.969	0.947	0.689	0.464
Sex	Male	80	1	–	1	–
	Female	70	1.248	0.469	1.316	0.407
Tumour size	<10 cm	86	1	–	1	–
	≥10 cm	64	2.504	0.003	2.170	0.015
Tumour localisation	Other	35	1	–	1	–
	Lower extremity	115	1.731	0.184	1.500	0.338
Tumour depth	Subcutaneous	26	1	–	1	–
	Deep	124	5.158	0.024	4.348	0.044
Dose intensity	≥80%	129	1	–	1	–
	<80%	21	2.142	0.042	2.334	0.027

n = number of patients, RR = relative risk

Table 3
Potential prognostic factors for overall survival.

Cox analysis of overall survival						
Factors		n	RR (univariate)	p-value (univariate)	RR (multivariate)	p-value (multivariate)
Age	<70 y	130	1	–	1	–
	≥70 y	20	1.155	0.788	0.776	0.653
Sex	Male	80	1	–	1	–
	Female	70	1.612	0.180	1.639	0.202
Tumour size	<10 cm	86	1	–	1	–
	≥10 cm	64	2.381	0.018	1.937	0.077
Tumour localisation	Other	35	1	–	1	–
	Lower extremity	115	1.417	0.442	1.131	0.795
Tumour depth	Subcutaneous	26	1	–	1	–
	Deep	124	8.129	0.039	7.016	0.056
Dose intensity	≥80%	129	1	–	1	–
	<80%	21	1.745	0.220	1.768	0.215

n = number of patients, RR = relative risk

either ifosfamide and/or doxorubicin. Dose reduction or delay of chemotherapy was registered in 22 patients.

Dose intensity was analysed for doxorubicin and ifosfamide separately and combined. Twenty-one patients received less than 80% of combined dose intensity. Dose intensity reduction below 80% was associated with an increased risk of metastasis with a factor of 2.3 ($p = 0.027$; Table 2).

3.6. Chemotherapy toxicity

The chemotherapy toxicity was recorded according to Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Almost all patients experienced some adverse events (AEs) from chemotherapy, and the majority had at least one toxicity event grade III–IV (Table 4). One single case of each of the following serious AEs was documented: pulmonary embolism, syncope and severe diarrhoea. No treatment-related death was observed.

Table 4
Toxicity according to CTCAE score.

Toxicity	All CTCAE grades[a]	CTCAE grade 3–4[b]
	Number of patients	Number of patients
Neutropenia without fever	112	82
Neutropenia with fever	25	25
Thrombocytopenia	132	32
Anaemia	11	2
Urinary tract infection	7	0
Wound infection	8	2
Other infections, normal ANC	22	8
Mucositis/stomatitis	27	1
Nausea/vomiting	19	3
Fatigue	8	1
Thrombosis	7	6
Musculoskeletal pain	8	2
ALAT increased	37	0
CNS toxicity	14	0
Haematuria	11	0
Peripheral fluid retention	7	0

[a] All grades of toxicities encountered in at least five patients.
[b] Number of patients experiencing CTCAE grade III–IV.

Long-term cardiac and renal toxicity were measured by left ventricular ejection fraction (LVEF) and glomerular filtration rate (GFR), respectively, at several times during and after treatment. Renal toxicity was somewhat more frequent and had a lower tendency to recover than cardiac toxicity, but almost all toxicities were of grades I or II, according to the CTCAE criteria. Only one case each of grade III for cardiac (1 year after treatment) and renal toxicity (5 years after treatment) occurred.

More data of long-term toxicity are presented in Appendix C.

3.7. Second malignancies

Six patients had a second malignancy after a median observation period of 4 years (range 2–7): three with prostate cancer, one with follicular thyroid adenocarcinoma and two with breast cancer.

4. Discussion

This study explored the possible benefit of adjuvant chemotherapy in STS patients with defined poor prognostic factors. A 5-year cumulative incidence of metastases in patients with the same risk profile as in our cohort, but not treated with chemotherapy, was around 50% in a previous report [7]. By comparison, the estimated 5-year MFS in our study was 70%. The chemotherapy toxicity was modest, and the vast majority fulfilled all six planned chemotherapy cycles.

A low chemotherapy dose intensity was found to have a negative effect on MFS in our previous SSG XIII protocol [3]. Therefore, we increased the doses in the current SSG XX with an increased effort to maintain dose intensity. This strategy appeared to have a

significant and positive impact on MFS and further confirms the value of chemotherapy.

Previous clinical studies on adjuvant chemotherapy in STS have reported conflicting benefit [16–19]. A challenge is that the patient groups are too heterogeneous. A meta-analysis of 14 trials (doxorubicin alone or in combination with other drugs) demonstrated significantly reduced rates of local failures and distant metastasis and also improved survival in a later update [20,21].

However, in a pooled analysis of the two randomised European Organisation for Research and Treatment of Cancer (EORTC) trials (819 patients), adjuvant chemotherapy did not demonstrate any survival benefit [22,23]. In a randomised study by Frustaci *et al.* [24], a survival benefit at 4 years in patients treated with adjuvant epirubicin and ifosfamide was demonstrated. After a median follow-up of 7 years, the benefit of chemotherapy regarding OS rate lost its statistical significance [25].

The Italian and Spanish Sarcoma groups conducted a randomised study between three preoperative chemotherapy cycles only, compared with a more 'conventional arm' consisting of three preoperative cycles of epirubicin (120 mg/m^2) and ifosfamide (9 g/m^2) and two further cycles postoperatively. Five-year overall and recurrence-free survivals were about 70% and 60%, respectively, with no difference between the two groups [19]. The groups concluded that adjuvant chemotherapy may be omitted after three administered preoperative cycles. The inclusion criteria were deep-seated primary STS $\geq$5 cm or any size of locally recurrent STS. Hence, the results cannot be directly compared to our study cohort. It should also be noted that they reported histological subtypes to be significantly associated with different outcome, with leiomyosarcoma showing the worst outcome and undifferentiated pleomorphic sarcoma the best [26]. In our study, no difference was observed between the histological subgroups, but our groups were relatively small.

Furthermore, a recent trial investigated whether histotype-tailored neoadjuvant chemotherapy would improve the outcome compared to standard chemotherapy but showed that the latter was significantly better [27].

The local control rate of 86% observed in the present study was deemed satisfactory and in line with a figure stated in a recent review [28]. The accelerated and hyperfractionated radiotherapy interposed between chemotherapy cycles applied in the present study was also used in our former protocol, SSG XIII, with acceptable treatment-related morbidity [3].

The non-randomised design and the fairly low sample size may limit the interpretation of the results obtained in SSG XX. Study strengths were the prospective setting and the strict inclusion criteria concerning the morphology and tumour-biological characteristics assessed by the review pathologists, defined surgical approaches and that all patients were treated at sarcoma centres by experienced multidisciplinary teams.

We conclude that patients with STS and poor prognostic factors according to the SING system may benefit from adjuvant doxorubicin and ifosfamide with maintained dose intensity.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejca.2018.05.011.

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Conflict of interest statement

None declared.

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