



Preoperative radiotherapy with concomitant chemotherapy in extremity soft tissue sarcomas: long-term results of a single center

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Abstract

Purpose To assess oncological outcomes of patients receiving neoadjuvant radiochemotherapy (RCT) for soft tissue sarcoma (STS) of the extremities.

Methods Patients who were treated with preoperative radiotherapy and concomitant chemotherapy—3 cycles of mitomycin/doxorubicin/cisplatin (MAP) or 2–4 cycles of doxorubicin/cisplatin (AP)—followed by surgery were analyzed retrospectively. Survival rates were estimated, and prognostic factors were identified.

Results Between 1994 and 2017, a total of 108 patients were included. Median ages were 43 years and 51 years for patients receiving MAP and AP, respectively. The 5-year local relapse-free survival (LRFS), disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS) were 94.1, 63.6, 75.3, and 71.9%, respectively. In the multivariate analysis, significant predictors were identified as follows: de novo or R1/R2 resected tumor on admission before RCT ($p=0.017$; hazard ratio [HR] 0.112, 95% confidence interval [CI] 0.019–0.675) and R0 resection after RCT ($p=0.010$; HR 0.121, 95% CI 0.024–0.598) for LRFS; female gender ($p=0.042$; HR 0.569, 95% CI 0.330–0.979) and liposarcoma histology ($p=0.014$; HR 0.436, 95% CI 0.224–0.845) for DFS; liposarcoma histology ($p=0.003$; HR 0.114, 95% CI 0.027–0.478) and AP regimen ($p=0.017$; HR 0.371, 95% CI 0.165–0.836) for DSS; age ≤ 45 years ($p=0.043$; HR 0.537, 95% CI 0.294–0.980) and liposarcoma histology ($p=0.006$; HR 0.318, 95% CI 0.141–0.716) for OS, respectively.

Conclusion An increased risk for local failure seems to exist for patients with relapsed tumor on admission and having positive surgical margins after neoadjuvant RCT. Intensity of chemotherapy influenced DSS but not OS, which could be due to younger patients receiving MAP.

Keywords Extremities · Neoadjuvant radiochemotherapy · Doxorubicin/cisplatin · Mitomycin/doxorubicin/cisplatin · Second primary cancers

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Introduction

Soft tissue sarcomas (STS) are uncommon tumors having more than 50 histologically subtypes [1]. Approximately half of the STS are located in the extremities [2]. Leiomyosarcoma, undifferentiated pleomorphic sarcoma, and liposarcoma are the most common forms of STS in adults [3]. Tumor histologic grade was shown to be the most important prognostic factor and to be the best indicator of metastatic risk [4].

Mainstay of the STS treatment is surgery. Historically amputation was the standard surgery of STS located at the extremities; however, this brutal approach was replaced by limb-sparing surgery followed by postoperative radiotherapy (XRT) in the 1980s. Although postoperative XRT prevents loss of the limb, it requires irradiation of

a large volume of the extremity up to 60–70Gy and may potentially cause serious permanent late toxicity such as fibrosis [5, 6]. In the last two decades, preoperative XRT was used more commonly than postoperative XRT in the management of extremity STS. Preoperative XRT requires lower doses around 44–50Gy to a smaller volume [5–7]. A phase III trial comparing preoperative vs postoperative XRT showed that both methods provide similar tumor control; however, although the postoperative complication rate was higher with preoperative XRT, serious late effects were much lower compared to postoperative XRT [8].

Surgery and XRT provide good local control in high-grade STS; however, distant metastases to lungs, brain, and bones are common, and determine the survival. A trend towards improved overall survival (OS) was shown following the use of adjuvant chemotherapy (CHT) [9]. However, more improved survival data come from the phase 2 studies where preoperative XRT was combined with neoadjuvant CHT, but these were not randomized or multi-institutional studies [10, 11].

This study presents the retrospective data of a single center's patients with the diagnosis of extremity STS, who had received neoadjuvant radiochemotherapy (RCT) before surgery. Our institute is the reference center for sarcoma management and all sarcoma patients are evaluated by the weekly multidisciplinary sarcoma board which was shown to have a significant impact on treatment success [3].

Materials and methods

This study was approved by the institutional ethics committee.

Study population

Patients with biopsy-proven, nonmetastatic high-grade or large STS of the extremities who were treated with neoadjuvant RCT followed by limb-sparing surgery from 1994–2017 were retrospectively analyzed. Patient and tumor characteristics including age, date of diagnosis, imaging studies, histology, tumor size and location as well as treatment parameters including surgery, XRT and CHT details were extracted from the patient charts. Treatment response, tumor progression, and follow-up notes were carefully recorded.

Neoadjuvant treatment protocol

The treatment schedule for each patient was decided at the weekly multidisciplinary bone and soft tissue sarcoma meetings. We recommended neoadjuvant RCT for most patients with high-grade STS and a few patients with low-

grade STS. Indications were deep-seated grade 2–3 soft tissue sarcoma of the extremities which were larger than 5 cm. Principally all patients fulfilling these criteria were considered for neoadjuvant RCT; however, exclusions included superficial tumors which were amenable to safe resection with wide margins, patients medically unfit for CHT, and patients unsuitable for long treatment period. Although high-grade histology was the main selection criteria, there were few selected patients with low-grade STS in whom we decided to use RCT. These were the cases for whom obtaining negative surgical margin or preserving extremity function could be difficult without RCT due to the size and location of the tumor.

Radiotherapy

XRT was administered to 50.4Gy in 28 fractions. The tumor-bearing extremity was immobilized using vacuum bags, and proper patient positioning was provided. Magnetic resonance imaging (MRI) was ordered to define the size, exact location, and borders of the tumor prior to XRT planning. Until 2004, two-dimensional XRT planning was used—usually two oblique portals with wedges, to include macroscopic tumor plus 5 cm margins longitudinally and 2 cm margins radially. Extra care was given for not to irradiate the whole circumference of the limb. From 2004, a three-dimensional conformal XRT technique was used in all patients. Clinical target volume (CTV) included gross tumor volume plus 3–4 cm margins longitudinally and 1–1.5 cm margins radially. These margins were modified to allow lymphatic flow and not to cross intact bone and fascial barriers. Planning target volume was created by adding 0.5–1 cm uniform expansion margin to the CTV.

An additional dose of 18Gy was given after surgery to those patients with R1 resection, or those with very close surgical margins (1–2 mm) with the decision of the multidisciplinary tumor board if postoperative wound healing was achieved.

Chemotherapy

Doxorubicin-based CHT was administered concomitantly with XRT, at the first irradiation day (D1), and 3rd week of XRT (D22). The third cycle was given at D43 prior to surgery. From 1995–2007, 3 cycles of MAP (mitomycin 8 mg/m², D1–22; doxorubicin 40 mg/m², D1–22–43; cisplatin 60 mg/m², D1–22–43), which was inspired by the phase 3 trial, were used [12]. From 2007–2017, mitomycin was not used anymore and patients received 4 cycles of AP (doxorubicin 60–75 mg/m²; cisplatin 60–75 mg/m²). The first CHT cycle was 3 weeks before the first day of XRT and the other 3 cycles were given at D1–22–43 (cisplatin was only given at D1 and D22). Later, intensity of this schedule was reduced

to 2 cycles (D1–22) due to high toxicity observed with 4 cycles of AP. Overall 63 patients received MAP and 45 received AP. The total median drug doses were as follows: mitomycin 16 mg/m², doxorubicin 120 mg/m² and cisplatin 180 mg/m² for MAP regimen, and doxorubicin 225 mg/m² and cisplatin 150 mg/m² for patients for AP regimen.

Additional CHT cycles were given to 25 patients post-operatively who had large and/or high-grade tumors at presentation.

Surgery

One month after the completion of XRT, tumor response was evaluated with dynamic contrast-enhanced MRI scan, and limb-sparing surgery was performed in 2–3 weeks. The goal of the surgery was to remove the tumor completely with wide margins to provide R0 resection without compromising the extremity function.

Follow-up procedure

During follow-up, physical examination, MRI of the treated extremity, and chest X-ray or chest computed tomography were performed. Follow-up was scheduled every 3 months for the first 2 years, every 6 months between the third and fifth year, and then annually.

Outcomes

Outcome measures were as follows: local relapse-free survival (LRFS), metastasis-free survival (MFS), disease-free survival (DFS), disease-specific survival (DSS), and OS. All times to event were measured from the first day of the treatment and patients without an event were censored at the last contact date known alive for all survival metrics. Event was defined for each survival metric as follows: LRFS, recurrence at local site confirmed by either pathology or imaging; MFS, distant metastasis, or death from any cause, whichever occurred first; DFS, local recurrence, regional lymph node recurrence, distant metastasis, second malignancy, or death from any cause, whichever occurred first; DSS, dying of cause related to sarcoma; OS, death from any cause. Patients who died of unrelated causes were censored for DSS. Patients were also censored at the date of death if no prior local recurrence was observed when calculating LRFS.

Toxicities were scored using the common toxicity criteria for adverse events (CTCAE) version 5.0 [13].

Statistics

The data processing and statistical analysis were performed with statistical software package SPSS Statistics for Win-

dows (version 22.0, IBM Corp., Armonk, NY, USA). Patient or treatment related characteristics including age (≤ 45 years vs > 45 years), gender, status on admission (de novo or R1/R2 resected tumor vs relapsed tumor after previous surgery), size of tumor (T1&T2 vs T3&T4), histology (liposarcoma vs non-liposarcoma), tumor location (upper extremity vs lower extremity), neoadjuvant CHT (MAP vs AP), surgical resection after neoadjuvant RCT (R0 vs R1), adjuvant XRT (present vs not present), and adjuvant CHT (present vs not present) were evaluated as categorical data. Time to event data was calculated using the Kaplan–Meier method. For time-to-event endpoints, a univariate test comparing categorical variables was conducted using a log-rank test along with Kaplan–Meier estimates. Variables statistically significant on the log rank method were subsequently entered into Cox proportional hazards regression model for multivariate analysis. Hazard ratio (HR) and 95% confidence interval (CI) were calculated.

Toxicities were compared among MAP and AP applied groups with the use of Fisher's exact test and Yate's continuity correction chi-square (χ^2) test.

Two-sided *p*-values were reported, and *p* < 0.05 was considered statistically significant.

Results

Patient and treatment characteristics

A total of 108 patients were included in the study. Median age was 45 years (43 years for patients receiving MAP and 51 years for patients receiving AP), and 58 patients (54%) were male and 50 (46%) were female. Tumor was located at lower extremity in 81% of patients. Median size of the tumors was 10.3 cm. Undifferentiated pleomorphic sarcoma (*n* = 41, 38%) and liposarcoma (*n* = 31, 29%) were the most common histologies. Most patients (76%) had no previous surgery, whereas one out of every four patients had previous resections with positive margins (R1–R2), or recurrence after previous surgery. Data regarding patient and treatment-related characteristics are presented in Table 1.

Tumor control and limb preservation

Limb preservation was possible in 103 patients (95.4%). Primary closure or skin grafts were mostly sufficient for wound closure; however, pedicled flaps and rarely free flaps were required. Five (4.6%) patients were amputated due to insufficient tumor shrinkage not allowing R0 or R1 resection despite neoadjuvant RCT. Margins were clear (R0) in 91 (88.4%) of the resections and microscopic residue left (R1) in 12 (11.6%). There were no patients with gross tumor left (R2) after surgery. In addition, 2 patients under-

Table 1 Patient and treatment-related characteristics (*n* = 108)

Characteristics	<i>n</i> (%)
Age, years	
Median (range)	45 (17–72)
Gender	
Female	50 (46.3)
Male	58 (53.7)
Status on admission	
No previous surgery	82 (75.9)
Previous surgery, R1	1 (0.9)
Previous surgery, R2	16 (14.8)
Relapsed after previous surgery	9 (8.3)
Tumor size (cm) ^a	
Median (range)	10.3 (0–30)
Tumor size classification ^{b,c}	
T1	9 (9.3)
T2	39 (40.2)
T3	25 (25.8)
T4	24 (24.7)
Histology	
Undifferentiated pleomorphic sarcoma	41 (38.0)
Liposarcoma	31 (28.7)
Well differentiated	2
Myxoid	18
Round cell	5
Pleomorphic	2
Not known	4
Others	36 (33.3)
Synovial sarcoma	18
Malignant peripheral nerve sheath tumor	8
Leiomyosarcoma	6
Angiosarcoma	2
Spindle cell sarcoma	1
Malignant mesenchymal tumor	1
Tumor location	
Upper extremity	21 (19.4)
Upper limb	14
Shoulder girdle	7
Lower extremity	87 (80.6)
Lower limb	81
Pelvic girdle	6
Neoadjuvant CHT	
Mitomycin, doxorubicin, cisplatin	63 (58.3)
Doxorubicin, cisplatin	45 (41.7)
Surgery type after neoadjuvant RCT	
Limb-sparing surgery	103 (95.4)
Amputation	5 (4.6)
Surgical resection after neoadjuvant RCT	
R0	96 (88.9)
R1	12 (11.1)
Postoperative XRT boost	
Present	19 (17.6)
Not present	89 (82.4)

Table 1 (Continued)

Characteristics	<i>n</i> (%)
Postoperative CHT	
Present	25 (23.1)
Not present	83 (76.9)

RCT Radiochemotherapy, XRT Radiotherapy, CHT Chemotherapy

^aAccording to the magnetic resonance imaging of the tumor before the initiation of neoadjuvant radiochemotherapy

^bAmerican Joint Committee on Cancer Staging System for soft tissue sarcoma of the trunk and extremities (8th ed, 2017) was used for determination of tumor size classification of TNM

^cTumor size was not known for 10 patients, and 1 patient had R1 resection before neoadjuvant radiochemotherapy so those were not included in tumor size classification. Thus, valid percents were estimated

went amputation during the follow-up period: one was due to postoperative complication and the other was due to local recurrence. Overall extremity preservation rate was 93.5%.

Recurrence and survival

The mean follow-up time was 114 months (range 5–311 months). Eleven of 108 (10.2%) patients were lost to follow-up; however, we were able to follow these 11 patients at least 3 years (median 102 months, range 35–206 months).

Eight (7.4%) patients developed local recurrence with a median time of 16 months (range 8–87 months). LRFS was 94.1% at 5 years and 91.2% at 10 years (Fig. 1a). Distant metastases occurred in 38 (35.2%) patients with a median time of 19 months (range 5–155 months). Lung metastases were observed in 31 patients. Other metastatic sites were soft tissue in 7 patients, bones in 4 patients, brain in 3 patients, and adrenal gland in 1 patient. MFS was 67.1% and DFS was 63.6% at 5 years; 58.3% and 51.4% at 10 years, respectively (Fig. 1b,c). In all, 11 (10%) patients developed 13 second primary cancers during follow-up (Table 2).

A total of 32 (29.6%) patients died due to tumor progression and 12 (11.1%) patients died of other causes and 2 (1.9%) patients died of second primary cancer. DSS and OS were 75.3–71.9% at 5 years and 70.8–64.2% at 10 years, respectively (Fig. 1d,e).

The univariate and multivariate associations of patient and tumor characteristics with LRFS, MFS, DFS, DSS, and OS are listed in Tables 3 and 4, respectively.

LRFS was improved for patients whom were treated for de novo or R1/2 resected tumor (tumor status on admission) compared to patients whom were treated for a relapsed tumor following a previous surgery ($p=0.030$ [5-year LRFS 95.7% vs 75.0%]) and for patients applied R0 resection compared to patients applied R1 resection after neoadjuvant RCT ($p=0.010$ [5-year LRFS 96.6% vs 74.1%]). Also in

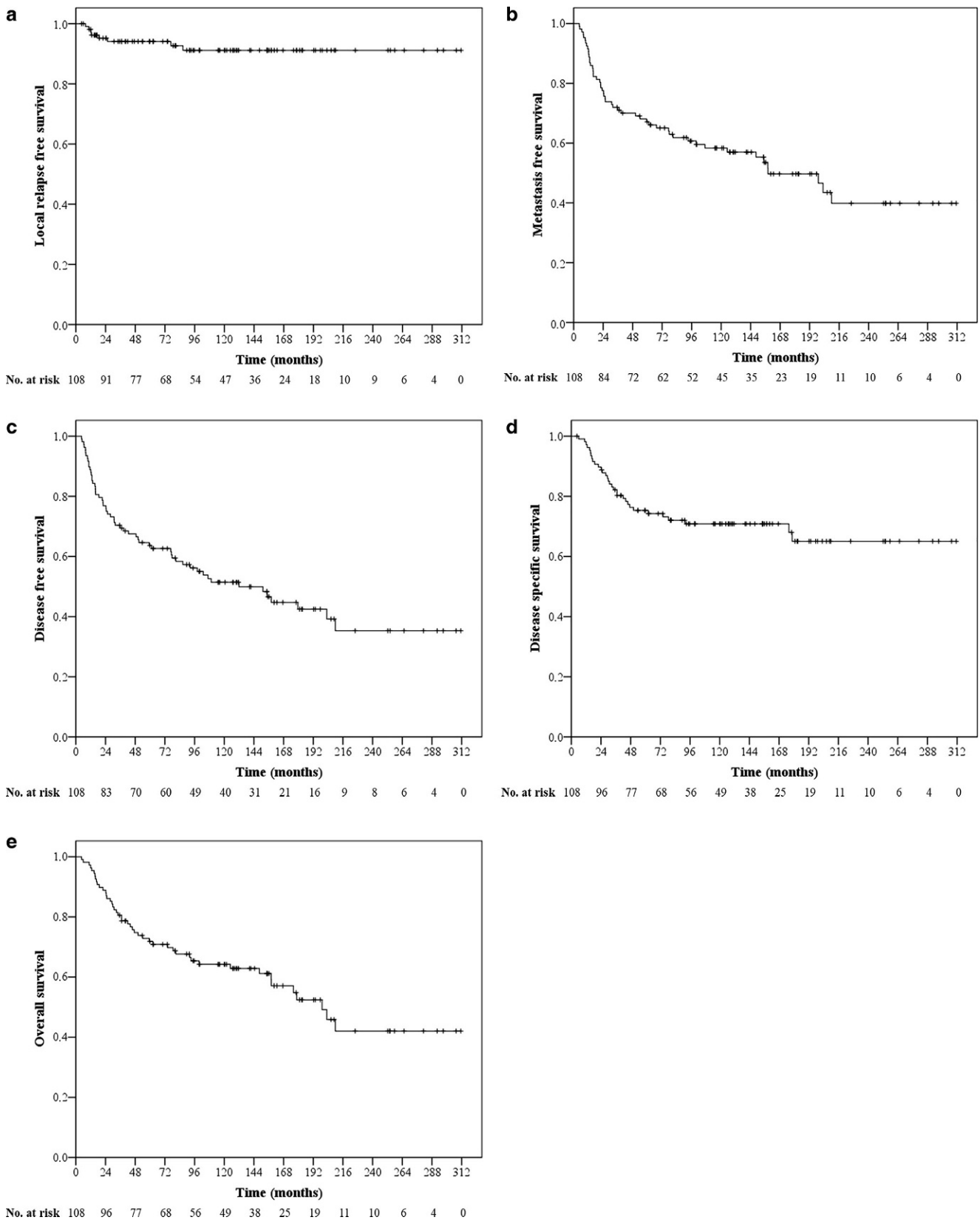


Fig. 1 The graphs show Kaplan–Meier estimates of local relapse-free survival (a); metastasis-free survival (b); disease-free survival (c); disease-specific survival (d); overall survival (e)

the multivariable analysis, de novo or R1/R2 resected tumor on admission ($p=0.017$; HR 0.112, 95% CI 0.019–0.675) and R0 resection after neoadjuvant RCT ($p=0.010$; HR 0.121, 95% CI 0.024–0.598) were found as the significant predictors of improved LRFS.

Only liposarcoma histology compared to non-liposarcoma histologies was associated with improved MFS ($p=0.006$ [5-year MFS 90.2% vs 57.7%]) on univariate analysis; therefore, no multivariate analysis was performed. On univariate analysis, female gender compared to male gender ($p=0.022$ [5-year DFS 69.8% vs 58.3%]) and liposarcoma histology compared to non-liposarcoma histologies ($p=0.007$ [5-year DFS 90.2% vs 53%]) were associated with improved DFS. In the multivariable analysis; female gender ($p=0.042$; HR 0.569, 95% CI 0.330–0.979) and liposarcoma histology ($p=0.014$; HR 0.436, 95% CI 0.224–0.845) remained to be the significant predictors of improved DFS.

Patients with liposarcoma histology compared to patients with non-liposarcoma histologies ($p=0.001$ [5-year DSS 100.0% vs 65.5%]), and patients receiving AP compared to patients receiving MAP ($p=0.039$ [5-year DSS 86.6% vs 67.0%]) had improved DSS. These results were also confirmed by multivariate analysis that patients with liposarcoma histology performed better than patients with other histologic subtypes ($p=0.003$; HR 0.114, 95% CI 0.027–0.478), and patients applied AP performed better than patients applied MAP ($p=0.017$; HR 0.371, 95% CI 0.165–0.836).

On univariate analysis, age ≤ 45 years compared to >45 years ($p=0.027$ [5-year OS 76.6% vs 66.7%]), female

gender compared to male gender ($p=0.036$ [5-year OS 77.6% vs 66.9%]), and liposarcoma histology compared to non-liposarcoma histologies ($p=0.003$ [5-year OS 96.8% vs 61.8%]) were associated with improved OS. Multivariate analysis revealed that age ≤ 45 years ($p=0.043$; HR 0.537, 95% CI 0.294–0.980) and liposarcoma histology ($p=0.006$; HR 0.318, 95% CI 0.141–0.716) were significant predictors of increased OS.

Adverse events

Treatment-related toxicities were compared between patients receiving MAP regimen and those receiving AP regimen (Table 5). Thrombocytopenia of grade 3, grade 4 neutropenia, and febrile neutropenia were significantly higher in patients who received AP regimen compared to those received MAP regimen ($p=0.029$, $p=0.035$, and $p=0.040$, respectively). Other adverse events were not statistically different.

Discussion

Five-year LRFS of entire patient cohort was 94.1% which was similar with the phase 3 randomized trial that compared preoperative vs postoperative XRT [8]. At 10 years, it was 91.2%, demonstrating that high local control benefit with XRT persists over time. We were able to preserve the extremity in 93.5% of the patients, which was very satisfactory.

Table 2 Second primary cancers diagnosed during follow-up

Patient	Primary cancer location and diagnosis	Second primary cancer location and diagnosis	Time frame ^c (months)
1	Thigh, UPS	Neck, DLBCL	110
		Bladder and ureter, urothelial ca	135
		Rectum, intramucosal ca	168
2	Thigh, liposarcoma	Stomach, poorly cohesive ca	180
3	Thigh, liposarcoma	Lung, NSCLC	151
4	Thigh, MPNST	Brain tumor ^a	93
5	Cruris, liposarcoma	Colon tumor ^b	98
6	Thigh, liposarcoma	Stomach, poorly cohesive ca	132
7	Pelvic girdle, angiosarcoma	Bladder, urothelial ca	104
8	Thigh, UPS	Brain, glioblastoma	43
9	Forearm, UPS	Lung, NSCLC (adenoca)	31
10	Thigh, UPS	Stomach, GIST	49
11	Cruris, UPS	Malar, LMM	45

ca Carcinoma, UPS Undifferentiated pleomorphic sarcoma, DLBCL diffuse large b cell lymphoma, NSCLC Non-small cell lung cancer, MPNST Malignant peripheral nerve sheath tumor, GIST Gastrointestinal stromal tumor, LMM Lentigo maligna melanoma

^aNot histologically confirmed. Magnetic resonance imaging revealed tumor (5 centimeter in size) in lateral ventricle in brain

^bNot histologically confirmed. Carcinoembryonic antigen level was 1128 $\mu\text{g/L}$ and positron emission tomography/computed tomography revealed colon tumor (5 cm in size) with multiple metastases in lung and liver

^c The date from the initiation of neoadjuvant radiochemotherapy to the diagnosis of second primary cancer

Table 3 Univariate analysis of patient and treatment related factors influencing local relapse-free survival, metastasis-free survival, disease-free survival, disease-specific survival, and overall survival

Characteristics	5-year LRFS (in %)	<i>p</i>	5-year MFS (in %)	<i>p</i>	5-year DFS (in %)	<i>p</i>	5-year DSS (in %)	<i>p</i>	5-year OS (in %)	<i>p</i>
<i>Age</i>		0.061		0.069		0.066		0.571		0.027
≤ 45 years	90.7		71.3		71.3		76.6		76.6	
> 45 years	98		62.5		55.5		73.9		66.7	
<i>Gender</i>		0.180		0.100		0.022		0.194		0.036
Female	95.6		71.8		69.8		81.5		77.6	
Male	92.8		63		58.3		69.9		66.9	
<i>Status on admission</i>		0.030		0.329		0.442		0.512		0.197
De novo, or R1/2 resected tumor	95.7		69.3		65.5		76.4		74.5	
Relapsed tumor	75		41.7		41.7		62.5		41.7	
<i>Size of tumor</i>		0.496		0.445		0.299		0.230		0.620
T1&T2	93.5		70.2		68.7		77.1		72.9	
T3&T4	95.7		63.1		58.9		74.6		71.2	
<i>Histology</i>		0.224		0.006		0.007		0.001		0.003
Liposarcoma	96.2		90.2		90.2		100		96.8	
Non-liposarcoma	91.6		57.7		53		65.5		61.8	
<i>Tumor location</i>		0.165		0.701		0.378		0.576		0.688
Upper extremity	89.9		61.5		56.7		66.3		66.3	
Lower extremity	95.1		68.4		65.3		77.5		73.2	
<i>Neoadjuvant CHT</i>		0.281		0.756		0.863		0.039		0.150
MAP	91.5		64.5		61.7		67.0		64.7	
AP	97.7		71		66.6		86.6		81.9	
<i>Surgical resection^a</i>		0.01		0.730		0.514		0.733		0.904
R0	96.6		67.2		63.3		76.5		72.6	
R1	74.1		66.7		66.7		66.7		66.7	
<i>Adjuvant XRT</i>		0.156		0.174		0.540		0.368		0.302
Present	89.5		73.3		68		84.2		78.6	
Not present	95.1		65.8		62.7		73.3		70.3	
<i>Adjuvant CHT</i>		0.258		0.508		0.552		0.366		0.733
Present	87.2		60		55.7		63		63	
Not present	96.1		69.3		66		79		74.4	

Statistically significant *p* values are italicised

CHT Chemotherapy, *MAP* Mitomycin, Doxorubicin, Cisplatin, *AP* Doxorubicin, Cisplatin, *XRT* Radiotherapy, *LRFS* Local relapse-free survival, *DFS* Disease-free survival, *DSS* Disease specific survival, *OS* Overall survival

^aSurgical resection after neoadjuvant radiochemotherapy

As stated in the previous studies, tumor positivity at the surgical margins after neoadjuvant RCT was also an independent predictor of decreased local control in our study [14, 15]. Although local recurrence rate significantly decreased after the utilization of XRT in extremity STS, adequate surgical margin still remains a predictor of local control. Another subgroup of patients with inferior local control rate included patients irradiated for a local relapse after previous surgery. Although at first sight a relapsed tumor may exhibit more aggressive clinical behavior, survival of this group was similar with others and increase in local relapse rate did not translate into decrease of survival.

The 5-year OS was 71.9% in our entire patient cohort. It was 67% in the EORTC 62931 phase 3 randomized trial involving high-risk STS patients [16]. In that trial, surgery

was compared with surgery plus CHT and 73% of all patients received XRT. In the two notable phase 2 studies for neoadjuvant RCT, 5-year OS was 71.2% in the RTOG 9514 trial and 80% in the study conducted by Edmonson et al. [7, 10]. Our result appears consistent with the literature. Multivariate analysis revealed that younger age (≤ 45 years) and liposarcoma histology were associated with improved OS, as expected.

Patients with a diagnosis of liposarcoma histology fared better compared to patients with non-liposarcoma histologies in all survival metrics except LRFS (which was also improved for non-liposarcoma histologies) and 5-year DSS was 100% for liposarcoma histology in our study. In a similar study conducted by Fiore et al., 5-year DSS was 83% for all patient cohort consisting of primary and recurrent

Table 4 Multivariate analysis of statistically significant variables determined by univariate analysis those are influencing local relapse-free survival, metastasis-free survival, disease-free survival, disease-specific survival, and overall survival

Characteristics	Variation	HR	95% CI	p
<i>LRFS</i>				
Status on admission	De novo tumor or R1/R2 resection	0.112	0.019–0.675	<i>0.017</i>
	Relapsed tumor	1		
Surgical resection ^a	R0	0.121	0.024–0.598	<i>0.010</i>
	R1	1		
<i>DFS</i>				
Gender	Female	0.569	0.330–0.979	<i>0.042</i>
	Male	1		
Histology	Liposarcoma	0.436	0.224–0.845	<i>0.014</i>
	Non-liposarcoma	1		
<i>DSS</i>				
Histology	Liposarcoma	0.114	0.027–0.478	<i>0.003</i>
	Non-liposarcoma	1		
Neoadjuvant CHT	AP	0.371	0.165–0.836	<i>0.017</i>
	MAP	1		
<i>OS</i>				
Age	≤45 years	0.537	0.294–0.980	<i>0.043</i>
	>45 years	1		
Gender	Female	0.619	0.334–1.146	0.127
	Male	1		
Histology	Liposarcoma	0.318	0.141–0.716	<i>0.006</i>
	Non-liposarcoma	1		

Statistically significant *p* values are italicised

LRFS Local relapse-free survival, *DFS* Disease-free survival, *DSS* Disease-specific survival, *OS* Overall survival, *CHT* Chemotherapy, *MAP* Mitomycin, Doxorubicin, Cisplatin, *AP* Doxorubicin, Cisplatin, *CI* confidence interval, *HR* hazard ratio

^aSurgical resection after neoadjuvant radiochemotherapy

liposarcoma. However, although limited patients received XRT (39%) and CHT (18%), DSS was 90% for those presenting with primary tumor [17]. The much better DSS in our group may be due to the relatively high ratio of myxoid liposarcoma cases.

The role of CHT in the treatment of non-metastatic STS of the extremities has not been clarified exclusively. Furthermore, very limited data exist for neoadjuvant CHT compared to adjuvant CHT. Although no randomized trials addressing the benefit of neoadjuvant CHT given concomitantly with XRT are available, various doxorubicin-based CHT regimens were frequently used with preoperative XRT for the treatment of locally advanced STS [10, 11, 18–20]. Eilber et al. showed that the tumor necrosis rate increased from 60 to 70% when cisplatin was added to doxorubicin in concomitant use of CHT with XRT [21]. Following two cycles of ifosfamide, mitomycin, and cisplatin, XRT and three concomitant cycles of MAP were given preoperatively to the patients with limb or pelvic girdle high-grade soft tissue sarcoma in the phase 2 trial conducted by Edmonson et al., and 5-year survival rate was 80% [10]. In the RTOG 9514 phase-2 trial, patients having a high-grade STS larger than 8 cm were treated preoperatively with three cycles of the modified mesna, doxorubicin, ifosfamide, and dacarbazine (MAID) regimen and XRT, and additional three cycles

of MAID were given postoperatively. The results showed 5-year OS rate of 71.2% albeit with significant toxicity as grade 3 or higher in 97% and death due to toxicity in 5% of patients [7]. Our study was not a randomized trial; however, DSS was better with the AP regimen although XRT dose schedule and approach of target volume delineation were similar in all patients. We think that despite increased treatment-related toxicities, the intense doxorubicin dose might play an important role for improved DSS. However, although patients receiving AP had improved OS compared to patients receiving MAP (81.9% vs 64.7% at 5 years), the difference did not reach statistical significance. We suppose this statistically nonsignificant result for OS could be related to the fact that patients receiving MAP were younger than those receiving AP (median age 43 years vs 51 years). Nonetheless, one needs to be careful when interpreting this result, since our patient cohort comprises several tumor types and are thereby not appropriate for subgroup estimation. Thus, further research on the role of concomitant CHT and XRT for specific tumor types is required.

We are aware of the limitations of this study which were retrospective design and consisting of heterogeneous tumor types; however, prospective trials for STS are quite limited. Nonetheless, apart from survival outcomes, prognostic factors, and treatment-related toxicities, we also highlighted

Table 5 Cumulative incidence of adverse events

Toxicities	MAP n (%) ^a	AP n (%) ^a	<i>p</i> -value
Anemia^b			
Grade 3	2 (3.4)	6 (14)	0.067
Grade 4	1 (1.7)	1 (2.3)	1
Neutropenia^b			
Grade 3	15 (25.4)	8 (18.6)	0.566
Grade 4	11 (18.6)	17 (39.5)	<i>0.035</i>
Thrombocytopenia^b			
Grade 3	–	4 (9.3)	<i>0.029</i>
Grade 4	–	2 (4.7)	0.175
Febrile neutropenia			
Present	1 (1.7)	6 (14)	<i>0.040</i>
Not present	58 (98.3)	37 (86)	
Acute RD			
Grade 3	8 (12.7)	1 (2.2)	0.077
Grade 4	–	–	–
Surgery required postoperative complications			
Present	7 ^c (11.1)	8 (17.8)	0.481
Not present	56 (88.9)	37 (82.2)	
Chronic neuropathy			
Present	1 (1.6)	1 (2.2)	1
Not present	62 (98.4)	44 (97.8)	

Statistically significant *p* values are italicised

RD Radiation dermatitis

^aValid percents, missing data excluded

^bData were missing for 4 patients receiving MAP and 2 patients receiving AP regimen

^cAmputation was performed in 1 patient

the details of second primary cancers occurring during follow-up. We believe in that experience of our center will contribute to the sarcoma literature.

Conclusion

Neoadjuvant RCT followed by surgery provides long-term and very high local control in high-grade or large STS of the extremities. Treating a relapsed tumor and surgical margin positivity after neoadjuvant RCT pose an increased risk for local failure. Finally, apart from relatively innocent histological subtype such as liposarcoma, CHT intensity also seems to significantly influence DSS. However, CHT intensity did not have a statistically significant impact on OS. Nonetheless, this could be due to younger patients receiving MAP.

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Declarations

Conflict of interest U. Yilmaz, S. Kamer, H. Kaya, D. Sabah, U.A. Sanli, I. Tamsel, B. Yaman, T. Akalin and Y. Anacak declare that they have no competing interests.

Ethical standards This study was approved by the institutional ethics committee (21-8T/56).

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