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Oncological Outcome and Prognostic Factors of Surgery for Soft Tissue Sarcoma After Neoadjuvant or Adjuvant Radiation Therapy: A Retrospective Analysis over 15 Years

HEINRICH M.L. MUEHLHOFER[1], BENJAMIN SCHLOSSMACHER[1], ULRICH LENZE[1], FLORIAN LENZE[1], RAINER BURGKART[1], ALEXANDRA S. GERSING[2], JAN C. PEEKEN[3,4,5], STEPHANIE E. COMBS[3,4,5], RUEDIGER VON EISENHART-ROTHE[1] and CAROLIN KNEBEL[1]

[1]*Department of Orthopedics and Sports Orthopedics, Technical University of Munich, Klinikum rechts der Isar, Munich, Germany;*
[2]*Department of Radiology, Technical University of Munich, Klinikum rechts der Isar, Munich, Germany;*
[3]*Department of Radiation Oncology, Technical University of Munich, Klinikum rechts der Isar, Munich, Germany;*
[4]*Institute of Radiation Medicine (IRM), Department of Radiation Sciences (DRS), Helmholtz Zentrum München, Munich, Germany;*
[5]*Deutsches Konsortium für Translationale Krebsforschung (DKTK), Partner Site Munich, Munich, Germany*

Abstract. *Background/Aim: Surgical resection for soft tissue sarcomas (STSs) is the gold standard for a curative oncologic therapy in combination with neoadjuvant or adjuvant radiation therapy (NRT/ART). The aim of this study was to determine prognostic factors influencing the survival of patients with STS undergoing NRT or ART considering various parameters in a retrospective, single-centre analysis over 15 years. Patients and Methods: We included 119 patients (male 59) and the median follow-up period was 69 months (4-197). The patients received NRT (n=64) or ART (n=55). We recorded the histopathologic subtype of STS, tumour grade, localization, tumour margins, complications, survival, local recurrence, and metastases. Survival analysis was performed using the Kaplan–Meier method. Results: The overall survival rate was 68.9% at 5 years. The localization (epifascial/subfascial), resection margin and type of radiation therapy (NRT/ART) had no significant impact on survival. Tumour grade, tumour size, local recurrence and metastases were significantly correlated with patient survival (p<0.05). Local recurrence was significantly higher in patients with ART (p=0.044). Conclusion: Tumour grade and tumour size were independently associated with disease-specific survival, and patients with local recurrence and metastases had lower survival rates.*

Correspondence to: Carolin Knebel, MD, Department of Orthopedics and Sports Orthopedics, Ismaninger Strasse 22, 81675 Munich, Germany. Tel: +49 8941402283, Fax: +49 8941404849, e-mail: carolin.knebel@tum.de

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Soft tissue sarcomas (STSs) are rare entities with an incidence of approximately 2-5 per 100,000 per year (1-3). A distinction can be made between approximately 50 histopathological subtypes in STS (4). Optimal treatment of STS is achieved by an interdisciplinary approach and depends on the histopathological subtype that is determined after tissue biopsy and histopathological analysis (2). The therapy max varies from primary surgical resection to NRT/ART and/or neoadjuvant or adjuvant cytotoxic chemotherapy with different chemotherapy drugs and secondary surgical resection. Primary or secondary surgical resection is the gold standard and the curative basis in oncologic therapy. The aim of every strategy is to have maximum local control while preserving function (5). A systematic literature analysis by Albertsmeier *et al.* (6) concluded that NRT results in a statistical trend towards improved local control and slightly increased overall survival. However, this previous study showed a significant three times higher wound complication rate associated with NRT. Nevertheless, regarding marginal positive effects, no clear conclusion was drawn. A study by Shelby *et al.* reported that NRT improves the margin-negative resection rates but overall not the survival of patients with extremity sarcoma (7).

Our cohort represents a larger number of patients with sarcomas with extensive clinical patient records. Therefore, the aim of this study was to determine prognostic factors influencing the survival of patients with STS undergoing NRT or ART with consideration for tumor grading, histological subtype, resection margin, size, localization,

Table I. *Patient parameters of the radiation groups (neoadjuvant/adjuvant).*

	Neoadjuvant RT (n=64)	%	Adjuvant RT (n=55)	%	Total (n=119)
Median age (years)	57.0		60.7		58.0 (range=18-89)
Gender					
Male	34	53.1	25	45.5	59
Female	30	46.9	30	54.5	60
Median follow-up years (range)	3.94 (0.55-9.86)		4.95 (0.28-16.19)		4.41 (0.28-16.19)
Mean radiation dose Gy (range)	49.9 (45.0-52.0)		61.2 (55.0-66.6)		------
Grading					
G1	6	9.4	3	5.5	9
G2	23	35.9	18	32.7	41
G3	34	53.1	34	61.8	68
Gx	1	1.6	0	0	1
Localization/Depth					
Epifascial	5	7.8	13	23.6	18
Subfascial	59	92.2	42	76.4	101
Size					
<5 cm	8	12.5	9	16.4	17
5-10 cm	27	42.2	22	40.0	49
10-15 cm	24	37.5	13	23.6	37
>15 cm	4	6.2	9	16.4	13
missing	1	1.6	2	3.6	3
Resection margin					
R0	62	96.8	40	72.7	102
R1	1	1.6	10	18.2	11
R2	0	0	0	0	0
Rx	1	1.6	5	9.1	6

local recurrence, and metastases in a retrospective, single-centre analysis over 15 years.

Patients and Methods

We retrospectively analysed our institution's database for patients who underwent treatment for the diagnosis of STS from January 2002 to December 2017. The approval of the Institutional Review Board was obtained before initiating the study (Ethics Committee of Medical Faculty, Technical University of Munich). Written informed consent was obtained from all patients included in the study.

We identified 516 patients treated with STS of the limbs or trunk in our clinic. The inclusion criteria were as follows: i) histopathologically proven STS confirmed by two experienced skeletal pathologists, based on the WHO classification of STS; ii) tumour localized in the trunk or the extremities; iii) neoadjuvant or adjuvant radiotherapy at our clinic; and iv) surgical therapy at our clinic. We recorded the age at time of diagnosis, sex (male/female), histologic subtype of sarcoma, grade (G1, G2, and G3), localization, tumour margins (R0: negative/clean margins; R1: positive/involved margins (microscopic); R2: positive/involved margins (macroscopic); Rx: the presence of residual tumour cannot be assessed), radiation therapy (neoadjuvant, adjuvant, dose), complications, survival, local recurrence, metastases, and follow-up (months from time of diagnosis). Regarding complications, the parameters of wound healing disorder, seroma, deep wound infection, restricted movement of the adjacent joints (> 20% after a period of 6 months postoperatively as part of the follow-up examination compared to the contralateral side) and fracture (femur fracture when sarcoma was located in the area of the thigh and intraoperative deperiostation of the femoral shaft) were evaluated. Wound healing disorder, seroma (no infection), and deep wound infection were only considered relevant complications if they led to a surgical revision. A total of 119 patients (male/female=59/60) with a median age of 58.3 years (range=18-89 years) at the time of STS diagnosis were included in the study (Table I). The median follow-up period was 69 months (range=4-197 months for the whole group). The patients received NRT (n=64) or ART (n=55, start of RT within a period of 3 months postoperatively) in addition to surgical resection of the tumour as part of their multimodal treatment in our clinic, with complete documentation of the treatment data. The mean dose of NRT was 49.9 Gy (range=45.0-52.2 Gy), and in the adjuvant group, the mean dose was 61.2 Gy (range=55.0-66.6 Gy). In one case in each group, radiotherapy was stopped early due to complications or acute tumour progression. Exclusion criteria of the patients who had received radiation therapy were combined NRT and ART, additional brachytherapy, chemotherapy, sarcoma recurrence at the first presentation in sarcoma centre, patients with external surgical interventions, an unclear histology regarding the grading, and incomplete documentation of treatment data. Survival analysis was performed using the Kaplan–Meier method. Prognostic factors and the influence on mortality were determined with the log-rank test (Mantel–Cox). All data are reported as the mean, deviation, and percentage, where applicable. Statistical analysis was performed using SPSS 25.0 (IBM, Armonk, NY, USA).

Table II. *Histopathological subtype of STS.*

	Number of patients (%)
Pleomorphic sarcoma	46 (38.66%)
Myxoid liposarcoma	21 (17.65%)
Synovial sarcoma	13 (10.92%)
Myxofibrosarcoma	17 (14.29%)
Fibrosarcoma	1 (0.84%)
MPNST	2 (1.68%)
Leiomyosarcoma	4 (3.36%)
Rhabdomyosarcoma	3 (2.52%)
Epithelioid sarcoma	1 (0.84%)
Angiosarcoma	3 (2.52%)
Alveolar sarcoma	1 (0.84%)
Inflammatory sarcoma	1 (0.84%)
Spindle cell sarcoma	3 (2.52%)
Pleomorphic liposarcoma	3 (2.52%)
	n=119 (100%)

Table III. *Localization of sarcomas.*

	Number of patients (%)
Thigh	75 (63.03%)
Lower leg	9 (7.57%)
Forearm	8 (6.72%)
Upper arm	8 (6.72%)
Shoulder	6 (5.04%)
Thorax wall	4 (3.36%)
Pelvis	3 (2.52%)
Neck	3 (2.52%)
Paravertebral muscle	2 (1.68%)
Food	1 (0.84%)
	n=119 (100%)

Results

Regarding histopathological findings, a typical distribution pattern of sarcomas was observed in the patient cohort (n=119), as shown in Table II. Most patients were diagnosed with undifferentiated pleomorphic sarcoma (n=46, 38.66%), followed by myxoid liposarcoma (n=21, 17.65%), myxofibrosarcoma (MFS; n=17, 14.29%) and synovial sarcoma (n=13, 10.92%). Overall, we determined that there were 75 sarcomas (63.03%) located in the thigh, and approximately the same numbers were observed in the lower leg (n=9, 7.57%), forearm (n=8, 6.72%) and upper arm (n=8, 6.72%), as shown in detail in Table III.

Overall survival considering all 119 patients was 94.9% (95%CI=91.0-98.8) at 1 year, 68.9% (95%CI=59.3-78.5) at 5

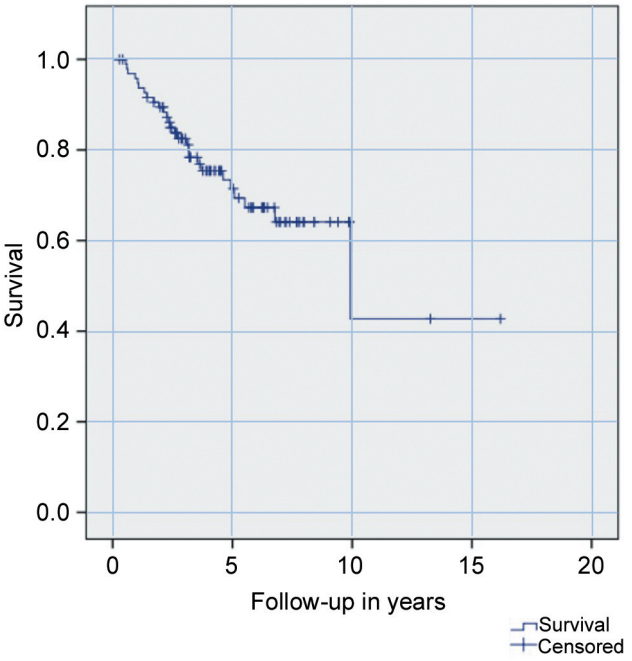

Figure 1. *Kaplan–Meier curve showing the statistical analysis of overall survival in years after initial diagnosis of sarcoma.*

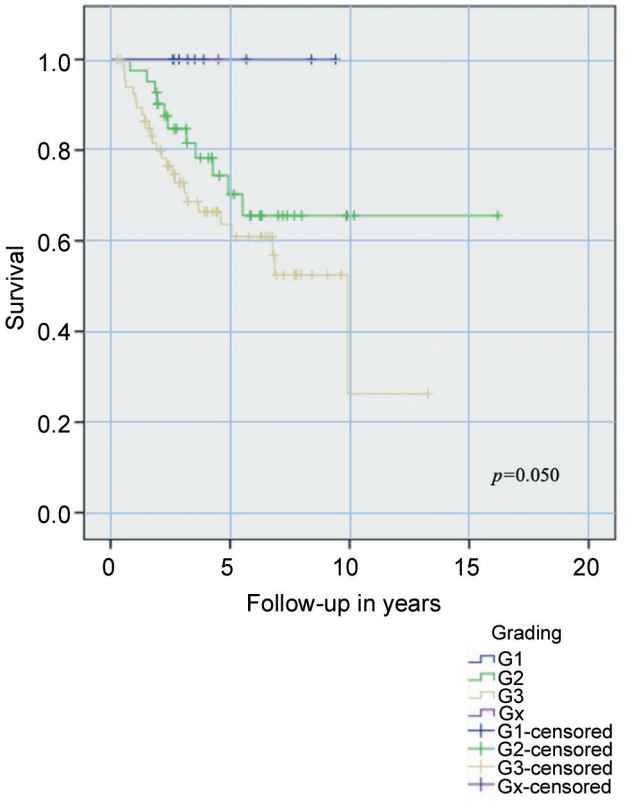

Figure 2. *Kaplan–Meier curve showing the statistical analysis of survival in years after initial diagnosis according to grading of sarcoma.*

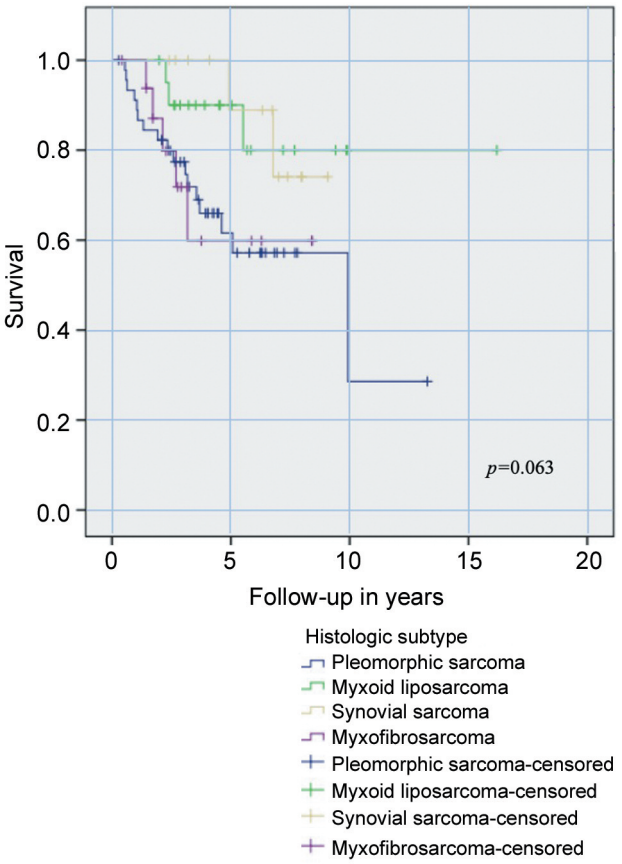

Figure 3. *Kaplan–Meier curve showing the statistical analysis of survival in years after initial diagnosis according to subtype of sarcoma.*

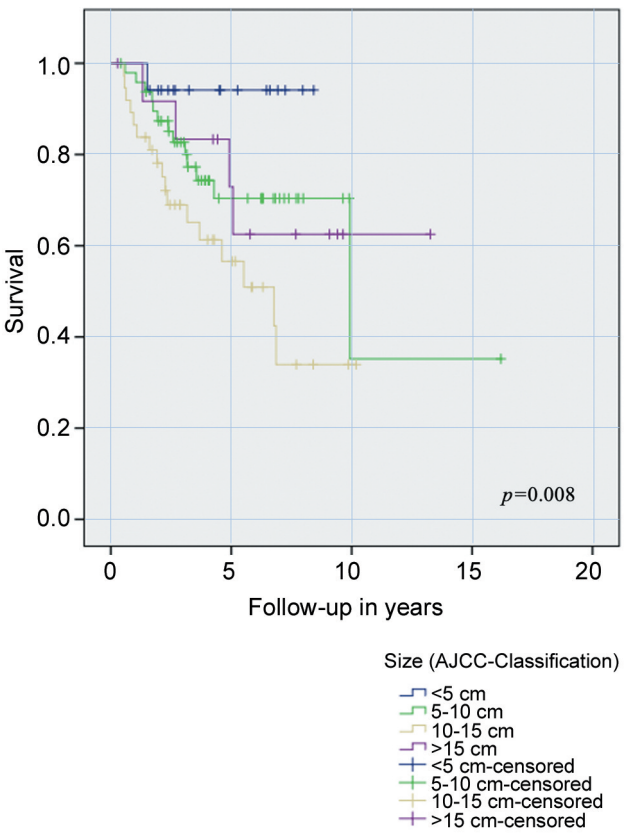

Figure 4. *Kaplan–Meier curve showing the statistical analysis of survival in years after initial diagnosis according to size of sarcoma.*

years, and 45.3% (95%CI=18.3-72.4) at 10 years after the initial diagnosis (Figure 1). Concerning the tumour grade (FNCLCC system), there were 9 (7.6%) G1 tumours, 41 (34.5%) G2 tumours, 68 (57.1%) G3 tumours and 1 (0.8%) Gx tumour. The following two sub-entities received NRT or ART for G1 sarcomas: myxoid liposarcoma n=8 (neoadjuvant/adjuvant radiation therapy=6/2) and MFS n=1 (adjuvant radiation therapy). The grading significantly correlated (log rank-test p=0.050) with patient survival, with G1 tumours as expected having the best survival (Figure 2). While the 5-year survival rate in the G1 group was 100%, it dropped to 70.3% (95%CI=54.2-86.4) in G2 tumours and 63.7% G3 tumours (95%CI=50.8-76.6). With regard to the prognostic factor of the histopathological subtypes of the most common four sub-entities, the 5-year survival rates were as follows: for undifferentiated pleomorphic sarcoma, 61.6% (95%CI=45.5-77.7); for synovial sarcoma, 88.9% (95%CI=68.3-100.0); for MFS, 59.8% (95%CI=30.6-89.0); and for myxoid liposarcoma, 90% (95%CI=76.9-100.0). There was a tendency for better survival rates in myxoid liposarcoma and synovial sarcoma (p=0.055) but these were not statistically significant compared to poorer survival of undifferentiated pleomorphic sarcoma and MFS (Figure 3). The hazard ratio (HR) was 3.2 (95%CI=0.9-11.0; p=0.063) for undifferentiated pleomorphic sarcoma, 0.9 (95%CI=0.1-5.8; p=0.967) for synovial sarcoma and 3.2 (95%CI=0.7-13.4; p=0.116) for MFS compared to myxoid liposarcoma. Concerning localization of the sarcomas, 18 (15.1%) tumours were epifascial and 101 (84.9%) tumours were subfascial. However, tumour localization had no impact on overall survival (p=0.190). The HR was 2.5 (95%CI=0.6-10.5; p=0.206). The following results were found regarding tumour size. Seventeen cases (14.7%) showed a tumour size of less than 5 cm, 49 tumours (42.2%) were between 5 cm and 10 cm, and 37 tumours (31.9%) were between 10 cm and 15 cm. Thirteen sarcomas (11.2%) were larger than 15 cm, and the corresponding pathology findings regarding the tumour size were missing in 3 cases (2.1%). Only the difference between the tumour size <5 cm and tumour size 10-15 cm groups was clearly significant (p=0.008), with the difference between the 5-10 cm and 10-15 cm groups being nearly significant (70.4% *vs*. 56.6%; p=0.052). For the HR, sarcoma <5 cm was set as a reference. For the size 5-10 cm group, the HR was 4.5

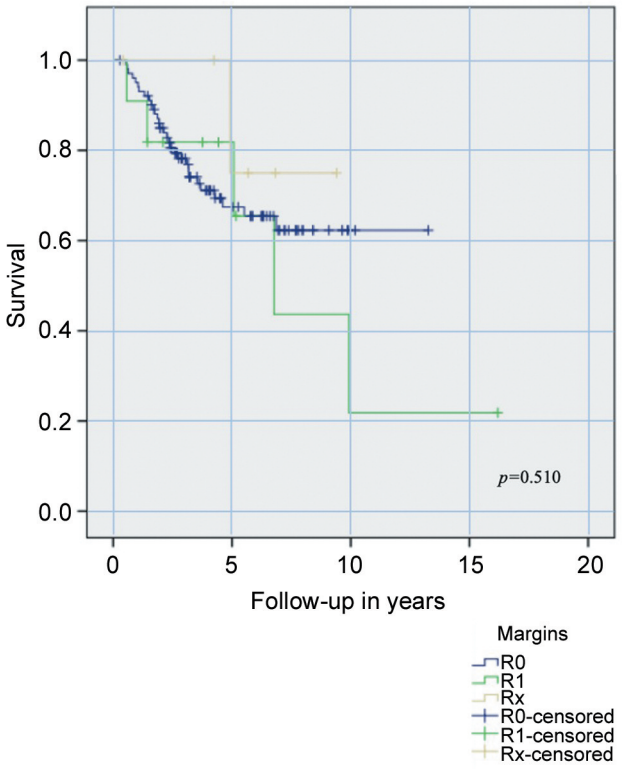

Figure 5. *Kaplan–Meier curve showing the statistical analysis of survival in years after initial diagnosis according to resection margins of sarcoma.*

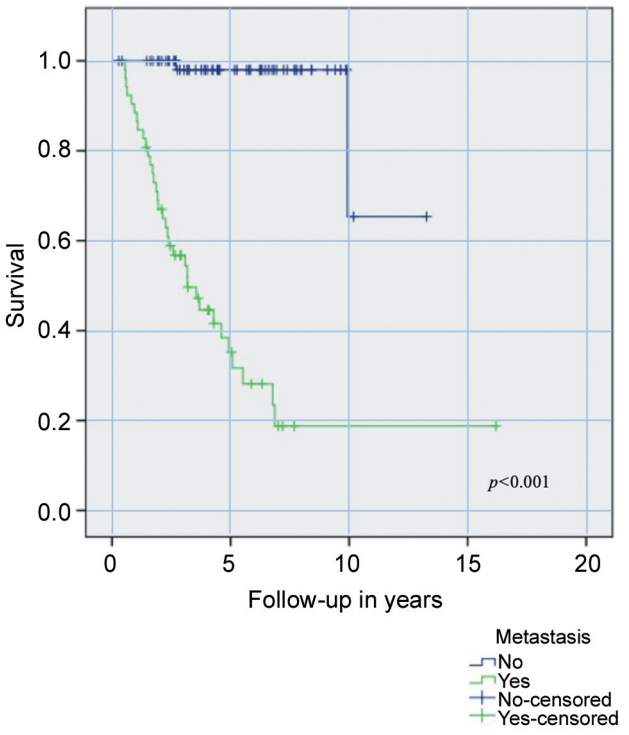

Figure 6. *Kaplan–Meier curve showing the statistical analysis of survival in years after initial diagnosis according to metastasis of sarcoma.*

(95%CI=0.6-34.7; p=0.145); for the size 10-15 cm group, the HR was 9.1 (95%CI=1.2-68.5; p=0.032); and for the size >15 cm group, the HR was 4.3 (95%CI=0.5-39.0; p=0.190). The Kaplan–Meier curve regarding the tumour size is shown in Figure 4. The following results were obtained regarding the resection status. There were 6 cases with Rx resections (5.1%), 102 cases with R0 resections (85.7%) and 11 cases with R1 resections (9.2%, 1 patient with NRT/10 patients with ART). The 5-year survival rate was 67.5% (95%CI=51.7-77.9) for R0 resection, 81.8% (95%CI=59.1-100.0) for R1 resection, and 75.0% (95%CI=32.4-100.0) for Rx resection. However, these differences were not statistically significant (p=0.510) in any way (Figure 5). For the HR, the R0 resection was set as a reference. The Rx resection HR was 0.5 (95%CI=0.0-3.6); p=0.481), and the R1 resection HR was 1.4 (95%CI=0.5-3.6); p=0.521). The appearance of metastases means the transition from a local disease to systemic progression, which translates in a significant increase in the likelihood of survival. The survival analysis showed that patients with tumours that metastasized over the course of the disease had a 5-year survival rate of 37.2% (95%CI=22.5-51.9) compared to 98.0% (95%CI=94.1-100.0) in metastasis-free patients (p<0.001), as shown in Figure 6. The HR for the occurrence of metastases was 31.0 (95%CI=7.4-129.4); p<0.001). Local recurrence occurred in a total of 14 patients (4 patients with NRT/10 patients with ART, p=0.044). The HR was 2.2 (95%CI=1.0-4.8; p=0.041). For patients with local recurrence, the analysis showed a significantly lower 5-year survival rate of 51.0% (95%CI=21.8-80.2) compared to the 71.8% (95%CI=62.0-81.6) rate for relapse-free patients (p=0.036, Figure 7). The HR was 2.2 (95%CI=1.0-4.8; p=0.041). There was a significant correlation between metastases and local recurrences. While only 21.4% (95%CI=0.0-46.1) of patients who developed local recurrence in the course of the disease were free of metastases after 5 years, 56.3% (95%CI=45.7-66.9) of patients were free of metastases when they were free of local recurrence (p=0.011). The HR was 2.3 (95%CI=1.1-4.9; p=0.029).

Looking at the difference between NRT and ART, the 5-year survival rate for NRT-treated patients was 62.6% (95%CI=49.3-76.0) compared to 77.8% (95%CI=65.3-90.3) in patients with ART. This difference was not significant in the statistical analysis (p=0.328), as shown in Figure 8. The HR for NRT was 0.8 (95%CI=0.6-1.2, p=0.330). The survival data of the patients separated according to NRT and ART with regard to the different parameters mentioned above are shown in detail in Table IV. There was no statistically significant

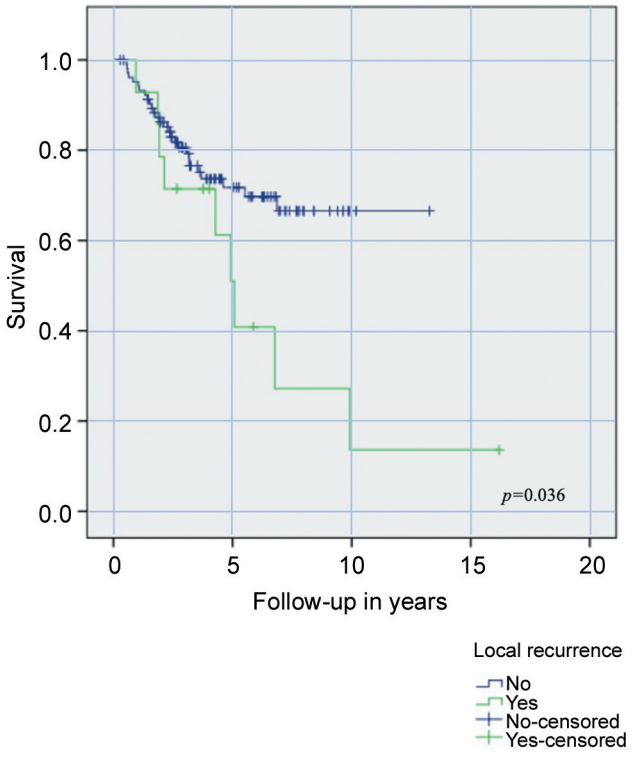

Figure 7. *Kaplan–Meier curve showing the statistical analysis of survival in years after initial diagnosis according to local recurrence of sarcoma.*

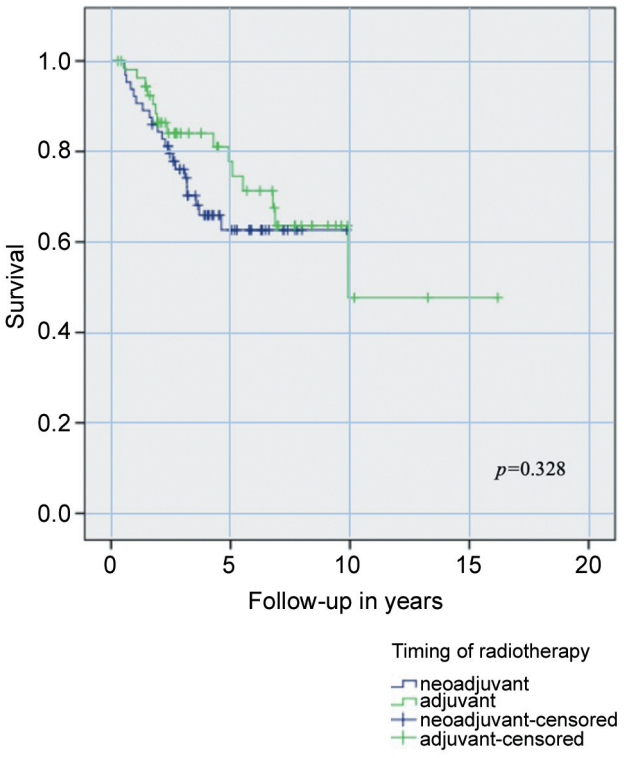

Figure 8. *Kaplan–Meier curve showing the statistical analysis of survival in years after initial diagnosis according to neoadjuvant radiation therapy versus adjuvant radiation therapy of sarcoma.*

difference in the two groups, with a tendency towards poorer survival of the patients with G3 tumours in the neoadjuvant group (p=0.131). Finally, multivariate analysis Cox regression should be used to investigate whether the significant influencing factors in the Kaplan–Meier analyses are actually independent. Due to the small number of cases, however, no valid and reliable statements can be made here.

Regarding complications, an amputation (hip joint disarticulation) as a result of an infection had to be carried out in one patient (NRT). No difference was observed in the overall complication rate of the collective groups when distinguishing between NRT and ART (p=0.971). The incidence of wound healing disorders was higher in the group of NRT-treated patients (21 NRT patients *vs*. 15 ART patients), but this difference was not statistically significant (p=0.512). The incidence of postoperative seromas and deep wound infections was approximately the same in both groups and therefore also not significantly different (seroma, p=0.802; deep wound infection, p=0.957), as shown in detail in Table V.

Discussion

In the current study, our working group retrospectively analysed a single-centre cohort treated in a national sarcoma centre. We determined the outcome and prognostic factors of STSs patients after surgical treatment and compared ART and NRT. To the best of our knowledge, this is the most up-to-date report providing a prognostic evaluation of STS with comparison of ART versus NRT.

Localization and overall survival. In the present study, the localization of STS was comparable to that noted in existing literature. Our cohort had an equal distribution of sexes, with a median age of 58.3 years. The most common tumour site was the thigh (approximately 60% tumours), followed by the lower leg and upper extremity, which is similar to results from the cohorts of Kikuta *et al*. and Bonvalot *et al*. (8, 9). The subtypes of STSs in our cohort are comparable to those of large epidemiologic studies with undifferentiated pleomorphic sarcoma as the most common subtype, followed by myxoid liposarcoma and MFS (3).

The overall survival rate in our cohort was 94.1% one year after initial diagnosis and dropped to 68.9% after 5 years. The 5-year survival rate in our cohort is slightly lower than that in some cohorts in the literature, *e.g*., Sanfillipo *et al*. (10), who found a rate of 80% in a homogenous cohort of mostly MFS patients. Our data confirm the results of Harati, who indicated a 5-year survival rate of 65.3% in a

Table IV. *Comparison of 5-year survival data after neoadjuvant (NRT) and adjuvant radiation therapy (ART) based on various parameters.*

Parameter	Neoadjuvant RT (NRT) (percentage, 95%CI)	Adjuvant RT (ART) (percentage, 95%CI)	*p*-Value
Overall survival	62.6 (49.3-76.0)	77.8 (65.3-90.3)	0.328
Grading			
G1	100.0	100.0	-------
G2	72.4 (53.4-91.4)	69.1 (42.4-95.8)	0.821
G3	49.8 (30.8-68.8)	79.9 (65.4-94.4)	0.131
Localization/Depth			
Epifascial	100.0	81.8 (59.0-100.0)	0.329
Subfascial	60.4 (46.6-74.1)	77.3 (62.9-91.6)	0.304
Size			
<5 cm	100.0	88.9 (68.3-100.0)	0.346
5-10 cm	63.3 (43.7-82.9)	82.7 (64.2-100.0)	0.148
10-15 cm	52.1 (29.3-74.8)	65.3 (37.0-93.5)	0.795
>15 cm	50.0 (1.0-99.0)	85.7 (59.8-100.0)	0.163
Resection margin			
R0	61.3 (47.6-75.0)	79.1 (65.2-93.0)	0.256
R1	100.0	80.0 (55.3-100.0)	0.498
Rx	100.0	75.0 (32.5-100.0)	0.462
Local recurrence			
No	63.3 (49.3-77.2)	85.0 (73.8-96.2)	0.169
Yes	50.0 (1.0-99.0)	53.3 (18.8-87.8)	0.679
Metastases			
No	96.3 (89.2-100.0)	100.0	0.367
Yes	31.9 (13.2-50.5)	46.7 (23.3-70.0)	0.680

Table V. *Comparison of complications after neoadjuvant (NRT) and adjuvant radiation therapy (ART).*

	NRT	NRT (%. n=64, 95%CI)	ART	ART (%, n=55, 95%CI)	*p*-Value	Total	Total (%, n=119, 95%CI)
Wound healing disorder	21	32.8 (22.3-44.9)	15	27.3 (16.9-40.0)	0.512	36	30.3 (22.5-38.9)
Restricted joint mobility	6	9.4 (4.0-18.3)	4	7.3 (2.5-16.4)	0.680	10	8.4 (4.4-14.4)
Thrombosis	3	4.7 (1.3-12.0)	1	1.8 (0.2-8-2)	0.387	4	3.4 (1.1-7.8)
Deep wound infection	6	9.4 (4.0-18.3)	5	9.1 (3.6-18.8)	0.957	11	9.2 (5.0-15.4)
Wound seroma	5	7.8 (3.0-16.3)	5	9.1 (3.6-18.8)	0.802	10	8.4 (4.4-14.4)
Fracture	1	1.6 (0.2-7.1)	1	1.8 (0.2-8.2)	0.914	2	1.7 (0.4-5.3)
Amputation	1	1.6 (0.2-7-1)	0	0.0	0.352	1	0.8 (0.1-3.9)

comparable cohort of STS patients (10, 11). The survival rate of STSs is multifactorial and depends on different parameters, such as grading, tumour size, surgical experience/resection margins, metastatic status, distribution of subtypes and local recurrence; therefore, the study cohorts are not easy to compare (1, 12, 13). Comparing the NRT and ART groups, the ART group seemed to have advantages in terms of 5-year survival, but the difference was not significant (62.6% *vs*. 77.8%; p=0.328).

Many patients in our cohort had subfascial tumour localization, slightly over 85%. We could not detect statistical significance for tumour localization as a prognostic parameter for overall survival. Pfister *et al*. have reported a significant difference between subfascial and epifascial localization in their cohort (5-year survival; 69.4% *vs*. 91.7%) (14). In the literature, there is no agreement concerning this prognostic factor; the results of Weitz *et al*. are comparable to our findings, but it must be stated that their cohort had many more patients with epifascial tumours (15).

The high number of subfascial tumours in our cohort can be explained by the study location being a national reference sarcoma centre treating complex and complicated cases. However, comparing the adjuvant *vs*. neoadjuvant radiation groups, a trend was detected; subfascial tumours had poorer

survival rates in the NRT group, though the difference was not statistically significant (60.4% *vs*. 77.3%). This observation agrees with the surgical assessment of experienced tumour surgeon, as tumours with deep localization and neoadjuvant radiation tend to develop liquid tumour necrosis with the risk of bursting during resection, contaminating the surgical site. Despite the lack of statistical power, our study detects this trend.

However, tumour size is an important prognostic factor. Tumour size between 10-15 cm had a dramatic HR of 9.1 (95%CI=1.2-68.5; p=0.032), statistical significance (Reference < 5 cm) and indicated poor 5-year survival (Figure 4). These findings are in complete contrast to HR reported (1.64-2.54) by Eilber *et al*. comparing the tumour size <5 group with the >10 cm group (16). It should be mentioned that the working group of Eilber did not subclassify tumours larger than 10 cm as we did in our cohort (Table I). Additionally, their cohort included only approximately 50% high-grade sarcoma with overrepresentation of liposarcoma, whereas in our cohort, high-grade (G2+G3) tumours were overrepresented, and only myxoid and pleomorphic liposarcoma were included. This fact clearly demonstrated the problems of studies with rare entities and heterogeneous study designs. Other cohorts with homogenous tumour types, *e.g*., MFS, show comparable results to our study concerning tumour size (11, 17).

Comparing the tumour size groups divided into ART and NRT groups, again, the trend of lower 5-year survival in the NRT group can be observed. This trend was particularly clear in patients with tumour size 5-10 cm, which had a 5-year survival rate of 63.3% with NRT *vs*. 82.7% with ART.

In terms of histopathology, most of the tumours in our cohort were classified as high grade, as mentioned above. In total, 109 of 119 patients had histopathologic classification of G2 (n=41) or G3 (n=68). This fact could explain the lower overall survival rate compared to other cohorts (9). Grading of STSs correlated significantly with the 5-year survival of the patients (Figure 2), which decreased from 100% in the G1 group to 63% in the G3 group. According to Biau *et al*., patients with a histological G3 tumour have different negative predictors for long-term survival, such as a greater risk of local recurrence and metastasis (12). Different studies have investigated the probability of local recurrence comparing high-grade *vs*. low-grade STS. Coindre *et al*. and Eilber *et al*. have reported an HR of approximately 2 (16, 18), which at first glance seems to be relatively low. However, high-grade STS tend to have an even greater risk of metastasis; therefore, patients with high-grade sarcoma are more likely to die from systemic disease before local recurrence can occur (12). We detected equal results comparing NRT and ART in the G2 group but again detected a trend of poorer outcome in the G3 group (49.8 *vs*. 79.9%) among those who received NRT.

Despite being a rare disease, STS represents a heterogeneous group of tumour entities (4). Our cohort includes the most common tumour entities of STS. We detected highly variable 5-year survival rates among the different entities (Figure 3), with a low 5-year survival rate of approximately 60% for undifferentiated pleomorphic sarcoma and MFS and a high 5-year survival rate for synovial sarcoma and myxoid liposarcoma. However, in the statistical analysis, we could not state statistical significance (p=0.05-0.9). This trend stands in part in contrast to the findings of Weitz *et al*., who have reported a 5-year survival rate of 63% for synovial sarcoma and 87% for MFS (15). However, we confirmed their findings regarding the survival rate of undifferentiated pleomorphic sarcoma (formerly known as MFH) (15). This difference could be explained by the heterogeneous study design and lack of statistical power in our cohort.

Surgical margins are an ongoing and controversial issue in STS treatment. The literature is characterized by inconsistent findings regarding the prognostic value. Some authors state that surgical margins influence local recurrence but not overall survival (19, 20). On the other hand, some authors have stated the importance of negative margins for overall survival (14, 21). Our study lacks statistical power to give any further informative value to this pattern.

Our study proved local recurrence as a prognostic factor for the survival of STS patients. The 5-year survival rate decreased from 74% to 51% (p=0.036), and the HR increased to 2.2 in patients with and without local recurrence. Local recurrence occurred independent of the state of the margins; in fact, most of the patients with local recurrence had histologically negative margins. Local recurrence is a major problem for surgeons and patients. Reoperation is much more difficult due to neurovascular structures and scar tissue because most STSs are located deep in the thigh. This fact was examined by Kikuta *et al*. in their cohort of MFS patients with local recurrence, who had a 5-year re-recurrence-free survival rate with positive histopathological margins of 9.8% and those with negative margin of 62.3% (22).

Local recurrence of STS can be seen as a biological marker of the aggressiveness of the tumour (14, 20). In line to the findings of Albertsmeier *et al*., the local recurrence rate in our study was significantly higher in patients with ART compared to those with NRT (6).

In total, 54 patients (45.4%) developed distant metastases during the study period. Basically, the appearance of metastases indicates a transition from a local disease to a systemic disease accompanied by a dramatic decrease in 5-year survival, dropping to 37.2% (95%CI=22.5-51.9) compared to 98.0% (95%CI=94.1-100.0) in metastasis-free patients (p<0.001), as shown in Figure 6. We proved a strong relationship between distant metastasis and tumour-related mortality in our cohort. Metastasis formation is a statistically significant prognostic factor for poor outcome of STS. We

confirmed the results of other working groups, such as Zagars *et al*. and Pisters *et al*., who have reported an even poorer outcome with a 5-year survival of 28% (14, 21). The HR of 31 is another parameter that reflects the dramatic rise in mortality when metastasis occurs.

Surgical complications are common after radiation and are well known. Patients suffer from wound complications, deep wound infections, seroma, and fractures that sometimes lead to amputation of the affected extremity. These complications are well described for adjuvant radiation therapy (23-25). Neoadjuvant radiation therapy could contribute to reducing these problems. The main problem we were facing was wound healing disorders (total of 36 patients/119 30%) followed by deep wound infections in 11/119 patients. We confirmed the findings of O'Sullivan *et al*. (5), who reported a 18% wound healing complication rate in their cohort . The significantly higher rate of wound healing problems in the NRT group compared to the ART group was not reproduced in our cohort. We had equal distribution in the NRT and ART groups (Table V). Several explanations for this are feasible. In the cohort of O'Sullivan (5) not all patients had primary wound closure and sometimes plastic surgery reconstruction was performed in the adjuvant group. In our cohort, patients had primary wound closure. Second, the radiation protocol varied in the two studies; some of the patients in their NRT group received a second dose of radiation after primary wound closure. However, NRT or ART, though an important step in the treatment of STS, is followed by important surgical complications that the patient and the surgeon must be aware of (1). Devastating complications such as limb amputation are rare but may occur.

Our study has certain limitations. The number of patients included in the study limits the statistical analysis. STS remains a rare disease with different histopathological subtypes that respond differently to radiation therapy. Therefore, a multicentre study with a detailed analysis of the histopathological subtypes and their response to radiation therapy would be desirable. Furthermore, no patients were included in our study who received additional chemotherapy that could possibly contribute to an improved outcome, but this would have led to a further subdivision of the total cohort. As a future outlook for individualized radiation therapy, it may be expected that models using clinical and radiomic features could improve therapy in patients with STS (26-28).

Conclusion

Analysis of retrospective data from a single institution could identify specific prognostic risk factors for overall survival, such as tumour size, grading, local recurrence and metastasis, whereas tumour localisation did not affect the overall survival. Surgeons must be aware of these findings preoperatively as much as treating a very rare and heterogenous disease. NRT and ART did not differ significantly in overall survival or risk of complication, but local recurrence was significantly lower for NRT. Further prospective studies, particularly focusing on indication, outcome and complication rates for NRT or chemotherapy, are required.

Conflicts of Interest

The Authors declare that they have no financial or non-financial competing interests.

Authors' Contributions

HM, BS and CK performed patient recruitment, clinical investigation and data analysis. UL, FL, AG, RB, JCP, SC and RvER helped draft the article and correct the manuscript. HM and CK wrote the manuscript. All Authors read and approved the final article.

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