Introduction

Soft tissue sarcoma (STS) is a heterogeneous group of malignant tumors which, with the exception of the reticulo-endothelial system, originates from extra-skeletal mesenchymal and neuroectodermal tissues. The majority of tumors occur in adults in their 60s. The cornerstone of treatment is surgery, which is often combined with radiotherapy and chemotherapy. The prognosis is generally considered poor.

The Regional Musculoskeletal Tumor Center, University Hospital, Lund, Sweden, is the repository for a population-based database which contains clinicopathologic, treatment, and follow-up data on adult patients with STS of the extremity and trunk wall.

This presentation of information from the database summarizes and expands upon earlier findings from our center. It addresses epidemiology and clinical course, prognosis, and the association between local recurrence and metastases.

Epidemiology and clinical course

Few authors have used population-based series in studies of STS. We believe that this may facilitate more accurate assessment of the clinical behavior of STS.

Histopathologic classification has evolved considerably over the last few decades with the aid of new diagnostic techniques, such as immunohistochemistry, electron microscopy and cytogenetic analysis. These advances and refinements have resulted in the reclassification of several tumors. For example, rhabdomyosarcoma and fibrosarcoma, which were common histotypes 30 years ago, are today considered rare. In their place, malignant fibrous histiocytoma (MFH) is now recognized to be the commonest.

Prognostic factors

The clinical course in STS varies between uneventful follow-up after simple surgery to metastases and local recurrences despite extensive treatment. Chemotherapy, which has significantly improved survival in osteosarcoma and Ewing sarcoma, has not proved effective in STS. A suitable selection of patients is necessary for assessing possible benefits of chemotherapy. To this end, a number of prognostic systems are available. Not all distinguish helpfully between survival groups and this may, in part, be attributed to the selection of weak prognostic factors. One aspect, still uncommon amongst reports, is the study of prognostic factors in histotypes in isolation.

Metastases and local recurrence

The influence of primary tumor treatment on survival remains controversial. It is accepted that inadequate local treatment is often responsible for local recurrence. The frequent development of local recurrence in patients who also develop metastases has been interpreted as causal, with the local recurrence being the source of the metastases. This has led to aggressive and mutilating treatment to increase survival. This view has been questioned by studies which have failed to demonstrate any major impact from local treatment on survival.

This study aims to

- describe the epidemiology and clinical course in a population-based series of STS.
- identify prognostic factors, and propose a prognostic system.
- elucidate the association between local recurrence and metastases.

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The database can be obtained from the author. Please provide unformatted 3.5 inch floppy disk (StatView II® for Macintosh®).

Patients and methods

Since 1958, all patients with a malignant tumor are recorded in the Swedish Cancer Registry and since 1982, this has occurred via the Regional Tumor Registries. A double-reporting system is used that requires the pathologist and the physician to report every patient with a diagnosis of malignancy. As a result, nearly all cases are registered (Mattsson 1984, Kreicbergs et al. 1987). Furthermore, all residents of Sweden can be identified via a unique civic registration number, which permits the compilation of a population-based series of patients with complete follow-up, irrespective of where the treatment has been given. In almost all instances, pertinent medical records are available from other hospitals.

In 1970, the Musculoskeletal Tumor Center was founded at the Department of Orthopedics, University Hospital in Lund, to serve the Southern Swedish Health Care Region. The population in this area has increased from 1.2 million in 1964 to 1.5 million in 1989. The members of this center are orthopedic surgeons, radiologists, cytopathologists, pathologists and oncologists.

Inclusion criteria

We collected all adult (16 years or older) patients with a STS of the extremity and trunk wall who, at the time of diagnosis, were living permanently in the region, and had been diagnosed from 1964 through 1989. These patients were identified with the assistance of the Swedish Cancer Registry and Regional Tumour Registry. Patients with Mb Recklinghausen, Kaposi's sarcoma, dermatofibrosarcoma protuberans, desmoid tumors, Stewart-Treves syndrome, and post-irradiation sarcomas were excluded, as were patients with strictly dermal tumors. An additional 19 patients were excluded because of unretrievable histologic slides or medical records.

The medical records of all patients treated at our center since 1970 were examined, as were those of patients treated elsewhere—i.e., preoperative examinations, radiographic reports, operation records, histopathologic reports, and postoperative examinations. Every histologic specimen was reexamined by pathologists in our center.

Altogether, 508 patients were entered into the database, which is population-based, i.e., it contains information about *all patients in a defined area irrespective of where treatment has been given.*

The use of a population-based series has several advantages. Selection bias in referral and follow-up is avoided. Bias in referral may affect center-based series by limiting the referral of patients with small and superficial tumors. Bias in follow-up may distort the results of a center-based series in that patients who do not develop a local recurrence and / or metastasis, tend to be underrepresented. In a population-based series, the records of patients treated outside the center includes all procedures performed, thereby permitting an analysis of the impact on outcome of various treatments. Such analyses are more difficult to carry out at tumor centers which maintain optimal standards of treatment.

Referral pattern

Patients referred before surgery were classified as *virgin,* or *after fine-needle aspiration cytology.* Patients referred after surgery were classified as referred after *incisional biopsy, surgery with a marginal margin, local recurrence,* or as referred after *metastasis.* Non-center patients were designated *not referred.*

Localization

Upper extremity, proximal, shoulder, upper arm, elbow.
Upper extremity, distal, lower arm, hand.
Trunk wall.
Lower extremity, proximal, hip girdle, thigh, knee.
Lower extremity, distal, lower leg, foot.

Depth

Subcutaneous tumors, superficial to and not involving the deep fascia.
Deep-seated tumors, below the deep fascia and / or involving this fascia.

Size

Tumor size was recorded as the largest diameter, either in the surgical specimen or on preoperative examinations.

Surgery

Surgical margins and compartmentalization were classified according to Enneking et al. (1980) and Rydholm and Rööser (1987).

An *intralesional* margin was defined as excision

with macroscopic residual tumor.

A *marginal* margin was referred to when the pseudocapsule formed any part of the resection border.

A *wide* margin was subdivided depending on tumor depth: wide-S (subcutaneous) for subcutaneous tumors, where the tumor had to be sideways surrounded by a minimum of a 2-cm cuff of macroscopically normal tissue, and the deep fascia in the bottom. For a deep-seated tumor the margin was called wide-AM (areolar or muscular). The tumor was removed with a cuff of macroscopically normal tissue surrounding it entirely. The thickness of this cuff varied, but was never less than 2 cm. Provided the tumor was intramuscular, and a primary myectomy (removal of the tumor-bearing muscle or group of muscles) was performed, the margin was called wide-F (fascia), if there were unbroken fascial planes (fascia or periosteum) around the tumor. For this margin, fine-needle aspiration cytology was allowed as a diagnostic procedure, but not open biopsy.

A *radical* margin was achieved if the whole tumor-bearing compartment was removed en bloc.

Surgery was also classified as a *local procedure* or an *amputation*. These terms designated the procedure, not the margin.

Radiotherapy

Target volume included the entire tumor-involved anatomic structure with appropriate margins. The specified target's absorbed dose was 51 Gy / 17 fractions in 1981 through 1986 (Alvegård et al. 1989b). Before 1981 and after 1986, the dose was 50 Gy / 25 fractions.

Local treatment

The local treatment was classified as *inadequate* (surgery with an intralesional margin regardless of adjuvant radiotherapy, or surgery with a marginal margin without radiotherapy) or *adequate* (surgery with a marginal margin with adjuvant radiotherapy or surgery with a wide or radical margin, regardless of radiotherapy).

Chemotherapy

Chemotherapy was given to 57 patients, according to several different regimens, and they were not analyzed separately.

Histopathologic classification and malignancy grading

Archival tumor tissue from all patients were reexamined by the pathologists at our center (Helena Willén, MD, PhD, and Måns Åkerman, MD, PhD). All tumors were described according to current classification systems (Enzinger and Weiss 1988). (For details see Rööser et al. 1989, Rööser et al. 1991, Gustafson et al. 1992b, Gustafson et al. 1993b). Malignancy grading was on a four-grade scale (Broders et al. 1939, Angervall et al. 1986) and was based on estimation and a combination of cell and tissue differentiation, cellularity, cellular atypia, necrosis and mitotic frequency.

The value of peer review of STS has been stressed by Baker and Benjamin (1978), and by Alvegård and Berg (1989), who found that in one fourth of the tumors the histotype was reclassified, and in two fifths the malignancy grade was changed, when STS was reviewed by an expert pathology committee.

Tumor necrosis

Necrosis was said to be present if the diameter of one necrotic area in any of the examined slides exceeded 4 mm. This has been shown to be of prognostic value for a mixed series of soft tissue sarcomas and for malignant fibrous histiocytoma (Rööser 1987, Rööser et al. 1991).

Vascular invasion

Vascular invasion was defined as only a definite and well-established growth of tumor cells within the lumen of microscopic intratumoral blood or lymphatic vessels. Vascular invasion is of prognostic value in carcinoma of the uterine cervix (Willén 1984), and in sarcoma (Mandard et al. 1981, Trojani et al. 1984, Chase and Enzinger 1985).

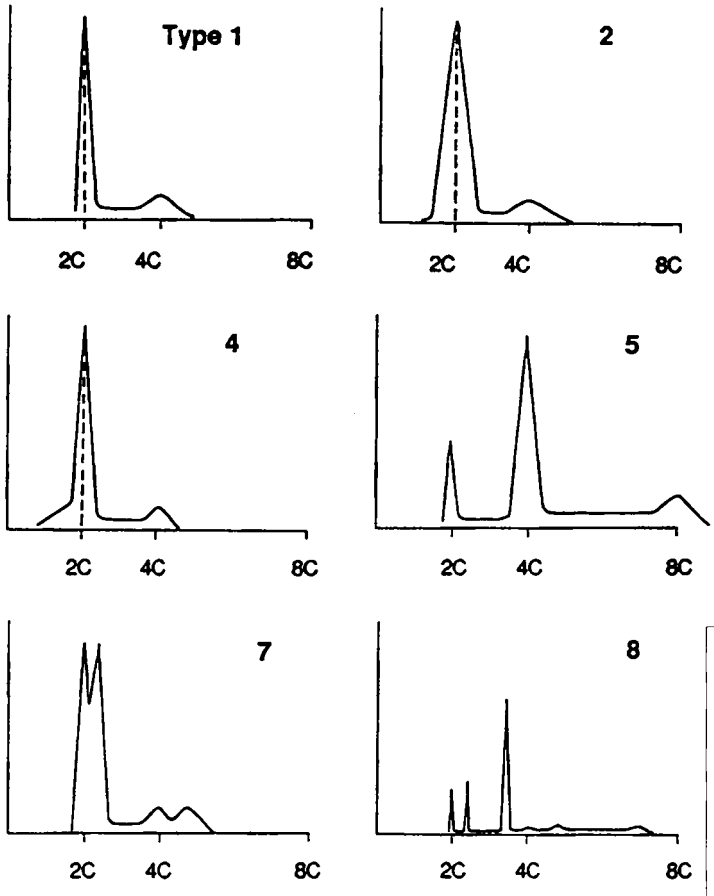
DNA analysis

Flowcytometric DNA analysis was performed on either disintegrated formalin-fixed and paraffin-embedded tissue (n 258) or fresh/frozen (n 59) operative specimens. These two methods were considered equivalent with regard to ploidy status (Fernö et al. 1990). For details, see Appendix. All analyses were performed by Bo Baldetorp, PhD, and Mårten Fernö, PhD, at our center.

Eight different types of histograms were identified (Figure 1). Histogram types 1 and 2 were grouped together and called "DNA type 1–2". Histogram types 3 through 8 were grouped together and called "DNA type 3–8". This gave the best prognostic separation and was based on a Scandinavian Sarcoma Group study with pooled data from 777 patients with STS of the extremity and trunk wall (Gustafson 1994).

Completeness of data

There were complete data on all 508 patients, with the exception of DNA analysis, vascular invasion,



Type 1. A narrow gaussian distribution.
2. A broad gaussian distribution.
3. A non-gaussian distribution.
4. A dominant narrow and gaussian distribution with a clearly distinguishable small skewness at either side of its base.
5. A tetraploid distribution.
6. An aneuploid distribution.
7. An aneuploid distribution with two distinguishable G_0/G_1 peaks.
8. Multiple non-diploid G_0/G_1 peaks.

Figure 1. Representative examples of different types of FCM DNA histograms. The distribution is 'narrow' when the coefficient of variation (CV) is less than 7.5 percent and 'broad' when larger. Tetraploid samples required the number of events in the 4C peak to be larger than 20 percent of the total diploid DNA distribution, and a G_2 peak in the octaploid region.

and tumor necrosis. DNA content could be analyzed in 317 patients, vascular invasion in 356 patients, and tumor necrosis in 445 patients. These analyses were less commonly performed in patients from the earlier years of our series, otherwise we found no specific selection bias.

Follow-up

All follow-up times were calculated from the day of diagnosis of the primary tumor. Patients treated at our center were followed by clinical examinations, including chest radiographs, at regular intervals for at least 6 years. Patients treated outside our center were, in many instances, followed as described above, but several patients were followed at irregular intervals or for a shorter time. All patients were also followed via the Swedish Population Registry. Patients who died with tumor, but from other causes, were classified as "died with tumor but from other causes", as opposed to "died from tumor".

The occurrence of metastases was chosen as the end-point in prognostic analyses. 14 patients dying of local consequences of the tumor, but without metastases, were regarded as censored. At latest follow-up, 178 of the 202 patients with metastases had died from tumor. In the majority, the diagnosis of a local recurrence was based on histopathologic examinations, otherwise by clinical findings, which in later years were confirmed by fine-needle aspiration cytology. The diagnosis of pulmonary metastases was based on radiography. The autopsy frequency was 76 percent in patients judged to have died from tumor, 73 percent in patients who died with tumor but from other causes, and 56 percent in patients who died without

tumor. No patient was lost to follow-up. The cumulative follow-up for all 508 patients was 3,596 person-years.

Statistics

The data were analyzed using the Mann-Whitney U-test, the Chi-square test with the Yates continuity correction when indicated, the Kruskal-Wallis test, and Pearson's correlation coefficient. Analyses of metastasis-free survival were univariately performed using the Kaplan-Meier methods and the Generalized Wilcoxon test. Cox multivariate analyses of independent prognostic factors for metastasis-free survival were performed, and the Wald statistic was used for assessment of significant factors. A P-value < 0.05 was considered significant. The analyses were performed by Jonas Ranstam, PhD, Department of Community Health Sciences, Malmö General Hospital, Sweden. The relative survival analysis was done according to Hakulinen and Abeywickrama (1985), and was performed by Harald Anderson, PhD, Regional Tumour Registry, University Hospital in Lund, Sweden.

Epidemiology and clinical course

Clinicopathologic data

STS was more common in men. The annual incidence was 18 per million population. The thigh was the single commonest localization. Subcutaneous tumors were smaller than deep-seated ones (Table 1). Proximal tumors were larger than distal ones (mean sizes 9 cm versus 5 cm). Malignant fibrous histiocytoma (MFH) and grade IV tumors were the commonest (Table 2). At latest follow-up, 192 patients had died from tumor, 15 had died with tumor but from other causes, 95 had died from unrelated disease, and 206 patients were alive, 2 of whom with disease. The median follow-up for all 508 patients was 5 years (1 month – 28 years), and for the 206 survivors 11 (3–28) years.

Association with histotype

The typical patient with a MFH was 70 years old and had a 7-cm deep-seated grade IV tumor in the thigh. A leiomyosarcoma typically occurred in a patient of similar age, localization and malignancy grade, but it was smaller. In contrast, a liposarcoma typically presented as a larger tumor of grade II in a patient one decade younger. Patients with synovial sarcoma were typically young and the tumors were distally located, small and deep-seated (Table 3).

Covariations

Tumor necrosis had the greatest number of covariates: vascular invasion, DNA content, malignancy grade, size, histotype and depth. Malignancy grade and DNA content had fewer but similar covariates. Depth correlated only with size and necrosis (Table 4).

Local recurrence

Of 508 patients, 471 were surgically treated. At latest follow-up, 139 patients had developed a local recur-

Table 1. Epidemiology in 508 patients with a soft tissue sarcoma of the extremity and trunk wall

Annual incidence / million		17.5	
Age, median (range)		64	(16–96)
Sex male		288	
female		220	
Localization			
upper extremity	prox	76	
	dist	46	
trunk wall		68	
lower extremity	prox	239	
	dist	79	
Tumor depth			
subcutaneous	mean size 5 cm	154	
deep-seated	mean size 9 cm	354	
Tumor size, cm	median (range)	6.5	(1–40)
	mean	8	
Tumor necrosis	no	224	
	yes	221	
Vascular invasion	no	265	
	yes	91	
DNA analysis	type 1–2	94	
	type 3–8	223	

Tumor necrosis determined in 445 patients, vascular invasion in 356 patients, and DNA analysis performed in 317 patients. In 5 patients DNA analysis was performed but was considered inconclusive.

Table 2. Histotypes and malignancy grades in 508 patients with soft tissue sarcoma of the extremity and trunk wall

	Malignancy grade				
Histotype	I	II	III	IV	Total
MFH	7	16	49	137	209
Leiomyosarcoma	2	6	19	39	66
Liposarcoma	5	23	13	12	53
Synovial sarcoma	0	3	18	15	36
Nerve tumor[a]	1	5	8	9	23
Malign. hemangiopericytoma	0	13	5	3	21
Fibrosarcoma	2	3	8	3	16
Rhabdomyosarcoma	0	0	2	13	15
Hemangiosarcoma	0	0	3	5	8
Epithelioid cell sarcoma	0	0	5	3	8
Malignant mesenchymoma	1	1	0	4	6
Clear cell sarcoma	0	0	1	5	6
Extraskeletal					
myxoid chondrosarcoma	1	3	0	1	5
mesenchymal chondrosarc.	0	0	2	0	2
osteosarcoma	0	0	1	1	2
Ewing's sarcoma	0	0	0	2	2
Alveolar soft part sarcoma	0	0	1	0	1
Soft tissue sarcoma, unclass.	2	3	3	21	29
Total	21	76	138	273	508

[a]Malignant peripheral nerve sheath tumor

Table 3. Clinicopathologic data versus subtype in a population-based series of patients with soft tissue sarcoma of the extremity and trunk wall

		Histotype			
		MFH	Leiomyosarc.	Liposarc.	Synovial sarc.
Number (percent of all STS)		209 (41)	66 (13)	53 (10)	36 (7)
Age, median (range)		68 (19–96)	67 (22–94)	59 (29–90)	39 (17–85)
Tumor size, median (range), cm		7 (1–40)	5 (1–25)	9 (2–30)	5 (1–16)
Depth (percent)	subcutaneous	77 (37)	28 (42)	11 (21)	5 (14)
	deep-seated	132 (63)	38 (58)	42 (79)	31 (86)
Malignancy grade (percent)	I	7 (3)	2 (3)	5 (9)	0 (0)
	II	16 (8)	6 (9)	23 (43)	3 (8)
	III	49 (23)	19 (29)	13 (25)	18 (50)
	IV	137 (66)	39 (59)	12 (23)	15 (42)
Localization (percent)	upper extr. prox	29 (14)	8 (12)	7 (13)	0 (0)
	upper extr. dist	13 (6)	10 (15)	1 (2)	5 (14)
	trunk wall	26 (12)	4 (6)	6 (11)	6 (17)
	lower extr. prox	103 (50)	32 (49)	35 (66)	11 (31)
	lower extr. dist	38 (18)	12 (18)	4 (8)	14 (39)

Table 4. Covariations between tumor characteristics in 471 patients surgically treated for soft tissue sarcoma of the extremity and trunk wall

	DNA content	Malignancy grade	Vascular invasion	Histotype	Tumor size	Tumor depth
Tumor necrosis	+	+	+	+	+	+
DNA content		+	+			
Malignancy grade			+			
Histotype					+	
Tumor size						+

Footnote: MFH and leiomyosarcoma were more often necrotic.

Table 5. Localization and time to diagnosis of first metastasis in the commonest histotypes in soft tissue sarcoma

Histotype	Total	Pulmonary	Skeletal	Soft tissues	Lymph nodes	Multiple	Months to diagnosis median (range)
MFH	70	54	4	7	2	3	9 (0–93)
Liposarcoma	18	5	2	6	0	5	16 (0–163)
Leiomyosarcoma	28	15	1	1	3	8	12 (0–85)
Rhabdomyosarcoma	12	3	0	1	4	4	4 (0–36)
Synovial sarcoma	19	14	0	2	2	1	12 (0–144)
Nerve tumor	10	6	1	1	1	1	20 (6–153)
Soft tissue sarcoma, unclass.	12	8	0	0	1	3	4 (0–139)

rence; 123 within 3 years and all within 13 years. 47 patients had more than one local recurrence. Half of all local recurrences (77 of 139) were seen in patients treated outside our center, while one fifth (62 of 295) of patients treated at our center developed a local recurrence.

Metastases

38 patients had a metastasis at the time of diagnosis of the primary tumor. At latest follow-up, 202 patients had developed metastases; 176 within 3 years and all within 14 years. Metastases were first detected in the lungs in 125 patients, in the soft tissues in 19, in the lymph nodes in 16, in the skeleton in 11 and in multiple localizations in 31 patients.

In MFH, leiomyosarcoma, synovial sarcoma, nerve tumors, and in unclassified STS, the commonest localization of the first metastasis was the lung. In liposarcoma, soft tissue metastases were relatively frequent (3 in the locomotor system, 1 in the liver, 1 in the retroperitoneal space, and 1 in the right

Table 6. Median months to metastasis and local recurrence in subsets of 159 patients with soft tissue sarcoma of the extremity and trunk wall

Median time to	Small/low-grade (n 76)	Large/high-grade (n 83)
metastasis in patients without local recurrence	24	8
metastasis in patients with local recurrence	30	7
local recurrence	20	8

Small = ≤ 10 cm. Low–grade = malignancy grades I and II.

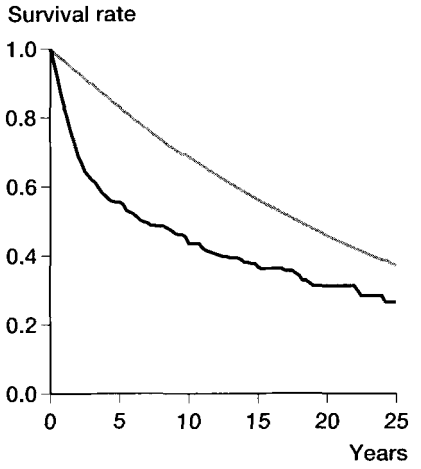


Figure 2. Observed total survival (black line) in 508 patients with soft tissue sarcoma of the extremity and trunk wall, compared to expected total survival (grey line) in a Swedish reference population.

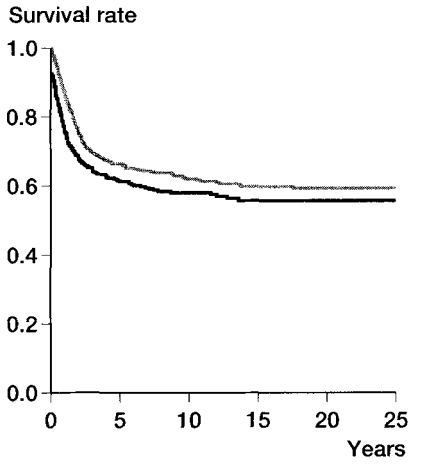


Figure 3. Tumor-related survival (grey line) and metastasis-free survival (black line) in 508 patients with soft tissue sarcoma of the extremity and trunk wall.

ventricle of the heart, out of 18), and in rhabdomyosarcoma the lymph nodes and multiple locations were equally common (Table 5).

The median time to detection of pulmonary metastases was 0.8 (0–13) years, for skeletal metastases 2 (0–7) years, for soft tissue metastases 2.5 (0–14) years, for lymph node metastases 0.3 (0–3) years, and for multiple localizations 0.5 (0–4) years. Local recurrence and metastasis were found 3 times later in small and low-grade tumors than in large and high-grade tumors (Table 6).

Survival

The crude metastasis-free survival was 306 / 508 (60 percent), and the crude tumor-related survival was 316 / 508 (62 percent). The observed 10-year total survival rate was 0.44, and the expected total survival in a standardized population was 0.68 (Figure 2). The 5-year metastasis-free survival rate (MFSR) was 0.61, and the 5-year tumor-related survival was 0.66 (Figure 3).

Referral

43 percent of the patients were referred before surgery. Since 1970, one half of the patients in the uptake area have been referred to our center before surgery. In 1985 to 1989 this figure was two thirds (Table 7), for patients with subcutaneous tumors one half, and for patients with deep-seated tumors four fifths (Table 8). Patients who were not referred were older and comprised two groups; one group had metastases at the time of diagnosis of the primary tumor, while the other group had subcutaneous and small tumors. Despite the favorable surgical conditions of the latter group, inadequate treatment was common (Table 9).

Discussion

The 5-year tumor-related survival rate was comparatively high, 0.66. One explanation is the high fraction of subcutaneous and small tumors. These may, due to

Table 7. Referral pattern in a population-based series of patients with soft tissue sarcoma of the extremity and trunk wall

	Calender year			
Referrals	1964–1989	1970–1989	1970–1974	1985–1989
Virgin	116	116	20	44
After aspiration cytology	105 [a]	105	1	47
After incisional biopsy	23	23	7	4
After marginal surgery	83 [b]	83	12	19
After local recurrence	18	18	2	7
After metastasis	0	0	0	0
Not referred	163	75	39	11
Total	508	420	81	132

[a] Includes 2 patients with coarse needle biopsy.
[b] includes 1 patient referred after surgery with a wide margin.

Table 8. Referral pattern versus tumor depth in 1970–1974 and 1985–1989 in patients with soft tissue sarcoma of the extremity and trunk wall. 420 patients were diagnosed between 1970 and 1989

	1970–1974			1985–1989		
	subcutaneous	deep-seated	total	subcutaneous	deep-seated	total
Before surgery[a]	3	18	21	17	74	91
After surgery[b]	7	14	21	15	15	30
Not referred	17	22	39	5	6	11
Total	27	54	81	37	95	132

[a]Virgin or after fine-needle aspiration cytology.
[b]After incisional biopsy, marginal surgery, local recurrence.

Table 9. Clinicopathologic data in 420 patients with soft tissue sarcoma of the extremity and trunk wall. Comparison of patients referred and not referred to tumor center

		Referred (n 345)	Not referred (n 75)	*P*-value
Age	mean (range)	60 (17–96)	68 (26–91)	0.0001
Sex	male / female	190 / 155	43 / 32	0.8
Localization	upper extremity prox	52	8	0.2
	upper extremity dist	32	10	
	trunk wall	38	14	
	lower extremity prox	168	31	
	lower extremity dist	55	12	
Tumor depth	subcutaneous	93	36	0.0003
	deep-seated	252	39	
Size	mean (range) cm	8 (1–30)	7 (1–20)	0.09
Metastasis at diagnosis	yes	21	10	0.05
	no	324	65	
Local treatment	inadequate	62	41	0.0001
	adequate	265	25	
	no operation	18	9	

selection bias, be underrepresented in center-based series. We previously reported that subcutaneous tumors had a better prognosis than deep-seated tumors since they were often small and less malignant. The local recurrence rate after surgery with a wide margin but without radiotherapy was less than 10 percent (Rydholm et al. 1991). Therefore, the identification of this large group of patients is of importance.

MFH was the commonest histotype, followed by leiomyosarcoma, liposarcoma, and synovial sarcoma. This distribution concurs with the data of Enzinger and Weiss (1988) and apart from minor differences generally holds true for most other series. We have used the four-grade scale for malignancy grading as originally proposed by Broders et al. (1939) and as applied to STS by Angervall et al. (1986). There are other grading systems that employ 2 to 4 grades and utilize different criteria. The increasing efforts to introduce newer grading systems attest to the difficulty of classifying malignancy.

Another difficulty with grading systems is to assign the relative weights of each histologic parameter. Multivariate analysis can discern the relative risks of specific prognostic factors. In this way, the strongest prognostic factors can be isolated for use in a grading system. This method, however, has been restricted to a few studies (Trojani et al. 1984, van Unnik et al. 1993), and several grading systems have used histologic factors which were not tested for strength or independence. Furthermore, as specific factors are recognized to be important, they may influence malignancy grading. For example, since the prognostic importance of necrosis has been recognized, our pathologists have classified more necrotic tumors as grade IV.

90 percent of all local recurrences and metastases occurred within 3 years. We have chosen 6 years as the length of regular follow-up for all patients. Follow-up of patients with liposarcoma, synovial sarcoma, and nerve tumors, however, should be extended, as these patients may have late local recurrences and metastases. In addition, our observations of late events like these after small and low-grade tumors raise the question whether such patients should be followed for a longer period. Apart from regular pulmonary radiographs and physical examinations, the value of other measures, such as CT scans of chest and abdomen or skeletal scintigraphy, remains to be established. In our series the commonest localization of the first metastasis was the lungs in patients with MFH, leiomyosarcoma, synovial sarcoma, nerve tumors, and unclassified STS, whereas it was the soft tissues in patients with liposarcoma. Lymph node metastases were more often seen with synovial, angio- and rhabdomyosarcoma. These findings concur with those of others (Lawrence et al. 1987, Huth and Eilber 1988, Evans 1988, Ariel 1988, Fong et al. 1992).

Patients treated outside our center more often received inadequate local treatment, which explains their higher local recurrence rates. We previously reported that both the number of operations for the primary tumors and the local recurrence rates can be reduced if patients with suspected STS are referred to a tumor center before surgery (Gustafson et al. 1994). In 1985 through 1989 more than two thirds—for deep-seated tumors almost four fifths—of the patients were referred to our center before surgery. This favorable referral pattern is a result of strict guidelines for referral in our uptake area. This has been made possible by repeated information given to to physicians at local hospitals who are encouraged to refer before surgery all patients with soft tissue tumors that are larger than 5 cm, or deep-seated, or otherwise suspected of malignancy. As a result of these recommendations, for every patient with a soft tissue sarcoma, 10 patients are referred with a tumor which turns out to be benign, a cost considered to be reasonable (Rööser et al. 1987a).

Prognostic factors

Most studies have used histotypically mixed series of STS to evaluate prognosis. The benefits include a larger sample size, and hence greater statistical strength. The identification of prognostic factors in such series enhances their value in a prognostic system, which should ideally be applicable to all histotypes. One disadvantage, however, is that prognostic factors, which could be specific to certain histotypes, may not be recognized.

This section evaluates prognostic factors in a mixed series, and in MFH, leiomyosarcoma, liposarcoma, and synovial sarcoma.

Univariate analyses were performed using the Kaplan–Meier technique. All factors were then included in a Cox model. Inclusion criteria in the Cox model were: surgical treatment for the primary tumor, no metastasis at diagnosis of the primary tumor, and complete data.

All histotypes (mixed series)

Patients

The analysis comprised 471 patients. The median follow-up time for the 204 patients who were alive at the latest follow-up was 11 (3–28) years.

Clinicopathologic data

A male preponderance of 1.4:1 was seen. The median age was 64 (16–96) years.

Localization in the proximal part of the lower extremity and grade IV were commonest (Table 11).

Local treatment

Two thirds of the patients received adequate local treatment for the primary tumor and in one tenth this entailed amputation. In one sixth of the patients, surgery was combined with adjuvant radiotherapy (Table 10).

Local recurrence

132 of the 139 patients who developed a local recurrence did so within 6 years. One third (47) of the patients had more than one local recurrence. The local recurrence rate (0.6) for patients with inadequate local treatment was three times higher than for patients with adequate local treatment (0.2) (Table 10). Patients with a local recurrence had twice the metastatic rate of patients without a local recurrence (79/139 versus 98/332).

Metastases

Of the 471 patients, 21 had metastases at diagnosis of the primary tumor. Of the remaining 450 patients 156 developed metastases, 146 of them within 6 years.

At the latest follow-up, 154 of the 177 patients with metastases had died from tumor. 165 patients died from tumor, 141 of them within 5 years. The cumulative 5-year metastasis-free survival rate (MFSR) for all 471 patients was 0.64.

Results

Prognostic factors for metastases

By univariate analysis, male sex, deep-seated tumor, increasing size and grade, necrosis, vascular invasion, DNA type 3–8, inadequate local treatment, and local recurrence reduced the metastasis-free survival.

A Cox model of 244 patients revealed that tumor size larger than 10 cm, tumor necrosis, vascular invasion, leiomyosarcoma, and local recurrence independently reduced the metastasis-free survival (Table 11). The other factors lost their significance due to covariations with the independent prognostic factors.

Prognostic factors for local recurrence

Localization in the distal part of the upper extremity (relative risk (RR) 5), size larger than 10 cm (RR 5), inadequate treatment (RR 3), necrosis (RR 3), and leiomyosarcoma (RR 3) were independent prognostic factors for local recurrence.

Table 10. Local treatment and local recurrence rates in 471 patients treated for soft tissue sarcoma of the extremity and trunk wall. 426 patients were treated with local excision and 45 with amputation

Local treatment	n	Local recurrence rate	Fraction
Intralesional	5		
Intralesional + RT[a]	10	5/10	0.5
Marginal	128	73/128	0.6
Marginal + RT[a]	52	18/52	0.3
Wide[b]	246	43/246	0.2
Radical[c]	30	0/30	
Total	471	139/466	0.3

[a] Radiotherapy. 50 patients given adjuvant chemotherapy not separately analyzed.
[b] Includes 16 patients with RT.
[c] Includes 2 patients with RT.

Table 11. Clinicopathologic data, metastasis-free survival, and uni- and multivariate prognostic factors for metastases in 471 surgically treated patients with soft tissue sarcoma of the extremity and trunk wall

Factor	Criteria	n	5-year MFSR	*P*-value univariate analysis	Crude metastasis n	Multivariate analysis RR (95% CI)
Age	≤ 64 yrs	249	0.65	0.6	94	
	> 64 yrs	222	0.62		83	
Sex	male	271	0.60	0.04	109	
	female	200	0.69		68	
Localization	upper extremity prox	70	0.68	0.2	25	
	upper extremity dist	44	0.76		10	
	trunk wall	62	0.54		27	
	lower extremity prox	219	0.61		89	
	lower extremity dist	76	0.71		26	
Depth	subcutaneous	154	0.74	0.0003	40	
	deep-seated	317	0.59		137	
Tumor size (cm)	1 to 5	185	0.80	<0.00001	39	
	6 to 10	185	0.59		80	
	11 to 15	65	0.47		37	3.5 (1.6–8)
	16 and larger	36	0.39		21	
Histotype	MFH	203	0.69	0.2	65	
	leiomyosarcoma	60	0.59		24	2.1 (1.1–4)
	liposarcoma	50	0.73		16	
	synovial sarcoma	36	0.56		19	
	all other	122	0.58		53	
Malignancy grade	I	21	1.00	<0.00001	0	
	II	73	0.87		12	
	III	134	0.71		44	
	IV	243	0.50		121	
Tumor necrosis[a]	no	222	0.84	<0.00001	39	
	yes	209	0.45		120	3.2 (1.7–6)
Vascular invasion[b]	no	262	0.76	<0.00001	65	
	yes	88	0.37		60	2.2 (1.3–4)
DNA type[c]	1–2	94	0.75	0.004	28	
	3–8	221	0.57		93	
Local treatment	inadequate	143	0.55	0.003	67	
	adequate	328	0.68		110	
Local recurrence	no	332	0.71	<0.00001	98	
	yes	139	0.47		79	3.4 (2.0–6)

[a] Necrosis determined in 431 patients.
[b] Vascular invasion determined in 350 patients.
[c] DNA analysis performed in 315 patients.
MFSR metastasis-free survival rate.
RR relative risk.
CI confidence interval.

Malignant fibrous histiocytoma

Patients

The analysis comprised 203 patients. The median follow-up time for the 91 patients who were alive at the latest follow-up was 8 (3–28) years.

Clinicopathologic data

A male preponderance of 1.2:1 was seen. The median age was 68 (19–96) years. The majority of tumors were located in the proximal part of the lower extremity. Grade IV and pleomorphic MFH were the commonest (Table 12). Pleomorphic and storiform tumors were more often large, deep-seated, of grade IV, of DNA type 3–8, and more often had necrosis and vascular invasion than myxoid tumors (Table 14).

Local treatment

Three fourths of the patients received adequate local treatment for the primary tumor (Table 13).

Table 12. Clinicopathologic data, metastasis-free survival, and uni- and multivariate prognostic factors for metastasis in 203 surgically treated patients with malignant fibrous histiocytoma of the extremity and trunk wall

Factor	Criteria	n	5-year MFSR	*P*-value univariate analysis	Crude metastasis n	Multivariate analysis RR (95% CI)
Age	≤ 68 yrs	102	0.66	0.8	34	
	> 68 yrs	101	0.71		31	
Sex	male	109	0.66	0.2	38	
	female	94	0.72		27	
Localization	upper extremity prox	29	0.86	0.10	5	
	upper extremity dist	13	0.92		1	
	trunk wall	25	0.59		10	
	lower extremity prox	99	0.62		37	
	lower extremity dist	37	0.70		12	
Depth	subcutaneous	77	0.79	0.007	17	
	deep-seated	126	0.62		48	
Tumor size (cm)	1 to 5	77	0.89	<0.00001	9	
	6 to 10	77	0.62		30	
	11 to 15	33	0.42		19	4.1 (1.1–15)
	16 and larger	16	0.50		7	
Malignancy grade	I	7	1.00	0.0001	0	
	II	16	0.88		2	
	III	49	0.85		8	
	IV	131	0.58		55	
Subtype	myxoid	76	0.93	<0.00001	6	
	storiform	30	0.36		19	13 (3.5–53)
	pleomorphic	94	0.59		39	5.9 (1.8–19)
	inflammatory	2	0.50		1	
	angiomatoid	1	1.00		0	
Tumor necrosis[a]	no	91	0.90	<0.00001	10	
	yes	111	0.50		55	5.9 (1.8–20)
Vascular invasion[b]	no	150	0.75	<0.00001	39	
	yes	41	0.42		24	
DNA type[c]	1–2	17	0.82	0.07	3	
	3–8	116	0.64		42	
Local treatment	inadequate	52	0.52	0.006	24	
	adequate	151	0.74		41	
Local recurrence	no	137	0.74	0.01	35	
	yes	66	0.57		30	5.9 (2.5–14)

[a] Necrosis determined in 202 patients.
[b] Vascular invasion determined in 191 patients.
[c] DNA analysis performed in 133 patients.
MFSR metastasis-free survival rate.
RR relative risk.
CI confidence interval.

Local recurrence

Almost all local recurrences (65/66) developed within 6 years. Half (13/29) of those with multiple local recurrences had myxoid tumors. Two thirds of the inadequately treated patients developed a local recurrence compared to one fifth of those who received adequate local treatment (Table 13). The metastatic rate of those with local recurrence (30/66) was almost twice that of those without local recurrence (35/137).

Metastases

Of the 203 patients, 6 had metastases at diagnosis of the primary tumor. Of the remaining 197 patients 59 developed metastases, 51 of them within 6 years.

Table 13. Local treatment and local recurrence rates in 203 patients treated for malignant fibrous histiocytoma (MFH) of the extremity and trunk wall. 191 patients were treated with local procedures and 12 with amputation

Local treatment	n	Local recurrence rate	Fraction
Intralesional	3		
Intralesional + RT[a]	1	0/1	
Marginal	48	32/48	0.7
Marginal + RT[a]	21	8/21	0.4
Wide[b]	111	26/111	0.2
Radical[c]	19	0/19	
Total	203	66/200	0.3

[a] Radiotherapy. 14 patients given adjuvant chemotherapy not separately analyzed.
[b] Includes 4 patients with RT. [c] Includes 1 patient with RT.

Table 14. Clinicopathologic data by subtype in 200 patients with myxoid, pleomorphic or storiform subtype of malignant fibrous histiocytoma of the extremity and trunk wall

Factor		Myxoid	Storiform	Pleomorphic	*P*-value
Number		76	30	94	...
Age, mean		64	65	67	0.6
Sex	male	37	15	57	0.2
	female	39	15	37	
Localization	upper extremity prox	12	1	16	0.4
	upper extremity dist	6	1	6	
	trunk wall	8	7	9	
	lower extremity prox	35	15	47	
	lower extremity dist	15	6	16	
Depth	subcutaneous	43	10	24	0.0002
	deep-seated	33	20	70	
Malignancy grade	I	5	2	0	0.0001
	II	13	2	0	
	III	37	11	1	
	IV	21	15	93	
Size, mean, cm		5.9	9.2	9.2	0.0001
Tumor necrosis	no	57	13	19	0.0001
	yes	19	17	74	
	not evaluated	0	0	1	
Vascular invasion	no	67	20	61	0.002
	yes	6	6	28	
	not evaluated	3	4	5	
DNA type	1–2	13	3	1	0.0004
	3–8	35	12	68	
	not evaluated / inconcl.	28	15	25	

There was no correlation between subtype and the site where the first metastasis appeared.

At latest follow-up, 54 of the 65 patients with metastases had died from tumor. 57 died from tumor, 55 of them within 5 years. The cumulative 5-year MFSR for all 203 patients was 0.69.

Results

By univariate analysis, deep-seated tumor, increasing size and grade, subtype other than myxoid, tumor necrosis, vascular invasion, inadequate treatment, and local recurrence reduced metastasis-free survival.

122 patients were analyzed in a Cox model. Subtype other than myxoid, tumor necrosis, tumor larger than 10 cm, and local recurrence independently reduced the metastasis-free survival (Table 12).

Leiomyosarcoma

Patients

The analysis comprised 60 patients. The median follow-up time for the 16 patients who were alive at the latest follow-up was 12 (4–28) years.

Clinicopathologic data

A male preponderance of 1.5:1 was seen. The median age was 66 (22–87) years. Localization in the proximal part of the lower extremity and grade IV were commonest (Table 15).

Local treatment

Two thirds of the patients received adequate local treatment for the primary tumor (Table 16).

Local recurrence

All 11 local recurrences developed within 2 years. 2 patients had more than one local recurrence. One fourth of inadequately-treated patients developed a local recurrence, while this occurred in one sixth of those adequately treated (Table 16). Of the 11 patients with a local recurrence, 7 also had metastases, compared to 17 of the 49 patients without a local recurrence.

Metastases

Of the 60 patients, 3 had metastases at diagnosis of the primary tumor. Of the remaining 57 patients, 21 developed metastases, 20 of them within 6 years. At the latest follow-up, 22 of the 24 patients with metas-

Table 15. Clinicopathologic data, metastasis-free survival, and uni- and multivariate prognostic factors for metastasis in 60 surgically treated patients with leiomyosarcoma of the extremity and trunk wall

Factor	Criteria	n	5-year MFSR	*P*-value univariate analysis	Crude metastasis n	Multivariate analysis RR (95% CI)
Age	≤ 66 yrs	31	0.64	0.4	11	
	> 66 yrs	29	0.50		13	
Sex	male	36	0.65	0.7	12	
	female	24	0.51		12	
Localization	upper extremity prox	7	0.51	0.09	4	
	upper extremity dist	8	0.56		3	
	trunk wall	3	0		3	
	lower extremity prox	30	0.57		12	
	lower extremity dist	12	0.83		2	
Depth	subcutaneous	28	0.73	0.04	7	
	deep-seated	32	0.46		17	
Tumor size (cm)	1 to 5	31	0.61	0.002	12	
	6 to 10	20	0.73		5	
	11 to 15	3	0.33		2	
	16 and larger	6	0.17		5	
Malignancy grade	I	2	1.00	0.4	0	
	II	4	0.75		1	
	III	19	0.59		8	
	IV	35	0.55		15	
Tumor necrosis	no	30	0.81	0.0001	6	
	yes	29	0.37		17	11 (1.3–92)
Vascular invasion	no	37	0.79	0.0001	7	
	yes	21	0.33		15	6.9 (1.7–29)
DNA type	1–2	12	0.64	0.6	4	
	3–8	39	0.55		17	
Local treatment	inadequate	17	0.57	0.6	7	
	adequate	43	0.59		17	
Local recurrence	no	49	0.65	0.006	17	
	yes	11	0.27		7	

[a] Necrosis determined in 59 patients.
[b] Vascular invasion determined in 58 patients.
[c] DNA analysis performed in 51 patients.
MFSR metastasis-free survival rate.
RR relative risk.
CI confidence interval.

Table 16. Local treatment and local recurrence rates in 60 patients surgically treated for leiomyosarcoma of the extremity and trunk wall. 58 patients were treated with local excision and 2 patients with amputation

Local treatment	n	Local recurrence rate	Fraction
Intralesional + RT[a]	1	0/1	
Marginal	16	4/16	0.3
Marginal + RT[a]	10	3/10	0.3
Wide[b]	33	4/33	0.1
Total	60	11/60	0.2

[a] Radiotherapy. 8 patients given adjuvant chemotherapy not separately analyzed.
[b] Includes 3 patients with RT.

tases had died from tumor. 23 patients died from tumor, 19 of them within 5 years. The cumulative 5-year MFSR for all 60 patients was 0.59.

Results

By univariate analysis, deep-seated tumor, increasing size, tumor necrosis, vascular invasion, and local recurrence impaired metastasis-free survival.

A Cox model of 49 patients showed that tumor necrosis and vascular invasion independently reduced the metastasis-free survival (Table 15).

Liposarcoma

Patients

The analysis comprised 50 patients. The median follow-up time for the 30 patients who were alive at the latest follow-up was 13 (4–28) years.

Three subtype groupings were made. In the first, the tumors were classified according to the predominant subtype—i.e., well-differentiated, myxoid, round cell, and pleomorphic (Enzinger and Winslow 1962), and, in the second, according to the least dif-

Table 17. Clinicopathologic data, metastasis-free survival, and uni- and multivariate prognostic factors for metastasis in 50 surgically treated patients with liposarcoma of the extremity and trunk wall

Factor	Criteria	n	5-year MFSR	*P*-value univariate analysis	Crude metastasis n	Multivariate analysis RR (95% CI)
Age	≤ 59 yrs	28	0.81	0.1	8	
	> 59 yrs	22	0.61		8	
Sex	male	28	0.74	0.9	8	
	female	22	0.72		8	
Localization	upper extremity prox	6	0.50	0.3	3	
	upper extremity dist	1	1.00		0	
	trunk wall	6	0.75		1	
	lower extremity prox	33	0.75		9	
	lower extremity dist	4	0.75		3	
Depth	subcutaneous	11	0.73	0.6	3	
	deep-seated	39	0.73		13	
Tumor size (cm)	1 to 5	5	1.00	0.1	0	
	6 to 10	24	0.74		6	
	11 to 15	14	0.79		5	
	16 and larger	7	0.43		5	
Malignancy grade	I	5	1.00	0.02	0	
	II	22	0.86		4	
	III	11	0.62		6	
	IV	12	0.40		6	
Subtype[a] (Predominant)	well-differentiated	5	1.00	0.08	0	
	myxoid	26	0.80		8	
	round-cell	4	0.75		1	
	pleomorphic	11	0.32		6	
Subtype[a] (Least differentiated)	well-differentiated	5	1.00	0.01	0	
	myxoid	21	0.85		4	
	round-cell	7	0.69		4	
	pleomorphic	13	0.37		7	
Subtype[a] (Pure and mixed)	well-differentiated	5	1.00	<0.00001	0	
	myxoid	17	0.88		2	
	round-cell	1	0		1	
	pleomorphic	5	0.40		2	
	mixed	18	0.59		10	
Tumor necrosis[b]	no	33	0.90	<0.00001	4	
	yes	16	0.36		12	19 (3.9–88)
Vascular invasion[c]	no	40	0.81	0.001	9	
	yes	7	0.29		6	
DNA type[d]	1–2	18	0.89	0.3	5	
	3–8	25	0.61		9	
Local treatment	inadequate	18	0.71	0.7	6	
	adequate	32	0.74		10	
Local recurrence	no	39	0.78	0.08	10	
	yes	11	0.55		6	

[a] Subtype determined in 46 patients.
[b] Necrosis determined in 49 patients.
[c] Vascular invasion determined in 47 patients.
[d] DNA analysis performed in 43 patients.

MFSR metastasis-free survival rate.
RR relative risk.
CI confidence interval.

Table 18. Local treatment and local recurrence rates in 50 patients treated for liposarcoma of the extremity and trunk wall. 46 patients were treated with local procedures and 4 patients with amputation

Local treatment	n	Local recurrence rate	Fraction
Intralesional + RT[a]	1	0/1	
Marginal	17	7/17	0.4
Marginal + RT[a]	5	2/5	0.4
Wide[b]	25	2/25	0.1
Radical[c]	2	0/2	
Total	50	11/50	0.2

[a] Radiotherapy. 5 patients given adjuvant chemotherapy not separately analyzed.
[b] Includes 2 patients with RT.
[c] Includes 1 patient with RT.

ferentiated subtype regardless of its amount of the tumor. The third subtype grouping included, not only the pure forms (well-differentiated, myxoid, round cell, or pleomorphic), but also a fifth mixed group comprising all tumors with more than one distinct component.

Clinicopathologic data

A male preponderance of 1.3:1 was seen. The median age was 59 (29–90) years. Localization in the proximal part of the lower extremity and grade II were the commonest (Table 17). Apart from the absence of subcutaneous round-cell liposarcoma, there was no difference between subcutaneous and deep-seated tumors with regard to subtypes.

Local treatment

Two thirds of the patients received adequate local treatment for the primary tumor (Table 18).

Local recurrence

10 of 11 local recurrences developed within 6 years. Multiple local recurrences were uncommon (1/11). The local recurrence rate for the patients with inadequate local treatment was 7/18, while this rate was almost three times lower following adequate local treatment (Table 18). Of the 11 patients with local recurrence, 6 also had metastases, compared to 10 of the 39 patients without local recurrence.

Metastases

Of the 50 patients, 2 had metastases at diagnosis of the primary tumor. Of the remaining 48 patients 14 developed metastases, 12 of them within 6 years. Predominantly myxoid tumors more often metastasized to soft tissues other than the lungs (6/8) in comparison to metastasizing pleomorphic tumors (1/6). At the latest follow-up, 14 of the 16 patients with metastases had died, 10 of them within 5 years. The cumulative 5-year MFSR for all 50 patients was 0.73.

Results

By univariate analysis increasing malignancy grade, subtype other than well-differentiated, tumor necrosis, and vascular invasion reduced the metastasis-free survival.

Tumor necrosis was the sole prognostic factor found to be independent by a Cox model of 38 patients (Table 17). Metastasis was commoner in necrotic tumors (Table 19).

Table 19. Metastatic rates with regard to subtype and tumor necrosis in 45 surgically treated patients with liposarcoma of the extremity and trunk wall

Classification	Necrosis	No necrosis	Total
According to predominant subtype			
Well-differentiated	–	0/5	0/5
Myxoid	4/5	4/21	8/26
Round-cell	1/2	0/2	1/4
Pleomorphic	6/7	0/3	6/10
Total	11/14	4/31	15/45
According to pure and mixed subtypes			
Well-differentiated	–	0/5	0/5
Myxoid	1/1	1/16	2/17
Round-cell	1/1	–	1/1
Pleomorphic	2/2	0/2	2/4
Mixed	7/10	3/8	10/18
Total	11/14	4/31	15/45

Synovial sarcoma

Patients

The analysis comprised all 36 patients. The median follow-up time for those 18 patients alive at latest follow-up was 9 (4–22) years.

Clinicopathologic data

A male preponderance of 1.6:1 was seen. The median age, 39 (17–85) years, was lower than that found in the other histotypes. Localization in the distal part of the lower extremity and grade III were commonest (Table 20).

Local treatment

Four fifths of the patients received adequate local treatment for the primary tumor (Table 21).

Table 20. Clinicopathologic data, metastasis-free survival, and univariate prognostic factors for metastasis in 36 surgically treated patients with synovial sarcoma of the extremity and trunk wall.

Factor	Criteria	n	5-year MFSR	*P*-value univariate analysis	Crude metastasis n
Age	≤ 39 yrs	19	0.53	0.7	11
	> 39 yrs	17	0.59		8
Sex	male	22	0.45	0.2	14
	female	14	0.71		5
Localization	upper extremity prox	0	–	0.3	0
	upper extremity dist	5	0.60		2
	trunk wall	6	0.50		3
	lower extremity prox	11	0.45		8
	lower extremity dist	14	0.64		6
Depth	subcutaneous	5	0.60	0.8	2
	deep-seated	31	0.55		17
Tumor size (cm)	1 to 5	19	0.74	0.003	6
	6 to 10	12	0.50		8
	11 to 15	4	0		4
	16 and larger	1	0		1
Malignancy grade	I	0	–	0.09	0
	II	3	1.00		1
	III	18	0.67		8
	IV	15	0.33		10
Tumor necrosis[a]	no	19	0.63	0.5	9
	yes	9	0.44		6
Vascular invasion[b]	no	16	0.69	0.07	6
	yes	11	0.45		8
DNA type[c]	1–2	14	0.71	0.06	4
	3–8	8	0.38		6
Local treatment	inadequate	7	0.29	0.3	6
	adequate	29	0.62		13
Local recurrence	no	28	0.68	0.06	11
	yes	8	0.13		8

[a] Necrosis determined in 28 patients.
[b] Vascular invasion determined in 28 patients.
[c] DNA analysis performed in 22 patients.
MFSR metastasis-free survival rate.

Local recurrence

7 of 8 local recurrences developed within 6 years. 2 patients had more than one local recurrence. 5 of 7 patients with inadequate local treatment developed a local recurrence compared to 3 of 29 patients with adequate local treatment (Table 21). All patients with a local recurrence developed metastases, compared to 11 of the 28 patients without a local recurrence.

Metastases

Of the 36 patients, 2 had metastases at diagnosis of the primary tumor. Of the remaining 34 patients, 17 developed metastases, all except 2 within 6 years. At the latest follow-up, 14 of the 19 patients with metastases had died, 10 of them within 5 years. The cumulative 5-year MFSR for all 36 patients was 0.56.

Results

Univariate analysis showed that only increasing tumor size reduced the metastasis-free survival (Table 20). Due to the small sample size a Cox model could not be fitted.

Table 21. Local treatment and local recurrence rates in 36 patients treated for synovial sarcoma of the extremity and trunk wall. 24 patients were treated with local procedures and 12 patients with amputation

Local treatment	n	Local recurrence rate	Fraction
Intralesional + RT[a]	1	1/1	
Marginal	6	4/6	0.7
Marginal + RT[a]	3	0/3	
Wide[b]	24	3/24	0.1
Radical	2	0/2	
Total	36	8/36	0.2

[a] Radiotherapy. 7 patients given adjuvant chemotherapy not separately analyzed.
[b] Includes 2 patients with RT.

Discussion

Univariate analysis has identified a number of prognostic factors in STS in series of different sizes, collected under various circumstances, and analyzed by different methods. Univariate analysis, however, does not reveal covariations between prognostic factors (Table 4); the degree of independence cannot be ascertained. Multivariate analysis is required for identifying independent prognostic factors.

The factors that emerge as prognostic depend on the factors introduced into the model, the unselected nature and the size of the series analyzed. For example, the exclusion of a strong prognostic factor like tumor size may allow a weaker factor, like tumor depth, to emerge as prognostic. Furthermore, it is not uncommon that series on epidemiology and prognosis are composed of patients with both primary and locally recurrent tumors presenting at the center without metastases. This may confound the results because patients with locally recurrent tumors presenting without metastases comprise a prognostically favorable subset (Gustafson et al. 1993a). Different criteria for histologic evaluation may also complicate comparisons and interpretations of the results.

We tried to avoid these difficulties by performing multivariate analyses on a large and unselected series of patients with only primary tumors, whose histotype and malignancy grade were determined by only two pathologists.

We found that *age* and *sex* were of no prognostic importance. However, some series of mixed and specific histotypes have reported that high age and male sex are prognostic (Hajdu et al. 1977, Chase and Enzinger 1985, Collin et al. 1987). Recently, it has been suggested that estrogen has a favorable effect on prognosis in premenopausal females with STS (Ohsawa et al. 1991), a finding our series could not verify; pre- and postmenopausal women had similar metastases rates (data not shown).

Proximal *localization* and *tumor depth* have been reported to be unfavorable prognostic factors (Enzinger and Weiss 1988, Tsujimoto et al. 1988, Gaynor et al. 1992). We found no influence of localization, while deep-seated tumors had a worse prognosis when univariately analyzed. However, when size was accounted for, tumor depth lost its importance; deep-seated tumors are larger than subcutaneous ones. The prognostic value of localization may be explained by its covariation with size; proximal tumors are larger than distal.

Our observations confirm the consistency of *tumor size* as one of the strongest prognostic factors, which has been repeatedly reported in mixed series and in specific tumor types (Dahl and Angervall 1974, Wile et al. 1981, Markhede et al. 1982, Reitan et al. 1985, Hashimoto et al. 1986, Orson et al. 1987, Ueda et al. 1988, Enzinger and Weiss 1988, Mandard et al. 1989, Bauer et al. 1991, Pezzi et al. 1992, Brodsky et al. 1992, Oda et al. 1993).

Malignancy grade is another well-known and strong prognostic factor in STS (Markhede et al. 1982, Costa et al. 1984, Trojani et al. 1984, Collin et al. 1987, Torosian et al. 1988, Ueda et al. 1988, Lack et al. 1989, Berlin et al. 1990, Stotter et al. 1990, Becker et al. 1991, Gaynor et al. 1992, Pezzi et al. 1992). Unexpectedly, we found that malignancy grade lost its prognostic value when *tumor necrosis* and *vascular invasion* were adjusted for in the multivariate analysis. Microscopic tumor necrosis was prognostic in our series and this agrees with Lack et al. (1989) and Becker et al. (1991). Macroscopic tumor necrosis (Costa et al. 1984, Mandard et al. 1989, van Unnik et al. 1993, Oda et al. 1993) and tumor necrosis as determined on CT scans (Gustafson et al. 1992a) have also been correlated with survival. Vascular invasion has been reported to be prognostic by Mandard et al. (1981), and Alvegård et al. (1989a) and we have confirmed their findings in our mixed, MFH, leiomyosarcoma, and liposarcoma series. Our observations suggest that greater emphasis should be placed on tumor necrosis and vascular invasion when deciding malignancy grade.

Abnormal *DNA-ploidy* status has been reported to have independent prognostic value in mixed series (Alvegård et al. 1990, Bauer et al. 1991), leiomyosarcoma (Keen et al. 1985), and synovial sarcoma (El-Naggar et al. 1990). The series of Bauer et al. (1991) did not include tumor necrosis and vascular invasion, which may explain why DNA analysis was prognostic there. DNA type was a univariate prognostic factor in our series, but weaker than size, tumor necrosis, and vascular invasion. In an earlier study of leiomyosarcoma (Gustafson et al. 1992b) we reported a weak prognostic influence from abnormal cellular DNA content. In our present series we found no such influence.

The quality of *local treatment* per se is usually not related to survival (Collin et al. 1987). Like many others, we found that inadequate local treatment often was prognostic in the univariate analysis, but failed to retain its significance in the multivariate analysis. In contrast, *local recurrence* is a well-known prognostic factor (Cantin et al. 1968, Markhede et al. 1982, Collin et al. 1987, Rööser 1987, Emrich et al. 1989) reaffirmed by our observations.

The significance and strength of prognostic factors vary between different histotypes. Overall, we found

that tumor size, tumor necrosis, and vascular invasion were strong, independent, and consistent prognostic factors. The interobserver reproducibility of tumor necrosis and vascular invasion has to be validated.

Prognostic system

An optimal prognostic system for STS should identify two groups, one with a good prognosis which benefits from local treatment alone, and the other with a poor prognosis which may require adjuvant systemic therapy. The system must use strong variables that are easy to define to make possible the identification of large groups with an extreme prognosis.

Two prognostic systems for STS are in common use. The American Joint Committee (AJC) system was introduced in 1977 and revised in 1988. It is based on malignancy grade (low-grade, intermediate, or high-grade) and tumor size (cut-off 5 cm) (Russell et al. 1977, Bears et al. 1988). Three major groups specified by the grade are each subdivided into two, depending on size. The Surgical Staging System (SSS) for STS is based on malignancy grade (low-grade or high-grade) and compartmentalization (intra or extra), the combination of which creates four stages (Enneking et al. 1980). Both systems group patients with lymph node or distant metastasis at diagnosis of the primary tumor separately. Rööser (1987) showed that prognostication using these systems was only as good as the histologic malignancy grade alone.

We constructed a prognostic system using tumor size, tumor necrosis, and vascular invasion and compared it with the AJC and the SSS.

Patients and methods

There were 354 patients with data on size, tumor necrosis, and vascular invasion. 16 of these patients had metastases at diagnosis of the primary tumor. The MFSR of different subsets of these factors was compared to those predicted by AJC and SSS. For the AJC system, our malignancy grades I and II were called low-grade, our grade III intermediate, and our grade IV was called high-grade. For the SSS, our grades I and II were called low-grade and our grades III and IV were called high-grade.

Results

8 subsets were formed from the combination of tumor size, tumor necrosis, and vascular invasion (Figure 4, Table 22). Patients with no or one risk factor constituted two thirds of all patients and patients with two or three risk factors constituted one third. The 5-year MFSR of these groups were 0.81 and 0.32, respectively (Figure 5).

Table 22. Crude metastasis rates in subsets of 354 patients with soft tissue sarcoma of the extremity and trunk wall, formed by combinations of tumor size, tumor necrosis and vascular invasion

Tumor size ≥11 cm	Tumor necrosis	Vascular invasion	Crude metastasis rate	
–	–	–	16/143	52/245
+	–	–	5/19	
–	+	–	23/66	
–	–	+	8/17	
+	+	–	22/35	76/109
+	–	+	2/3	
–	+	+	32/45	
+	+	+	20/26	

The best and the worst 5-year MFSR for the 6 AJC groups were 0.96 and 0.56, respectively (Figure 6). The corresponding figures for the 4 SSS groups were 0.93 and 0.56 (Figure 7). Patients with metastases at diagnosis are not shown in Figures 6 and 7.

Discussion

The value of a prognostic system depends on its ability to identify patients who will either respond to local treatment or who may require adjuvant therapy. Good and poor survivors must be widely separated. However, this often results in dwindling patient numbers at the extremes of prognosis and a large intermediate group whose management remains unclear.

The AJC system uses three malignancy grades, which are poorly defined, and tumor size dichotomized at 5 cm, which may not be optimal. We have found in several analyses, including this one, that a 10 cm dichotomization is of stronger prognostic value.

The SSS combines grade and compartmentalization. This is a surgical staging system and, as such, was designed for the surgeon. It was introduced together with a classification of surgical margins which has gained widespread acceptance. The concept of compartmentalization was used to help the surgeon to determine the outcome of different surgical margins. However, when used to predict survival, the system is principally dependent on malignancy grade. Compartmentalization is a weak prognostic factor because it is a covariant of tumor size; intracompartmental tumors, to which SSS includes all subcutaneous tumors, are smaller.

We found that a better prognostication resulted from the use of tumor size > 10 cm, tumor necrosis,

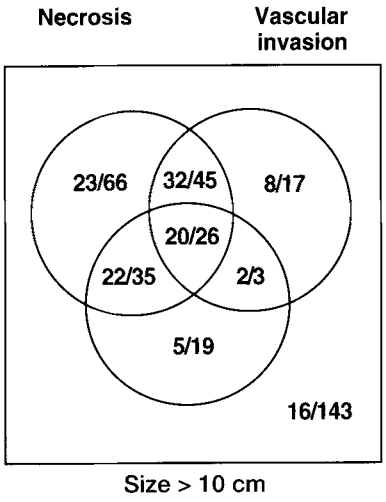


Figure 4. Number of patients with metastasis / total number of patients in each group in subsets of 354 patients with soft tissue sarcoma of the extremity and trunk wall, using tumor size > 10 cm, tumor necrosis, and vascular invasion.

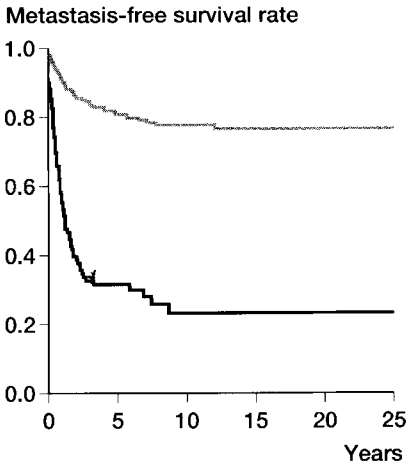


Figure 5. Metastasis-free survival in subsets of 354 patients with soft tissue sarcoma of the extremity and trunk wall, using tumor size > 10 cm, tumor necrosis, and vascular invasion. 245 patients with 0 or 1 factor (grey line). 109 patients with 2 or 3 factors (black line).

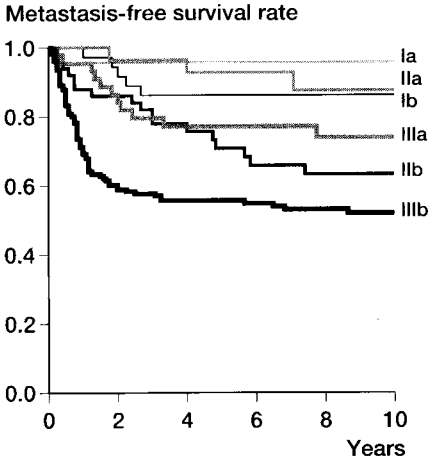


Figure 6. Metastasis-free survival in 338 patients with soft tissue sarcoma of extremity and trunk wall, staged according to the AJC system. 23 patients stage Ia, 36 patients stage Ib, 29 patients stage IIa, 50 patients stage IIb, 44 patients stage IIIa, and 156 patients stage IIIb. 16 patients with metastasis at diagnosis of primary tumor (stage IV) not shown in graph.

Stage Ia = malignancy grades I+II, tumor size < 5cm.
Ib = grades I+II, size ≥ 5cm.
IIa = grade III, size < 5cm.
IIb = grade III, size ≥ 5cm.
IIIa = grade IV, size < 5cm.
IIIb = grade IV, size ≥ 5cm.

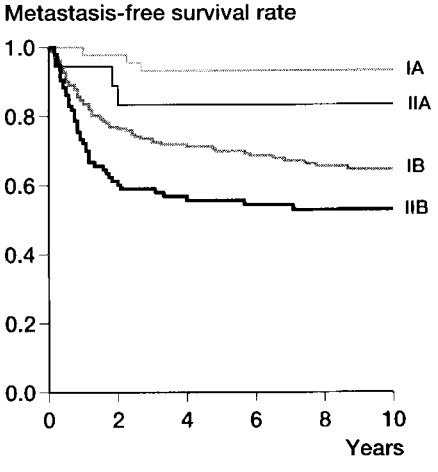


Figure 7. Metastasis-free survival in 338 patients with soft tissue sarcoma of extremity and trunk wall, staged according to the Surgical Staging System. 44 patients stage IA, 18 patients stage IB, 182 patients stage IIA, and 94 patients stage IIB. 16 patients with metastasis at diagnosis of primary tumor (stage III) not shown in graph.

Stage IA = malignancy grades I+II, intracompartmental.
IB = grades I+II, extracompartmental.
IIA = grades III+IV, intracompartmental.
IIB = grades III+IV, extracompartmental.

and vascular invasion which could identify two thirds of all patients with a 5-year MFSR of 0.8 and one third with a corresponding rate of 0.3. The treatment of the patients in the good prognosis group should be focused on removal of the primary tumor. The other patients may be candidates for trials of chemotherapy.

Metastases and local recurrence

Patients with a local recurrence more often have metastases. This holds true for several solid malignant tumors, such as breast cancer, malignant melanoma, and soft tissue sarcoma. This relationship has been interpreted as causal, i.e., the metastases are thought to emanate from the local recurrence (Cantin et al. 1968, Markhede et al. 1982, Suit and Tepper 1986, Emrich et al. 1989, Berlin et al. 1990, Stotter et al. 1990, Barr et al. 1991, Suit 1992). However, this notion has been questioned, and alternative explanations have been given, suggesting that highly malignant tumors combine local and distant aggressiveness, and that if tumor dissemination occurs, it would be an early event taking place before diagnosis of the primary tumor (Collins et al. 1956, Schwartz 1961, Pearlman 1979, Koscielny et al. 1985, Potter et al. 1986, Rööser et al. 1987b, Torosian et al. 1988, Rööser et al. 1990, Fischer et al. 1991, Gustafson et al. 1991, Williard et al. 1992a, Williard et al. 1992b, Gaynor et al. 1992, Benjamin 1993, Evans 1993).

Selection bias in treatment may also confound the interpretation of the association between local recurrence and metastasis. We found that surgery for highly malignant, deep-seated and large tumors with poor survival, more often resulted in a marginal margin with a high risk of local recurrence (Table 23).

There are different explanations for local recurrence. It may be an effect of local reseeding by systemically circulating tumor cells that deposit at the site of the primary tumor after its removal. Murthy et al. (1989) have shown in animals that surgical trauma renders an organ susceptible to the formation of metastases. Local recurrence may also result from residual tumor—persistent tumor—left following inadequate treatment or, especially in the case of adequate treatment, because the tumor has given rise to satellite tumors (local metastases) outside the resection margin. Residual tumor cells probably explain the majority of local recurrences. This is supported by the strong covariation between increasing good quality of the local treatment and decreasing local recurrence rate.

The nature of the association between local recurrence and metastasis has wide clinical implications. If the local recurrence is the source of metastases, then gains in survival also motivate mutilating treatment. If, on the other hand, the local recurrence is a marker of risk for metastases, then aggressive local treatment to reduce mortality is questionable. In this case the extent of surgery has only to be balanced between loss of function and local control.

Evans (1993) underscored the difficulty of analyzing the impact of local recurrences since these amount only to 10 or 15 percent in center-based series. In comparison, our population-based database has a 30 percent local recurrence rate. This high number permits an analysis of the association between local recurrence and metastasis.

In our series, over half of the patients with local recurrence had metastases, compared to one third of patients without local recurrence. If a univariate analysis of survival in patients with or without local

Table 23. Data for 225 patients with extremity-localized soft tissue sarcoma, treated by limb-sparing surgery, according to surgical margin. Actual number (percent)

		n	High-risk[a] n 50	Low-risk[b] n 175	Difference	Relative risk	95% CI[c]
Mean age		225	63	59	3.9		−1.2–8.9
Localization[d]	proximal	179	38 (21)	141 (79)		1.1	0.9–1.3
	distal	46	12 (26)	34 (74)			
Depth	subcutaneous	66	5 (8)	61 (92)		1.3	1.1–1.5
	deep-seated	159	45 (28)	114 (72)			
Mean size	cm	225	10.6	6.9	3.7		2.2–5.2
Malignancy grade	I and II	50	16 (32)	34 (68)		0.9	0.7–1.0
	III and IV	175	34 (19)	141 (81)			

[a] Intralesional or marginal margin.
[b] Wide or radical margin.
[c] 95 percent confidence interval.
[d] Distal = lower arm, hand, lower leg and foot. Proximal = all other localizations.

Table 24. Distribution of prognostic factors in subsets of 149 patients with metastatic soft tissue sarcoma of the extremity and trunk wall of 438 patients with soft tissue sarcoma operated on with marginal or better margin and without metastasis at diagnosis

Factor	Local recurrence		*P*-value
	yes	no	
Number	73	76	
Size, mean, cm	9.7	9.4	0.9
Malignancy grade IV	51/73	51/76	0.7
Necrosis	55/69	49/65	0.6
Vascular invasion	23/49	32/59	0.5
DNA type 3–8	43/55	40/49	0.7
Local treatment inadequate	41	8	0.0001
adequate	32	68	

recurrence is performed, patients without local recurrence invariably do better, assuming that local recurrence causes a poor prognosis. This association, however, is statistical and gives no indication of causality. Statistical analyses identify markers of risk, including local recurrence, of metastases, but they do not answer the question whether the local recurrence is the source of metastases.

Evidence questioning causal relationship

1. In patients who have local control, but still develop metastases, the metastases obviously emanated from the primary tumor. It has been suggested that tumor dissemination occurs long before diagnosis (see above). If so, patients with the most malignant tumors—i.e. those who develop metastases—should have a similar pattern of prognostic factors, irrespective of whether they develop a local recurrence. This was the case in our series: of 438 patients who were operated on with a marginal margin or better and who had no metastasis at diagnosis of the primary tumor, 149 patients subsequently developed metastases, 73 of whom also had a local recurrence. These 73 patients had a similar pattern of prognostic factors compared to the 76 patients in whom only metastases were seen. The only difference between the two groups was the higher rate of inadequate local treatment in those with a local recurrence (Table 24). This finding indicates that the incidence of metastases may be independent of local recurrence.

2. If metastases were to emanate from the local recurrence, then patients with a local recurrence should manifest their metastases later than those without a local recurrence, provided the growth rate of the metastases does not differ. We found that the timings of metastases in the 149 patients described above were similar, irrespective of the presence of local recurrence (Figure 8). This pattern was similar in the individual histotypes. Furthermore, in half of the patients who had both metastases and a local recurrence the diagnosis of a metastasis preceded or coincided with that of a local recurrence. These observations seem contrary to the notion that local recurrence is the source of metastases.

3. The increased metastasis rates in patients with local recurrence may reflect combined distant and local aggressiveness of highly malignant tumors. If this is true, the local recurrence rates should be higher in patients with numerous unfavorable prognostic factors for metastasis. In support of this, we found that in all 318 adequately treated patients without metastasis at diagnosis, the local recurrence rates were about twice as high in patients having tumors with unfavorable prognostic factors for metastasis as in those without such factors (Table 25).

4. Further evidence that highly malignant tumors combine a potential for both local recurrence and distant metastases was found in the series of 438 patients operated on with a marginal margin or better and who had no metastasis at diagnosis of the primary tumor. Of these patients, 120 were given inadequate treatment, 131 had local recurrence and 149 developed metastases. The local recurrence rate after inadequate

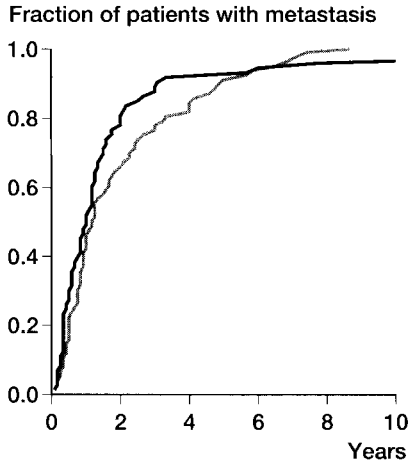


Figure 8. Fraction of patients with metastasis versus time to diagnosis of metastasis in 149 patients with metastatic soft tissue sarcoma of extremity and trunk wall. 76 patients with metastasis only (grey line). 73 patients with both local recurrence and metastasis (black line).

Table 25. Local recurrence rates versus prognostic factors for metastasis in 318 primarily non-metastatic adequately treated patients with soft tissue sarcoma of the extremity and trunk wall

		Metastasis			Local recurrence		
Factor		rate	(percent)	*P*-value	rate	(percent)	*P*-value
Size, cm	1 to 10	64/255	(25)	0.0001	43/255	(17)	0.03
	11 and larger	36/63	(57)		18/63	(29)	
Malignancy grade	I and II	2/49	(4)	0.0001	5/49	(10)	0.08
	III and IV	98/269	(36)		56/269	(21)	
Necrosis	no	16/146	(11)	0.0001	18/146	(12)	0.001
	yes	75/147	(51)		40/147	(27)	
Vascular invasion	no	34/186	(18)	0.0001	27/186	(15)	0.002
	yes	44/66	(67)		21/66	(32)	
DNA analysis	type 1–2	15/61	(25)	0.1	7/61	(11)	0.04
	type 3–8	59/165	(36)		40/165	(24)	

Table 26. Local recurrence and metastasis related to treatment in 438 patients with soft tissue sarcoma of the extremity and trunk wall. Actual number (percent)

	Proportion local recurrence			Proportion with metastasis
Treatment	No metastasis	Metastasis	Total	
Inadequate	29/71 (41)	41/49 (84)	70/120 (58)	49/120 (41)
Adequate	29/211 (14)	32/107 (30)	61/318 (19)	100/318 (31)
Total	58/282 (21)	73/156 (47)	131/438 (30)	149/438 (34)

treatment was 58 percent and after adequate treatment 19 percent. Combinations of treatment, local recurrence, and metastasis formed 8 subsets (Figure 9, Table 26) showing that (i) after inadequate local treatment, local recurrence was 3 times commoner but metastases were only 1.3 times commoner than after adequate local treatment, (ii) in patients with metastases, local recurrence was twice as common as in those without metastases, (iii) in patients with metastases, the local recurrence rate, regardless of the adequacy of local treatment, was twice that of patients without metastases.

In conclusion, local recurrence seems to be a marker of the adequacy of treatment and of a highly malignant tumor that combines local and distant aggressiveness. The fact that local recurrence may not be the common source of the metastases should not discourage appropriate surgery. Indeed, in patients who have not developed metastases, good local surgery may be curative.

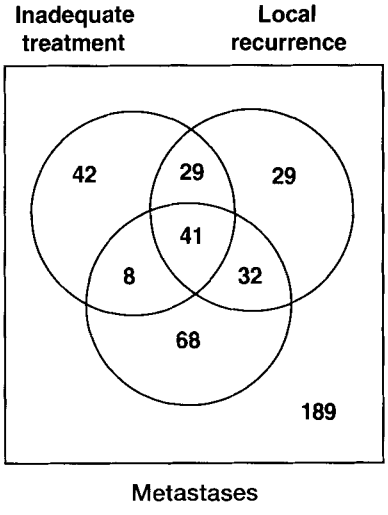


Figure 9. Distribution of 438 patients with soft tissue sarcoma of the extremity and trunk wall in subsets formed by combination of treatment, local recurrence, and metastases.

Summary

We have evaluated epidemiology, prognosis and the association between metastases and local recurrence in a series of adult patients with soft tissue sarcoma (STS) of the extremity and trunk wall. 508 patients were diagnosed in the Southern Swedish Health Care Region from 1964 through 1989. The series was population-based, i.e., all patients within a defined area were included, irrespective of where treated, thereby avoiding selection bias in referral and follow-up.

Epidemiology

The annual incidence was 18 per million. The median age was 64 years. One third of the tumors were subcutaneous, and these were smaller than the deep-seated tumors. Malignant fibrous histiocytoma and grade IV were the commonest. Differences were noted in clinicopathologic features among histotypes.

The 5-year metastasis-free survival rate (MFSR) was 0.6. The crude local recurrence rate was 0.3. The majority of metastases and local recurrences occurred within 3 years.

The referral pattern to the tumor center has become more favorable over time; in the last 5 years half of the subcutaneous and four fifths of the deep-seated tumors were referred before surgery.

Prognostic factors

Tumor size, tumor necrosis, and vascular invasion were strong and independent prognostic factors for metastasis in a histologically mixed series. In MFH, storiform and pleomorphic subtype, tumor necrosis and tumor size were associated with a poor prognosis. Tumor necrosis and vascular invasion independently worsened the prognosis in leiomyosarcoma. In liposarcoma, tumor necrosis and in synovial sarcoma, tumor size were the only important prognostic factors.

Tumor size, tumor necrosis, and vascular invasion were used in a prognostic system which identified two thirds of all patients with a 5-year MFSR of 0.8 and one third of the patients with a 5-year MFSR of 0.3.

Metastasis and local recurrence

The causal association proposed for local recurrence and metastasis should be interpreted with caution. We suggest that highly malignant tumors combine local and distant aggressiveness, and that local recurrence is a marker of risk, and not necessarily a cause of, metastasis.

Conclusions

1. Population-based series are preferable when studying epidemiology in soft tissue sarcoma.
2. We propose that tumor size, tumor necrosis, and vascular invasion are strong and reliable factors that can be used to improve prognostic accuracy.
3. There is a growing body of evidence against a causal relationship between local recurrence and metastasis.

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Appendix

Flowcytometric DNA analysis

Frozen tumor tissue

Tissue for DNA analysis was stored at –80 °C until required. For analysis the tissue was prepared in a one-step procedure. 100–200 mg of the tumor specimen was thawed in 0.2 mL citrate buffer (sucrose 250 mM, trisodium citrate 40 mM, dimethyl sulfoxide 5 percent, pH 7.6) containing chicken and trout red blood corpuscles (CRBC and TRBC, 10^6/mL). To enhance cell elution, the tissue was mechanically disintegrated with 2 forceps, after which 1–2 mL of a nuclear isolation medium (NIM) containing propidium iodide (PI) was added (50 µg PI/mL, Sigma P-5264; RNAse 0.1 mg/mL, Sigma R-5125; Nonidet P 40 0.6 percent (v/v); Sigma N-3516 in isotonic buffered saline; Gibco). The samples were filtered (50 µm), incubated in the dark at room temperature for 10 minutes, and then kept at +4 °C until FCM analysis, which was performed within 2 hours.

Paraffin archival tumor tissue (modification I)

A 100 µm and an adjacent 5 µm section were cut from each block. The 5-µm section was stained with hematoxylin and eosin for routine histopathological examination and was used as a control to ensure that sarcoma tissue was analyzed. The 100 µm section was dewaxed in a glass tube by 4 treatments with 3 mL Histoclear (HS 200, National Diagnostics) at room temperature for 10 minutes. After the third and fourth treatments, the tissue sections were centrifuged at 800 g before the removal of the Histoclear. Rehydration was then performed in a sequence of 3 ml rinses of absolute (twice), 90 percent (twice), and 70 percent (once) ethanol, and centrifuged at 800 g after each step. The tissue was washed twice in isotonic phosphate-buffered saline (PBS) without Ca^{2+} and Mg^{2+} and treated with 1 mL of a 0.5 percent (w/v) pepsin solution (Sigma P-7012, with 0.9 percent NaCl; pH 1.5) at 37 °C for 30 minutes with a continuous shaking interrupted by a more heavy vortexing every 5 minutes. This incubation was finished by centrifugation, and the sample was washed twice in ice-cold PBS. After the second centrifugation, the tissue was mechanically disintegrated in 2 mL of PBS by syringing with a Pasteur pipette; the resulting suspensions were filtered through a 50-µm nylon-mesh filter. The filter was washed with 1 mL of PBS to obtain a final volume of 3 mL, which was centrifuged. The pellet was then resuspended in a DNA-staining solution (see above frozen tissue).

Paraffin archival tumor tissue (modification II)

The 100 µm section was deparaffinized by treating the sample twice with 5 mL Histoclear (HS 200; National Diagnostics) during continuous shaking at room temperature for 1 hour each time, after which the sections were rehydrated in a sequence of 5 mL of absolute, 95 percent, 70 percent, 40 percent ethanol and distilled water. The samples were centrifuged at 800 g for 10 minutes and thereafter incubated with a trypsin solution (0.25 percent (w/v) trypsin, Sigma T-8128 in buffer (trisodium citrate 3.0mM, Nonidet P 40 0.1 percent (v/v), Sigma N-6507; spermine-tetrachloride 1.5 mM and TRIS 0.5 mM, pH 7.6)) overnight at 37 °C (waterbath) with continuous shaking. After this incubation, the section was further disintegrated by syringing with a Pasteur pipette, filtered through a 50 µm nylon mesh and centrifuged at 800 g. The pellet was then resuspended in a DNA-staining solution (see above frozen tissue).

The two modifications of DNA analysis in paraffin archival material have previously been shown to give comparable results as regards DNA ploidy status (Gustafson et al. 1992b).

FCM DNA analysis

Just prior to FCM DNA analysis, the nuclear suspension was syringed 5 times through a 29 gauge needle and filtered through a 50-µm nylon mesh. FCM DNA analysis was performed according to Baldetorp et al. (1989) with an Ortho Cytofluorograph 50-H system (Ortho Instruments, Westwood, MA, USA) equipped with a Lexel 4 W argon ion laser (Lexel Mod 10-4, Palo Alto, CA, USA). The 488 nm laser line with an output of 200 mW was used for quantitating the relative amount of DNA per nucleus. The inside of the quartz flow chamber had a circular cross-section. The PI emission was measured above 600 nm, and the signal coupled to each measured nucleus was processed in the peak-area detector of the Cytofluorograph in order to distinguish subsequently the contribution of false signals, i.e., nuclear doublets. These two analog signals, the area

and the peak, were digitized to a resolution of 1,000 discrete levels, corresponding to the same number of channels in the DNA histograms, and were recorded in list mode on floppy diskettes with an Ortho 2140 data-handling system. Up to 20,000 events were recorded per sample at a rate of 100 per second.

Coefficient of variation (CV)

The CV (percent) of all G_0/G_1-peaks was calculated with the formula SD/MV of the full peak, assuming the peaks to be Gaussian with a mean value (MV) and a standard deviation (SD).

DNA index (DI)

Frozen tissue. After zero point adjustment of the DNA histogram, using the modal values of the CRBC and TRBC G_0/G_1 peaks, the mean channel numbers of all G_0/G_1 peaks were adjusted and used to calculate the DI with TRBC as reference standard.

Paraffin archival tissue. The DI for the abnormal cell population was calculated using the first (diploid) peak as the reference.