

Survival in soft tissue sarcoma

Prognostic variables identified by multivariate analysis

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The prognostic influence of 15 separate factors on local recurrence and survival was analyzed in 144 patients with highly malignant (histologic Grades III and IV) soft tissue sarcoma of the locomotor system. The minimum follow-up time was 6 years, or until death. Three factors, marginal excision, tumor necrosis, and extracompartmental tumor location were identified as risk factors for local recurrence. Five factors, local recurrence, Grade IV, male sex, tumor necrosis, and increasing tumor size were associated with decreased life expectancy.

A high histologic malignancy grade decreases the chance for survival in soft tissue sarcoma (Enneking et al. 1980, Markhede et al. 1982, Merck et al. 1983). Other factors that have been found to negatively influence the outcome are high age, large tumor size, central location, pain from the tumor, deep site, male sex, and extracompartmental tumor location (Kindblom et al. 1975, Sears et al. 1980, Abbas et al. 1981, Enneking et al. 1980, Wright et al. 1982, Merck et al. 1983, Rydholm 1983). Recently, extensive tumor necrosis has also been shown to have an adverse effect on prognosis (de Stefani et al. 1982, Costa et al. 1984, Trojani et al. 1984).

When a system with four histologic malignancy grades is used, patients with Grades I and II tumors generally have 5-year survival rates of 85-100 per cent, whereas the survival rates in Grades III and IV tumors are lower (Kindblom et al. 1975, Markhede et al. 1982, Rydholm 1983).

We report a multivariate analysis of 15 different factors having potential effect on local recurrence and survival in the material of high-grade soft tissue sarcoma described by Rydholm (1983).

Patients and methods

Our patients were collected from an unselected series of all 278 patients with soft tissue sarcoma of the locomotor system diagnosed from 1964 through 1978 (Rydholm et al. 1984) in the 1.3 million population of southern Sweden. Thus, patients treated outside the Center were also included. Follow-up has continued in all the patients, and the present analysis is based on a minimum follow-up time of 6 years or until death and a maximum follow-up time of 21 years.

The tumor malignancy was graded histologically on a four-point scale (Kindblom et al. 1975, Angervall 1980, Markhede et al. 1982, Merck et al. 1983, Rydholm et al. 1984). Sixty-four patients with low-grade tumors (I and II) were excluded. Of the 214 patients with Grades III and IV tumors, 18 were excluded because of overt metastases when the primary tumor was diagnosed. A further 18 patients, whose tumors for various reasons were not removed, were also excluded. In the remaining 178 patients, data on tumor size were missing in 1 case, information about tumor compartmentalization in 8 cases, and the histologic slides were unavailable in 25 cases. Complete clinical data and histologic specimens permitting a multivariate analysis were thus available in 144 cases, 87 males and 57 females.

The original histology slides were reexamined (N.O.B.) without knowledge of the clinical course.

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Fifteen variables were analyzed for influence on survival and 14 for influence on local recurrence (Table 1). The *mean age* was 56 (16–88) years. The *mean tumor size* was 7 (1–30) cm. Subcutaneous

tumors were classified as *superficial* when the deep fascia was uninvolved; all the other tumors were classified as *deep*. *Surgical margins* were classified according to Enneking et al. (1980).

Table 1. Variables multivariately analyzed for prognostic influence on local recurrence and survival in 144 patients with Grades III and IV soft tissue sarcoma

Variable	n	Patients with local recurrence	Patients dead of tumor
Age			
< 50 years	51	14	17
> 50 years	93	34	38
Sex			
Male	87	27	40
Female	57	21	15
Symptoms			
No pain	105	32	29
Pain	39	16	26
Histologic type			
Malignant fibrous histiocytoma	38	13	15
Leiomyosarcoma	22	7	10
Liposarcoma	19	5	6
Neurogenic sarcoma	17	8	10
Synovial sarcoma	16	6	6
Other types	32	9	8
Malignancy Grade			
III	63	19	15
IV	81	29	40
Tumor necrosis			
None or minimal	69	17	14
Extensive	75	31	41
Tumor depth			
Superficial	47	11	10
Deep	97	37	45
Size			
< 6 cm	77	22	19
> 6 cm	67	26	36
Compartmentalization			
Intracompartamental	90	20	26
Extracompartamental	54	28	29
Fine needle aspiration			
Performed	93	31	38
Not performed	51	17	17
Number of operations for primary tumor			
1	72	28	30
> 1	72	20	25
Surgical margin			
Marginal	62	37	33
Wide or radical	82	11	22
Radiotherapy			
No	122	38	43
Yes	22	10	12
Chemotherapy			
No	126	43	45
Yes	18	5	10
Local recurrence			
No	96	—	19
Yes	48	—	36

Because the previous multivariate analysis (Rydholm 1983) could not demonstrate any significant difference in local recurrence risk and survival between the surgical margins superior to the marginal one, we grouped 16 radical and 66 wide excisions together in our analysis. *Amputations* were not classified per se, but according to the margin achieved. The tumors were also classified as *intracompartmental* or *extracompartmental* (Enneking et al. 1980).

We introduced a variable not analyzed previously: namely, *tumor necrosis*. The extent of necrosis was determined by microscopic examination of slides from different parts of the tumor. The tumors were classified into two groups: none or minimally necrotic (*nonnecrotic*) and extensively necrotic (*necrotic*). The tumor was considered necrotic when the longest cross-section of one necrotic area in a slide occupied at least the diameter of one low power field = 4.3 mm (Carl Zeiss 10× ocular and 2.5× plane lens).

Statistics

The Cox proportional hazards model was used in a stepwise multivariate modeling of the variables jointly influencing the *expected* local recurrence and survival. An account was taken of the follow-up time and censoring (Kalbfleisch & Prentice 1980). From the Cox model the prognostic weights of the variables could be expressed as relative risks: the higher the value, the stronger the influence. The variables were tested for prognostic significance by the Wald statistic, and individual variables were retained in the model if their significance value was at least 0.05. When analyzing survival, local recurrence was included as a time-dependent prognostic variable; the model used here was thus nonproportional for that variable.

A two-sided chi-square test with Yates continuity correction was used to test the independence of the dichotomous prognostic variables significant in the Cox analysis. When analyzing independence of size, the two-sided Student's *t*-test for difference of means was used. When evaluating independence, several tests were performed simultaneously, and therefore the correction formula of Fisher was used; i.e., to achieve a significance level of 0.05, the *P* value of an individual test had

to be 0.05 divided by the number of tests performed.

Kaplan-Meier plots of the *observed* cumulative survival rate were generated for groups of patients defined by different values in significant prognostic variables. Global significance values, evaluating different trends in a graph were calculated by the generalized Wilcoxon test.

Results

Local recurrence

Forty-eight patients (33%) had local recurrence. Marginal excision, tumor necrosis, and extracompartmental tumor location carried an increased risk of local recurrence by factors 6, 2, and 2 (Table 2).

Table 2. Risk factors for local recurrence in 144 patients with Grades III and IV soft tissue sarcoma of the locomotor system

	Relative Risk	Significance
Marginal surgery	5.9	0.0001
Extensive necrosis	2.1	0.013
Extracompartmental location	1.9	0.033

Survival

Fifty-five patients (38%) died of their tumor illness. Local recurrence, malignancy Grade IV, male sex, and tumor necrosis increased the risk of tumor-related death by factors 9, 3, 3, and 2 (Table 3, Figures 1 and 2). Continuously increasing tumor size carried an increased risk of tumor-related death by about 10 percent for one centimeter of increment (Table 3). This translates into an exponentially increased risk with increasing tumor size. For instance, the relative risk associ-

Table 3. Risk factors for tumor-related death in 144 patients with Grades III and IV soft tissue sarcoma of the locomotor system

	Relative Risk	Significance
Local recurrence	9	0.0000
Malignancy Grade IV	3.4	0.0002
Male sex	3.4	0.0002
Extensive necrosis	2.4	0.007
Increasing size for 1 cm increment	1.1	0.0002

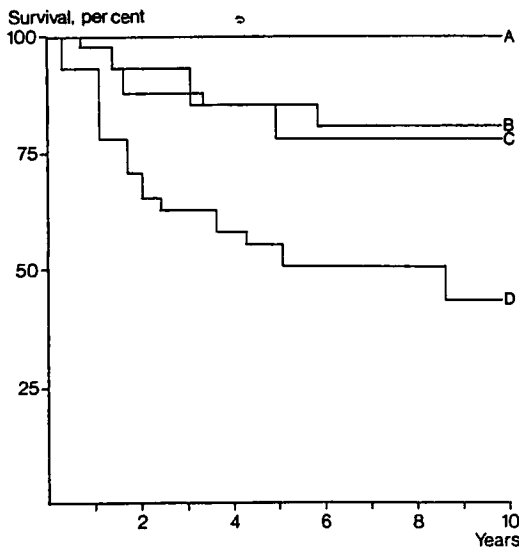


Figure 1. Cumulative survival rate related to sex and malignancy grade in 82 patients with soft tissue sarcoma operated on with a wide or radical margin.
 A Females, Grade III tumors, n 12
 B Males, Grade III tumors, n 28
 C Females, Grade IV tumors, n 15
 D Males, Grade IV tumors, n 27
 Global significance, $P = 0.003$

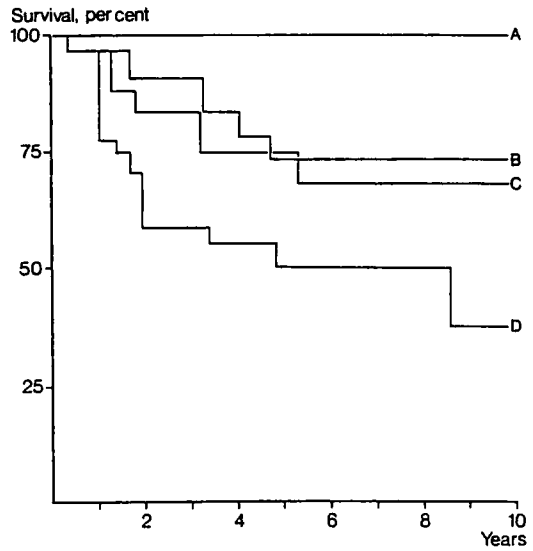


Figure 2. Cumulative survival rate related to malignancy grade and tumor necrosis in 82 patients with soft tissue sarcoma operated on with a wide or radical margin.
 A Grade III, no necrosis, n 23
 B Grade IV, no necrosis, n 19
 C Grade III, necrosis, n 17
 D Grade IV, necrosis, n 23
 Global significance, $P = 0.002$

ated with an increase in tumor size from 5 to 10 cm was 1.7, from 10 to 15 cm 1.7, and from 5 to 15 cm 3.0.

Marginal surgery was associated with an increased risk of death from tumor by a factor of 2. By using a separate interaction variable in the multivariate model, the higher local recurrence rate after marginal surgery was fully taken into account. The relative risk of death from tumor after marginal surgery per se was then 0.98 ($P = 0.1$).

Independence of prognostic variables

Twenty-one test of combinations of pairs of the significant prognostic variables were carried out. Using the Fisher correction formula by which a P value of $0.05/21 = 0.0024$ was required for significance, the only significant covariations found were between size and necrosis ($P = 0.001$), between compartmentalization and surgical margin ($P = 0.002$), and between local recurrence and surgical margin ($P = 0.0001$). The mean size

of the necrotic tumors was 8 cm as compared with 5 cm for the nonnecrotic ones.

Omitting the Fisher formula, there were significant covariations also between malignancy grade and necrosis ($P = 0.03$), between local recurrence and necrosis ($P = 0.05$), and between compartmentalization and local recurrence ($P = 0.005$). Forty-nine out of 81 Grade IV tumors were necrotic compared with 26 of 63 Grade III tumors, and altogether 75 of the 144 Grades III and IV sarcomas were necrotic as compared with 8 of 49 of the Grades I and II tumors available for analysis from the base series (bivariate significance, $P < 0.0001$).

When considering the relation between necrosis and pain caused by the tumor, 29 of 39 painful tumors and 46 of 105 painless tumors were necrotic (bivariate significance, $P < 0.01$).

Discussion

The patients in this study were previously analyzed by the same multivariate technique as in the present investigation (Rydholm 1983). However,

in the former analysis patients with sarcoma of Grades I and II malignancy were also included, and the minimum follow-up time was only 3 years. The 5-year survival rate for patients with Grades I and II tumors was 90 per cent in that study. These patients thus formed a low risk group well defined solely by histologic malignancy grade; no other variable was necessary for prognostication. We therefore analyzed only patients with Grades III and IV tumors; the crude survival rate for these patients was 62 per cent. This figure is higher than usually reported for patients with high-grade sarcoma and is probably due to the fact that our series is population-based and therefore unselected. Thus, more than half of the tumors were smaller than 6 cm and one third of them were superficial.

The significant variables found were the same as in the former analysis, except that age and pain from the tumor could not be demonstrated to influence survival in this study. The pain variable may have disappeared owing to a relationship to tumor necrosis, which was not analyzed previously. It is not clear why age did not influence survival in the present study.

The negative effect of marginal surgery on survival could be explained by the association between marginal excision and local recurrence, the latter being a strong predictor of fatal outcome. A relation between local recurrence and poor prognosis is previously reported by Markhede et al. (1983) and Merck et al. (1983). Besides residual tumor causing metastasis, the reason for this correlation may be that the risk of surgery becoming marginal, and thus for local recurrence, is higher in tumors prone to dissemination. Mandard et al. (1981) found that the prognosis in soft tissue sarcoma in the extremities was better after "adequate excision" than when macroscopic or microscopic tumor was left in the patient. Infiltrating sarcomas, especially large ones, however, were adequately excised in a lower frequency than small, well-delineated tumors. These results were interpreted as indicating a correlation between loco-regional and general malignancy. Infiltrative growth was not evaluated as a potential prognostic variable in our analysis.

Extracompartmental tumor location increased the risk of local recurrence, probably because removal of a sarcoma with a margin wholly constituted of a fascial tumor barrier is never

achieved for extracompartmental tumors (Enneking et al. 1980, Rydholm & Rööser 1987).

The number of operations for the primary tumor did not influence the local recurrence risk and neither did the fine-needle aspiration procedure confirming the report by Markhede and co-workers (1982). Adjunctive radiotherapy or chemotherapy could not be proved to influence local recurrence or survival. However, no standardized protocols were used for these therapies.

The adverse effect of a high histologic malignancy grade on survival in soft-tissue sarcoma was confirmed in our study; malignancy Grade IV versus Grade III increased the risk of death from tumor, but not of local recurrence.

Successively increasing tumor size had a negative effect on survival, confirming reports of Kindblom et al. (1975) and Eilber et al. (1985). The increase in relative risk was the same for the same increment in size regardless of the absolute values. This may indicate that the larger of two tumors, alike in other respects, has grown for a longer period of time, thus increasing the risk of tumor-cell emboli. A relationship between tumor size, and thus duration, and the risk of metastasis has been shown by Martinez et al. (1956) in animal models.

Widespread necrosis has previously been considered a sign of a high malignancy (Broders et al. 1939, Hajdu 1979). Tumor necrosis, as defined in our study, increased the risk of both local recurrence and tumor-related death. In the study of Costa et al. (1984), moderate to massive tumor necrosis, defined as more than 15 per cent of the analyzed area, was the single best predictor of metastatic disease. Also in multivariate studies by de Stefani et al. (1982) and by Trojani et al. (1984) and in bivariate analyses by Ekfors & Rantakokko (1978) and by Donhuijsen et al. (1986), extensive tumor necrosis worsened the prognosis. Thus, by different criteria, widespread necrosis has been found to be a strong negative prognostic factor in soft tissue sarcoma. This indicates that tumor necrosis is a major indicator of biological aggressiveness. However, an optimal system of classification of necrosis separating different prognostic groups of patients remains to be established.

Also the development of tumor necrosis and the fact that limited necrosis does not seem to carry a bad prognosis are unclear. Widespread necrosis may be a consequence of rapid growth with

insufficient vascular supply, most likely to occur in histologic high-grade tumors. It has also been shown by Young et al. (1959) and by Wiig et al. (1981) in animal experiments that malignant tumors may develop high internal pressures, eventually leading to necrosis analogous to muscular compartment syndromes. In our study there seemed to be a relation between necrosis and pain caused by the tumor. This could lend some support to the hypothesis of a tumor compartment syndrome as one cause of extensive necrosis. More Grade IV than Grade III tumors were necrotic, but the higher malignancy grade could not explain the whole effect of necrosis on survival. There was also a strong relation between extensive necrosis and large tumor size; but again, this could not explain the whole prognostic effect of either variable. Increasing tumor size could increase the risk of necrosis. On the other hand, a gross central necrosis could expand the tumor, especially if bleeding occurs.

Men had a lower expected survival than women. This prognostic sex difference is not commonly reported for soft tissue sarcoma when using multivariate analysis (Kindblom et al. 1975,

Sears et al. 1980, Markhede et al. 1982, Merck et al. 1983). However, Wright et al. (1982), in an analysis of 185 cases of synovial sarcoma, found a higher survival rate for females, as did Hajdu et al (1977) in a series of 136 patients with synovial sarcoma. Also, Alvegård (1986), using multivariate analysis, reported a higher mortality from tumor in males in 146 patients with high-grade soft tissue sarcoma.

There is no consensus on a staging system for soft-tissue sarcoma. This may in part be explained by the lack of identification of prognostic factors and their relative strengths by multivariate analysis. Of the present, commonly used systems, only the variables of the American Joint Committee (AJC system (histologic grade, size including tumor extension, regional and distant metastases) have been multivariately analyzed (Heise et al. 1986). In that study, all analyzed variables were found to be of prognostic value, but the surgical margin achieved was not considered. Our findings indicate that besides histologic malignancy grade and tumor size, also sex and tumor necrosis should be considered for prognostication of patients with soft tissue sarcoma.

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