

Prognosis in high-grade soft tissue sarcomas

The Scandinavian Sarcoma Group experience in a randomized adjuvant chemotherapy trial

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From 1981 to 1986, 240 patients with primary, malignancy grade III or IV soft-tissue sarcoma were entered into a randomized adjuvant chemotherapy multicenter trial, conducted by the Scandinavian Sarcoma Group. After a median follow-up time of 46 (2-97) months, a multivariate analysis of risk factors for metastases was performed in 138 radically operated on patients with tumors of the extremities. Adjuvant single-agent doxorubicin did not improve the metastasis-free survival. Histologic malignancy grade IV, tumor size > 10 cm, vascular invasion by tumor, and male sex were identified as risk factors. Patients with no or one risk factor had a 5-year metastasis-free survival of 0.7, with two risk factors 0.5, and with three or four risk factors 0.2. The combination of different risk factors provides a prognostic model for soft tissue sarcomas, which could be a basis for therapeutic trials.

Except for histologic malignancy grade and tumor size, there is no consensus on which tumor and host factors are prognostic in soft tissue sarcoma. There are conflicting reports as regards the importance of sex, age, tumor depth, and localization (Enneking et al. 1980, Angervall 1981, Markhede et al. 1982, Merck et al. 1983, Rösser et al. 1987, Tsujimoto et al. 1988). In recent years, also the extent of tumor necrosis and intratumoral vascular invasion has been reported to be of prognostic value (De Stefani et al. 1982, Costa et al. 1984, Trojani et al. 1984, Rösser et al. 1987a). We analyzed the prognostic importance of all these factors in 138 patients with soft tissue sarcoma of the extremities treated by carefully defined surgery without adjuvant radiotherapy. Because the series is part of a randomized trial on adjuvant doxorubicin treatment conducted by the Scandinavian Sarcoma Group (Alvegård 1989b), one half of the patients were also given chemotherapy, which, however, in the whole series did not effect local recurrence rate, metastasis-free survival, or overall survival (Alvegård 1986, 1989b).

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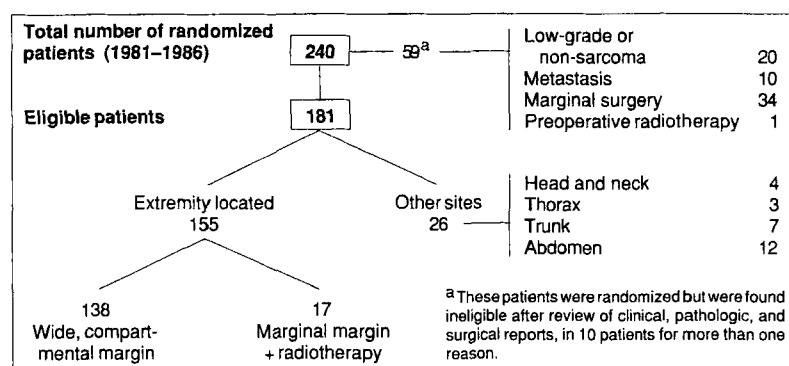
Patients and methods

Eligibility criteria

From January, 1981, through February, 1986, totally 240 patients with primary, high-grade soft tissue sarcoma, without evidence of metastatic disease, were entered into a randomized, adjuvant, postoperative chemotherapy multicenter trial, using single-agent doxorubicin 60 mg/m², given as an intravenous bolus once a month for 9 months. The trial was conducted by the Scandinavian Sarcoma Group (Alvegård 1989b). Patients were eligible for inclusion if they were between 15 and 70 years of age and had a sarcoma classified as grade III or IV on a four-grade scale (Broders 1964, Angervall 1981). Histologic typing was based on the WHO classification, updated by Enzinger and Weiss (1983). Coded data for all the patients have been reported by Alvegård (1989a).

Out of the 240 randomized patients, 181 patients fulfilled all the study entrance criteria (Figure 1). The tumor was located in the extremities in 155 patients, of whom 138 had a wide or compartmental margin by local or ablative surgery. In these patients a multivariate analysis of risk factors for the occurrence of metastasis was performed.

Figure 1. Accrual of patients with high-grade soft tissue sarcoma in the randomized single doxorubicin Scandinavian multicenter trial.



Surgery

Classification of the surgery was according to Stener (Alvegård et al. 1989b). A *wide excision* was the same as defined by Enneking et al. (1980). *Anatomic compartment*: A single muscle including its fibrous boundary may constitute an anatomic compartment, as may a group of muscles with their common fibrous boundary. A tumor is confined to an anatomic compartment as long as the fibrous boundary of the latter is not invaded by tumor tissue and has not been transgressed by biopsy procedures. *Compartmental excision*: The anatomic compartment in which the tumor is located is removed unopened along with its fibrous boundary (sometimes bone). For a tumor located between muscles, a compartmental excision means that all the muscles around the tumor are included in the surgical specimen along with their common fibrous boundary. For an excision to be described as compartmental, any anatomic compartment that has possibly been contaminated by tumor cells as a result of a biopsy must be included in the surgical specimen. *Amputations* were classified according to the surgical margin.

The classification of surgical margin was reviewed by the surgical panel of the Scandinavian Sarcoma Group at annual meetings without knowledge of the clinical course.

Pathology

Only grades III and IV soft tissue sarcomas were accepted in this trial. All the specimens were reviewed blindly by the Scandinavian Sarcoma Pathology Panel including malignancy grading on a four-grade scale, as previously reported (Alvegård 1989b). For this study, a further histologic classification as regards tumor necrosis and vascular invasion by tumor was performed by one of the authors (NOB).

Table 1. Variables multivariately analysed for prognostic influence on occurrence of metastasis in 138 patients with malignancy-grades III and IV soft tissue sarcomas of the extremities

Factor	No. of patients	No. with metastasis	Relative risk and confidence interval	P-value
Sex				
Male	73	37		
Female	65	23	2.0 (1.1-3.5)	0.02
Age				
≤50 years	55	25		
>50 years	83	35	1.1 (0.6-1.9)	0.8
Extremity				
Upper	23	6		
Lower	115	54	1.8 (0.7-4.2)	0.2
Tumor depth				
Superficial	37	12		
Deep	101	48	1.0 (0.5-2.2)	0.97
Tumor size				
≤10 cm	102	36		
>10 cm	36	24	2.3 (1.2-4.4)	0.01
Malignancy grade				
III	43	11		
IV	95	49	2.3 (1.1-4.6)	0.02
Tumor necrosis				
None	52	18		
5-16 mm	15	7	1.2 (0.5-3.2)	0.61
≥17 mm	71	35	1.1 (0.6-2.0)	0.83
Vascular invasion				
None	105	40		
+	10	5	1.5 (0.5-4.1)	0.44
++	23	15	2.7 (1.4-5.0)	0.002
Chemotherapy				
No	67	24		
Yes	71	28	1.0 (0.6-1.7)	0.9

Tumor necrosis: The extent of necrosis was defined as the length in millimeters of the longest cross section of necrosis found after examination of all the slides. In the analysis, two parameters of necrosis were used: 5-16 mm and ≥17 mm. Only areas of coagulation nec-

Table 2. Metastasis-free survival probability related to sum of Cox-coefficients and number of risk factors in 138 patients with malignancy grades III and IV soft-tissue sarcoma, operated with a wide or compartmental margin

Sum of coefficients (B)	No. of risk factors	Pattern of risk factors				No. of metastases	No. of patients	5-years metastasis-free survival
		Sex	Grade	Size ^a	Vascular invasion			
0	0	F	III	--	-	12	2	0.76
0.64	1	M	III	-	-	20	3	0.84
0.86	1	F	III	+	-	0	0	-
0.87	1	F	III	-	+	5	3	0.40
0.91	1	F	IV	--	-	29	9	0.69
1.50	2	M	III	+	-	4	2	0.50
1.50	2	M	III	-	+	2	1	0.50
1.55	2	M	IV	-	-	25	13	0.43
1.72	2	F	III	+	+	0	0	-
1.77	2	F	IV	+	-	14	7	0.48
1.80	2	F	IV	-	+	5	2	0.60
2.36	3	M	III	+	+	0	0	-
2.41	3	M	IV	+	-	11	9	0.18
2.42	3	M	IV	-	+	4	3	0.25
2.64	3	F	IV	+	+	0	0	-
3.27	4	M	IV	+	+	7	6	0.00

a - ≤ 10 cm; + > 10 cm

rosis, with or without leukocytic infiltration, were taken into account.

Vascular invasion ++ was defined as microscopic evidence of tumor extension into the lumen and/or through the wall of a blood or lymphatic vessel of any dimension with distinct endothelial lining; + was defined as tumor proliferation in spaces with necrotic walls (necrotic tumor) or in spaces with questionable endothelial lining.

Characteristics of patients

The median age was 56 (15-70) years, and 73 patients were males and 65 were females. The tumor was superficial in 37 patients and deep-seated in 101. The tumor was located in the upper extremity in 23 patients and in the lower extremity in 115. The median tumor size was 8 (1-20) cm with grade III in 43 and IV in 95 patients. The tumor types were as follows: malignant fibrous histiocytoma (n 65), synovial sarcoma (n 23), liposarcoma (n 12), leiomyosarcoma (n 10), unclassified soft tissue sarcoma (n 7), malignant Schwannoma (n 6), malignant mesenchymoma (n 4), fibrosarcoma (n 2), hemangiosarcoma (n 2), malignant hemangiopericytoma (n 2), extraskeletal osteosarcoma (n 2), extraskeletal chondrosarcoma (n 1), rhabdomyosarcoma (n 1), and extraskeletal Ewing's sarcoma (n 1). In 81 patients a wide excision was performed, while respectively in

24, 21, and 12 patients a compartmental excision, a wide amputation, and a compartmental amputation was carried out. Sex, age, site, tumor depth, tumor size, malignancy grade, tumor necrosis, intratumoral vascular invasion, and chemotherapy were multivariately analyzed (Table I).

The median follow-up time was 46 (2-97) months for all the patients and 58 (35-97) months for the 90 survivors. No patient was lost to follow-up.

Sixty patients developed metastases after a median follow-up of 12 (1-48) months, most commonly in the lungs. At the time of analysis, 48 of these patients had died. Eight patients had a local recurrence, of whom 6 also developed metastases. The metastases were diagnosed before, at the time of, and after local recurrence, in 1, 4, and 1 patients, respectively.

Statistics

Metastasis-free survival was estimated using the Kaplan-Meier method and the generalized Wilcoxon test. Simultaneous analyses of several risk factors were performed using the Cox's proportional hazards model with *P*-values calculated by Wald's statistic. Confidence intervals are given at the 95 percent level.

The internal independence among the risk factors was tested using chi-square tests. Simultaneous inference was thereby achieved using the Bonferroni meth-

Table 3. Test for independence in pairs of analysed variables. Significant covariation with Bonferroni's correction, $P < 0.004$, and without, $P < 0.05$

	Size	Vascular invasion	Sex	Necrosis	
				≤5 mm	≥17 mm
Malignancy					
Grade IV	0.005	1.0	0.31	0.2	0.18
Size, > 10 cm		0.8	0.34	1.0	0.007
Vascular invasion (++)			0.88	1.0	0.45
Sex				1.0	0.72

od (Jones et al. 1982); the P -value required for significance in an individual test, of the 14 performed, was set at $0.05/14 = 0.004$.

Results

Vascular involvement (++) by the tumor (versus none or +), malignancy grade IV (versus grade III), tumor size >10 cm, and male sex decreased metastasis-free survival (Tables 1 and 2); all of these had similar relative risk values (2.0–2.7). Forty-seven percent of the patients had a 0–1 risk factor and a 5-year metastasis-free survival of 73 percent. Thirty-six percent had two factors and a survival of 46 percent, whereas 16 percent had 3–4 factors and a metastasis-free survival of only 17 percent (Figure 1).

A covariation was found between increasing malignancy grade and size, and between necrosis and increasing size (Table 3).

Discussion

Adjuvant chemotherapy for soft tissue sarcoma has not been shown to be effective. Further randomized trials require identification of the high-risk patients, because only these should be included. Histologic malignancy grade is the principal prognostic variable (Röösér et al. 1987b) in the two commonly used staging systems: viz., the Surgical Staging system with a two-grade scale (Enneking et al. 1980) and the AJC system with a three-grade scale (Russel et al. 1977). We used a four-grade scale, found reproducible (Angervall 1981, Angervall et al. 1986, Rydholm et al. 1984, Röösér et al. 1987a). The 5-year survival for patients with grade I sarcomas on this scale is close to 100 percent and for patients with grade II sarcomas well over 80 percent (Markhede 1982 et al., Rydholm et al. 1984).

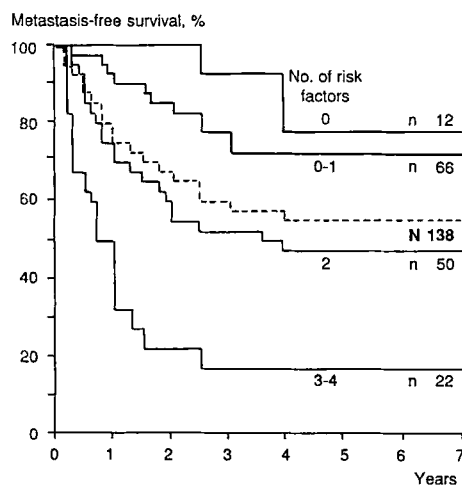


Figure 2. Cumulative metastasis-free survival with different number of risk factors in 138 patients with malignancy grades III and IV soft tissue sarcoma, operated with a wide or compartmental margin. --- all 138 patients.

Several factors, other than histologic malignancy grade, have been reported to be prognostic. The well-known importance of tumor size was confirmed in our series, as was the negative influence of male sex and vascular invasion, reported by Hajdu (1977), De Stefani et al. (1982), Trojani et al. (1984), Chasets and Enzinger (1985), Potter et al. (1986), and Röösér et al. (1988). In contrast to earlier reports (De Stefani et al. 1982, Costa et al. 1984, Trojani et al. 1984, Röösér et al. 1988), we found no influence of tumor necrosis when analyzed multivariately. There was, however, a close covariation between tumor size and necrosis; by omitting tumor size in our analysis, necrosis emerged as a prognostic factor.

Prognostic factors and their strength may vary between different histotypes, which therefore ideally should be analyzed separately. Our series was too small to permit this.

The local recurrence rate was low in our series, and can probably be explained by the strict criteria applied for the definition of surgical margins (Alho et al. 1989). We did not analyze the prognostic importance of local recurrence. The association of local recurrence and tumor-related death is well-known, but whether causal or statistical is controversial. In none of our patients did the interval between the diagnosis of local recurrence and metastases exceed 6 months, making a causal association less probable.

Only patients with histologic high-grade malignant tumors (grades III and IV on a four-grade scale) were

included in the randomized trial from which the patients in the present series originated. As in several other studies on adjuvant chemotherapy for soft tissue sarcoma, histologic malignancy grade was the only tumor characteristic necessary for inclusion. However, by inclusion of all the prognostic factors identified—vascular invasion, large tumor size, male sex, and malignancy grade IV—one half (66/138) of our patients had a 5-year survival rate around 75 percent. Sixty-four of these patients were females, demonstrat-

ing the prognostic importance of sex in this series. In retrospect, the prognosis of these patients did not justify their inclusion in the trial. A small group of 22 patients, all males, had a poor prognosis with only 17 percent, with 5 years' metastasis-free survival. Half of these patients were under 40 years of age.

Our findings confirm that several clinicopathologic factors should be added to histologic malignancy grade to identify soft tissue sarcoma patients with a poor prognosis.

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