Local recurrence of soft tissue sarcoma a risk factor for late metastases

379 patients followed for 0.5–20 years

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We performed a retrospective analysis of 379 adult patients treated for soft tissue sarcoma. None had metastasis at the time of diagnosis and all were treated surgically. Patients who developed metastatic disease before the local recurrence were excluded. The 8-year metastasis-free survival rate in the group of 261 patients with local tumor control was 0.72, compared to 0.67 in the 118 patients with local recurrence (*P* 0.2). Multiple regression analysis showed that high-grade malignancy and large tumor size were risk factors for metastases. Local recurrence was not a risk factor. However, when patients with small and/or low-grade tumors were analyzed separately, local recurrence emerged as a risk factor. In this group of patients, the 8-year survival rate was 0.87 for those with local control and 0.64 for those with local recurrence (*P* 0.004). Local recurrence appears to be a risk factor for the development of late metastases in patients who otherwise have a low risk of metastases.

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Several reports on prognostic factors following surgical treatment of soft tissue sarcoma have been published. Host and tumor features often claimed to be of prognostic value are tumor depth, size, malignancy grade, necrosis, vascular invasion, and DNA ploidy (Enneking et al. 1980, Markhede et al. 1982, Rydholm et al. 1984, Collin et al. 1987, Rööser et al. 1987, Collin et al. 1988, Rööser et al. 1988, Alvegård et al. 1989a, El-Jabbour et al. 1990, Bauer et al. 1991, Rydholm et al. 1991, Saddegh et al. 1992, Westbury 1992).

Controversy prevails about the importance of local tumor control for metastasis-free survival (Stotter et al. 1990, Barr et al. 1991, Singer et al. 1992, Westbury 1992, Williard et al. 1992). Improved local tumor control does not appear to translate into improved overall survival (Brennan et al. 1987, Emrich et al. 1989). Furthermore, in population based studies from southern Sweden, local recurrence has not been found to increase the risk of metastases (Rööser et al. 1990, Rydholm et al. 1991). The fact that patients with local recurrence also often have concomitant metastases is interpreted as different manifestations of a highly malignant tumor (Gustafson et al. 1991).

In the most recent study from the southern Sweden sarcoma database, patients with local recurrence without concurrent metastases were reported to have a similar survival rate as primary sarcoma patients, i.e., the 5-year metastsis-free survival was 0.73 after the last recurrence (Gustafson et al. 1993). The patients with local recurrence were prognostically favourable, with more low-grade and small tumors compared to an unselected group of primary sarcoma patients. Hence, one might question whether the survival rate would not have been even better without the local recurrence.

We made a multivariate analysis of factors related to metastasis in soft tissue sarcoma, with a special focus on local recurrence.

Patients and methods

This retrospective study was based on 429 adult patients with soft tissue sarcoma of the trunk wall or extremities treated at the Karolinska Hospital in 1970–1992. 32 patients with metastases at the time of diagnosis and 7 who were not treated surgically were excluded, leaving 390 patients. Another 11 patients with metastases preceding the local recurrence were also excluded, leaving 379 patients for study. These 379 patients were divided into a local control

Table 1. Tumor site (number of patients and *percent*)

Margin	Local control group	Local recurrence group	Total	Local recurrence rate
Subcutaneous	85 *32*	35 *30*	120	0.36
Intracompartmental deep	104 *40*	38 *32*	142	0.29
Extracompartmental deep	72 *28*	45 *38*	117	0.38

Difference between groups P 0.11.

Table 2. Surgical margins obtained at surgery for primary tumor (number of patients and *percent*)

Margin	Local control group	Local recurrence group	Total	Local recurrence rate
Marginal	114 *44*	89 *75*	203	0.47
Wide	131 *50*	28 *24*	159	0.20
Radical	16 *6*	1 *1*	17	–

Difference between groups $P < 0.0001$.

Table 3. Malignancy grade (number of patients and *percent*)

Malignancy grade	Local control group	Local recurrence group	Total	Local recurrence rate
I	31 *12*	5 *4*	36	0.16
II	45 *17*	24 *20*	69	0.33
III	121 *47*	65 *55*	186	0.38
IV	64 *24*	24 *21*	88	0.35

Difference between groups P 0.06.

group of 261 patients and a local recurrence group of 118 patients. There were 192 men and 187 women, and the median age at diagnosis was 63 (15–95) years. 218 (58 percent) of the patients were referred with untouched tumors or after a fine needle biopsy only. Among the remaining 161 patients, 54 were referred after an incision biopsy or intralesional excision and 61 after a marginal excision. 46 patients were referred with a local recurrence.

29 percent of the tumors were located on the trunk (including shoulder, groin and gluteal regions) and 71 percent on extremities. The most common tumor location was the thigh (35 percent). The lesions were subcutaneous in 32 percent, deep intracompartmental in 37 percent, and deep extracompartmental in 31 percent (Table 1). The median tumor size was 7 cm. Size could not be established in 13 patients.

22 (6 percent) patients were amputated and 357 had local surgery. The surgical margins were classified according to the Surgical Staging System (Enneking et al. 1980). Patients referred after an intralesional excision were reoperated to achieve at least a marginal margin. The final surgical margin was marginal in 54 percent and wide or radical in 46 percent (Table 2). Among the 203 patients in whom only a marginal margin was obtained, 77 received postoperative radiation therapy, commonly 51 Gy. 13 patients had adjuvant chemotherapy (Alvegård et al. 1989b).

All specimens have been examined at the Department of Pathology, including those from patients referred after surgery, whose histologic slides were reviewed. The tumors were classified according to histotype (Enzinger et al. 1969) and malignancy grade (I–IV) (Broders et al. 1939). The definition of malignant fibrous histiocytoma was that of Enzinger and Weiss (1988). The most common histotypes were malignant fibrous histiocytoma (40 percent), liposarcoma (17 percent), fibrosarcoma (10 percent), and synovial sarcoma (5 percent). 72 percent of the le-

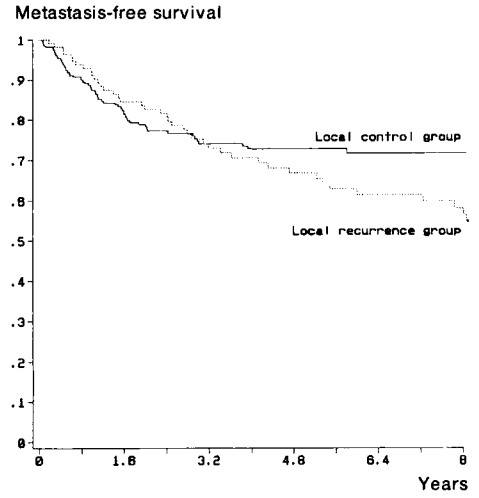

Figure 1. Metastasis-free survival for patients surgically treated for soft tissue sarcoma. There were 261 patients in the local control group and 118 in the local recurrence group. *P* 0.18.

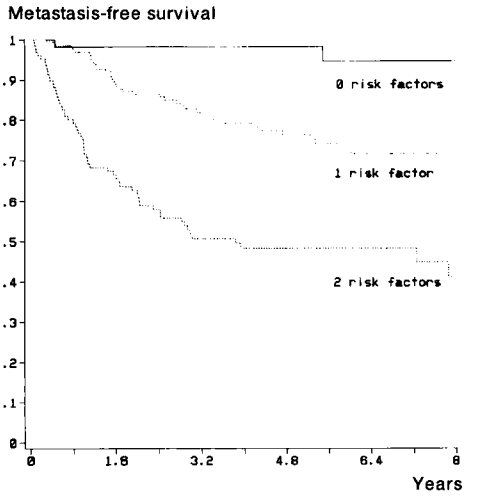

Figure 2. Metastasis-free survival in relation to presence of the risk factors high grade and large tumor size. 57 patients with 0 risk factors, 195 with 1, and 131 with 2. $P < 0.0001$.

sions were of high (III–IV) grade (Table 3).

All patients were followed until May, 1993, or until metastases or death. The median follow-up time was 5 (0.5–22) years.

Statistics

Descriptive data and surgical margins of patients with and without local recurrence, given in the text and tables, were analyzed using the Chi-square test or the Wilcoxon Rank Sum Test. Local recurrence and metastasis-free survival rates were estimated using Kaplan-Meier methods. The Mantel-Haenszel log-rank test was applied to check for equality of survival curves. The data bank collection and statistical analysis were performed on Medlog (Information Analysis Corp., Nevada , U. S. A.).

Sex, age, grade, size, location, depth, surgical margin, and local recurrence were analyzed for influence on metastasis-free survival assessed from the date of diagnosis. Patient age and tumor size were treated as continuous variables. Cox multivariate regression analysis of prognostic factors for metastasis-free survival with a likelihood-ratio test for significance of covariates was performed. 13 patients with incomplete data were excluded from the multivariate analyses. A *P*-value < 0.05 was considered significant. The increased risk of metastases associated with the identified prognostic variables was expressed as the Relative Risk equal to e^x, where x was the coefficient estimate obtained from the multivariate regression analysis.

Results

The 5-year metastasis-free survival rate for the whole group of 379 patients was 0.70. It was 0.73 in the local control group and 0.66 in the local recurrence group (Figure 1). The 8-year survival rates were 0.72 and 0.58 for the 2 groups, respectively (*P* 0.18).

Only 2 risk factors for metastases were identified: high malignancy grade and increasing tumor size (Table 4). Neither surgical margin nor local recurrence was a risk factor for metastases. Survival was closely related to the number of risk factors, i.e., high grade or large tumor size (> 7cm). 8-year survival rates for patients with 0, 1, or 2 risk factors were 0.95, 0.72, and 0.41, respectively (Figure 2). The median time between diagnosis of local recurrence and that of a subsequent metastasis was 31 months for patients with 0–1 risk factors and 16 months for those with 2 risk factors (*P* 0.003).

To assess the influence of local recurrence in patients with a good prognosis, a second multivariate analysis was performed after exclusion of patients with 2 risk factors. In this analysis of 252 patients with 0–1 risk factor, local recurrence was a risk factor for metastases, together with large tumor size, high grade and location on the trunk (Table 5). In fact, the 8-year survival rate was 0.87 for patients with local control and 0.64 for those with local recurrence (Figure 3). The median time between treatment of the primary tumor and subsequent metastasis was

Table 4. Multivariate analysis of risk for metastases based on 366 patients with soft tissue sarcoma

Variable	Definition	*P*-value	Relative risk
Age	Continuous	0.3	
Sex	Female vs male	0.3	
Tumor location	Trunk vs extremity	0.7	
Site	Intra- vs extracompartmental	0.06	
Size	Continuous	<0.0001	1.5 per 5 cm increment
Malignancy grade	Low (I, II) vs high (III, IV)	<0.0001	5
Surgical margin	Wide or radical vs marginal	0.9	
Local recurrence	No vs yes	0.9	

Table 5. Multivariate analysis of risk for metastases based on 252 patients with small and/or low grade lesions

Variable	Definition	*P*-value	Relative risk
Age	Continuous	0.2	
Sex	Female vs male	0.8	
Tumor location	Extremities vs trunk	0.02	2
Site	Intra- vs extracompartmental	0.07	
Size	Continuous	0.02	1.5 per 5 cm increment
Malignancy grade	Low (I, II) vs high (III, IV)	0.001	5
Surgical margin	Wide or radical vs marginal	0.1	
Local recurrence	No vs yes	0.05	2

1.4 years for patients without local recurrence (n 17) and 3.3 years for those with local recurrence (n 23, $P < 0.001$).

The 5-year local recurrence rate, based on all 379 patients, was 0.34. Significant risk factors for local recurrence were a poor surgical margin and high malignancy grade. The risk of local recurrence was 0.46 for patients treated surgically before referral to the Tumor Service and 0.23 for those referred with untouched lesions (Figure 4).

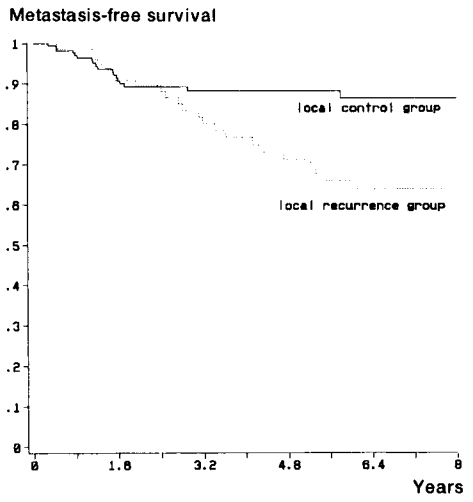

Figure 3. Metastasis-free survival for patients with 0–1 risk factor, 179 patients with local control and 73 with local recurrence. *P* 0.004.

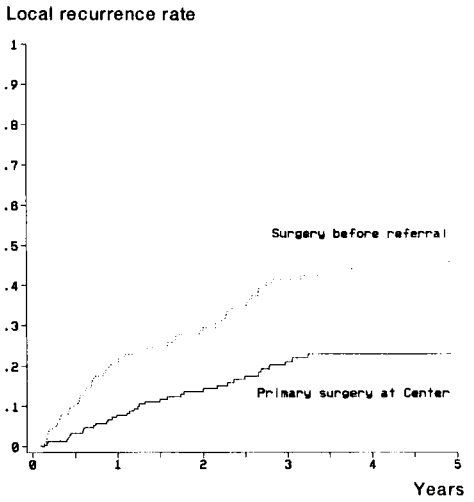

Figure 4. Local recurrence rates and referral status, 161 patients had undergone surgery before referral and 218 had their primary surgery at the Tumor Service. $P < 0.0001$.

Discussion

This study of surgically-treated soft tissue sarcoma patients shows that the survival rate was similar for patients with or without local recurrence. However, for patients who have an inherently good prognosis, i.e., with small and/or low-grade lesions, local recurrence does appear to be a risk factor for metastases.

A major concern with this type of survival study is that the patient material is not population-based. Especially the inclusion of patients with a local recurrence who were primarily treated outside of the Tumor Service may have biased the results. However, there was no difference in the distribution of pertinent clinical features, such as tumor size and grade, between the local control group and the local recurrence group. Only the quality of the surgical margin differed between the 2 groups. Furthermore, the clinical features of the whole series were almost identical to the most recent population-based study from Southern Sweden (Gustafson et al. 1993). In fact, their overall 5-year metastasis-free survival rate was also the same, 0.68 versus 0.70 in our series. Hence, we consider the series as representative.

Several studies have shown that wide or radical local resection improves local tumor control, but have been unable to demonstrate that better local control improves survival (Emrich et al. 1989, Rööser et al. 1990, Brennan et al. 1991). It has been argued that those who die shortly after the primary operation do not have time to develop a local recurrence and therefore a group of patients without local recurrence could be biased by a greater number of more malignant tumors which quickly prove fatal.

From the survival curve in Figure 1 we can conclude that the risk of metastases after 3 years was almost nil for patients with local tumor control, whereas those with local recurrence had a continued risk of metastases, even 8 years after diagnosis of the primary tumor. However, the analysis of possible weak risk factors is confounded by high-risk patients who develop early metastases. By excluding patients with both risk factors for metastases, we could analyze a large group of patients with a favorable prognosis. Interestingly, the interval between the diagnosis of local recurrence and appearance of metastases was more than 2 years, which supports the concept of a causal relation between the two. This concept is also supported by the large difference between patients with and without local recurrence in the interval between primary treatment and metastases. Hence, among patients with small and/or low-grade tumors, local recurrence was a significant risk factor, a finding which is in agreement with a similar study from the Memorial Sloan-Kettering Cancer Center (Gaynor et al. 1992).

The importance of referring soft tissue sarcoma patients before surgery to musculoskeletal tumor centers was evidenced by the difference in local recurrence rates among patients treated for their primary tumor outside and at the Tumor Service.

One important implication that can be drawn from this and other similar studies is that survival of patients with soft tissue sarcoma will only be improved by effective adjuvant chemotherapy aimed at eliminating micrometastases. The reported 5-year metastasis-free survival rate of 0.70 is slightly higher than in most other series, probably because low-grade and small tumors associated with a low risk of metastasis are referred to our Service (Rydholm et al. 1984, 1991). This relatively high overall survival rate underlines the importance of identifying high-risk patients for trials of adjuvant chemotherapy. The risk factors of high malignancy grade and large tumor size are among those that have been consistently identified previously. Assessment of DNA ploidy or of tumor necrosis may be objective substitutes for subjective histologic grading of malignancy (Rööser et al. 1987, Alvegård et al. 1989a, Bauer et al. 1991). A narrow surgical margin should not be per se a criterion for inclusion in trials of adjuvant chemotherapy.

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