Size and timing of local recurrence predicts metastasis in soft tissue sarcoma

Growth rate index retrospectively analyzed in 134 patients

Peter F M Choong, Pelle Gustafson and Anders Rydholm

Our study combined size and timing of the first local recurrence to create a growth rate index (GRI - ratio of size (cm) to timing (mo)) which we analyzed for an association with metastasis. We analyzed 134 locally recurrent tumors from a series of 460 adult patients with soft tissue sarcoma of the extremities and trunk wall who were diagnosed and treated between 1964 and 1990, with a median follow-up of 10 (2–28) years for survivors. None of the patients had metastases at diagnosis. One half (74) of local recurrences were from inadequately treated primaries, one half (71) were associated with metastases, and two thirds (89) were seen in non-center-treated patients. There were equal numbers of patients with GRI ≤ 0.4 (low) and > 0.4 (high). Patients with a low GRI had a better 2-year metastasis-free survival (80 percent) than those with a high GRI (30 percent). High GRIs were associated with large, high grade primary tumors and a short metastasis-free interval in comparison to low GRI tumors. Time to local recurrence strongly correlated with the time to metastasis (R^2 0.85, $p < 0.001$). GRI was a good discriminator of metastasis in patients with tumors larger than 5 cm and of malignancy grade IV. Our study suggests that clinical characteristics (e.g., GRI) of local recurrence rather than presence, per se, are important in predicting tumor behavior.

Department of Orthopedics, University Hospital, S-221 85 Lund, Sweden. Tel +46 46-171500. Fax -130732
Correspondence: Dr. A Rydholm
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Local control of soft tissue sarcoma is directly related to the quality of local treatment, which in general consists of surgery and adjuvant radiotherapy. There appears to be, however, only a weak correlation between the type of local treatment and the incidence of metastasis. Therefore, some groups have questioned a causal relationship between local recurrence and metastasis (Potter et al. 1986, Lawrence et al. 1987). Rööser (1987) and Gustafson et al. (1991) concluded that local recurrence, occurring especially after surgery with wide margins, was probably a predictor of grave prognosis rather than the cause of metastasis. Recently, our group identified a population of patients with local recurrence who had a good prognosis (Gustafson et al. 1993).

Local recurrence may accompany metastasis or occur in its absence, suggesting that the presence or absence of local recurrence, per se, may be less accurate as predictors. We analyzed whether the nature of local recurrence, rather than its presence alone, was a more useful guide to prognosis. To this end, we examined the relationship of size and timing of local recurrence to metastasis in patients with soft tissue sarcoma of the extremities and trunk wall.

Patients

This is a retrospective population-based study of adult patients with soft tissue sarcoma of the extremity and trunk who were diagnosed and operated on between 1964 and 1990 in the Southern Swedish Health Care region (population of 1.5 million). For details regarding the database, see Gustafson (1994). Patients referred to as being center-treated are those who had the management of their primary tumor at the Musculoskeletal Tumor Center in Lund. Patients who did not receive treatment (38), who had metastases at diagnosis (39) or whose local recurrence size could not be determined (5) were excluded from the total of 525 cases recorded in the data bank during this period, leaving 460 patients. Of these 460 patients, 134 developed local recurrences, of whom 71 also had metastases. The median follow-up time was 10 (2–28) years for survivors. All patients are reviewed at 3-monthly intervals for the first 2 years, following which 6-monthly reviews are undertaken. Chest radiographs are performed at each review. While it is clear that CT-scanning can detect miniscule pulmonary metastases, our specialists believe

Table 1. Comparison between patients with or without local recurrence in 460 patients with STS of extremity and trunk wall

Characteristic	Local recurrence		p-value
	Yes	No	
Number	134	326	
Median age (range)	66 (16–91)	64 (17–96)	0.06 [b]
Sex			
Male	75	185	0.9 [a]
Female	59	141	
Median size of primary (cm)	7 (1–30)	6 (1–30)	0.2 [b]
Treatment center			
Center	45	168	0.0001[a]
Non-center	89	158	
Treatment			
Adequate	60	267	0.0001[a]
Inadequate	74	59	
Metastasis			
Yes	71	80	0.0001[a]
No	63	246	

[a] differences, [b] mean rank

that serial standard radiographic imaging is sufficient for this purpose and it has been adopted in our review protocol.

Clinicopathologic features

Pathologists from our sarcoma group reviewed all slides and described the tumors according to the histopathological classification of Enzinger and Weiss (1988). The criteria for histologic malignancy grading have been previously described (Angervall et al. 1986). The actuarial 5-year survival from the entire database of patients with histologic malignancy grade I, II, III and IV tumors are 100, 90, 70, and 50 percent, respectively. On this basis, we have chosen in this study to regard patients with grade I–III tumors as a low malignancy group, and patients with grade IV tumors as a high malignancy group. We classified surgical margins according to Enneking et al. (1980) and for patients treated between 1964 and 1980, a retrospective classification was performed from the original operation case notes. We defined adequate treatment as marginal excision combined with radiotherapy (53) or surgery with wide (249) or radical (25) margins, regardless of radiotherapy. 133 patients received inadequate treatment either because treatment was intralesional (12) or by marginal excision (121) alone. 33 patients had postoperative and 4 received preoperative chemotherapy. As a previous study by the Scandinavian Sarcoma Group failed to show any effect of chemotherapy upon metastases (Alvegård et al. 1989), these patients were not analyzed separately.

We determined the size of the primary tumor and the first local recurrence from measurements of unfixed surgical specimens, pathologists' notes (usually of the unfixed specimen, except prior to 1970) or computer tomography. When all 3 measurements were available, CT measurements were used, followed by measurements of the unfixed specimen. The recurrence-free period was defined as the time between definitive surgery for the primary tumor and the time when the recurrence was diagnosed.

The clinical endpoint was the development of metastasis. The metastasis-free interval was the time from initial surgery to the diagnosis of metastatic disease. Any patients who died of other causes before the onset of metastasis were treated as censored cases. Differences between groups were compared using contingency tables and the Mann-Whitney U test. The predictive potentials of different factors were evaluated using the Cox model of proportional hazards. Metastasis-free survival of patients was analyzed using Kaplan-Meier methods and differences were compared using the Breslow test. A p-value < 0.05 was regarded as significant.

Results

Local recurrence and metastasis (Table 1)

The overall incidence of local recurrence was 29 percent (134/460) and these cases occurred between 1 and 156 months. There was no relationship between the incidence of local recurrence and sex, age, primary tumor size or histotype. In contrast, centralized and adequate treatment had a major bearing on the quality of local control. 45/213 center-treated patients developed local recurrence compared to 89/247 non-center patients. Center treatment accounted for 23 percent of the 133 patients who were inadequately treated, while this was 77 percent in non-center-treated patients. The incidence of metastasis in center- and non-center-treated groups was the same (33 percent vs. 34 percent). There was a strong positive association between the incidence of metastasis and local recurrence; 71 patients developed both local recurrence and metastasis.

Size and timing of local recurrence (Table 2)

The median local recurrence size was 4 (0.3–19) cm. Small (≤ 4 cm) local recurrences were associated with low-grade primary tumors, while large local recurrences were more commonly associated with high-grade primary tumors. Regardless of timing, large local recurrences were more often associated with metastases. The median metastasis-free interval

Table 2. Comparison of size and timing of local recurrence in 134 patients with local recurrence after STS of extremity and trunk wall

	Size (cm)			Timing (months)		
	≤ 4	> 4	Median	≤ 12	> 12	Median
Metastasis						
Yes (71)	28	43	5	51	20	8
No (63)	41	22	3	30	33	13
p-value	0.003 [a]		0.0003 [b]	0.004 [a]		0.006 [b]
Grade						
High (76)	32	44	5	53	23	8
Low (58)	37	21	3	28	30	15
p-value	0.01 [a]		0.004 [b]	0.02 [a]		0.003 [b]

[a] differences, [b] mean rank

Table 3. Growth rate indices and 2-year metastasis-free survival in 134 patients with local recurrence after STS of extremity and trunk wall

GRI		Survival rate	n
0.3	≤	0.84	57
	>	0.35	77
0.4	≤	0.79	67
	>	0.33	67
0.5	≤	0.74	79
	>	0.29	55
0.6	≤	0.75	84
	>	0.25	50
1.0	≤	0.63	110
	>	0.22	24

p-values of differences for all indices < 0.0001

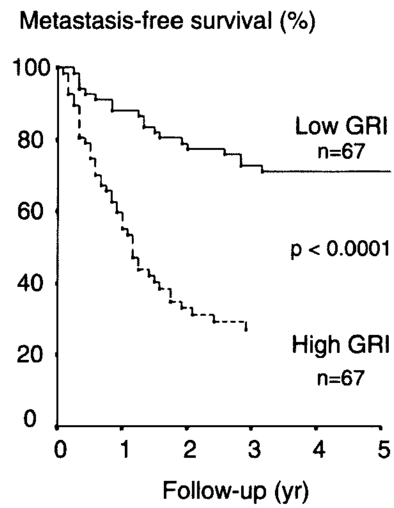

Figure 1. 5-year metastasis-free survival curves related to GRI (low ≤ 0.4, high > 0.4).

was 18 months for patients with large local recurrences and over 5 years for those with small local recurrences.

The median time to local recurrence was 11 (1–156) months. Regardless of size, earlier local recurrences were associated with a lower metastasis-free survival rate than recurrences occurring later. The median survival for patients who developed local recurrence ≤ 1 year was 14 months and over 5 years in whom local recurrence developed after 1 year.

In the 71 patients who developed both local recurrence and metastasis, there was a strong correlation between the time to local recurrence and metastasis (R^2 0.85, p 0.001). No correlation was noted between the size of the local recurrence and the time to metastasis (R^2 0.001, p 0.8).

Growth rate index

The positive association between local recurrence size and timing with the incidence of metastasis led us to examine whether a combination of the two parameters was a still better predictor of metastasis. We divided the size (cm) of the local recurrence by the time (mo) of its appearance following surgery of the primary tumor to give a growth rate index (GRI). We found a positive correlation between GRI and incidence of metastasis that was much better than for size alone, and at least as good, if not better, than for the timing of the local recurrence. We constructed Kaplan-Meier curves for the metastasis-free survival of a range of indices, and all those tested discriminated between metastatic and non-metastatic groups at 2 years (Table 3). We chose a GRI of 0.4 as our index because there were equal numbers of patients ≤ 0.4 and > 0.4 (Figure 1). Large, high-grade primary tumors, with a greater incidence of metastasis and a relatively short metastasis-free interval were associated with GRI > 0.4 (High GRI). In contrast, low-grade primary tumors, a lower incidence of

Table 4. Comparison between patients with GRI ≤ 0.4 (Low) and > 0.4 (High) in 134 patients with local recurrence after STS of extremity and trunk wall

Characteristic	GRI		p-value
	Low	High	
Median age (range)	63 (16–90)	67 (26–91)	0.06 [b]
Sex			
Male	36	39	0.60 [a]
Female	31	28	
Treatment			
Adequate	30	30	
Inadequate	37	37	
Malignancy grade			
Low	40	18	0.0001 [a]
High	27	49	
Primary tumor size			
≤ 5 cm	34	14	0.0003 [a]
> 5 cm	33	53	
Local recurrence size			
≤ 4 cm	48	21	0.0001 [a]
> 4 cm	19	46	
Timing of local recurrence			
≤ 12 months	23	58	0.0001 [a]
> 12 months	44	9	
Metastasis			
Yes	25	46	0.0003 [a]
No	42	21	

[a] differences, [b] mean rank

metastasis and a longer metastasis-free interval were associated with GRI ≤ 0.4 (Low GRI) (Table 4). The 2-year metastasis-free survival rate for those with Low GRI was approximately 80 percent with a median survival of over 5 years, and that for a High GRI was approximately 30 percent, with a median survival of 14 months (Figure 1).

Relationship of GRI to metastasis in selected groups (Table 5)

To test further the ability of GRI to identify patients with metastasis, we selected a group with the best and worst potential prognosis based upon the size and histologic malignancy grade of their primary tumors and applied this index to them. There were 28 good-prognosis patients who had low-grade tumors that were ≤ 5 cm in diameter, and 56 bad-prognosis patients who had high-grade tumors that were > 5 cm. As anticipated, the good-prognosis group had very few metastases and GRI was of little use in this group. In contrast, of the 56 bad-prognosis patients, 34 of the 40 who developed metastases had high GRIs.

Predictive potential of GRI, and size and malignancy grade of primary tumor

We used the Cox proportional hazards model to

Table 5. Relationship of GRI to metastasis in low and high risk groups

		Low risk [a] (28) Metastasis		High risk [b] (56) Metastasis	
		Yes	No	Yes	No
GRI	≤ 0.4	4	18	6	9
	> 0.4	1	5	34	7
p-value		0.9		0.002	

[a] Low malignancy grade and size ≤ 5 cm of primary tumor
[b] High malignancy grade and size > 5 cm of primary tumor

compare the relative risks (RR) of metastasis as determined by high GRI, and large size (> 5 cm) and high malignancy grade of the primary tumor. The analyses show that high GRI (RR 3, CI 1.8–4.4) carries, at least, the same risk as high malignancy grade (RR 2.6, CI 1.6–4) and that high GRI involves a greater risk of metastasis than the size of the primary tumor (RR 1.3, CI 1–2).

Discussion

There is a well-known association between local recurrence and metastasis in soft tissue sarcomas. Certainly, local recurrence may be either an indication of inadequate treatment or of a highly malignant tumor with aggressive local growth. Therefore, the prognostic importance of local recurrence, per se, may vary and may be one explanation for the variation in results seen following treatment of patients with local recurrence. Our study examined 2 clinical characteristics of local recurrence, i.e., size and timing, to see if these had prognostic value.

Markhede et al. (1982) examined the prognosis after surgical treatment of malignant soft tissue tumors and reported on various factors which influenced or were influenced by local recurrence. Like them, we found an increased risk of metastasis as well as a shorter metastasis-free interval with earlier local recurrence. They concluded that the timing of recurrence was not influenced by the malignancy grade. In contrast, we found that local recurrences within 1 year of surgery were more often associated with high malignancy grade primary tumors and this may be one explanation for the association between early local recurrence and mortality. Markhede et al.'s study did not comment on aspects related to the size of local recurrence. We found that a larger local recurrence led to a poorer prognosis than a smaller recurrence.

We found that primary tumors of a high malignancy grade were, in general, associated with local recurrences that were larger or occurred earlier than low malignant tumors. As size is the numerator and time is the denominator in GRI, this index is higher for tumors that recur early and/or are large, such as those with more aggressive neoplasms. Our findings show that GRI results in a wider division in the survival curves than the size of the local recurrence alone. There needs to be, however, an analysis of greater numbers to show whether the better discrimination of survival seen with GRI, as compared to timing of the local recurrence alone, is maintained. Our analysis of poor-prognosis patients who had high grade and large tumors showed that GRI was a good discriminator of metastasis in this group, indicating that it is of independent value.

Prior to this study, only Ruka et al. (1988) alluded to a similar index by examining the importance of tumor size to a symptom-duration ratio as a prognostic factor in patients with high-grade soft tissue sarcomas. They concluded that this ratio was helpful in identifying the metastastic risk. Their study differed from ours in that they combined primary and recurrent tumors in deriving their ratio. We have drawn a distinction between primary and recurrent tumors, as it is still unclear if they share a similar biological behavior.

In an earlier report (Gustafson et al. 1991), we found no difference in timing of metastasis following definitive surgery in either the presence or the absence of local recurrence in 2 groups with similar clinicopathological features at presentation. In the present study, we found a strong correlation between the timings of both the local recurrence and the metastasis. Patients with a local recurrence who subsequently developed metastasis, did so within months after the local recurrence was diagnosed. One possible explanation would be that the metastatic shower(s) which gave rise to a distant metastasis may be partly responsible for the local metastasis and that may explain why the two events are closely related in time. If true, local metastases which exist outside the treatment field may explain the incidence of local recurrence, even after adequate treatment. This explanation is not contrary to the notion that local recurrence after adequate treatment is the result of tumor aggressiveness, while local recurrence after inadequate local treatment can mainly be attributed to the quality of treatment.

In regard to the time span for detection of metastases, we acknowledge that this varies, depending upon the screening method used. Centers which employ computed tomography at short follow-up intervals are more likely to detect metastases sooner. In comparison, our traditional method of serial chest radiographs may be less exact and may underestimate the actual incidence of metastases. However, the consistent use of this method has allowed us to identify a pattern of metastases related to local recurrence which may benefit from similar scrutiny, using computed tomography.

The importance of GRI as a potential predictor of metastasis in this study is highlighted by the greater risk that a high GRI carries in comparison to tumor grade and size, both of which are recognized independent predictors of survival. Soft tissue sarcoma series have reported up to 40 percent of patients who may present for the first time with local recurrence following surgery elsewhere and information, such as size or grade of the primary tumor, may not be available to the treating group (Serpell et al. 1991). In these situations, the GRI may be helpful in determining the probable outcome and the treatment of the patients with local recurrence. While retrospective studies such as ours have problems of analysis, as also do prospective trials, the relative scarcity of soft tissue sarcoma (< 1 percent of all cancers) necessitates retrospective collection of patients in order to assemble sufficient numbers to examine specific disease parameters. Having identified GRI as a potential indicator of disease, the value of its role as a prognostic factor must be established by prospective studies. We await the results of such studies.

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