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Surgical margins, local recurrence and metastasis in soft tissue sarcomas: 559 surgically-treated patients from the Scandinavian Sarcoma Group Register

C.S. Trovik [a,*], H.C.F. Bauer [b], T.A. Alvegård [c], H. Anderson [d], C. Blomqvist [e], Ö. Berlin [f], P. Gustafson [g], G. Sæter [h], A. Wallöe [i]

[a] *Department of Orthopaedics, Haukeland University Hospital, Bergen, Norway*
[b] *Oncology Service, Department of Orthopaedics, Karolinska Hospital, Stockholm, Sweden*
[c] *Department of Oncology, University Hospital, Lund, Sweden*
[d] *Department of Cancer Epidemiology, University Hospital, Lund, Sweden*
[e] *Department of Oncology, University Hospital, Helsinki, Finland*
[f] *Department of Orthopaedics, Sahlgren University Hospital, Gothenburg, Sweden*
[g] *Department of Orthopaedics, University Hospital, Lund, Sweden*
[h] *Department of Oncology, The Norwegian Radium Hospital, Oslo, Norway*
[i] *Department of Orthopaedics, Ullevål Hospital, Oslo, Norway*

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Abstract

The prognostic importance of surgical margins on local recurrence rates and metastasis-free survival (MFS) was studied in 559 patients with soft tissue sarcoma of the extremities and trunk wall. The patients were all surgically treated, but received no adjuvant treatment. The median follow-up for the survivors was 7.4 (range: 0.1–12.5) years. Independent prognostic factors for MFS were analysed by Cox models. The overall 5-year MFS was 0.72 (95% confidence intervals (CI) 0.68–0.76). High histopathological malignancy grade (relative risk (RR) 3.0; 95% CI 1.5–6.3) and an inadequate surgical margin (RR 2.9; 95% CI 1.8–4.6) were independent risk factors for local recurrence. High histopathological malignancy grade and large tumour size (>7 cm) were the most important risk factors for metastasis. Local recurrence was associated with an increased risk of metastasis (RR 4.4; 95% CI 2.9–6.8), but an inadequate surgical margin was not a risk factor for metastasis (RR 1.1; 95% CI 0.8–1.7). This study confirms that, as regards metastasis, tumour-related risk factors (malignancy grade and tumour size) are more important risk factors than treatment-related factors. Local recurrence was associated with an increased metastasis rate, whereas inadequate surgical margin was a risk factor for local recurrence but not for metastasis. Hence, the proposed causal association between local recurrence and metastasis is doubtful, and if it exists is a weak association.

Keywords: Soft tissue sarcoma; Surgical margins; Local recurrence; Metastasis; Multicentre study; Multivariate analysis

1. Introduction

Several studies on soft tissue sarcomas (STS) have shown that in the strong correlation between local recurrence and metastasis, local recurrence can be thought of as both a marker of the adequacy of the local treatment, and of a highly malignant tumour with a propensity for both local and distant aggressiveness [1–8]. Thus, lower local recurrence rates, achieved by aggressive local treatment, should not lead to lower metastasis rates and hence better survival. This view is supported by the fact that better local control did not translate into better survival in either a series comparing limb-sparing surgery and adjuvant radiation therapy with amputation [9], or in a randomised series of adjuvant brachytherapy [10]. However, local recurrence analysed as a time-dependent variable has been shown to be a risk factor for metastasis, even when correcting for tumour grade and size [11–13]. It is also well known that poor surgical margins lead to high local

* Corresponding author at The SSG-Secretariat, Regional Tumor Registry, University Hospital, SE-221 85 Lund, Sweden. Tel.: +46-46-17-75-55; fax: +46-46-18-81-43.
E-mail address: evy.nilsson@onk.lu.se (C.S. Trovik).

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recurrence rates [14–17], and these findings may support the hypothesis that local recurrence is the source of metastasis.

A correct understanding of the prognostic impact of a local recurrence is important, as it is closely linked to the local treatment. If local recurrence is merely a problem of local control that does not affect the metastasis rate and survival of the patient, closer surgical margins and thus less loss of function, may be advantageous. However, if local recurrence has by itself a substantial influence on survival, wider surgical margins and more liberal use of adjuvant radiotherapy would be indicated, and larger sequelae accepted.

In Scandinavia, indication for adjuvant radiotherapy has been an intralesional or marginal surgical excision [18]. Adjuvant chemotherapy has until recently only been used in a randomised Scandinavian Sarcoma Group (SSG) trial [19]. Thus, the prospective database of the SSG (the SSG Register) offers an opportunity to study a large group of patients with a uniform and well defined surgical treatment as a single treatment modality. We have used this database to examine the prognostic impact of clinical variables, surgical margin and local recurrence on metastasis in patients with STS.

2. Patients and methods

2.1. Patients, referral and treatment

The nine participating institutions (Appendix A) followed the SSG guidelines regarding treatment modalities, classification of surgical margins and histopathological classification and malignancy grading [20]. 975 adult patients with STS in the extremities or trunk wall and with complete data on tumour histology, malignancy grading, treatment and follow-up were reported to the Register in 1986 to 1991. For this series the following patients were excluded: 131 referred after local recurrence or metastasis, 67 with metastasis at diagnosis, and 26 with non-operative treatment. 147 patients had adjuvant chemo- or radiotherapy, and 45 had all their surgical treatment done outside a sarcoma centre; these were also excluded. The remaining 559 patients with primary STS, treated at a centre and with surgery as single therapy, constitute the study group.

There were 251 women and 308 men with a median age of 64 (range: 16–92) years. 224/558 (40%) of the patients were referred to a sarcoma centre without prior invasive diagnostic procedures, 102 (18%) after fine needle cytology, 63 (11%) after open biopsy, and 169 (30%) after an intralesional or marginal surgical excision. These patients were re-operated upon with an extended surgical excision at the sarcoma centre. No information on the diagnostic procedures was available for the remaining patient. 409 of the tumours (73%) were located in the extremities and 150 (27%) in the trunk wall, shoulder, groin or gluteal regions. 203 tumours (36%) were subcutaneous (s.c.) and 356 (64%) were deep seated. The tumour size (greatest diameter) was assessed by computed tomography (CT), magnetic resonance imaging (MRI), or in the fresh pathological specimens. The median tumour size was 7 (1–32) cm. This median was used as a cut-off point when defining patient sub-groups for tumour size. The histopathological classification and malignancy grading were performed by pathologists at the different centres following SSG guidelines [21]. The most frequent histotypes were malignant fibrous histiocytoma and liposarcoma (Table 1). A four grade scale of histopathological malignancy grading was used; 420 tumours (75%) were high-grade (III or IV) lesions.

The primary assessment of the surgical margins was done at the centre by the operating surgeon, or investigating oncologist and the pathologist. Margins were classified according to Enneking as intralesional, marginal, wide or compartmental [22]. The term *contaminated wide* was not used. Based on pathology reports and surgical records from the participating hospitals, the surgical margins have been re-evaluated by the authors. The revised surgical margins were 24/559 (4%) intralesional, 115 marginal (21%) and 420 (75%) wide or compartmental. Intralesional and marginal margins were regarded as inadequate margins in the survival analyses.

2.2. Follow-up

The standard follow-up protocol included clinical examination and a chest X-ray, every 2–4 months for the first 2 years, every 4–6 months for the next 5 years, and yearly thereafter until 10 years after diagnosis. The varying figures are based on local tradition at the centres. 136 patients (24%) developed metastases or died from disease, whilst 123 patients died (22%) from non-tumour related causes. The median follow-up for the 300 survivors was 7.4 (0.1–12.5) years. 9 patients had a follow-up of less than 2 years. Local recurrence was diagnosed in 101 (18%) patients; 60 of these had both local recurrence and metastases. In 33 of these 60 patients the local recurrence preceded the metastases or the patient was reported dead from disease, in 10 the local recurrence and the metastases were diagnosed simultaneously and in 17 patients the metastases preceded the local recurrence.

2.3. Statistics

The proportion of patients with inadequate margins was compared in subgroups of patients by Pearson Chi-square tests. Univariate evaluation of possible prognostic factors was done using Kaplan–Meier technique

Table 1
Histotypes and grouping for stratification in survival analyses in 559 patients with soft tissue sarcoma of extremity and trunk wall

Group	*n* (%)
Malignant fibrous histiocytoma	251 (45)
Liposarcoma	80 (14)
Synovial sarcoma	50 (9)
Leiomyosarcoma	44 (8)
Malignant schwannoma	25 (4)
Fibrosarcoma	18 (3)
Extraskeletal myxoid chondrosarcoma	13 (2)
Rare sarcomas, usually of high grade malignancy	32 (6)
Epithelioid sarcoma	8
Extraskeletal osteosarcoma	8
Clear cell sarcoma	6
Haemangiosarcoma	3
Rhabdomyosarcoma	3
Lymphangiosarcoma	3
Mesenchymoma	1
Other rare sarcomas	26 (5)
Unclassified sarcomas	20 (4)

with Greenwood confidence bands and log-rank tests [23]. Multiple Cox regression models were used to analyse the simultaneous effect of several prognostic factors on time to local recurrence and metastasis-free survival [24]. In the Cox analyses, histotypes were stratified into 10 groups (Table 1) [25]. Local recurrence was analysed as a time-dependent variable when assessing the effect on metastases, not including the 10 local recurrences diagnosed at the same time as the metastases [26]. In the analyses of time to local recurrence, the same 10 local recurrences were considered as events, but otherwise follow-up was censored if a patient got metastases or died. Patients who develop metastases probably have a larger risk to get later local recurrence than those alive without metastases and, in this respect, due to informative censoring, the analysis of local recurrence should be considered with caution.

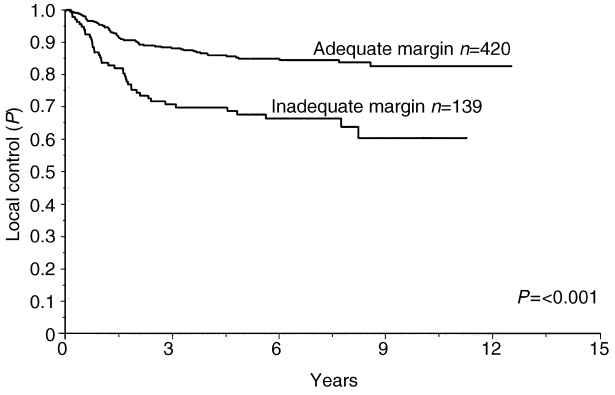

Fig. 1. Local recurrence rates based on surgical margins in 559 patients with soft tissue sarcoma of extremity and trunk wall, analysed with Kaplan–Meier technique. Inadequate = intralesional or marginal surgical margin. Adequate = wide or compartmental surgical margin.

The statistical analyses were performed on anonymised data using Medlog (Information Analysis Corp., Nevada, USA) and Stata [27]. All tests were two-sided and a P value of 0.05 was considered significant.

3. Results

The overall estimated 5-year MFS was 0.72 (95% CI 0.68–0.76). 420 of the patients were operated on with an adequate surgical margin, which was more often seen in patients aged 50 years or younger, in tumours of high histopathological malignancy grade, in tumours 7 cm or smaller, in superficial tumours and in extremity located tumours (Table 2).

3.1. Local recurrence

The local recurrence rates were more than twice as high after inadequate surgery (Fig. 1). In a multivariate

Table 2
Surgical margins versus clinical variables in 559 patients with soft tissue sarcoma of extremity and trunk wall. There were 420 patients operated on with an adequate margin and 139 with an inadequate margin. Pearson Chi-square tests on differences in margin distribution between variable subgroups

Variable	Definition	Adequate margin *n* (%)	Inadequate margin *n* (%)	*P* value
Malignancy grade	Low (I–II)	95 (68)	44 (32)	0.003
	High (III–IV)	325 (77)	95 (23)	
Tumour size	⩽7 cm	237 (80)	61 (20)	0.01
	>7 cm	183 (70)	77 (30)	
Age	⩽50 years	147 (80)	36 (20)	0.05
	>50 years	273 (73)	103 (27)	
Site	Superficial	166 (82)	37 (18)	0.006
	Deep	254 (71)	102 (29)	
Location	Extremity	322 (79)	87 (21)	0.001
	Central	98 (65)	52 (35)	
Sex	Male	237 (77)	71 (23)	0.3
	Female	183 (73)	68 (27)	

Table 3
Analysis of time to local recurrence and risk factors for local recurrence in 559 patients with soft tissue sarcoma of extremity and trunk wall. Cox regression analysis stratified by histotype into 10 groups

Factor	Categories	RR (95% CI)	*P* value
Malignancy grade	High (III–IV) Low (I–II)	3.0 (1.5–6.3)	0.002
Tumour size	>7 cm ⩽7 cm	1.3 (0.8–2.2)	0.2
Site	Deep-seated Subcutaneous	1.4 (0.8–2.4)	0.2
Age at diagnosis	>50 years ⩽50 years	1.3 (0.8–2.3)	0.3
Surgical margin	Inadequate[a] Adequate[b]	2.9 (1.8–4.6)	<0.001
Location	Central Extremity	1.1 (0.7–1.8)	0.7
Sex	Male Female	1.0 (0.6–1.5)	0.9

[a] Intralesional or marginal surgical margin.
[b] Wide or compartmental surgical margin. RR, relative risk; CI, confidence interval.

analysis of risk factors for local recurrence, only inadequate surgical margins and malignancy grades III and IV emerged as independent risk factors (Table 3).

3.2. Metastasis

A multivariate analysis of risk factors for metastasis (local recurrence not included) showed that malignancy grades III and IV and large tumour size were the strongest risk factors, whereas an inadequate surgical margin was not a risk factor (Table 4, model A). When local recurrence (as a time-dependent variable) was introduced into the model, this factor was associated with an increased risk for metastasis, but the relationship between risk for metastasis and the original tumour-related factors was not changed (Table 4, model B).

3.3. Subgroups

Amongst the 207 patients with tumours of both high malignancy grade and large size, the 5-year MFS was 0.55 (95% CI 0.47–0.62). Here, local recurrence was an independent risk factor for metastasis [RR 3.4 95% CI (1.8–6.5); *P* value < 0.001] (Table 5, model A). The remaining 351 patients with no or only one of the risk factors high malignancy grade or large tumour size had a 5-year MFS of 0.83 (95% CI 0.78–0.86). Here, the increase in RR for metastasis associated with a local recurrence was most pronounced (RR 7.2 95% CI (3.7–14); *P* value < 0.001). Deep tumour site, age over 50 years, large tumour size and high malignancy grade were also independent risk factors for metastasis (Table 5, model B). In both these analyses, surgical margins were not independently significant. This pattern was not altered by exclusion of local recurrence.

4. Discussion

The purpose of this study was to test the hypothesis that there is a causal relationship between local recurrence and metastasis, i.e. whether local recurrence

Table 4
Cox regression analysis of time to metastasis and risk factors for metastasis in 559 patients with soft tissue sarcoma of the extremities and trunk wall stratified by histotype into 10 groups. Model A includes variables identified by univariate analysis. Model B includes also local recurrence (as a time-dependent factor)

		Model A		Model B	
Factor	Categories	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Malignancy grade	High (III–IV) Low (I–II)	3.3 (1.8–6.3)	<0.001	3.3 (1.8–6.3)	<0.001
Tumour size	>7 cm ⩽7 cm	2.3 (1.6–3.3)	<0.001	2.2 (1.5–3.1)	<0.001
Site	Deep-seated Subcutaneous	1.8 (1.1–2.8)	0.02	1.7 (1.1–2.7)	0.02
Age at diagnosis	>50 years ⩽50 years	1.4 (0.9–2.0)	0.1	1.3 (0.9–2.0)	0.2
Surgical margin	Inadequate Adequate	1.3 (0.9–2.0)	0.1	1.1 (0.8–1.7)	0.6
Local recurrence	Yes No	Not included		4.4 (2.9–6.8)	<0.001
Location	Central Extremity	1.0 (0.7–1.5)	0.8	1.0 (0.7–1.5)	1.0
Sex	Male Female	1.0 (0.7–1.3)	0.8	1.0 (0.7–1.4)	1.0

Inadequate = intralesional or marginal surgical margin. Adequate = wide or compartmental surgical margin. RR, relative risk; CI, confidence interval.

Table 5
Cox regression analysis of time to metastasis and risk factors for metastasis in 559 patients with soft tissue sarcoma of extremity and trunk wall stratified by histotype into 10 groups. Model A includes 207 patients with high-risk tumours (tumour size >7 cm and malignancy grade III or IV). Model B includes 351 patients with low risk tumours (no or only one of these risk factors)

		Model A High-risk		Model B Low-risk	
Factor	Categories	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Site	Deep-seated Subcutaneous	1.2 (0.6–2.3)	0.6	2.0 (1.1–3.8)	0.03
Age	>50 years ⩽50 years	0.8 (0.5–1.4)	0.5	3.0 (1.5–6.0)	0.002
Local recurrence	Yes No	3.4 (1.8–6.5)	<0.001	7.2 (3.7–14)	<0.001
Surgical margin	Inadequate[a] Adequate[b]	1.2 (0.8–2.0)	0.4	0.7 (0.3–1.3)	0.3
Malignancy grade	High (III–IV) Low (I–II)			2.9 (1.1–7.7)	0.03
Tumour size	>7 cm ⩽7 cm			2.3 (0.7–7.7)	0.2

Local recurrence was analysed as a time-dependent variable.
[a] Intralesional or marginal surgical margin.
[b] Wide or compartmental surgical margin. RR, relative risk; CI, confidence interval.

contributes to metastases or not. For this, we used a large Scandinavian multicentre database on STS patients. The SSG Register is not population-based, but is considered fairly representative of the entire population of STS patients, as two sensitive indicators of referral bias (the median tumour size and the fraction of s.c. tumours) were comparable to a large population-based database [8]. A challenge in all multi-centre studies is the heterogeneity in classification of the clinical variables. The SSG Register is the result of over 15 years of collaboration between Scandinavian tumour centres [19,28–30]. Reporting routines, as well as guidelines for treatment, have repeatedly been discussed and harmonised. For this study, all surgical margins have been re-evaluated, and histological subtype was stratified for all analyses. Therefore, we consider our findings valid, and our results should not be dismissed on the grounds that they stem from a multicentre series.

In Scandinavia, until recently, most patients with inadequate margins, i.e. intralesional or marginal margins, have been treated with adjuvant radiotherapy in accordance with the SSG treatment guidelines. Nevertheless, not all such patients have received adjuvant radiotherapy. The most common reasons for this were wound complications, old age and complicating additional disease [31]. Patients who received adjuvant radiotherapy were excluded from the present study. When these latter patients were included in the analyses the pattern of prognostic factors remained similar although the effect of surgical treatment on survival is difficult to interpret in series that include adjuvant local treatment. If the causal mechanisms relating surgical margins, local recurrence and metastasis are modified by adjuvant radiotherapy, the results of this study may not be valid. A local recurrence after both surgery and adjuvant radiotherapy suggests an even higher inherent malignancy of the tumour. However, the present patient material was more homogeneous, allowing focus on the effect of surgical treatment alone on local recurrence and metastasis.

A strong association between inadequate surgical margins and local recurrence and between local recurrence and metastasis was found in this study. However, a direct association between inadequate surgical margins and metastasis could not be demonstrated. When local recurrence was introduced as a time-dependent factor in the analysis of MFS, it emerged as an independent risk factor whilst none of the other risk factors changed markedly. This suggests a causal relationship. Since inadequate surgical margins was a major risk factor for local recurrence, if there was such a relationship, inadequate surgical margins should be a prognostic factor for MFS in an analysis not including local recurrence. However, this was not the case in our analyses (Table 4, model A). Even in the low-risk group of tumours, where there was a considerable increase in RR for metastasis associated with a local recurrence, inadequate surgical margin was not an independent risk factor for metastasis (Table 5, model B). Hence, our results did not support the hypothesis of a causal relationship between local recurrence and metastasis.

There was a strong statistical correlation between local recurrence (analysed as a time-dependent variable) and metastasis. This may be explained by incomplete known prognostic factors. At diagnosis, prognostic factors such as tumour size and malignancy grade provide incomplete prognostic information about the true malignancy of the tumour, due to both due the genuine

lack of information and to measurement errors. For given values of these factors, the patients will remain heterogeneous regarding the risk for metastasis. Local recurrence could in this aspect be regarded as a biological marker for malignancy, and when a local recurrence is diagnosed the patient is at a higher risk for metastasis compared with a patient with the same original risk factors but without a local recurrence. In a multivariate analysis, this emerges as an increased relative risk when local recurrence was used as a time-dependent factor, regardless of a causal relationship. A consequence of the increased risk for metastasis is that adjuvant chemotherapy may be considered for some local recurrence patients. However, earlier studies have shown that patients with local recurrence but without concurrent metastasis have as a group a similar prognosis to those patients who never develop local recurrence [6]. Therefore, further evaluation is needed to identify those patients with local recurrence who will benefit from adjuvant chemotherapy.

In the present series, the low-risk group comprised two-thirds (63%) of the patients. Amongst these patients, deep tumour site and age >50 years were independent risk factors for metastasis together with local recurrence, or high malignancy grade. Thus, by using simple clinical features it is possible to identify patients in this low risk group that have an increased risk for metastasis. The increase in relative risk for metastasis associated with a local recurrence was greater in the low risk group than in the high risk group. This could also be explained by the heterogeneity of the patient population; the patients who develop local recurrence are compared with reference patients with a lower risk of metastasis. Several reports analysing local recurrence as a time-dependent variable have reported a similar association between local recurrence and subsequent metastasis. Gaynor and colleagues [25] showed in a large series that the larger the number of favourable characteristics, the larger was the increase in relative risk for metastasis associated with local recurrence.

Lewis and colleagues [13] did not find any indication for a causal relationship between local recurrence and metastasis, and concluded that local recurrence must be regarded primarily as a biological marker of malignancy. Recently, several other series have shown improved local control after adequate surgical margins failed to translate into a survival benefit associated with these better surgical margins [32–34].

To conclude, an inadequate surgical margin is a risk factor for local recurrence but not for metastasis. High malignancy grade and large tumour size, but not surgical margins, are together with local recurrence important and independent prognostic factors for metastasis. The well-known association between local recurrence and metastasis must be interpreted as non-causal; highly malignant tumours combine both local and distant aggressiveness.

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Appendix A. Participating institutions

The Norwegian Radium Hospital, Oslo, Norway, G. Sæter; Karolinska Hospital, Stockholm, Sweden, H.C.F. Bauer; University Hospital, Lund, Sweden, P. Gustafson; Sahlgren University Hospital, Gothenburg, Sweden, Ö. Berlin; The National Cancer Hospital, Helsinki, Finland, C. Blomqvist; Haukeland Hospital, Bergen, Norway, A. Walløe; University Hospital, Linköping, Sweden, O. Wahlström; University Hospital, Umeå, Sweden, M. Erlanson; University Hospital, Trondheim, Norway, R. Klepp.

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