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Local recurrence of soft tissue sarcoma
A Scandinavian Sarcoma Group Project

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THESIS

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List of Papers

This presentation is based on the following studies, referred to in the text by their Roman numerals:

I Monitoring Referral and Treatment in Soft Tissue Sarcoma: Study based on 1851 patients from the Scandinavian Sarcoma Group Register

Henrik C F Bauer, Clement S Trovik, Thor A Alvegård, Örjan Berlin, Martin Erlanson, Pelle Gustafson, Ragnhild Klepp, Torgil R Möller, Anders Rydholm, Gunnar Sæter, Ola Wahlström, Tom Wiklund.

Acta Orthop Scand 2000; 71 (accepted for publication).

II Local Recurrence in Deep-Seated, High-Grade, Soft Tissue Sarcoma. 459 patients from the Scandinavian Sarcoma Group Register

Clement S Trovik, Henrik C F Bauer, Harald Anderson, Örjan Berlin, Erkki Tukiainen, Martin Erlanson, Pelle Gustafson, Ragnhild Klepp, Gunnar Sæter, Ola Wahlström.

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III Fine Needle Aspiration (FNA) Cytology in the Diagnosis of Recurrent Soft Tissue Sarcoma

Clement S Trovik, Henrik C F Bauer, Otte Brosjö, Lambert Skoog, Veli Söderlund.

Cytopathology 1998; 9(5): 320-8

IV Consequences of Local Recurrence of Soft Tissue Sarcoma. 205 patients from the Scandinavian Sarcoma Group Register

Clement S Trovik, Pelle Gustafson, Henrik C F Bauer, Gunnar Sæter, Ragnhild Klepp, Örjan Berlin, Martin Erlanson, Ola Wahlström, Nils Raabe.

Acta Orthop Scand 2000; 71 (in press).

V Local Recurrence of Soft Tissue Sarcoma, a Risk Factor for late Metastases. 379 patients followed for 0.5–20 years

Clement S Trovik, Henrik C F Bauer

Acta Orthop Scand 1994; 65(5): 553-8

VI Surgical Margin, Local Recurrence and Metastasis in Soft Tissue Sarcoma; 559 surgically-treated patients from the Scandinavian Sarcoma Group Register

Clement S Trovik, Henrik C F Bauer, Thor A Alvegård, Harald Anderson, Carl Blomqvist, Örjan Berlin, Pelle Gustafson, Gunnar Sæter, Anders Wallöe.

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Summary

The aim of this project was to investigate the diagnosis, treatment and consequences of local recurrence of soft tissue sarcoma (STS). It is based on patients reported to the Karolinska Hospital Sarcoma Register and the Scandinavian Sarcoma Group Register.

Demographic and treatment data, based on 1613 adult patients reported to the Scandinavian Sarcoma Group Register by sarcoma centers in Norway, Sweden and Finland are presented. They all had STS of the extremities or trunk wall, and were diagnosed between 1986 and 1995. One third of the tumors were subcutaneous and two thirds deep-seated. The median size was 7 (1–35) cm and 75% were high grade. Metastases at presentation were diagnosed in 8% of the patients. Two thirds of the patients were referred to a sarcoma center before surgery. The preoperative morphologic diagnosis was made by fine-needle aspiration cytology in 72%.

Among patients with final treatment for primary tumor at a sarcoma center (n=1331), the surgical margins were wide or better in 76% of subcutaneous lesions, and in 58% of deep-seated lesions. Adjuvant radiotherapy has not generally been considered indicated after wide or compartmental excisions in Scandinavia. Overall, 23% of patients managed by surgery had adjuvant radiotherapy. Among patients with an intralesional or marginal excision, 44% had postoperative radiotherapy. Patients treated outside of sarcoma centers were seldom referred for radiotherapy.

The crude local recurrence rate was 225/1331 (17%) among the patients with final treatment for primary tumor at a sarcoma center. The local recurrence rate after local surgery for high-malignant deep-seated STS was 103/391 (26%). The rate was 25/64 (39%) after an intralesional/marginal margin without postoperative radiotherapy *versus* 28/119 (24%) when radiotherapy was given.

Fine-needle aspiration cytology (FNAC) was used to diagnose suspected local recurrences. 95 FNAC were performed in 86 patients from Karolinska Hospital. There were 47 local recurrences, of which 44 were diagnosed correctly by FNAC; one biopsy was inconclusive, and two lesions were incorrectly assessed as benign. 39 patients proved to have benign lesions in the scar examined cytologically on 50 occasions. None of the specimens was regarded as malignant, but in 4 cases FNAC was inconclusive. The inconclusive or false cytological diagnoses had no serious clinical consequences.

Among 205 patients with local recurrence identified in the SSG Register 1987–1995, 169 patients were surgically treated. An intralesional or marginal margin was achieved in 110 of these patients, 59 of whom were also given radiotherapy. 54 of the 169 patients had a second local recurrence. The second local recurrence rate was 0.50 if the first local recurrence was treated using surgery with a marginal margin alone, compared to 0.28 if treated using either surgery with a marginal margin and radiotherapy, or a wide margin (p = 0.0008). In extremity STS, the amputation rate for local recurrences was 0.22, compared to 0.09 for primary tumors.

The overall 5-year MFS was 0.72 (95% CI 0.68–0.76). High histopathological malignancy grade (Relative Risk 3.0; 95% CI 1.5–6.3) and an inadequate surgical margin (2.9; 95% CI 1.8–4.6) were independent risk factors for local recurrence. High histopathological malignancy grade and large tumor size (>7 cm) were the most important risk factors for metastasis. Local recurrence was associated with an increased risk of metastasis (4.4; 95% CI 2.9–6.8), but an inadequate surgical margin was not a risk factor for metastasis (1.1; 95% CI 0.8–1.7).

In conclusion, it is unlikely that local recurrence of STS is a major source of metastases. It nevertheless represents a costly, complicated and emotionally difficult problem. More radical surgical margins would improve the local recurrence rate, but this can hardly be achieved for center-operat-

ed patients without increasing the amputation rate. Instead, local control will improve by giving radiotherapy to all patients after marginal surgery, and to selected patients with wide margins. Radiotherapy is indicated especially after a previous open biopsy or when a local recurrence might lead to an amputation. Furthermore, radiotherapy seems indicated after local recurrence, regardless of margin or grade. The most effective way of reducing costs and detriment associated with local recurrence is to increase referral to sarcoma centers before biopsy or surgery as primary surgical margins would then improve.

Introduction

Amputation was the only safe operation for soft tissue sarcoma (STS) of the extremities 30 years ago; local excision was followed by local recurrence in most patients. Today, most limbs are saved and the risk of local recurrence is low after centralized specialist treatment. In Scandinavia, diagnosis and surgical treatment of patients with extremity and trunk wall localized STS are the responsibility of orthopedic surgeons. At the sarcoma centers, this responsibility is exercised in the context of a multidisciplinary sarcoma group, consisting of pathologist/cytologist, oncologist and radiologist with experience in sarcoma management. This project focuses on STS of the extremities or trunk wall in adult patients.

Treatment failures associated with STS comprise local recurrence, metastases and death. One-third of soft tissue sarcoma patients die because of metastatic disease, and this is commoner in patients with local recurrence. However, the causal relation between local recurrence and metastasis is unclear. The interpretation of the association between local recurrence and metastasis implies different treatment approaches for the primary tumor. One extreme would be narrow surgical margins and no radiotherapy, resulting in less loss of function but many local recurrences that would not kill the patient, but would require further local treatment. On the other hand, if local recurrences give rise to metastases, wider margins and more liberal use of radiotherapy are indicated. The latter strategy would be more expensive initially and increase loss of function, but the local recurrence rate would be low. However, even if local recurrences do not increase the risk of metastases, they necessitate more, often expensive operations, and may eventually lead to loss of the affected limb.

With more than 70 entities defined, STS represent diagnostic and treatment challenges because they show a wide variation in their biological capabilities. Established prognostic factors include histological malignancy grade, tumor size and presence of metastases at diagnosis. It is also agreed that surgical margins and radiotherapy are of major importance for local control but that no substantial effect on rate of metastasis has been shown. No chemotherapy regimen gives a major survival benefit in STS so far, either when given for metastatic disease or as an adjuvant to surgical treatment in non-metastatic patients. However, although no change in overall survival was obtained, in a meta-analysis of randomized chemotherapy trials adjuvant doxorubicin treatment has been found to reduce local recurrence by 6% and distant recurrence by 10% at 10 years (Tierney et al. 1997).

The principal local treatment options are surgical resection alone or surgery and adjuvant radiation treatment. Controversy exists on the way to select patients for radiotherapy. At many centers, nearly all patients with STS will be treated with radiotherapy, while in Scandinavia, only 20% were so treated. Currently reported local recurrence rates among sarcoma centers varies between 10% and 30%.

The aims of this project were to explore the phenomenon of local recurrence of STS by:

- Assessing local recurrence rates in relation to clinical features and treatment;
- Describing diagnosis and treatment of local recurrence;
- Estimating costs and surgical consequences of a local recurrence;
- Determining whether local recurrence leads to metastases.

Patients and methods

Sarcomas comprise about 1% of adult malignancies. 80% of these are soft tissue sarcomas, and about 70 % are located in the extremities or trunk wall. This project was based on three patient series. The first series comprised patients treated at Karolinska Hospital from 1970 to 1992 (Study V). Patients in this series, treated from 1986 to 1995, had also been reported to the Scandinavian Sarcoma Group Register. The second series consisted of patients reported to the SSG Register from 1986 to 1995 (Studies I, II, IV and VI). The third series of patients, dealing with the cytological diagnosis of local recurrence (Study III), was based on patients followed at Karolinska Hospital from 1991 to 1997. These studies and accrual years are summarized in **Table 1**.

Study I considers all patients reported to the SSG register in 1986–1997 from Norway and Sweden. It includes comparisons between early and late referral and treatment practices. As this project focus on local recurrence, only patients registered from 1986 to 1995 are included, and patients from Finland are added. The purpose is to describe the database from which patient information for studies II, IV and VI have been drawn.

Table 1. Survey of studies

Study	Years	n	Description
Based on Karolinska Hospital Register			
III	1991–1997	86	Suspected of having a local recurrence during clinical follow-up.
V	1970–1992	379	All STS, surgically treated, without metastasis at diagnosis.
Based on SSG Register			
I	1986–1997	1851	All extremity and trunk STS patients reported to SSG register. Data concerning 1613 patients reported from 1986-1995 were obtained for this presentation.
II	1986–1993	459	Patients with deep-seated high-grade STS operated on at a sarcoma center.
IV	1987–1995	205	Patients with local recurrence of STS. Based on 1224 operated patients. Patients from Finland not included.
VI	1986–1991	559	STS patients with primary tumors, operated on at a sarcoma center and not given radio- or chemotherapy.

Karolinska Hospital Register (Studies III and V)

This register was organized in 1986, and patients were entered prospectively. Previous patients were identified by a comprehensive search in hospital files. All patient files were examined and data entered retrospectively. Data quality was further checked at patient's follow-ups. The demographic and treatment data for this Register were similar to those described below in detail for the SSG register.

Scandinavian Sarcoma Group Register (Studies I, II, IV and VI)

In 1986, the Scandinavian Sarcoma Group (SSG) started a register of sarcoma patients referred to centers in Finland, Norway and Sweden. The aim was to create a large database of patients treated according to generally accepted guidelines for comparison with non-referred patients, to determine how SSG treatment guidelines were implemented, and to permit multi-center studies of rare tumor entities. The design of the SSG Register was based on experience with smaller, hospital-based registers at the large sarcoma centers in Scandinavia.

Patients were reported to the Register by SSG centers in Finland, Norway and Sweden (18 million inhabitants), but there was no compulsory participation. Since the Register is not population-based, except in southern Sweden (1.5 million inhabitants), patients never referred to SSG centers were not included. However, in Sweden and Norway, all referral hospitals are participating SSG

centers. In Finland, only one - the largest,- center participates.

Quality of data

The SSG Register is based at the Southern Sweden Tumor Register in Lund. The data forms regarding the primary tumor and follow-up (Appendix B) are filled in by the treating institutions (Appendix A). Each center appoints a coordinator to collect data from the multidisciplinary teams. These coordinators meet twice yearly for discussions on reporting routines and data management.

The quality of data is ensured by consensus on terminology in the SSG, established by collaboration among Scandinavian tumor centers for more than 20 years (Ahlo et al. 1989, Alvegård et al. 1989a, Alvegård et al. 1989b, Wiklund et al. 1993). Reporting routines, and guidelines for treatment, have repeatedly been discussed and harmonized. In-depth studies, site visits by the register sub-committee members, and reevaluations of data entered by coordinators at the centers have provided a continuous quality control. All reported data were checked for inconsistencies and corrected. For example, if the patient was reported to having been referred before surgery, but the first procedure was performed outside a sarcoma center, the data had to be corrected by the reporting institution. Thereby inconsistent entries regarding referral, site and location, biopsy and surgical treatment were detected and corrected.

The primary assessment of the surgical margin was done at the center by the operating surgeon and the pathologist. Margins were classified by Enneking's (1980) terminology as *intralesional, marginal, wide or compartmental* (radical). Intralesional margin was recorded when the plane of the excision was considered to pass through the tumor, leaving microscopic or macroscopic tumor tissue behind. A marginal margin was recorded when the plane of excision passed through the tumor pseudocapsule or too close to the tumor for a wide margin to be recorded. Both of these margins were regarded as inadequate and further surgery to improve the margin should be considered before a final margin was recorded. When the tumor was removed, surrounded by a cuff of normal tissue, it was a wide margin and, if the entire compartment containing the tumor was removed, it was a compartmental margin. The term myectomy is regarded as meaning a subtype of the wide margin, and applies to intramuscular lesions in which the involved muscle, from origin to insertion, is completely removed (Stener 1978, Rydholm and Rööser 1987). The terms negative/positive microscopic margins or contaminated wide margins were not used.

A formal reevaluation of all reported margins in the register has not been completed. However, on the basis of pathology reports and surgical records from the participating hospitals, all surgical margins have been reevaluated for the study of the prognostic importance of local recurrence (Study VI). Margin assessments not in accordance with the above have been corrected. In the study of the consequences of local recurrence (Study IV), the complete charts of the patients with local recurrence were reviewed at all centers in Norway and Sweden. The large centers have a continuous quality-check of data entered in their own database, and up-dates of data have been transferred to the Register.

A complete peer review of histopathological material has not been concluded. Consequently, the histological diagnoses were made at the various centers. In a retrospective analysis by the SSG Pathology Board of 1000 sarcomas from the register, the diagnosis of sarcoma was retained in 90% (Meis-Kindblom et al., 1999). In 2%, non-sarcomatous malignancy was diagnosed, in 1% a borderline lesion was considered and in 2% the material was not diagnostic. The lesions were regarded as benign in 5%, all except one were diagnosed primarily as low-grade MFH or liposarcoma. Overall, the peer review changed the grading from high to low or from low to high in 5%, although the histological subtype was changed in 20%.The greatest changes were made among lesions first diagnosed as MFH whereas the lowest incidence of revised diagnoses were among synovial sarcomas.

Patients selected for the studies in this project were those with complete information regarding tumor and treatment factors, and final treatment at a sarcoma center. Thus, among 293/459 extracted for the study of local recurrence in deep-seated, high-malignant tumors (Study II), all were sarco-

Table 2. Histotypes

Type	n	%
Malignant fibrous histiocytoma	727	*45*
Liposarcoma	226	*14*
Leiomyosarcoma	144	*9*
Synovial sarcoma	117	*7*
Malignant schwannoma	73	*5*
Fibrosarcoma	52	*3*
Myxoid chondrosarcoma	29	*2*
PNET/Ewing of soft tissue	27	*2*
Osteosarcoma of soft tissue	24	*2*
Malignant pericytoma	23	*1*
Rhabdomyosarcoma	21	*1*
Epithelioid sarcoma	17	*1*
Clear-cell sarcoma	14	*1*
Hemangiosarcoma	13	*1*
Others	14	*1*
Unclassified	92	*5*
Total	1613	*100*

mas at peer review. In 78 (26%) of these, the grade was altered, mostly from grade III to IV or *vice versa*. In only 11 (4%) cases was the tumor first classified as low grade while called high-grade on review. Calculations based on the revised grade had no influence on the result.

Demographic and treatment data, SSG register (Study I)

1613 adult (16 years or older) patients with STS of the extremities or trunk wall, diagnosed between March 1, 1986 and December 31, 1995, were reported to the SSG Register. Patients with sarcomas in the head and neck region, viscera or retroperitoneal space were not included nor were patients with Kaposi's sarcoma or dermatofibrosarcoma protuberans.

Age and sex

The median age at diagnosis was 64 (16–99) years. The male to female ratio was 51:49.

Site and location

The commonest sites were the thigh, trunk wall, and the lower leg. 35% of tumors were subcutaneous, 29% intramuscular, and 36% deep, extramuscular.

Table 3. Surgical stage according to the UICC/AJCC staging system (Fleming et al. 1997) based on 1576 patients

Stage	Definition		n	%
IA	Low-grade,	≤ 5 cm	166	*11*
IB	Low grade, subcutaneous,	> 5 cm	37	*2*
IIA	Low-grade, deep,	> 5 cm	132	*8*
IIB	High-grade,	≤ 5 cm	405	*26*
IIC	High-grade, subcutaneous,	> 5 cm	137	*9*
III	High-grade, deep,	> 5 cm	569	*36*
IV	Metastases at diagnosis		130	*8*

Metastatic status at presentation

Metastases at presentation were diagnosed in 8% of the patients. There was no difference in the median age of patients with or without metastases, but patients with metastases had larger primary tumors, *i. e.*, median 12cm *versus* 7 cm. Metastases at diagnosis were seen in only 3% of subcutaneous and 7% of intramuscular lesions, but in 14% of extramuscular lesions.

Histological type and grade

The commonest histotypes were MFH (45%) and liposarcoma (14%) (Table 2) (Enzinger and Weiss 1988 and 1995). Histological grading using a four-grade scale (Angervall et al. 1986, Angervall and Kindblom 1993), based on biopsy or surgical specimens, showed that 78% of STS were of high grades (III–IV). Liposarcomas were not subgrouped, but 59% were classified as low-grade (I–II).

Size

Tumor size was assessed by preoperative imaging or examination of the surgical specimens by the pathologist. The median size was 7 (1–47) cm. The median size increased with patient age, *i.e.*, from 6 cm in patients younger than 40 years to 8 cm in those older than 80 years ($p<0.001$) (Standardized S-value 5.1, $p<0.0001$).

Surgical staging

For a comprehensive description of the database, enabling comparison with other series, the UICC/AJCC staging system was employed. One third were deep, high-grade and larger than 5 cm (Table 3).

Table 4. Status on referral to sarcoma center

Referred after	Subcutaneous n	%	Deep n	%	Total n	%
No biopsy or excision	101	*18*	519	*50*	620	*39*
Fine-needle biopsy	71	*12*	187	*18*	258	*16*
Core-needle biopsy	5	*1*	30	*3*	35	*2*
Incisional biopsy	50	*9*	77	*7*	127	*8*
Excision [a]	271	*48*	168	*16*	439	*27*
Local recurrence	66	*12*	65	*6*	131	*8*

Referral status was not recorded in 3 patients.
[a] 10/439 had wide excisions.

Referral

57% of STS patients were referred before incisional biopsy or surgical excision (Table 4). Patients who had a biopsy or were operated on before referral to a sarcoma center had smaller lesions (5cm *vs* 9 cm, $p<0.001$) and more than one half were subcutaneous (56% *vs* 19%, $p<0.0001$).

Biopsy

The preoperative diagnosis was made at sarcoma centers by fine-needle aspiration cytology in 66%, by core-needle or true-cut biopsy in 6% and incisional biopsy in 20 %. In 78 patients (8%), the tumor was removed without prior morphological diagnosis. Among these patients, 19 had a wide margin and in 10, a second operation was done to improve margins.

Surgical procedures

75 (5%) patients were not operated on, 60% of whom had metastases at the time of diagnosis. The remaining 31 non-operated patients were older (median 78 years *vs* 64 years, p=0.001) and had larger (median 15 cm *vs* 7 cm, p<0.001) lesions than operated STS patients.

Among the 1533 operated patients, 969 (63%) had the first operation at a sarcoma center. Of the remaining 564 (37%) who were operated on outside a center, 362 were referred and had a second operation for primary tumor at a sarcoma center. Hence, only 202 (13%) patients had all surgical treatment for primary tumor outside of a sarcoma center. They were reported to the Register when referred to the sarcoma center for radiation treatment or local recurrence. Amputation for primary extremity sarcomas was performed in 129/1331 (10%) of the center-operated patients. To this number must be added amputations performed after a local recurrence.

Surgical margins

A wide or compartmental margin was achieved in only 10% of patients with final operation outside a sarcoma center and later reported to the Register. Among those operated on, primarily at a center, 60% had wide or compartmental margins. A wide or better margin was achieved in 70% of subcutaneous lesions and 58% of deep-seated lesions.

Adjuvant treatment

Adjuvant radio- or chemotherapy was registered in temporal relation to surgery, *i. e.,* whether it was given pre-, per-, or postoperatively. No details about drugs, dosage, radiation target volume, fractionation or duration of treatment were recorded. The SSG had no recommendations or trials during the study period for adjuvant chemotherapy in primary STS.

Postoperative radiotherapy in STS was recommended after a marginal excision. Radiotherapy was also indicated after an intralesional or marginal excision if the margin could not be improved by further surgery. Adjuvant radiotherapy has not generally been considered indicated after wide or compartmental excisions (Berlin et al. 1990, Wiklund et al. 1993, Alho et al. 1989, Rydholm et al. 1991b). The recommended target-absorbed dose was 50 Gy in 25 fractions with a 10/20 Gy boost after an intralesional margin.

Overall, 23% of patients managed by surgery had adjuvant radiotherapy. Among patients with an intralesional or marginal excision, 44% had postoperative radiotherapy. Patients treated outside of sarcoma centers were seldom referred for radiotherapy, *i.e.,* only 21% with an intralesional or marginal excision receiving radiotherapy, compared to 52% treated at a sarcoma center.

Follow-up

The standard follow-up protocol included clinical examination and chest radiographs 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. Of the 1613 patients, 796 (50%) had no evidence of disease, 70 (4%) were

alive with disease, and no follow-up was reported in 39 (2%). 708 (44%) were dead, of whom 463 had died of disease. The median follow-up time for the 902 patients who were alive was 6 (0.1–12.5) years.

Comments

The SSG register is a typical site-specific register based on voluntary reporting by dedicated specialists, in contrast to the Nordic National Cancer Registers, which are based on compulsory reporting by any physician who strongly suspects or diagnoses a malignant disease. Therefore a direct comparison of their respective data contents is misleading. The aim of the Nordic National Cancer Registers is to act as incidence registers, recording all new cases of cancer occurring in the entire population, while the aim of the SSG register is to study types of treatment and outcome at specialized centers.

The register is not population based. A population-based register contains a record of all patients with the disease in a specific area, regardless of where and how they are treated. Those with all treatment outside a sarcoma center and no recurrences would less often be referred to the sarcoma center and reported to the SSG register. Consequently there is a larger proportion of local recurrence cases among those patients reported, but who have received all their treatment for primary tumor outside a sarcoma center. These patients were therefore excluded in the studies concerning local recurrence rates (Studies II, VI). The Swedish patients in the SSG Register were compared with the Swedish National Cancer Register for the year 1995. 90% of all sarcomas of the trunk wall and extremities, recorded in the National Register, were also found in the SSG Register. The remaining 10% were mostly diagnosed in patients with other severe diseases, diagnosed at autopsy, or they were small subcutaneous lesions. The SSG Register contains a high proportion, 35%, of patients with subcutaneous sarcomas, which are those least likely to be referred to a sarcoma center, as they often pose a less obvious clinical problem. The population-based database from southern Sweden contains a similar fraction of subcutaneous sarcomas, which also testifies to the completeness of the accrual. Hence, the SSG Register can be regarded as representative as a population-based register.

The referral of sarcoma patients before surgery was adhered to more closely in Sweden than in Finland or Norway. Sweden has borne the fruits of a more than 20-year educational process in southern Sweden to centralize STS treatment to Lund (Rydholm 1983, Gustafson et al. 1994b). The referral practice in the Scandinavian countries is better than in the U.S.A. In a large study carried out by the Musculoskeletal Tumor Society, 145/235 (62%) had a biopsy or partial removal of the STS at referring institutions before referral to a specialized center. In 17%, it was considered that the patients' outcome had been impaired by the biopsy (Mankin et al. 1996).

Fine-needle biopsy for cytological diagnosis of soft-tissue lesions was developed and popularized in Sweden and is also being used in Norway (Åkerman et al. 1985, Willén et al. 1995). Increasing use of fine-needle biopsy at local hospitals may be one reason for referral before surgery to SSG centers in Sweden; today, Swedish surgeons refrain from open biopsies or excisions without a cytological diagnosis. In a study of treatment patterns in the U S A 1983–1984, one half of the diagnoses were made with excisional biopsy and needle biopsy was used in only 9% of their cases (Lawrence et al. 1987). In a study from London, only one third of the patients even had a biopsy, the remainder had their first operation as an intralesional or marginal excision, without prior knowledge of the histological diagnosis (Clasby et al. 1997).

Overall, a wide or compartmental surgical margin was achieved in 6 of 10 patients. Many were not given adjuvant radiotherapy after intralesional or marginal surgical margins. This lack of compliance with SSG recommendations applied not only to patients treated outside of a SSG center but also to many operated on at a center. Common reasons for abstaining from radiotherapy included a low histological grade, old age or concomitant disease, and protracted wound-healing following the primary operation. (Bauer et al. 1997).

Amputation was performed in 10% of patients which is in line with other large series (Fleming et al. 1999, Pisters et al. 1996b). It has been pro-

posed that multimodality treatment should make amputations necessary in less than 5% of cases (Brennan et al. 1991, Wylie et al. 1999), but to achieve this, over treatment of many patients who could successfully be managed by local excision alone would be necessary .

Statistical analysis

Descriptive data given in the text or tables were compared in subgroups of patients by chi-square tests with Yates' continuity correction when indicated. Statistical methods and analyses, concerning SSG-register data, have been discussed with Harald Anderson, Department of Cancer Epidemiology, University Hospital, Lund, Sweden. All statistical analyses were performed on anonymized data using Medlog (Information Analysis Corp., Nevada, USA) and Stata[1] . Tests were two-sided and a *p*-value of 0.05 was considered significant.

For testing linear trends over time for dichotomous categorical variables, standardized S values with one-tailed p-values are given (Cochran 1954).

Local recurrence rates (Study II). All local recurrences, including those occurring after metastasis, were used in the analysis. Recurrence rates were recorded as actually observed local recurrence rates. Comparisons of recurrence rates based on clinical and treatment factors were assessed by chi-square tests. 85% of local recurrences occur within 3 years of diagnosis (Gustafson 1994a). Since all patients were followed for more than 3 years, and median follow-up was 7.5 (3–12) years, an analysis based on the actually observed local recurrences was considered adequate and more informative than Kaplan-Meier estimates. There is also the problem of competing risks when using Kaplan-Meier methodes in this context, as deaths of disease and local recurrences are not independent events (Schulgen et al. 1998). More than half of the patients died during the observation period and would have been censored when using actuarial methods to analyze local recurrence. With a high rate of early censoring, such methods would tend to overestimate the clinical problem of local recurrence. Metastasis-free survival and relapse-free survival were estimated, using Kaplan-Meier methodes. The Mantel–Haenszel log-rank test was used to check for equality of survival curves.

Prognostic importance of local recurrence and surgical margins (Study VI). The proportion of patients with inadequate margins was compared in subgroups of patients by chi-square tests. Univariate evaluation of possible prognostic factors was done using the Kaplan-Meier method, with Greenwood confidence bands and log-rank tests. Multiple Cox regression models were used to analyze the simultaneous effect of several prognostic factors on time to local recurrence and metastasis-free survival. In the Cox analyses, histotypes were stratified into 10 groups (Gaynor et al. 1992). Local recurrence was analyzed as a time-dependent variable when assessing the effect on risk of metastases. 10 local recurrences diagnosed simultaneously with metastases were not considered as events in this analysis. (Kalbfleisch and Prentice 1980). In the analyses of time to local recurrence, the same 10 local recurrences were considered as events. Otherwise, follow-up was censored if a patient had metastases or died. Patients who develop a metastasis probably run a greater risk of later local recurrence than those who are alive without metastases and, in this respect, due to informative censoring, the result of the analysis of local recurrence should be considered with caution (Schulgen et al. 1980).

Patients who received adjuvant radiotherapy were excluded from the study. The isolated effect of surgical treatment on survival is difficult to interpret in series including patients with adjuvant local treatment. However, when the analyses included such patients the patterns of prognostic factors remained similar.

[1] StataCorp. 1997. Stata Statistical Software: Release 5.0. College Station, Texas, USA: Stata Corporation.

Primary treatment and local recurrence rate

Among the patients reported to the SSG Register from 1986 to 1995, who had had final surgical treatment at a sarcoma center (n=1331), the crude local recurrence rate was 225/1331 (17%). Median follow-up of local recurrence-free survivors was 6 years.

A detailed analysis of local recurrence was done in patients registered from 1986 to 1993 for longer follow-up, enabling reliable crude rates to be calculated. We excluded patients who had had definitive treatment for the primary tumor outside of a center. Treatment and local recurrence were assessed in patients with high-grade deep-seated lesions. The same analyses were then done for subcutaneous and for low-grade deep-seated lesions for comparative purposes.

High-grade deep-seated sarcomas (Study II)

Patients

613 surgically-treated patients with deep-seated, high-grade, soft-tissue sarcoma of the trunk wall or extremities diagnosed from March 1, 1986 to December 31, 1993 were extracted from the SSG Register. After exclusion of 76 patients who had all surgical treatment for the primary tumor before referral to a SSG center and 47 patients with metastases at the time of diagnosis, 490 patients remained. We then excluded 17 patients who had had adjuvant chemotherapy, 6 without follow-up, and 8 recurrence-free survivors followed for less than 3 years, which left 459 patients for study.

351 (76%) patients were referred with untouched lesions or after needle biopsy, 41 had had an open biopsy and 67 an incomplete excision before referral to a SSG center. 224/459 (49%) lesions were intramuscular and 235 were extramuscular. The median size of the lesions was 9 (1–35) cm.

The median follow-up was 7.5 (3–12) years for the 171 patients alive without local recurrence or metastasis. 35 patients are alive with a tumor.

Treatment

68 (15%) patients had had an amputation and 391 a local excision. The surgical margins after amputation were intralesional or marginal in 4/68, wide in 35, and compartmental in 29. After local excision, there were 10% intralesional, 37% marginal, 51% wide, and 3% compartmental margins (Table 5). 62 (31%) of the wide margins were sub-classified as myectomies.

Radiotherapy was given to 137 of 391 (35%) of the patients. 119 of 183 (65%) patients had had radiotherapy after an intralesional or marginal margin and 18 of 198 (9%) after a wide margin.

Findings

In all, 107/459 (23%) local recurrences were reported. The Kaplan-Meier estimate of the local recurrence rate at 7 years was 0.28 (95% CI 0.23–0.33). 90 (84%) of the recurrences occurred within 3 years of diagnosis, and only 7 after 5 years. 58 patients had both a local recurrence and metastases, 49 had a local recurrence alone, 141 had metastases only, and 211 had no recurrent disease.

3 of the 68 amputated patients had local recurrences, as compared to 103/391 (26%) after local surgery.

The following analyses of local recurrence pertain only to the 391 patients who had local surgery. There were no strong associations between clinical features and local recurrence (Table 5). The group of patients referred with untouched lesions had a local recurrence rate of 0.25 compared to 0.33 for those referred after biopsy or incomplete excision ($p = 0.2$). There was also a tendency towards more inadequate final margins, but this was counteracted by increased use of radiotherapy among these patients.

Local recurrence rates were higher for lesions in the lower trunk wall, groin or below the knee. Open biopsy was associated with a higher rate of local recurrence, 29 of 81 patients (36%), compared to needle or no biopsy, 74 of 310 patients (24%) ($p = 0.04$).

Table 5. Univariate analysis of prognostic factors related to local recurrence in 391 patients operated on for deep, high-grade soft-tissue sarcoma. Amputated patients were not included

Variable	Criteria	Patients	Observed local recurrence rate n	%	*p*-value
All patients		391	103	*26*	
Referral	Untouched	306	76	*25*	0.16
	After open biopsy/excision	85	28	*33*	
Diagnosis	Open biopsy	81	29	*36*	0.04
	Needle or no biopsy	310	74	*24*	
Site	Shoulder, upper trunk	60	15	*25*	
	Arm	57	12	*21*	
	Lower trunk, gluteal, groin	58	19	*33*	
	Thigh	171	40	*23*	0.08 [x]
	Lower leg, foot	45	17	*38*	
Location	Intramuscular	214	57	*27*	1.0
	Extramuscular	177	46	*26*	
Treatment	Intralesional/ marginal (**a**)	64	25	*39*	0.04 [y]
	Intralesional/ marginal + radiotherapy (**b**)	119	28	*24*	0.05 [z]
	Wide (**c**)	198	50	*25*	
	Compartmental	10	0	*0*	

[x] Thigh and arm compared to all other sites.
[y] a and b compared.
[z] a and c compared.

Regarding treatment, the local recurrence rate was 39% after an intralesional or marginal margin and no radiotherapy. 11/64 patients had an intralesional margin. The rate was 24% after the same margin, but with postoperative adjuvant radiotherapy, and 25% after a wide margin (**Figure 1**). There was no difference in recurrences between a wide margin without fascial containment of the lesion in 34/136 (25%) or a myectomy 16/62 (26%). Among the 208 patients who had a wide or compartmental margin, 27 of 116 patients (23%) with lesions of the thigh had a local recurrence, compared to 23 recurrences among 92 patients (25%) with other tumor sites.

Subcutaneous sarcomas

293 patients with local surgical treatment for subcutaneous sarcoma were selected from the SSG Register, using the same criteria as for deep-seated tumors. The crude local recurrence rate was 45/293 (15%). Only 40% of subcutaneous tumors were referred before excision. All patients referred after surgery had extended surgery at a sarcoma center, and the local recurrence rate was the same as for those referred "untouched". 12/64 (19%) had a local recurrence after an intralesional/marginal final margin compared to 33/229 (14%) after a wide margin. 9 of 64 inadequate margins were intralesional. Only 31 patients had radiotherapy and the effect on local recurrence

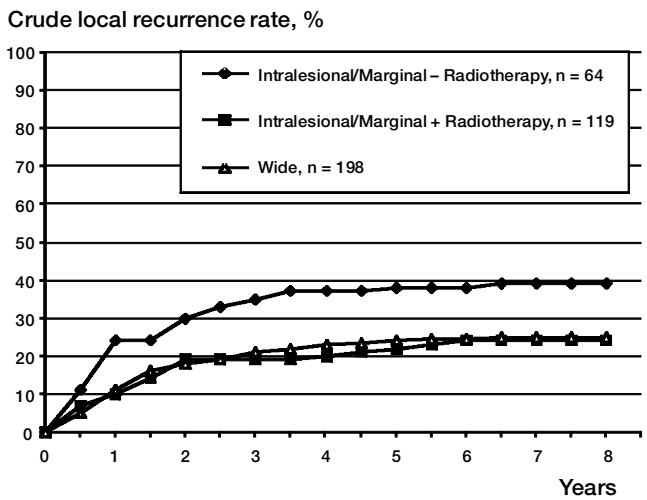

Figure 1. Local recurrence after treatment of high-grade deep-seated tumors.

Table 6. Analysis of time to local recurrence and risk factors for local recurrence in 559 patients with soft-tissue sarcoma of extremity or trunk wall. Both subcutaneous and deep-seated tumors are included. Patients who have received radiotherapy are excluded. Cox regression stratified on histotype in 10 groups. (Study VI)

Factor	Categories	RR	(95%CI)	*p*-value
Malignancy grade	High (III–IV) Low (I–II)	3.0	(1.5–6.3)	0.002
Tumor 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 Adequate	2.9	(1.8–4.6)	<0.001
Location	Central Extremity	1.1	(0.7–1.8)	0.7
Gender	Male Female	1.0	(0.6–1.5)	0.9

Inadequate: intralesional or marginal surgical margin.
Adequate: wide or compartmental surgical margin.

rates could not be assessed. None of the potential prognostic factors analyzed in Table 6 was significantly related to local recurrence in this series of subcutaneous sarcomas.

Low-grade deep-seated sarcomas

122 patients with low-grade deep-seated sarcomas were extracted according to the same criteria as in Study II. 13 (11%) of the 122 patients had a local recurrence. 8 of 36 patients with a marginal margin and no radiotherapy had local recurrences. The local recurrence rates were similar after marginal surgery and radiotherapy or after wide surgery, *i. e.,* 1/15 and 4/68, respectively.

Local recurrence (Studies V and VI)

Local recurrence rates were also assessed in the series of 379 patients referred to Karolinska Hospital from 1970 to 1992 (Study V). The overall local recurrence rate was 34%. The local recurrence rates after an intralesional/marginal surgical margin was 47% and after a wide margin 20%. The local recurrence rate was twice as high in patients referred after surgical treatment for primary tumor than in those operated at the center. However, to determine precisely the local recurrence rates for patients treated outside of centers, population-based series are needed (Rydholm 1983).

Risk factors for local recurrence were assessed among the 559 patients of Study VI who had had surgical treatment for primary STS at a sarcoma center and no radiotherapy. In a multivariate analysis of risk factors for local recurrence, only inadequate surgical margin and malignancy grades III and IV emerged as independent risk factors (Table 6).

Comments

Local control in soft tissue sarcoma is based on surgical excision and radiotherapy. At many centers, radiotherapy is given routinely for high-grade malignant lesions to all patients with deep-seated and subcutaneous soft-tissue sarcoma (Whylie et al. 1999, Yang et al. 1998, Lewis and Brennan 1996, Tanabe et al. 1994, Sadoski et al. 1993). In the Scandinavian countries, indications for radiotherapy have been based on the surgical margin obtained, and considered indicated only after an intralesional or marginal excision (Wiklund et al. 1993). Interestingly though, Rööser (1987), analyzing a Swedish series, stated that radiotherapy should be considered after a wide margin for deep STS, except after myectomies. Myectomy was reported to provide lower local recurrence rates than other wide margins (Rydholm and Rööser 1987).

In patients with surgery as the sole treatment modality (Study VI), inadequate margin emerged as the most important adverse prognostic factor for a local recurrence, together with high-grade malignancy. In this study, the Cox analysis was based on tumors in all locations taken together.

The following discussion applies to deep-seated tumors of high-grade malignancy. In subcutaneous and deep-seated low-malignant tumors, the same pattern of prognostic factors emerged, but was less pronounced.

The overall local recurrence rate for deep-seated, high-grade soft tissue sarcoma was 23%. Most patients were treated with local surgery, and most had marginal margins and postoperative radiotherapy or wide margins without radiotherapy.

The recurrence rates are in line with other reported series (Table 10) (Guillou et al. 1997, Heslin et al. 1996). The local recurrence rate after intralesional or marginal margins was lower than in other reports for both high-grade deep-seated, subcutaneous and low malignant sarcomas (Enneking et al. 1980, Gustafson 1994a).

One might assume that margin classification was unreliable because the local recurrence rate after inadequate margins without radiotherapy was only 39%. However, margin assessment was performed by experienced orthopedic oncology surgeons and pathologists, applying the guidelines strictly. Accordingly, cases where the margin of excision was wide, except in a small area, were nevertheless classified as marginal. Furthermore, surgical margins were reassessed by reviewing surgical and pathology reports in connection with other studies in this project. Excisions assessed as wide seem to have been correctly classified and this margin is associated with more than 20% local recurrences without radiotherapy (Rööser 1987). Therefore, indications for adjuvant radiotherapy, based mainly on margin assessment, seem debatable.

Myectomy showed no advantage over other wide margins as regards local recurrence. We applied Stener's (1978) classification of myectomy strictly. Cases reported as myectomy, but involving an open biopsy or with extramuscular location of the lesion, were reclassified. The series is not large enough to determine whether tumors situated in certain muscles permit better local control than others.

Open biopsy has many side effects, such as increased pain, infection and tumor seeding of adjacent compartments. Univariate analysis based on high-grade, deep-seated sarcomas showed a higher local recurrence rate after open biopsy. However, this adverse effect of open biopsy probably could not generally be attributed to the procedure as such, but also to the fact that few open biopsies were performed at sarcoma centers. Therefore, correctly placed and performed open biopsy may not substantially increase the risk of local recurrence.

High-grade deep-seated lesions of the lower trunk, groin, and gluteus were associated with a local recurrence rate of 33%, and those below the knee a rate of 38%. Clearly, adjuvant radiotherapy is more often indicated in these sites. The local recurrence rate was still 23% after wide excisions for lesions of the thigh, considered the most favorable location.

Recently, Fleming et al. (1999) reported on local recurrence rates among 111 patients with small (<5cm) STS of extremities treated at M. D. Anderson Cancer Center, Houston, Texas. The crude local recurrence rate was 21%. Among 151 comparable patients with small extremity STS selected from the SSG Register the local recurrence rate was 16%. The proportions of subcutaneous lesions and of amputations were similar, although the M. D. Anderson series included more patients operated on before referral. The major difference was that 62% of their patients had radiotherapy and 30% chemotherapy, as opposed to 16% radiotherapy and no chemotherapy among SSG patients. Although comparisons among series are difficult, radiotherapy appeared to provide little benefit in this selected group of patients with small sarcomas, which has also been shown in other series (Brooks et al. 1997, Rydholm et al. 1991a). It appears, however, that the general use of radiotherapy for all deep-seated, high-grade soft-tissue sarcomas yields better local control, but that better control does not improve survival (Rööser et al. 1990, Gustafson 1994a, Lewis et al. 1997, Study VI) The morbidity associated with radiotherapy treatment (Sugerbaker et al. 1982, Bell et al 1989, Stinson et al. 1992, Wiklund et al. 1993, O'Sullivan et al.1999) must be weighed against the benefit of a low local recurrence rate. With modern radiation volume design, this morbidity may be reduced. In a recent randomized study of functional outcome after combined surgery and radiotherapy, the conclusion was that complications were transient and had little effect on overall function (Yang et al. 1998). The morbidity and costs associated with a local recurrence may also be substantial enough to justify the radiation morbidity.

In conclusion, a wide surgical margin in subcutaneous and low-grade, deep STS provides adequate local control in most patients. Radiotherapy is therefore only rarely indicated in these patients. However, a wide surgical margin in high-grade, deep STS appears to be associated with a 25% risk of local relapse. Radiotherapy should be considered for most of these patients.

Diagnosis of local recurrence

Local recurrence of soft tissue sarcoma is often diagnosed by the patient who feels a new lump in the previously treated region. Although the recurrence may seem obvious, the diagnosis should be confirmed by radiological or cytological/histological examinations.

205 patients with a local recurrence were included in Study IV. Following clinical examination, the diagnosis was made by needle biopsy in 108/205 patients, by open biopsy in 12, and by radiological examination in 27. Routine radiological studies of the tumor bed were not part of the follow-up examination protocol, but CT or MRI was performed in patients where the tumor bed could not be easily palpated. In 58 patients, the palpable recurrence was removed without prior diagnostic procedures, but was verified by histological examination after removal.

The diagnosis of soft tissue sarcoma by fine needle aspiration cytology (FNAC) remains controversial. (Enzinger and Weiss 1995, Springfield and Rosenberg 1996) The core-needle biopsy, providing a tiny piece of tissue for histological diagnosis, has become widely used (Skrzynski et al. 1996), whereas FNAC has replaced open biopsy at most sarcoma centers in Scandinavia (Åkermann et al.1980, Åkermann et al. 1985, Rydholm et al. 1982, Willén et al. 1995). So far, most reports on FNAC deal with the diagnosis of primary sarcoma, and hardly any on the accuracy of FNAC in the diagnosis of recurrent lesions (Arya et al. 2000).

Patients and methods (Study III)

Between 1991 and 1997, 86 patients at Karolinska Hospital had tumor-like palpable lesions in the wound area after treatment of a soft tissue sarcoma. A local recurrence was suspected on 95 occasions and the lesion was evaluated by FNAC (Study III). 47 patients proved to have a local recurrence while 39 only had scar tissue or other benign lesions.

Of the 47 patients with recurrences, 19 had been treated for the primary tumor at other hospitals and were referred because of a suspected local recurrence, while 28 had been treated for their primary tumor at the center.

The fine-needle aspiration biopsy was performed as an outpatient procedure by a cytopathologist, without the aid of ultrasound or CT, except when the lesion was impalpable, and local recurrence was suspected based on radiological routine examination. The smears were stained with May-Grünwald-Giemsa, supplemented with immunohistochemical stains when indicated.

Findings

Among the 96 FNACs performed there, were 5 specimens with insufficient material for a cytological diagnosis; 4 from patients who proved not to have a local recurrence and 1 from a patient who had a local recurrence. Among the remaining 90 FNAC specimens, 46 were regarded as benign and 44 as malignant. Two patients with benign FNAC later proved to have recurrences. All specimens diagnosed as malignant by FNAC had histologically—or clinically—verified recurrent sarcomas. Hence, the rate of false benign cytological diagnoses was 5% and none were false malignant. In all cases, and after a comparative study of slides from the primary tumor, cytological diagnosis correctly distinguished between low- and high-grade lesions, including two cases where the tumor had undergone dedifferentiation from low- to high-grade.

Comments

This study on the efficacy of FNAC in diagnosing recurrent soft tissue sarcoma shows a high diagnostic accuracy. A local recurrence could be confirmed or excluded in 88 of 95 FNAC.

The use of FNAC in diagnosing mesenchymal tumors is still discouraged by some authors

(Simon and Springfield 1998, Lewis and Brennan 1996). However, FNAC has now largely replaced open biopsy in the primary diagnostic work-up of patients with soft tissue lesions in most Scandinavian sarcoma centers. A high level of diagnostic accuracy can be achived with experience and by utilizing immunohistochemical and cytogenetic techniques (Miralles et al. 1986, Gonzales-Campora et al. 1992, Kreicbergs et al 1996). In the case of a recurrent sarcoma, the situation is simpler since the histological details are available from the primary tumor, and the problem is more often one of sampling. In fact, both of our falsely benign results were due to sampling error in nonpalpable tumors. However, the problem of sampling is not confined to FNAC, but may also be encountered when a course needle- or open biopsy is undertaken. A recent study of recurrent sarcomas showed improved accuracy with ultrasonic-guided FNAC in 14/17 cases (Arya et al. 2000).

In the present series, half of the suspected recurrences proved to be benign conditions, with postoperative changes commonly mimicking tumor recurrence. FNAC is a much simpler, cheaper and faster method for ruling out a local recurrence than an open biopsy. In many instances the presence of a local recurrence is clinically obvious. Nevertheless, cytological or histological confirmation is mandatory, especially if major resections or adjuvant treatment is to be considered.

As MRI capacity increases, this diagnostic modality alone may provide an adequate first evaluation of suspected recurrences. Currently, most center-treated, extremity STS patients in USA undergoes a yearly MRI for local recurrence control for the first two years (Beitler et al. 2000). The cost-benefit associated with such active surveillance remains to be determined. Morphological confirmation of the recurrence will still be needed before major surgery should be undertaken.

This series shows that FNAC can be used as the primary technique to diagnose a suspected local recurrence of soft-tissue sarcoma. A cytopathologist as member of a multidisciplinary team at sarcoma centers can provide a very high diagnostic accuracy precluding open biopsy in almost all cases.

Morbidity of local recurrence

Two decades ago, amputation was recommended for local recurrences because limb-sparing procedures were too often followed by a second recurrence (Shiu 1975, Romsdahl 1983, Williard 1992). Today a second limb salvage procedure is usually considered feasible (Gibbs 2000).

Several studies have been done on wound complications after surgery of primary sarcomas. Depending on how a complication was defined, a rate of 3–40 % has been reported. No systematic analysis of the complication rate after treatment for local recurrence has been done.

In this section we assessed treatment for a local recurrence in 205 patients with 284 local recurrences reported to the SSG Register between 1987 and 1995. Local recurrences and treatment are summarized in Figure 2. The cost of surgical treatment for a local recurrence was also estimated.

Patients

209 patients with a local recurrence were selected from the SSG register. 63 of them had a local recurrence on referral to a sarcoma center. Complete information was available about 205 patients who had had 284 local recurrences. Among these, 106 were men and the median age at diagnosis of the primary tumor was 67 (20–91) years. The thigh was the commonest site (n = 54), followed by the trunk wall (n = 32). 65 of the primary tumors were subcutaneous, and 140 were deep-seated. Surgical complications were categorized as major, moderate or minor as recommended by Arbeit et al. (1987).

To compare the cost of treating a local recurrence to the cost of a standard orthopedic procedure (hip arthroplasty) we calculated basic costs. In Swedish patients, the costs of surgery were calculated using the tariffs negotiated between hospitals and county health boards. In Norwegian patients, the costs of surgery and radiotherapy were based on the tariffs used by counties to bill each other when treating patients across county boundaries.

The median time to the first local recurrence was 12 (2–94) months. 158 (77%) were diagnosed within 2 years, and 201 (98%) within 5 years. 169 of the 205 patients with a first recurrence were surgically treated. An intralesional or marginal margin was achieved in 110 patients, of whom 59 were also given adjuvant radiotherapy, and a wide or compartmental margin was achieved in 59 patients. Adjuvant chemotherapy was part of the total treatment for a local recurrence in 32 of the 205 patients (Table 7).

Findings

Among the 169 patients surgically treated for their first local recurrence, 54 had a second local recurrence after a median of 10 (1–70) months. The overall 3-year risk of having a second local recurrence was 0.33. Among 118 first local recurrences treated with a marginal margin and adjuvant radiotherapy or with a wide margin, the risk was 0.28 versus 0.50 of 51 first local recurrences treated with surgery alone with a marginal margin (p = 0.0008).

Of the 39 patients who had surgery for their second local recurrence, 17 had a third local recurrence after a median 12 (2–36) months. 4 patients

Table 7. Treatment of 205 patients with local recurrence of soft tissue sarcoma of extremity or the trunk wall. The number of patients with metastasis at the time of diagnosis of the local recurrence is given in parentheses

	No surgery	Intralesional/ marginal	Wide	Total
Radiotherapy	9 (3)	55 (5)	13 (2)	77 (10)
Chemotherapy	8 (4)	11 (8)	5 (2)	24 (14)
Radio- and chemotherapy	4 (3)	4 (2)	0	8 (5)
None	15 (5)	40 (3)	41 (2)	96 (10)
Total	36 (15)	110 (18)	59 (6)	205 (39)

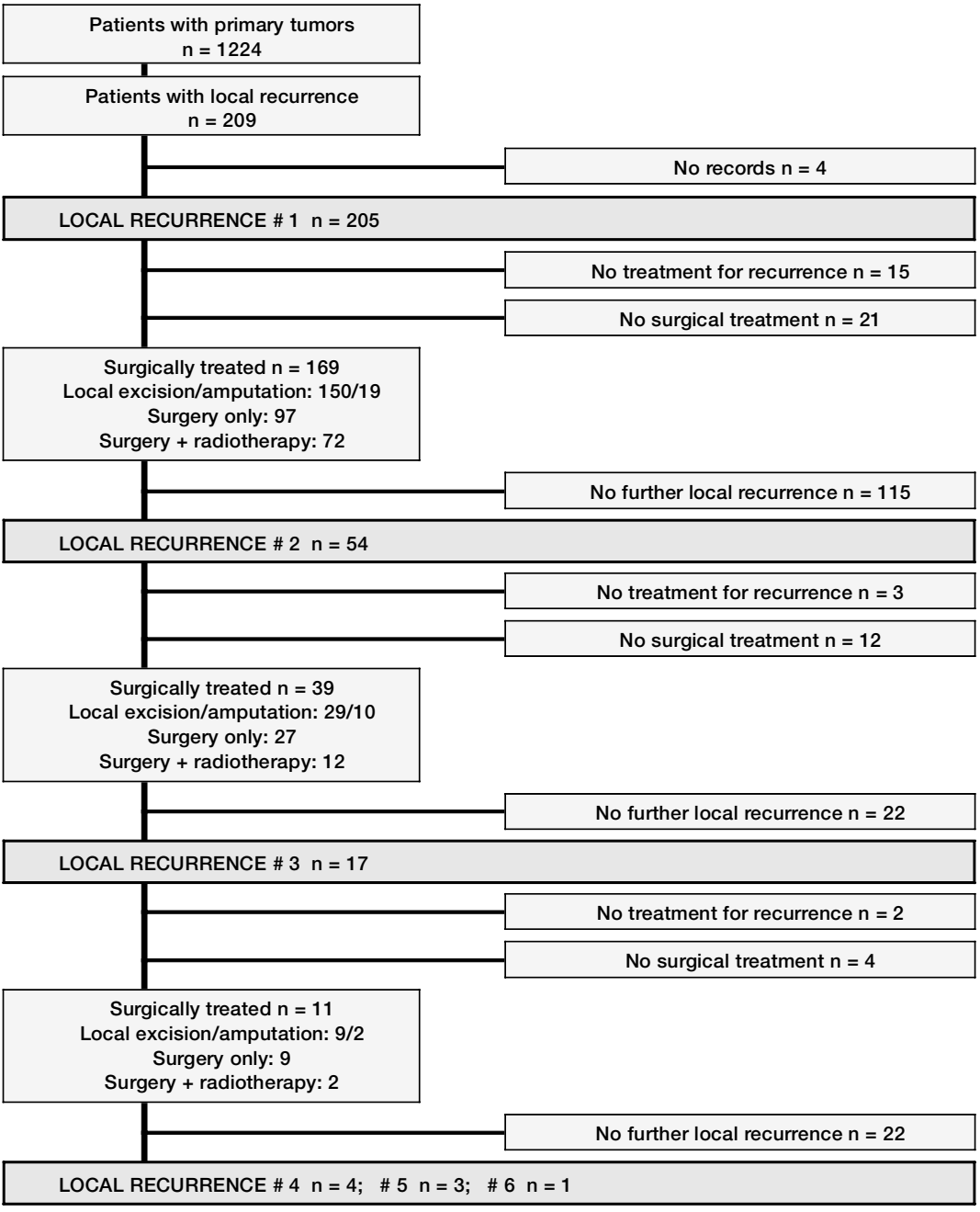

Figure 2. Flowsheet of local recurrences, treatment and outcome based on 1224 patients with primary STS.

had 4, 3 had 5, and 1 had 6 local recurrences.

The amputation rate for a primary tumor in the extremities was 9%. However 22% of patients with local recurrences required amputation, leading to a final amputation rate of 12%.

Wound complications could be evaluated in 199 of the 224 operations performed for a local recurrence. The wound healed uneventfully after two thirds of the operations. Major complications occurred after 20 operations, moderate complica-

tions after 32, and minor complications after 20 operations. There was no association between previous radiotherapy and wound complications in this series.

The patients were hospitalized for a median of 9 days for surgery of a local recurrence and 29 days for those in need of hospitalization for their oncological treatment. The median cost of surgery was USD 11,000 (5,700–86,000) per local recurrence. This includes the basic cost of operation and hospitalization. By way of comparison, the cost of a standard total hip replacement in the two countries was USD 8,500. The cost of standard 54 Gy radiotherapy at the outpatient clinic was USD 2,000. When hospitalization was necessary for radio- or chemotherapy, this entailed a cost of USD 12,000 (3,400–22,000).

Comments

As has been previously reported, local control was more difficult to achieve after local recurrence than after primary tumors (Robinson et al. 1990). For local recurrences, the possibility of achieving wide margins without resorting to amputation may be limited, partly due to distorted anatomy after previous treatment. Previous radiotherapy may also preclude further use of this modality. In this series, a reduction in second and subsequent local recurrence rates would be likely if more patients had been given radiotherapy after the first recurrence. In all only half of the patients had radiotherapy for primary tumor or the local recurrence. Radiotherapy is definitely indicated after local recurrence, probably regardless of margin or grade.

The rate of wound complications reportedly increases after radiation treatment (Robinson et al. 1990, Brennan et al. 1991). Limb-sparing surgery for a local recurrence has been associated with a higher complication rate than for a primary tumor (Stotter et al. 1988). The complication rate in this series of recurrent sarcoma was similar to those after primary surgery (Arbeit et al. 1987, Skibber et al. 1987, Bell et al. 1989, Chang et al. 1989, Paz et al. 1992, Saddegh and Bauer 1993, Peat et al. 1994, Chemell and Schwartz 1996). However, it is difficult to compare complication rates, as there is no universally accepted method for categorizing wound complications.

Only 10% of patients required hospitalization during radiotherapy, so the adjuvant treatment adds relatively little to the total costs. In a cost-benefit analysis, multimodality treatment for a primary tumor must be weighed against the cost for surgical treatment of a local recurrence, *i. e.* in excess of USD 11,000.

In conclusion, local recurrences are expensive and complicated to treat. Both amputation rates and second local recurrence rates were twice as high as for primary tumor treatment. One third of the patients were referred to a sarcoma center with local recurrence after inadequate treatment elsewhere. The most effective means of reducing costs associated with a local recurrence is to improve referral practices in the community.

Prognostic importance of local recurrence

The first study in this project on the prognostic importance of local recurrence on metastases was based on 379 STS patients treated surgically at Karolinska Hospital over a 20 year period (Study V). The 5-year metastasis-free survival rate for the whole group was 0.70. It was 0.73 in the local control group and 0.66 in the local recurrence group (p=0.18). Multivariate analysis indicated that only high histological malignancy grade and increasing tumor size were risk factors for metastases. Neither surgical margin nor local recurrence were related to metastases. After exclusion of patients with high-grade and large tumors, a new subset was formed. In this group of 252 patients, the survival rate was 0.87 in the local control group and 0.64 in the local recurrence group (p=0.004). Multivariate analysis showed that a local recurrence was associated with an increased risk of metastases among these low risk patients. Interestingly, the median interval between the local recurrence and subsequent metastases was more than two years in this group, which allows for a causal relation between them. These findings are in agreement with a similar study from the Memorial Sloan-Kettering Cancer Center (Gaynor et al. 1992). As the conclusion was controversial, a new study was done based on the SSG Register; it included 559 patients treated between 1986 and 1991 at a sarcoma center, and with surgery as the sole modality.

Patients (Study VI)

409 of the tumors were located in the extremities and 150 in the trunk wall, shoulder, groin or gluteal regions. 203 were subcutaneous and 356 were deep-seated. The median tumor size was 7 (1–32) cm. 420 tumors were high-grade lesions.

The reassessed surgical margins were 24 intralesional-, 115 marginal- and 420 wide or compartmental margins. Intralesional and marginal margins were regarded as inadequate in the survival analyses. 420 of the patients were operated on with an adequate surgical margin. Univariate analysis showed that this was more often achieved among younger patients, in tumors of high grade, in small (≤ 7 cm) superficial tumors, located in an extremity.

136 patients developed metastases or died of metastasizing disease, while 123 patients died of non-tumor-related causes. The median follow-up for the 300 survivors was 7.4 (0.1–12.5) years. Nine patients had a follow-up of less than 2 years. Local recurrence was diagnosed in 101 patients; 60 of these had both a local recurrence and metastases. In 33 of these 60 patients, local recurrence preceded the metastases, in 10 the local recurrence and the metastases were diagnosed simultaneously, and in 17, the metastases preceded the local recurrence.

Findings

The overall estimated 5-year MFS was 0.72 (95% CI 0.68–0.76). A multivariate analysis of risk factors for metastasis (local recurrence not included) showed that malignancy grades III and IV and large tumor size were the strongest risk factors, whereas an inadequate surgical margin was not a risk factor. When local recurrence (time-dependent variable) was introduced into a new model, this factor was associated with an increased risk of metastasis, but the relationship between the original tumor-related factors regarding risk of metastasis was not changed (Table 8).

Subgroups

Among the 207 patients with tumors of both high malignancy grade and large size, the 5-year MFS was 0.55 (95% CI 0.47–0.62). Local recurrence was an independent risk factor for metastasis. The remaining 351 patients with no or only one of the risk factors of high malignancy grade or large tumor size had a 5-year MFS of 0.83 (95% CI 0.78–0.86). Here, the increase in relative risk of metastasis associated with a local recurrence was

Table 8. Cox regression analysis of time to metastasis and risk factors for metastasis in 559 patients with soft tissue sarcoma in an extremity or the trunk wall, stratified by histotype in 10 groups (Study VI)

Factor	Categories	RR	(95%CI)	*p*-value
Malignancy grade	High (III–IV) Low (I–II)	3.3	(1.8–6.3)	<0.001
Tumor size	> 7 cm ≤ 7 cm	2.2	(1.5–3.1)	<0.001
Site	Deep-seated Subcutaneous	1.7	(1.1–2.7)	0.02
Age at diagnosis	> 50 yrs ≤ 50 yrs	1.3	(0.9–2.0)	0.2
Surgical margin	Inadequate Adequate	1.1	(0.8–1.7)	0.6
Local recurrence	Yes No	4.4	(2.9–6.8)	<0.001
Location	Central Extremity	1.0	(0.7–1.5)	1.0
Gender	Male Female	1.0	(0.7–1.4)	1.0

most pronounced (Table 9). In both these analyses, surgical margin was of no independent importance even if a local recurrence was excluded.

Comments

The aim of this study was to test the hypothesis that there is a causal relation between local recurrence and metastasis, *i.e.,* whether a local recurrence contributes to metastasis development. There is a strong statistical association between inadequate surgical margin and local recurrence. When local recurrence was introduced as a time-dependent factor, it emerged as an independent risk factor for metastases. If there was a causal relationship, inadequate surgical margin should also be prognostic in an analysis not including local recurrence. However, this was not the case. Even in the low-risk group of tumors, where there was a considerable increase in relative risk of metastasis associated with a local recurrence, inadequate surgical margin was not a risk factor for metastasis. Furthermore, the Cox analyses of prognostic factors for local recurrence (Table 6) indicated a different pattern of factors for local recurrence than for metastasis (Table 8). Hence, the results do not support the hypothesis of a causal relation between local recurrence and metastasis (Figure 3).

Table 9. Cox regression analysis of time to metastasis and risk factors for metastasis among 351 patients with low-risk tumors (small and/or low grade)

Factor	Categories	RR	(95%CI)	*p*-value
Site	Deep-seated Subcutaneous	2.0	(1.1–3.8)	0.03
Age at diagnosis	> 50 years ≤ 50 years	3.0	(1.5–6.0)	0.002
Local recurrence	Yes No	7.2	(3.7–14)	<0.001
Surgical margin	Inadequate Adequate	0.7	(0.3–1.3)	0.3
Malignancy grade	High (III–IV) Low (I–II)	2.9	(1.1–7.7)	0.03
Tumor size	> 7 cm ≤ 7 cm	2.3	(0.7–7.7)	0.2

At diagnosis, prognostic factors, such as tumor size and malignancy grade, provide insufficient information about the true malignancy of the tumor,- *i.e.,* the risk of metastases. In this respect, a local recurrence may be regarded as a biological marker for malignancy and, when it is detected the risk is higher than in a patient with the same initial risk factors, but no local recurrence. In a multivariate analysis it emerges as an increased relative risk, even if there is no causal relation. Since the risk of metastasis increased, adjuvant chemotherapy may be considered for patient with a local recurrence. However, some data show that patients with a local recurrence, but no concurrent metastasis have, as a group, a prognosis similar to those who never develop a local recurrence (Gustafson et al. 1993). On the other hand, clinical characteristics,— *i.e.,* high rate of growth and early appearance of a local recurrence,—run a higher risk of metastasis (Choong et al. 1995). More studies are needed to determine which patients with a local recurrence might benefit from adjuvant chemotherapy.

We excluded patients who received adjuvant radiotherapy from this study. When they were included, the patterns of prognostic factors remained similar. The effect of surgical treatment on survival is difficult to interpret in patients who are also given adjuvant local treatment. If the causal mechanisms relating surgical margin, local recur-

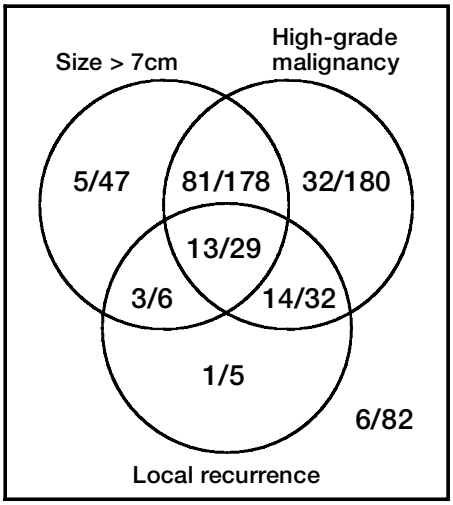

Figure 3. Venn diagram showing the relation between prognostic factors and metastases. Number with metastases/number of patients in each subset of 559 patients. Only local recurrences diagnosed prior to metastasis were considered.

rence and metastasis are modified by adjuvant radiotherapy, the results of this study (Study VI) may not be valid. A local recurrence after both surgery and adjuvant radiotherapy suggests an even higher inherent malignancy of the tumor. Our patient material was more homogeneous, and allowed us to evaluate the effect of surgical treatment alone on local recurrence and metastasis.

In the present series, the low-risk group (no or only one of the risk factors large tumor and high grade) comprised two-thirds of the patients. Among these, deep tumor site and age >50 years were independent risk factors for metastasis together with local recurrence, large tumor size or high malignancy grade. Thus, by using simple clinical features one can detect patients with an increased risk of metastasis, although they belong to the low-risk group. The increase in relative risk of metastasis associated with a local recurrence was larger in the low-risk group than in the high-risk group. This may also be due to heterogeneity since the patients who develop a local recurrence are compared to reference patients with a lower risk of metastasis. Other investigators who have regarded local recurrence as a time-dependent variable have found a similar relation between local recurrence and subsequent metastasis (Emrich et al. 1989, Stotter et al. 1990). Gaynor et al. (1992) in a large series showed that the relative risk of metastasis associated with a local recurrence increased with the number of favorable characteristics, e.g low-grade malignancy, small size and superficial location.

An early study from Lund questioned the causal relationship between local recurrence and metastasis, and suggested that highly malignant tumors combined local and distant aggressiveness (Gustafson et al. 1991). This view was supported by Lewis et. al. (1997) who found no causal relationship between local recurrence and metastasis. They concluded that local recurrence must primarily be regarded as a biological marker of malignancy. Two randomized series evaluating local control (Pisters et al. 1996a, Yang et al. 1998) failed to show a survival benefit when local control was improved. More recent series of improved local control after adequate surgical margins have shown no survival benefit associated with better margins (Tanabe et al. 1994, Li et al. 1996).

To confound the situation further, Lewis and coworkers from the Memorial Sloan-Kettering Cancer Center have recently suggested that inadequate surgical margins might provide a nidus for late metastases (Lewis et al. 1999). This study was based on the same patient material as their study from 1997, but only patients who had survived 5 years werez now included. On multivariate analysis only a positive microscopic margin was associated with late metastases; neither high grade nor large tumor size was of significance. This accords with our study of Karolinska Hospital patients (Study V) and other studies from single institutions (Peiper et al. 1997, Ueda et al. 1997), which show that inadequate local treatment can lead to metastases in patients with an otherwise inherent good prognosis.

Recently, Gibbs et al. (2000) found no difference in survival after early or late local recurrence, but they emphasized that 16% of initially low-grade tumors recur as high-grade lesions. Therefore, referral especially of patients with small and low-grade sarcomas for adequate treatment and follow-up at a sarcoma center may be important for long-term survival.

Discussion

In the study based on the SSG Register, the crude local recurrence rate was 17% among 1331 STS patients operated on at a sarcoma center. This result compares favorably with those of other large series, especially because it was multi-institutional, had a long follow-up, and no patients had been excluded because of age or disease (Table 10). However, subgroups of patients were identified who had high local recurrence rates. These included patients operated on with an intralesional/marginal margin and who were not treated with radiotherapy. In addition we found that a wide margin for deep, high-grade STS was associated with a 25% local recurrence rate. Local control might have been improved by adding radiotherapy to the surgical treatment of these patients.

The data in Table 10 should be interpreted with caution. Moreover, the local recurrence rates are not entirely comparable. The methods of terminology and assessing surgical margins vary, but 20–30% of margins were probably less than wide in these series. Most patients, except in the SSG series, also had been give various types of chemotherapy regimens. The ratio of primary to secondary operations varied also. Two randomized trials have been done on the effect of radiotherapy in multimodality settings. Pisters et al. (1996) reported 9% local recurrence in the treatment arm of high-malignant STS after postoperative brachytherapy, while Yang et al. (1998) had no local recurrences in the treatment arm of high-malignant STS after postoperative external beam radiotherapy.

The diagnosis of a local recurrence can safely be made by fine-needle aspiration for cytology at a sarcoma center. We found that approximately half of the suspected recurrences were benign lesions or scar tissue. Hence, it is important to firmly establish the diagnosis of a local recurrence before treatment.

The association between surgical margins, local recurrence and subsequent metastases was evaluated in two studies (Studies V and VI). They indicated that local recurrence is seldom a source of metastases, but rather a marker of the malignant potential of the lesion. However, it cannot be ruled out that persistence of tumor tissue may eventually lead to metastases, in some cases after many local recurrences or dedifferentiation of the tumor. In a recent study that found a positive correlation between positive microscopic margins and late

Table 10. Crude local recurrence rates after treatment for extremity STS

Institution [a] Accrual years	Patients	Follow-up years	Med age	Med Size	% High-grade	% Deep-seated	% Radio-therapy	% Ampu-tation	% Local recurrence	Reference
MSKCC 82–94	1041	4	51	6-7	65	76	40	10	17	Pisters 1996b
FNCLCC 80-89	546	5	52	7	84	79	56	4	29	Coindre 1996
NCI 83-91	132	10	NR	6-7	70	NR	50 [b]	0	11	Yang 1998
RPCI 77-94	194	3	54	NR	86	88	42	7	15	Karakousis 1999
MDACC 84-92	111	6	40	3	100	50	62	9	19	Fleming 1999
SSG-register 86-95	1331	6	64	7	78	66	24	10	17	

[a] MSKCC = Memorial Sloan-Kettering Cancer Center;
FNCLCC = French Federation of Cancer Centers Sarcoma Group,
NCI = National Cancer Institute;
RPCI = Roswell Park Cancer Institute;
MDACC = M.D.Anderson Cancer Center.
NR = Not Reported.
[b] randomized

disease-specific mortality (Lewis et al. 1999), this possibility was emphasized. The study supports our early findings, which were based on a long follow-up of patients at Karolinska Hospital (Study V).

Consequences of local recurrence were also assessed in terms of morbidity and costs. The amputation rate was twice as high after a local recurrence as after primary tumors. Many local recurrences could not be treated surgically and among those operated on, one of three had more recurrences. Hence, the consequences of a local recurrence for the patient are such that increased efforts to improve local control are merited even if survival will is not greatly affected.

There are several ways to improve local control of soft tissue sarcoma. First, increase compliance with treatment recommendations so that all patients receive radiotherapy after intralesional/marginal excisions. Thus, radiotherapy should be given even if the patient is old or has other ailments. Secondly, radiotherapy is indicated in many patients with wide margins (Rööser 1987, Pisters 1998), especially when an open biopsy has been taken, or a local recurrence might lead to an amputation. However, the most effective method is to further improve referral practices so that more patients receive primary treatment at sarcoma centers.

Appendix A – Participating institutions

Participating institutions

Center	City	Country	Coordinators
Norwegian Radium Hospital	Oslo	Norway	Gunnar Sæter
Karolinska Hospital	Stockholm	Sweden	Henrik C. F. Bauer
University Hospital	Lund	Sweden	Pelle Gustafson
Sahlgren University Hospital	Gothenburg	Sweden	Örjan Berlin
National Cancer Hospital	Helsinki	Finland	Carl Blomqvist
Haukeland Hospital	Bergen	Norway	Clement Trovik
University Hospital	Linköping	Sweden	Ola Wahlström
University Hospital	Umeå	Sweden	Martin Erlanson
University Hospital	Trondheim	Norway	Ragnhild Klepp

Appendix B – Forms for reporting primary tumor and follow-up of patients to the SSG Register

BONE AND SOFT TISSUE SARCOMA
FOLLOW-UP **SSG Central Registry**

Patient identification

This form should be sent to:
Regionala tumörregistret, Universitetssjukhuset i Lund
S-221 85 LUND Tel: +46-(0)46-17 75 60 Fax: +46-(0)46-18 81 43

Hospital

Doctor

Follow-up

year month day
Latest follow-up date

☐ No evidence of disease (NED)

☐ Local recurrence

☐ Distant metastasis(es) ☐ Lung ☐ Lymph node ☐ Skeletal ☐ Other

☐ Persistent disease (previously recorded)

Treatment of first local recurrence

Where
☐ Center ☐ Outside

Tumor size
☐☐ cm (largest diameter) ☐ Not determinable

Surgical procedure
☐ Local excision ☐ Amputation ☐ No treatment

Surgical margin
☐ Intralesional ☐ Marginal ☐ Wide ☐ Compartmental

Other treatment
☐ Radiotherapy ☐ Chemotherapy ☐ None

Treatment of metastatic disease

☐ Lung surgery ☐ Other surgery ☐ Chemotherapy ☐ Lung radiotherapy ☐ No treatment

According to SSG-treatment protocol number ☐☐

Death

year month day
Date of death

Reason
☐ From tumor ☐ With tumor ☐ Without tumor ☐ Unknown