Local recurrence of deep-seated, high-grade, soft tissue sarcoma

459 patients from the Scandinavian Sarcoma Group Register

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ABSTRACT – This study was based on 459 adult patients with deep, high-grade, soft tissue sarcoma of extremities or trunk wall reported to the Scandinavian Sarcoma Group Register (1986–1993). All patients had their definitive surgery for primary tumor at a sarcoma center. The median follow-up was 7.5 (3–12) years. 204 patients are still alive.

68 patients had amputations and 391 underwent limb-sparing surgery. Among 183 patients with intralesional or marginal margins after limb-sparing surgery, 65% had postoperative radiotherapy and 9% of the 198 patients with wide margins.

The local recurrence rate after limb-sparing surgery was 26%. The rate with an intralesional or marginal margin was 39% without postoperative radiotherapy versus 24% when radiotherapy was given. It was 25% after a wide margin, and no recurrences were noted among the 10 patients with a compartmental surgical margin. Among patients with a wide margin, a subset fulfilling criteria for a myectomy was defined. The local recurrence rate was 26% among these 62 and there was no advantage of myectomy over other wide margins.

More radical surgical margins would improve the local recurrence rate, but this can hardly be achieved in center-operated patients without increasing the amputation rate. Instead, increased use of radiotherapy in all patients with inadequate margins, and to a larger extent in those with wide margins will improve local control.

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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, pre- or postoperatively, to all patients with deep-seated soft tissue sarcoma (Sadoski et al. 1993, Tanabe et al. 1994, Lewis and Brennan 1996, Yang et al. 1998, Wylie et al. 1999). In Scandinavia, indication for radiotherapy has been based on assessment of the surgical margin. Radiotherapy has been given after an intralesional or marginal excision, i.e., when the plane of the excision passes through the tumor or the tumor pseudocapsule, and further surgery to improve the margin is not considered feasible (Wiklund et al. 1993). Radiotherapy has usually not been given after a wide margin, i.e., the tumor is removed surrounded by normal tissue (Alho et al. 1989). The term myectomy is regarded as a subtype of wide margin and is applied when intramuscular lesions are removed with the muscle involved, from origin to insertion (Stener 1978). Myectomy has been reported to give lower local recurrence rates than other wide margins (Rydholm and Rööser 1987).

This study aimed to evaluate local recurrence in deep-seated, high-grade soft tissue sarcoma in relation to tumor and treatment factors. We especially wished to assess whether the indications for postoperative radiotherapy, based on margin assessment, are appropriate.

Patients and methods

Soft tissue sarcoma patients treated at centers in Finland, Norway and Sweden have been reported prospectively, and with follow-up data, to the Scandinavian Sarcoma Group (SSG) Register since March 1, 1986 (Bauer et al. 1999). The present study was based on 613 surgically-treated adult patients (16 years or older) with deep-seated, high-grade, soft tissue sarcoma of the trunk wall or extremities reported to the SSG Register, and diagnosed from March 1, 1986 to December 31, 1993. Some centers started reporting later than the first inclusion date, and the number of patients reported does not necessarily reflect the size of the center (Appendix A). Patients with PNET, dermatofibrosarcoma protuberans or Kaposi sarcoma were not included. All patients had complete data regarding tumor location, site, size, and treatment. After exclusion of 76 patients who had all been operated on for primary tumor before referral to a SSG sarcoma center, and 47 with metastases at diagnoses, 490 patients remained. In addition, we excluded 17 who had adjuvant chemotherapy, 6 without follow-up and 8 recurrence-free survivors followed for less than 3 years, leaving 459 patients for study. Patients were reported from 1 sarcoma center in Finland, 3 in Norway and 5 in Sweden (Appendix A).

Patients

The median age was 65 (16–94) years and there was an equal sex distribution. 40% of the lesions were located in the thigh (224/459 (49%) were intramuscular and 235 extramuscular). There was a predominance of intramuscular lesions in the upper arm and thigh (Table 1). Tumor size was assessed by CT, MRI or in fresh surgical specimens. Their median size was 9 (1–35) cm.

Preoperative diagnosis was based on fine needle aspiration biopsy for cytology in 257 (56%) patients, coarse needle biopsy in 21 (5%) and open biopsy in 121 (26%). 60 (13%) patients were operated on without previous biopsy. Patients referred after incomplete excision were often operated on without prior biopsy, i.e., 28/67 (42%).

Histological classification and malignancy grading on a four-grade scale were performed by pathologists at the various centers using SSG guidelines (Angervall and Kindblom 1993). Grading was based on pleomorphism, mitoses, cellularity and necrosis. The most frequent histotype was malignant fibrous histiocytoma (54%), followed by synovial sarcoma (12%), and liposarcoma (7%). A complete peer review of histopathological material has not been concluded. Consequently, the histological diagnoses are those given by the centers. 293 tumors have been subjected to peer review by the SSG Pathology Board (Meis-Kindblom et al. 1999). In 78 (26%) of these, the grade was changed, mostly from grade III to IV or vice versa. In only 11 (4%) patient, was the tumor primarily classified as low-grade, but called high-grade on review. Calculations based on the revised grade had no effect on the result.

Table 1. Tumor location and site

Location	Intramuscular	Extramuscular	Total
Trunk wall	18	32	50
Shoulder	8	18	26
Upper arm	26	11	37
Lower arm, elbow and hand	10	20	30
Gluteal	17	14	31
Groin	–	14	14
Thigh	124	59	183
Lower leg and knee	21	52	73
Foot	–	15	15
Total	224	235	459

Treatment

68 (15%) patients were amputated and 391 had limb-sparing surgery. 367 (80%) had 1 surgical procedure for the primary lesion, 83 (18%) 2, and 9 (2%) 3 procedures. The surgical margins after amputation were intralesional or marginal in 4 (5%), wide in 35 (52%), and compartmental in 29 (43%) (Enneking et al. 1980). After limb-sparing excisions, there were 10% intralesional, 37% marginal, 51% wide, and 3% compartmental margins (Table 2). 62 (31%) of the wide margins were subclassified as myectomies. The surgical margin obtained was classified as wide in 150 of 214 (70%) intramuscular lesions and 58 of 177 (33%) extramuscular ($p<0.001$). Lesions of the thigh were excised with a wide margin in 116 of 171 (68%) patients, compared to 92 of 220 (42%) in all other locations ($p<0.001$).

Table 2. Univariate analysis of prognostic factors related to local recurrence in 391 patients operated on for deep, high-grade soft tissue sarcoma. Amputated patients are not included

Variable	Patients	Observed local recurrence rate		P-value
		n	%	
All patients	391	103	26	
Age				
≤ 60 years	157	41	26	1.0
> 60 years	234	62	27	
Sex				
male	200	49	25	0.5
female	191	54	28	
Referral				
untouched	306	75	25	0.2
after open biopsy/excision	85	28	33	
Site				
shoulder, upper trunk	60	15	25	
arm	57	12	21	
lower trunk, gluteal, groin	58	19	33	
thigh	171	40	23	0.08 [a]
lower leg, foot	45	17	38	
Location				
intramuscular	214	57	27	1.0
extramuscular	177	46	26	
Tumor size				
≤ 9 cm	210	51	24	0.4
> 9 cm	181	52	29	
Treatment				
a) intralesional/marginal	64	25	39	0.04 [b]
b) intralesional/marginal & Rt [d]	119	28	24	0.05 [c]
c) wide	198	50	25	
d) compartmental	10	0	–	
Malignancy grade				
Grade III	146	36	25	0.6
Grade IV	245	67	27	

[a] Thigh and arm compared to all other sites.
[b] Treatment a vs b.
[c] Treatment a vs c.
[d] Radiotherapy.

According to SSG guidelines, the recommended target-absorbed dose for postoperative radiotherapy was 50 Gy in 25 fractions with a boost to 64 Gy after intralesional surgery.

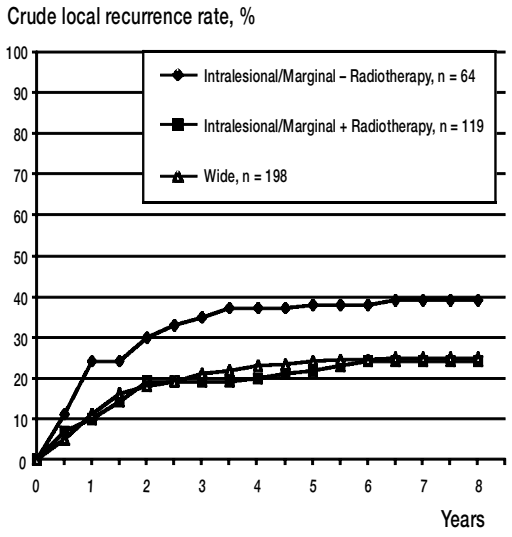
Overall, radiotherapy was given to 137 of 391 (35%) of the patients. 119 of 183 (65%) patients had radiotherapy after an intralesional or marginal margin and 18 of 198 (9%) after a wide margin. Common reasons why patients with intralesional or marginal margins did not receive radiotherapy were old age, intercurrent disease or wound complications (Bauer et al. 1997).

Follow-up and statistics

The median follow-up was 7.5 (3–12) years in the 171 patients alive without recurrences. 204 patients are still alive. 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 1994). Since all patients were followed for more than 3 years, and median follow-up is long, 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 techniques in this context, as death from disease and local recurrence are not independent events (Schulgen et al. 1998). In this patient cohort, more than half of the patients died during the observation period and would therefore be censored when using actuarial methods in the analysis of 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 techniques. The Mantel-Haenszel log-rank test was used to check for equality of survival curves.

Results

351 (76%) patients were referred with untouched lesions or after needle biopsy, while 41 had an open biopsy and 67 an incomplete excision before referral to a SSG center. Patients who were referred with untouched lesions had larger tumors (10 versus 6 cm, $p<0.001$). Patients with intra-



Local recurrence and treatment. Crude local recurrence rate (%).

muscular tumors as opposed to extramuscular ones were more often referred before biopsy or resection, 186/224 (83%) versus 165/235 (70%), p= 0.002.

107 (23 %) local recurrences were reported. 90 (84%) of these occurred within 3 years of diagnosis, and only 7 (7%) after 5 years. The 5-year metastasis-free survival was 0.56 (95% CI 0.51–0.61) and relapse-free survival for either metastasis or local recurrence was 0.46 (95% CI 0.41–0.51). 58 patients had both a local recurrence and metastases, 49 had a local recurrence alone, 141 had metastases alone, and 211 had no recurrence disease.

Among 68 amputated patients, there were 3 (4%) local recurrences versus 103/391 (26%) after limb-sparing surgery. The difference in metastasis-free survival did not suggest a survival benefit from improved local control. Local recurrences among amputated patients were seen in 1 patient, after a marginal margin and postoperative radiotherapy and in 2 patients, after compartmental excisions without radiotherapy.

The following analyses of local recurrence pertain only to the 391 patients who had limb-sparing surgery. There were no strong associations between clinical features and a local recurrence (Table 2). 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, a difference that may not exist in the target population (p= 0.2). 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). Local recurrence rates were higher in lesions located on the lower trunk wall, groin or below the knee. The rates were the same for intra- and extramuscular lesions.

Regarding treatment, the local recurrence rate was 39% after an intralesional or marginal margin, but 24% after the same margin but with postoperative adjuvant radiotherapy, and 25% after a wide margin (Figure). There were no recurrences among the 10 patients with a compartmental margin. In this study, there was only an insignificant difference in recurrence rate between a wide margin without fascial containment of the lesion (34/136 (25%) or a myectomy 16/62 (26%)). Regarding 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 (p= 0.9).

Discussion

This study of local treatment for deep-seated, high-grade soft tissue sarcoma shows an overall local recurrence rate of 23%. This is higher than in other reports. The final result in a randomized series of high-grade sarcomas of all depths was 11% local recurrences in the radiotherapy arm, and 34% local recurrences without radiotherapy (Pisters et al. 1996b). The vast majority of our patients were treated with limb-sparing surgery and most had marginal margins and postoperative radiotherapy or wide margins without radiotherapy. The recurrence rates are in line with other reported series with similar patient characteristics (Heslin et al. 1996, Guillou et al. 1997). The local recurrence rate after intralesional or marginal margins was lower than in other reports (Enneking et al. 1980, Gustafson 1994). However, it was higher than we expected after a wide margin without radiotherapy, as compared to single institution reports (Rydholm et al. 1991, Karakousis and

Driscoll 1999). Hence, indications for adjuvant radiotherapy based mainly on margin assessment appear debatable.

One might assume that margin classification was unreliable as the local recurrence rate after wide excisions was 25%. However, margin assessment was performed by experienced orthopedic surgeons and pathologists who have participated in margin assessment in various SSG trials. Guidelines for margin assessment are given in the SSG Central Register Protocol (SSG VII), based on Stener (1978), Enneking et al. (1980) and Rydholm and Rööser (1987). Surgical margins have also been reassessed, by reviewing surgical and pathology reports in connection with other studies. Accordingly, cases where the margin of excision was wide, except in a small area, were classified as marginal. In fact, the strict application of these guidelines resulted in a relatively low rate of local recurrence after an intralesional or marginal margin without radiotherapy. Hence, we believe that excisions assessed as wide were correctly classified, but that this margin is associated with a more than 20% local recurrence rate without radiotherapy. This accords with other series of deep-seated sarcomas (Heslin et al. 1996, Guillou et al. 1997, Yang et al. 1998).

Treatment policy in Scandinavia for the last 20 years has relied upon accurate margin assessment to decide whether to use radiotherapy. In Scandinavian studies, a wide surgical margin has been associated with a local recurrence rate of less than 15% (Berlin et al. 1990, Rydholm et al. 1991, Wiklund et al. 1993). In a SSG randomized study of doxorubicin, the rate of local recurrence was 2/21 after marginal surgery with radiotherapy and 7/84 after a wide margin without radiotherapy (Alho et al. 1989). However, this study was highly selected for age and the chemotherapy may have contributed to local control (Alvegård et al. 1989, Tierney et al. 1997).

There was no evidence that myectomy was better than other wide margins with respect to local recurrence. We applied the strict classification of myectomy and reclassified all cases reported as myectomy if there had been an open biopsy or the lesion was located extramuscularly. We cannot explain why myectomy did not have a better outcome. Our series is not large enough to determine whether tumors in certain muscles permit better local control than others.

Local recurrence rates down to 10% may be obtained when all patients are treated with radiotherapy regardless of surgical margin (Sadoski et al. 1993, Pisters et al. 1996a, Yang et al. 1998). The studies cannot be readily compared with ours since patients with recurrent sarcoma were included in some of these one-center studies, and more patients were treated with chemotherapy. It does appear, however, that the general use of radiotherapy for all deep-seated, high-grade soft tissue sarcomas yields better local control, but better control does not improve survival (Rööser et al. 1990, Gustafson 1994, Lewis et al. 1997, Trovik et al. 2000a). Hence, the morbidity associated with radiotherapy may not be justified to attain a 10% reduction in the recurrence rate (Sugerbaker et al. 1982, Bell et al. 1989, Stinson et al. 1992, Wiklund et al. 1993, O'Sullivan et al. 1999). Even if most patients outside Scandinavia, with high-grade soft tissue sarcomas have received radiotherapy for the last two decades, the longer-term effects of radiotherapy may still not be fully appreciated. We cannot predict which patients will develop complications. However, 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. Local recurrences lead to amputation in 2 of 10 patients with extremity soft tissue sarcomas (Karakousis and Driscoll 1999, Trovik et al. 2000b). Hence, in sites where local recurrence would have devastating consequences, especially in the upper limb, modern radiation therapy, based on optimal dose-fractionation to obtain adequate volumes, will be indicated in most cases, regardless of margins (Pisters 1998, Wylie et al. 1999).

One of the aims of the present study was to ascertain whether certain tumor sites gave better results. Lesions of the lower trunk, groin, and gluteus were associated with a local recurrence rate of 33%, and those below the knee of 38%. Clearly, adjuvant radiotherapy is more often indicated in these sites. The local recurrence rate was still 23% after wide excisions for lesions in the

thigh, which could be considered as the most favorable location. An intramuscular location also did not yield better local control than an extramuscular one and there was no difference between Grade III and IV lesions.

There are several ways to improve local control in soft tissue sarcoma. The most effective is to improve referral practices, so that more patients are given primary treatment at sarcoma centers (Gustafson et al. 1994). Secondly, sarcoma centers in Scandinavia should increase the use of radiotherapy to improve compliance with treatment recommendations, so that all patients receive radiotherapy after intralesional or marginal excisions. Hence, radiotherapy is indicated, even if the patient is old or has other ailments. Thirdly, radiotherapy is indicated in many patients with wide margins (Rööser 1987, Pisters 1998), especially in those with a previous open biopsy or if a local recurrence might lead to an amputation.

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Appendix A. Participating institutions and number of patients reported

Center	City	Patients
Karolinska Hospital	Stockholm	105
University Hospital	Lund	84
Norwegian Radium Hospital	Oslo	71
Sahlgren University Hospital	Götenborg	60
University Hospital	Helsinki	38
University Hospital	Linköping	34
Haukeland Hospital	Bergen	31
University Hospital	Trondheim	22
University Hospital	Umeå	14
Total		459

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