Surgical margin in soft tissue sarcoma

The Scandinavian Sarcoma Group experience

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Two-hundred and forty adult patients with a high-grade soft tissue sarcoma were treated surgically in 18 hospitals participating in the Scandinavian Sarcoma Group Protocol I. The patients were randomized to either postoperative doxorubicin or control; patients whose surgical margin was judged marginal also received radiotherapy. The outcome after different surgical margins was analyzed in 185 tumors of Grades III or IV in the extremities. The total cumulative local tumor control was 91 percent (168 of 185) after a median of 47 months. The cumulative local control rates in the surgical groups were: compartmental or wide amputation—37/37 (100 percent), compartmental local excision—23/24 (96 percent), wide local excision—77/84 (92 percent), marginal excision and radiotherapy—19/21 (90 percent), and marginal excision alone (reevaluated margin)—12/19 (63 percent, significantly lower than others). The risk of local recurrence was 13 times higher after marginal than after compartmental surgery ($P = 0.02$) and 3 times higher if the tumor was larger than 10 cm ($P = 0.05$). The treatment with doxorubicin did not influence the risk of local recurrence. The survival rates did not differ significantly in the groups.

Increased knowledge of the local behavior of soft tissue sarcoma has made limb salvage possible in an increasing number of patients. Centralization of diagnostic work-up and treatment, with strict adherence to approved guidelines, has been one of the decisive factors (Mankin et al. 1982, Rööser 1987). However, Enneking (1983) reported a 50–70 percent local recurrence rate in high-grade sarcomas after wide margin surgery alone. By contrast, other authors have reported lower figures (Karakousis et al. 1986, Berlin et al. 1978, Rydholm and Rööser 1987). To decrease the local recurrence rates after local surgery, radiotherapy is often combined with surgery (Rosenberg et al. 1982, Suit et al. 1985). Adjuvant chemotherapy has also been used, but the results are equivocal (Antman et al. 1984, Bramwell et al. 1985, Eilber et al. 1986, Gherlinzoni et al. 1986, Alvegård et al. 1989).

In an effort to standardize the treatment principles, the Scandinavian Sarcoma Group was founded in 1979. The first protocol of the group was on adjuvant chemotherapy for surgically treated soft tissue sarcoma (Working Committee SSG 1981, Alvegård et al. 1989). The use of common guidelines for surgical treatment and precise definition of surgical margins (Stener 1979, Working Committee SSG 1981) allowed for the present analysis of the local recurrence rate after surgery with those strictly defined margins.

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Patients and methods

Patients

From January 1981 to February 1986, 240 patients were treated in 17 hospitals (see Appendix) according to the Scandinavian Sarcoma Group Protocol I (SSG I 1981). The requirements for inclusion were age ≥15 years, previously untreated soft tissue sarcoma Grade III or IV (Broders 1964, Angervall et al. 1986), no metastases, no other malignancies, and no contraindications for doxorubicin (Adriamycin). The patients operated on with a compartmental or wide margin were randomized to doxorubicin or control groups. The patients with marginal margin were randomized in the same way after postoperative radiotherapy 51 Gy/17 fractions/24 days. The adjuvant postoperative chemotherapy consisted of doxorubicin 60 mg/m^2 i.v. on day 1, the cycle length was 28 days, and 9 cycles were given (Alvegård et al. 1989). After exclusion of patients who at the review did not fulfill the inclusion criteria and tumors in other than extremity locations, 185 tumors in 101 males and 84 females with a median age of 56 (15–73) years were eligible for the present analysis.

Thirty-one tumors (17 percent) were located in the upper extremities, 104 (56 percent) in the hip and thigh area, and 50 (27 percent) more distally in the lower extremities. Forty-four tumors were superficial, 122 deep, and 19 both deep and superficial. The median tumor size was 8 (1–25) cm.

In the final histologic review, which was the basis for inclusion of the patients in the present analysis, 54 tumors were designated Grade III and 131 Grade IV. The most common histiotypes were malignant fibrous histiocytoma—81 (44 percent), synovial sarcoma—34 (18 percent), and liposarcoma—19 (10 percent).

Coded data for all the patients have been reported by Alvegård (1989).

Diagnostic procedures

Among the patients with compartmental or wide amputations, the preoperative diagnosis was clinical in 4 cases, cytologic in 6 cases, and histologic by open biopsy or marginal excision in 27 cases. The corresponding figures were 8, 9, and 7 for compartmental local excisions, and 8, 24, and 52 for wide excisions. Thus, the diagnosis in compartmental and wide surgery was clinical in 20, cytologic in 39, and histologic in 86 cases. The diagnosis in marginal surgery with radiotherapy was clinical in 11 patients, cytologic in 9 patients, and histologic in 1 patient. The diagnosis in the cases of marginal surgery without radiotherapy (reclassified margins) was cytologic in 3 and histologic in 16 patients.

Surgical guidelines

The surgical guidelines were according to the following definitions (Stener 1979): A single muscle including its fibrous boundary in both the longitudinal and transverse planes or a group of muscles with their common fibrous boundary constitutes an anatomic compartment. A tumor is confined to a compartment as long as the fibrous boundary is not invaded by tumor and has not been transgressed by biopsy procedures.

In *compartmental excision*, the anatomic compartment where the tumor is located is removed unopened along with its fibrous boundary or, occasionally, is removed with bone. For a tumor located between muscles, a compartmental excision means that all the muscles around the tumor are included in the surgical specimen. For an excision to be described as compartmental, any compartment possibly contaminated by tumor cells initially or as a result of biopsy must be included in the specimen. Compartmental excision is preferable whenever possible, and it is especially indicated if an incisional biopsy has been carried out. In case of biopsy of any kind, great care has to be taken to include the entire biopsy route with an adequate margin into the surgical specimen.

In *wide excision*, an adequate safe margin of healthy tissue is included in the specimen, although the knife may cut within the compartment where the tumor is located. Where muscle tissue is being cut transversely to its fibers, the margin must be especially wide, at least 2.5 cm, even if the tumor is small.

In *marginal excision*, the knife cuts close to the tumor, through the pseudocapsule or reactive zone, in one or more places, even all around. If during an operation intended to be compartmental or wide the tumor is exposed in one single place or if histologic examination reveals that the margin is marginal in one single place, the excision is marginal.

Amputation can be compartmental, wide, or marginal. It should be noted that the term compartmental is not synonymous with the term radical used by the Musculoskeletal Tumor Society (Enneking 1983). In many cases it means the preservation of much more function, as in myectomy, which does not comprise a whole anatomic compartment as de-

Table 1. Local tumor control and survival in relation to the surgical margin. Cumulative results at median 47 (23–85) months' follow-up and estimated results at 3 years

Procedure	Number of patients	Local recurrence-free patients	Proportion of Grade IV tumors	Tumor size, median, cm	Local tumor control at 3 years	Survival at 3 years
Compartmental or wide amputation	37	37	0.81	8	1.00	0.65
Compartmental local excision	24	23	0.79	10	0.96	0.75
Wide local excision	84	77	0.61	6	0.92	0.78
Marginal local excision and radiotherapy	21	19	0.80	9	0.90	0.60
Reclassified marginal excision	19	12	0.73	12	0.63[a]	0.50
Total	185	168	0.71	8	0.91	0.69

[a] Significantly lower than in compartmental or wide amputation ($P = 0.0003$), compartmental excision ($P = 0.007$), or wide excision ($P = 0.007$).

fined by the Musculoskeletal Tumor Society.

The operation and pathology reports were regularly reviewed by the Surgery and Pathology Subcommittees without knowledge of the clinical course. Nineteen reported compartmental or wide margins were reclassified to marginal margins. In 14 of these patients, the margin was reclassified based on the information in the operation reports and in another 5 patients because of the findings in the histology reports. These 19 patients did not receive postoperative radiotherapy.

Postoperative radiotherapy

Postoperative radiotherapy was given if the operation was primarily classified as marginal. Target volume for radiotherapy included the entire tumor-involved anatomic structure with appropriate margins, depending on tumor site. Anatomic compartment volumes were defined for extremity-localized deep-seated intracompartmental tumors. Irradiation of the entire circumference was avoided. The definition of the target was based on all the available information, including preoperative examination and CT, by reviewing the operative and pathologic reports, and sometimes with the aid of radiopaque clips placed by the surgeon at the periphery of the operative field. Surgical scars and drainage canals were included in the target. Two opposing beams were usually used, and megavoltage radiation was employed (Cobalt-60-8MV photons). The specified target absorbed dose was 51 Gy/17 fractions/24 days (Cumulative Radiation Effect, CRE = 18.2).

Follow-up

A clinical examination, including chest radiographs, was made every third month during the first 2 years and every 6 months up to 5 years, and thereafter once a year up to 10 years. The median follow-up period for surviving patients was 47 (23–85) months.

Statistical analysis

Tumor-related survival and local recurrence were analyzed univariately by the Kaplan-Meier method, and statistical significance was evaluated using the Generalized Wilcoxon tests. Multivariate analyses were performed using the Cox proportional hazards model.

Results

Surgical margins and local tumor control

The total cumulative local tumor control was 91 percent (168 of 185; Table 1). No local recurrencies were experienced in the patients with compartmental or wide amputations. One local recurrence occurred in 24 patients with compartmental excision, and in 7 of 84 patients with wide excision. The numbers for marginal excision with and without radiotherapy were 2 of 21 and 7 of 19, respectively. Ten of the 17 patients with local recurrence also had metastases, most of them in the lungs. When adjusting multivar-

Table 2. Variables multivariately analyzed for prognostic influence on occurrence of local recurrence in 185 patients with malignancy Grades III and IV soft tissue sarcomas of the extremities

Factor	Relative risk	*P*-value
Sex		
Male	0.8	0.8
Female		
Age		
≤50 years	0.5	0.2
> 50 years		
Site		
Proximal	3.0	0.2
Distal		
Tumor depth		
Superficial	2.0	0.2
Deep		
Tumor size		
≤10 cm	3.0	0.05
> 10 cm		
Malignancy grade		
III	1.6	0.5
IV		
Tumor type		
MFH	0.5	0.3
Other types		
Tumor necrosis		
None	3.0	0.2
5–6 mm	2.0	0.2
≥17 mm		
Diagnostic procedure		
Clinical	0.9	0.9
Needle biopsy	1.3	0.7
Open biopsy		
Type of surgery		
Compartmental amputation and excision	3.7	0.2
Wide amputation and excision	5.3	0.2
Marginal excision with or without radiotherapy	12.5	0.02
Chemotherapy		
No	1.3	0.6
Yes		

iately for sex, age, tumor site, tumor depth, tumor size, tumor type, malignancy grade, tumor necrosis, diagnostic procedure, type of surgical margin, and chemotherapy, the only risk factor for local recurrence was marginal surgery with a 13 times higher risk than after compartmental amputation and excision (P = 0.02, Table 2). Tumor size (> 10 cm) reached almost significance (P = 0.05), with a relative risk of local recurrence of 3.0.

The postoperative treatment with doxorubicin did not influence the risk of local recurrence.

Reporting institutions with higher numbers of tumors included in the study had closer agreement between the margin planned preoperatively and the one achieved at operation than institutions with lower numbers ($P < 0.001$, chi-square test). The larger centers also used clinical and cytologic diagnoses more often than the centers with fewer tumor patients included in the study.

Survival

The cumulative tumor-related survival was 69 per cent at 3 years (Table 1) and 56 per cent at 5 years. Three patients died of cardiomyopathy as a complication of Adriamycin therapy. The survival rates did not differ significantly in the surgical groups (Table 1).

Discussion

When the present study was started, no randomized study with doxorubicin as the sole adjuvant drug for high-grade soft tissue sarcomas operated on according to modern surgical principles existed. Also, the surgical principles and the definitions of surgical margins were not standardized in the Scandinavian countries. In agreement with previous results (Antman et al. 1984), no adjuvant effect of doxorubicin could be demonstrated (Alvegård et al. 1989). On the other hand, the study gives interesting information concerning the surgical treatment. The guidelines that were agreed upon could be followed in most patients. Obviously, a more critical attitude towards the width of the margin as observed clinically and histologically and towards intraoperative contamination would have improved the results.

Limb-saving surgery was performed in 80 percent of the patients, including postoperative radiotherapy in 11 percent. The local tumor control was high in this series for nonablative surgery with compartmental or wide margins (94 percent), and also for marginally operated on patients who received postoperative radiotherapy (90 percent). Our low local recurrence rates after wide and compartmental operations can probably be explained by the strict criteria applied for the definition of surgical margin.

The centers treating the largest numbers of tumors applied compartmental excisions more often than others and reached a compartmental or wide margin more often than centers treating smaller numbers. In each center, several patients were treated who were not included in the study because of the exclusion

criteria. Therefore, the series does not allow any statement of the minimum number of patients to be treated in a center so that adequate expertise may be developed.

Several risk factors have previously been found predictive of local recurrence and tumor-related death (Collin et al. 1988, Rööser 1987). Thus, high-grade, limb-saving surgery, marginal surgery, extra-compartmental tumor location, and tumor necrosis have increased the risk of local recurrence. In the present series, to date, only marginal surgery without radiotherapy has been shown to entail such a risk. The tumor size appeared also to be an important factor. On the other hand, we found no association between the type of surgical margin and survival.

We conclude that a strict adherence to surgical guidelines improves local tumor control. An exact definition of surgical margins is essential in multicenter studies and when comparing results of separate studies. Critical evaluation of surgical margins is warranted to give the benefit of postoperative radiotherapy, necessary only for patients operated on with marginal or contaminated margins.

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APPENDIX. Participating hospitals and principal investigators

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