# Surgery for soft tissue sarcoma in the extremities

## A multivariate analysis of the 6–26-year prognosis in 137 patients

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**In 137 patients with soft tissue sarcomas in the extremities, the influence of patient and tumor characteristics and surgical procedures on prognosis was studied using a multivariate statistical analysis. The minimum follow-up time was 6 years, and no patient was lost to follow-up.**

**Eighty-nine patients were referred with the tumor intact (primary series), while 48 were referred after biopsy or with local recurrence after previous surgery (secondary series). The frequency of amputation was 15 percent in the primary series and 48 percent in the secondary series. A local, function-preserving operation with a wide margin was performed in 37 patients without biopsy (clinical diagnosis alone). Local control of the disease was obtained in all but one of these patients without any adjunctive treatment.**

**Independent, unfavorable factors concerning local recurrence were advancing age, open biopsy, and marginal surgery. Independent, unfavorable factors concerning survival were advancing age, increasing histologic malignancy grade, and ablative surgery. A tumor-related death was observed in 0, 29, 47, and 67 percent of the patients with tumors of malignancy grades I, II, III, and IV, respectively.**

There is still no agreement on the best treatment of soft tissue sarcomas of the extremities. To promote the understanding of this problem, long-term follow-up studies of the results of various modes of treatment by multivariate statistical analysis are needed to disclose factors of independent prognostic importance (Kindblom et al. 1975, Markhede et al. 1982, Merck et al. 1983). Multivariate statistical analyses have shown the histologic malignancy grade, patient age, tumor size, the occurrence of local recurrence, and the surgical treatment to be of major prognostic importance (Collin et al. 1986, 1987, Heise et al. 1986, Kindblom et al. 1975, Markhede et al. 1982, Merck et al. 1983, Rydholm et al. 1984, Rööser et al. 1987).

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In the present report, the influence of patient and tumor characteristics and surgical procedures on the risk of local recurrence and tumor-related death was studied using a nonparametric multivariate statistical analysis including hazard function tests. The study included a comparison between three different diagnostic procedures: clinical diagnosis alone, clinical diagnosis combined with aspiration cytology, and clinical diagnosis confirmed by histologic examination of biopsy specimens.

## Patients and methods

During the period 1956 through 1976, we treated 137 patients with a soft tissue sarcoma in an extremity; all of them were free from evidence of metastasis. No adjunctive treatment was used for the primary tumor. Eighty-nine patients, the primary series, were referred to our department before any surgical intervention, whereas 48 patients, the secondary series, were referred after biopsy or with local recurrence after previous surgery.

*Sex.* Totally, 78 patients were men and 59 were women with a similar distribution in the primary and secondary series.

*Age.* The median age was 63 (14–90) years in the primary series and 49 (13–89) years in the secondary series.

The minimum follow-up time was 6 years. All the patients that were alive were examined clinically and with chest radiographs. No patient was lost to follow-up.

## Diagnostic procedures

In the *primary series,* biopsy was omitted in many patients in whom the history, a careful physical examination, and various radiographic studies all agreed as regards a diagnosis of malignancy, and the tumor was judged as removable with a sufficient margin without any substantial loss of function. If a fairly certain clinical diagnosis of malignancy was not arrived at, the preoperative investigation included a fine-needle aspiration biopsy (needle diameter < 0.8 mm). An incisional biopsy was performed when the planned surgery was expected to result in a nonacceptable loss of function if the lesion should unexpectedly turn out to be benign. When the incisional biopsy specimen was examined by frozen-section technique, the circulation of the tumor was either stopped using a torniquet or restricted to a minimum by temporarily clamping the main artery of the limb (Stener and Stener 1958). The definitive surgical intervention was carried out before the circulation was released.

In the *secondary series,* a histologic examination had been carried out before referral in all the patients. An incisional biopsy had been performed in 17 patients, an excisional biopsy in 13 patients, and a coarse-needle biopsy in 1 patient. These patients were referred for treatment within 1 month. Seventeen patients were referred after a median time of 33 (2–177) months with a local recurrence after previous surgery. These patients were included in our study since the surgical problems they posed, such as the calculation of necessary margins, were similar to those encountered in the patients referred soon after incisional or excisional biopsy. Further, an analysis showed that the risk of tumor-related death did not differ between the patients referred with local recurrence and those referred after incisional biopsy of the primary tumor. In the comparison between the three different diagnostic procedures mentioned above, the patients referred with local recurrence were excluded.

All surgical procedures at our department, including biopsy when needed, were based on available knowledge of the site of origin of the tumor and its topographic relation to important anatomic structures. For this purpose, angiography, using the stereoscopic technique, was most useful (Stener and Stener 1958, Stener 1979).

## Tumor site and surgical margin

Although using basically the same definitions as those adopted by the Musculo-skeletal Tumor Society (Enneking et al. 1980), we distinguished between an extramuscular wide margin and an intramuscular wide margin (Berlin et al. 1987). The extramuscular margin is somewhere between a radical margin and a wide margin; it is radical in the longitudinal planes of the extremities, but not in the transverse planes. The definition of an intramuscular wide margin is that the knife has cut in one or more places within the muscle affected by the tumor, but always through normal tissue well away from the reactive tissue zone about the tumor. In several cases, there was no great difference between an extramuscular margin and an intramuscular one since in the latter case only a small part of a long muscle was left behind proximally and/or distally. We also distinguished between deep and subcutaneous wide and marginal margins.

## Pathologic-anatomic examination

In the gross examination of the surgical specimen, usually performed by the pathologist and surgeon in collaboration, the size of the tumor was measured and the topographic relation to surrounding anatomic structures was examined. The microscopic analysis included studies of the growth characteristics of the tumor, and the adequacy of the surgical procedure was assessed by examination of resection margins (Angervall et al. 1986). A four-grade scale of histologic malignancy was used and the principles for the histologic typing and grading were the same as in previous studies (Kindblom et al. 1975, Markhede et al. 1982, Merck et al. 1983).

## Variables recorded

Descriptive variables were recorded at the time of surgery at our department (definitive surgery) with one exception: for patients referred with a local recurrence, the size of the tumor was related to the initial operation. The following descriptive variables were recorded:

*Patient.* Sex, age, symptoms (mass and pain), and sedimentation rate.

*Tumor.* Anatomic location (upper versus lower extremity), site (intracompartmental versus extracompartmental), depth (four categories: subcutaneous; subcutaneous attached to deep fascia; intramuscular or intermuscular; affecting major nerves, vessels, or periosteum of bone), size (five categories; see Table 1), histologic type (eight categories; see Table 2), grade (I–IV), and stage according to the Surgical Staging System (IA, IB, IIA, and IIB) (Enneking et al. 1980). It was assumed that our grades I and II tumors can be regarded as low grade and our grades III and IV tumors as high grade.

*Diagnostic procedure.* Clinical diagnosis alone versus clinical diagnosis combined with aspiration cytology, and clinical diagnosis alone versus clinical diagnosis confirmed by histologic examination of biopsy specimens. These variables were restricted to local surgery with radical or wide margins, and patients referred with local recurrence were excluded.

*Surgical treatment.* Local surgery versus amputation (for both, only radical and wide margins), and radical and wide margins versus marginal margin.

*Outcome.* Two outcome variables were studied: local recurrence and tumor-related death. The time from the operation at our department to the occurrence of the event was recorded.

### Statistics

The statistical analysis aimed to assess whether the descriptive variables, independent of one another, had an influence on local recurrence and tumor-related death. The analysis was performed in the following stepwise manner:

*Bivariate analysis.* Fisher's exact test was used for the comparison of proportions (Odén and Wedel 1975). Pitman's test was used to study the correlation between pairs of descriptive variables (Bradley 1968). Hazard function test was used to study the correlation between descriptive and result variables (Bradley 1968, Mantel 1963, Merck et al. 1983).

*Multivariate analysis.* When the hazard function test showed a significant correlation between a descriptive variable and a result variable, the descriptive variable was used as a test variable in a nonparametric multivariate analysis (Cox 1972, Merck et al. 1983). The method offers a strict means of assessing whether a descriptive variable has a correlation to a result variable that cannot be explained by a correlation between the descriptive variable and another descriptive variable that is also correlated with the result variable.

All $P$-values, except for Fisher's exact test, were obtained by using the Edgeworth expansion (Cramer 1946).

## Results

### Clinicopathologic observations

*Symptoms.* All the patients but one or their doctor had felt a mass as a sign of the disease. Sixty patients had experienced pain related to the tumor.

*Sedimentation rate.* The sedimentation rate was not recorded at the time of operation in 15 patients. Of the remaining 122 patients, 60 had a sedimentation rate of 20 mm or below, 31 between 21–50 mm, 24 between 51–100 mm, and 7 over 100 mm.

*Anatomic location.* One-hundred and fifteen sarcomas were located in the lower extremity (84 percent) and 22 in the upper extremity (16 percent), with no difference in distribution between the two series. Of the 115 sarcomas in the lower extremity, 12 were in the hip or gluteal region or groin, 77 in the thigh, and 26 at or below the knee. Fifty-six percent of the sarcomas of the total series were located in the thigh. Of the 22 sarcomas in the upper extremity, 19 were in the shoulder or upper arm.

*Site of tumor.* Of the 137 sarcomas, 76 were intracompartmental (55 percent) and 61 were extracompartmental (45 percent). The ratio of intracompartmental versus extracompartmental tumors was approximately three to one in the primary series and one to three in the secondary series.

*Depth of tumor.* Twenty-seven sarcomas were subcutaneous and 15 of these were attached to the deep fascia. In the primary series 14 of 89 tumors were subcutaneous compared with 12 of 48 tumors in the secondary series. Totally, 110 sarcomas (80 percent) were deeply located within or between muscles. Fifteen of these sarcomas affected major nerves (seven malignant schwannomas), vessels (six leiomyosarcomas), or periosteum of bone.

*Size of tumor.* Two fifths of the tumors were larger than 10 cm (Table 1).

*Histologic type and grade of malignancy.* One third of the tumors were malignant fibrous histiocytomas, and 56 percent were grade IV (Table 2).

*Stage.* Of the 137 sarcomas, 10 were stage IA, 8 IB, 66 IIA, and 53 IIB.

Table 1. Size of 130 soft tissue sarcomas of the extremities in the primary and the secondary series

| Size (cm) | Primary series | Secondary series[a] | Total series | Percent (n 130) |
|---|---|---|---|---|
| ≤ 5 | 10 | 10 | 20 | 16 |
| 5.1–10 | 40 | 16 | 56 | 43 |
| 10.1–15 | 24 | 10 | 34 | 26 |
| 15.1–20 | 8 | 5 | 13 | 10 |
| > 20 | 7 | 0 | 7 | 5 |
| Total | 89 | 41 | 130 | 100 |

[a]Size could not be estimated for 7 tumors.

Table 2. Histologic type and malignancy grade in 137 soft tissue sarcomas of the extremities

| | I | II | III | IV | n | Percent |
|---|---|---|---|---|---|---|
| Malignant fibrous histiocytoma | – | 1 | 11 | 28 | 40 | 29 |
| Myxofibrosarcoma | – | 4 | 5 | 4 | 13 | 9.5 |
| Fibrosarcoma | 1 | 1 | 6 | 1 | 9 | 7 |
| Liposarcoma | 2 | 4 | 9 | 10 | 25 | 18 |
| Leiomyosarcoma | – | 1 | 3 | 6 | 10 | 7 |
| Malignant schwannoma | – | 2 | 4 | 7 | 13 | 9.5 |
| Synovial sarcoma | – | – | 1 | 11 | 12 | 9 |
| Miscellaneous types | 1 | 1 | 4 | 9 | 15 | 11 |
| Total | 4 | 14 | 43 | 76 | 137 | |
| Percent | 3 | 10 | 31 | 56 | | 100 |

Table 3. Surgical and diagnostic procedures in 137 patients with soft tissue sarcomas of the extremities

| | Primary series | Secondary series | Total series |
|---|---|---|---|
| Radical local resections | 1 | 5 | 6 |
| Wide local excisions | 56 | 14 | 70 |
| Clinical diagnosis alone | 38 | – | 38 |
| Aspiration cytology | 16 | – | 16 |
| Frozen-section biopsy[a] | 2 | – | 2 |
| Incisional biopsy | 1 | 6 | 7 |
| Excisional biopsy | – | 6 | 6 |
| Recurrence after previous surgery | – | 7 | 7 |
| Total | 57 | 19 | 76 |
| Marginal local excisions | | | |
| Clinical diagnosis alone[b] | 11 | – | 11 |
| Aspiration cytology | 8 | – | 8 |
| Incisional biopsy | – | 1 | 1 |
| Excisional biopsy | – | 3 | 3 |
| Recurrence after previous surgery | – | 2 | 2 |
| Total | 19 | 6 | 25 |
| Radical amputations | 10 | 15 | 25 |
| Wide amputations | 2 | 8 | 10 |
| Clinical diagnosis alone | 1 | – | 1 |
| Aspiration cytology | 5 | – | 5 |
| Frozen-section biopsy[a] | 3 | – | 3 |
| Incisional biopsy | 3 | 10 | 13 |
| Excisional biopsy | – | 4 | 4 |
| Coarse-needle biopsy | – | 1 | 1 |
| Recurrence after previous surgery | – | 8 | 8 |
| Total | 12 | 23 | 35 |
| Marginal amputation | | | |
| Clinical diagnosis alone | 1 | – | 1 |

[a]Incisional biopsy followed by immediate surgery (occluded blood circulation).
[b]Intentionally marginal in 3 cases.

Table 4. Number of patients with local recurrence in relation to surgical and diagnostic procedure in 137 patients with soft tissue sarcomas of the extremities

| Surgical procedure | Clinical diagnosis | Aspiration cytology alone | Histologic examination | Total |
|---|---|---|---|---|
| Radical local resection | 0/1 | – | 1/5 | 1/6 |
| Wide local excision | | | | |
| Extramuscular | 1/26 | 2/13 | 1/5 | 4/44 |
| Intramuscular | 0/6 | 1/2 | 1/3 | 2/11 |
| Subcutaneous | 0/5 | 0/1 | 3/9 | 3/15 |
| Total | 1/38 | 3/16 | 6/22 | 10/76 |
| Marginal local excision | | | | |
| Deep | 5/7[a] | 5/5 | 1/4 | 11/16 |
| Subcutaneous | 3/4 | 1/3 | 1/2 | 5/9 |
| Total | 8/11 | 6/8 | 2/6 | 16/25 |
| Radical amputation | 0/1 | 0/5 | 0/19 | 0/25 |
| Wide amputation | – | – | 1/10 | 1/10 |
| Total | 0/1 | 0/5 | 1/29 | 1/35 |
| Marginal amputation | 1/1[b] | – | – | 1/1 |

[a]Intentionally marginal in 3 patients.
[b]Palliative surgery.

*Diagnostic and surgical procedures* (Table 3). Of the 25 marginal local excisions, 5 were intentionally marginal since such a margin was the only option for various reasons. Two patients in the primary series underwent amputation without biopsy. One of them had an extremely vascular tumor which had largely destroyed the skeleton of the foot. A leg amputation was the only option whatever the diagnosis, which turned out to be a synovial sarcoma. The other patient who had a huge malignant fibrous histiocytoma in the right shoulder and neck region suffered severe pain because of the involvement of the

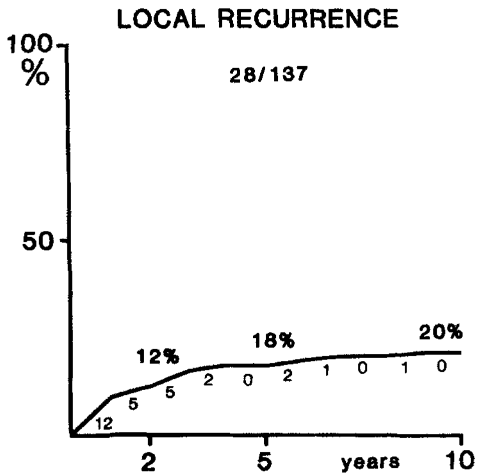


Figure 1. Observed frequency of local recurrence in relation to postoperative time in 137 surgically treated soft tissue sarcomas of the extremities. Eleven of the local recurrences (39 percent) occurred more than 2 years after operation.

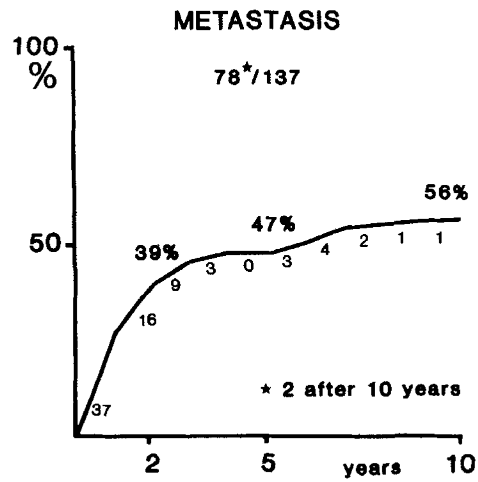


Figure 2. Observed frequency of metastasis in relation to postoperative time in 137 surgically treated soft tissue sarcomas of the extremities.

nerve plexus of the arm. An interscapulothoracic marginal amputation was performed for palliation. The frequency of amputation was 13/89 in the primary series and 23/48 in the secondary series ($P<$ 0.001).

*Local recurrence* (Table 4). Twenty-eight of the 137 patients (20 percent) had a local recurrence, 11 of them after more than 2 years and 4 after more than 5 years (Figure 1). There was no difference in the time of occurrence between the primary and the secondary series. After radical and wide local operations, local recurrence occurred in 5 of 57 patients in the primary series and 5 of 19 patients in the secondary series.

*Treatment for local recurrence.* Of the 28 patients in whom local recurrence developed, 10 received only palliative treatment because of generalized tumor disease; they were all dead at follow-up. Twelve patients were treated by local excision of one or more local recurrences. Six of these patients died of the tumor disease and 3 died of an unrelated disease. Three patients were alive without evidence of disease. Six patients underwent amputation for one or more local recurrences. Five died of the tumor disease and one of an unrelated disease. When amputations performed for local recurrence were included, the frequency of amputation was 18/89 in the primary series and 24/48 in the secondary series.

*Metastasis.* Seventy-eight patients, 51 in the primary and 27 in the secondary series, developed distant metastases (Figure 2). Thirty-three patients had only pulmonary metastases, 10 had metastases only outside the lungs, and 35 had pulmonary metastases in combination with other locations. The average time from definitive surgery to metastatic spread was shorter the higher the grade of malignancy (Table 5).

*Treatment for metastasis.* Of the 78 patients in whom metastasis developed, 74 were dead at follow-up. Seven of these 74 patients underwent surgical treatment for metastasis, and 5 had such treatment combined with chemotherapy and/or radiotherapy. These 12 patients died with a mean survival time of 28 months after the appearance of metastasis. Twenty-two patients received chemotherapy and/or radiotherapy without surgery; their mean survival time after metastasis was 11 months. The

Table 5. Absolute and relative number of patients with distant metastasis and the average time from definitive surgery to the appearance of metastasis in relation to histologic grade of malignancy

| Grade | Number | Percent | Months |
|---|---|---|---|
| I | 0/4 | 0 | – |
| II | 4/14 | 29 | 62 |
| III | 23/43 | 53 | 45 |
| IV | 51/76 | 67 | 15 |
| Total | 78/137 | 57 | 26 |

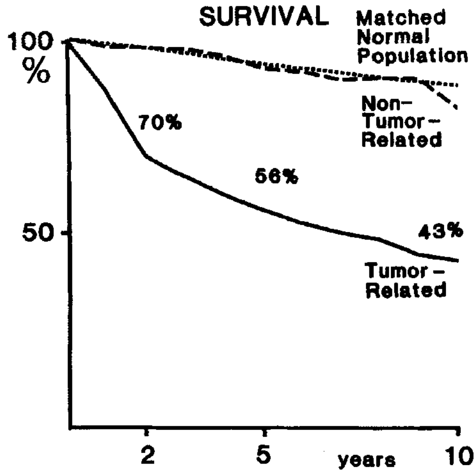


Figure 3. Survival in relation to time in 137 surgically treated soft tissue sarcomas of the extremities (hazard function technique). Patients dying from nontumor-related diseases closely follow an age- and sex-matched normal population indicating that the tumor-related death has not been overestimated or underestimated.

remaining 40 patients had only palliative treatment; their mean survival time after metastasis was 6 months.

Of the 4 patients who were alive at follow-up, 3 were without evidence of disease after surgical treatment, and one was receiving palliative treatment for pulmonary metastasis.

*Survival.* Seventy-five patients, 50 in the primary and 25 in the secondary series, had sustained a tumor-related death at the time of follow-up (Figure 3). One of those who died because of the tumor had no evidence of metastasis. Nontumor-related death was noted in 13 of 89 patients in the primary series and 4 of 48 patients in the secondary series. Of the 45 patients who were alive at the follow-up, 44 were without evidence of tumor disease (one had metastases).

## Factors influencing the prognosis

### Bivariate analysis

The upper section of Table 6 shows the correlations between descriptive variables in Pitman's test and the lower section shows the correlations between descriptive and result variables in the hazard function test. Sex, symptoms, and sedimentation rate are excluded because they were not correlated with any of the result variables. Concerning age and the various tumor variables, only such results are presented in the text that are not given in Table 6.

*Age.* The patients in the primary series were older than those in the secondary series ($P < 0.001$). Older patients had higher sedimentation rates ($P < 0.01$). Patients with malignant fibrous histiocytoma

Table 6. Correlations between descriptive variables in Pitman's test (upper section) and between descriptive and result variables in the hazard function test (lower section)

| | Age | Site | Depth | Size | Grade | Stage | Diagn–A | Diagn–B | Surg–A | Surg–B |
|---|---|---|---|---|---|---|---|---|---|---|
| n | 137 | 137 | 137 | 130 | 137 | 137 | 54 | 51 | 111 | 137 |
| Pitman's test | | | | | | | | | | |
| Site | –** | | | | | | | | | |
| Depth | –*** | +*** | | | | | | | | |
| Size | NS | NS | +** | | | | | | | |
| Grade | NS | NS | NS | NS | | | | | | |
| Stage | NS | +*** | +** | NS | +** | | | | | |
| Diagnosis–A[a] | NS | NS | NS | NS | NS | NS | | | | |
| Diagnosis–B[b] | NS | NS | –** | NS | NS | NS | | | | |
| Surgery–A[c] | –* | +*** | +*** | NS | NS | +*** | | | | |
| Surgery–B[d] | NS | NS | NS | NS | NS | NS | | | | |
| Hazard function test | | | | | | | | | | |
| Local recurrence | +* | NS | NS | NS | NS | NS | NS | +** | NS | +* |
| Tumor-related death | +* | NS | +* | +* | +*** | +*** | NS | NS | +* | NS |

+ Positive correlation (e.g., increasing size with increasing depth).
– Negative correlation (e.g., decreasing depth with increasing age).
*, **, and *** mean $P < 0.05$, $P < 0.01$, and $P < 0.001$, respectively.
NS not significant.
[a]Clinical diagnosis alone versus aspiration cytology.
[b]Clinical diagnosis alone versus open biopsy. Both diagnostic variables were restricted to local surgery with radical or wide margins (see Table 7).
[c]Local surgery versus amputation (radical and wide margins).
[d]Radical and wide margins versus marginal margin.

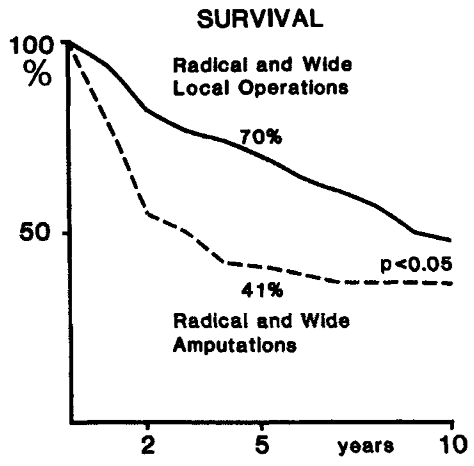


Figure 4. Tumor-related survival in relation to postoperative time in 76 patients who underwent radical and wide local operations versus 35 patients who underwent radical and wide amputations (hazard function technique). The estimated 10-year survival was 48 and 37 percent, respectively.

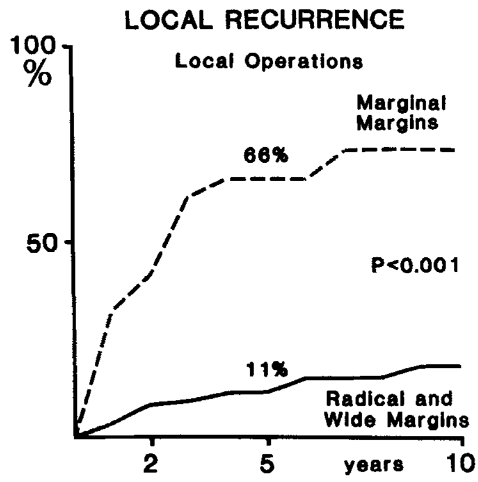


Figure 5. Frequency of local recurrence in relation to postoperative time in 76 patients who underwent radical and wide local operations versus 25 patients who underwent marginal local operations (hazard function technique). The estimated 10-year frequency of local recurrence was 18 and 73 percent, respectively.

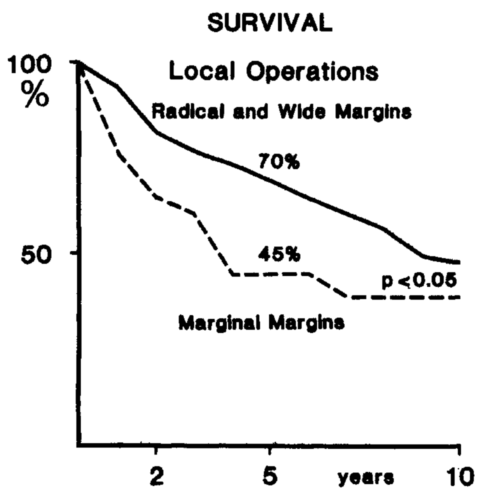


Figure 6. Tumor-related survival in relation to postoperative time in 76 patients who underwent radical and wide local operations versus 25 patients who underwent marginal local operations (hazard function technique). The estimated 10-year survival was 48 and 39 percent, respectively.

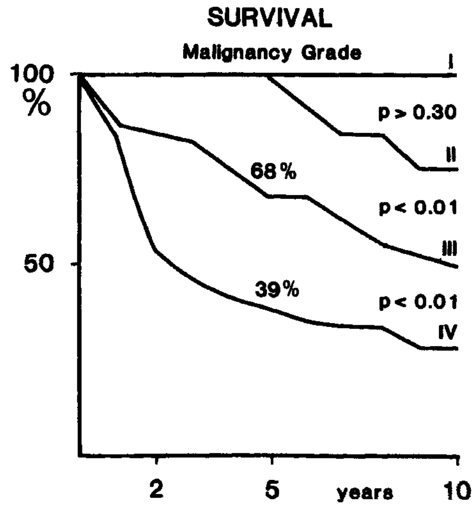


Figure 7. Tumor-related survival in relation to postoperative time and to histologic malignancy grade in 137 surgically treated soft tissue sarcomas of the extremities (hazard function technique). The estimated 10-year survival was 100, 76, 50, and 29 percent for grades I, II, III, and IV, respectively.

were older than patients with other types of sarcoma as a group ($P < 0.001$).

*Anatomic location.* Liposarcomas were found more often in the thigh as compared with all other locations combined ($P < 0.05$).

*Site of tumor.* The 51 patients in the primary series whose surgical treatment was based on clinical diagnosis alone had an intracompartmental tumor more often than the 29 patients whose treatment was based on aspiration cytology as well ($P < 0.05$). There was no difference, however, when only those patients who had undergone local surgery with radical or wide margin, 38 and 16 patients, respectively (Table 3), were included.

*Depth of tumor.* Malignant fibrous histiocytomas and myxofibrosarcomas were superficially located more often than all other tumors as a group ($P<$ 0.001).

*Size of tumor.* Liposarcomas were larger than other histologic types as a group ($P<$ 0.05). Sarcomas in the thigh were larger than sarcomas located elsewhere as a group ($P<$ 0.05).

*Histologic type and grade of malignancy.* Compared with all other histologic types as a group, liposarcomas were more often low grade ($P<$ 0.05), whereas malignant fibrous histiocytomas were more often high grade ($P<$ 0.01).

*Diagnostic procedure.* In 67 patients who had undergone a radical or wide local operation, clinical diagnosis alone was compared with clinical diagnosis combined with aspiration cytology (diagnosis–A) and with clinical diagnosis confirmed by histologic examination of biopsy specimens (diagnosis–B). These two diagnostic variables were not correlated with age, site, size, grade, and surgical stage, but the patients whose treatment was based on clinical diagnosis alone had more deeply located tumors than the patients whose treatment was based on histologic diagnosis ($P<$ 0.01).

*Surgical treatment.* Patients who underwent a radical or wide local operation had a tumor-related death less often than those who underwent a radical or wide amputation ($P<$ 0.05); the 5-year survival was 70 and 41 percent, respectively (Figure 4). The risk of local recurrence was lower after radical and wide operations than after marginal operations ($P<$ 0.05), and this variable was not correlated with any other descriptive or result variable. After local operations (Figure 5), the 5-year frequency of local recurrence was 11 and 66 percent, respectively ($P<$ 0.001). There was no difference in tumor-related death between patients who underwent a radical or wide operation and those who underwent a marginal operation; however, when only local operations were compared (Figure 6), there was a difference ($P < 0.05$).

*Local recurrence.* Local recurrence was more common after open biopsy than after clinical diagnosis alone in patients treated by local operations with radical or wide margins (Table 7).

*Tumor-related death.* Survival was strongly correlated with grade (Figure 7). None of the 4 patients with a grade I tumor had a tumor-related death, whereas 4 of the 14 patients with a grade II tumor did—all of them later than 5 years postoperatively. A tumor-related death was observed in 20 of 43 and 51 of 76 of the patients with tumors of malignancy grade III and IV, respectively. After radical and wide amputations the survival rate was higher for grade III tumors than for grade IV tumors ($P<$ 0.01). The risk of tumor-related death increased if the tumor recurred locally ($P<$ 0.001), especially if the recurrence appeared soon after operation. There was no difference in tumor-related death between the primary and secondary series, and in the latter series, there was no difference between the patients who had undergone incisional biopsy and those who were referred with local recurrence.

Table 7. Absolute and relative number of patients with local recurrence in relation to diagnostic procedure in 67 patients with a soft tissue sarcoma of an extremity treated with radical local resection (n 4) or wide local excision (n 63)[a]

| Diagnostic procedure | Local recurrence related to diagnostic procedure | | Comparison with clinical diagnosis alone (Fisher's exact test) |
|---|---|---|---|
| | Ratio | Percent | |
| Clinical diagnosis alone | 1/38[b] | 2.6 | – |
| Aspiration cytology | 3/16 | 19 | $P = 0.14$ |
| Open biopsy | 4/13 | 31 | $P < 0.05$ |
| Incisional | 3/7[c] | 43 | $P < 0.01$ |
| Excisional | 1/6 | 17 | $P > 0.30$ |

[a]Nine of the 76 patients treated with such surgery have been excluded: 7 who were referred with local recurrence after previous surgery and 2 who underwent frozen-section biopsy followed by immediate surgery, with precautions taken to minimize the risk of local recurrence (see text p. 476).
[b]Radical margin 1, wide margin 37 (1 recurrence).
[c]Radical margin 3 (1 recurrence), wide margin 4 (2 recurrences).

### Multivariate analysis

Such analysis was performed when the Pitman's test showed a correlation between a descriptive variable and one or more other descriptive variables that were also correlated with the result variable (Table 6). The influence of stage on other descriptive variables was excluded from the multivariate analysis since the influence of each of its two components, grade and site, was analyzed.

*Local recurrence.* All three of the descriptive variables that were correlated with local recurrence at the bivariate analysis, namely age ($P<$ 0.05), no biopsy versus open biopsy ($P<$ 0.01), and radical and wide margins versus marginal margin ($P<$ 0.05), had an independent influence.

*Tumor-related death.* Of the descriptive variables that were correlated with tumor-related death at the bivariate analysis, age ($P< 0.05$), grade ($P< 0.001$), and local surgery versus amputation (radical and wide margins; $P< 0.05$) had an independent influence.

## Discussion

The referral of a patient with a soft tissue sarcoma in a virgin state permits the application of the following surgical principle: to omit biopsy when the history, the physical examination, and various radiographic studies all agree on the diagnosis of malignancy and the location of the tumor allows its complete removal without any substantial loss of function (Stener 1979). This principle is based on early observations that malignant soft tissue tumors tend to respect preformed fibrous barriers, such as intermuscular septa and fasciae, for a long time (Stener and Stener 1958, 1963, Stener 1971). In our opinion the surgical margin in the transverse planes of the extremities need not be larger than such a barrier, provided that this barrier has not been infiltrated by the tumor, nor cut through for biopsy purposes. Like some skeletal parts, such as rib, clavicle, and fibula, many muscles are expendable; remaining synergistic muscles compensate for the loss by hypertrophy (Markhede and Nistor 1979, Gunterberg et al. 1981, Markhede and Stener 1981, Markhede et al. 1985). Because the principle of operating without biopsy was applied in the primary series, a comparison could be made between two categories of radical and wide local operations, namely those performed without biopsy and those performed after incisional or excisional biopsy. Open biopsy was shown to have a significant and independent adverse influence on the risk of local recurrence. When studying the influence of the diagnostic procedure on the risk of local recurrence we found it important to exclude (1) patients with a minimal risk of local recurrence, namely those who had been treated with a radical or wide amputation, and (2) patients with a high risk of local recurrence, irrespective of the diagnostic procedure, namely those who had been treated with marginal surgery. We also excluded the patients who had been referred with local recurrence after previous surgery. A restriction to radical and wide local operations has not been done in previous studies analyzing the influence of diagnostic procedures on the risk of local recurrence (Collin et al. 1986, Alho et al. 1989).

When using the principle of operating without biopsy, there is a risk that a benign tumor may be removed with an unnecessarily wide margin. In our opinion this risk does not outweigh the benefit of preserved function with a minimal risk of local recurrence that the vast majority of patients enjoy. When the history, the physical examination, and radiographic studies of various kinds together indicate malignancy, it is, in our experience, exceedingly rare that the lesion unexpectedly turns out to be benign. If this happens, no great harm is done since a prerequisite for operating without biopsy is, as a rule, that the surgery does not result in any substantial loss of function.

Generally, incisional biopsy must be performed when the planned surgery is expected to result in a considerable loss of function (Stener 1979). Even in such instances, however, incisional biopsy sometimes can be avoided provided the clinical presentation indicating malignancy can be confirmed by the morphologic findings in fine-needle aspirates. The increased knowledge of the cytology of various types of soft tissue lesions gained during recent years has increased the potentials of the fine-needle aspiration technique in the preoperative diagnostic investigation of soft tissue tumors (Åkerman 1988, Walaas 1990). With further growing experience and use of refined methods and adjunctive techniques in the analysis of the aspirates, such as electron microscopy, immunohistochemistry, quantitative DNA-analysis, chromosome analysis, and molecular genetic studies, fine-needle aspiration may become even more useful in the future. Especially the embedding technique for combined light- and electron-microscopic examination of fine-needle aspirates has proved to be of diagnostic value (Kindblom 1983, Kindblom et al. 1986). Occasionally, the clinical diagnosis of malignancy is so definite that even a fine-needle aspiration can be omitted despite that the surgery will result in a considerable loss of function. Two patients in the primary series underwent amputation without biopsy because the malignancy was obvious and such treatment was the only option.

The histologic grade of malignancy proved to have a strong influence on tumor-related death, and this influence was independent of all the other factors studied. The value of using a four-grade scale of malignancy, demonstrated previously in several studies at our institutions (Kindblom et al. 1975, Markhede et al. 1982, Merck et al. 1983), was further shown in the present study. As to the risk of a tumor-related death, there was a difference between grade II and grade III, as well as between grade III and grade IV. No patient with a grade I tumor died, whereas 4 of the 14 patients with a grade II tumor had a tumor-related death.

Objections can be raised to the use of a histologic malignancy grading of soft tissue sarcomas as a group when investigating the influence of malignancy grade and other morphologic and clinical variables on prognosis (Angervall et al. 1986). A general principle for malignancy grading that is valid for all kinds of soft tissue sarcomas cannot be formulated. Mitotic activity, for instance, seems to be of greater significance when assessing the malignancy grade of leiomyosarcoma than of liposarcoma. A discrepancy between cell atypia and cell and tissue differentiation may be seen, especially in leiomyosarcoma, thus giving rise to considerable difficulties in the grading. For some rare tumors the grading is based more on the knowledge of prognosis than on the histologic appearance, e.g., for alveolar soft part sarcoma, clear cell sarcoma and epithelioid sarcoma. Moreover, various types of soft tissue sarcoma, despite having the same malignancy grade, do not present identical behavior in terms of local recurrence, metastasis and survival. Previous studies indicated that a myxofibrosarcoma (Merck et al. 1983) of grade IV has a better prognosis than a liposarcoma (Kindblom et al. 1975) of the same grade. It is therefore obvious that the histologic grading of malignancy using a four-grade scale is most valuable in prognostic studies of single soft tissue sarcoma entities.

The Surgical Staging System adopted by the Musculoskeletal Tumor Society is based on the combination of grade and site: stage IA = low-grade, intracompartmental; stage IB = low-grade, extracompartmental; stage IIA = high-grade, intracompartmental; stage IIB = high-grade, extracompartmental (Enneking et al. 1980). In order to use this system as a variable in the statistical analysis we assumed that our grade I and II tumors could be regarded as low-grade tumors and our grade III and IV tumors as high-grade tumors. Furthermore, the analysis depended on the assumption that increasing stage (IA, IB, IIA, IIB) means increasing risk of tumor-related death. Because grade and site are combined in the staging system, it is of interest to clarify which part each of them plays in the prognosis. The present study indicated that the prognostic significance of stage mainly depends on the histologic malignancy grade. Site was not correlated with the risk of tumor-related death. The dominant role of grade in this staging system was also observed by Rööser (1987).

Preoperative assessment of the stage according to the Surgical Staging System necessitates open biopsy so that the malignancy grade of the tumor can be determined. It has been argued that this knowledge is important since a low-grade tumor (stage I) can be treated with a wide margin, whereas a high-grade tumor (stage II) should be removed with a radical margin to minimize the risk of local recurrence (Enneking et al. 1980). In the present study, however, the frequency of local recurrence was low (1/37) after wide local excisions performed without biopsy, even though about 90 percent of the tumors were highly malignant (grades III and IV). Thus, when surgery can be performed without biopsy, preoperative knowledge of the malignancy grade does not seem essential. A wide margin, which is required for a low-grade tumor, then seems to be sufficient for a high-grade tumor as well, especially if the wide margin is extramuscular, as it was in most of the wide local excisions performed without biopsy (26/37).

The value of a long-term follow-up was demonstrated by the fact that two fifths of the local recurrences occurred more than 2 years after operation and that 13 patients developed metastasis after more than 5 years, 2 of them after more than 10 years.

The long-term survival did not differ between the primary and the secondary series. When comparing these two series one must remember, however, that they differed as regards several factors with an influence on survival. Increasing age meant increased risk of tumor-related death, and this factor disfavored the primary series. This series was also disfavored by two other factors: it contained proportionately more deeply located and larger tumors than the secondary series. Bivariate analysis showed that both deep location and large size increased the risk of tumor-related death. Thus, with several factors favoring the secondary series, one would expect a better survival in this series than in the primary series. In at least one respect, however, the secondary series was disfavored. The frequency of amputation was much higher in this series than in the primary series and, as was shown by multivariate analysis, ablative surgery with radical and wide margins entailed—independently of other factors—a higher risk of tumor-related death than local surgery with such margins. Also in a previous study, amputation proved to be an independent predictor of decreased survival (Collin et al. 1987). The high frequency of amputation in the secondary series can be explained by the fact that the tumor was not in a virgin state when the patient was referred for treatment: this entailed an increased risk of ablative surgery being necessary in order to obtain a safe margin. Our study supports the opinion (Mankin et al. 1982, Rydholm 1983, Rydholm et al. 1983, 1984, Berlin et al. 1987) that better results can be achieved if patients suspected of having a malignant soft tissue tumor in an extremity are referred for musculoskeletal oncologic treatment before any surgical intervention takes place.

When an adequate surgical margin was aimed at, it was obtained in 38 of 46 patients who underwent local surgery based on clinical diagnosis alone, and only one of these patients had a local recurrence despite that most tumors were highly malignant (35/38). Thus, the vast majority of the patients in whom the tumor according to our principles can be removed without previous biopsy do not seem to need any adjunctive treatment for obtaining local control of the disease at the same time as good function is preserved. Such treatment, for instance, irradiation as an alternative to extended surgery (Suit et al. 1987), can be restricted to those patients in whom an adequate margin is not obtained.

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