From the University Department of Orthopaedics in Lund, Sweden

Management of patients with soft-tissue tumors

Strategy developed at a regional oncology center

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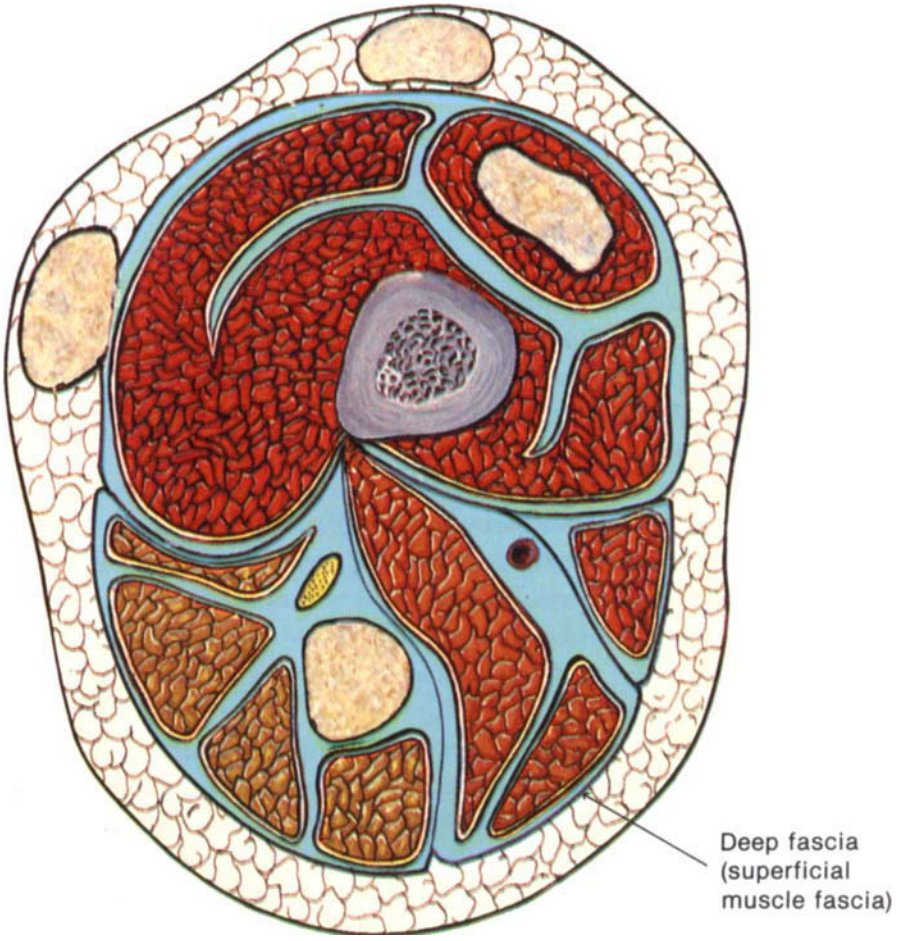
Contents

Figures

Tables



Superficial:
Subcutaneous
Subcutaneous, attached to the deep fascia

Deep:
Intramuscular
Extramuscular

All tumors are intracompartmental, except for the subcutaneous tumor attached to the deep fascia.

The three muscle compartments (quadriceps, adductor, hamstring) are indicated by different colors.

Figure 1 Tumor sites and compartments in the mid-thigh

Definitions

Soft-tissue tumor		Soft-tissue tumor in the locomotor system, benign or malignant. Tumors of the head, viscera, retroperitoneum and dermis were excluded as were Kaposi's sarcoma, dermatofibrosarcoma protuberans, desmoid tumor and sarcomas in previously irradiated fields.
Malignancy grade		Four-grade scale based on histologic criteria *(1-4)*. Low-grade sarcomas: Malignancy Grades I and II. High-grade sarcomas: Malignancy Grades III and IV.
Size		Largest diameter (cm) usually as recorded by the pathologist's examination of the formalin fixed specimen.
Geometric size		Natural logaritm of the product of three dimensions *(5)*.
Tumor site	Location	Part of the body (Table 5).
	Depth	1) subcutaneous 2) subcutaneous and attached to the deep fascia (superficial muscle fascia) 3) subfascial = below the deep fascia, intra- or extramuscular 1 + 2 = superficial tumor; 3 = deep tumor (Figure 1).
Compartmentalisation		Intra- or extracompartmental tumor site according to Enneking et al *(6, 7)*. Thus, tumors located in the fascial compartments of the extremities, intra- or extramuscular, were termed intracompartmental, as were also subcutaneous tumors without extension to the deep fascia. All other tumors were classified as extracompartmental (Figure 1).

Aspiration cytology

Fine needle aspiration biopsy. Needle diameter not exceeding 0.8 mm.

Surgical margins

Intralesional. Incisional biopsy and partial excision (incomplete, piecemeal, debulking).

Marginal. The tumor pseudocapsule formed all *or part* of the specimens periphery (shelling out). Thus, an excision intended with broader margins was classified as marginal, even if the pseudocapsule was exposed in only a small part of the specimen.

Wide. The tumor was removed *en bloc,* completely surrounded by a cuff of macroscopically uninvolved tissue as recorded in the surgical note. No microscopic tumor-growth should be seen at the resection margin. For a subcutaneous sarcoma, a wide margin required inclusion of the deep fascia beneath the tumor.

Compartmental: Excisions of subfascial intracompartmental tumors with a "radical margin" (total compartment) according to the definitions of Enneking et al *(6, 7)* were called compartmental excisions. For *intramuscular* tumors, provided the muscle fascia was unopened and not transgressed by a biopsy, complete myectomies were also called compartmental excisions even if they did not include the total compartment as it has been defined by Enneking et al *(6, 7).* These latter operations were thus performed as a primary procedure without surgical biopsy.

Broad: Wide or compartmental margin.

Amputation was not regarded as a surgical procedure *per se,* but classified according to the surgical margin obtained.

Final surgery

When the primary tumor was treated by several surgical procedures at short intervals in order to increase the surgical margin, the last intervention was called the final surgery.

Clinical incidence

Number of patients consulting a physician because of a tumor, irrespective of histological verification.

Referral pattern

Patients were classified as "referred before surgery" if referred before any intervention other than aspiration cytology. As "referred after surgery" were classified patients referred soon after surgery for further therapy. All other patients, including those referred with local recurrence were termed "not referred".

Introduction

The great majority of soft-tissue tumors are benign; local recurrence is unusual and metastatic spread does not occur. By contrast, soft-tissue sarcomas are rare and their prognosis is considered poor due to a high incidence of local recurrence and metastatic spread.

The clinical evaluation of a soft-tissue mass is often inaccurate *(8);* sarcomas are frequently misinterpreted as being benign tumors and shelled out, their real nature disclosed only at microscopic examination. However, the shelling out of a sarcoma is inappropriate therapy and, in the majority of cases, should not be considered even for diagnostic purposes; the risk of local recurrence is high *(3, 9)* and the extended surgery may be complicated by tumor spread in the wound hematoma *(3, 10)*. The diagnostic value of aspiration cytology for various types of carcinoma is well established. However, its role in the preoperative evaluation of soft-tissue tumors is still controversial *(11, 12)*.

Local control by surgery is essential; local recurrence greatly increases the risk for distant spread *(3)*. Surgery with low potential for local recurrence means extensive margins; in most series reporting low local recurrence rate the number of amputations is high *(7, 10, 13)*. Therefore surgery with pre- and/or postoperative radiotherapy has been tried to a) reduce the risk of local recurrence and b) avoid amputation *(14-16)*. Despite local control death due to metastasis, most often occult at the time of diagnosis of the primary tumor, is common. Adjuvant chemotherapy has been tried to erradicate such micrometastases *(17, 18)*.

However, the results of multimodality therapy are difficult to evaluate as prognostic variables as regards both local recurrence and survival are imperfectly known and sometimes contradictory. As a result there is no concensus on staging systems for soft-tissue sarcomas. Most series reporting on treatment results are not randomized; unidentified subsets of patients with low local recurrence rate following local surgery alone and with low mortality despite having tumors of high histological malignancy grade may thus make comparison between different series unreliable.

To improve the prognosis centralised treatment is recommended. An Orthopaedic Oncology Group (the Center) was formally established in 1970 at the Uni-

versity Hospital in Lund by agreement of all heads of departments within orthopaedic surgery and general surgery in southern Sweden (1.3 million inhabitants or 15 per cent of the population in Sweden). The Center acts as a referral institution for patients with proven or suspected musculoskeletal malignancies. The group includes representatives from orthopaedic surgery, radiology, cytology, pathology and oncology who examine patients together at a weekly tumor clinic for choice of further diagnostic and therapeutic procedures *(19)*.

Within the Center soft-tissue tumors have been studied from several aspects; epidemiologic *(19-21)*, radiologic *(22-27)*, cytologic *(28-32)* and prognostic *(33)*. The epidemiologic and prognostic studies concern unselected, population-based series of patients in contrast to most reports which deal with *subsets* of patients; certain histologic types and/or groups of patients defined by their referral to a treating center. In this presentation some of the results from previous studies were summarised and further analysed as regards: the epidemiology of soft-tissue sarcoma and lipoma (pp 21-26); the reliability of aspiration cytology (pp 29-32); the treatment, clinical course and prognostic variables in soft-tissue sarcoma (pp 35-51); the changes in the surgical treatment of soft-tissue sarcoma over the years in southern Sweden (pp 58-61).

The *purpose* was:

To determine guidelines for the management of soft-tissue tumors outside the Center, i.e., which patients should be referred before surgery?

To evaluate the role of aspiration cytology in the diagnostic work-up of soft-tissue tumors.

To determine if subsets of patients with good prognosis following surgery alone can be identified, i.e., patients for whom trials with adjuvant chemo- and radiotherapy are not indicated.

To examine the importance of the Center.

Patients and methods

Demographic data

The southern region of Sweden comprises 4 counties with a total area of 23,000 km^2. The population was 1.23 million in 1964 and 1.35 million in 1978. Between 11 and 15 % of the total population was found in each of the first seven decades and 10 % were older than 70 years. In 1965 (75), 11 (4) per cent of the population over 16 years of age were occupied in agriculture, and 34 (21) in industry. In 1965 (75, 83), 2 (5, 10) per cent were engaged in health care. The region was in 1964 (1978) served by 2 (2) University Hospitals, 15 (14) County Hospitals and about 100 (90) Health Care Centers. (Regional census data.)

Lipoma series

Clinical data were recorded from the clinical and pathological notes in all patients with a lipoma in the locomotor system histologically diagnosed in 1979 in any of the four departments of pathology in the southernmost county of Sweden (Malmöhus län, 743,000 inhabitants) *(20)*. Patients with multiple lipomas were not included. A lipoma was classified as being deep when the surgical report described it as such or when the histological sections showed infiltration of muscle.

Sarcoma series

Patients

All soft-tissue malignancies reported from the southern region of Sweden to the Swedish National Cancer Registry (1964—79) and to the Regional Cancer Registry (1980—81) were histologically reexamined without knowledge of the clinical course; 326 cases (basic series) were accepted as soft-tissue sarcoma *(19, 21)*. Different subsets of the basic series were used in the further analyses (Table 1).

Table 1 Soft-tissue sarcoma. Basic series and subsets.

	Time	n
Basic series	1964-81	326
Epidemiology	1964-78	278
Clinical course, bivariate analyses	1964-78	237[1]
Prognosis, multivariate analysis	1964-78	229[1, 2]
Treatment and referral pattern related to the Center	1964-81	261[3]

Excluded patients:
[1] Metastatic disease at the time of diagnosis (n 19) and patients not treated by surgery (n 22).
[2] Patients with missing data (n 8).
[3] Metastatic disease at the time of diagnosis (n 20), patients not treated by surgery (n 30), patients who primarily consulted the Orthopaedic Department in Lund (n 5) and patients with neck tumors (n 10), usually referred to and treated by the ENT-Department.

Histogenetic classification

The system of classification and nomenclature used was that applied at the WHO International Reference Centre for Histological Definition and Classification of Soft-Tissue Tumors. The definitions of myxofibrosarcoma and malignant fibrous histiocytoma were used in accordance with the description by Merck et al *(4)* and Weiss and Enzinger *(34)*, respectively. For the diagnosis of hemangiopericytoma the criteria given by Enzinger and Smith *(35)* were employed.

Malignancy grading

Histologic grading was based on cellular anaplasia and pleomorphism, mitotic frequency and cellularity. In tumors dominated by small cells, special attention was given to the frequency of mitoses. In tumors consisting of pleomorphic and/or large cells the frequency of mitoses as well as the occurrence of atypical mitoses were noted. The frequency of mitoses was related more to the cellularity of the specimen than to a certain number of mitoses per high power field. Synovial sarcomas, rhabdomyosarcomas, epithelioid sarcomas, clear cell sarcomas, osteosarcomas and Ewing sarcomas were all referred to one of the high-grade malignancy groups.

Liposarcomas were graded according to the system of Angervall *(1)* and Kindblom et al *(2)*: well-differentiated, Grade I; myxoid, Grade II; round cell and pleomorphic, Grade IV. Mixed liposarcomas i.e. well-differentiated or myxoid tumors with pleomorphic and/or round cell areas or areas of malignant fibrous histiocytomas were in most cases referred to as being Grade III.

The histologic reevaluation was performed by NO Berg, Department of Pathology, University Hospital in Lund.

Clinical and morphologic data

From the medical records, available in all cases, pertinent clinical and morphologic data were recorded. The tumor symptoms which were recorded were a lump noticed by the patients and/or pain. Only patients with spontaneous pain at rest as noted in the medical record were registered as having pain, whereas those with paraesthesia or tenderness were not included in this category. Patients in whose record the absence of pain was noted were assigned to a "no pain" category while patients without information concerning pain were placed in a "no data" group. The surgical margins were classified in retrospect from the surgical notes and pathology reports.

Follow-up

The clinical course in all 278 patients diagnosed 1964-78 was analysed by the medical records. A diagnosis of local recurrence was histologically proven in the reoperated patients but was otherwise based on the clinical findings of the attending physician, in later years often supported by cytodiagnosis. The diagnosis of pulmonary metastases was based on radiographic examination. In a majority of the patients these were confirmed by autopsy. The interval between diagnosis and local recurrence and/or death and whether the tumor was the cause of death was recorded. Because the interval between diagnosis and therapy was very short or non-existent, treatment failure, either local recurrence, metastases or death, was calculated from the date of diagnosis. The minimum follow-up time was 3 (3-18) years. Ninety-nine patients died during the follow-up time, 72 because of tumor and 27 because of other diseases. In 195 patients the follow-up was 5 years or more, and in 107, 10 or more years. No patient was lost to follow-up.

Comments

Since 1958 all physicians practicing in Sweden have been required to report all malignant tumors to the Swedish National Cancer Registry. In addition, pathologists and cytologists are required to report every microscopic cancer diagnosis. With this double reporting system it is estimated that close to 100 per cent of all malignant tumor cases reach the Registry *(36)*.

Cytology series

Retrospective series

Included were all 178 patients (cases 1-178) who were referred before surgery, with suspected soft-tissue malignancies, *and* examined by aspiration cytology at the Center from 1972 through 1977 *(28)*.

Prospective series

Included were 109 consecutive patients (cases 201-309) with unbiopsied, suspected soft-tissue malignancies referred to the Center during 1980 and 1981 *(30)*. These patients were all examined by aspiration cytology.

Technique

The aspiration biopsy was performed without anaesthesia. A special holder for disposable plastic syringes was used with needles with an outer diameter of 0.7-0.8 mm (gauge 22-21) and length 50-80 mm. The puncture site, determined by the surgeon, was usually at the vertex of the lesion and the puncture canal was later included in the surgical specimen. The lesion was usually punctured only once but, well inside the tumor, aspirations were frequently obtained from different regions. Perforation of the deep tumor border was avoided. The obtained material was smeared on glass-slides. Some slides were immediately fixed in 95 per cent ethanol and stained with hematoxylin and erythrosin. This staining takes 10 minutes; a preliminary report could be given within 15 minutes. The other slides were air-dried and stained according to the method of May-Grünwald-Giemsa.

Classification of cytodiagnoses

The cytologist had to specify his diagnosis as benign, suspicious for malignancy, malignant or inconclusive (possibly because of insufficient material). In addition a diagnosis of malignancy or suspected malignancy had to be specified as sarcoma, carcinoma or other malignancy. If this was not possible the diagnosis was classified as "unspecified malignancy". In the prospective series the diagnosis of sarcoma was further divided into low- or high-grade malignancy.

The cytologic examination were performed by M Åkerman and I Idvall, Department of Cytology, University Hospital in Lund.

Follow-up

The patients not operated had a clinical follow-up of at least two and one years in the retrospective and prospective series, respectively. At follow-up all lesions were still clinically classified as benign, that is, they had not increased in size or had actually diminished. No scheduled follow-up was then performed but all patients were instructed to contact the Center again if the tumor should increase in size or cause trouble. After an additional 4 and 1 years no malignancy has yet been disclosed in any of the patients. Therefore, the lesions in these patients were considered benign in the analyses and grouped together with the histologically benign tumors.

Reliability

All histologic material from operative specimens and autopsies was reviewed. The cytodiagnosis was then compared to the histological or clinical follow-up diagnosis in the two cytologic series, comprising altogether 287 patients.

Influence of cytodiagnosis on choice of surgical procedure

In the prospective series referred patients were examined at the weekly tumor clinic and a form was completed stating whether the history, symptoms and signs indicated that the tumor was *probably benign* or *probably malignant,* or, when intermediate between these was of *doubtful malignancy.* Four alternative schemes of treatment were then planned. In probably benign tumors:

1. No surgery when the tumor was believed to be benign and of no concern to the patient;

2. Marginal excision when the tumor was believed to be benign and was disturbing the patient;

In tumors of doubtful malignancy and probably malignant tumors:

3. Incisional biopsy and, in some selected cases, marginal excision when a broad excision could not be undertaken without considerable loss of function;

4. Excision with wide or compartmental margins when operation was considered to be possible with little loss of function.

Angiography and computed tomography were planned when considered to be of value for the anatomical planning of an operation.

After this form was completed, aspiration cytology was performed and the influence of the cytodiagnosis on the previously planned examination and treatment was then evaluated in each individual case.

Statistical methods

According to the scale of the variables various of the following techniques were used: t-test, Chi-square-test with Yates' correction when indicated, product moment correlation, multiple regression and analysis of variance. The classification of histologic groups was made by loglinear modelling. When analysing the survival and local recurrence for different categories within a single variable the Lee-Desu test *(37)* was used. In the multivariate analysis Cox's proportional hazard regression test *(38)* was applied in a stepwise manner. Thus all variables could be entered at each step and we did not apply any form of primary selection of variables based on bivariate association. The survival curves were constructed by the lifetable technique. All tests were two-sided.

In the text and Tables the symbols indicate statistical significance according to the following definitions:

*** $P<0.001$
** $P<0.01$
* $P<0.05$
NS $P>0.05$

The statistical analyses were performed by B Gullberg and J Ranstam, Southern Swedish Regional Tumor Registry, University Hospital in Lund.

Observations

Epidemiology

Most reports on soft-tissue tumors are not population-based; there are great differences in the reported location and size of the tumor, histogenesis, malignancy-grade and in patient age.

Lipoma

A *superficial lipoma* was found in 324 patients with a mean age of 47 years and with no significant sex difference (Figure 2). The annual incidence was $0.5/10^3$. The mean (median) size was 3.9 (3.3) cm. Four fifths (260/324) of the tumors were smaller than 5 cm (Figure 3). They were uncommon in the hands and lower extremities (Table 2). Notes on the duration of symptoms were found for 110 patients, being 3 years or more in one third, less than 1 year in one half and less than 3 months in one fifth.

A *deep lipoma* was found in 13 patients with a mean age of 58 years (Table 3). These patients were older ** than those with superficial lipomas. The mean (median) size was 9 (6) cm, i.e. larger *** than that of superficial lipoma (Figure 3).

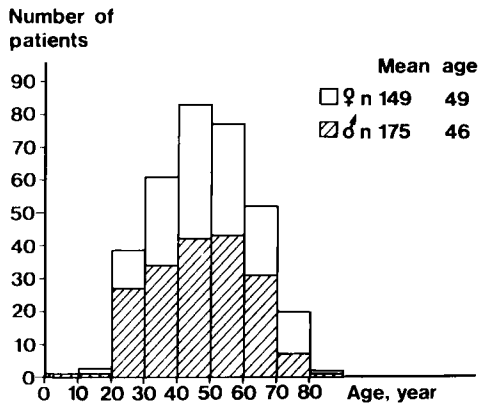


Figure 2 Solitary superficial lipoma. Age and sex.

Table 2 Solitary superficial lipoma. Location.

Location	n	%
Shoulder — upper arm	58	*18*
Lower arm	28	*9*
Hand	4	*1*
Trunk	194	*60*
Hip-buttock-groin	22	*7*
Thigh	10	*3*
Below knee	8	*2*
Total	324	*100*

Table 3 Deep lipoma. Age, sex, location and size.

Age	Sex	Location	Size
12	F	Shoulder	7
63	F	Shoulder	5
74	F	Shoulder	6
59	F	Upper arm	10
72	F	Upper arm	6
76	M	Upper arm	6
45	F	Lower arm	5
59	F	Upper back	6
59	F	Upper back	4
69	M	Upper back	8
50	M	Thigh	20
58	F	Thigh	28
55	F	Lower leg	6

Comments

Lipoma is the most common soft-tissue tumor *(39-41)*. Our observations were similar to those of other series except for: 1) Lipomas have been reported as being more common in females *(42, 43)*; 2) In our series only 3 per cent of the solitary lipomas were located in the thigh. In the only report *(43)* where the thigh was separately recorded the figure was 13 per cent probably because multiple lipomas, which are common in the trunk, arm and thigh *(42-44)*, were included.

Our findings support Kindblom et al *(45)* who stated that deep lipomas are more frequent than previously thought and constitute the most common deep tumor. A deep lipoma which does not infiltrate muscular tissue has no histologic features to differentiate it from a superficial lipoma. This may well be an explanation for the low frequency of deep *versus* superficial lipoma (3/640, 0/102) in earlier reports *(41, 44)*. For the same reason the incidence found in this study is a minimum figure.

The annual *clinical incidence* of lipoma was estimated as twice the number of lipomas sent for histologic examination, or $1/10^3$. This figure was based on an analysis of patients with a clinical diagnosis of lipoma, whether histologically verified or not *(20)*.

Sarcoma

Malignant fibrous histiocytoma, liposarcoma and leiomyosarcoma were the most common *histologic types* comprising about one half of the material. Twenty-three per cent of the tumors were classified as low-grade malignant, 33 per cent as Grade III and 44 per cent as Grade IV (Table 4).

Half of the tumors occurred in patients older than 60 years. They were most common in the seventh decade. From the fifth decade there was a continuous increase in the age specific annual incidence up to $8/10^5$ at 80 years and older. The *annual incidence rate* over all ages were $1.4/10^5$. The mean *age* was, for males, 56 years and for females 60 years. Males (159 patients) predominated *** (Figure 4).

Slightly more than one half of the tumors were *deep* and one third were smaller than 5 cm. The median *size* for superficial tumors was 4 cm and for deep tumors 8 cm *** (Figure 3). More than one third of the tumors were *located* in the thigh (Table 5).

The most common *symptom* was a palpable mass (97 %). One fifth of the patients had pain whereas in one half the absence of pain was recorded (Table 6). The *duration of symptoms* could be determined in 257 patients. It was less than 3 months in one third of the patients and less than a year in three-fourths. Patient's delay could be analysed in 197 cases and was less than 3 months in half of these. In 204 cases the doctor's delay could be analysed and was found to be less than 3 months in 90 per cent.

Table 4 Soft-tissue sarcoma. Histologic type and malignancy-grade.

Histologic type	Malignancy-grade I	II	III	IV	Total	% *Type*	% *Group*
Malignant fibrous histiocytoma	5	7	16	34	62	*22.3*	*22.3*
Liposarcoma							*14.4*
Well differentiated	3				3	*1.1*	
Myxoid		12			12	*4.3*	
Round cell				2	2	*0.7*	
Pleomorphic				6	6	*2.2*	
Mixed			14	3	17	*6.1*	
Leiomyosarcoma	1	2	13	15	31	*11.2*	*11.2*
Neurogenic sarcoma	2	3	9	12	26	*9.4*	*9.4*
Tendosynovial sarcoma							*8.9*
Synovial sarcoma			8	9	17	*6.1*	
Epithelioid sarcoma			2	2	4	*1.4*	
Clear cell sarcoma				4	4	*1.4*	
Angiosarcoma							*6.9*
Hemangiosarcoma NOS				2	2	*0.7*	
Mal hemangioendothelioma		1	2	2	5	*1.8*	
Mal hemangiopericytoma		7	4		11	*4.0*	
Lymphangiosarcoma				1	1	*0.4*	
Fibrosarcoma	2	7	6	1	16	*5.8*	*5.8*
Myxofibrosarcoma	1	7	6	1	15	*5.4*	*5.4*
Rhabdomyosarcoma			2	12	14	*5.1*	*5.1*
Other types							*2.6*
Malignant mesenchymoma	2			1	3	*1.1*	
Soft-tissue osteosarcoma			1	1	2	*0.7*	
Soft-tissue chondrosarcoma			1		1	*0.4*	
Soft-tissue Ewing sarcoma				1	1	*0.4*	
Alveolar soft tissue sarcoma			1		1	*0.4*	
Sarcoma NOS	1	1	6	14	22	*7.9*	*7.9*
Total	17	47	91	123	278		
Percent	*6.1*	*16.9*	*32.7*	*44.2*		*100*	*100*

The types are divided into 11 different *groups* used in the statistical analysis. Values given are number of tumors and percentage of total.

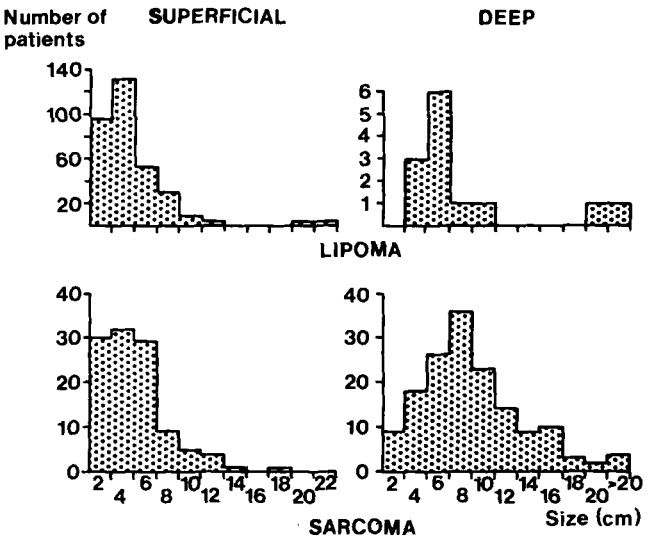


Figure 3 Lipoma and sarcoma. Size related to depth.

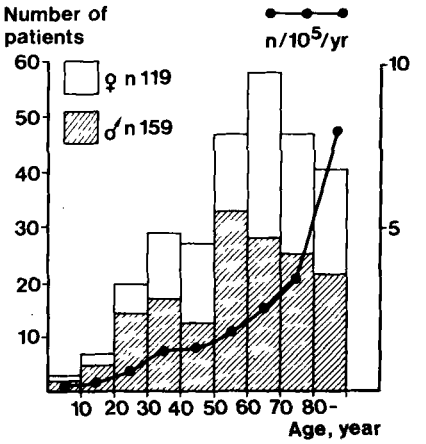


Figure 4 Soft-tissue sarcoma. Age, sex and age-specific incidence.

Comments

The location, the male preponderance and the distribution among the different histologic groups in our study was similar to that in two recent series *(3, 46)*. The incidence and the numbers of cases reaching a peak in the sixth and seventh decade also agreed with earlier reports *(47, 48)*. The increasing age specific incidence was similar to the pattern seen in almost all types of malignant disease. However, the fraction of small-sized and/or superficial tumors was greater than in most other series; certainly a result of patient selection in series reported from referral centers.

The majority of the tumors were painless and accidentally noted by the patients which explains the differences in size between superficial and deep tumors.

Table 5 Soft-tissue sarcoma. Location.

Location	n	%
Shoulder — upper arm	45	*16*
Below elbow	25	*9*
Trunk	45	*16*
Hip — buttock — groin	30	*11*
Thigh	100	*36*
Below knee	33	*12*
Total	278	*100*

Table 6 Soft-tissue sarcoma. Symptoms.

Symptoms	n	%
Mass, no pain at rest	138	*50*
Mass, pain not recorded	77	*28*
Mass, pain at rest	56	*20*
Pain only	7	*2*
Total	278	*100*

Comparison of clinical data and guidelines for referral of patients with soft-tissue tumors

Age, sex and duration of symptoms were of minor value for the clinical differentiation of lipoma and sarcoma. The median size was 4 and 8 cm for superficial and deep sarcomas respectively. These figures were about the same as those found for lipomas. Obviously a certain tumor volume forces the patient to see a doctor. The type of tumor, sarcoma or lipoma, seems to be less important. Tumor size related to tumor depth was thus of no help in differentiation. Considering only tumor size, irrespective of tumor location and depth, the ratio of lipoma to sarcoma was 150/1 for tumors smaller than 5 cm and 20/1 for tumors 5 cm or larger. For tumors larger than 10 cm, this ratio was 6/1. In the thigh, irrespective of size and depth, the ratio of lipoma to sarcoma was 6/1. Among deep tumors, irrespective of size and location, the ratio of lipoma to sarcoma was 4/1. These calculations were based on an estimated annual *clinical incidence* for lipoma of $1/10^3$ *(20)*. It may be concluded that in the clinical differential diagnosis between a

lipoma and sarcoma, a tumor 5 cm or larger, a tumor in the thigh or a deep tumor, is relatively more likely to be a sarcoma.

An analysis of clinical data for benign soft-tissue tumors in general (considering only depth and size; the rareness of lipomas in the thigh being not shared by other benign soft-tissue tumors *(41)*) can be made with the following assumptions:

1) The annual incidence of histologically diagnosed lipoma is $0.5/10^3$ (p 21)
2) Lipoma accounts for 1/3 of all benign soft-tissue tumors *(39-41)*
3) The clinical incidence of benign soft-tissue tumors is about double that of those histologically verified
4) One per cent of all histologically diagnosed benign soft-tissue lesions are deep-seated and 5 per cent measure 5 cm or more *(41)*

This translates into an annual clinical incidence of $\sim 300/10^5$ benign soft-tissue tumors of which ~ 20 are 5 cm of larger and/or deep seated. A policy of recommending referral of all patients with deep-seated tumors or tumors 5 cm or larger before surgery in our population (1.3 million inhabitants) would imply an annual referral of 250 patients with benign lesions. At the same time ~ 15 sarcomas would be referred before surgery and the remaining ~ 3 sarcomas, smaller than 5 cm and superficial (Table 7) will probably be removed with a marginal excision. However, as shown below (p 50) superficially located sarcomas without extension to the deep fascia form a favourable subset as regards surgery; local recurrence is unusual after wide reexcision.

It may thus be argued that all superficial tumors can be primarily excised by a marginal excision; a histological diagnosis of sarcoma can then be followed by a wide reexcision. However, for an unexperienced examiner is it not always easy to

Table 7 Soft-tissue sarcoma. Size related to depth.

	Size			
	<5		≥5	
	n	%	n	%
Subcutaneous	43	*16*	33	*12*
Subcutaneous, attached to deep fascia	17	*6*	18	*7*
Deep	28	*11*	128	*48*
Total	88	*33*	179	*67*

Epidemiology series (n 278), no data on depth in 11 patients.

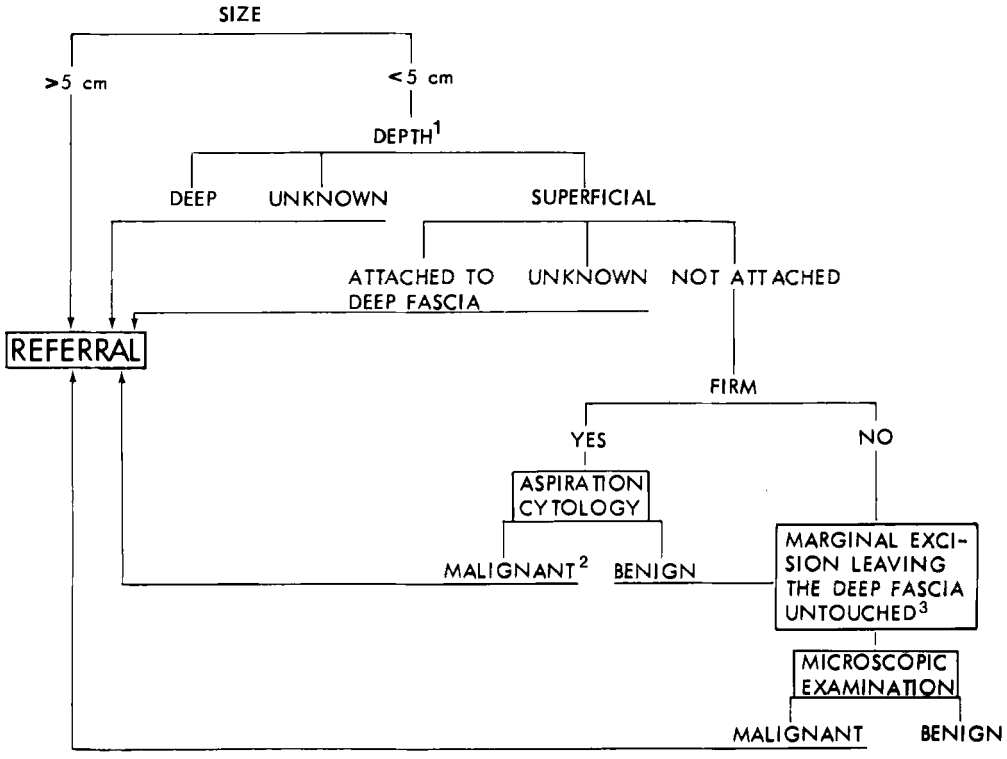


Figure 5 Guidelines for the management of soft-tissue tumors outside the Center.

[1] A *superficial* tumor is mobile and easily delineated. On muscular contraction its longitudinal position does not change and it becomes more prominent. If somewhat less movable on muscular contraction it is *attached* to the deep fascia. A *deep* tumor is not well delineated and becomes even less so on muscle contraction (except for intramuscular lipoma) which makes it much less movable and sometimes changes its position. All tumors fixed to the skeleton are deep but most deep tumors are not fixed.

[2] Includes inconclusive cytodiagnosis.

[3] Superficial tumors which by history, clinical findings and aspiration biopsy are diagnosed as benign can be left without surgery.

determine tumor depth. Actually, 5 cm is safety border as regards deep-seated sarcomas; four fifths of these are larger than 5 cm (Table 7).

The palpable findings as regards the firmness of a tumor could not be evaluated in retrospect. In a Swedish series on soft-tissue sarcoma *(49)* near one half were reported as soft or fairly firm: a soft tumor does not exclude a sarcoma. In contrast, a firm tumor speaks in favor of a sarcoma.

A decision tree for the management of patients with soft-tissue tumors outside the Center based on the findings in this study is shown in Figure 5.

Comments

When the 10 sarcoma patients who were referred after a marginal excision during 1980-81 (p 60) were analysed, it was found that only 1 tumor was superficial and smaller than 5 cm while 8 were deep and 1 was subcutaneous but larger than 5 cm. At the same time about 95 patients whose tumors turned out to be benign were referred. Nine tenths of these patients had deep tumors or tumors larger than 5 cm. An additional annual referral of 200 patients, according to the calculations above, would mean that an additional 4 patients with deep sarcoma would have been referred before marginal excision. This figure compares favourably to those of other screening procedures such as gastroscopy *(50)* and breast cytology. Out of 1360 breast lesions examined by aspiration cytology in Lund, 1982, a carcinoma was diagnosed in 93 (unpublished observations). The desired increase, thus calculated, of patients referred would double the number actually seen last year. The next step in the screening of these patients in the Center is based on history, clinical examination *and* aspiration cytology.

If only patients with tumors considered deep were referred the increase would be considerably less. However, by including *both* depth and size in the screening system a safety margin is built in; the effect of misjudged tumor depth is minimized. In addition, most benign tumors larger than 5 cm are lipomas *(41)*. A cytodiagnosis of lipoma from aspirations performed at the Center in recent years has a high specificity and sensitivity (unpublished observations). Thus, further examinations are not indicated for the majority of these patients.

Aspiration cytology

The diagnostic value of aspiration cytology for various types of carcinoma is well established. However, there are only a few reports on the use of this method in soft-tissue tumors and the series reported are small *(29, 31, 32, 51-53)*.

Reliability, retrospective and prospective series

The final diagnosis was *sarcoma* in 46 patients, *other malignancies* in 11 patients (all malignancies histologically verified) and a *benign lesion* in 230/287 patients (140 histological and 90 clinical follow-up diagnoses). A cytodiagnosis was formulated in 92 per cent (265/287). There were 8 false malignant and 7 false benign cytodiagnoses (Table 8).

Table 8 Correlation between cytodiagnosis and final diagnosis.

Final diagnosis	Cytodiagnosis					Total
	Sarcoma	Other mal	Mal NOS	Benign	Insufficient material or inconclusive diagnosis	
Histologic diagnosis						
Sarcoma	37	—	—	6	3	46
Other malignancy	1	5	3	1 [b]	1	11
Benign lesion	5	—	2	124	9	140
Clinical diagnosis, benign at follow-up	1	—	— [a]	80	9	90
Total	44	5	5	211	22	287

Retrospective and prospective series.

[a] Falsely malignant cytodiagnosis, (n 8) see Table 9.
[b] Falsely benign cytodiagnosis, (n 7) see Table 10.

In the *sarcoma* group 37/46 had a correct cytodiagnosis, 6 cases were erroneously diagnosed as benign tumors and in 3 cases the material was insufficient for diagnosis.

The *other malignant tumors* comprised 7 carcinomas, all but 1 metastatic, and 4 malignant lymphomas. In 5 patients the cytodiagnosis was carcinoma or lymphoma and in 3 patients is was "unspecified malignancy". One adenocarcinoma was misdiagnosed as a sarcoma, 1 pulmonary oat-cell carcinoma was misinterpreted as granulation tissue and from 1 malignant lymphoma only necrotic material was aspirated.

Of the 230 *benign lesions,* 204 (89 %) had a correct cytodiagnosis, 8 (3 %) had a falsely malignant cytodiagnosis and in 18 cases (8 %) the material was insufficient for diagnosis (Table 8).

When the 15 *false cytologic diagnoses* were analysed, difficulties in cytodiagnosis as regards malignancy were evident for certain types of tumors, e.g. neurogenic tumors, aggressive fibromatosis and some fibrous sarcomas (Table 9 and 10) *(28).* In case 55 (Table 9) the aspirate consisted of young, large fibroblasts with loose chromatin, swollen nuclei and also bizarre forms of nucleoli, misinterpreted as

Table 9 Falsely malignant cytodiagnoses.

Case no	Cytology	Histology
55	Polymorphic cell sarcoma	Non-operated. Tumor disappeared
62	Sarcoma	Aggressive fibromatosis
76	Difficult to interpret. Tumor with bleeding — malignancy?	Intramuscular hemangioma
120	Atypia in fat cells — suspicion of malignancy	Lipoma
130	Highly differentiated liposarcoma	Lipoma
138	Cellular mesenchymal tumor. Malignancy cannot be excluded	Neurinoma
223	Suspected malignancy. Highly differentiated liposarcoma?	Lipoma with nodular osteocartilaginous metaplasia
286	Low-grade sarcoma	Intramuscular hemangioma

Retrospective and prospective series.

sarcoma cells. Two intramuscular hemangiomas and 3 lipomas (cases 76, 120, 130, 223, 286, Table 9) were cytologically diagnosed as low grade sarcomas. On reevaluation of the cytologic material all were readily classified as benign tumors and it was difficult to understand the previous misinterpretations. In the 11 malignant tumors other than soft-tissue sarcomas there was one falsely benign cytodiagnosis (Case 185, Table 10). The patient had pulmonary tuberculosis with a gravity abscess in the right groin. Aspiration biopsy and a later incisional biopsy showed only granulation tissue. The patient died later and autopsy showed also a bronchial carcinoma of oat-cell type with metastasis to the right pelvis.

In 22 cases, 3 of them sarcomas and one malignant lymphoma, the cellular material was *insufficient* for diagnosis (20 cases) or the diagnosis was *inconclusive* in spite of sufficient material (2 cases). On reevaluation it was obvious that the reasons that the cytologic material was insufficient in the malignant cases was the presence of necrosis and cystic changes in the tumors. In 3 fibrous lesions it was difficult to aspirate sufficient material. One benign hemangiopericytoma and one muscle rupture was diagnosed as a mesenchymal tumor of uncertain malignancy.

The probability of a benign cytodiagnosis being correct was 0.97 (204/211), of a malignant cytodiagnosis being correct 0.85 (46/54) and for a cytodiagnostic report of sarcoma the probability of correct diagnosis was 0.84 (37/44) (Table 8).

Table 10 Falsely benign cytodiagnoses.

Case no	Cytology	Histology[1]
150	Cellular but probably benign neurofibroma	Neurofibroma with progress into sarcoma (III)
153	Cellular mesenchymal tumor, probably benign	Sarcoma NOS (III)
172	Granulation tissue with reactively changed cells	Myxofibrosarcoma (IV)
173	Aggressive fibromatosis?	Malignant fibrous histiocytoma (II)
185	Granulation tissue	Metastasis of pulmonary oat-cell carcinoma
208	Non-specific inflammation	Epithelioid sarcoma (IV)
308	Benign mesenchymal tumor	Haemangiopericytoma (I)

Retrospective and prospective series.

[1] Grade of malignancy in parentheses.

The histologic type in case 153, 172 and 173 is reclassified compared to an earlier report *(28)*.

Comments

The scheduled clinical follow-up time of the cases not operated, was rather short. However, none of the cases in the retrospective series (1972-77) had a sarcoma reported to the Regional Cancer Registry up to and including 1981. As regards the prospective series (1981) it is highly unlikely that a sarcoma diagnosed in the years 1982-83 in a patient with a lesion earlier examined at the Center and considered benign should not have been reported to our group. Thus, the benign diagnosis in these patients appears reliable.

Influence of cytodiagnosis on choice of surgical procedure, prospective series

A clinical diagnosis of a *probably malignant tumor* was made in 42 patients. A sarcoma was histologically diagnosed in 9 of these patients, other malignancies in 3 and benign lesions in 24 patients. Six patients had no surgery. A diagnosis of *doubtful malignancy* was assigned clinically to 31 tumors, 2 of which had a histologic

Table 11 Changes in choice of surgical margin following aspiration cytology.

Clinical diagnosis by the Center	Planned	Incisional				Marginal	Wide			Compartmental		Total
	Performed	No	M	W	C	No	No	I	M	M	W	
Probably malignant (42)		2	3	1	1		3	1	4	1	4	20
Doubtful malignancy (31)							3		2		2	7
Probably benign (36)						6						6

Prospective series.

No = no surgery, M = marginal, W = wide, C = compartmental

diagnosis of sarcoma and 19 of a benign tumor. Ten patients had no surgery. *Probably benign* tumors were found in 36 patients, 11 of which were histologically verified and 25 were left without surgery.

The cytodiagnosis changed the surgery planned on clinical findings in 20/42 of the "probably malignant" tumors, in 7/31 of the lesions with "doubtful malignancy" and in 6/36 tumors which were clinically considered"probably benign" (Table 11). Incisional biopsy was omitted in 3 sarcomas. The most common tumors for which the cytodiagnosis reduced the extent of the planned surgery were deep lipomas (6 cases) and intramuscular myxomas (6 cases) *(30, 32)*. Planned computed tomography and/or angiography was avoided in 14 patients.

The cytodiagnosis was falsely benign in 2 patients (cases 208, 308), falsely malignant in 2 (cases 223, 286) (Table 9 and 10) and inconclusive in 7 patients. In case 208 with an ill defined deep-seated epithelioid sarcoma in the lower arm, incisional biopsy was planned and considered necessary even after the falsely benign cytodiagnosis. One falsely benign cytodiagnosis (hemangioma) of an intramuscular hemangiopericytoma, grade I, did not change the planned wide excision in case 308.

In case 223 with a deep lipoma in the axilla the cytodiagnosis could not exclude a low grade liposarcoma. The planned diagnostic marginal excision was performed. Case no 286 was a 33-year old man with a deep tumor in the upper arm unchanged for several years but growing considerably the last 6 months. Clinical and angiographic examinations of a 15 x 10 cm tumor were consistent with a sarcoma. The cytodiagnosis was low-grade sarcoma and a wide excision including the ulnar nerve was performed. The histologic diagnosis was a benign infiltrating intramuscular hemangioma.

Comments

Recent surveys on soft-tissue lesions consider aspiration cytology to be of little value, concluding that "in general ... all of these conditions require surgical treatment" *(12)* or "aspiration biopsy has virtually no role in the diagnosis" *(11)*. The objection is that it "seldom yields tissue for full pathologic evaluation" *(12)*. However, histogenetic classification is of minor interest for the surgical planning. Pack *(54)* when reporting the value of aspiration cytology for soft-tissue lesions stated 30 years ago: "The critics of aspiration biopsy are too specific in their demands of the method. The procedure is successful if it permits the differential diagnosis between inflammatory and neoplastic tissues, or, in the case of tumor, between the benign and the malignant variety."

In a 1982 Current Concepts Review, Simon *(8)* stated: "The clinical evaluation of primary soft-tissue tumor, unlike that of bone tumor, is notoriously inaccurate." This statement is substantiated by our observations. Aspiration cytology should be used as an adjunct to clinical evaluation and such further examinations as angiography and computed tomography to assist the surgeon in the probability analysis of sarcoma versus benign lesions. This means that not only sarcoma patients can benefit by surgery without prior open biopsy (p 51) but even other patients can be safely assigned to the benign group without resorting to surgery. This has been important when evaluating the increasing number of patients referred to the Center because of suspected malignancy in lesions subsequently found to be benign.

Stener reports a high reliability without prior biopsy when he, by history and clinical and radiographic examinations, selects patients suitable for treatment according to the surgical concept introduced by him, i.e., a primary surgical procedure with margins adequate for a sarcoma (personal communication). This is based on a considerable experience with soft-tissue lesions but it should also be noted that in the report on Stener's series *(3)* nine tenths of the sarcomas were deep-seated and also nine tenths were larger than 5 cm. This is not the case for sarcomas in general and can only be explained by referral selection. There is a high probability that lesions of that size and location are sarcomas.

The risk of distant tumor spread because of fine needle biopsy seems to be neglible *(55-56)*. In the multivariate analysis of this series (p 42) the use of aspiration cytology was of no prognostic importance confirming Markhede et al *(3)*.

Treatment and clinical course in soft-tissue sarcoma

There are only a few reports on the treatment and clinical course in population-based series of patients with soft-tissue sarcomas *(2, 4, 46)*. Of the several variables which may influence the clinical course there is consensus about the prognostic importance of histologic malignancy-grade, surgical margin and the occurrence of metastases. Malignancy-grade and type of surgical procedure are, however, the most difficult to define of all the variables discussed as prognostic predictors and there are considerable differences in the reported rates of local recurrence and metastasis. The implications of a certain malignancy-grade and type of surgical procedure can be estimated by the survival and local recurrence rate, respectively. For these reasons the clinical course related to the type of surgical margin and the malignancy-grade was analysed in the 278 patients with a soft-tissue sarcoma diagnosed in southern Sweden 1964-1978 (Table I). The clinical course in patients with metastases at the time of diagnosis of the primary tumor and in patients not treated by surgery was separately analysed.

Patients with metastases at the time of diagnosis and patients not treated by surgery

At the time of diagnosis of the primary tumor metastases were found in 19 patients all of whom died from their tumors. The median survival time was 4 (1-22) months. The primary tumor was for various reasons not excised in 22 other patients. Five of these patients died from intercurrent disease within 6 months after the diagnosis of the sarcoma. Another 15 died due to the tumor, with a median survival time of 12 months. One patient is alive with disease and one is alive with no evidence of disease after partial excision and radiation therapy 12 years ago.

These 19 patients with metastases and 22 not treated by surgery were excluded from the further analyses which therefore were based on 237 patients.

Patients treated by surgery and without metastases at the time of diagnosis

Treatment

The *final surgical margin* was marginal in 111 patients, wide in 94 and compartmental in 32 patients. Twenty patients had a major amputation and 3 a minor. One surgical procedure for the primary tumor was performed in 116 patients, two in 98 patients and 3 or more in 23 patients. The *first local recurrence* was treated by a marginal excision in 36/72 patients, and by a broad excision in 10 patients. Twenty-six patients had no surgery; 5 because the recurrence was judged inoper-

able and 21 because metastases were found prior to or concurrently with the local recurrence. *Pulmonary metastases* were treated by surgery in 12/62 patients. Eight of these patients died in new pulmonary metastases. Two are apparently disease-free, 6 and 8 years after surgery, respectively, and 2 are living with new pulmonary metastases.

Adjuvant *chemotherapy* was given in 12 patients, 3 of whom died from tumor. *Radiotherapy* was given for the primary tumor in 8 patients following a marginal excision with 1 local recurrence and in 7 patients following a broad excision with 3 recurrences. Chemo- and/or radiotherapy was given in an additional 35 patients. Thirteen of these patients had generalized disease and all died due to tumor.

Comments

The cytostatic agents used were mainly cyclophosphamide and doxorubicin (Adriamycin) given as single drugs and CYVADIC (cyclophosphamide, vincristine, doxorubicin and dacarbazine) as combination regimen. There was a wide range in the total amount given and many patients did not complete the planned treatment because of side-effects. Likewise, the radiotherapy technique used, the number of fractions and the target absorbed dose varied considerably from case to case.

Local recurrence, metastases and tumor-related death

Local recurrence was diagnosed in 72/237 patients (30 per cent); 50 had 1 recurrence, 16 had 2 and 6 patients had 3 or more local recurrence. In 23 patients distant spread was diagnosed before or at the same time as the local recurrence. The time interval to the first local recurrence decreased with increasing malignancy-grade (Table 12). One year after diagnosis half of the recurrences in

Table 12 Time interval for treatment failure related to malignancy-grade.

Grade	N	Time interval, median (range) in months					
		Local recurrence	n	Metastasis	n	Death	n
I-II	59	18 (4- 71)	13	27 (14- 30)	4	30 (24- 87)	5
III	80	13 (4-120)	24	22 (5-120)	20	28 (9-130)	18
IV	98	6 (1- 48)	35	12 (1-120)	52	19 (1-132)	49
Total	237		72		76		72

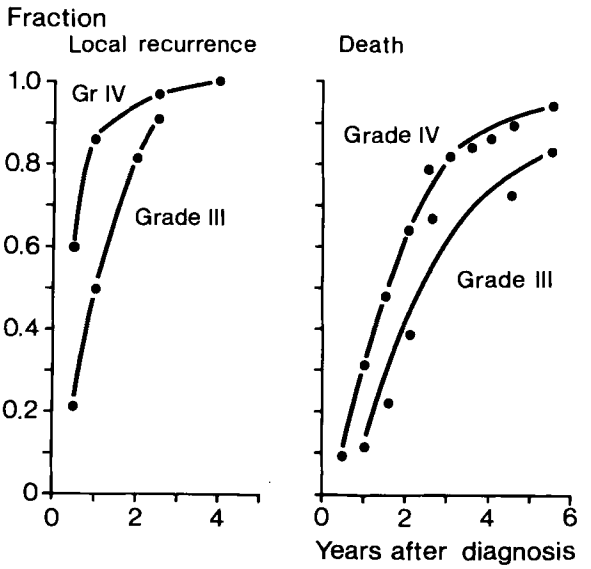


Figure 6 Time to local recurrence and tumor-related death among patients having respective outcome. Grades III and IV tumors

patients with Grade III sarcoma had occurred, compared to almost nine tenths in those with Grade IV sarcoma (Figure 6). For all malignancy grades the vast majority (68/72) of the recurrences had occurred within 30 months.

Metastases, most often pulmonary, were diagnosed in 76/237 (32 per cent) patients. None of the patients with Grade I tumors developed metastases. Fifty-six patients with pulmonary metastases died because of tumor, 1 died of other disease, 3 are still alive with pulmonary metastases and 2 are disease-free after thoracic surgery. There were 13 patients in whom metastases were exclusively extra pulmonary and all of these died. The time interval to metastases decreased with increasing malignancy-grade (Table 12). One year after diagnosis one of every five of the metastases in patients with Grade III tumors had occurred compared to three fifths for those with Grade IV tumors. This difference decreased with time till at 4 years nine tenths of the metastases had occurred in all malignancy grades. The median survival time after the diagnosis of metastases was 5 months.

Tumor-related death occurred in 72 patients, in all but 3 because of metastases (Table 12). Slightly more than four fifths of the deaths among Grade IV-tumor patients had occurred by 3 years compared to about two thirds of those who died with Grade III-tumors (Figure 6).

Comments

The correlation found between malignancy-grade and treatment failure and also between malignancy-grade and the time interval to treatment failure implies a

Table 13 Local recurrence related to surgical margin and malignancy-grade.

Surgical margin	Malignancy-grade			Total
	I-II		III-IV	
Marginal	9/31 (.29)	•	46/80 (.58)	55/111 (.50)
	NS		***	***
Broad	4/28 (.14)	*NS*	13/98 (.13)	17/126 (.13)
Total	13/59 (.22)	*NS*	59/178 (.33)	72/237 (.30)

3-18 year follow-up. No patient censored.

biological difference between Grades I-II and III and IV tumors. In the multivariate analysis (p 42) malignancy-grades III and IV were found to be the strongest predictors of survival.

To evaluate the local recurrence rate following surgery alone a follow-up time of 2.5 years is sufficient when all but one tenth of local recurrences were manifest. With regard to survival, 6 years of follow-up is required; at that time almost nine tenths of the tumor-related deaths had occurred. When evaluating the effect of adjuvant therapy this time period should probably be extended *(10)*.

Local recurrence related to surgical margin and malignancy-grade

The local recurrence risk following a marginal, a wide and a compartmental excision was .50, .17 and .03 respectively. The difference between a marginal excision and the more extensive procedures was significant *** in Grades III and IV tumors but not in Grade I and II tumors (Table 13). The difference between a wide and a compartmental excision was not significant ($P = 0.09$) (Table 14).

Table 14 Local recurrence related to surgical and malignancy-grade.

Surgical margin	Malignancy-grade			Total
	I-II		III-IV	
Wide	4/24 (.17)	*NS*	12/70 (.17)	16/ 94 (.17)
	NS		*NS*	*NS*
Compartmental	0/ 4 (.0)	*NS*	1/28 (.04)	1/ 32 (.03)
Total	4/28 (.14)	*NS*	13/98 (.13)	17/126 (.13)

3-18 year follow-up. No patient censored.

Comments

One half of the tumors treated by a marginal excision recurred locally. Considerably higher figures, in some series close to 100 per cent, have been presented *(9, 57)*, probably as a result of "referral selection". Our wide excision is probably comparable to procedures termed by others as *en bloc* wide soft part resection *(13)*, wide local excision *(58)*, wide monobloc soft part resection *(12)*, wide *en bloc* resection *(59)*, radical *en bloc* excision *(60)* and wide soft-tissue resection *(61)*. All these procedures had local recurrence rates which were comparable to those found in our series. The low local recurrence rate following compartmental excision is similar to that reported by Enneking et al *(7, 10)* for tumors excised with a "radical margin".

The histologic malignancy-grade has been shown to influence the local recurrence rate *(3, 62)*. We observed a significantly lower local recurrence rate following a marginal excision of low-grade compared to high-grade tumors by bivariate analysis. A difference in the local recurrence rate was not found when comparing a wide or a compartmental excision relative to malignancy-grade. In addition, by multivariate analysis malignancy-grade did not emerge as a prognostic variable with regard to the local recurrence risk (p 43).

Death related to malignancy-grade and local recurrence

There was a positive correlation between increasing mortality related to malignancy-grade and local recurrence (Table 15). Only 5 of the 59 patients with Grades I or II tumors died because of tumor. Only 1 patient with a Grade I tumor died because of tumor; a local recurrence invaded the cervical spinal cord. Three patients with Grade II tumors died because of pulmonary metastases (2 of these

Table 15 Tumor-related death related to malignancy-grade and local recurrence.

Grade	No local recurrence		Local recurrence	Total
I-II	1/ 46 (0.02)	**	4/13 (0.3)	5/ 59 (0.1)
	NS		*NS*	*
III	6/ 56 (0.1)	***	12/24 (0.5)	18/ 80 (0.2)
	*		*	***
IV	20/ 63 (0.3)	***	29/35 (0.8)	49/ 98 (0.5)
Total	25/165 (0.15)	***	45/72 (0.6)	72/237 (0.3)

3-18 year follow-up. No patient censored.

also had local recurrence) and 1 patient died because of multiple soft-tissue metastases and local recurrence. The well known prognostic importance of malignancy-grade and local recurrence as shown bivariately is quantified in the multivariate analysis (p 46).

Death related to type of surgical procedure for local recurrence

Surgery was performed for 46/72 first local recurrences. A *broad* excision was performed in 10 patients, none of them had a second recurrence. One patient died in metastatic disease, one from intercurrent disease and 8 are alive with no evidence of disease. A *marginal* excision was performed in 36 patients of whom 2 had metastatic disease diagnosed before surgery and are dead. Ten are alive while 2 died from intercurrent disease, all without evidence of tumor disease. Twenty-two patients had a second local recurrence and 16 of these died because of the sarcoma. Local recurrence was *not treated* by surgery in 26 patients of whom 21 had distant spread diagnosed before or at the same time as the local recurrence.

Comments

In cases of local recurrence with no signs of metastasis a more aggressive surgical approach than was taken in this series is clearly indicated. Of 10 patients whose first local recurrence was treated by a wide or compartmental excision none had a second local recurrence and only one developed metastatic disease. It may be that this good result can be an effect of patient selection as cases with more aggressive tumor may be found to have metastases at the same time as they have a local recurrence.

Prognostic variables, multivariate analysis

The prognosis in soft-tissue sarcoma may be influenced by several variables. To identify these and to determine their relative importance, multivariate statistical analysis is necessary *(3, 4, 63)*. Because of the uniformly dismal prognosis demonstrated above (p 35) in patients with metastases at the time of diagnosis and in patients not treated by surgery, these 41 patients were excluded as were also 8 patients with no data on tumor compartmentalisation. The analysis was then based on 229 patients with surgically treated (marginal, wide or compartmental excisions) sarcomas and without signs of metastases at the time of diagnosis (Table 16 and 17).

Table 16 Variables studied by multivariate statistical analysis.

Variable	Definition	No of patients
Histologic group	11 groups[1]	229
Malignancy-grade	4 Grades	229
Patients age at diagnosis	Years	229
Sex	Male	135
	Female	94
Depth	Superficial	104
	Deep	125
Size	Geometric	229
Location	Shoulder — upper arm	38
	Below elbow	22
	Trunk	35
	Hip — buttock — groin	18
	Thigh	88
	Below knee	28
Compartmentalisation	Intracompartmental	132
	Extracompartmental	97
Presenting symptoms	Pain recorded	47
	No pain	182
Duration of symptoms	Months	229
Aspiration cytology	Performed	69
Number of surgical procedures for primary tumor[2]	One	110
	More than one	119
Final surgery for primary tumor[2]	Marginal	105
	Wide	93
	Compartmental	31
Radiotherapy	Yes	50
Chemotherapy	Yes	33

[1] As in Table 4.
[2] Does not include surgery for local recurrence.

Table 17 Histologic group and malignancy-grade in patients studied by multivariate statistical analysis.

Histologic group	Malignancy-grade I	II	III	IV	Total	%
Malignant fibrous histiocytoma	5	5	14	30	54	*24*
Liposarcoma	3	10	14	8	35	*15*
Leiomyosarcoma	1	2	12	12	27	*12*
Neurogenic sarcoma	2	3	9	10	24	*10*
Tendosynovial sarcoma			8	12	20	*9*
Angiosarcoma		8	3	3	14	*6*
Fibrosarcoma	2	7	5	1	15	*7*
Myxofibrosarcoma	1	7	6	1	15	*7*
Rhabdomyosarcoma			2	6	8	*3*
Other types	2		2	3	7	*3*
Sarcoma NOS		1	3	6	10	*4*
Total	16	43	78	92	229	*100*
Percentage	*7*	*18*	*34*	*41*		

Survival

The significant negative prognostic variables in order of decreasing relative risk (RR) were *malignancy-grade* IV and III, the occurrence of *pain, male sex, age, tumor-size, marginal surgery* and *extracompartmental tumor site* (Table 18). No other clinical or morphologic variable could be proven to influence the survival.

Table 18 Negative prognostic variables for survival.

Negative prognostic variable	Relative risk	Coefficient[1]	P-value	Occurrence[2] *(%)*
Malignancy-grade IV	5.94	1.78	0.0001	*41*
" " III	2.73	1.00	0.0314	*34*
Pain at rest	2.57	0.94	0.0008	*21*
Male sex	2.56	0.94	0.0008	*59*
Age over 50 years	2.36	0.86	0.0021	*64*
Size over 6 cm	2.33	0.84	0.0016	*43*
Marginal excision	2.16	0.77	0.0029	*46*
Extracompartmental site	1.94	0.66	0.0097	*42*

[1] Coefficient of the survival function, see p 46.
[2] Occurrence of the variables in the total material.

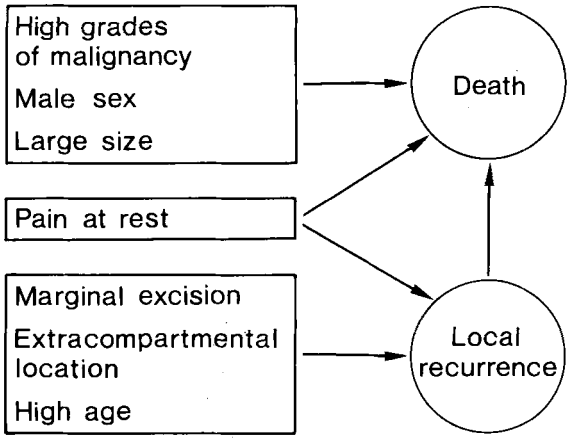


Figure 7 Relationship of prognostic variables and outcome.

Local recurrence

When the occurrence of *local recurrence* was included among the significant variables it was found to have a stronger negative influence on survival than any of the other variables (RR = 8.3, $P = 0.0001$).

The variables which significantly increased the probability of local recurrence were: *marginal excision* (RR 4.3, $P = 0.0001$), *extracompartmental* tumor site (RR 1.9, $P = 0.007$), *age* above 50 years (RR 1.9, $P = 0.02$), and the occurrence of *pain* (RR 1.9, $P = 0.03$). The analysis indicated that patients treated by compartmental excision had a tendency to have fewer recurrences when compared to those treated by wide excision but the difference could not be proven statistically significant when multivariately analysed.

When comparing the prognostic variables related to local recurrence and survival, marginal surgery, extracompartmental tumor site and age were found to influence survival *only* via local recurrence. The occurrence of pain was the only factor with genuine importance for both survival and local recurrence whereas malignancy grade, sex and tumor-size had a direct influence on survival, irrespective of local recurrence (Figure 7).

As the majority of the patients with metastases died and almost all tumor-related deaths were due to metastases, no separate analysis regarding prognostic varibles for metastasis was performed.

Comments

Multivariate analysis could not prove the *histologic type* to be prognostic when adjustment was made for malignancy-grade; a finding supported by data from previous studies *(3, 10, 59, 62)*. An especially low survival rate reported for certain histologic types i.e. neurogenic sarcoma, tendosynovial sarcoma and rhabdomyo-

sarcoma *(13, 14, 57)* may be related to the preponderance of high-grade lesions among these tumors. Thus, in a multivariate analysis by Markhede et al *(3)* correlations between histologic type and survival could be explained by the histological malignancy-grade. In two large Swedish series, using the same system for grading of malignancy the 5-year survival was 45 per cent in Grade IV myxofibrosarcomas *(4)* compared to 10 per cent for Grade IV liposarcomas *(2)*. Although these series were not subjected to a common multivariate analysis, the results may indicate that the histologic type, as well as the malignancy-grade, could have prognostic value.

The importance of *local control* of the primary tumor has been emphasized in most reports on soft-tissue sarcoma. In this series it was shown to be the most important factor influencing survival. A more active treatment in the patients with local recurrence would have diminished the magnitude of the relative risk associated with local recurrence. However, it should be noted that 23 of 72 patients had metastases when the local recurrence appeared.

Tumor compartmentalisation (extra/intra) and *malignancy-grade* (low/high) were combined in a surgical staging system introduced by Enneking et al *(6)*. In a retrospective analysis they found a significant difference in survival rates for high-grade extracompartmental tumors compared to high-grade intracompartmental tumors whereas no difference related to compartmentalisation could be found for the low-grade tumors. In our series extracompartmental tumors also had a worse prognosis; this was related to a higher local recurrence rate. Lesions situated outside a compartment grow in ill-defined spaces without natural proximal and distal tumor barriers such as preformed fibrous septae. There is thus a greater risk of microscopic tumor growth at a distance from the main lesion. In another report Enneking et al *(7)* demonstrated a local recurrence rate of 20 per cent for extracompartmental tumors, compared to 5 per cent for intracompartmental tumors.

Several authors have demonstrated a correlation between increasing *age* and mortality *(2, 58, 64)* as was observed here also. It was surprising that this effect was mediated via local recurrence, and we have no clear-cut explanation for our findings. It is unlikely that the classification of surgical margins should be biased by age. We have found two reports concerning the relationship between age and local recurrence rate. Both Markhede et al *(3)* and Merck et al *(4)* reported an increase with age of the local recurrence rate. However, when adjusted for the type of surgery this correlation disappeared in the former series whereas in the latter it remained even after malignancy-grade and type of surgical procedure were allowed for.

Tumor size has most often been dichotomized at 5 cm, smaller tumors have been shown to carry a better prognosis in several series *(2, 4, 13, 14, 34, 46, 61, 63-65)*.

When geometric size was used as a continuous variable, increasing size was correlated to an increasingly poor prognosis. When size was dichotomized a 6 cm largest diameter gave maximal separation. The influence of size on survival was not a function of a higher rate of local recurrence. Size did not influence the rate of local recurrence when the surgical margin was taken into account.

The occurrence of *pain* in soft-tissue sarcoma has not been related to prognosis. One fifth of our patients had pain while in one half of the patients the occurrence of pain was denied in the medical records. For the remaining patients there were no data. When these three groups were analysed for survival, the group with no data occupied an intermediate position with a significantly different survival rate compared to the other two groups. In the further analysis the group with recorded absence of pain was combined with the group with no data. Thus, the importance of pain is certainly not overestimated. This was also confirmed when the analysis was made with the no data patients omitted. The occurrence of pain was positively correlated with increasing age, size, depth and malignancy grade (p 57). However, when these variables were allowed for, pain was still of prognostic importance for survival, both directly and via local recurrence. Pain may thus be a clinical indicator of high malignancy with regard to both metastasis and local recurrence. The pain may be caused by increased intratumoral pressure or the release of chemical substances from necrotic areas in rapidly growing tumors. Pain is common also in highly malignant bone tumors such as Ewing sarcoma and osteosarcoma.

A tendency toward a worse prognosis for *males* with soft-tissue sarcomas has been demonstrated in one series *(64)*. It has been reported in osteosarcoma *(66)* and is well known for some other malignancies e.g. malignant melanoma *(67)* and childhood leukemia *(68)*. Our findings indicate that sex should be included in a staging-system for soft-tissue sarcoma.

Like Markhede et al *(3)* we found that *tumor location* and *depth* did not influence survival. Contrasting opinions have been expressed by several authors *(57, 58, 60, 64)* who report a better prognosis for distal and superficial tumors. However, there are significant correlations between both malignancy grade and location related to size and depth, as well as a strong correlation between size and depth (p 57). Thus, the apparent discrepancies in this regard may be explained by these other factors not having been taken into account in previous studies. If size was omitted in our analysis, deep-seated tumors carried a worse prognosis. However, this was related to their larger size.

Prediction of survival

To predict the survival for an individual patient the prognostic variables identified here were assigned different weights (coefficient of the survival function, Table 18) as determined by the multivariate proportional hazard regression analysis. The values of the weighted variables were then summed into a linear discriminant function (D). This function was first calculated with age and geometric size as continuous variables. To facilitate later applications of the function these variables were then dichotomized by determining the point where the maximum separation was found between death and survival. Furthermore, since geometric size is cumbersome in manual calculations the largest recorded tumor diameter was used instead; it follows the geometric size very closely. The cut-points determined in this way were 50 years and 6 cm, and the function was:

D = 1.78 (Grade IV) or 1.00 (Grade III) + 0.94 (Pain) + 0.94 (Male sex) + 0.86 (Age > 50 yrs) + 0.84 (Size > 6 cm) + 0.77 (Marginal surgery) + 0.66 (Extracompartmental site)

Using the D-value for a certain patient, probability of 5- and 10-year survival can thus be determined (Figure 8). Survival curves based on continuous values for age and geometric size were almost identical to those calculated with the dichotomized variables.

An example: For a female below 50 years of age with a painless intracompartmental Grade III tumor, less than 6 cm in diameter, and broadly excised, the sum of survival coefficients is 1 and the probability for surviving 5 years was well over 90 per cent. By contrast, for a male over 50 with a painful, large, extracompart-

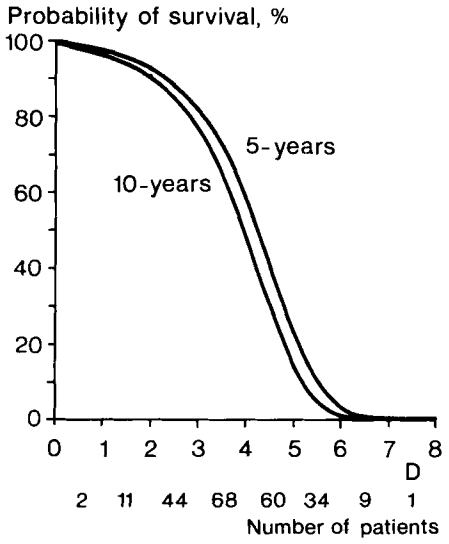


Figure 8 Probability of survival related to the survival function (D).

mental Grade IV tumor the probability of surviving 5 years was close to 0 regardless of type of surgery performed (Figure 8). The effect of surgery was most pronounced in the middle part of the curves where the slope is greatest. The greatest difference in the probability of 5-year survival following a marginal compared to a broad excision was 28 per cent.

Comments

It is possible to estimate survival with the function even if a variable is missing or intendedly omitted. In these cases the mean value for the particular prognostic variable as found in this material (Table 18) is used. This mean value should be multiplied by its survival coefficient and then entered into the equation. This may introduce a bias, however, as there is a covariation between the prognostic variables (p 57). Thus malignancy-grade is correlated with tumor size and the occurrence of pain; Grades I and II tumors are smaller and most often painless *(21)*. A more correct calculation can be made by estimating the survival as being between the figures found with and without the missing variable.

This analysis was based on retrospective investigations and the validity as regards the classification of surgical margins, tumor compartmentalisation and pain may be questioned. However, the results of the statistical analyses support the basis of the classification used here for surgical margins and compartmentalisation. Misclassified cases may change the weight of the individual prognostic variables. This applies particularly to the pain variable, here defined as pain of such magnitude that the patient mentioned it *and* the physician noted it in the medical record. A more stoic attitude in females would be a bias, however, there was no correlation between pain and sex when bivariately analysed (p 57).

Survival, subsets

The number of prognostic variables makes it difficult to use a staging system based on different combinations of all these variables. Instead, by the prognostic variables identified the patients can be stratified into different subsets as regards survival. The 5-year survival for all 278 patients was 61 per cent; for Grade I tumors 100 per cent, Grade II 91 per cent, Grade III 69 per cent and for Grade IV tumors 38 per cent. Survival related to the type of surgery performed (marginal *versus* broad excision) differed in Grades III and IV tumors but not in Grades I and II (Figure 9). The 5- (10) year survival following a marginal and a broad excision of Grade I-II tumors was 93 (81) and 97 (97) per cent. By combinations of the other prognostic variables of primary significance for survival (pain, sex and tu-

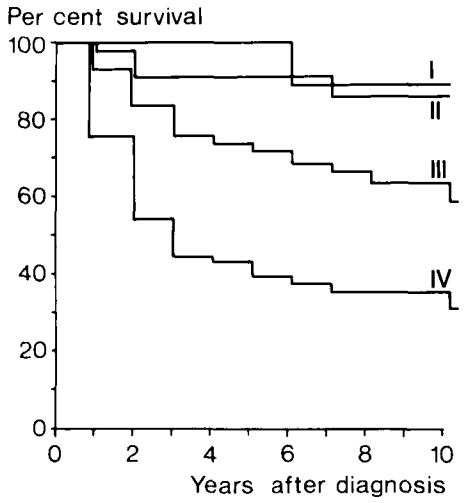


Figure 9a Survival related to malignancy-grade in epidemiologic series, 278 patients. Statistical significance between differences in survival (number of patients): Grade I (17) *v.* Grade II (47) *NS*, Grade II *v.* Grade III (91)**, Grade III *v.* Grade IV (123)***

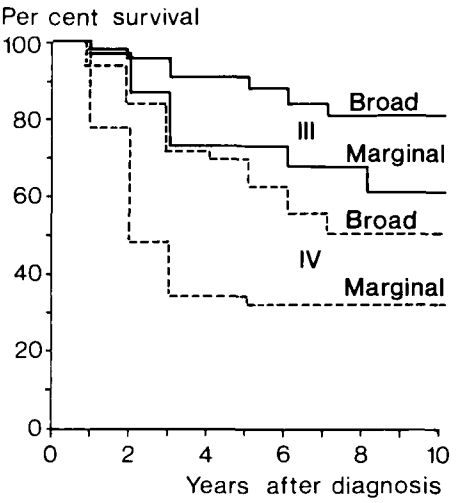


Figure 9b Survival related to surgical margin and malignancy-grade in patients with no metastases at diagnosis, epidemiologic series. Statistical significance between differences in survival (number of patients): Grade III broad (48) *v.* marginal (32)*, Grade IV broad (50) *v.* marginal (48)***

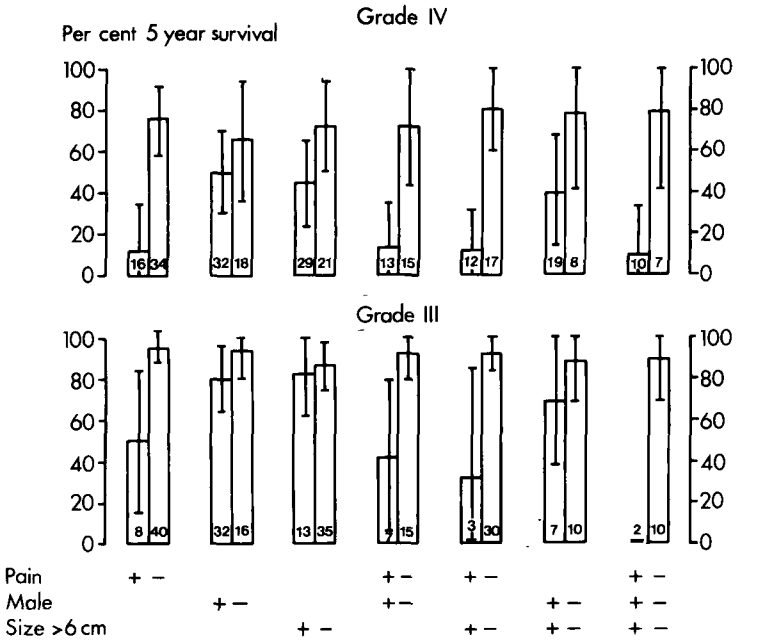


Figure 10 5-year survival following a broad excision in Grades III and IV tumors related to pain, sex and tumor-size. ⊡ = number of patients, I = 95 % confidence interval.

mor size) subsets with different 5-year survival following broad excisions for Grades III and IV tumors, could be identified (Figure 10). The variable of pain was involved in all the subsets with a significantly different survival. Out of 8 patients with painful Grade III tumors 4 died whereas 38/40 with no pain survived 5 years. Painless or small Grade IV tumors had a 5-year survival 50 per cent or higher.

Comments

There is no generally accepted 5-year survival rate appropriate for inclusion of patients in trials with adjuvant chemo-therapy. The fraction of patients destined to survive irrespective of adjuvant therapy, should be considered from two viewpoints:

1. Unless the tumor has a 100 per cent mortality some patients will always be subjected to the risks of chemotherapy unnecessarily;

2. Inclusion of patients with good prognosis increases the number of patients required to disclose possible effects of chemotherapy.

For these reasons a 5-year survival below 50 per cent is a reasonable prerequisite for inclusion of patients in trials with adjuvant chemotherapy. Thus, patients with Grade I, II and III sarcomas treated by broad excision should not be included in trials. A retrospective analysis of the distribution of the variables pain, sex and size should be made in trials where patients were selected for randomization exclusively on the basis of high malignancy grade.

Local recurrence, subsets

The type of surgical margin, and to a lesser degree, tumor compartmentalisation, age and the occurrence of pain were related to the incidence of local recurrence (Figure 7). Subsets with significantly different local recurrence risk following a broad excision could not be identified by different combinations of these variables. However, strictly *subcutaneous* and *intramuscular* tumors treated by wide and compartmental excisions, respectively, seldom recurred. Information as to whether deep tumors were intra- or extramuscular was incomplete so it was not possible to perform a further multivariate analysis including these specific positions.

Table 19 Local recurrence related to tumor depth and surgical margin.

	Surgical margin		
Tumor depth	Marginal	Wide	Compartmental
Superficial			
Subcutaneous	13/34	3/39 (1/3)	—
Subcutaneous, attached to deep fascia	7/11	4/23 (1/3)	—
Deep	35/66 (2/10)	9/32 (2/5)	1/32 (0/5)
Total	55/111	16/94	1/32

3-18 year follow-up. No patient censored.
Figures in parentheses denotes those patients given adjuvant chemo- or radiotherapy.

Subcutaneous tumors

Thirty-nine subcutaneous tumors, not attached to the deep fascia, were excised with a wide margin (Table 19). A *local* excision not followed by chemo- or radiotherapy was performed for 33 tumors (22 high- and 11 low-grade), 27 of which were treated by 2 or more surgical procedures until a wide margin was obtained. There were only 2 local recurrences (both Grade III tumors) and both occurred in the group treated by several excisions. By contrast, 9 out of the 32* deep tumors treated by wide excision recurred locally.

Intramuscular tumors

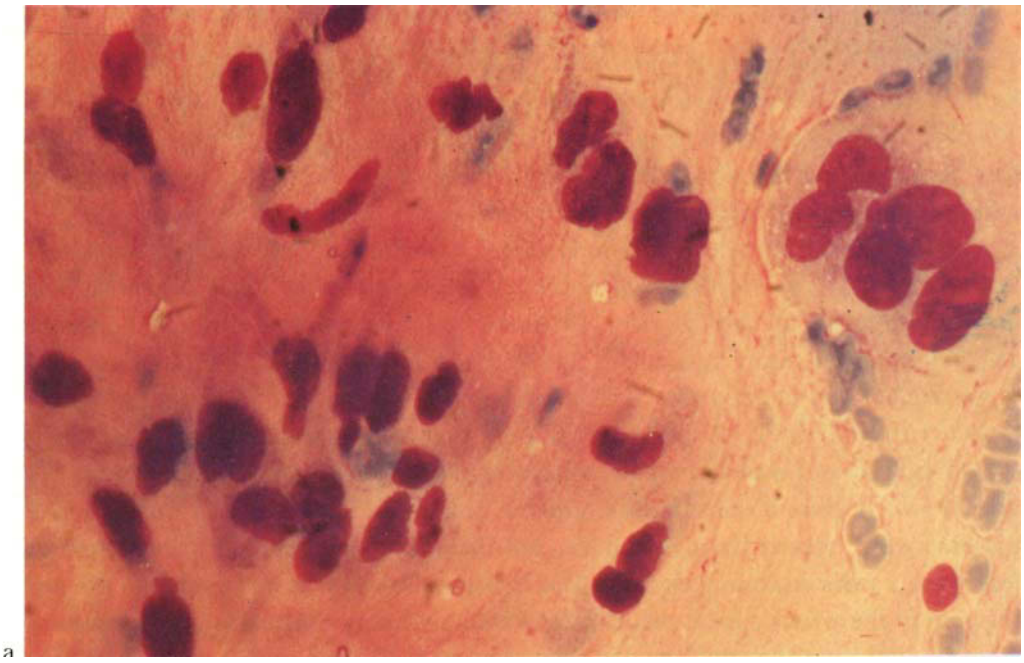
Thirty-two deep tumors (25 high- and 7 low-grade) were treated by a compartmental excision, in 9 by amputation (Table 19). The compartmental margin was in the amputated patients the same as Enneking's radical margin as it also was in two patients treated by local excision of the complete adductor compartment in the thigh. The other 21 patients were treated by local myectomies (not encompassing the complete compartment) for intramuscular tumors with one local recurrence. Sixteen (14 high- and 2 low-grade) were treated by surgery alone, 3 had also adjuvant chemotherapy and 2 had postoperative radiotherapy. In these 2 latter patients a tumor close to an unengaged fascia was considered a "a doubtful" margin by the pathologist. Both patients were treated more than 10 years ago when the quality of this type of margin was not fully recognized. The only local recurrence among these 32 patients appeared as a purely subcutaneous tumor 5 cm away from the scar at the same time as pulmonary metastases were diagnosed.

Comments

The morbidity following a wide local excision of a subcutaneous tumor is negligible. Also, the functional loss following myectomies is usually small *(69, 70)*. There is thus no need for trials with pre- and/or postoperative radiotherapy in subcutaneous and intramuscular tumors to reduce the surgical margins required and/or diminish the risk for local recurrence.

The local compartmental excisions were all performed as primary procedures at the Center without prior surgical biopsy. However, the clinical diagnosis was usually supported by cytodiagnosis (Figure 11-13). Following a surgical biopsy for an intramuscular tumor excision of the total compartment as defined by Enneking et al is probably needed *(6, 7)*. For example, a sarcoma in the rectus femoris muscle can be treated by myectomy of only that muscle if a biopsy has not been made. Otherwise, excision of the total quadriceps compartment is probably required which gives a considerable greater functional loss. Early in this series, 2 patients were treated by myectomies, not including the complete compartment, following a prior marginal excision and incisional biopsy, respectively. In the latter patient there was a local recurrence. Probably many of the deep tumors which were treated by a marginal or wide excision were intramuscular and could have been primarily treated by a myectomy.

The difference in local recurrence risk following wide excisions of subcutaneous as compared to deep sarcomas may indicate different resistance to tumor spread for fat tissue as compared to muscle and intermuscular tissue. Perhaps, interlacing fibrous septae in the subcutaneous fat layer act as barriers to extensive tumor spread. Interestingly, Enneking defines the subcutaneous space as intracompartmental in his classification despite the absence of fascial boundaries in the longitudinal direction.

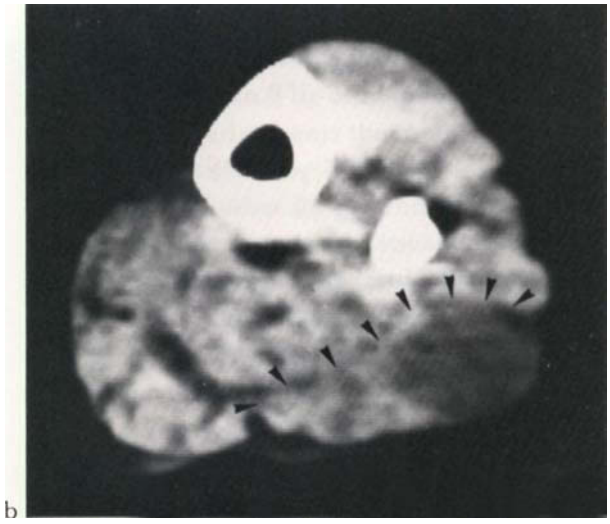


a

MGG, × 500

Figure 11 Aspiration cytology, computed tomography and primary myectomy.

A 65 year old woman with a painless 6 × 4 cm tumor in the left calf. Aspiration cytology (a) diagnosed a high-grade sarcoma. Computed tomography (b) showed a tumor in the lateral gastrocnemius head. At surgery without open biopsy the lateral gastrocnemius head and a lateral part of the soleus muscle was excised. A generous portion of skin and subcutis surrounding the puncture canal was included in the specimen. Transsection (c) of the specimen in the sagittal plane down to but not through the fascia of the soleus muscle showed a macroscopically well delineated tumor confined to the gastrocnemius muscle. The microscopic diagnosis was malignant fibrous histiocytoma, Grade III. The tumor is in part very close to the muscle fascia of the gastrocnemius, but the fascia is unengaged (d). In contrast to the macroscopic appearance there is no sharp demarcation between the tumor and muscle tissue, which is infiltrated (e). Three years after operation there is no evidence of disease and the patient can stand tip-toe on the left leg (f).



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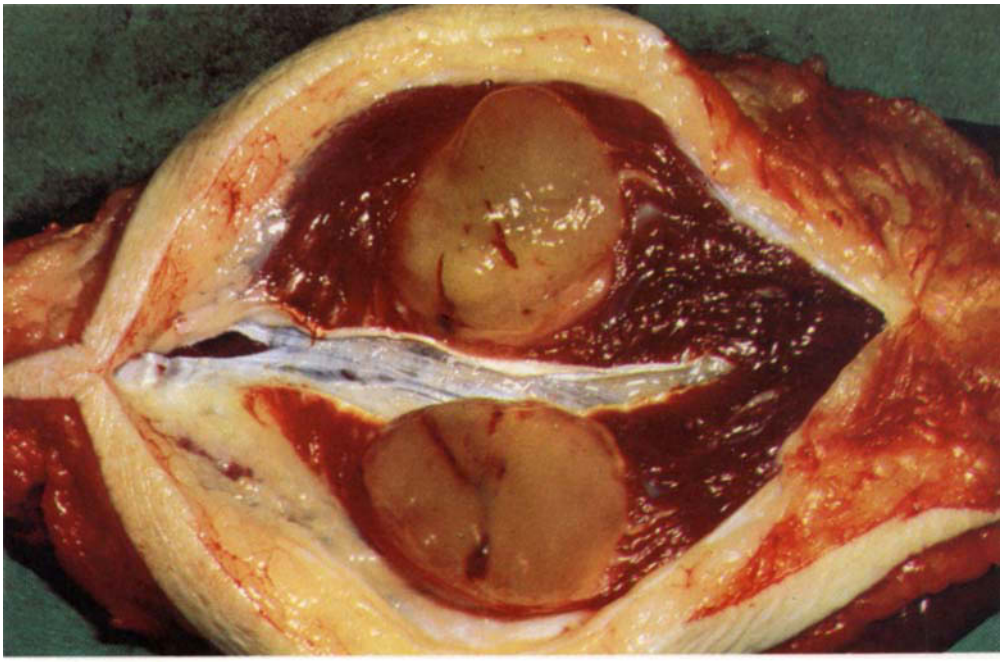
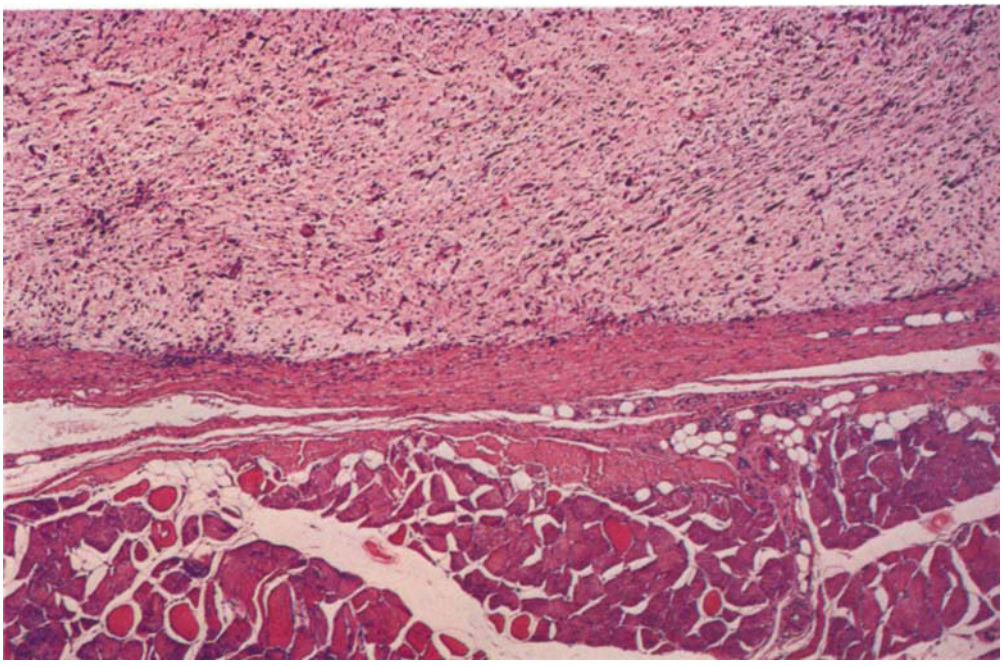


Fig 11c



H & E, × 70

Fig 11d

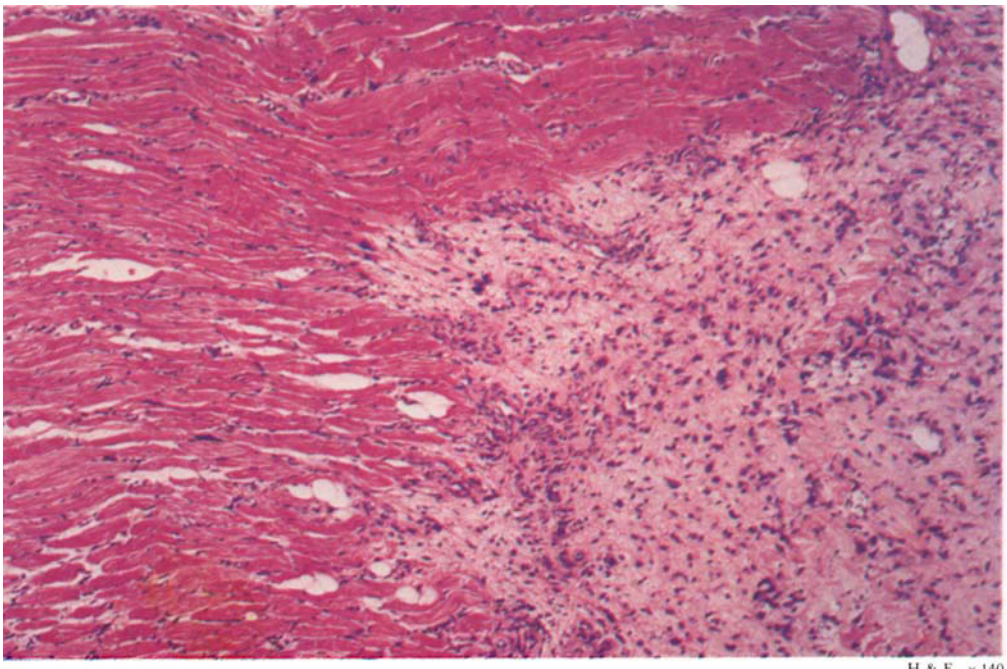


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Fig 11e

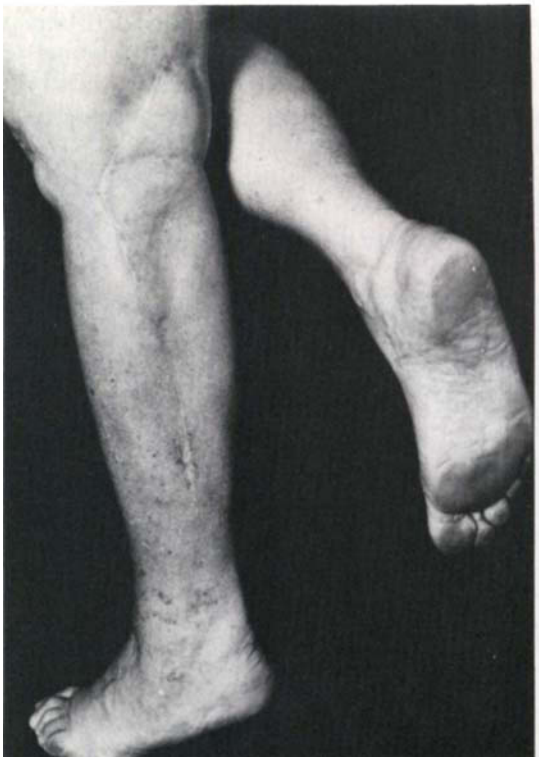
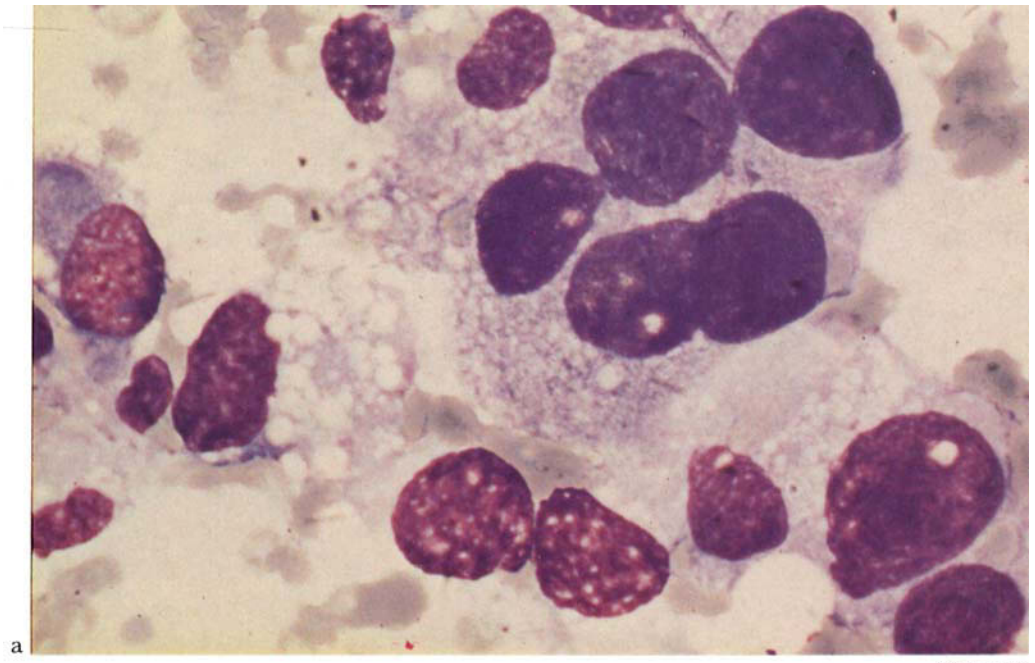
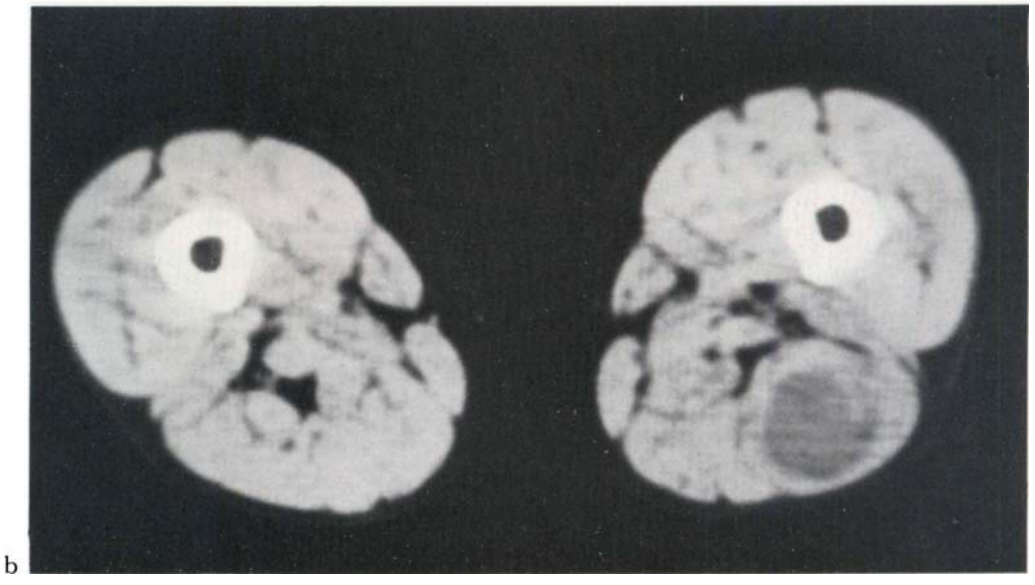


Fig 11f



a

MGG, × 800



b

Figure 12 Aspiration cytology, computed tomography and primary myectomy.

A 56 year old man with a painless, 7 × 5 cm tumor in the left thigh. Aspiration cytology (a) diagnosed a high-grade sarcoma. Computed tomography (b) demonstrated a tumor in the long head of the biceps muscle which was extirpated without surgical biopsy. Microscopic examination showed a malignant fibrous histiocytoma, Grade IV. There was only slight loss of function. The patient died 17 months later in metastatic disease but with no local recurrence.

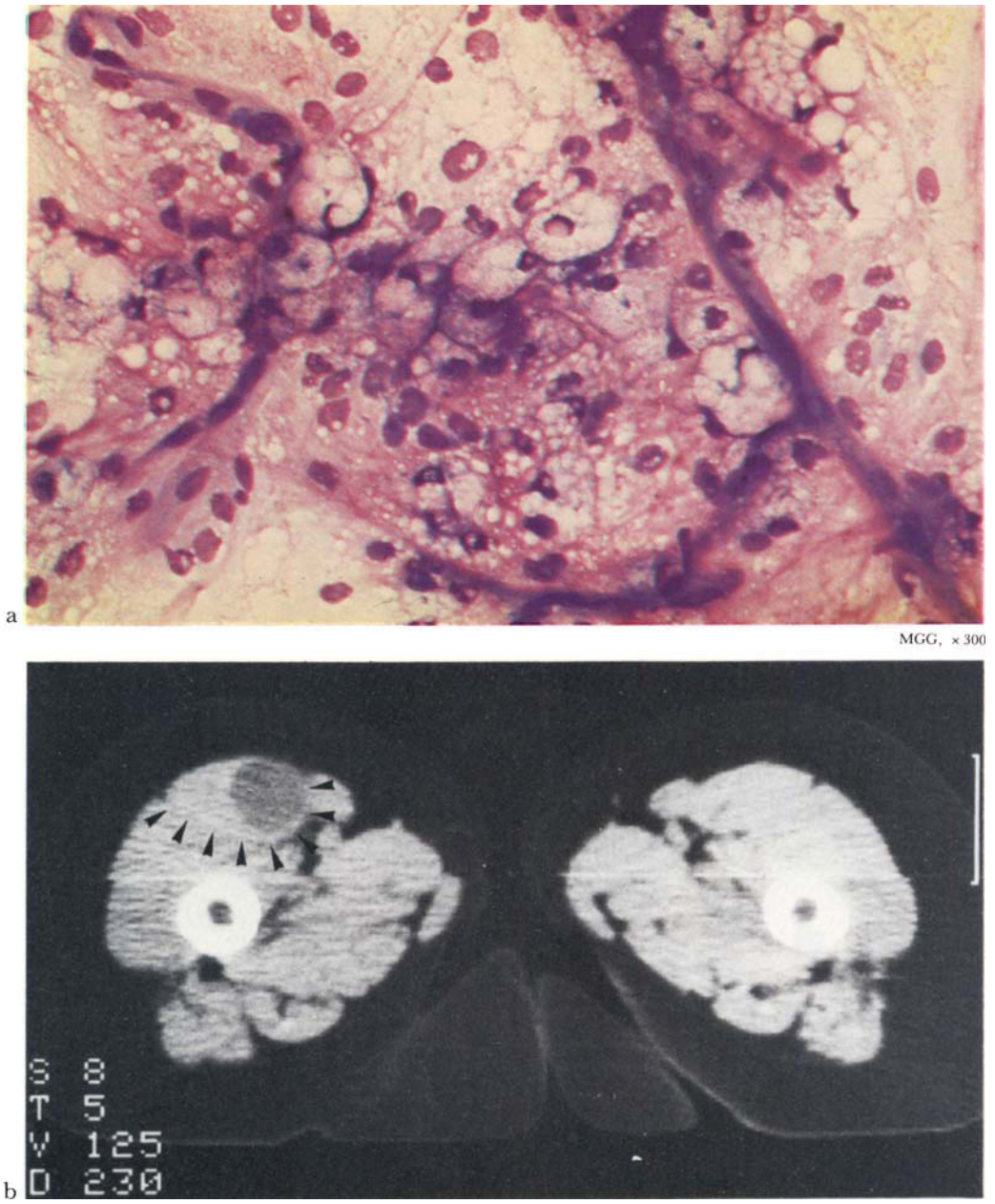


Figure 13 Aspiration cytology, computed tomography and primary myectomy.

A 35-year old woman with a painless 10 × 5 cm tumor in the right thigh. Aspiration cytology (a) diagnosed a myxoid liposarcoma. Computed tomography (b) demonstrated a tumor in the rectus femoris muscle which was extirpated without biopsy. Microscopic examination showed a myxoid liposarcoma. At latest follow-up, 9 months after surgery, the patient is disease-free. There is a full range of knee movement and the patient experiences no loss of function.

Covariation between prognostic variables

That there exist different opinions as regards the prognostic importance of a number of clinical and morphologic variables may in part be explained by covariation between them. Most studies have not analysed for such a covariation but rather have emphasized some variables and neglected others. This problem was examined by analysis of clinical and morphologic data in the epidemiologic sarcoma series (Table 1).

Pairwise correlation between variables

Sex, compartmentalisation and duration of symptoms were not significantly correlated to any of the other variables. (Correlations between compartmentalisation *versus* depth and location were not calculated since subcutaneous tumors were by definition intracompartmental and tumors located in the trunk were extracompartmental.) The majority of other variables were pairwise correlated (Table 20).

Simultaneous correlations, multiple regression analysis

The strongest associations were depth — size, depth — histologic group, size — histologic group, size — malignancy-grade (I, II, III *v.* IV), malignancy-grade — histologic group, and age — histologic group. Using multiple regression (path analysis) the genuine associations between these variables could be explained

Table 20 Soft-tissue sarcoma. Correlations between morphologic and clinical variables.

	Hist group	Mal grade	Age	Depth	Size	Location
Malignancy-grade[1]	***	—				
Age	***	*NS*	—			
Depth	**	**	*NS*	—		
Size	***	***	•	***	—	
Location	*NS*	*NS*	*NS*	**	**	—
Symptoms[2]	**	***	**	***	•	*NS*

[1] Malignancy-grade analysed for Grades I + II + III *v.* IV. When the tumors were divided into malignancy-grades I + II *v.* III + IV there were no significant correlations to depth and size.
[2] Symptoms analysed for patients with recorded pain *v.* all other patients.

The correlations between malignancy-grade (increasing), depth (deep tumors), size (increasing) and symptoms (pain) are positive.

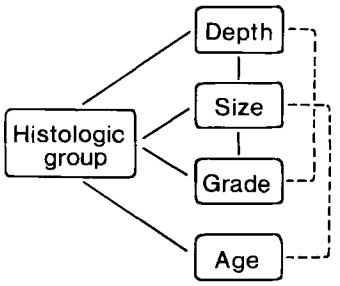


Figure 14 Soft-tissue sarcoma. Associations between different variables (malignancy-grade = I-II-III *v.* IV). Solid lines = genuine associations, broken lines = associations mainly explained by correlation to different histologic groups.

(Figure 14). In different pairwise correlations with histologic groups various histologic groups caused the significance. Thus the correlation between size and histologic group was mainly explained by the fact that fibrosarcomas were small and that liposarcomas were large. The correlation between age and histologic group was mainly related to malignant fibrous histiocytoma and leiomyosarcoma (older) and tendosynovial sarcoma (younger). The pairwise correlations found between depth — malignancy grade and size — age were mainly explained by correlations to different histologic groups *(21)*.

Comments

The close association between several variables is of importance when analysing prognosis. Thus, the prognostic importance of tumor-depth *(34, 58, 60)* may be explained by the greater size of deep-seated tumors. In addition, size and malignaney-grade were correlated, but both these variables are of prognostic importance. The better prognosis for distal tumors *(57, 58, 60)* can be related to their small size.

When the histologic groups were characterized by malignancy-grade, age, depth, size, and symptoms, each group differed significantly from all the other groups with respect to at least one of the variables *(21)*. Thus histogenetic classification seems to identify biologically different tumor entities.

Changes in the surgical treatment and referral pattern to the Center

A broad excision is the main principle in the surgical treatment of soft-tissue sarcomas. Appropriate surgical techniques were clearly described some 30 years ago *(54, 71, 72)* with authoratative reemphasis in later years *(7, 10, 73, 74)*. To evaluate the practice of these principles in southern Sweden, patterns of surgical treatment were analysed over time. For the subset analysed below, see Table 1.

Table 21 Soft-tissue sarcoma. Final surgical margin in different time periods.

Surgical margin	1964-69	1970-81	1964-81
Marginal	48	62	110
Broad	25	126	151
Total	73	188	261

Surgical treatment 1964—81

The final surgical procedure for the primary tumor was a marginal excision in 110 patients and a broad excision in 151 patients (Table 21).

Treatment related to the Center

The final surgical procedure for the primary tumor was a marginal excision in two thirds of the patients treated between 1964-69 compared with one third 1970-81 (Table 21). The final surgery was still marginal in two thirds of the patients not referred to the Center from 1970 through 1981 as compared with one fifth for referred patients (Table 22).

The first surgical procedure was a broad excision, diagnostic and therapeutic, in 71 per cent of the patients referred before surgery compared with 5 per cent for the other patients. The diagnostic surgical procedure was a marginal excision in 139/183 (76 per cent) of sarcomas diagnosed outside the Center.

The tentative preoperative diagnosis for patients referred before surgery, was malignancy in nine out of ten as compared with one third for patients not referred or referred after surgery. Lipoma was the most common falsely benign, preoperative diagnosis (Table 23).

Table 22 Soft-tissue sarcoma. Final surgical margin in patients referred or not referred 1970-81.

Surgical margin	Referred	Not referred
Marginal	31	31
Broad	111	15
Total	142	46

Table 23 Soft-tissue sarcoma. Pre-operative diagnosis.

Pre-operative diagnosis	Patients referred before surgery	Patients referred after surgery or not referred
Malignancy	62	40
Benign lesion (lipoma)	8 (2)	67 (27)
No recorded diagnosis	8	76
Total	78	183

Referral pattern

Of 188 sarcoma patients treated during 1970-81, 24 per cent were not referred to the Center, 34 per cent were referred after surgery and 42 per cent before surgery. The fraction of patients referred both before and after surgery increased over the years (Figure 15). When the referral pattern was separately analysed for two subpopulations, where Area I is the county in which Lund is situated (0.7 million inhabitants) and Area II comprises the 3 more distant counties of the region (0.6 million inhabitants) the same change in referral pattern was found except for a 5-year delay in Area II (Figure 16). During 1980-81 nine tenths (35/38) of the patients were referred; 10 after marginal excision and 25 before surgery.

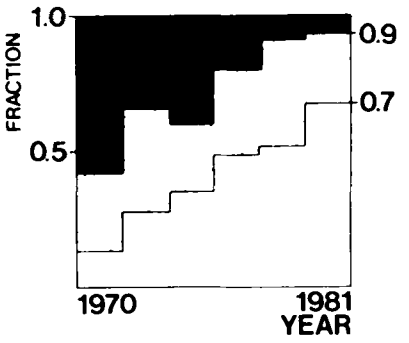
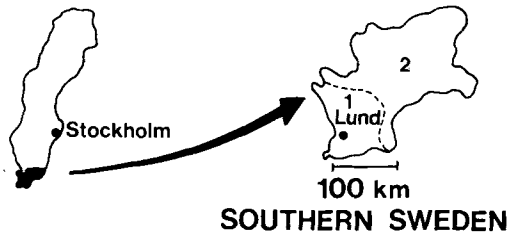


Figure 15 Soft-tissue sarcoma. Referral pattern for 188 patients in southern Sweden. ■ patients not referred; ▨ referred after surgery; □ referred before surgery. (By permission reproduced from Acta Orthopaedica Scandinavica *(19)*).



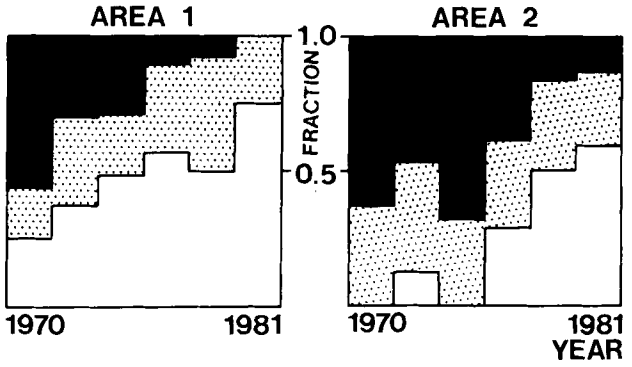


Figure 16 Soft-tissue sarcoma. Referral pattern for 188 patients from two different areas in southern Sweden. ■ patients not referred; ▨ referred after surgery; □ referred before surgery. (By permission reproduced from Acta Orthopaedica Scandinavica *(19)*).

Comments

For two reasons patients with soft-tissue sarcoma should preferably be referred to a treating center before any surgery:

1. Interpretation of clinical findings and radiograms are more reliable in a virgin tumor *(10)*.
2. An incisional biopsy or a marginal excision may spread tumor into unengaged tissue spaces *(3, 10)*.

The rather high fraction (50-80 per cent) of patients referred after marginal surgery as reported from treating centers *(10, 61)* may be partly explained by the difficulties encountered in the clinical evaluation of soft-tissue masses. No reports of the fraction of referred patients related to *all* soft-tissue sarcomas diagnosed in the catchment area of a treating center has been found. To increase the fraction of soft-tissue sarcomas referred before surgery the treating center must accept a large number of patients most of whom have benign lesions. Thus the increasing number of sarcoma patients referred to our Center before surgery has been accompanied by increasing numbers of patients with benign lesions.

The treatment outside the Center did not change during the period 1964 to 1981; two thirds of the patients were treated by marginal excision. This pattern agrees with two other Scandinavian population-based series of liposarcomas *(2)* and soft-tissue sarcomas in the extremities *(46)*.

Discussion

The prognosis in soft-tissue sarcoma can be improved by better therapy given to more of the patients.

Better therapy

Randomized prospective trials

The evaluation of different therapies should preferably be by randomized prospective trials. Due to the rareness of these tumors and the subsets of patients with good prognosis such trials require large base populations. The following calculations can be made for a randomized study evaluating effect of adjuvant chemotherapy after broad excision if only patients with non-metastatic disease and Grade IV tumors be included. The annual incidence of such patients is $5/10^6$. To demonstrate an increase in 5-year survival (significance 5 per cent, power 80 per cent) from the expected 50 per cent to 80 per cent, 90 patients would be required *(75)*. For a study collecting patients over 5 years a base population of 18 million would be needed. As one third of such patients are older than 70 year and some have concomitant disease making them unsuitable for chemotherapy and, as the number of patients who achieve a broad excision is limited, the required base population could easily be doubled. With a 5-year survival of 70 per cent in the chemotherapy group the figure would once again need to be doubled!

Non-randomized trials, prognostic variables and staging systems

The effect of different treatments could also be estimated in non-randomized series. To make possible a comparison of tumors with the same prognosis, knowledge of prognostic variables and concensus on the definitions of these variables is necessary. However, except for histologic malignancy-grade *(2-4, 6, 13, 14, 59,*

61-63, 65, 76-79) and the type of surgery performed *(3, 7, 9, 61, 80)* there is at present no agreement as regards prognostic variables for soft-tissue sarcoma. Furthermore, these variables are the most difficult ones to define; a multitude of classification systems exists.

Malignancy-grades

Our Grades I-II and Grades III-IV tumors probably correspond to the low-grade and high-grade tumors of Enneking et al *(6)* and Hajdu *(81)*. Information is lost by using a 2-grade system, however; like Markhede et al *(3)* we observed significant differences in survival for Grades I-II, Grade III and Grade IV tumors. The survival rate for Grades I and II tumors did not differ significantly. However, it appears that the potential for metastases among Grade I tumors is even lower than that in Grade II tumors *(2-4)*. A system with 3 grades of malignancy has been evaluated by Russel et al *(65)*. The 5-year survival rate for their Grade I tumors was 75 per cent and for Grades II and III tumors, 55 and 29 per cent, respectively. A disadvantage with their system is that a group of low-grade tumors with a good prognosis is not defined.

We used the same system as Markhede et al *(3)* and found survival rates in close accordance with theirs. The application of this system seems reliable and it can be recommended.

Surgical procedures

Neither is there any consensus concerning the definitions of different surgical margins for soft-tissue sarcoma; a bewildering terminology exists. Some authors have simply defined the margin required for a "radical excision" as being a specific thickness of apparently healthy tissue surrounding all the tumor. Some authors *(63, 64)* require 5 cm, a margin virtually unobtainable for most tumors without amputation. In a retrospective study it is certainly impossible to measure the obtained margin. Such measurements are difficult to make even in prospective studies. Many sarcomas are poorly delineated, making intraoperative estimations by palpation difficult. In addition, intraoperative exposure of the tumor is contraindicated as this makes the excision marginal. Postoperative measurement of the specimen is often inaccurate; surrounding tissues, especially muscles, retract and slide away. The *quality* of the margin, however, is more important than its dimensions, a point seldom mentioned but especially stressed by Stener *(73, 74)*. Sarcomas tend to respect preformed fibrous barriers (muscle fascia and aponeurosis, deep fascia and intermuscular septae), till very late *(10)*; an unengaged fascia, even if only millimeters away from the gross tumor, is an adequate margin. Thus when discussing surgical margins, *the type of the tissue* constituting the margin, must be specified.

Enneking and coworkers *(6, 7, 10)* recently defined four types of surgical margins obtainable by local or ablative surgery: *intralesional, marginal, wide* and *radical.* The wide margin was considered adequate for a low-grade sarcoma and the radical margin necessary for a high-grade lesion. They also defined two anatomic tumor sites: intracompartmental for tumors confined to "the closed fascial compartments" of the extremities and for tumors superficial to the deep fascia, and extracompartmental for all other tumors. Their definitions of intralesional marginal and wide margin and of the type of compartmentalisation were used in this study.

However, the definition of the radical margin is sometimes problematical as is the concept of compartmentalisation. This can be exemplified by reference to tumor sites and surgical margins in the thigh (Figure 1):

1. The subcutaneous space, regarded as intracompartmental, has no boundaries except for the deep fascia; the difference between a wide and a radical margin for a subcutaneous sarcoma is unclear.
2. A subfascial but extracompartmental (femoral triangle, popliteal fossa) and extramuscular tumor grows in a space with no boundaries in the longitudinal plane; the difference between a wide and a radical margin for these lesions is arbitrary. The same holds for a subcutaneous tumor with extension to the deep fascia.
3. The borderline between intra- and extracompartmental site for subfascial but extramuscular tumors is not always clear-cut. Thus, the subfascial, extramuscular space in the posterior mid-thigh between the hamstrings is considered intracompartmental. However, the loose areolar tissue in this space is continous with the popliteal fossa, which is defined as extracompartmental. Likewise, a subfascial lesion in the extramuscular space adjacent to the rectus femoris muscle in the mid-thigh is intracompartmental. This space communicates with the femoral triangle which is extracompartmental.

Thus, an extramuscular tumor in the anterior mid-thigh removed with a radical margin (the whole quadriceps muscle including the deep fascia and intermuscular septae) has fascial boundaries in the transverse directions. However, in the proximal longitudinal direction there are no defined boundaries. In this direction the margin is, instead, extremely wide which well may explain the low local recurrence rate with this procedure.

As regards subcutaneous tumors not attached to the deep fascia the problem is theoretical; there was a low local recurrence rate following excision with wide margins (including the deep fascia beneath the tumor) even when performed for high-grade tumors. However, as regards classification of compartmentalisation and surgical margins for subfascial tumors the problem is more substantial. A compartment more easy to define anatomically is the intramuscular one, closed

by the muscle fascia and the tendinous origins and insertions. For these reasons a *compartmental* margin was defined in this study. In this category were included procedures with the radical margin of Enneking as well as myectomy for intramuscular tumors, not including the total compartment as defined by Enneking, provided the muscle fascia was unopened and not transgressed by a prior surgical biopsy. The tumor must be removed without biopsy by a myectomy including the muscle fascia and through tendinous origins and insertions. If the muscle has a broad, not tendinous, attachment to bone near the tumor, the bone itself or a cortical layer next to the muscle should be included.

This procedure is *radical* in the longitudinal plane but only *wide* in the transverse plane according to the terminology of Enneking. However, there seems to be a very low potential for local recurrence with this procedure even when performed for high-grade lesions, as shown in this study. The same has been found by Stener (personal communication) who actually introduced the surgical concept of myectomy without biopsy *(3, 73, 74)*. The functional loss is usually slight *(69, 70)* and often considerably less than that following Enneking's radical margin. Thus, a radical margin in the anterior thigh requires excision of the whole quadriceps muscle and in the posterior thigh the sciatic nerve must be sacrified, making amputation more realistic.

The small loss of function which is usual following myectomy justifies the prerequisite for this procedure: surgery without biopsy (Figure 11-13). When clinical and radiographic preoperative examinations all indicate a malignant tumor the small risk of excising a benign tumor with unnecessarily large margins can be accepted *(3)*. This risk can be further diminished by the use of aspiration cytology. Thus, it is unnecessary to investigate whether this surgical technique would be safe if also combined with pre- or intraoperative incisional biopsy. This is one reason why frozen-section analysis was not used at our Center.

With the advent of computed tomography it became easier to stage tumors preoperatively as being subcutaneous or intramuscular *(24, 25)* (Figure 11-13). These tumors can be safely treated by surgery alone with low morbidity; trials with adjuvant chemo- or radiotherapy to further diminish the surgical margins and/or the local recurrence rate are clearly not indicated. Further, these locations should be specified when reporting the results of surgery and radiotherapy for soft-tissue sarcoma.

In this series compartmentalisation according to Enneking proved prognostic for local recurrence. This was related to the very low local recurrence rates for subcutaneous, by definition intracompartmental tumors, treated by a wide excision and intramuscular, usually intracompartmental tumors, treated by myectomies.

Except for the compartmental margin for intramuscular tumors surgical margins are more quantitative then qualitative; the risk of leaving microscopic tumor, direct microextensions or skip metastases, decreases with increasing distance from

the gross tumor. This risk seems to be related also to the tissue type; local recurrence was uncommon following a wide excision of a superficial compared to a deep tumor. It seems unlikely that the actual thickness of the margins obtained in the excisions classified as wide should differ for superficial and deep tumors. Our observations motivate a modification of Enneking's classification of tumor compartmentalisation. *Contained* tumors are intramuscular tumors and subcutaneous tumors not attached to the deep fascia. Tumors in other sites are *non-contained.* The reasons for such a classification are:

1. The anatomical definitions of these tumor-sites are clear-cut;
2. Contained tumors can be treated by local surgical procedures with low morbidity and low potential for local recurrence.

This system could not be tested in the multivariate analysis since in a majority of the deep tumors excised with marginal or wide margins it could not in retrospect be determined if the tumor had been intra- or extramuscular.

Other prognostic variables and staging systems

Staging systems have been developed for almost all types of carcinoma. They identify the most significant prognostic variables and combine them into a classification system which describes progressive degrees of risk. By combining malignancy-grade (high and low) and compartmentalisation (intra and extra) Enneking et al *(6)* formulated a surgical staging system for sarcomas. Compartmentalisation has specific implications for the surgical management as well as prognostic significance; local recurrence is more common following surgery for extracompartmental lesions. Enneking also suggested that a surgical staging system should provide guidelines for the use of adjuvant therapy. However, as shown in this study several variables other than malignancy-grade and compartmentalisation should be used to stratify patients into subsets with different survival.

Tumor size was one of these significant variables. It should be noted that size was of no importance for local recurrence; tumor size has no bearing on surgical margins or compartmentalisation. Size was incorporated in a staging system developed by the American Joint Committee for Cancer Staging and End Results Reporting *(65).* However, some other factors in this system are controversial: "Gross involvement of a major nerve, artery and bone" is poorly defined. Second, lesions with regional lymph node metastasis are separately classified. Lymph node metastases are uncommon in sarcoma and when they occur, the prognosis is poor. These patients are better grouped in common with others with distant tumor spread.

Hajdu *(81)* combined *malignancy grade* (high-low), *size* (>5> cm) and *depth* (superficial-deep) into a staging system where the variables were assigned the same importance. As shown in this study size and depth are closely related and could replace each other in the prognostic multivariate analysis; no further information was obtained by including both. In addition, by this system a deep and low-grade lesion is the same stage as a superficial and high-grade lesion of comparable size, which is inconsistent with the great prognostic importance of malignancy grade.

Seven prognostic variables were identified in this study. Staging systems based on appropriate variables can stratify patients into several different survival groups (p 47-48) and should be subjected to further studies.

Extent of surgery and adjuvant therapy

Optimal treatment means first, maximal survival and, second, minimal loss of function. The loss of function and mortality risk are inversely correlated; marginal surgery to save function is a principal reason for failure. Local recurrence greatly increases the risk for metastases. This has been repeatedly demonstrated and was shown also in this study. In three recent, well controlled surgically treated series, from tumor centres well known for their experience, four fifths of the patients obtained a surgical procedure with low potential (~5 per cent) for local recurrence *(3, 7, 10)*.

In Markhede's *(3)* analysis of Stener's material the amputation rate in the 97 patients referred before any surgery was 20 per cent. In addition, by avoiding surgical biopsy in most patients treated by local excisions, function was spared. At the same time, 1956-76, amputation was carried out in 50 per cent of the patients referred after marginal surgery. (Berlin and Stener, personal communication). In the two series presented by Enneking and co-workers *(7, 10)* one half of the patients had an amputation. However, most of their patients had already had an excisional biopsy or a recurrence when first seen. This clearly demonstrates the advantages and difficulties in getting these patients referred before surgery. However, high amputation rates have been reported also in previously untreated patients; the amputation rate was 42 per cent in one series *(13)* .

To decrease the amputation rate limited surgery combined with radiotherapy has been introduced. With this treatment Lindberg et al *(14)* and Suit et al *(15)* could preserve a functional limb in four fifths of the patients and the local recurrence rate was 20 per cent. However, as compared with the above mentioned series with only surgical treatment their patient material seems different; the tumors were smaller, more distally located and of lower malignancy. Suit et al *(16)* reported on preoperative radiotherapy followed by "conservative surgery" or amputation. Local control was achieved in 32/36 patients with follow-up time

between 3 months and 8 years. The results in these series with combined therapy has not been compared with an adequately defined surgically treated group of patients with lesions of the same prognostic characteristics. To date, limited surgery supported by radiotherapy seems not to give better results than surgery alone. However, when local control is not readily obtained by surgery due to the anatomic position, limited surgery combined with radiotherapy may be indicated.

Despite local control, metastatic disease, not clinically manifest at the time of diagnosis of the primary tumor, is common. Adjuvant chemotherapy has thus been investigated (for references see Sutow and Maurer *(17)*). Most series are not randomized and the effects are difficult to evaluate. However, Rosenberg et al *(18)* in a recent prospective randomized study of 65 patients with median follow-up of 2 years, reported a significantly improved prognosis in patients treated by adjuvant chemotherapy (doxorubicin, cyclophosphamide and high-dose methotrexate). In 1981 a multi-center, randomized prospective study of adjuvant doxorubicin (Adriamycin) treatment was started in Scandinavia (Scandinavian sarcoma group trial, SSG: I/81. Oncology Center, Lund). Up to October, 1983, 135 patients have entered the study but it is still too early to draw any conclusions.

Optimal treatment to more patients

Over the years the treatment of sarcoma patients outside the Center remained the same; two thirds had a marginal excision. In several series reported from other treating centers a substantial number of the patients are referred with local recurrences or following a marginal excision, and there are no data as regards the treatment of the patients not referred at all. Most probably, many of these later patients are treated by marginal excisions. The catchment area of Stener's tumor center in Gothenburg, Sweden, comprises about 2 million inhabitants. In an analysis *(3)* of the patients treated during 1956-76, 97 patients were referred before any surgery and at the same time 87 were referred for extended surgery. Using the annual incidence found in this study ($1.4/10^5$) the expected number of soft-tissue sarcoma during this time in that region should be about 600. Thus, two thirds of the sarcoma patients were not referred.

The most rapid and reliable way to improve the prognosis in soft-tissue sarcoma would be to refer patients to a tumor center before any surgery; a greater number of patients is then operated with a broad margin, with decreased mortality (Figure 17) and morbidity. If all patients in our region with soft-tissue lesions which are 5 cm or larger and/or deep were referred before any surgery about 250 patients would be referred anually to the Center. Slightly less than 10

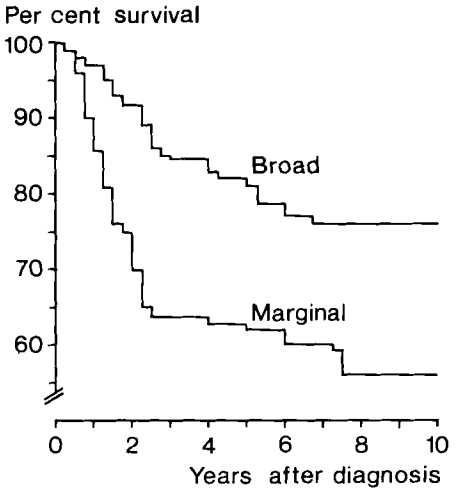


Figure 17 Survival related to surgical margin in patients with no metastases at diagnosis, epidemiologic series. Statistical significance between difference in survival (number of patients): Broad excision (n 126) *v.* marginal (n 111)***

per cent of these patients would have a sarcoma. At the same time only a few patients with small and superficial sarcomas would be referred after first having had a marginal excision. During 1980-81 seven tenths of the patients with soft-tissue sarcoma were referred before surgery, it seems difficult to significantly increase this referral rate. However, some of the patients referred before surgery had small superficial tumors and most patients referred after a marginal excision had large and/or deep tumors. By reversing this pattern the prognosis would improve; patients with superficial tumors form a favourable subset as regards surgery with low local recurrence risk following reexcision with wide margins. With the recommended principles for referral it thus seems possible to further increase the already high fraction of sarcoma patients referred before surgery and to have a favourable selection of those patients who are referred first after surgery.

The increasing number of patients referred before surgery, the majority of them with benign lesions, makes a well-founded strategy in the preoperative evaluation mandatory; the risk and cost for different investigations and the availability of resources, notably computed tomography and angiography, must be considered.

Therefore, the management of patients with soft-tissue tumors referred to the Center before biopsy is based on a step-wise evaluation by history, clinical findings, aspiration cytology and radiographic examinations but only infrequently open biopsy. All patients do not run through all these steps (Figure 18). None of these diagnostic measures can prove the existence of a sarcoma versus a benign tumor. The probability of malignancy following each step is instead weighed against the possible information which could be obtained by further preoperative examinations *and* the risk that a certain surgical procedure turns out to

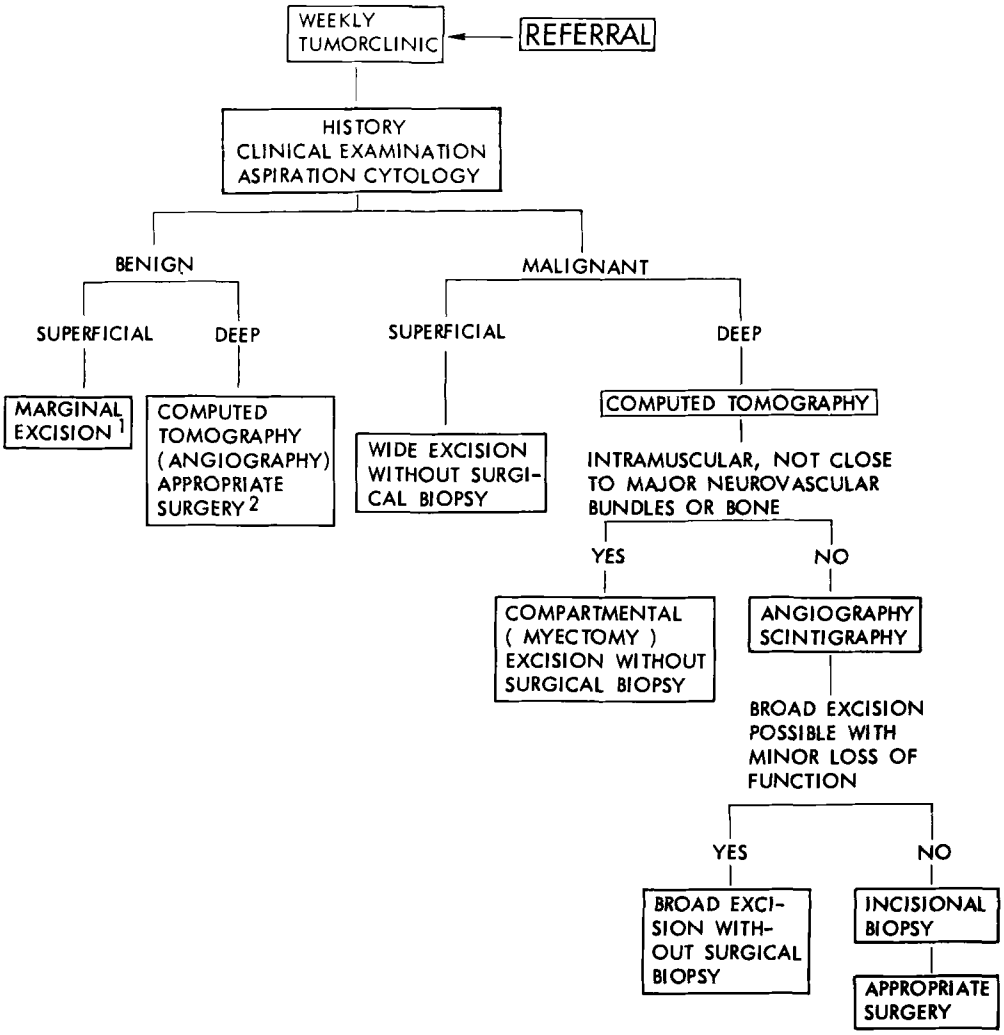


Figure 18 Management of soft-tissue tumors at the Center.

[1] Superficial tumors which by history, clinical findings and aspiration biopsy are diagnosed as benign can be left without surgery.

[2] Some benign deep tumors (e.g. desmoids and infiltrating lipomas) are best treated by wide or compartmental excisions.

be inappropriate; too small or too extensive. Thus, a marginal excision of a strictly subcutaneous sarcoma can be salvaged by reoperation with wide margins, and a myectomy without prior open biopsy often gives a small loss of function, acceptable should the tumor turn out to be benign.

Summary and conclusion

Clinical and morphologic variables in soft-tissue sarcomas and lipomas were retrospectively analysed and compared in consecutive, unselected population-based series from southern Sweden 1964-1981. Among the sarcoma patients these variables and the treatment given were evaluated by multivariate analysis with regard to the clinical course. The results of aspiration cytology and its influence on the choice of surgical procedure were evaluated in two series of patients referred to the Orthopaedic Oncology Group (the Center) because of suspected malignant soft-tissue tumors. Changes in the surgical treatment over time was determined.

The annual incidence of sarcoma was $1.4/10^5$ with a 30 per cent male preponderance. The mean age was 58 years. The most common histologic types were malignant fibrous histiocytoma, liposarcoma and leiomyosarcoma. Twenty-three per cent were histologically classified as low-grade malignant (Grades I and II), 33 per cent as Grade III and 44 per cent as Grade IV tumors. Slightly more than one half of the tumors were deep and these had a median size of 8 cm compared to 4 cm for the superficial tumors. One third of the tumors were located in the thigh.

The annual clinical incidence of solitary subcutaneous lipoma was estimated to $1/10^3$. Four fifths of the lipomas were smaller than 5 cm and they were most common in the trunk, shoulder and upper arm.

By comparing clinical data for benign tumors and sarcomas it was found that a tumor 5 cm or larger or a deep tumor is relatively more likely to be a sarcoma. Patients with tumors of that size and depth should be referred before surgery.

The probability of a benign cytodiagnosis being correct was 0.97 while that of a malignant one was 0.85. For a cytodiagnostic report of sarcoma the probability of correct diagnosis was 0.84. In a prospective evaluation the planned surgery was changed by subsequent cytodiagnosis in one third of the patients.

Negative prognostic variables as regards survival in the order of decreasing relative risks were: Malignancy Grades IV and III, pain, male sex, increasing age and tumor size, marginal surgery and extracompartmental tumor site. Marginal excision, extracompartmental tumor site and age exerted their effect only via local recurrence which had a stronger negative influence on survival than any of the other variables. A linear survival function based on the prognostic variables was

related to the probability of survival and the patients could be stratified into subsets with significantly different survival.

Strictly subcutaneous and intramuscular sarcomas had a local recurrence risk less than 6 per cent even when treated by local excisions, done as a primary myectomy for the intramuscular tumors.

A close correlation was found between several of the variables for soft-tissue sarcoma, a fact which may explain some of the different viewpoints as regards prognostic variables.

The surgical treatment of sarcomas outside the Center has not changed over the years; two thirds of the patients have had marginal excisions only. By contrast four fifths of the patients treated in the Center obtained a broad excision. The number of patients referred increased over the years; in 1980-81 nine tenths of the sarcoma patients were referred and two thirds of these before any surgery.

In *conclusion:* By the use of simple clinical data in the evaluation of a soft-tissue tumor, high risk patients can be selected for referral to a treating center before any surgery while low risk patients can be treated outside the center by marginal excision. By aspiration cytology referred patients can be further selected for radiographic examinations and different surgical procedures. In the majority of cases, the definitive surgery can then be done as a one-stage procedure, thereby saving function in patients with intramuscular sarcomas. A number of variables are of prognostic importance and can be used to identify patients with good prognosis for whom trials with adjuvant chemotherapy are not indicated. The prognosis is improved by centralised treatment.

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CODED DATA, EPIDEMIOLOGIC SARCOMA SERIES

Key to data

A	Age at diagnosis, years	
B	Sex	1=Male, 2=Female
C	Year of diagnosis (64–78)	
D	Length of anamnesis, months	
E	Symptoms	1=Pain, 2=No pain, 3=No data
F	Location	1=Shoulder, 2=Upper arm, 3=Elbow, 4=Lower arm, 5=Hand, 6=Buttock, 7=Hip, groin, 8=Thigh, 9=Knee, 10=Lower leg, 11=Foot, 12=Neck, 13=Trunk
G	Depth	1=Subcutaneous, 2=Subcutaneous, attached to deep fascia, 3=Intramuscular, 4=Deep-seated NOS
H	Compartmentalisation	1=Intracompartmental, 2=Extracompartmental
I	Metastases at diagnosis	0=No, 1=Yes
J	Malignancy-grade (1–4)	
K	Histologic type	1=Malignant fibrous, histiocytoma, 2=Well differentiated liposarcoma, 3=Myxoid liposarcoma, 4=Round cell liposarcoma, 5=Pleomorphic liposarcoma, 6=Mixed liposarcoma, 7=Leiomyosarcoma, 8=Neurogenic sarcoma, 9=Synovial sarcoma, 10=Epithelioid sarcoma, 11=Clear cell sarcoma, 12=Hemangiosarcoma NOS, 13=Malignant hemangioendothelioma, 14=Malignant hemangiopericytoma, 15=Lymphangiosarcoma, 16=Fibrosarcoma, 17=Myxofibrosarcoma, 18=Rhabdomyosarcoma, 19=Malignant mesenchymoma, 20=Soft-tissue osteosarcoma, 21=Soft-tissue chondrosarcoma, 22=Soft-tissue Ewing sarcoma, 23=Alveolar soft-tissue sarcoma, 24=Sarcoma NOS
L	Size, largest diameter in cm	
M	Aspiration cytology	0=No, 1=Yes
N	Surgical margin at first operation, if more than one, for the primary tumor	0=No surgery, 1=Incisional biopsy, 2=Partial excision, 3=Marginal, 4=Wide, 5=Compartmental,
O	Margin at final surgery for the primary tumor	(same as for N)
P	Number of surgical procedures for the primary tumor	
Q	Chemo- and/or radiotherapy	0=No, 1=Yes
R	Time for first local recurrence, months	
S	Surgical margin	(Same as for N)
T	Time for second local recurrence, months	
U	Surgical margin	(Same as for N)
V	Number of local recurrences	
X	Time for pulmonary metastases, months	
Y	Other metastases	0=No, 1=Yes
Z	Time for death, months	
Å	Cause for death	1=Tumor, 2=Other disease
Ä	Follow-up time, years	

n	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	X	Y	Z	Å	Ä
1	95	1	66	6	3	10			0	1	24	13	1	0	0	0	1					0		0	9	1	
2	32	2	74	10	2	2	4	2	0	1	17	14	1	1	3	2	0					0		0			7
3	67	2	73	2	1	7	1	1	0	1	16	02	0	3	3	2	0	24	3			1		0			8
4	47	2	65	24	3	8	1	1	0	1	1	01	0	3	3	2	0					0		0			16
5	36	1	78	3	2	5	4	2	0	1	16	02	0	0	3	1	0					0		0			3
6	42	2	74	2	2	13	4	2	0	1	2	07	0	0	3	1	0					0		0			7
7	59	1	67		3	1	1	1	0	1	2	07	0	0	3	1	0	30	3			1		0			14
8	70	1	66	24	3	12	4	2	0	1	8	07	0	0	3	1	0	71				1		0	72	1	
9	70	1	70	24	2	12	1	1	0	1	1	02	0	3	4	2	0					0		0			11
10	51	1	71		3	6	1	1	0	1	7	05	0	3	4	2	0					0		0			10
11	57	1	78		2	1	1	1	0	1	8	02	0	3	4	2	0					0		0			3
12	66	2	75	10	1	6	3	2	0	1	19	04	1	0	4	1	0					0		0			6
13	79	1	78	60	2	13	1	1	0	1	1	06	1	0	4	1	0					0		0			3
14	61	1	68	6	2	11	2	2	0	1	1	02	0	1	4	2	0					0		0			13
15	22	1	64	6	3	13	1	1	0	1	1	02	0	3	4	3	0					0		0			17
16	66	2	73	24	2	1	3	1	0	1	19	08	0	0	5	1	0					0		0	36	2	
17	55	1	77	24	2	8	4	1	0	1	2	23	1	0	5	1	0					0		0			4
18	64	1	75	24	2	7	3	2	0	2	1	05	1	0	2	1	0					0		0			6
19	85	1	72	4	2	2	2	2	0	2	1	05	0	2	2	2	0					0		0	103	1	
20	87	2	71	5	2	6	4	2	0	2	3	15	0	2	2	2	0					0		0	69	2	
21	79	1	73	26	3	1	2	2	0	2	14	13	0	0	3	1	0					0		0	21	2	
22	52	1	75	60	2	6	1	1	0	2	8	16	1	0	3	1	0					0		0			6
23	88	2	67	12	3	4	4	1	0	2	16	05	0	0	3	1	0					0		0	3	2	
24	45	2	65	1	2	7	1	1	0	2	3	04	0	3	3	2	0					0		0			16
25	64	2	68	12	2	10	4	1	0	2	17	14	0	1	3	2	0					0		0			13
26	55	2	72	2	2	8	4	1	0	2	3	26	0	0	3	1	0					0		0			9
27	57	1	77	60	2	10	2	2	0	2	1	04	0	3	3	2	0					0		0			4
28	79	2	65	1	2	9	1	1	0	2	17	03	0	0	3	1	0	6	3	99		2		0	132	2	
29	81	1	65	12	3	13	1	1	0	2	14	12	0	0	3	1	0					0		0	43	2	
30	64	2	75	3	2	1	3	2	0	2	14	02	0	3	3	2	0					0		0			6
31	69	1	72	14	3	4	1	1	0	2	17	03	0	3	3	2	0					0		0			9
32	61	1	71	1	2	10	1	1	0	2	17	03	0	0	3	1	0	18	4			1		0			10
33	49	2	78	48	2	12	3	2	0	2	13	06	1	1	3	2	1					0		0			3
34	55	1	67	30	2	6	4	1	0	2	8	07	0	0	3	1	0	20	3	36	2	3	30	0	87	1	
35	68	1	70	2	2	8	3	1	0	2	14	10	1	1	3	3	0	26				1		1	30	1	
36	26	1	78		2	7	4	2	0	2	14	05	0	0	3	1	0					0		0			3
37	29	1	69	2	1	6	4	2	0	2	3	15	0	1	3	2	1	4				1	14	1	24	1	
38	84	2	75	3	3	11	4	2	0	2	7	08	1	0	3	1	0					0		0	50	2	
39	40	1	70	60	3	13	1	1	0	2	17	05	0	3	3	2	0					0		0			11
40	64	2	73	6	1	11	4	2	1	2	3	07	0	0	3	1	0	12	5			1		1	22	1	
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50	70	1	75	6	2	8	3	1	0	2	3	07	1	0	4	1	0	30	4			1		0			6
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55	78	2	77	12	3	13	1	1	0	2	1	11	0	1	4	2	0					0	27	1	27	1	
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57	28	2	75	2	3	2	1	1	0	2	14	04	0	3	4	3	0					0		0			6
58	71	1	70	99	2	10	1	1	0	2	14	05	1	0	4	1	0					0		0			11
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61	15	2	76	7	2	10	1	1	0	2	16	02	0	3	4	2	0					0		0			5
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63	42	1	76	3	2	8	3	1	0	2	3	05	1	0	5	1	0					0		0			5
64	52	2	71	72	2	8	3	1	0	2	3	08	1	1	5	2	0					0		0			10
65	94	2	75	3	2	5			0	3	24	04	1	0	0	0	1					0		0	26	2	
66	78	2	76	2	2	1		2	0	3	24	12	1	0	0	0	1					0		0	2	1	
67	79	1	71	2	1	5	4	2	1	3	10	05	0	0	1	1	1					0		1	4	1	
68	86	1	65		3	13	4	2	1	3	24	04	0	0	1	1	0					0	1	1	3	1	
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70	81	1	66	2	1	11	4	2	0	3	9	08	0	0	1	1	1					0	8	0	12	1	
71	82	2	77	18	2	6	4		0	3	1	10	0	0	2	1	0					0		0	16	1	
72	50	1	68	9	3	13	3	2	0	3	14	19	1	0	2	1	1					0	4	1	12	1	
73	68	1	70	12	2	7	4	2	0	3	7	08	0	1	2	2	1					0	22	1	26	1	
74	86	1	75	36	3	13	1	1	0	3	7	05	0	0	3	1	0					0	15	0	16	1	
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84	84	2	66	12	3	8	1	1	0	3	8	06	0	0	3	1	0					0		1	27	1	
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86	54	2	76		3	8	4	1	0	3	6	17	1	0	3	1	1					0		0			5
87	54	1	65	10	2	13	3	2	0	3	1	11	0	2	3	2	1	4				1	5	0	9	1	
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94	66	1	74		3	5	1	1	0	3	7	01	0	0	3	1	0					0		0	3	2	
95	47	2	76	8	1	9		2	1	3	16	06	1	0	3	1	1					0	1	1	13	1	

n	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	X	Y	Z	Å	Ä
96	63	2	74	6	3	4	2	2	0	3	6	02	1	3	3	3	0	17	3			1		0			7
97	81	2	74	9	1	1	4	2	0	3	16	04	1	0	3	1	0	4	3	18	2	2	18	0	24	1	
98	78	2	66	2	3	2	4		0	3	1	14	1	0	3	1	1	18				1	14	0	19	1	
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114	66	1	68	1	1	8	3	1	0	3	7	18	1	0	4	1	1	12	3	16		2	30	1	30	1	
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119	51	1	77	12	2	8	1	1	0	3	7	02	0	3	4	2	0					0		0			4
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121	57	2	71	10	2	2	1	1	0	3	16	02	0	3	4	2	0					0		0			10
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123	17	1	69	5	2	8	4	1	0	3	21	08	0	3	4	2	0					0		0			12
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125	45	2	74	4	3	10	2	2	0	3	24	03	1	3	4	2	0					0		0			7
126	21	1	78	30	2	5	1	1	0	3	18	02	0	3	4	3	1					0		0			3
127	38	1	67	72	1	8	3	1	0	3	8	11	1	0	4	1	1					0	36	1	53	1	
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