STAGING OF SOFT-TISSUE SARCOMAS

PROGNOSTIC ANALYSIS OF CLINICAL AND PATHOLOGICAL FEATURES

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In a retrospective study of all 137 patients with soft-tissue sarcoma treated by surgery between 1972 and 1984, the clinical course was related to several host and tumour features, including the Surgical Staging System of Enneking, Spanier and Goodman (1980). Only patients free from metastasis with untreated primary lesions on admission were included. According to the Surgical Staging System, nine tumours were IA, 18 IB, 38 IIA and 72 IIB. Only 12 patients underwent amputation; 125 were treated by local surgery. The mean follow-up time was ten years (minimum five).

For the whole series the probability of seven-year survival was 0.65; 42 patients (31%) died from tumour disease. All these had metastases and 24 also had local recurrence. The local recurrence rate was 36%. Multivariate analysis identified large tumour size and high histological grade as significant risk factors for metastatic disease and tumour-related death. Sex, age, tumour site, surgical margin and local recurrence showed no correlation with survival. The prognostic contribution of compartmentality was virtually nil. Histological grade combined with tumour size was found to give better prognostic information than that obtained by the Surgical Staging System.

Of several systems for staging soft-tissue sarcoma, the Surgical Staging System (SSS) proposed by Enneking et al (1980) and Enneking (1983, 1986) seems to be the most widely used. It has been claimed to be of value both for surgical planning and for prognosis. By combining assessments of tumour biology and extent, that is histological grade and anatomical compartment, the system provides guidelines on the feasibility of limb-salvage procedures. The use of local excisional procedures appears to have increased since the introduction of SSS. None the less, controversy prevails about its validity, particularly for prognostication (Rööser et al 1987a, 1988). One reason for this is that there have been few prognostic studies on the basis of multivariate analysis (Ueda et al 1988; Berlin et al 1990). Quite apart from the method of treatment, the prognosis for soft-tissue sarcoma depends on a wide variety of host and tumour features (Markhede, Angervall and Stener 1982; Heise et al 1986; Rööser et al 1988; Ruka et al 1988; Tsujimoto

et al 1988; Alvegård et al 1989a; Stotter et al 1990), and appropriate statistical analysis is essential to assess the usefulness of SSS.

The present study was undertaken to this end.

PATIENTS AND METHODS

We studied the clinical and pathological records of all 137 patients with soft-tissue sarcoma treated by surgery at the Karolinska Hospital from 1972 to 1984, excluding only those who presented with metastases.

Table I. Histological diagnoses in 137 soft-tissue sarcomas

Final diagnosis	Grade		Initial diagnosis	Number
	I	II		
Malignant fibrous histiocytoma	6	57	Liposarcoma Fibrosarcoma Rhabdomyosarcoma Leiomyosarcoma	18 10 2 1
Liposarcoma	8	17	Fibrosarcoma	1
Synovial sarcoma	3	14	Fibrosarcoma	5
Fibrosarcoma	10	12	Liposarcoma Leiomyosarcoma	1 1
Rhabdomyosarcoma	0	3		
Leiomyosarcoma	1	2	Fibrosarcoma	2
Angiosarcoma	0	2	Liposarcoma	1
Haemangiopericytoma	1	1		

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There were 75 men (mean age 57 years) and 62 women (mean age 58 years). Tumours of the trunk wall, shoulder and groin were classified as proximal (39%) and those of the extremities as distal (61%). The most common location was the thigh (41%). Tumour size was defined as the largest diameter measured on radiographs or on the surgical specimen. The mean size of the tumours was 9 cm.

We performed the histological classification according to the principles of the World Health Organisation (Enzinger, Lattes and Torloni 1969) and the malignancy grading (I to IV) according to Broders, Hargrave and Meyerding (1939). All histological slides were reviewed by one pathologist. In 42 cases the original diagnosis was changed. The distribution of the tumours by histological type and grade is given in Table I. The most common tumour type (46%) was malignant fibrous histiocytoma (MFH).

All tumours were classified according to the SSS as low-grade (I) or high-grade (II) and as intracompartmental (A) or extracompartmental (B). Nine tumours were stage IA, 18 stage IB, 38 stage IIA and 72 stage IIB. The pre-operative diagnosis had been based on open biopsy in 50 cases and fine-needle aspiration biopsy in 64. In the remaining 23 cases, the diagnosis before treatment had been assessed solely on clinical and radiological signs.

The surgical procedures were classified as local or ablative and the margins obtained as intralesional, marginal, wide or radical. Local surgery had been used in 125 cases (91%) and amputation in 12. The surgical margin was intralesional in 12 cases, marginal in 56, wide in 59 and radical in 10. Local radiotherapy (35 to 60 Gy) had been given pre-operatively to 19 patients and postoperatively to 17. These two groups had undergone intralesional surgery (3 cases), marginal excision (16), wide excision (16) or radical excision (1). Adjuvant chemotherapy (adriamycin) had been given to ten patients with high-grade tumours, according to the protocol of the Scandinavian Sarcoma Group (Alvegård et al 1989b). This study was discontinued in 1986 as no improvement of survival had been observed. Metastases were diagnosed by plain radiography. Of 39 patients who developed pulmonary metastases, five had had combined therapy and none had been treated by surgery only.

Clinical follow-up, for the period 1972 to 1989, focused on local recurrence, metastases and survival. The mean follow-up time was ten years, the minimum five years. No patient was lost to follow-up. Patients who died of causes not related to the tumour were included in the prognostic analysis until the time of death.

Statistics. Survival and local recurrence rates were estimated by Kaplan-Meier life-table analysis of the data (Peto et al 1977). Prognosis was related to the following variables: sex, age, tumour location and size, histological type and grade, surgical stage, surgical procedure and margin. Tumour size was simplified into < 7 cm and > 7 cm, for better prognostic discrimination.

Cox's multivariate proportional regression analysis was used to test the relative significance of the different variables and to calculate the relative risk of tumour-related death, metastasis or local recurrence. For tumour grade, this risk was calculated as that for occurrence in high-grade tumours compared with low-grade tumours. For tumour size it was calculated for each 1 cm increment.

RESULTS

Relationship between various clinical and pathological features. There was no relationship between the histological type, grade, site, size and compartmentality of the tumour or between any of these and the age and sex of the patient. The mean size of each tumour in relation to sex, age, site, compartmentality, etc., ranged only from 7 to 9 cm. There was, however, a greater variation in mean tumour size between the histological types; the minimum was in leiomyosarcoma (5 cm) and the maximum in rhabdomyosarcoma (12 cm).

Treatment in relation to clinical and pathological features. The margins obtained at the operation, whether local or ablative, are given in Table II. The surgical procedure chosen and the margin obtained did not relate to tumour grade, size or compartmentality, but the tumours treated by amputation were all extracompartmental. The margin obtained was inadequate (intralesional or marginal) in 68 cases, of which 71% had high-grade lesions, 69% had tumours > 7 cm in diameter and 49% were extracompartmental. An adequate margin was achieved in 69 cases, of which 87% had high-grade lesions, 62% had tumours > 7 cm in diameter and 59% were extracompartmental.

Clinical course in relation to clinical and pathological features

Local recurrence. There was local recurrence in 49 patients (36%); in 33 within two years, in 13 within five years and in three patients after five years. The local recurrence rate was not related to tumour location, size, compartmentality or grade. The rate was 40% in extracompartmental compared with 28% in intracompartmental lesions; and 38% in high-grade compared with 28% in low-grade lesions. The local recurrence rates according to type of biopsy, surgical procedure and surgical margin are shown in Table III. The recurrence rate was higher after local surgery than after amputation, for obvious reasons, and higher after intralesional surgery than after other procedures. The statistical analysis of the local recurrence rate in relation to various clinical and pathological features is presented in Table IV.

Table II. Surgical margins in relation to surgical procedure

	Intralesional	Marginal	Wide	Radical
Local	12	56	59	1
Ablative	0	0	3	9

Of 19 patients who received pre-operative radiotherapy, eight had local recurrence; of 17 who had postoperative radiotherapy, four had local recurrence.

Comparison between the surgeon's and the pathologist's assessment of surgical margin showed agreement in 105 cases (77%). The local recurrence rate in those considered to have had an adequate margin (marginal/wide/radical) was 17 (25%) out of 69; in those with an inadequate margin the rate was 32 (47%) out of 68. There were 39 (32%) recurrences in the 121 patients in whom there was an adequate surgical margin according to the surgeon; 25 of the recurrences were within two years. The corresponding rates based on the pathologist's assessment were 31 (30%) recurrences in 103; 20 of these were within two years.

Metastasis. Distant metastases occurred in 49 (36%) patients. The lesions were diagnosed within two years in 29 patients, and within five years in 42; 39 patients had pulmonary and ten extrapulmonary metastases. A statistical analysis of the metastatic rate in relation to various

clinical and pathological features, and to local recurrence, is presented in Table V. Of the histological types the highest metastatic rate was observed in patients with MFH.

In patients who had received pre- or postoperative radiotherapy the metastatic rates were 13 out of 19, and 12 out of 17, respectively.

Metastases developed in 21 (43%) of 49 patients with local recurrence, compared with 28 (32%) of 88 patients without local recurrence. Metastasis preceded local recurrence in two patients.

Survival. Of the 137 patients 42 (31%) died from tumour disease; all had metastases and 24 also had local recurrence; 13 patients died from causes unrelated to tumour disease. For the whole series, the probability of a

Table III. Local recurrence in relation to type of biopsy, surgical procedure and surgical margin

	Local recurrence	
	Number	Per cent
Biopsy		
No biopsy	8	35
Fine-needle	23	36
Incisional	5	28
Both	13	41
Surgery		
Local	48	38
Ablative	1	8
Margin		
Intralesional	10	83
Marginal	22	39
Wide	17	29
Radical	0	0

Table IV. Local recurrence in relation to some clinical and pathological features

Covariate	Univariate			Multivariate	
	A*	B†	p value	RR‡	p value
Sex	32	39	0.3	–	NS
Age	28	43	0.1	–	NS
Location	36	36	0.9	–	NS
Size	28	49	0.02	–	NS
Grade	28	38	0.4	–	NS
Compartmentality	28	40	0.2	–	NS
Local surgery	8	38	0.08	–	NS
Adequate margin	25	47	0.01	1.8	0.02

* A, percentage of patients who developed local recurrence of those with respectively: female sex, age <60 years, distal location, tumour size <7 cm, low-grade, intracompartmental location, amputation, adequate margin

† B, percentage of patients who developed local recurrence of those with respectively: male sex, age >60 years, proximal location, tumour size >7 cm, high-grade, extracompartmental location, local surgery, inadequate margin

‡ RR, relative risk of local recurrence

Fig. 1a

Fig. 1b

Survival curves from Kaplan-Meier life-table analysis (a) related to the SSS combination; and (b) related to combined histological grade (LO = low-grade; HI = high-grade) and tumour size (small = <7 cm; large = >7 cm).

seven-year survival was 0.65. The seven-year survival rate for patients with local recurrence was 0.55, compared with 0.69 for those without recurrence. A statistical analysis of factors related to death is given in Table VI. Probability of survival in relation to SSS, that is to grade and compartmentality, is shown in Figure 1a; the survival rate for patients with IA tumours was 1.0; IB, 0.94; IIA, 0.48; and IIB, 0.57. A similar analysis in relation to grade and size is presented in Figure 1b; the survival rate for patients with small low-grade tumours was 1.0; large low-grade tumours, 0.93; small high-grade tumours, 0.63; and large high-grade tumours, 0.42. As can be seen, the lowest survival rate among all subsets was in patients with large high-grade tumours. It is notable that, among patients with high-grade tumours, there was no difference in survival between those with intracompartmental or extracompartmental tumours.

DISCUSSION

The present study confirms that histological grade and tumour size are the most important prognostic factors in soft-tissue sarcoma (Shiu et al 1975; Suit, Russell and Martin 1975; Russell et al 1977; Abbas et al 1981; Wright et al 1982; Trojani et al 1984; Bramwell et al 1985; Potter et al 1985; Rööser et al 1987, 1988; Ruka et al 1989; Rööser, Gustafson and Rydholm 1990; Stotter et al 1990). Previous studies have shown that, apart from high-grade and large size, male sex, proximal location and extracompartmental extension are ominous features (Simon, Spanier and Enneking 1979; Sears et al 1980; De Stéfani et al 1982; Enneking 1983, 1986; Trojani et al 1984; Rööser et al 1987; Alvegård et al 1989a; Kulander et al

1989), and possibly also tumour necrosis and vascular invasion (De Stéfani et al 1982; Costa et al 1984; Trojani et al 1984; Rööser et al 1987). It seems that some factors are consistently prognostically relevant, whereas others are so only occasionally. There are several conceivable explanations for the latter observation. One is that the criteria used in defining the variables may themselves vary. Another is that the variable, although relevant, is prognostically weak. The prognostic strength of a variable may depend on the series analysed and the design of the study.

The fact that only tumour size and grade gave prognostic information agrees with several other studies and implies that our results are valid. Conversely, our failure to detect other prognostic factors could reflect deficiencies in the design of the study. It must be remembered that our study was retrospective, that the numbers were small, and the series heterogeneous with respect to various clinical and pathological features. Some subgroups were too small to allow statistical evaluation. Finally, chemotherapy and radiotherapy, used in a limited number of cases, were not taken into consideration. On the other hand, the strength of our study is the absence of a referral bias. All patients in the study were treated primarily at our tumour centre and were free from metastases on admission; all clinical records were still available; and, all slides could be retrieved and were reviewed by one pathologist. No patient was lost to follow-up, the mean time of which was ten years. We believe therefore that our study, despite its minor shortcomings, offers valid information.

As for the two identified prognostic factors, histo-

Table V. Metastasis in relation to some clinical and pathological features and to local recurrence

Covariate	Univariate			Multivariate	
	A*	B†	p value	RR‡	p value
Sex	34	38	0.8	–	NS
Age	33	39	0.6	–	NS
Location	37	32	0.8	–	NS
Size	24	43	0.03	1.1§	0.0001
Grade	3	44	0.0001	15	0.0077
Compartmentality	40	33	0.5	–	NS
Adequate margin	38	34	0.8	–	NS
Local recurrence	32	43	0.2	–	NS

* A, percentage of patients who developed metastatic disease of those with respectively: female sex, age < 60 years, distal location, tumour size < 7 cm, low-grade, intracompartmental location, adequate margin, no local recurrence

† B, percentage of patients who developed metastatic disease of those with respectively: male sex, age > 60 years, proximal location, tumour size > 7 cm, high-grade, extracompartmental location, inadequate margin, local recurrence

‡ RR, relative risk of metastasis

§ size, per cm increment in tumour size

Table VI. Tumour-related deaths in relation to some clinical and pathological features and to local recurrence

Covariate	Univariate			Multivariate	
	A*	B†	p value	RR‡	p value
Sex	29	32	0.9	–	NS
Age	25	36	0.3	–	NS
Location	30	32	0.9	–	NS
Size	21	36	0.1	1.06§	0.04
Grade	3	38	0.0008	13	0.01
Compartmentality	32	30	0.9	–	NS
Local surgery	58	28	0.06	–	NS
Adequate margin	32	29	0.9	–	NS
Local recurrence	27	37	0.4	–	NS

* A, percentage of patients who died due to the tumour disease of those with respectively: female sex, age < 60 years, distal location, tumour size < 7 cm, low-grade, intracompartmental location, amputation, adequate margin, no local recurrence

† B, percentage of patients who died due to the tumour disease of those with respectively: male sex, age > 60 years, proximal location, tumour size > 7 cm, high-grade, extracompartmental location, local surgery, inadequate margin, local recurrence

‡ RR, relative risk of tumour-related death

§ size, per cm increment in tumour size

logical grade and tumour size, we were unable to show a correlation with other clinical or pathological features. Surprisingly, size was not related to site or compartmentality or to sex or age. The same applied to the grade of the tumour, which did not show a relationship to any other feature, not even tumour size. The latter observation clearly shows that grade and size are independent prognostic variables.

As mentioned before, several factors other than tumour size and grade have been claimed to have prognostic importance. Many investigators have, however, used only univariate analysis (Costa et al 1984; Ruka et al 1988) and this risks identifying factors as prognostic when they are merely intercorrelated with true prognostic factors. Some of the prognostic observations reported previously are therefore questionable. This risk can be avoided by using multivariate analysis and in our study, the information obtained in this way did not differ significantly from that obtained by univariate analysis. The reason was that there were no significant intercorrelations between the different factors analysed. None the less, it may be assumed that in some studies certain factors emerge falsely as prognostic due to statistical inadequacy, that is, the failure to identify intercorrelations.

Considering the wide application of the Surgical Staging System proposed by Enneking, it is reassuring that we were able to confirm some relationship between stage and survival. The difference in survival, however, between stage IA and IB patients was only 5% and there was no difference between stage IIA and stage IIB patients, indicating that the prognostic significance of compartmentality is virtually nil. In fact, the difference in survival between patients with intracompartmental (IA + IIA) and extracompartmental (IB + IIB) lesions was only 2%; it was the grade that proved to be the prognostically discriminating factor. For patients with low-grade tumours the survival rate was 97%, compared with 62% for those with high-grade tumours. Thus, the prognostic significance of SSS can be attributed almost exclusively to histological grade. This finding is in accordance with the only previous studies to use multivariate analysis on population-based material (Röösér, Attewell and Rydholm 1987; Röösér et al 1987, 1988). We therefore question the prognostic importance of SSS, as it is based largely on tumour compartmentality. For obvious reasons, its limited predictive strength applied not only to survival but also to metastatic rate.

Although the surgical stage of the tumours proved to be of only minor importance for survival, it seemed plausible that SSS would predict the local recurrence rate. In this study, however, we could not show any relationship between stage and local recurrence. In fact, not even clear-cut compartmentality was related to local recurrence; nor grade, which is less surprising. The only factors which did correlate with a higher rate of local recurrence were an inadequate surgical margin and large

tumour size. Although tumour size appears to be of importance for both survival and local recurrence, it is not considered in the SSS. Size was not found to correlate with compartmentality; there was no difference in size between the intracompartmental and the extracompartmental tumours.

Tumour size is a better predictor of clinical outcome in soft-tissue sarcoma than is compartmentality, and it should replace the latter in any staging system used for prognosis. Size is also more relevant than compartmentality in the surgical planning, as shown by its relationship to local recurrence. It would seem to be best to use a surgical staging system in which histological grade is combined with tumour size but, to our knowledge, there is no such system for soft-tissue tumours, although both factors are incorporated in the American Joint Committee system (Russell et al 1977). Only a report by Sears et al (1980) suggests a staging system based exclusively on histological grade and tumour size. The crucial problem with tumour size in such a system is to find the prognostic cut-off point in terms of tumour diameter or volume. Presumably, this could be established by using modern imaging techniques such as CT and MRI to measure the tumour in a prospective study of a well-defined series of soft-tissue tumours with adequate follow-up.

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