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Original Paper

Prognostic Factors in Soft Tissue Sarcomas: The Aarhus Experience

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In the present study, the outcome, patterns of local recurrence and survival, as well as prognostic factors, were evaluated in patients surgically treated for soft tissue sarcomas. Between January 1979 and July 1993, 316 consecutive patients were referred to the Sarcoma Centre in Aarhus with localised malignant soft tissue sarcoma of the extremities or trunk. If possible, the patients were treated with a limb-sparing resection, primarily by use of a wide excision. 50 patients received adjuvant radiotherapy. There were 161 men (51%) and 155 women (49%) median age 56 years (range 1–94 years). 94 patients (30%) had tumours in the trunk, including shoulder and buttock lesions, 163 (52%) in the lower extremity and 59 (19%) in the upper extremity. 52 patients (16%) had grade 1 tumour, 60 (19%) grade 2 and 204 (65%) grades 3A–3B. The 5-year local recurrence rate was 18% and the 5-year survival rate was 75%. Multivariate analysis indicated the following variables as independent unfavourable factors for local recurrence: extracompartmental location, histological high grade, local excision, no adjuvant radiotherapy and intralesional/marginal excision. Independent unfavourable factors for survival were advanced age, extracompartmental location, histological high grade, lower extremity location and large tumour size. If the variable local recurrence was included in the analysis, it was found to have a very strong influence on survival. Based on these variables, a prognostic model was developed. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: soft tissue sarcoma, surgical treatment, multivariate analysis, local recurrence, survival, prognostic factors
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INTRODUCTION

SOFT TISSUE sarcomas comprise a heterogeneous group of rare tumours arising from mesenchymal tissue. In Denmark approximately 200 new cases of non-visceral malignant soft tissue sarcomas are diagnosed annually [1]. Because of the small number, treatment is centralised in a few centres. The Sarcoma Centre in Aarhus serves a population which is approximately 1.5 million. A number of studies from different treatment centres have investigated prognostic factors in the treatment of soft tissue sarcoma [2–8]. It is well known that the histological grading and tumour size are the most important prognostic factors for patients with soft tissue sarcomas. Other factors, such as age, sex, anatomical location, compartmental site and surgical margin, have been investigated, but the importance of these parameters for overall survival is still questionable. Therefore, it is important to continue to look for prognostic parameters that may optimise the treatment of patients. The aim of the present study was to investigate possible prognostic factors and their influence on local recurrence risk and survival.

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PATIENTS AND METHODS

Between January 1979 and July 1993, 336 consecutive patients received surgical treatment for a localised malignant soft tissue sarcoma at the Sarcoma Centre in Aarhus. 20 patients were excluded from the study because of tumour location in viscera, retroperitoneum or in the head or neck region, thus leaving 316 patients for the study.

Surgery and adjuvant therapy

48 patients (15%) were referred with a local recurrence after inadequate treatment at a local hospital and the other 268 patients (85%) were referred after a biopsy (46 patients),

an inadequate resection (126 patients) or without any treatment (96 patients).

The patients were diagnosed using an incisional biopsy. During the observation period, surgery at the centre was primarily performed by two surgeons according to the same principles. The extent of the surgical treatment was primarily dependent on the histopathological grade. Furthermore, treatment was planned according to tumour location and size. When possible, a local, limb-sparing operation with a wide margin was performed. Patients having undergone surgery elsewhere or referred with local recurrence were treated according to the same surgical principles as that of previously non-treated patients.

49 patients (16%) received adjuvant radiotherapy, 12 patients (4%) received adjuvant chemotherapy and 1 patient received both adjuvant radiation and chemotherapy. Adjuvant radiotherapy was given pre-operatively for 16 patients and postoperatively for 34 patients and was, primarily given to patients treated with an intralesional or marginal excision. In most cases, the total dose given was 50 Gy in 25 fractions. Adjuvant chemotherapy was given to patients with extraskeletal osteosarcomas (cisplatin and doxorubicin) and to 3 patients with soft tissue sarcomas who were included in a protocol performed by the Scandinavian Sarcoma Group (doxorubicin). The details of the adjuvant chemotherapy were not analysed further in the present study.

Pathology

The histopathological evaluation was performed at the University Department of Pathology and exclusively by the same pathologist, based on examinations of biopsy and/or surgical specimens. The microscopic analysis evaluated the adequacy of the surgical procedure by examination of resection margins. If tumour cells were present at the margin or within 1 cm of the margin, the surgery was classified as a marginal resection. The histopathological grading was based on mitotic activity, cellularity, anaplasia and necrosis using a three grade scale, as described elsewhere [9]. High grade tumours were furthermore divided into grade 3A or 3B based on the number of mitoses alone [10].

Patient follow-up

All patients were seen every 3–4 months for the first 3 years after surgery, at 6 month intervals for 5 years and yearly up to a total of 10 years. A physical examination and a chest X-ray (grade 2 and 3) were performed at the follow-up visits. Other investigations, such as computer tomography (CT) scanning of the lungs, were only carried out in cases of observations suspicious of metastasis.

Any patient with a local recurrence or distant metastasis was fully evaluated to determine the extent of disease. If possible, surgical resection was offered to patients with a locally recurrent tumour. Patients with metastasis were offered surgical treatment, chemotherapy or no treatment, depending on the number, localisation and size of the metastasis. In the present analysis, the following were defined as tumour-related death: death following treatment, death due to tumour or metastasis or death from an intercurrent disease with tumour or metastasis. All patients were followed until June 1997 or until death. The minimum follow-up period was 46 months or until death. The median follow-up time was 71 months. 2 patients emigrated in the follow-up period and were lost to follow-up.

Statistics

The log-rank test was used to evaluate the significance of individual factors. If the log-rank test showed a correlation between a descriptive variable and local recurrence or survival, this variable was included in Cox's proportional hazards model for multivariate analysis. Size and age were treated as ordinal variables in the multivariate analysis. The Cox proportional hazard identifies independent prognostic factors and each factor has a coefficient which reflects the importance of this specific factor. The prognostic factors concerning survival and their respective coefficients were included in a prognostic grading model that enables patients to be identified with good or poor prognosis. The level of significance was set at $P < 0.05$. Local recurrence and survival rates were estimated using the method of Kaplan–Meier.

RESULTS

Univariate analysis

The univariate analysis of possible prognostic factors for local recurrence and survival is shown in Table 1. Neither the 5-year local recurrence rate nor survival rate were affected by sex, duration of symptoms, wound complication or adjuvant radiotherapy.

The median age at diagnosis was 56 years (range 1–94 years). The distribution of age and sex is shown in Figure 1. Patients older than the median age had a greater risk of local recurrence ($P = 0.004$) and shorter 5-year survival ($P < 0.0001$).

Table 2 shows the anatomical location of the tumours. The thigh was the most common location (34%). Shoulder and buttock lesions were classified as trunk lesions. Location did not affect local recurrence risk, but patients with a tumour in the lower extremity had a poorer survival than patients with a tumour in the upper extremity or trunk (Table 1; $P = 0.005$).

Patients with a deep tumour had a significantly poorer survival than those with a subcutaneous or a cutaneous tumour, although tumour depth did not significantly influence local recurrence risk. Patients with tumours placed in only one muscle compartment ('intracompartmental') fared better in terms of local recurrence or survival, than those with tumours placed outside an ordinary compartment ('extracompartmental', e.g. the axillary region and the popliteal fossa or tumours spreading into the adjacent compartment; Table 1).

Tumour size was measured using the pathological specimen, if available, or alternatively by magnetic resonance imaging (MRI) or CT-scanning. For patients surgically treated

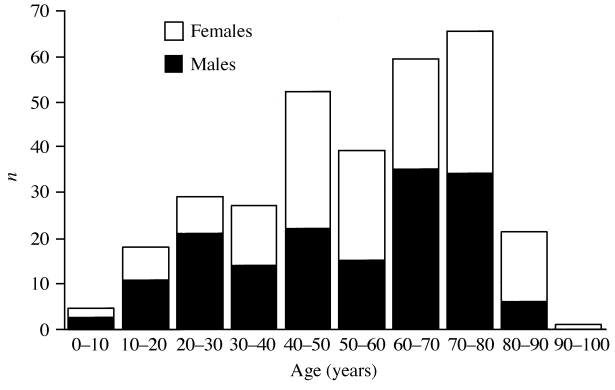

Figure 1. Distribution of 316 patients according to age and sex.

Table 1. *Actuarial local recurrence-free rates and survival rates according to various clinical factors*

Factors	No. of patients (%)	Local recurrence-free rate 5-year	Local recurrence-free rate *P*-value	Survival rate 5-year	Survival rate *P*-value
Age (years)					
0–56	156 (49)	0.87	0.004	0.87	< 0.0001
≥ 56	160 (51)	0.76		0.62	
Sex					
Male	161 (51)	0.81	NS	0.76	NS
Female	155 (49)	0.82		0.72	
Location					
Trunk*	94 (30)	0.78	NS	0.77	NS
Upper extremity	59 (19)	0.86		0.91	
Lower extremity	163 (52)	0.77		0.68	0.005
Duration of symptoms (years)					
≤ 1	216 (69)	0.82	NS	0.73	NS
> 1	96 (32)	0.84		0.78	
Tumour size (cm)†					
≤ 5	154 (49)	0.82	NS	0.88	< 0.0001
> 5	158 (51)	0.82		0.62	
Tumour depth					
Superficial	130 (41)	0.85	NS	0.87	< 0.0001
Deep	186 (59)	0.79		0.66	
Histological grade					
Grade 1	52 (16)	0.94	NS	1.00	NS
Grade 2	60 (19)	0.90	0.01	0.93	0.005
Grade 3A	97 (31)	0.77	NS	0.75	0.0001
Grade 3B‡	107 (34)	0.74		0.50	
Compartmentalisation					
Intracompartmental	198 (63)	0.88	0.0006	0.80	< 0.0001
Extracompartmental	118 (37)	0.71		0.65	
Surgical treatment					
Local excision	249 (79)	0.79	0.03	0.77	0.005
Amputation	67 (21)	0.92		0.63	
Surgical margin					
Intralesional/marginal	47 (15)	0.63	0.002	0.70	NS
Wide	223 (71)	0.85	NS	0.79	0.001
Compartmental	46 (15)	0.85		0.57	
Wounds complication					
Yes	61 (19)	0.77	NS	0.73	NS
No	255 (81)	0.83		0.75	
Adjuvant radiotherapy					
Performed	50 (16)	0.88	NS	0.80	NS
Not performed	266 (84)	0.80		0.73	
Local recurrence					
Yes	58 (18)			0.50	< 0.0001
No	258 (82)			0.81	

NS, not significant. *Including shoulder and buttocks lesions. †Data missing for 4 patients. ‡Including 22 patients with a high grade tumour not otherwise specified.

elsewhere before referral, the size measured at the referring hospital was used. Tumour size could not be obtained in 4 cases. The maximum diameter ranged from 1 to 37 cm with a median of 6 cm. The patients were divided into two groups according to the largest diameter: ≤ 5 cm or > 5 cm. There was no significant difference in local recurrence risk in the two groups, but patients with large tumours had poorer survival ($P < 0.0001$, Table 1).

Table 3 lists the histological types. Malignant fibrous histiocytoma (MFH), liposarcoma and leiomyosarcoma were the commonest tumours representing 31, 13 and 12%, respectively. None of the 11 patients presenting an extraskeletal osteosarcoma were paediatric patients, since the youngest patient was 32 years of age. However, among the 11 patients with a rhabdomyosarcoma, 3 patients were aged 15 years or younger at the time of surgery. Apart from these three rhabdomyosarcomas, no other paediatric tumours were included in the study.

Table 1 shows the histological grade of the tumours. For 22 lesions, it was not possible to distinguish between grade 3A and 3B so these patients were classified as grade 3B lesions, although this could minimise any difference between

Table 2. Anatomical location of soft-tissue sarcomas

Anatomical location	Number (%)
Trunk	94 (30)
Thoracic wall	31 (10)
Abdominal wall	17 (5)
Shoulder	24 (8)
Buttock	22 (7)
Upper extremity	59 (19)
Upper arm	21 (7)
Elbow	6 (2)
Lower arm	23 (7)
Hand	9 (3)
Lower extremity	163 (52)
Thigh	109 (34)
Knee	13 (4)
Lower leg	35 (11)
Foot	6 (2)
Total	316

the two groups. There was a significantly higher number of local recurrences ($P = 0.01$) among patients with high grade 3 tumours than patients with low grade (grade 1) or intermediate grade 2 tumours. The difference in survival between patients with grade 2 and 3A ($P = 0.005$) and between patients with grade 3A and 3B ($P = 0.0001$) were significant.

67 (21%) patients had amputations and 249 (79%) underwent local resection. Patients treated with a limb-sparing resection had a greater risk of local recurrence ($P = 0.03$), but better overall survival ($P = 0.005$). However, the two groups are not comparable, since tumours which were small and favourably situated tended to be treated with a local resection, whereas large extracompartmental tumours were more often treated with an amputation. According to the surgical margins as defined by Enneking and colleagues [11, 12], the patients were treated as follows: intralesional excision in 5 patients, marginal excision in 42, wide excision in 223 and compartmental excision in 46. In the analysis, patients treated with an inadequate surgical margin, i.e. intralesional or marginal excision, were grouped together, and had a greater risk of local recurrence ($P = 0.002$), although survival was not affected. Those who received a wide excision had a better survival ($P = 0.001$) than those given a compartmental excision.

58 patients (18%) developed a local recurrence, and 46 of these had the recurrence surgically removed. Patients who developed a local recurrence had a significantly poorer overall survival than patients who did not ($P < 0.0001$).

Table 3. Histological types of soft tissue sarcomas

Histological type	Number (%)
MFH	97 (31)
Liposarcoma	41 (13)
Fibrosarcoma	16 (5)
Leiomyosarcoma	39 (12)
Malignant schwannoma	22 (7)
Synovial sarcoma	20 (6)
Dermatofibrosarcoma	26 (8)
Rhabdomyosarcoma	11 (3)
Angiosarcoma	15 (5)
Extraskeletal osteosarcoma	11 (3)
Other types	18 (6)
Total	316

91 patients (29%) developed distant metastases, of whom 54 (59%) had lung metastases, 20 (22%) had other metastases (especially bone metastases) and 17 (19%) had both lung metastases and other types. The metastases were diagnosed at a median of 12 months after the primary surgery. Distant metastases were the direct cause of death in 79 of the 91 patients (87%) with disseminated disease, and the other 12 (13%) are still alive.

90 patients (28%) had a tumour-related death. 2 of these patients died because of a postoperative lung embolism. 40 patients (13%) died of other causes with no signs of a tumour.

Multivariate analysis

Figure 2 illustrates the local recurrence-free rate. At 5 years, 18% of the patients had developed a local recurrence. Eighty-six per cent of the total number of recurrences occurred within 3 years. 7 patients had a local recurrence more than 5 years after the date of surgery. The factors that were significant for the development of a local recurrence using the univariate analysis were further tested in a multivariate analysis. Radiotherapy was included as a variable in this analysis, although it did not show significance by univariate analysis. In this study, radiotherapy was primarily given to patients having an inadequate surgical treatment (marginal resection). The patients in the group treated with adjuvant radiotherapy, therefore, contained a disproportionately high number of patients with an inadequate surgical treatment. It is a well-known fact that surgical adequacy is one of the most important factors in the development of a local recurrence. Therefore, this unequal distribution could diminish any difference in the risk of local recurrence between the group treated with adjuvant radiotherapy and the group not treated with adjuvant radiotherapy. The following factors, therefore, were tested in the multivariate analysis: age, compartmentalisation, histological grade, type of surgery, surgical margin and radiotherapy. Table 4 shows the result of the analysis. Only age lost its significance. Radiotherapy reduced the number of local recurrences significantly.

Figure 3(a) illustrates the overall survival rate. The 5-year survival rate was 75%, the 10-year survival rate was 67%. The variables which showed significance in the univariate analysis were tested in the multivariate analysis. Again we included radiotherapy as a variable, so the following variables

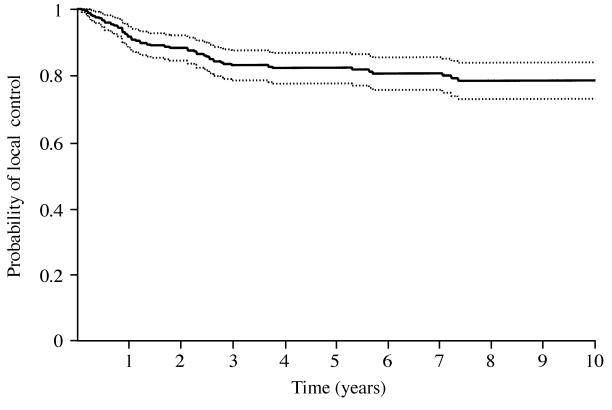

Figure 2. Local recurrence-free rate for all 316 patients (95% confidence intervals are shown by the broken lines).

Table 4. *Unfavourable prognostic variables for local recurrence. The result of a multivariate statistical analysis*

Variable	Coefficient*	S.D.	*P* value
Compartmentalisation	0.95	0.27	0.0004
Histological grade	0.67	0.14	< 0.0001
Type of surgery	1.69	0.48	0.0004
Radiation therapy	1.31	0.46	0.005
Surgical margin	0.58	0.26	0.03

*Coefficient of the local recurrence-free function. S.D., standard deviation.

Table 5. *Unfavourable prognostic variables for survival. The result of a multivariate statistical analysis*

Variable	Coefficient*	S.D.	*P* value
Age	0.85	0.25	0.0007
Compartmentalisation	0.72	0.22	0.0005
Histological grade	0.94	0.15	< 0.0001
Anatomical location	0.44	0.15	0.003
Tumour size	0.6	0.14	0.004

*Coefficient of the survival function. S.D., standard deviation.

were included in the analysis: age, anatomical location, tumour depth, compartmentalisation, tumour size, histological grade, type of surgery, surgical margin, radiotherapy and local recurrence. The result of the analysis is shown in Table 5. Age, compartmentalisation, histological grade, anatomical location and tumour size were independent prognostic factors for survival. Local recurrence, if included in the model, also showed significance.

The variables affecting survival excluding local recurrence were included in a prognostic grading model. Local recurrence as a variable was excluded because the purpose was to produce a model which gives the clinician a reasonable estimation of the prognosis for every single patient at a very early stage of treatment. The prognostic model was based on the five variables which were found to be independent prognostic factors for survival; age, compartmentalisation, histological grade, tumour size and anatomical location. Every prognostic factor was given a certain weight, which was the coefficient calculated in the Cox regression analysis (Table 6), and each patient was assigned five values according to their specific characteristics. Adding these five values resulted in an overall score with 0 as the minimal value and 5.86 as the maximum, with small values correlated with good survival and large values with poor survival. For example, a 50 year old man with an intracompartmental tumour in the thigh, 7 cm in diameter and grade 3A would score 0 + 0 + 1.88 + 0.6 + 0.87 = 3.35. The patients in the study were divided into four equally sized groups according to the score (Table 7 and Figure 3b). The mortality rates differed significantly between the groups. The score made it possible to identify patients with good, poor and very poor prognosis.

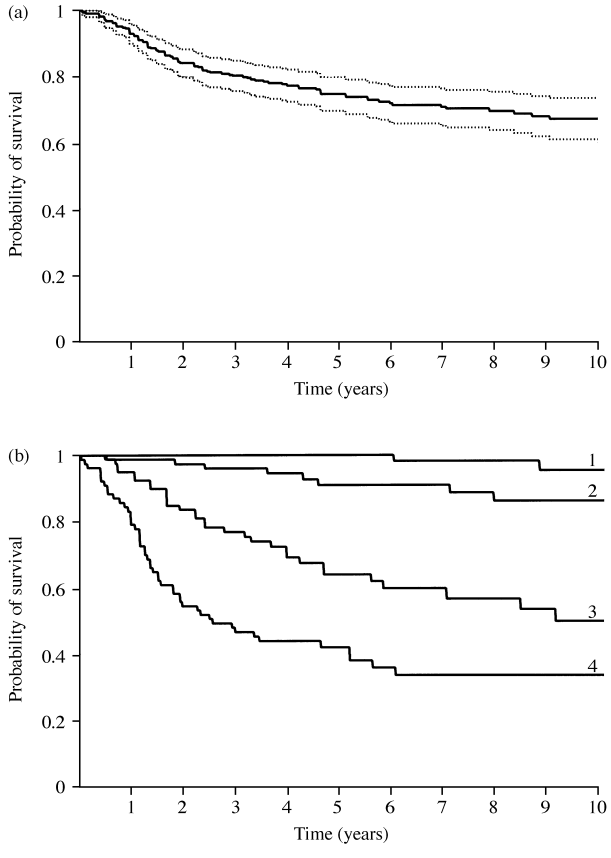

Figure 3. (a) Survival rate for all 316 patients (95% confidence intervals are shown by the broken lines). (b) Survival rates in 316 patients divided into four equal size groups according to calculated score by using the prognostic grading model. Group 1 contains patients with the lowest score and group 4 contains patients with the highest score (see text and Table 7 for further details).

DISCUSSION

The present study analysed prognostic factors for local recurrence and survival in 316 consecutively treated sarcoma patients. The patients in this study had tumours localised in

Table 6. *The values used in the prognostic score*

Factor	Variable	Value
Age (years)	< 56	0
	> 56	0.85
Compartmentalisation	Intracompartmental	0
	Extracompartmental	0.72
Histological grade	Grade 1	0
	Grade 2	0.94
	Grade 3A	1.88
	Grade 3B	2.82
Tumour size (cm)	≤ 5	0
	> 5	0.6
Anatomical location	Upper extremity	0
	Trunk site	0.44
	Lower extremity	0.87

Table 7. *The four groups from the prognostic model*

Group	Prognostic score	Number of patients	5-year survival (%)	*P* value
1	≤ 2.20	78	100	
				0.01
2	> 2.20 ≤ 3.53	80	88	
				0.0002
3	> 3.53 ≤ 4.39	77	69	
				0.0003
4	> 4.39	77	43	

the extremities or trunk. We excluded patients with tumours in the head and neck region because these patients offer great difficulties for the surgeon, as it is very difficult to remove a tumour in these regions with an adequate margin without mutilating the patient.

It is well-documented that an inadequate surgical margin increases the risk of local recurrence [2, 3, 5, 6, 8, 13–16 and present study]. So, it is of great importance to plan surgery so as to remove the tumour with a free margin to minimise the risk of local recurrence. Similarly to what has been seen in some [5, 15], but not in other studies [3, 6, 13, 17], we found that patients with high grade tumours had an increased risk of local recurrence compared with patients with low grade tumours. In the present study, we found a greater number of local recurrences among patients with extracompartmental tumours. Extracompartmental tumours may be more aggressive and offer greater surgical difficulties and, therefore, have a higher risk of local recurrence than compartmental tumours. This is supported by a study by Rydholm [18], whilst Bell and colleagues [13] and Gaynor and associates [8] could not correlate the compartmental site with the risk of local recurrence.

The 5-year local recurrence rate was 18% in the present study. This is in concordance with other similar studies [6, 15, 16] which found 5-year local recurrence rates between 18 and 26%. Enneking [19] found better local control in patients treated with a radical resection compared with patients treated with a wide resection, but he did not further comment on the distribution of the patients in the two groups. The present study was not able to show an improved local control in patients treated with a radical resection compared with those treated with a wide resection. In order to improve local control without performing a radical resection, e.g. an amputation, adjuvant radiotherapy has been used. Radiotherapy has been proven effective in the treatment of soft tissue sarcomas and a number of randomised prospective studies have shown that a wide resection and adjuvant radiotherapy is as effective as radical surgery [20, 21]. Some studies even found a reduced local recurrence risk when using adjuvant radiotherapy or brachytherapy [3, 5, 22]. However, these studies were primarily retrospective analyses and it may be questionable to evaluate the effect of radiation from such data, as the radiotherapy technique, total dose and indications may differ. To show a clear correlation, it is necessary to perform prospective and, if possible, randomised studies.

Histological grading as the most important indicator for overall survival has been widely accepted and again confirmed in the present study. Also, tumour size has been accepted to be of prognostic importance in all except a few studies [16, 17]. The influence of patient age and compartmental site of the tumour are not so well defined. Some investigations, including the present study, found age to be of importance for survival [7, 16, 18, 23], but many other studies were not able to find any correlation between age and survival [3, 6, 14, 15, 17, 24, 25]. Similarly, the present analysis very clearly showed a poor prognosis in patients with an extracompartmental tumour—a finding also reported by Rydholm and colleagues [18, 23], whilst other studies have not found this correlation [16, 26, 27]. In the present analysis, patients with a tumour in the lower extremity had increased mortality as compared with patients with tumours of the trunk or upper extremity. Although tumours in the lower extremity in the present analysis were larger and more malignant, the multivariate analysis took this into account and adjusted for these biases. This agrees with Pisters and colleagues [6] who found a worse prognosis for patients with a tumour in the thigh, whilst Ravaud and associates [17] and Levay and colleagues [15] found the poorest prognosis for patients with a tumour in the trunk. In contrast, most other studies have not found any correlation between anatomical location and survival [14, 16, 18, 23–25].

In the present study, the univariate analysis surprisingly showed a better survival rate among patients treated with a wide surgical margin compared with patients treated with a compartmental margin. Subsequently, the multivariate analysis failed to show any statistical significant correlation between surgical margin and survival. These findings could be due to the definition of wide and compartmental margin or could be explained by the fact that the two groups were not comparable. In a number of other studies [5, 14, 16, 28], as in the present study, no statistical correlation was found between inadequate surgery and distant metastases, although there was a strong relationship between adequacy of surgery and local recurrence. It is known that metastatic spread may occur early in tumour development [29] and patients with small, undetectable metastasis could very likely be equally spread among those who receive adequate surgery and those who receive inadequate surgery, which would tend to minimise any difference. Our analysis showed local recurrence to be an unfavourable prognostic factor for survival, a finding also observed in other studies [3, 16, 23].

Based on the five prognostic factors for survival, a prognostic model was produced. A similar model was used by Rydholm and colleagues [23], although other variables were included. Patients in groups 1 and 2 had a good prognosis, whereas patients in groups 3 and 4 had a poor prognosis. It is of importance that 25% of the patients with a high grade sarcoma were placed in group 1 or group 2 with good prognosis. Thereby the score could further subdivide patients with high grade sarcomas and identify those patients who had a good prognosis. However, this score was based on the specific selection of patients included in the present study in the period between 1979 and 1993. The treatment of sarcoma patients at the Sarcoma Centre in Aarhus has, as in other centres, been changed and adjuvant radiotherapy is now more widely used and the number of amputated patients has reduced. These alterations in the treatment could change the prognostic value of the score. Therefore, to show a predictive value of the prognostic score it has to be applied prospectively to newly referred patients. Alternatively, it could be tested in a group of patients from another institution. At the Sarcoma Centre in Aarhus the prognostic score will be tested in future patients referred to the centre to examine the usefulness of the model.

Although a relatively large group of patients with soft tissue sarcomas responds well to treatment and has a high disease-free survival rate, a number of patients will have a poor prognosis. In the future, the primary challenge must be to identify patients with a high risk of developing disseminated disease at an earlier stage than is possible today and, if available, to offer these patients adjuvant systemic treatment. The prognostic grading model presented in this study may help to identify the patients with a very poor prognosis. At present, adjuvant systemic chemotherapy has not proven effective in prospective studies. A recent meta-analysis showed an effect

of adjuvant chemotherapy on progression-free survival, but not on overall survival [30]. Our data suggest that future randomised trials should test chemotherapy only in the group of patients with a high risk of metastasis.

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