DNA content prognostic in soft tissue sarcoma

102 patients followed for 1–10 years

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In a prospective study of 102 patients with soft tissue sarcoma, the prognostic importance of DNA content and clinicopathologic features was analyzed. Based on DNA flow cytometry, 37 lesions were diploid (normal DNA content) and 65 were nondiploid (abnormal DNA content). The 5-year metastasis-free survival rate of the whole series was 0.59. The survival rate was 0.77 for patients with diploid tumors and 0.48 for those with nondiploid tumors ($P = 0.01$). Multivariate analysis identified two independent metastatic risk factors: increasing tumor size and nondiploidy. Unexpectedly, high malignancy grade (III–IV) was not found to be an independent risk factor for metastasis. The risk of metastasis was strongly related to the number of risk factors present. Thus, the 5-year survival for the 76 patients with no or one risk factor was 0.69, as compared with 0.30 for the 26 patients with two risk factors ($P < 0.0001$).

Our study shows that metastatic disease in soft tissue sarcoma is closely related to nondiploidy. A prognostication model based on DNA content and tumor size was found to discriminate between patients with a good and a poor prognosis after surgical treatment. The model can be used to identify patients who should be excluded from trials with adjuvant chemotherapy.

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Prediction of the clinical course in soft tissue sarcoma is difficult mainly because of the histologic heterogeneity of the tumors, which is associated with great uncertainty. Although histogenetic classification has become more accurate with the aid of immunohistochemical markers and electron microscopy, it remains of limited prognostic value. Malignancy grading appears to be of greater relevancy. Still, there is a need of improved characterization of soft tissue sarcomas for both prognostic and therapeutic purposes.

The considerable treatment morbidity associated with adjuvant chemotherapy makes it imperative to identify and exclude those patients with soft tissue sarcoma who have a good prognosis after surgical treatment alone. Various staging systems, based on clinical and histologic features, have been proposed to improve prognostication and patient allocation to different treatment protocols (Russel et al. 1977, Hajdu 1979, Rydholm 1983, Enneking 1986, Rööser 1987, Alvegård et al. 1989a). However, the validity of various clinical and histologic features is controversial. Some found to be of decisive prognostic importance, such as sex and local recurrence, have emerged as irrelevant when applied to new series of patients (Rööser 1987).

Cellular DNA content in soft tissue sarcoma is related to histologic grade (Kreicbergs et al. 1987, Xiang et al. 1987, Matsuno et al. 1988). Low-grade lesions generally seem to be diploid (normal DNA content), whereas the majority of high-grade lesions are nondiploid (abnormal DNA content). However, of greater interest are lesions exhibiting a discrepancy between DNA content and histologic grade, i.e., nondiploid low-grade tumors and diploid high-grade tumors. Whether or not DNA analysis provides prognostic information beyond that obtained by histologic malignancy grading is still unclear. Thus, Matsuno et al. (1988) could not relate ploidy level to the clinical course; on the other hand, the Scandinavian Sarcoma Group reported that nondiploidy was an independent risk factor for metastasis in soft tissue sarcoma (Alvegård et al. 1989b).

In this prospective study of soft tissue sarcoma, DNA content has been related to the clinical course of the disease. The prognostic significance of ploidy has been analyzed separately, but also in relation to different clinical and histologic features.

Patients and methods

The study was based on a prospective series of 102 patients with soft tissue sarcoma of the extremities and trunk treated at our hospital between 1980 and

Table 1. Patient and tumor characteristics in 102 soft tissue sarcoma cases

Case	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U
0	86	1	44	2	3	1	3	1	1	1	0	0	0	2	1	0	15	7	0	22	2
2	86	1	29	0	9	8	3	0	1	27	0	2			1	0		4	0	16	2
20	86	0	68	0	0	1	3	0	0	17	0	0	0	2	0	0		3	0	10	2
26	84	1	79	0	10	0	2	1	0	9	0	0			1	0	43	13	0	55	2
28	86	1	70	0	9	0	2	1	1	20	0	1			0	0		18	0	30	2
31	81	1	38	0	9	1	3	0	1	9	0	4			0	0	92	96	1	102	1
41	86	0	20	1	0	0	2	0	0	12	0	1			0	0	10			40	0
50	85	1	73	0	11	1	3	0	0	15	0	0			1	0	23			46	3
60	86	1	32	1	12	12	3	1	1	6	0	1			1	0				44	0
62	86	1	64	1	2	1	3	1	1	12	0	2			0	0				46	0
65	86	1	75	0	2	1	4	1	1	20	1	2			0	0	2	3	0	3	2
69	84	0	74	0	7	1	4	0	2	17	0	0			0	0	17	23	0	31	2
74	86	0	60	1	0	1	4	0	1	4	0	2			0	0				47	0
85	86	0	48	0	9	10	3	0	1	8	0	3			0	1		5	0	11	2
86	86	1	90	1	5	2	3	0	1	9	0	2			0	0		24	0	26	2
125	86	1	36	2	9	6	3	0	0	6	0	0	0	2	0	0		13	0	38	2
148	86	0	73	1	4	1	4	0	1	7	0	1			1	0				45	0
154	84	1	71	1	9	2	2	0	0	7	0	3			0	0				75	0
158	86	1	31	1	2	1	3	1	0	11	0	1			1	0				36	0
160	86	0	66	1	5	9	3	0	0	3	0	2			0	0				36	0
170	86	0	47	0	9	1	3	0	1	12	0	2			0	0	4	12	0	24	2
182	86	1	76	2	4	1	3	1	1	9	0	0			1	0				40	0
184	82	0	35	0	11	7	3	0	0	19	0	3			1	1				62	0
190	82	1	61	1	1	1	3	1	0	14	0	1			0	0				65	0
203	85	1	77	1	9	1	4	0	1	14	0	3			0	0				51	0
235	86	1	66	1	5	3	4	0	1	7	0	2			0	0				43	0
237	83	0	74	1	0	1	3	0	0	11	0	2			0	0	27			72	0
252	86	0	61	2	11	1	4	0	1	3	0	0	0	2	0	0				39	0
255	87	0	75	0	9	1	4	0	1	8	0	1			0	0				19	3
257	86	1	81	2	3	9	2	1	0	15	0	0			0	0	8	14	0	15	2
258	87	1	78	1	5	1	3	0	1	13	0	2			0	0	14			41	0
261	87	0	79	0	11	2	2	0	1	5	0	0			0	0	20			41	0
270	83	1	37	0	2	0	2	1	0	6	0	2			0	0				86	0
277	83	0	68	1	11	1	3	0	1	3	0	2			0	0				80	0
282	82	1	51	1	0	1	3	0	1	6	0	1			0	0	28			90	
283	82	1	70	1	11	1	3	1	2	15	1	4			0	0		5	0	23	2
286	84	0	46	1	5	1	3	0	1	4	0	4			0	0				53	3
292	80	0	67	1	0	1	3	0	0	8	0	2			0	0				116	0
293	84	0	79	1	9	1	3	0	1	8	0	4			0	1		6	0	21	2
294	84	1	87	1	9	1	4	0	1	10	0	2			0	0	6	10	0	20	2
295	83	1	84	1	9	1	4	0	1	10	0	2			0	0				81	0
297	84	0	73	1	9	1	4	0	1	12	0	3			0	0				15	3
298	81	1	63	1	9	1	3	0	1	20	0	0			0	0		9	0	9	2
299	84	0	69	1	9	1	4	0	1	8	0	2			0	0	2	8	0	8	1
300	81	0	65	0	9	1	3	0	1	5	0	2			0	0		13	0	24	0
301	84	0	47	0	9	1	4	0	1	8	0	3			0	1		11	2	60	0
308	83	1	62	1	9	4	2	0	0	12	0	3			0	0				82	0
309	84	0	73	1	11	2	2	1	0	10	0	1			0	0	31			36	3
310	82	1	30	2	11	0	2	1	0	3	0	0	0	2	0	0				97	0
311	81	0	79	1	12	7	4	1	0	7	0	0			0	0	36			89	3
313	82	1	24	1	11	2	2	0	0	9	0	1			0	0				72	0
314	82	0	49	1	11	2	2	0	0	10	0	3			0	0				97	0
322	83	1	88	0	2	0	2	1	0	17	0	1			0	0		14	0	15	2
323	83	0	80	0	11	9	3	1	1	12	0	0	1	4	0	0		5	0	9	2
324	83	0	83	0	11	2	3	0	1	7	0	0			1	0	62	63	2	66	3
325	84	0	49	1	6	7	4	1	0	12	0	1			1	0				61	0
326	82	1	12	0	9	7	3	0	1	12	0	2			0	1		7	0	22	2
333	82	1	75	1	7	5	3	0	0	30	1	2			0	0				57	3
363	81	0	40	1	9	2	2	0	2	9	0	2			0	0		34	1	55	2
365	82	0	70	0	6	0	3	1	1	6	0	1			1	0				25	3
367	80	1	64	2	12	7	3	1	1	4	1	2			0	0		17	0	58	2
381	84	0	55	1	3	10	4	0	1	20	0	1			0	1	11	7	0	19	2
397	83	1	62	1	11	1	4	0	2	9	0	2			1	1				72	0
416	84	1	80	1	11	0	3	0	0	7	0	2			0	0				23	3
423	81	1	61	1	12	7	3	1	1	8	1	4			0	0		35	0	71	2
439	83	0	73	1	4	10	3	1	2	20	0	1			0	0	10	4	0	13	2
440	82	0	75	1	9	1	3	0	1	15	0	1			1	0		1	0	13	2

Case	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U
446	81	1	73	1	9	2	2	0	0	15	0	2			0	0				109	0
465	81	0	66	0	0	1	3	0	1	20	0	2			0	0		1	0	2	2
467	84	0	82	0	9	7	4	0	0	25	1	4			0	0		1	0	1	2
473	87	1	46	1	9	1	3	0	1	6	0	1			0	0				36	0
502	87	0	59	0	9	0	1	0	0	10	0	4			0	0				37	0
519	87	0	69	0	9	2	2	0	1	11	0	3			0	0				30	0
539	87	0	58	0	9	1	3	0	1	14	0	2			0	0		7	0	18	2
556	87	1	63	0	9	1	4	1	0	15	0	0			1	0		36	0	36	1
558	87	1	60	1	2	1	4	0	1	5	0	2			1	0				30	0
571	81	1	28	0	5	0	1	0	0	2	0	2			0	0				91	0
617	87	1	19	0	11	4	3	1	1	15	1	4			0	0		19	0	25	2
624	87	0	39	0	2	3	3	0	1	8	0	2			0	0		28	0	36	1
632	87	1	67	0	11	2	2	0	2	20	0	2			0	0	15			27	0
641	88	1	73	1	0	1	3	1	0	8	0	0			0	0				17	0
642	88	0	55	0	9	14	4	0	1	10	0	1			0	0	7	12	0	13	2
647	87	0	77	2	10	1	3	0	1	8	0	0	0	0	1	0	5			26	0
654	87	0	52	0	0	14	1	0	0	6	0	1			0	0				27	0
668	88	1	74	0	9	10	3	1	1	9	0	2			0	0				23	0
675	88	0	77	1	5	1	4	1	1	10	0	1			1	0				23	0
706	88	1	65	2	3	8	3	1	1	6	0	1			1	0	20			24	0
725	88	0	70	0	9	1	3	1	1	15	0	2			0	0		11	0	19	1
726	88	1	70	0	3	8	3	1	1	8	0	1			1	0				23	0
734	88	0	67	1	3	10	3	1	0	13	0	2			0	0		10	0	19	1
760	88	0	76	0	9	11	4	1	1	12	0	1			1	0		13	2	13	2
774	88	0	39	0	9	2	3	1	0	5	0	3			0	0				20	0
780	88	0	38	0	2	2	3	0	0	6	0	2			0	0				16	0
786	88	1	79	0	11	1	3	0	1	21	0	1			1	0				15	0
848	89	0	63	0	1	6	2	1	0	17	0	0			0	0				14	0
849	89	0	30	1	9	0	2	0	0	4	0	2			0	0				12	0
852	89	0	73	1	5	1	4	0	2	13	0	1			1	0				12	0

A Year of diagnosis (1980–1988)
B Sex
- 0 Male
- 1 Female

C Age at diagnosis (years)
D Referral status
- 0 Virgin
- 1 After fine-needle aspiration cytology
- 2 Open biopsy

E Location
- 0 Trunk
- 1 Retroperitoneally
- 2 Buttock
- 3 Groin
- 4 Shoulder
- 5 Upper arm
- 6 Elbow
- 7 Lower arm
- 8 Hand
- 9 Thigh
- 10 Knee
- 11 Lower leg
- 12 Foot

F Histotype
- 0 Fibrosarcoma
- 1 Malignant fibrous histiocytoma
- 2 Liposarcoma
- 3 Rhabdomyosarcoma
- 4 Hemangiosarcoma
- 5 Lymphangiosarcoma
- 6 Malignant hemangiopericytoma
- 7 Synovial sarcoma
- 8 Malignant schwannoma
- 9 Extraskeletal chondrosarcoma
- 10 Extraskeletal osteosarcoma
- 11 Malignant mesenchymoma
- 12 Clear-cell sarcoma
- 13 Myxofibrosarcoma
- 14 Sarcoma NOS

G Malignancy grade (1–4)
H Surgical stage
- 0 IA
- 1 IB
- 2 IIA
- 3 IIB

I Ploidy
- 0 Diploid
- 1 Aneuploid
- 2 Tetraploid

J Size (cm)

Treatment
K First surgical procedure
- 0 Local resection
- 1 Amputation

L Margin
- 0 Intralesional
- 1 Marginal
- 2 Wide
- 3 Myectomy
- 4 Radical

M Second surgical procedure
- 0 Local resection
- 1 Amputation

N Margin
- 0 Intralesional
- 1 Marginal
- 2 Wide
- 3 Myectomy
- 4 Radical

O Local postoperative radiotherapy 51 Gy
- 0 No
- 1 Yes

P Adjunct chemotherapy doxorubicin
- 0 No
- 1 Yes

Follow-up
Q Time to first local recurrence (months)
R Time to first metastasis (months)
S Metastasis
- 0 Lung
- 1 Skeletal
- 2 Other

T Time to last follow-up (months)
U Status at last follow-up
- 0 NED
- 1 Metastasis
- 2 Died of tumor disease
- 3 Death nontumor related

Table 2. Histogenetic type and surgical stage

Diagnosis	Surgical stage				Total
	IA	IB	IIA	IIB	
Malignant fibrous histiocytoma	–	–	35	12	47
Liposarcoma	8	1	3	1	13
Fibrosarcoma	4	5	1	1	11
Synovial sarcoma	–	–	3	4	7
Miscellaneous	2	2	10	4	24
Total	14	8	52	28	102

Table 3. Malignancy grade and ploidy level

Ploidy	Grade				Total
	I	II	III	IV	
Diploid	2	14	16	5	37
Nondiploid	1	5	39	20	65
Total	3	19	55	25	102

Table 4. Treatment of primary tumor and local recurrence

Margin	Radiotherapy	Local recurrence
Intralesional	no	4/7
	yes	5/7
Marginal	no	7/14
	yes	1/14
Wide	no	6/43
	yes	2/7
Radical	no	1/10
Total		26/102

1988. There were 53 males and 49 females with a median age of 67 (12–95) years (Table 1). None of the patients had lung metastases at admission based on standard chest radiography. Forty-two patients were referred without prior diagnostic procedures, 47 had undergone an aspiration biopsy, and 13 had had an open biopsy or intralesional surgery.

Tumor characteristics

According to location, 29 lesions were proximal (in the trunk, shoulder, glutei, or groin) and 73 were distal (in the extremities). The median tumor size was 9 (1–30) cm. Histologically, the lesions were classified according to type (Enzinger et al. 1969; Table 2) and malignancy grade (Broders et al. 1939; Table 3). There was a predominance of high-grade malignant fibrous histiocytoma. The majority of the tumors were IIA lesions (Enneking 1986).

Flow DNA cytometry was performed according to methods previously described in detail (Bauer et al. 1986, Kreicbergs et al. 1987, Tribukait 1987). Briefly, tissue samples from the surgical specimens were prepared as nuclear suspensions followed by DNA staining in ethidium bromide. Human lymphocytes were used as controls of the diploid DNA value. Specimens containing more than 15 percent tetraploid cells were considered tetraploid. Aneuploid and tetraploid lesions were classified as nondiploid lesions. There were 37 diploid lesions and 65 nondiploid lesions. The incidence of nondiploidy increased with increasing histologic grade ($P = 0.0002$ with the chi-square test; Table 3).

Treatment

All the patients were treated surgically without prior chemotherapy or radiotherapy. Local surgery was performed in 94 patients and ablative surgery in 8 patients (Table 4). Eight patients underwent two operations before the definitive surgical margin was attained. Myectomy as described by Stener (1978), performed in 10 cases, was considered to provide a wide surgical margin (Rydholm et al. 1986). Postoperative local radiation (51 Gy) was administered to 32 patients; in 7 patients the surgical margin was intralesional, in 15 patients marginal, and in 10 patients wide. Eight patients were randomized to adjuvant chemotherapy (doxorubicin 60 mg/m^2 × 9) in a trial of high-grade soft tissue sarcoma conducted by the Scandinavian Sarcoma Group (Alvegård et al. 1990). The study was discontinued in 1986, when no effect of the treatment could be proved. Hence, these patients were not analyzed separately.

Patients with high-grade tumors underwent a chest radiographic examination every 3 months during the first 2 years, and then every 6 months; those with low-grade tumors had a chest radiographic examination every 6 months. The median follow-up time was 4 (1–10) years. Ten patients died without evidence of tumor disease. Finally, 1 patient moved abroad during the follow-up period after having developed lung metastases.

Statistics

The 5-year, metastasis-free survival rate was determined by Kaplan-Meier life-table analysis of censored data (Peto et al. 1977). Multivariate Cox

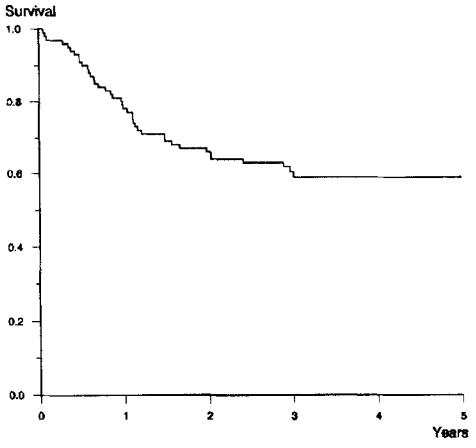


Figure 1. Life-table curve of metastasis-free survival of the whole series of 102 patients.

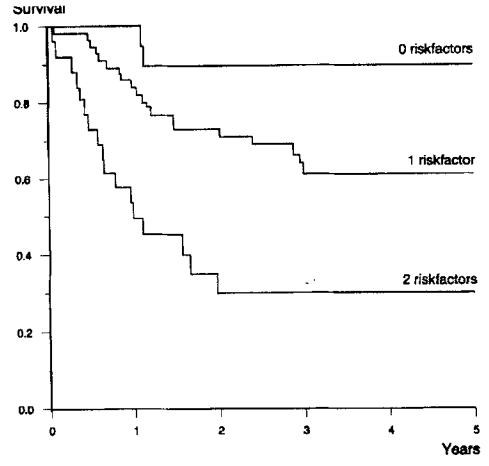
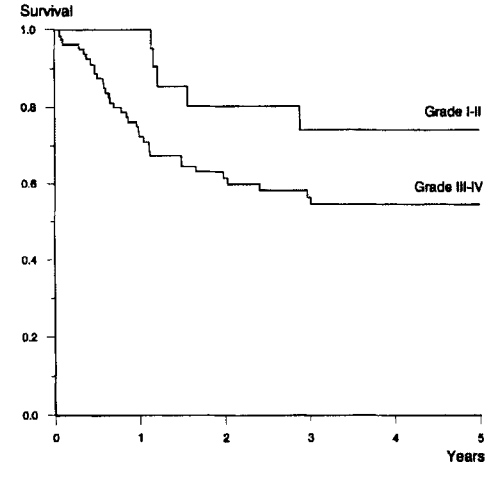


Figure 3. Life-table curve of metastasis-free survival in relation to risk factors.



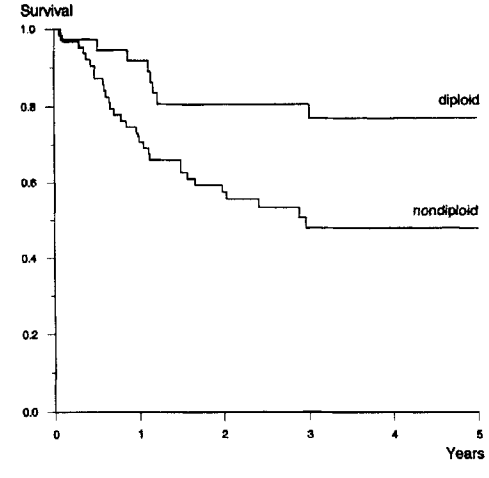


Figure 2. Life-table curves of metastasis-free survival in relation to A (tumor grade) and B (ploidy). Analysis of difference in survival: $P = 0.05$ between patients with Grade I/II and III/IV lesions, $P < 0.01$ between patients with diploid and nondiploid lesions.

(1972) proportional regression analysis was used to test the relative significance of different clinicopathologic features: age, sex, compartmentalization, size, histologic grade (Grade I/II versus Grade III/IV) and DNA ploidy level. Age and tumor size were treated as continuous variables.

The risk of metastasis, relative risk (RR), associated with a variable was expressed as $e^{\beta x}$, where ß was the Cox multiple regression coefficient and x was the difference between the actual value of the variable and another value (x = 1 in case of a dichotomous variable). The bivariate log rank Mantel-Haenzel test was used to compare survival for subgroups of patients according to different clinicopathologic features.

Results

The 5-year metastasis-free survival rate of the whole series of 102 patients was 0.59 (Figure 1). At 5 years, 39 patients had developed metastatic disease, 20 were free from disease, and 43 had been censored, i.e., were followed less than 5 years or had died of nontumor-related causes. The metastases were diagnosed within 2 years of surgery in 34 of the 39 patients who developed metastatic disease.

Bivariate analysis showed that survival was related to both tumor grade and ploidy level. The 5-year survival rate was 0.74 for patients with low-grade (I/II) lesions as compared with 0.55 for patients with high-grade (III/IV) lesions ($P = 0.05$; Figure 2). For patients with diploid tumors, the rate

Table 5. Multivariate analysis of risk of metastasis

Covariate	Definition	Regression coefficient ß	Relative risk	P
Sex	0 Females, 1 Male	0.72	2.0	0.04
Age	Years (Continuous)	-0.01		0.2
Compartment	0 Intra, 1 Extra	0.62		0.06
Size	Cm (Continuous)	0.13	1.16[1]	0.0001
Grade	0 Low, 1 High	0.57		0.2
Ploidy	0 Diploid, 1 Nondiploid	1.5	4.5	0.001

[1]For each centimeter increase in tumor size.

Table 6. Five-year metastasis-free survival according to risk factors present

Risk factor		Patients	Survival
Nondiploid	Size >10cm		
-	-	20	0.89
-	+	17	0.64
+	-	39	0.60
+	+	26	0.30

was 0.77, and for those with nondiploid tumors, 0.48 ($P = 0.01$; Figure 2).

Cox regression analysis identified three independent risk factors for metastasis (Table 5): tumor size (RR 1.2 for each centimeter increase), nondiploidy (RR 4.5), and male sex (RR 2). As to tumor size, the increase in risk of metastasis was 2.1 from 5 to 10 cm, and 4.5 from 5 to 15 cm.

The two strongest risk factors, tumor size (> 10 cm) and nondiploidy were considered in different combinations to form four subgroups of patients (Table 6). The risk of metastasis was strongly related to the number of risk factors present. Thus, the 5-year survival rate was 0.9 for the 20 patients with no risk factors, 0.6 for the 56 with one risk factor, and 0.3 for the 26 with two risk factors ($P < 0.0001$; Figure 3).

Discussion

Our study shows that the risk of developing metastasis in soft tissue sarcoma is related to DNA content and tumor size. These features can be assessed by objective means: by flow cytometry and radiographic-imaging techniques. Based on a combined assessment of these features, patients with soft tissue sarcoma can be separated into subsets with a different prognosis.

Our series, like most other studies on soft tissue sarcoma, was not population-based. In fact, not even all the patients treated at our department during the period could be included, because flow cytometry of primary specimens was not feasible in cases referred after previous marginal and wide procedures, or after local recurrence. However, the distribution of the patients according to pertinent features was comparable to that reported from population-based studies of soft tissue sarcoma (Rydholm 1983, Rööser 1987). Hence, the series can be considered representative.

The finding that nondiploidy was strongly related to metastatic disease accords with the results of other DNA studies of musculoskeletal tumors (Kreicbergs 1990). In chondrosarcoma, nondiploidy has been found to be associated with early metastasis and death (Kreicbergs et al. 1982). In high-grade osteosarcoma, the vast majority of tumors are nondiploid (Heliö et al. 1985, Mankin et al. 1985, Hiddeman et al. 1987, Xiang et al. 1987, Bauer et al. 1989). In soft tissue sarcoma, a relationship has been demonstrated between histologic grade and ploidy level; the fraction of nondiploid tumors increases with increasing histologic grade (Kreicbergs et al. 1987, Matsuno et al. 1988, Stenfert Kroese et al. 1990). Interestingly, synovial sarcoma does not comply with this relationship, because the lesions are considered to be high-grade, but the majority of them are diploid (Alvegård 1989b). This agrees with cytogenetic studies of synovial sarcoma, which have shown that a balanced X;18 translocation is often the sole cytogenetic aberration (Turc-Carel et al. 1987). Accordingly, the total DNA content is not increased. However, nondiploid synovial sarcomas, accounting for approximately one third of the lesions, have recently been reported to be associated with a worse prognosis than diploid synovial sarcomas (El Naggar et al. 1990).

As to the other risk factor identified, the prognostic significance of tumor size is well recog-

nized (Russell 1977, Hajdu 1979, Rydholm 1983, Alvegård et al. 1989a). In a study by Rööser (1987), every 1-cm increment in tumor size entailed an increased relative risk of 1.2. Notably, our finding was almost identical: namely, a risk of 1.2.

Our most surprising finding was that histologic malignancy grading gave no independent prognostic information. This is contrary to most comprehensive studies of soft tissue sarcoma and also to the staging systems proposed over the last two decades (Russell et al. 1977, Hajdu 1979, Enneking 1986, Rööser 1987, Alvegård et al. 1989a). However, the issue of histologic grading is complex. Although considered to be of predictive value, there is still no consensus regarding the morphologic criteria and grading systems to be employed. Enneking (1986) and Hajdu (1979) suggest two levels of malignancy grade, Russell (1977) three, and Rööser (1987) four, the latter based on Broders et al. classification (1939). Further, in the systems of Enneking and Hajdu, the distinction between low- and high-grade tumors is claimed to be prognostic, whereas in Rööser's study the discrimination among high-grade lesions, i.e., Grade III versus Grade IV, proved to be the most relevant. These differences illustrate the inherent problems of using prognostic factors based mainly on subjective interpretation of histology. Bell et al. (1989) recently found that the histologic grade, retrospectively assessed, was not an important prognostic factor in a series of 100 soft tissue sarcomas analyzed using multivariate analysis.

If the slides of the histologic preparations of the present series had been reviewed, malignancy grade might have become prognostic. However, histologic reassessment is something quite different from routine histopathologic diagnosis, and does not reflect the clinical situation. Therefore, our results of malignancy grading do not necessarily imply that the histologic assessment was inadequate, although prognostically not significant. Instead, it illustrates the limitation of applying grading systems prospectively, based on experience from retrospective studies. The rationale for prognostication models is to allocate patients to different treatment protocols. Thus, prognostic factors identified in prospective studies may prove to be of greater clinical relevance than those assessed retrospectively.

From the present study, the relative risk value associated with a given ploidy level and tumor size can be used to calculate the risk of metastasis. If the relative risk of metastasis for a patient with a diploid 5-cm tumor is set at 1, the relative risk associated with a nondiploid 10-cm tumor would be nine, and that with a nondiploid 15-cm tumor would be 18. These examples reflect the relative power of the identified risk factors in providing prognostic stratification. The presence of both risk factors was associated with only a 0.3 survival rate. Identification of such high-risk patients may be valuable in trials with adjuvant chemotherapy. More importantly, in 75 percent of the patients, the survival rate after surgical treatment alone was so high (0.69) that it would be difficult to prove any beneficial effect of adjuvant treatment. In sum, the prognostication model that we propose here may be useful to identify patients who should be excluded from adjuvant chemotherapy.

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