Synovial sarcoma—identification of favorable and unfavorable histologic types

A Scandinavian sarcoma group study of 104 cases

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Synovial sarcoma has traditionally been regarded as a high-grade sarcoma and treated as such. Recently, specific types of poorly differentiated synovial sarcoma have been defined and shown to affect prognosis adversely. We studied 104 primary synovial sarcomas of the extremities and trunk wall without metastasis at diagnosis that were retrieved from the Scandinavian Sarcoma Group Registry (SSG) and the Swedish Cancer Registry from 1986 to 1994. Follow-up was available in all patients, median 6 (3–11) years for the survivors. There were local recurrences in 15% of patients and metastases in 33%.

Histologically, the tumors were divided into favorable and unfavorable types. The favorable type had no significant cytologic atypia, and in most instances, no necrosis and a mitotic count of < 10/10 hpf. The unfavorable type included so-called poorly differentiated synovial sarcomas as well as recognizable biphasic and monophasic synovial sarcomas with prominent nuclear atypia, extreme cellularity and nuclear crowding. Designation of a tumor as having favorable vs. unfavorable histology conveyed more prognostic information than any single histologic factor. Kaplan-Meier estimates of metastasis-free survival at 5 years were 83% for patients with histologically favorable tumors and 31% for patients with histologically unfavorable tumors (95% confidence intervals 72–92% and 13–51%, respectively). These findings may influence future treatment protocols for synovial sarcoma.

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Synovial sarcoma accounts for approximately 10% of all soft tissue sarcomas and tends to occur in the extremities of young and middle-aged adults (Cadman et al. 1965, Mackenzie 1966, Moberger et al. 1968, Gerner and Moore 1975, Wright et al. 1982, Tsuneyoshi 1983 et al., Soule 1986, Oda et al. 1993, Choong et al. 1995, Enzinger and Weiss 1995, Bergh et al. 1999). Biphasic synovial sarcoma has a stereotypic histologic appearance and is readily diagnosed. However, the monophasic variant is more difficult to recognize due to overlapping appearances with other spindle and round-cell sarcomas (Evans 1980, Meis-Kindblom et al. 1996, Folpe et al. 1998, Bergh et al. 1999, van de Rijn et al. 1999). In such cases, adjunctive morphologic or cytogenetic techniques are needed to confirm the diagnosis of synovial sarcoma (Evans 1980, Fisher 1986, El-Naggar et al. 1990, Clark et al. 1994, de Leeuw et al. 1994a, b, Crew et al. 1995, Enzinger and Weiss 1995, Shipley et al. 1996).

Although synovial sarcoma is generally viewed as a high-grade sarcoma, late metastases and a protracted clinical course are not uncommon, with 5- and 10-year survivals of 40–70% and 30–56%, respectively (Wright et al. 1982, Choong et al. 1995, Bergh et al. 1999). Few prognostic studies have been published based on large series of cases

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that have been diagnosed and treated using modern principles and have longterm follow-up. Moreover, recent studies of synovial sarcoma have indicated that it is not a homogeneous tumor in terms of disease course and outcome (Choong et al. 1995, Bergh et al. 1999, Skytting et al. 1999). Certain patient factors, clinical features, treatment, morphologic, flow cytometric, and cytogenetic characteristics have been found to be prognostically significant in synovial sarcoma (Wright et al. 1982, Cagle et al. 1987, Rööser et al. 1989, El-Naggar et al. 1990, Golouth et al. 1990, Schmidt et al. 1991, Brodsky et al. 1992, Ladenstein et al. 1993, Oda et al. 1993a, b, Pappo et al. 1994, de Leeuw et al. 1994a, Yokoyama et al. 1995, Singer et al. 1996, Folpe et al. 1998, Kawai et al. 1998, Lopes et al. 1998, Bergh et al. 1999). A recent study has indicated that distinct groups of patients with synovial sarcoma have a favorable prognosis and other groups have a distinctly poor prognosis (Bergh et al. 1999). These findings have important implications for current treatment protocols.

This study aimed to review the morphologic spectrum of synovial sarcoma and to identify through statistical analysis those histologic factors that are prognostically significant and predictive. The analysis was based on a series of 104 patients whose treatment and clinical course are reported in this issue of Acta Orthop Scand (Skytting et. al. 1999).

Patients and methods

Patient series, clinical features, treatment and follow-up

104 patients with primary synovial sarcoma of the extremities or trunk wall without metastasis at presentation and diagnosed between 1986 and 1994 constituted the basis for this study. There were 53 men and 51 women in the series; median patient age was 38 (6–81) years. 69 tumors were located in the lower extremity or groin, 26 were in the upper extremity or shoulder, and 9 involved the trunk wall. Median tumor size was 5 (1–20) cm.

The definitive or final surgical margin of the primary tumor was wide or compartmental in 63 patients and marginal or intralesional in 41. The primary tumor was treated with local surgery in 77 patients and amputation in 27 patients. None of the patients received preoperative radiotherapy. 21 of the 41 patients who had inadequate surgery received postoperative radiotherapy. 7 patients, all children or young adults, received postoperative chemotherapy according to non-standardized protocols.

Follow-up information was obtained for all 104 patients. 73 patients (70%) had no evidence of disease at a median interval of 6 (3–11) years; 26 patients (25%) died of disease at a median interval of 3 (0.4–6.5) years; and 5 patients were alive with either local recurrence or metastasis at a median interval of 4.5 (3.2–10.5) years.

There were local recurrences in 16 of 104 patients. The median interval to local recurrence was 1.8 (0.3–4) years.

34 of 104 patients (33%) developed metastases, predominantly in the lungs, but also in bone and lymph nodes. The median interval to metastasis was 1.5 (0.2–6) years. The estimated median survival (Kaplan-Meier) after metastasis was 1.8 years.

Histologic and immunohistochemical analysis

The original histologic review included 148 cases. Of these, 130 were accepted as synovial sarcoma. The remaining 18 cases were excluded as another type of sarcoma (15 cases), metastatic carcinoma (2 cases), or benign epithelioid schwannoma (1 case). An additional 26 cases were excluded from the series because they did not fulfill the clinical criteria (see Skytting et. al. 1999). Histologic stains included hematoxylin and eosin (H&E) and/or van Gieson. Immunohistochemical stains were reviewed in all available cases and new stains were performed in selected cases, including immunostains for cytokeratins (KL-1, AEI/AE3, MNF116, CAM 5.2) and EMA. Focal positivity for cytokeratins and/or EMA was required for the diagnosis of monophasic synovial sarcoma, fibrous type.

The tumors were all subclassified as monophasic fibrous or biphasic synovial sarcoma, and evaluated for the presence of poorly differentiated areas, tumor necrosis, vascular invasion, type of tumor interface with normal tissues, mitotic activity, and tumor grade as defined below.

Subtype: The subclassification of the tumors as biphasic or monophasic fibrous type was based entirely on light microscopic features. A lesion was classified as biphasic synovial sarcoma, if it had any areas with a distinct biphasic pattern including epithelioid tumor cells forming glands, solid cords or strands as well as a spindle cell, fibrosarcoma-like component. Features supporting the diagnosis of monophasic synovial sarcoma included the presence of highly uniform spindled cells with a high nuclear to cytoplasmic ratio arranged in sweeping fascicles and whorls, uniform chromatin pattern, foci of calcification, mast cell infiltration, and a hemangiopericytoma-like pattern, as well as alternating cellular and paucicellular areas. Occasional monophasic fibrous type tumors showed extensive fibrosis, while others revealed extensive, paucicellular areas dominated by bland-looking, spindled and stellate tumor cells in a poorly vascularized, myxoid matrix. A few tumors contained large cystic areas.

Poorly differentiated synovial sarcomas: These synovial sarcomas were classified as previously described (Meis-Kindblom et al. 1996, Folpe et al. 1998, van de Rijn et al. 1999)—that is, tumors contained areas of classical biphasic or monophasic fibrous synovial sarcoma, as well as poorly differentiated areas comprising more than one-fourth of the area of the tumor in microscopic sections. Three main types of poorly differentiated synovial sarcoma were observed and included tumors with: (1) a high-grade spindled and fascicular pattern, simulating high-grade fibrosarcoma and malignant peripheral nerve sheath tumor, frequently with extensive necrosis, perivascular tumor preservation and high mitotic activity; (2) larger, atypical cells with transitional features intermediate between clearly spindled and epithelioid cells, sometimes having rhabdoid features; and (3) densely packed, poorly differentiated, small cells resembling Ewing's sarcoma and primitive neuroectodermal tumor (PNET). Some of the poorly differentiated synovial sarcomas had a prominent hemangiopericytoma-like vascular pattern, thereby resembling a malignant hemangiopericytoma.

Tumor necrosis: This was evaluated on the basis of histologic sections rather than macroscopic inspection. Any convincing microscopic focus was viewed as necrosis, regardless of its size. Microscopic tumor necrosis was evaluable in 103 cases.

Vascular invasion: This was defined as tumor floating freely in a vessel lumen of any size or type, as well as tumor invading the vessel wall into the lumen and without covering endothelium. Vascular invasion was evaluable in 103 cases.

Growth pattern: The interface between the tumor and the surrounding tissue was evaluated as "pushing" or "infiltrative". Tumors that revealed any areas of infiltrative growth were categorized as such. The tumor's growth pattern was evaluable in 93 cases.

Mitotic activity: Mitotic rate was evaluated by counting the number of mitotic figures per 10 consecutive high-power fields (hpf) and registered as low (0–2 mitotic figures/10 hpf), moderate (3–9 mitotic figures/10 hpf), and high (10 or more mitotic figures/10 hpf, 1 hpf = 0.8 mm^2).

Tumor grade: According to SSG protocols, all soft-tissue sarcomas were graded on a IV-tiered scale, depending on the degree of cellularity, atypia, differentiation, mitotic activity, tumor necrosis, and vascular invasion (Broders et al. 1939, Angervall et al. 1986), as well as taking into consideration the inherent grade of the tumor entity per se. In this grading system, grades I and II are equated with low grade and grades III and IV with high grade (Markhede et al. 1982). Since synovial sarcoma is generally viewed as a high-grade sarcoma, all tumors in this series were graded as grade III or IV. All tumors containing poorly differentiated, areas as defined in this study, were classified as grade IV tumors, also called unfavorable histology. In addition, synovial sarcomas of classical biphasic or monophasic, fibrous type but with unusually prominent nuclear atypia, high cellularity and nuclear crowding, usually combined with high mitotic activity (10 or more mitoses per 10 hpf) and necrosis, were also classified as grade IV (unfavorable histology). All other biphasic and monophasic synovial sarcomas were classified as grade III, also called favorable histology.

Statistics

Univariate comparisons of subgroups with regard to metastasis-free and overall survival were based on Kaplan-Meier survival estimates and the log-

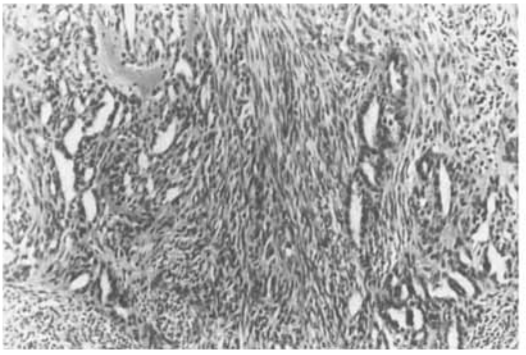


Figure 1. Biphasic synovial sarcoma of favorable histology showing distinct glands and a spindle cell component characterized by uniform cells with relatively small, bland, oval nuclei.

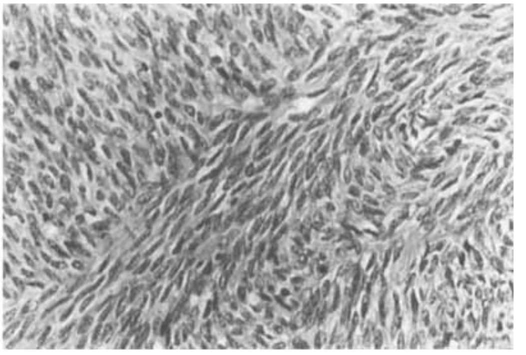
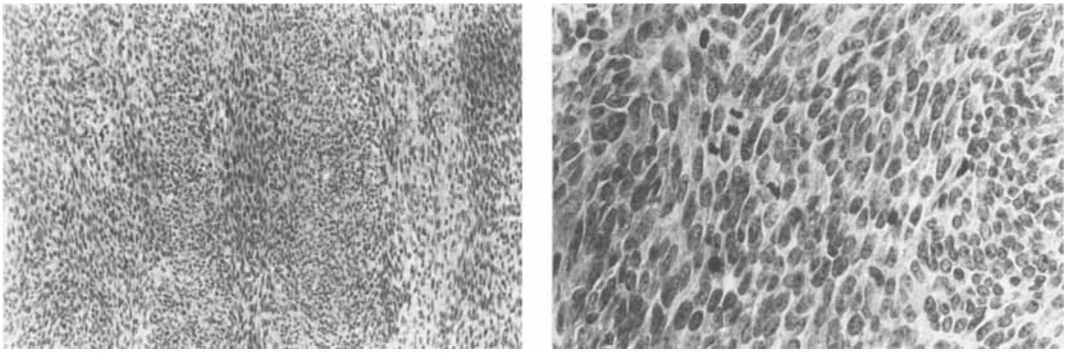


Figure 2. Monophasic fibrous synovial sarcoma of favorable histology, showing oval and elongated nuclei that are uniform with an evenly distributed chromatin pattern and inconspicuous nucleoli.



Figures 3A and B. Monophasic fibrous synovial sarcoma with a poorly differentiated area resembling a malignant peripheral nerve sheath tumor and characterized by increased cellularity, nuclear crowding and atypia, nucleolar prominence, and high mitotic activity (i.e., unfavorable histology).

rank test. The joint effect of tentative prognostic factors was analyzed multivariately according to Cox's proportional hazards regression model. Tumor size was entered as a categorical covariate with three levels: 1–3, 4–5 and > 5–20 cm. 2 patients who did not develop metastases but died of other causes were treated as censored at the time of death when evaluating the time to metastasis.

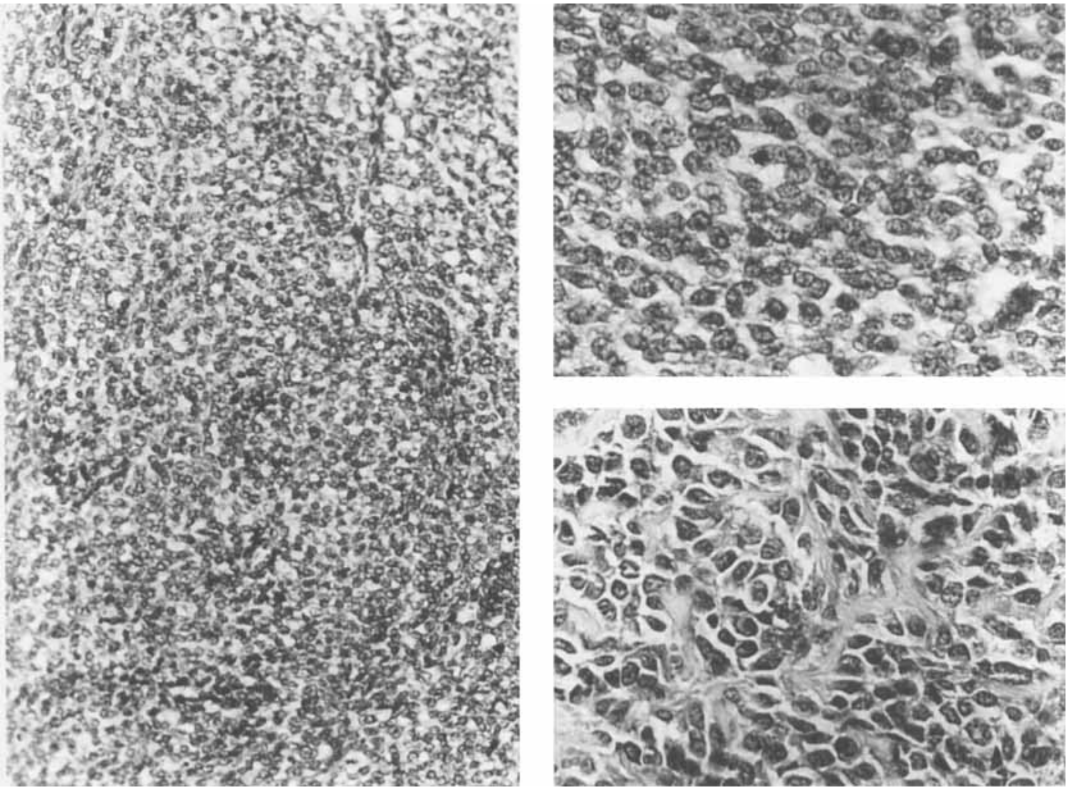
Results

Histologic features

33 tumors (32%) were classified as biphasic synovial sarcoma (Figure 1) and 71 cases as monophasic, fibrous type (Figure 2). Poorly differentiated areas, as defined previously, were seen in 22 (21%) cases (Figures 3–6); 2 of these were biphasic and the remainder were monophasic fibrous synovial sarcomas. 74 tumors (71%) were classified as grade III (favorable histology) and 30 as grade IV synovial sarcoma (unfavorable). Of the 30 grade IV tumors, 8 had no poorly differentiated areas; 3 of these were biphasic and 5 were monophasic (Figure 7). Immunostains for cytokeratins (Figure 6) and EMA highlighted the epithelial component in the biphasic synovial sarcomas and revealed at least focal positivity for one or both of these markers in the spindle cell components of the monophasic fibrous variants.

Prognostic factors

Among the factors initially examined in the univariate analysis, tumor size, poorly differentiated areas, microscopic tumor necrosis, mitotic activity, vascular invasion and malignancy grade (III, favorable vs. IV, unfavorable) were all significantly associated (log-rank $p < 0.05$) with me-



Figures 4A , B, and C. Monophasic fibrous synovial sarcoma with poorly differentiated areas (unfavorable histology). Sheets of densely packed, small round cells with nuclear atypia and focal nesting in a fibrous stroma are similar to Ewing's sarcoma—primitive neuroectodermal tumor.

tastasis-free survival (Table 1). Age > 20 years, monophasic subtype and diffuse infiltrating growth pattern also tended to be associated with decreased metastasis-free survival, but were not statistically significant. Figures 8–10 illustrate the impact of tumor grade (III, favorable vs. IV, unfavorable), tumor size, and the presence of poorly differentiated areas on survival.

In Table 2, the effects of histologic variables have been adjusted for the impact of age and tumor size in separate Cox regression hazard models. The inclusion of age at diagnosis, whether dichotomized at 20 years or analyzed as a continuous variable, did not essentially change the hazard ratio estimates for the histologic variables. Both the univariate analyses (Table 1) and the adjusted analyses (Table 2) suggest that histologic grading as favorable or unfavorable type provides more prognostic information than any single histologic factor. Figure 10 illustrates the combined impact of tumor size and grade on survival.

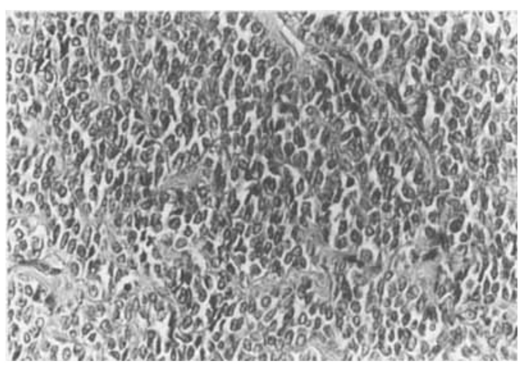
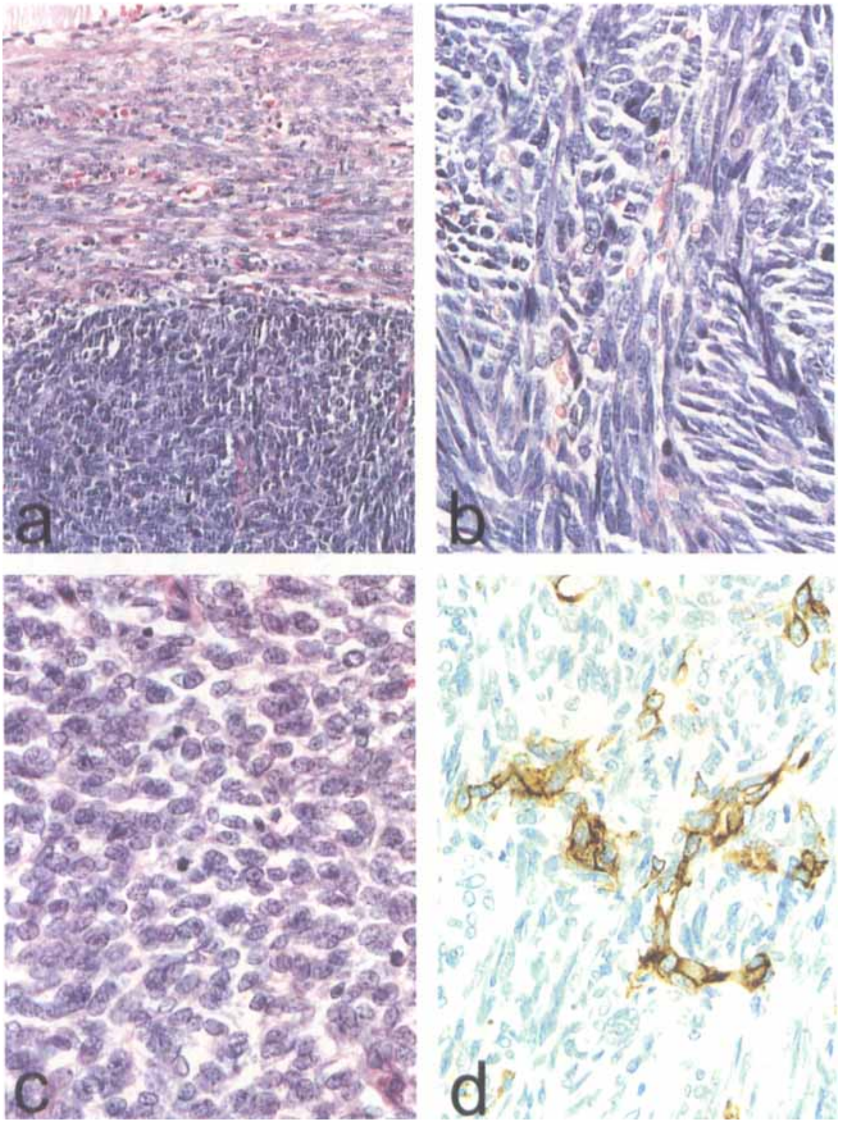


Figure 5. Biphasic synovial sarcoma with a poorly differentiated area (unfavorable histology), composed of tumor cells with features intermediate between spindle and epithelial cells of synovial sarcoma. Note the nuclear atypia. The poorly differentiated areas had high mitotic activity and microscopic tumor necrosis.

The interpretation of the multivariate models in this study is complicated, since the histologic variables are all more or less associated with each other and with tumor size. The analysis is further

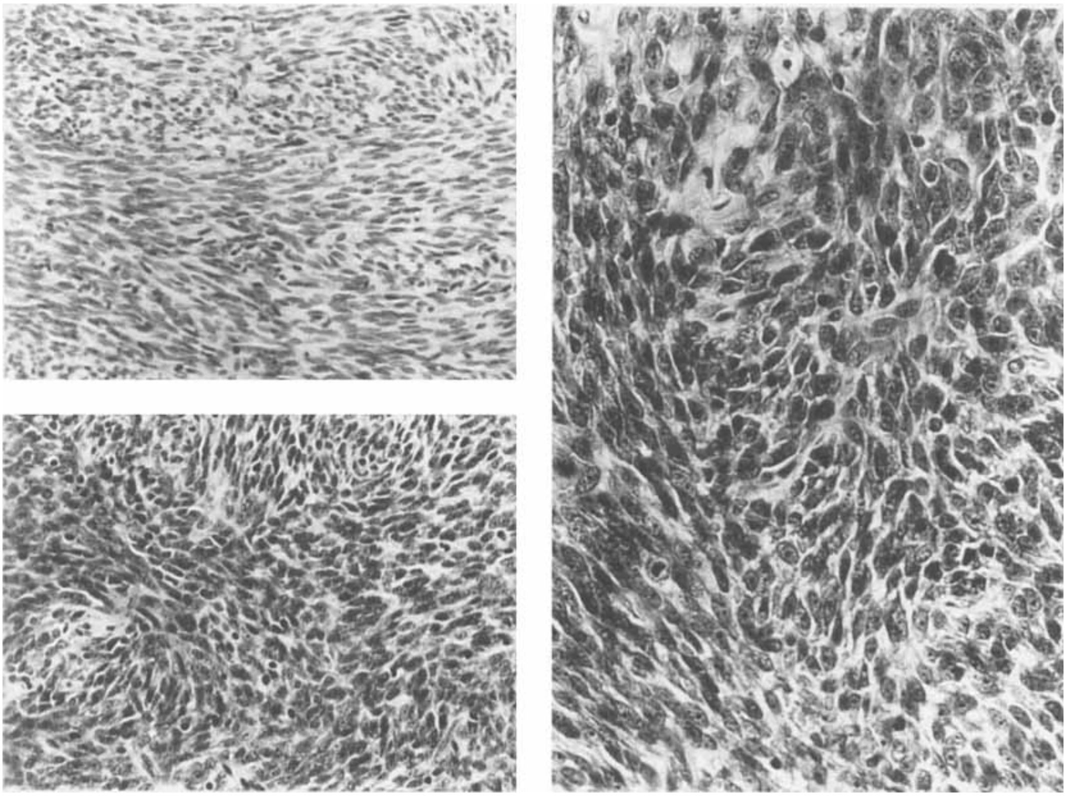


Figures 6A, B, C, D. Synovial sarcoma with an abrupt transition between well differentiated (A, top) and poorly differentiated areas (A, bottom). The poorly differentiated areas were partially spindled and fascicular (B); other areas had a Ewing's sarcoma-like appearance (C). In well differentiated areas, nests of epithelioid tumor cells with cytokeratin positivity (AE1/AE3) were seen (D).

impaired by the relatively small size of the series. In Table 3 an attempt was made to describe the simultaneous effects of the histologic factors. Due to the size of the material, the point estimates in Table 3 are, fairly imprecise and the results should be interpreted with caution.

Discussion

Since synovial sarcoma was first recognized as an entity over 100 years ago, numerous prognostic studies have indicated that it is a high-grade sarcoma prone to metastasize to the lungs (Mackenzie 1966, Moberger et al. 1968, Gerner and Moore 1975, Evans 1980, Ryan et al. 1982, Wright et al. 1982, Tsuneyoshi et al. 1983, Soule 1986, Rööser



Figures 7A, B, and C. Monophasic fibrous synovial sarcoma of classical type with uniform, bland spindle cells (A). A gradual transition to areas with increased cellularity, nuclear crowding and atypia, nucleolar prominence, and high mitotic activity is seen (B and C). This case was considered to have an unfavorable histology, without poorly differentiated areas.

et al. 1989, Oda et al. 1993a, b, Mullen and Zagars 1994, Singer et al. 1996). Numerous patient, treatment, and tumor factors have been found to influence disease outcome (Varela-Duran and Enzinger 1982, Cagle et al. 1987, Rööser et al. 1989, El-Naggar et al. 1990, Golouth et al. 1990, Schmidt et al. 1991, Brodsky et al. 1992, Ladenstein et al. 1993, Oda et al. 1993a, b, de Leeuw et al. 1994, Pappo et al. 1994, Yokoyama et al. 1995, Singer et al. 1996, Folpe et al. 1998, Kawai et al. 1998, Lopes et al. 1998, Bergh et al. 1999, van de Rijn et al. 1999). However, a comparison of these studies is hampered by their heterogeneous nature. Some series include cases collected over a very long period in which the principles for diagnosis and treatment have changed considerably. In other studies, detailed information regarding patient age, tumor size, histologic features, and surgical and adjuvant treatment is incomplete or lacking. The quality of follow-up is also highly variable, metastatic status is not always clearly stated, and the cause of death is uncertain in some cases.

The current study was based on a well-defined group of patients with synovial sarcoma, representing a population-based cohort from Sweden, as well as patients treated at SSG centers in Norway and Finland during a recent 8-year period. The patients received relatively uniform treatment; the clinical and histologic criteria for inclusion in the study were in accordance with current standards; and only extremity and trunk-wall tumors that were primary lesions without metastasis at the time of diagnosis were included in the study. Moreover, no patient was lost to follow-up.

It is of interest to note that 130 of 148 tumors, initially diagnosed as synovial sarcoma, were accepted as such by the peer-review committee and that only 1 of these cases was reclassified as benign. This is in contrast to an earlier Swedish study of synovial sarcoma in which 16 of 143 cases were reclassified as benign lesions, primarily pigmented villonodular synovitis (Moberger et al.

Table 1. Univariate analysis of prognostic factors related to metastasis-free survival

Variable	Criteria	No.	5-yr MFSR [a]	Hazard ratio	P-value [b]
All patients		104	0.68		
Tumor size, cm	1–3	31	0.89	1	0.0005
	4–5	31	0.70	3.6	
	> 5–20	38	0.54	7.5	
Age, years	≤ 20	26	0.80	1	0.21
	> 20	78	0.64	1.7	
Grade	III-favorable	74	0.83	1	<0.0001
	IV-unfavorable	30	0.31	7.0	
Histologic subtype	Biphasic	33	0.78	1	0.08
	Monophasic	71	0.64	2.1	
Poorly differentiated areas	Yes	22	0.38	4.0	<0.0001
	No	82	0.76		
Microscopic necrosis	Yes	32	0.45	3.0	0.0009
	No	71	0.82	1	
Tumor growth pattern	Diffusely infiltrating	70	0.64	1.7	0.3
	Pushing	23	0.83	1	
Vascular invasion	Yes	16	0.47	2.2	0.04
	No	87	0.71	1	
Mitotic activity	Low	39	0.74	1	0.002
	Moderate	32	0.82	0.56	
	High	33	0.48	2.5	

[a] Metastasis-free survival rate at 5 years according to Kaplan-Meier estimate
[b] P-values obtained by a log-rank test

Table 2. Hazard ratios from separate Cox regression models of metastases-free survival with each variable adjusted for tumor size and patient age

Variable	Adjusted hazard ratio	95% confidence interval
High mitotic activity	2.4	1.1–5.0
Necrosis	2.2	1.1–4.0
Poor differentiation	2.6	1.1–5.8
Vascular invasion	1.3	0.5–3.0
Infiltrative growth pattern	1.9	0.7–5.0
Monophasic subtype	2.0	0.9–4.7
Grade IV (unfavorable histology)	5.2	2.4–11

Table 3. Multvariate Cox regression model of metastasis-free survival for histologic factors and tumor size

Variables	Hazard ratio	P-value	95% CI [a]
Biphasic without PD [b]	1 [c]		
Monophasic without PD [b]	2.5	0.08	0.9–7.1
PD [b]	2.9	0.07	0.9–9.1
High mitotic activity	2.1	0.06	1.0–4.6
Necrosis	1.8	0.12	0.8–4.0
Size 1–3 cm	1 [c]		
Size 4–5 cm	3.0	0.10	0.8 - 11
Size >5–20 cm	4.2	0.03	1.1–15

[a] 95% confidence interval
[a] PD, poorly differentiated areas.
[b] Reference value.

1968). This difference is explained by the fact that the latter series was based on cases diagnosed between 1925 and 1963; criteria for the diagnosis of synovial sarcoma have been refined since then; the monophasic variant of synovial sarcoma had not been clearly defined at that time; and ancillary diagnostic techniques have recently been developed that improve diagnostic accuracy. Moreover, the initial pathologic diagnoses in the current series were, to a large extent, made at SSG centers. 15 cases excluded from our study were reclassified as fibrosarcoma, malignant peripheral nerve sheath tumor, malignant fibrous histiocytoma, and clear-cell sarcoma of tendons and aponeuroses. All of these are high-grade tumors that would have been handled in a manner similar to synovial sarcoma. 2 additional tumors, initially diagnosed as predominantly epithelioid biphasic synovial

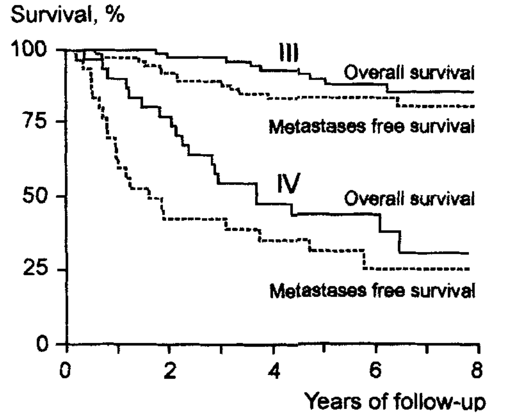


Figure 8. Kaplan-Meier estimate of survival of patients with grade III and grade IV synovial sarcomas. Grade IV is synonymous with unfavorable histology.

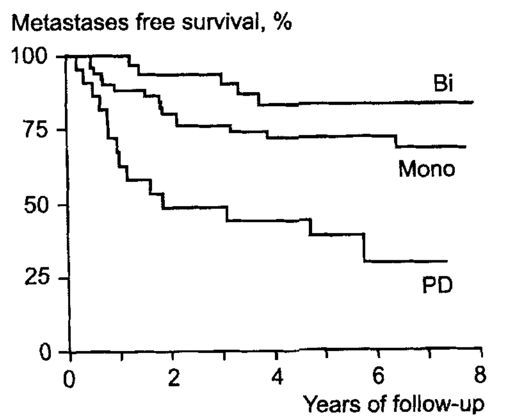


Figure 9. Kaplan-Meier estimate of survival of patients with synovial sarcomas, comparing those with poorly differentiated areas and those without such differentiated areas.

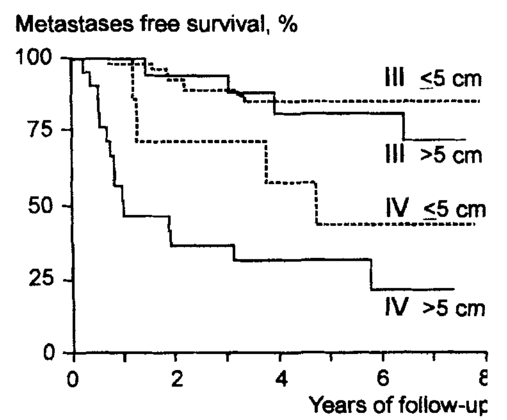


Figure 10. Kaplan-Meier estimate of survival, illustrating the combined impact of tumor grade and tumor size for grade III and grade IV synovial sarcomas ≤ and > 5 cm in size.

sarcoma, were reclassified as metastatic carcinoma and would therefore have been treated differently.

The occurrence of synovial sarcomas with primitive, high-grade areas has been referred to in the literature as poorly differentiated synovial sarcoma (Cagle et al. 1987, Enzinger and Weiss 1995). In a previous study, we described three main morphologic variants of poorly differentiated synovial sarcoma (Meis-Kindblom et al. 1996). Poorly differentiated tumors were included in this study only if they had focal areas of classical synovial sarcoma light microscopically and immunohistochemically. Since the poorly differentiated areas of synovial sarcoma usually lose the classical immunophenotype, the diagnosis of an entirely poorly differentiated synovial sarcoma becomes difficult or impossible. Demonstration of the X;18 translocation, using tissue culturing and karyotyping as well as fluorescence in situ hybridization (FISH) and other DNA- and RNA-based molecular techniques, appears to be the only way to establish unequivocally the diagnosis in cases that are entirely poorly differentiated (Clark et al. 1994, de Leeuw et al. 1994, Folpe et al. 1998, Kawai et al. 1998, van de Rijn et al. 1999).

The prognostic significance of poorly differentiated areas in synovial sarcoma has previously been shown (Bergh et al. 1999, van de Rijn et al. 1999). This study suggests that there is, in addition, a subset of synovial sarcomas without so-called poorly differentiated foci (as previously defined) that is also associated with a significantly worse prognosis. Histologically, these cases may be biphasic, but are more commonly monophasic, characterized by prominent nuclear atypia, extreme cellularity and nuclear crowding, high mitotic activity, and microscopic tumor necrosis. Such histologic features are also seen in the poorly differentiated types of synovial sarcoma. Hence, the distinction between these two groups is somewhat subjective and not prognostically important; we believe that both groups are best referred to as histologically unfavorable synovial sarcomas.

The statistical analysis clearly showed the strong predictive value of certain histologic features. Individual factors found to be associated with a worse prognosis included classification of a tumor as grade IV (unfavorable histology), presence of poorly differentiated areas, microscopic tumor necrosis, 10 or more mitotic figures/10 hpf, and vascular invasion. All of these features are mutually associated, which may, along with the relatively small size of our series, explain the failure of the multivariate analysis to show that any single histologic factor was statistically significant. The important result of this study is that it clearly shows synovial sarcomas can be histologically separated into prognostically favorable and unfavorable subgroups.

As in several previous studies of soft tissue sarcoma, vascular invasion was found to be an adverse prognostic factor (Rööser et al. 1989, Gustafson 1994). Its value as a predictor of poor outcome is limited, however, because of the rarity with which it is observed in synovial sarcomas (i.e., it is relatively insensitive). Only 16 of 103 cases in which vascular invasion could be evaluated showed convincing vascular invasion—most patients with metastases had no histologically identifiable vascular invasion. The histologic assessment of vascular invasion is unreliable, even when immunostains are used. In addition, assessment of vascular invasion is dependent on the extent of sampling, particularly around the periphery of the tumor.

The interface of the tumor with surrounding non-tumor tissues, referred to as the tumor growth pattern in this study, and judged as infiltrative vs. pushing, was not significantly associated with disease outcome. This could be because infiltrative growth does not necessarily reflect more aggressive behavior. In fact, many tumors with unfavorable histology tended to grow in an expansive, pushing manner, while many of the bland synovial sarcomas with a favorable histology showed extensive diffuse infiltration.

In addition to histologic grading, the only other factor found to have a very strong impact on prognosis was tumor size. Previous studies have shown that synovial sarcomas larger than 5 cm. in size have a significantly worse prognosis than smaller tumors (Wright et al. 1982, Choong et al. 1995, Bergh et al. 1999). Our analysis also showed that patients with tumors 1–3 cm. in size tended to have a better prognosis than patients with tumors 3–5 cm. (hazard ratio 3.6, $p = 0.06$). These results, we believe, show that the effect of tumor size on prognosis as well as the critical tumor size must be determined for each individual type of sarcoma. Because of its strong prognostic influence, tumor size was taken into consideration (or "adjusted for") in the multivariate analysis of various histologic factors.

Previous studies have found that favorable and unfavorable prognostic groups of synovial sarcoma can be identified. Patients less than 25 years of age with tumors less than 5 cm. in size and a classical morphology have a favorable prognosis, in contrast to patients 25 years of age or older with poorly differentiated tumors that are 5 cm. or more in size (Bergh et al. 1999). The present study further indicates the strong predictive value of tumor grade—that is, the identification of favorable and unfavorable histology in synovial sarcoma.

Considering the relatively small size of this study, we believe that it is prudent to view both tumor grade (favorable vs. unfavorable histology) and tumor size as important prognostic factors in synovial sarcoma. In this study, the estimated metastasis-free survival at 5 years was 85% for patients with histologically favorable tumors up to 5 cm. in size, in contrast to 31% at 5 years for patients with histologically unfavorable tumors over 5 cm. in size. The extremely good clinical outcome in the subset of synovial sarcomas with favorable histology is more in keeping with a grade II sarcoma (in a IV-tiered grading system), such as myxoid liposarcoma. Therefore, we believe that the blandest looking synovial sarcomas may justifiably be regarded as relatively low-grade and patients with small tumors having such a favorable histology should probably be excluded from chemotherapy trials.

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