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Clinical course in synovial sarcoma

A Scandinavian sarcoma group study of 104 patients

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We analyzed treatment and outcome in 104 Scandinavian patients with synovial sarcoma in the extremities or trunk wall, diagnosed between 1986 and 1994. Only surgically treated patients without metastases at diagnosis were included. Median follow-up of survivors was 6 (3–11) years. 34 patients developed metastases. The overall 5- and 7-year survival rates were 0.76 (95% CI 0.66–0.83) and 0.69 (0.58–0.78), respectively. Large tumor size and amputation were significantly associated with impaired metastasis-free survival. Patients with local recurrence had a higher risk of metastases following the local event. Local excision with inadequate margin was associated with a higher risk of local recurrence.

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Synovial sarcoma accounts for approximately 10% of soft tissue sarcomas (Cadman et al. 1965, Choong et al. 1995). Unlike other soft tissue sarcomas, synovial sarcoma is commoner among younger persons. The treatment has been surgical, and some centers include radiotherapy to improve local control. Adjuvant chemotherapy is frequently given to children (Ladenstein et al. 1993), but its value remains unknown (Mullen and Zagars 1994).

The reported 5-year overall survival rate varies from 40% to 70% (Cadman et al. 1965, Hajdu et al. 1977, Shiu et al 1979, Wright et al. 1982, Brodsky et al. 1992, Ladenstein et al. 1993, Mullen and Zagars 1994, Choong et al. 1995). Metastases from soft tissue sarcoma are uncommon after 5 years, but such late systemic recurrences are well known in synovial sarcoma. Therefore, the reported survival rates have dropped to 30–50% at 10 years (Wright et al. 1982, Mullen and Zagars 1994, Choong et al. 1995).

The survival rates have continuously improved, but it remains unclear whether this is due to a change in the selection of patients or to changes in treatment. Only two centers, the Mayo Clinic and the Memorial Sloan Kettering Cancer Center, have published series of more than 100 patients and their findings may reflect referral policies unique to the United States.

We report survival and local recurrence data based on 104 patients treated during a 9-year period. Our aim was to identify clinical factors related to outcome.

Patients and methods

This study was based on 130 patients diagnosed with primary synovial sarcoma of the extremities or trunk wall between 1986 and 1994. 107 patients recruited from the Scandinavian Sarcoma Group (SSG) Register, all treated for primary tumor at an

SSG center, and 23 Swedish patients in the SSG Register or the National Swedish Cancer Register receiving all treatment outside an SSG center, were analyzed. Hence, the Swedish patients may be regarded as a population-based cohort.

All tumors were reviewed by the SSG Pathology Board, without knowledge of the clinical course, using established histopathological criteria (Enzinger and Weiss 1995). 18 patients were excluded, 12 because the diagnosis of synovial sarcoma was not accepted and 6 because of inadequate histological tissue for review. 7 patients had lung metastases at diagnosis and 1 patient had refused surgery, leaving 104 for study. 88 patients were treated for primary tumor at an SSG center and 16 had all treatment outside. Histological review revealed 71 monophasic and 33 biphasic lesions. Medical records were reviewed in all cases to verify and complete reported clinical data.

Patient characteristics

Our study had 53 men and 51 women with a median age of 38 (6–81) years. 9 of the primary tumors were located in the trunk wall, 26 in the upper extremities and 69 in the lower extremities. The median tumor size was 5 (1–20) cm. 29 lesions were intracompartmental, 69 were extracompartmental and 6 were unclassified (Enneking et al. 1980). 45 patients (44 deep-seated and 1 subcutaneous tumor) were referred to an SSG center without prior surgery, 9 after incisional biopsy, 37 after intralesional or marginal excision and 1 after wide excision. 4 patients were referred after local recurrence. 8 patients were never referred to an SSG center. There was no systematic bias regarding clinical characteristics between patients primarily treated at an SSG center vs. outside.

Treatment

54 patients had all surgery and 34 had re-excisions performed at an SSG center, while 16 had all surgery for a primary tumor outside. Local excision was performed in 77 patients and amputation in 27 (Table 1). 48 patients underwent two or more operations before the definitive surgical margin was attained. Surgical margins were classified according to Enneking et al. (1980). In 41 patients, the final surgical margin was intralesional or marginal, and in 63 wide or compartmental. None had preoperative radiotherapy, but 21 were treated postoperatively due to an intralesional or marginal surgical margin. 7 patients, all children or adolescents, had adjuvant chemotherapy for a primary tumor.

Follow-up

No patient was lost to follow-up. The median follow-up for survivors was 6 (3–11) years. 2 patients died of other causes than tumor.

Statistics

Univariate subgroup comparisons with respect to metastases-free survival were based on Kaplan-Meier survival estimates and the log-rank test. The joint impact of tentative prognostic factors was analyzed multivariately according to Cox's proportional hazards model. All covariates examined univariately and all patients with no missing covariate values were used in the model building process. The 2 patients who did not develop metastases, died of other causes, and were treated as censored at the time of death.

When considering factors of importance for local failure, we avoided modeling of the cause-specific hazard, since the resulting estimates can be seriously biased if the two modes of failure (local/distant) are not independent of one another (Gelman et al. 1990). Instead, we considered the type of the first-failure event and made simple comparisons between subgroups concerning the failure mode patterns at different times from diagnosis. Statistical significance concerning differences in the proportion of failing subjects with local recurrence as a first-failure event was evaluated with Fisher's exact test. Only patients diagnosed before January 1994 (n 85) were included in the comparisons to avoid possible bias resulting from differing lengths of follow-up. Selected patients were either free of disease with follow-up exceeding 4.5 years or encountered at least one failure event within 4.5 years of diagnosis.

Results

Metastasis-free survival and factors related to local recurrence

Among the 104 surgically treated patients without

Table 1. Prognostic factors related to metastasis-free survival in 104 patients with synovial sarcoma and no metastasis at time of diagnosis, including estimates from univariate Cox proportional hazards analyses

Variable	Criteria	No.	5-year MFSR [a]	95% CI	Hazard ratio	95% CI	P-value log-rank
All patients		104	0.68	0.58–0.76			
Age	<= 20	26	0.80	0.59–0.91	1		0.21
	> 20	78	0.64	0.52–0.74	1.7	0.72–4.2	
Sex	Male	53	0.62	0.48–0.74	1		0.32
	Female	51	0.74	0.59–0.84	0.71	0.36–1.4	
Localization [b]	Proximal	56	0.68	0.54–0.79	1		0.99
	Distal	48	0.68	0.52–0.79	0.99	0.51–2.0	
Depth [c]	Subcutaneous [d]	10	1.00	–			0.034
	Deep	88	0.64	0.53–0.73	–	–	
Compartment [c]	Extra	69	0.62	0.49–0.72	1		0.037
	Intra	29	0.81	0.55–0.88	0.38	0.15–0.98	
Tumor size, cm [e]	1–3	31	0.89	0.70–0.96	1		0.0005
	4–5	31	0.70	0.50–0.83	3.6	0.96–13	
	> 5–20	38	0.54	0.36–0.68	7.5	2.2–25	
Surgical procedure	Local excision	77	0.8	0.61–0.92	1		0.010
	Amputation	27	0.62	0.49–0.72	2.4	1.2–4.8	
Local treatment	Adequate [f]	79	0.69	0.57–0.78	1		0.98
	Inadequate [g]	25	0.66	0.43–0.81	1.0	0.46–2.2	
Treatment center	SSG center	88	0.71	0.60–0.79	1		0.38
	Outside	16	0.54	0.27–0.75	1.45	0.63–3.3	

[a] MFSR metastasis-free survival rate
[b] Location distal to elbow or knee
[c] Compartmentalization and depth determined in 98 patients
[d] Subcutaneous –no penetration of the subcutaneous fascia
[e] Tumor size determined in 100 patients
[f] Adequate –at least marginal margin and radiotherapy or wide/compartmental
[g] Inadequate–intralesional margin or marginal margin without radiotherapy

metastases at diagnosis, 34 developed metastases. The metastases first appeared in the lungs in 28 patients and in the lymph nodes or multiple other soft tissue sites in 6 patients. The median time to metastases was 1.5 (0.2–6.4) years. The metastasis-free survival rate of the whole series of 104 patients was 0.68 (95% CI 0.58–0.76) at 5 years and 0.65 (0.54–0.74) at 7 years (Figure 1). The corresponding overall 5-year survival rates were 0.76 (0.66–0.83) and 0.69 (0.58–0.78), respectively (Figure 2). The crude local recurrence rate was 0.08 among patients treated at an SSG center and 0.6 among patients treated outside an SSG center.

With univariate analyses, large tumor size, amputation, deep tumor site and extracompartmental location were associated with impaired metastases-free survival (Table 1). 14/27 patients who were amputated, as compared to 20/77 who had a local excision, developed metastases. The median metastasis-free survival time was 1.5 years in both groups. Compartmentalization and tumor depth were, to a different extent, both related to tumor size and surgical procedure. Local excision was used for all 29 intracompartmentally-located tumors, whereas amputation was chosen for 27/69 tumors with extracompartmental location. Among the 10 subcutaneous tumors, all but 2 were small and all patients had local excision.

Cox's proportional hazards model was used to evaluate the joint impact of covariables with respect to metastasis-free survival. Our final model includes local recurrence, entered as a time-dependent variable, tumor size and amputation vs. local excision (Table 2). Information concerning compartmentalization was of no additional value, probably because of the associations with size and surgical procedure. The effect of tumor depth could not be examined further, since none of the 10 patients with subcutaneous lesions developed metastases. The other covariates considered only

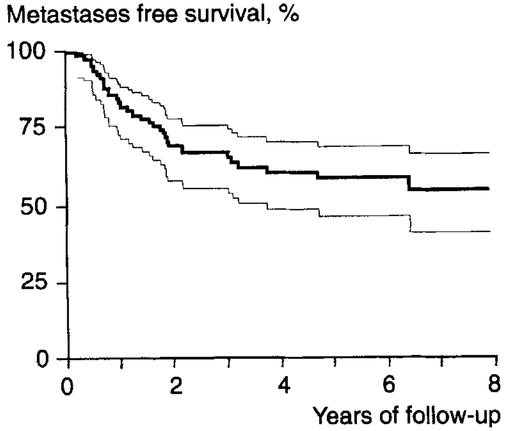

Figure 1. Kaplan-Meier survival estimate for metastasis-free survival in 104 patients with synovial sarcomas. 95% pointwise confidence band shown.

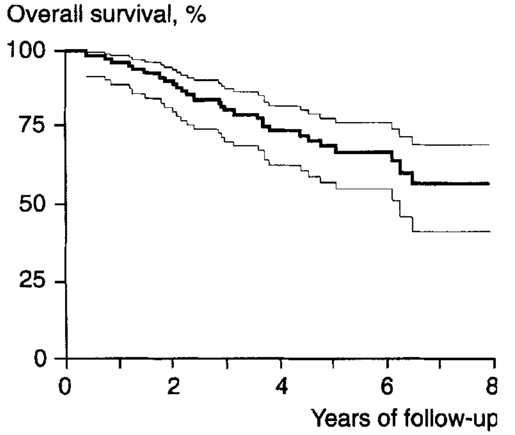

Figure 2. Kaplan-Meier survival estimate for overall survival in 104 patients with synovial sarcomas. 95% pointwise confidence band shown.

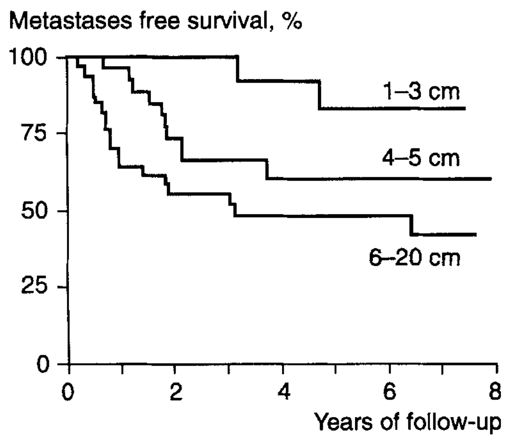

Figure 3. Kaplan-Meier survival estimates for metastasis-free survival based on tumor size. There were 31 patients with tumor size 1–3 cm, 31 with 4–5 cm, 38 with > 5 cm and 4 patients with missing data. P-log-rank 0.0003.

Table 2. Metastasis-free survival analyzed multivariately according to Cox's proportional hazards model. Local recurrence is entered as a time-dependent covariable

	Hazard ratio	95% CI	P-value
Tumor size, cm			
1–3 (reference)	1	–	–
4–5	4.3	1.2–16	0.03
> 5–20	7.2	2.1–24	0.001
Amputation	2.9	1.4–6.3	0.005
Local recurrence	9.8	3.6–26	< 0.001

Based on 100 patients

slightly affected the model parameters and were of little significance. These inncluded age (≤ 20 versus > 20 years) at diagnosis which resulted in an estimated hazard ratio of 1.25 (Wald test p-value 0.7) for age > 20 years and virtually no changes in the other model parameters. Tumor size was entered as a categorical covariate with three levels: 1–3, 4–5 and 6–20 cm, respectively. The categorization was used since the log hazard did not appear to increase linearly with tumor size, cf. Figure 3. Note that the hazard ratio estimates are rather imprecise, with fairly wide 95% confidence intervals for the effects (Table 2.).

When considering the type of first failure event (local or distant) for the 85 patients diagnosed before January 1994 (see statistics), we found that inadequate treatment significantly altered the proportions between the two failure modes, leading to a substantially larger proportion of local recurrences (Table 3). The proportion of patients with no evidence of disease was slightly larger in the group given an adequate treatment, but the difference was not significant in any cases, e.g., 44/85 (0.7) patients (68%) vs. 11/19 (0.6) patients (55%) at 4.5 years, p = 0.4. Note also that inadequate treatment had no impact on metastases-free survival (Table 1, p-value log-rank test 1). 4 of the 7 patients with a local recurrence as the first failure event developed metastases within 4.5 years from diagnosis.

The adequacy of the surgical treatment was closely related to where the patient was treated. Only 5 of 16 patients treated outside an SSG center were given adequate surgical treatment. The corresponding figures for SSG-treated patients

Table 3. Distributions of failure modes associated with time to first failure for 85 patients diagnosed before 940101. Adequate local treatment (n 65), inadequate local treatment (n 20). Figures in parenthesis are proportions (%)

	Adequate local treatment			Inadequate local treatment			
Time from diagnosis, years	No. of subjects with event n	Local recurrence n (%)	Metastasis n (%)	No. of subjects with event n	Local recurrence n (%)	Metastasis n (%)	P-value Fisher's
1	12	1 (8)	11 (92)	4	2 (50)	2 (50)	0.1
2	16	1 (6)	15 (94)	8	4 (50)	4 (50)	0.03
3	17	1 (6)	16 (94)	9	5 (56)	4 (44)	0.01
4	20	1 (5)	19 (95)	9	5 (56)	4 (44)	0.006
4.5	21	2 (10)	19 (90)	9	5 (56)	4 (44)	0.01

were 74 of 88; p-value with Fishers's exact test < 0.001.

Among the 34 patients who developed metastases, 11 had lung surgery plus chemotherapy and/ or radiotherapy, 7 underwent lung surgery only and 5 chemotherapy only. 11 patients were not treated. At the last follow-up, 26 of 34 patients with metastases had died of the tumor. 5 patients were alive with persistent disease up to 4 years after diagnosis of the metastases. 3 patients had no evidence of disease at 6, 7 and 11 years, respectively, after the diagnosis of metastases. 2 of these had been treated with lung surgery only and 1 patient had lung surgery, in combination with chemotherapy.

Discussion

Our study, based on the SSG and the National Swedish Cancer Registers, revealed an overall survival rate of 0.76 at 5 years and 0.69 at 7 years (Figure 1). Previous studies have reported a 5-year overall survival rate ranging from 0.40 (Hajdu et al. 1977) to 0.68 (Choong et al. 1995) and 0.23 (Wright et al. 1982) to 0.56 (Choong et al. 1995) at 10 years. Hence, our results compare favorably to previous series of synovial sarcoma and, in fact, the reported survival of patients with synovial sarcoma has continuously improved since the entity was first described. This improvement has been explained by more aggressive treatment (Choong et al. 1995), but it can also be ascribed to differences in patient selection due to changing referral practices. Unfortunately, most published series lack such essential data as treatment before referral, tumor size and location. A uniformly applied system of classification of surgical margin is also lacking. Hence, it is difficult to compare different patient series of synovial sarcoma.

All patients in Sweden with a primary synovial sarcoma were included. In comparison to Sweden, only patients from Norway and Finland treated at an SSG center were included in the study. Swedish patients having all primary surgery outside an SSG center were included in the analyses since Swedish patients with synovial sarcoma not reported to the SSG Registry were traced through the National Swedish Cancer Register. The importance of histological review of the National Cancer Register diagnoses was illustrated by the fact that the diagnosis of synovial sarcoma was accepted in only 16 of 23 patients treated outside of an SSG center.

Since our material was collected during a relatively short period, 9 years, in contrast to most other studies of synovial sarcoma, treatment policies have changed little during the accrual period. Compared to previous studies, more patients were referred before surgery, the lesions were smaller, and the patients were also older (Figure 3). These differences reflect the better referral practices in the Scandinavian countries compared to the USA (Mankin et al. 1996). The most striking difference was the amputation rate of 26%, as compared to the Mayo Clinic of 51% (Wright et al. 1982) and of 56% (Choong et al. 1995). The amputation rate is still high compared to mixed series of soft tissue sarcomas. This is due to the peripheral location of synovial sarcomas treated with minor amputation, e.g., forefoot.

The poor results of surgery among Swedish patients treated outside of SSG centers point to the importance of referral of patients with soft tissue tumors to sarcoma centers for treatment of primary tumor (Gustafson et al. 1994). Inadequate local treatment was almost exclusively performed outside of sarcoma centers.

The importance of local recurrence for survival is still under debate. Retrospective studies of soft tissue sarcoma show that local recurrence is associated with an increased rate of metastases. This does not necessarily mean that the local recurrence gives rise to metastases. Indeed, the analysis for types of first failure event (Table 3) revealed that inadequate local treatment was a strong risk-factor for local recurrence but not for metastases. This issue cannot be resolved by our study but it remains clear that local recurrence is an ominous finding and may warrant not only aggressive local but also systemic treatment.

Large tumor size proved to be the most important risk factor for metastases confirming previous findings (Wright et al. 1982, Zito 1984, Brodsky et al. 1992, Mullen and Zagars 1994, Choong et al. 1995, Singer et al. 1996). Our study failed to show prognostic significance of several clinical features such as site (Hajdu et al. 1977, Oda et al. 1993) and sex (Moberger et al. 1968) previously claimed to be of importance. There is no consensus that these features have any strong prognostic value and they do not warrant further discussion. Young age has been associated with increased survival and longer metastases-free survival in a number of studies (Hajdu et al. 1977, Wright et al. 1982, Choong et al. 1995). However, in our study only a slight trend for a better metastases-free survival rate was noted in patients < = 20 years old in the univariate analysis. This trend vanished in the multivariate analysis in accord with the findings Brodsky reported in his series of 95 patients from MSKCC. We have no explanation of the discrepancies between the studies, except that the median age in our series was 38 years, as compared to 30 years in both Choong's and Wright's material, possibly accounting for the difference.

With univariate analysis, there was a trend for a higher survival rate among patients with intracompartmentally-located tumors, but in the multivariate analysis, this effect disappeared, probably because of covariation with size, which was also shown by Rydholm et al. (1991). The poor prognosis of amputated patients was probably due to the selection of patients with more aggressive lesions.

Only 7 patients received adjuvant chemotherapy. All were children or adolescents and 1 developed metastases, but no conclusions can be drawn since they were so few. Nevertheless, the question arises whether all patients with synovial sarcoma should receive adjuvant chemotherapy. In a metaanalysis of randomized chemotherapy trials of adult soft tissue sarcoma, an increased 5-year metastases-free survival rate was noted but there was no overall survival benefit (Sarcoma Meta-analysis Collaboration 1997). The overall survival rate of 0.69 at 7 years is in our opinion too high to warrant such treatment. Patients with large tumors, e.g., > 5 cm, can be considered candidates for adjuvant chemotherapy. Among the remaining patients, chemotherapy may be indicated only after local or distant relapse.

The chance of salvage, i.e., 5 years of disease-free survival after diagnosis of metastatic disease, was only 0.1 in our series. This contrasts to the latest Mayo Clinic series (Choong et al. 1995) where the survival was twice as high (0.2). The difference in survival between the series may be due to selection of patients referred with operable metastatic disease to the Mayo Clinic. Unfortunately, the report contains no information on referral. It is also possible that the difference is attributable to more active treatment and monitoring of patients with metastatic disease at the Mayo Clinic. Larger population-based studies may show whether survival of synovial sarcoma patients with metastases improves with more aggressive treatment, as randomized trials are hardly feasible.

Supported by the Nordic Cancer Union, the Swedish Cancer Foundation, and the Swedish National Board of Health and Welfare. Data regarding children: VSTB (The Swedish Solid Childhood Tumor Register). 10 patients from the material in Anal Cell Pathol 1998; 16 (1): 45-62 "Synovial sarcoma. Evaluation of prognosis with emphasis on the study of DNA ploidy and proliferation (PCNA and Ki-67) markers" by Lopes J M, Hannisdal E, Bjerkehagen B, Brunland O S, Danielsen H E, Pettersen EO, Sobrinho-Simoes M, Nesland J M and 17 patients from the Gothen-

burg-Rizzoli study accepted in Cancer; "Synovial sarcoma: identification of high- and low-risk groups" by Berg P, Meis-Kindblom J, Gherlinzoni F, Berlin Ö, Bacchini P, Bertoni F, Gunterberg B, Kindblom L-G were included in our series. Detailed information about individual patients can be obtained on request.

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