Original Article

Long-Term Recurrence of Soft Tissue Sarcomas

Prognostic Factors and Implications for Prolonged Follow-Up

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BACKGROUND: To the authors' knowledge, the incidence of late recurrence (> 5 years after initial management) is unknown and no prognostic factors for late events have been characterized in patients with soft tissue sarcomas. **METHODS:** Follow-up data from patients with localized soft tissue sarcoma who were included in the French Sarcoma Group database from January 1990 to June 2005 were reviewed. The outcomes of interest were the cumulative probabilities of late (> 5 years) local and metastatic disease recurrence with death as a competing event. Estimations and 95% confidence intervals (95% CIs) were computed with the cumulative incidence function. **RESULTS:** A total of 719 patients who were alive and event free > 5 years after their initial diagnosis were included in the current study. Sixty-seven patients (9.3%) developed a late local recurrence and 42 patients (5.8%) developed a late metastatic recurrence, respectively. On multivariate analysis, internal trunk location (hazard ratio [HR], 3.9; 95% CI, 2.2-6.7 [$P < .001$]) and tumor size > 100 mm (HR, 2.1; 95% CI, 1.1-4 [$P = .035$]) were the 2 factors found to be independently associated with an increased risk of late local recurrence. Grade > 1 (graded according to the French Federation of Cancer Centers Sarcoma Group) (HR, 4.7; 95% CI 1.1-21 [$P = .04$]) was the sole factor found to be independently associated with an increased risk of late metastatic recurrence. **CONCLUSIONS:** Late recurrence of soft tissue sarcoma is relatively uncommon. However, the results of the current study emphasize the critical role of long-term follow-up to detect late local disease recurrence in patients with retroperitoneal or very large soft tissue sarcomas, and late metastatic recurrence in patients with high-grade disease. Conversely, the prolonged follow-up of patients with grade 1 disease is not needed. ***Cancer*** **2014;120:3003-6.** © *2014 American Cancer Society.*

KEYWORDS: soft tissue sarcoma, late recurrence, follow-up, prognosis.

INTRODUCTION

Soft tissue sarcoma (STS) is a rare and heterogeneous disease that comprises > 50 distinct histological subgroups.[1] The treatment of STS in specialized centers is expressly recommended.[2-4] However, to our knowledge, there is no consensus regarding the follow-up of patients with STS after initial management.[5]

Late disease recurrence is generally defined as recurrence that occurs > 5 years after initial management. The incidence of late recurrence, which would justify prolonged follow-up, is not well-documented and to our knowledge no prognostic factors specific for late events such as local recurrence or metastasis have been characterized in patients with STS. The diversity of STS in terms of anatomic location, histology, and biological behavior makes global analysis inappropriate. Early diagnosis of local recurrence or metastatic recurrence can lead to aggressive treatments with curative intent and prolonged survival in selected patients.[6] Prognostic factors for a tailored follow-up are therefore needed.

The primary objective of the current study was to determine prognostic factors for late local and metastatic disease recurrence to better distinguish those patients who should have a longer and more careful follow-up from those who do not need it.

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TABLE 1. Patient Characteristics

Characteristic	No. of Patients	%
Median age (range), y 52 (16-92)		
Sex		
Male	352	49
Female	367	51
Location		
Limb	509	70.8
Trunk wall	70	9.7
Head and neck	18	2.5
Internal trunk	122	17
Median tumor size (range), mm 80 (10-600)		
Histology		
Liposarcoma	233	32.4
Well differentiated/dedifferentiated	148	20.5
Myxoid/round cell	66	9.2
Pleiomorphic	19	2.6
Undifferentiated sarcoma	184	25.6
Leiomyosarcoma	81	11.3
Synovial sarcoma	72	10
MPNST	25	3.5
Rhabdomyosarcoma	20	2.8
Fibrosarcoma	18	2.5
Other	86	11.9
FNCLCC grade		
1	189	26.3
2	265	36.9
3	244	33.9
Unknown	21	2.9
Surgical margins		
R0	326	45.3
R1	129	17.9
Unknown	264	36.7
Radiotherapy		
No	186	25.9
Neoadjuvant	3	0.4
Adjuvant	530	73.7
Chemotherapy		
No	434	60.4
Adjuvant	177	24.6
Neoadjuvant	108	15.0

Abbreviations: FNCLCC, French Federation of Cancer Centers Sarcoma Group; MPNST, malignant peripheral nerve sheath tumor.

MATERIALS AND METHODS

The current study was based on data from the French Sarcoma Group database (conticabase.sarcomabcb.org/). Inclusion criteria were 1) a primary diagnosis of localized deep STS after January 1990; 2) macroscopically complete surgery; and 3) complete remission maintained for at least 5 years after initial management.

The outcomes of interest were the cumulative probabilities of late (> 5 years) local and metastatic disease recurrence, respectively, with death as a competing event. In all cases, the histological diagnosis was established according to the World Health Organization Classification of Tumors[1] by an expert pathologist. The histological grade was determined as previously described according to the French Federation of Cancer Centers Sarcoma Group (FNCLCC) grading system.[7]

Statistical Analysis

Descriptive statistics were used to show the distribution of variables in the population. We used a proportional hazards model for the subdistribution of competing risks. Estimations and 95% confidence intervals (95%CIs) were computed with the cumulative incidence function. Patients who did not experience the event of interest or death over the course of the study were censored at the time of their last follow-up.

Variables tested in univariate analysis included age, sex, location, size, histology, grade, depth, bone/neurovascular involvement, surgical margins, adjuvant radiotherapy, and adjuvant chemotherapy. Variables associated with the respective endpoint of interest with a P value $< .05$ were planned to be included in the multivariate analysis.

RESULTS

A total of 3369 patients with STS underwent macroscopically complete surgery for a localized STS between 1990 and 2009. Among them, 719 patients were free of disease recurrence 5 years after the initial diagnosis and were therefore included in the current study. Their characteristics are described in Table 1.

The median follow-up was 9.1 years (95% CI, 8.7 years-9.8 years). At the time of analysis, 96 patients were dead of any cause. Sixty-seven patients (9.3%) developed a late local disease recurrence whereas 42 patients (5.8%) developed a late metastatic recurrence.

Prognostic Factors Associated With Late Local Recurrence

On univariate analysis, internal trunk location, a liposarcoma histological subtype, tumor size > 100 mm, R1 surgical margins, and lack of adjuvant radiotherapy were found to be significantly associated with an increased risk of late local recurrence (Table 2).

On multivariate analysis, internal trunk location (hazard ratio [HR], 3.9; 95% CI, 2.2-6.7 [$P < .001$]) and tumor size > 100 mm (HR, 2.1; 95% CI, 1.1-4 [$P = .035$]) were the 2 factors found to be independently associated with an increased risk of late local disease recurrence.

Prognostic Factors Associated With Late Metastatic Recurrence

On univariate analysis, leiomyosarcoma histological subtype and grade > 1 were significantly associated with an increased risk of late metastatic recurrence (Table 3).

On multivariate analysis, grade > 1 (HR, 4.7; 95% CI, 1.1-21 [$P = .04$]) was found to be the sole factor

TABLE 2. Prognostic Factors for Local Disease Recurrence (Univariate Analysis){TC}

	No. of Patients	Events	%	HR (95% CI)	*P*	*P*
Location						
Limb	509	29	5.7	Reference	.708	
Trunk wall/head and neck	88	7	8.0	1.18 (0.50-2.77)	<.001	<.0001
Internal trunk	122	31	25.4	4.98 (3.01-8.25)		
Histology						
Liposarcoma	233	31	13.3	Reference	.108	
Leiomyosarcoma	81	6	7.4	0.49 (0.20-1.17)	.045	.0480
Undifferentiated sarcoma	184	14	7.6	0.52 (0.28-0.99)	.024	
Other	221	16	7.2	0.50 (0.27-0.91)		
Tumor size, mm						
<51	195	12	6.2	Reference	.689	
51-101	246	13	5.3	0.85 (0.39-1.88)	.009	.0006
>100	249	34	13.7	2.43 (1.25-4.72)		
Unknown	29	8	27.6	—		
Surgical margins						
R0	326	22	6.7	Reference	.001	.0005
R1	129	21	16.3	2.85 (1.56-5.21)		
Unknown	264	24	9.1	—		
Radiotherapy						
No	186	25	13.4	Reference	.004	.0038
Yes	533	42	7.9	0.48 (0.29-0.79)		

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio.

TABLE 3. Prognostic Factors for Metastatic Disease Recurrence (Univariate Analysis)

	No. of Patients	Events	%	HR (95% CI)	*P*	*P*
Histology						
Liposarcoma	233	9	3.9	Reference	.016	
Leiomyosarcoma	81	10	12.3	3.06 (1.23-7.61)	.280	.0027
Undifferentiated sarcoma	184	4	2.2	0.52 (0.16-1.69)	.059	
Other	221	19	8.6	2.14 (0.97-4.70)		
FNCLCC grade						
1	189	3	1.6	Reference	.021	
2	265	3	6.8	4.21 (1.24-14.3)	.016	.0253
3	244	18	7.4	4.54 (1.33-15.5)		
Unknown	21	18	14.3	—		

Abbreviations: 95% CI, 95% confidence interval; FNCLCC, French Federation of Cancer Centers Sarcoma Group; HR, hazard ratio.

independently associated with an increased risk of late metastatic disease recurrence.

DISCUSSION

The results of the current study demonstrate that late disease recurrence among patients with STS is relatively uncommon. By distinguishing local recurrence from metastatic recurrence in the current analysis, we found that each pattern of recurrence occurs preferentially in distinct subtypes of STS and that they are quite different in terms of prognostic factors.

Late local recurrence occurred in 25% of patients with internal trunk sarcoma and 14% of patients with a tumor size > 100 mm. Retroperitoneal sarcomas share both negative prognostic features for local recurrence. More specifically, retroperitoneal liposarcomas, especially when well differentiated, can have a very indolent course interspersed with iterative recurrences. Indeed, a recent work from our group demonstrated that the local recurrence-free survival of patients with retroperitoneal well-differentiated and dedifferentiated liposarcomas is divided by 2 between 5 years and 10 years.[2] Therefore, a tailored long and regular follow-up appears justified for these patients.

Although the majority of metastatic recurrences occur within 2 years from the time of the initial diagnosis, the data from the current study indicate that 1 in 14 patients with high-grade STS who was free of recurrence at 5 years developed a late metastatic recurrence. One mechanism that could explain the late recurrence of high-

grade, highly proliferating tumors is tumor dormancy. To the best of our knowledge, cancer dormancy is poorly understood, and various mechanisms have been reported, including angiogenic dormancy, cellular dormancy (G_0-G_1 arrest), and immunosurveillance.[8] A large set of compelling preclinical data have suggested that the angiogenesis switch could be a crucial trigger in reversing tumor dormancy.[9,10] These data indicate the need for a deeper understanding of the underlying tumor biology driving dormancy in patients with high-grade sarcomas.

To the best of our knowledge, there are no published data to indicate the optimal routine follow-up policy for patients with localized STS who are treated surgically. Current recommendations suggest following surgically treated patients with intermediate-grade to high-grade disease every 3 to 4 months in the first 2 to 3 years, then twice yearly up to the fifth year and once a year thereafter.[2] It is also proposed to follow patients with low-grade sarcomas for local recurrence every 4 to 6 months in the first 3 to 5 years and then annually thereafter. It is interesting to note that recent data have suggested no difference in time to detection and overall survival between less costly (eg, chest x-ray at 6-month intervals) and more expensive (computed tomography scans at 3-month intervals) testing or follow-up regimens.[11,12]

The results of the current study emphasize the critical role of long-term follow-up to detect late local disease recurrence in patients with retroperitoneal or very large STS, and late metastatic recurrence in patients with high-grade disease. In addition to current European Society for Medical Oncology recommendations for the first 5 years, we suggest that patients with retroperitoneal sarcoma and patients with high-grade tumors be followed biannually for up to 10 years (eg, with biannual chest x-ray and annual computed tomography scans). However, the data from the current study also suggest that the prolonged follow-up of patients with grade 1 nonretroperitoneal disease is not needed.

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CONFLICT OF INTEREST DISCLOSURES

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