Original Article

Prognostic Factors and Impact of Adjuvant Treatments on Local and Metastatic Relapse of Soft-Tissue Sarcoma Patients in the Competing Risks Setting

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BACKGROUND: In the medical literature many analyses of outcomes of sarcoma patients were performed without regard to the problem of "competing risks." **METHODS:** We analyzed local relapse–free and metastasis-free survival in a population of 3255 adult patients with a primary soft-tissue sarcoma (STS) included in the French Sarcoma Group database. Cumulative incidence of local and metastatic relapse was estimated by accounting for death as a competing event. **RESULTS:** On multivariate analysis, age, tumor site, histological subtype, and grade were independent adverse prognostic factors for local relapse, whereas tumor depth and size had no influence. Histological subtype, tumor depth, tumor size, and grade were independent adverse prognostic factors for metastatic relapse. Despite a higher incidence of competing deaths in patients managed with adjuvant radiotherapy than in patients not receiving radiotherapy, adjuvant radiotherapy was associated with a significant benefit in terms of local relapse–free survival. Despite a similar cumulative incidence of competing deaths in patients with grade 2 and grade 3 disease, we found that the benefit of adjuvant chemotherapy was present only in patients with grade 3 and not in patients with grade 2 disease. **CONCLUSIONS:** In the setting of competing risks, tumor biology reflected by histological grade is a crucial predictor of local relapse, whereas tumor depth and size have poor if any influence. Grade could also predict the benefit of adjuvant chemotherapy in patients with STS. ***Cancer* 2014;120:3361-9.** © *2014 American Cancer Society.*

KEYWORDS: competing risks, soft-tissue sarcoma, prognosis, treatment.

INTRODUCTION

Prognostication is of crucial importance in cancer patients. Indeed, an accurate prediction of local or metastatic relapse and of overall survival will help clinicians to plan specific care and follow-up strategies according to the specific risks of their own patients.

Statistical methods for analyzing time-to-event data such as Kaplan-Meier curves, the log rank test, hazard ratios, and the Cox proportional hazard model are widely used in the medical literature. These methods evaluate time to a specific event with data that are often subject to censored observations. For instance, to determine time to local relapse, every patient is followed from the date of local treatment until the date of local relapse or study final date. However, with the above methods, patients who first develop metastatic disease or die before local relapse are considered censored for time to local relapse. Such events (metastatic relapse or death) are typically called "competing risks."[1-3] In fact, the main limit of actuarial methods cited above is that they are based on the assumption that "competing risks" are independent. For most cancers, such an assumption does not make sense. Indeed, the occurrence of a competing risk (for instance, death by suicide or by metastatic disease) may preclude the onset of the event of interest (for instance, local relapse) or at least modify its probability.[1-3]

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TABLE 1. Patient Characteristics (N = 3255)

		n	%
Sex	Male	1612	49.5
	Female	1643	50.5
Age, years	≥55	1590	48.8
	>55	1665	51.2
	n	3255	
	Median (range)	56 (16-100)	
Tumor site	Limb	2175	66.8
	Trunk wall	319	9.8
	Head and neck	112	3.4
	Internal trunk	649	19.9
Histological subtype	Well-differentiated/ dedifferentiated LPS	667	20.5
	Myxoid/round cell LPS	303	9.3
	Pleomorphic LPS	82	2.5
	Angiosarcoma	78	2.4
	Leiomyosarcoma	484	14.9
	Malignant schwannoma	108	3.3
	Myxofibrosarcoma	249	7.6
	Undifferentiated sarcoma	663	20.4
	Synovialosarcoma	314	9.6
	Other	307	9.4
Tumor location	Unknown	26	0.8
	Deep	2785	85.6
	Superficial	444	13.6
Tumor size	Unknown	105	3.2
	<5 cm	895	27.5
	≥5 and < 10 cm	1043	32.0
	≥10	1212	37.2
FNCLCC grade	Unknown	124	3.8
	1	728	22.4
	2	1143	35.1
	3	1260	38.7
Radiotherapy	Unknown	4	0.1
	No	1292	39.7
	Yes	1959	60.2
Chemotherapy	Unknown	6	0.2
	No	2525	77.5
	Yes	724	22.3

Abbreviations: LPS, liposarcoma.

Soft-tissue sarcomas represent a heterogeneous group of rare tumors accounting for about 1% of cancers in adults.[4,5] Surgery represents the cornerstone of treatment for patients with localized disease. Despite adequate locoregional treatment, 10%-30% and 35%-40% of patients will develop local relapse and metastatic disease, respectively. Isolated local relapse may lead to patient death even in the absence of metastatic disease, particularly when the primary tumor is retroperitoneal. In contrast, high-grade tumors are associated with a risk of early metastatic relapse leading to patient death and as a consequence minimizing the risk of local failure.[6,7]

The role of adjuvant treatments such as radiation therapy and chemotherapy is controversial. Indeed, because of their rarity, data from randomized trials assessing the role of adjuvant radiation therapy and chemotherapy are scarce and the level of evidence poor. Although adjuvant radiation therapy is considered standard treatment in high-grade deep lesions, >5 cm, its role is more controversial in low-grade or <5-cm lesions.[8,9] Moreover, although adjuvant chemotherapy has been shown to improve metastasis-free survival, its impact on overall survival has not been demonstrated.[10] Several studies aimed to refine the prognosis of soft-tissue sarcomas to help clinicians to more accurately select patients for adjuvant treatments.[2-17] For all these studies, survival analysis was performed for each event type (local relapse, metastatic relapse, or death) separately, whereas the other (competing) event types were treated as censored categories. This approach may substantially overestimate the absolute risk of the event of interest because subjects with a competing (and thus censored) event are treated as if they could experience the event of interest in the future. The aim of this study was to use a competing risk model for the definition of prognostic factors for local and metastatic relapse in soft-tissue sarcomas and the assessment of the impact of adjuvant treatments.

MATERIALS AND METHODS

Patients

From 1990 to 2010, 3255 nonpediatric patients (≥16 years old) with a nonmetastatic soft-tissue sarcoma underwent R0 or R1 surgery of the primary tumor and were included in the French Sarcoma Group (GSF) database. Patient with tumors of intermediate malignancy (dermatofibrosarcoma protuberans) or with Ewing or alveolar/embryonal rhabdomyosarcoma were excluded. All the cases were reviewed by the members of the pathological subcommittee of the GSF. Histological diagnosis was established according to the World Health Organization Classification of Tumors.[4] Histological grade was determined after central review as previously described according to the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system.[7,18] The patients' characteristics are described in Table 1. Nineteen hundred fifty-nine patients (60.2%) received adjuvant radiotherapy (median dose, 50.4 Gy). Seven hundred twenty-four (22.3%) received adjuvant chemotherapy. In all the cases, doxorubicin was delivered either alone or in combination with other drugs (dacarbazine with or without cyclophosphamide and vincristine; CYVADIC protocol, or ifosfamide with or without dacarbazine and mesna; AI or MAID protocols).

Statistical Analysis

Qualitative descriptive statistics were reported as counts and proportions and compared using the chi-square test. The outcomes assessed were local relapse–free survival

(LRFS) and metastatic relapse–free survival (MRFS). LRFS was defined as the interval between histological diagnosis and the time of local recurrence or the last follow-up. MRFS was defined as the interval between histological diagnosis and the time of distant recurrence or the last follow-up. Competing risk was death from all causes in the analyses of LRFS and MRFS. The LRFS and MRFS were described using cumulative incidence rates with 95% confidence intervals (CIs).

The cumulative incidence function is the cumulative probability of failure from a specific cause over time and is particularly useful in the presence of competing risks. The effect of covariates on failure time can be assessed using regression analysis based directly on the cumulative incidence function using, for example, the method introduced by Fine and Gray.[19] Details regarding this approach have already been described.[20,21]

Following this approach, the possible prognostic factors were analyzed using a proportional hazard model, estimating subhazard ratios (sHRs) with 95% CIs both univariately and multivariately. Univariate analysis included the following variables: age, sex, anatomic site, tumor size, tumor location (superficial or deep), margin status, presence of bone or neurovascular invasion, histological subtype, and FNCLCC grade. Significant factors ($P < .05$) were included in a multivariate model and selected in a descending process. The final model was adjusted on treatment. Median follow-up was determined using the reverse Kaplan-Meier estimator.[22] Analyses were performed using Stata statistical software, version 11.2.

RESULTS

The median follow-up of patients was 4.5 years (95% CI, 4.3-4.7 years).

Local Relapse–Free Survival (LRFS)

At the time of analysis, 737 patients (22.6%) had local recurrence. The 1-year, 5-year, and 10-year cumulative incidence of local relapse was 6.5% (95% CI, 5.6%-7.3%), 26.1% (95% CI, 24.2%-27.6%), and 31.5% (95% CI, 29.3%-33.5%), respectively (Fig. 1). On multivariate analysis, age, tumor site, histological subtype, and grade were independent adverse prognostic factors for LRFS (Table 2, Fig. 2).

Impact of Adjuvant Radiotherapy

The incidence of competing deaths was higher in patients managed with adjuvant radiotherapy than in patients not receiving radiotherapy. Despite this, adjuvant radiotherapy was associated with a significant benefit in local relapse–free survival, with an overall sHR of 0.52 (95% CI, 0.44-0.61; $P < .001$) after adjustment for other prognostic factors in competing settings.

Metastasis-Free Survival

At the time of analysis, 754 patients (23.2%) had metastatic relapse. The 1-year, 5-year, and 10-year cumulative incidence of metastatic relapse was 7.5% (95% CI, 6.5%-8.3%), 26.8% (95% CI, 25.2%-28.7%), and 32.0% (95% CI, 29.9%-34.1%), respectively (Fig. 3). On multivariate analysis, histological subtype, tumor location, tumor size, and grade were independent adverse prognostic factors for metastasis-free survival (Table 2, Fig. 3).

Impact of Adjuvant Chemotherapy

On multivariate analysis, adjuvant chemotherapy was associated with a significant benefit metastasis-free survival, with an overall sHR of 0.70 (95% CI, 0.57-0.86; $P = .001$) after adjustment for other prognostic factors. Because we have previously reported that the benefit of adjuvant chemotherapy was limited to patient with grade 3 disease, we performed an analysis by grade. Despite a similar cumulative incidence of competing deaths in patients with grade 2 and grade 3 disease, we found that the benefit of adjuvant chemotherapy was present only in patients with grade 3 (sHR, 0.57; 95% CI, 0.45-0.73; $P < .001$) and not in patients with grade 2 disease (sHR, 1.06; 95% CI, 0.74-1.54; $P = .436$) after adjustment for other prognostic factors in competing settings (Fig. 4).

DISCUSSION

In the presence of competing events, the Kaplan-Meier method generally overestimates the risk of the event of interest.[1-3] Therefore, the cumulative incidence of metastatic relapse accounting for competing risk as reported in the results section above is a more accurate estimation of the risk of metastatic relapse than the risk estimated by the Kaplan-Meier method. This also appears obvious when comparing the risk of an event in different categories of a specific variable. In fact, the risk of a competing event may not be identical in categories of the same variable. For instance, as shown in the results section, patients with a deep tumor or a tumor >5 cm were at a higher risk of competing death than patients with a superficial or a small-size tumor. This may be explained by the finding that patients with deep and/or large tumors have a higher risk of metastatic relapse and death from disease, which is in keeping with previous reports.[6-8,13-16].This may explain why deep location and tumor size were not

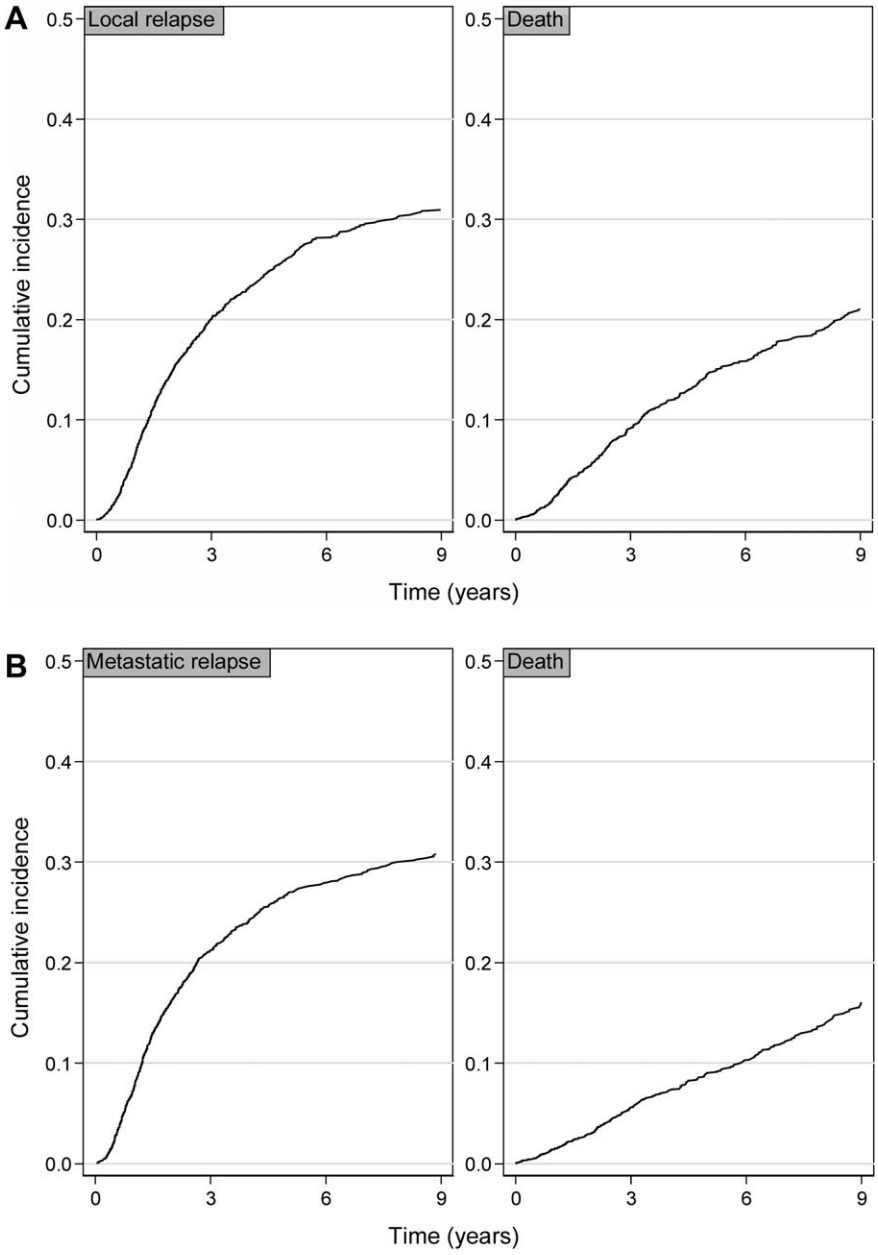

Figure 1. Cumulative incidences of local relapse (A), metastasis (B), and related competing deaths.

identified as independent prognostic factors for local relapse in our series. In regard to the other prognostic factors of local relapse, the majority of them were in agreement with those of previous reports.[6,8,13-16] However, we also found that despite a higher incidence of competing deaths for patients with high-grade tumors, distinctions between low-grade and high-grade tumors may help to identify patients who are at higher risk of local relapse. These findings are not in agreement with a recent study that analyzed the risk of local relapse of soft-tissue sarcoma (STS) in the setting of competitive risks.[23] However, that study also included patients with recurrent disease at presentation, which may have biased the interpretation of the results. Adjuvant radiotherapy is considered standard treatment in high-grade, deep lesions >5 cm.[10] Indeed, these characteristics have been identified as prognostic factors for local relapse in several series using actuarial statistical methods.[6,12-16] Adjuvant radiotherapy is also

TABLE 2. Significant Prognostic Factors for Local Relapse and Metastasis Incidence (Multivariate Analysis)

	LRFS		MFS	
Variable	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Whole population				
Age	REF	.014		
<55 years	1.237 (1.044-1.466)			
≥55 years				
Tumor site	REF	<.001		
Limb	1.645 (1.282-2.11)	.005		
Trunk wall	1.856 (1.21-2.848)	<.001		
Head and neck	2.155 (1.751-2.652)			
Internal trunk				
Histological subtype	REF	.693	REF	
Well-differentiated/dedifferentiated LPS	0.926 (0.633-1.356)	.386	2.963 (1.999-4.393)	<.001
Myxoid/round cell LPS	1.237 (0.765-2.001)	.332	1.856 (1.074-3.208)	.027
Pleomorphic LPS	1.303 (0.763-2.227)	<.001	3.852 (2.063-7.193)	<.001
Angiosarcoma	0.585 (0.442-0.773)	.875	3.199 (2.245-4.558)	<.001
Leiomyosarcoma	1.038 (0.653-1.651)	.596	1.308 (0.719-2.377)	.379
Malignant schwannoma	1.1 (0.774-1.563)	.516	1.504 (0.952-2.375)	.080
Myxofibrosarcoma	0.911 (0.688-1.207)	.142	1.747 (1.217-2.508)	.002
Undifferentiated sarcoma	0.752 (0.513-1.1)	.708	3.484 (2.351-5.163)	<.001
Synovialosarcoma	0.94 (0.679-1.301)		2.992 (2.042-4.386]	<.001
Other				
Tumor location			REF	.002
Superficial			1.622 (1.197-2.196)	
Deep				
Tumor size			REF	.001
<5 cm			1.453 (1.173-1.8)	<.001
≥5 and <10 cm			1.88 (1.483-2.384)	
≥10				
FNCLCC grade	REF	<.001	REF	<.001
1	2.051 (1.615-2.605)	<.001	3.621 (2.526-5.192)	<.001
2	2.854 (2.19-3.719)		7.018 (4.796-10.269)	
3				
Radiotherapy	REF	<.001	REF	.070
No	0.516 (0.437-0.608)		0.851 (0.715-1.013)	
Adjuvant				
Chemotherapy	REF	.101	REF	.001
No	0.832 (0.667-1.037)		0.697 (0.568-0.856)	
Aduvant				

recommended for high-grade, deep, <5-cm tumors, whereas it remains only an option for deep-seated low-grade tumors. Our results clearly confirm the higher risk of recurrence of high-grade lesions based on competing risks models. However as discussed above, we did not find any prognostic impact of tumor size and tumor location (deep or superficial). Altogether, these data suggest that the benefit of adjuvant radiotherapy depends mainly on the biological characteristics of the tumor and its intrinsic risk of life-threatening metastatic relapse rather than its deep or superficial location or size.

Prognostic factors for metastatic relapse identified in our study are similar to those reported previously.[6,8,13-16] The role of adjuvant chemotherapy in soft-tissue sarcomas is a matter of debate. A 1997 individual patient meta-analysis of all known randomized clinical data failed to show a significant benefit of adjuvant chemotherapy in terms of overall survival (OS).[24] A more recent meta-analysis including the published data of 4 additional trials published from 2000 to 2002 recently reported that adjuvant chemotherapy was actually associated with a significant benefit in terms of OS, with a hazard ratio (HR) of 0.77 and an absolute risk reduction of death of 6%.[25] These results have been contradicted by the report of a randomized trial by the European Organisation for Research and Treatment of Cancer group, which was not included in the more recent meta-analysis and which has failed to demonstrate any benefit of adjuvant chemotherapy.[26] The apparent lack of benefit of chemotherapy in localized soft-tissue sarcomas may be because many trials have included heterogeneous types of sarcomas with different biological characteristics and clinical outcomes.[24,25]

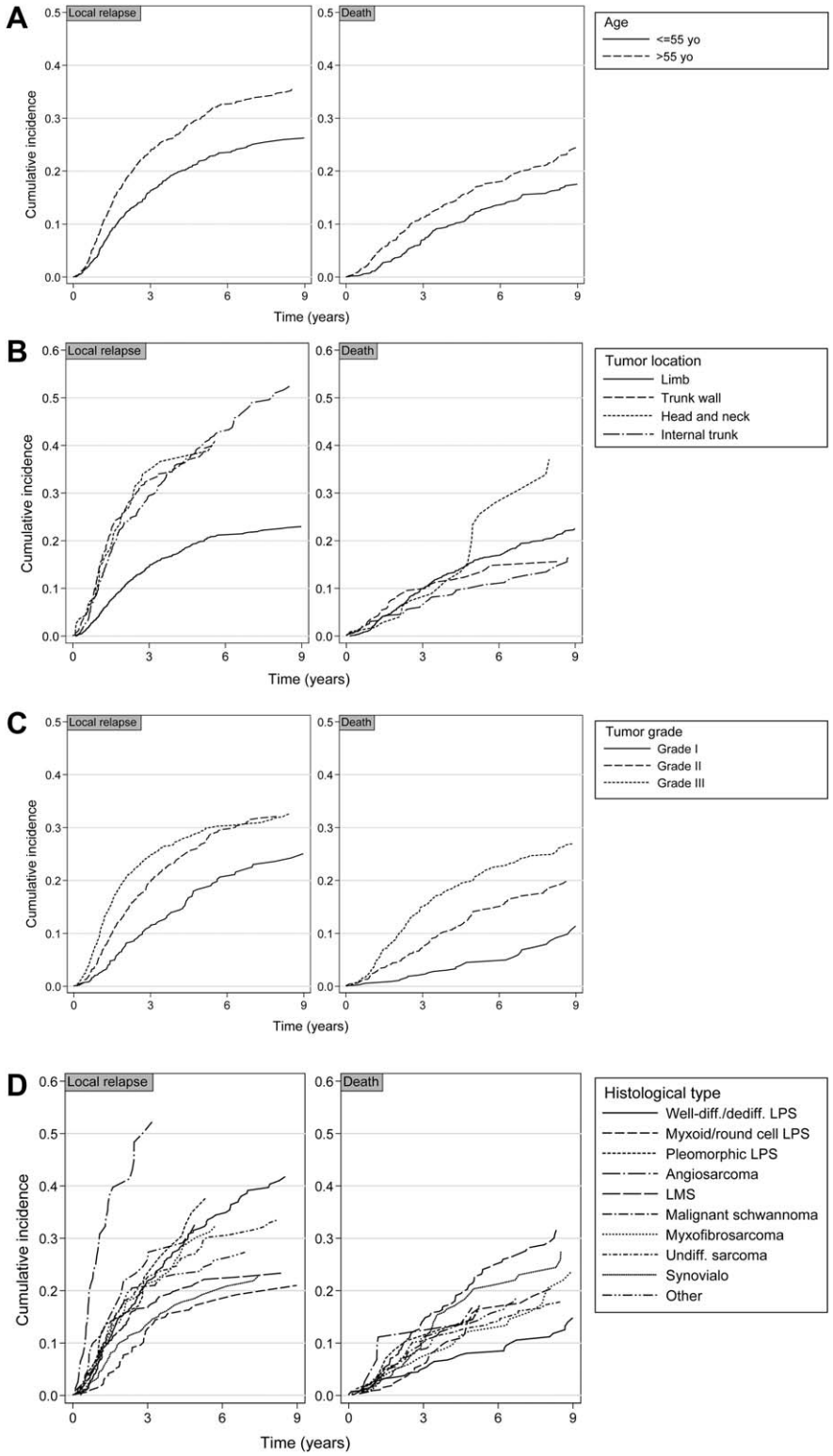

Figure 2. Cumulative incidences of local relapse according to age (A), tumor site (B), tumor grade (C), and histological subtype (D) and related competing deaths.

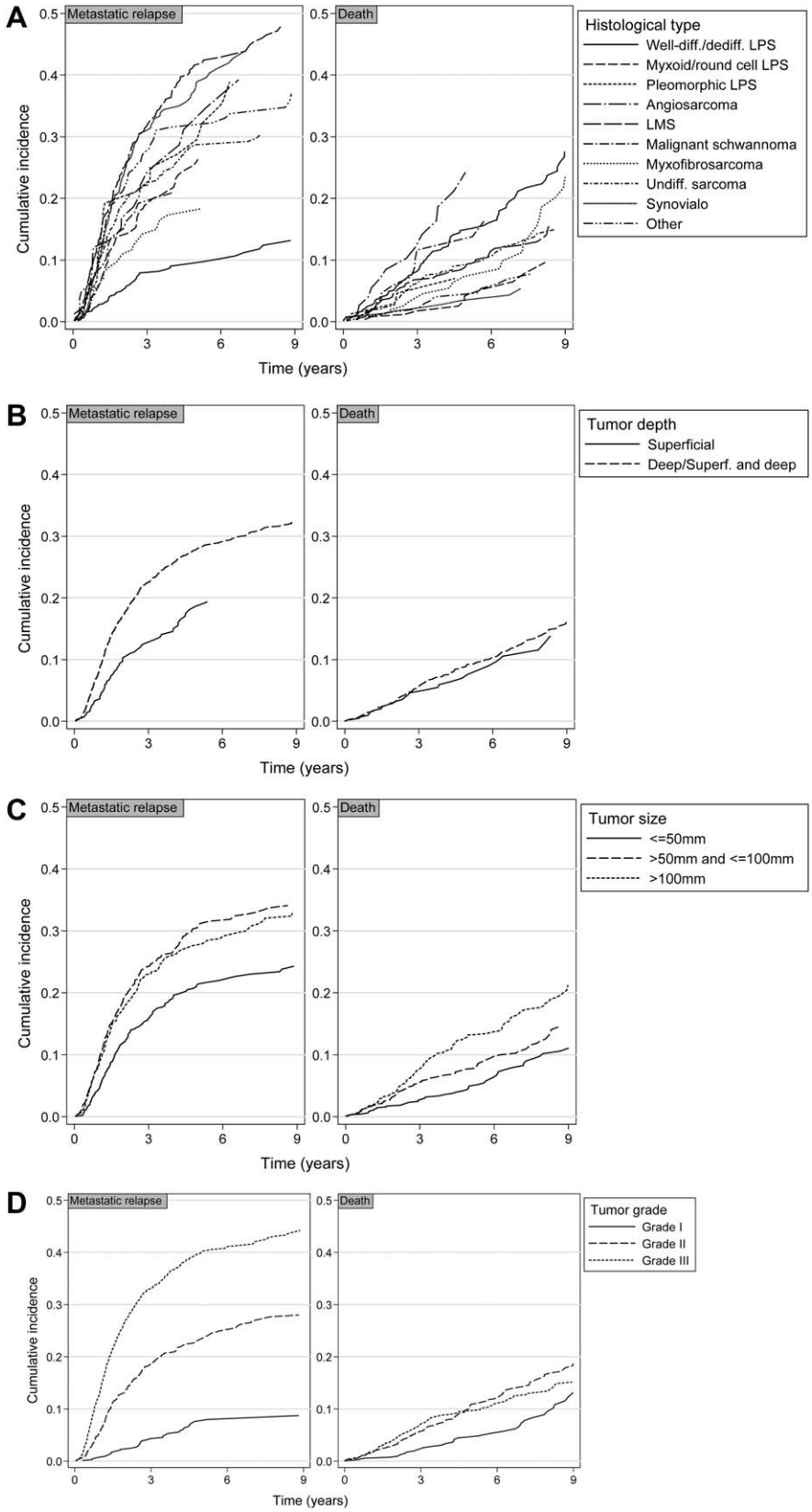

Figure 3. Cumulative incidence of metastatic relapse according to histological subtype (A), tumor depth (B), tumor size (C), and tumor grade (D) and related competing deaths.

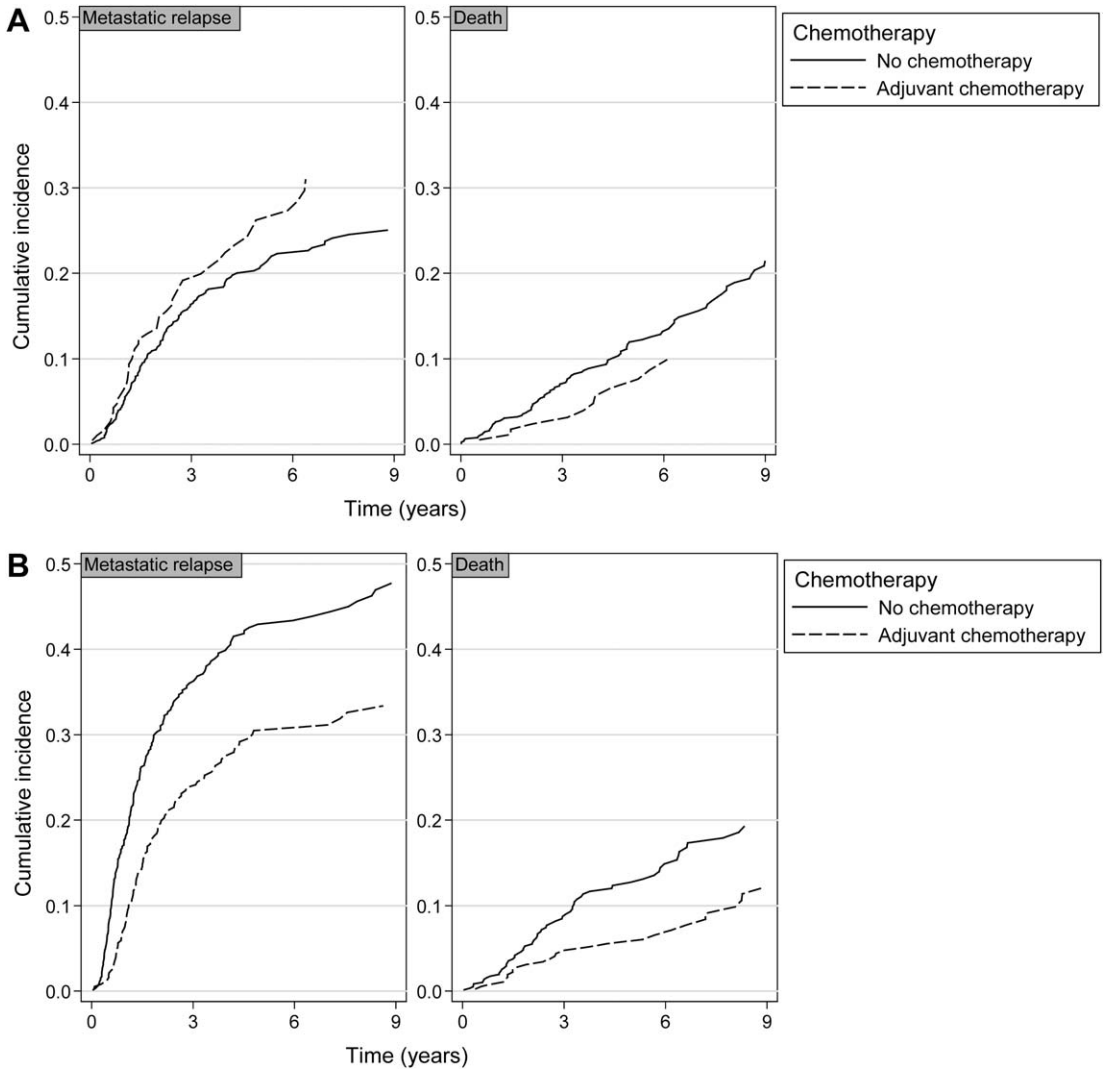

Figure 4. Cumulative incidences of metastatic relapse and related competing deaths in grade 2 (A) and grade 3 (B) patients.

We recently reported a large cohort-based analysis including 1513 patients with 9-year follow-up suggesting that FNCLCC grade 3 but not grade 2 was predictive of a benefit from adjuvant chemotherapy.[27] None of the adjuvant retrospective or prospective studies as well as the meta-analyses were analyzed in the competitive risk settings. Indeed, the aim of chemotherapy is to reduce the risk of metastatic relapse. However, a significant proportion of patients die of disease without metastatic recurrence, particularly patients with retroperitoneal tumors, which are associated with an important risk of local recurrence whatever their grade. Our present results indicate that the differences we observed in chemotherapy benefit between grade 2 and grade 3 patients were not related to differences in competing risk of death but more likely to disease biology. Altogether, these data suggest that it is unlikely that future clinical trials in the adjuvant setting would show a benefit in metastasis-free and overall survival in STS patients if their design is not improved to include a more homogenous population in terms of metastatic risk.

Overall, our results suggest that in the setting of competing risks, tumor biology reflected by histological grade is a crucial predictor of local relapse, whereas tumor depth and size have poor if any influence. Grade could also predict the benefit of adjuvant chemotherapy in patients with STS. Overall, these data should be considered to tailor the indications and choice of adjuvant treatments in STS patients.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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