Original Article

Local Recurrence of Localized Soft Tissue Sarcoma

A New Look at Old Predictors

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BACKGROUND: The objective of this study was to examine the effect of known predictors of local recurrence of soft tissue sarcoma in a competing risk setting. **METHODS:** The outcome of interest was the cumulative probability of local recurrence per category of relevant predictors, with death as a competing event. In total, 1668 patients with a localized soft tissue sarcoma of the extremity or trunk were included. **RESULTS:** Tumor size (hazard ratio, 3.3), depth (hazard ratio, 3.2), and histologic grade (hazard ratio, 4.5) were the variables that had the most effect on the risk of metastasis and, accordingly, were the most likely to induce competition. Surgical margins (hazard ratio, 3.3), histologic grade (hazard ratio, 2.1), presentation status (hazard ratio, 2.4), and tumor depth (hazard ratio, 1.5) were the variables that had the most effect on the risk of local recurrence. The 10-year cumulative probabilities of local recurrence were markedly different within categories for presentation status ($P < .001$) and surgical margin status ($P < .001$). However, because of the competing effect of death, there was little difference in the 10-year cumulative probabilities of local recurrence with regard to tumor depth (12% and 11.4% for deep and superficial tumors, respectively; $P = .2$), tumor size (10.6% and 13.3% for large and small tumors, respectively; $P = .99$), or histologic tumor grade (12.6%, 10.7%, and 11.1% for high, intermediate, and low-grade tumors, respectively; $P = .17$). **CONCLUSIONS:** Because of the competition between local recurrence and death, histologic tumor grade, tumor size, and tumor depth had little influence on the cumulative probability of local recurrence. The authors concluded that local management should be based on presentation status and surgical margins rather than other, previously acknowledged factors. ***Cancer* 2012;000:000–000.** *© 2012 American Cancer Society.*

KEYWORDS: sarcoma, neoplasm recurrence, local, competing risk, histologic grade, tumor size, tumor depth, radiation, surgical margins.

INTRODUCTION

Approximately 11,000 soft-tissue sarcomas are diagnosed every year in the United States, accounting for <1% of the incidence of all cancers.[1] The local control of soft tissue sarcomas involves surgical resection with adjuvant radiation if wide margins cannot be obtained circumferentially.[2,3] At 5 years, the cumulative probability of local recurrence reported in large series ranges from 12% to 28%,[4-8] and the cumulative probability of metastasis ranges from 21% to 40%.[4,5,7-9]

Numerous predictors, such as patient age, presentation status, tumor size, tumor depth, histologic grade, surgical margins, and radiation, reportedly have a significant influence on the cause-specific hazard of local recurrence.[4-8,10] Accordingly, it also has been reported that the cumulative probabilities between categories of these predictors are markedly different. For instance, at 5 years, the cumulative probability of local recurrence for patients with high-grade tumors versus low-grade tumors has been reported as 40% and 24%,[4] 25% and 18%,[11] and 20% and 12%,[8] respectively. However, in those series, cumulative probabilities were computed using the Kaplan-Meier estimator, which is known as biased in the presence of competition.[12]

Competition arises when the occurrence of 1 event precludes the occurrence of the event of interest[13]; for instance, death competes with the occurrence of a local recurrence. If the competition is different between categories of a variable, then the hazard ratio may not be an appropriate measure of the difference in cumulative probabilities between these categories. Patients who present with high-grade tumors have a higher risk of local recurrence than those who present with low-grade tumors.[4-6,9,11] However, the finding that the former patients are at even higher risk of death from metastatic disease,[4,6-11] which precludes them from developing a local recurrence, suggests that, in reality, there may be little difference in the cumulative probability of local recurrence between these 2 groups of patients. To our knowledge, no investigation to date has thoroughly studied the effect of the main predictors of local recurrence in the setting of competing risks.

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Table 1. Presentation and Treatment Characteristics, n = 1668

Variable	No. of Patients (%)
Age	
>60 y	751 (45)
Sex	
Men	913 (55)
Tumor site	
Upper extremity	455 (27)
Lower extremity	1094 (66)
Trunk	114 (7)
Presentation status	
Recurrent disease	136 (8)
Histologic subtype	
Angiosarcoma	32 (2)
Solitary fibrous tumor	36 (2)
Fibrosarcoma	83 (5)
Liposarcomas, pleo/dediff	102 (6)
MPNST	111 (7)
Synovial sarcomas	115 (7)
Sarcomas, other	148 (9)
Leiomyosarcomas	185 (11)
Liposarcomas, myxoid/round cell	207 (12)
Pleomorphic undifferentiated sarcoma	644 (39)
Tumor size	
Large	976 (62)
Tumor depth	
Deep	1153 (70)
Tumor grade	
1	205 (12)
2	529 (32)
3	920 (56)
Surgery type	
Amputation	91 (5)
Surgical margin status	
Positive	246 (15)
Radiotherapy	
Yes	1150 (69)
Chemotherapy	
Yes	72 (4)

Abbreviations: MPNST, malignant peripheral nerve sheath tumor; Pleo/Dediff, pleomorphic/dedifferentiated.

Because predictors like histologic grade, tumor depth, tumor size, and other variables play an important role in the treatment decision for patients who present with soft tissue sarcoma,[14-16] the objective of the current study was to reinterpret the clinical significance of the main predictors of local recurrence in a competing risk setting.

MATERIALS AND METHODS

Patients and Treatments

Between 1989 and 2010, 2048 consecutive patients with a soft tissue sarcoma of the extremity or trunk were treated at the combined Sarcoma Unit of Mount Sinai Hospital and Princess Margaret Hospital, Toronto, Canada. Of these, we excluded 136 patients who developed metastasis before definitive surgery as well as 145 patients who presented with well differentiated liposarcomas and 99 patients who presented with dermatofibrosarcoma protuberans because of their different biology and low risk of local recurrence. This study was approved by the local research ethics board.

All treatment decisions were made at dedicated sarcoma multidisciplinary tumor boards. The surgical objective was to obtain a circumferential wide resection margin with a 1-cm to 2-cm cuff of normal tissue, or fascia, surrounding the specimen; otherwise, patients typically received radiation therapy. Follow-up visits were planned every 3 months for the first 2 years, then every 6 months until the fifth year, and then annually until the 10th year, at which time, follow-up normally was discontinued.

Local status at presentation was classified as primary if the patient underwent surgery for the first time or as part of the re-excision of a previously excised soft tissue sarcoma with inadequate margins ("whoops" procedure); otherwise tumors were classified as recurrent. Tumors of that measured ≤ 5 cm were classified as small, and other tumors were classified as large. The depth of the tumor was classified as superficial for tumors above the fascia superficialis and deep for tumors that were deep to or involving this fascia. The histologic grade of the tumor was based on the 3-tier grading system of the French Federation of Cancer Centers Sarcoma Group.[17] Surgical resection margins were considered positive if tumor cells extended to the inked margins and negative otherwise.

The cohort included 1668 patients, 913 [55%] men, and 751 patients aged > 60 years old (Table 1). One thousand ninety-four patients (66%) presented with a tumor affecting the lower limb, and 136 patients (8%) with a recurrent tumor. Tumors more frequently were deep (1153 tumors; 70%), large (976 tumors; 62%), and of intermediate or high grade (1449 tumors; 88%). Pleomorphic undifferentiated sarcoma was the most common diagnosis (644 patients; 39%). Ninety-one patients (5%) underwent amputation, 72 patients (4%) received chemotherapy, and 1150 patients (69%) received radiation; of these latter patients, radiation was received preoperatively by 67% of patients, postoperatively by 27% of patients, and both preoperatively and postoperatively by 6% of patients. The median follow-up was 38 months (first to third quartile, 15-84 months).

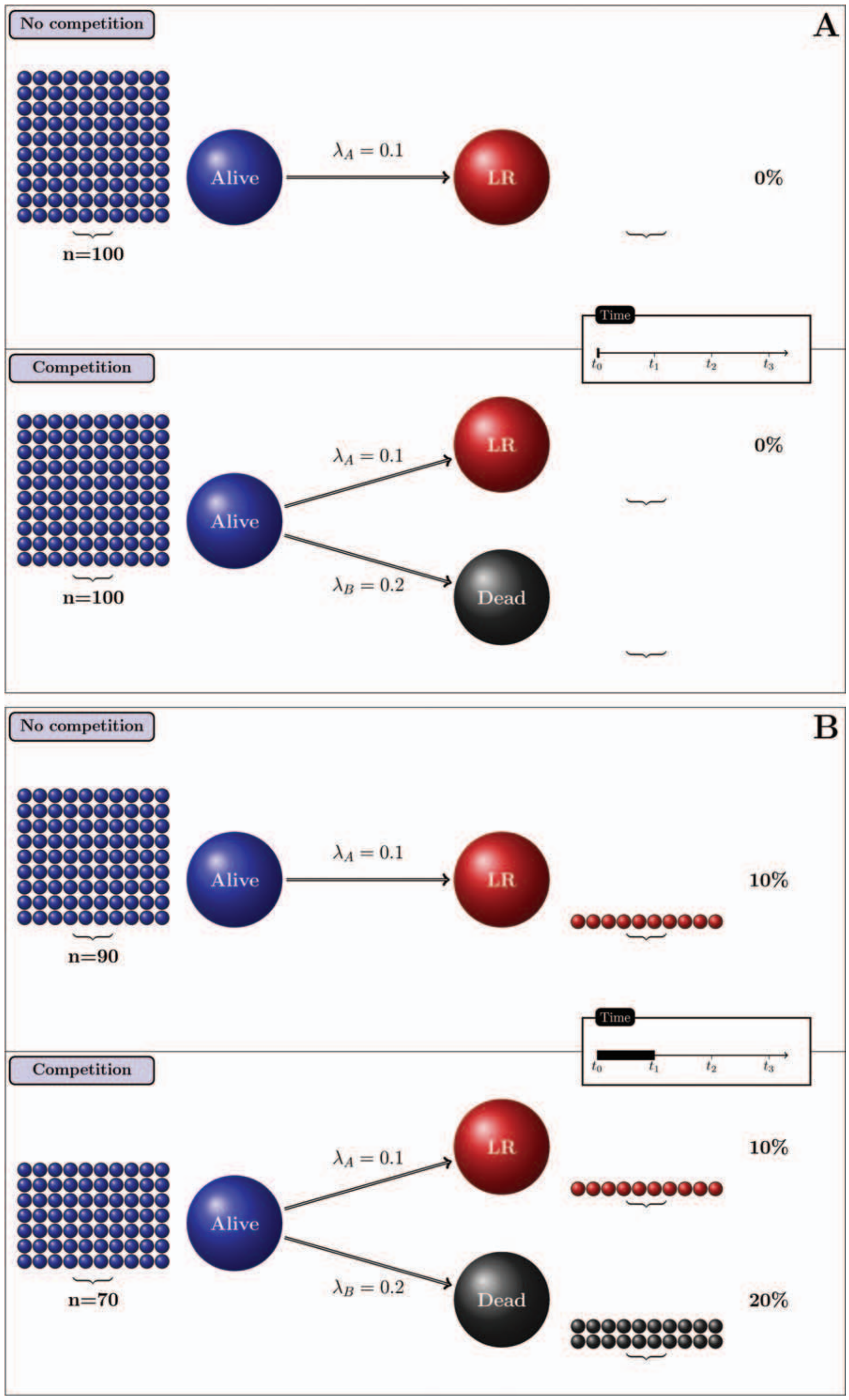

Figure 1. This is a representation of the models for local recurrence in noncompeting (Kaplan-Meier) and competing settings over time. In the noncompeting scenario, patients may only experience a local recurrence (LR) over follow-up; in the competing scenario, patients may experience LR or death (competing event). Over each period (from time zero t_0 to t_1, t_1 to t_2, ...), patients who remain alive are transferred to the other state(s) according to some risk or hazard (λ). The hazard of local recurrence (λ_A) is 0.1 in this example and is the same in both settings; namely, 10% of the patients who are alive at the beginning of each period will be transferred to the LR state during that period. However, patients in the competing scenario also are subject to the competing risk ($\lambda_B = \lambda_A \times 2$) and are transferred accordingly. (A-D) The end and beginning of successive periods are illustrated, indicating that, over time, the cumulative probability of LR (percentages on the right) is overestimated in the noncompeting (Kaplan-Meier) scenario, because no account is made for the competition. It is noteworthy that, for clarity, censoring is not represented, because it would not change the estimation of cumulative probabilities.

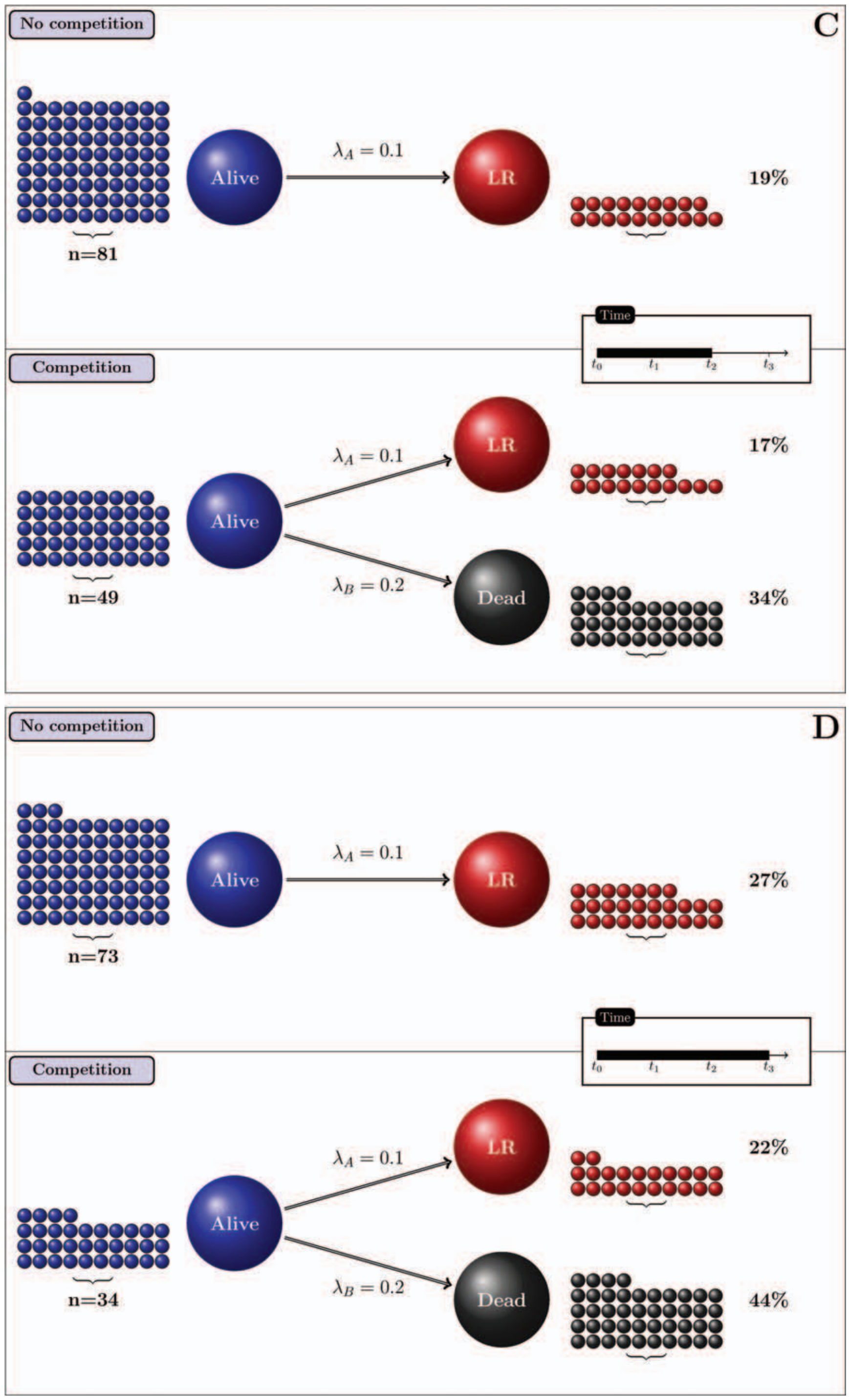

Figure 1. Continued

Methods

The outcome of interest was the cumulative probability of local recurrence with death as a competing event. Estimations and 95% confidence intervals (CIs) were computed with the cumulative incidence function.[13] Patients who did not experience the event of interest or death over the course of the study were censored at their last follow-up.

To interpret the effect of the competition between local recurrence and death on relevant variables, first, we estimated the hazard ratio for these variables for both local

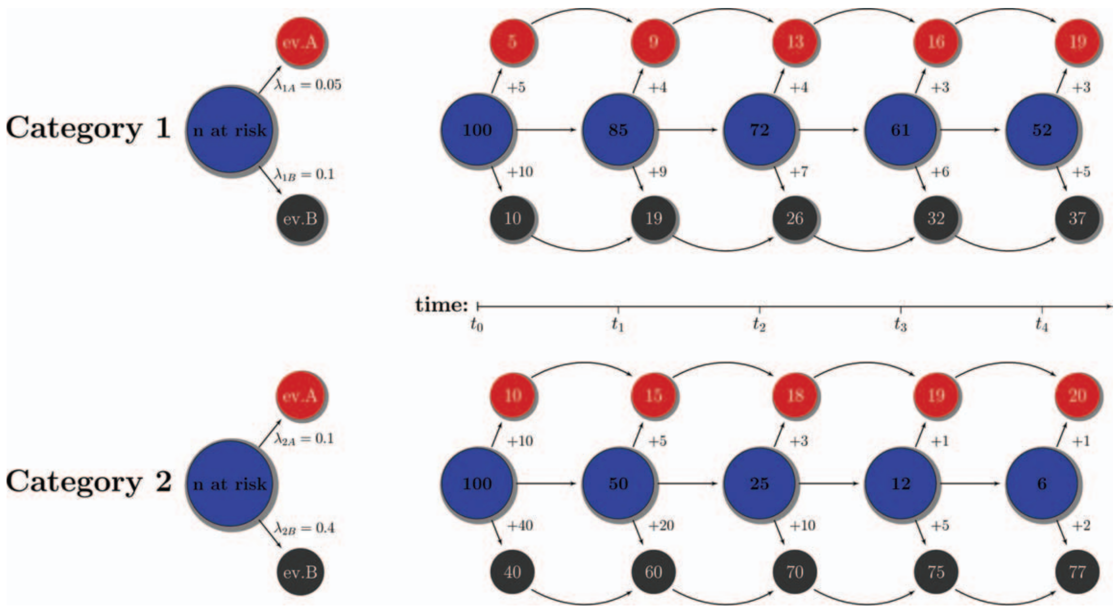

Figure 2. The cumulative probability of an event A (ev.A) is illustrated for 2 categories of a variable (eg, low-grade and high-grade tumor) in a competing risk scenario. Patients in category 1 have a low probability of event A (eg, local recurrence; $\lambda_{1A} = 0.05$) and event B (ev.B) (death; $\lambda_{1B} = 0.1$). Patients in category 2 are at greater risk for event A ($\lambda_{2A} = 0.1$) and are at even greater risk for the competing event B ($\lambda_{2B} = 0.4$). Consequently, for that variable, the hazard ratio of event A is $\lambda_{2A}/\lambda_{1A} = 2$, and the hazard ratio of the competing event B is $\lambda_{2B}/\lambda_{1B} = 4$. It is observed that, over time, the cumulative probability of event A for patients in category 1 gradually reaches that of patients in category 2. At the end of the fourth period, the cumulative probability is 19% for patients in category 1 and 20% for patients in category 2. The reason is that, over time, more patients in category 2 fail from the competing event, and fewer are available for event A. Conversely, patients in category 1 have a lower risk but, on average, they will carry that risk for a longer time.

recurrence and metastasis in unadjusted and adjusted Cox proportional hazard models.[18] On the basis of previous reports from the literature,[4-11] the following variables were considered to be of importance: age ($\leq$60 years and >60 years), local status at presentation (primary or recurrent), tumor size, tumor grade (1, 2, and 3), tumor depth (superficial or deep), histologic subtype, radiation (yes or no), chemotherapy (yes or no), and surgical margins (positive or negative). Age had a complex, nonlinear effect on both local recurrence and metastasis that yielded a separate analysis and report; for simplicity, models were stratified on age, but its effect is not presented here[19]; Cox proportional hazard models also were stratified according to histologic subtypes. Continuous predictors were categorized to facilitate the interpretation. All tests were bilateral at the .05 level and were based on the Wald test except when specified otherwise. Cumulative incidence curves were compared with a Gray test.[20] All computations were performed using R (R Foundation for Statistical Computing, Vienna, Austria).[21] Unless specified otherwise, the words "risk" and "hazard" refer to the cause-specific hazard,[13] and estimates refer to that from the univariable regression models. Figures 1 and 2 illustrate the effect of competition on the cumulative probability of an event and its relevance with regard to categories of a predictor.

RESULTS

Tumor size, tumor depth, and histologic tumor grade were the variables that had the most effect on the risk of metastasis (Table 2). Patients who had high-grade tumors had 4.5 times greater risk (95% CI, 2.8-7.3) of developing metastasis than patients who had low-grade tumors. Patients who presented with deep tumors or large tumors had 3.2 times greater risk (95% CI, 2.4-4.2) and 3.3 times greater risk (95% CI, 2.6-4.3) of developing a metastasis compared with those who presented with superficial or small tumors, respectively. Surgical margins, histologic grade, presentation status, tumor depth, and radiotherapy were the variables that had the most effect on the risk of local recurrence (Table 2). Patients with positive surgical margins had 3.3 times greater risk (95% CI, 2.3-4.7) of developing a local recurrence compared with those who had negative surgical margins. Patients who presented with locally recurrent tumors, high-grade tumors, and deep tumors had 2.4 times greater risk (95% CI, 1.5-3.7), 2.1 times greater risk (95% CI, 1-4.1), and 1.5 times

Table 2. Univariable and Multivariable Regression Models on the Cause-Specific Hazard of Metastasis and Local Recurrence

	HR (95% CI)			
	Metastasis		Local Recurrence	
Variable	Univariable Model	Multivariable Model	Univariable Model	Multivariable Model
Presentation status				
Recurrent	0.65 (0.44-0.96)	0.68 (0.45-1.03)	2.38 (1.52-3.73)	1.83 (1.13-2.97)
Tumor size				
Large	3.34 (2.62-4.25)	2.57 (1.99-3.32)	1.17 (0.82-1.68)	1.05 (0.71-1.55)
Tumor depth				
Deep	3.16 (2.39-4.19)	2.50 (1.83-3.44)	1.47 (0.97-2.20)	1.61 (1.00-2.59)
Tumor grade				
2	1.98 (1.20-3.27)	1.66 (0.97-2.83)	1.52 (0.74-3.12)	1.78 (0.84-3.79)
3	4.53 (2.82-7.29)	3.47 (2.08-5.80)	2.07 (1.04-4.13)	2.16 (1.05-4.43)
Surgical margin status				
Positive	1.50 (1.19-1.89)	1.37 (1.08-1.75)	3.25 (2.27-4.66)	3.43 (2.30-5.13)
Radiotherapy				
Yes	1.44 (1.15-1.80)	0.78 (0.61-0.99)	0.75 (0.52-1.07)	0.48 (0.32-0.73)
Chemotherapy				
Yes	1.69 (1.15-2.48)	1.09 (0.72-1.63)	1.39 (0.65-2.99)	1.49 (0.66-3.37)

Abbreviations: CI, confidence interval; HR, hazard ratio.
The effects presented are that of the category presented in comparison to the category not presented. For instance, "Large" tumors have a 3.34 increased risk of metastasis compared to "Small" tumors.

Table 3. Cumulative Probability of Local Recurrence and Death at 10 Years

	10-Year CP (95% CI)		
Variable	Death[a]	Local Recurrence	*P*
Presentation status			
Primary	30.2 (27-33.5)	10.8 (8.7-13.1)	< .001
Recurrent	26 (17.2-35.7)	22 (13.9-31.3)	
Tumor size			.99
Small	14.8 (10.9-19.3)	13.3 (9.6-17.6)	
Large	39.5 (35.3-43.7)	10.6 (8.3-13.2)	
Tumor depth			.2
Superficial	15.8 (11.3-21.1)	11.4 (7.1-16.7)	
Deep	35.1 (31.4-38.8)	12 (9.7-14.5)	
Tumor grade			.17
1	17.2 (9.3-27.3)	11.1 (4-22.2)	
2	21.6 (16.9-26.8)	10.7 (7.7-14.3)	
3	37.6 (33.3-41.9)	12.6 (9.8-15.8)	
Surgical margin status			< .001
Negative	27.5 (24.2-30.8)	9.2 (7.2-11.6)	
Positive	41.2 (33.3-49)	23.9 (17.6-30.8)	
Radiotherapy			.085
No	25 (19.5-30.8)	16.5 (11.3-22.4)	
Yes	31.7 (28.1-35.4)	10 (8-12.4)	
Chemotherapy			.48
No	29.9 (26.8-33.1)	11.7 (9.6-14.1)	
Yes	29.9 (18-42.8)	12.5 (5.4-22.7)	

Abbreviations: CI, confidence interval; CP, cumulative probability.
[a] With death as a competing event, that is, death occurring as the first event.

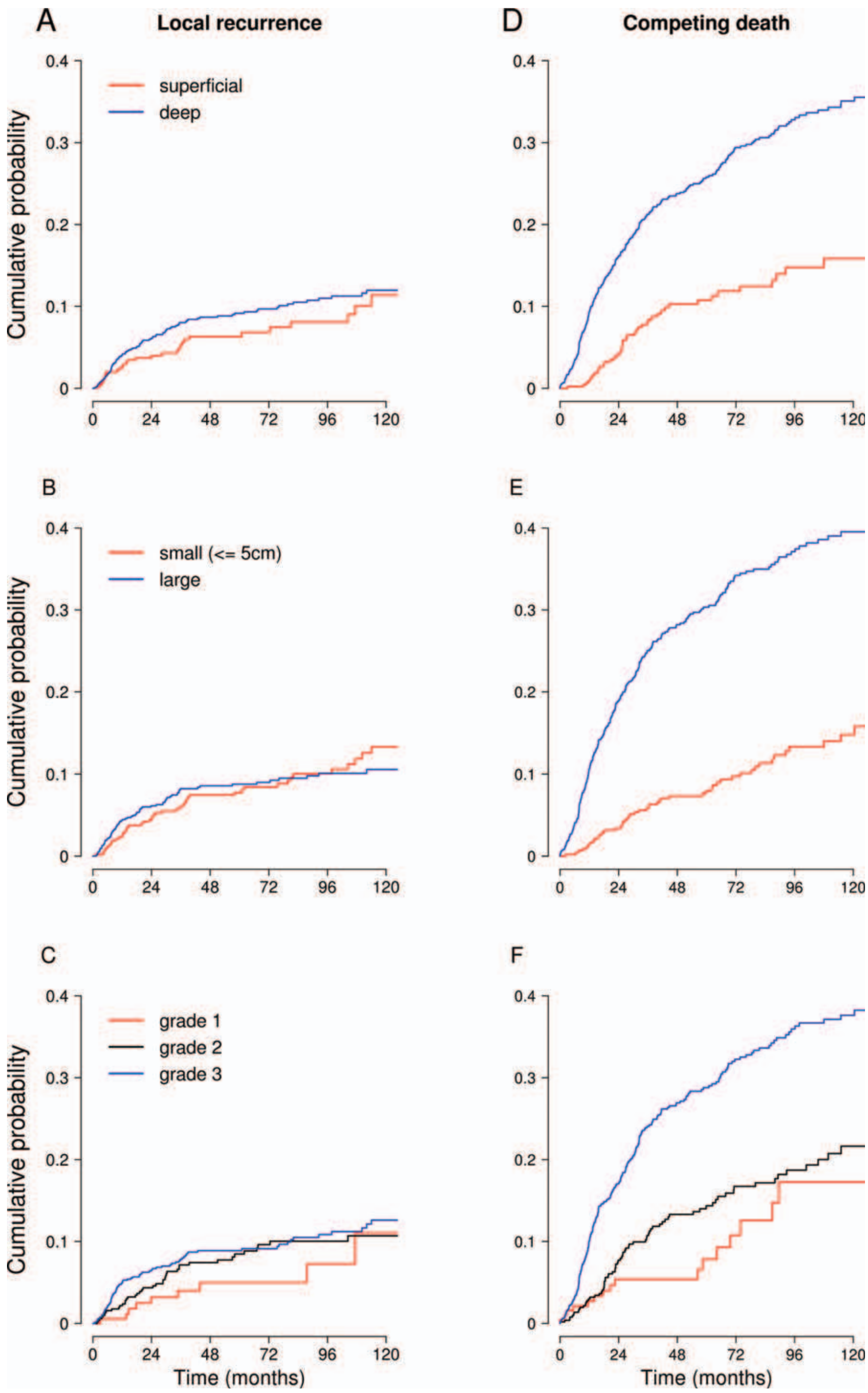

Figure 3. Cumulative probabilities of local recurrence are illustrated according to (A) tumor depth, (B) tumor size, and (C) tumor grade with (D-F) death as a competing event.

greater risk (95% CI, 1-2.2) of developing a local recurrence, respectively, than their counterparts with primary tumors, low-grade tumors, and superficial tumors, respectively. Patients who received radiation had their risk of local recurrence reduced by a factor of 1.3 times (95% CI, 0.5-1.1).

The 10-year cumulative probabilities of local recurrence were markedly different within categories for presentation status ($P < .001$) and surgical margins ($P < .001$) (Table 3, Fig. 3). Patients who presented with recurrent sarcoma and those who had positive surgical margins had a 10-year cumulative probability of local recurrence

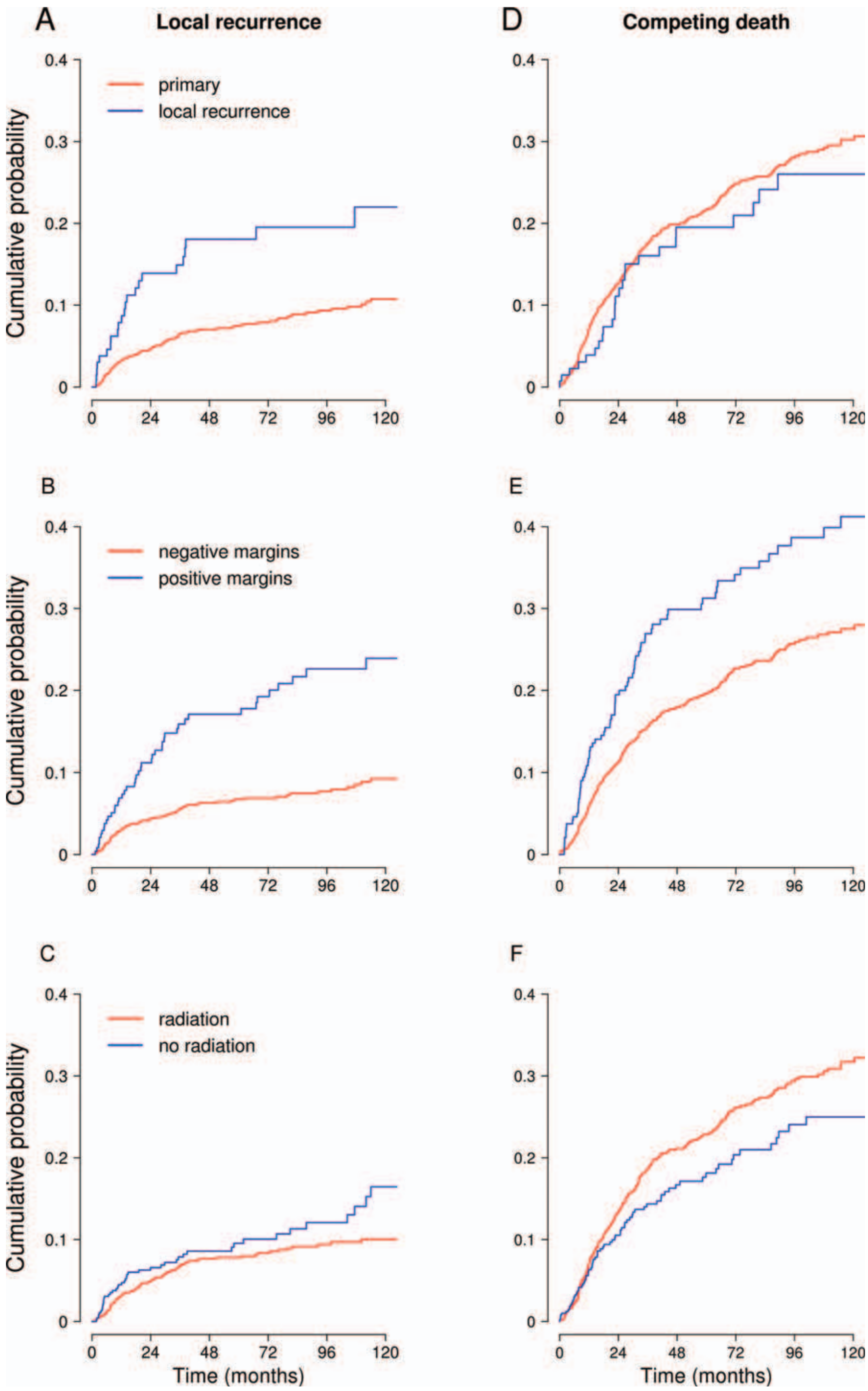

Figure 4. Cumulative probabilities of local recurrence are illustrated according to (A) presentation status, (B) surgical margin status, and (C) radiotherapy with (D-F) death as a competing event.

of 22% and 23.9%, respectively; in contrast, at 10 years, the cumulative probability of local recurrence for patients who presented with primary sarcoma and those who had negative surgical margins were 10.8% and 9.2%, respectively (Table 3, Fig. 3). The 10-year cumulative probability of local recurrence for patients who received radiation was 10% compared with 16.5% for those who did not receive radiation ($P = .085$) (Table 3, Fig. 3). However, there was little difference in the 10-year cumulative probabilities of local recurrence with regard to tumor depth ($P = .2$), tumor size ($P = .99$), or histologic tumor grade ($P = .12$) (Table 3, Fig. 4). At 10 years, the cumulative probability of local recurrence for patients who presented with small tumors was 13.3% compared with 10.6% for those who presented with large tumors. The 10-year cumulative probability of local recurrence for patients who had deep tumors was 12% compared with 11.4% for those who had superficial tumors. The 10-year cumulative probability of local recurrence was 11.1% for patients who presented with low-grade tumors, 10.7% for those who presented with intermediate-grade tumors, and 12.6% for those who presented with high-grade tumors.

DISCUSSION

Competition arises when the occurrence of an event precludes the occurrence of the event of interest.[13] In the presence of competition, the Kaplan-Meier method overestimates the probability of the event of interest, because it considers that patients who experienced the competing event are still at risk for the event of interest. In the current study, this means that patients who die would be censored, but they would still be considered at risk of having a local recurrence when this is obviously no longer possible. Therefore, in the presence of competition, the cumulative incidence estimator developed by Prentice et al[13] should be the preferred method for comparing clinical outcomes instead of the Kaplan-Meier method. Moreover, if the amount of competition differs between the categories of a variable, such as the risk of death between patients with low-grade tumors and high-grade tumors, then the difference in the risk of local recurrence, as measured by the hazard ratio, may be very different from that reported by cumulative probabilities, because the former does not take competition into account. The reason for this is that patients in 1 category may be so affected by the competing event and be withdrawn from the risk of having the event of interest that, over time, the latter event will only occur in a small number of patients (Fig. 2). Consequently, interpreting the effect of a variable on the local recurrence of soft tissue sarcomas requires assessment of both the hazard ratio and the cumulative incidence[22]; the former provides a measure of the instantaneous difference in the risks of local recurrence per category of the variable disregarding the competition, and the latter provides the probability of local recurrence within each category, accounting for the competition that has occurred over time.

In large series, the hazard ratio of local recurrence for high-grade tumors versus low-grade tumors ranges from 1.2 to 2.6[4-6,11] and is in keeping with findings in the current study (Table 2). However, there was little difference in the cumulative probabilities of local recurrence between histologic grade categories when competition was considered (Fig. 4, Table 3). The reason for this apparent discrepancy is that, although patients with high-grade tumors have an increased risk of local recurrence, they demonstrate an even greater risk of metastasis (Fig. 4, Table 3). Therefore, with increasing follow-up, patients with high-grade tumors are more likely to die and be withdrawn from the risk of developing a local recurrence than those with low-grade tumors. Accordingly, it can be observed (Fig. 4) that the cumulative probability of local recurrence for patients with high-grade tumors quickly plateaus, whereas that for patients with low-grade tumors keeps slowly increasing over time. The difference in competition between the 3 categories of histologic grade is so important that, ultimately, at 10 years, the cumulative probabilities of local recurrence of all 3 categories merge despite significant differences in risks. Other series that reported large differences in cumulative probabilities between groups of patients with different histologic grades (40% and 24%,[4] 25% and 18%,[11] and 20% and 12%[8] for high-grade and low-grade tumors, respectively) used the more conventional Kaplan-Meier methodology, which does not take into account the competition between local recurrence and death.[4,8,11]

The effect of tumor depth on local recurrence follows a similar pattern: Patients who have deep-seated tumors have an increased risk of local recurrence compared with those who have superficial tumors based on cause-specific hazard ratios (Table 2), which is in keeping with previous reports, but the difference in competition between local recurrence and death that exists for deep and superficial tumors helps to explain the absence of a difference in cumulative probabilities between these 2 categories at 10 years (Fig. 4, Table 3).

In the current cohort, large tumors were not associated with an increased risk of local recurrence. The effect of tumor size on local recurrence reported in the literature is contradictory. Two centers reported that large tumors were significantly associated with an increased risk of local recurrence with hazard ratios of 1.4 and 1.6,[5,11] and 2 others reported no significant association with hazard ratios of 1.3 and 0.9.[7,9] One explanation why tumor size was not a predictor of local recurrence in the current series is that, given the appropriate surgical means (eg, frequent use of soft tissue flaps and vascular resection and reconstruction) the extent of resection of large tumors did not have to be compromised. In keeping with previous reports,[4,9-11] patients with large tumors had a higher risk of metastasis, and the competition between death and local recurrence in this group is more prevalent than in patients with small tumors (Fig. 4). Accordingly, because there is no difference in the risk of local recurrence, as follow-up increases, the cumulative probability of local recurrence in patients with small tumors eventually overtakes that of patients with large tumors (Fig. 3, Table 3).

The status of surgical margins is the factor that has the most profound effect on local recurrence, and this has been reported consistently in the literature.[4,6,7,9,11] The competition is similar to that for tumor grade and depth: Patients who have positive surgical margins have an increased cumulative probability of death compared with those who gave negative margins (Fig. 3). However, the increased risk of local recurrence for patients with positive surgical margins is so important (hazard ratio, 3.25) that the cumulative probability of local recurrence for these patients remains higher than that for patients with negative surgical margins. The absence of significant competition between patients who presented with primary sarcoma and those who presented with recurrent sarcoma explains why the effect estimated by the hazard ratio yields a good approximation of the cumulative probability of local recurrence. Indeed, at 10 years, the cumulative probability of local recurrence in patients with recurrent sarcoma was twice that in patients with primary sarcoma, in keeping with a hazard ratio of 2.4 (Fig. 3).

The current findings have significant implications with regard to the current local management of soft tissue sarcomas. Some national guidelines and authors suggest that the use of radiation should take into account the grade, the size, and the depth of the tumor because of the estimated effect of these variables in a noncompeting scenario. For instance, the latest National Comprehensive Cancer Network guidelines[14] recommend that, for American Joint Committee on Cancer stage IA sarcoma (low grade, small, superficial or deep) of the extremity and trunk, radiotherapy or observation should be considered if margins are <1 cm; for American Joint Committee on Cancer stage IB tumors (low grade, large, superficial or deep) with margins <1 cm, again, only radiotherapy should be considered. The latest European Society for Medical Oncology clinical practice guidelines[15] for the treatment of sarcoma of the extremity and trunk recommend adding radiation therapy to surgery in selected patients with low-grade, superficial, >5 cm and low-grade, deep, <5 cm soft tissue sarcomas. In patients with low-grade, deep, >5 cm soft tissue sarcoma, they recommend a discussion of radiation therapy. Clark et al,[16] in a recent review of the treatment of soft tissue sarcoma published in the *New England Journal of Medicine* reported that there was little role for radiotherapy in the treatment of primary, low-grade soft tissue sarcoma. Our approach is more aggressive, and we believe that the use of radiotherapy should be based mainly on surgical margin status and the biology of the sarcoma in terms of presentation status (ie, primary vs recurrent); whereas the size, depth, and grade of the tumor play little in this decision. The findings of the current study support this approach to local control. In keeping with the report by Clark et al, however, we do agree that treatment decisions regarding local control should be made on a case-by-case basis and should rely on dedicated sarcoma multidisciplinary tumor boards involving the participation of all sarcoma care providers.

This study has several limitations. First, the competing risk scenario used here is only a simplification of a more complex, multilevel situation in which patients transfer freely between the following transient states: disease free, local recurrence, metastasis, and death, which is an absorbing state.[23] In the current study, only the occurrence of the first of 2 competing events was modeled, because this was the main clinical scenario of interest with regard to local recurrence. Second, when assessing the effect of a variable on the cumulative incidence of an event, the investigator may choose to regress directly on the cumulative incidence with the subdistribution hazard.[24] We decided not to take this approach, because, in this instance, patients who experience the competing event remain in the risk set, and this has little clinical meaning.

In conclusion, because of the competition between local recurrence and death, histologic grade, tumor size, and tumor depth have little influence on the cumulative probability of local recurrence; whereas presentation status and surgical margins are the predictors at presentation with the most influence. Accordingly, local management, such as the use of adjuvant radiation, should be based on presentation status and surgical margins rather than other previously acknowledged factors. Current guidelines and recommendations should be amended with regard to the current findings.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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