A Synovial Sarcoma-Specific Preoperative Nomogram Supports a Survival Benefit to Ifosfamide-Based Chemotherapy and Improves Risk Stratification for Patients

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Abstract

Purpose: To identify prognostic factors related to outcome in 255 patients with synovial sarcoma and to construct a preoperative nomogram to predict the risk of disease-specific death.

Design: Between July 1982 and June 2006, 301 patients underwent treatment at our institution for primary synovial sarcoma of all anatomic sites and 255 patients with localized disease at presentation were resected with curative intent. Data were collected prospectively and analyzed retrospectively.

Results: Five-, 10-, and 15-year disease-specific survival (DSS) was 72%, 60%, and 53%, respectively. Multivariate analysis revealed size and primary tumor site as the only independent adverse predictors of disease-specific death. A nomogram based on preoperative data for surgical patients not receiving anthracycline-ifosfamide (AI) chemotherapy ($n = 196$) estimates 3- and 5-year DSS with a concordance index of 77.3%. For the first 3 years following diagnosis, the observed DSS for patients treated with AI chemotherapy ($n = 59$) was greater than that predicted by the preoperative nomogram based on patients not receiving AI chemotherapy. SYT-SSX fusion transcript data were available for 132 patients. Multivariate analysis of this subset showed that SYT-SSX1 fusion type was predictive of early, but not late, distant recurrence.

Conclusion: Size and location govern prognosis in primary synovial sarcoma resected with curative intent. A nomogram based on preoperative variables provides individualized patient survival estimates and shows an early survival benefit to chemotherapy that may dissipate over time. This nomogram may improve decision-making with regards to selecting patients most likely to benefit from neoadjuvant/adjuvant chemotherapy.

Synovial sarcomas comprise 5% to 10% of soft-tissue sarcomas and contain unique chromosomal translocations forming the SYT-SSX1 or SYT-SSX2 genes (1, 2). Accumulating evidence suggests that synovial sarcoma is relatively chemosensitive (3, 4) and that patient outcomes in appropriately selected cases are improved by the use of neoadjuvant/adjuvant chemotherapy (5, 6).

Multiple studies have individually identified age (7), size (5, 7–12), sex (13), margin status (11), location (8, 13), mitotic activity (11), bone or neurovascular invasion (10), grade (11), and possibly SYT-SSX fusion type (12, 14) as significant prognostic factors in synovial sarcoma. Although larger tumor size has consistently emerged as an important predictor of worse survival across these studies, the relative prognostic value of the other factors remains equivocal.

The administration of adjuvant chemotherapy for adult patients with soft-tissue sarcoma remains controversial (1). A minority of positive studies shows a survival benefit to chemotherapy, whereas numerous other studies do not. Among patients with synovial sarcoma undergoing resection with curative intent, anthracycline-ifosfamide (AI) chemotherapy was associated with improved survival in a retrospective analysis (5). Because individual assessments of the risk of synovial sarcoma-specific death and the potential benefit of adjuvant/neoadjuvant AI chemotherapy are needed to guide treatment decisions, we chose to analyze the clinicopathologic predictors of distant recurrence and sarcoma-specific death in a large cohort of synovial sarcoma patients who presented with primary, localized disease of any site. We constructed a nomogram based on preoperative variables to more precisely define individual patient risk for disease-specific death for surgical patients not receiving AI chemotherapy and compared the predicted survival based on this nomogram with the observed survival for the subgroup of patients who received AI chemotherapy.

Materials and Methods

Between July 1982 and June 2006, 416 patients aged ≥16 years underwent inpatient treatment for primary, locally recurrent, and

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Translational Relevance

A nomogram was developed based on preoperative variables to more precisely define individual patient risk for disease-specific death for surgical patients presenting with synovial sarcoma. This synovial sarcoma-specific nomogram enables the patient and physician to make more informed decisions regarding neoadjuvant/adjuvant chemotherapy based on assessment of predicted risk for an individual patient rather than employing traditional size cutpoints alone.

metastatic synovial sarcoma at Memorial Sloan-Kettering Cancer Center. Of the 301 patients who presented with primary disease, 38 patients presented with synchronous primary and metastatic disease and were excluded from this analysis. An additional 8 patients did not undergo resection of the primary tumor because of poor performance status or progression on neoadjuvant chemotherapy. The remaining 255 patients were resected with curative intent and form the basis of this study.

Following approval for this retrospective study by the Institutional Review Board of Memorial Sloan-Kettering Cancer Center, clinical, pathologic, and treatment data were reviewed and analyzed with respect to distant recurrence-free survival (DRFS) and disease-specific survival (DSS). Histologic diagnosis of synovial sarcoma was assigned using published criteria (15). Margin status was determined as part of the histopathologic assessment. Depth was categorized as either superficial or deep to the investing fascia.

Therapeutic decisions regarding the administration of radiotherapy and chemotherapy were based on the consensus judgment of the treating physicians and therefore represent aggregate institutional practice, which has evolved over time. A proportion of the patients were administered radiotherapy as part of a clinical trial (16), whereas chemotherapy was not administered in the setting of a clinical protocol. Doxorubicin was typically given at 75 mg/m^2/cycle as divided doses by intravenous bolus over 3 days, and ifosfamide was given at a dose of 6 to 9 g/m^2/cycle in divided doses over 3 days.

For patients who received neoadjuvant chemotherapy before resection of the primary tumor, tumor size was defined as the maximum diameter measured by computed tomography or magnetic resonance imaging before treatment. For patients who received adjuvant chemotherapy or no chemotherapy following resection of the primary tumor, size was defined both by cross-sectional imaging and by maximum diameter on pathologic analysis. The differences between these measurements were negligible. One hundred thirty-two patients (52%) had tumor tissue submitted for SYT-SSX fusion type analysis. SYT-SSX1 and SYT-SSX2 were distinguished by reverse transcription-PCR as described previously (14, 17).

Fisher's exact test and Wilcoxon rank-sum test were used to compare categorical and continuous variables, respectively, across groups. The associations of the examined clinical, pathologic, and treatment variables with DRFS, DSS, and overall survival were examined using the log-rank test for categorical variables and the score test for continuous variables. To examine the association of DRFS, DSS, and overall survival while adjusting for important prognostic factors, variables significant on univariate analysis at the 0.10 level were entered into a Cox proportional hazards model. An accelerated failure time analysis (18, 19) with the Gehan estimator was used to examine the association of SYT-SSX fusion type with DRFS and DSS because the proportional hazards assumption does not hold for this variable. These analyses were done with R software using the Survival and Rankreg libraries.

The variables considered for the creation of the nomogram were anatomic site (upper extremity, lower extremity, other), size, depth (superficial, deep), and histologic variant (monophasic, biphasic). The nomogram modeling and validation procedure were similar to that used previously (20, 21). An individual patient's predicted probability of DSS was assumed to be a function of two components: the baseline hazards function shared by all patients and a linear combination of an individual patient's predictor variable values. For validation, the nomogram was subjected to bootstrapping to calculate an unbiased measure of its ability to discriminate among patients. This effect is quantified by the concordance index. The concordance index is similar to the area under the receiver operating characteristic curve and ranges from 0.5 (no discrimination) to 1.0 (perfect discrimination). Given a randomly selected pair of patients, the concordance index is the probability that the patient who dies first had the higher predicted probability of death. These analyses were done with R software using the Design and Hmisc libraries.

Table 1. Clinicopathologic characteristics of 132 patients with known fusion transcript data

Characteristics	SYT-SSX1 (*n* = 73), *n* (%)	SYT-SSX2 (*n* = 59), *n* (%)	Univariate *P*
Gender*			
Male	47 (64)	22 (37)	0.005
Female	26 (36)	37 (63)	
Age at diagnosis, median (range)	41 (16-80)	35 (18-78)	0.07
Site			
Lower extremity	43 (59)	33 (56)	0.56
Upper extremity	15 (20)	11 (19)	
Trunk	5 (7)	3 (5)	
Head and neck	4 (6)	2 (3)	
Thoracic	4 (6)	9 (15)	
Retroperitoneal/ intraabdominal	2 (3)	1 (2)	
Grade			
High	71 (97)	59 (100)	0.50
Low	2 (3)	0 (0)	
Depth			
Deep	70 (96)	57 (97)	1.00
Superficial	3 (4)	2 (3)	
Primary tumor size (cm)			
≤5	21 (29)	16 (27)	0.86
5-10	34 (47)	26 (44)	
>10	18 (25)	17 (29)	
Margin status			
R0	66 (90)	49 (83)	0.36
R1	5 (7)	9 (15)	
R2	1 (1)	1 (2)	
Unknown	1 (1)	0 (0)	
Subtype*			
Monophasic	41 (56)	50 (85)	0.001
Biphasic	32 (44)	9 (15)	
Extent of resection*			
Limb-sparing	60 (82)	57 (97)	0.01
Amputation	13 (18)	2 (3)	
Adjuvant radiotherapy			
Yes	48 (66)	44 (75)	0.34
No	25 (34)	15 (25)	
Perioperative chemotherapy			
Ifosfamide-based	24 (33)	18 (30)	0.68
Non-ifosfamide-based	10 (14)	6 (10)	
None	38 (52)	35 (59)	
Unknown	1 (1)	0 (0)	

NOTE: Because of rounding, not all percentages sum to 100.
*Statistically significant differences.

Results

Clinicopathologic and treatment characteristics. Among this cohort of 255 patients, there was an equal gender distribution, the median age was 34 years, and 81% of the tumors were located on the extremity (58% lower, 23% upper). There were a comparable number of primary tumors from the thorax, trunk, and head and neck locations. Only 2% of tumors were located intraabdominally or within the retroperitoneum. Given the sample size, all nonextremity sites (48 patients, 19% of the cohort) were grouped together for purposes of statistical analysis.

Ninety-nine percent of the tumors were high grade, 93% were deep, and the median maximal dimension was 6 cm (range, 0.5-30 cm; with 44% of the tumors <5 cm). The monophasic subtype was more prevalent than the biphasic one (66% compared with 34%). SYT-SSX fusion type was available for 52% of patients with SYT-SSX1 and SYT-SSX2 fusions detected in 73 and 59 tumors, respectively. As depicted in Table 1, the median age for patients with the SYT-SSX1 and SYT-SSX2 fusion type was 41 and 35 years, respectively (P = 0.07). The gender distribution for SYT-SSX1 patients was 26 females and 47 males compared with 37 females and 22 males for patients with the SYT-SSX2 fusion transcript (P = 0.005). Fusion transcript distribution was significantly different for the 91 monophasic tumors (41 SYT-SSX1 and 50 SYT-SSX2) compared with the 41 biphasic tumors (32 SYT-SSX1 and 9 SYT-SSX2; P = 0.001). Fusion transcript type was not significantly associated with tumor size, depth, or location, although there was a trend toward a higher frequency of distal extremity tumors, defined as tumors at or distal to the wrist or ankle, among the SYT-SSX1 subtype (21% versus 11% for SYT-SSX2; P = 0.16). This may explain, in part, the statistically significant increase in the rate of amputation among patients with the SYT-SSX1 subtype (18% versus 3% for SYT-SSX2; P = 0.01).

A R0 resection was achieved in 86% of patients, and limb salvage was possible in 88% of patients (85% of patients with extremity tumors). Sixty-three percent of patients received radiotherapy, and the vast majority (151 patients) were treated with postoperative radiation. External beam radiation predominated over brachytherapy by an ~3:2 ratio. In this nonrandomized cohort of patients, radiotherapy was not statistically associated with DSS, overall survival, or local recurrence-free survival (data not shown). Thirty-nine percent (99 patients) were administered perioperative chemotherapy of whom 50 received adjuvant and 49 received neoadjuvant therapy. After 1990, chemotherapy was almost exclusively AI-based (59 of 65 patients, 91%).

Predictors of DSS and DRFS. With a median follow-up of 72 months for survivors (range, 0-287), median DSS was not reached. Five-, 10-, and 15-year DSS were 72% [95% confidence interval (95% CI), 66-78], 60% (95% CI, 52-68), and 53% (95% CI, 45-63), respectively. Median DRFS was 103 months, and 5-, 10-, and 15-year DRFS were 55% (95% CI, 549-62), 47% (95% CI, 40-55), and 44% (95% CI, 36-54), respectively.

The factors associated with DSS on multivariate analysis were primary tumor size [2.75 hazard ratio (HR) for sarcoma-specific death for tumors 5-10 cm relative to ≤5 cm (P = 0.01) and 5.17 HR for tumors >10 cm relative to ≤5 cm (P < 0.001)] and primary tumor site [2.01 HR for sarcoma-specific death for lower extremity location relative to upper extremity (P = 0.06) and 3.63 HR for death for other sites relative to upper extremity (P = 0.01)]. These results are depicted graphically in Fig. 1A and B, respectively. For the subset of patients with data available on SYT-SSX fusion type, the median and 3-year DSS for the SYT-SSX1 and SYT-SSX2 were 123 months and 71%

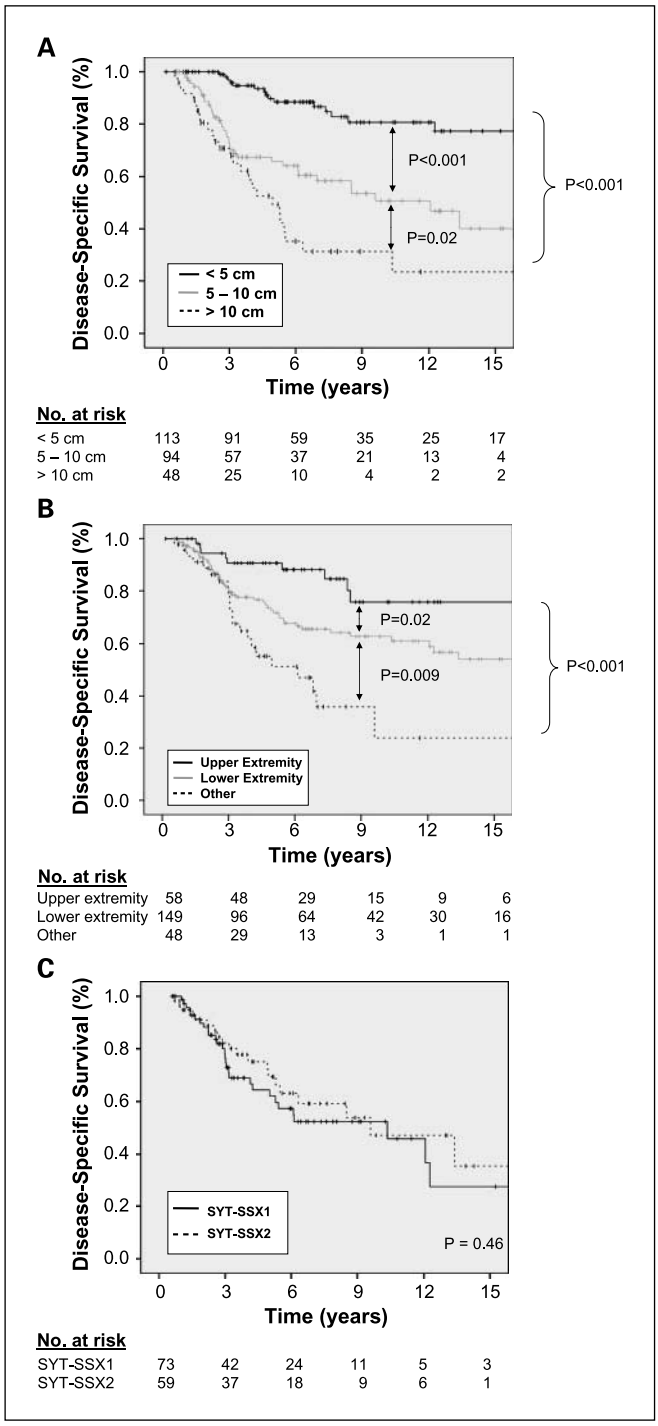

Fig. 1. *A,* Kaplan-Meier curve depicting DSS grouped by primary tumor size. Univariate *P* values are shown. *B,* Kaplan-Meier curve depicting DSS grouped by site of primary tumor. Univariate *P* values are shown. *C,* Kaplan-Meier curve depicting DSS grouped by type of fusion transcript. Univariate *P* values are shown.

versus 115 months and 78%, respectively (see Fig. 1C; $P = 0.7$, using an accelerated failure time analysis).

Multivariate analysis of independent variables associated with DRFS revealed that primary tumor size was strongly predictive of DRFS [2.72 HR for distant recurrence for tumors 5-10 cm relative to ≤5 cm ($P < 0.001$) and 5.72 HR for distant recurrence for tumors >10 cm relative to ≤5 cm ($P < 0.001$)] as was primary tumor site [1.77 HR for distant recurrence for lower extremity location relative to upper extremity ($P = 0.05$) and 2.51 HR for distant recurrence for other sites relative to upper extremity ($P = 0.005$)]. Kaplan-Meier curves of DRFS grouped by primary tumor size, site, and fusion type are shown in Fig. 2A to C, respectively. For the subset of patients with data available on SYT-SSX fusion type, the median and 3-year DRFS for the SYT-SSX1 and SYT-SSX2 were 29 months and 44% versus 45 months and 56%, respectively ($P = 0.07$, using an accelerated failure time univariate analysis). Multivariate analysis of this 132 patient subset using an accelerated failure time analysis showed that SYT-SSX1 fusion type was independently predictive of early distant recurrence ($P = 0.02$; acceleration rate = -1.15; see Table 2).

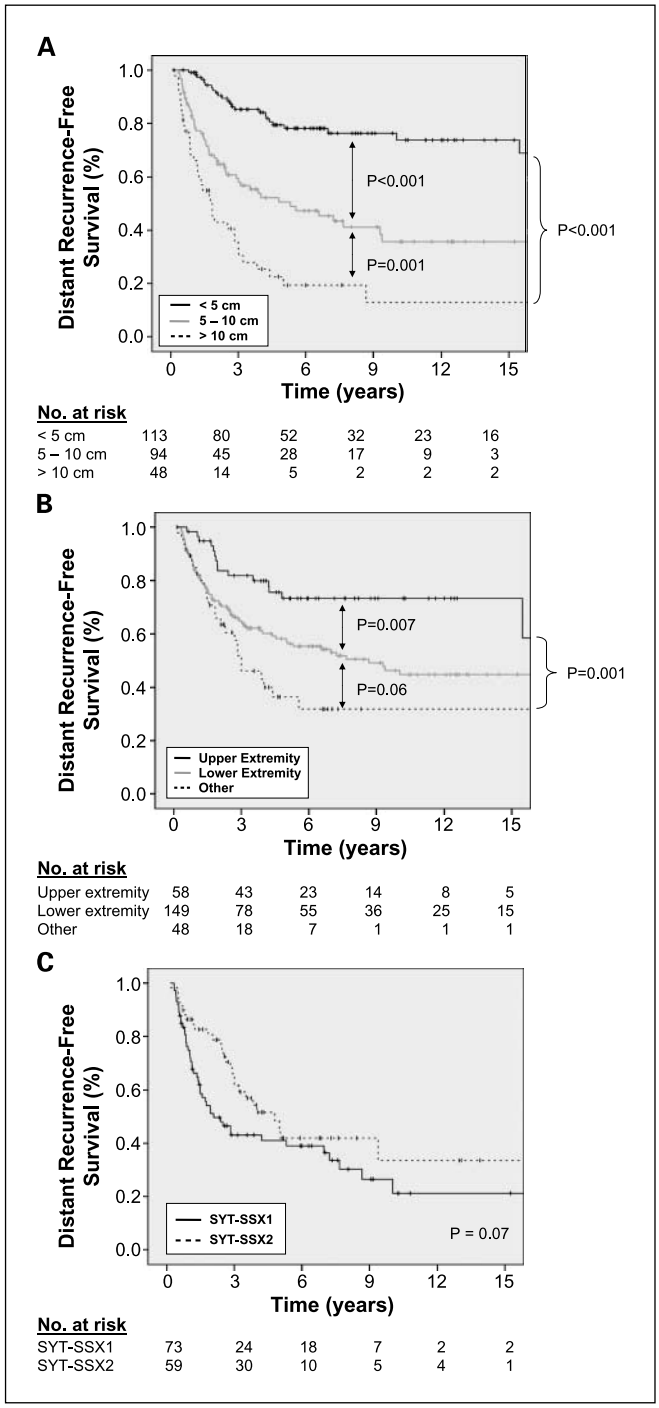

Fig. 2. *A,* Kaplan-Meier curve depicting DRFS grouped by primary tumor size. Univariate *P* values are shown. *B,* Kaplan-Meier curve depicting DRFS grouped by site of primary tumor. Univariate *P* values are shown. *C,* Kaplan-Meier curve depicting DRFS grouped by type of fusion transcript. Univariate *P* values are shown.

Preoperative nomogram. A nomogram to calculate synovial sarcoma-specific 3- and 5-year DSS for surgical patients not receiving AI chemotherapy (149 patients received no chemotherapy and 47 patients received non-ifosfamide chemotherapy) based on preoperative variables is depicted in Fig. 3. We choose to focus on variables readily available to the clinician to enable improved prognostication for an individual patient before any definitive therapy. We purposely avoided variables such as mitotic activity and necrosis because, on a core biopsy, these variables are often difficult to quantify, not representative of the entire tumor, and not reproducible among different pathologists (22). The fusion transcript type was not included in the nomogram because it had no significant association with DSS using an accelerated failure time analysis.

Although the data were mature enough to reliably predict DSS up to 10 years with reasonably narrow 95% CIs, we chose to focus on the earlier time points because decisions regarding neoadjuvant/adjuvant therapy seem better informed by the risk of early/intermediate recurrence and death. The nomogram predicts the probability that a patient will be alive 3 and 5 years following the diagnosis and surgical resection of synovial sarcoma, excluding death from another cause. The bootstrapping concordance index was 77.3 %.

Predicted versus observed survival based on type of chemotherapy. Using our preoperative nomogram, we plotted the predicted survival curve of DSS for resected patients receiving ifosfamide-containing chemotherapy (Fig. 4) and compared this with the observed survival (with 95% CIs) for these patients. As depicted in Fig. 4, during the first 3 years following diagnosis, the observed DSS for patients treated with AI chemotherapy ($n = 59$) was greater than that predicted by the preoperative nomogram. After 3 years, the nomogram-predicted survival and the observed survival for AI-treated patients then converge. Median follow-up for AI-treated patients was 37 months (range, 1-124) for survivors.

Discussion

Because synovial sarcoma constitutes a minority of cases of an already rare disease (soft-tissue sarcoma), it has been difficult to definitively characterize the unique behavior, prognostic factors, and outcome with multimodality therapy among patients with this histology. Of the retrospective studies that have examined the natural history of this disease, size has clearly emerged as the dominant predictor of outcome (5, 7–12). However, controversy exists regarding the relative influence of other prognostic variables, including age (7),

Table 2. Association of SYT-SSX fusion type with DRFS and DSS (n = 132) using accelerated failure time analysis

Characteristics	DRFS		DSS	
	Univariate *P*	Multivariate *P* [AR* (95% CI)]	Univariate *P*	Multivariate *P* [AR* (95% CI)]
SYT-SSX fusion type	0.066		0.722	
SYT-SSX2				
SYT-SSX1		0.019 [-1.15 (-2.12 to -0.19)]		0.794 [-0.22 (-1.87 to 1.43)]
Primary tumor size (cm)				
≤5				
5-10		0.039 [-2.19 (-4.27 to -0.12)]		0.058 [-3.58 (-7.29 to 0.13)]
>10		0.004 [-3.11 (-5.21 to -1.01)]		0.046 [-3.93 (-7.78 to -0.07)]
Primary tumor site				
Upper extremity				
Lower extremity		0.041 [-1.63 (-3.20 to -0.07)]		0.014 [-3.90 (-7.02 to -0.78)]
Other sites †		0.048 [-1.68 (-3.35 to -0.01)]		0.020 [-3.93 (-7.24 to -0.63)]

*Acceleration rate.
† Includes truncal, thoracic, retroperitoneal/intraabdominal, and head and neck locations.

neurovascular invasion (10), mitotic rate (11), sex (13), grade (23), and type of fusion transcript (14, 23).

Our study identified size and site as significant predictors of DSS and DRFS on multivariate analysis (although there was only a trend toward statistical significance for lower extremity tumors relative to upper extremity for both DSS and DRFS). Although Trassard et al. (13) found truncal location to be adversely associated with DSS but not metastasis-free survival, the current study is the first study to show that primary tumor location is associated with DSS and DRFS differences even after adjusting for size.

In the current series, SYT-SSX fusion transcript data were available for 52% of patients and largely reflects the patients who were diagnosed later in the study period and/or those who had their definitive resection done at our institution, providing sufficient material for molecular analysis. In the subset of patients with available fusion transcript data, SYT-SSX1 was independently associated with an increased risk of early distant recurrence after adjusting for tumor size and location (P = 0.02) but was not associated with an increased risk of DSS (P = 0.8). In the present study, we confirmed a significant association between fusion type and patient sex with SYT-SSX1 and SYT-SSX2 cases having a male to female ratio of 1.7:1 and 0.6:1, respectively. Most large studies have observed that synovial sarcoma among women is twice as likely to contain the SYT-SSX2 fusion type compared with those arising in men (12, 23, 24).

Histologic subtype was also associated with fusion type. Biphasic tumors predominantly showed the SYT-SSX1 fusion type. In a prior study from our institution of 45 synovial sarcoma patients (39 localized and 6 metastatic), patients with the SYT-SSX1 fusion type had a significantly shorter DRFS than patients with SYT-SSX2 (14). These findings were subsequently confirmed in a large multi-institutional analysis of 243 patients (12). The present study suggests that fusion type is more important in early (<3 years) distant recurrence and that late recurrence is largely dependent on tumor size and location. Other investigators have made different observations. A study of 141 patients with localized synovial sarcoma employing the three-tier Federation Nationale des Centres de Lutte Contre le Cancer grading system found histologic grade, and not fusion type, to be a significant predictor of DSS and DRFS on multivariate analysis (23). Using a grading system similar to the Federation Nationale des Centres de Lutte Contre le Cancer, Takenaka et al. observed tumor size but not fusion transcript type to be prognostic for both overall survival and DRFS in 91 patients with localized disease (24).

Although retrospective analyses are important to identify factors independently associated with prognosis, they are limited in their ability to provide survival estimates for individual patients. Nomograms are increasingly accepted as models in which identified prognostic factors can be incorporated into a scoring system and used to predict likelihood of DSS. These statistically based tools not only use the factors included in a clinical staging system but also may incorporate

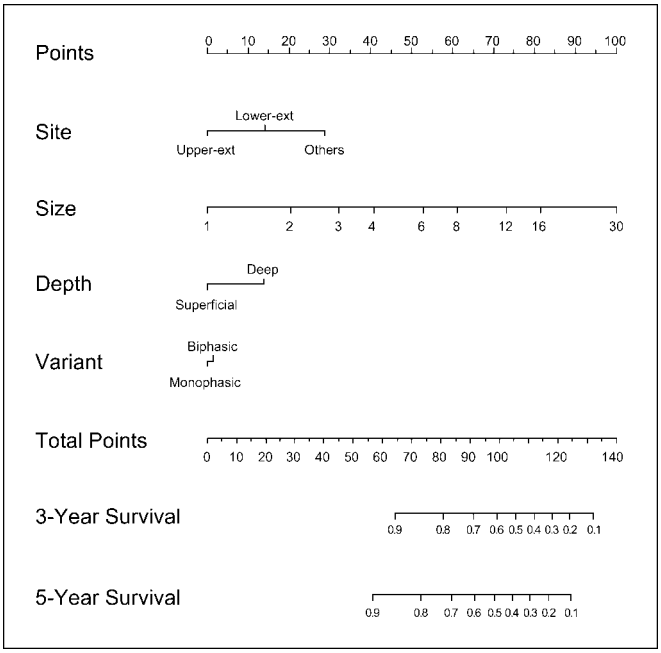

Fig. 3. Nomogram based on preoperative variables used to calculate synovial sarcoma-specific 3- and 5-y survival.

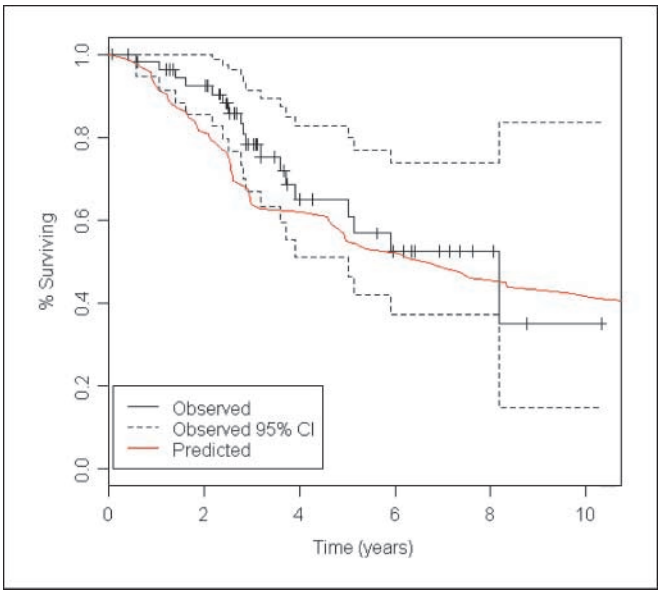

Fig. 4. Kaplan-Meier curve depicting observed DSS (with 95% CIs) for patients treated with ifosfamide-containing chemotherapy compared with DSS predicted by the preoperative nomogram for otherwise similar patients treated without ifosfamide-based chemotherapy.

additional factors suspected to have an effect on outcome. A postoperative nomogram calculating 12-year DSS for all patients with resected soft-tissue sarcoma has been published previously with the goal of providing more individualized patient counseling for follow-up scheduling and consideration for additional therapy or clinical trials (20).

We provide a synovial sarcoma-specific nomogram based on preoperatively known clinical and pathologic variables. Although the only independent determinants of outcome were size and location, we also included depth and histologic variant in the nomogram because of their ability to incrementally enhance the prognostic value of the nomogram. This nomogram shows the magnitude of the risk of sarcoma death as well as the variability in survival estimates that exist among individual patients with synovial sarcoma. For example, with a deep, monophasic tumor of the lower extremity, a 5 cm tumor has a favorable predicted 3-year survival of 85% and 5-year survival of 82%. However, this predicted survival drops significantly to 73% at 3 years and to 64% at 5 years if the tumor increases to 8 cm in size. For a 10 cm tumor, the predicted survival is 65% at 3 years and 55% at 5 years. The generic postoperative sarcoma nomogram provides the same 12-year estimate for DSS of 71% for all these hypothetical patients because tumor size is grouped by increments of 5 cm. Similarly, for a 15 cm deep, biphasic synovial sarcoma of the thorax, the synovial specific nomogram estimates a 3- and 5-year survival of 25% and 15%, whereas the generic sarcoma nomogram estimates a 12-year DSS of 28%.

We chose to focus on 3- and 5-year time points for this synovial-specific nomogram because decisions regarding adjuvant/neoadjuvant chemotherapy are typically based on shorter-term estimations of recurrence and death. This makes direct comparisons between synovial-specific and generic sarcoma nomograms difficult. Given the 95% CIs for the respective nomograms, the differences between nomograms may represent less pronounced true differences. Nevertheless, it is noteworthy that the synovial-specific nomogram predicts a more favorable survival than the generic sarcoma nomogram for the low-risk patient and a worse survival for the higher-risk patients. Ultimately, the synovial sarcoma-specific nomogram may prove to be a more sensitive tool for predicting outcome, consistent with the idea that sarcomas exhibit unique patterns of recurrence and mortality depending on histologic type.

The synovial sarcoma-specific nomogram may also allow more informed decision-making with regard to risk, particularly for the typical size cutpoints clinicians use for consideration of neoadjuvant chemotherapy. For example, most clinicians would consider a young patient with a 5 cm synovial sarcoma a potential candidate for systemic chemotherapy.[5] From the synovial sarcoma nomogram (Fig. 3), it is evident that the 3-year DSS can vary significantly for a 5 cm tumor. A hypothetical patient with a deep, 5 cm, biphasic synovial sarcoma of the trunk has a total point score of 93. According to the synovial sarcoma nomogram, this corresponds to a 3-year sarcoma-specific survival of 68%. In contrast, another hypothetical patient with a superficial, 5 cm, monophasic synovial sarcoma of the upper extremity has a total point score of 46. This corresponds to an estimated 3-year sarcoma-specific survival that exceeds 90%.

Based on these risk assessments, although both hypothetical patients have 5 cm tumors, it would be reasonable to consider neoadjuvant or adjuvant ifosfamide-based chemotherapy for the first patient, whereas it would be difficult to justify it for the second because it is difficult to improve significantly on the excellent predicted outcome for this patient by the addition of chemotherapy. Thus, this synovial sarcoma-specific nomogram enables the patient and physician to make more informed decisions regarding neoadjuvant/adjuvant chemotherapy based on assessment of predicted risk for an individual patient rather than employing traditional size cutpoints alone.

Our nonrandomized data also lend support to the premise that AI-based chemotherapy is associated with improved survival in synovial sarcoma patients resected with curative intent (5). When comparing the DSS predicted by the nomogram constructed from non-AI treated patients with the observed survival for AI-treated patients, controlling for other factors, the DSS for patients treated with AI chemotherapy was greater than that predicted by the preoperative nomogram for the first 3 years following diagnosis (Fig. 4). After 3 years, the nomogram-predicted survival was no longer statistically different from untreated patients, and after 4 years, the curves converge and are essentially superimposable. It is conceivable that, with longer follow-up of the AI-treated patients (median, 40 months; range 8-140), statistically significant differences in survival may be extended. However, it may be that there is a time-varying effect to AI-chemotherapy with a loss of DSS benefit over time as has been observed in other randomized and nonrandomized studies of heterogeneous cohorts of soft-tissue sarcoma patients (25, 26). Ultimately, the hypothesis that chemotherapy provides a survival advantage for patients with synovial sarcoma requires confirmation in randomized trials.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

[5] www.nccn.org/professionals/sarcoma

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