Chapter 2
Natural History: Importance of Size, Site, and Histopathology

Natural History

The natural history of soft tissue sarcoma is highly influenced by the site of the primary lesion, tumor histopathology, and tumor size. Multiple approaches have been developed to define outcome variables based on these factors, and as data accumulate with sufficient numbers, progressively more refined staging or predictive systems can be provided for rare tumors with multiple variables.

Influence of Site

The anatomic site of the primary lesion is clearly a determinant of outcome. This is most dramatically illustrated when one looks at the risk of local recurrence at various sites (Fig. 2.1). Retroperitoneal and intra-abdominal lesions have a significant risk of local recurrence, whereas extremity lesions have a much lower risk. When one considers disease-specific survival (Fig. 2.2), it is clear that disease-specific survival in retroperitoneal lesions is associated with similar prevalence to local recurrence, whereas for visceral lesions, systemic disease is the cause of death as local recurrence is relatively infrequent. This emphasizes the value of prospective, long-term databases in determining aspects of biology as well as outcome.

Staging

Staging of soft tissue sarcoma continues to evolve. Most staging systems depend on the grade and presence or absence of metastasis. The original system was initially based on data from 1977 (Fig. 2.3). Stage was subdivided based on the primary size of the initial tumor, into categories of <5 cm and >5 cm (T1/T2). By 1992, the absence or presence of nodal metastasis was included (N0/N1).

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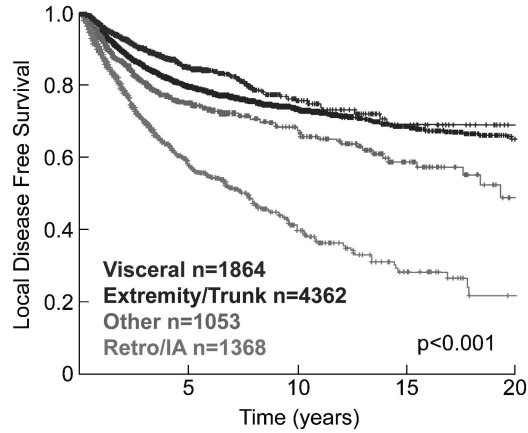

Fig. 2.1 All adult sarcomas, local disease-free survival by site. MSKCC 7/1/1982–6/30/2010 n = 8,647

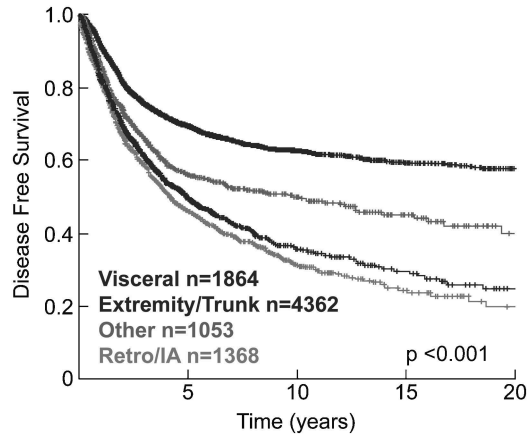

Fig. 2.2 All adult sarcomas, disease-specific survival by site. MSKCC 7/1/1982–6/30/2010 n = 8,647

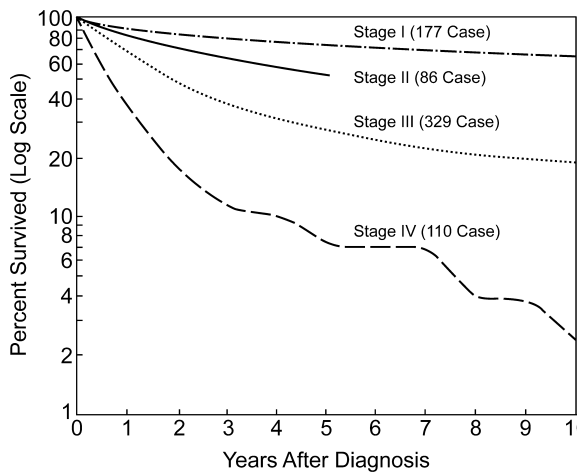

Fig. 2.3 1977 AJCC staging system (Used with permission from Russell et al. [1])

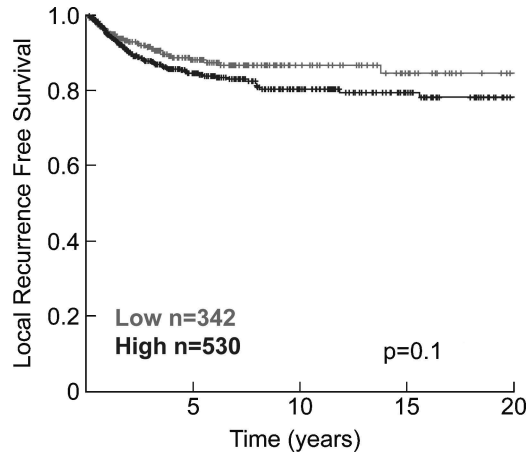

Fig. 2.4 Local recurrence-free survival, primary extremity ≤5 cm by grade. MSKCC 7/1/1982–6/30/2010 n = 872

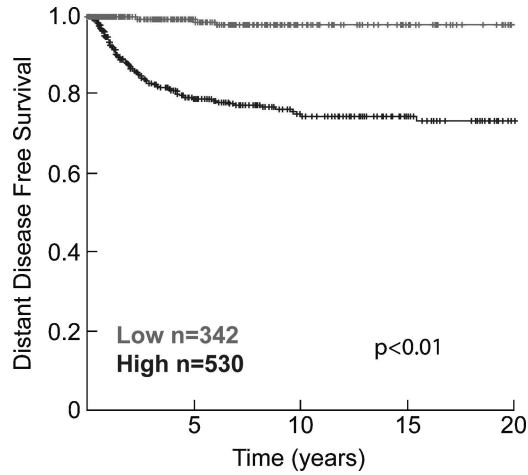

Fig. 2.5 Distant disease-free survival, primary extremity ≤5 cm by grade. MSKCC 7/1/1982–6/30/2010 n = 872

It has become progressively clear that tumors of very small size have a much better prognosis than was predicted by the initial American Joint Committee on Cancer (AJCC) staging system. Small (<5 cm) high-grade lesions (Fig. 2.4) have a favorable local recurrence-free survival similar to low-grade lesions. Small, low-grade tumors have a negligible risk of death from sarcoma, and small high-grade tumors have a 10-year disease-specific survival of approximately 80% (Fig. 2.5) [2]. We have shown that grade, depth, and size are independent predictors of outcome, and most systems base the risk of developing distant metastases giving each factor equal weight. However, tumor grade is dominant in the initial presentation where patients with high-grade lesions are more likely to have an early distant metastasis, whereas patients with lower grade but large tumors have progressive and prolonged risk of metastatic recurrence (Fig. 2.6) [3, 4]. Early metastatic disease is dominated by the grade of the tumor.

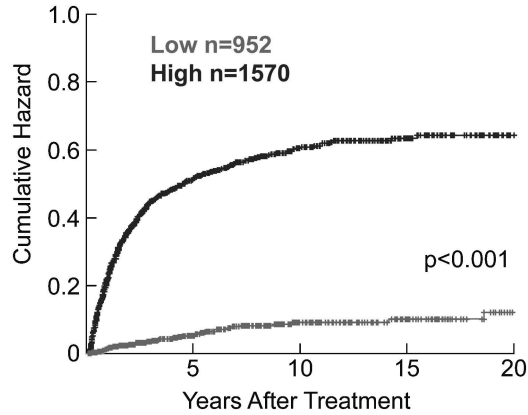

Fig. 2.6 Distant metastasis, extremity primary, and local recurrent by grade. MSKCC 7/1/1982–6/30/2010 n = 2,522

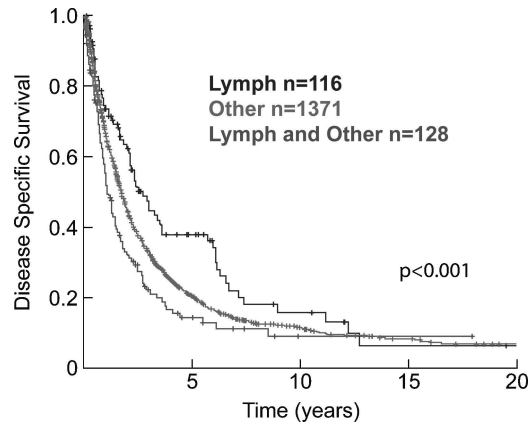

Fig. 2.7 Disease-specific survival by lymph node metastases alone or with other metastasis and other metastasis. MSKCC 7/1/1982–6/30/2010 n = 1,615

The outcome for patients with lymph node metastasis is similar, but not identical, to patients with other metastases (Fig. 2.7). It is important to emphasize that lymph node metastasis is infrequent in soft tissue sarcoma (Table 2.1) with an overall prevalence of <5% for all sarcomas and occurring predominantly in those having epithelioid features. There clearly are patients with limited nodal metastasis who are salvaged by resection, and such patients tend to do better than those with metastasis to other sites (Fig. 2.7).

A study comparing three different staging systems [6] was published in 2000. At that time, the authors found that depth, grade, and size were significant prognostic indicators and that inclusion of these criteria could better define patients who might benefit from systemic therapy. This was in contradistinction to the Musculoskeletal Tumor Society study [7] which employed a staging system based on extra compartmental extension (which is itself influenced by size).

The latest staging system by the AJCC (7th edition, 2010) [8] has made a number of changes to the prior edition of 2002 (Tables 2.2 and 2.3). Gastrointestinal stromal

Table 2.1 Histologic type of sarcomas and lymph node metastasis (Adapted with permission from Fong et al. [5])

	No. of nodal metastases/all sarcoma patients			% of all lesions		
Histologic findings	Weingrad[a]	Mazeron[b]	This study[c]	Weingrad	Mazeron	This study
Fibrosarcoma	55/1083	54/215	0/162	5.1	4.4	0
Malignant fibrous histiocytoma	1/30	84/823	8/316	3.3	10.2	2.6
Undifferentiated spindle cell	–	–	0/42	–	0	–
Rhabdomyosarcoma (all types)	108/888	201/1354	–	12.2	14.8	–
Rhabdomyosarcoma (non-embryonal)	–	–	1/35	–	–	2.9
Embryonal rhabdomyosarcoma	–	–	12/88	–	–	13.6
Leiomyosarcoma	10/94	21/524	9/328	10.6	4.0	2.7
Malignant peripheral nerve sheath tumor	0/60	3/476	2/96	0	0.6	2.1
Vascular	–	43/376	–	–	11.4	–
Angiosarcoma	–	–	5/37	–	–	13.5
Hemangiopericytoma	3/23	–	0/21	13.0	–	0
Lymphangiosarcoma	–	–	1/4	–	–	25.0
Osteosarcoma	20/327	–	0/11	6.1	–	0
Chondrosarcoma	–	–	1/46	–	–	2.2
Synovial sarcoma	91/535	117/851	2/145	19.1	13.7	1.4
Epithelioid sarcoma	–	14/70	2/12	–	20	16.7
Liposarcoma	15/288	16/504	3/403	5.7	3.2	0.7
Alveolar soft part sarcoma	6/62	3/24	0/13	9.7	12.5	0
Clear cell sarcoma	–	11/40	–	–	27.5	–
Other	11/125	–	0/27	8.8	–	0
Total	320/3515	567/5257	47/1772	9.1	10.8	2.6

[a]Adapted from a review by Weingrad and Rosenberg summary of 47 studies (Weingrad DN, et al. Surgery 1978; 84:231–40)

[b]Adapted from a review of Mazeron and Suit summary of 122 studies (Mazeron JJ, Suit HD. Cancer 1987; 60:1800–8)

[c]Database only includes extraskeletal osteo- and chondrosarcomas

tumors, desmoid tumors, Kaposi sarcoma, and infantile fibrosarcoma are now excluded from the staging system. New histopathologies including angiosarcoma, extraskeletal Ewing sarcoma, and dermatofibrosarcoma protuberans have been added. Nodal disease, included as stage IV previously, has been reclassified as stage III, although the differences in outcome between patients with nodal and other metastases are small (Fig. 2.7). This reclassification highlights the ability to rescue patients with lymph node metastasis alone by further treatment, usually surgical resection. Anatomic stage and prognostic groups are defined in Table 2.2. This

Table 2.2 Anatomic stage and prognostic groups from AJCC Cancer Staging Manual, 7th edition (Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, seventh edition (2010) published by Springer Science and Business Media LLC, www.springer.com)

Anatomic stage – prognostic groups									
Clinical					Pathologic				
Group	T	N	M		Group	T	N	M	
IA	T1a	N0	M0	G1, GX	IA	T1a	N0	M0	G1, GX
	T1b	N0	M0	G1, GX		T1b	N0	M0	G1, GX
IB	T2a	N0	M0	G1, GX	IB	T2a	N0	M0	G1, GX
	T2b	N0	M0	G1, GX		T2b	N0	M0	G1, GX
IIA	T1a	N0	M0	G2, G3	IIA	T1a	N0	M0	G2, G3
	T1b	N0	M0	G2, G3		T1b	N0	M0	G2, G3
IIB	T2a	N0	M0	G2	IIB	T2a	N0	M0	G2
	T2b	N0	M0	G2		T2b	N0	M0	G2
III	T2a, T2b	N0	M0	G3	III	T2a, T2b	N0	M0	G3
	Any T	N1	M0	Any G		Any T	N1	M0	Any G
IV	Any T	Any N	M1	Any G	IV	Any T	Any N	M1	Any G
Stage unknown					Stage unknown				

Table 2.3 Stage grouping from AJCC Cancer Manual, 6th edition (Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, seventh edition (2010) published by Springer Science and Business Media LLC, www.springer.com)

Stage grouping						
Stage I	T1a, 1b, 2a, 2b	N0	M0	G1–2	G1	Low
Stage II	T1a, 1b, 2a	N0	M0	G3–4	G2–3	High
Stage III	T2b	N0	M0	G3–4	G2–3	High
Stage IV	Any T	N1	M0	Any G	Any G	High or low
	Any T	N0	M1	Any G	Any G	High or low

defines T stage as less than or greater than 5 cm. We and others have shown that size is a continuous variable with increasing risk of death from high-grade sarcoma as size increases. Wherever possible, size should be recorded three dimensionally (Fig. 2.8).

In the AJCC Staging Manual, 7th edition, depth continues to be recorded relative to the investing fascia of the extremity and trunk, but has no meaning for retroperitoneal or visceral primary tumors. Because depth is an independent prognostic value, depth is included in relationship to tumor size. Thus, a superficial tumor <5 cm is classified T1A, while T1B is deep. Similarly, a primary superficial tumor >5 cm is superficial, while T2B is deep. Survival is however still influenced by both depth and size (Fig. 2.9 and Table 2.2). However, if we examine the staging table in the AJCC 7th edition, depth has functionally been discarded. It should be emphasized that superficial lesions >5 cm are rare (<1%) in the extremity.

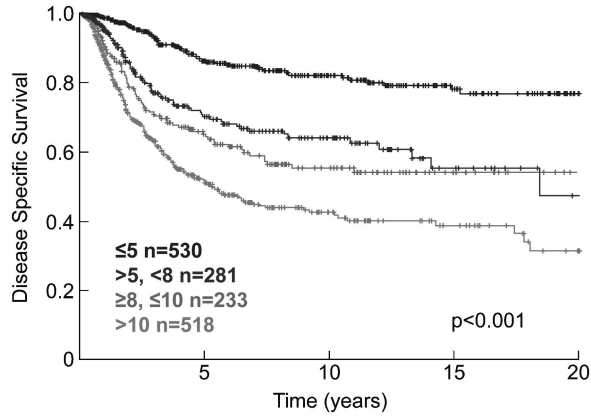

Fig. 2.8 Disease-specific survival, primary extremity high grade by size. MSKCC 7/1/1982–6/30/2010 n = 1,562

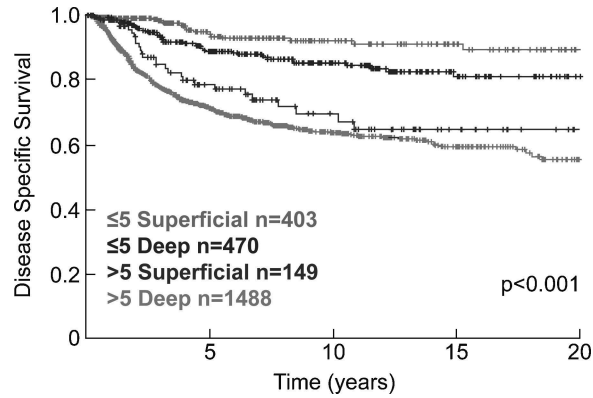

Fig. 2.9 Disease-specific survival, primary extremity high grade by size and depth. MSKCC 7/1/1982–6/30/2010 n = 2,510

Grade has historically been a dominant factor in outcome for soft tissue sarcoma. Previous AJCC systems used four grade levels, but this has been effectively functioning as a two-grade system, i.e., grades I and II as low grade and grades III and IV as high grade. This was the system employed at Memorial Sloan-Kettering for many years with good discrimination. Grade is interpreted not only by differentiation but also by specific histological subtype, mitotic rate, and degree of necrosis. The new AJCC staging system has incorporated a 3-tier grading system, but the AJCC does have a dichotomy in that the grade 2 and 3 tumors are both considered high grade.

Where a three-tier system is utilized, i.e., the FNCLCC grading system (Fédération Nationale des Centres de Lutte Contre le Cancer), grade is determined by three different parameters, specifically differentiation, mitotic activity, and extent of necrosis. Each parameter is then scored, and the sum score used to assign grade. Specifically, differentiation is scored 1–3, mitotic activity scored 1–3, and necrosis scored 0–2. Summation then makes grade I (2 or 3 points), grade II (4 or 5 points), and grade III (6–8 points). Most encouraging is the attempt to place measurable

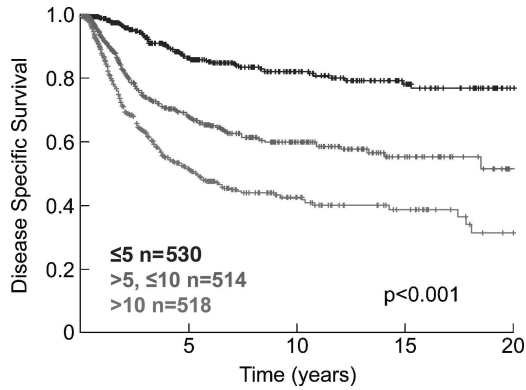

Fig. 2.10 Disease-specific survival, primary extremity high grade by size. MSKCC 7/1/1982–6/30/2010 n = 1,562

numbers on the mitotic count, i.e., a score of 1 for 0–9 mitoses per 10 high-powered fields, score of 2 for 10–19 mitoses per 10 high-powered fields, and score of 3 for 20 or more mitoses per 10 high-powered fields. A score of 2 is defined by histologic type, much as some sarcomas are automatically classified as high grade by their cellular subtype. The functional outcome of this grading system is that grade I–II tumors are tumors of defined histological types with less than 10 mitoses per 10 high-powered fields and no tumor necrosis, whereas grade III tumors require lack of differentiation and greater than 10 mitoses and some tumor necrosis. All others then become intermediate lesions.

We have previously shown that in high-grade lesions, size is better considered as a continuous variable or at least considered as three categories, i.e., <5, 5–10, and >10 (Fig. 2.10). Future staging systems will be aided by inclusion of at least a three-tier size system and a reevaluation of the value of depth and anatomic site. As more variables are added, staging systems become exponentially more complex, an argument that relies on new tools such as nomograms or Bayesian belief networks for risk estimation (see Prognostic Factors: Nomograms below).

Neurovascular and bone invasions are negative prognostic factors, but are not included in current staging systems. Molecular markers are currently being evaluated as determinants of outcome, and they are discussed in the histology-specific sections that follow.

Staging of Retroperitoneal Visceral Sarcoma

As noted immediately above, it is important to emphasize that no adequate staging system to date has specifically addressed retroperitoneal or visceral sarcomas. The historical components of size, grade, and depth become meaningless when the majority of retroperitoneal lesions are large and low grade, while visceral lesions may present as small, high-grade lesions. While death from local recurrence is possible with a large, low-grade tumor, death from visceral lesions is usually from

Table 2.4 Analysis of local recurrence-free survival in 231 primary retroperitoneal sarcoma patients with resectable disease (Used with permission from Lewis et al. [9])

	N	*p*-value[a] (univariate)	*p*-value (multivariate)	Relative risk[b] (95% CI)
Sex		0.06		
Male	140			
Female	91			
Age		0.9		
>50 years	156			
<50 years	75			
Grade		0.05		
High	134		0.01	2.1 (1.2–3.4)
Low	97			
Size		0.07		
>10 cm	170			
≤10 cm	59			
Histologic subtype		0.02		
Liposarcoma	109		0.01	2.6 (1.5–4.6)
Others	58			
Leiomyosarcoma	48			
Fibrosarcoma	16			
Surgical resection margins		0.2		
Negative micro and gross margins	136			
Positive micro and negative gross margins	49			
Positive micro and gross margins	46			

95% CI: 95 percent confidence interval
[a]Univariate *p* refers to log-rank test of no difference versus any difference between categories
[b]Relative risk to other categories of the same factor

systemic disease. This emphasizes the importance of approaches to therapy, as the predominant factor in outcome for retroperitoneal sarcoma is the adequacy of the initial resection. Without complete gross resection, essentially all patients recur regardless of grade. Only following complete resection does grade become a factor for outcome, i.e., high that are completely resected. This finding is consistent with the fact that many of the high-grade lesions have a risk of metastatic spread. This makes meaningful staging more difficult for these anatomic sites [9]. This is one reason for development of a specific AJCC version 7 staging system for GIST.

We described the factors that influence outcome for primary retroperitoneal patients [9]. Local recurrence-free survival for such lesions is summarized in Table 2.4 and for distant metastasis-free survival in Table 2.5. Important sites of metastasis include the lung and liver. Once metastasis develops, then survival is poor, at a median of 13 months (Fig. 2.11). It is important to emphasize that recurrence is common in retroperitoneal tumors, such primary sarcomas can occur late, and that many patients can undergo further resection, which is associated with prolonged survival (Figs. 2.1 and 2.2). The complete resection rate diminishes

Table 2.5 Analysis of distant metastasis-free survival in 231 primary retroperitoneal sarcoma patients with resectable disease (Used with permission from Lewis et al. [9])

	N	*p*-value[a] (univariate)	*p*-value (multivariate)	Relative risk[b] (95% CI)
Sex		0.8		
Male	140			
Female	91			
Age		0.8		
>50 years	156			
<50 years	75			
Grade		0.01		
High	134		0.01	5.0 (1.7–15)
Low	97			
Size		0.06		
>10 cm	170			
≤10 cm	59			
Histologic subtype		0.01		
Liposarcoma	109		0.01	0.2 (0.07–0.7)
Others	58			
Leiomyosarcoma	48			
Fibrosarcoma	16			
Surgical resection margins		0.01		
Negative micro and gross margins	136			
Positive micro and negative gross margins	49			
Positive micro and gross margins	46		0.01	3.9 (1.6–9.5)

95% CI: 95 percent confidence interval
[a]Univariate *p* refers to log-rank test of no difference versus any difference between categories
[b]Relative risk to other categories of the same factor

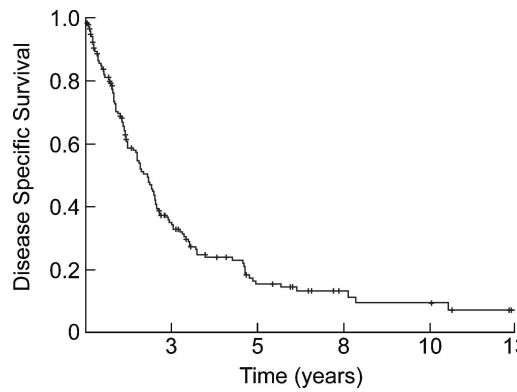

Fig. 2.11 Disease-specific survival for retroperitoneal sarcoma patients who had surgery at MSKCC (n = 745) and then developed metastases (n = 173). MSKCC 7/1/1982–6/30/2010

with each subsequent local recurrence (Fig. 2.12). If one looks at multivariate analysis of disease-specific survival of patients who undergo complete resection, the important factors for overall survival include grade and size, as emphasized previously (Table 2.6).

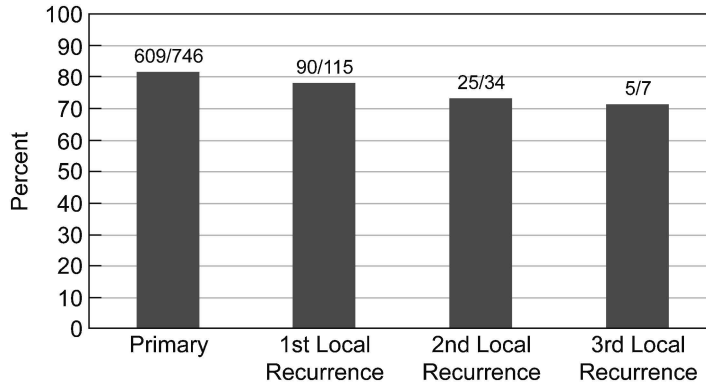

Fig. 2.12 Complete resection rate at primary operation and then following recurrence. MSKCC 7/1/1982–6/30/2010

Table 2.6 Analysis of disease-specific survival in 278 primary retroperitoneal sarcoma patients (Used with permission from Lewis et al. [9])

	N	*p*-value[a] (univariate)	*p*-value (multivariate)	Relative risk[b] (95% CI)
Sex		0.6		
Male	170			
Female	108			
Age		0.08		
>50 years	183			
<50 years	95			
Grade		0.001		
High	168			
Low	119		0.001	3.2 (2.0–5.0)
Size		0.2		
>10 cm	196			
≤10 cm	170		0.02	1.7 (1.1–2.7)
Histological subtype		0.08		
Liposarcoma	116			
Others	87			
Leiomyosarcoma	109			
Fibrosarcoma	22			
Surgical resection margins		0.001		
Negative micro and gross margins	136			
Positive micro and negative gross margins	49		0.001	4.7 (2.9–7.5)
Positive micro and gross margins	46		0.001	4.0 (2.5–6.5)

[a]Univariate *p* refers to log-rank test of no difference versus any difference between categories
[b]Relative risk to other categories of the same factor

Prognostic Factors for Extremity and Superficial Soft Tissue Sarcoma

We published [10] an analysis of a single-institution study of over 1,000 patients with extremity soft tissue sarcoma treated between 1982 and 1994. In this analysis, patient, tumor, and pathological factors were all analyzed by univariate and multivariate analysis to better define prognostic factors for local recurrence, metastatic recurrence, death from sarcoma, and post-metastasis survival. Prognostic factors identified are illustrated in Table 2.7. It was clear that age >50, recurrent presentation, positive initial microscopic margin, and the histopathological subtype of fibrosarcoma or malignant peripheral nerve tumor were all factors in multivariate analysis and were associated with a higher risk of local recurrence. Local recurrence is not grade dependent, and an analysis of extremity lesions is shown in Fig. 2.13. Local recurrence for all is approximately 25%. Local recurrence by size is illustrated (Fig. 2.14) emphasizing the progressive increase in local recurrence as the lesion increases in size, whether low grade (Fig. 2.15) or high grade (Fig. 2.16).

Table 2.7 Prognostic factors in extremity soft-tissue sarcoma – summary of significant adverse prognostic factors. MSKCC 1982–1994 n = 1,041 (Adapted from Pisters et al. [10]. Adapted with permission.)

Local recurrence	Distant recurrence	Post-metastasis survival	Disease-specific survival
LR at presentation	High grade	Size >10 cm	High grade
Positive margins	Size >5 cm		Size >10 cm
MPNST	Size >10 cm		Deep location
Age >50	Deep location		Positive margins
	LR at presentation		LR at presentation
			Lower extremity site
			MPNST
			Leiomyosarcoma

MPNST malignant peripheral nerve sheath tumor

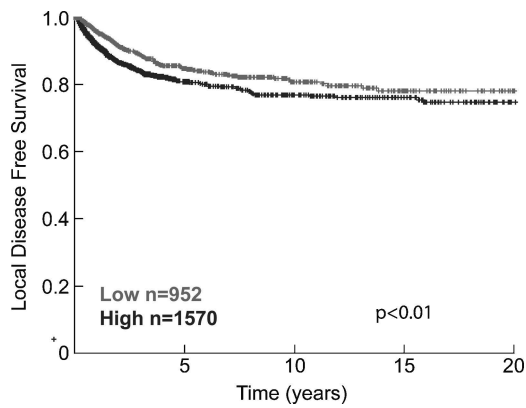

Fig. 2.13 Local disease-free survival for all primary extremity by grade. MSKCC 7/1/1982–6/30/2010 n = 2,522

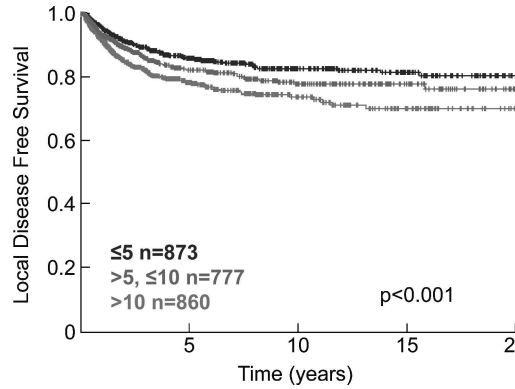

Fig. 2.14 Local disease-free survival for all primary extremity by size. MSKCC 7/1/1982-6/30/2010 n = 2,510

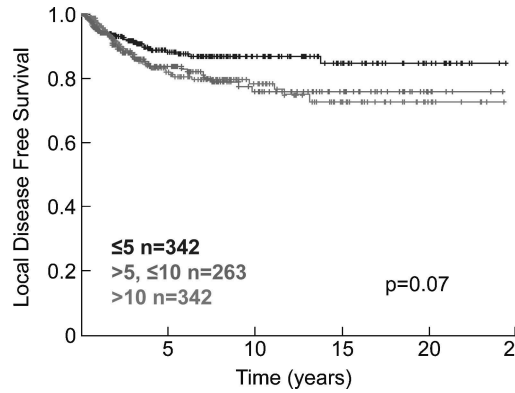

Fig. 2.15 Local recurrence-free survival primary extremity low grade, by size. MSKCC 7/1/1982–6/30/2010 n = 947

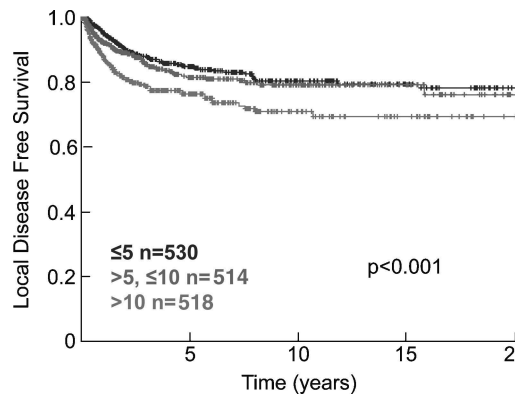

Fig. 2.16 Local recurrence-free survival for primary high-grade extremity, by size. MSKCC 7/1/1982–6/30/2010 n = 1,562

Disease-Specific Survival

Disease-specific survival or death from disease can be characterized by grade, size, and location; presence of positive margins; and local recurrence at presentation (Table 2.7). As with all of these issues, many of these factors are not arbitrary, but

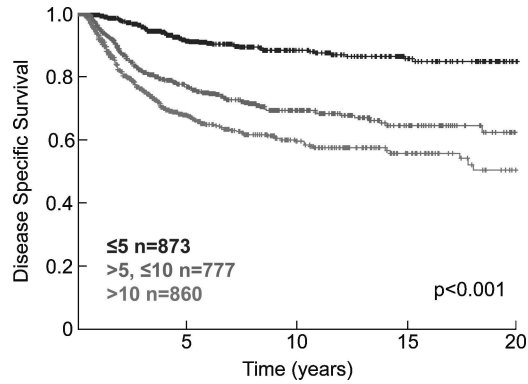

Fig. 2.17 Disease-specific survival all primary extremity by size. MSKCC 7/1/1982–6/30/2010 n = 2,510

dependent and continuous. For example, in size, increase in size (Fig. 2.17) shows an increasing risk of disease-specific death.

Prognostic Factors for Survival Following Local Recurrence of Extremity Sarcoma

Prognostic factors for outcome after a patient has recurred have been defined [11]. We found that the median time to local recurrence was 19 months, 65% of patients had developed local recurrence by 2 years, and 90% of all patients who will recur will do so within 4 years. Transition from low to high grade is uncommon, and independent predictors for disease-specific survival after recurrence are high grade, the local recurrence tumor size, and the recurrence-free interval. Patients who developed a local recurrence >5 cm in less than 16 months had a 4-year disease-specific survival of 18% compared to 81% for patients who developed a local recurrence less than or equal to 5 cm in greater than 16 months. These data are reflected in Figs. 2.18 and 2.19.

Prognostic Factors: Nomograms

Nomograms can yield improved specificity of a given clinical outcome for an individual patient, but at the present time are available for a limited number of histological types and subtypes, e.g., liposarcoma and GIST.

Nomograms are graphical representations of statistical models that provide the probability of outcome based on patient-specific covariates following specific treatment. They are usually expressed as time to a specific event, such as local recurrence or survival. They require large datasets in which there are a significant number of both negative and positive events, and they require extended length of follow-up.

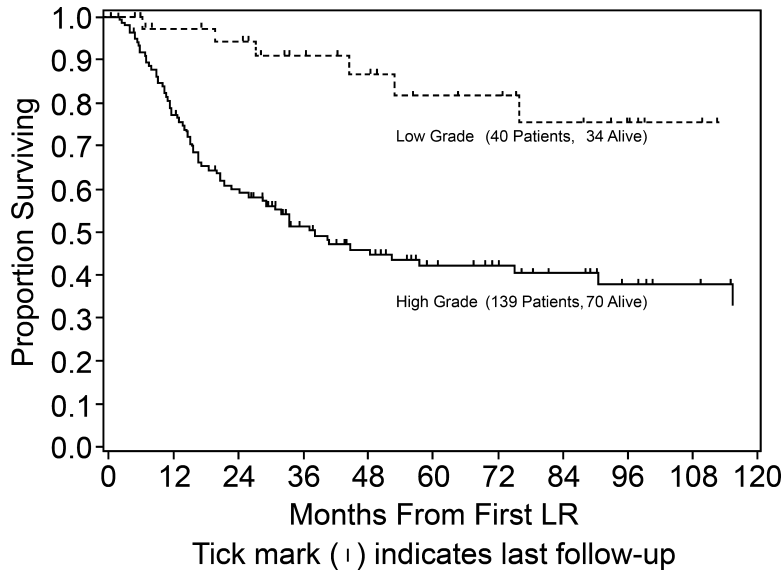

Fig. 2.18 Disease-specific survival extremity by primary tumor grade from time of local recurrence (Used with permission from Eilber et al. [11])

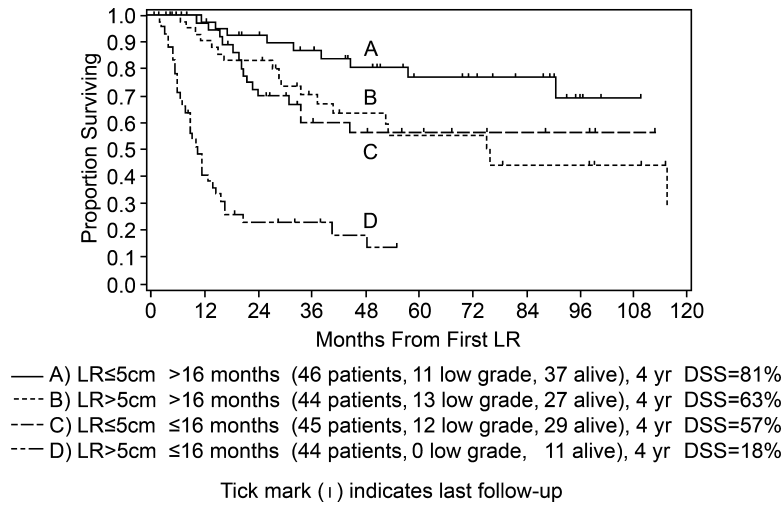

Fig. 2.19 Disease-specific survival extremity by local recurrence-free interval and size of local recurrence (Used with permission from Eilber et al. [11])

We have been actively involved in defining nomograms for prediction of sarcoma outcome. As we have a defined population with defined outcomes, known risk factors, and selected covariates, we are able to construct such nomograms in a meaningful way. Our initial attempt was a postoperative nomogram for 12-year

sarcoma-specific death [12]. In that study, we are clearly able to utilize the known factors of our large dataset to predict outcome. As there were only sufficient data for six defined histologies, i.e., fibrosarcoma, liposarcoma, leiomyosarcoma, synovial sarcoma, undifferentiated pleomorphic sarcoma (UPS), and malignant peripheral nerve sheath tumor (MPNST), outcomes were only defined for these categories. Other barriers to defining outcomes better using nomograms include the knowledge that different liposarcoma subtypes each have distinct recurrence risk or chance of death and the definition of myxofibrosarcoma as a unique sarcoma subtype, differing from malignant fibrous histiocytoma, which is now itself called undifferentiated pleomorphic sarcoma (UPS) [12]. The original sarcoma nomogram subsequently has been validated using an independent dataset [13] and has been further validated by others [14].

Because of the multiple subtypes of liposarcoma, we developed a specific liposarcoma nomogram for disease-specific survival [15]. Such nomograms can then be developed to be site or histology specific; they can be considered to develop in time-altered sequence and have the potential to add biological variables. We further developed nomograms for probability of death from sarcoma following a local recurrence [16].

Nomograms have the potential to be utilized as a tool for evaluating the effects of treatment. While this requires validation by testing in a randomized trial, it has been suggestive [17] in our study of ifosfamide-based chemotherapy in adults with synovial sarcoma. Similar nomograms have been developed for predicting local recurrence both for all histologies and for desmoid tumors and can provide useful tools in patient management.

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