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

2.1 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.

2.2 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.

2.3 Staging

Staging of soft tissue sarcoma continues to evolve. Most staging systems depend on the grade and presence or absence of metastasis. The original soft tissue sarcoma staging system was based on data from 1977 (Fig. 2.3). Stage was subdivided based

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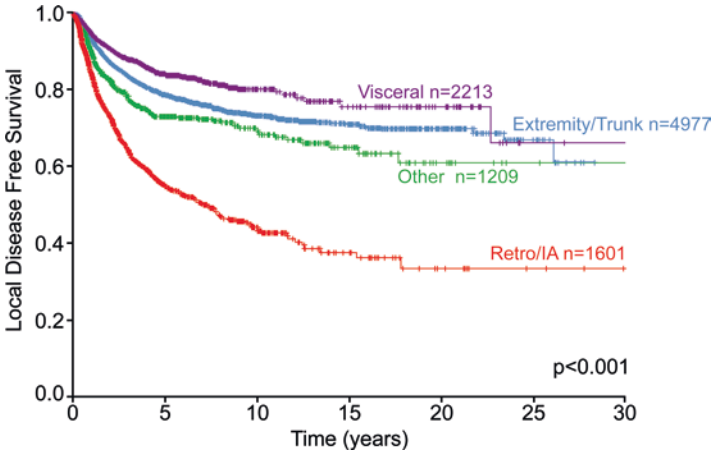

Fig. 2.1 All adult sarcomas, local disease-free survival by site. MSKCC 7/1/1982–5/31/2013 $n = 10{,}000$

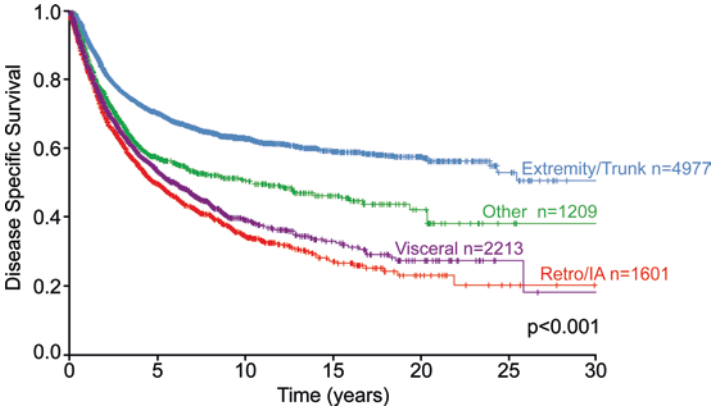

Fig. 2.2 All adult sarcomas, disease-specific survival by site. MSKCC 7/1/1982–5/31/2013 $n = 10{,}000$

on the primary size of the initial tumor, into categories of <5 and >5 cm (T1/T2). By 1992, the absence or presence of nodal metastasis was included (N0/N1).

It became progressively clear that tumors of very small size have a much better prognosis than was predicted by the initial 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) [1]. 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

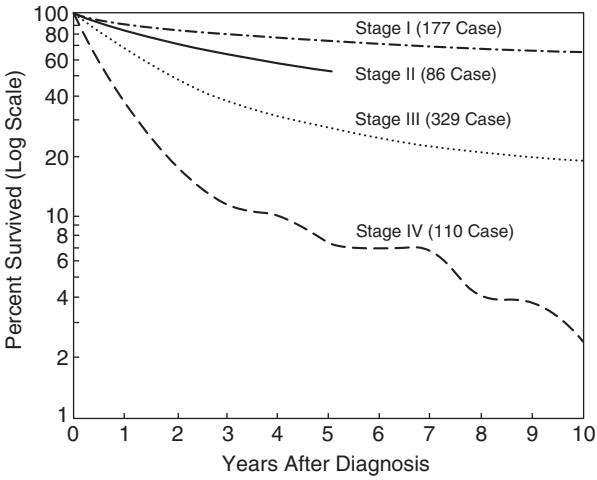

Fig. 2.3 1977 AJCC staging system. From: Russell WO, et al. Cancer 40:1562–1570, 1977

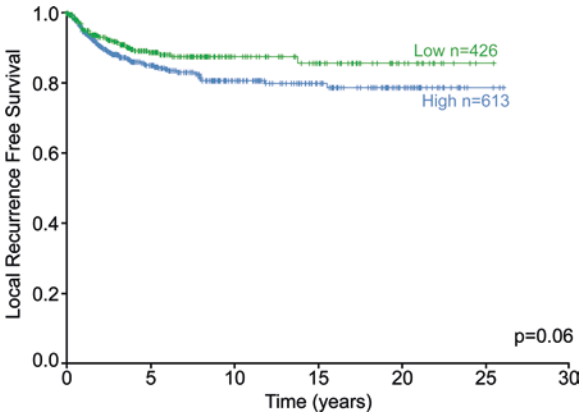

Fig. 2.4 Local recurrence-free survival, primary extremity ≤5 cm, by grade. MSKCC 7/1/1982–5/31/2013 $n = 1039$

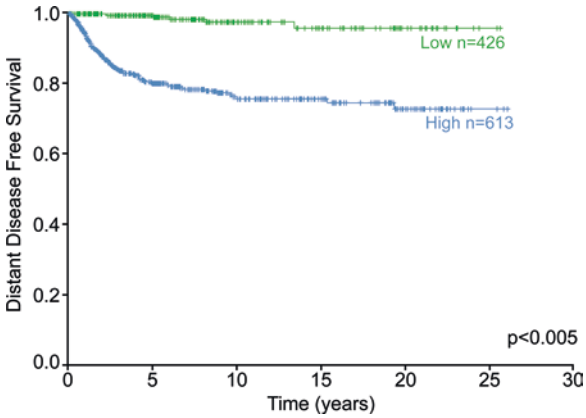

Fig. 2.5 Distant disease-free survival, primary extremity ≤5 cm, by grade. MSKCC 7/1/1982–5/31/2013 $n = 1039$

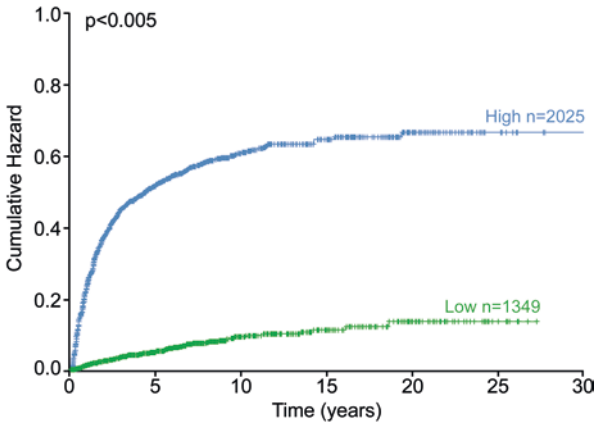

Fig. 2.6 Distant metastasis, extremity primary and local recurrent by grade. MSKCC 7/1/1982–5/31/2013 $n = 3374$

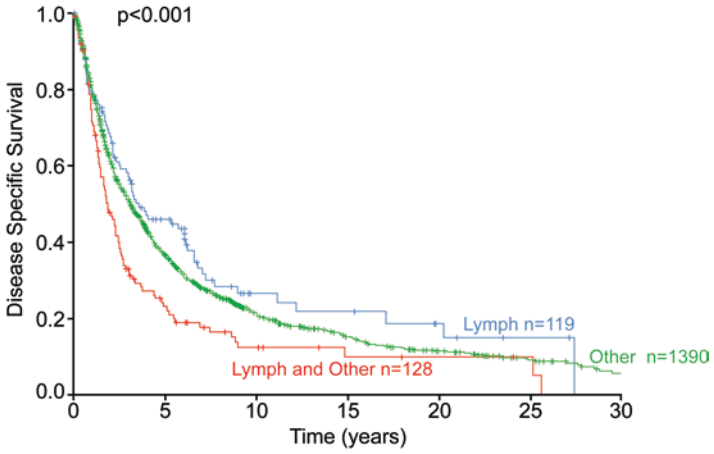

Fig. 2.7 Disease-specific survival by lymph node metastases alone or with other metastasis and other metastasis MSKCC 7/1/1982–5/31/2013 $n = 1637$

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) [2, 3]. Early metastatic disease is dominated by the grade of the tumor.

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).

Table 2.1 Histologic type of sarcomas and lymph node metastasis

	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

MPNST malignant peripheral nerve sheath tumor

Adapted from: Fong Y, Coit DG, Woodruff JM, Brennan MF. Ann Surg 218:72–77, 1993

Review of past studies of nodal metastasis from sarcomas and current study

[a]Adapted from a review by Weingrad and Rosenberg summary of 47 studies (Weingrad DN, et al. Surgery 1978; 84:231–240)

[b]Adapted from a review of Mazeron and Suit summary of 122 studies (Mazeron JJ, Suit HD. Cancer 1987; 60:1800–1808)

[c]Database only includes extraskeletal osteo- and chondrosarcomas

Table 2.2 Cox proportional hazard regression analysis for disease-specific survival including all database patients

Variable	Categories	*p* value	HR	95 % CI for HR
Age	<54.4, ≥54.4 years (median)	<0.001	0.749	0.641–0.874
Gender	Male, female	0.914	–	–
Anatomic primary site	Other site, retroperitoneal and visceral, extremity	0.005	1.221	1.061–1.405
Primary tumor size (cm)	>15, >10–15, >5–10, <5	<0.001	1.198	1.106–1.299
Depth	Superficial, deep	0.166	–	–
Grade	Low, high	0.042	0.556	0.316–0.978
Metastatic disease	None, nodal metastases (N1M0), other metastases (N0M1), both nodal and other metastases (N1M1)	<0.001		
	N0M0 vs. N1M0	0.011	0.392	0.190–0.807
	N1M0 vs. N0M1	<0.001	0.197	0.109–0.353
	N1M0 vs. N1M1	0.613	–	–

With permission from: Maki RG, et al. Ann Surg Oncol. 2013 20(11):3377–83
Tumors >10 cm were excluded if their exact sizes were not specified
HR hazard ratio; *95 % CI* 95 % confidence interval—omitted since not statistically significant

A study comparing three different staging systems [4] 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 [5], which employed a staging system based on extra compartmental extension (which is itself influenced by size).

Disease-specific survival including all patients from our database (Table 2.2) suggests age, site, size, grade, nodal metastases alone and systemic metastases alone, but not N1 M1, to all be independent predictors of survival (Fig. 2.8). All categories, local disease-free survival, recurrence-free survival, and disease-specific survival, are shown in Fig. 2.9. In the AJCC Staging Manual, 8th edition, depth was removed as a stratification factor, given its lesser role in recurrence compared to grade and primary tumor size. However, disease-specific survival is still influenced by both size and depth in our own analyses (Fig. 2.10 and Table 2.2).

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.

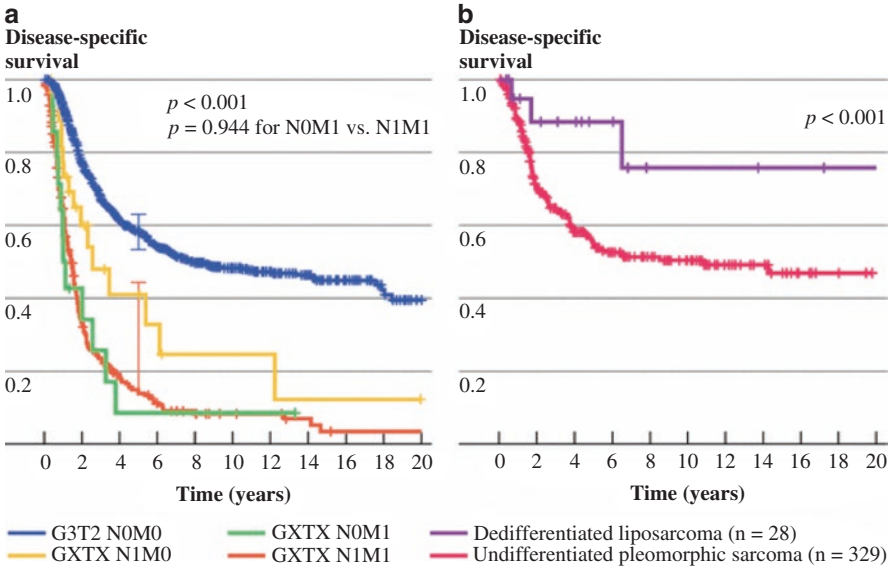

Fig. 2.8 (**a**) Disease-specific survival comparing G3T2N0M0 primary STS to GXTXN1M0 and GXTXN1M1 STS, $n=1440$ total; G3T2N0M0 disease ($n=1123$), GXTXN1M0 ($n=33$), GXTXN1M1 ($n=15$), and GXTXN0M1 disease ($n=269$); log rank, $p<0.001$. Comparing GXTXN0M1 and GXTXN1M1 patients; log rank, $p=0.944$. 95 % confidence intervals are noted at 5 years for the two largest groups; they are not meaningful for the smallest groups with so few events. (**b**) Disease-specific survival comparing extremity dedifferentiated liposarcoma ($n=28$) and undifferentiated pleomorphic sarcoma ($n=329$); log rank, $p<0.001$. With permission from: Maki RG, et al. Ann Surg Oncol. 2013 20(11):3377–3383

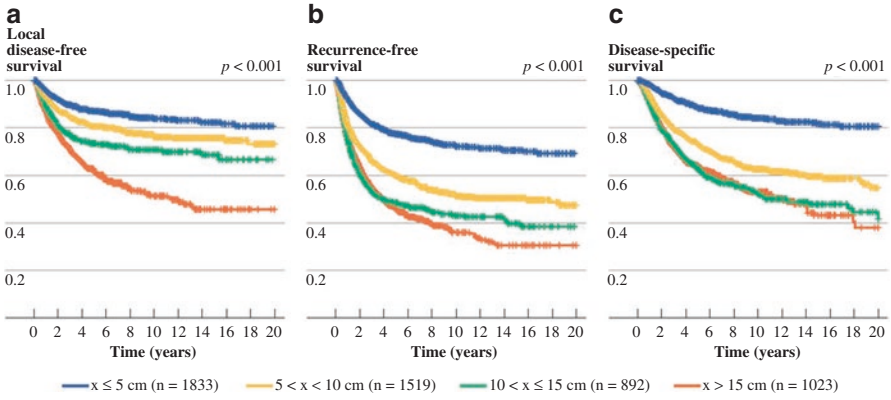

Fig. 2.9 Local recurrence-free survival (RFS), overall recurrence-free survival, and disease-specific survival (DSS) by size category, ≤5, 5–10, 10–15, and >15 cm. (**a**) Local recurrence-free survival (time from primary surgery to first local recurrence), $n=5267$ patients, excludes 75 patients with unknown size categories; log rank, $p<0.001$. (**b**) Recurrence-free survival (time from primary surgery to first local or distant recurrence), $n=5267$, excludes 75 patients with unknown size categories; log rank, $p<0.001$. (**c**) Disease-specific survival (time from primary surgery to death from disease), $n=5267$, excludes 75 patients with unknown size categories; log rank, $p<0.001$; log rank, p value $=0.91$ comparing >10–15 and >15 cm groups. With permission from: Maki RG, et al. Ann Surg Oncol. 2013 20(11):3377–3383

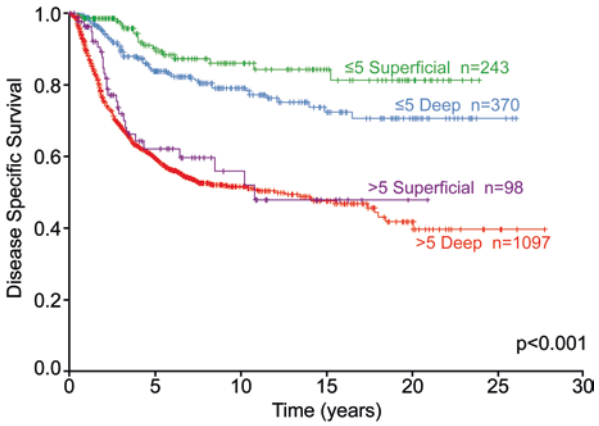

Fig. 2.10 Disease-specific survival, primary extremity high grade, by size and depth. MSKCC 7/1/1982–5/31/2013 $n = 1808$

The AJCC staging system, 8th edition, continues to incorporate the FNCLCC three-tier grading system, though the 8th edition of the AJCC system for extremity and trunk tumors still has a dichotomy in that both grade 2 and 3 tumors are considered higher-risk tumors.

The FNCLCC grading system (Fédération Nationale des Centres de Lutte Contre le Cancer) is determined by three different parameters, specifically differentiation, mitotic activity, and extent of necrosis. Each parameter is then scored and the sum yields 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 numbers on the mitotic count, i.e., a score of 1 for 0–9 mitoses per 10 high-powered fields, score 2 for 10–19 mitoses per 10 high-powered fields, and score 3, 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.

For trunk, extremity, head, and neck primary alone, local disease-free survival, recurrence-free survival, and disease-specific survival are illustrated in Fig. 2.11. These differences in outcome were a significant reason in justifying separating soft tissue sarcoma staging systems by 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.

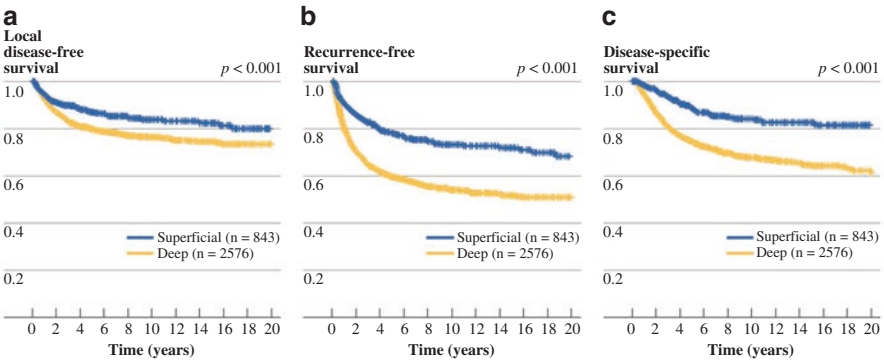

Fig. 2.11 (**a**) Local relapse-free survival (time from primary surgery to first local relapse, trunk/extremity/head-neck primary sites only). $n = 3419$, excludes six patients with unknown size categories; (**b**) Recurrence-free survival (time from primary surgery to first local or distant relapse, trunk/extremity/head-neck primary sites only), $n = 3419$, excludes six patients with unknown size categories; (**c**) Disease-specific survival (time from primary surgery to death from disease, trunk/extremity/head-neck primary sites only), $n = 3419$, excludes six patients with unknown size categories. With permission from: Maki RG, et al. Ann Surg Oncol. 2013 20(11):3377–3383

(see Prognostic Factors—Nomograms below) In principle, single histology staging systems should provide the most accuracy in prognostication. While difficult to achieve, GIST and rhabdomyosarcoma stand out as two histologies in which histology-specific staging systems exist; the AJCC version 8 staging system is the first to reference a nomogram to aid in staging, in the case of retroperitoneal sarcomas.

Neurovascular and bone invasion are negative prognostic factors, but are not included in current staging systems. Molecular markers are currently being evaluated as determinants of outcome, but are not part of traditional staging systems; *KIT* or *PDGFRA* mutation will likely be incorporated in future iterations of the staging system for GIST, but no such markers have been found with such impact in other soft tissue sarcomas. Given their importance in defining characteristics of a variety of soft tissue sarcomas, molecular markers are discussed in the histology-specific sections that follow.

2.4 Staging of Retroperitoneal and 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; this was the impetus behind changes to the AJCC version 8 staging system for soft tissue sarcomas, which now employs a nomogram to stage retroperitoneal sarcomas, based on development and validation of a nomogram across multiple large volume institutions. In addition, there is a separate staging system for visceral soft tissue sarcomas.

These nomogram data highlight the data that while death from local recurrence is possible with a large, low-grade tumor, death from visceral lesions is usually from 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.

We have previously described the factors that influence outcome for primary retroperitoneal patients [6]. Local recurrence-free survival for such lesions is summarized in Table 2.3 and distant metastasis-free survival in Table 2.4. Important

Table 2.3 Analysis of local recurrence-free survival in 231 primary retroperitoneal sarcoma patients with resectable disease

	N	*p* value* (univariate)	*p* value (multivariate)	Relative risk[a] (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
From: Lewis JJ, Leung D, Woodruff JM, Brennan MF. Ann Surg 228:355–365, 1998
*Univariate p refers to log rank test of no difference vs. any difference between categories
[a]Relative risk to other categories of the same factor

Table 2.4 Analysis of distant metastasis-free survival in 231 primary retroperitoneal sarcoma patients with resectable disease

	N	*p* value* (univariate)	*p* value (multivariate)	Relative risk[a] (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
From: Lewis JJ, Leung D, Woodruff JM, Brennan MF. Ann Surg 228:355–365, 1998
*Univariate p refers to log rank test of no difference vs. any difference between categories
[a]Relative risk to other categories of the same factor

sites of metastasis include the lung and liver. Once metastasis develops, survival is poor, at a median of 13 months (Fig. 2.12). 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. 2.2 and 2.1). The complete resection rate diminishes with each subsequent local recurrence (Fig. 2.13). 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 2.5). These and other data have directly impacted upon the AJCC version 8 sarcoma staging systems.

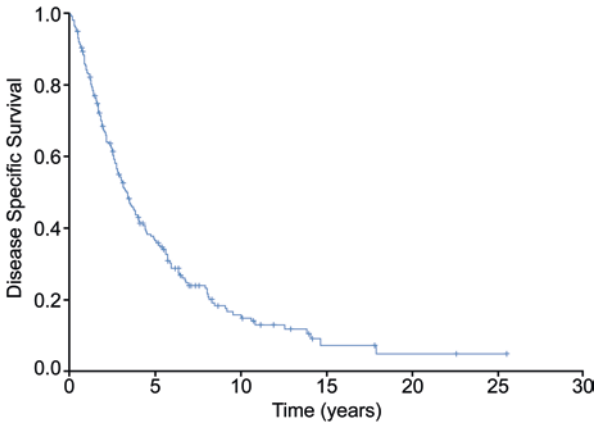

Fig. 2.12 Disease-specific survival for retroperitoneal sarcoma who had operation at MSKCC ($n = 899$) and then developed metastases ($n = 196$). MSKCC 7/1/1982–5/31/2013

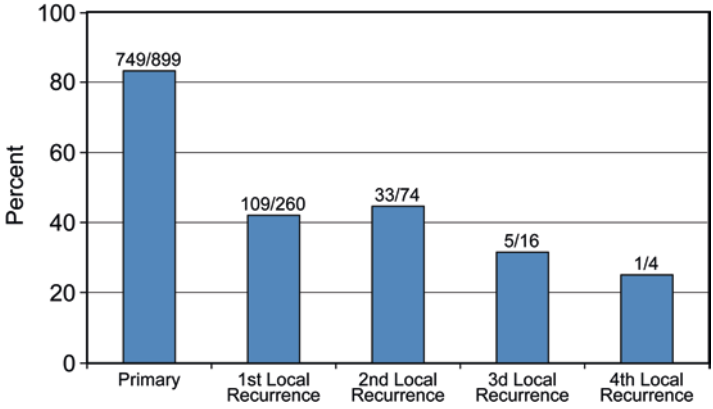

Fig. 2.13 Complete resection rate at primary operation and then following recurrence. MSKCC 7/1/1982–5/31/2013

2.5 Prognostic Factors for Extremity and Superficial Soft Tissue Sarcoma

Highlighting outcomes that eventually were incorporated into sarcoma staging systems, we published [7] an analysis of a single institution study of over 1000 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 2.6. 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

Table 2.5 Analysis of disease-specific survival in 278 primary retroperitoneal sarcoma patients

	`	*p* value* (univariate)	*p*-value (multivariate)	Relative risk[a] (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			
Other	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)

From: Lewis JJ, Leung D, Woodruff JM, Brennan MF. Ann Surg 228:355–365, 1998
*Univariate p refers to log rank test of no difference vs. any difference between categories
[a]Relative risk to other categories of the same factor

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. 2.14). Local recurrence for all is approximately 25 %. Local recurrence by size is illustrated (Fig. 2.15), emphasizing the progressive increase in local recurrence as the lesion increases in size, whether low grade (Fig. 2.16) or high grade (Fig. 2.17).

2.6 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 2.6). As with all of these issues, many of these factors are not arbitrary, but interdependent and continuous. For example in size, increase in size (Fig. 2.18) shows an increasing risk of disease-specific death.

Table 2.6 Prognostic factors in extremity soft tissue sarcoma—summary of significant adverse prognostic factors

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

MSKCC 1982–1994 $n=1041$
MPNST malignant peripheral nerve sheath tumor
Adapted from: Pisters P, Leung D, Woodruff J, Shi W, Brennan MF. J Clin Oncol 14:1679–1689, 1996

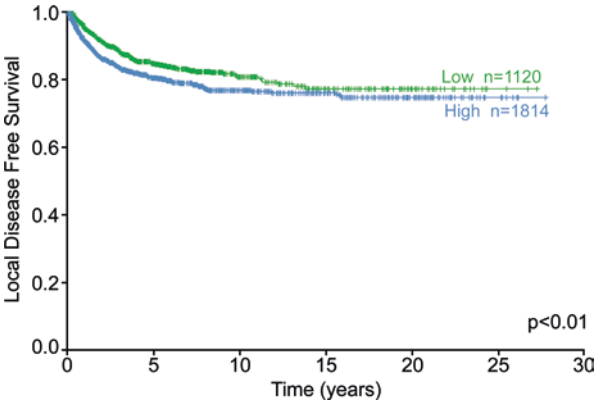

Fig. 2.14 Local disease-free survival for all primary extremity, by grade. MSKCC 7/1/1982–5/31/2013 $n=2934$

2.7 Prognostic Factors for Survival Following Local Recurrence of Extremity Sarcoma

Prognostic factors for outcome after a patient has developed a local recurrence have been defined [8]. 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

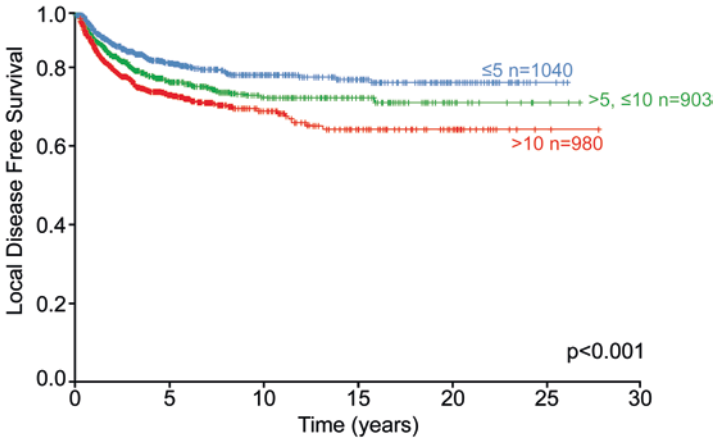

Fig. 2.15 Local disease- free survival for all primary extremity, by size. MSKCC 7/1/1982–5/31/2013 $n = 2923$

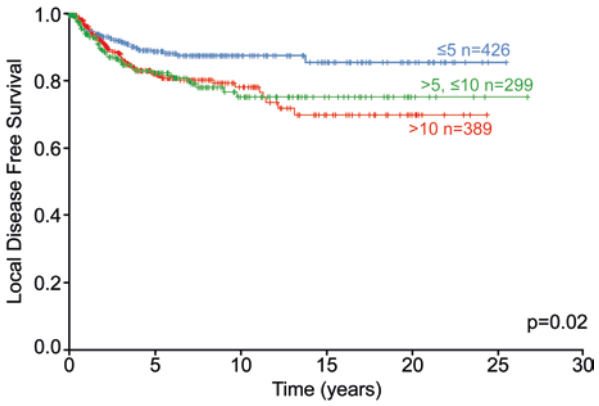

Fig. 2.16 Local recurrence-free survival primary extremity low grade, by size. MSKCC 7/1/1982–5/31/2013 $n = 1114$

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. 2.19 and 2.20.

2.8 AJCC Staging

The 8th edition of the American Joint Commission on Cancer soft tissue sarcoma staging system is expanded from prior editions with a greater emphasis on site-specific staging than in previous editions. For example, from prior editions of the staging manual, since all retroperitoneal tumors are deep, the designation of superficial or deep is meaningless and is removed from the staging system(s) in the 8th edition. We will emphasize here the staging of extremity and trunk tumors, the most common primary

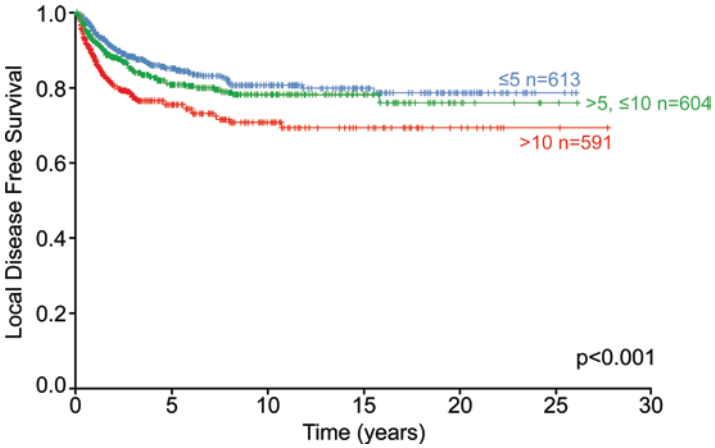

Fig. 2.17 Local recurrence-free survival for primary high-grade extremity, by size. MSKCC 7/1/1982–5/31/2013 $n = 1808$

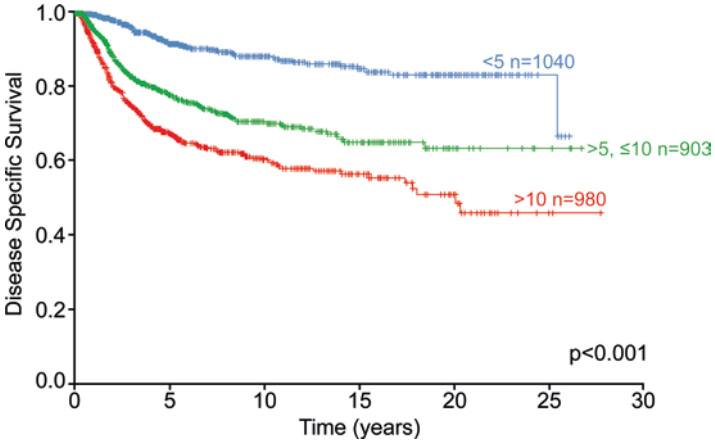

Fig. 2.18 Disease-specific survival all primary extremity, by size. MSKCC 7/1/1982–5/31/2013 $n = 2923$

site, and refer to the staging manual for a more detailed discussion of other anatomic sites, all of which are staged differently from extremity/trunk tumors.

Desmoid tumors and Kaposi sarcoma continue to be excluded from the staging system, given their very different biology compared to other soft tissue sarcomas. Nodal disease, included as stage IV in older editions, is considered stage IIIb in the 7th and 8th edition, although the differences in outcome between patients with nodal and other metastases are small (Fig. 2.7). This reclassification highlights the ability to cure some patients with lymph node metastasis alone with further treatment, usually surgical resection. Anatomic stage and prognostic groups for extremity and truncal

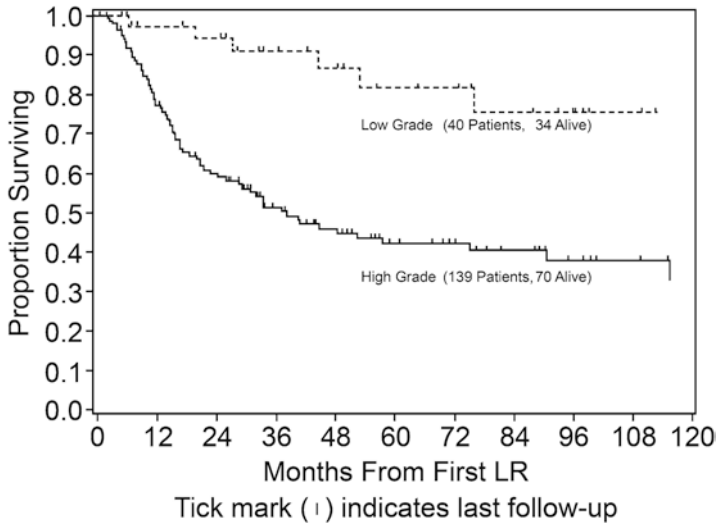

Fig. 2.19 Disease-specific survival extremity by primary tumor grade from time of local recurrence. From: Eilber FC, Brennan MF, Riedel E, et al. Ann Surg Oncol 12:228–236, 2005

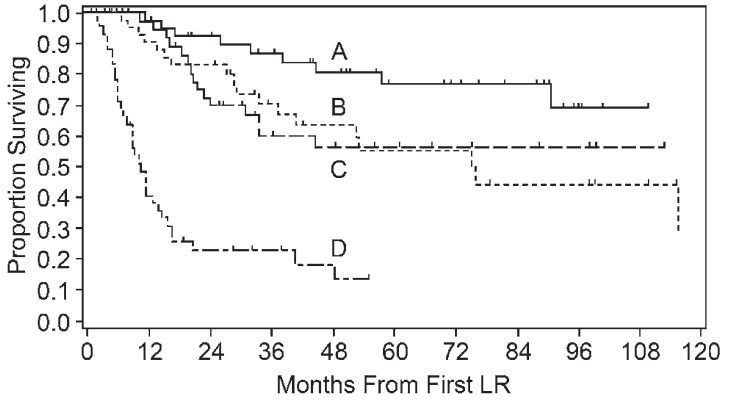

Fig. 2.20 Disease-specific survival extremity by local recurrence-free interval and size of local recurrence. From: Eilber FC, Brennan MF, Riedel E, et al. Ann Surg Oncol 12:228–236, 2005

Table 2.7 AJCC 8 staging system for extremity and trunk sarcoma (in press 2017)

T category	*T criteria*
Definition of primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 5 cm or less in greatest dimension
T2	Tumor more than 5 cm and less than or equal to 10 cm in greatest dimension
T3	Tumor more than 10 cm and less than or equal to 15 cm in greatest dimension
T4	Tumor more than 15 cm in greatest dimension

N category	*N criteria*
Definition of regional lymph node (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

M category	*M criteria*
Definition of distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

G	*G Definition*
Definition of grade (G)	
GX	Grade cannot be assessed
G1	Grade 1
G2	Grade 2
G3	Grade 3

Modified from Amin, M.B., Edge, S., Greene, F.L., et al. (Eds.) (2017) *AJCC Cancer Staging Manual*
Proposed for 8th Edition:
Stage Ia: T1; N0; M0; G1; GX
Stage Ib: T2;T3;T4; N0; M0; G1; GX
Stage II: T1; N0; M0; G2; G3
Stage IIIa: T2; N0; M0; G2; G3
Stage IIIb: T3; T4; N0; M0; G2; G3; Any T: N1; M0; Any G
Stage IV: Any T; Any N; M1; Any G

primary tumors are defined in Table 2.7. Prognostic groups are defined by T stage as 5 cm or less (T1), over 5 and up to 10 cm (T2), over 10 and up to 15 cm (T3), and over 15 cm in greatest dimension (T4), in keeping with data that metastasis and recurrence continue to increase in frequency in primary tumors larger than 5 cm, as we had shown previously [9]. (Figs. 2.21 and 2.22). T3 and T4 lesions are distinguished from one another by the increased local recurrence risk of T4 vs. T3 tumors, though the metastatic potential appears to plateau and is similar for both T3 and T4 tumors. It should

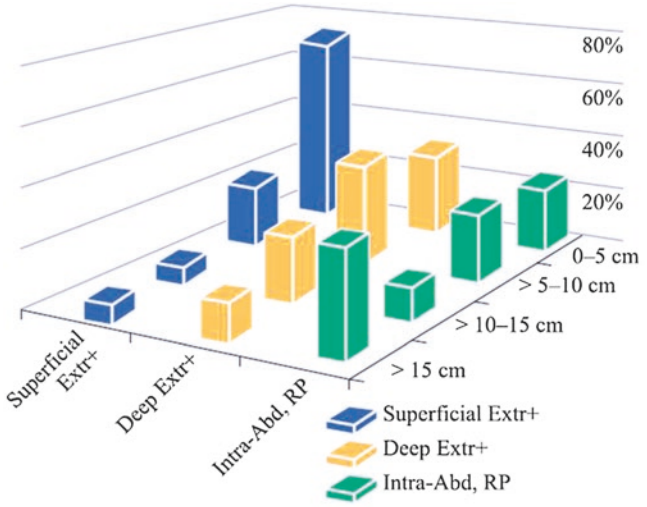

Fig. 2.21 Frequency of different size categories by superficial or deep site. All intra-abdominal, retroperitoneal, and visceral tumors are deep and are noted separately. Percentages of each tumor class by size are indicated. Extr + = extremity and head and neck, Intra-abd, RP = intra-abdominal, retroperitoneal, and visceral. With permission from: Maki RG, et al. Ann Surg Oncol. 2013 20(11):3377–3383

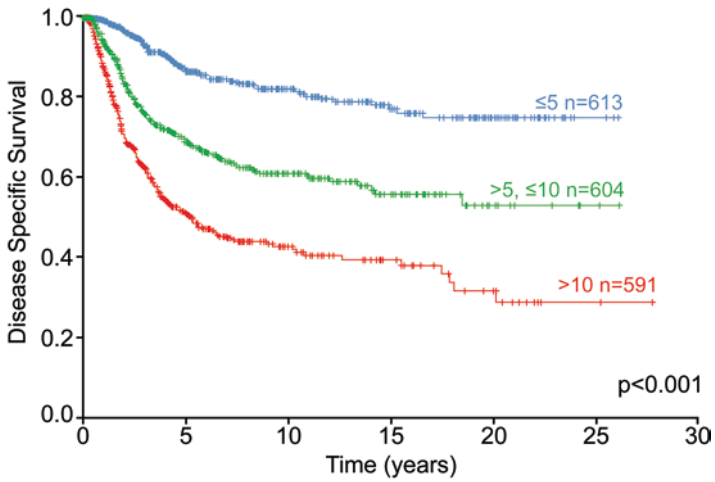

Fig. 2.22 Disease-specific survival, primary extremity high grade, by size. MSKCC 7/1/1982–5/31/2013 $n = 1808$. With permission from: Brennan MF, et al. Ann Surg 260(3):416–422, 2014

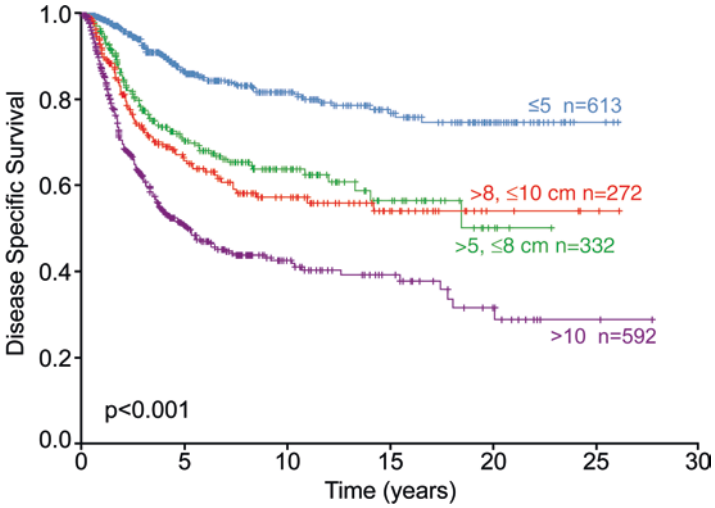

Fig. 2.23 Disease-specific survival, primary extremity high grade, by size. MSKCC 7/1/1982–5/31/2013 $n = 1808$

be emphasized that superficial lesions >5 cm are rare (< 1 %) in the extremity. Wherever possible, size should be recorded three dimensionally, since future efforts will be made to examine risk based on tumor volume (Fig. 2.23).

2.9 Prognostic Factors—Nomograms

Nomograms provide a powerful means to 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, as well as for specific anatomic sites, such as retroperitoneum.

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. 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 [10]. In that study, we were clearly able to utilize the multiple 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 sar-

coma, 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 has 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) [10]. The original sarcoma nomogram subsequently has been validated using an independent dataset [11] and has been further validated by others [12].

Because of the multiple subtypes of liposarcoma, we developed a specific liposarcoma nomogram for disease-specific survival [13]. With larger data sets, nomograms can be developed to be site- or histology-specific, 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 [14].

The use of nomograms has spread to other specific soft tissue tumor subtypes. Nomograms have been described for local recurrence of a soft tissue sarcoma without radiation, which will hopefully identify populations appropriate for a closer examination of radiation therapy [15]. More recently, a nomogram specific for uterine leiomyosarcoma has been developed [16]. An important nomogram has now been developed for the desmoid tumor, demonstrating the importance of size, site, and age, but not microscopic margin [17].

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 [18] 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.

An alternative approach to yield better clinical prognostication is the development of Bayesian Belief Networks [19] where dominant factors in predication of survival and recurrence can be identified. Such networks can also identify within the network primary/dependent relationships.

References

1. Geer RJ, Woodruff J, Casper ES, et al. Management of small soft-tissue sarcoma of the extremity in adults. Arch Surg. 1992;127:1285–9.
2. Grosso F, Sanfilippo R, Virdis E, et al. Trabectedin in myxoid liposarcomas (MLS): a long-term analysis of a single-institution series. Ann Oncol. 2009;20:1439–44.
3. De Wever I, Dal Cin P, Fletcher CD, et al. Cytogenetic, clinical, and morphologic correlations in 78 cases of fibromatosis: a report from the CHAMP Study Group. Chromosomes and morphology. Mod Pathol. 2000;13:1080–5.
4. Wunder JS, Healey JH, Davis AM, et al. A comparison of staging systems for localized extremity soft tissue sarcoma. Cancer. 2000;88:2721–30.

5. Wolf RE, Enneking WF. The staging and surgery of musculoskeletal neoplasms. Orthop Clin North Am. 1996;27:473–81.
6. Lewis JJ, Leung D, Woodruff JM, et al. Retroperitoneal soft-tissue sarcoma: analysis of 500 patients treated and followed at a single institution. Ann Surg. 1998;228:355–65.
7. Pisters PW, Leung DH, Woodruff J, et al. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol. 1996;14:1679–89.
8. Eilber FC, Brennan MF, Riedel E, et al. Prognostic factors for survival in patients with locally recurrent extremity soft tissue sarcomas. Ann Surg Oncol. 2005;12:228–36.
9. Maki RG, Moraco N, Antonescu CR, et al. Toward better soft tissue sarcoma staging: building on American Joint Committee on Cancer Staging Systems versions 6 and 7. Ann Surg Oncol. 2013;20:3377–83.
10. Kattan MW, Leung DH, Brennan MF. Postoperative nomogram for 12-year sarcoma-specific death. J Clin Oncol. 2002;20:791–6.
11. Eilber FC, Brennan MF, Eilber FR, et al. Validation of the postoperative nomogram for 12-year sarcoma-specific mortality. Cancer. 2004;101:2270–5.
12. Mariani L, Miceli R, Kattan MW, et al. Validation and adaptation of a nomogram for predicting the survival of patients with extremity soft tissue sarcoma using a three-grade system. Cancer. 2005;103:402–8.
13. Dalal KM, Kattan MW, Antonescu CR, et al. Subtype specific prognostic nomogram for patients with primary liposarcoma of the retroperitoneum, extremity, or trunk. Ann Surg. 2006;244:381–91.
14. Kattan MW, Heller G, Brennan MF. A competing-risks nomogram for sarcoma-specific death following local recurrence. Stat Med. 2003;22:3515–25.
15. Cahlon O, Brennan MF, Jia X, et al. A postoperative nomogram for local recurrence risk in extremity soft tissue sarcomas after limb-sparing surgery without adjuvant radiation. Ann Surg. 2012;255:343–7.
16. Zivanovic O, Jacks LM, Iasonos A, et al. A nomogram to predict postresection 5-year overall survival for patients with uterine leiomyosarcoma. Cancer. 2012;118:660–9.
17. Crago AM, Denton B, Salas S, et al. A prognostic nomogram for prediction of recurrence in desmoid fibromatosis. Ann Surg. 2013;258:347–53.
18. Canter RJ, Qin LX, Maki RG, et al. A synovial sarcoma-specific preoperative nomogram supports a survival benefit to ifosfamide-based chemotherapy and improves risk stratification for patients. Clin Cancer Res. 2008;14:8191–7.
19. Forsberg JA, Healey JH, Brennan MF. A probabilistic analysis of completely excised high-grade soft tissue sarcomas of the extremity: an application of a Bayesian belief network. Ann Surg Oncol. 2012;19:2992–3001.