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REVIEW ARTICLE

Diagnosis and Management of Lipomatous Tumors

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Lipomatous tumors range from benign lipomas to high-grade liposarcomas. Liposarcomas are classified into five histologic subtypes: well-differentiated, dedifferentiated, myxoid, round cell, and pleomorphic, which differ in outcomes and patterns of recurrence. Surgical resection is the mainstay of curative treatment; however, large, high grade liposarcomas may benefit from multimodality treatment with chemotherapy and radiation. A histologic-subtype specific nomogram provides accurate survival predictions. Prospective randomized clinical trials will continue to improve our care of patients with liposarcoma.
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KEY WORDS: liposarcoma; management; prognosis; diagnosis; treatment

EPIDEMIOLOGY

Lipomatous tumors comprise 50% of soft tissue neoplasms and are commonly encountered by primary care physicians, surgeons, and pathologists. Occurring at almost any site in the body, lipomatous tumors range from benign lipomas to aggressive, high-grade liposarcomas.

Liposarcoma is the most common soft tissue sarcoma (STS), accounting for 20% of all STS in adults [1]; 10,000 cases and 3,600 deaths attributable to STS are expected in the U.S. in 2007 [2]. Mortality rates for patients with liposarcoma range from 1% to 90%, and recurrence rates range from 5% to 83% depending on the histologic subtype and location [3–10]. Liposarcomas are thought to arise de novo and not from pre-existing benign lesions. In most patients, no specific etiology is found. Although trauma is often implicated as an inciting agent, it is unclear whether it is a true causal factor. Genetic alterations are becoming increasingly recognized as causal and have been used to improve the accuracy of subtype classification when combined with morphology; they are discussed later in the chapter.

SITES OF INVOLVEMENT

Lipomatous tumors may occur in any area of the body. Lipomas most commonly arise in the subcutaneous tissues, frequently located in the trunk and proximal limbs. Although benign lipomas may occur in the mediastinum, gastrointestinal tract, and retroperitoneum, fatty neoplasms in the retroperitoneum are usually well-differentiated liposarcomas (WDLS). Spindle cell lipomas, often seen in men between the ages of 45 and 65, occur in the posterior neck and shoulder area. Intramuscular lipomas, usually poorly circumscribed and infiltrative, typically present in mid-adult life as slow-growing, deep masses located in the thigh or trunk; however, approximately 10% of intramuscular lipomas are non-infiltrative and well-circumscribed. In a patient with a large, deep-seated lipomatous tumor, it is important to exclude an atypical lipomatous tumor (ALT)/WDLS, which is more common than an intramuscular lipoma. Angiolipomas present as subcutaneous nodules in the upper extremity, usually in young adults, and are multiple in more than 50% of cases. Hibernomas may arise in the trunk, retroperitoneum, and extremities.

Liposarcomas may occur anywhere in the body, although the most common sites are the thigh and the retroperitoneum. Liposarcoma is classified into three biological types encompassing five subtypes: (1) well-differentiated/dedifferentiated, (2) myxoid/round cell, and (3) pleomorphic, based on strict morphologic features, natural history and cytogenetic aberrations [11]. These five subtypes have different biology and patterns of behavior [9–13]. The well-differentiated and dedifferentiated subtypes account for 46% and 18% of liposarcomas, respectively, and are more commonly found in the retroperitoneal location [13]. The myxoid/round cell and pleomorphic subtypes account for 28% and 8% of liposarcomas, respectively, and are usually located in the extremity; more than 66% of cases arises within the thigh [13].

HISTOPATHOLOGY

Except for subcutaneous lipomas, there is little evidence that these lesions arise from their mature tissue counterparts. In fact, many liposarcomas arise at sites devoid of adipose tissue.

Lipoma

Lipomas are well-circumscribed, lobulated lesions composed of fat cells, but are demarcated from surrounding fat by a thin fibrous capsule. In spindle cell lipoma, mature fat is replaced by collagen-forming

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spindle cells while pleomorphic lipoma, a closely related lesion, typically shows pleomorphic, florette-type cells. Angiolipomas consist of adipocytes with interspersed clusters of capillaries containing fibrin thrombi. Lipomatosis is a term used to describe a poorly circumscribed overgrowth of mature adipose tissue that grows in an infiltrating pattern.

Hibernoma

Hibernomas are rare, slow-growing benign neoplasms which arise within the thorax and resemble the glandular brown fat found in hibernating animals [14].

Lipoblastoma and Lipoblastomatosis

Lipoblastoma and lipoblastomatosis are variants of lipoma that occur almost exclusively in infancy and early childhood [15]. They differ from lipomas by their cellular immaturity and their extensive myxoid stroma, resembling myxoid liposarcomas.

Liposarcoma

There are five histologic subtypes of liposarcoma: well-differentiated, dedifferentiated, myxoid, round cell, and pleomorphic [11]. Well-differentiated liposarcomas (WDLS) are non-metastasizing, low-grade lipomatous tumors with a propensity for local recurrence [16]. WDLS can be classified as lipoma-like, sclerosing, inflammatory, and spindle cell. They can be found in the extremity, retroperitoneal, and truncal locations [17]. Lipoma-like WDLS may also be termed atypical lipomatous tumor (ALT), a term introduced in 1974 [18,19]. ALTs share similar histologic features with lipoma-like WDLS and typically occur in subfascial locations of the extremity and trunk (this term is not used for retroperitoneal lipomatous tumors). ALT/WDLS are composed of mature adipocytes with significant variation in cell size and focal nuclear atypia [10]. They typically show scattered atypical stromal cells with hyperchromatic nuclei embedded within mature adipose tissue. This morphologic appearance is in keeping with a lipoma-like WDLS. Rare multivacuolated lipoblasts are also commonly found, but they are not a requirement for histologic diagnosis. Fibrous septa are often present, dividing the tumor into irregular lobules and being infiltrated by atypical stromal cells. If this pattern predominates, the diagnosis is consistent with a sclerosing variant of WDLS [20] (Fig. 1).

Dedifferentiated liposarcoma is defined as a WDLS that shows abrupt transition to a non-lipogenic sarcoma at least several millimeters in diameter. The process of dedifferentiation is often seen de novo in the primary tumor and less commonly occurs in the subsequent local recurrences. Morphologically, these regions may have heterogeneous appearances, ranging from low to high grade components, resembling myxofibrosarcoma and malignant fibrous histiocytoma (MFH) (Fig. 2). Grossly, dedifferentiated liposarcoma consists of large multinodular yellow masses (WDLS components) containing discrete solid, often fleshy, tan-gray non-lipomatous (dedifferentiated) areas.

Myxoid/round cell liposarcoma accounts for approximately 40% of liposarcomas. The tumor consists of uniform round primitive mesenchymal cells and a variable number of small signet-ring lipoblasts within a prominent myxoid stroma and a characteristic branching vascular pattern. High histologic grade, often defined as having greater than 5% round cell component and termed ''round cell''

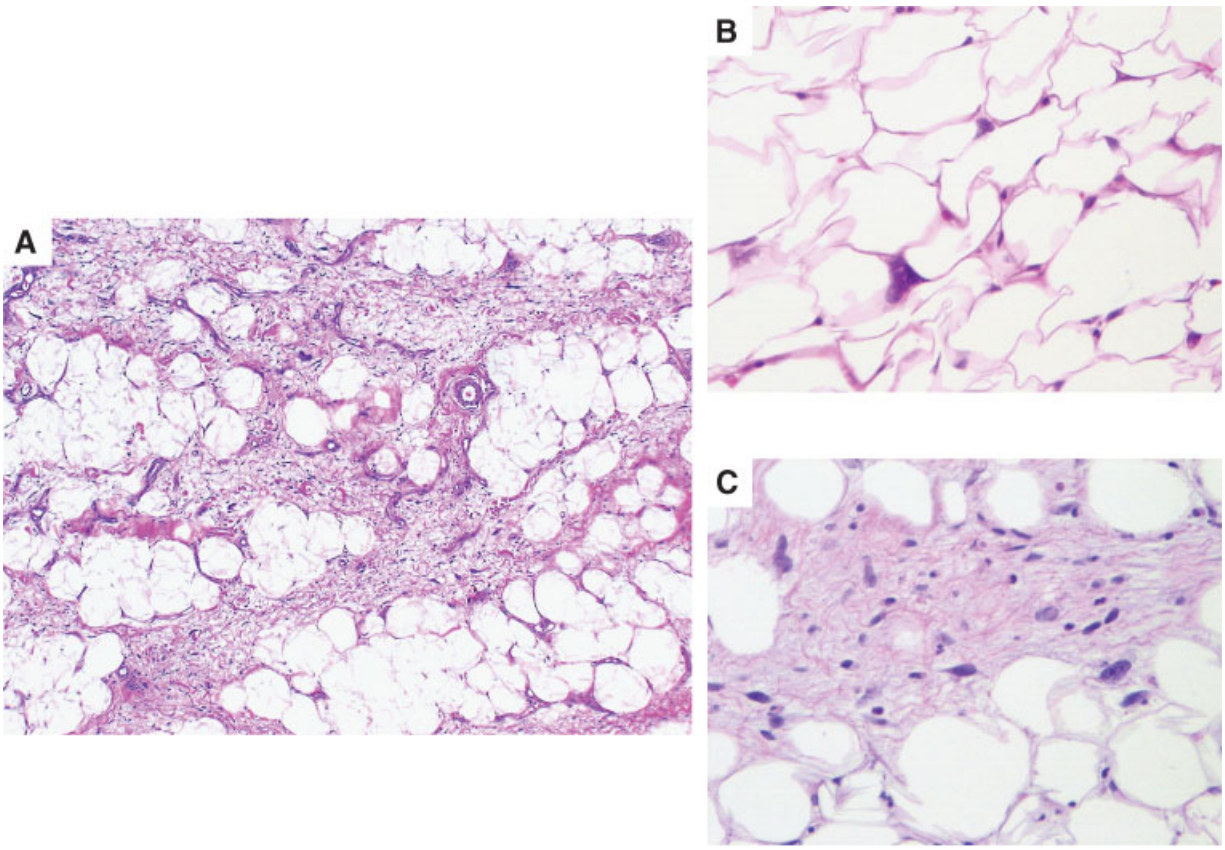

Fig. 1. Well-differentiated liposarcoma (WDLS; **A**). Lipoma-like WDLS may also be termed atypical lipomatous tumor (ALT; **B**). ALT/WDLS are composed of mature adipocytes with significant variation in cell size and focal nuclear atypia. They typically show scattered atypical stromal cells with hyperchromatic nuclei embedded within mature adipose tissue. Fibrous septa are often present, dividing the tumor into irregular lobules and being infiltrated by atypical stromal cells. If this pattern predominates, the diagnosis is consistent with a sclerosing variant of WDLS (**C**).

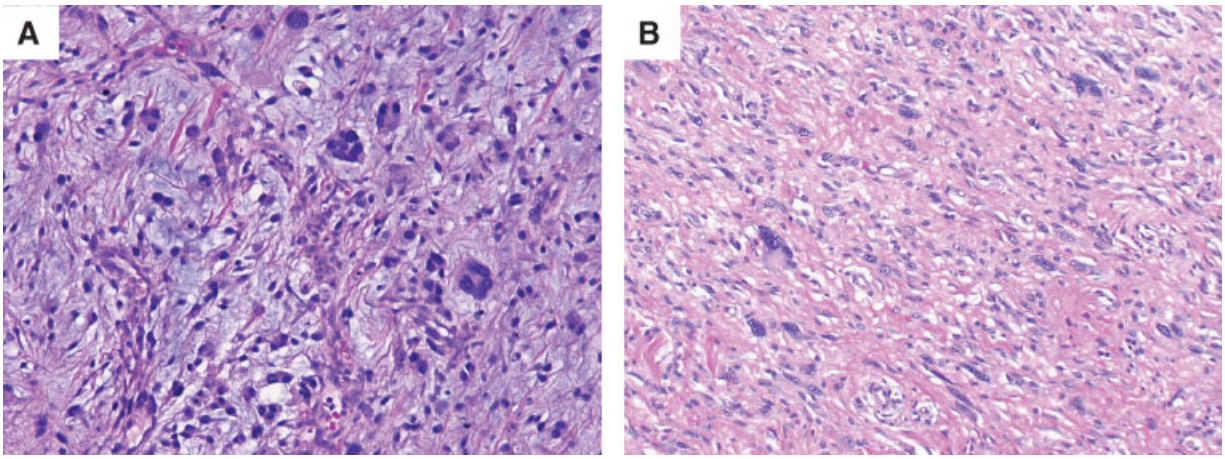

Fig. 2. Dedifferentiated liposarcoma is defined as a WDLS that shows abrupt transition to a non-lipogenic sarcoma at least several millimeters in diameter. Morphologically, these regions may have heterogeneous appearances, ranging from low to high grade components, resembling myxofibrosarcoma (**A**) and malignant fibrous histiocytoma (**B**).

liposarcoma, is a predictor of worse outcome in localized myxoid/round cell liposarcoma (Fig. 3).

Pleomorphic liposarcoma accounts for fewer than 5% of all liposarcomas and is a high-grade, highly malignant sarcoma seen in the older population. It contains a variable number of pleomorphic lipoblasts. Mitotic activity is high, and hemorrhage or necrosis is common [21] (Fig. 4).

CLINICAL FEATURES

Benign lipomas

Most lipomas are solitary, soft, well-circumscribed, superficial, painless, and slow-growing lesions; however, 2% to 3% of patients have multiple lesions that have a familial pattern.

While they rarely grow larger than 2 cm in size, angiolipomas often are painful, especially during their initial growth period.

Liposarcoma

In a study of 910 patients with liposarcoma at a single institution, there were 330 women and 471 men with a median age of 56 years (Table I). The histologic subtype was well-differentiated (46%), dedifferentiated (18%), myxoid (18%), round cell (10%), and pleomorphic (8%). With regard to presentation status, 34% had undergone a previous biopsy, 41% had not had prior surgical treatment, and 25% presented with a prior excision. Nearly half of the LS tumors were located in the lower extremity. Retroperitoneal LS was seen in 34% of patients; half of these patients required resection of at least one contiguous organ. Most patients (91%) had tumors deep to the fascia. The median tumor burden was 15 cm. Margins were evaluated both grossly and microscopically in six dimensions (superior, inferior, medial, lateral, anterior, and posterior). Two-thirds of patients had negative margins, and 7% had grossly positive margins.

The pattern of growth of liposarcomas is by direct local extension infiltrating adjacent tissues and structures along tissue planes; however, liposarcomas rarely violate major fascial planes or bones. Lymphatic spread to nodes is rare [22].

Histologic Subtypes

ALT/WD liposarcoma can be subdivided morphologically into four subtypes: adipocytic (lipoma-like), sclerosing, inflammatory, and

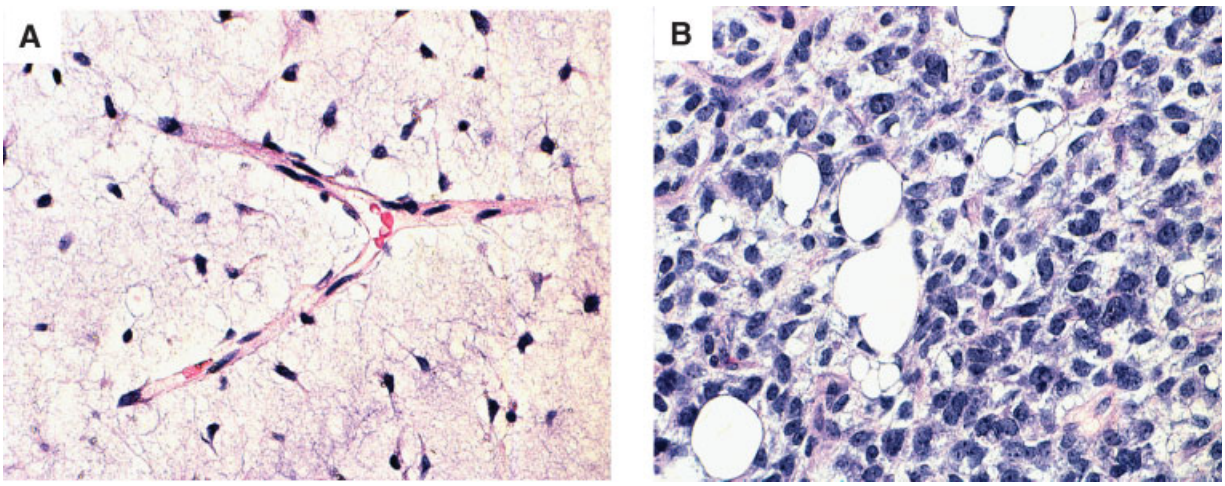

Fig. 3. Myxoid/round cell liposarcoma consists of uniform round primitive mesenchymal cells and a variable number of small signet-ring lipoblasts within a prominent myxoid stroma and a characteristic branching vascular pattern. Myxoid is defined as $<5\%$ round cell component (**A**) whereas round cell is defined as having $\geq 5\%$ round cell component (**B**).

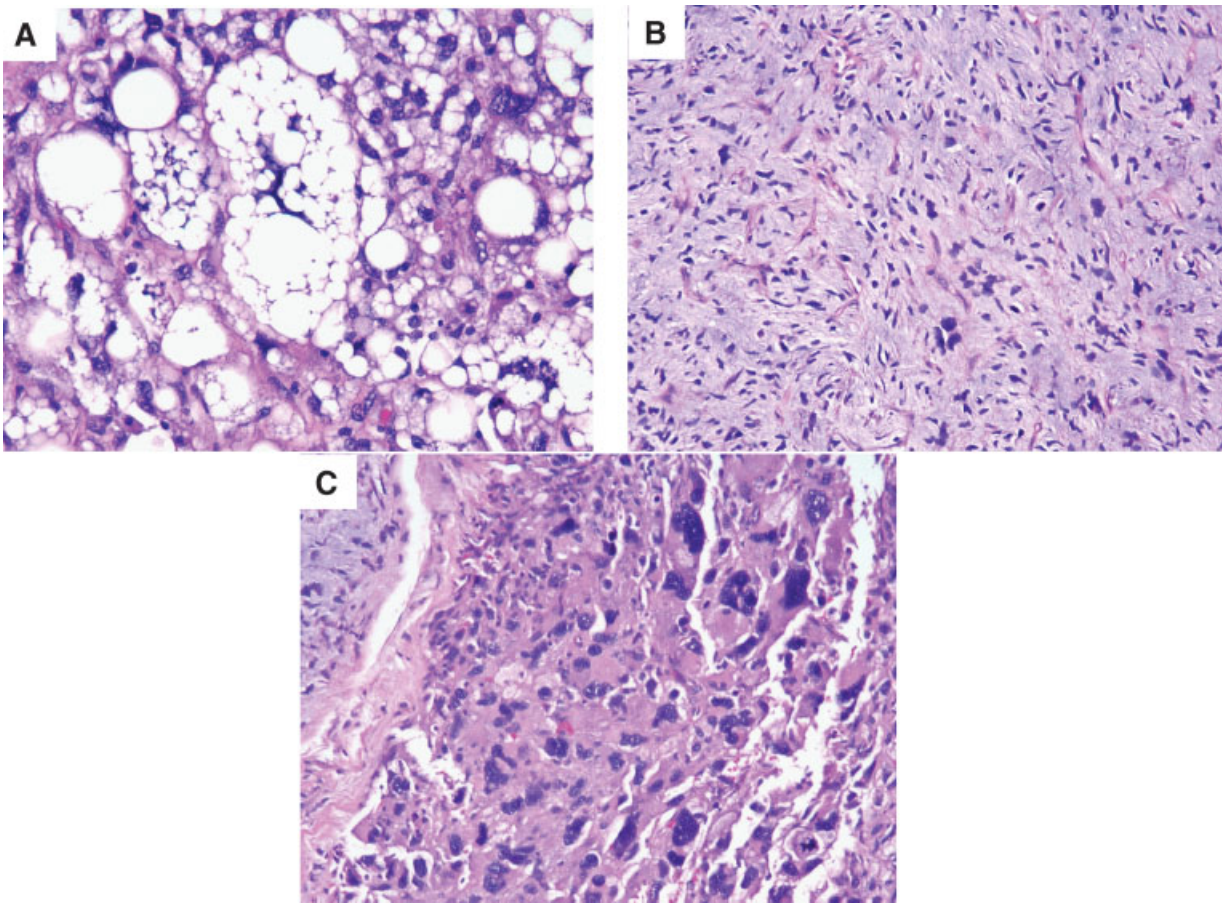

Fig. 4. Pleomorphic liposarcoma contains a variable number of pleomorphic lipoblasts (**A**). Mitotic activity is high, and hemorrhage or necrosis is common. They can have a myxofibrosarcoma-like (**B**) or MFH-like component (**C**).

spindle cell. The average age at presentation ranges between 50 and 60 years with a male predominance. In one study [10], 90% were found on the extremity with a mean size of 16 cm. Ninety percent were deep to the superficial fascia. After a median follow-up time of 47 months, local recurrence-free survival (LRFS) was 100% and 78% at 5 and 10 years, respectively. Patients who recurred locally all had a significant component of sclerosing morphology, positive margin, and recurred after 5 years [10]. The 10-year LRFS for margin-positive sclerosing WDLS was 17%, which emphasized that in this patient group with positive margins and sclerosing WDLS, the treating physician should consider function-preserving re-excision for negative margins when possible or adjuvant external beam radiotherapy. However, patients without a significant sclerosing component even in the presence of positive margins are best managed by surgery alone. Dedifferentiation was a rare event in WDLS of the extremity and trunk (3% of patients) and typically occurred in female patients with sclerosing WDLS extremity lesions. In contrast, WDLS in the retroperitoneum and mediastinum recur repeatedly and eventually result in patient death as a result of local effects such as adjacent organ compression, or dedifferentiation with subsequent increased risk of distant metastasis (7–30%) [23]. Retroperitoneal dedifferentiated liposarcoma has a lower metastatic rate compared to other high grade soft tissue sarcomas, which is strongly related to de novo dedifferentiated histology. The latter component typically predominates and often shows a myxofibrosarcoma-like growth pattern [23]. In a series of 177 patients with primary retroperitoneal liposarcoma, the WD histology was associated with a 5-year disease-specific survival and local recurrence rates of 83% and 46%, respectively [9].

Dedifferentiation in retroperitoneal liposarcoma occurs de novo in 47% of patients over the age of 63 and in 32% of patients less than 63 years of age. The incidence of dedifferentiation at first recurrence of what was initially retroperitoneal WDLS is about 20% and at second recurrence is as high as 40%. Radiologic imaging typically shows coexistence of both fatty, or well-differentiated components, and discontiguous non-fatty, solid components. In a study of primary retroperitoneal liposarcoma, 65 of 177 patients had tumors with dedifferentiated histology, which was associated with a 5-year DSS of 20% and a LRFS and distant recurrence-free survival (DRFS) at 3 years of 17% and 70%, respectively [9].

Pure myxoid liposarcomas (no round cell areas) are considered low-grade and are associated with a 90% 5-year survival. In contrast, those lesions containing a greater than 5% round cell component are considered high grade and are associated with a 5-year survival of 50% [7]. In contrast to other liposarcoma types, myxoid/round cell liposarcomas tend to metastasize to unusual soft tissue and bone locations, with multifocal synchronous or metachronous spread to fat pad areas in the retroperitoneum and axilla occurring even without pulmonary metastasis [7]. Round cell liposarcomas are generally responsive to chemotherapy with ifosfamide and ET-743.

The majority of pleomorphic liposarcomas arises in elderly patients older than 50 years of age and occurs in the deep-seated soft tissue of

TABLE I. Clinicopathologic and Treatment Characteristics in 801 Patients With Primary Liposarcoma of the Extremity, Trunk, or Retroperitoneum [13] (Used With Permission)

Patient characteristic	N	% of total
Age, years median (range)	56 (16–95)	
Gender		
Female	330	41.2
Male	471	58.9
Histologic variant		
Well-differentiated	369	46.1
Dedifferentiated	143	17.9
Myxoid	144	18.0
Round cell	81	10.0
Pleomorphic	64	8.0
Presentation status		
Biopsy	274	34.2
No treatment	331	41.3
Prior excision	196	24.5
Primary site		
Lower extremity	389	48.6
Upper extremity	63	7.9
Trunk	85	10.6
Retroperitoneum		
With contiguous organ resection	129	16.1
Without contiguous organ resection	139	17.4
Tumor depth		
Superficial	73	9.1
Deep	728	90.9
Tumor burden, cm median (range)	15 (1–139)	
Margins		
Negative margins	533	66.5
Positive micro margins	211	26.3
Positive gross margins	57	7.1

the extremities (lower more frequently than upper limbs). Clinically, they metastasize early to lung in 75% of patients [24].

MOLECULAR GENETICS

Most subcutaneous, solitary lipomas show reproducible cytogenetic aberrations: translocations involving 12q13-15, rearrangements of 13q, or rearrangements involving 6p21-33 [25]. Spindle cell lipomas bear chromosomal aberrations of 13q and 16q [26].

Karyotyping of liposarcomas demonstrates the presence of a supernumerary ring and long marker chromosomes composed of an amplified chromosomal region 12q13-15 in both ALT and WDLS [27]; the World Health Organization classification of soft tissue groups these lesions into one category [11]. FISH combined with Southern blotting showed that MDM2, CDK4, and HMGIC were consistently amplified; all of these genes are located in the 12q14-15 region of the ring and giant marker chromosomes. Dedifferentiated liposarcoma is in the same biological group as WDLS and is also characterized by ring or giant marker chromosomes on cytogenetic analysis and by amplification of the 12q13-21 region on FISH analysis [28].

Myxoid/round cell liposarcoma typically has a t(12;16)(q13-14;p11) translocation, which is present in more than 90% of cases. The translocation leads to the fusion of the *CHOP* and *TLS* genes at 12q13 and 16p11, respectively, and the generation of the *TLS-CHOP* hybrid protein. The presence of the *TLS-CHOP* gene rearrangement is highly sensitive and specific for the myxoid/round cell subtype despite their strikingly different morphologic characteristics. This fusion protein is absent in other morphologic mimics, such as retroperitoneal WDLS with extensive myxoid changes and myxofibrosarcomas [29].

Pleomorphic liposarcomas have nonspecific genetic alterations and complex unbalanced karyotypes, representing numerous genetic losses and gains.

CLINICAL MANAGEMENT

All patients require a thorough history and physical examination, with a focus on defining the anatomic involvement of major nerves and vessels of extremity lesions and surrounding visceral structures in retroperitoneal tumors. For a subcutaneous, mobile, soft lesion that is suggestive of lipoma, local excision of lipoma is generally curative, with a local recurrence after simple excision in 1–2% of cases.

Extremity Liposarcoma

Patients with extremity liposarcoma may present with a deep-seated, painless, enlarging mass that can grow slowly over many years (ALT/WDLS) or rapidly (myxoid/round cell, pleomorphic) to attain a very large size. The majority present at a size larger than 5 cm. Size becomes an important feature, and definitive diagnosis is dependent on biopsy results and histologic confirmation.

The incidence of distant metastasis is a function of histologic subtype which defines grade and tumor size. For patients who develop distant metastatic disease from extremity sarcomas, the first site is the lung in 70% of patients, which is the predominant cause of death from metastatic disease [30]. Pulmonary metastasectomy is associated with improved overall survival in patients with complete surgical resection and no evidence of disease elsewhere [31]. The unusual presentation of extrapulmonary metastasis, such as to fat pad regions, intraabdominal soft tissue, pelvic or spinal bony metastasis, may occur with an extremity myxoid/round cell liposarcoma [32].

Retroperitoneal Liposarcoma

Approximately 55% of retroperitoneal liposarcomas are well-differentiated with tumors in roughly 40% of patients showing dedifferentiated features at primary presentation. Most patients present with an asymptomatic abdominal mass. Occasionally, pain is present, and less common symptoms include gastrointestinal bleeding, incomplete obstruction, and neurologic symptoms related to retroperitoneal invasion or pressure on neurovascular structures [33]. Weight loss is uncommon. On physical examination, a large abdominal mass is often present. Important issues of differential diagnosis are germ cell tumor, lymphoma, or primary adrenal tumor. The most common site for metastases is the lung, with the liver a secondary site.

Magnetic Resonance Imaging and Computed Tomography

Radiographic imaging studies for liposarcoma vary, depending on the site. They involve evaluation of both the primary lesion and the potential site of metastasis. Once the diagnosis and subtype/grade have been established, evaluation for sites of potential metastasis should be performed. Lymph node metastases occur in less than 3% of adult soft tissue sarcoma [22] and is exceedingly rare in liposarcoma.

For extremity lesions, if a lesion is greater than 3 cm and seems deep to the superficial fascia, imaging should be considered. Magnetic resonance imaging (MRI) is the imaging of choice for extremity and head and neck lesions due to its ability to attenuate bone artifact and discern the relationship of the tumor to fascial planes, vessels, bones, and nerves [34,35].

The lung is the principal site of metastasis for high-grade dedifferentiated, round cell and pleomorphic extremity liposarcomas [30], and these patients should have a baseline chest computed tomography (CT) scan at the time of diagnosis [36,37]. The round cell subtype also has a predilection for fat pad metastasis in the retroperitoneum and axilla as well as bone [32]. Patients with the round cell subtype should undergo an abdominal/pelvic CT scan in addition to chest CT scan for full staging prior to treatment. For

evaluation of metastasis for small, superficial low grade extremity liposarcoma, a chest radiograph will suffice.

Patients with retroperitoneal liposarcoma should undergo a chest, abdominal and pelvic CT scan prior to surgery which enables planning for resection of the primary lesion as well as serving as a baseline scan for lung or liver metastasis.

Biopsy

In an adult, any soft tissue extremity or truncal mass that is symptomatic or enlarging, larger than 3 cm, or new and persists beyond 4 weeks should be biopsied. Fine-needle aspiration biopsy may be of value in the documentation of recurrence but is not helpful for the diagnosis of the primary tumor as it typically only provides cells in the absence of tissue architecture. A core needle biopsy is the preferred first step and for extremity lesions this can usually be performed under local anesthetic guided by direct palpation. Heslin et al. [38] demonstrated that core needle biopsy provides accurate diagnostic information for diagnosis, malignancy and grade when read by an experienced pathologist. After examining 164 primary extremity soft tissue masses, 93% of core needle biopsies had adequate tissue to make a diagnosis. Of the adequate biopsy specimens, 95% correlated with the final resection diagnosis for malignancy, 88% for histologic grade, and 75% for histologic subtype [38]. False negative and false positive rates were 5% and 0% for malignancy. Advantages of core needle biopsy include minimal morbidity, low cost, and ease of performance. Adequate core needle biopsy obviates the need for open biopsy and can be used for treatment planning. Should tissue be inadequate, an open linearly placed incisional biopsy along the longitudinal axis of the limb is then indicated.

If an incisional biopsy is planned, limb masses are best sampled through a longitudinal incision centered over the mass in its most superficial location; a longitudinal incision is made so that the entire biopsy tract can be excised at the time of definitive resection and closed primarily. No tissue flap should be raised, and meticulous hemostasis should be ensured to prevent cellular dissemination by hematoma. Excisional biopsy is recommended for cutaneous or subcutaneous tumors, smaller than 3 cm, in which a necessary wide re-excision is usually straightforward.

For retroperitoneal liposarcomas, the diagnosis is usually suspected on finding a soft tissue mass on abdominal CT. Fine-needle aspiration biopsy or CT-guided core biopsy has a limited role in the routine diagnostic evaluation of these patients. In most patients, exploratory laparotomy should be performed and the diagnosis made at operation, unless the patient's tumor is clearly unresectable or the patient will be undergoing preoperative investigational treatment. Retroperitoneal tumors may require contiguous organ resection (e.g., kidney, colon, small bowel, pancreas, spleen, bladder, uterus). In one study, half of the operations required at least one contiguous organ resection [13].

Staging

The present 2002 staging system focuses on histologic grade and size of the primary tumor as well as the presence or absence of lymph node or distant metastasis to characterize four stages.[39,40] This staging system takes into account the relative infrequency of high-grade, large, superficial sarcomas and simplifies the category of stage III tumors to represent only large, deep, high-grade sarcomas (Table II). Stage III can be further divided into tumors larger than 5–10 cm and those larger than 10 cm. Histologic grade is a major prognostic determinant and is based on degree of mitosis, cellularity,

TABLE II. 2002 American Joint Committee on Cancer (AJCC) Staging System for Soft Tissue Sarcoma [84] (Used With Permission)

Primary tumor (T)						
TX	Primary tumor cannot be assessed					
T0	No evidence of primary tumor					
T1	Tumor 5 cm or less in greatest dimension					
T1a	Superficial tumor[a]					
T1b	Deep tumor[a]					
T2	Tumor more than 5 cm in greatest dimension					
T2a	Superficial tumor[a]					
T2b	Deep tumor[a]					
Regional lymph nodes (N)						
NX	Regional lymph nodes cannot be assessed					
N0	No regional lymph node metastasis					
N1[b]	Regional lymph node metastasis					
Distant metastases (M)						
MX	Distant metastasis cannot be assessed					
M0	No distant metastasis					
M1	Distant metastases					
Histologic grade						
GX	Grade cannot be assessed					
G1	Well differentiated					
G2	Moderately differentiated					
G3	Poorly differentiated					
G4	Poorly differentiated or undifferentiated (four-tiered systems only)					
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

[a]Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor is located either exclusively beneath the superficial fascia, superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumors.

[b]Presence of positive nodes (N1) is considered stage IV.

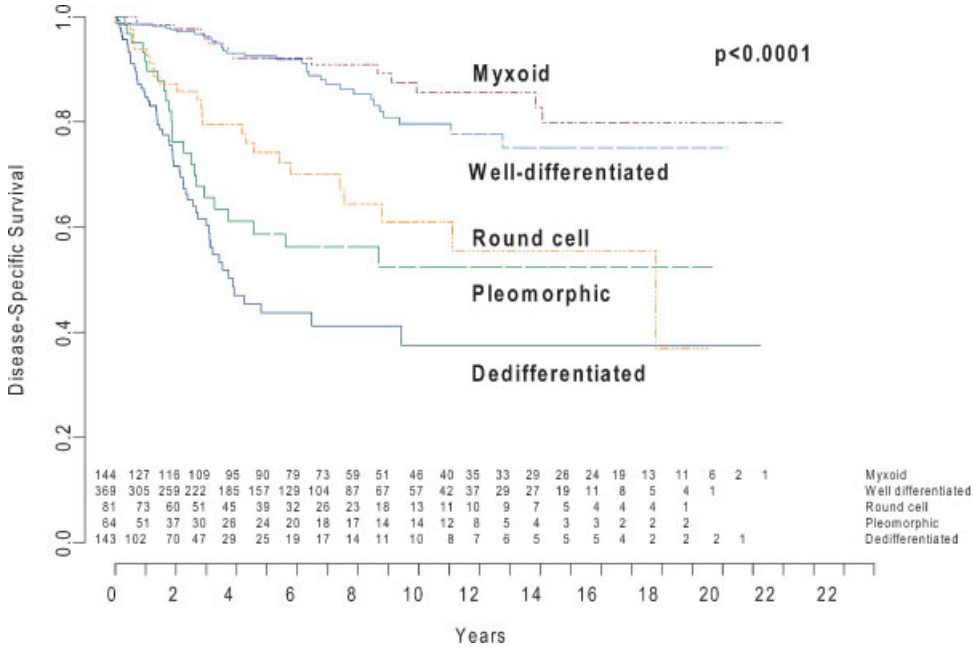

Fig. 5. Liposarcoma-specific survival by histologic subtype. Figures at bottom indicate number of patients at risk [13] (used with permission).

presence of necrosis, differentiation, and stromal content. Low-grade lesions are assumed to have a low (<15%) risk of subsequent metastasis, and high-grade lesions have a high (>50%) risk of subsequent metastasis. Size has been considered a less important determinant of biologic behavior, but large lesions can be associated with late recurrence. Very small, high-grade lesions less than 5 cm in maximal diameter have limited risk for metastatic disease if treated appropriately at the first encounter. Analysis of the primary extremity soft tissue sarcomas seen at Memorial Sloan-Kettering Hospital from July 1, 1982 to June 30, 2002 suggests that the probability of metastasis by stage is better discriminated in the new AJCC 2002 staging system [41]. Staging systems apply to risk of metastasis, disease-specific survival, or overall survival and are almost exclusively confined to extremity lesions. There is as yet no adequate staging system for retroperitoneal and visceral lesions.

Follow-up

Patients are observed in our STS program at approximately 6-month intervals for low grade liposarcoma (WDLS and myxoid) and at 4-month intervals for high grade lesions (dedifferentiated, round cell, and pleomorphic) during the first 3 years and 6-month intervals thereafter. Retroperitoneal and visceral liposarcomas are followed with a chest, abdomen, and pelvic CT scan. Extremity lesions are followed by local palpation of the primary site obtaining an MRI for symptoms, suspicious findings, or patients with a tumor location that is difficult to examine. High grade lesions are followed by chest CT and low grade lesions by plain film to screen for lung metastases.

PROGNOSTIC FACTORS

Histologic grade, reflected in the extent of differentiation, remains the most important prognostic factor regarding clinical course and prognosis. This has been shown in several multivariate studies [42] and is clearly stated in the World Health Organization classification [11]. The pathologic features that define grade include cellularity, histological type and subtype and/or differentiation, pleomorphism, necrosis, and number of mitoses. Low-grade myxoid and well-differentiated variants each have a 5-year survival of 90% [3–5,7]. Conversely, high grade variants, such as round cell (defined by >5% round cell component), pleomorphic, and dedifferentiated tumors, have 5-year survival rates of 60% [7], 30–50% [8], and 75% [6], respectively. DSS stratified by histologic subtype is demonstrated in Figure 5 [13]. The 5- and 12-year DSS on univariate analysis are also shown in Table III [13]. The 5-year DSS for low grade lesions, namely well-differentiated and myxoid tumors, were 93% and 92%,

TABLE III. Univariate Analysis of Histologic Variant in Disease-specific Survival [13] (Used With Permission)

Histologic variant	Total	No. of events	5-year DSS (95%CI)	*P*-value
Well-differentiated	157	19	0.93 (0.88–0.95)	<0.0001
Dedifferentiated	25	55	0.44 (0.33–0.54)	
Myxoid	90	9	0.92 (0.85–0.96)	
Round cell	39	18	0.74 (0.62–0.83)	
Pleomorphic	24	21	0.59 (0.44–0.71)	
Histologic variant	Total	No. of events	12-year DSS (95% CI)	*P*-value
Well-differentiated	37	15	0.78 (0.69–0.84)	<0.0001
Dedifferentiated	7	2	0.38 (0.25–0.50)	
Myxoid	35	4	0.86 (0.76–0.92)	
Round cell	10	6	0.55 (0.38–0.70)	
Pleomorphic	8	2	0.53 (0.37–0.66)	

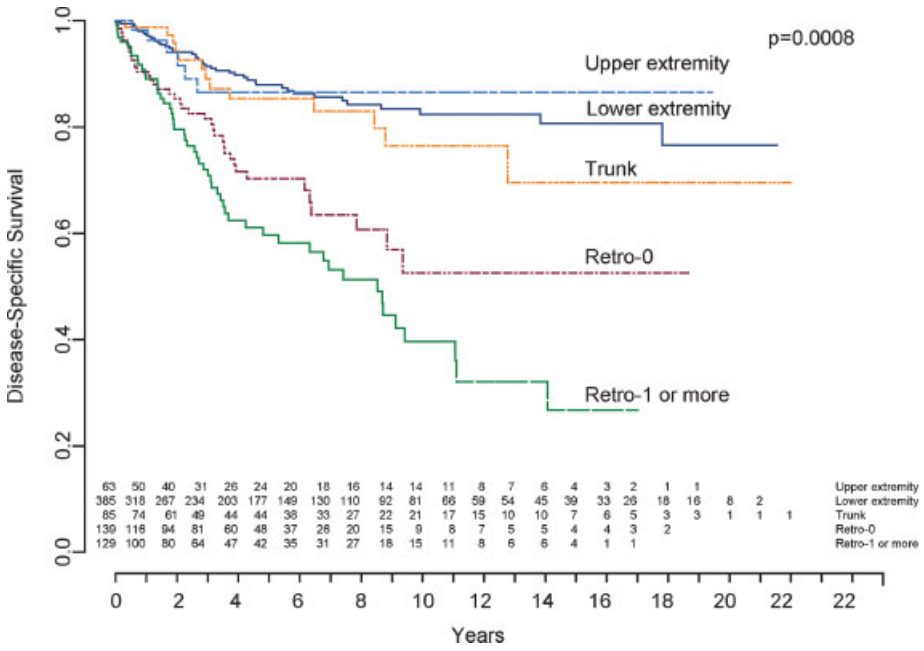

Fig. 6. Liposarcoma-specific survival by primary location (extremity, trunk, retroperitoneum). Figures at bottom indicate number of patients at risk [13] (used with permission).

respectively. For high grade tumors, the 5-year DSS rates were: dedifferentiated 44%; round cell 74%; and pleomorphic 59%.

The primary site of disease is another important factor in determination of outcome for patients with liposarcoma. For example, patients with large low-grade liposarcomas of the extremity show lower relapse rates than patients with low-grade liposarcomas of the retroperitoneum; the latter are more difficult to control locally. DSS stratified by primary site is illustrated in Figure 6 [13]. Extremity lesions (upper extremity, 87%; lower extremity, 82%) enjoyed a higher 12-year DSS compared with truncal LS (77%). In a recent study of 126 patients with primary extremity LS, a multivariate analysis revealed that size, histologic subtype, and treatment with ifosfamide-based chemotherapy were independently associated with DSS [12]. Conversely, retroperitoneal tumors had a significantly decreased 12-year DSS, with patients requiring resection of one or more contiguous organs having the lowest 12-year DSS at 32%. Those patients with retroperitoneal tumors which did not require contiguous organ resection had a 12-year DSS of 53% ($P = 0.0008$).

Another important factor is margin status. DSS stratified by margin status is depicted in Figure 7 [13]. While patients with microscopically negative and positive margins had 12-year DSS rates of 74% and 68%, respectively, those with grossly positive margins had a significantly decreased 12-year DSS of 25 ($P < 0.0001$).

A recent multivariate analysis illustrated prognostic factors of importance to DSS for 801 patients with primary liposarcoma, including both extremity and retroperitoneal disease, who underwent surgical resection at Memorial Sloan-Kettering Cancer Center (MSKCC) [13] (Table IV). The independent predictors of DSS were histologic variant/tumor grade ($P < 0.0001$), age ($P = 0.008$), presentation status ($P = 0.004$), primary site ($P = 0.0008$), tumor burden ($P = 0.0001$), and gross margin status ($P < 0.0001$). The median follow-up was 45 months (range, 1–264) for all patients and 51 months for survivors. The 5- and 12-year DSS probabilities were 83% and 72%, respectively (Fig. 8) [13].

Nomogram

Nomograms are being increasingly more readily accepted as models in which identified prognostic factors can be combined and used to predict risk of DSS [43–46]. Our group published a postoperative nomogram for DSS for all primary [43] and locally recurrent extremity sarcomas [44], which we found useful for patient counseling, follow-up scheduling, and clinical trial eligibility determination. These statistically based tools not only use the factors included in a clinical staging system but also incorporate additional factors suspected to have an impact on outcome. The sarcoma nomogram for all primary sarcomas accounted for LS subtype only as it is reflected in grade, high versus low [43]. Subsequently, we developed a subtype-specific nomogram for patients with LS that integrates various prognostic factors and predicts disease-specific death so as to provide an individualized prognosis for each patient [13]. The variables considered for the basis of the nomogram were age at diagnosis, gender, histologic variant (well-differentiated, dedifferentiated, myxoid, round cell, pleomorphic), presentation status (biopsy, no prior treatment, prior excision), primary site (lower extremity, upper extremity, trunk, retroperitoneum with or without contiguous organ resection), primary depth (superficial, deep) and primary tumor burden, and margins (negative, microscopically positive, grossly positive). A nomogram based on the Cox model is illustrated in Figure 9 [13]. Each variable in the Cox model was associated with LS-specific survival ($P < 0.05$) on univariate analysis. The nomogram predicts the probability that the patient will die of LS within 5 and 12 years of his initial surgery, assuming he or she does not die of another cause first. The higher concordance index for a LS nomogram (0.827) demonstrates the improvement in prediction of DSS that is achieved when a model employing histologic subtype as opposed to grade (concordance index 0.776) is utilized [43].

For example, if we have a 50-year-old gentleman with a 10 cm, deep, dedifferentiated liposarcoma of the upper extremity, in the

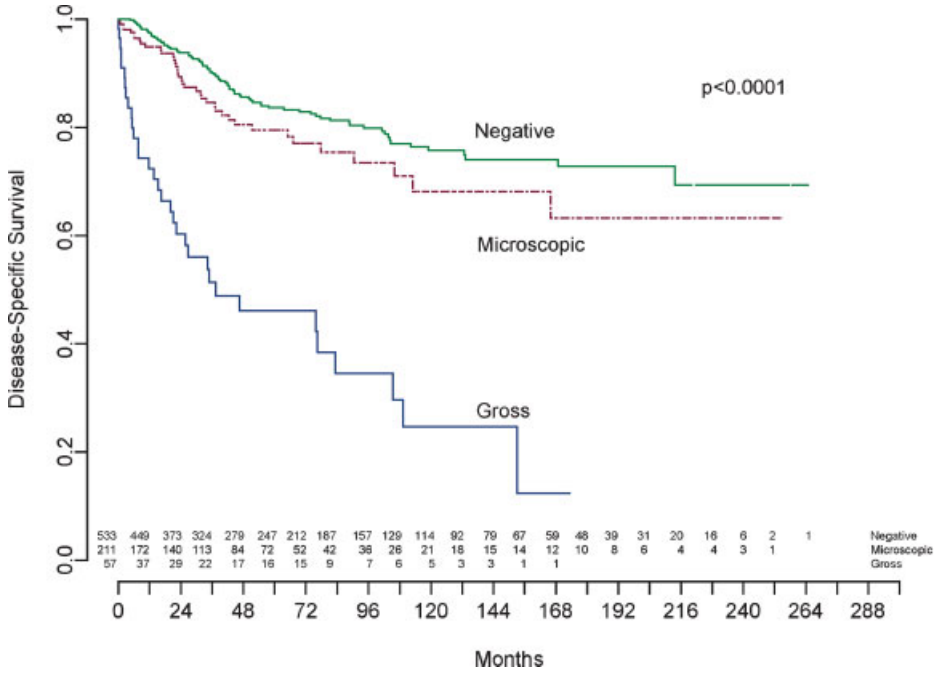

Fig. 7. Liposarcoma-specific survival by margin of resection. Figures at bottom indicate number of patients at risk [13] (used with permission).

LS-specific nomogram, he would have 170 points. His 12-year sarcoma-specific survival rate would be 78%. In the previously established generic nomogram, in which grade is used instead of histologic subtype, his predicted 12-year sarcoma-specific survival is substantially different at 46%. If we change our patient's histologic subtype to pleomorphic, which is also considered high grade, but keep all of the same clinicopathologic features, his 12-year DSS is 38%, which is lower than the 46% predicted DSS in the generic nomogram. This illustrates how the liposarcoma-specific nomogram discriminates better than the previously established nomogram. In the first example, the GPS nomogram results in a 40% inaccuracy in predictive value if a dedifferentiated subtype, it underestimates 12-year DSS by 30%, and if a pleomorphic subtype, the old nomogram overestimates 12-year DSS by 10%.

A LS nomogram model that utilizes histologic subtype as opposed to grade improves prediction of DSS. In the future, improved understanding of molecular markers may allow their inclusion in these nomograms to further enhance their predictive power. These nomograms can be readily transferred to handheld personal organizers for instant calculation of disease-specific survival probability.

TABLE IV. Multivariate Analysis of Clinicopathologic Variables for Disease-Specific Survival in 801 Patients With Primary Liposarcoma of the Extremity, Trunk, or Retroperitoneum [13] (Used With Permission)

Factor	Chi-square	d.f.	*P*-value
Age	6.97	1	0.0083
Gender	2.66	1	0.1028
Presentation status	11.09	2	0.0039
Primary site	19.01	4	0.0008
Histologic variant	96.67	5	<0.0001
Tumor depth	0.26	1	0.6126
Tumor burden	19.43	2	0.0001
Margin status	28.93	2	<0.0001

Recurrence

An important factor in outcome is the type of recurrence [47]. Moreover, for early recurrence, grade appears to be the predominant characteristic, whereas for late recurrence, size is more important [48]. Patients with a >5 cm local recurrence within 16 months of resection had a 4-year disease specific survival of 18%, compared to 81% for patients with a local recurrence which was ≤5 cm after 16 months [47].

Factors that increased distant recurrence rates in an analysis of prospective data collected from 1,041 patients with localized soft tissue sarcoma of the extremity were tumor size larger than 5 cm, high histologic grade, deep location, and recurrent disease at the time of presentation [42]. Histologic subtype of liposarcoma was favorable for decreased distant recurrence rate when compared with other histologic types [42]. The important prognostic factors for local recurrence were age greater than 50, recurrent disease at the time of presentation, microscopically positive surgical margins, and the histologic subtypes fibrosarcoma and malignant peripheral nerve tumor.

In our recent study of 801 patients with liposarcomas, median time to distant recurrence was 41 months. Independent predictors of distant recurrence on multivariate analysis were presentation status ($P < 0.0001$), histologic variant ($P < 0.0001$), and tumor burden ($P = 0.0005$). In addition, median time to local recurrence was 35 months. The independent predictors of local recurrence on multivariate analysis were age ($P = 0.0225$), gender ($P = 0.0045$) primary site ($P = 0.0001$), histologic variant ($P = 0.0009$), and tumor burden ($P = 0.0001$) (unpublished data).

Although we typically discuss survival in terms of the 5-year mark, 5-year survival does not guarantee cure. An analysis of patients disease free 5 years after the diagnosis and treatment of extremity lesions showed that 9% would go on to have a further recurrence in the next 5 years [49]. Unfortunately, survival has not measurably improved with time when corrected for stage [50]. A review of 1261 completely resected extremity soft tissue sarcomas by 5-year increments for 1982 to 2001 suggests that disease-specific actuarial 5-year survival is 79%

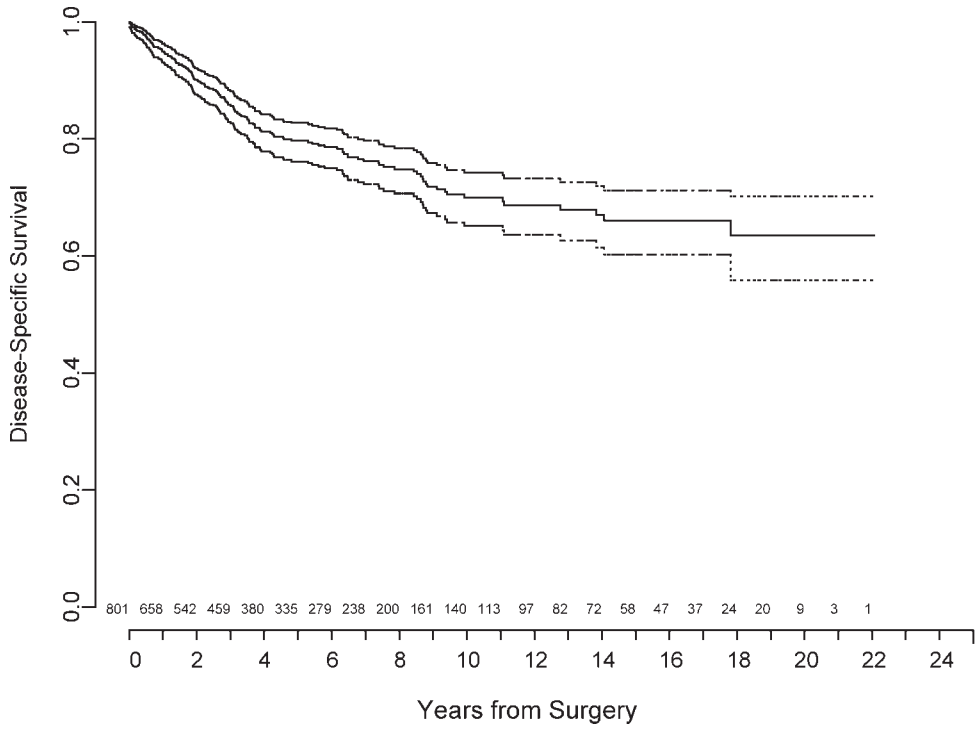

Fig. 8. Liposarcoma-specific survival for 801 patients treated at Memorial Sloan-Kettering Cancer Center. Dotted-line bands represent 95% CI. Figures at bottom indicate number of patients at risk [13] (used with permission).

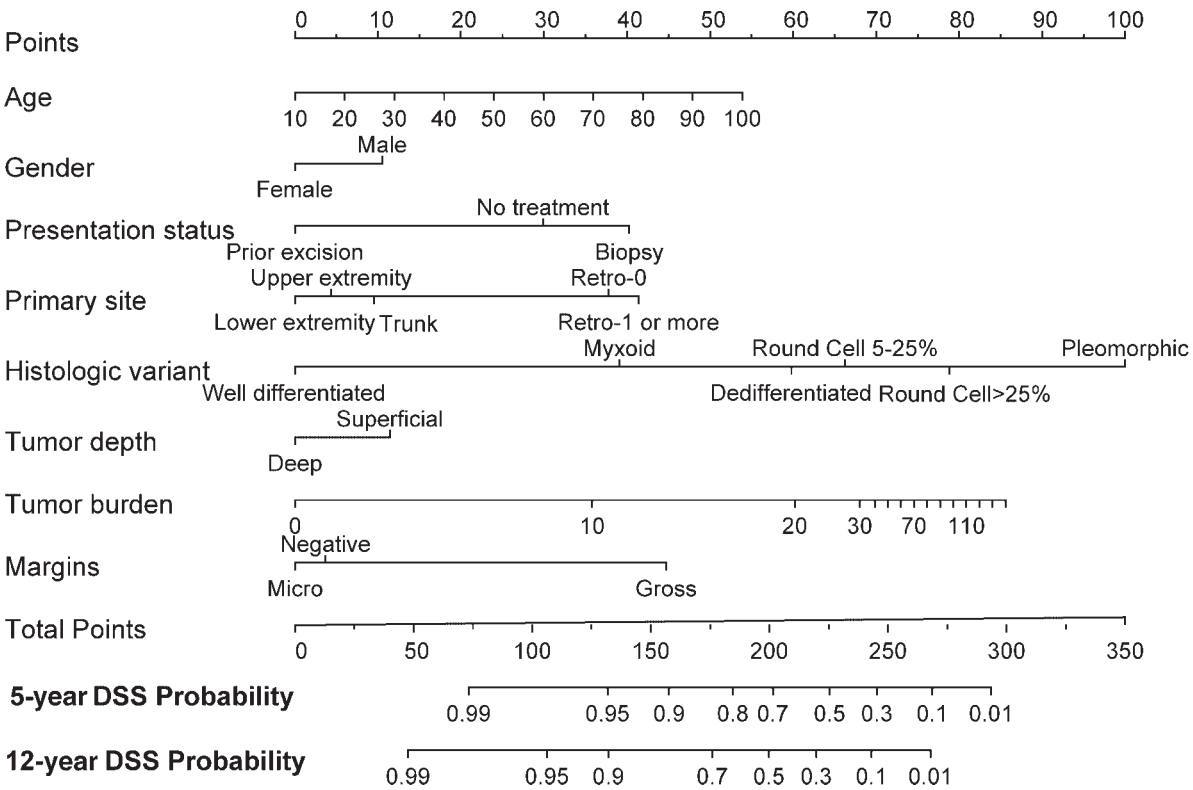

Fig. 9. Nomogram for predicting 5- and 12-year liposarcoma-specific survival probabilities [13] (used with permission).

and remains unchanged over 20 years. For high-risk patients (i.e., those with high-grade, larger than 10-cm, deep tumors), DSS remains around 50%. It is essential to emphasize long-term follow-up for all patients with liposarcoma.

SURGICAL APPROACH

Extremity and Superficial Trunk Sarcoma

Surgical excision remains the dominant modality of curative therapy. Whenever possible, limb-sparing resections preserving function [51] should be performed with a 1–2 cm margin of normal tissue including a fascial plane, which is important because of the propensity for local spread which does not traverse fascial planes. For sarcomas that closely approximate bone, the periosteum, if removed intact, can serve as a sufficient intact fascial margin. Deliberate sacrifice of major neurovascular structures can be avoided, provided meticulous attention is paid to dissection [51,52]. With complete resection, less radical procedures do not adversely affect local recurrence or outcome. Experience over the last 25 years at MSKCC indicates that the 50% amputation rate in the late 1960s has now been replaced by a limb-salvage rate of 95% [51]. Amputation should be reserved for tumors not able to be resected by any other means, without evidence of metastatic disease, and the propensity for good long-term functional rehabilitation. Often these are patients with large, low-grade tumors with marked cosmetic and functional deformity who can be rendered symptom-free by a major amputation.

Liposarcomas uncommonly involve the skin, so major skin resection should be limited. In situations of primary or recurrent tumors in which skin is involved, or which the tumor is so extensive that skin is involved, then consideration of free flap or rotational flap closure becomes important, particularly in those patients who are candidates for subsequent adjuvant radiation therapy.

Retroperitoneal Liposarcoma

Primary surgical resection is the dominant therapeutic modality with the most important prognostic factors for survival being completeness of resection, and histologic subtype or grade. In a study from MSKCC [9] that analyzed 177 patients with primary retroperitoneal liposarcoma operated on for curative intent, 99 (56%) presented with well-differentiated (WD), 65 (37%) with dedifferentiated (DD), 9 (5%) with myxoid and 4 (2%) with round cell morphology. In this study a substantial number of patients that had been previously classified as MFH were found on re-examination to be dedifferentiated liposarcoma. No pleomorphic liposarcomas were found in this large series of retroperitoneal tumors. The tumor burden was determined by the sum of the maximum tumor diameters. The median tumor burden was 26 cm (5–139 cm). Median follow-up time for 92 (52%) surviving patients was 37 (0.5–192) months. Multivariate analysis showed that dedifferentiated liposarcoma subtype was associated with a sixfold increased risk of death compared to well-differentiated histology ($P < 0.0001$). In addition to histologic subtype, incomplete resection ($P < 0.0001$), contiguous organ resection (excluding nephrectomy) ($P = 0.05$) and age ($P = 0.03$) were important independent prognostic factors for survival in retroperitoneal liposarcoma. Retroperitoneal dedifferentiated liposarcoma was associated with an 83% local recurrence rate and 30% distant recurrence rate at 3 years.

Surgical treatment for retroperitoneal liposarcoma should consist of an aggressive approach to achieve a complete surgical resection. En bloc resection of adjacent organs should be performed if necessary to achieve a complete resection. However, kidney parenchymal sparing renal capsular resections can be performed without any measurable influence on DSS as long as complete resection is achieved. Despite an aggressive surgical approach, over 80% of patients with dedifferentiated histology will recur locally and 30% will metastasize to distant sites within 3 years of diagnosis. The high rates of local recurrence seen with liposarcoma may relate to the often multi-focal involvement of disease throughout the retroperitoneal space as well as the difficulty in distinguishing liposarcoma from adjacent normal fat. In the series from MSKCC cited above, 39 of the 99 patients who presented with well-differentiated liposarcoma developed at least one local recurrence at the time of last follow-up. Of these first time local recurrences that underwent resection, 83% remained well-differentiated and 17% recurred as high grade dedifferentiated liposarcoma. Of the patients with well-differentiated first local recurrences who then developed a second recurrence, 44% recurred as dedifferentiated liposarcoma and 56% remained well-differentiated. Thus, the fraction of well-differentiated tumors that progress and dedifferentiate seems to increase with each subsequent recurrence.

Preoperative bowel preparation is important due to the frequent technical difficulty of performing resection without encompassing the intestine. Evaluation of renal function, particularly the establishment of contralateral adequate renal function, is important to allow nephrectomy when appropriate. In retroperitoneal and visceral lesions, surgery remains the dominant method of therapy [5,9].

Jaques et al. [33] reported the experience at MSKCC from 1982 to 1987 in which half the patients presented with liposarcoma. Sixty-five percent of patients with primary sarcomas underwent a complete resection, whereas half the patients with recurrent retroperitoneal sarcomas underwent a complete resection. Despite complete resection, local recurrence developed in 50% of cases. The median time for recurrence was 15 and 42 months, respectively. Fifty-three percent of patients required adjacent organ resection, and 40% of patients required more than one adjacent organ resection.

Although resection of adjacent organs is common [33], proof that a more extensive resection of adjacent organs has impact on long-term survival seems very limited. Complete surgical resection is the primary factor in outcome. Once fully resected, the predominant factor in outcome is histologic subtype/grade.

The major issue in resection of retroperitoneal liposarcomas is adequate exposure, which usually can be provided by a large midline incision and occasionally may require a thoracoabdominal incision, rectus-dividing incision, or incision extending through the inguinal ligament into the thigh. Resectability rates vary widely but seem independent of histologic type, grade, or size [33].

Complete resection is usually possible in 60–70% of patients presenting with a second or subsequent recurrence. Although nephrectomy was performed in 46% of cases, the kidney itself was rarely involved. In the report by Jaques et al. [33], only 2 of 30 nephrectomy specimens showed true parenchymal invasion. Nevertheless, the involvement of the hilar renal vasculature makes nephrectomy often necessary.

The overriding principle of retroperitoneal liposarcoma resection is to include removal of adjacent organs if they are involved by tumor; however, one should not resect uninvolved organs if they are not the limiting factor for the tumor margin. Overall, the use of debulking for recurrent lesions is of limited value in terms of long-term survival. In retroperitoneal liposarcoma, there is some evidence that incomplete resection is associated with prolonged survival [53]. The basis for unresectability is usually the presence of peritoneal implants or extensive vascular involvement. Unless palliation can be achieved, operation should be reserved for those patients for whom complete resection is possible.

ADJUVANT THERAPY FOR RETROPERITONEAL LIPOSARCOMA

Retroperitoneal liposarcomas remain a major clinical challenge. Most of these tumors are large, making it difficult to obtain adequate

margins of resection. The presence of normal organs such as small bowel, large bowel, kidney, and liver make delivery of therapeutic doses of radiation therapy difficult or impossible.

There are data to suggest some improvement in local control with moderate doses of adjuvant external-beam irradiation for retroperitoneal sarcoma despite the low tolerance of surrounding normal organs. Tepper and co-workers [54] reviewed a cohort of 23 patients with retroperitoneal sarcomas treated with surgery and radiation therapy. Radiation dose appeared to influence tumor control, with patients receiving doses less than 5,000 cGy or greater than 6,000 cGy having local control rates of 30% and 83%, respectively.

There has been an interest in using intraoperative radiotherapy (IOR) to deliver higher doses of radiation to the tumor and lower doses to surrounding tissue [55]. Sindelar [56] reported on a prospective, randomized clinical trial using intraoperative radiation therapy at the NCI. Thirty-five patients with surgically resected sarcomas of the retroperitoneum were randomly assigned to receive IORT (20 Gy) followed by low-dose external beam radiotherapy (EBRT) (35–40 Gy) or EBRT alone (50–55 Gy). The study revealed a significant improvement in local control for those who received IORT with misonidazole but no impact on survival. Of note, patients who received IORT had a higher incidence of peripheral neuropathy but a lower incidence of radiation enteritis than those who received EBRT alone.

At MSKCC, resection was combined with EBRT and high dose-rate intraoperative brachytherapy (HDR-IOBRT) [57]. A phase I and II trial was reported in which 32 patients with primary and recurrent retroperitoneal sarcoma underwent resection and HDR-IOBRT (1,200–1,500 cGy). Twenty-five patients were treated with EBRT (4,500–5,040 cGy) after resection. Median follow-up was 33 months and overall 5-year local recurrence-free survival was 62%. Five-year actuarial rates of local control for primary and recurrent tumors were 74% and 54%, respectively. These rates were not significantly different when analyzed according to histologic grade. Treatment-related morbidity was observed in 34% of patients, with the most common complication being gastrointestinal obstruction and gastrointestinal fistula.

A report from the University of Alabama of dose-painting preoperative intensity modulated radiation therapy (IMRT) in 14 patients showed the feasibility of delivering 4,500 cGy to the tumor, and the area that was judged to be at risk for positive margin at the time of resection was separately boosted with IMRT to bring the total dose to 5,750 cGy. Eleven patients had complete resection with negative margins. With a median follow-up of 12 months there was no late toxicity related to radiation [58]. The benefit of preoperative IMRT with dose painting in addition to resection for improving local control and survival in patients with primary retroperitoneal sarcoma awaits evaluation in a prospective randomized trial.

ADJUVANT THERAPY FOR EXTREMITY LIPOSARCOMA

The goals of adjuvant radiotherapy in the management of liposarcoma are to enhance local control, preserve function, and achieve acceptable cosmesis by contributing to tissue preservation. Superficial lesions and smaller, contained lesions confined to individual muscles may be managed with surgery alone in expert hands [59,60]. The effectiveness of adjuvant radiation for improving local control has been shown not only through retrospective data but also through three prospective randomized trials that compared surgery alone to surgery and radiation [51,61,62]. This includes using either brachytherapy for high-grade lesions or external-beam radiation therapy for large (>5 cm) high- or low-grade lesions [61,62]. For subcutaneous or intramuscular high-grade sarcoma smaller than 5 cm, or any size low-grade sarcoma, surgery alone is adequate as long a negative margin of 1–2 cm of surrounding fat and muscle can be achieved; several studies have shown these patients have a local recurrence rate of 5–10% [60,63]. If the excision margin is close, particularly with extramuscular involvement, or if a local recurrence would result in the sacrifice of a major neurovascular bundle or amputation, adjuvant radiation therapy should be added to the surgical resection to reduce local failure [61].

Postoperative EBRT was the first and remains the most widely practiced local adjuvant approach, in part because it is rational and convenient to sterilize microscopic nests of residual disease without postponing surgery. Postoperative radiotherapy acquired a veneer of superiority compared to preoperative radiotherapy after the first report of the Canadian Sarcoma Group randomized trial, which demonstrated that preoperative radiotherapy doubles the risk of early acute wound complication, almost exclusively to lower limb lesions [64]. Several limitations of postoperative EBRT include less precise target volumes compared to those of preoperative EBRT. Postoperative volumes are larger and associated with higher doses, both of which impact negatively on late tissue morbidity. With 2-year follow-up in the same trial, postoperative radiotherapy was associated with significantly deteriorating later tissue effects, including increased tissue fibrosis and edema. Late bone fracture may be related in part to higher radiotherapy doses and larger volumes associated with postoperative delivery.

Given the established benefit of radiotherapy in improving local control, several clinical studies have now shifted toward reducing the morbidity of adjuvant radiotherapy or improving local control in subsets of patients where there is still room for improvement in local control, such as those with microscopic positive margins [65,66] or upper extremity lesions [67]. One alternative approach to improve the morbidity profile of adjuvant radiotherapy has been to use intensity modulated radiation therapy (IMRT). IMRT techniques can reduce the dose to the femur without compromising target coverage and at the same time has been shown to significantly reduce hot spots in the surrounding soft tissues and skin. IMRT has been shown to provide excellent local control in patients with high-risk primary extremity sarcoma with a favorable morbidity profile [68].

ADJUVANT AND NEO-ADJUVANT CHEMOTHERAPY FOR LIPOSARCOMA

Surgery remains the mainstay of therapy for liposarcoma in the control of local disease. Nonetheless, despite adequate local control of disease, as many as 50–75% of patients with round cell and pleomorphic liposarcoma will develop distant metastasis, usually to the lungs, bone or fat pad sites in the retroperitoneum and trunk. Due to the high rate of response of myxoid/round cell liposarcoma to ifosfamide-based chemotherapy in the metastatic setting, it was hoped that neoadjuvant or adjuvant chemotherapy for high-risk primary liposarcoma would help decrease the frequency of distant metastases and, thus, increase overall survival.

One of the most important studies of adjuvant chemotherapy for extremity soft tissue sarcomas is that from the Italian Sarcoma Study Group, who examined an anthracycline (epirubicin) and ifosfamide in the adjuvant setting [69]. After surgery with or without local radiation, 104 patients were randomly assigned to receive no chemotherapy or to receive ifosfamide (1.8 g/m^2 on 5 consecutive days) with epirubicin (60 mg/m^2 on 2 consecutive days), with filgrastim support. Interim analysis in 1996 led to early conclusion of the trial because the study had reached its primary end point of improved disease-free survival. At a median follow-up of 36 months, overall survival in the chemotherapy arm was 72%, compared to 55% in the control arm ($P = 0.002$). Interpretation of the study was made more difficult by the finding of equal rates of distant or local recurrence or both at 4 years as well as by subtle imbalances in the distribution of patients on the control and treatment arms of the study. With longer follow-up, overall and

disease-free survival no longer reached a statistical significance level of $P = 0.05$. Nonetheless, 5-year overall survival is still significantly better with chemotherapy, and this study has been used as a rationale to give combination ifosfamide and an anthracycline in the adjuvant setting. A smaller confirmatory study of epirubicin alone versus epirubicin-ifosfamide, which closed due to poor accrual, also showed a nearly statistically significant difference in favor of the combination [70].

The most recent study of adjuvant chemotherapy for primary soft tissue sarcoma is a comparison of surgery and radiation therapy alone with or without 5 cycles of doxorubicin (75 mg/m^2) and a 24-hr infusion of ifosfamide (5 g/m^2) every 21 days, given with supportive mesna and lenogastrim [71]. A total of 351 patients were recruited, and 175 were allocated to chemotherapy. One hundred sixty-three patients started chemotherapy, and 127 completed 5 cycles of treatment. The estimated 5-year relapse free survival was 52% in both arms; estimated 5-year overall survival was 69% in the observation arm and 64% in the chemotherapy arm. Though there are arguments that the ifosfamide dose was too low to be effective, this remains the largest adjuvant study of chemotherapy with doxorubicin and ifosfamide in the adjuvant setting for soft tissue sarcomas. These data will need more time to mature to confirm these conclusions. Unfortunately, the randomized trial data with ifosfamide-based therapy in high grade extremity sarcoma is limited due to poor patient accrual and the heterogeneity of sarcoma types that are included in these randomized trials. Thus, adjuvant chemotherapy for soft tissue sarcoma should be regarded as investigational and is rarely indicated, except in a clinical trial.

From treatment of advanced disease, we have learned that the response rate to adriamycin and ifosfamide therapy is histology specific (e.g., myxoid/round cell and pleomorphic liposarcoma have much higher response rates than do dedifferentiated liposarcoma). The randomized trial data typically do not stratify by histologic subtype; therefore, there is a paucity of data regarding the benefit of adjuvant/neoadjuvant chemotherapy for specific histologic subtypes of sarcoma.

The preoperative use of neoadjuvant combination chemotherapy, usually with doxorubicin and ifosfamide, for adult soft tissue sarcoma has several potential advantages in that it can make subsequent surgery easier, treat micrometastatic disease early before the acquisition of resistance, leave the vasculature intact for improved drug delivery, and enable assessment of therapeutic response or resistance to therapy. A retrospective analysis of patients with high grade extremity sarcoma from prospectively acquired databases of patients from MSKCC and Dana Farber Cancer Institute demonstrated an overall improvement in DSS for the complete cohort of patients, and this improvement appears to be driven by the benefit of neoadjuvant chemotherapy in patients with extremity sarcomas >10 cm [72]. In this high risk group, there was a 21% improvement in DSS at 3 years. Conversely, no association was seen between improved DSS in patients with extremity sarcomas between 5 and 10 cm. Although this study was stratified by histologic type, there were not enough patients within a given subtype to determine which subtypes benefit the most from chemotherapy. To address this issue, we then sought to evaluate the association of chemotherapy with survival in patients with extremity liposarcoma [12]. All patients with >5 cm, high-grade, primary extremity liposarcoma (n = 245) were identified from the prospective sarcoma databases at MSKCC (1982–2003) and UCLA (1976–2003). Patients were treated with doxorubicin (DOX) alone (n = 83, 34%), ifosfamide (IF) containing regime (n = 63, 26%) and no chemotherapy (NoC) (n = 99, 40%). Although the patients treated with NoC span the entire study period (1975–2003), the DOX alone patients were treated in a different decade (1975–1990) than the IF treated patients (1990–2003). To accurately assess the impact of treatment with DOX and IF, two separate contemporary cohort analyses were performed. A cohort of patients treated from 1975 to 1990 was used to analyze the impact of DOX on DSS. Of the 129 patients identified, there was a similar number of patients treated at MSKCC (n = 62, 48%) and at UCLA (n = 67, 52%). Eighty-three (64%) patients received treatment with DOX and 46 (36%) with NoC. The clinical and pathologic characteristics of the DOX treated patients, including size, were very similar to the NoC treated patients. The major difference between these treatment groups was institutional treatment. The majority of patients from UCLA were treated with DOX (n = 62, 75%), and the majority of patients from MSKCC were treated with NoC (n = 41, 89%). With a median follow-up of over 14 years for survivors, treatment with DOX alone was not found to be significantly associated with DSS either on univariate or multivariate analysis.

A cohort of patients treated from 1990 to 2003 was used to analyze the impact of IF-containing regimes on DSS. Of the 126 patients identified, there was a similar number of patients treated at MSKCC (n = 62, 49%) and at UCLA (n = 64, 51%). Sixty-three (50%) patients received treatment with IF and 63 (50%) with NoC. The clinical and pathologic characteristics of the IF treated patients, including size and histologic subtype, were very similar to the NoC treated patients. Again, the major difference between these treatment groups was institutional treatment. The majority of patients from UCLA were treated with IF (n = 55, 87%), and the majority of patients from MSKCC were treated with NoC (n = 54, 86%).

With a median follow-up of 5 years for survivors, treatment with IF was found to be significantly associated with DSS ($P = 0.0003$). The 5-year DSS was 92% (84–100%) in the IF treated patients and 65% (51–79%) in the NoC patients. By multivariate analysis, smaller size, myxoid/round cell histologic subtype, and treatment with IF were independently associated with an improved DSS. Patients that did not receive IF had a threefold increased risk of death from disease compared to patients that received IF. In addition, patients with pleomorphic liposarcoma had a four-fold increased risk of death from disease compared to patients with the myxoid/round cell subtype.

Additional analyses were performed to determine if there was a tumor size range and/or histologic subtype that benefited most from treatment with IF. Although there appears to be a modest (14%) survival benefit at 5 years for 5–10 cm tumors in IF treated patients, there was a 31% survival benefit at 5 years for >10 cm IF treated patients. The 5-year DSS for >10 cm IF treated patients was 89% (78–100%) compared to 58% (40–75%) for >10 cm NoC patients. Interestingly, both myxoid/round cell and pleomorhic histologic subtypes benefited from treatment with IF. There was a 22% survival benefit at 5 years for myxoid/round cell IF treated patients and a 31% survival benefit at 5 years for pleomorphic IF treated patient [12]. Taken together, these results suggest that neoadjuvant chemotherapy may be justified in carefully selected high-risk patients >5 cm, high-grade extremity liposarcoma.

COMPLICATIONS

The risk of wound complication appears to be almost entirely confined to lower extremity lesions [64,73]. It is well established that radiation and chemotherapy inhibit wound healing. Early studies defined the effects of doxorubicin and radiation on wound healing in animal models [74]. The authors suggested that radiation or antineoplastic drugs delivered more than 7 days before or after the wound creation were accompanied by minimal inhibition of wound healing. However, the application of radiation or chemotherapy just before surgery resulted in significant impairment of wound healing, as demonstrated by wound-breaking strength due to inhibition of newly synthesized collagen.

The most comprehensive study on the influence of preoperative chemotherapy on the risk of wound complications was reported by the M.D. Anderson Cancer Center [75]. The authors compared morbidity of resection of soft tissue sarcoma in 104 patients who received neoadjuvant chemotherapy and in 204 patients who had surgery first.

The most common complications were wound infections; however, the incidence of surgical complications was no different for patients undergoing preoperative chemotherapy than for patients undergoing surgery alone in those with extremity sarcomas (34% vs. 41%) or retroperitoneal or visceral sarcomas (29% vs. 34%). Simultaneous neoadjuvant chemotherapy and radiotherapy resulted in greater morbidity than when radiotherapy is given alone [76].

Wound complications requiring operative intervention were analyzed in the randomized BRT trial at MSKCC.[66] The overall complication rate was 24% in the BRT arm compared to 15% in the control arm ($P = 0.18$). However, reoperation rates were 9% and 1% in patients whose width of skin was more than 4 cm or less than 4 cm, respectively ($P = 0.02$). These types of complications have been shown with external-beam irradiation as well [64,77]. In the Canadian trial comparing preoperative and postoperative irradiation, patients undergoing preoperative radiation had a significantly higher rate of wound complications requiring secondary wound surgery, hospital admission, or need for deep packing or prolonged dressings within 120 days of surgery (35% vs. 17%; $P = 0.01$) [64]. The authors found that the wound complication rate after preoperative radiotherapy and primary direct wound closure was 16% and seemed to be lower in those treated with vascularized tissue transfer [77]. This lower rate contrast with those found in the prospective trial of adjuvant radiotherapy alone [78].

In situations in which wound complications may be anticipated because of the magnitude of the wound, extent of the resection, prior radiation, transpositional or free grafts should be employed to cover the defect before the delivery of radiation therapy. With this approach, postoperative morbidity can be markedly diminished. For soft tissue reconstruction (e.g., tissue transfer in the form of pedicle flaps, free flaps, or skin grafts) to repair surgical defects, postoperative radiotherapy can be administered 3–4 weeks after grafting without detriment [79]. Wound breakdown is less than 5%, and most tissue transfers tolerate subsequent adjuvant radiation therapy well [80].

The impact of adjuvant radiation and chemotherapy on the development of bony fracture has been reported in the literature, but the data are scant [81,82]. Another complication encountered with adjuvant radiation is peripheral nerve damage, which can occur with postoperative and preoperative radiation. In the MSKCC randomized trial, the rate was 5% in the control arm compared to 9% in the BRT arm ($P = 0.5$) [83].

CONCLUSION

Liposarcomas are classified into three biological types encompassing five subtypes: (1) well-differentiated/dedifferentiated, (2) myxoid/round cell, and (3) pleomorphic, based on morphological features and cytogenetic aberrations. These five subtypes have different biology, growth rates, and patterns of behavior. Surgical resection is the mainstay of curative treatment; however, many patients with large, >5 cm, high grade round cell or pleomorphic liposarcomas of the extremity may benefit from treatment with neoadjuvant/adjuvant ifosfamide-based chemotherapy. Radiation is generally applied either pre-operatively or postoperatively to enhance local control for high grade (round cell, pleomorphic) extremity liposarcomas that are ≥ 5 cm. Low grade (well-differentiated and myxoid) liposarcomas, even those large in size, and small (<5 cm) high grade extremity/truncal liposarcomas can often be managed by surgery alone if the surgery is carefully planed and adequate clean margins are achieved. Surgery remains the only proven therapy for well-differentiated and dedifferentiated liposarcoma of the retroperitoneum. A histologic subtype specific nomogram provides accurate survival predictions for patients with primary liposarcoma, and this nomogram aids in counseling of patients, identification of patients appropriate for adjuvant therapy, and stratification of patients for clinical trials and molecular analysis. Future, prospective randomized clinical trials and the development of new targeted agents that are subtype-specific will continue to improve our care of patients with liposarcoma.

REFERENCES

1. Mack T: Sarcomas and other malignancies of soft tissue, retroperitoneum, peritoneum, pleura, heart, mediastinum, and spleen. Cancer 1995;75:211–244.
2. Jemal A, Siegel R, Ward E, et al.: Cancer Statistics. CA Cancer J Clin 2007;57:43–66.
3. Henricks WH, Chu YC, Goldblum JR, et al.: Dedifferentiated liposarcoma: A clinicopathological analysis of 155 cases with a proposal for an expanded definition of dedifferentiation. Am J Surg Pathol 1997;21:271–281.
4. Linehan DC, Lewis JJ, Leung D, et al.: Influence of biologic factors and anatomic site in completely resected liposarcoma. J Clin Oncol 2000;18:1637–1643.
5. Lewis J, Leung D, Woodruff J, et al.: Retroperitoneal soft-tissue sarcoma. Ann Surg 1998;228:355–365.
6. McCormick D, Mentzel T, Beham A, et al.: Dedifferentiated liposarcoma: Clinicopathologic analysis of 32 cases suggesting a better prognostic subgroup among pleomorphic sarcomas. Am J Surg Pathol 1994;18:1213–1223.
7. Antonescu CR, Tschernyavsky SJ, Decuseara R, et al.: Prognostic impact of P53 status. TLS-CHOP fusion transcript structure, and histological grade in myxoid liposarcoma: A molecular and clinicopathologic study of 82 cases. Clin Cancer Res 2001;7: 3977–3987.
8. Gebhard S, Coindre JM, Michels JJ, et al.: Pleomorphic liposarcoma: Clinicopathologic, immunohistochemical, and follow-up analysis of 63 cases: A study from the French Federation of Cancer Centers Sarcoma Group. Am J Surg Pathol 2002;26:601–616.
9. Singer S, Antonescu CR, Riedel E, et al.: Histologic subtype and margin of resection predict pattern of recurrence and survival for retroperitoneal liposarcoma. Ann Surg 2003;238:358–370.
10. Kooby DA, Antonescu CR, Brennan MF, et al.: Atypical lipomatous tumor/well-differentiated liposarcoma of the extremity and trunk wall: Importance of histological subtype with treatment recommendations. Ann Surg Oncol 2003;11:78–84.
11. Fletcher C, Unni K, Mertens F, editors. Pathology and genetics of tumors of soft tissue and bone. Lyon, France: International Agency for Research on Cancer Press; 2002.
12. Eilber FC, Eilber FR, Eckardt J, et al.: The impact of chemotherapy on the survival of patients with high-grade primary extremity liposarcoma. Ann Surg 2004;240:686–695.
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;244:381–391.
14. Ahn C, Harvey J: Mediastinal hibernoma, a rare tumor. Ann Thorac Surg 1990;50:828–830.
15. Mentzel T, Calonje E, Fletcher C: Lipoblastoma and lipoblastomatosis: A clinicopathological study of 14 cases. Histopathology 1993;23:527–533.
16. Brennan M: Diagnosis and management of soft tissue sarcoma. London: Martin Dunitz, 2002.
17. Mentzel T, Fletcher CD: Lipomatous tumours of soft tissues: An update. Virchows Arch 1995;427:353–363.
18. Kindblom LG, Angervall L, Stener B, et al.: Intermuscular and, intramusclar lipomas and hibernomas. A clinical, roentgenologic, histologic, and prognostic study of 46 cases. Cancer 1974;33: 754–762.
19. Rozental TD, Khoury LD, Donthineni-Rao R, et al.: Atypical lipomatous masses of the extremities: Outcome of surgical treatment. Clin Orthop Relat Res 2002;398:203–211.
20. Weiss SW: Lipomatous tumors. Monogr Pathol 1996;38:207–239.
21. Brown FM, Fletcher CD: Problems in grading soft tissue sarcomas. Am J Clin Pathol 2000; S82–S89.
22. Fong Y, Coit DG, Woodruff JM, et al.: Lymph node metastasis from soft tissue sarcoma in adults: Analysis of data from a prospective database of 1772 sarcoma patients. Ann Surg 1993; 217:72–77.

23. Huang HY, Brennan MF, Singer S, et al.: Distant metastasis in retroperitoneal dedifferentiated liposarcoma is rare and rapidly fatal: A clinicopathological study with emphasis on the low-grade myxofibrosarcoma-like pattern as an early sign of dedifferentiation. Mod Pathol 2005;18:976–984.
24. Downes KA, Goldblum JR, Montgomery EA, et al.: Pleomorphic liposarcoma: A clinicopathologic analysis of 19 case. Mod Pathol 2001;14:179–184.
25. Willen H, Akerman M, Dal Cin P, et al.: Comparison of chromosomal patterns with clinical features in 165 lipomas: A report of the CHAMP study group. Cancer Cytogenet 1998; 102: 46–49.
26. Dal Cin P, Sciot R, Polito P, et al.: Lesions of 13q may occur independently of deletion of 16q in spindle cell/pleomorphic lipomas. Histopathology 1997;31:222–225.
27. Fletcher CD, Akerman M, Dal Cin P, et al.: Correlation between clinical pathological features and karyotype in lipomatous tumors. Am J Pathol 1996;148:623–630.
28. Meis-Kindblom JM, Sjogren H, Kindblom LG, et al.: Cytogenetic and molecular genetic analyses of liposarcoma and its soft tissue simulators: Recognition of new variants and differential diagnosis. Virchows Arch 2001;439:141–151.
29. Antonescu CR, Elahi A, Humphrey M, et al.: Specificity of TLS-CHOP rearrangement for classic myxoid/round cell liposarcoma; absence in predominantly myxoid well-differentiated liposarcoma. J Mol Diagn 2000;2:132–138.
30. Gadd MA, Casper ES, Woodruff JM, et al.: Development and treatment of pulmonary metastases in adult patients with extremity soft tissue sarcoma. Ann Surg 1993;218:705–712.
31. Temple LK, Brennan MF: The role of pulmonary metastasectomy in soft tissue sarcoma. Semin Thorac Cardiovasc Surg 2002;14: 35–44.
32. Cheng EY, Springfield DS, Mankin HJ: Frequent incidence of extrapulmonary sites of initial metastases in patients with liposarcoma. Cancer 1995;75:1120–1127.
33. Jaques D, Coit DG, Hajdu S, et al.: Management of primary and recurrent soft tissue sarcoma of the retroperitoneum. Ann Surg 1990;212:51–59.
34. Varma DG: Optimal radiologic imaging of soft tissue sarcomas. Semin Surg Oncol 1999;17:2–10.
35. Demas BE, Heelan RT, Lane J, et al.: Soft-tissue sarcomas of the extremities: Comparison of MR and CT in determining the extent of disease. AJR Am J Roentgenol 1988;150:615–620.
36. National Comprehensive Cancer Network www.nccn.org. 2007.
37. Pollack R, Brennan MF, Lawrence W Jr: Soft tissue sarcoma surgical practice guidelines. Oncology 1997;11:1327–1332.
38. Heslin MJ, Lewis JJ, Woodruff JM, et al.: Core needle biopsy for diagnosis of extremity soft tissue sarcoma. Ann Surg Oncol 1997; 4:425–431.
39. Gaynor JJ, Tan CC, Casper ES, et al.: Refinement of clinicopathologic staging for localized soft tissue sarcoma of the extremity: A study of 423 adults. J Clin Oncol 1992;10:1317–1329.
40. Greene FL, Page DL, Fleming I, et al.: AJCC cancer staging manual. Heidelberg: Springer-Verlag; 2002.
41. Wunder JS, Heale JH, Davis AM, et al.: A comparison of staging systems for localized extremity soft tissue sarcoma. Cancer 2000; 88:2721–2730.
42. Pisters PWT, Leung DHY, Woodruff J, et al.: Analysis of prognostic factors in 1041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol 1996;14:1679–1689.
43. Kattan MW, Leung DH, Brennan MF: Postoperative nomogram for 12-year sarcoma-specific death. J Clin Oncol 2002;20:627–629.
44. Kattan MW, Heller G, Brennan MF: Competing risks nomogram. Stat Med 2003;22:3515–3525.
45. Brennan MF, Kattan MW, Klimstra D, et al.: Prognostic nomogram for patients undergoing resection for adenocarcinoma of the pancreas. Ann Surg 2004;240:293–298.
46. Kattan MW, Karpeh MS, Mazumdar M, et al.: Postoperative nomogram for disease-specific survival after an R0 resection for gastric carcinoma. J Clin Oncol 2003;21:3647–3650.
47. Eilber FC, Brennan MF, Reidel E, et al.: Prognostic factors for survival in patients with locally recurrent extremity soft tissue sarcoma. Ann Surg Oncol 2005;12:228–236.
48. Stojadinovic A, Leung DH, Allen P, et al.: Primary adult soft tissue sarcoma: Time-dependent influence of prognostic factors. J Clin Oncol 2002;20:4344–4352.
49. Lewis J, Leung D, Casper E, et al.: Multifactorial analysis of long-term follow-up (more than five years) of primary extremity sarcoma. Arch Surg 1999;134:190–194.
50. Weitz J, Antonescu CR, Brennan MF: Localized extremity soft tissue sarcoma: Improved knowledge with unchanged survival over time. J Clin Oncol 2003;21:2719–2725.
51. Rosenberg SA, Tepper J, Glatstein E, et al.: The treatment of soft-tissue sarcomas of the extremities: Prospective randomized evaluations of 1) limb-sparing surgery plus radiation therapy compared with amputation and 2) the role of adjuvant chemotherapy. Ann Surg 1982;196:305–315.
52. Williard WC, Collin C, Casper ES, et al.: The changing role of amputation for soft tissue sarcoma of the extremity in adults. Surg Gynecol Obstet 1992;175:389–396.
53. Shibata D, Lewis JJ, Leung D, et al.: Is there a role for incomplete resection in the management of retroperitoneal liposarcomas? J Am Coll Surg 2001;193:373–379.
54. Tepper JE, Suit HD, Wood WC, et al.: Radiation therpayof retorperitoneal soft tissue sarcomas. Int J Radiat Oncol Biol Phys 1984;10:825–830.
55. Willett C, Suit H, Tepper J, et al.: Intraoperative electron beam radiation therapy for retroperitoneal soft tissue sarcomas. Cancer 1991;68:278–283.
56. Sindelar W, Kinsella T, Chen PW, et al.: Intraoperative radiotherapy in retroperitoneal sarcomas. Final results of a prospective, randomized, clinical trial. Arch Surg 1993;128:402–410.
57. Alektiar KM, Hu K, Anderson L, et al.: High-dose-rate intraoperative radiation therapy (HDR-IORT) for retroperitoneal sarcomas. Int J Radiat Oncol Biol Phys 2000;47:157–163.
58. Fiveash JB, Murshed H, Duan J, et al.: Effect of multileaf collimator leaf width on physical dose distributions in the treatment of CNS and head and neck neoplasms with intensity modulated radiation therapy. Med Phys 2002;29:1116–1119.
59. Geer R, Woodruff J, Casper E, et al.: Management of small soft tissue sarcoma of the extremity in adults. Arch Surg 1992; 127: 1285–1289.
60. Baldini EH, Goldberg J, Jenner C, et al.: Long term outcomes after function-sparing surgery without radiotherapy for soft tissue sarcoma of the extremities and trunk. J Clin Oncol 1999;17: 3252–3259.
61. Yang JC, Chang AE, Baker AR, et al.: Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol 1992;16: 197–203.
62. Pisters PW, Harrison LB, Leung DH, et al.: Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. J Clin Oncol 1996;14:859–868.
63. Alektiar KM, Leung D, Zelefsky MJ, et al.: Adjuvant radiation for stage II-B soft tissue sarcoma of the extremity. J Clin Oncol 2002; 20:1643–1650.
64. O'Sullivan B, Davis AM, Turcotte R, et al.: Preoperative versus postoperative radiotherapy in soft tissue sarcoma of limbs: A randomised trial. Lancet 2002;359:2235–2241.
65. Zagars K, Ballo MT: Significance of dose in postoperative radiotherapy for soft tissue sarcoma. Int J Radiat Oncol Biol Phys 2003;56:473–481.
66. Alektiar KM, Velasco J, Zelefsky MJ, et al.: Adjuvant radiotherapy for margin-positive high-grade soft tissue sarcoma of the extremity. Int J Radiat Oncol Biol Phys 2000;48:1051–1058.
67. Alektiar KM, Brennan MF, Singer S: Influence of site on the therapeutic ratio of adjuvant radiotherapy in soft-tissue sarcoma of the extremity. Int J Radiat Oncol Biol Phys 2005;63: 202–208.
68. Alektiar KM, Hong L, Brennan MF, et al.: Intensity modulated radiation therapy for primary soft tissue sarcoma of the extremity: Preliminary results. Int J Radiat Oncol Biol Phys 2007;68:458–464.

69. Frustaci S, Gherlinzoni F, De Paoli A, et al.: Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: Results of the Italian randomized cooperative trial. J Clin Oncol 2001;19:1238–1247.
70. Petrioli R, Coratti A, Correale P, et al.: Adjuvant epirubicin with or without ifosfamide for adult soft tissue sarcomas. Am J Clin Oncol 2002;25:468–473.
71. Woll PJ, van Glabbeke M, Hohenberger P, Le Cesne A, Gronchi A, Hoekstra HJ, Radford JA, van Coevorden F, Blay J-Y, for the EORTC Soft Tissue and Bone Sarcoma Group. Adjuvant chemotherapy (CT) with doxorubicin and ifosfamide in resected soft tissue sarcoma (STS): Interim analysis of a randomized phase III trial. J Clin Oncol, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007; 10008.
72. Grobmyer SR, Maki RG, Demetri GD, et al.: Neo-adjuvant chemotherapy for primary high-grade extremity soft tissue sarcoma. Ann Oncol 2004;15:1667–1672.
73. DeLaney TF, Spiro IJ, Suit HD, et al.: Neoadjuvant chemotherapy and radiotherapy for large extremity soft-tissue sarcomas. Int J Radiat Oncol Biol Phys 2003;56:1117–1127.
74. Devereux D, Kent H, Brennan M: Time dependent effects of adriamycin and x-ray therapy on wound healing in the rat. Cancer 1980;45:2805–2810.
75. Meric F, Milas M, Hunt KK, et al.: Impact of neoadjuvant chemotherapy on postoperative morbidity in soft tissue sarcomas. J Clin Oncol 2000;18:3378–3383.
76. Arbeit JM, Hilaris BS, Brennan MF: Wound complications in the multimodality treatment of extremity and superficial truncal sarcomas. J Clin Oncol 1987;5:480–488.
77. Peat BG, Bell RS, Davis A, et al.: Wound-healing complications after soft-tissue sarcoma surgery. Plast Reconstr Surg 1994;93: 980–987.
78. O'Sullivan B, Bell RS: Has ''MAID'' made it in the management of high-risk soft-tissue sarcoma. Int J Radiat Oncol Biol Phys 2003;56:915–916.
79. Spear MA, Dupuy DE, Park JJ, et al.: Tolerance of autologous and allogeneic bone grafts to therapeutic radiation in humans. Int J Radiat Oncol Biol Phys 1999;45:1275–1280.
80. Spierer MM, Alektiar KM, Zelefsky MJ, et al.: Tolerance of tissue transfers to adjuvant radiation therapy in primary soft tissue sarcoma of the extremity. Int J Radiat Oncol Biol Phys 2003; 56:1112–1116.
81. Alektiar KM, Zelefsky MJ, Brennan MF: Morbidity of adjuvant brachytherapy in soft tissue sarcoma of the extremity and superficial trunk. Int J Radiat Oncol Biol Phys 2000;47:1273–1279.
82. Holt GE, Griffin AM, Pintilie M, et al.: Fractures following radiation therapy and limb salvage surgery for soft tissue sarcomas: A comparison of high-dose and low-dose radiotherapy. J Bone Joint Surg Am 2005;87:315–319.
83. Alektiar KM, Leung DH, Brennan MF, et al.: The effect of combined external beam radiotherapy and brachytherapy on local control and wound complications in patients with high-grade soft tissue sarcomas of the extremity with positive microscopic margin. Int J Radiat Oncol Biol Phys 1996;36:321–324.
84. Greene FLPD, Fleming ID, Fritz A, et al.: AJCC cancer staging manual. New York: Springer-Verlag; 2002.