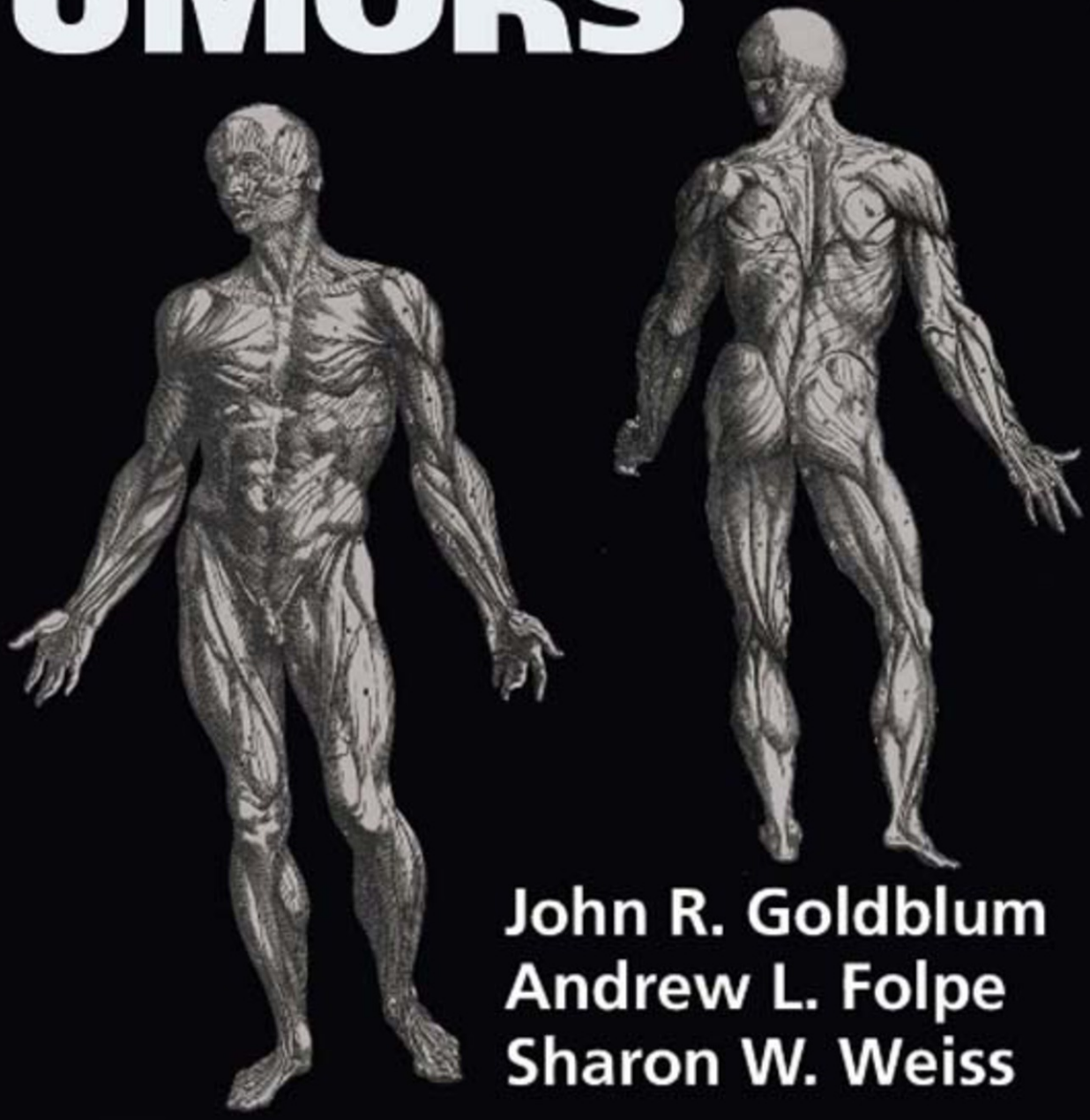
Enzinger & Weiss's

SOFT TISSUE TUMORS

SIXTH EDITION



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Preface to the Sixth Edition

Just over a hundred years ago, in 1910 to be exact, two events changed the landscape of American medicine. Dr. Abraham Flexner published his now famous report, The Flexner Report, which revolutionized American medical education and forever integrated science and the practice of clinical medicine into our medical curricula. And, coincidentally, that same year, as if to reinforce the interdependence of basic science and clinical medicine, Peyton Rous discovered a transmissible, sarcoma-producing virus in chickens (Rous sarcoma virus). Although initially not well accepted, this finding ultimately ignited interest in sarcomas as a specific form of cancer. In the several decades following that seminal event, work on sarcomas focused on defining and classifying these tumors; however, the last three decades have witnessed an explosive growth in understanding genetic alterations of these tumors. More recently, elucidation of the downstream consequences of the genetic alterations has spawned optimism for the identification of druggable targets. It has been six years since the fifth edition of *Enzinger and Weiss's Soft Tissue Tumors*, and although this may seem like a short interval between editions, the preceding advances suggest an exponential growth of new information worthy of dissemination. The editors and contributors of this edition, therefore, have extensively revised areas related to the molecular genetic alterations of soft tissue tumors, incorporated myriad recently described entities, reorganized chapters so that they are consistent with new views, and provided recent behavioral data that inform clinical decision-making. Our challenge and commitment have been to incorporate these recent advances into a framework that remains useful for the daily practice of pathology and related specialties. It is our hope that we have achieved this balance.

As we look forward to the release of the sixth edition of our textbook, we are also reminded that on the eve of the last edition we lost Dr. Franz Enzinger, whose name has forever become a part of this book's title. His contributions to soft tissue pathology were manifold, and his diagnostic virtuosity legendary. The exquisite detail and nuances embodied in his descriptions of epithelioid sarcoma and clear cell sarcoma, to name just two, are unmatched even today. Viewed in a larger context, his work offers more than an introduction to new entities; it underscores the importance of laying a sturdy foundation—based on accurate, consistent, and reproducible pathologic observations—on which subsequent scientific and clinical work can build and progress. For that lesson alone we owe him an enormous debt of gratitude.

We have many individuals to thank for assisting with the completion of this textbook. We would like to thank our superb group of co-authors, who have crafted outstanding and up-to-date chapters, and our superlative assistants, Ms. Kathleen Ranney and Ms. Susan Raven, who have yet again worked tirelessly on the manuscript. Many thanks to our dedicated young faculty, Drs. Alison Cheah, Darya Buehler, and Konstantinos Linos, for their excellent proofreading skills, and to Dr. Rish Pai for his technical support. Our most sincere thanks to each of you.

Sharon W. Weiss
John R. Goldblum
Andrew L. Folpe

I would like to dedicate this book to my lovely wife Asmita, who has been my dearest companion for 33 years; to my four amazing children, Andrew, Ryan, Janavi, and Raedan; to my dear mother, Bette Jean, and my late father, Raymond; and to the rest of the Goldblum and Shirali families, whom I cherish.

—John R. Goldblum, MD, FCAP, FASCP, FACG

I would like to thank my wife, Ana, our children, Leah, Elizabeth, and Benjamin, my father, Herbert, and late mother, Susan, and all of our families for their support in this and all my other endeavors.

—Andrew L. Folpe, MD

To Bernie and Francine, who have brought sublime happiness and purpose to my life.

—Sharon W. Weiss, MD

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Preface to the First Edition

Since the publication of the *AFIP Fascicle on Soft Tissue Tumors* by A.P. Stout in 1957 and the revised edition by A.P. Stout and R. Lattes in 1967, there have been numerous advances and changes both in the diagnosis and treatment of soft tissue tumors. This book combines traditional views, which have stood the test of time, and newer concepts and observations accrued over the past 20 years. Because a precise diagnosis is essential for planning of treatment and assessment of prognosis, emphasis has been placed throughout the book on clear and concise descriptions and differential diagnoses of the tumors discussed. Each chapter has been freely illustrated, and comprehensive references have been added with emphasis on recent publications.

The WHO Classification of Soft Tissue Tumors provided the basis for the classification in this book. However, since its publication in 1969 several modifications have become necessary. Fibrohistiocytic and extraskeletal cartilaginous and osseous tumors have been included as separate groups, and a number of changes have been made, especially in the classification of fibrous, vascular, and neural tumors. The role of histochemistry, electron microscopy, and immunohistochemistry has been noted when applicable. Relatively less emphasis, however, has been placed on the specifics of therapy because of the rapidly changing nature of this discipline. It is our hope that this blending of old and new will make this book valuable not only as a reference book for those specifically interested in soft tissue tumors but also as a diagnostic aid for the practicing general pathologist.

In many areas the contents of this book reflect our personal experience derived from approximately 5000 cases reviewed annually in the Department of Soft Tissue Pathology of the Armed Forces Institute of Pathology. The large number of cases has afforded us a unique opportunity for which we are extremely grateful.

We also wish to express our appreciation and gratitude to the many contributing pathologists who not only shared their interesting and problematic cases with us but also provided additional teaching material in the form of photographs, roentgenograms, and electron micrographs. We also owe thanks to our professional colleagues for their advice and support in this endeavor, to the photographic staff of the Institute, especially Mr. C. Edwards and Mr. B. Allen, for their skill and assistance in preparing the photographs, and to Mrs. P. Diaz and Mrs. J. Kozlay for typing the manuscript. We are also greatly indebted to our publishers for their cooperation and help throughout the production of this book. We are particularly indebted to our families for their patience and tolerance.

Franz M. Enzinger
Sharon W. Weiss

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Contents

Chapter 1

General Considerations

CHAPTER CONTENTS

Soft tissue can be defined as nonepithelial extraskeletal tissue of the body exclusive of the reticuloendothelial system, glia, and supporting tissue of various parenchymal organs. It is represented by the voluntary muscles, fat, and fibrous tissue, along with the vessels serving these tissues. By convention, it also includes the peripheral nervous system because tumors arising from nerves present as soft tissue masses and pose similar problems in differential diagnosis and therapy. Embryologically, soft tissue is derived principally from mesoderm, with some contribution from neuroectoderm.

Soft tissue tumors are a highly heterogeneous group of tumors that are classified by the line of differentiation, according to the adult tissue they resemble. Lipomas and liposarcomas, for example, are tumors that recapitulate to a varying degree normal fatty tissue; and hemangiomas and angiosarcomas contain cells resembling vascular endothelium. Within the various categories, soft tissue tumors are usually divided into benign and malignant forms.

Benign tumors, which more closely resemble normal tissue, have a limited capacity for autonomous growth. They exhibit little tendency to invade locally and are attended by a low rate of local recurrence following conservative therapy.

Malignant tumors, or *sarcomas*, in contrast, are locally aggressive and are capable of invasive or destructive growth, recurrence, and distant metastasis. Radical surgery is required to ensure the total removal of these tumors. Unfortunately, the term *sarcoma* does not indicate the likelihood or rapidity of metastasis. Some sarcomas, such as dermatofibrosarcoma protuberans, rarely metastasize, whereas others do so with alacrity. For these reasons, it is important to qualify the term *sarcoma* with a statement concerning the degree of differentiation or the histologic grade. "Well differentiated" and "poorly differentiated" are qualitative, and therefore subjective, terms used to indicate the relative maturity of the tumor with respect to normal adult tissue. Histologic grade is a means of quantitating the degree of differentiation by applying a set of histologic criteria. Usually, well-differentiated sarcomas are low-grade lesions, whereas poorly differentiated sarcomas are high-grade neoplasms. Tumors of intermediate or borderline malignancy are characterized by frequent recurrence but rarely metastasis.

INCIDENCE OF SOFT TISSUE TUMORS

The incidence of soft tissue tumors, especially the frequency of benign tumors relative to malignant ones, is nearly impossible to determine accurately. Benign soft tissue tumors outnumber malignant tumors by a wide margin. The fact that many benign tumors, such as lipomas and hemangiomas, do not undergo biopsy makes direct application of data from most hospital series invalid for the general population.

Malignant soft tissue tumors, on the other hand, ultimately come to medical attention. Soft tissue sarcomas, compared with carcinomas and other neoplasms, are relatively rare and constitute fewer than 1.5% of all cancers with an annual incidence of about 6 per 100,000 persons.[1] However, according to an analysis of the Surveillance, Epidemiology and End Results (SEER) database, the incidence changes with age[1]; for children younger than 10 years of age, the annual incidence was 0.9/100,000 children but rose to 18.2/100,000 adults over the age of 70 years. The most dramatic increases occurred at 30 and 70 years of age (Table 1-1).

There seems to be an upward trend in the incidence of soft tissue sarcomas, but it is not clear whether this represents a true increase or reflects better diagnostic capabilities and greater interest in this type of tumor. Data from the SEER database showed a marked increase in the age-adjusted incidence of soft tissue sarcomas between 1981 and 1987.[2] However, when patients with Kaposi sarcoma were eliminated from this analysis, the rates remained relatively unchanged throughout that time period. Judging from the available data, the incidence and distribution of soft tissue sarcomas seem to be similar in different regions of the world. Soft tissue sarcomas may occur anywhere in the body, but most arise from the large muscles of the extremities, the chest wall, the mediastinum, and the retroperitoneum. They occur at any age and, like carcinomas, are more common in older patients.

Soft tissue sarcomas occur more commonly in males, but gender and age-related incidences vary among the histologic types: for instance, embryonal rhabdomyosarcoma occurs almost exclusively in young individuals, whereas undifferentiated pleomorphic sarcoma is predominantly a tumor of old age and is rare in children younger than 10 years. There is also no proven racial variation.

PATHOGENESIS OF SOFT TISSUE TUMORS

As with other malignant neoplasms, the pathogenesis of most soft tissue tumors is still unknown. Recognized causes include various physical and chemical factors, exposure to ionizing

Table 1-1 Characteristics of Select Soft Tissue Sarcomas from the Surveillance Epidemiology and End Results Database (SEER)

SARCOMA TYPE	NUMBER OF CASES	MEDIAN AGE OF DIAGNOSIS	PERCENTAGE OF PATIENTS ≤19 YEARS (%)
Fibroblastic/ myofibroblastic tumors	3,037	54	9.4
Fibrohistiocytic tumors	14,599	57	3.7
Rhabdomyosarcomas	2,831	15	58.9
Malignant peripheral nerve sheath tumor	2,186	46	9.9
Ewing family of tumors	589	24	39.6
Liposarcomas	7,419	60	1.2
Leiomyosarcomas	13,135	59	0.9
Synovial sarcomas	1,859	35	17.6
Vascular tumors (not Kaposi)	2,742	65	2.1
Chondroosseous soft tissue tumors	680	55	3.8
Alveolar soft part sarcomas	164	25	28.7

Data from SEER database from 1973-2006. Modified from: Ferrari A, Sultan I, Huang TT, et al. Soft tissue sarcoma across the age spectrum: a population-based study from the surveillance epidemiology and end results database. Pediatr Blood Cancer 2011;57(6):943–9.

radiation, and inherited or acquired immunologic defects. An evaluation of the exact cause is often difficult because of the long latent period between the time of exposure and the development of sarcoma, as well as the possible effect of multiple environmental and hereditary factors during the induction period. The origin of sarcomas from benign soft tissue tumors is exceedingly rare, except for malignant peripheral nerve sheath tumors arising in neurofibromas, which are nearly always in patients with the manifestations of type 1 neurofibromatosis (von Recklinghausen disease).

Environmental Factors

Trauma is frequently implicated in the development of sarcomas. Many of these reports are anecdotal, however, and the integrity of the injured part was not clearly established before the injury. Consequently, trauma often seems to be an event that merely calls attention to the underlying neoplasm. Occasionally, there is reasonable evidence to suggest a causal relation. Rare soft tissue sarcomas have been reported as arising in scar tissue following surgical procedures or thermal or acid burns, at fracture sites, and in the vicinity of plastic or metal implants, usually after a latent period of several years.[3] Kirkpatrick et al. studied the histologic features in capsules surrounding the implantation site of a variety of biomaterials.[4] Interestingly, these authors noted a spectrum of change from focal proliferative lesions through preneoplastic proliferations to incipient sarcomas and suggested a model of multistage tumorigenesis akin to the adenoma-carcinoma sequence.

Environmental carcinogens have been related to the development of sarcomas, but their role is largely unexplored, and only a few substances have been identified as playing a role in the induction of sarcomas in humans. A variety of animal models now exist to induce sarcomas, allowing a better understanding of their pathogenesis.

Phenoxyacetic acid herbicides, chlorophenols, and their contaminants such as 2,3,7,8-tetrachlorodibenzo-para-dioxin (dioxin) have been linked to sarcomagenesis.[5-9] A series of case-control studies from Sweden from 1979 to 1990 reported an up to sixfold increased risk of soft tissue sarcoma associated with exposure to phenoxyacetic acids or chlorophenols in individuals exposed to these herbicides in agricultural or forestry work.[10-12] Similar reports of an increased risk of sarcoma associated with these herbicides were reported from Italy,[13] Great Britain,[14] and New Zealand.[15] Although a study by Leiss and Savitz linked the use of phenoxyacetic acid lawn pesticides with soft tissue sarcomas in children,[16] several other studies with more detailed exposure histories did not confirm this association.[17] These inconsistencies may be due in part to the predominant phenoxyacetic herbicide used in different locations. In the United States, 2,4-dichlorophenoxyacetic acid is the primary phenoxyacetic herbicide used, whereas in Sweden the main herbicides contain 2,4,5-trichlorophenoxyacetic acid and 2-methyl-4-chlorophenoxyacetic acid, both of which are more likely contaminated with dioxin.[18,19] High levels of dioxin exposure due to accidental environmental contamination near Seveso, Italy, from an explosion at a chemical factory was followed by a threefold increased risk of soft tissue sarcomas reported among individuals living near this factory.[13,20] Similarly, Collins et al. found a significantly higher risk of soft tissue sarcomas in trichlorophenol workers in Midland, Michigan, who were exposed to 2,3,7,8-tetrachlorodibenzo-para-dioxin.[9] In addition, the possibility of an increased incidence of sarcomas was claimed for some of the two million soldiers stationed in Vietnam between 1965 and 1970 who were exposed to Agent Orange, a defoliant that contained dioxin as a contaminant.[21,22] However, in several case-control and proportional mortality studies, no excess risk of soft tissue sarcoma was reported among those Vietnam veterans who were directly involved with the spraying of Agent Orange.[18]

Vinyl chloride exposure is clearly associated with the development of hepatic angiosarcoma.[23,24] There are also rare reports of extrahepatic angiosarcoma associated with this agent.[25]

Radiation exposure has been related to the development of sarcomas, but considering the frequency of radiotherapy, radiation-induced soft tissue sarcomas are quite uncommon. The incidence of postradiation sarcoma is difficult to estimate, but reports generally range from 0.03% to 0.80%.[26,27] Much of the data regarding the incidence of postradiation sarcomas are derived from large cohorts of breast cancer patients treated with postoperative radiation therapy.[28,29] To qualify as a postradiation sarcoma, there must be documentation that the sarcoma developed in the irradiated field, a histologic confirmation of the diagnosis, a period of latency of at least 3 years between irradiation and the appearance of a tumor, and documentation that the region bearing the tumor was normal before the administration of the radiation.[30] Nearly all postradiation sarcomas occur in adults, and women develop these tumors more frequently, an observation that reflects the common use of radiation for the treatment of breast and gynecologic malignancies.

Postradiation sarcomas do not display the wide range of appearances associated with sporadic non–radiation-induced tumors. The most common postradiation soft tissue sarcoma is undifferentiated pleomorphic sarcoma, which accounts for nearly 70% of cases. Unfortunately, most postradiation sarcomas are high-grade lesions and are detected at a relatively higher stage than their sporadic counterparts. Therefore, the survival rate associated with these lesions is quite poor.

The prognosis of postradiation sarcomas is most closely related to the anatomic site, which, in turn, probably reflects resectability. Patients with radiation-induced sarcomas of the extremities have the best survival (approximately 30% at 5 years), whereas those with lesions arising in the vertebral column, pelvis, and shoulder girdle generally have survival rates of less than 5% at 5 years.[28,31,32]

The total dose of radiation seems to influence the incidence of postradiation sarcoma; most are reported to occur at doses of 5000 cGy or more.[33] Mutations of the *p53* gene have been implicated in the pathogenesis of these tumors.[34] Extravasated Thorotrast (thorium dioxide), although no longer used for diagnostic or therapeutic purposes, has induced soft tissue sarcomas, particularly angiosarcomas, at the site of injection.[35,36]

Oncogenic Viruses

The role of oncogenic viruses in the evolution of soft tissue sarcomas is still poorly understood, although there is strong evidence that the human herpesvirus 8 (HHV8) is the causative agent of Kaposi sarcoma.[37,38] In addition, there is a large body of literature supporting the role of the Epstein-Barr virus in the pathogenesis of smooth muscle tumors in patients with immunodeficiency syndromes or following therapeutic immunosuppression in the transplant setting.[39] Aside from these settings, there is no conclusive evidence that human-transmissible viral agents constitute a major risk factor in the development of soft tissue sarcomas.

Immunologic Factors

As mentioned previously, immunodeficiency and therapeutic immunosuppression are also associated with the development of soft tissue sarcomas, particularly smooth muscle tumors and Kaposi sarcoma. In addition, acquired regional immunodeficiency, or loss of regional immune surveillance, may play a central role in the development of the relatively rare angiosarcomas that arise in the setting of chronic lymphedema,[40] secondary to radical mastectomy (Stewart-Treves syndrome)[41] or congenital or infectious conditions.[41,42]

Genetic Factors

A number of genetic diseases are associated with the development of soft tissue tumors, and the list will undoubtedly lengthen as we begin to understand the molecular underpinnings of mesenchymal neoplasia. Neurofibromatosis type 1, neurofibromatosis type 2, and familial adenomatous polyposis (FAP)/Gardner syndrome are classic examples of genetic diseases associated with soft tissue tumors. Familial cancer syndromes associated with soft tissue sarcomas are more fully described in Chapter 4.

CLASSIFICATION OF SOFT TISSUE TUMORS

The development of a useful, comprehensive histologic classification of soft tissue tumors has been a relatively slow process. Earlier classifications have been largely descriptive and based more on the nuclear configuration than the type of tumor cells. Terms such as *round cell sarcoma* and *spindle cell sarcoma* may be diagnostically convenient but should be discouraged because they convey little information as to the nature and potential behavior of a given tumor. Moreover, purely descriptive classifications do not clearly distinguish between tumors and tumor-like reactive processes. More recent classifications have been based principally on the line of differentiation of the tumor, that is, the type of tissue formed by the tumor rather than the type of tissue from which the tumor theoretically arose.

Over the past four decades, there have been several attempts to devise a useful, comprehensive classification of soft tissue tumors. The classification used herein is very similar but not identical to the revised 2013 World Health Organization (WHO) classification, a collective effort by pathologists throughout the world.

Each of the histologic categories is divided into a benign group and a malignant group. In addition, for several tumor categories, some tumors are classified as being of intermediate (borderline or low malignant potential) malignancy, implying a high rate of local recurrence and a small risk of metastasis. Most tumors retain the same pattern of differentiation in the primary and recurrent lesions, but, occasionally, they change their pattern of differentiation or may even differentiate along several cellular lines.

Undifferentiated pleomorphic sarcoma (formerly known as *malignant fibrous histiocytoma*) and liposarcoma are the most common soft tissue sarcomas of adults; together they account for 35% to 45% of all sarcomas. Rhabdomyosarcoma, neuroblastoma, and the Ewing family of tumors are the most frequent soft tissue sarcomas of childhood.

GRADING AND STAGING SOFT TISSUE SARCOMAS

With a few notable exceptions, histologic typing does not provide sufficient information for predicting the clinical course of a sarcoma and, therefore, must be accompanied by grading and staging information. *Grading* assesses the degree of malignancy of a sarcoma and is based on an evaluation of several histologic parameters (described in the following two sections), whereas *staging* provides shorthand information regarding the extent of the disease at a designated time, usually the time of initial diagnosis. Many variables affect the outcome of a sarcoma. Their relative importance may vary with time and with the sarcoma subtype. Grading and staging systems of necessity simplify these variables and emphasize the most important ones that seem to have the most universal applicability for all sarcomas. An extensive discussion related to grading systems and issues was provided by Deyrup and Weiss.[45]

Grading Systems

Grading of soft tissue sarcomas was first proposed in 1939 by Broders, who used a combination of mitotic activity, giant-cell tumors, and fibrous stroma in assigning a grade to fibrosarcomas.[46] Broders also acknowledged the importance of cellular differentiation in grading. He suggested that fibrosarcomas could be divided into several subtypes (fibrous, fibrocellular,

and cellular), and that those that were highly cellular should be considered grade 4 regardless of the level of mitotic activity. These principles persist in grading systems today, namely that certain parameters (e.g., mitotic activity) should be evaluated in sarcomas, that some histologic subtypes *a priori* dictate a grade, and that the level of differentiation must be factored into the assignment of a grade. Over the ensuing decades following that publication, numerous studies reaffirmed the importance of grading and emphasized the primacy of necrosis and mitotic activity in assessing a grade.[47–50] Some studies have further proposed the use of Ki-67 immunoreactivity or MIB-1 score/index to accurately assess mitotic activity.[51–54]

The first large-scale effort to grade and stage sarcomas occurred in 1977 when Russell et al., using a database of 1000 cases and the tumor node metastasis (TNM) staging system showed that incorporating a grade into the staging system achieved predictions of outcome.[55] Most important, in the absence of metastatic disease, grade essentially defined the clinical stage. This study is most often cited as providing the first reliable grading system in the United States, yet, paradoxically, it did not provide objective criteria for grading. Rather, the grade was determined by a panel of experts based on their years of experience. The real contribution that the paper provided to grading was the implied concept that certain histologic types of sarcomas were inherently low grade and others were high grade, a premise of many grading systems.

Following that seminal publication, many grading systems were published internationally,[49,56-60] including one from the National Cancer Institute (NCI) (Table 1-2). Although differing in emphasis, most relied on mitotic activity and necrosis in deriving a grade, and some proposed that sarcoma-specific parameters should be used. The number of grades varies among the staging systems, ranging from two to four. Three-grade systems seem best suited for predicting patterns for survival and a likely response to therapy (Fig. 1-1). Four-grade systems usually show little difference between the two lowermost grades; two-grade systems, which distinguish between only low-grade and high-grade sarcomas, are more readily related to the type of surgical therapy but make it difficult to deal with sarcomas that lie between these two extremes.

The French system published by Trojani et al. in 1984 was developed by the French Federation of Cancer Centers Sarcoma Group (FNCLCC), based on an analysis of 155 adult patients with soft tissue sarcomas.[61] On the basis of a multivariate analysis of histologic features, a combination of cellular differentiation, mitotic rate, and tumor necrosis was determined to be the most useful parameters for sarcoma grading. This system assigns a score to each parameter and adds the scores together for a combined grade (Table 1-3). This study concluded that histologic grade was the single most important factor for predicting survival rates; tumor depth (superficial versus deep) was another important prognostic parameter. The reproducibility of this system was tested by 15 pathologists; an agreement was reached in 81% of the cases for tumor necrosis, 74% for tumor differentiation, 73% for mitotic rate, and 75% for overall tumor grade, although the agreement as to histologic type was 61% only.

Although the French system relies on a balanced evaluation of parameters (differentiation score, mitoses, necrosis), its principal weakness lies in the assignment of the differentiation score. The *differentiation score* is defined as the extent to which a tumor resembles adult mesenchymal tissue (score 1), the extent to which the histologic type is known (score 2), or the observation that the tumor is undifferentiated (score 3). Although a listing of the differentiation scores for the common tumors has been reported (Table 1-4), the rationale for some of these scores is not clear. It must also be remembered that this system has been derived from resected specimens unmodified by treatment, a situation that is not analogous to our current practices, which are heavily weighted toward grading on biopsies or on resection specimens following preoperative radiation or chemotherapy.

Despite these issues, the French system appears to be the most widely used grading system for sarcomas throughout the world. In a study of soft tissue pathologists from 30 countries, more preferred the French system (37.3%) over the NCI (24%), Broders' criteria (12%), Markhede's system (1.3%), and other (15.3%)[62] systems, probably because it is more precisely defined and, therefore, reproducible. It also performs superiorly to the NCI system in a large dataset comparison. The two systems were compared by Guillou et al. in adult patients with nonmetastatic soft tissue sarcomas.[63] By a univariate analysis, both systems were of prognostic value for predicting metastasis and overall survival. By a multivariate analysis, a tumor size of 10 cm or more, a deep location, and a high tumor grade, regardless of the system used, were found to be independent prognostic factors for predicting metastases. Interestingly, there were grade discrepancies using these two

Table 1-2 Assigned Histologic Grade According to Histologic Type in the NCI System

HISTOLOGIC TYPE	GRADE 1	GRADE 2	GRADE 3
Well-differentiated liposarcoma	+		
Myxoid liposarcoma	+		
Round cell liposarcoma		+	+
Pleomorphic liposarcoma			+
Fibrosarcoma		+	+
MFH, pleomorphic type*		+	+
MFH, inflammatory type*		+	+
MFH, myxoid type*		+	
MFH, pleomorphic type*		+	
DFSP	+		
Leiomyosarcoma	+	+	+
Malignant solitary fibrous tumor	+	+	+
Rhabdomyosarcoma (all types)			+
Chondrosarcoma	+	+	+
Myxoid chondrosarcoma	+	+	
Mesenchymal chondrosarcoma			+
Osteosarcoma			+
Extraskeletal Ewing sarcoma			+
Synovial sarcoma			+
Epithelioid sarcoma		+	+
Clear cell sarcoma		+	+
Superficial MPNST		+	
Epithelioid MPNST		+	+
Malignant triton tumor			+
Angiosarcoma		+	+
Alveolar soft part sarcoma			+
Kaposi sarcoma		+	+

Modified from Costa J, Wesley RA, Glatstein E, et al. The grading of soft tissue sarcomas: results of a clinicopathologic correlation in a series of 163 cases. Cancer 1984;53(3):530.

DFSP, dermatofibrosarcoma protuberans; MFH, malignant fibrous histiocytoma; MPNST, malignant peripheral nerve sheath tumor; NCI, National Cancer Institute.
*MFH is now referred to as undifferentiated pleomorphic sarcoma.

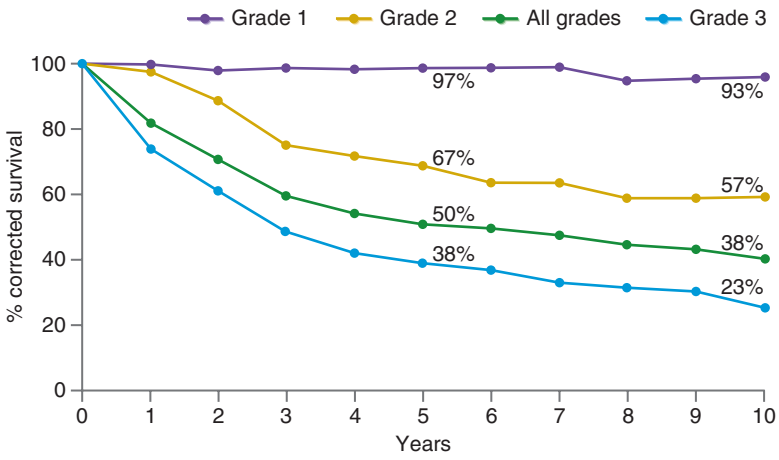


FIGURE 1-1. Grading system for soft tissue sarcomas based on three grades of malignancy. *(From Myhre Jensen O, Kaae S, Madsen EH, et al. Histopathological grading in soft-tissue tumours: relation to survival in 261 surgically treated patients. Acta Pathol Microbiol Immunol Scand 1983;91A:145.)*

TABLE 1-3 Definitions of Grading Parameters for the FNCLCC System

PARAMETER	CRITERION
Tumor Differentiation	
Score 1	Sarcoma closely resembling normal adult mesenchymal tissue (e.g., well-differentiated liposarcoma)
Score 2	Sarcomas for which histologic typing is certain (e.g., myxoid liposarcoma)
Score 3	Embryonal and undifferentiated sarcomas; sarcoma of uncertain type
Mitosis Count	
Score 1	0-9/10 HPF
Score 2	10-19/10 HPF
Score 3	≥20/10 HPF
Tumor Necrosis (Microscopic)	
Score 0	No necrosis
Score 1	≤50% tumor necrosis
Score 2	>50% tumor necrosis
Histologic Grade	
Grade 1	Total score 2, 3
Grade 2	Total score 4, 5
Grade 3	Total score 6, 7, 8

Modified from Coindre JM, Trojani M, Contesso G, et al. Reproducibility of a histopathologic grading system for adult soft tissue sarcomas. Cancer 1986;58(2):306.

FNCLCC, Fédération Nationale de Centres de Lutte Contre le Cancer; HPF, high-power field.

grading systems in 34.6% of the cases. The use of the FNCLCC system resulted in an increased number of grade 3 tumors, a reduced number of grade 2 tumors, and a better correlation with overall and metastasis-free survival when compared with the results from using the NCI system.

Limitations of Grading

Despite the widespread use of some form of grading system in the diagnosis and management of sarcomas, there is agreement among experts that no grading system performs well on every type of sarcoma. There are several reasons for this. In

TABLE 1-4 Tumor Differentiation Score According to Histologic Type in the Updated Version of the FNCLCC System

HISTOLOGIC TYPE	TUMOR DIFFERENTIATION SCORE
Well-differentiated liposarcoma	1
Myxoid liposarcoma	2
Round cell liposarcoma	3
Pleomorphic liposarcoma	3
Dedifferentiated liposarcoma	3
Fibrosarcoma	2
Myxofibrosarcoma	2
MFH*, pleomorphic type (patternless pleomorphic sarcoma)	3
Giant-cell and inflammatory MFH* (pleomorphic sarcoma, NOS, with giant cells or inflammatory cells)	3
Well-differentiated leiomyosarcoma	1
Conventional leiomyosarcoma	2
Poorly differentiated/ pleomorphic/epithelioid leiomyosarcoma	3
Biphasic/monophasic synovial sarcoma	3
Poorly differentiated synovial sarcoma	3
Pleomorphic rhabdomyosarcoma	3
Mesenchymal chondrosarcoma	3
Extraskeletal osteosarcoma	3
Ewing sarcoma/PNET**	3
Malignant rhabdoid tumor	3
Undifferentiated (spindle cell and pleomorphic) sarcoma	3

Rubin BP, et al. Protocol for the Examination of Specimens From Patients With Tumors of Soft Tissue. College of American Pathologists, June 2012. Modified from Guillou L, et al.[63]

Grading of malignant peripheral nerve sheath tumor, embryonal and alveolar rhabdomyosarcoma, angiosarcoma, extraskeletal myxoid chondrosarcoma, alveolar soft part sarcoma, clear cell sarcoma, and epithelioid sarcoma is not recommended.

*MFH is now referred to as undifferentiated pleomorphic sarcoma.

**PNET, primitive neuroectodermal tumor.

the most obvious situation, there are sarcomas in which the histologic subtype essentially defines behavior and, therefore, grade becomes redundant. This is best illustrated by a well-differentiated liposarcoma (atypical lipomatous neoplasm), an inherently low-grade, nonmetastasizing lesion, and the majority of round cell sarcomas (e.g., alveolar rhabdomyosarcoma), which are inherently high grade.

Also problematic are the rare sarcomas that are considered difficult, if not impossible, to grade. Epithelioid sarcoma, clear cell sarcoma, and alveolar soft part sarcoma are the most commonly cited examples of ungradable sarcomas, yet it is difficult to find a cogent explanation for this long-standing bias in the literature. It is possible that our grading systems fail to capture the correct histologic information in grading these rare sarcomas or, perhaps, when compared to other sarcomas, nonhistologic factors are far more influential in determining outcome than histologic factors. What is clear, however, is that there is a substantial risk of distant metastasis in the long term, whereas in the short term (5 years) where the interval for which traditional grading systems are most accurate, the risk may be low. Therefore, the assignment of grade to these tumors does not guarantee biologic equivalency to other sarcomas of comparable grade.

In a number of sarcomas, clinical features play a larger role in determining a prognosis. Cutaneous angiosarcomas are usually ungraded because multifocality and size are more predictive of outcome; paradoxically, angiosarcomas of deep soft tissue are probably amenable to grading. The difficulty of grading synovial sarcomas by histologic features has been noted in many studies, leading Bergh et al. to stratify synovial sarcoma into low- and high-risk groups using a combination of age, size, and presence or absence of poorly differentiated areas.[64] Myxoid chondrosarcoma, long considered a low-grade lesion histologically, has late metastasis in approximately 40% of cases. By stratifying lesions by age, distal versus proximal location, and grade, Meis-Kindblom et al. were able to predict an outcome.[65]

Leiomyosarcomas present another interesting paradigm. Various studies present conflicting views as to the predictive power of grading leiomyosarcomas, and there is some evidence that, as a group, myogenic tumors have a worse prognosis when matched for other variables.[66-68] The reasons for this are not clear. However, a study documenting the vascular origin of most somatic leiomyosarcomas speculated that early hematogenous dissemination may account in part for this aggressive behavior, and the authors proposed a risk model, taking into account the age, grade, and whether a tumor had been "disrupted" by prior surgical intervention.[69] Even among sarcomas that have traditionally been graded, we have begun to recognize the limitations of grading. For example, malignant peripheral nerve sheath tumors have customarily been graded, but the FNCLCC has indicated that an assigned grade does not predict metastasis.

Strictly speaking, these models are not grading systems because they incorporate histologic, clinical, and demographic variables. Nonetheless, their use gives some indication that we may gradually move in the direction of sarcoma-specific analyses, which may be used in conjunction with or, in some cases, instead of grade. The advantage of such an approach is that it allows the most appropriate criteria to be used for each sarcoma type to theoretically improve the ability to prognosticate. The disadvantage of this approach is that it presupposes an inordinate amount of clinical information for each sarcoma type, a challenge considering the rarity of some subtypes of these tumors. Moreover, the more specific these systems become, the more complicated they also become.

Another means of integrating clinical and pathologic data in a manner that accounts for sarcoma subtypes is the use of nomograms. This method collates multiple clinical and histologic parameters in a given patient and compares the data against a large population of patients with similar parameters whose outcome is known. A nomogram for a 12-year sarcoma-specific mortality has been devised by the Memorial Sloan–Kettering Cancer Center.[70,71] Ultimately, nomograms could incorporate new molecular information with a prognostic import.

Despite the limitations noted previously, grading remains one of the most powerful and inexpensive ways of assessing the prognosis in a sarcoma and is currently regarded as a major independent predictor of metastasis in the major histologic types of adult soft tissue sarcomas.[72] Consequently, a grade should be provided by the pathologist, whenever possible. Putative grade ranges for various sarcomas are shown in Figure 1-2. It should not be considered a substitute for an accurate histologic diagnosis, however. Grading, like diagnosing soft tissue sarcomas, requires representative, well-fixed, well-stained histologic material that should be obtained before neoadjuvant therapy because this process alters many of the features necessary for accurate grading. Thick or heavily stained sections are misleading because they may suggest less cellular differentiation than is actually present. Selection of the tissue sample and the length of fixation may also influence the degree of necrosis and the mitotic index. Necrosis may be prominent in tumors of which a biopsy has been previously performed or that have been irradiated or embolized and, therefore, cannot be accurately assessed in these situations. Grading is usually based on the least differentiated area of a tumor, unless it comprises a very minor component of the overall tumor.

Staging Systems

Several staging systems have been developed for soft tissue sarcomas in an attempt to predict a prognosis and to evaluate therapy by stratifying similar tumors according to prognostic factors such as the histologic grade, tumor size, compartmentalization of the tumor, and the presence or absence of metastasis. The two major staging systems used at present for adult soft tissue sarcomas were developed by The American Joint Committee on Cancer (AJCC)[55,73-75] and the Musculoskeletal Tumor Society.[76-78] Each of these systems has advantages and disadvantages, as described in the following sections.

AJCC Staging System

The original AJCC staging system was based on data obtained from a retrospective study of 702 sarcomas collected from 13 institutions. The study included only tumors that were diagnosed during the 15-year period of 1954 to 1969, were histologically confirmed, had adequate follow-up information, and underwent primary treatment in the institution that contributed the specimen. Because the sample was too small to gain sufficient data on all well-defined soft tissue sarcomas,

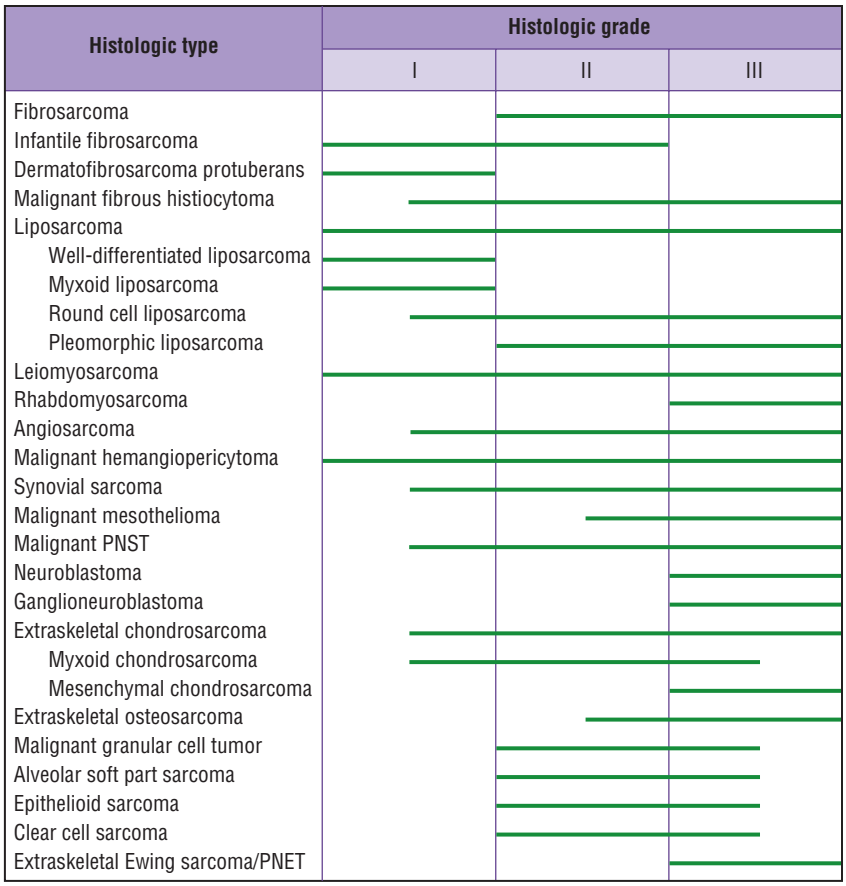


FIGURE 1-2. Soft tissue sarcomas. Estimated range of degree of malignancy based on histologic type and grade. Grade within the overall range depends on specific histologic features such as cellularity, cellular pleomorphism, mitotic activity, amount of stroma, infiltrative or expansive growth, and necrosis.

the staging system was limited to the eight most common types.[55,79] This system is based on the TNM staging system used for staging carcinomas, with the addition of histologic grade as a prognostic variable. The AJCC system published in 1992 was based on the size of the primary tumor (T), the involvement of lymph nodes (N), the presence of metastasis (M), and the type and grade of sarcoma (G).[80] In 1997, several important modifications were made to the AJCC staging system.[73] Tumor depth was subsequently incorporated into this staging system. In addition, grades 1 and 2 were grouped as low grade and grades 3 and 4 as high grade, whereas in a three-tiered grading system, grade 1 is considered low grade and grades 2 and 3 are high grade. In 2010, the AJCC published the seventh edition of its staging manual, updating the staging system for soft tissue sarcomas, as shown in Table 1-5.[75]

Musculoskeletal Tumor Society Staging System

The Enneking system, designed for sarcomas of soft tissue and bone, distinguishes two anatomic settings: T1, intracompartmental tumors confined within the boundaries of well-defined anatomic structures, such as a functional muscle group, joint, and subcutis; and T2, extracompartmental neoplasms that arise within or involve secondarily extrafascial spaces or planes that have no natural anatomic barriers to extension. There are two grades (G1 and G2) and three stages. In this system, two grades are favored because they can be better related to the two surgical procedures (wide and radical excisions) and because of the reported lack of any difference in the metastatic rate between intermediate- and high-grade tumors.[76,81] This staging system is summarized in Tables 1-6 and 1-7.

Advantages and Disadvantages of Staging Systems

These two principal staging systems serve as a valuable guide to therapy and provide useful prognostic information. Although the AJCC system is applicable to soft tissue sarcomas at any site, the development of this system was based on studies that included lesions from a variety of anatomic locations, including the extremities, retroperitoneum, and head and neck. It is difficult to compare data from patients with tumors at these sites, given the differences in the ability to eradicate tumors surgically in these anatomic locations.[82,83] The AJCC system also uses 5 cm as an important dimension for determining a prognosis, although the designation is somewhat arbitrary because size is a continuous variable. The Musculoskeletal Tumor Society system, with its emphasis on compartmentalization, is most popular with surgeons and is best tailored for lesions in the extremities. It does not include the type, size, or depth of the tumor as separate parameters; and its two-tiered grading system may be too narrow for the wide biologic range of soft tissue sarcomas. Because of the need for adequately defining compartmentalization, the system does not lend itself to retrospective staging. Furthermore, this system was devised before the routine use of

Table 1-5 Definitions and Staging System of the American Joint Committee on Cancer, 7th Edition

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
T1b	Deep tumor
T2	Tumor more than 5 cm in greatest dimension*
T2a	Superficial tumor
T2b	Deep tumor
*Note: 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.	
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1*	Regional lymph node metastasis
*Note: Presence of positive nodes (N1) in M0 tumors is considered Stage III.	
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

	PRIMARY TUMOR	REGIONAL LYMPH NODES	DISTANT METASTASIS	GRADE
Stage IA	T1a	N0	M0	G1, GX
	T1b	N0	M0	G1, GX
Stage IB	T2a	N0	M0	G1, GX
	T2b	N0	M0	G1, GX
Stage IIA	T1a	N0	M0	G2, G3
	T1b	N0	M0	G2, G3
Stage IIB	T2a	N0	M0	G2
	T2b	N0	M0	G2
Stage III	T2a, T2b	N0	M0	G3
	Any T	N1	M0	Any G
Stage IV	Any T	Any N	M1	Any G

Histopathologic Grade (FNCLCC System Preferred)	
GX	Grade cannot be assessed
G1	Grade 1
G2	Grade 2
G3	Grade 3

From AJCC Cancer Staging Handbook, 7th edition. Springer, New York, 2010.

Table 1-6 Definitions of Anatomic Extent in the Musculoskeletal Tumor Society Staging System

INTRACOMPARTMENTAL (T1)		EXTRACOMPARTMENTAL (T2)
Intra-articular	→	Soft tissue extension
Superficial to deep fascia	→	Deep fascial extension
Paraosseous	→	Intraosseous or extrafascial extension
Intrafascial compartment	→	Extrafascial compartment

Modified from Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop 1980; 153:106; and Peabody TD, Gibbs CP, Simon MA. Evaluation and staging of musculoskeletal neoplasms. J Bone Joint Surg [Am] 1998;80(8):1204.

Table 1-7 Musculoskeletal Tumor Society Staging System

STAGE	GRADE	SITE	METASTASIS
IA	G1	T1	M0
IB	G1	T2	M0
IIA	G2	T1	M0
IIB	G2	T2	M0
III	G1 or G2	T1 or T2	M1

Modified from Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop 1980; 153:106; and Peabody TD, Gibbs CP, Simon MA. Evaluation and staging of musculoskeletal neoplasms. J Bone Joint Surg [Am] 1998;80(8):1204.

advanced imaging techniques such as magnetic resonance imaging and before the widespread use of adjuvant therapy.[84] Obviously, staging soft tissue sarcomas requires a multidisciplinary approach with close cooperation among the clinician, oncologist, and pathologist. In view of the relative rarity of these tumors, staging and grading are ideally carried out in large medical centers with special interest and experience in the diagnosis and management of soft tissue sarcomas. Moreover, prospective rather than retrospective studies are necessary to test the value of the various staging systems.

References

1. Ferrari A, Sultan I, Huang TT, et al. Soft tissue sarcoma across the age spectrum: A population-based study from the surveillance epidemiology and end results database. Pediatr Blood Cancer 2011;57(6): 943–9.
2. Ross JA, Severson RK, Davis S, et al. Trends in the incidence of soft tissue sarcomas in the United States from 1973 through 1987. Cancer 1993;72(2): 486–90.
3. Piscitelli D, Ruggeri E, Fiore MG, et al. Undifferentiated high-grade pleomorphic sarcoma in a blind eye with a silicone prosthesis implant: a clinico-pathologic study. Orbit 2011;30(4):192–4.
4. Kirkpatrick CJ, Alves A, Köhler H, et al. Biomaterial-induced sarcoma: A novel model to study preneoplastic change. Am J Pathol 2000;156(4): 1455–67.
5. Zambon P, Ricci P, Bovo E, et al. Sarcoma risk and dioxin emissions from incinerators and industrial plants: a population-based case-control study (Italy). Environ Health 2007;6:19.
6. Fingerhut MA, Halperin WE, Marlow DA, et al. Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. N Engl J Med 1991;324(4):212–8.
7. Kogevinas M, Becher H, Benn T, et al. Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins. An expanded and updated international cohort study. Am J Epidemiol 1997;145(12): 1061–75.
8. Tessari R, Canova C, Canal F, et al. [Environmental pollution from dioxins and soft tissue sarcomas in the population of Venice and Mestre: an example of the use of current electronic information sources]. Epidemiol Prev 2006;30(3):191–8.
9. Collins JJ, Bodner K, Aylward LL, et al. Mortality rates among workers exposed to dioxins in the manufacture of pentachlorophenol. J Occup Environ Med 2009;51(10):1212–9.
10. Eriksson M, Hardell L, Adami HO. Exposure to dioxins as a risk factor for soft tissue sarcoma: a population-based case-control study. J Natl Cancer Inst 1990;82(6):486–90.
11. Hardell L, Eriksson M. The association between cancer mortality and dioxin exposure: a comment on the hazard of repetition of epidemiological misinterpretation. Am J Ind Med 1991;19(4):547–9.
12. Hardell L, Eriksson M, Axelson O. Agent Orange in war medicine: an aftermath myth. Int J Health Serv 1998;28(4):715–24.
13. Bertazzi PA, Consonni D, Bachetti S, et al. Health effects of dioxin exposure: a 20-year mortality study. Am J Epidemiol 2001;153(11): 1031–44.
14. Balarajan R, Acheson ED. Soft tissue sarcomas in agriculture and forestry workers. J Epidemiol Community Health 1984;38(2):113–6.
15. Smith AH, Patterson DG Jr, Warner ML, et al. Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin levels of New Zealand pesticide applicators and their implication for cancer hypotheses. J Natl Cancer Inst 1992;84(2): 104–8.
16. Leiss JK, Savitz DA. Home pesticide use and childhood cancer: a case-control study. Am J Public Health 1995;85(2):249–52.
17. Pahwa P, McDuffie HH, Dosman JA, et al. Hodgkin lymphoma, multiple myeloma, soft tissue sarcomas, insect repellents, and phenoxyherbicides. J Occup Environ Med 2006;48(3):264–74.
18. Zahm SH, Fraumeni JF Jr. The epidemiology of soft tissue sarcoma. Semin Oncol 1997;24(5):504–14.
19. Zahm SH, Ward MH. Pesticides and childhood cancer. Environ Health Perspect 1998;106(Suppl. 3):893–908.
20. Bertazzi PA, Zocchetti C, Guercilena S, et al. Dioxin exposure and cancer risk: a 15-year mortality study after the "Seveso accident." Epidemiology 1997;8(6):646–52.
21. Clapp RW, Cupples LA, Colton T, et al. Cancer surveillance of veterans in Massachusetts, USA, 1982–1988. Int J Epidemiol 1991;20(1):7–12.
22. Kramárová E, Kogevinas M, Anh CT, et al. Exposure to Agent Orange and occurrence of soft-tissue sarcomas or non-Hodgkin lymphomas: an ongoing study in Vietnam. Environ Health Perspect 1998;106(Suppl. 2): 671–8.
23. Sahmel J, Unice K, Scott P, et al. The use of multizone models to estimate an airborne chemical contaminant generation and decay profile: occupational exposures of hairdressers to vinyl chloride in hairspray during the 1960s and 1970s. Risk Anal 2009;29(12):1699–725.
24. Sherman M. Vinyl chloride and the liver. J Hepatol 2009;51(6): 1074–81.
25. Rhomberg W. Exposure to polymeric materials in vascular soft-tissue sarcomas. Int Arch Occup Environ Health 1998;71(5):343–7.
26. Mark RJ, Poen JC, Tran LM, et al. Angiosarcoma. A report of 67 patients and a review of the literature. Cancer 1996;77(11):2400–6.
27. Inoue YZ, Frassica FJ, Sim FH, et al. Clinicopathologic features and treatment of postirradiation sarcoma of bone and soft tissue. J Surg Oncol 2000;75(1):42–50.
28. Billings SD, McKenney JK, Folpe AL, et al. Cutaneous angiosarcoma following breast-conserving surgery and radiation: an analysis of 27 cases. Am J Surg Pathol 2004;28(6):781–8.
29. Weaver J, Billings SD. Postradiation cutaneous vascular tumors of the breast: a review. Semin Diagn Pathol 2009;26(3):141–9.
30. Arlen M, Higinbotham NL, Huvos AG, et al. Radiation-induced sarcoma of bone. Cancer 1971;28(5):1087–99.
31. Fang Z, Matsumoto S, Ae K, et al. Postradiation soft tissue sarcoma: a multi-institutional analysis of 14 cases in Japan. J Orthop Sci 2004;9(3): 242–6.
32. Patel SG, See AC, Williamson PA, et al. Radiation induced sarcoma of the head and neck. Head Neck 1999;21(4):346–54.
33. Yap J, Chuba PJ, Thomas R, et al. Sarcoma as a second malignancy after treatment for breast cancer. Int J Radiat Oncol Biol Phys 2002;52(5): 1231–7.
34. Nakanishi H, Tomita Y, Myoui A, et al. Mutation of the p53 gene in postradiation sarcoma. Lab Invest 1998;78(6):727–33.
35. Balamurali G, du Plessis DG, Wengoy M, et al. Thorotrast-induced primary cerebral angiosarcoma: case report. Neurosurgery 2009;65(1): E210–211; discussion E211.
36. Lipshutz GS, Brennan TV, Warren RS. Thorotrast-induced liver neoplasia: a collective review. J Am Coll Surg 2002;195(5):713–8.
37. Chang Y, Cesarman E, Pessin MS, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science 1994; 266(5192):1865–9.
38. Mesri EA, Cesarman E, Boshoff C. Kaposi's sarcoma and its associated herpesvirus. Nat Rev Cancer 2010;10(10):707–19.
39. Deyrup AT, Lee VK, Hill CE, et al. Epstein-Barr virus-associated smooth muscle tumors are distinctive mesenchymal tumors reflecting multiple infection events: a clinicopathologic and molecular analysis of 29 tumors from 19 patients. Am J Surg Pathol 2006;30(1): 75–82.
40. Shon W, Ida CM, Boland-Froemming JM, et al. Cutaneous angiosarcoma arising in massive localized lymphedema of the morbidly obese: a report of five cases and review of the literature. J Cutan Pathol 2011;38(7): 560–4.
41. Dawlatly SL, Dramis A, Sumathi VP, et al. Stewart-treves syndrome and the use of positron emission tomographic scanning. Ann Vasc Surg 2011;25(5):699.e1–3.
42. Roy P, Clark MA, Thomas JM. Stewart-Treves syndrome–treatment and outcome in six patients from a single centre. Eur J Surg Oncol 2004;30(9): 982–6.
43. Fletcher CDM. The evolving classification of soft tissue tumours: an update based on the new WHO classification. Histopathology 2006;48(1): 3–12.
44. Fletcher C, Bridges J, Hogendoorn P, et al. WHO classification of tumours of soft issue and bone. Lyon: IARC; 2013.
45. Deyrup AT, Weiss SW. Grading of soft tissue sarcomas: the challenge of providing precise information in an imprecise world. Histopathology 2006;48(1):42–50.
46. Broders A, Hargrave R, Meyerding H. Pathological features of soft tissue fibrosarcoma: with special reference to the grading of its malignancy. Surg Gynecol Obstet 1939;(69):267.
47. Coindre JM, Terrier P, Bui NB, et al. Prognostic factors in adult patients with locally controlled soft tissue sarcoma. A study of 546 patients from the French Federation of Cancer Centers Sarcoma Group. J Clin Oncol 1996;14(3):869–77.
48. Coindre JM, Trojani M, Contesso G, et al. Reproducibility of a histopathologic grading system for adult soft tissue sarcoma. Cancer 1986; 58(2):306–9.
49. Costa J, Wesley RA, Glatstein E, et al. The grading of soft tissue sarcomas. Results of a clinicohistopathologic correlation in a series of 163 cases. Cancer 1984;53(3):530–41.
50. Parham DM, Webber BL, Jenkins JJ 3rd, et al. Nonrhabdomyosarcomatous soft tissue sarcomas of childhood: formulation of a simplified system for grading. Mod Pathol 1995;8(7):705–10.
51. Jensen V, Høyer M, Sørensen FB, et al. MIB-1 expression and iododeoxyuridine labelling in soft tissue sarcomas: an immunohistochemical study including correlations with p53, bcl-2 and histological characteristics. Histopathology 1996;28(5):437–44.
52. Jensen V, Sørensen FB, Bentzen SM, et al. Proliferative activity (MIB-1 index) is an independent prognostic parameter in patients with high-grade soft tissue sarcomas of subtypes other than malignant fibrous

histiocytomas: a retrospective immunohistological study including 216 soft tissue sarcomas. Histopathology 1998;32(6):536–46.
53. Hasegawa T. Histological grading and MIB-1 labeling index of soft-tissue sarcomas. Pathol Int 2007;57(3):121–5.
54. Hasegawa T, Yamamoto S, Yokoyama R, et al. Prognostic significance of grading and staging systems using MIB-1 score in adult patients with soft tissue sarcoma of the extremities and trunk. Cancer 2002;95(4): 843–51.
55. Russell WO, Cohen J, Enzinger F, et al. A clinical and pathological staging system for soft tissue sarcomas. Cancer 1977;40(4):1562–70.
56. Jensen OM, Høgh J, Ostgaard SE, et al. Histopathological grading of soft tissue tumours. Prognostic significance in a prospective study of 278 consecutive cases. J Pathol 1991;163(1):19–24.
57. Hashimoto H, Daimaru Y, Takeshita S, et al. Prognostic significance of histologic parameters of soft tissue sarcomas. Cancer 1992;70(12): 2816–22.
58. van Unnik JA, Coindre JM, Contesso C, et al. Grading of soft tissue sarcomas: experience of the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer 1993;29A(15):2089–93.
59. Gustafson P. Soft tissue sarcoma. Epidemiology and prognosis in 508 patients. Acta Orthop Scand Suppl 1994;259:1–31.
60. Markhede G, Angervall L, Stener B. A multivariate analysis of the prognosis after surgical treatment of malignant soft-tissue tumors. Cancer 1982;49(8):1721–33.
61. Trojani M, Contesso G, Coindre JM, et al. Soft-tissue sarcomas of adults; study of pathological prognostic variables and definition of a histopathological grading system. Int J Cancer 1984;33(1):37–42.
62. Golouh R, Bracko M. What is the current practice in soft tissue sarcoma grading? Radiol Oncol 2001;35(1):47.
63. Guillou L, Coindre JM, Bonichon F, et al. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. J Clin Oncol 1997;15(1):350–62.
64. Bergh P, Meis-Kindblom JM, Gherlinzoni F, et al. Synovial sarcoma: identification of low and high risk groups. Cancer 1999;85(12): 2596–607.
65. Meis-Kindblom JM, Bergh P, Gunterberg B, et al. Extraskeletal myxoid chondrosarcoma: a reappraisal of its morphologic spectrum and prognostic factors based on 117 cases. Am J Surg Pathol 1999;23(6):636–50.
66. Deyrup AT, Haydon RC, Huo D, et al. Myoid differentiation and prognosis in adult pleomorphic sarcomas of the extremity: an analysis of 92 cases. Cancer 2003;98(4):805–13.
67. Fletcher CD, Gustafson P, Rydholm A, et al. Clinicopathologic re-evaluation of 100 malignant fibrous histiocytomas: prognostic relevance of subclassification. J Clin Oncol 2001;19(12):3045–50.
68. Koea JB, Leung D, Lewis JJ, et al. Histopathologic type: an independent prognostic factor in primary soft tissue sarcoma of the extremity? Ann Surg Oncol 2003;10(4):432–40.
69. Farshid G, Pradhan M, Goldblum J, et al. Leiomyosarcoma of somatic soft tissues: a tumor of vascular origin with multivariate analysis of outcome in 42 cases. Am J Surg Pathol 2002;26(1):14–24.
70. Eilber FC, Kattan MW. Sarcoma nomogram: validation and a model to evaluate impact of therapy. J Am Coll Surg 2007;205(Suppl. 4):S90–95.
71. Kattan MW, Heller G, Brennan MF. A competing-risks nomogram for sarcoma-specific death following local recurrence. Stat Med 2003;22(22): 3515–25.
72. Coindre JM, Terrier P, Guillou L, et al. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. Cancer 2001;91(10):1914–26.
73. Fleming ID, Cooper J, Henson D. AJCC Cancer Staging Manual. 5th ed. Philadelphia: Lippincott-Raven; 1997.
74. Greene F, Page D, Fleming I. AJCC Cancer Staging Manual. 6th ed. New York: Springer; 2002.
75. Edge S, Byrd D, Compton C, et al. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.
76. Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop Relat Res 1980;(153): 106–20.
77. Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. 1980. Clin Orthop Relat Res 2003;(415):4–18.
78. Saddegh MK, Lindholm J, Lundberg A, et al. Staging of soft-tissue sarcomas. Prognostic analysis of clinical and pathological features. J Bone Joint Surg Br 1992;74(4):495–500.
79. Russell W, Cohen J, Cutler S, et al. Staging system for soft tissue sarcoma. In: Task Force on Soft Tissue Sarcoma. American Joint Committee for Cancer Staging and End Results Reporting. Chicago: American College of Surgeons; 1980.
80. Beahrs O, Henson D, Hutter R, et al. Manual for Staging of Cancer. 3rd ed. Philadelphia: Lippincott; 1992.
81. Enneking WF, Spanier SS, Malawer MM. The effect of the Anatomic setting on the results of surgical procedures for soft parts sarcoma of the thigh. Cancer 1981;47(5):1005–22.
82. Kotilingam D, Lev DC, Lazar AJF, et al. Staging soft tissue sarcoma: evolution and change. CA Cancer J Clin 2006;56(5):282–91; quiz 314–315.
83. Lahat G, Tuvin D, Wei C, et al. New perspectives for staging and prognosis in soft tissue sarcoma. Ann Surg Oncol 2008;15(10):2739–48.
84. Peabody TD, Gibbs CP Jr, Simon MA. Evaluation and staging of musculoskeletal neoplasms. J Bone Joint Surg Am 1998;80(8):1204–18.

Chapter 2

Clinical Evaluation and Treatment of Soft Tissue Tumors

PETER W.T. PISTERS

CHAPTER CONTENTS

INTRODUCTION

Although soft tissue sarcomas (STS) are a heterogeneous group of neoplasms, their clinical evaluation and treatment follow common principles. This chapter will focus on the clinical evaluation, determinants of prognosis and outcome, and treatment of patients with STS.

The frequency and anatomic distribution of 7563 consecutive patients with STS, referred to the University of Texas MD Anderson Cancer Center, are outlined in Figure 2-1. The data illustrate that the extremity is the most common anatomic site, accounting for approximately one-half of all cases. Other important anatomic sites include the retroperitoneum, head and neck, and body wall. The site-specific distribution of histologic subtypes is outlined in Figure 2-1. Of note, the distribution of histologic subtypes is very dependent on the anatomic site; for example, in the extremity, undifferentiated pleomorphic sarcoma (so-called malignant fibrous histiocytoma), liposarcoma, and synovial sarcoma are common. In contrast, in the retroperitoneum, synovial sarcoma and undifferentiated pleomorphic sarcoma are relatively uncommon, and other histologic subtypes, particularly leiomyosarcoma and liposarcoma, predominate. The reasons for this regional variation in histologic subtype are not understood.

CLINICAL EVALUATION

Clinical Presentation and Assessment

Most patients with suspected soft tissue neoplasms present with a painless mass, although pain is reported in one-third of cases.[1] A delay in diagnosis is common; the most common

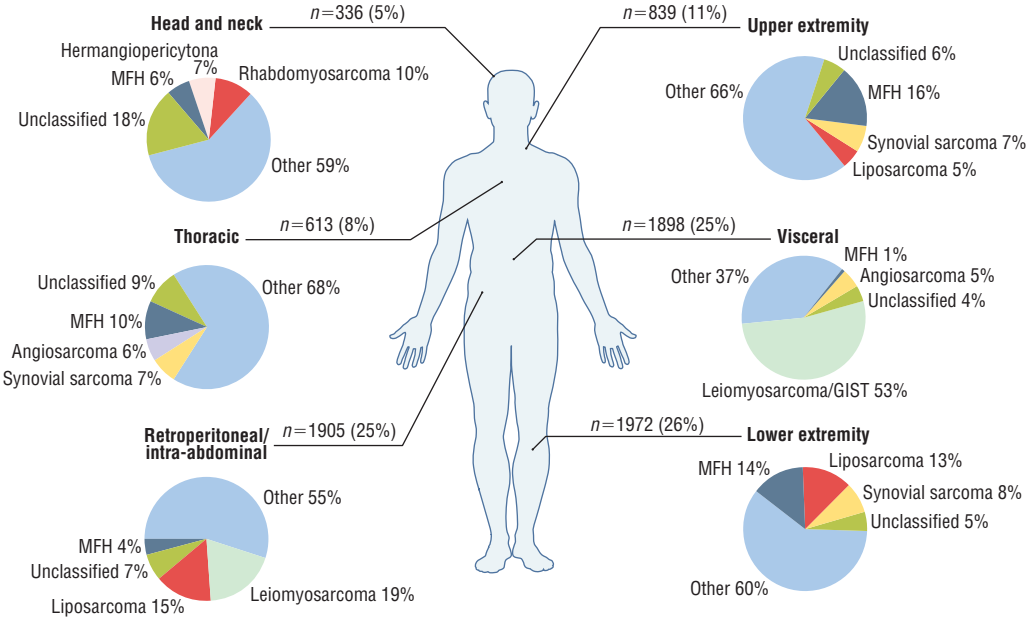


FIGURE 2-1. Anatomic distribution and site-specific histologic subtypes of 7563 consecutive STS seen at the University of Texas MD Anderson Cancer Center. *(From MDACC Sarcoma Database, June 1996 to June 2006.)*

misdiagnoses include posttraumatic or spontaneous hematoma and lipoma. A late diagnosis of patients with retroperitoneal sarcomas is very common because of the large size of the retroperitoneal space, generally slow growth rate, and the tendency of sarcomas to gradually displace rather than to invade and compromise adjacent viscera. Therefore, retroperitoneal sarcomas can reach a considerable size before the diagnosis (Fig. 2-2).

The physical examination should include an assessment of tumor size, relative mobility, and fixation. Patients with extremity soft tissue tumors should be evaluated for tumor-related neuropathy. An examination of regional lymph node basins should also be performed with the understanding that nodal metastases are relatively uncommon, occurring in less than 15% of patients with extremity STS.[2]

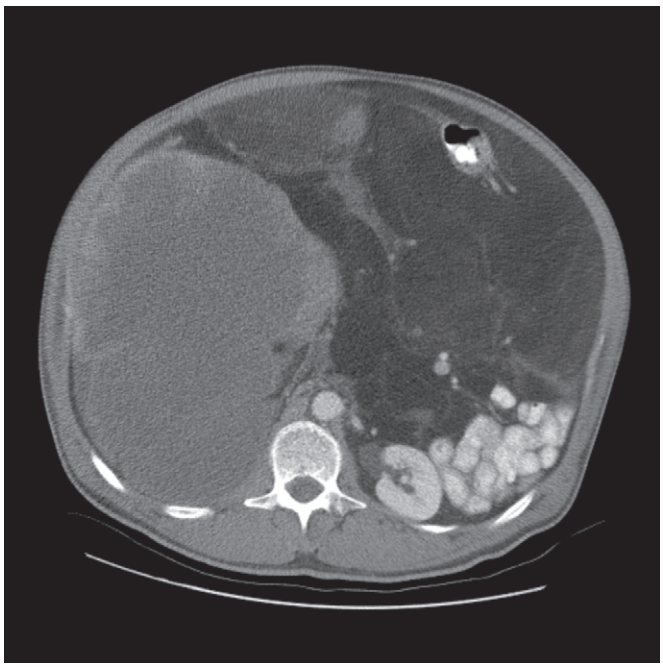


FIGURE 2-2. Contrast-enhanced CT scan of a 52-year-old patient with retroperitoneal dedifferentiated liposarcoma. The CT findings illustrate features of both well-differentiated and dedifferentiated forms of liposarcoma that frequently coexist. The dedifferentiated component is the more solid-appearing, low-density mass situated in the right retroperitoneum, whereas the well-differentiated component has similar density to the subcutaneous (normal) fat and fills the retroperitoneum, displacing the contrast-filled small bowel to the anatomic left side and posterior.

Pretreatment Evaluation

The pretreatment evaluation of the patient with a suspected soft tissue malignancy includes a biopsy diagnosis and radiologic staging to establish the extent of the disease. Practical algorithms for the evaluation of patients with extremity and retroperitoneal soft tissue masses are outlined in Figures 2-3 and 2-4.

Biopsy

A pretreatment biopsy of the primary tumor is essential for most patients presenting with soft tissue masses. In general, any soft tissue mass that is enlarging or is larger than 5 cm should be considered for a biopsy. The preferred biopsy method is generally the least invasive technique that allows for a definitive histologic assessment, including an assessment of grade. Grade is particularly important to clinicians because it impacts treatment planning and treatment options.

A percutaneous core-needle biopsy (CNB) provides satisfactory diagnostic tissue for the diagnosis of most soft tissue neoplasms. A CNB can be performed "blindly" in the clinic by clinicians without real-time radiologic control. However, many centers have moved to an image-guided CNB performed by interventional radiologists. Image-guided approaches allow for a biopsy from the areas of the tumor felt to be most likely to harbor a viable tumor (i.e., avoiding centrally necrotic areas). The use of real-time imaging also minimizes the risks for biopsy-related vascular or adjacent organ injury. In many centers, image-guided biopsy also allows for real-time pathology quality control by having a pathologist immediately available in the biopsy suite to evaluate the quality of tissue retrieved and its probable suitability for a definitive diagnosis. Studies comparing a CNB to the traditional open surgical biopsy have demonstrated the safety, reliability, and cost-effectiveness of this approach.[3-5] Additional issues related to a pathologic interpretation of the CNB are discussed in Chapter 5.

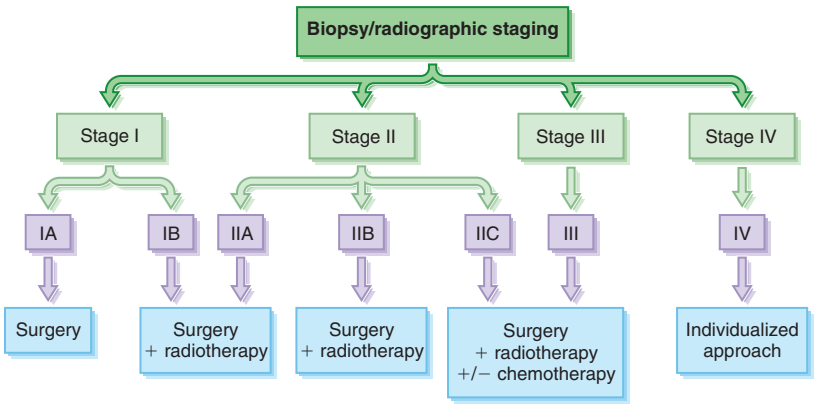


FIGURE 2-3. Pretreatment evaluation and staging algorithm for assessment of the patient presenting with an extremity soft tissue mass. AJCC, American Joint Committee on Cancer. *(From Pisters PW. Combined modality treatment of extremity soft tissue sarcomas. Ann Surg Oncol 1998;5(5):464–72.)*

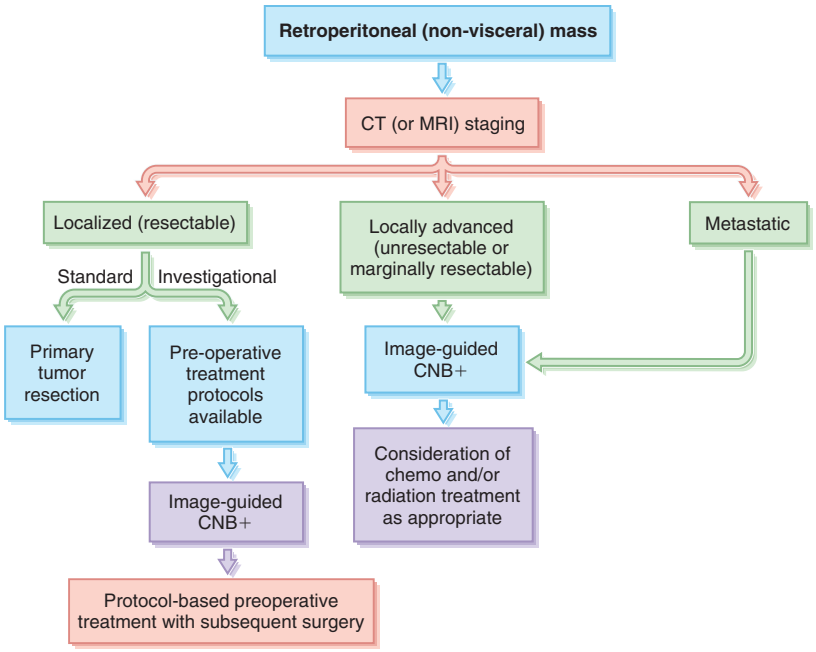


FIGURE 2-4. Pretreatment evaluation, staging, and treatment algorithm for assessment of the patient presenting with a retroperitoneal (nonvisceral) mass. Patients should undergo pretreatment cross-sectional imaging by CT or MRI. Localized, radiologically resectable masses that are believed to be neoplastic can be treated by diagnostic and therapeutic primary tumor resection. In clinical settings, where preoperative treatment protocols are available, pretreatment image-guided CNB should be used to establish the diagnosis of sarcoma for protocol eligibility. Patients with locally advanced (radiologically unresectable) or metastatic disease should undergo CNB for diagnosis followed by consideration of nonsurgical treatments. In general, CNB is sufficient for diagnosis, and surgery performed exclusively for diagnostic purposes (e.g., laparotomy for incisional biopsy) should be avoided whenever possible. CNB, core-needle biopsy.

Tumor recurrence in the needle track after a percutaneous CNB is extremely rare. Indeed, there are only case reports in the literature. However, these rare cases have led some physicians to advocate tattooing the biopsy site for subsequent excision.[6]

We have generally taken a practical approach to this issue and perform an en-bloc resection of the needle track and percutaneous entry point when feasible but not if a resection of the biopsy track requires a second incision or substantial modification of the surgical plan. The rare risks for needle track recurrence do not justify the added morbidity risk imposed by major alterations in the surgical plan.

An incisional biopsy is occasionally required to establish a definitive diagnosis for some soft tissue neoplasms. It has the advantage over a CNB of providing more tissue for a pathologic analysis and often additional tissue for tumor banking purposes. However, the morbidity of an incisional biopsy can be considerable and includes the risks for anesthesia, bleeding, and wound healing problems. Given these risks and the greater financial costs of an incisional biopsy, the incisional biopsy is generally a secondary technique that may best be reserved for cases where a definitive diagnosis cannot be established by a CNB.

An excisional biopsy may be appropriate for some patients who present with small superficial neoplasms located on the extremity or superficial body wall where the morbidity from this procedure is minimal. Although an incisional biopsy may allow for a single diagnostic and therapeutic procedure in some clinical settings, its main disadvantage is that the malignant potential of the neoplasm is unknown at the time of the biopsy, and informed decisions on surgical margins are not possible. This leaves the operating surgeon with the choice of narrow or nonexistent surgical margins with generally lower risks for wound and functional morbidity or deliberately wide margins with generally greater risks for wound and functional morbidity. The oncologic appropriateness of the surgical margin cannot be assessed preoperatively and is difficult to assess with precision intraoperatively. This disadvantage makes an excisional biopsy appropriate for only a small subset of patients who have small, superficial neoplasms and for whom a re-excision is feasible if the final diagnosis indicates a malignant lesion with compromised margins.

A percutaneous fine-needle aspiration (FNA) biopsy can also be used for cytologic assessment of some soft tissue neoplasms.[7,8] Accurate FNA diagnosis requires the availability of an expert cytopathologist experienced in the diagnosis of STS by cytology. From a practical standpoint, most centers (even academic centers) will not have a cytopathologist with sufficient experience to allow for the use of FNA for routine diagnosis and classification of primary soft tissue neoplasms. Given the frequent difficulty in histopathologic diagnosis and classification of STS, the major utility of FNA cytology in most centers is for the diagnosis of patients with suspected recurrent sarcoma. In such settings, there is already an established pathologic diagnosis such that only confirmation of a recurrence with similar features is required.

Staging

The relative rarity of STS, the anatomic heterogeneity of these lesions, and the presence of more than 50 recognized histologic subtypes of variable grades have made it difficult to establish a functional system that can accurately stage all forms of this disease. The staging system (seventh edition) of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) (formerly named International Union Against Cancer) is the most widely used staging system for STS and is presented in Chapter 1.[9] The system is designed to optimally stage extremity tumors but is also applicable to the torso, head and neck,

and retroperitoneal lesions; it should not be used for sarcomas of the gastrointestinal tract or other parenchymal organs.

A major limitation of the present staging system is that it does not take into account the anatomic site of STS. The anatomic site, however, has been recognized as an important determinant of the outcome.[10,11] Although site is not a specific component of any present staging system, outcome data should be reported on a site-specific basis.

PROGNOSTIC FACTORS

Clinicopathologic Factors

Understanding the clinicopathologic factors that affect outcome is essential in formulating a treatment plan for the patient with STS. The three major clinicopathologic factors that establish the risk profile for a given patient are tumor size, anatomic depth relative to the investing fascia of the extremity or body wall musculature (superficial versus deep), and histologic grade.[12-14] Indeed, these factors are all components of the AJCC staging system for STS.

In addition to the foregoing factors, the anatomic site, histologic subtype, and margin status are also significant, but this information is not captured by the current staging system. Moreover, unlike other solid tumors, factors that predict local recurrence are different from those that predict distant metastasis and tumor-related death (Table 2-1).[12] In other words, patients with a constellation of adverse prognostic factors for local recurrence are not necessarily at increased risk for distant metastasis or tumor-related, death, and vice versa. Therefore, clinicians and pathologists should be careful about using the terminology *high-risk disease* without qualification of which end point (local recurrence or overall survival) for which the patient is believed to be at increased risk.

TABLE 2-1 Multivariate Analysis of Prognostic Factors in Patients with Extremity STS

END POINT	ADVERSE PROGNOSTIC FACTOR	RELATIVE RISK (%)
Local recurrence	Fibrosarcoma	2.5
	Local recurrence at presentation	2.0
	Microscopically positive margin	1.8
	Malignant peripheral nerve sheath tumor	1.8
	Age >50 years	1.6
Distant recurrence	High grade	4.3
	Deep location	2.5
	Size 5.0-9.9 cm	1.9
	Leiomyosarcoma	1.7
	Nonliposarcoma histology	1.6
	Local recurrence at presentation	1.5
	Size ≥10.0 cm	1.5
Disease-specific survival	High grade	4.0
	Deep location	2.8
	Size ≥10.0 cm	2.1
	Malignant peripheral nerve sheath tumor	1.9
	Leiomyosarcoma	1.9
	Microscopically positive margin	1.7
	Lower extremity site	1.6
	Local recurrence at presentation	1.5

From Pisters PW, Leung DH, Woodruff J, et al. Analysis of prognostic factors in 1041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol 1996;14(5):1679–89.

Adverse prognostic factors identified are independent by Cox regression analysis.

Classification and Prognostic Significance of Surgical Margins

Surgeons should use the UICC resection (designated by the letter *R*) classification system for integration of the operative findings and the final microscopic surgical margins. Under this classification system, an R0 resection is defined as a macroscopically complete sarcoma resection with microscopically negative surgical margins; an R1 resection is a macroscopically complete sarcoma resection with microscopically positive surgical margins, and an R2 resection is a macroscopically incomplete (i.e., with gross residual disease) and microscopically positive surgical margins.

All therapeutic surgical procedures should be described in medical records using the R classification. To do so, surgeons must await the final pathology report, including margin assessment and then integrate the observed operative findings, including the presence or absence of a residual gross tumor with the final assessment of microscopic surgical margins. The operative report, discharge summary, and related medical records should describe the procedure using the R classification. As an example, a surgical procedure that involved a wide local resection of a left anterior thigh soft tissue leiomyosarcoma with satisfactory gross tumor margins, no operatively defined residual gross tumor, and negative microscopic surgical margins would be described as "R0 resection of left anterior thigh leiomyosarcoma."

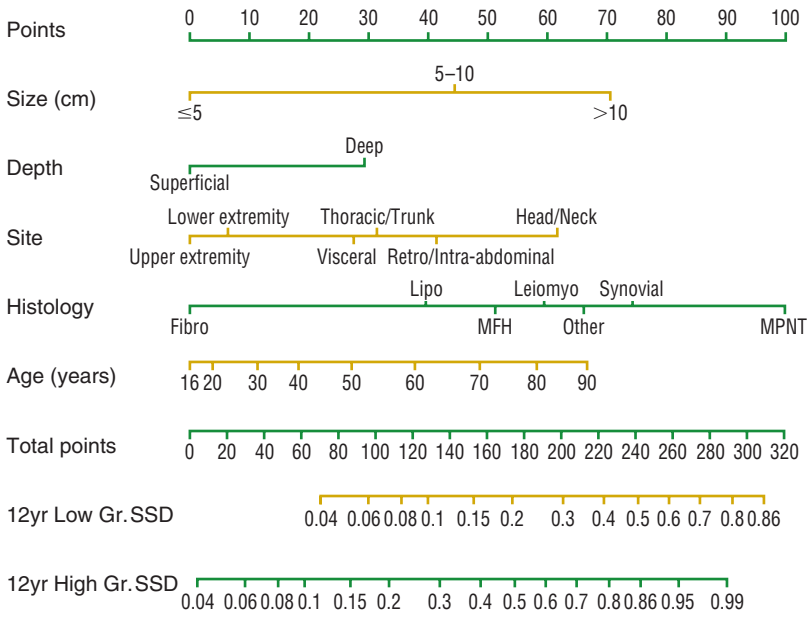
The type of microscopically positive surgical margins also appears important. For example, an R1 resection for a low-grade liposarcoma or an R1 after preoperative radiation treatment in which a microscopically positive margin is anticipated (and accepted) in order to preserve critical structures has a relatively low risk (<10%) for local recurrence.[15]

In contrast, patients undergoing "unplanned" excision followed by a re-excision with positive margins (i.e., R1 re-resection) or patients with unanticipated positive margins after primary resection are at increased risk for local recurrence, with rates approaching 30%. Therefore, the specific clinical setting needs to be considered when interpreting the relative risk for local recurrence after an R1 resection.

Nomograms for Assessment of Individual Patient Prognosis

Kattan et al. from the Memorial Sloan–Kettering Cancer Center (MSKCC) have used a database of over 2000 prospectively followed adult patients with STS to predict the probability of sarcoma-specific death by 12 years.[10]

The results have been used to construct and internally validate a nomogram to predict sarcoma-specific death (Fig. 2-5). This nomogram matches a patient's prognostic score against those of previously treated patients with comparable tumor and patient factors to estimate individual patient risk for sarcoma-related death. The MSKCC nomogram has been externally validated[16,17] and is considered to be an extremely valuable tool for individual patient counseling and determination of the frequency for individual



Instructions for physician: Locate the patient's tumor size on the size axis. Draw a line straight upwards to the points axis to determine how many points towards sarcoma-specific death the patient receives for his tumor size. Repeat this process for the other axis, each time drawing straight upward to the points axis. Sum the points achieved for each predictor and locate this sum on the Total Points axis. Draw a line straight down to either the Low Grade or High Grade axis to find the patient's probability of dying from sarcoma within 12 years assuming he or she does not die of another cause first.

Instruction to patient: "If we had 100 patients exactly like you, we would expect between <predicted percentage from nomogram −8%> and <predicted percentage + 8%> to die of sarcoma within 12 years if they did not die of another cause first, and death from sarcoma after 12 years is still possible."

FIGURE 2-5. Postoperative nomogram for 12-year sarcoma-specific deaths, in 2163 patients treated at the MSKCC. Fibro, fibrosarcoma; GR, grade; Lipo, liposarcoma; Leiomyo, leiomyosarcoma; MFH, malignant fibrous histiocytoma; MPNT, malignant peripheral-nerve sheath tumor; SSD, sarcoma-specific death. *(From Kattan MW, Leung DH, Brennan MF. Postoperative nomogram for 12-year sarcoma-specific death. J Clin Oncol 2002;20(3):791–6.)*

patient follow-up. The nomogram is available online at www.nomograms.org.

TREATMENT OF LOCALIZED PRIMARY EXTREMITY SARCOMAS

Surgery

Surgical resection remains the cornerstone of therapy for localized primary STS. The following discussion focuses on STS in the limbs, the most common anatomic site of origin, but the principles of treatment are generally applicable for patients with sarcomas at other anatomic sites.

Historically, amputation was the primary treatment for patients with extremity STS. However, there has been a marked decline in the rate of amputation as the primary therapy for extremity STS. With the widespread application of multimodality treatment strategies, the vast majority of patients with localized STS of the extremities undergo limb-sparing treatment, and less than 10% of patients presently undergo amputation.[18,19]

Satisfactory local resection involves resection of the primary tumor with a margin of normal tissue around the lesion. Dissection along the tumor pseudocapsule (enucleation or "shelling out") is associated with local recurrence rates ranging between 33% and 63%.[20-22]

In contrast, wide local excision with a margin of normal tissue around the lesion is associated with lower local recurrence rates in the range of 10% to 31%, as demonstrated in the surgery-alone control arms of randomized trials evaluating postoperative radiotherapy (RT) and in single-institution reports.[23-25]

The issue of what constitutes an acceptable gross surgical margin is complex, and there are limited prospective data specifically addressing surgical margins in STS surgery. Circumferential margin assessment in sarcomas is imprecise owing to the complex anatomy of each tumor and the tendency of soft tissue around the tumor to collapse and adopt its inherent shape when not under the continuous tension that is applied to the tissues as part of modern soft tissue surgery. This can result in significant discordance between the intraoperative perception and the pathologic evaluation of the gross surgical margin.

Unlike resections for cutaneous melanoma in which gross surgical margins can be measured with a ruler at the time of surgery, a gross margin assessment for STS cannot be measured so precisely. In addition, it is likely that not all soft tissues provide an equivalent barrier to tumor extension. For example, it is believed that a smaller gross margin that includes a fascial barrier is, in general, a more secure margin than a comparable gross margin that does not include fascia. For many of these reasons, a margin assessment for sarcomas by both surgeons and pathologists will continue to have an

PART IX

FUTURE TRENDS IN PRIMATE TOXICOLOGY

unavoidable degree of imprecision that probably exceeds the inherent imprecision in the assessment of gross margins of other solid tumors.

Combined Modality Limb-Sparing Treatment

Currently, approximately 90% of patients with localized extremity sarcomas undergo limb-sparing treatment.[18,26]

The use of limb-sparing multimodality treatment approaches for extremity sarcoma was based on an important phase III trial from the U.S. National Cancer Institute (NCI) in which patients with extremity sarcomas amenable to limb-sparing surgery were randomly assigned to receive amputation or limb-sparing surgery with postoperative RT.[27,28]

Both arms of this trial included postoperative chemotherapy with doxorubicin, cyclophosphamide, and methotrexate. With more than 9 years of follow-up information, this study established that for patients for whom limb-sparing surgery is an option, limb-sparing surgery combined with postoperative RT and chemotherapy yielded disease-related survival rates comparable to those for amputation and simultaneously preserved a functional extremity.[27,28]

This trial established limb-sparing treatment as the standard treatment for patients with localized extremity STS. Amputation is used in only clinical settings in which local tumor anatomy precludes limb-sparing approaches, most commonly as a result of tumor involvement of functionally significant neurovascular structures.

Today, a discussion of limb-preserving approaches must be linked to a discussion of the role of adjuvant therapies, most commonly radiation treatment. Several randomized, controlled trials have addressed issues surrounding the use of adjuvant therapy and collectively have established important milestones in the evolution of the local management of STS.

Yang et al. randomized 91 patients with high-grade extremity lesions following limb-sparing surgery to receive adjuvant chemotherapy alone or concurrent chemotherapy and RT.[24]

An additional 50 patients with low-grade tumors were to receive adjuvant RT or no further treatment following limb-sparing surgery. The local control rate for those who received RT was 99% compared to 70% in the non-RT group (p <0.0001).[24]

The results were similar for high- and low-grade tumors (Table 2-2).

Adjuvant radiation using brachytherapy (BRT) was also evaluated at the MSKCC in a randomized trial of 126 cases treated between 1982 and 1987 (see Table 2-2).[23]

Patients with localized extremity and superficial trunk sarcomas undergoing surgery were randomly assigned to be treated by surgery alone or by a combination of surgery and BRT. BRT was administered postoperatively through an iridium-192 implant that delivered 42 to 45 Gy over 4 to 6 days. At 5 years, the local control rate for high-grade tumors was 91% with BRT compared to 70% in surgery-alone controls (p <0.04). Of note, no improvement in local control with BRT was evident for patients with low-grade tumors. The local control rate was 74% with surgery alone and 64% with BRT. The full explanation for grade-specific differences in local control with BRT remains unresolved, although one suggestion implicates the relatively long cell cycle of low-grade tumors; low-grade tumor cells may not enter the radiosensitive phases of the cell cycle during the relatively short BRT time.[23]

Taken together, the NCI and MSKCC randomized trials have provided the evidence to support surgery plus radiation as the standard approach for most patients with operable extremity and superficial trunk sarcomas. At this time, there are no controlled trials evaluating the use of radiation treatment for patients with sarcomas in non-extremity sites. However, most multidisciplinary groups have extrapolated from the foregoing data and have assumed that radiation improves local control for patients with non-extremity sarcomas as well.

Treatment by Surgery Alone—without Radiotherapy

Radiation provides the unquestioned clinical benefit of decreasing local recurrence for the majority of patients with STS. However, the known secondary adverse effects of radiation, which include edema, fibrosis, and radiation-induced second malignancies, have also prompted clinicians to try to identify a subset of patients who could be treated by surgery alone without compromising local disease control. Careful patient selection for unimodality treatment by surgery alone is essential. Important criteria include an R0 resection in clinical settings in which the anatomic site clearly allows for adequate surgical margins. The importance of anatomic site in considering treatment by surgery alone is illustrated by the hypothetical cases of two patients with 4-cm, high-grade sarcomas: one in the anterior thigh and the second case with an identically sized tumor located in the wrist. Clearly, the first patient could undergo satisfactory treatment by surgery alone because the surgical margins can and should be satisfactory. However, this is not the case for the second patient because

Table 2-2 Phase III Trials of Adjuvant Radiotherapy for Localized Extremity and Trunk Sarcoma Stratified by Grade

HISTOLOGIC GRADE	FIRST AUTHOR/ INSTITUTION	TREATMENT GROUP	RADIATION DOSE, GY	NO. OF PATIENTS	NO. OF LOCAL FAILURES (%)	LRFS (%)	OS (%)
High grade	Pisters/MSKCC[23]	Surgery + BRT	42-45	56	5 (9)	89	27
		Surgery	–	63	19 (30)	66	67
	Yang[24]	Surgery + XRT	45 + 18 (boost)	47	0 (0)	100	75
		Surgery	–	44	9 (20)	78	74
Low grade	Pisters[23]	Surgery + BRT	42-45	22	8 (36)	73	96
		Surgery	–	23	6 (26)	73	95
	Yang[24]	Surgery + BRT	45 + 18 (boost)	26	1 (4)	96	NR
		Surgery	–	24	8 (33)	63	NR

MSKCC, Memorial Sloan-Kettering Cancer Center; BRT, brachytherapy; LRFS, local recurrence-free survival; OS, overall survival; NCI, National Cancer Institute; XRT, external-beam radiotherapy; NR, not reported.

the wrist or other anatomically similar site is not amenable to wide margins without amputation and sacrifice of neurovascular structures. Table 2-2 summarizes recent reports of patients treated by surgery alone and demonstrates that very acceptable local control rates of 10% or less can be achieved in carefully selected patients treated by surgery alone.

Amputation

Although sparingly used, amputation is still the appropriate treatment for a subset of patients who present with locally advanced primary tumors. The criteria for patient selection for amputation include:

- Radiologically defined major vascular, bony, or nerve involvement such that a "limb sparing" primary tumor resection will result in critical loss of function or tissue viability
- Localized nonmetastatic disease (Amputation is usually not considered for patients with established metastatic disease.)

For patients without limb-sparing surgical options, amputation offers excellent local tumor control and the prospect of prompt rehabilitation; therefore, there remains a small but well-defined role for amputation in the management of patients with extremity STS.

Management of Regional Lymph Nodes

There is no role for routine regional lymph node dissection in most patients with localized STS given the low (2% to 3%) incidence of lymph node metastasis in adults with sarcomas.[2,29] However, patients with angiosarcoma, embryonal/alveolar rhabdomyosarcoma, clear cell sarcoma, and epithelioid sarcoma are at increased risk for lymph node metastasis and should be carefully examined for lymphadenopathy. These patients should be considered for a sentinel lymph node biopsy as part of a definitive surgical treatment. A therapeutic lymph node dissection should be considered for patients with pathologically proven lymph node involvement who do not have radiologically defined metastatic disease. A therapeutic lymph node dissection may result in survival rates as high as 34%.[2]

The prognosis of patients with pathologically positive metastatic disease to lymph nodes has been generally regarded as similar to patients with visceral metastatic disease. However, a recent series of patients with isolated lymph node metastasis treated intensively with combined modality treatment showed somewhat better outcomes, approaching those of patients with localized, high-risk (stage III) disease. This report and the relative rarity of nodal involvement in patients with STS raise questions as to whether nodal involvement should be reconsidered in the future editions of the AJCC staging system.[30,31]

Radiotherapy

Rationale for Combining Radiotherapy with Surgery

The use of RT in combination with surgery for STS is supported by two phase III clinical trials (see Table 2-2)[23,24] and is based on two premises: microscopic foci or residual disease can be destroyed by RT, and less radical surgery can be performed when surgery and RT are combined. Although the traditional belief was that STS is resistant to RT, radiosensitivity assays performed on sarcoma cell lines grown in vitro have confirmed that the radiosensitivity of sarcomas is similar to that of other malignancies; this confirmation supports the first premise.[32,33]

The second premise stresses the philosophy of preservation of form (including cosmesis where possible) and function as a goal for many patients with extremity, truncal, breast, and head and neck sarcomas.[34-36]

Similar principles govern the frequent use of RT for sarcomas at anatomically challenging sites, such as the retroperitoneum, head and neck, or paravertebral regions.

Sequencing of Radiotherapy and Surgery

The optimal sequencing of surgery and radiation is a subject of considerable controversy and debate. Advantages of preoperative radiation include a generally lower radiation dose (50 Gy) and small field size with reduced risks for long-term treatment sequelae, including edema and fibrosis. These advantages occur at the cost of increased risk for surgical wound complications resulting from radiation-related impairment in wound healing. Advantages of postoperative radiation treatment include the ability to treat pathologically diagnosed and staged patients with known margin status. However, postoperative radiation is usually administered to a higher dose (65 Gy) and is associated with greater risks for treatment-related, long-term complications, including edema and fibrosis. Therefore, treatment-sequencing involves complicated trade-off issues that need to be individualized and carefully discussed with the patient.

The NCI of Canada/Canadian Sarcoma Group SR2 clinical trial (Fig. 2-6) is the only prospective, randomized comparison of preoperative versus postoperative RT.[37]

Patients were randomly assigned to be treated by surgery with either preoperative or postoperative radiation (with a radiation boost dose for patients with microscopically positive surgical margins). The primary end point of the trial was major wound complications. The SR2 trial demonstrated that wound complications were twice as common with preoperative RT as with postoperative RT (35% versus 17%, respectively), although the increased risk was almost exclusively confined to patients with sarcomas of the lower extremity. Of interest, a recent report from the University of Texas MD Anderson Cancer Center, using the same criteria for classifying wound complications as were used in the Canadian NCI trial, found almost identical results.[38]

The SR2 trial also provided important data on long-term, treatment-related complications. Patients randomized to postoperative radiation had significantly greater rates of generally irreversible fibrosis and edema.[39]

This observation is potentially important because patients with significant fibrosis, joint stiffness, or limb edema had significantly lower-limb function scores at these later time points.[39]

The analysis of late-treatment effects demonstrated that the radiation field size was associated with greater degrees of fibrosis and joint stiffness and also may be related to edema.[40]

The SR2 trial was neither designed nor statistically powered to compare traditional oncologic end points such as local control and overall survival (these were secondary end points in the trial). The 5-year results for preoperative versus postoperative, respectively, include: local control, 93% versus 92%;

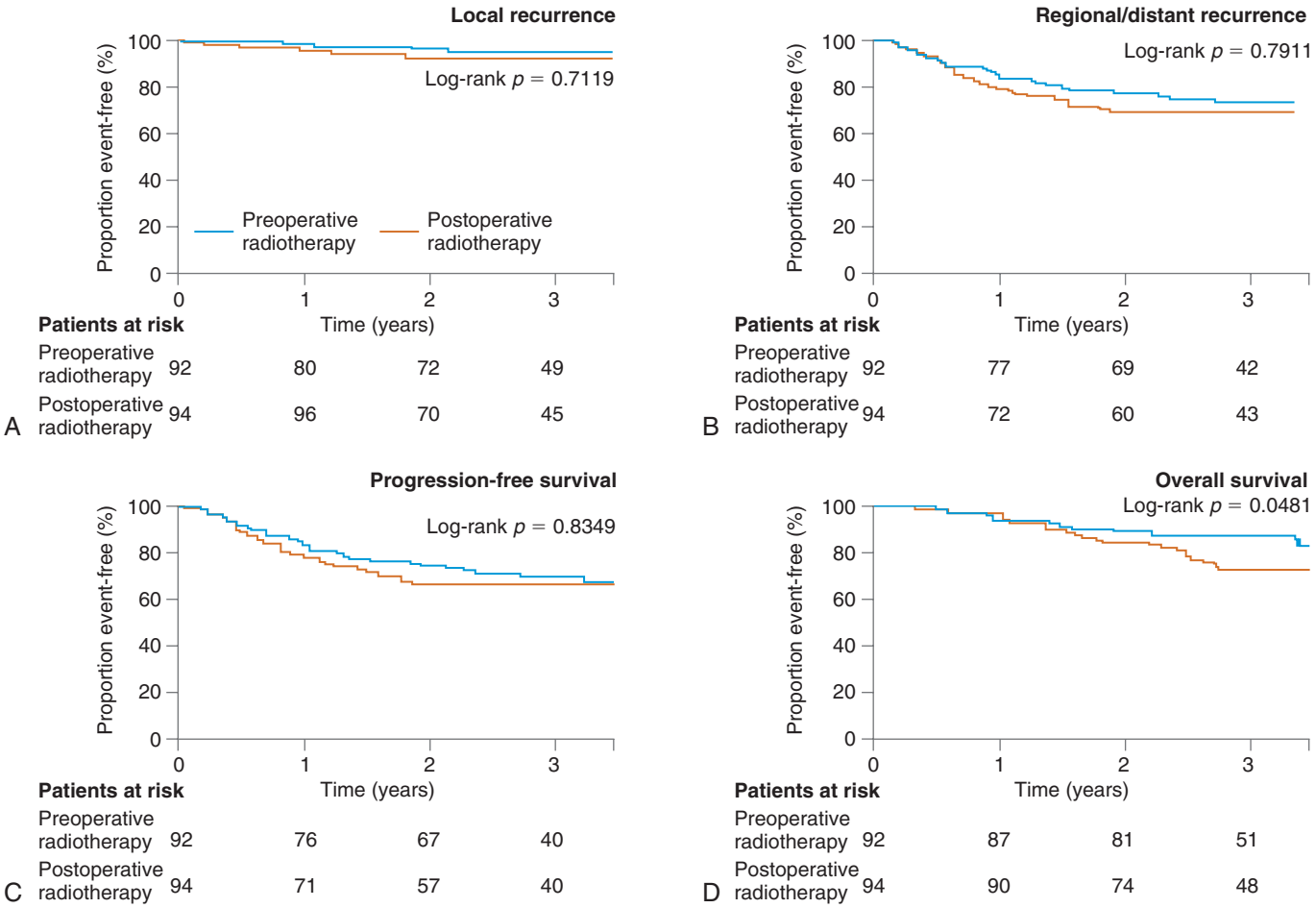


FIGURE 2-6. A-D, Kaplan–Meier plots for probability of local recurrence, metastasis (local and regional recurrence), progression-free survival, and overall survival in the Canadian Sarcoma Group randomized trial of the National Cancer Institute of Canada Clinical Trials Group comparing preoperative and postoperative radiotherapy. *(Reproduced with permission of The Lancet Ltd. from O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet 2002;359(9325):2235–41.)*

metastatic-relapse free, 67% versus 69%; recurrence-free survival, 58% versus 59%; overall survival, 73% versus 67% ($p = 0.48$); cause-specific survival, 78% versus 73% ($p = 0.64$).[41]

Cox modeling showed only resection margins as significant for local control. Tumor size and grade were the only significant factors for metastatic relapse, overall survival, and cause-specific survival. Grade was the only consistent predictor of recurrence-free survival.[41]

For the present, decisions about preoperative versus postoperative RT should be individualized, taking into account tumor location, tumor size, RT field size, comorbidities, and risks. In general, preoperative RT provides some advantages over postoperative RT but exposes the patient to significantly increased risks of serious (generally reversible) postoperative wound complications. A summary of the relative indications that can be used to select patients for preoperative RT is provided in Table 2-3.

Radiation Treatment Techniques

External beam radiation treatment (EBRT) and BRT are used for patients with STS. There are no prospective trials that directly compare EBRT and BRT, but each of these techniques has been compared with surgery alone.[23,24]

EBRT is the most commonly used radiation treatment technique for patients with STS. EBRT is widely available and can be administered by all radiation oncologists. It is also effective for patients with both high- and low-grade sarcomas. Treatment is usually administered on an outpatient basis in daily fractions of 1.8 to 2.0 Gy (Monday to Friday) to total doses of 50 Gy (preop dose; 5-week duration) or 60 to 66 Gy (postop dose; 6½ weeks).

In contrast, BRT for STS is available in only specific centers where there are trained radiation oncologists and appropriate radiation isotope storage and handling facilities, but BRT does offer several advantages. Because of the shorter treatment time (4 to 6 days) compared to EBRT, it is usually administered on an inpatient basis during the same hospital stay and is more easily integrated into treatment protocols that include systemic chemotherapy. Because irradiated tissue volume is less, BRT may confer long-term functional advantages. BRT also costs $1200 per patient, which is less than the cost of EBRT.[42]

One specific limitation of BRT is that it should be used for patients with only high-grade sarcomas (as well as R0 cases) because the only randomized trial that evaluated this technique demonstrated that BRT does not appear effective for

Table 2-3 Relative Indications for Preoperative RT, Despite Concerns Related to Wound Complications

TREATMENT CONTEXT/SARCOMA SITE	ISSUES OF CONCERN	COMMENTS
Head and neck Paranasal sinus	Proximity to optic apparatus (eye, orbit, chiasma)	Major visual functional deficit can be minimized
Skull base	Proximity to spinal cord, brainstem	Other "lesser" morbidities (dental, xerostomia) may also be less due to reduced doses and volumes
Cheek and face		
Split-thickness skin graft reconstruction (especially lower limb)	Skin graft breakdown and consequent infection	Many months to years of recreational and/or vocational disability may occur during healing (rare)
Retroperitoneum	Proximity to bowel, liver, kidney	Critical organs may be displaced by tumor or not fixed or adherent as is likely in postoperative setting
	Large-volume GTV or CTV occupying coelomic cavities	Entire tumor treated before possible contamination of cavity
Some small bowel lesions	Proximity to critical anatomy, especially intestine with side wall adherence	Contamination of abdominal cavity renders postoperative RT unsuitable
Thoracic wall/pleura	Proximity to lung or cardiac structures	Lung may be displaced by chest wall or pleural tumor and can be avoided with preoperative RT, or permits GTV to be treated before operative contamination
Abdominal trunk walls, pelvic side wall	Proximity to kidney, bowel, liver, ovaries	Avoid CT encroachment on vulnerable anatomy GTV adjacent to dose-limiting critical anatomy
Thoracic inlet/upper chest	Proximity to brachial plexus	Dose limitation of critical anatomy lends itself to preoperative wall low neck RT. Additional volume considerations
Medial thigh (young male)	Proximity to testes	Permanent infertility may be avoided
Central limb tumor	Proximity to other compartments	Permits partial circumferential sparing, which would not be feasible in postoperative setting

From O'Sullivan B, Wylie J, Catton C, et al. The local management of soft tissue sarcoma. Semin Radiat Oncol 1999;9(4):328–48

CTV, clinical target volume; GTV, gross tumor volume; RT, radiotherapy.

patients with low-grade sarcomas (see Table 2-2),[24,43-44] and retrospective data suggest that BRT may not provide optimal local control for R1 cases.[45]

BRT may also have an advantage in the following situations in which normal-tissue tolerance to conventional external beam radiation has been compromised: (1) a postoperative boost in patients who have received preoperative RT or (2) radiation for local recurrence in a previously irradiated field.[46-49]

Intensity modulated radiation treatment is a radiation delivery technique that allows external beams designed with variable intensity to be delivered across their profiles, in contrast to the uniform flat profile used in traditional external beam RT. These variable-intensity beams are not only shaped according to the needs of the target but also take into account the dose provided by the others. This allows the beams to closely conform to the target while avoiding other structures. It may be particularly valuable for tumors of complex shape, such as sarcomas, and has recently been used to treat large intra-abdominal targets, including retroperitoneal sarcomas.[50] Clinical results are anticipated from studies of these improvements in RT planning and delivery.

Chemotherapy

Chemotherapy is the mainstay of therapy for patients with metastatic (stage IV) STS. The use of chemotherapy in the adjuvant setting has been controversial but is gaining increased acceptance when used selectively.

Chemotherapy Following Primary Surgical Resection

Although local or locoregional recurrence is a problem for a small subset of patients following primary therapy, the major risk to life in sarcoma patients is uncontrolled microscopic or macroscopic systemic disease. Increasingly, major sarcoma centers are taking a histology-specific approach to selecting patients for consideration of adjuvant treatment.

Adjuvant chemotherapy is an appropriate standard of care for the Ewing family of tumors and for rhabdomyosarcoma.[51-53] However, for more common STSs such as leiomyosarcoma, liposarcoma, and high-grade undifferentiated pleomorphic sarcoma, the benefit for chemotherapy, if there is one, is small.[54] Because adjuvant therapy is used by many practitioners for more common diseases where the benefit is a relatively small one, such as stage I breast cancer and stage II colon cancer, this small potential benefit is an issue that needs to be discussed on an individual basis with patients. Certainly, the lack of available effective agents for metastatic sarcoma has impeded progress in this area, but the utility of imatinib in a gastrointestinal stromal tumor gives hope that new agents will contribute to the ultimate goal of any type of systemic therapy, specifically to increase the cure rate of new patients.

There have been over a dozen studies of anthracycline-based adjuvant chemotherapy for STS, which date back nearly as long as the initial development of doxorubicin.[55,56] These will not be reviewed here because anthracycline/ifosfamide-based therapy constitutes a better standard of care in patients offered adjuvant chemotherapy, and only one of the studies completed by 1992 had used ifosfamide. The best summary of