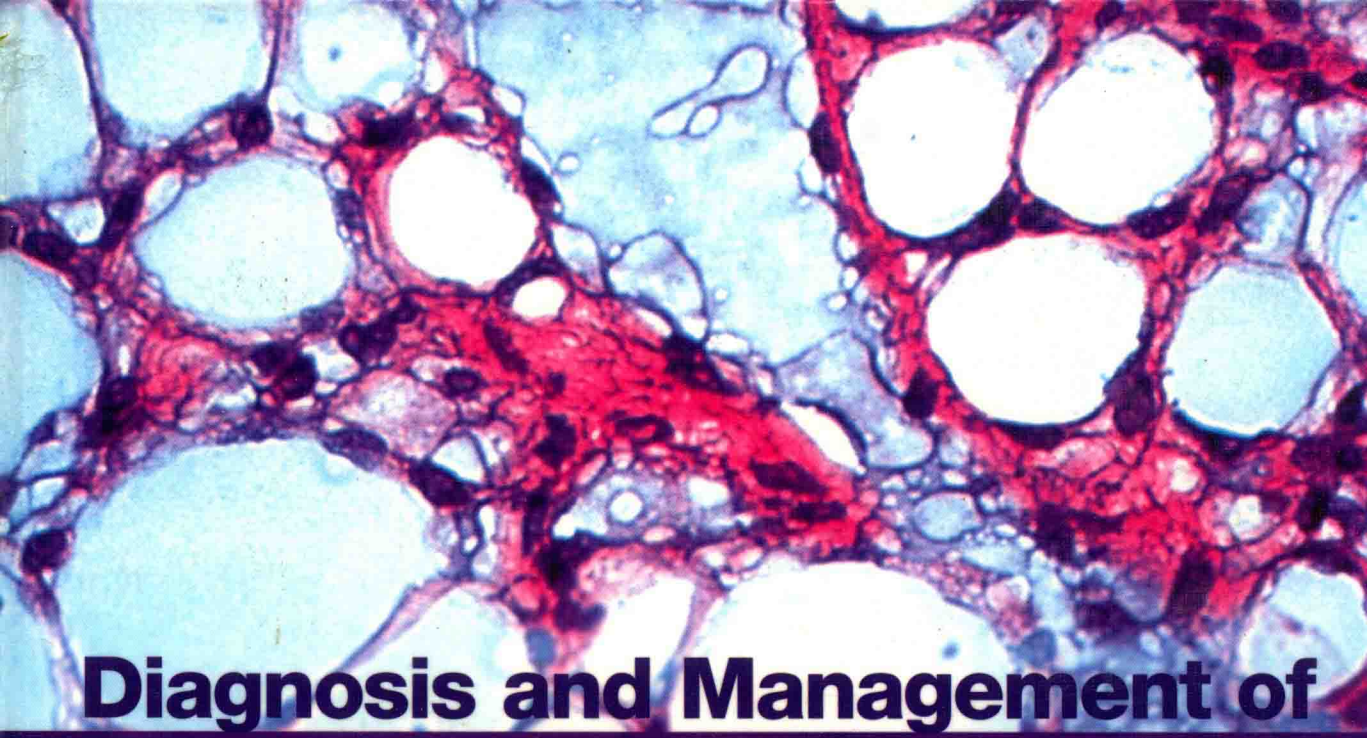

Diagnosis and Management of Soft Tissue Sarcoma

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Diagnosis and Management of Soft Tissue Sarcoma

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Introduction

Once a rare and unfamiliar disease, of interest to a small group of clinicians and pathologists, soft tissue sarcoma has progressively 'come of age'. In the USA, the incidence is still relatively low, 7000–8000 cases each year, about half of whom will go on to die of their disease. Sufficient experience has now been accumulated by the appropriate use of prospective databases, to define the important issues in management. Major advances have been made in defining prognostic factors for outcome, such that predictions can be made prior to treatment for high-risk and low-risk groups. Appropriate low morbidity treatment can then be applied to the low-risk group, whereas high-risk subgroups can be identified for investigational treatment in efforts to minimize local recurrence, metastasis and death.

This text draws heavily on the experience at Memorial Sloan-Kettering Cancer Center, based on a prospective database begun by the senior author in 1982 and maintained by the institution with extensive support from many colleagues.

Acknowledgements

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Many colleagues have been involved in the management of these patients, particularly Dr John Healey in Orthopedic Oncology, Dr Ephraim Casper in Medical Oncology, Dr Louis Harrison and Dr Kaled Alektiar in Radiation Oncology, Dr David Panicek in Radiology, Dr James Woodruff, Dr Steven Hajdu and Dr Christina Antonescue in Pathology, Dr Jeffrey Gaynor and Dr Denis Leung in Biostatistics, Dr Michael Burt and Dr Robert Downey in Thoracic Surgical Oncology, and numerous Surgical Fellows with whom the authors have had the privilege to work.

Finally, none of the information described herein would have been possible without the quite extraordinary involvement of our patients. They, above all, have taught us more than we can possibly acknowledge.

The publishers would like to thank the editors of the journals from which material has been acknowledged for permission to use data and illustrations.

Contents

1 Historical perspectives and evolution of treatment

Historical perspectives

The term 'sarcoma' is derived from the Greek word 'sarkoma', meaning a fleshy excrescence. In his writings, Galen (AD 130–200) regarded these fleshy tumors as cancerous and cautioned against surgical intervention.[1] With the advent of the light microscope in 1592, a few descriptions were recorded of soft tissue sarcoma, including that of a myxoid liposarcoma by Marcus Severinius (1580–1637)[2] and a retroperitoneal liposarcoma by Morgagni (1682–1771).[3] The use of thin sections and the achromatic lens, along with other refinements of the microscope, permitted further advances in the recognition of soft tissue sarcoma.

In the eighteenth and nineteenth centuries, Bichat (1771–1801), Abernathy (1780–1848) and Laennec (1781–1826) were among those who made important contributions to the morphologic understanding of cancer. As best we know, the term 'soft cancer' was introduced by Wardrop (1782–1869), an Edinburgh surgeon who studied in Vienna, but the name in terms of the definition of soft cancer, as differentiated from carcinoma, has been attributed to Charles Bell (1774–1842), a neuroanatomist. Bell's book, *Surgical Observations*, was published in 1816.[4]

Bichat postulated that anatomic structures consisted of parenchymal cells, which he called 'filaments', and stroma, which he called 'fiber' or 'tissue', thus beginning the science of histology. He saw that the stroma was common to many tumors, while the parenchymal cells were specific.[5] Abernathy, a pupil of John Hunter, was a prominent surgeon of London who recognized the difference between true neoplasms and non-neoplastic swellings such as cysts, aneurysms, and abscesses. He suggested that tumors be classified by their anatomic structure and offered the first classification of sarcomas.[6] Early descriptions to which names have been applied include those of Dupuytren, who in 1832 reported on bladder soft tissue lesions and plantar fibromatosis.

Understanding of the nature of soft tissue sarcoma progressed in the nineteenth century through the studies of cellular pathologists, particularly those of Cruveilhier (1791–1874) and Johannes Muller (1801–1858), who described the cellular origin of various soft tumors. He seems to have coined the term 'desmoid' in 1838.[4] Many of his ideas were reinforced by Rokitansky (1804–1878). Most importantly, Virchow (1821–1902) advanced the significant view that 'annis cellula et cellulare', which literally means 'where a cell arises, there a cell previously existed'. Sarcomas he defined as 'new formations of the connective tissue ... distinguishable from the corresponding fully evolved tissue by their immaturity', thereby laying the foundation for

the histogenetic classification. His further classification according to microscopic features, which separated sarcomas from carcinomas of epithelial origin, was published in 1863, and is similar to what is accepted today.[7] His observations and concepts formed some of the most important milestones in the study of soft tissue sarcomas and paved the way for the development of our current understanding and treatment of these neoplasms.

At that time sarcomas were considered essentially benign, and 'local growths' and 'carcinoma' were still reserved for lesions that had potential for metastasis. Samuel Gross (1805–1884) described distinctions between sarcoma and carcinoma in the fourth edition of his book, *A System of Surgery*, in 1866.

When Mallory (1862–1941) introduced his method of staining tissues at the beginning of the twentieth century, the study of soft tissue sarcoma by histopathologic techniques began, and the description and histogenetic classification of sarcomas was advanced by others.

At the Mayo Clinic in the 1920s, Broders suggested that the number of dividing cells in a tumor, mitotic index, might reflect its malignant potential, and gave an illustration of its application in fibrosarcomas.[8] The histopathologic grading of sarcomas, vital to the study and treatment of these tumors, was thus begun.

Stout (1885–1967), in a monograph published in 1932, also elucidated on the nature, morphology and treatment of sarcomas.[9] His classification of soft tissue sarcoma included the histogenesis, grade of malignancy, including mitotic activity, and cellular as well as stromal organization. Except for minor modifications, this classification remains in use today. The first comprehensive treatise on soft tissue sarcomas[10] was the product of his studies.[11]

Murray and Stout published their classic tissue culture studies of Schwann cells in 1942.[12] With their later studies of synovial tissue and synovial sarcoma, they confirmed the mesenchymal origin of synovial sarcomas, even though these tumors may show epithelial characteristics.[13]

Classic contributions to the description and histogenetic classifications of sarcoma were made at the Memorial Hospital for Cancer and Allied Diseases, starting with Dr James Ewing (1866–1943) (Figure 1.1). James Ewing was the first Professor of Pathology at Cornell University Medical Center. Having graduated in 1891 with his MD degree, he assumed the position of Chief of Pathology at Memorial Hospital in 1899 at the age of 33. When he published the first edition of his monograph, *Neoplastic Diseases*, in 1919, his observations

Figure 1.1
Dr James Ewing.

and concepts of tumors laid the foundation for the surgical pathology of neoplasms.[14] He completed the book despite trigeminal neuralgia. In 1926 neurosurgery by Dr Harvey Cushing replaced the paroxysms of tic douloureux with a painful anesthesia which disabled him for the rest of his life.

In a succession of editions, he gave a clear classification of soft tissue sarcoma and stated that 'Sarcoma is a malignant tumor composed of cells of the connective tissue type ... This definition is based on the morphology of the tumor cells and on their histogenesis.' He listed benign and malignant counterparts of tumors arising from fibrous tissue, cartilage, bone, myxomatous tissue, fatty tissue, blood and lymphatic vessels, smooth and striated muscle, and vascular endothelium. He also recognized that the accepted scope of sarcomas has been subject to much revision, since there is often much difficulty in determining the origin of cellular tumors. One of his most important contributions was his description of Ewing's sarcoma, first described in 1920.[15] The suggestion that grade was of importance in the outcome of sarcomas was first emphasized in the fourth edition of *Neoplastic Diseases*, published in 1931.[4]

William Coley (Figure 1.2) in 1889 had treated the 17-year-old Elizabeth Dashiell at Memorial Hospital for Cancer and Allied Diseases for an extremity sarcoma. Despite his surgical efforts, this young friend of John D Rockefeller Jr died from her disease in June 1890. This had a significant effect on Coley and influenced him to study sarcoma. He continued to study the treatment and outcome of patients of his mentor, William Tillinghast Bull. In the lower east side of Manhattan, Coley found a patient with recurrent sarcoma. After the patient had multiple recurrences resected from his neck, he was then surprisingly cured by a postoperative erysipelas infection. Based on this, Coley started using Coley's toxins in 1892 and instituted the advent of immunotherapy in cancer.

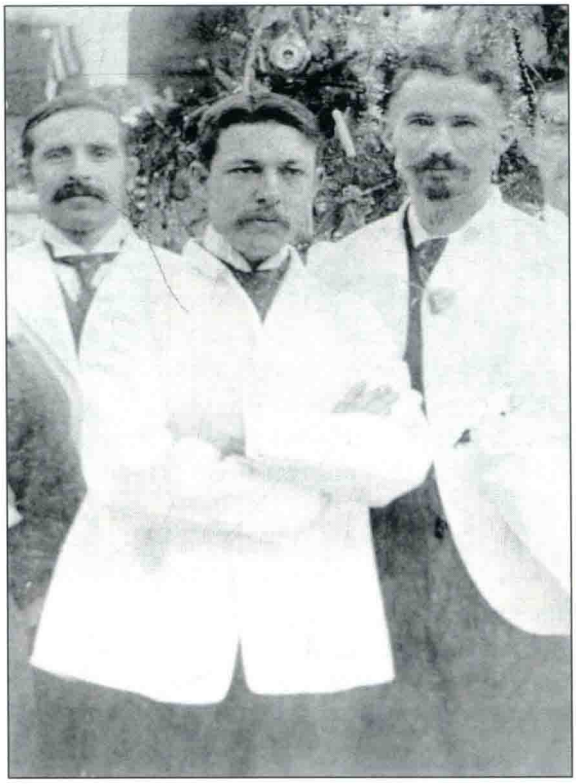

Figure 1.2
Dr William Coley.

A great many contributions to pathologic evaluation have come from Memorial Sloan-Kettering Cancer Center, from Ewing to Stout in 1942, who introduced the term 'hemangiopericytoma'. Moreover, Stout's classification of liposarcomas in 1944 was a first, as was his description, with Ackerman, of leiomyosarcoma of soft tissue in 1947. He published a comprehensive listing of tumors of soft tissue in an Armed Forces Institute of Pathology fasicle in 1953.[10]

In 1948, Stewart and Treves at Memorial Hospital (Figures 1.3 and 1.4) described

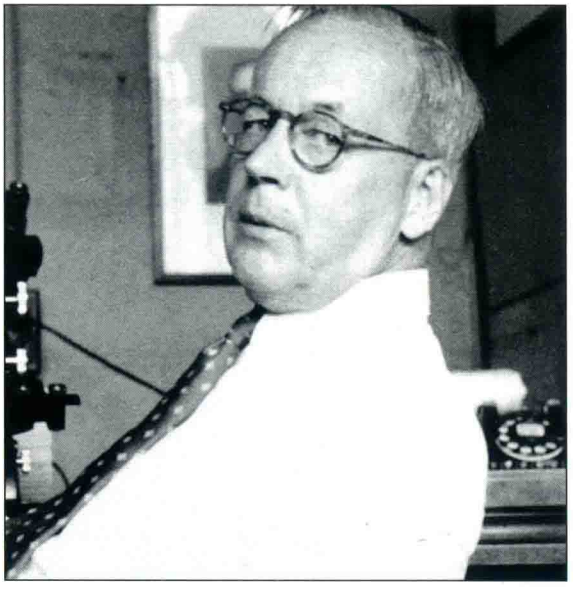

Figure 1.3
Dr Frederick Stewart.

Figure 1.4
Dr Norman Treves.

lymphangiosarcoma, a highly malignant tumor, in post-mastectomy patients with chronic lymphedema of the upper limb.[16] Since their original description, lymphangiosarcoma has been found in non-edematous post-mastectomy upper limbs[17] and in patients with limbs congenitally lymphadematous or edematous due to filariasis or trauma.[18] Stewart, in 1952, reported the first case of alveolar soft part sarcoma.

In the 1940s to1960s, the term 'giant and spindle cell sarcoma' was often used as a descriptive pathologic diagnosis for many soft tissue sarcomas. Myxoid and histiocytic cellular elements often combined with a varying amount of collagenous tissue in the stroma in these neoplasms. In 1967, Stout and Lattes described the morphology of these tumors and coined the term (malignant) *fibrous histiocytoma*, which they considered to be embryonal forms of fibroblastic neoplasms. Steven Hajdu, for long the recognized authority on soft tissue sarcoma at Memorial Hospital, collated much of the rich resources into his text *Pathology of Soft Tissue Tumors* in 1979, and a further version, from his 25 years of experience, in 1985.[4]

In the evolution of the classification of soft tissue sarcoma, leukemias, lymphomas, and myelomas, which were of mesenchymal origin, were separated from the broad classification of sarcomas in the 1940s, along with bone sarcomas. Malignant peripheral nerve tumors, derived from Schwann cells of neurocrest origin, were included with sarcomas. Often excluded in our present classification are lesions of presumed endothelial (Kaposi's sarcoma) or mesothelial (mesothelioma) origin. Ewing's words, 'Future investigation will doubtless reveal many new and more precise facts regarding the etiology, conditions of incidence, histogenesis, and clinical course which will warrant the recognition of many

sarcomas as specific pathological entities', continue to hold true.[14]

Evolution of treatment of soft tissue sarcoma

The progress that has been made in soft tissue sarcoma therapy has come about gradually, by early recognition of risk factors and, by trial and error, judiciously combining the available modalities of treatment, including surgery, radiation and chemotherapy. Such combined therapy has improved local tumor control, enabling surgeons to salvage many limbs that previously would have required amputation.[19,20] There have been advances in the control as well as the prevention of pulmonary metastases, the most common cause of death from soft tissue sarcoma. Surgical resection of pulmonary metastases started in the middle of the twentieth century, and oncologists have vigorously treated metastatic soft tissue sarcoma with chemotherapeutic agents. Starting in the 1970s, accounts of successful resection of lung metastases from soft tissue sarcoma were recorded in the literature, with prolonged survival of 20–40% of the patients.[21] Today, surgical resection of lung metastases in appropriately selected patients has become a treatment of recognized efficacy.[22–24]

A succession of studies has shown increasing tumor responses to chemotherapy as new drugs became available, including the alkylating agents, methotrexate, actinomycin D, the nitrosoureas, and doxorubicin (adriamycin). The introduction of chemotherapy in an adjuvant setting was a natural development of the 1970s, but was also met with considerable scepticism. Rosenberg et al, at the National Cancer Institute, showed in a prospective randomized trial, using doxorubicin, cyclophosphamide and methotrexate, that patients who received such adjuvant therapy enjoyed a significantly higher local recurrence-free survival rate.[25] It still remains unclear as to whether current chemotherapy impacts on disease-specific survival. Ifosfamide is the most active recent drug addition.

As much is being learned about the molecular and genetic biology of these tumors, newer treatments will evolve. Several translational studies are currently being conducted which include immunotherapy, gene therapy and the use of small DNA molecules. It is likely that some of these will be included as standard therapies in the future.

References

1. Long ER. *History of Pathology*. Baltimore: Williams & Wilkins, 1928.
2. Mettler CC. *History of Medicine*. Philadelphia: Blakiston, 1947.
3. Morgagni JB. *The Seats and Causes of Disease Investigated by Anatomy*, letter 39, Vol. 2. London: Millen & Cadell, 1769.
4. Hajdu SI. *Differential Diagnosis of Soft Tissue and Bone Tumors*. Philadelphia: Lea & Febiger, 1986.
5. Bichat X. *Anatomic General 1801*, Vol. 3, translated by Hayrook. Boston: Richardson and Ford, 1822.
6. Abernathy J. Tumor classification. In: *Surgical Observations*. London: Longman & O'Rees, 1804.
7. Virchow R. *Die Krankhaften*, Vol. 3. Berlin: Geschwuelste, 1863:1–15.
8. Broders AC, Hargrave R, Meyerding HW. Pathologic features of soft tissue fibrosarcoma. *Surg Gynecol Obstet* 1939;**69**:267.
9. Stout AP. *Human Cancer: Etiologic Factors, Precancerous Lesions, Growth, Spread, Symptoms, Diagnosis, Prognosis, Principles of Treatment*. Philadelphia: Lea & Febiger, 1932.
10. Stout AP. Tumors of the soft tissues. In: *Atlas of Tumor Pathology*, section 2, fascicle 5.

Washington, DC: Armed Forces Institute of Pathology, 1953.
11. Stout AP. Sarcomas of soft parts. *J Missouri Med Assoc* 1947;**44**:329.
12. Murray MR, Stout AP. Demonstration and formation of reticulin by schwannian tumor cells in vitro. *Am J Pathol* 1942;**18**:585.
13. Murray MR, Stout AP, Pogogeff IA. Synovial sarcoma and synovial tissue cultivated in vitro. *Ann Surg* 1949;**31A**:619.
14. Ewing J. *Neoplastic Diseases: A Treatise on Tumors*. Philadelphia: WB Saunders, 1919.
15. Ewing J. Further report on endothelial myeloma. *Proc NY Pathol Soc* 1924;**24**:93–101.
16. Stewart FW, Treves N. Lymphangiosarcoma in postmastectomy lymphedema: a report of six cases of elephantiasis chirurgica. *Cancer* 1948;**1**:64–81.
17. Woodward AM, Ivins JC, Soule EM. Lymphangiosarcoma arising in chronic lymphedematous extremities. *Cancer* 1972;**30**:562–72.
18. Muller R, Hajdu SI, Brennan MF. Lymphangiosarcoma associated with chronic filarial lymphedema. *Cancer* 1987;**59**:179–83.
19. Rosenberg SA, Kent H, Costa J et al. Prospective randomized evaluation of the role of limb-sparing surgery, radiation therapy and adjuvant chemoimmunotherapy in the treatment of adult soft tissue sarcomas. *Surgery* 1978;**84**:62–9.
20. Rosenberg SA, Tepper J, Glatstein E et al. The surgical treatment of soft tissue sarcoma of the extremities. *Ann Surg* 1982;**196**:305–15.
21. McCormack PM, Martini A. The changing role of surgery for pulmonary metastases. *Ann Thorac Surg* 1979;**28**:139.
22. Gadd MA, Casper ES, Woodruff J et al. Development and treatment of pulmonary metastases in adult patients with extremity soft tissue sarcoma. *Ann Surg* 1993;**218**:705.
23. Verazin GT, Warneke JA, Driscoll DL et al. Resection of lung metastases from soft tissue sarcomas: a multivariate analysis. *Arch Surg* 1992;**127**:1407.
24. Casson AG, Putnam JB, Natarajan G et al. Five-year survival after pulmonary metastectomy for adult soft tissue sarcoma. *Cancer* 1992;**69**:662.
25. Rosenberg SA, Tepper J, Glatstein E et al. Prospective randomized evaluation of adjuvant chemotherapy in adults with soft tissue sarcoma of the extremities. *Cancer* 1983;**52**:424–34.

2 Incidence, etiology

Incidence, prevalence by site and type

In the USA, the incidence of soft tissue sarcoma is approximately 7000–8000 new cases per year. This incidence is comparable to that of tumors of the testis and of the tongue (Figure 2.1). These tumors account for approximately 1% of all adult malignancies and 15% of pediatric malignancies.

The data presented here are derived from a prospective database of all patients over the age of 16 who had been admitted and treated in Memorial Sloan-Kettering Cancer Center (MSKCC) with a diagnosis of soft tissue sarcoma, from 1 July 1982 to 31 December 2000. The number of patients admitted each year is illustrated in Figure 2.2. The distribution by sex and site for patients is illustrated in Figures 2.3 and 2.4. Although sarcoma may develop in any anatomic site, approximately half occur in the extremities (Figure 2.5). Figures 2.6–2.8 depict the regional sites for lower extremity, upper extremity and gastrointestinal/visceral tumors.

Approximately two-thirds of the tumors are high grade and one-third low grade (see Chapter 3) (Figure 2.9). Size distribution is shown in Figure 2.10: one-third of all patients have tumors greater than 10 cm. Size distribution in the extremities is shown in Figure 2.11. Only 13% are superficial (Figure 2.12) (see Chapter 3). The histopathologic subtype varies widely, but is dominated by liposarcoma, malignant fibrous histiocytoma (MFH) and leiomyosarcoma (Figure 2.13). Age distributions for these subtypes are illustrated in Chapter 4. There is clearly a variability in age for all histopathologic

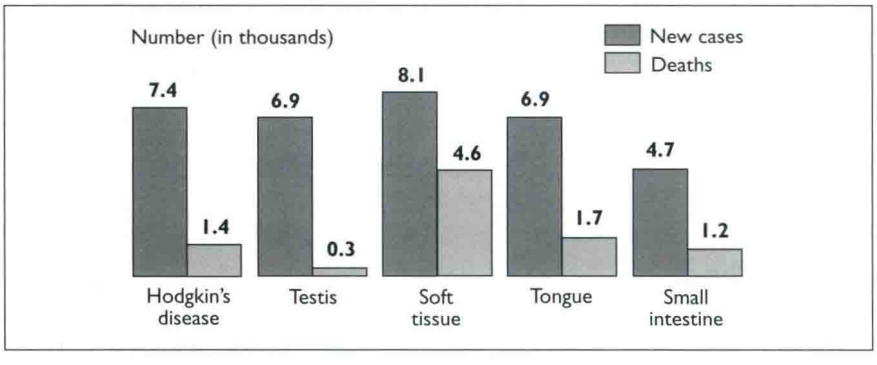

Figure 2.1
Incidence of soft tissue sarcoma in the USA, 2000. From Greenlee et al.[1]

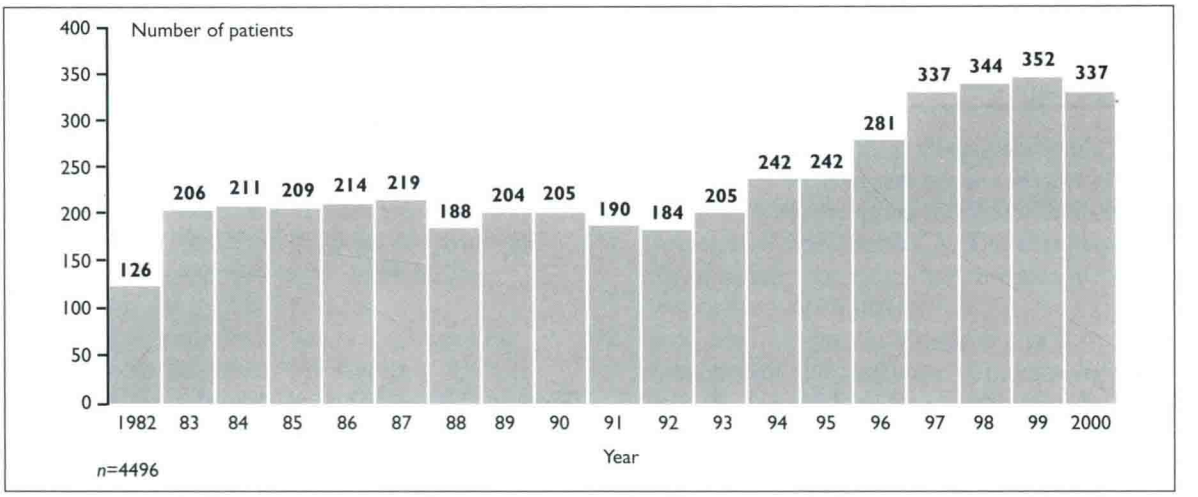

Figure 2.2
The number of sarcoma patients admitted each year to MSKCC, 12/82–12/00.

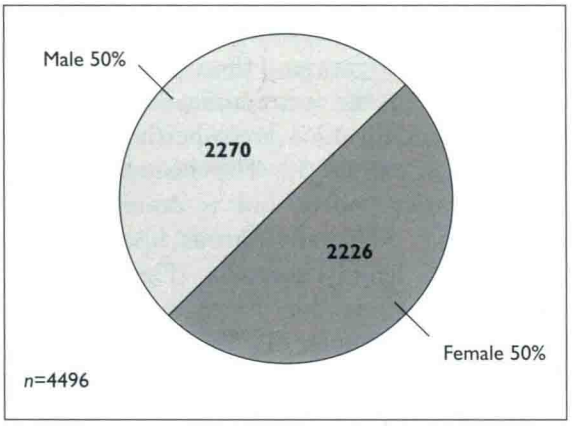

Figure 2.3
Distribution by sex for total patients admitted, MSKCC, 7/82–12/00.

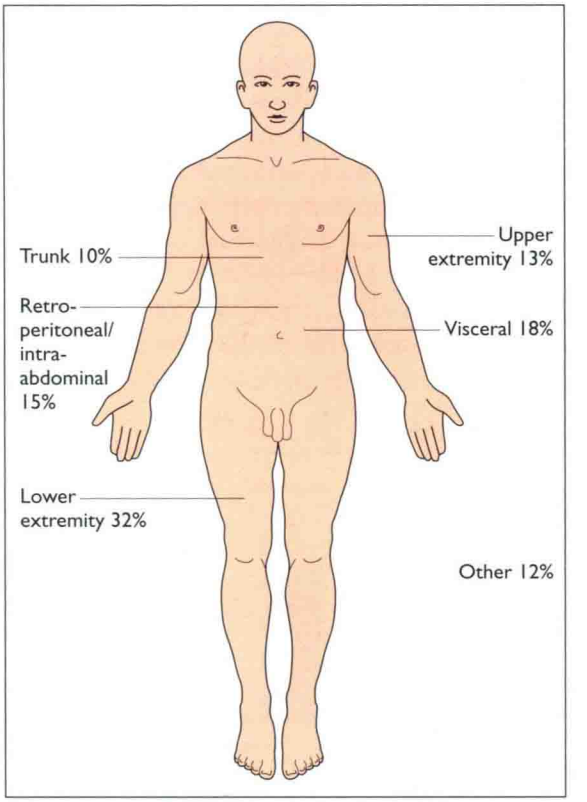

Figure 2.4
Distribution by site for total patients admitted, MSKCC, 7/82–12/00.

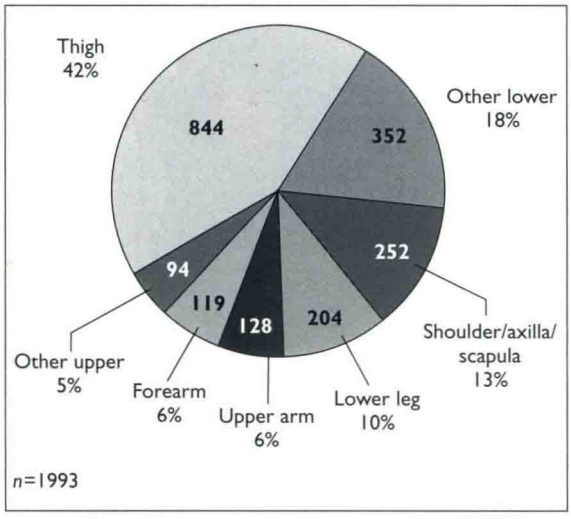

Figure 2.5
Extremity distribution of soft tissue sarcoma, MSKCC, 7/82–12/00.

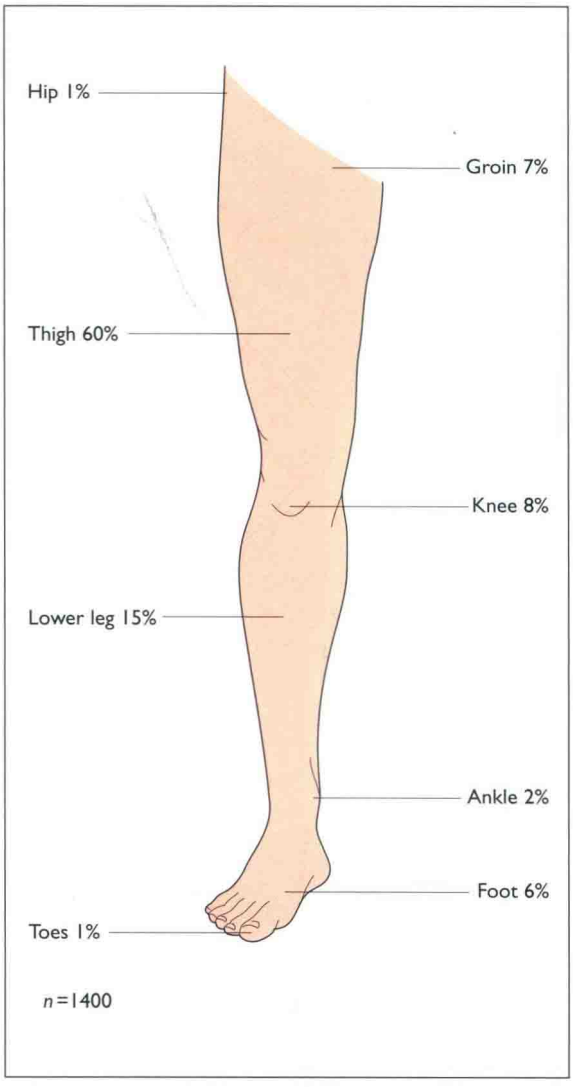

Figure 2.6
Regional sites: lower extremity, MSKCC, 7/82–12/00.

subtypes. Fibrosarcoma and synovial sarcoma are more commonly seen in patients less than 40 years of age, while MFH tends to be a tumor of the older age group. Age groups for liposarcoma and leiomyosarcoma are more uniformly distributed. Histopathology also varies by site (see Chapter 3). The majority of extremity lesions are liposarcoma and MFH, and the majority of visceral tumors are gastrointestinal stromal tumors (GIST), either leiomyosarcoma or GANT (gastrointestinal autonomic nerve tumors), or GIST–NOS (not otherwise specified). In the retroperitoneum, liposarcoma dominates, followed by leiomyosarcoma.

Etiology and predisposing factors

Soft tissue sarcomas comprise a widely diverse group of neoplasms. They vary in site of origin, occurring in all parts of the body and, in the main, are thought to share a common mesodermal embryologic origin. However, even that shared commonality varies, and there may be exceptions. For example, tumors derived from nerve and nerve sheath are predominantly neuroectodermal in origin. It is of interest that the incidence of tumors arising

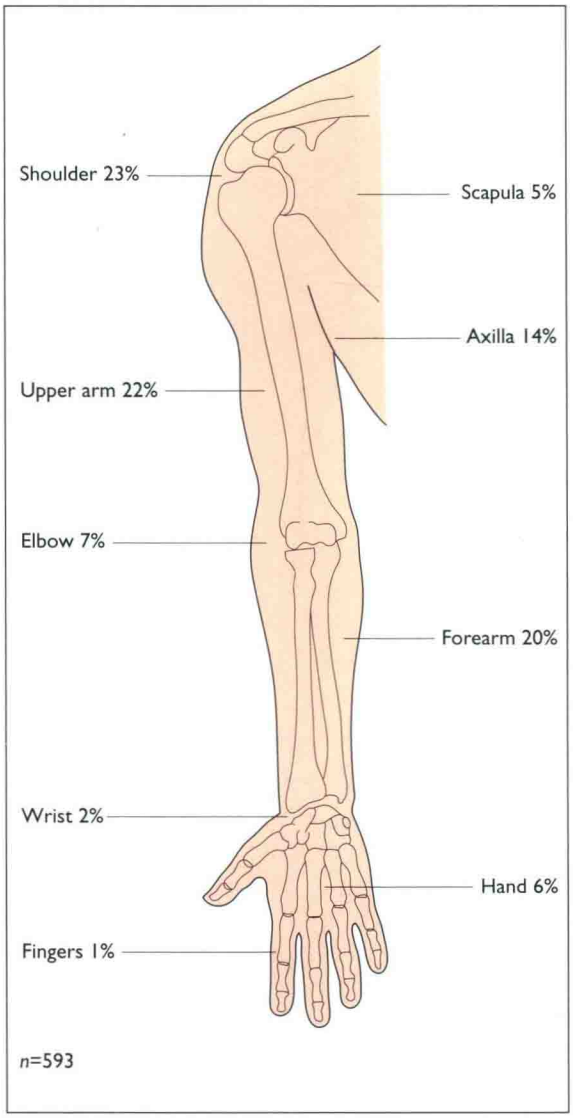

Figure 2.7
Regional sites: upper extremity, MSKCC, 7/82–12/00.

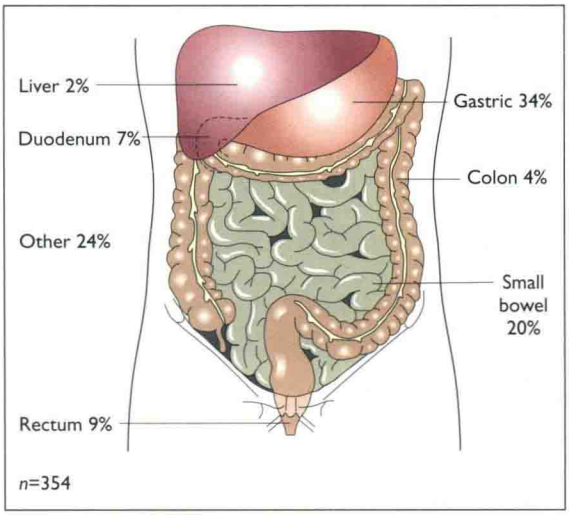

Figure 2.8
Regional sites for gastrointestinal/visceral tumors, MSKCC, 7/82–12/00.

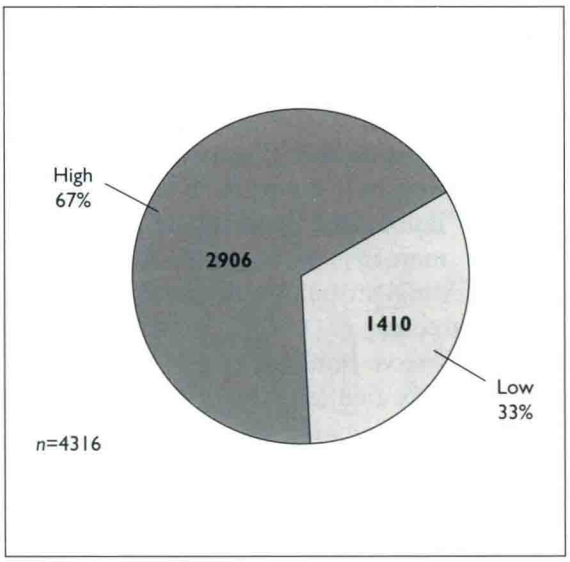

Figure 2.9
Distribution of soft tissue sarcoma by grade (all available data), MSKCC, 7/82–12/00.

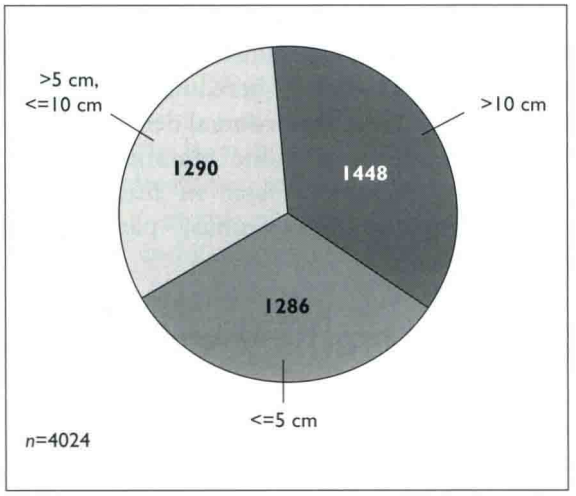

Figure 2.10
Distribution of soft tissue sarcoma by size (all available data), MSKCC, 7/82–12/00.

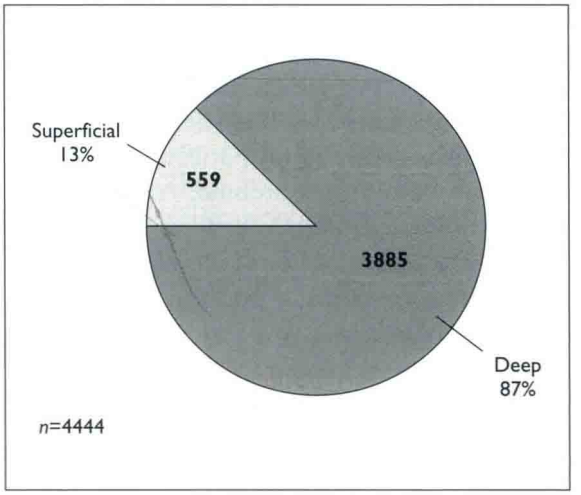

Figure 2.12
Distribution of soft tissue sarcoma by depth (all available data), MSKCC, 7/82–12/00.

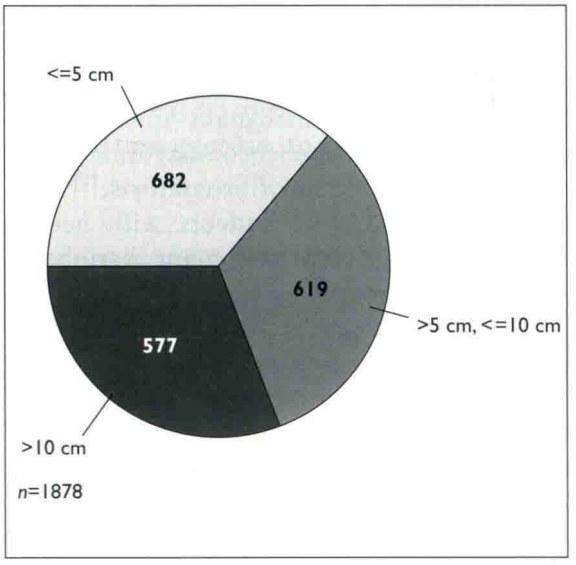

Figure 2.11
Distribution in the extremities by size, MSKCC, 7/82–12/00.

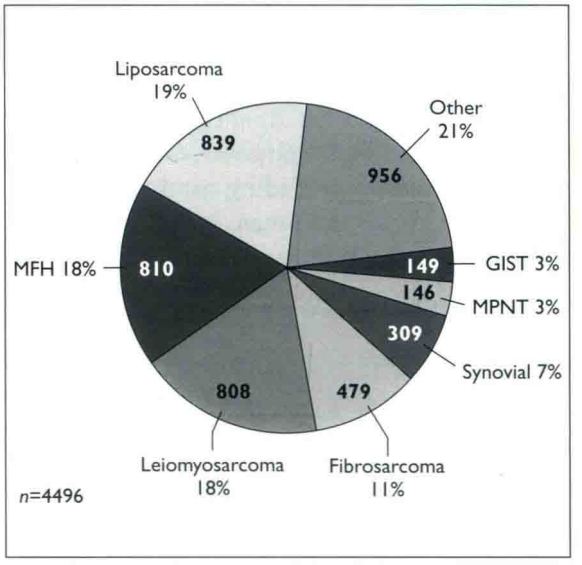

Figure 2.13
Distribution of soft tissue sarcoma by histopathologic subtype, MSKCC, 7/82–12/00. MPNT, malignant peripheral nerve tumor.