Dorothy Fox. *Fifth Avenue Springtime.* Watercolor, 30″ × 36″.

Soft tissue sarcomas present challenges in diagnosis and management.

Diagnosis, Classification, and Management of Soft Tissue Sarcomas

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Background: *Soft tissue sarcomas are challenging to oncologists due to their unique character, the infrequency of their occurrence, and the difficulties in predicting outcomes. Advances in imaging, as well as improvements in surgical techniques and adjunctive treatment methods, have improved care for patients with these unusual disorders.*

Methods: *The various types of soft tissue tumors are defined, and the statistics for the Orthopaedic Oncology Group in relation to them are reviewed and compared with literature references.*

Results: *The overall survival rate for 1,220 tumors treated at our institute from June 1972 to June of 2001 was 72%, with a wide range. Patients with leiomyosarcomas, clear cell sarcomas, and malignant fibrous histiocytomas had a poorer survival rate, while those with fibrosarcomas, liposarcomas, and neurofibrosarcomas fared better. Outcome was affected by patient age, tumor anatomic site, tumor stage, and a history of recurrence.*

Conclusions: *Competent imaging, predictive immunological and genetic studies, improved surgery, and newer methods of adjunctive and neoadjunctive treatment should result in improvements in outcomes for patients with these tumors.*

Introduction

Soft tissue sarcomas represent a major group of lesions that are often subtle in presentation and have wide variation in extent of aggressive or malignant behavior.[1-6] By standards of carcinomatous tumors such as cancers of the breast, prostate, lung, bowel, and kidney, each of which has a frequency of over 150,000 per annum in the United States, soft tissue sarcomas are relatively infrequent with probably fewer than 5,000 cases appearing annually.[7] Benign soft tissue tumors such as fibromas, lipomas, myxomas, or schwannomas may be confused with malignant soft tissue tumors and, in some cases, may lead to either excessive treatment for benign lesions or inadequate treatment for malignant ones.[2,8-15] The relative infrequency and

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Abbreviations used in this paper: CT = computed tomography, GTNM staging system = grading, tumor, node, metastases staging system, MAID protocol = mesna, doxorubicin, ifosfamide and dacarbazine, MRI = magnetic resonance imaging, MSTS = Musculoskeletal Tumor Society, PET = positron emission tomography.

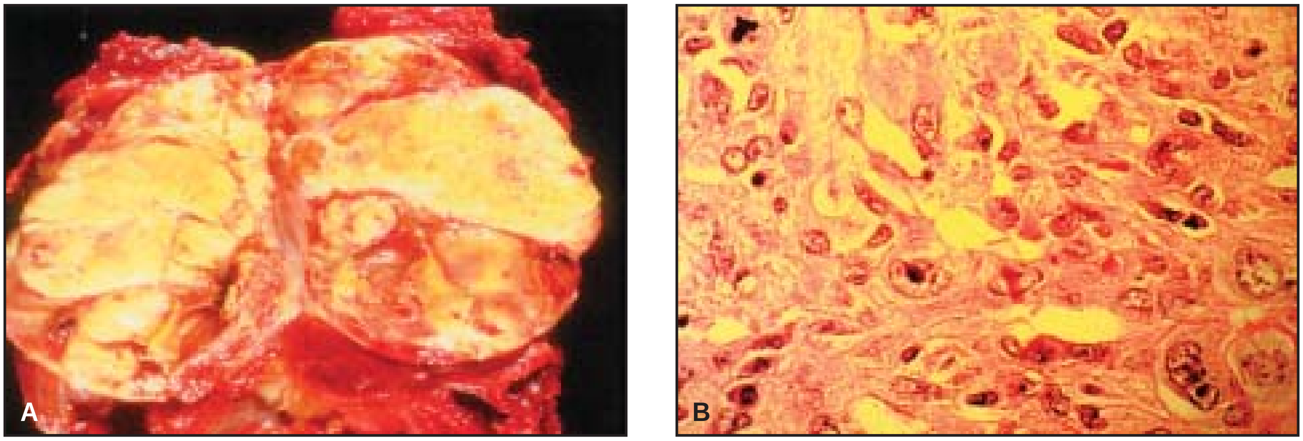

Fig 1A-B. — Photographs of tissue from a patient with a malignant fibrous histiocytoma of the thigh. (A) shows the mass and demonstrates the irregularity of contour and lack of a limiting membrane. (B) shows the histologic picture demonstrating the marked pleomorphism and nuclear abnormalities seen in this poorly differentiated tumor.

sometime subtle presentations make soft tissue sarcomas difficult to detect. Even experienced oncologists may not appreciate their presence or, equally important, their potential threat to the patient.

Many of the soft tissue tumors have a relationship to normal soft tissue structures so that the lesions may arise in relation to the fascia, elastic tissue, fat, smooth muscle, fibrous capsule, blood vessels, and nerves. The symptomatology of these tumors may be related in part to the effect they have on the function of the normal tissue adjacent to them. Malignant bone tumors occur less frequently but are more easily diagnosed because of their relation to bony structure and the limited number of cells of origin (principally osseous, cartilaginous, and marrow elements). However, soft tissue lesions such as clear cell sarcomas, malignant fibrous histiocytomas, alveolar soft part sarcomas and epithelioid sarcomas, spindle cell sarcomas, and synovial sarcomas seem to have no well-defined cells of origin.[16-25]

A number of texts describe the benign and malignant connective tissue tumors in detail, including their anatomic locations, histology, imaging characteristics, treatment, and outcomes.[4,5,26,27] Using data from a computer system created over 25 years ago and containing information regarding over 16,000 connective tissue tumors treated by the Harvard Orthopaedic Oncology Group,[28] this report briefly identifies the almost 2,000 soft tissue sarcomas, describes the treatment rendered to them at our institute over the years, and discusses the clinical results and the survival data.

Types of Soft Tissue Sarcomas

The most common soft tissue sarcoma in most series, including ours with 224 cases, is the malignant fibrous histiocytoma, an entity that, until approximately 20 years ago, was identified by a series of other names, principally fibrosarcoma.[25,29,30] Our series contains data on 530 such lesions with a male-female ratio 52 to 48 and a mean age of 58 ± 18 years (range 3 to 96 years). These tumors are often undifferentiated, and they are classified by some pathologists as pleomorphic sarcoma. They may have a broad range of histologic appearances[4,31-33] and can be generally divided into four subtypes: storiform, myxoid, giant cell, and inflammatory, each of which has a relatively distinctive appearance and may vary to some extent in malignity.[4,31-34] The tumors principally occur in late adult life and arise more frequently in men. They are usually located in the thigh, pelvis, arm, or trunk, and present below the knees and elbows only occasionally.[4,30-33] The tumors are often described as rapidly enlarging, and in most cases, they are painless and nontender.[30,35] They may involve adjacent structures including bone, especially of the femur or pelvis.[4] Although multiple reports used immunohistochemical markers to identify these lesions, none are overly helpful in predicting outcome.[36-40] However, a recent report from Japan suggests that the presence of bone morphogenetic protein-2 in malignant fibrous histiocytomas offers a considerably better prognosis for the patients.[41] Malignant fibrous histiocytomas may occur in relation to radiation exposure and occasionally in bone as a result of an infarction.[42-44] Several reports now describe malignant fibrous histiocytomas occurring in relation to implanted metallic and especially plastic devices.[44,45] Examples of the gross and histologic features of malignant fibrous histiocytoma are shown in Figs 1A-B.

The second most frequent lesion in our series is liposarcoma. The male-female ratio is 57 to 43, and the mean age is 51 ± 17 years (range 5 to 94 years). According to the World Health Organization and others, the tumors are divided into five subtypes: well-differentiated, myxoid, round cell, dedifferentiated, and pleomorphic.[4,10,26,46-51] The well-differentiated variant closely resembles the lipoma and is of concern in terms of potential likelihood of over-or under-treatment.[11,13,52-54] A reciprocal translocation has been identified between chromosomes 12 and 16 for most of the round cell and myxoid liposarcoma variants, which may be considered as one entity.[55-60] The principal anatomic sites for liposarcomas are similar to those for the malignant fibrous histiocytoma, with possibly a greater number more distally placed.[61,62] Some of the tumors seem to have a lower tendency for metastasis and may be present for a considerable length of time prior to discovery.[63] They have no known relation to radiation injury, to implanted devices, or in fact to lipomas in patients with diffuse lipomatosis syndromes. Examples of the gross and histologic characteristics of a liposarcoma are shown in Figs 2A-B.

The synovial sarcoma is a common lesion that is often malignant in its behavior. The Orthopaedic Oncology Group database includes 177 synovial sarcomas, with an average patient age of 33 ± 16 years (range 2 to 80 years) and a slightly greater frequency in men (55%) than women (45%). Although the tumor occurs more often in the region of joints, tendons, and ligamentous structures and especially more frequently in acral parts,[64-67] there is no evidence to support the concept that the tumor arises from synovial cells or in fact that it ever really begins inside the synovial lining of a joint.[68] The synovial sarcoma is believed to have three types: a biphasic type, a monophasic epithelial type, and a monophasic fibrous type. However, there do not appear to be any differences in the malignant character or anatomic location based on these structural characteristics.[4,65,69,70] Many of the lesions are myxoid in character, and these are reported to contain hyaluronic acid and heparan and most show immunoreactivity to cytokeratin and epithelial membrane antigen.[4] A consistent specific translocation between chromosome 18 and chromosomes 11 or 12 has been noted, which can be useful in distinguishing this tumor from some of the other soft tissue sarcomas.[71-76] Of some clinical importance is the fact that synovial sarcomas may seem to be dormant for a long period of time before behaving aggressively, and they may have irregular, small flecks of calcification in their substance, which sometimes provides a radiographic clue regarding their diagnosis.[77,78] A characteristic set of gross and histologic studies for synovial sarcoma are shown in Figs 3A-B.

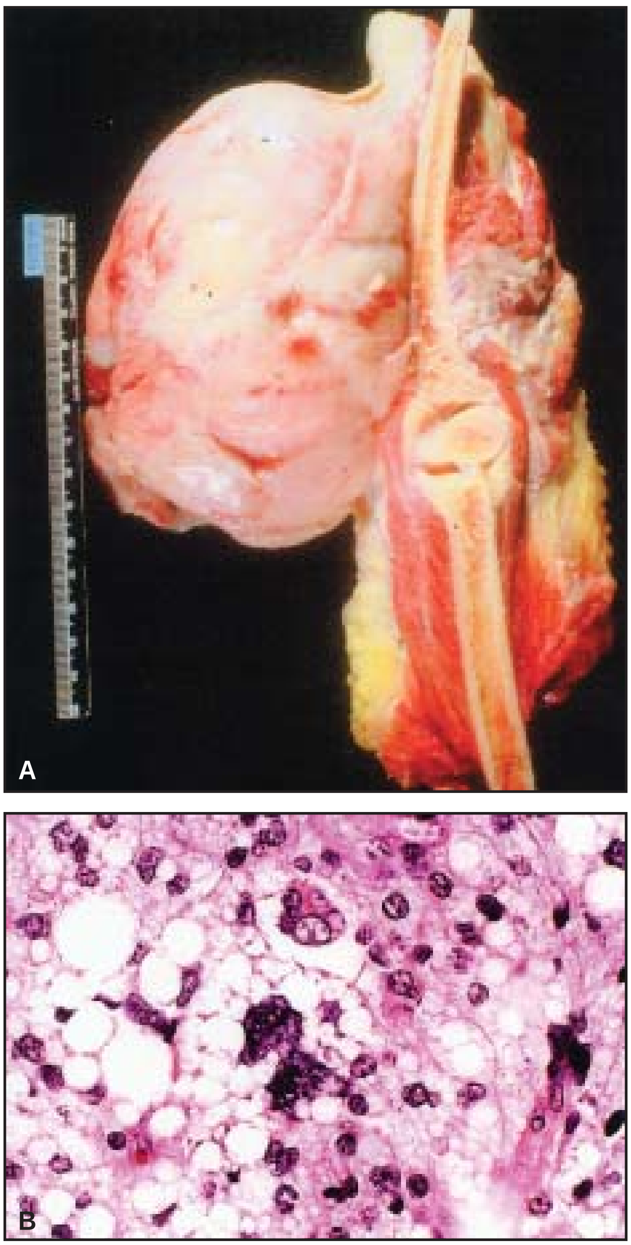

Fig 2A-B. — (A) shows the gross structure of a high-grade malignant liposarcoma of the arm. An amputation was necessary due to the large size. (B) shows the histologic picture — an undifferentiated pattern with several areas of fat within the tumor. Note the atypical forms.

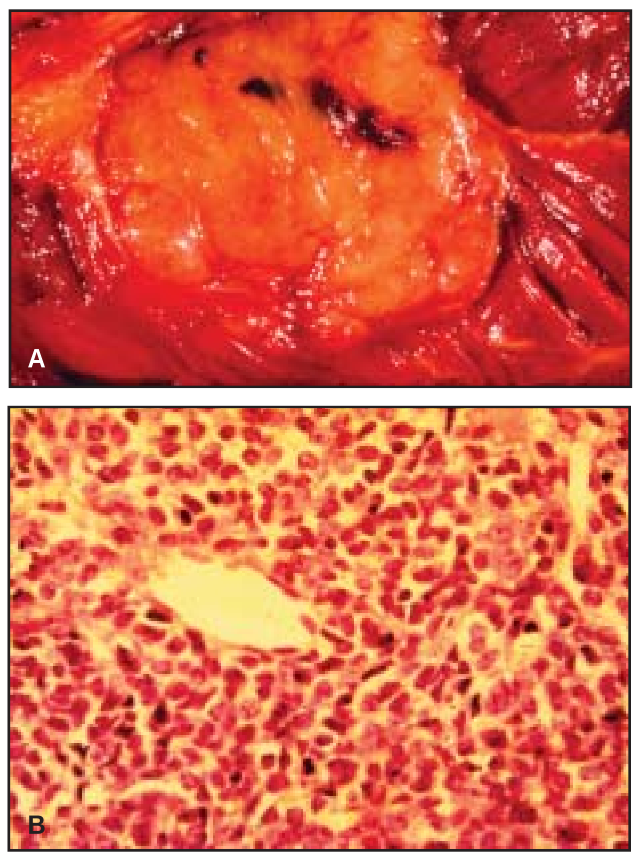

Fig 3A-B. — (A) shows the gross specimen of a synovial sarcoma that arose adjacent to but not within the knee. (B) shows the histologic picture, and the cells seem to resemble synovial tissue.

Neurofibrosarcoma is more appropriately termed a malignant schwannoma, since the tumors arise from the sheath of Schwann covering neural tissues. Since in many cases the tumors have few characteristics of Schwann cells, they are also known as malignant peripheral nerve sheath tumors, which may be a more appropriate name.[8,9,79-81] The tumors appear to occur more frequently in patients with neurofibromatosis type 1[82-85] and also seem to arise as a result of radiation exposure.[86,87] The lesions are generally considered malignant, and until recently it was thought that patients with neurofibromatosis type 1 who develop a malignant peripheral nerve sheath tumor had a poorer prognosis than patients in whom the tumor arose spontaneously.[82,83,88,89] Part of the reason for this concern was that patients with plexiform tumors — or their physicians — may not recognize the malignant variant until it becomes greatly enlarged.[90] Our series now contains data on 93 patients with this lesion, 18 of whom had neurofibromatosis type 1. The mean patient age is 36 ± 17 years (range 10 to 85 years) and women were more frequently affected than men (53% and 47%, respectively). The tumors occurred most frequently in the thigh, shoulder, spine, and pelvis. The tissue can often be identified immunologically by markers, including S-100, CD57, collagen type 4, laminin and, less commonly, cytokeratin, and occasionally P53.[91-93] Examples of the gross and histologic characteristics of a malignant neurofibrosarcoma are shown in Figs 4A-B.

Leiomyosarcoma is an uncommon malignant neoplasm that arises from smooth muscle. The tumors occur most frequently in the uterus, abdominal, and urologic viscera.[94-97] However, in the series of tumors from our Orthopaedic Oncologic Group database, they are present in the soft somatic tissues with sufficient frequency to be the fifth on our list of tumors. Our group has treated 76 such lesions, most of which were present in the extremities. The tumors are more common in men (57%) than women (43%), and the mean age is 56 ± 19 years (range 18 to 85 years). The tumors produce a different behavioral pattern in peripheral soft tissues than in viscera such as the uterus, possibly related to the tissue of origin. In the uterus, they arise from the smooth muscle of that structure, but in peripheral parts, they appear to arise from the

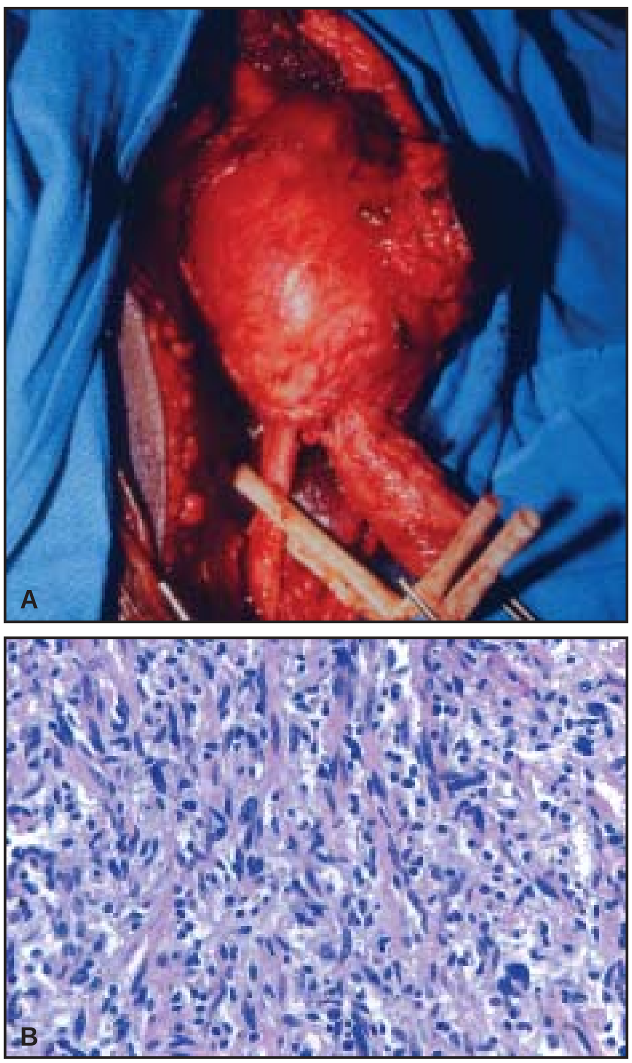

Fig 4A-B. — (A) is a gross photograph of a malignant neural tumor rising from the sciatic nerve. The patient has neurofibromatosis type 1, and the sciatic nerve is enormously enlarged. (B) shows the histologic picture, which appears atypical and malignant with the cells showing a fibroid pattern some pleomorphic cells.

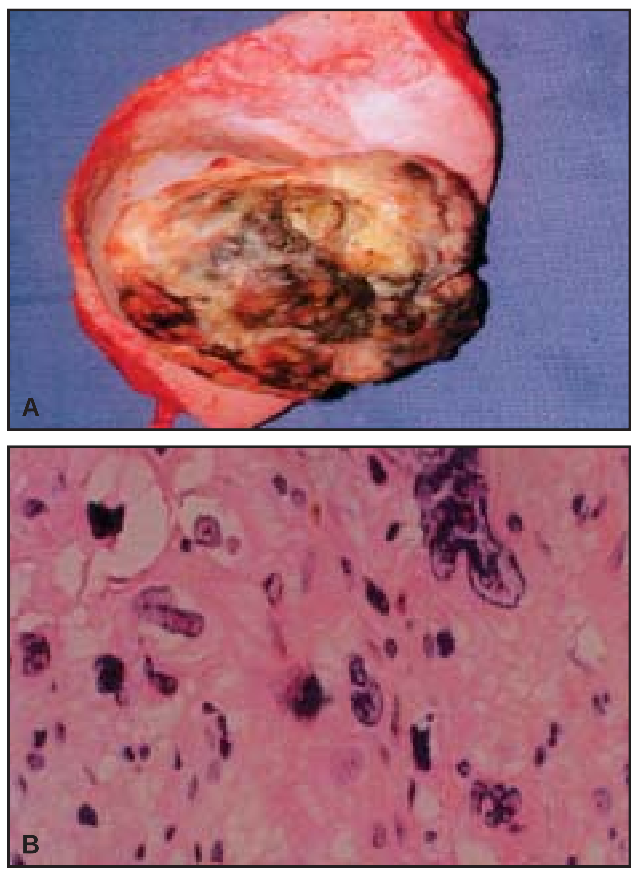

Fig 5A-B. — The gross appearance of a leiomyosarcoma that was located superficially in the buttock and has broken out of the skin (A). The tumor appears to be surrounded by fat. Histologically, the tumor consists of many bizarre cells in myxoid matrix (B).

smooth muscle surrounding blood vessels often in the thigh, calf, or even distal parts.[98,99] Thus, these tumors seem to have increased access to blood vessels since there is no necessity to break through the smooth muscle covering of a vein or artery and hence can lead to earlier and more extensive metastatic spread.[99-101] This appears to be the case, since leiomyosarcoma seem to be the most malignant of all of the soft tissue tumors in terms of metastasis and poor survival rates.[101-104] Examples of the gross and histologic characteristics of a leiomyosarcoma are shown in Figs 5A-B.

Clear cell sarcomas are also known as malignant melanoma of soft parts, chiefly because the tumors often contain melanin, which may be difficult to identify on hematoxylin and eosin stains but do show immunohistochemical evidence of melanocytic differentiation.[4,22,105,106] Unlike melanomas, clear cell sarcomas are located deep to the surface, often in the foot and ankle and sometimes closely bound to tendons.[107-109] Despite their peripheral location the lesions are considered to be highly malignant. Our series includes 26 patients with clear cell sarcomas, affecting more men (58%) than women (42%) and having a mean patient age of 39 ± 21 years (range 7 to 78 years). Histologically, the tumors often have dark-staining sites containing melanin, and almost all express S-100 protein and antigens associated with melanin synthesis.[4,22,110] Examples of the gross and histologic characteristics of a clear cell sarcoma are shown in Figs 6A-B.

Fibrosarcomas were formerly thought to occur frequently. with the earliest studies suggesting that most soft tissue sarcomas seemed to arise from fibroblasts. However, the tumors varied considerably in histologic pattern and in fact in biologic behavior. Thus, the term malignant fibrous histiocytoma was introduced to describe the majority of these lesions and more particularly the malignant ones.[4,16,17,25,30] The diagnosis of fibrosarcoma is now almost always applied by exclusion when the lesion is found to have a fibroblastic stroma and a limited amount of atypia or number of bizarre cells. However, whether it represents a form of malignant fibrous histiocytoma remains a concern.[111] The tumors occur in fibrous soft tissues in the upper and lower extremities, in the pelvis, and even inside bone.[112-117] Several reports suggest that these lesions are more common in children and even young infants and can be identified by a specific t(12;15) translocation.[118,119] In the Harvard Orthopaedic Oncology Group case series, we describe 95 such lesions, and they appear to occur more frequently in men (60%) than women (40%). The average age is 48 ± 20 years (range 2 to 87 years). It should be noted that the patients identified as having fibrosarcoma were entered into our system prior to 1980, and the diagnosis has been rarely applied in recent

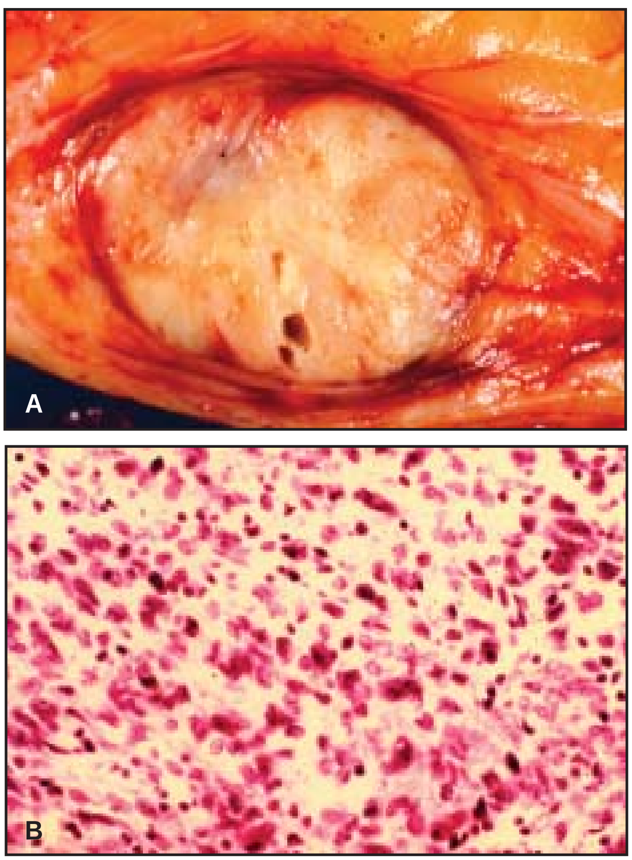

Fig 6A-B. — (A) shows a clear cell sarcoma arising in the foot. The histologic picture shows the presence of multiple cells with clear cytoplasm and considerable pleomorphism and some bizarre forms (B).

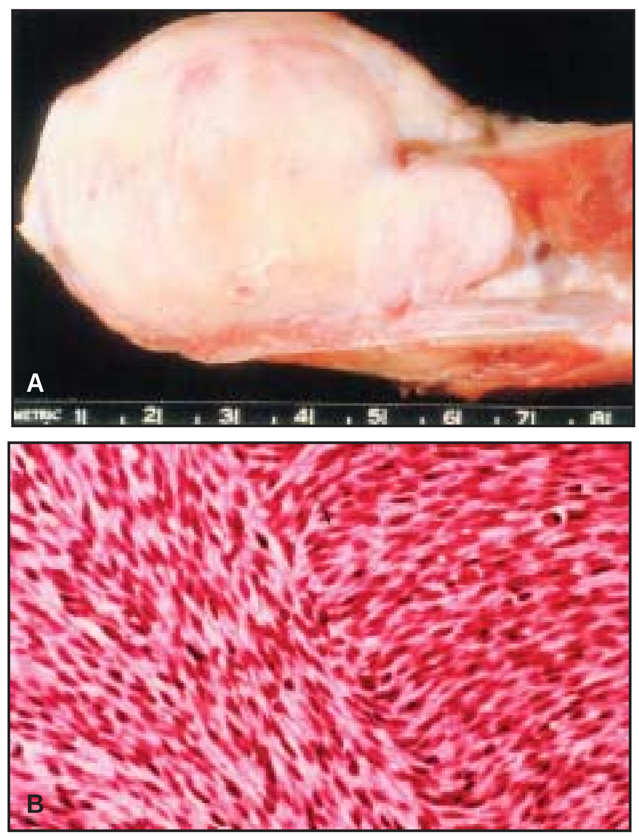

Fig 7A-B. — Photograph of a fibrosarcoma of soft tissues invading the femur and requiring a femoral resection (A). Histologically, the tumor shows a distinct fibrous pattern consisting of uniform spindle cells in fascicular pattern (B).

years. Some confusion arises in relation to other diagnoses such as fibromyxoid sarcoma, myxofibrosarcoma, and myofibroblastic sarcoma.[4] Low-grade fibrosarcomas, although having malignant characteristics, may resemble desmoid tumors, which may be locally aggressive but do not metastasize.[4] Examples of the gross and histologic characteristics of a fibrosarcoma are shown in Figs 7A-B.

Rhabdomyosarcomas are unusual lesions with an extraordinary history. The first such tumors were thought to occur in adults and were labeled pleomorphic rhabdomyosarcoma.[120] With the identification of the malignant fibrous histiocytomas, it became apparent that for the most part, adult rhabdomyosarcomas fell into that category. However, there is another group of these lesions that are highly malignant, occur principally in young children, and are often called embryonal or alveolar rhabdomyosarcomas.[121-124] These tumors were thought to arise from striated muscle (hence the name), but there is little evidence for this.[122] Our series contains 36 such cases, with an average age of 17 ± 10 years (range 6 to 33 years). Women exceeded men in frequency (56% and 44%, respectively). An abnormality has been described in chromosome 11p15.5, which is considered diagnostic, and some tumors display a trisomy 8.[4,123,125,126] Until the 1970s, patients with childhood rhabdomyosarcoma had a nearly uniformly fatal course, with widespread metastases occurring early in the course. Since the introduction of chemotherapy, most children survive.[122,125] Examples of the gross and histologic characteristics of a rhabdomyosarcoma are shown in Figs 8A-B.

Epithelioid sarcomas are uncommon lesions that often affect the upper extremities. They appear to be relatively benign in appearance but are malignant in behavior.[127-130] The tumors are often confused with a number of other lesions, including granulomatous processes.[131] The tumors have a predilection for the finger, hand, and forearm and occur in the subcutis and deeper tissues.[132,133] They occasionally present as ulcerations in the skin and may grossly resemble squamous cell carcinoma.[134] Calcification may be present in some lesions and is sometimes evident on imaging studies.[128-131] Our series includes 49 such lesions, occurring more frequently in men (65%) than in women (35%), with a mean age of 34 ± 18 years (range 8 to 81 years). Examples of the gross and histologic characteristics of an epithelioid sarcoma are shown in Figs 9A-B.

Alveolar soft part sarcomas are unusual tumors that, because of the presence of various muscle-associated pro-

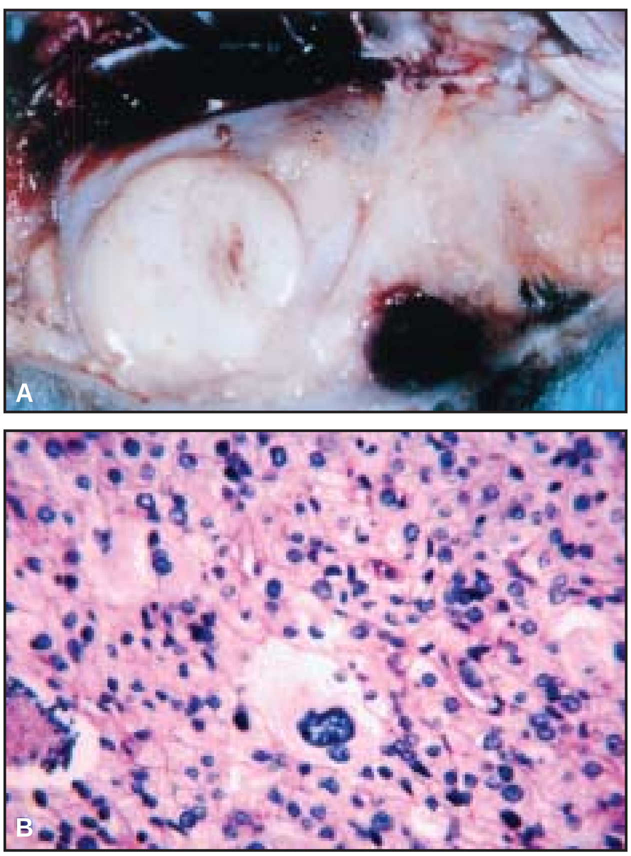

Fig 8A-B. — A rhabdomyosarcoma arising in the thigh of a young child (A). Histologically, the pattern is embryonal with primitive ovoid cells with scattered bizarre cells known as rhabdomyoblasts (B).

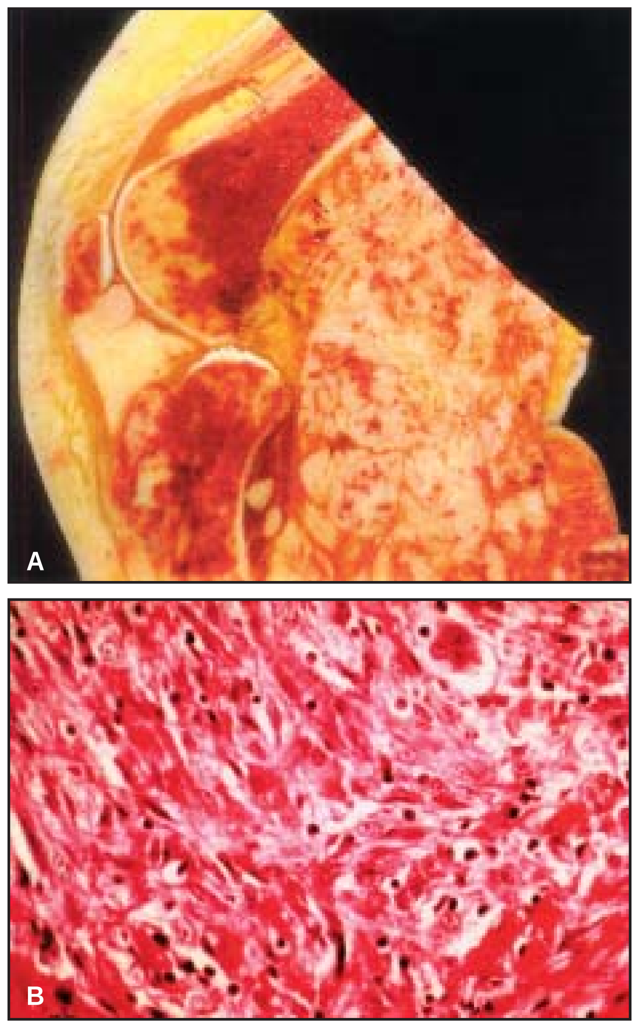

Fig 9A-B. — A highly malignant epithelioid sarcoma arising in the post aspect of the knee and invaded the bone. The lesion was highly malignant and required an amputation (A). Histologically the lesion shows spindle cells with densely eosinophilic cytoplasm and giant cells with marked atypism (B).

teins, especially desmin, are thought by some investigators to arise from skeletal muscle.[20,23,135-138] The structure of the tumor is unusual in that it has an organoid pattern and produces some characteristic crystals that contain monocarboxylate transporter protein 1 and CD147.[139-141] The tumors are located in fascial planes and skeletal muscles of the lower extremities of adults and occasionally in other sites, especially the head and neck region in children and in bone in adults.[136,138,142,143] The tumors are highly malignant with a rapid spread to other sites.[137,138,144] Our experience with this rare tumor includes 18 patients with a mean age of 27 ± 12 years (range 13 to 69 years). In our series, more women (67%) are affected than men (33%). Examples of the gross and histologic characteristics of an alveolar soft part sarcoma are shown in Figs 10A-B.

A number of other tumors have been identified in addition to these 11 lesions, most of which are rare and to some extent less well defined. These include an array of tumors arising from blood vessels, which have various characteristics and nomenclature. One of these is the relatively low-grade epithelioid hemangioendothelioma, which in many cases arises from a vein and is not likely to metastasize.[4,26,27] Another is a true angiosarcoma, which is often subcutaneous and aggressive.[145-147] Another tumor in this category is Kaposi's sarcoma, which affects the skin and may be virus-associated.[148-150] Fifty-one patients in our database fell into the general category of vascular sarcomas. The mean patient age was 56 ± 19 years (range 20 to 53 years), affecting 47% of men and 53% of women. Two other groups of tumors — spindle cell sarcoma not otherwise classified and undifferentiated sarcoma of soft parts — are sometimes included in discussions of soft tissue sarcomas but are difficult to identify or characterize. The spindle cell sarcoma not otherwise classified may be a form of fibrosarcoma or malignant fibrous histiocytoma; 40 patients in our series have been so categorized. Seven cases were identified as undifferentiated sarcoma of soft parts.[4,26,27] Examples of the gross and histologic characteristics of angiosarcomas are seen in Figs 11A-B.

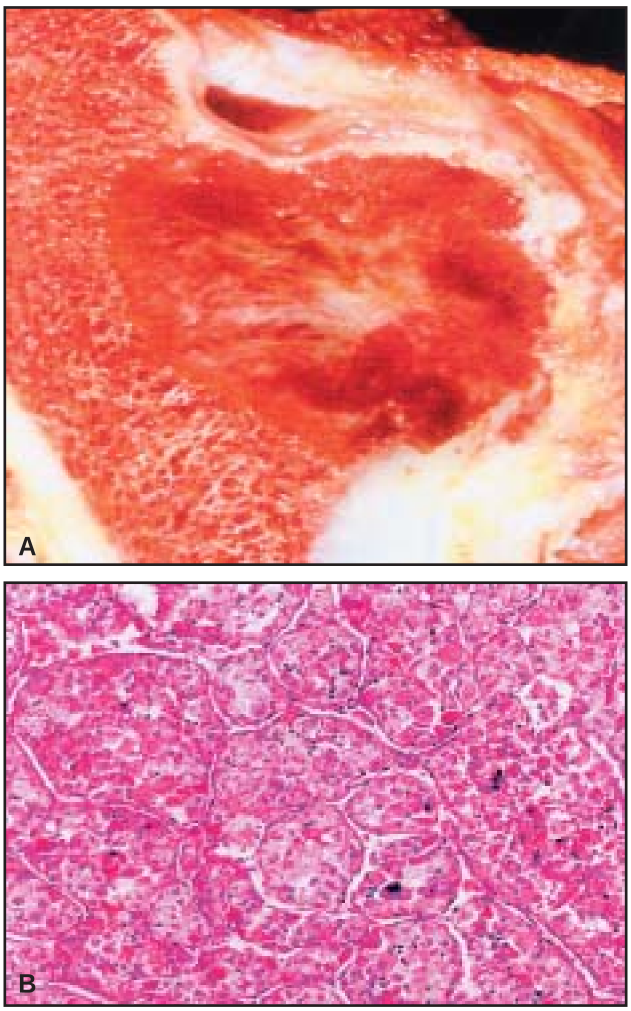

Fig 10A-B. — An alveolar soft part sarcoma arising in the soft tissues adjacent to the greater trochanter and breaking into the bone (A). Histologically, the tumor shows an organoid characteristic with the cells in an alveolaroid pattern separated by vascular spaces (B). Reprinted from Weiss SW, Goldblum JR, eds. *Enzinger and Weiss's Soft Tissue Tumors*. 4th ed. Philadelphia, Pa: Mosby; 2001:1511. With permission from Elsevier.

Diagnosis of Soft Tissue Sarcomas

The diagnosis of soft tissue sarcomas can be difficult due to the fact that the tumors are often painless, and they can be located in the soft somatic tissues of the proximal parts of the body that may be difficult to examine in muscular or obese patients. Tumors in the shoulder or hip may

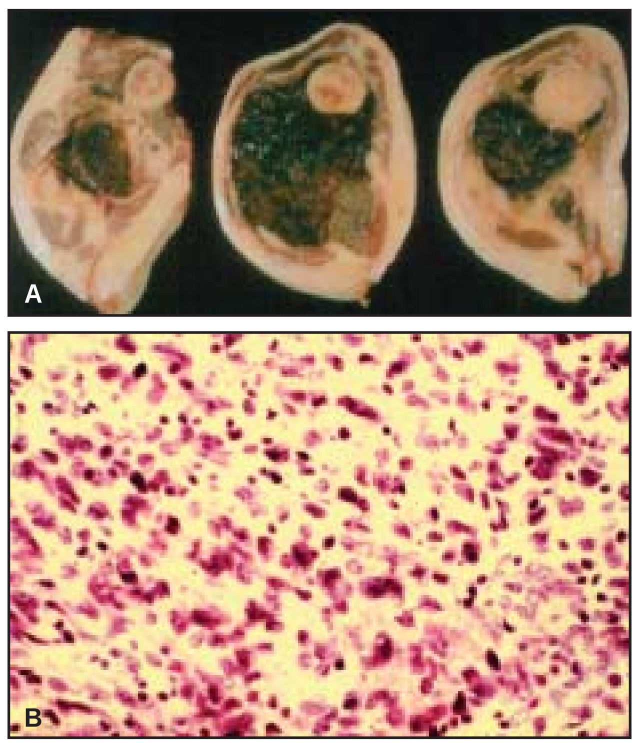

Fig 11A-B. — An angiosarcoma arising in the pelvis and surrounding the proximal femur. Note the hemorrhagic contents of the tumor (A). The histologic pattern is abnormal cellular elements with a collection of red cells within the tissue (B).

cause some restriction of motion, and those in the forearm and hand may present considerable limitation of hand function or pronation and supination. Tumors such as malignant neurofibrosarcomas that arise adjacent to nerves may present with neural abnormalities such as a sensory deficit or minor motor paralysis. In some circumstances, when the patients or their families finally notice the tumors, the size may be remarkable and on occasion the lesions may have broken through the skin (Fig 12).

Identification or definition of soft tissue tumors by physical examination may be difficult. Most of the tumors are firmer than the surrounding soft tissues and are often attached to bone, fibrous membranes, or even vascular or neural structures. Except for the liposarcoma, most soft tissue tumors are easily distinguished from normal fat in the subcutaneous layers, but they may appear to be related to recent or even earlier trauma. The tumors may be tender, particularly if they are surrounded by neural or vascular structures or if they become large enough to compress or cause a significant stretching of a muscular structure such as the deltoid or quadriceps. The history of radiation to the site may offer some diagnostic importance since this is believed to be a significant factor in the induction of some forms of soft tissue sarcoma.[94,95,151-153]

Imaging of soft tissue sarcomas is often helpful and in many cases may be diagnostic.[154] Roentgenograms are useful when the lesion is large or causes injury or damage to a bone (Fig 13), but small lesions in some locations such as the pelvis or shoulder are sometimes difficult to see on radiographs. A computed tomography (CT) scan is frequently valuable in clearly displaying the alteration in the shape and size of a part and the character of the soft tissue material (Fig 14).[154] The material may appear homogeneous on such studies or may show irregularity in the structure, suggesting areas of necrosis or hemorrhage within the tumor (Fig 15).

The magnetic resonance image (MRI) provides the most information about soft tissue sarcomas and not only demonstrates the shape and size of the lesion often with remarkable clarity, but also provides some clues as to the nature of the lesion.[15,154-157] Most of the connective tissue sarcomas are dark on T1 (hypo-intense) and light on T2 (hyper-intense), as is shown in Fig 16. However, the presence of fat and its increased vascularity make the tumor appear light on both T1 and T2, while a dense lesion such as the desmoid or fibrosarcoma may appear dark on both.[154,158-160] The use of gadolinium helps to define the extent of the lesion and its vascularity, and it also demon-

Fig 12. — Photograph showing a large liposarcoma that has invaded and destroyed the elbow and has also broken through the skin.

Fig 13. — Antero-posterior and lateral views of a radiograph of the distal femur showing an enormous soft tissue mass, which on biopsy proved to be a high-grade liposarcoma.

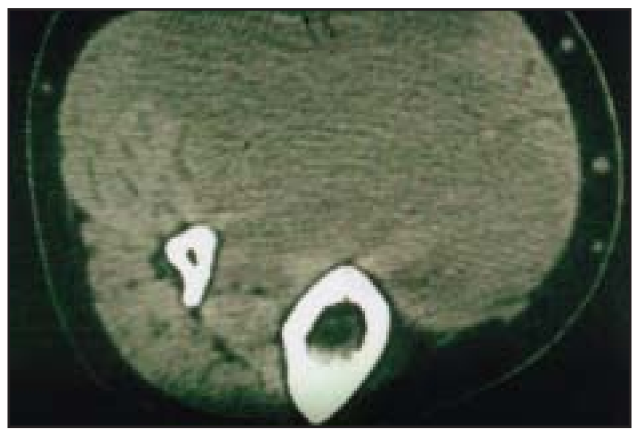

Fig 14. — CT image of a soft tissue tumor of the calf that was diagnosed as a malignant fibrous histiocytoma.

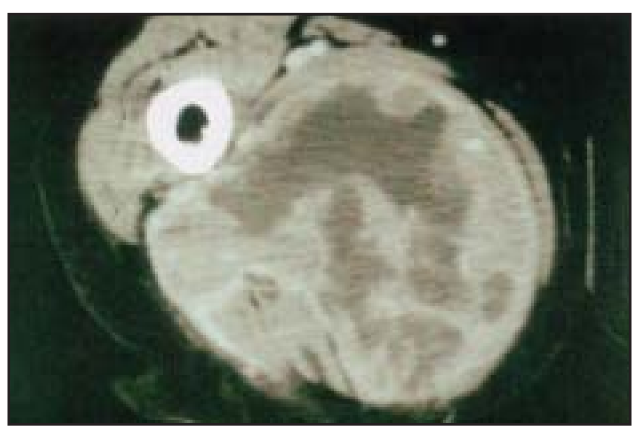

Fig 15. — CT image of a malignant synovial sarcoma of the thigh. Note the variation of pattern of the internal aspect of the tumor suggesting hemorrhage or necrosis.

strates the proximity to the nerves and blood vessels, which can be helpful to the surgeon planning a resection.[15,154-156,159,160]

Bone scans are likely to be positive only if the tumor has damaged the bone or if the lesion itself is highly vascular.[154] Positron emission tomography (PET) scans are for the most part active over the soft tissue sarcoma, but more importantly, they are useful if seeking metastases, additional lesions, or particularly lymph node extensions.[161,162]

Screening the patient for metastatic spread is essential. Among the 1,626 patients in our series who had been completely assessed at the time of admission, 278 (17%) had metastatic disease at presentation. A chest CT is essential in the workup, and for some tumors that are likely to appear at multiple sites in the soft tissues, a PET scan may be useful.[5,161,162] Laboratory screening provides little information of importance in relation to the tumor other than to assess the possible problems related to surgical procedures.

The biopsy is also an essential part of the workup and in most cases will identify the type of tumor and provide key information in determining the treatment protocol.

Open biopsies have a relatively high risk of complication but a small likelihood of a misdiagnosis,[163] while needle biopsies are less likely to present with problems but are also frequently less definitive and accurate.[164] An open biopsy should be performed through a small incision, which should be designed with consideration of the subsequent definitive resective operative procedure. Thus, transverse incisions in the extremities are generally to be avoided, and pelvic biopsies should be planned to avoid placing neural or vascular structures in danger of exposure or injury. Sufficient tissue should be obtained to provide the pathologist with material for a frozen section in order to verify that the lesional tissue is present.[163] The remainder of the tissue should be used for permanent sections for identification of the type of tumor, the grade (most pathologists grade them 1–3), and immunologic studies for identification of some of the special materials present in some of the tumors such as S-100, cytokeratin, or P53.[4,36-40,93-95] Some tissue should be reserved for electron microscopy, and in some laboratories tissue may be used for flow cytometry studies to define the rate of DNA synthesis, the apoptotic activity, and the presence or absence of aneuploidy.[126,164] The latter sometimes correlates with outcome.[164]

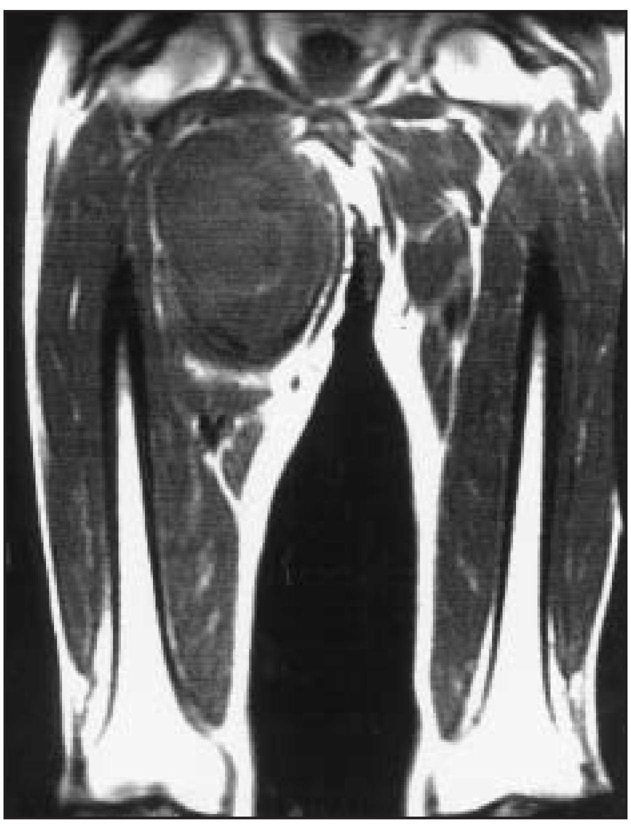

Fig 16. — T1 MRI of a high-grade malignant fibrous histiocytoma arising in the proximal thigh.

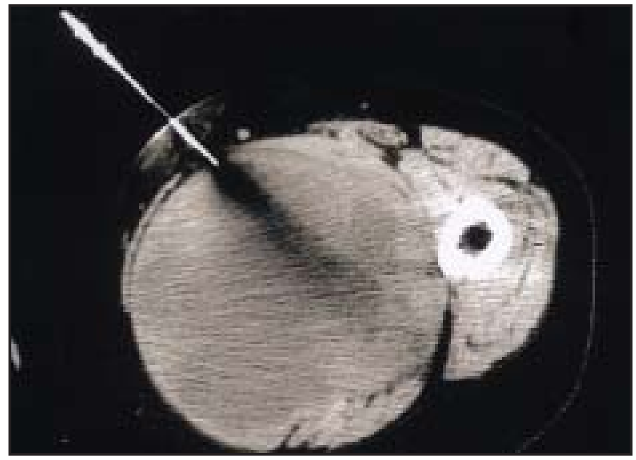

Fig 17. — Technique of a CT-guided biopsy under local anesthesia for a high-grade leiomyosarcoma of the proximal thigh.

As indicated, the needle biopsy is safer in terms of complications, but its accuracy is an area of concern. There are two forms of needle biopsies: (1) fine-needle aspiration[5,165-168] and (2) core biopsies usually performed under CT or, less commonly, ultrasound guidance.[165] With the latter technique, it should be possible to obtain several cores, possibly from different sites, to ensure that the biopsies are representative and also to apply some of the special stains and perform flow cytometric studies (Fig 17).[164] These additional studies are difficult with fine-needle aspiration techniques due to the limited amount of available tissue.[165]

Staging of Soft Tissue Sarcomas

Once the imaging studies have been performed and the biopsy obtained, it should be possible to stage the tumor.[4,5] Staging is essential for treatment planning.[169] Tumors that are low-grade histologically, small in size, and confined within a compartment have a good prognosis and may require only surgical excision, while those that are high-grade histologically and large in size or have metastasized or recurred locally often require adjunctive or neoadjunctive chemotherapy and radiation therapy.[5,169-171]

Two staging systems are available — the Musculoskeletal Tumor Society (MSTS) staging system and the GTNM (grading, tumor, nodes, metastases) staging system. Both of these systems define the extent and severity of the tumor.

The MSTS system[14,172] is based on three components, including the grade of the tumor (G1 is low-grade, G2 is high-grade), the anatomic location (T1 is within a compartment, T2 is extracompartmental), and absence (M0) or presence (M1) of metastases. The tumors are thus defined as stage IA (G1, T1, M0) *or* stage IB (G1, T2, M0) *or* stage IIA (G2, T1, M0) *or* stage IIB (G2, T2, M0). Stage III (any G, any T, M1) indicates the presence of metastatic focus. Thus, a high-grade (G2) malignant fibrous histiocytoma that has broken out of the quadriceps compartment where it is located (T2) but shows no metastatic spread is classified as an MSTS stage IIB tumor. A low-grade liposarcoma (G1) that is small in size, remains confined within the biceps (T1) and has not metastasized is classified as an MSTS stage IA tumor. A patient with a synovial sarcoma who at the time of discovery has a pulmonary metastasis is defined as stage III (any G, any T, M1).

The second protocol for staging is the GTNM system, which is described by the American Joint Commission on Cancer.[173] This system requires the grade (G1, G2, or G3), the size of the primary tumor (less than 5 cm in greatest diameter is T1 and greater than 5 cm in diameter is T2), and the absence or presence of regional lymph node involvement (N0 or N1) or distant metastases (M0 or M1). Stage IA is G1, T1, N0, M0, stage IB is G1, T2, N0, M0, stage IIA is G2, T1, N0, M0, stage IIB is G2, T2, N0, M0, stage IIIA is G3, T1, N0, M0, stage IVA is any G, any T, N1, M0, and stage IVB is any G, any T, any N, and M1. Thus, using the GTNM system, the score for a malignant fibrous histiocytoma is stage IIIB (G3, T2, N0, M0), while the small liposarcoma would be designated as stage IA (G1, T1, N0, M0). The synovial sarcoma would be stage IVB (any G, any T, any N, M1).

Treatment of Soft Tissue Sarcomas

To assist in developing appropriate treatment regimens, all patients with possible soft tissue sarcomas must have a careful history, physical diagnosis, laboratory studies, a bone scan, roentgenograms of the lesional site, a CT of the lesional site and the chest, an MRI of the lesional site and, if indicated, and a PET scan to assess the presence or absence of local or distal spread. A biopsy must be performed; most centers prefer CT-guided needle biopsies since they are often diagnostic and have a limited likelihood of a negative effect on the surgical or other treatment protocols.

The treatment protocols performed for soft tissue sarcomas depend to some extent on the size and site of the tumor, its proximity to neurovascular or visceral structures, the patient's age and general health status, the presence or absence of metastatic spread, and the desires of the patient and the patient's family. For the most part, the principal treatment protocol is surgical.[170-172,174-177] Surgical procedures can be intralesional (within the tumor mass, often leaving gross tumor), marginal (through the surrounding fibrous membrane, often leaving microscopic foci of tumor), wide (outside the membrane and compartment, leaving no tumor other than "skip metastases"), and radical (most often involving the entire limb and including the entire compartment in which the tumor was located). In general, most oncologic surgeons prefer to achieve a wide margin if possible for high-grade sarcomas. However, in some circumstances, particularly in cases with neurologic or vascular proximity, marginal surgery is utilized for some of the lesions. Surgeons usually include the site of prior biopsy and at times, if the resection is wide enough, need to perform muscle transfer and skin grafting. If major blood vessels are included in the specimen, the possibility of a vascular graft is reasonable. If bone is involved, resection and metallic or allograft implant may be used to restore function and limb length. A radical margin usually involves an amputation; this is principally reserved for cases when the lesion cannot be resected safely or when the resection would so affect the vascular or neural system as to render the limb markedly impaired.[178,179] Patients who undergo amputation often require prolonged bed rest in a hospital setting and antibiotics and anticoagulant therapy in order to avoid complications.

Radiation is often helpful in decreasing the likelihood of local recurrence and possibly metastasis. It may be given preoperatively, intraoperatively, and sometimes postoperatively.[180-187] Brachytherapy, which consists of inserting a catheter and implanting a radioactive source for usually a 3-day period, appears to decrease the likelihood of local recurrence.[188-191] Postoperative radiation may be necessary if intralesional or even marginal tumors are discovered on pathologic study at the time of surgical resection. The amount of radiation given to a patient may range from 40 to 60 Gy or more depending on the extent of the surgery, the anatomic site, and likelihood of microscopic or macroscopic retention of diseased tissue.

In recent years, chemotherapy has been useful for soft tissue sarcomas.[124,144,192-203] The principal agents are ifosfamide and doxorubicin, both of which are particularly effective for high-grade tumors. They may be given preoperatively or postoperatively, and if administered prior to surgery, they may allow the surgeon to reduce the extent of the resection. Members of the Connective Tissue Oncology Service at the Massachusetts General Hospital have developed a protocol known as MAID (mesna, doxorubicin, ifosfamide, and dacarbazine), which is adminis-

Table 1. — Analysis of Results for Soft Tissue Sarcomas Treated Between May 1972 and May 2001

Diagnosis	No. of Patients	No. of Patients Died of Disease	% Surviving	No. of Recurrences	No. of Patients With Stage III Disease
Malignant fibrous histiocytoma	471	171	63.7	5 (1.1%)	45 (9.5%)
Liposarcoma	196	43	78.1	8 (4.1%)	16 (8.2%)
Synovial sarcoma	146	34	76.7	3 (2.1%)	17 (11.6%)
Fibrosarcoma	100	15	85.0	6 (6.0%)	6 (6.0%)
Malignant schwannoma	87	15	82.8	10 (11.5%)	7 (8.0%)
Leiomyosarcoma	65	32	50.8	7 (10.8%)	16 (24.6%)
Epithelioid sarcoma	45	5	88.9	2 (4.4%)	6 (13.3%)
Angiosarcoma	43	4	90.7	3 (7.0%)	12 (27.9%)
Rhabdomyosarcoma	32	5	84.4	1 (3.1%)	7 (21.9%)
Clear cell sarcoma	22	9	59.1	2 (9.1%)	4 (18.2%)
Alveolar soft part sarcoma	13	5	61.5	0 (0.0%)	3 (23.1%)
Total	1,220	338	72.3	47 (3.9%)	139 (11.4%)

tered preoperatively and appears to be effective for large, high-grade soft tissue sarcomas.[204] The I.V. chemotherapy regimen consists of the following:

Mesna 2,500 mg/m^2 per day for 4 days
Doxorubicin 20 mg/m^2 per day for 3 days
Ifosfamide 2,000 mg/m^2 per day for 3 days
Dacarbazine 250 mg/m^2 per day for 4 days

This course of chemotherapy is followed by a 2-day rest period, and then radiation (2 Gy) is administered daily for 11 days, totaling 22 Gy. After another 2-day rest period, a second MAID treatment is administered, which is followed by a second course of radiation, bringing the total radiation dose to 44 Gy. A third course of MAID is then administered, and surgery is performed at approximately 3 weeks after completion of the preoperative chemotherapy and radiation. The specimen is assessed for the percentage of nonviable tumor tissue and margins, and additional radiation or chemotherapy is administered if necessary. The current status of the MAID protocol suggests that it has substantially decreased the rate of local recurrence and metastasis and has increased the survival time when compared with a historical control population.[204] Complications from the procedure are principally related to skin and gastrointestinal and hematologic problems. However, only 1 patient in the series of 48 has died of late-onset neutropenia.

Treatment of Soft Tissue Sarcomas by the Massachusetts General Hospital Orthopaedic Oncology Group

The results for 1,220 patients treated by our group between 1972 and June 2001 are shown in Table 1 and Fig 18. The overall survival rate for the entire series is 72%, which generally reflects the results reported from other institutions. Variation in survival data is noted for some of the tumors, with the poorest survival prognosis for patients with leiomyosarcoma, clear cell sarcoma, alveolar soft part sarcoma, and malignant fibrous histiocytoma (51%, 59%, 62%, and 64% surviving, respectively). The best prognoses are for epithelioid sarcoma and fibrosarcoma (89% and 85% surviving, respectively). The percentage survival for angiosarcoma is higher (91%), but this should not be considered accurate since in our computerized system all vascular tumors, even the very low-grade ones, were classified as angiosarcoma.

Eighty-four percent of patients with rhabdomyosarcomas survived. However, our experience and outcome information are limited due to the small numbers of patients we treated compared with the larger series under control of the hematology-oncology team, particularly at Children's Hospital of Boston.

Part of the reason for the poor prognosis for some of the tumors is the number of MSTS stage III patients in our series. Table 1 demonstrates that 11.4% of the patients presented with metastases at the time of first contact, particularly for leiomyosarcoma (25%), angiosarcoma (28%), and alveolar soft part sarcoma (23%). The recurrence rates fol-

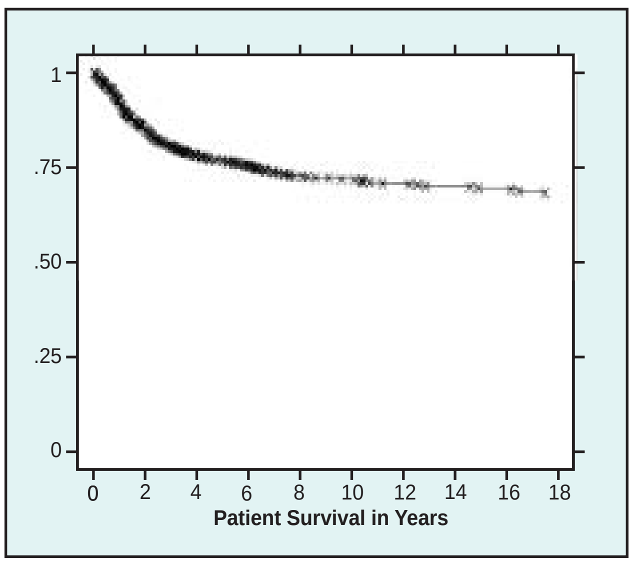

Fig 18. — A Kaplan-Meier plot demonstrating the life table pattern for the 1,220 patients described in our series (Tables 1 and 2).

lowing treatment are generally low, accounting for less than 4% for the entire series. Only the patients with malignant neurofibrosarcomas and leiomyosarcomas had recurrence rates over 10%.

Table 2 provides some statistical analysis for survival rates for the entire series of 1,220 patients. No difference was noted for gender, but the survival rate markedly decreased for patients 40 years of age or older (67%) compared with those less than 40 years (81%) (Fig 19). Patients whose tumors were located in the thigh, hip, or

Table 2. — Statistical Analysis for Percent Survival for the Entire Series (N = 1,220)

Characteristic	Survival	*P* Value
Gender		NS
Men	73%	
Women	72%	
Age		*P*<.0006
<40 years	81%	
≥40	67%	
Anatomic Site		*P*<.0005
Thigh, hip, pelvis	64%	
Shoulder, arm, elbow	75%	
Hands and feet	77%	
MSTS Stage		*P*<.0001
Stage IA, IB	90%	
Stage IIA,IIB	73%	
Stage III	57%	
Intracompartmental vs Extracompartmental Location		*P*<.0003
Stage IA, IIA	84%	
Stage IB, IIB	73%	
Recurrence		*P*<.0006
Recurrence (67 pts)	51%	
No recurrence	74%	

NS = not significant

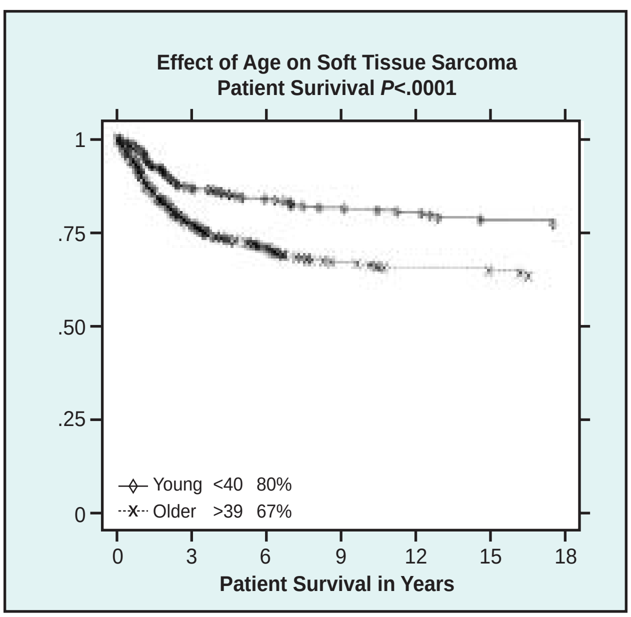

Fig 19. — Kaplan-Meier plot showing the effect of age on survival in our series. The graph shows that patients under 40 years of age have a survival rate of 80% compared with 67% for those 40 years of age or older. These data are highly significant.

pelvis had a lower survival rate (64%) than those whose tumors were in the proximal upper extremity (75%) or in the hand or foot (77%); this is particularly evident in review of foot tumors.[205] Patients with MSTS stage I tumors fared better than those with stage II tumors (90% and 73% survival rates, respectively). For patients with metastases present at the time of admission (stage III), the survival rate was less than 60% (Fig 20). A similar analysis for the "T1" or "T2" characteristic (intracompartmental vs extracompartmental location) showed a marked differ-

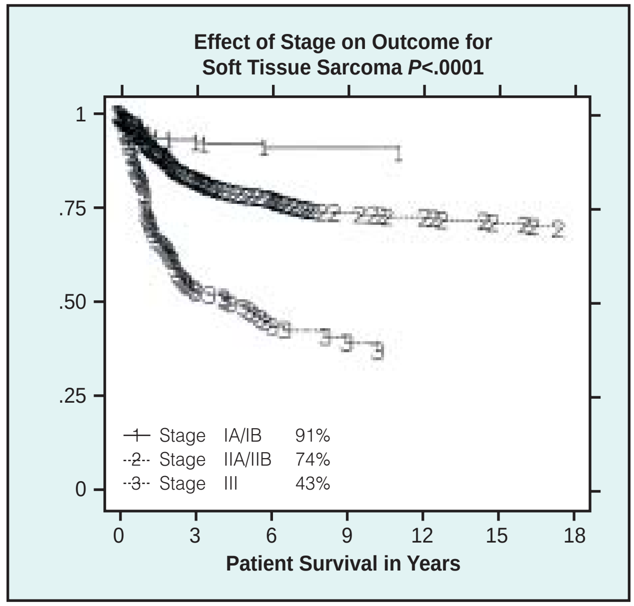

Fig 20. — MSTS staging system showing the effect on outcome in our series of soft tissue sarcomas. Patients with stages IA and IB tumors have a survival rate of 91% compared with 74% for those with stage IIA and IIB. Patients with metastases at outset (stage III) have a poor outcome (43% survival).

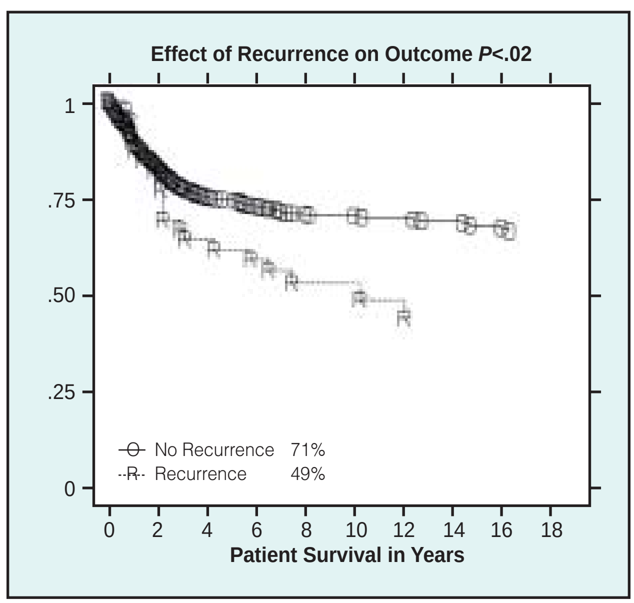

Fig 21. — Plot showing the negative effect of tumor recurrence on outcome. Patients with a tumor recurrence have a 49% survival rate compared with 71% for those without a recurrence (Table 1).

ence; patients whose tumors were designated T1 had a survival rate of 84% compared with 73% for those with tumors classified as T2. Local recurrence developed in 67 of the total series of patients, representing an important effect on outcome (only 51% surviving) (Fig 21).

Table 3 presents an analysis of the effects of surgery and other treatment protocols on patients' quality of life. The data are based on a questionnaire program developed by our group to assess the clinical, functional, sociologic, and psychologic effects of tumor treatment on surviving patients treated for malignant lesions at the Massachusetts General Hospital.[178] Some of the data from questionnaires received from 448 patients with soft tissue tumors are included in Table 3. Eleven percent of the patients still have sufficient pain to require medication, 10% require a crutch or a cane, over 30% have difficulty going up or down stairs, 20% have a discernible limp when walking, and over 30% cannot participate in sports. Of note is that 9% are sometimes depressed, and 14% still have some anxiety about their tumors. These data did not differ materially from those patients who were treated for other types of lesions such as osteosarcoma, chondrosarcoma, and lymphoma.

Table 3. — **Disability Evaluation for 448 Patients With High-Grade Soft Tissue Sarcomas**

Data below are based on a questionnaire sent to approximately 4,000 patients treated by our group for malignant connective tissue tumors. In each case, data from patient responses were recorded in a computerized file, which has served as a study base for evaluating the clinical, functional, sociologic, and psychologic effects of tumor treatment on surviving patients.

	Yes	Percent
Are you unable to drive?	23	5%
Do you have sufficient pain to require medication?	48	11%
Are you confined to a bed or chair?	10	2%
Do you require a crutch or cane?	43	10%
Do you wear a brace?	22	5%
Do you have difficulty going up or down stairs?	140	31%
Do you limp when you walk?	90	20%
Are you unable to participate in sports?	139	31%
Are you often depressed?	39	9%
Do you occasionally feel anxious about your tumor?	63	14%

Discussion and Conclusions

Soft tissue sarcomas are an unusual entity in the oncology field. While many centers rarely encounter patients with the lesions, they are a major concern to connective tissue oncology groups that have treated many of these lesions over the past several decades. The definition of the extent of disease and the determination of the presence or absence of metastases to lung, lymph nodes, or other anatomical sites require a complex protocol using imaging studies such as CT, MRI, and PET scanning.

Once the tumor extent is defined, tissue is obtained for diagnostic histologic analysis. Grading is somewhat complex, and the use of immunologic and genetic studies of the tissue and flow cytometric analyses of DNA characteristics may help to define the tumor type, as well as serve to some extent as indicators of prognosis.

Surgery remains complex in many cases, particularly for large tumors within the pelvis. Currently, the use of preoperative radiation and chemotherapy is increasing for the treatment of large, high-grade, proximally placed tumors in order to reduce the likelihood of local recurrence and distant metastases. Despite attempts at reducing the complication rate for the treatment protocols, many patients who survive are disabled and to some extent limited in their capacity to walk, go up and down stairs, and engage in sports (Table 3).

In the future, patient outcomes may be improved by the addition of diagnostic modalities such as PET scanning to assess the presence of metastases at an earlier time and genetic studies to determine which tumors are likely to metastasize so that chemotherapy and radiation therapy can be selectively used. A protocol such as the MAID system can be utilized, which appears to improve the patient's survival rate with only a moderate increase in complications. It is hoped that gene identification and repair will assist in developing treatments that decrease the malignity of the tumors and reduce the complications of surgical management.

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