Clinical presentation, histopathology, diagnostic evaluation, and staging of soft tissue sarcoma

Authors: Christopher W Ryan, MD, Janelle Meyer, MD
Section Editors: Robert Maki, MD, PhD, Raphael E Pollock, MD
Deputy Editor: Diane MF Savarese, MD

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Apr 2018. | **This topic last updated:** Apr 27, 2017.

INTRODUCTION — Sarcomas are a rare and heterogeneous group of malignant tumors of mesenchymal origin that comprise less than 1 percent of all adult malignancies and 12 percent of pediatric cancers [1-3]. Approximately 80 percent of sarcomas originate from soft tissue, and the rest originate from bone new cases [3].

The histopathologic spectrum of sarcomas is broad, presumably because the embryonic mesenchymal cells from which they arise have the capacity to mature into striated skeletal and smooth muscle, adipose and fibrous tissue, bone, and cartilage, among other tissues. Although ectodermal in origin, malignant tumors affecting peripheral nerves are included because of similarities in their clinical behavior, management, and outcome.

This topic review will cover the clinical presentation, diagnostic evaluation, and staging of soft tissue sarcoma other than gastrointestinal stromal tumor (GIST), the most common sarcoma, which is discussed in detail elsewhere. Issues specific to soft tissue sarcomas arising in the head and neck, retroperitoneum, and breast are discussed elsewhere, as are bone sarcomas, Kaposi sarcoma, and dermatofibrosarcoma protuberans (DFSP). (See "Head and neck sarcomas" and "Clinical features, evaluation, and treatment of retroperitoneal soft tissue sarcoma" and "Breast sarcoma: Epidemiology, risk factors, clinical presentation, diagnosis, and staging" and "Osteosarcoma: Epidemiology, pathogenesis, clinical presentation, diagnosis, and histology" and "AIDS-related Kaposi sarcoma: Staging and treatment" and "Classic Kaposi sarcoma: Clinical features, staging, diagnosis, and treatment" and "Dermatofibrosarcoma protuberans: Epidemiology, pathogenesis, clinical presentation, diagnosis, and staging".)

HISTOPATHOLOGY — As classified by the World Health Organization (WHO), the group of soft tissue neoplasms includes more than 100 different histologic subtypes [2]. The most common subtypes that arise in adults are outlined in the figure (figure 1).

WHO classifies most soft tissue neoplasms according to the presumptive tissue of origin (ie, the normal tissues the tumor most closely resembles) [2]. Examples include liposarcoma, synovial sarcoma, leiomyosarcoma, rhabdomyosarcoma (RMS), fibrosarcoma, and angiosarcoma. In some cases, histogenesis is uncertain, and the designation reflects the architectural pattern (eg, alveolar sarcoma of soft parts, epithelioid sarcoma, clear cell sarcoma).

Histologically, the diagnosis of a soft tissue sarcoma is made on the basis of morphologic pattern. Immunohistochemical staining (IHC) often aids in the identification of the presumptive tissue of origin. Some IHC markers are more characteristic than others, and it is the spectrum of markers examined that determines the histological subtype. As examples:

- Desmin is particularly valuable in the identification of myogenic differentiation: RMS and, to a lesser degree, leiomyosarcoma. (See "Rhabdomyosarcoma in childhood and adolescence: Epidemiology, pathology, and molecular pathogenesis", section on 'Tissue diagnosis'.)
- The presence of S100 antigen and neurofilaments suggests cells arising from the neural sheath, but this is also found in tumors with melanocytic differentiation. Among sarcomas, these include clear cell sarcoma and perivascular epithelioid cell tumors (PEComa).
- Cytokeratin is rarely expressed in most sarcomas but can help distinguish between synovial or epithelioid sarcoma (which both contain cytokeratin) and fibrosarcomas (which do not).
- Factor VIII-related antigen identifies tumors of endothelial origin.

Molecular diagnostics — A number of histologic subtypes are associated with specific chromosomal translocations; several examples are provided in the table (table 1), and molecular techniques (including fluorescence in situ hybridization [FISH] and reverse transcriptase polymerase chain reaction [RT-PCR] to detect the protein products of these fusion genes) can aid

in the diagnosis of these tumors. A prospective study has shown that molecular methods can modify expert histologic diagnoses in certain sarcomas, and argument has been made that such testing should be considered mandatory [4]. However, in our view, the decision of such testing should be made by an experienced sarcoma pathologist taking into account the clinical information provided by a multidisciplinary care team.

Routine cytogenetics on fresh sarcoma specimens have largely been supplanted by FISH probes that can be performed on paraffin-embedded material. FISH testing can be definitive in ruling-in a specific sarcoma subtype in certain cases when the differential diagnosis has been narrowed but histology and IHC staining remain equivocal (eg, synovial sarcoma). However, when a translocation-associated tumor is highly suspected based upon the clinical presentation (eg, Ewing sarcoma), it is reasonable to send fresh tissue for cytogenetic analysis at the time of biopsy in consultation with the pathologist. This topic is discussed in detail elsewhere. (See "Pathogenetic factors in soft tissue and bone sarcomas", section on 'Chromosomal translocations'.)

Most common subtypes — The most common soft tissue sarcoma subtypes in adults are undifferentiated/unclassified soft tissue sarcoma, undifferentiated pleomorphic sarcoma, liposarcoma, leiomyosarcoma, and gastrointestinal stromal tumors (GIST) (figure 1) [5,6]. GIST are discussed elsewhere. (See "Epidemiology, classification, clinical presentation, prognostic features, and diagnostic work-up of gastrointestinal stromal tumors (GIST)".)

A brief description of some of the common subtypes follows:

- **Liposarcoma** – Liposarcomas appear to arise from precursors of adipocytes (fat cells) and are most commonly found in the extremities and retroperitoneum. The three main morphologic subgroups are well-differentiated/dedifferentiated, myxoid/round cell, and pleomorphic liposarcomas [2,7]. There is a great range of biologic behavior amongst these subtypes, spanning from well-differentiated liposarcomas with low metastatic potential to the high-risk round cell or pleomorphic types, which tend to be higher grade and are associated with a high rate of distant metastases [8]. (See 'Histologic grade' below.)

  Some well-differentiated liposarcomas arising on the extremities and trunk are referred to as "atypical lipomas" or atypical lipomatous tumors to denote the fact that, at these sites, excision is usually curative and that there is no potential for metastases, as compared with sites in the retroperitoneum, mediastinum, and spermatic cord [9]. However, in our view, this is a confusing name that underestimates the risk of local recurrence of such tumors.

  The metastatic pattern of the various subtypes of liposarcomas is also unique, with metastases to other soft tissue sites and bone marrow (myxoid/round cell liposarcoma, dedifferentiated liposarcoma) more common than metastases to liver or lung (as may occur for pleomorphic liposarcomas or undifferentiated/unclassified sarcomas). (See 'Pattern of recurrence' below.)

  Myxoid and round cell liposarcomas share the same reciprocal translocation t(12;16)(q13;p11), in which the *CHOP* gene (also called the DNA damage inducible transcript 3 [*DDIT3*] gene or *GADD153*) is inserted adjacent to a novel gene called *FUS* or *TLS* (translocated in liposarcoma). While no specific chromosomal translocations have been identified in well-differentiated/dedifferentiated liposarcomas, amplification of *MDM2* and *CDK4* is very frequent in these subtypes, and their identification may be useful diagnostically. Furthermore, overexpression of the *MDM2* and *CDK4* genes is also being exploited for therapeutic gain [7,10]. Pleomorphic liposarcomas genetically most closely resemble the pleomorphic variant of undifferentiated/unclassified sarcomas. (See "Pathogenetic factors in soft tissue and bone sarcomas", section on 'Myxoid and round cell liposarcomas' and "Pathogenetic factors in soft tissue and bone sarcomas", section on 'Somatic gene mutations'.)

- **Leiomyosarcoma** – Leiomyosarcomas, which are characterized by smooth muscle differentiation, can be found throughout the body, including the retroperitoneum, any location where there is a vein, and the uterus. Leiomyosarcomas that originate in the uterus may be a distinct subgroup of tumors as they have different gene expression patterns when compared with nonuterine leiomyosarcomas [11]. Uterine leiomyosarcomas are discussed in detail separately. (See "Uterine sarcoma: Classification, clinical manifestations, and diagnosis", section on 'Leiomyosarcoma'.)

  Unlike superficial and deep tumors, cutaneous leiomyosarcomas typically have a more indolent course and are less likely to metastasize [12].

- **Undifferentiated/unclassified soft tissue sarcoma** – This subgroup was formerly included in a broad category of soft tissue sarcomas that were termed malignant fibrous histiocytoma (MFH), which was the most common subtype of soft tissue sarcoma [6]. However, many sarcomas that were previously identified as MFH could be reclassified by many pathologists as other subtypes when reanalyzed using histology and IHC [13]. The term undifferentiated/unclassified soft tissue sarcoma is now reserved specifically for sarcomas that lack specific lines of differentiation [2], although some pathologists use the term "sarcoma, not otherwise specified (NOS)" for these sarcomas.

Subsets of undifferentiated/unclassified soft tissue sarcomas include the pleomorphic (undifferentiated pleomorphic sarcoma), round cell, and spindle cell variants, which simply describe histological morphology. One version of what was formerly termed myxoid MFH is now classified as a distinct sarcoma subtype, myxofibrosarcoma. In comparison with undifferentiated/unclassified soft tissue sarcoma, myxofibrosarcomas may be associated with a greater local recurrence risk [14-16].

- **Synovial sarcoma** – Synovial sarcoma initially derived its name from a histologic resemblance to synovial cells, but its cell of origin is unknown. There are two morphologic subtypes, monophasic and biphasic. The most common presentation is a soft tissue tumor of the extremities in young adults.

  The majority of synovial sarcomas are characterized by the chromosomal translocation t(X;18)(p11;q11). The breakpoint of this translocation fuses the *SS18* (previously called *SYT*) gene from chromosome 18 to one of three homologous genes, *SSX1*, *SSX2*, and *SSX4* on the X chromosome. *SS18-SSX1* is associated with biphasic tumors (glandular epithelial differentiation on a background of spindle tumor cells), while *SS18-SSX2* is associated with monophasic tumors that lack glandular epithelial differentiation.

  Cytogenetic analysis, FISH, or RT-PCR can be used to detect the translocation or the protein product of the fusion gene, thus aiding in the diagnosis of synovial sarcoma. The specific *SS18-SSX* fusion type may have prognostic importance, with better outcomes reported for patients with the *SS18-SSX2* fusion in many, but not all, reports. (See "Pathogenetic factors in soft tissue and bone sarcomas", section on 'Synovial sarcoma'.)

- **Malignant peripheral nerve sheath tumor (MPNST)** – MPNSTs are of ectodermal origin and originate from peripheral nerves. Approximately 50 percent of these tumors occur in patients with neurofibromatosis type I and result from degeneration of plexiform neurofibromas. (See "Peripheral nerve tumors", section on 'Malignant peripheral nerve sheath tumors' and "Pathogenetic factors in soft tissue and bone sarcomas", section on 'Neurofibromatosis' and "Neurofibromatosis type 1 (NF1): Pathogenesis, clinical features, and diagnosis", section on 'Soft tissue sarcomas'.)

  MPNSTs are commonly found in the trunk, extremities, and head and neck. The diagnosis of an MPNST can be difficult due to variable histomorphology. There are no characteristic chromosomal translocations. The presence of S100 protein can aid in the diagnosis, but it is not uniformly expressed in these tumors, since the line of differentiation appears to be lost to some degree in many.

- **Angiosarcoma** – Angiosarcomas are uncommon tumors that arise in the subcutaneous tissue of many sites of the body, typically head and neck, or breast. It is one of the most common tumors caused by therapeutic radiation, often after treatment of breast cancer or Hodgkin lymphoma, with a median time of development of 8 to 10 years. (See "Breast sarcoma: Epidemiology, risk factors, clinical presentation, diagnosis, and staging", section on 'Ionizing radiation' and "Head and neck sarcomas", section on 'Angiosarcoma'.)

  In IHC, the tumor cells stain positive for vascular markers such as CD31 and factor VIII. Mutations in the vascular endothelial growth factor receptor-2 (VEGFR2; also called Flk1/KDR) are seen in a subset of these patients, with unclear clinical implications. (See "Overview of angiogenesis inhibitors", section on 'VEGF receptors'.)

- **Solitary fibrous tumor (SFT)** – SFTs are slow-growing tumors that arise most commonly in the pleura, pelvis, or dura, where they can reach a very large size before detection due to their slow change over time. (See "Solitary fibrous tumor" and "Uncommon brain tumors", section on 'Solitary fibrous tumor/hemangiopericytoma'.)

  While many SFTs are classified as benign tumors with a very low risk of metastasis, others are classified as malignant because of hypercellularity, at least focal cytologic atypia, tumor necrosis, numerous mitoses, and/or infiltrative borders [17]. These lesions have a greater ability to metastasize, usually at an interval of several years, most commonly to bone, liver, and lung. Tumor cells stain positive for stem cell marker CD34.

  Rare patients will present with hypoglycemia on the basis of overexpression of a form of insulin-like growth factor II (IGF-II). This finding resolves with resection of the tumor.

  These tumors are commonly associated with an *NAB2-STAT6* fusion gene, which functions as a chimeric transcription factor. (See "Solitary fibrous tumor", section on 'Molecular pathogenesis and molecular diagnostics'.)

- **Desmoid tumor/deep fibromatosis** – Desmoid tumors, also referred to as aggressive or deep fibromatosis, are not sarcomas, but they represent neoplasms of fibroblastic tissue that lack the ability to metastasize. However, desmoid tumors have a propensity for local recurrence, even after complete resection, and they have the capacity to cause local morbidity and death in rare cases. (See "Desmoid tumors: Epidemiology, risk factors, molecular pathogenesis, clinical presentation, diagnosis, and local therapy".)

Desmoid tumors typically arise in the extremity in sporadic cases or in the abdominal wall in association with pregnancy (where they usually improve postpartum) and arise in the mesenteric root in the setting of familial adenomatous polyposis (FAP). FAP is characterized by loss of expression of the gene *APC*. The development of desmoid tumor in the setting of FAP is a characteristic of Gardner syndrome, a specific version of FAP. Mesenteric desmoids are those with the highest degree of mortality.

CTNNB1 gene mutations are found in most sporadic desmoids, although some, instead, have loss of the *APC* gene. The specific type of *CTNNB1* mutation may predict for risk of recurrence.

Among children, who account for 10 to 15 percent of all cases of soft tissue sarcoma, the "small round blue cell" sarcomas predominate (eg, Ewing sarcoma, embryonal RMS, and peripheral primitive neuroectodermal tumor [PNET]). Central (supratentorial) PNET tumors are discussed elsewhere. (See "Clinical presentation, staging, and prognostic factors of the Ewing sarcoma family of tumors" and "Rhabdomyosarcoma in childhood and adolescence: Clinical presentation, diagnostic evaluation, and staging".)

It is important to differentiate between the various subtypes of sarcoma for both prognosis and potential differences in treatment. This is especially true for typical pediatric tumors that arise in adults, such as RMS. Both embryonal and alveolar RMS are more susceptible to chemotherapy and carry a better prognosis than many types of adult soft tissue sarcomas. Nevertheless, pleomorphic RMS has a relatively poor prognosis compared with other RMS subtypes and predominates in adults, and outcomes are worse than in children. (See "Rhabdomyosarcoma in childhood and adolescence: Epidemiology, pathology, and molecular pathogenesis", section on 'Histologic classification' and "Rhabdomyosarcoma in childhood, adolescence, and adulthood: Treatment".)

Histologic grade — Several grading systems have been developed to increase the prognostic value of histologic assessment, some of which use a three-tier system (ie, grade 1 [well differentiated, low grade], 2 [moderately differentiated] or 3 [poorly differentiated, high grade]) and others a four-tier system. The three-tiered system is incorporated into the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging system for soft tissue sarcomas and is preferred [2,18]. (See 'Staging' below.)

The French Federation of Cancer Centers Sarcoma Group (FNCLCC) grading system is preferred by the College of American Pathologists (CAP), and is based on three parameters: differentiation, mitotic activity, and necrosis [19,20]. Grading should be used only for untreated primary soft tissue sarcomas. The histologic grade does not differentiate between benign and malignant soft tissue tumors and is not a substitute for morphologic diagnosis.

Grading is not applicable to all soft tissue sarcomas. It is of little prognostic value for MPNST (the majority of which are considered high grade [21,22]), and it is not recommended for angiosarcoma, alveolar soft part sarcoma, extraskeletal myxoid chondrosarcoma, clear cell sarcoma, and epithelioid sarcoma [2,18]. The impact of histologic grade on prognosis is discussed below. (See 'Prognostic factors' below.)

ETIOLOGY AND PATHOGENESIS — In nearly all instances, sarcomas are thought to arise de novo and not from a preexisting benign lesion. Most cases have no clearly defined etiology, but a number of associated or predisposing factors have been identified. These include genetic predisposition (eg, Li Fraumeni syndrome, neurofibromatosis type I), retinoblastoma, exposure to radiation therapy or chemotherapy, chemical carcinogens, chronic irritation, and lymphedema. In addition, human immunodeficiency virus (HIV) and human herpes virus 8 have been implicated in the pathogenesis of Kaposi sarcoma. These topics are discussed separately. (See "Pathogenetic factors in soft tissue and bone sarcomas" and "AIDS-related Kaposi sarcoma: Clinical manifestations and diagnosis" and "Classic Kaposi sarcoma: Epidemiology, risk factors, pathology, and molecular pathogenesis" and "Retinoblastoma: Treatment and outcome", section on 'Second malignancies'.)

CLINICAL PRESENTATION — The most common presenting complaint for a soft tissue sarcoma is a gradually enlarging, painless mass. These tumors can become quite large, especially in the thigh and retroperitoneum. Some patients complain of pain or symptoms associated with compression by the mass, including paresthesias or edema in an extremity. Rarely, a patient may present with constitutional symptoms, such as fever and/or weight loss.

Distribution — Soft tissue sarcomas occur at all anatomic body sites, but the majority are in the extremities. The anatomic distribution of soft tissue sarcomas in 4550 adults reviewed by the American College of Surgeons was as follows [23]:

- Thigh, buttock, and groin – 46 percent
- Upper extremity – 13 percent
- Torso – 18 percent
- Retroperitoneum – 13 percent

- Head and neck – 9 percent

Some histologic types of soft tissue sarcoma have a predilection for certain anatomic sites. As examples:

- While only 14 percent of all soft tissue sarcomas present in the upper extremity, 40 to 50 percent of all epithelioid sarcomas arise on the forearm and finger [24-26].
- Desmoplastic small round cell tumors, which have a predilection for adolescent and young adult males, primarily involve the abdominal cavity and pelvis [27,28].

The anatomic distribution of histologic subtypes is not a simple function of abundance of the tissue type. Liposarcomas are not common in the large fatty deposits of the abdominal wall, while in the thigh, a frequent site, they often arise deep in the muscle mass, rather than in the subcutaneous fat.

Clinical presentation of retroperitoneal sarcomas, uterine sarcomas, and sarcomas of the head and neck is discussed in more detail elsewhere. (See "Clinical features, evaluation, and treatment of retroperitoneal soft tissue sarcoma" and "Uterine sarcoma: Classification, clinical manifestations, and diagnosis" and "Head and neck sarcomas".)

Pattern of growth — Soft tissue sarcomas grow at various rates depending on the aggressiveness of the tumor. Tumors tend to grow along tissue planes and only rarely traverse or violate major fascial planes or bone. The growing tumor compresses surrounding normal tissue, leading to the formation of a so-called pseudocapsule that is comprised of compressed normal tissue with poorly defined margins and fingerlike tumor projections that infiltrate adjacent tissues. Dissection along the pseudocapsule plane will invariably leave residual disease and should be avoided. (See "Overview of multimodality treatment for primary soft tissue sarcoma of the extremities and chest wall", section on 'Resection'.)

Pattern of spread — The most common pattern of spread is hematogenous, predominantly to the lung. (See 'Pattern of recurrence' below.)

The presence of distant metastatic disease at the time of initial diagnosis is uncommon, but is more likely in large, deep, high-grade sarcomas and with specific histologies. In a retrospective review of 1170 patients over a 7.5 year period, the following were noted [29]:

- The incidence of distant metastatic disease at the time of diagnosis was 10 percent, and 83 percent of metastases were located in the lungs.
- There was a higher risk of lung metastases in tumors that were deep to the fascia (9 versus 4 percent).
- The risk of having lung metastases at diagnosis also increased with higher histologic grade of differentiation (12, 7, and 1.2 percent for high-grade, intermediate-grade, and low-grade tumors, respectively).
- The histologic subtypes most likely to present with lung metastases were soft tissue Ewing sarcoma, malignant peripheral nerve sheath tumor (MPNST), and extraskeletal chondrosarcoma (25, 16.2, and 13.6 percent respectively). (See "Chondrosarcoma".)

Regional nodes — Overall, spread to regional nodes is infrequent for soft tissue sarcomas. An analysis of 1772 sarcoma patients in a prospective database at Memorial Sloan-Kettering Cancer Center (MSKCC) identified 46 (2.6 percent) with lymph node metastases [30]. However, certain histologies have a higher risk of nodal metastases than do others. The histologies with the greatest risk of lymph node metastases are rhabdomyosarcoma, synovial sarcoma, epithelioid sarcoma, clear cell sarcoma, and the vascular sarcomas (including angiosarcomas) [24-26,30-35].

Nodal metastases carry a poor prognostic implication but somewhat less than do overt bloodborne metastases in soft tissue sarcoma [31,32,34,35]. This finding prompted a change in the 2010 joint American Joint Committee on Cancer (AJCC)/Union for international Cancer Control (UICC) staging system (which covered all soft tissue sarcomas regardless of primary location) to reclassify N1 disease as stage III instead of stage IV [36]. However, in the 2017 revision of the AJCC/UICC staging system, this is only the case for soft tissue sarcomas arising in the retroperitoneum (table 2); nodal metastases are once again classified as stage IV disease for primary sites in the extremity and trunk (table 3) [37,38]. Implementation of the staging tables in the 2017 revision has been delayed to January 2018. However, outside of the United States, the UICC has implemented the eighth edition changes as of January 1, 2017. (See 'Staging' below.)

Management of the regional lymph nodes, including the role of sentinel node biopsy, is discussed elsewhere. (See "Surgical resection of primary soft tissue sarcoma of the extremities", section on 'Lymphadenectomy'.)

Pattern of recurrence — Recurrent disease after treatment of a soft tissue sarcoma can present as a local recurrence or metastatic disease [39,40]. The incidence of local recurrence depends on anatomic location, extent of resection, use of perioperative radiation therapy, and histology. (See "Surgical resection of primary soft tissue sarcoma of the extremities",

section on 'Recurrence' and "Clinical features, evaluation, and treatment of retroperitoneal soft tissue sarcoma", section on 'Preoperative therapy for large high-grade or locally advanced tumors' and "Clinical features, evaluation, and treatment of retroperitoneal soft tissue sarcoma", section on 'Outcomes and prognostic factors'.)

Overall, approximately 25 percent of patients will develop distant metastatic disease after successful treatment of their primary tumor; the incidence increases to 40 to 50 percent with tumors that are >5 cm in size, deep to the fascia, and intermediate or high grade [41,42].

In 70 to 80 percent of cases, metastatic disease is to the lungs [29,40,43,44]. Rare sites of metastatic disease spread include the skin, soft tissues, bone, liver, and brain [39,40,45,46].

There are some exceptions to the typical pattern of metastatic disease:

- In round cell/myxoid liposarcomas, where extrapulmonary metastases to the retroperitoneum, abdomen, bone (particularly the spine), and paraspinal soft tissue are common [47,48].
- Retroperitoneal sarcomas, in particular leiomyosarcomas, also commonly metastasize to the liver as well as the lung. Conversely, retroperitoneal liposarcomas, nearly all the well-differentiated/dedifferentiated subtype, recur local-regionally instead of with metastatic disease. (See "Clinical features, evaluation, and treatment of retroperitoneal soft tissue sarcoma".)

DIAGNOSTIC EVALUATION — Histologic examination of a soft tissue mass is essential for diagnosis and treatment planning. Radiographic imaging is used to assist in defining the etiology of a soft tissue mass, determining the extent of a primary tumor for surgical planning, and establishing the presence or absence of metastatic disease.

The initial evaluation of a patient with a suspected soft tissue sarcoma begins with a history of when the mass was first noticed, how quickly it has been growing, and whether there are symptoms to suggest distal neurovascular compromise. The physical examination should focus on the size and depth of the mass, fixation to adjacent structures, and associated edema or signs of nerve impingement.

Delay in diagnosis of soft tissue sarcomas is common. Patients frequently do not seek prompt medical attention due to the painless nature of the tumor, and delays on the part of the physician are likewise common due to assumptions of benignity [49].

Differential diagnosis — The differential diagnosis of a soft tissue mass includes benign soft tissue tumors, such as a lipoma, as well as malignant tumors, including sarcoma, metastatic carcinoma, melanoma, or lymphoma.

Given that benign soft tissue masses are at least 100 times more common than malignant soft tissue sarcomas [2], it can be difficult to determine which soft tissue masses warrant further evaluation. The United Kingdom Department of Health has published criteria for urgent referral of a patient with a soft tissue lesion [50]:

- Soft tissue mass >5 cm (golf ball size or larger)
- Painful lump
- Lump that is increasing in size
- A lump of any size that is deep to the muscle fascia
- Recurrence of a lump after previous excision

In a prospective review of 365 patients with confirmed soft tissue sarcoma, tumor depth was found to be the most sensitive marker of malignancy, followed by size >5 cm and a history of rapid growth [51].

Importance of biopsy planning — Because the diagnosis of soft tissue sarcoma is often unsuspected, unplanned and inappropriate excisions of these tumors frequently occur before a proper pathologic diagnosis has been made [52]. Partial excision of the tumor before referral to a tertiary center does not appear to compromise limb preservation, local control, or in most series, survival. However, a higher incidence of distant metastatic disease has been reported in such patients [53], and reresection may entail a larger procedure than a de novo procedure and impact the functional result. These data underscore the importance of transferring patients with soft tissue masses of uncertain identity to centers that specialize in treating sarcomas so that they can undergo adequate initial resection. Studies have shown improved outcomes in patients treated at a specialist sarcoma center [54,55]. (See 'Biopsy' below and "Surgical resection of primary soft tissue sarcoma of the extremities", section on 'Inadequate initial resection'.)

Radiographic studies — Various imaging techniques are used to assist in defining the etiology of a soft tissue mass, determining the extent of a primary tumor for surgical planning, and establishing the presence or absence of metastatic disease.

Imaging of the primary tumor — Our practice for the diagnostic workup of a soft tissue mass includes cross-sectional imaging with magnetic resonance imaging (MRI) for a primary extremity or trunk lesion and contrast-enhanced multidetector-row computed tomography (MDCT) for a primary abdominal, visceral, or retroperitoneal lesion.

Plain radiography — Plain films of the primary site can be useful to rule out soft tissue masses that arise from bone and to detect intratumoral calcifications such as those that appear within soft tissue (extraskeletal) osteosarcomas and synovial sarcomas.

MRI and CT — Magnetic resonance imaging (MRI) is the preferred imaging modality for the evaluation of soft tissue masses of the extremities, trunk, and head and neck, while computed tomography (CT) is the most commonly used imaging technique for retroperitoneal and visceral sarcomas. Several studies report that MRI is superior to CT in evaluating soft tissue sarcomas of the extremity as MRI provides multiplanar images with better spatial orientation. MRI is superior for delineating the extent of the neoplasm and the relation to surrounding structures, especially individual muscle involvement (image 1) [56-58]. However, a multicenter prospective study that included 133 patients who underwent both CT (image 2) and MRI within four weeks of surgery for a soft tissue sarcoma of the arm, shoulder, pelvis, hip, or lower extremity found no statistically significant difference between the two modalities in determining tumor involvement of muscle, bone, joints, or neurovascular structures [59]. Combined interpretation of CT and MRI did not improve accuracy of preoperative assessment.

PET and PET/CT — A number of studies report that positron emission tomography (PET) and integrated PET/computed tomography (CT) using fluorodeoxyglucose (FDG) can distinguish benign soft tissue tumors from sarcomas with the greatest sensitivity for high-grade sarcomas [60-62]. However, the ability to differentiate benign soft tissue tumors from low- or intermediate-grade sarcomas is limited, and PET and PET/CT are not routinely recommended for the initial workup of a soft tissue mass [63-65]. One exception may be in the characterization of a suspected peripheral nerve sheath tumor in a patient with neurofibromatosis; in this scenario, PET imaging can be helpful in distinguishing a malignant peripheral nerve sheath tumor (MPNST) from a neurofibroma [66-68]. Gallium scans may also differentiate between neurofibromas and MPNSTs [69]. (See "Neurofibromatosis type 1 (NF1): Pathogenesis, clinical features, and diagnosis", section on 'Soft tissue sarcomas'.)

Consensus guidelines for workup of a soft tissue sarcoma of the extremity and trunk issued by the National Comprehensive Care Network (NCCN) suggest that PET scan may be useful in prognostication, grading, and determining response to neoadjuvant chemotherapy in patients with soft tissue sarcoma [70]. However, this recommendation is based upon a single study from the University of Washington that found that FDG-PET was useful to predict the outcomes of patients with high-grade extremity soft tissue sarcomas who were treated initially with chemotherapy [71]. Patients with a baseline tumor standard uptake value (SUV) maximum ≥6 who had a <40 percent decrease in FDG uptake after neoadjuvant chemotherapy were found to be at high risk of systemic disease recurrence.

The clinical utility of having this information prior to surgical treatment is unclear. At present, the use of PET for prognostication or assessment of treatment response is not considered routine at most institutions.

Functional imaging with PET/CT may have a role in patients with a clinical suspicion of recurrent sarcoma. In one study, the sensitivity of FDG-PET for recurrence of soft tissue sarcoma was higher than that of contrast-enhanced CT (83 versus 50 percent), though specificity was equally good (100 percent with both tests) [72]. However, MRI is still considered the most useful modality for detecting local recurrences [73].

Evaluation for metastatic disease — We recommend chest imaging to evaluate for pulmonary metastatic disease in all patients; we use chest CT rather than chest radiograph (CXR) in patients with a high risk of pulmonary metastases (tumors >5 cm or deep seated, or intermediate or high grade). We also recommend CT of the abdomen and pelvis in round cell/myxoid liposarcomas due to the common presentation of extrapulmonary metastases to the abdomen and retroperitoneum. Imaging of the brain is suggested for patients with angiosarcoma and alveolar soft part sarcoma due to the high propensity of these tumors for central nervous system metastases. PET or integrated PET/CT is not routinely recommended as a component of the initial staging workup of soft tissue sarcoma for evaluation of either pulmonary or extrapulmonary metastatic disease.

Given the propensity for lung metastases, chest imaging is recommended for newly diagnosed patients with soft tissue sarcoma of the extremity/trunk [70]. (See 'Pattern of spread' above.)

While CT scan is often preferred due to its greater sensitivity in detecting small lung nodules, it is unknown whether this provides benefit over CXR alone. Both modalities are considered highly appropriate for this purpose by the American College of Radiology (ACR) [74]. A retrospective review performed in the United Kingdom found that CXR alone detected two-thirds

of pulmonary metastases in patients with soft tissue sarcoma; when compared with CT as the "gold standard," the sensitivity, specificity, positive predictive value, and negative predictive value of CXR were 60.8, 99.6, 93.3, and 96.7 percent, respectively [29]. The use of CXR only to stage the lungs would have missed one-third of all patients with lung metastases, but because of the infrequency of lung metastases overall (96 of 1170 patients), the initial staging would have been inaccurate in only 3.1 percent of cases. A greater proportion (4.9 percent) would have been incorrectly staged if CXR alone had been used in patients with high-grade, large, deep tumors. The authors recommended that all patients with a suspected soft tissue sarcoma should have a CXR, with chest CT reserved for those with an abnormality on CXR or who have the highest risk of pulmonary metastases (primary tumor >5 cm and deep-seated, or intermediate/high grade). We agree with this recommendation.

However, we note that recommendations for chest imaging from expert groups differ:

- Consensus-based NCCN guidelines suggest chest imaging with either CXR or CT for soft tissue sarcoma of the extremity or trunk, but chest CT for retroperitoneal/abdominal soft tissue sarcoma.
- On the other hand, guidelines from the European Society of Medical Oncology (ESMO) recommend spiral chest CT for all patients with newly diagnosed soft tissue sarcoma, regardless of site of origin [75].
- The most recent eighth edition of the American Joint Committee on Cancer (AJCC) staging manual suggests the use of chest CT to assess for pulmonary metastases [76].

A CT of the abdomen and pelvis is recommended to evaluate for metastatic disease in round cell/myxoid liposarcomas due to the common presentation of extrapulmonary metastases to the abdomen and retroperitoneum. In addition, guidelines from NCCN also recommend abdominal/pelvic CT for epithelioid sarcomas, angiosarcomas, and leiomyosarcomas of the extremity/trunk, but the rationale for this recommendation, particularly for leiomyosarcomas, is not clear.

Bone scan is usually **not** helpful for initial staging. Bone metastases are unusual in adults in the absence of multiple metastases in other sites, except possibly in round cell/myxoid liposarcomas. Bone scan can be insensitive in these patients, so MRI is the recommended imaging modality for symptomatic patients [77]. (See 'Pattern of spread' above.)

Another problem is that a positive bone scan adjacent to a soft tissue tumor is insufficient evidence of bone invasion and, instead, may represent a reactive process. The diagnosis of bone invasion is best made by demonstration of loss of cortical bone on plain radiographs or CT with bone windows.

In addition, guidelines from NCCN suggest imaging of the central nervous system in patients with angiosarcoma and alveolar soft part sarcoma due to the propensity of these tumors to metastasize to the central nervous system. We agree with this approach. (See 'Pattern of spread' above.)

Role of PET scanning — Positron emission tomography (PET) scanning can achieve whole body imaging, and it is widely considered to be more sensitive than CT for the detection of occult distant metastases in a variety of solid tumors (image 3). However, the utility of PET alone or with integrated CT for staging of distant disease extent in soft tissue sarcoma is unclear, as evidenced by the following reports [78-82]:

- In several reports, chest CT is more sensitive than PET for detection of thoracic metastases in patients with sarcoma [78,80,82,83]. In the largest report of 106 patients with bone or soft tissue sarcomas who had PET or integrated PET/CT, pulmonary metastases were found in 40 [80]. CT identified 17 lesions larger than 1 cm, while PET identified only 13 of them. The authors concluded that subcentimeter CT lesions should not be considered false-positive if inactive on PET and that a negative PET scan in the presence of suspicious CT findings in the chest cannot reliably exclude pulmonary metastases.
- One purported benefit of PET is its ability to detect additional sites of extrapulmonary metastatic disease [78,81]. However, the risk of extrapulmonary metastases is so low with most soft tissue sarcomas that the routine use of PET for this purpose is unlikely to change the therapeutic plan. This was illustrated in a report of 75 patients who underwent PET during staging evaluation for a soft tissue sarcoma [82]. Only one patient was upstaged as a result of PET imaging, and PET did not alter the management of patients already known to have metastatic disease (ie, no new organ sites were identified).

Biopsy — Histologic examination of a soft tissue mass is essential for diagnosis and treatment planning. Our preferred method for obtaining tissue is with a core needle biopsy, if technically feasible. If incisional biopsy is required, it should be carefully planned and performed by the surgeon who will be doing the definitive resection. A poorly placed initial biopsy may preclude subsequent surgical resection, preparation of flaps, and/or cosmetic repair, or result in the need for a more extensive surgery to encompass the biopsy site at the time of definitive resection. We recommend that all pathology

specimens of suspected soft tissue sarcoma be reviewed by a pathologist who specializes in the evaluation of soft tissue tumors.

There are several methods for obtaining a diagnostic biopsy, which are reviewed below. Ideally, the biopsy should be performed after an MRI has been obtained, as postprocedural edema may make the MRI difficult to interpret.

The diagnostic biopsy must be carefully planned to ensure that adequate tissue is obtained in a manner that does not compromise definitive therapy.

Incisional biopsy — Although incisional biopsy was the historic gold standard procedure for obtaining diagnostic tissue for a suspicious soft tissue mass, core needle biopsy has become the most common procedure used for diagnosis in recent years (see 'Core needle biopsy' below). A biopsy that contains enough material to ascertain the histologic subtype and grade of the tumor is essential prior to commencement of therapy [84].

If definitive diagnosis may require flow cytometry, cytogenetics, or molecular analysis for chromosomal translocations (table 4), an incisional biopsy may be preferred. The larger sample provides the pathologist with more tissue and a greater degree of confidence in the diagnosis, in part because of the degree of morphologic heterogeneity throughout the tumor.

If needed, incisional biopsy should ideally be performed by the surgeon planning the definitive resection. Errors, complications, and changes in patient outcome occur more frequently when an incisional biopsy is performed in a referring institution instead of a treatment center [85,86]. Open biopsy incisions should be placed longitudinally along the extremity so that the scar can be resected along with the tumor at the time of definitive surgical resection. Adequate hemostasis is important to prevent dissemination of tumor cells.

Core needle biopsy — Core needle biopsy is considered the preferred method to achieve an initial biopsy in most cases due to its low incidence of complications and high diagnostic accuracy [87-90]. In a study of 530 patients with suspected soft tissue tumors, core needle biopsy differentiated malignant soft tissue sarcomas from benign soft tissue tumors in 97.6 percent of patients. Histologic grade was accurately determined in 86.3 percent of patients, and the subtype was accurately identified in 88 percent [88].

CT or ultrasound guidance can assist in the biopsy of deep lesions and improve the diagnostic accuracy in lesions with cystic areas and necrosis by allowing the operator to select the site to be biopsied [91,92]. In cases where core needle biopsy is unsuccessful in obtaining adequate material for diagnosis, a subsequent incisional biopsy is usually considered. The incidence of follow-up biopsy has been reported as high as 20 percent [93].

Fine needle aspiration — Fine needle aspiration (FNA) is not recommended in the initial diagnostic evaluation of a suspicious soft tissue mass as it has a lower diagnostic accuracy than core needle biopsy [94,95]. In addition, FNA may not provide the histologic subtype or grade of the sarcoma, which are both important for treatment planning. FNA can be useful in confirming disease recurrence, however [96].

STAGING — The most widely used staging system for soft tissue sarcomas is the tumor, node, metastasis (TNM) system developed as a collaborative effort of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC). The AJCC TNM system uses tumor size (T), lymph node involvement (N), presence or absence of distant metastases (M), and histologic grade (G) to determine the stage grouping for soft tissue sarcomas.

The most recent (eighth edition, 2017) version of the TNM staging classification contains separate T staging criteria and prognostic stage groups for soft tissue sarcomas arising in the extremity/trunk (table 3) and retroperitoneum (table 2); there are also unique primary tumor definitions for soft tissue sarcoma of the viscera of the abdomen and thorax but no recommended prognostic stage groupings at this site (table 5) [37,97].

The AJCC staging system has not been in widespread use for retroperitoneal sarcomas. It does not account for disease site or histology, two major prognostic indicators. In addition, its ability to discriminate outcome is limited [98]. Because of this, the AJCC specifically recommends the use of a prognostic nomogram to estimate the likelihood of postoperative survival (figure 2) [99]. Given that histologic grade, the presence or absence of metastatic disease, and achieving macroscopic total resection are the major determinants of survival for patients with retroperitoneal sarcoma, alternative staging systems have been proposed, one of which is depicted in the table (table 6), but they are not in widespread use. (See "Clinical features, evaluation, and treatment of retroperitoneal soft tissue sarcoma", section on 'Staging'.)

PROGNOSTIC FACTORS — A number of prognostic factors have been identified in patients with soft tissue sarcoma, the most important of which are histologic grade, tumor size [5,100-102], and pathologic stage at the time of diagnosis. These factors are the main determinants of the primary tumor (T) stage (see 'Staging' above). In a series derived from Memorial Sloan Kettering Cancer Center (MSKCC) and using the tumor, node, metastasis (TNM) stage groupings from the 2010

seventh edition, five-year rates disease-free survival for stage I, II, and III disease were 86, 72, and 52 percent, respectively [103]. The corresponding values for overall survival were 90, 81, and 56 percent.

Histologic grade — Histologic grading is an independent indicator of the degree of malignancy and the probability of distant metastases and death from sarcoma [2,5,6,104]. In contrast, histologic grade is a poor predictor of local recurrence, which is mainly a function of surgical margins.

A histologic grade should be assigned to all sarcomas. Comprehensive grading incorporates differentiation (which is histology specific), mitotic rate, and the extent of necrosis. In accordance with recommendations from the College of American Pathologists (CAP) [105], the 2017 American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) cancer staging manual recommends use of the three-tiered French Federation of Cancer Centers Sarcoma Group (FNCLCC) grading schema, which is based on the resected tumor or pretreatment biopsy material, for soft tissue sarcomas at all sites (table 7) [76].

Tumor size — The risk of developing a local recurrence and distant metastases increases substantially as tumor size increases [100,106,107]:

- In a review from Massachusetts General Hospital (MGH), the frequency of distant metastases in high-grade tumors as a function of tumor size was [106]:
  - Tumors ≤2.5 cm – 6 percent
  - Tumors 2.6 to 4.9 cm – 23 percent
  - Tumors 5 to 10 cm – 38 percent
  - Tumors 10.1 to 15 cm – 49 percent
  - Tumors 15.1 to 20 cm – 58 percent
  - Tumors >20 cm – 83 percent
- Another study grouped 316 patients with soft tissue sarcomas into four subgroups on the basis of tumor size (less than 5 cm, 5 to less than 10 cm, 10 to less than 15 cm, and greater than 15 cm). Each subgroup was found to have a different prognosis, with five-year survival rates of 84, 70, 50, and 33 percent, respectively [100].
- The impact of tumor size category on local disease-free survival, overall recurrence-free interval, and disease-specific survival in a series of 5267 patients with soft tissue sarcoma of the extremities or trunk is illustrated in the figure (figure 3) [107].

These data form the basis of the primary tumor (T) stage classification in the 2017 AJCC/UICC cancer staging manual for extremity/trunk (table 3) and retroperitoneal (table 2) primary soft tissue sarcomas.

Prognostic tools — Estimating prognosis in patients with soft tissue sarcoma is important for both individual patient counseling as well as for therapeutic decision-making. In addition to stage, grade, and tumor size, factors that are associated with survival include anatomic site, age, and histologic subtype. Prognostic nomograms incorporating such variables are useful tools in patient management.

The most widely used nomogram (which applies to all anatomic sites) is the postoperative nomogram for 12-year sarcoma-specific death from MSKCC (figure 4) [108]. This nomogram is also available online [109] and has been validated with an external cohort of patients who were treated at University of California-Los Angeles (UCLA) [110]. Histologic grade in the MSKCC nomogram was defined as high or low according to previously published criteria [111]. A subsequent adapted nomogram has been published incorporating the FNCLCC three-grade classification [112]. In our practice, we use the MSKCC nomogram and categorize both grade 2 and 3 tumors as high grade for the purposes of predicting prognosis.

A separate prognostic nomogram is available for retroperitoneal sarcoma that also includes the FNCLCC grade and the extent of resection (figure 2) [99]. (See "Clinical features, evaluation, and treatment of retroperitoneal soft tissue sarcoma".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Soft tissue sarcoma (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Soft tissue sarcomas are a rare and heterogeneous group of tumors of mesenchymal origin, which includes more than 100 different histologic subtypes. Pathologic diagnosis is based on histologic morphology, immunohistochemistry, and sometimes, molecular testing. (See 'Histopathology' above.)

- Soft tissue sarcomas most commonly present as an enlarging, painless mass in the extremities or trunk. The presence of distant metastatic disease at the time of initial diagnosis is uncommon but more likely in large, deep, high-grade sarcomas. Approximately 80 percent of metastases are located in the lungs. (See 'Clinical presentation' above.)

- The diagnosis of a soft tissue sarcoma is often unsuspected. Partial excision of the tumor before referral may be associated with a higher incidence of distant metastatic disease and the need for an extensive reresection that may impact the functional result. In addition, an inappropriately placed diagnostic biopsy may preclude subsequent surgical resection, preparation of flaps, and/or cosmetic repair, or result in the need for a more extensive surgery to encompass the biopsy site at the time of definitive resection. Because of these issues, early referral of a patient with a suspicious soft tissue mass to a specialized center with a multidisciplinary sarcoma team is recommended. (See 'Diagnostic evaluation' above.)

- Our practice for the diagnostic workup of a soft tissue mass includes (see 'Diagnostic evaluation' above):

  - Magnetic resonance imaging (MRI) of a primary extremity lesion and computed tomography (CT) of a primary abdominal, visceral, or retroperitoneal lesion. (See 'Imaging of the primary tumor' above.)

  - Our preferred method of obtaining tissue is with a core needle biopsy, if technically feasible. If incisional biopsy is required, it should be carefully planned and performed by the surgeon who will be doing the definitive resection. A poorly placed initial biopsy may preclude subsequent surgical resection, preparation of flaps, and/or cosmetic repair, or result in the need for a more extensive surgery to encompass the biopsy site at the time of definitive resection.

    We recommend that all pathology specimens of suspected soft tissue sarcomas be reviewed by a pathologist who specializes in the evaluation of soft tissue tumors. (See 'Biopsy' above.)

  - Once the diagnosis of a sarcoma is established, we recommend chest imaging to evaluate for pulmonary metastatic disease in all patients; we use chest CT rather than chest radiograph in patients with a high risk of pulmonary metastases (tumors >5 cm, deep-seated, or intermediate or high grade). We also recommend CT of the abdomen and pelvis in round cell/myxoid liposarcomas due to the common presentation of extrapulmonary metastases to the abdomen and retroperitoneum.

    Imaging of the brain is suggested for patients with angiosarcoma and alveolar soft part sarcoma due to the high propensity of these tumors for central nervous system metastases. (See 'Evaluation for metastatic disease' above.)

  - We do not routinely perform positron emission tomography (PET) or PET/CT in the initial staging evaluation of a newly diagnosed soft tissue sarcoma. PET or gallium scan may be of value in a patient with neurofibromatosis as an aid to differentiating between a plexiform neurofibroma and a malignant peripheral nerve sheath tumor. (See 'PET and PET/CT' above and 'Role of PET scanning' above.)

  - Bone scan is not helpful for initial staging of soft tissue sarcomas. (See 'Evaluation for metastatic disease' above.)

- Soft tissue sarcomas are staged according to the combined American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor, node, metastasis (TNM) system, which is based on tumor size (T), lymph node involvement (N), distant metastases (M), and histologic grade (G).

  The most recent (eighth edition, 2017) version of the AJCC/UICC staging manual has separate T staging criteria and prognostic stage groups for soft tissue sarcoma arising in the extremity/trunk (table 3) and retroperitoneum (table 2); in addition, there are unique primary tumor definitions for sarcomas of the viscera of the abdomen and thorax but no recommended prognostic stage groupings at this site (table 5) [37,97]. (See 'Staging' above.)

  The TNM staging system is not in widespread use for retroperitoneal sarcomas. It does not account for disease site or histology, two major prognostic indicators. In addition, its ability to discriminate outcome is limited. Because of this, the

AJCC specifically recommends the use of a prognostic nomogram to estimate the likelihood of postoperative survival (figure 2) [99].

- In addition to tumor stage, other prognostic variables include anatomic site, patient age, and histologic subtype. A nomogram developed by Memorial Sloan-Kettering Cancer Center (MSKCC) is available online to aid in predicting survival and treatment decision-making for individual patients. (See 'Prognostic factors' above.)

REFERENCES

1. Miller RW, Young JL Jr, Novakovic B. Childhood cancer. Cancer 1995; 75:395.
2. Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F. World Health Organization Classification of tumours of soft tiss ue and bone, 4th ed, IARC Press, Lyon 2013.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018; 68:7.
4. Italiano A, Di Mauro I, Rapp J, et al. Clinical effect of molecular methods in sarcoma diagnosis (GENSARC): a prospective, multicentre, observational study. Lancet Oncol 2016; 17:532.
5. Zagars GK, Ballo MT, Pisters PW, et al. Prognostic factors for patients with localized soft-tissue sarcoma treated with conservation surgery and radiation therapy: an analysis of 1225 patients. Cancer 2003; 97:2530.
6. 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; 91:1914.
7. Conyers R, Young S, Thomas DM. Liposarcoma: molecular genetics and therapeutics. Sarcoma 2011; 2011:483154.
8. Ghadimi MP, Liu P, Peng T, et al. Pleomorphic liposarcoma: clinical observations and molecular variables. Cancer 2011; 117:5359.
9. Dei Tos AP, Pedeutour F. Atypical lipomatous tumour. In: WHO Classification of tumours of soft tissue and bone, 4th, Fl etcher CDM, Bridge JA, Hogendoorn PCW, Mertens F (Eds), IARC, Lyon 2013. p.33.
10. Italiano A, Bianchini L, Gjernes E, et al. Clinical and biological significance of CDK4 amplification in well-differentiated and dedifferentiated liposarcomas. Clin Cancer Res 2009; 15:5696.
11. Rao UN, Finkelstein SD, Jones MW. Comparative immunohistochemical and molecular analysis of uterine and extrauterine leiomyosarcomas. Mod Pathol 1999; 12:1001.
12. Svarvar C, Böhling T, Berlin O, et al. Clinical course of nonvisceral soft tissue leiomyosarcoma in 225 patients from the Scandinavian Sarcoma Group. Cancer 2007; 109:282.
13. Fletcher CD, Gustafson P, Rydholm A, et al. Clinicopathologic re-evaluation of 100 malignant fibrous histiocytomas: prognostic relevance of subclassification. J Clin Oncol 2001; 19:3045.
14. Sanfilippo R, Miceli R, Grosso F, et al. Myxofibrosarcoma: prognostic factors and survival in a series of patients treated at a single institution. Ann Surg Oncol 2011; 18:720.
15. Gronchi A, Lo Vullo S, Colombo C, et al. Extremity soft tissue sarcoma in a series of patients treated at a single institution: local control directly impacts survival. Ann Surg 2010; 251:506.
16. Look Hong NJ, Hornicek FJ, Raskin KA, et al. Prognostic factors and outcomes of patients with myxofibrosarcoma. Ann Surg Oncol 2013; 20:80.
17. Fletcher CDM, Bridge JA, Lee J-C. Extrapleural solitary fibrous tumour. In: World health organization classification of tu mours of soft tissue and bone, 4th, Fletcher CDM,Bridge JA, Hogendoorn PCW, Mertens F (Eds), IARC, Lyon 2013. p.8 0.
18. Deyrup AT, Weiss SW. Grading of soft tissue sarcomas: the challenge of providing precise information in an imprecise world. Histopathology 2006; 48:42.
19. Rubin BP, Fletcher CD, Inwards C, et al. Protocol for the examination of specimens from patients with soft tissue tumors of intermediate malignant potential, malignant soft tissue tumors, and benign/locally aggressive and malignant bone tumors. Arch Pathol Lab Med 2006; 130:1616.
20. 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; 15:350.

21. Woodruff JM, Kourea HP, Louis DN, Schiethauer BW. Malignant peripheral nerve sheath tumour (MPNST). In: World H ealth Organization Classification of Tumours: Pathology and genetics of Tumours of the nervous system, Kleihues P, C avenee WK (Eds), IARC Press, Lyon 2000. p.172.
22. Stucky CC, Johnson KN, Gray RJ, et al. Malignant peripheral nerve sheath tumors (MPNST): the Mayo Clinic experience. Ann Surg Oncol 2012; 19:878.
23. Lawrence W Jr, Donegan WL, Natarajan N, et al. Adult soft tissue sarcomas. A pattern of care survey of the American College of Surgeons. Ann Surg 1987; 205:349.
24. Baratti D, Pennacchioli E, Casali PG, et al. Epithelioid sarcoma: prognostic factors and survival in a series of patients treated at a single institution. Ann Surg Oncol 2007; 14:3542.
25. Sakharpe A, Lahat G, Gulamhusein T, et al. Epithelioid sarcoma and unclassified sarcoma with epithelioid features: clinicopathological variables, molecular markers, and a new experimental model. Oncologist 2011; 16:512.
26. Levy A, Le Péchoux C, Terrier P, et al. Epithelioid sarcoma: need for a multimodal approach to maximize the chances of curative conservative treatment. Ann Surg Oncol 2014; 21:269.
27. Mora J, Modak S, Cheung NK, et al. Desmoplastic small round cell tumor 20 years after its discovery. Future Oncol 2015; 11:1071.
28. Zhang J, Xu H, Ren F, et al. Analysis of clinicopathological features and prognostic factors of desmoplastic small round cell tumor. Pathol Oncol Res 2014; 20:161.
29. Christie-Large M, James SL, Tiessen L, et al. Imaging strategy for detecting lung metastases at presentation in patients with soft tissue sarcomas. Eur J Cancer 2008; 44:1841.
30. Fong Y, Coit DG, Woodruff JM, Brennan MF. Lymph node metastasis from soft tissue sarcoma in adults. Analysis of data from a prospective database of 1772 sarcoma patients. Ann Surg 1993; 217:72.
31. Riad S, Griffin AM, Liberman B, et al. Lymph node metastasis in soft tissue sarcoma in an extremity. Clin Orthop Relat Res 2004; :129.
32. Mazeron JJ, Suit HD. Lymph nodes as sites of metastases from sarcomas of soft tissue. Cancer 1987; 60:1800.
33. de Visscher SA, van Ginkel RJ, Wobbes T, et al. Epithelioid sarcoma: Still an only surgically curable disease. Cancer 2006; 107:606.
34. Blazer DG 3rd, Lazar AJ, Xing Y, et al. Clinical outcomes of molecularly confirmed clear cell sarcoma from a single institution and in comparison with data from the Surveillance, Epidemiology, and End Results registry. Cancer 2009; 115:2971.
35. Johannesmeyer D, Smith V, Cole DJ, et al. The impact of lymph node disease in extremity soft-tissue sarcomas: a population-based analysis. Am J Surg 2013; 206:289.
36. AJCC (American Joint Committee on Cancer). Cancer Staging Manual, 7th edition, Edge SB, Byrd DR, Compton CC, et al (Eds), Springer, New York 2010. p.291.
37. Pollock RE, Maki RG, Baldini EH, et al.. Soft Tissue Sarcoma of the Retroperitoneum. In: AJCC Cancer Staging Manua l, 8th, Amin, MB (Eds), AJCC, Chicago 2017. p.531.
38. Yoon SS, Maki RG, Asare EA, et al.. Soft Tissue Sarcoma of the Trunk and Extremities. In: AJCC Cancer Staging Manu al, 8th, Amin. MB (Ed), AJCC, Chicago 2017. p.507.
39. Vezeridis MP, Moore R, Karakousis CP. Metastatic patterns in soft-tissue sarcomas. Arch Surg 1983; 118:915.
40. Potter DA, Glenn J, Kinsella T, et al. Patterns of recurrence in patients with high-grade soft-tissue sarcomas. J Clin Oncol 1985; 3:353.
41. Lindberg RD, Martin RG, Romsdahl MM, Barkley HT Jr. Conservative surgery and postoperative radiotherapy in 300 adults with soft-tissue sarcomas. Cancer 1981; 47:2391.
42. Weitz J, Antonescu CR, Brennan MF. Localized extremity soft tissue sarcoma: improved knowledge with unchanged survival over time. J Clin Oncol 2003; 21:2719.
43. Billingsley KG, Lewis JJ, Leung DH, et al. Multifactorial analysis of the survival of patients with distant metastasis arising from primary extremity sarcoma. Cancer 1999; 85:389.
44. Rydholm A, Berg NO, Gullberg B, et al. Prognosis for soft-tissue sarcoma in the locomotor system. A retrospective population-based follow-up study of 237 patients. Acta Pathol Microbiol Immunol Scand A 1984; 92:375.
45. Ryzewicz M, McLoughlin HA, Freudenberger C, et al. Unusual metastases from extremity soft tissue sarcomas. Orthopedics 2008; 31:439.

46. Wang WL, Bones-Valentin RA, Prieto VG, et al. Sarcoma metastases to the skin: a clinicopathologic study of 65 patients. Cancer 2012; 118:2900.
47. Schwab JH, Boland P, Guo T, et al. Skeletal metastases in myxoid liposarcoma: an unusual pattern of distant spread. Ann Surg Oncol 2007; 14:1507.
48. Moreau LC, Turcotte R, Ferguson P, et al. Myxoid\round cell liposarcoma (MRCLS) revisited: an analysis of 418 primarily managed cases. Ann Surg Oncol 2012; 19:1081.
49. Chotel F, Unnithan A, Chandrasekar CR, et al. Variability in the presentation of synovial sarcoma in children: a plea for greater awareness. J Bone Joint Surg Br 2008; 90:1090.
50. Sinha S, Peach AH. Diagnosis and management of soft tissue sarcoma. BMJ 2010; 341:c7170.
51. Hussein R, Smith MA. Soft tissue sarcomas: are current referral guidelines sufficient? Ann R Coll Surg Engl 2005; 87:171.
52. Noria S, Davis A, Kandel R, et al. Residual disease following unplanned excision of soft-tissue sarcoma of an extremity. J Bone Joint Surg Am 1996; 78:650.
53. Rehders A, Stoecklein NH, Poremba C, et al. Reexcision of soft tissue sarcoma: sufficient local control but increased rate of metastasis. World J Surg 2009; 33:2599.
54. Bhangu AA, Beard JA, Grimer RJ. Should Soft Tissue Sarcomas be Treated at a Specialist Centre? Sarcoma 2004; 8:1.
55. Gustafson P, Dreinhöfer KE, Rydholm A. Soft tissue sarcoma should be treated at a tumor center. A comparison of quality of surgery in 375 patients. Acta Orthop Scand 1994; 65:47.
56. Sundaram M, McGuire MH, Herbold DR. Magnetic resonance imaging of soft tissue masses: an evaluation of fifty-three histologically proven tumors. Magn Reson Imaging 1988; 6:237.
57. Demas BE, Heelan RT, Lane J, et al. Soft-tissue sarcomas of the extremities: comparison of MR and CT in determining the extent of disease. AJR Am J Roentgenol 1988; 150:615.
58. Aisen AM, Martel W, Braunstein EM, et al. MRI and CT evaluation of primary bone and soft-tissue tumors. AJR Am J Roentgenol 1986; 146:749.
59. Panicek DM, Gatsonis C, Rosenthal DI, et al. CT and MR imaging in the local staging of primary malignant musculoskeletal neoplasms: Report of the Radiology Diagnostic Oncology Group. Radiology 1997; 202:237.
60. Nieweg OE, Pruim J, van Ginkel RJ, et al. Fluorine-18-fluorodeoxyglucose PET imaging of soft-tissue sarcoma. J Nucl Med 1996; 37:257.
61. Schwarzbach MH, Dimitrakopoulou-Strauss A, Willeke F, et al. Clinical value of [18-F]] fluorodeoxyglucose positron emission tomography imaging in soft tissue sarcomas. Ann Surg 2000; 231:380.
62. Bastiaannet E, Groen H, Jager PL, et al. The value of FDG-PET in the detection, grading and response to therapy of soft tissue and bone sarcomas; a systematic review and meta-analysis. Cancer Treat Rev 2004; 30:83.
63. Dimitrakopoulou-Strauss A, Strauss LG, Schwarzbach M, et al. Dynamic PET 18F-FDG studies in patients with primary and recurrent soft-tissue sarcomas: impact on diagnosis and correlation with grading. J Nucl Med 2001; 42:713.
64. Folpe AL, Lyles RH, Sprouse JT, et al. (F-18) fluorodeoxyglucose positron emission tomography as a predictor of pathologic grade and other prognostic variables in bone and soft tissue sarcoma. Clin Cancer Res 2000; 6:1279.
65. Lucas JD, O'Doherty MJ, Cronin BF, et al. Prospective evaluation of soft tissue masses and sarcomas using fluorodeoxyglucose positron emission tomography. Br J Surg 1999; 86:550.
66. Benz MR, Czernin J, Dry SM, et al. Quantitative F18-fluorodeoxyglucose positron emission tomography accurately characterizes peripheral nerve sheath tumors as malignant or benign. Cancer 2010; 116:451.
67. Ferner RE, Golding JF, Smith M, et al. [18F]2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET) as a diagnostic tool for neurofibromatosis 1 (NF1) associated malignant peripheral nerve sheath tumours (MPNSTs): a long-term clinical study. Ann Oncol 2008; 19:390.
68. Warbey VS, Ferner RE, Dunn JT, et al. [18F]FDG PET/CT in the diagnosis of malignant peripheral nerve sheath tumours in neurofibromatosis type-1. Eur J Nucl Med Mol Imaging 2009; 36:751.
69. Levine E, Huntrakoon M, Wetzel LH. Malignant nerve-sheath neoplasms in neurofibromatosis: distinction from benign tumors by using imaging techniques. AJR Am J Roentgenol 1987; 149:1059.
70. National Comprehensive Cancer Network (NCCN) guidelines www.nccn.org (Accessed on May 18, 2011).
71. Schuetze SM, Rubin BP, Vernon C, et al. Use of positron emission tomography in localized extremity soft tissue sarcoma treated with neoadjuvant chemotherapy. Cancer 2005; 103:339.

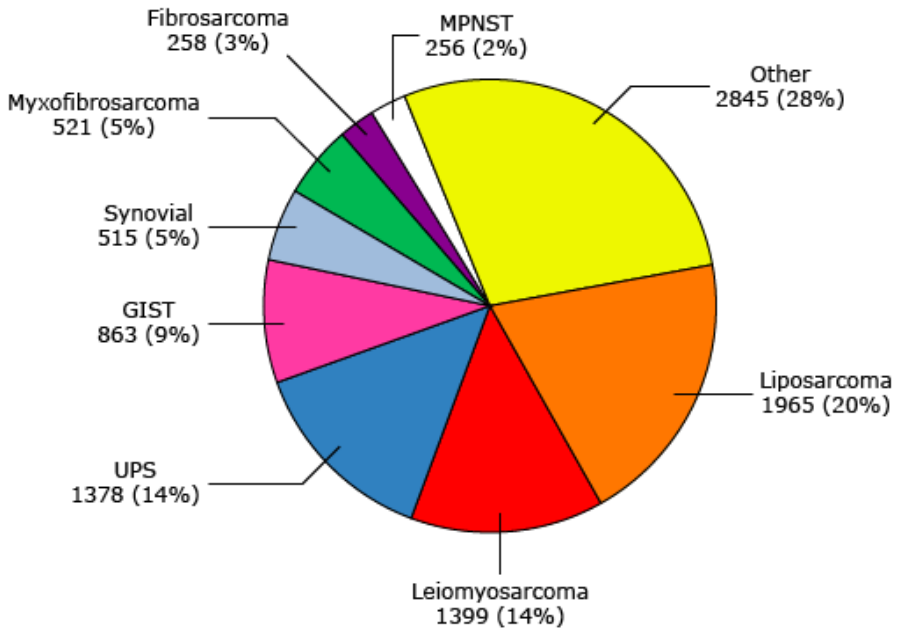
72. Al-Ibraheem A, Buck AK, Benz MR, et al. (18) F-fluorodeoxyglucose positron emission tomography/computed tomography for the detection of recurrent bone and soft tissue sarcoma. Cancer 2013; 119:1227.
73. American College of Radiology (ACR) appropriateness criteria for follow-up of malignant or aggressive musculoskeletal tumors available online at http://www.acr.org/~/media/ACR/Documents/AppCriteria/Diagnostic/FollowupMalignantOrAggressiveMusculoskeletalTumors.pdf (Accessed on May 13, 2013).
74. Mohammed TL, Chowdhry A, Reddy GP, et al. ACR Appropriateness Criteria® screening for pulmonary metastases. J Thorac Imaging 2011; 26:W1.
75. ESMO/European Sarcoma Network Working Group. Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25 Suppl 3:iii102.
76. Pollock RE, Maki RG.. Introduction to Soft Tissue Sarcoma. In: AJCC Cancer Staging Manual, 8th, Amin, MB. (Eds), AJCC, Chicago 2017. p.489.
77. Noble JL, Moskovic E, Fisher C, Judson I. Imaging of skeletal metastases in myxoid liposarcoma. Sarcoma 2010; 2010:262361.
78. Lucas JD, O'Doherty MJ, Wong JC, et al. Evaluation of fluorodeoxyglucose positron emission tomography in the management of soft-tissue sarcomas. J Bone Joint Surg Br 1998; 80:441.
79. Johnson GR, Zhuang H, Khan J, et al. Roles of positron emission tomography with fluorine-18-deoxyglucose in the detection of local recurrent and distant metastatic sarcoma. Clin Nucl Med 2003; 28:815.
80. Iagaru A, Chawla S, Menendez L, Conti PS. 18F-FDG PET and PET/CT for detection of pulmonary metastases from musculoskeletal sarcomas. Nucl Med Commun 2006; 27:795.
81. Pastorino U, Veronesi G, Landoni C, et al. Fluorodeoxyglucose positron emission tomography improves preoperative staging of resectable lung metastasis. J Thorac Cardiovasc Surg 2003; 126:1906.
82. Roberge D, Hickeson M, Charest M, Turcotte RE. Initial McGill experience with fluorodeoxyglucose pet/ct staging of soft-tissue sarcoma. Curr Oncol 2010; 17:18.
83. Völker T, Denecke T, Steffen I, et al. Positron emission tomography for staging of pediatric sarcoma patients: results of a prospective multicenter trial. J Clin Oncol 2007; 25:5435.
84. National Comprehensive Cancer Network (NCCN) guidelines available online at www.nccn.org (Accessed on May 19, 2011).
85. Mankin HJ, Lange TA, Spanier SS. The hazards of biopsy in patients with malignant primary bone and soft-tissue tumors. J Bone Joint Surg Am 1982; 64:1121.
86. Mankin HJ, Mankin CJ, Simon MA. The hazards of the biopsy, revisited. Members of the Musculoskeletal Tumor Society. J Bone Joint Surg Am 1996; 78:656.
87. Heslin MJ, Lewis JJ, Woodruff JM, Brennan MF. Core needle biopsy for diagnosis of extremity soft tissue sarcoma. Ann Surg Oncol 1997; 4:425.
88. Strauss DC, Qureshi YA, Hayes AJ, et al. The role of core needle biopsy in the diagnosis of suspected soft tissue tumours. J Surg Oncol 2010; 102:523.
89. Woon DT, Serpell JW. Preoperative core biopsy of soft tissue tumours facilitates their surgical management: a 10-year update. ANZ J Surg 2008; 78:977.
90. Serpell JW, Pitcher ME. Pre-operative core biopsy of soft-tissue tumours facilitates their surgical management. Aust N Z J Surg 1998; 68:345.
91. Hau A, Kim I, Kattapuram S, et al. Accuracy of CT-guided biopsies in 359 patients with musculoskeletal lesions. Skeletal Radiol 2002; 31:349.
92. Dupuy DE, Rosenberg AE, Punyaratabandhu T, et al. Accuracy of CT-guided needle biopsy of musculoskeletal neoplasms. AJR Am J Roentgenol 1998; 171:759.
93. Verheijen P, Witjes H, van Gorp J, et al. Current pathology work-up of extremity soft tissue sarcomas, evaluation of the validity of different techniques. Eur J Surg Oncol 2010; 36:95.
94. Rougraff BT, Aboulafia A, Biermann JS, Healey J. Biopsy of soft tissue masses: evidence-based medicine for the musculoskeletal tumor society. Clin Orthop Relat Res 2009; 467:2783.
95. Wakely PE Jr, Kneisl JS. Soft tissue aspiration cytopathology. Cancer 2000; 90:292.
96. Trovik CS, Bauer HC, Brosjö O, et al. Fine needle aspiration (FNA) cytology in the diagnosis of recurrent soft tissue sarcoma. Cytopathology 1998; 9:320.

97. Raut CP, Maki RG, Baldini EH, et al.. Soft Tissue Sarcoma of the Abdomen and Thoracic Visceral Organs. In: AJCC Cancer Staging Manual, 8th, Amin MB (Ed), AJCC, Chicago 2017. p.517.
98. Cates JMM. Performance Analysis of the American Joint Committee on Cancer 8th Edition Staging System for Retroperitoneal Sarcoma and Development of a New Staging Algorithm for Sarcoma-Specific Survival. Ann Surg Oncol 2017; 24:3880.
99. Gronchi A, Miceli R, Shurell E, et al. Outcome prediction in primary resected retroperitoneal soft tissue sarcoma: histology-specific overall survival and disease-free survival nomograms built on major sarcoma center data sets. J Clin Oncol 2013; 31:1649.
100. Ramanathan RC, A'Hern R, Fisher C, Thomas JM. Modified staging system for extremity soft tissue sarcomas. Ann Surg Oncol 1999; 6:57.
101. Pisters PW, Leung DH, Woodruff J, et al. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol 1996; 14:1679.
102. Rööser B, Attewell R, Berg NO, Rydholm A. Prognostication in soft tissue sarcoma. A model with four risk factors. Cancer 1988; 61:817.
103. American Joint Committee on Cancer Staging Manual, Edge SB, Byrd DR, Compton CC, et al (Eds), Springer, New York 2010. p.291.
104. Lahat G, Tuvin D, Wei C, et al. New perspectives for staging and prognosis in soft tissue sarcoma. Ann Surg Oncol 2008; 15:2739.
105. Rubin BP, Cooper K, Fletcher CD, et al. Protocol for the examination of specimens from patients with tumors of soft tissue. Arch Pathol Lab Med 2010; 134:e31.
106. Suit HD, Mankin HJ, Wood WC, et al. Treatment of the patient with stage M0 soft tissue sarcoma. J Clin Oncol 1988; 6:854.
107. Maki RG, Moraco N, Antonescu CR, et al. Toward better soft tissue sarcoma staging: building on american joint committee on cancer staging systems versions 6 and 7. Ann Surg Oncol 2013; 20:3377.
108. Kattan MW, Leung DH, Brennan MF. Postoperative nomogram for 12-year sarcoma-specific death. J Clin Oncol 2002; 20:791.
109. http://www.mskcc.org/mskcc/html/6181.cfm (Accessed on May 18, 2011).
110. Eilber FC, Brennan MF, Eilber FR, et al. Validation of the postoperative nomogram for 12-year sarcoma-specific mortality. Cancer 2004; 101:2270.
111. Hajdu SI, Shiu MH, Brennan MF. The role of the pathologist in the management of soft tissue sarcomas. World J Surg 1988; 12:326.
112. Mariani L, Miceli R, Kattan MW, et al. Validation and adaptation of a nomogram for predicting the survival of patients with extremity soft tissue sarcoma using a three-grade system. Cancer 2005; 103:402.

Topic 14259 Version 40.0

GRAPHICS

Distribution of histologic subtypes in a modern database series of 10,000 adult soft tissue sarcomas, Memorial Sloan Kettering Cancer Center (MSKCC)



Distribution by histology for adult patients with soft tissue sarcoma, all sites. MSKCC 7/1/1982-5/31/2013 n = 10,000.

MPNST: malignant peripheral nerve sheath tumor; GIST: gastrointestinal stromal tumor; UPS: undifferentiated pleomorphic sarcoma.

Graphic 112600 Version 2.0

Selected translocations associated with sarcomas

Translocation	Genes	Type of fusion gene
Ewing's sarcoma (OMIM#133450)		
t(11;22)(q24;q12)	*EWSR1-FLI1*	Transcription factor
t(21;22)(q22;q12)	*EWSR1-ERG*	Transcription factor
t(7;22)(p22;q12)	*EWSR1-ETV1*	Transcription factor
t(17;22)(q12;q12)	*EWSR1-ETV4*	Transcription factor
t(2;22)(q35;q12)	*EWSR1-FEV*	Transcription factor
t(2;16)(q35;p11)	*FUS-FEV*	Transcription factor
t(16;21)(p11;q24)	*FUS-ERG*	Transcription factor
Ewing-like undifferentiated sarcoma (OMIM#300485)		
t(X;X)(p11;p11)	*BCOR-CCNB3*	Cell cycle progression
Clear cell sarcoma (OMIM#123803)		
t(12;22)(q13;q12)	*EWSR1-ATF1*	Transcription factor
Desmoplastic small round cell tumor of the abdomen (OMIM#133450)		
t(11;22)(p13;q12)	*EWSR1-WT1*	Transcription factor
Myxoid chondrosarcoma (OMIM#600542)		
t(9;22)(q22-31;q11-12)	*EWSR1-NR4A3*	Transcription factor
Myxoid liposarcoma (OMIM#126337, #137070)		
t(12;16)(q13;p11)	*FUS-CHOP* (*FUS-DDIT3*)	Transcription factor
t(12;22)(q13;q12)	*EWSR1-CHOP* (*EWSR1-DDIT3*)	Transcription factor
Alveolar rhabdomyosarcoma (OMIM#268220)		
t(2;13)(q35;q14)	*PAX3-FOXO1A**	Transcription factor
t(1;13)(p36;q14)	*PAX7-FOXO1A**	Transcription factor
Congenital infantile spindle cell rhabdomyosarcoma		
t(6;6)(q24.1;q22.1)	*VGLL2-CITED2*	Transcription factor
t(6;8)(q22.1;q13.3)	*VGLL2-NC0A2*	Transcription factor
t(11;8)(p15.3;q13.3)	*TEAD1-NCOA2*	Transcription factor
t(2;8)(q36;q13.3)	*PAX3-NCOA2*	Transcription factor
t(6;8)(p21.1;q13.3)	*SRF-NCOA2*	Transcription factor
Synovial sarcoma (OMIM#312820)		
t(X;18)(p11;q11)	*SS18-SSX1*, *SSX2*, or *SSX4*	Remodels chromatin to alter transcription
Dermatofibrosarcoma protuberans (OMIM#607907)		
t(17;22)(q22;q13)	*COL1A1-PDGFB*	Growth factor
Congenital fibrosarcoma (OMIM#191316)		
t(12;15)(p13;q25)	*ETV6-NTRK3*	Transcription factor receptor
Inflammatory myofibroblastic tumor		
2p23 rearrangements	*TMP3-ALK*	Growth factor receptor
	TMP4-ALK	Growth factor receptor
Alveolar soft part sarcoma (OMIM#606243)		
t(X;17)(p11.2;q25)	*ASPL-TFE3*	Transcription factor
Solitary fibrous tumor (OMIM#602381)		
Inversion 12q13	*NAB2-STAT6*	Transcription factor
Epithelioid hemangioendothelioma		
t(1;3)(p36;q25)	*WWTR1-CAMTA1*	Transcription factor

Note that for some tumors, notably Ewing's sarcoma, multiple variant translocations have been observed involving related genes.

OMIM: Online Mendelian Inheritance in Man, available at http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim.
* *FOXO1A* gene, also known as the *FKHR* gene.

Adapted with permission from: Helman LJ, Meltzer P. Mechanisms of sarcoma development. Nature Reviews: Cancer 2003; 3:685. Copyright © 2003 MacMillan Magazines Ltd.

http://www.nature.com

Graphic 64666 Version 6.0

Retroperitoneal soft tissue sarcoma TNM staging AJCC UICC 2017

Primary tumor (T)

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

Regional lymph nodes (N)

N category	N criteria
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastasis

Distant metastasis (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

Definition of grade (G)

G	G definition
GX	Grade cannot be assessed
G1	Total differentiation, mitotic count and necrosis score of 2 or 3
G2	Total differentiation, mitotic count and necrosis score of 4 or 5
G3	Total differentiation, mitotic count and necrosis score of 6, 7, or 8

Prognostic stage groups

When T is...	And N is...	And M is...	And grade is...	Then the stage group is...
T1	N0	M0	G1, GX	IA
T2, T3, T4	N0	M0	G1, GX	IB
T1	N0	M0	G2, G3	II
T2	N0	M0	G2, G3	IIIA
T3, T4	N0	M0	G2, G3	IIIB
Any T	N1	M0	Any G	IIIB
Any T	Any N	M1	Any G	IV

Tumor differentiation

Tumor differentiation is histology specific and is generally scored as follows:

Differentiation score	Definition
1	Sarcomas closely resembling normal adult mesenchymal tissue (eg, low-grade leiomyosarcoma)
2	Sarcomas for which histologic typing is certain (eg, myxoid/round cell liposarcoma)
3	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, soft tissue osteosarcoma, Ewing sarcoma/primitive neuroectodermal tumor (PNET) of soft tissue

Mitotic count

In the most mitotically active area of the sarcoma, 10 successive high-power fields (HPF; one HPF at 400x magnification = 0.1734 mm^2) are assessed using a 40x objective.

Mitotic count score	Definition
1	0 to 9 mitoses per 10 HPF
2	10 to 19 mitoses per 10 HPF
3	≥20 mitoses per 10 HPF

Tumor necrosis

Evaluated on gross examination and validated with histologic sections.

Necrosis score	Definition
0	No necrosis
1	<50% tumor necrosis
2	≥50% tumor necrosis

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 110713 Version 4.0

Soft tissue sarcoma of the extremities and trunk TNM staging AJCC UICC 2017

Primary tumor (T)

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

Regional lymph nodes (N)

N category	N criteria
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastasis

Distant metastasis (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

Definition of grade (G)

G	G definition
GX	Grade cannot be assessed
G1	Total differentiation, mitotic count and necrosis score of 2 or 3
G2	Total differentiation, mitotic count and necrosis score of 4 or 5
G3	Total differentiation, mitotic count and necrosis score of 6, 7, or 8

Prognostic stage groups

When T is...	And N is...	And M is...	And grade is...	Then the stage group is...
T1	N0	M0	G1, GX	IA
T2, T3, T4	N0	M0	G1, GX	IB
T1	N0	M0	G2, G3	II
T2	N0	M0	G2, G3	IIIA
T3, T4	N0	M0	G2, G3	IIIB
Any T	N1	M0	Any G	IV
Any T	Any N	M1	Any G	IV

Tumor differentiation

Tumor differentiation is histology specific and is generally scored as follows:

Differentiation score	Definition
1	Sarcomas closely resembling normal adult mesenchymal tissue (eg, low-grade leiomyosarcoma)
2	Sarcomas for which histologic typing is certain (eg, myxoid/round cell liposarcoma)
3	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, soft tissue osteosarcoma, Ewing sarcoma/primitive neuroectodermal tumor (PNET) of soft tissue

Mitotic count

In the most mitotically active area of the sarcoma, 10 successive high-power fields (HPF; one HPF at 400x magnification = 0.1734 mm^2) are assessed using a 40x objective.

Mitotic count score	Definition
1	0 to 9 mitoses per 10 HPF
2	10 to 19 mitoses per 10 HPF
3	≥20 mitoses per 10 HPF

Tumor necrosis

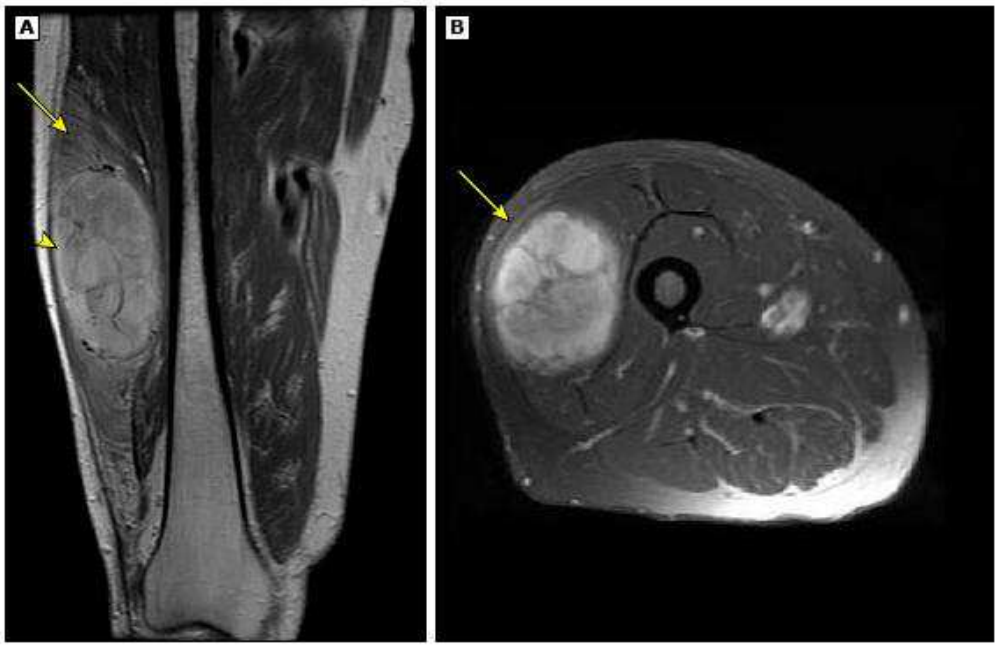
Evaluated on gross examination and validated with histologic sections.

Necrosis score	Definition
0	No necrosis
1	<50% tumor necrosis
2	≥50% tumor necrosis

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 110711 Version 5.0

Pleomorphic undifferentiated sarcoma on MRI

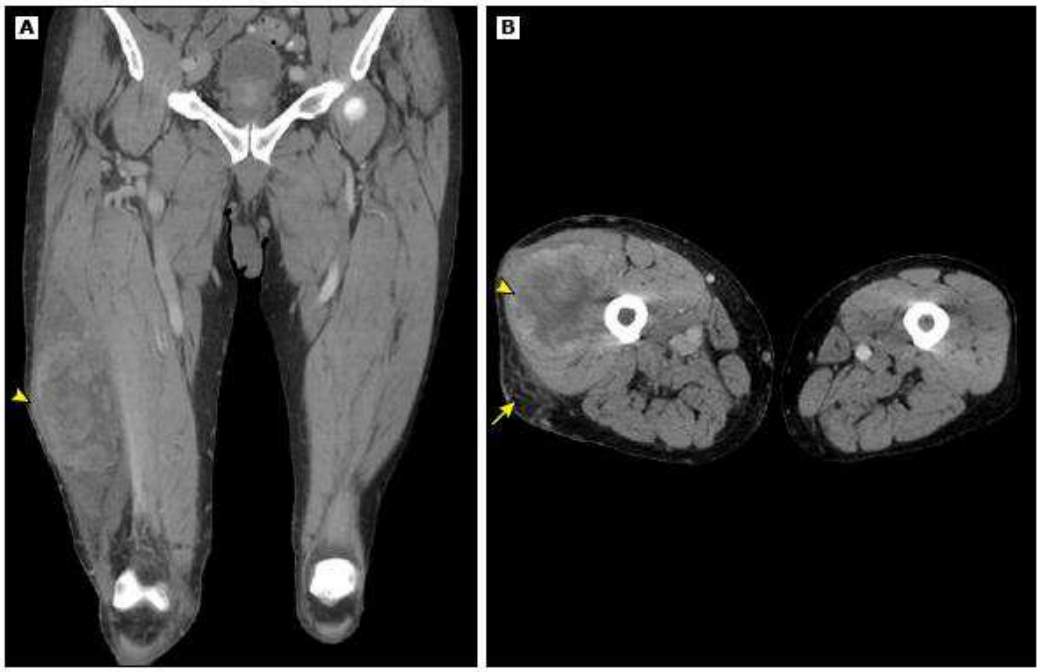


A T1-weighted MRI in the coronal projection prior to contrast (A) shows a mass in the vastus lateralis muscle of the right thigh. There are surrounding soft tissue changes (arrow). The mass enhances following gadolinium administration (arrow B).

MRI: magnetic resonance imaging.

Graphic 91158 Version 1.0

Pleomorphic undifferentiated sarcoma on CT scan

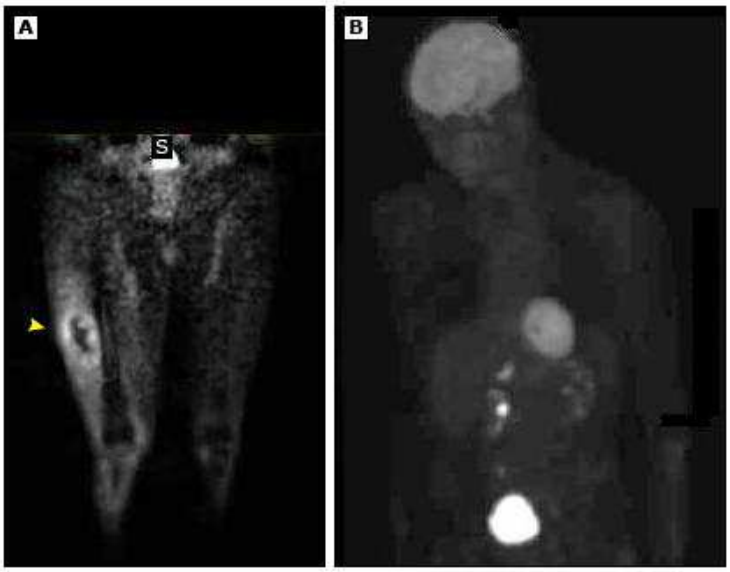


A CT scan reformatted in the coronal plane following contrast administration (A) shows an enhancing heterogeneous mass in the vastus lateralis muscle of the right thigh. An axial image (B) shows the mass as well as the edema in the surrounding soft tissues (short arrow).

CT: computed tomography.

Graphic 91159 Version 1.0

Pleomorphic undifferentiated sarcoma on PET scan



A PET scan projected in the coronal plane (A) shows a hypermetabolic mass in the vastus lateralis muscle of the right thigh. The central portion of the mass has diminished FDG uptake. A 3D reconstruction of the head, chest, and abdomen (B) shows no evidence of metastatic disease. Normal accumulation of FDG is seen in the brain, heart, kidneys, and bladder.

PET: positron emission tomography; FDG: fluorodeoxyglucose; 3D: three dimensional.

Graphic 91160 Version 2.0

Procedure for optimal tissue processing for a soft tissue mass

Tissue preparation	Studies
Intraoperative samples	Frozen tissue with cryopreservative
	Cytological, touch preparations, scrape and squash imprints for histologic diagnosis and FISH
Formalin-fixed tissue	Routine histopathology
	Immunohistochemical staining
	RT-PCR
	FISH for cytogenetics (tissue sections)
Glutaraldehyde-fixed tissue	Electron microscopy
Fresh tissue (tissue culture media)	Cytogenetics
	Molecular studies (FISH, RT-PCR for translocations)
	Tissue culture
Fresh tissue	Flow cytometry (DNA ploidy, cell surface markers)
Frozen tissue (no cryopreservative)	Molecular studies, gene rearrangement (FISH, RT-PCR), immunocytochemistry, microarray gene analysis, next-generation sequencing, precision medicine for tumor gene fusion and gene mutation panels
Alcohol-fixed tissue	Immunocytochemistry (if required improved cytoplasmic preservation)
	Microarray gene analysis
	Cytologic imprinting for FISH studies

FISH: fluorescence in situ hybridization; RT-PCR: reverse transcriptase polymerase chain reaction.

Graphic 62670 Version 4.0

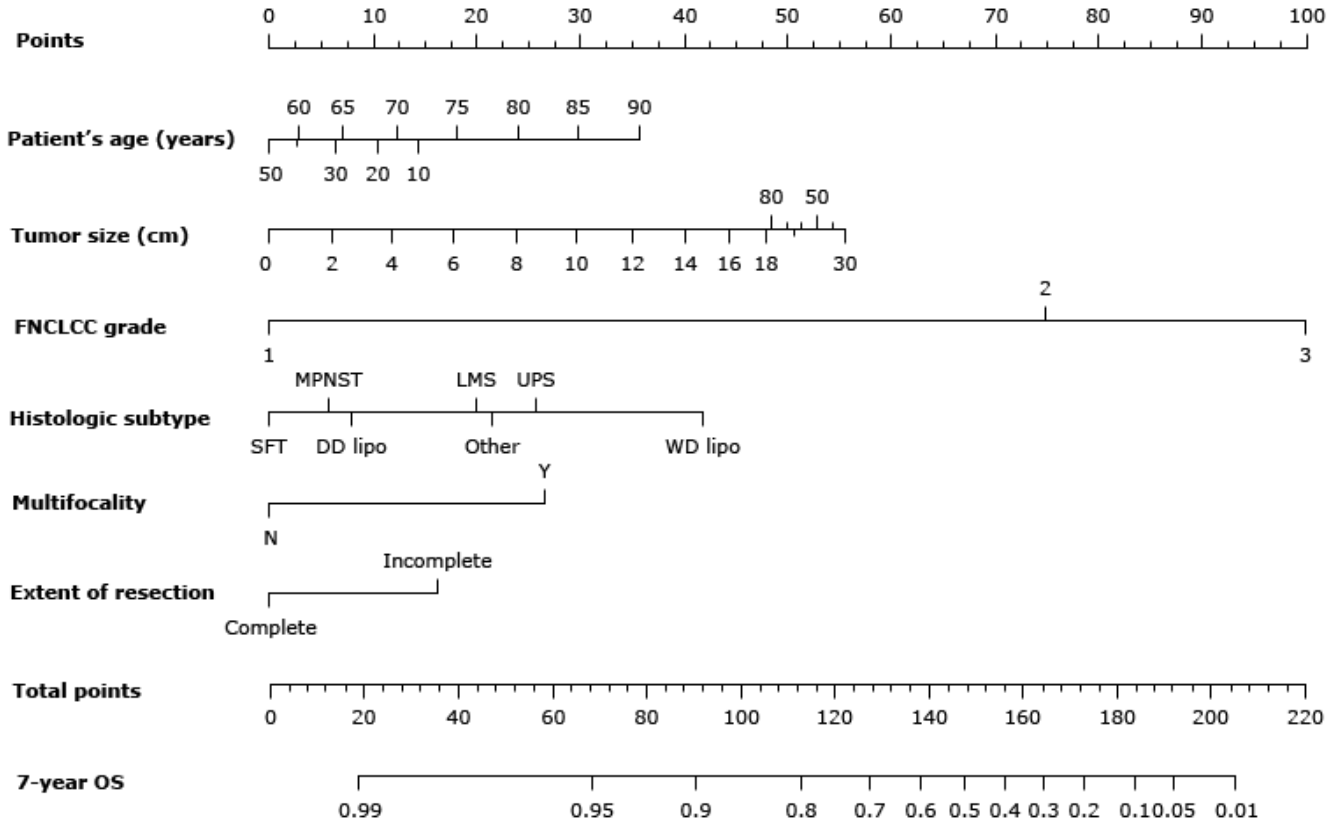
Soft tissue sarcomas arising in the abdominal and thoracic viscera TNM staging AJCC UICC 2017*

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T1	Organ confined
T2	Tumor extension into tissue beyond organ
T2a	Invades serosa or visceral peritoneum
T2b	Extension beyond serosa (mesentery)
T3	Invades another organ
T4	Multifocal involvement
T4a	Multifocal (two sites)
T4b	Multifocal (three to five sites)
T4c	Multifocal (>5 sites)
Regional lymph nodes (N)	
N category	**N criteria**
N0	No lymph node involvement or unknown lymph node status
N1	Lymph node involvement present
Distant metastasis (M)	
M category	**M criteria**
M0	No metastases
M1	Metastases present

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.
* There is no recommended prognostic stage grouping at this time.

Graphic 110739 Version 4.0

Nomogram for survival of retroperitoneal soft tissue sarcoma



The nomogram allows the user to obtain the seven-year OS probability corresponding to a patient's combination of covariates. For instance, locate the patient's tumor size and draw a line straight upward to the "Points" axis to determine the score associated with that size. Repeat the process for patient's age, FNCLCC grade, histologic subtype, multifocality, and extent of resection, then sum the scores achieved for each covariate and locate this sum on the "Total Points" axis. Draw a line straight down to the "7-year OS" axis to find the predicted probability.

FNCLCC: French National Federation of the Centers for the Fight Against Cancer; SFT: solitary fibrous tumor; MPNST: malignant peripheral nerve sheath tumor; DD lipo: dedifferentiated liposarcoma; LMS: leiomyosarcoma; UPS: undifferentiated pleomorphic sarcoma; WD lipo: well-differentiated liposarcoma; OS overall survival.

From: Gronchi A, Miceli R, Shurell E, et al. Outcome Prediction in Primary Resected Retroperitoneal Soft Tissue Sarcoma: Histology-Specific Overall Survival and Disease-Free Survival Nomograms Built on Major Sarcoma Center Data Sets. J Clin Oncol 2013; 31:1649-55. Reprinted with permission.

Graphic 98038 Version 2.0

The Dutch/Memorial Sloan-Kettering cancer center classification system for retroperitoneal soft tissue sarcomas

Classification	Definition
Stage I	Low-grade, complete resection, no metastases
Stage II	High-grade, complete resection, no metastases
Stage III	Any grade, incomplete resection, no metastases
Stage IV	Any grade, any resection, distant metastases

Modified from: van Dalen T, Hennipman A, Van Coevorden F, et al. Evaluation of a clinically applicable post-surgical classification system for primary retroperitoneal soft-tissue sarcoma. Ann Surg Oncol 2004; 11:483.

Graphic 61503 Version 3.0

Definition of histologic grade for soft tissue sarcomas at various sites AJCC UICC 2017

Tumor differentiation

Tumor differentiation is histology specific and is generally scored as follows:

Differentiation score	Definition
1	Sarcomas closely resembling normal adult mesenchymal tissue (eg, low-grade leiomyosarcoma)
2	Sarcomas for which histologic typing is certain (eg, myxoid/round cell liposarcoma)
3	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, soft tissue osteosarcoma, Ewing sarcoma/primitive neuroectodermal tumor (PNET) of soft tissue

Histology-specific tumor differentiation score

Histologic type	Score
Atypical lipomatous tumor/well-differentiated liposarcoma	1
Myxoid liposarcoma	2
Round cell liposarcoma	3
Pleomorphic liposarcoma	3
Dedifferentiated liposarcoma	3
Fibrosarcoma	2
Myxofibrosarcoma	2
Undifferentiated pleomorphic sarcoma (formerly termed malignant fibrous histiocytoma, pleomorphic type)	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 sarcoma, not otherwise specified	3

NOTE: Grading of gastrointestinal stromal tumor, malignant peripheral nerve sheath tumor, embryonal and alveolar rhabdomyosarcoma and angiosarcoma (rapid growth, dissemination common), as well as extraskeletal myxoid chondrosarcoma, alveolar soft part sarcoma, clear cell sarcoma, and epithelioid sarcoma (slower growth, dissemination common) is not recommended under this system. The case for grading malignant peripheral nerve sheath tumor is debated. Although all these histologies have a high rate of dissemination, survival with metastatic disease varies widely.

Mitotic count

In the most mitotically active area of the sarcoma, 10 successive high-power fields (HPF; one HPF at 400x magnification = 0.1734 mm^2) are assessed using a 40x objective.

Mitotic count score	Definition
1	0 to 9 mitoses per 10 HPF
2	10 to 19 mitoses per 10 HPF
3	≥20 mitoses per 10 HPF

Tumor necrosis

Evaluated on gross examination and validated with histologic sections.

Necrosis score	Definition
0	No necrosis
1	<50% tumor necrosis
2	≥50% tumor necrosis

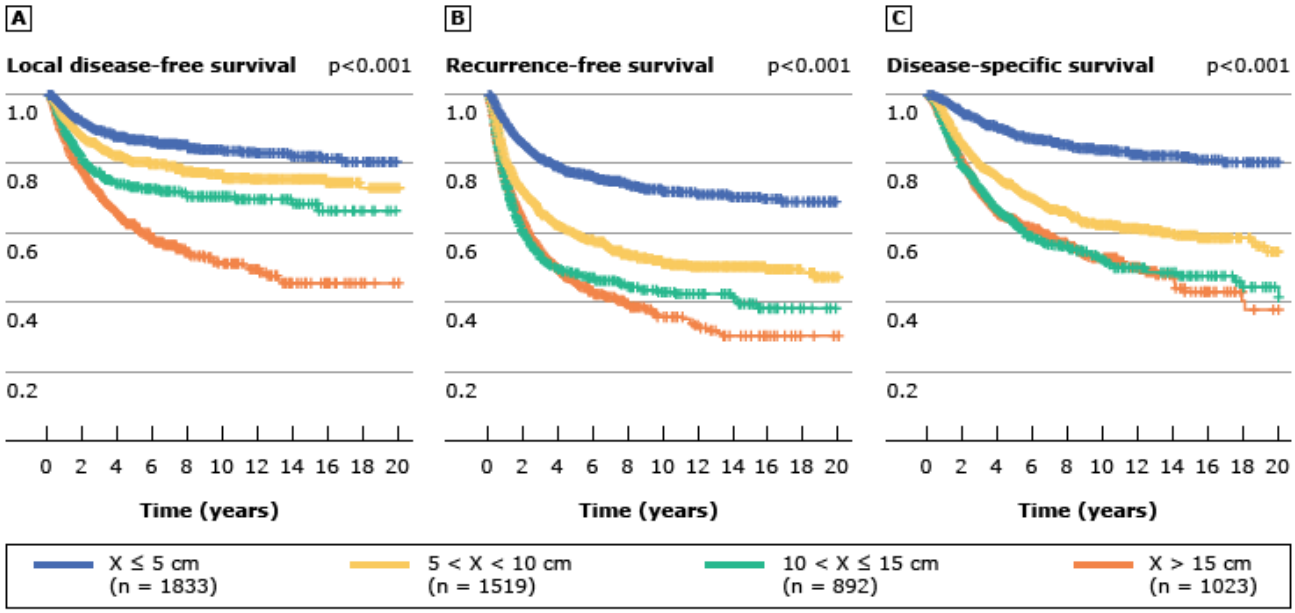
FNCLCC histologic grade

G	G definition
GX	Grade cannot be assessed
G1	Total differentiation, mitotic count and necrosis score of 2 or 3
G2	Total differentiation, mitotic count and necrosis score of 4 or 5
G3	Total differentiation, mitotic count and necrosis score of 6, 7, or 8

AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 110709 Version 3.0

Impact of primary tumor size on local recurrence-free survival, overall recurrence-free survival, and disease-specific survival in a series of 5267 patients with soft tissue sarcoma of the extremities or trunk

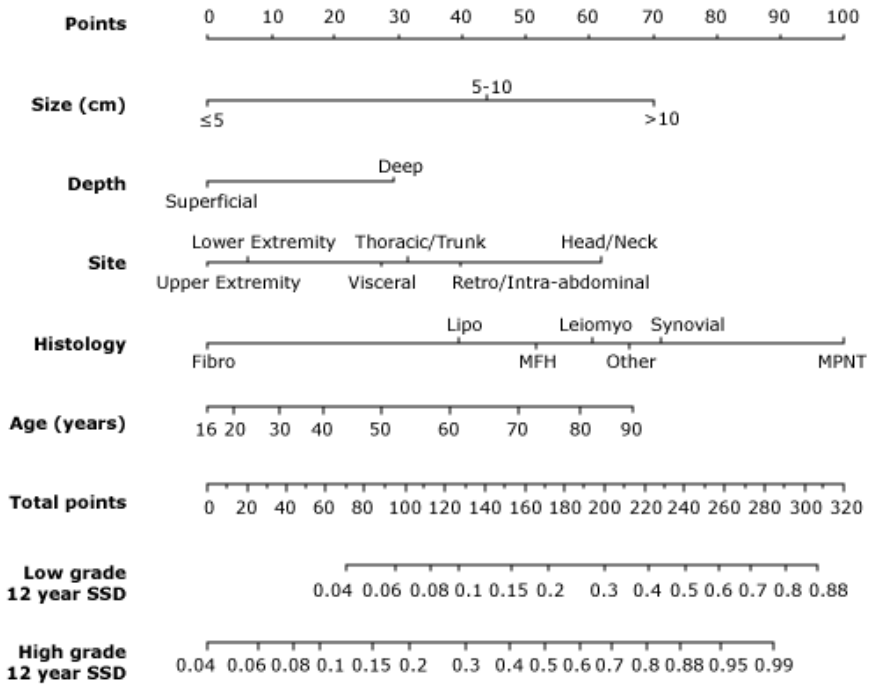


Local recurrence-free survival, overall recurrence-free survival, and disease-specific survival by size category, ≤5, 5-10, 10-15, and >15 cm.
(A) Local recurrence-free survival (time from primary surgery to first local recurrence), n = 5267 patients, excludes 75 patients with unknown size categories; log rank, p<0.001.
(B) Recurrence-free survival (time from primary surgery to first local or distant recurrence), n = 5267, excludes 75 patients with unknown size categories; log rank, p<0.001.
(C) Disease-specific survival (time from primary surgery to death from disease), n = 5267, excludes 75 patients with unknown size categories; log rank, p<0.001; log rank, p value = 0.91 comparing >10-15 and >15 cm groups.

Annals of Surgical Oncology, Toward better soft tissue sarcoma staging: building on american joint committee on cancer staging systems versions 6 and 7, Vol. 20, 2013, p. 3377, Maki RG, Moraco N, Antonescu CR, et al, © Society of Surgical Oncology 2013, with permission of Springer.

Graphic 110761 Version 2.0

Postoperative nomogram for 12-year sarcoma-specific death based upon data from 2163 patients treated at Memorial Sloan Kettering Cancer Center



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 tumor size. Repeat this process for the other axes, 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. **Instructions to patient:** "If we had 100 patients exactly like you, we would expect between (predicted percentage from nomogram - 8 percent) and (predicted percentage + 8 percentage) to die of sarcoma within 12 years if they did not die of another cause first. Death from sarcoma after 12 years is still possible."

Fibro: fibrosarcoma; Lipo: liposarcoma; Leiomyo: leiomyosarcoma; MFH: malignant fibrous histiocytoma; MPNT: malignant peripheral-nerve tumor; SSD: sarcoma-specific death.

Graphic 80175 Version 3.0

Contributor Disclosures

Christopher W Ryan, MD Grant/Research/Clinical Trial Support: Eisai [Sarcoma (Eribulin)]; Janssen [Sarcoma (Trabectedin)]; Bayer [Sarcoma (Sorafenib)]; Karyopharm [Sarcoma (Investigational agent)]; Threshold [Sarcoma (Investigational agent)]; Tracon [Renal carcinoma (Investigational agent)]; GSK/Novartis [Sarcoma (Pazopanib)]; Argos Therapeutics [Renal carcinoma (Investigational agent)]; Bristol Myers Squib [Renal carcinoma (Nivolumab, ipilumumab)]; CytRx [Sarcoma (Investigational agent)]; Exelexis [Renal carcinoma (Cabozantinib)]; Genentech [Renal carcinoma (Bevacizumab, atezolizumab)]; MabVax [Sarcoma (Investigational agent)]; Merck [Renal carcinoma (Pembrolizumab)]; Morphotek [Sarcoma (Investigational agent)]; OSI [Renal carcinoma (Erlotinib)]; Daiichi [Sarcoma (Investigational agent)]. Consultant/Advisory Boards: Eisai [Sarcoma and renal carcinoma (Eribulin)]; Pfizer [Renal carcinoma (Sunitinib, axitinib)]; Exelixis [Renal carcinoma (Cabozantinib)]; Novartis [Renal carcinoma (Pazopanib)]; Genentech/Roche [Renal carcinoma (Bevacizumab)]. **Janelle Meyer, MD** Nothing to disclose **Robert Maki, MD, PhD** Grant/Research/Clinical Trial Support: Bayer [Medical oncology (Regorafenib)]; Gem Pharmaceuticals [Medical oncology (GPX-150)]; Immune Design [Medical oncology (LV305+G305)]; Janssen/Pharma Mar [Medical oncology (Trabectedin)]; Karyopharm [Medical oncology (Selinexor)]; Sarcoma Alliance for Research through Collaboration (SARC) [Medical oncology (Regorafenib, pembrolizumab)], Tracon (TRC105). Speaker's Bureau: ABIM [Medical oncology]; Sarcoma Alliance for Research through Collaboration (SARC) [Medical oncology (Regorafenib, pembrolizumab)]. Consultant/Advisory Boards: ABIM [Medical oncology]; AADi [Medical oncology (Nab-rapamycin)]; Arcus (medical oncology); Bayer [Medical oncology (Regorafenib); Gem Pharmaceuticals [Medical oncology (GPX-150)]; Immune Design [Medical oncology (LV305+G305)]; Janssen/Pharma Mar [Medical oncology (Trabectedin)]; Karyopharm [Medical oncology (Selinexor)]; Lilly/Imclone [Medical oncology (Olaratumab)]; Sarcoma Alliance for Research through Collaboration (SARC) [Medical oncology (Regorafenib, pembrolizumab)]. **Raphael E Pollock, MD** Nothing to disclose **Diane MF Savarese, MD** Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy