Soft-tissue sarcomas (STSs) are a heterogeneous group of neoplasms arising from cells of mesenchymal origin. They are divided into tumors of adipocytic, fibroblastic, smooth muscle, skeletal muscle, vascular, osseous, fibrohistiocytic, and uncertain histogenesis. Tumors are generally categorized according to the 2002 World Health Organization (WHO) classification, which is based on the tissue or cell of origin. As the molecular genetics of STS becomes more clearly understood, current classifications will likely evolve into more prognostically useful groups. Tumors previously classified as malignant fibrous histiocytoma (MFH) have been reclassified into more specific entities (ie, leiomyosarcoma, dedifferentiated liposarcoma) based on their molecular genetics and cellular differentiation as determined by immunohistochemistry. This article discusses current epidemiology, diagnosis, and treatment of soft tissue sarcomas of the extremities, abdomen, and retroperitoneum.

EPIDEMIOLOGY

STSs account for less than 1% of all malignant neoplasms. The specific incidence patterns depend on the definition of STS used. Toro and colleagues studied the epidemiology of STS from 1978 to 2001 using the Surveillance, Epidemiology, and End Results database. Rates of STS ranged from 4.5 to 6.5 cases per 100,000
person-years. Rates were slightly higher in men than women, and highest in black women, possibly because of the inclusion of uterine leiomyosarcomas in the study. Generally, the rates of STS increase with age.

ETIOLOGY

Most STS are believed to arise spontaneously and are of an unknown cause; however, several observations have suggested specific etiologies. Rare heritable conditions are known to predispose patients to STS. Li-Fraumeni syndrome involves a cancer-predisposing mutation of the TP53 gene. Individuals who have this autosomal dominant condition have an increased rate of developing multiple primary malignancies, particularly STS, breast cancer, leukemia, osteogenic sarcoma, melanoma, and cancers of the colon, pancreas, adrenal cortex, and brain. TP53 is a tumor suppressor gene involved in regulating cell cycle and apoptosis.

Retinoblastoma, the most common malignant ocular neoplasm of childhood, is caused by mutation of the tumor suppressor gene, RB1, which may be sporadic or heritable. Childhood survivors of retinoblastoma are at risk for developing an STS later in life. TP53 and Rb1 gene mutations are commonly found mutated in sporadic STS. Mutation or deletion of the tumor suppressor gene, NF1, is associated with neurofibromatosis type I, and places patients at risk for developing malignant peripheral nerve sheath tumors.

Ionizing radiation has long been known to increase the risk for STS. Tumors typically develop approximately 7 to 10 years after radiation exposure. Radiation-induced mutations of the TP53 gene have been shown to play an integral role in radiation-induced STS. Severe, chronic lymphedema predisposes patients to developing cutaneous angiosarcoma. Stewart-Treves syndrome represents angiosarcoma arising in the setting of prolonged severe lymphedema from any acquired or congenital cause. It occurs in the upper extremity of approximately 0.07% of postmastectomy patients after axillary dissection. Postlymphedema angiosarcomas are fairly aggressive tumors, with an average survival of 19 months. Lymphedema of other sites and causes also predisposes patients to the development of STS. The only virus known to have a role in human STS is HHV-8, which plays a role in the development of Kaposi sarcoma.

When genetic syndromes and radiation-induced tumors are excluded, patients diagnosed with a STS have around a 16% risk for developing a second malignancy. These patients probably have an unknown and complex genetic predisposition to malignancy.

Although understanding the complex molecular genetics of STS may provide more useful prognostic classifications, this knowledge will undoubtedly provide insight for more specific therapeutic options. Currently, gastrointestinal stromal tumors, are the prototype of targeted molecular therapy with imatinib targeting the c-Kit (CD 117) receptor.

STAGING AND PROGNOSIS

Staging of STS is most commonly performed using the American Joint Committee on Cancer (AJCC) system in the United States and the WHO system in the rest of the world. These systems are very similar. Unique to the staging of STS is the addition of tumor grade to the traditional TNM system. Tumor grade is one of the most important prognostic factors. Grade is typically determined using either the National Cancer Institute or the French Federation of Cancer Centers Sarcoma Group systems. Both systems are three-tiered. The French system has a slightly greater ability to
predict metastases. Histologic grade considers cellularity, mitotic rate, cellular pleomorphism, and necrosis. How closely the tumor recapitulates normal tissue is also considered. STSs generally metastasize hematologically. Lymph node involvement is uncommon, and often represents aggressive disease. Nodal involvement is currently considered stage IV disease.

Limitations of traditional staging methods of determining survival have been noted. Sarcoma-specific death has been noted to be as high as 50%, but a wide variation is reported in the literature. A detailed and accurate method of determining risk for sarcoma-specific death in an individual patient would be useful. The current AJCC system does not incorporate many known prognostic factors, and risk for sarcoma-specific death can vary widely among stages.

Kattan and colleagues at the Memorial Sloan-Kettering Cancer Center (MSKCC) developed a nomogram to better predict risk for sarcoma-specific death (MSKCC Sarcoma Nomogram). The MSKCC nomogram considers age, histology, grade, location, depth, and size to determine the likelihood of 12-year sarcoma-specific survival. A prospective study of the validity of the nomogram proved it to have good predictive value. The proposed 7th edition of the AJCC staging manual, to be published within 2 years, should provide improved prognostic information.

Management, General Considerations

Optimal patient care of STS is best provided by a multidisciplinary team (consisting of radiology, medical and surgical oncology, radiation medicine, pathology, and psychosocial experts) with experience dealing with these types of tumors. Noria and colleagues found that approximately one third of patients who have excisional biopsies of an extremity sarcoma had residual disease on reexcision. A study in Florida showed that patients who had STS treated at high volume centers had improved survival and functional outcomes. Multidisciplinary centers generally treat more than 50 newly diagnosed sarcomas per year, participate in sarcoma research, and have an active sarcoma patient multidisciplinary management conference. Although all soft tissue masses and even soft tissue sarcomas cannot be treated at designated sarcoma centers, patients identified as having high-risk sarcomas and advanced sarcomas are best managed at these locations, with adherence to the principles of evaluating soft tissue masses as outlined here and elsewhere. The coordinated use of multiple disciplines and therapeutic modalities is necessary to achieve optimal outcome in patients who have STS.

MEDICAL IMAGING

Diagnostic imaging should be performed before invasive procedures so that soft tissue edema and hemorrhage do not complicate evaluation of the lesion. Anatomic localization of the mass and the extent of regional and metastatic disease may be established through state-of-the-art medical imaging techniques. Advanced imaging technology is used for monitoring response to chemotherapy, radiation treatment, and posttreatment follow-up of patients who have STS.

MRI

MRI is the most useful imaging modality for determining the extent of lesion, presurgical planning, and monitoring the disease during and after treatment. The superior soft tissue contrast resolution and multiplanar capabilities of MRI allow identification of the tumor margins and show the relationship of the tumor to muscle compartments and neurovascular and osseous structures. Different pulse sequences may assist in
tissue characterization. Fat, fluid, fibrous tissue, blood, and chondroid and osteoid matrix have distinctive imaging features. Intratumoral hemorrhage has a variable appearance depending on the stage of its evolution. Hematoma must be differentiated from a hemorrhagic neoplasm and should be followed up to ensure resolution of the soft tissue mass. If the presumed hematoma does not involute or continues to enlarge, then evaluation for an underlying tumor must be instituted.\textsuperscript{19}

Using intravenous contrast may distinguish areas of devitalized/necrotic tumor from cystic or myxomatous areas, and viable tumor must be identified to direct appropriate site of biopsy. Contrast-enhanced MRI may be used to evaluate the surgical bed in a postoperative patient who has positive tumor margins, monitor response to neoadjuvant chemotherapy and radiation therapy, and assess for tumor recurrence. Signal characteristics of the tumor will change over time and with treatment, thereby allowing differentiation of viable from nonviable tissue and scar formation from residual or recurrent tumor in many patients.\textsuperscript{19} Posttreatment changes may mimic residual and recurrent disease on MRI. Indeterminate findings may necessitate the need for functional imaging with positron emission tomography (PET).

MRI or CT angiography has replaced conventional angiography for the evaluation of tumor vascularity. Conventional angiography is needed for presurgical embolization.

**CT**

Recently manufactured multidetector/multichannel CT scans can acquire high-detail, submillimeter slice–thickness images. Two-dimensional and three-dimensional reformations can be generated in any plane or obliquity and may help determine the extent of the lesion and integrity of adjacent neurovascular and osseous structures, particularly in patients who cannot undergo MRI. CT and radiographs may show lucency in fat-containing tumors and intratumoral mineralization, such as dystrophic calcification, matrix mineralization, and phleboliths, in vascular tumors (Fig. 1). CT can determine the integrity of the cortex of an adjacent bone. CT is commonly used for image-guided biopsy of the mass and can be correlated with MRI for tumor localization.

Chest CT is required in all patients who have STS, because they have a high incidence of lung metastases. CT scanning of the abdomen and pelvis should be performed to evaluate for lymphadenopathy or other signs of metastatic disease.

**Ultrasound**

Ultrasound is a useful adjunct in the evaluation of STS when performed by experienced operators and in select patients. Lesion identification using ultrasound may be limited in the detection of deep masses and in patients who have large body habitus. Ultrasound can differentiate cystic from solid components of the tumor. Tumor vascularity may be assessed with Doppler ultrasonography. Ultrasound may be used to guide biopsy and may be preferable to CT guidance, depending on the expertise of the physician performing the procedure. Postoperative fluid collections may also be evaluated with ultrasound.

**POSITRON EMISSION TOMOGRAPHY**

Functional imaging evaluation of tumor metabolism is performed using whole-body PET and combined PET-CT scanning. The radiopharmaceutical glucose analog, fluorodeoxyglucose (FDG), may localize abnormally increased metabolic activity in primary and recurrent STS and allows evaluation of the entire patient. High- and intermediate-grade tumors have higher glycolytic metabolic activity as opposed to...
low-grade STS or benign tumors. The standardized uptake value (SUV) provides a semiquantitative measurement of glucose metabolism in a region of abnormal concentration and is typically greater than 2.0 in intermediate- and high-grade STS.

PET and combined PET-CT can direct biopsy of the most biologically active area in a large STS and may show unexpected nodal and distant metastases. These techniques can be used to identify the primary tumor in patients who present with metastatic disease.

PET and combined PET-CT may be used to monitor response to chemotherapy, radiation treatment, or radiofrequency ablation, and for long-term surveillance. PET and PET-CT scanning may help differentiate posttherapeutic changes from tumor recurrence in patients who have equivocal or indeterminate MRI findings. Metallic medical devices, such as orthopedic hardware, pacemakers, and dental devices, do not interfere with PET imaging.

EXTREMITY/TRUNK SOFT TISSUE SARCOMAS

Clinical Presentation

Although numerous exceptions exist, STSs of the extremities are generally painless and frequently become large before patients present. Lesions believed to be deep to fascia are suspicious for a STS and evaluated as such. Expert generally believe that superficial lesions smaller than 5 cm are unlikely to be malignant and can simply be excised. However, caution is advised, depending on the location (ie, hands, feet,
face, neck) and clinical characteristics. Lesions that cannot be explained should be properly evaluated.

**Tissue Sampling**

Incisional or excisional biopsy has been the traditional method. Mankin and colleagues\textsuperscript{22,23} showed the hazards of open biopsy in 1982 and again in 1992. They showed that complications from an inappropriate biopsy can have a negative impact on patient outcome, including increased use of radiation therapy and an increased rate of amputation. Core biopsy has become the preferred technique to establish diagnosis in soft tissue lesions.

Skrzynski and colleagues\textsuperscript{24} studied cost, comparing open versus percutaneous core biopsy, and showed that the cost of an open biopsy was around seven times higher than percutaneous biopsy. Several recent studies have shown the accuracy and low morbidity than can be achieved using image-guided (CT or ultrasound) core biopsies of these tumors.\textsuperscript{25,26} STS may be diagnosed with fine needle aspiration at institutions that have cytopathology expertise. It is advantageous for pathology to be present during the biopsy for real-time evaluation of the specimen to determine adequacy, triage tissue for special studies such as flow cytometry, or molecular diagnostics or cryopreservation. This stage is also favorable for obtaining tissue for banking and enrollment in clinical trials, if considered.\textsuperscript{27}

**Surgical Management**

Principles of good management begin when patients present with a soft tissue mass. In general, if an undiagnosed mass cannot be excised with widely negative margins, it should first be imaged and then an FNA, core needle biopsy (which the authors prefer), or an open incisional biopsy performed. When performing any diagnostic procedure, one should always plan for the next operation. Incisional and needle biopsies should be performed in the plane of any planned resection with the knowledge that the biopsy scar will have to be excised during the next procedure.

Current surgical treatment emphasizes function-preserving procedures with preoperative or postoperative radiation therapy. In their classic study comparing amputation with limb-sparing surgery plus radiation, Rosenberg and colleagues\textsuperscript{28} showed no difference in overall survival, although a small increase in local recurrence was seen in the limb-sparing group. Limb-sparing surgery entails compartmental resection or wide local excision. Compartmental resections can cause significant functional loss of the extremity; however, the approach can be modified in selected patients to allow improved function.

Standard care for surgical treatment is wide local excision that includes resection of the biopsy tract/scar with approximately 2 cm of normal tissue around the tumor. The goal of surgery is to achieve complete (R0) resection, because microscopic (R1) or grossly positive (R2) margins are associated with increased local recurrence and decreased survival.\textsuperscript{29} Small (<5 cm) tumors, regardless of grade, may be treated with surgical excision alone if an excision margin of uninvolved tissue of larger than 1 cm can be achieved. If margins of 1 to 2 cm cannot be obtained, preoperative or postoperative radiation therapy may result in an improved local control rate and adequate function.

Proximity of the tumor to major neurovascular structures has been considered a contraindication to limb-sparing surgery, but reports have shown encouraging results for en bloc resections coupled with major vascular reconstruction in the lower extremities and retroperitoneum.\textsuperscript{30,31} Tumors that require sacrifice of major lower extremity nerves, particularly the sciatic nerve, have traditionally been considered
an indication for amputation. Studies have shown an acceptable functional outcome with resection of the sciatic, peroneal, tibial, and femoral nerves. With appropriate reconstruction, tendon transfers, and rehabilitation, good functional outcomes have resulted. Considerable experience and judgment are required to estimate the potential for good quality of life when managing more advanced tumors. Local recurrence of STS in some patients may be treated with repeated wide local excision with no difference in survival compared with amputations.

Amputation is currently reserved for treatment of primary disease or extensive local recurrence when the function of the limb would be severely impaired after tumor resection. Generally, these are large, high-grade tumors located more distal in the extremity. Increased rates of distant, usually pulmonary metastases in these patients after primary amputation is likely because of the risk factors, size, and high tumor grade.

Hyperthermic isolated limb perfusion (HILP) with tumor necrosis factor and melphalan is used extensively in Europe for limb salvage in STSs of the extremities. Studies have shown response rates of approximately 75%, with long-term limb salvage rates of 80% in patients described as having advanced, frequently multicentric STSs. Radiation therapy is often given in addition to limb perfusion to increase local control.

Vascular insufficiency may develop as a late complication of limb perfusion and sometimes requires amputation.

Patients who have a previously unplanned excision of a STS present a special circumstance for surgical management. Routine reexcision has shown residual tumor in 50% of cases. Reexcision after an unplanned excision, although standard practice, is a challenging operation because the residual disease is rarely palpable to guide the surgical approach. After adequate reexcision, increased local relapse rates have been reported, whereas another series found rates similar to patients undergoing an adequate initial operation. Higher rates of distant metastasis have been noted in groups with residual disease in the reexcision specimen.

Radiation

To improve local control, radiation therapy is an effective adjuvant therapy, whether given pre- or postoperatively. Selected patients who have widely negative margins may not require radiation. Extremity STS can be treated with pre- or postoperative radiation. Preoperative radiotherapy allows a decreased radiation field and radiation dose, which may diminish complications associated with radiation. Giving radiation preoperatively avoids delays in giving radiation because of postoperative wound complications. However, an increased rate of postoperative wound complications is seen in patients undergoing preoperative radiation compared with those undergoing postoperative radiation. Coordination with a reconstructive surgery team may help limit these complications, although rates of major wound complications are still significant even when sophisticated reconstruction techniques are used. Postoperative radiation requires larger doses and can induce a greater long-term functional impairment.

A recent randomized trial of pre- versus postoperative radiation for extremity STS showed slightly better overall survival in the preoperative group (P<.05), although an increased rate of wound complications was seen (35% versus 17%). Surgical resection is generally performed 4 to 8 weeks after radiation therapy. Brachytherapy has resulted in reduced rates of local recurrence, especially for high-grade tumors.

Chemotherapy

Most randomized trials assessing the role of adjuvant chemotherapy in primary STSs are small and have had varying results. A large meta-analysis performed by the
Sarcoma Meta-Analysis Collaboration, including patients who had all grades, sizes, and locations of tumors, showed a 10% decrease in overall recurrence-free survival and a 4% increase in overall survival at 10 years (not statistically significant) with adjuvant chemotherapy. Criticisms of the study include concerns about inclusion of patients who had tumors in varied locations and inclusion of low-grade tumors, unlikely to metastasize, which could have overestimated the value of chemotherapy. Large (>5 cm), high-grade tumors have been shown to develop distant metastasis around 35% to 60% of the time. Although response to aggressive neoadjuvant and adjuvant chemotherapy has been documented using doxorubicin, ifosfamide, and dacarbazine, proof of efficacy in improving long-term survival remains controversial. This regimen and most others are extraordinarily toxic. The role of neoadjuvant chemotherapy and adjuvant chemotherapy in primary STSs remains controversial. New regimens, perhaps in combination with newer targeted therapies, are greatly needed for these tumors.

**Retroperitoneal/Abdominal Sarcomas**

**Clinical presentation**
Patients who have abdominal or retroperitoneal STS generally present with sensations of fullness or obstructive symptoms of the alimentary or renal systems. Given the slow onset and vague symptoms, tumors frequently grow to an enormous size and present at an advanced stage. Patients typically present to primary care doctors with vague symptoms and findings that contribute to the delay in diagnosis of these tumors. CT scan of the abdomen and pelvis with intravenous and oral contrast should be performed for any suspicious symptoms or physical findings. In addition to STS, the differential diagnosis for a retroperitoneal mass includes germ cell tumors, lymphoma, abscess, and renal, adrenal, and neurogenic tumors, and undifferentiated carcinoma (primary or metastatic).

**Tissue sampling**
Image-guided core biopsy is generally efficacious, safe, and accurate. In general, retroperitoneal masses are malignant and require resection. The authors prefer to biopsy retroperitoneal masses to confirm the diagnosis before resecting the tumor. This technique may also allow placement of selected patients on specific protocols. Biopsy would be required for neoadjuvant radiation therapy. However, retroperitoneal lipomatous lesions are difficult to biopsy with core needles unless the tumor of interest contains heterogenous enhancing areas.

**SURGICAL MANAGEMENT**

Retroperitoneal sarcomas are treated primarily with surgical excision. If neoadjuvant radiation is a therapeutic consideration, a core needle biopsy is essential. The lesion should be resected with as wide a margin as possible, even if neoadjuvant therapy is not used. The tumors should be removed en bloc with surrounding organs as necessary.

**Radiation**

Retroperitoneal tumors have shown some benefits with adjuvant or neoadjuvant radiation therapy, although definitive studies are not available. The presence of the tumor can help keep abdominal viscera out of the radiation field, making preoperative therapy attractive and reducing the incidence of radiation enteritis, bowel obstruction, and other complications associated with abdominal radiation. Intraoperative radiation and brachytherapy may also be used selectively. Using preoperative therapy with either an
intraoperative boost or brachytherapy could favorably affect local recurrence and 5-year survival for intermediate- and high-grade tumors.49

Chemotherapy
Chemotherapy for localized retroperitoneal sarcomas is controversial, and no large controlled studies have been reported. Patients who have metastatic disease may be considered for chemotherapy, but no evidence exists of significant benefit.50 Smaller, completely excised lesions without metastasis do not require chemotherapy. Clinical trials using chemotherapy are underway for patients who have unresectable retroperitoneal sarcomas.

SURVEILLANCE
Patients who have completed therapy and show no active disease require close observation and follow-up to monitor for recurrent or metastatic disease. For extremity/trunk STS, a recent update of the National Comprehensive Cancer Network (NCCN) recommends a history/physical and chest CT or radiograph be done every 3 to 6 months for 2 to 3 years, then every 6 months for the next 2 years and then should be done annually. Consideration should be given to imaging the primary site depending on the estimated risk for local recurrence and the primary site.51 Routine imaging of the affected extremity is beneficial if the patient’s body habitus prohibits a good physical examination.52 Having a good baseline image of the operative site is always advantageous. In selected patients, physical examination may be adequate, but for the most part imaging at least twice a year is the prudent course. Patients who have treated retroperitoneal sarcomas and no known active disease should have abdominal and pelvic CT scans every 3 to 6 months for 2 years and then annually.51

METASTATIC DISEASE
STS most commonly metastasizes to the lung. Isolated pulmonary metastasis occurs in approximately 20% of patients.53 Surgical resection (metastectomy) of these metastases is the mainstay of treatment. Resection can be performed using minimally invasive techniques, median sternotomy, unilateral posterolateral thoracotomy, staged bilateral thoracotomy, or a clamshell thoracotomy, depending on surgeon experience and the location of recurrence. Reports of 3-year survival rates after pulmonary metastectomy range from 28% to 54%.54,55 Factors associated with a prolonged survival include complete resection of pulmonary disease and greater than 1 year disease-free before development of metastatic disease.56 Between 40% and 80% of patients will develop recurrent disease in the lung after pulmonary resection. These patients should be considered for re-resection if complete resection of disease can be obtained.57 If the disease cannot be completely excised, little can be gained from metastectomy unless the patient is symptomatic.
Patients who have unresectable metastatic disease have few options. Doxorubicin-based palliative chemotherapy has not been shown to increase survival, and toxic side effects of the treatments are significant.58 Newer regimens using gemcitabine and docetaxel have shown some improvement in survival.59 Care must be taken when selecting patients for palliative chemotherapy.

FUTURE DIRECTIONS
Sarcomas are rare (approximately 7000 cases annually in the United States) heterogeneous tumors that involve multiple specialties in patient care. Research at individual
centers may be difficult. The Sarcoma Progress Review Group\(^{18}\) recommended the creation of a Sarcoma Research Consortium that would guide and focus research into more fruitful directions. This group recommended that research focus on the molecular characterization of STS.

STSs have recently been molecularly categorized into two broad groups. The first group includes tumors with simple karyotypes, simple translocations, or point mutations (c-KIT in gastrointestinal stromal tumors). The second group consists of tumors with complex karyotypes and nonspecific cytogenetic aberrations (approximately two thirds of all STS).\(^{60}\)

Newer molecular classification of tumors may result in a reclassification of many tumor types. Tumors previously classified as MFH have been shown to have similar gene expression patterns to liposarcomas and some leiomyosarcomas, supporting the hypothesis that MFH is a member of this group of tumors.\(^{61}\) Gene microarray analysis is crucial in determining these molecular patterns. Acquisition of fresh and archival formalin-fixed, paraffin embedded tissue obtained before treatment will provide resources for correlating outcomes with molecular patterns. Future hope for patients who have STSs is that more precise molecular genetic characterization of sarcomas will lead to an enhanced array of more specific and less toxic therapeutic options than currently exists.

REFERENCES


