The soft-tissue sarcomas are a group of rare but anatomically and histologically diverse neoplasms. This is due to the ubiquitous location of the soft tissues and the nearly three dozen recognized histologic subtypes of soft-tissue sarcomas. In the United States, approximately 10,500 new cases of soft-tissue sarcoma are identified annually, and about 3,800 patients die of the disease each year. The age-adjusted incidence is 2 cases per 100,000 persons.

**Epidemiology**

Unlike the more common malignancies, such as colon cancer, little is known about the epidemiology of soft-tissue sarcomas. This, again, reflects the uncommon nature of these lesions.

**Gender** There is a slight male predominance, with a male-to-female ratio of 1.1:1.0.

**Age** The age distribution in adult soft-tissue sarcoma studies is < 40 years, 20.7% of patients; 40 to 60 years, 27.6% of patients; and > 60 years, 51.7% of patients.

**Race** Studies in large cohorts of patients demonstrate that the race distribution of soft-tissue sarcomas mirrors that of the American population (86% Caucasian, 10% African American, 1% Asian American, and 3% other).

**Geography** Studies have suggested that the incidence and mortality of soft-tissue sarcomas may be increasing in New Zealand. There are no currently available data addressing this possibility in the United States.
In the majority of cases of patients with soft-tissue sarcoma, no specific etiologic agent is identifiable. However, a number of predisposing factors have been recognized.

**Radiation therapy** Soft-tissue sarcomas are recognized to originate in radiation fields following therapeutic irradiation for a variety of malignancies. Frequently, they are seen in the lower-dose regions at the edge of the radiation target volume. By definition, radiation-induced sarcomas arise no sooner than 3 years after radiation therapy and often develop decades later. The majority of these sarcomas are high-grade lesions (90%), and high-grade undifferentiated pleomorphic sarcoma (formerly termed MFH, malignant fibrous histiocytoma) is a predominant histology. Osteosarcoma, angiosarcoma, and other histologic subtypes have also been reported.

**Chemical exposure** Exposure to various chemicals in specific occupations or situations has been linked with the development of soft-tissue sarcoma. These chemicals include the phenoxy acetic acids (forestry and agriculture workers), chlorophenols (sawmill workers), vinyl chloride (individuals working with this gas, used in making plastics and as a refrigerant), and arsenic (vineyard workers).

**Chemotherapy** Soft-tissue sarcomas have been reported after previous exposure to alkylating chemotherapeutic agents, most commonly after treatment of pediatric acute lymphocytic leukemia. The drugs implicated include cyclophosphamide, melphalan (Alkeran), procarbazine (Matulane), nitrosoureas, and chlorambucil (Leukeran). The relative risk of sarcoma appears to increase with cumulative drug exposure.

**Chronic lymphedema** Soft-tissue sarcomas have been noted to arise in the chronically lymphedematous arms of women treated with radical mastectomy for breast cancer (Stewart-Treves syndrome). Lower-extremity lymphangiosarcomas have also been observed in patients with congenital lymphedema or filariasis complicated by chronic lymphedema.

**Trauma and foreign bodies** Although a recent history of trauma is often elicited from patients presenting with soft-tissue sarcoma, the interval between the traumatic event and diagnosis is often short; thus, a causal relationship is highly unlikely. Chronic inflammatory processes, however, may be a risk factor for sarcoma. Foreign bodies, such as shrapnel, bullets, and implants, have also been implicated.

**Signs and symptoms**

Signs and symptoms of soft-tissue sarcoma depend, in large part, on the anatomic site of origin. Due to the ubiquitous location of the soft tissues, these malignancies may arise at any site in the body where soft tissues are located. Since 50% of soft-tissue sarcomas arise in an extremity, the majority of patients present with a palpable soft-tissue mass. Pain at presentation is noted in only one-third of cases.

**Extremity and superficial trunk** Extremity and superficial trunk sarcomas account for 60% of all soft-tissue sarcomas. The majority of patients present with a painless primary soft-tissue mass. Lipomas are at least 100 times more common than soft-tissue sarcomas; however, any growing lesion or even a deep-seated fatty lesion should be biopsied to rule out a sarcoma.

**Retroperitoneum** Retroperitoneal sarcomas account for 15% of all soft-tissue
Viscera

Visceral soft-tissue sarcomas, which comprise 15% of all soft-tissue sarcomas, present with signs and symptoms unique to their viscus of origin. For example, gastrointestinal stromal tumors (GISTs) present with GI symptoms that are usually indistinguishable from those of the more common adenocarcinomas, such as anemia, melena, abdominal pain, or weight loss. Similarly, uterine leiomyosarcomas frequently present with painless vaginal bleeding, such as that often noted in patients with more common uterine malignancies.

Head and neck

Head and neck sarcomas comprise 10% of all soft-tissue sarcomas. Although generally smaller than sarcomas in other sites, they may present with important mechanical problems related to compression or invasion of adjacent anatomy (eg, orbital contents, airway, or pharynx). In addition, their proximity to critical anatomy can pose management difficulties due to compromise in the delivery of both surgery and radiotherapy.

Pathology

Histopathologic classification

As a consequence of the wide spectrum of soft tissues, a variety of histologically distinct neoplasms have been characterized. The current histopathologic classification is based on the putative cell of origin of each lesion. Such classification based on histogenesis is reproducible for the more differentiated tumors. However, as the degree of histologic differentiation declines, it becomes increasingly difficult to determine a potential cellular origin.

In addition, many of these tumors appear to have the ability to dedifferentiate. This process results in a variety of overlapping patterns, making uniform classification difficult. Experienced soft-tissue pathologists frequently disagree as to the cell of origin of an individual tumor. Comparative studies have demonstrated concordance in histopathologic diagnosis in only two-thirds of cases. MFH used to be the most common histologic subtype of soft-tissue sarcoma. However, in one study, reanalysis histologically, immunohistochemically, and ultrastructurally allowed reclassification of most of tumors to a specific line of differentiation. As a result, the term "malignant fibrous histiocytoma" is increasingly being replaced by the term "high-grade undifferentiated pleomorphic sarcoma" (UPS). GIST is now recognized as the most common form of sarcoma.

Staging and prognosis

AJCC/UICC staging system

The relative rarity of soft-tissue sarcomas, the anatomic heterogeneity of these lesions, and the presence of more than 30 recognized histologic subtypes of variable grade have made it difficult to establish a functional system that can accurately stage all forms of this disease. The staging system of the AJCC and the UICC, now in its 7th edition (2010), is the most widely employed staging classification for soft-tissue sarcomas (Table 1). In the 7th edition, the staging for GIST has been separated from other sarcomas for the first time (Table 2). All soft-tissue sarcoma subtypes are included, except desmoid tumors (deep fibromatosis), Kaposi sarcoma, and infantile fibrosarcoma. In keeping with the FNCLCC (Fédération Nationale des Centres de Lutte Contre la Cancer) sarcoma grading system, three distinct histologic grades are recognized, based on the degree of differentiation, mitotic activity, and necrosis.
Histologic grade and tumor size are the primary determinants of clinical stage. In the 6th version of the AJCC staging system, tumor size was further substaged as "a" (a superficial tumor that arises outside the investing fascia) or "b" (a deep tumor that arises beneath the fascia or invades the fascia). While these data are collected in AJCC/UICC version 7, these data are not used to stage the tumor.

<table>
<thead>
<tr>
<th>Table 1: AJCC version 7 staging for soft tissue sarcomas</th>
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<td>The AJCC/UICC system is designed to optimally stage extremity tumors but is also applicable to the trunk and head and neck. It is more difficult to employ for retroperitoneal or visceral (GI or other viscera) tumors, since the designation of superficial or deep is meaningless here, as all are deeply seated tumors in these anatomic sites.</td>
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Anatomic site is itself an important determinant of outcome. Patients with retroperitoneal, head and neck, and visceral sarcomas have an inferior overall prognosis compared with patients with extremity tumors. Although the anatomic site is not incorporated as a specific component of any current staging system, outcome data should be reported on a site-specific basis.

At Memorial Sloan-Kettering Cancer Center, a retrospective review of 369 patients with high-grade soft-tissue sarcoma of the extremity treated with postoperative radiation therapy was conducted to evaluate the influence of tumor site on local control and complications. The tumor site was upper extremity in 103 patients (28%) and lower extremity in 266 patients (72%). With a median follow-up of 50 months, the 5-year actuarial rates of local control, distant relapse–free, and overall survival for the entire population were 82%, 61%, and 71%, respectively. The 5-year local control rates in patients with upper extremity lesions vs lower extremity lesions were 70% and 86%, respectively ($P = .0004$). On multivariate analysis, upper extremity site ($P = .001$) and positive resection margin ($P = .02$) were significant predictors of poor local control.
TABLE 2

AJCC version 7 staging for GIST

Prognostic factors
Understanding relevant clinicopathologic prognostic factors is important in treatment planning for patients with soft-tissue sarcoma. Several reports document the adverse prognostic significance of tumor grade, anatomic site, tumor size, and depth relative to the investing fascia (for extremity and body wall tumors). Patients with high-grade lesions, large (T2) sarcomas, a nonextremity subsite, or deep tumor location are at increased risk for disease relapse and sarcoma-specific death.

Sarcoma-specific nomogram
Kattan and colleagues from Memorial Sloan-Kettering Cancer Center developed a sarcoma-specific nomogram for estimation of sarcoma-specific 12-year survival. The nomogram takes into account pretreatment clinicopathologic factors, including anatomic site, histologic subtype, tumor size, histologic grade, tumor depth, and patient age. The nomogram is based on prospectively collected data and has been validated in a population of 2,136 patients with sarcoma. The nomogram can be found at www.nomograms.org. The sarcoma nomogram may be useful for patient stratification for clinical trials and for risk assessment and treatment planning for individual patients. Similar nomograms have been generated for specific sarcoma subtypes, such as synovial sarcoma or the family of liposarcomas, and are validated for both 4-grade and 3-grade staging systems.

Risk assessment in GIST
Beyond the cumbersome AJCC/UICC staging system for GIST, there are other ways to assess tumor risk. Perhaps the most useful of these is the risk-stratification strategy from the Armed Forces Institute of Pathology (AFIP). Tumors are classified by anatomic site, size, and mitotic rate, and risk of recurrence (Table 3). This simple method allows one to discuss with a patient the risk of a particular GIST with respect to mortality or potential benefit of adjuvant imatinib (Gleevec). What is notable from this table is that even large gastric GISTs with a low mitotic rate, one of the most common scenarios for diagnosis, have a low 12%; thus, for the average patient adjuvant imatinib can be avoided.

TABLE 3

AFIP risk stratification strategy
**Prognostic factors for local vs distant recurrence** Unlike other solid tumors, the adverse prognostic factors for local recurrence of a soft-tissue sarcoma differ from those that predict distant metastasis and tumor-related mortality. In other words, patients with a constellation of adverse prognostic factors for local recurrence are not necessarily at increased risk for distant metastasis or tumor-related death.

This concept has been validated by an analysis of the SSG prospective database. In 559 patients with soft-tissue sarcomas of the extremities and trunk treated with surgery alone, inadequate surgical margin was found to be a risk factor for local recurrence but not for distant metastasis. Therefore, staging systems that are designed to stratify patients for risk of distant metastasis and tumor-related mortality using these prognostic factors (such as the AJCC/UICC system) do not stratify patients for risk of local recurrence.

**Screening and diagnosis**

Currently, there are no screening tests for soft-tissue sarcomas. Since the majority of patients with soft-tissue sarcoma have lesions arising in the extremities or superficial trunk, most of the comments here apply to soft-tissue lesions in those sites. A separate algorithm is usually employed for the evaluation of a primary retroperitoneal mass or visceral sarcoma.

**Physical examination** should include an assessment of the size of the mass and its mobility relative to the underlying soft tissues. The relationship of the mass to the investing fascia of the extremity (superficial vs deep) and nearby neurovascular and bony structures should be noted. Site-specific neurovascular examination and assessment of regional lymph nodes should also be performed.

**Biopsy** Any soft-tissue mass in an adult extremity should be biopsied if it is symptomatic or enlarging, is > 5 cm, or has persisted beyond 4 to 6 weeks.

*Percutaneous approaches* Percutaneous tissue diagnosis can usually be obtained with fine-needle aspiration (FNA) for cytology or by percutaneous core biopsy for histology. The needle track should be placed in an area to be excised or that can be encompassed in adjuvant radiotherapy fields if they are to be used. In most instances, when an experienced cytopathologist and/or histopathologist examines the specimen, a diagnosis of malignant soft-tissue sarcoma can be made. FNA is often viewed as a suboptimal method of establishing an initial diagnosis of soft-tissue sarcoma. Histology is usually preferred to cytology because more tissue is obtained, which allows for a more accurate delineation of tumor type and grade. Percutaneous tissue diagnosis is preferred to facilitate subsequent treatment planning and to permit surgical resection to be performed as a one-stage procedure.

*Open biopsy* In some cases, an adequate histologic diagnosis cannot be secured by percutaneous means. Open biopsy is indicated in these instances, with the exception of relatively small superficial masses, which can be easily removed by excisional biopsy with clear margins.

Biopsies should be incisional and performed with a longitudinal incision parallel to the long axis of the extremity. This approach facilitates subsequent wide local excision of the tumor, and the incisional scar results in minimal difficulties in wound closure. It also facilitates inclusion of any scars within the area of the tumor in adjuvant radiation fields without the excessive morbidity of large-field radiotherapy.
planning. The incision should be centered over the mass at its most superficial location. Care should be taken not to raise tissue flaps. Meticulous hemostasis should be ensured after the biopsy to prevent dissemination of tumor cells into adjacent tissue planes by hematoma.

**Retroperitoneal or intra-abdominal mass** Biopsy of primary retroperitoneal soft-tissue masses is generally not required for radiographically resectable masses, nor is biopsy recommended for suspected GISTs. The circumstances under which percutaneous or preoperative biopsy of retroperitoneal masses should be strongly considered include:

- tissue diagnosis for radiographically unresectable disease
- clinical suspicion of lymphoma or germ-cell tumor
- tissue diagnosis for neoadjuvant treatment, including radiotherapy and/or chemotherapy
- suspected metastases from another primary tumor.

**Primary tumor imaging** Optimal imaging of the primary tumor depends on the anatomic site. For soft-tissue masses of the extremities, MRI has been regarded as the imaging modality of choice because it enhances the contrast between tumor and muscle and between tumor and adjacent blood vessels and also provides multiplanar definition of the lesion. However, a study by the RDOG that compared MRI and CT in 183 patients with malignant bone and 133 patients with soft-tissue tumors showed no specific advantage of MRI over CT from a diagnostic standpoint.

For pelvic lesions, the multiplanar capability of MRI may provide superior single-modality imaging. In the retroperitoneum and abdomen, CT usually provides satisfactory anatomic definition of the lesion. Occasionally, MRI with gradient sequence imaging can better delineate the relationship of the tumor to midline vascular structures, particularly the inferior vena cava and aorta. In the future, MRI–CT fusion techniques may facilitate treatment planning using conformal radiotherapy techniques.

More invasive studies, such as angiography and cavography, are almost never required for the evaluation of soft-tissue sarcomas. The role of PET scan in sarcoma management is not well defined, although it correlates well with contrast-enhanced CT scans in patients with GIST. In particular, if the lack of IV contrast uptake as a sign of a responding tumor is taken into account, contrast-enhanced CT scans appear to yield results similar to PET scans in patients with GIST.

**Imaging for metastatic disease** Cost-effective imaging to exclude the possibility of distant metastatic disease depends on the size, grade, and anatomic location of the primary tumor. In general, patients with low-grade soft-tissue sarcomas <10 cm or intermediate-/high-grade tumors < 5 cm in diameter require only a chest x-ray for satisfactory staging of the chest. This reflects the fact that these patients are at comparatively low risk of presenting with pulmonary metastases. In contrast, patients with very large (10 cm) low-grade tumors or high-grade tumors 5 cm should undergo more thorough staging of the chest by CT.

Patients with retroperitoneal and intra-abdominal visceral sarcomas should undergo single-modality imaging of the liver to exclude the possibility of synchronous hepatic metastases. The liver is a common site for a first metastasis from these lesions.

**Treatment**
**Treatment of localized disease**

Surgical resection is the cornerstone of therapy for patients with localized disease. Over the past 20 years, there has been a gradual shift in the surgical management of soft-tissue sarcoma of the extremities away from radical ablative surgery, such as amputation or compartment resection, and toward limb-sparing approaches combining wide local resection with preoperative or postoperative radiotherapy. The development of advanced surgical techniques (eg, microvascular tissue transfer, bone and joint replacement, and vascular reconstruction) and the application of multimodality approaches have allowed most patients to retain a functional extremity without any compromise in survival.

**Surgery**

The surgical approach to soft-tissue sarcomas depends on careful preoperative staging with MRI or CT for lesions of the extremities and a percutaneous histologic diagnosis and assessment of tumor grade. In most instances, preoperative imaging studies allow for accurate prediction of resectability.

The surgical approach to soft-tissue sarcomas is based on an awareness that these lesions tend to expand and compress tissue planes, producing a pseudocapsule.

**Wide local resection** encompassing a rim of normal tissue around the lesion has led to improvements in local tumor control, with local recurrence rates of approximately 30% in the absence of adjuvant therapies. However, studies indicate that carefully selected patients with localized, small (T1), low-grade soft-tissue sarcomas of the extremity can be treated by wide resection alone, with local recurrence rates of < 10%.

A prospective trial examining local recurrence rates for T1 primary soft-tissue sarcomas of the trunk and extremities has been conducted. Patients underwent function-preserving surgery. Postoperative radiation was delivered for microscopically positive margins (R1 resection). No radiation was delivered if margins were negative (R0 resection). A total of 88 patients were evaluated in this trial. A total of 16% had R1 resection and received adjuvant radiation therapy, whereas 84% had R0 resection and did not receive radiation therapy. With a median follow-up of 75 months, isolated local recurrence was observed in six patients in the R1 arm (43%) and six patients in the R0 arm (8%). The 5- and 10-year local recurrence rates in the R0 arm were 7.9% and 10.6%, respectively, and the sarcoma-specific death rates were 3.2% at both 5 and 10 years in the R0 arm.

The need for adjuvant irradiation in small (< 5 cm), high-grade lesions has been studied. A retrospective review of 204 patients with stage IIB soft-tissue sarcoma of the extremity treated at Memorial Sloan-Kettering Cancer Center has been completed. A total of 57% of patients did not receive adjuvant radiation therapy, whereas 43% received either brachytherapy or external-beam radiation therapy. With a median follow-up of 67 months, there was no significant difference in 5-year local tumor control, distant relapse–free survival, or disease-specific survival when adjuvant irradiation was delivered.
Further studies will be required to define which subsets of patients with primary extremity sarcoma can be treated by wide excision surgery alone. Preoperative or postoperative radiotherapy should be employed for patients with primary T1 sarcomas in whom a satisfactory gross surgical margin cannot be attained without compromise of functionally important neurovascular structures.

**Limb-sparing surgery plus irradiation** Limb-sparing surgery employing adjuvant irradiation to facilitate maximal tumor local control has become the standard approach for large (T2) soft-tissue sarcomas of the extremities. In most centers, upward of 90% of patients are treated with limb-sparing approaches. Amputation is reserved as a last-resort option for local tumor control and is used with the knowledge that it does not affect survival. This approach was validated in a prospective National Cancer Institute (NCI) study, in which patients with a limb-sparing surgical option were randomized to receive limb-sparing surgery with postoperative radiation therapy or amputation. Both arms of the study included postoperative therapy with doxorubicin, cyclophosphamide, and methotrexate.

**Surgical procedure** The planned resection should encompass the skin, subcutaneous tissues, and soft tissues adjacent to the tumor, including the previous biopsy site and any associated drain sites. The tumor should be excised with a 2- to 3-cm margin of normal surrounding tissue whenever possible. Since good adjuvant approaches are available to facilitate local tumor control, this ideal margin is sometimes compromised rather than attempting resection of adjacent, possibly involved bone or neurovascular structures that would result in significant functional loss. In the rare circumstance of gross involvement of neurovascular structures or bone, they can be resected en bloc and reconstructed.

Metal clips should be placed at the margins of resection to facilitate radiation field planning, when and if external irradiation is indicated. Drain sites should be positioned close to the wound to allow inclusion in radiation therapy fields. As noted earlier, avoidance of transverse incisions greatly facilitates the ability to include the tissues at risk in radiation target volume without unduly large fields.

**Regional lymphadenectomy** Given the low, 2% to 3%, prevalence of lymph node metastasis in adult sarcomas, there is no role for routine regional lymphadenectomy. Patients with angiosarcoma, embryonal rhabdomyosarcoma, synovial sarcoma, and epithelioid histologies have an increased incidence of lymph node metastasis and should be carefully examined and radiographically imaged for lymphadenopathy. Clinically apparent lymphadenopathy should be treated with therapeutic lymphadenectomy. A recent analysis suggested that select patients undergoing lymphadenectomy, particularly in the absence of systemic metastases, may have a 5-year survival rate of 57%, far superior to the survival expected for patients with AJCC stage IV disease, as this is presently defined. As a result, the AJCC staging system (version 7) for sarcomas treats patients with lymph node metastasis as a different category from those patients with overt blood-borne metastases.

**Radiotherapy**
Radiation therapy is usually combined with surgical resection in managing soft-tissue sarcomas of the extremities. The decision of whether to use preoperative (neoadjuvant) or postoperative (adjuvant) irradiation remains somewhat controversial, but has been addressed in a phase III randomized trial.

**Preoperative irradiation** has a number of theoretic and practical advantages: (1) Smaller radiation portals can be utilized, as the scar, hematomas, and ecchymoses do not need to be covered. (2) Preoperative irradiation may produce tumor encapsulation, facilitating surgical resection from vital structures. (3) It is easier to spare a strip of skin and thereby reduce the risk of lymphedema. (4) The size of the tumor may be reduced, thus decreasing the extent of surgical resection. (5) Lower radiation doses can be utilized, as there are fewer relatively radioresistant hypoxic cells.
Preoperative irradiation also has several drawbacks, however. They include (1) the inability to precisely stage patients based on pathology due to downstaging and (2) increased problems with wound healing.

Studies of preoperative irradiation from the University of Florida, M. D. Anderson Cancer Center, and Massachusetts General Hospital demonstrated local tumor control rates of 90% using doses of approximately 50 Gy. Survival depended on the size and the grade of the primary tumor. Distant metastases were the primary pattern of failure.

Postoperative irradiation A number of retrospective reports, as well as a randomized trial from the NCI, have demonstrated that limb-sparing surgery plus postoperative irradiation produces local tumor control rates comparable to those achieved with amputation. Five-year local tumor control rates of 70% to 90%, survival rates of 70%, and limb-preservation rates of 85% can be expected.

Equivocal or positive histologic margins are associated with higher local recurrence rates, and, therefore, adjuvant external-beam irradiation should be considered in all patients with sarcoma of the extremities with positive or close microscopic margins in whom reexcision is impractical. Postoperative doses of 60 to 65 Gy should be used.

Interstitial therapy with iridium-192 is used at some institutions as a radiation boost to the tumor bed following adjuvant external-beam irradiation. At Memorial Sloan-Kettering Cancer Center, adjuvant brachytherapy is often used in place of external irradiation. In a randomized trial, the 5-year local tumor control rate was 82% in patients who received adjuvant brachytherapy, vs 69% in those treated with surgery alone. On subset analysis, the local tumor control rate was found to be 89%, vs 66% for those patients with high-grade lesions. This study and further studies have indicated that brachytherapy has no impact on local tumor control for low-grade lesions.

FIGURE 1A Kaplan-Meier plots for probability of local recurrence in the National Cancer Institute of Canada Clinical Trials Group phase III trial

FIGURE 1B Kaplan-Meier plots for probability of metastatic (regional and distant) recurrence in the National Cancer Institute of Canada Clinical Trials Group phase III trial.

FIGURE 1C Kaplan-Meier plots for probability of progression-free survival in the National Cancer Institute of Canada Clinical Trials Group phase III trial.
If an implant alone is used, the dose is 40 to 45 Gy to a volume that includes all margins; when a boost is combined with additional external-beam irradiation, a dose of 20 to 25 Gy is utilized. Some data suggest a higher rate of wound complications and a delay in healing when implants are afterloaded prior to the third postoperative day. Although some centers load implants sooner, this step must be performed with caution and strict attention to the incision site.

Over a 15-year period, 202 patients with high-grade sarcoma of the extremities underwent complete gross resection and adjuvant brachytherapy to a median dose of 45 Gy, delivered over 5 days. With a median follow-up of 61 months, the 5-year local tumor control, distant relapse-free survival, and overall survival rates were 84%, 63%, and 70%, respectively. These rates compared favorably with data on external-beam irradiation. Morbidity of brachytherapy was considered acceptable, with reoperation rates of 12%, bone fractures in 3%, and nerve damage in 5%.

Comparison of irradiation techniques Comparable local tumor control results (90%) are obtained with preoperative, postoperative, and interstitial techniques, although rates of wound complications are higher with preoperative techniques. Brachytherapy can offer a number of advantages. When brachytherapy is employed as the sole adjuvant, the entire treatment (surgery and irradiation) is completed in a 10- to 12-day period, compared with the 10 to 12 weeks required for typical external-beam irradiation (6 to 7 weeks) and surgery (4- to 6-week break before or after irradiation). Generally, smaller volumes can be irradiated with brachytherapy, which could improve functional results. However, smaller volumes may not be appropriate, depending on the tumor size, grade, and margin status.

The NCI of Canada Clinical Trials Group published 3-year median follow-up results of a randomized phase III trial comparing preoperative and postoperative radiotherapy for limb soft-tissue sarcoma (Figures 1A, 1B, 1C, 1D). Wound complications were observed in 31 of 88 patients (35%) in the preoperative group and 16 of 94 patients (17%) in the postoperative group (difference, 18% [95% CI: 5–30]; \( P = .01 \)). Tumor size and anatomic site were also significant risk factors in multivariate analysis. Local tumor control was identical in both arms of the trial. Five-year outcomes have been reported, and no difference in metastases, cause-specific survival, or overall survival was noted. Because preoperative radiotherapy is associated with a greater risk of wound complications than postoperative radiotherapy, but less late fibrosis and edema, the choice of regimen for patients with soft-tissue sarcoma should take into account the timing of surgery and radiotherapy and the size and anatomic site of the tumor.

Regardless of the technique employed, local control is a highly achievable and worthwhile endpoint, as demonstrated in a study of 911 patients treated by various techniques at Memorial Sloan-Kettering Cancer Center. Of the 116 patients who developed local recurrence, 38 patients subsequently developed metastases and 34 patients died. Metastases after local recurrence were predicted in patients with high-grade or large (> 5 cm) tumors.

Treatment recommendations Adjuvant radiotherapy should be employed for virtually all high-grade sarcomas of the extremities and larger (5 cm) low-grade lesions. If small (T1) lesions can be resected with clear margins, radiotherapy can be omitted. Postoperative therapy with either external-beam
irradiation (with or without an interstitial implant boost) or an implant alone will achieve a high likelihood of local tumor control and, therefore, limb preservation. Preoperative irradiation, although equally efficacious, does carry a higher wound complication rate than the postoperative approach.

**Primary radiation therapy**

Several studies on radiation therapy alone in the treatment of unresectable or medically inoperable soft-tissue sarcomas have reported 5-year survival rates of 25% to 40% and local tumor control rates of 30%. Local tumor control depends largely on the size of the primary tumor. Radiation doses should be at least 65 to 70 Gy, if delivery of such doses is feasible. The tumor's location may be particularly important in determining this dose because of the potential for damage to critical structures (eg, the spinal cord) with the higher doses normally used.

**Radiation therapy in retroperitoneal sarcomas**

Only 50% of patients with retroperitoneal sarcomas are able to undergo complete surgical resection. Of patients undergoing complete resection, one-half develop local recurrence. This significant local failure rate suggests a potentially important role for adjuvant treatment in all patients with retroperitoneal sarcomas. However, the role of radiation therapy for retroperitoneal sarcomas remains controversial due to the rarity of the tumor, the paucity of data, the retrospective nature of available studies, the low doses of radiation used in many studies, and the lack of consistent policies in determining the indications for radiation therapy.

**Preoperative irradiation**

The advantages of preoperative radiotherapy have already been discussed for soft-tissue sarcomas of the extremities. In the retroperitoneum, an additional advantage is that bowel is frequently displaced significantly by the tumor. In contrast to the postoperative setting, the bowel being treated is also unlikely to be tethered by adhesions from prior surgery. These features significantly offset acute toxicity of large-field intra-abdominal radiotherapy (eg, nausea, vomiting, and

**Intraoperative irradiation**

In a prospective trial from the NCI, 35 patients with completely resected retroperitoneal sarcomas were randomized to receive either intraoperative electron-beam irradiation (IORT) followed by low-dose (30 to 40 Gy) postoperative external-beam irradiation or high-dose postoperative external-beam irradiation (35 to 40 Gy plus a 20-Gy boost). Absolute local recurrence rates were significantly lower in the IORT group ($P < .05$), but disease-specific and overall survival rates did not differ between the two groups.

Similarly, a nonrandomized series from the Massachusetts General Hospital has suggested improved local tumor control with IORT for patients with retroperitoneal sarcoma. In 16 patients who underwent irradiation, complete gross resection, and IORT, overall survival and local tumor control rates were 74% and 83%, respectively. These numbers diminished to 30% and 61%, respectively, in the 13 patients treated with irradiation and complete gross resection without IORT. Although these local tumor control results are encouraging, IORT remains investigational and cannot be advocated on a routine basis at this time.

**Postoperative irradiation**

Two-year local tumor control rates of 70% have been reported with the addition of postoperative irradiation. However, irradiation of the retroperitoneum/abdomen in doses that have effected local tumor control in soft-tissue sarcoma of the extremities (50 to 65 Gy) is usually associated with significant GI toxicity. Obviously, the incidence of GI toxicity depends on the exact fields and technique used. However, as most retroperitoneal sarcomas are > 10 to 15 cm, the radiation
fields employed are generally also quite large, and bowel is often located and/or tethered in the high-risk area. Three-dimensional treatment planning and conformal techniques can now be utilized to maximize the radiation dose to the tumor bed while minimizing the dose to the surrounding normal tissues.

**Isolated limb perfusion**
Recent studies have evaluated the role of isolated limb perfusion (ILP) in the management of sarcomas of the extremities. These studies have generally been extrapolations from protocols initially designed to treat locally advanced melanoma.

The agents most commonly employed for ILP have been melphalan and tumor necrosis factor-alpha (TNF-), with or without interferon-gamma (IFN--1b [Actimmune]). The results of the largest series of ILP in patients with locally advanced soft-tissue sarcoma of the extremities were reported by Eggermont and colleagues. TNF- has now been approved in Europe for ILP in patients with locally advanced, grade 2/3 soft-tissue sarcomas of the extremities.

The Netherlands Cancer Institute published its results in patients with unresectable soft-tissue sarcoma of the extremities who were perfused with melphalan and TNF-. A total of 49 patients were treated and followed for a median of 26 months. One patient died shortly after perfusion, but 31 patients (63%) were able to undergo resection of the tumor. Based on clinical and pathologic grounds, an overall response was seen in 31 patients (63%), and a complete response was seen in 4 patients (8%). A total of 28 patients (57%) had local tumor control with limb preservation. Toxicity was frequent but usually mild.

**Role of adjuvant chemotherapy**

The striking success of combined-modality therapy in children with osteogenic sarcoma, rhabdomyosarcoma, and the Ewing sarcoma family of tumors has provided the stimulus for the use of aggressive combined-modality approaches in adults. The literature is replete with reports of the apparent benefit of combined-modality therapy in patients with resectable soft-tissue sarcoma. Yet most series are either retrospective or small nonrandomized trials.

**Preoperative chemotherapy**
Preoperative chemotherapy has been adopted at many centers for patients with large high-grade sarcoma. The specific regimens employed have evolved over the years but generally contain both an anthracycline and ifosfamide.

Aside from theoretic considerations, there are several pragmatic reasons to favor preoperative over postoperative treatment. First, a reduction in the size of a large lesion may permit surgical resection with less morbidity. Second, compliance may be better with preoperative therapy. One observation that supports the neoadjuvant approach is that response to preoperative chemotherapy, whether pathologic or radiographic, predicts improved tumor control and survival.

Neoadjuvant chemotherapy has been explored in a prospective randomized trial initiated by the EORTC. The trial was open to patients who had a sarcoma measuring at least 8 cm (of any grade), a primary or recurrent intermediate- to high-grade (grade 2/3) sarcoma of any size, or a locally
recurrent or inadequately excised grade 2/3 sarcoma. In spite of these broad eligibility criteria, accrual was slow, and the trial was closed after only 150 patients entered.

Patients were randomized to receive either immediate surgery, followed by radiation therapy for close or positive margins, or 3 cycles of chemotherapy with doxorubicin (50 mg/m² by IV bolus) plus ifosfamide (5 g/m² by 24-hour continuous infusion) with mesna (Mesnex). Among the 134 eligible patients, over 80% had primary tumors of the extremities, but only 4% had grade 2/3 lesions > 8 cm. Among 49 patients evaluable for response, 29% had major objective responses, including four complete responses. Only 18% had progression of disease before surgery. Chemotherapy was generally well tolerated and never prevented surgery. With a median follow-up of 7.3 years, the estimated 5-year survival rate was similar for both groups.

Trials have explored the role of neoadjuvant chemotherapy and radiation therapy to decrease the rate of distant failure and possibly impact survival. A study reported from Massachusetts General Hospital enrolled patients with high-grade soft-tissue sarcomas (8 cm or larger). Patients were treated with 3 cycles of preoperative chemotherapy consisting of MAID (mesna, doxorubicin [Adriamycin], ifosfamide, dacarbazine) interdigitated with 44 Gy of radiation therapy. This regimen was followed by surgical resection and 3 cycles of postoperative MAID chemotherapy. In cases with positive surgical margins, an additional 16 Gy of radiation therapy was delivered.

This regimen resulted in a significant improvement in 5-year freedom from distant metastasis (75% vs 44%; \( P = .0016 \)) when compared with historic control patients. Additionally, 5-year disease-free and overall survival rates were 70% vs 42% \( P = .0002 \) and 87% vs 58% \( P = .0003 \) for the MAID and control groups, respectively. There was a 29% rate of wound healing complications in the MAID group.

These data have been extended in a follow-up study of similar interdigitated 8 cm in diameter received a modified MAID regimen plus granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) and radiation therapy, followed by resection and postoperative chemotherapy. Preoperative radiotherapy and chemotherapy were successfully completed by 89% and 79% of patients, respectively. Grade 4 hematologic and nonhematologic toxicities affected 80% and 23% of patients, respectively. Two patients developed acute myelogenous leukemia (AML) following therapy. Delayed wound healing was noted in 31%. The estimated 3-year survival, disease-free survival, and local tumor control rates were 75%, 55%, and 79%, respectively.

The M. D. Anderson Cancer Center conducted a phase I trial to define the maximum tolerated dose of continuous infusion doxorubicin administered with preoperative radiation therapy to a dose of 50 Gy. In total, 27 patients with intermediate- or high-grade sarcomas were enrolled in the trial. The maximum tolerated dose of doxorubicin was 17.5 mg/m²/week. Twenty-six patients underwent surgery, and all had a macroscopic complete resection (R0 or R1). Two patients had a pathologic complete response. These studies suggest that further investigation of a preoperative approach combining chemotherapy and radiation therapy is warranted. The lack of randomized data regarding the addition of chemotherapy to radiation therapy for extremity sarcomas limits the ability to apply these treatment regimens outside the setting of a study.

**Postoperative chemotherapy**

A number of published trials have compared postoperative chemotherapy with observation alone in adults who had undergone resection of a primary or recurrent soft-tissue sarcoma. Most of these trials included fewer than 100 patients, and even the largest trial had inadequate statistical power to detect a 15% difference in survival. Other flaws confound the interpretation of many of the studies. Some trials included low-risk patients with small and/or low-grade sarcomas. In some trials, patient...
In five of the six trials in which doxorubicin monotherapy was studied, including one study limited to patients with uterine sarcoma, a significant improvement in survival could not be demonstrated. Among the trials of combination chemotherapy, most used the combination known as CyVADIC (cyclophosphamide, vincristine, doxorubicin [Adriamycin], dacarbazine). A significant survival advantage was seen in only one combination chemotherapy trial.

Nonetheless, some of the trials showed a trend or a statistically significant improvement in disease-free survival among patients who were administered adjuvant chemotherapy, especially among those with high-grade sarcomas of the extremities. Analyses of the pooled results of the published literature are consistent with this observation.

**Ifosfamide-containing trials** Only one trial included in a meta-analysis by SMAC used an ifosfamide-containing regimen; that trial involved only 29 patients. An attempt to conduct a large prospective trial of postoperative chemotherapy with the MAID regimen in the United States failed because of insufficient patient accrual.

An Italian cooperative group conducted a trial in which patients 18 to 65 years old with high-grade (> 5 cm) or any recurrent sarcoma of the extremities were randomized to receive postoperative chemotherapy or observation alone. The treatment consisted of 5 cycles of epirubicin, 60 mg/m² on days 1 and 2, plus ifosfamide, 1.8 g/m² on days 1 to 5. G-CSF was used to support the granulocyte counts during therapy.

The trial had been planned for 200 patients but was interrupted after accrual of 104 patients, when an interim analysis showed a significant survival advantage for the chemotherapy-treated group. At 36 months after the last randomization, with a median follow-up of 59 months, median overall survival among the patients who received adjuvant chemotherapy was 75 months, vs 46 months for control patients ($P = .03$). In a longer-term follow-up analysis, survival was not improved on an intention-to-treat analysis, although 5-year overall survival rates still favored the patients receiving chemotherapy.

An analysis of adjuvant chemotherapy using doxorubicin and ifosfamide was conducted by the EORTC. This study examined surgery and adjuvant radiation therapy vs the same local therapy and adjuvant chemotherapy with 5 cycles of doxorubicin (75 mg/m²) and ifosfamide (5 g/m²) every 21 days. The data indicated no benefit in overall survival for the chemotherapy arm and tempered some of the enthusiasm regarding adjuvant chemotherapy as demonstrated in a positive Italian study of epirubicin and ifosfamide.

Since the time of the original Italian study, two other randomized studies have been performed. They do not indicate a benefit for chemotherapy but were underpowered to detect small differences in outcome.

**SMAC and newer meta-analyses** A formal meta-analysis of individual data from 1,568 patients who participated in randomized trials of postoperative adjuvant chemotherapy vs no chemotherapy control patients was performed by the SMAC and published in 1997. Although not all data were available for all patients, the analysis demonstrated a significant reduction in the risk of local or distant recurrence in patients who received adjuvant chemotherapy.

The overall hazard ratio (HR) for distant relapse-free survival was 0.70; ie, the risk of distant relapse (metastasis) was reduced by 30% in treated patients. The absolute benefit at 10 years was 10%, so the recurrence-free survival rate at 10 years was improved from 60% to 70%. Also, the HR for local recurrence-free survival was 0.73 (27% reduction in the risk of local recurrence), and the absolute benefit was 6%.
The HR for overall survival, however, was 0.89, which did not meet the criteria for statistical significance. The observed survival at 10 years was 54% for patients who received chemotherapy and 50% for those who did not. Subset analysis failed to show that the effects of chemotherapy differed by primary site, although the best evidence for an effect of adjuvant chemotherapy was seen in patients with sarcoma of the extremities.

A newer meta-analysis, including more ifosfamide-based studies, although excluding the large randomized EORTC 62931 study, confirms the trend seen in the SMAC meta-analysis, with a modest overall survival benefit of chemotherapy in the adjuvant setting. In this updated meta-analysis, 18 trials, representing 1,953 patients, were $P = .02$. In terms of overall survival, use of doxorubicin-based therapy without ifosfamide had an OR of 0.84, which was not statistically significant ($P = .09$). However, the OR for doxorubicin/ifosfamide-based therapy was 0.56 ($P = .01$) in favor of chemotherapy. The updated meta-analysis confirmed the SMAC meta-analysis in that there was modest efficacy of adjuvant chemotherapy for resected soft-tissue sarcoma with respect to local recurrence, distant recurrence, overall recurrence, and overall survival. The authors concluded that benefits were further improved with the addition of ifosfamide to doxorubicin-based regimens but must be weighed against the toxicity of the addition of ifosfamide.

Analyses of other collected prospective data regarding adjuvant chemotherapy from large referral centers have yielded conflicting data. In two analyses of patients with synovial sarcoma and one involving myxoid/round cell liposarcoma, chemotherapy appeared to improve overall survival. In a large analysis of two prospective databases, patients receiving chemotherapy initially had superior survival but then suffered inferior survival compared with those who received no adjuvant chemotherapy. Notably, patients were not randomized as part of their treatment. Given the fact that this was a registry instead of a randomized study, there was by definition a bias to treat patients who had higher-risk tumors with chemotherapy, although this did not appear to correlate with a specific single variable in the analysis. The data from the most recent meta-analysis appear to be consistent with data from prior studies when taken as a whole. If there is a benefit in terms of overall survival with the use of adjuvant chemotherapy, it is a small one, and the risks and benefits should be discussed with patients on an individual basis.

**Treatment recommendations**

- Multidisciplinary treatment planning should precede the initiation of any therapy. An experienced multidisciplinary team should evaluate pathologic material and imaging studies and coordinate the integration of surgical resection, irradiation, and systemic therapy.

- Ideally, patients should be offered participation in clinical trials. Unfortunately, there are no active trials in the United States that will definitively answer the most important questions. Thus, a decision to treat must be made on an individual basis.

- Preoperative chemotherapy should be considered for fit, high-risk patients after a discussion of the risks and potential benefits. Older patients, especially those with cardiac or renal disease, are not optimal candidates for such treatment.

- Patients who do not receive preoperative chemotherapy may still be offered postoperative treatment. Adjuvant anthracycline/ifosfamide combinations improves relapse-free survival in selected patients and can be considered for the treatment of those with tumor size > 5 cm, deep.
tumor location, and high histologic grade. Overall survival was superior in the most recent meta-analysis for patients receiving doxorubicin-ifosfamide based therapy, and this should be the standard combination to consider if adjuvant therapy is to be administered.

• For patients who opt for preoperative or postoperative chemotherapy, a regimen that includes doxorubicin (60 to 75 mg/m²) or epirubicin ²) plus ifosfamide (9 to 10 g/m²), given for a total of four to six cycles, is a reasonable choice for patients younger than age 60.

• Outside the context of a clinical trial, it is difficult to recommend concurrent doxorubicin and radiation therapy, or closely spaced doxorubicin-based chemotherapy with radiation therapy, owing to the observed risk of second malignancies such as AML in clinical trials to date.

treatment of local recurrence

Despite optimal multimodality therapy, local recurrence develops in 10% to 50% of patients, with a median local recurrence-free interval of ~24 months. Local recurrence rates are a function of the primary site and are highest for patients with retroperitoneal and head and neck sarcomas, for which adequate surgical margins are difficult to attain. In addition, high-dose adjuvant irradiation of these sites is often limited by the relative radiosensitivity of surrounding structures. These factors result in local recurrence rates of 40% for retroperitoneal sarcomas and up to 50% for head and neck sarcomas, which are substantially higher than the 10% proximity typically seen for extremity sarcomas.

A large retrospective analysis of patients with high-grade sarcoma of the extremities was reported from UCLA. Local recurrence required amputation in 38% of cases and was associated with a threefold decrement in survival. This finding accentuates the necessity for adequate local therapy for sarcomas presenting primarily as well as for multidisciplinary management of local recurrence.

Reoperation Following staging evaluation, patients with isolated local recurrence should undergo reoperation. The results of reoperation in this setting are good, with two-thirds of patients experiencing long-term survival.

Adjuvant radiation therapy If no prior radiation therapy had been employed, adjuvant irradiation (50 to 65 Gy) should be used before or after surgery for locally recurrent disease. Radiation therapy (external-beam irradiation or brachytherapy) should be considered in patients for whom previous radiation doses were subtherapeutic or the previous radiation field design permitted additional treatment.

Reports from Memorial Sloan-Kettering Cancer Center, M. D. Anderson Cancer Center, and Princess Margaret Hospital suggest that patients who develop local recurrence following previous full-dose irradiation represent a difficult local tumor control challenge. A report from Memorial Sloan-Kettering Cancer Center suggests that limb-sparing surgery combined with adjuvant brachytherapy may produce excellent local tumor control and function in this group.

ILP Ongoing clinical investigations are defining the role of ILP in the management of patients with locally recurrent sarcoma. ILP is approved in Europe for treatment of otherwise unresectable extremity sarcomas.

treatment of Limited Pulmonary Metastasis
Thoracotomy and metastasectomy  The most common site of metastatic disease involvement of soft-tissue sarcoma is the lungs. Rates of 3-year survival following thoracotomy for pulmonary metastasectomy range from 23% to 42%. This fact, combined with the limited efficacy of systemic therapy, is the basis for the recommendation that patients with limited pulmonary metastases and no extrapulmonary disease should undergo thoracotomy and metastasectomy.

Appropriate patient selection for this aggressive therapeutic approach to metastatic disease is essential. The following are generally agreed upon criteria: (1) the primary tumor is controlled or controllable; (2) there is no extrathoracic metastatic disease; (3) the patient is a medical candidate for thoracotomy; and (4) complete resection of all disease appears to be possible.

Preresection chemotherapy  Chemotherapy is sometimes recommended before resection of pulmonary metastases. Although occasional patients may have tumor shrinkage to a degree that an unresectable tumor becomes resectable, there are no convincing data that chemotherapy impacts favorably on patient survival. It is also worth remarking that there are no randomized data on which to base this judgment.

Chemotherapy for Unresectable locally advanced or metastatic disease

Single agents
Doxorubicin Early trials of doxorubicin reported major responses in approximately 30% of patients with advanced soft-tissue sarcoma. In more recent randomized series, however, the rate of response has been closer to 17%.

Subset analysis of patients with soft-tissue sarcoma from a broad phase II trial in which patients were randomized to receive various doses of doxorubicin demonstrated a steep dose-response relationship; patients treated with doses below 60 mg/m² rarely responded. Whether dose intensification of doxorubicin is associated with improved survival remains an open question (see section on "Intensifying chemotherapy").

Pegylated liposomal doxorubicin (Doxil in the United States, Caelyx in Europe) has demonstrated limited activity in phase II trials, especially in patients whose disease is refractory to standard doxorubicin. In a randomized comparison among 95 previously untreated patients, however, the response rates to pegylated liposomal doxorubicin (50 mg/m² every 4 weeks; 10%) and to standard doxorubicin (75 mg/m² every 3 weeks; 9%) were similar, with no significant difference in time to disease progression or survival. Response rates improved to 14% and 12%, respectively, when GIST cases were excluded.

Ifosfamide  In a randomized phase II trial conducted by EORTC, 18% of patients treated with ifosfamide (5 g/m²) experienced major responses, in contrast to 12% of patients treated with cyclophosphamide (1.5 g/m²), despite the greater myelosuppression with the latter agent. In a large American phase II trial, 17 of 99 patients with soft-tissue sarcoma responded to ifosfamide (8 g/m²). All of the patients had been treated previously with doxorubicin-based therapy, suggesting a degree of non–cross-resistance.
Increasing ifosfamide dose Responses to ifosfamide (12 g/m²) have been observed in patients whose disease progressed while receiving lower doses, supporting the concept of a dose-response relationship.

In a randomized trial, the response to 9 g/m² of ifosfamide (17.5%) was superior to the 3% response observed among patients treated with 5 g/m². The reason for the low response to the lower dose was unclear. In a subsequent trial by the same investigators, the response to 12 g/m² was only 14%, however.

Among 45 evaluable patients enrolled in a Spanish phase II trial of ifosfamide (given by continuous infusion over 6 days), the response rate was 38%, but 47% of patients developed febrile neutropenia and 32%, grade 3 neurotoxicity.

At M. D. Anderson Cancer Center, ifosfamide (14 g/m² given by continuous infusion over 3 days) yielded responses in 29% of 37 patients with soft-tissue sarcoma and 40% of patients with bone sarcoma. Also within that report was a small cohort of patients in whom the response to the same total dose of ifosfamide was higher when the drug was given by an intermittent bolus rather than a continuous infusion; this finding led the authors to suggest that bolus therapy is more efficacious than continuous infusion. Pharmacokinetic studies, however, have shown no difference between a 1-hour infusion and bolus injection of ifosfamide with respect to the area under the concentration-time curve (AUC) for serum ifosfamide or its metabolites or the levels of ifosfamide metabolites in urine.

In an EORTC phase II trial, ifosfamide (12 g/m² given as a 3-day continuous infusion every 4 weeks) yielded a response rate of 17% among 89 chemotherapy-naive patients and 16% among 25 previously treated patients.

Ifosfamide doses as high as 14 to 20 g/m² have been given with hematopoietic growth factor support; reported response rates are high, but neurologic and renal toxicities often are dose-limiting. The available data suggest that synovial sarcoma is particularly sensitive to ifosfamide.

Dacarbazine The activity of dacarbazine in soft-tissue sarcoma has been recognized since the 1970s and was confirmed in a formal phase II trial. This marginally active agent has been used mostly in doxorubicin-based combinations. In particular, patients with leiomyosarcoma respond better to dacarbazine than do patients with other sarcoma subtypes.

Ecteinascidin (ET-743, trabectedin), a novel compound derived from a marine organism, has demonstrated promising activity as well. In phase I trials, trabectedin demonstrated activity in heavily pretreated patients with advanced sarcoma. Three phase II trials of trabectedin (1,500 mg/m² over 24 hours every 3 weeks) in refractory non-GIST soft-tissue sarcoma have been reported.

In one trial, two partial responses and four minor responses were seen among 52 patients; 9 additional patients had stable disease for at least 6 months. Twenty-four percent of patients were free of disease progression at 6 months. The median survival was 12.8 months, with 30% of patients alive at 2 years.

In a second trial, responses were observed in 3 of 36 patients, with one complete response and two partial responses, for an overall response rate of 8% (95% CI: 2–23). Responses, however, were durable, lasting up to 20 months.
TABLE 4: Chemotherapy regimens for soft-tissue sarcoma

Finally, a phase II study of patients treated in first line with the 24-hour infusion schedule of trabectedin demonstrated a 17% response rate. These data confirm that trabectedin is an active compound in the treatment of soft-tissue sarcomas, with a response rate similar to the 10% to 30% range seen for either doxorubicin or ifosfamide. The predominant toxicities were neutropenia and elevation of transaminase levels. Two phase II trials of trabectedin in patients with GIST showed no therapeutic activity. Trabectedin was approved for use in chemotherapy-refractory sarcomas in Europe in 2007.

Other agents Gemcitabine (Gemzar) has demonstrated modest activity in several phase II trials, although results of a recent SWOG trial were disappointing. Taxanes, vinca alkaloids, and platinum compounds have demonstrated only marginal activity, however. It should be noted that the taxanes, gemcitabine, and vinorelbine (Navelbine) have been observed to be active in angiosarcoma, especially involving the scalp and face.

Combination chemotherapy
Combination chemotherapy regimens have been used widely in the management of patients with soft-tissue sarcoma (Table 4). High response rates have been reported in a number of single-arm phase II trials. Most combination regimens include an anthracycline (either doxorubicin or epirubicin) plus an alkylating agent, dacarbazine, or both agents. Overall response rates are higher in these single-arm trials than when the same regimens are tested in larger, randomized studies.

CyVADIC and doxorubicin/dacarbazine regimens Combinations of doxorubicin with other agents have not proved to be superior to doxorubicin alone in terms of overall survival. Also, for over a decade, the CyVADIC regimen was widely accepted as the standard of care. In a prospective, randomized trial, however, CyVADIC did not prove to be superior to doxorubicin alone.

Doxorubicin (or epirubicin) plus ifosfamide Combinations of doxorubicin (or epirubicin) plus ifosfamide have consistently yielded responses in over 25% of patients in single-arm trials. In sequential trials conducted by the EORTC, doxorubicin at 75 mg/m² plus ifosfamide (5 g/m²) was superior to doxorubicin at 50 mg/m² plus ifosfamide (5 g/m²). A prospective randomized EORTC trial with 314 patients compared the two regimens. There was no difference in response rate or overall survival, but disease progression-free survival favored the more intensive regimen.

The strategy of intensifying the dosing of ifosfamide within the context of combination chemotherapy was explored in a randomized phase II trial. This study included both patients with localized disease treated with four cycles of preoperative chemotherapy as well as patients with metastatic disease.
Overall, there was no survival benefit for patients treated with doxorubicin (60 mg/m²) plus 12 g/m² of ifosfamide over those treated with doxorubicin (60 mg/m²) plus 2 g of ifosfamide. Also, there was no advantage to the patients with localized disease in terms of disease-free survival.

**MAID regimen** The MAID regimen yielded an overall response rate of 47% in patients in a large phase II trial. In a randomized comparison of AD (Adriamycin [doxorubicin]/dacarbazine) vs MAID regimens, the response to MAID was 32%, vs 17% with the two-drug regimen \( (P < .002) \). However, the price paid for the higher response was toxicity; of eight toxic deaths reported in this trial, seven occurred among the 170 patients treated with MAID. All treatment-related deaths occurred in patients > 50 years old. During the study, the doses of MAID were reduced to lessen toxicity. The median survival did not differ significantly between the two regimens, although a trend favoring the AD regimen was noted.

**Combination chemotherapy vs single-agent doxorubicin** Combination chemotherapy has been compared with single-agent doxorubicin in eight randomized phase III trials. Two trials were limited to patients with uterine sarcoma. Some of these studies showed superior response rates with combination chemotherapy, but none of the trials found a significant survival advantage. Kaplan-Meier plots of survival are virtually superimposable within each trial and from trial to trial. A meta-analysis confirmed the higher response rate when ifosfamide is added to other agents and showed no benefit at 1 year of combination therapy over single agents, likely due to the lack of synergy between anthracyclines and ifosfamide. Patients can achieve equal benefit by sequential use of such agents rather than by combinations.

It should be emphasized that approximately 20% to 25% of patients entered into such trials are alive 2 years after therapy was initiated. Complete responses are uncommon and do not appear to translate into prolonged survival.

**Gemcitabine plus docetaxel** In a phase II study of 34 patients with unresectable leiomyosarcoma, mostly uterine in origin, 53% responded to a combination of gemcitabine (given by 90-minute infusion) plus docetaxel (Taxotere), with G-CSF support. An additional 20% had stable disease. Almost half of the patients had disease progression after anthracycline-based therapy. The median time to disease progression was 5.6 months, and grade 3/4 toxicity was uncommon. The activity of the gemcitabine-docetaxel combination was confirmed in a variety of other sarcoma subtypes in another study, which also confirmed the rationale for the sequence used in the study in vitro.

A prospective, randomized trial comparing gemcitabine-docetaxel with gemcitabine alone in a spectrum of histologic types of sarcoma has been completed. The response rates were 8% for gemcitabine alone and 16% for gemcitabine-docetaxel. Time to disease progression and overall survival were superior with gemcitabine-docetaxel (17.9 months vs 11 months). Although this is one of the few studies in metastatic sarcoma to show a survival advantage, enthusiasm is tempered by toxicity, causing treatment discontinuation in up to 50% of patients after 6 months of gemcitabine-docetaxel chemotherapy. These data suggest that a dose reduction is needed in the off-study use of the therapy.

In the authors' experience, weekly administration of lower doses of each agent is more tolerable than the large day-8 dose of docetaxel and remains an active regimen. The randomized study previously noted that the response rate was higher in patients with high-grade undifferentiated pleomorphic sarcoma (UPS, formerly termed MFH [malignant fibrous histiocytoma]) than in patients with leiomyosarcoma.

**Gemcitabine plus vinorelbine** These agents given together were also active in one phase II study. It is not clear whether either vinorelbine or docetaxel is synergistic for all histologies tested or synergy is only observed for specific subtypes.
Kinase-targeted agents in non-GIST sarcomas Several of the commercially available tyrosine kinase inhibitors have been examined for activity in the setting of metastatic disease. In general, response rates have been low, and use of the agents is not recommended outside a clinical trial.

Exceptions to this statement may include a 15% response rate of patients with synovial sarcoma to pazopanib (Votrient), a 14% response rate of patients with angiosarcoma to sorafenib (Nexavar) (particularly those induced by therapeutic radiation) and similar activity of bevacizumab (Avastin) in angiosarcomas, and reports of the utility of imatinib in patients with the rare sarcoma subtype dermatofibrosarcoma protuberans. There appears to be at least modest activity of sunitinib (Sutent) in alveolar soft part sarcoma, clear cell sarcoma, and solitary fibrous tumor/hemangiopericytoma, and of cediranib (Recentin) in patients with metastatic alveolar soft-part sarcoma.

Intensifying chemotherapy Hematopoietic growth factors have facilitated the evaluation of dose-intensive chemotherapy in patients with sarcoma. The nonhematologic toxicities (cardiac, neurologic, and renal) of the agents most active in soft-tissue sarcoma prevent dramatic dose escalation.

Phase I/II trials of dose-intense anthracycline/ifosfamide regimens with hematopoietic growth factor support have shown that doxorubicin (70 to 90 mg/m²) can be used in combination with ifosfamide (10 to 12 g/m²) in selected patients. Response rates as high as 69% have been reported. Although toxicity increases, often dramatically, with these relatively modest dose escalations, the clinical benefit in terms of survival or palliation in patients with metastatic disease remains uncertain.

No randomized trial has demonstrated a survival advantage for patients treated with these more aggressive regimens. In one randomized trial, however, the FFCCSG demonstrated that, in comparison with standard doses, a 25% escalation in doses of MAID with G-CSF support did not improve outcome.

High-dose therapy with autologous stem-cell transplantation Most trials are small and presumably involve highly selected patients. In one trial involving 30 patients with metastatic or locally advanced sarcoma accrued over 6 years, more than 20% were free of disease progression at 5 years after high-dose therapy with stem-cell rescue. Complete response to standard induction chemotherapy predicted superior 5-year survival. Based on these favorable results, the investigators suggested a prospective randomized trial examining this approach. Although some groups are still exploring this approach, the appropriateness of generalizing these results to most patients with soft-tissue sarcoma remains speculative.

Prognostic factors for response to therapy Over the past 20 years, the EORTC has collected data on more than 2,000 patients with metastatic disease who participated in first-line anthracycline-based chemotherapy trials. Multivariate analysis of these data indicated that the patients most likely to respond to chemotherapy are those without liver metastases ($P < .0001$), younger patients, individuals with high histologic grade, and those with liposarcoma. In this Cox model, the factors associated with superior survival were good performance status, absence of liver metastases, low histologic grade, a long time to metastasis after treatment of the primary tumor, and young age.

More recently, these same investigators have reported that the observed response rate is superior in patients who have pulmonary metastases only, as compared with those who have metastases to the lungs and other sites or to other sites only. These findings highlight the danger of reaching broad conclusions based on extrapolations from small trials that include highly selected patients. The EORTC data are also consistent with the observation that patients with metastatic GI sarcoma rarely respond to standard chemotherapy regimens. This increasingly recognized observation has been used to explain the low response rates seen in some trials.
Targeted therapy for GISTs

Advances in our understanding of the biology of GIST, and the availability of an effective therapy for patients with advanced disease, have resulted in intense interest in this entity and rapid expansion of diagnosis of this disease. Because this entity had not been recognized, the incidence of GIST was underappreciated. GIST is the most common nonepithelial tumor of the GI tract, with an estimated annual incidence of 3,000 to 3,500 cases in the United States. Approximately 50% to 60% of GISTs arise in the stomach, and 25% in the small bowel. Other sites include the rest of the GI tract, the omentum, mesentery, and retroperitoneum. These tumors may range in size from millimeters to huge masses. It is not clear how many of these GISTs become clinically relevant and how many are noted anecdotally at the time of endoscopic ultrasonography or other abdominal procedures.

The demonstration of the efficacy of imatinib in GIST has been among the most dramatic and exciting observations in solid-tumor oncology. A randomized multicenter trial evaluated two doses of oral imatinib (400 vs 600 mg) in 147 patients with advanced GISTs. With a median follow-up of 288 days, 54% had a partial response, and 28% had stable disease, but there were no complete responses. Response was sustained, with a median duration exceeding 6 months. Most patients had mild grade 1 or 2 toxicity, but only 21% had severe grade 3 or 4 toxicity. GI or intra-abdominal hemorrhage occurred in 5% of patients. There was no difference in response or toxicity between the two doses.

These observations were expanded in two parallel, multi-institution trials in which patients with GISTs were randomized to receive imatinib (400 or 800 mg daily). The results were remarkably similar. In the American trial, among 746 registered patients, the overall response rate was 43% for patients treated with 400 mg and 41% for those treated with 800 mg. There were no differences in survival between the two arms. At 2 years, progression-free and overall survival rates in the 400-mg arm were 50% and 78%, respectively. In the 800-mg arm, the rate of progression-free survival at 2 years was 53%, and the rate of overall survival was 73%.

In a large European trial, 946 patients were randomized to receive imatinib (400 mg daily or twice a day). Among the 615 patients whose response could be evaluated, there was no difference in response frequency (43%) or survival between the two arms. Complete responses were seen in 3% and 2% of the lower-dose and higher-dose patients, respectively. Sixty-nine percent of patients whose disease was progressing on 400 mg of imatinib were allowed to cross over to the higher dose (800 mg). Further therapeutic activity was seen, with 26% of these patients free of disease progression at 1 year.

Based on these results, the EORTC, in conjunction with the ISG and the AGG, has reported its results to further identify factors predicting early and late resistance to imatinib in patients with GIST. Initial resistance was defined as disease progression within 3 months of randomization, and late resistance was disease progression beyond 3 months. Initial resistance was noted in 116 of 934 patients (12%). Low hemoglobin level, high granulocyte count, and the presence of lung and the absence of liver metastases were independent predictors of initial resistance. Late resistance occurred in 347 of 818 patients. Independent predictors were high baseline granulocyte count, primary tumor outside the stomach, large tumor size, and low initial imatinib dose. The impact of the dose on late resistance was significant in patients with high baseline granulocyte counts and in patients with GI tumors originating outside the stomach and small intestine.

Among a group of 127 patients with advanced GISTs, activating mutations of KIT or PDGFRA were identified in 87.4% and 3.9% of patients, respectively. In patients harboring an exon 11 mutation of KIT, the partial remission rate was 83.5%, whereas in patients without a discernible mutation in KIT or PDGFRA, the partial remission rate was 9.1%. The presence of an exon 11 mutation in KIT correlated with clinical response, decreased risk of treatment failure, and improved overall survival.
The National Comprehensive Cancer Network (NCCN) has established a GIST Task Force to develop guidelines for the evaluation and treatment of patients with GIST. This group recommended 400 mg daily as the initial starting dose of imatinib. Dose escalation should be considered in patients who do not respond initially or who demonstrate unequivocal disease progression. Surgery remains the primary modality for treatment of primary GIST, but adjuvant and neoadjuvant trials are ongoing. The efficacy, dose, and duration of imatinib therapy in these settings have not been established, so participation of patients in such trials should be encouraged.

Recent data indicate that sunitinib is an active agent in imatinib-refractory GIST. In both phase I/II and III studies, the response rate is on the order of 10%, with a greater than 60% chance of these patients remaining on treatment for 6 months or longer. Notably, the patients that showed the most benefit were those with the converse KIT genetic phenotype (exon 9 mutation or wild type KIT) to those who were sensitive to imatinib (exon 11 mutation). Nonetheless, imatinib remains the first line of therapy regardless of mutation type, because there is still a response rate seen for imatinib in patients with wild-type or exon 9 KIT mutations and because imatinib is less toxic than sunitinib in its present schedule (4 weeks on at 50 mg oral daily, 2 weeks off). Some studies are examining new schedules of sunitinib (eg, 37.5 mg oral daily continuously), whereas other studies are evaluating the benefit of other small-molecule inhibitors of KIT. Newer tyrosine kinase inhibitors such as sorafenib may have some activity in the imatinib- and sunitinib-refractory settings. A phase III study of Hsp90 (heat shock protein 90) inhibitor vs placebo for kinase inhibitor-resistant GIST was closed due to deaths observed on study.

The FSG has initiated a phase III randomized trial looking at intermittent vs continuous imatinib therapy after completion of 1 year of continuous imatinib therapy. A total of 159 patients have enrolled in the trial. A partial or complete response was achieved in 52% of patients. Twenty-three patients were randomized to join the intermittent arm, and 23 the continuous arm. After 3 months, five patients (21%) in the intermittent arm had evidence of disease progression, vs no patients in the continuous arm. Reintroduction of imatinib resulted in tumor control in all patients.

Assessment of response and treatment after disease progression on imatinib The use of standard (RECIST) response criteria in patients with GIST may be misleading. On CT or MR imaging, large tumor masses may become completely necrotic without a reduction in size for months in spite of dramatic clinical improvement. Indeed, such masses may actually increase. 18F-FDG (18 F-fluorodeoxyglucose)–PET imaging may be extremely useful in selected patients, because response may be seen as early as 24 hours after a dose of imatinib. It should be noted that the survival of patients with stable disease parallels that of patients with major objective responses using RECIST criteria.

Surgery does not cure GIST that recurs after resection of primary disease and should be managed as metastatic disease. However, multimodality therapy should be considered in patients with limited sites of disease. It has also been recognized that patients with disease progression in limited sites of disease, occasionally with a growing nodule within a previously necrotic metastasis, may experience rapid disease progression of previously controlled areas. Thus, imatinib should be continued indefinitely in such patients, who should be referred for investigational therapy.

FDA-approved therapy for metastatic disease includes imatinib in first-line and sunitinib in second-line. If there is disease progression on second-line sunitinib, patients may be able to receive another kinase inhibitor such as sorafenib or nilotinib (Tasigna), but neither drug is FDA approved for GIST. The results of the ACOSOG phase III study of adjuvant imatinib for 48 weeks vs placebo have been reported. The study examined patients with any GIST of at least 3 cm in maximum dimension. Dematteo et al indicated that there was only a 3% chance of disease progression after the 48 weeks of therapy, in comparison to 17% in those who underwent surgery alone. However, there was a decay in the progression-free survival curve after approximately 2 to 2.5 years of therapy back toward that of the
untreated patients. Furthermore, overall survival was no different between the two study arms, although median survival was only 15 months at the time of the report. These data indicate that although imatinib is a good salvage strategy for patients with recurrent GIST, it cannot be considered a new standard of care, given the lack of overall survival benefit noted with evidence of disease progression after therapy is complete. Thus, longer exposure to imatinib may be necessary; this is the subject of two studies in Europe (0 vs 2 years of imatinib, 1 vs 3 years of imatinib) and future studies by ACOSOG. Greater follow up in the potential use of adjuvant imatinib based on mutation status has been reported in preliminary form at ASCO 2010. In the presentation by Corless et al (Proc ASCO 2010, 28; abstract 10006), there was no improvement in overall survival with adjuvant imatinib, since relapsing patients so frequently responded to imatinib in the metastatic setting. Furthermore, there were certain mutational subtypes in which it was clear that 400 mg oral daily for 48 weeks did not improve progression-free survival over placebo, including patients with exon 9 mutations in \( KIT \), so-called wild type GIST, and those patients with \( PDGFRA \) mutation D842V.

Thus, if adjuvant therapy is to be given, patients with the more common exon 11 \( KIT \) mutations (or the rare \( PDGFRA \) mutant non-D842V) could be considered for therapy. It is not clear if longer exposure (eg, the 2 or 3 years' experimental arm of two European clinical trials) will demonstrate improved overall survival, the ultimate proof of the utility of adjuvant therapy.

If relapse-free survival is improved several years after the completion of therapy, one could deduce that this reflects a higher cure rate for patients, even without a presently demonstrable overall survival advantage. The cost of saving even one life with adjuvant remains unknown, however, given the ability to salvage nearly all recurring patients with imatinib in the metastatic setting—understanding that systemic therapy for recurrent metastatic disease is lifelong. Greater follow-up is needed to make definitive conclusions about this important topic.

**Recommendations for the treatment of metastatic sarcoma**

- For patients with rapidly progressive disease or with symptoms, combination chemotherapy with an anthracycline/ifosfamide combination is indicated. For most patients, however, sequential single-agent therapy is less toxic and not inferior in terms of survival.

- The management of metastatic GIST involves imatinib as first-line therapy, and increasing doses of imatinib, when feasible, before changing to sunitinib. Some patients can be maintained with good responses to imatinib for more than 5 years.

- Schedules other than the 50 mg oral daily dose of sunitinib (4 weeks on, 2 off) can be considered in an attempt to minimize the drug's toxicity (eg, 25 to 37.5 mg oral daily without interruption).

- Surgery is increasingly being performed at the time of best response (typically 6 to 9 months) and at the time of limited disease progression. There are no data that indicate that early surgery (at the time of best response) leads to superior survival than later surgery (at the time of limited disease progression). Surgery should generally be avoided in patients with multifocal progressive disease; a change in medical therapy is appropriate in this setting.

- The importance of histology relevant to selection of therapy is increasingly being appreciated. It is especially significant to distinguish GISTs from GI leiomyosarcomas. Patients with GIST that is progressive on standard therapy should be referred to subspecialty centers experienced in the multimodality management of this disease. Data regarding kinase-targeted agents will likely lead to the use of such agents for a limited number of rare sarcoma subtypes.
• Periods of watchful waiting may be appropriate for many patients with metastatic sarcoma who have no or only minimal symptoms.

SUGGESTED READING


Abbreviations in this chapter
ACOSOG = American College of Surgeons Oncology Group; AGG = Australasian Gastrointestinal Group; AJCC = American Joint Committee on Cancer; EORTC = European Organization for Research on the Treatment of Cancer; FFCCSG = French Federation of Cancer Centers Sarcoma Group; FSG = French Sarcoma Group; ISG = Italian Sarcoma Group; RDOG = Radiation Diagnostic Oncology Group; RTOG = Radiation Therapy Oncology Group; SMAC = Sarcoma Meta-Analysis Collaboration; SSG = Scandinavian Sarcoma Group; SWOG = Southwest Oncology Group; UICC = International Union Against Cancer