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Soft Tissue Sarcoma:

Clinical Practice Guidelines in Oncology

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Overview

Sarcomas constitute a heterogeneous group of rare solid tumors of mesenchymal cell origin with distinct clinical and pathological features, and are usually divided into 2 broad categories: sarcomas of soft tissues (including fat, muscle, nerve and nerve sheath, blood vessels, and other connective tissues) and sarcomas of bone.

Soft tissue sarcomas (STS) are the most frequent sarcomas; the annual incidence in the United States for 2009 is estimated to be approximately 10,660 cases, with an overall mortality rate of approximately 3820 cases per year, including adults and children.¹ The true incidence of sarcoma is underestimated, especially because a large proportion of patients with gastrointestinal stromal tumors (GIST) may not have been counted in tumor registry databases before 2001. GIST is expected to have an incidence of at least 5000 new cases per year in the United States.^{2,3}

Collectively, sarcomas account for approximately 1% of all adult and 15% of pediatric malignancies. Prior radiation therapy (RT) to the affected area given generally some years before the development of the sarcoma is a risk factor for STS.⁴ More than 50 different histologic subtypes of STS have been identified, with pleomorphic sarcoma (also known as *malignant fibrous histiocytoma*), GIST, liposarcoma, leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumors the most common.⁵ Rhabdomyosarcoma is the most common STS of childhood. The most common primary sites are the extremities

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(60%), trunk (19%), retroperitoneum (15%), and head and neck (9%).⁶ The anatomic site of the primary disease is an important variable influencing treatment and outcome. STS most commonly metastasize to the lungs; tumors arising in the abdominal cavity commonly metastasize to the liver and peritoneum.

NCCN encompasses institutions with extensive experience in managing sarcomas using multidisciplinary care and they function as referral centers of consultative support for community-based practitioners. The expertise of these institutions lends their extensive experience in defining the consensus guidelines for the management of patients with sarcomas. The guidelines appearing in this issue of *JNCCN* address sarcoma management in adult patients from the perspective of 2 disease subtypes: STS of the extremity/trunk and GIST. Two additional subtypes, retroperitoneal or intra-abdominal STS and desmoid tumors, are addressed online, in these guidelines, at www.NCCN.org. These guidelines do not include the management of rhabdomyosarcoma, Ewing's sarcoma, and desmoplastic small round cell tumor.

NOTE: This manuscript highlights only a portion of the NCCN Guidelines on Soft Tissue Sarcoma. Please refer to www.NCCN.org for the complete guidelines.

Pathology of STS

Biopsy

A pretreatment biopsy is highly preferred for diagnosing and grading sarcomas, and should be performed by an experienced surgeon or radiologist. Biopsy can be accomplished by core needle or open incisional techniques. Although fine needle aspiration (FNA) is a convenient technique, it can be difficult to make an accurate primary diagnosis with FNA alone.⁷ FNA may be acceptable in select institutions with clinical and pathologic expertise. Endoscopic or needle biopsy may be indicated for deep thoracic, abdominal, or pelvic sarcomas.

Principles of Pathologic Assessment

Pathologists with sarcoma expertise should review the pathologic assessment of biopsies and resected specimens, especially for initial histopathologic classification. Margins must be thoroughly evaluated in these specimens. Morphologic assessment based on microscopic examination of histologic sections remains the gold standard of sarcoma diagnosis. Differential diagnosis of a soft tissue mass includes malignant lesions (i.e., primary or metastatic carcinoma, melanoma, or lymphoma), desmoids, and benign lesions (i.e., lipomas, lymphangiomas, leiomyomas, and neuromas). Because identifying a histopathologic type of sarcoma is often difficult, several ancillary techniques, such as conventional cytogenetics, immunohistochemistry, and molecular genetic testing, are useful to support the morphologic diagnosis.

Pathologists should have access to optimal cytogenetic and molecular diagnostic techniques. Results of appropriate ancillary studies used as an adjunct to morphologic diagnosis should be included in the pathology report. The report should include specific details about the primary diagnosis (using standardized classification according to the WHO classification); organ; sarcoma site, depth, size, and histologic grade; presence or absence of necrosis; status

of excision margins and lymph nodes; TNM stage; and additional features of the tumor, such as mitotic rate, presence or absence of vascular invasion, and the type and extent of inflammatory infiltration (see page 646). The size at presentation depends on the location—tumors in the proximal extremities and retroperitoneum are often large, whereas distal extremity tumors are often small.

Molecular Diagnosis of STS

Molecular genetic testing has emerged as a particularly useful ancillary test because many STS subtypes are associated with characteristic genetic aberrations, including single base-pair substitutions, deletions, amplifications, and translocations (see pages 647 and 648). STS can be divided into 2 major genetic groups: 1) sarcomas with specific genetic alterations, such as chromosomal translocations or point mutations, and usually simple karyotypes, and 2) sarcomas with nonspecific genetic alterations and complex unbalanced karyotypes.⁸

STS with recurrent chromosomal translocations can be classified into subtypes depending on the presence of fusion gene transcripts (e.g., *EWS-ATF1* in clear cell sarcoma, *TLS-CHOP* in myxoid or round cell liposarcoma, *SYT-SSX* [*SYT-SSX1* or *SYT-SSX2*] in synovial sarcoma, and *PAX-FKHR* [*PAX3-FKHR* or *PAX7-FKHR*] in alveolar rhabdomyosarcoma). The fusion genes resulting from chromosomal translocations can provide useful diagnostic and prognostic information.

Common techniques used in molecular diagnosis include conventional cytogenetic analysis, fluorescence in-situ hybridization, and polymerase chain reaction (PCR)–based methods.⁹ In a prospective study, Hill et al.¹⁰ found that PCR–based molecular analysis is a useful adjunct and more sensitive than conventional cytogenetics for the diagnosis of certain STS subtypes, including alveolar rhabdomyosarcoma, synovial sarcoma, and myxoid liposarcoma, which have variation in fusion gene partners.

The molecular heterogeneity of fusion transcripts has been suggested to predict prognosis in certain sarcoma subtypes. In patients with alveolar rhabdomyosarcoma presenting with metastatic disease, *PAX7-FKHR* was associated with a favorable prognosis compared with *PAX3-FKHR*.¹¹ In those with synovial sarcoma, the prognostic impact of fusion gene transcripts *SYT-SSX1* and *SYT-SSX2* is less clear, with conflicting results in 2 large studies.^{12,13} In myxoid liposarcoma, the variability of fusion transcript has no effect on clinical outcome.¹⁴

Although molecular genetic testing appears promising, it involves highly complex techniques and the methods are not absolutely sensitive or provide specific results. In addition, technical limitations associated with molecular testing suggest that molecular evaluation be considered only as an ancillary technique. Molecular test results should therefore only be interpreted in the context of the morphologic features of a sarcoma.⁹

Staging

The American Joint Committee on Cancer (AJCC) STS staging system has historically used a 4-grade system, but within the STS staging groups this effectively functioned as a 2-tiered system (G1/G2 [low] and G3/G4 [high]). The 2 most widely used systems, the French

Federation of Cancer Centers Sarcoma Group (FNCLCC) and National Cancer Institute system, are 3-tiered grading systems. The latter is based on the evaluation of tumor histology, location, and amount of tumor necrosis, whereas the former is based on tumor differentiation, mitosis count, and tumor necrosis.

In a comparative study of these 2 systems in 410 adult patients with STS, the FNCLCC system showed a slightly increased ability to predict distant metastasis development and tumor mortality.¹⁵ The 2002 AJCC staging system accommodated some of the 3- and 4-tiered systems for establishing the grade. The revised 2010 AJCC staging system incorporates a 3-tiered grading system (see the staging table, available online, in these guidelines, at www.NCCN.org [ST-1]). Because many clinicians prefer the 2-tiered system, this system is also used in the algorithm (see page 633).

Principles of Surgery

Because surgery is the standard primary treatment for most sarcomas, the panel has included a separate section on principles of sarcoma surgery (see page 649). If a patient cannot be surgically treated according to these principles, preoperative RT or chemotherapy should be considered as alternate treatment options. Because the risk for failure in the surgical bed can be high, many clinicians choose to augment surgery with RT and chemotherapy, either pre- or postoperatively.^{16,17} When appropriate, the guidelines incorporate those therapies that are supported by clinical trial data or extensive clinical experience.¹⁸

Sarcoma Surgery

The biopsy site should be excised en bloc with the definitive surgical specimen. Dissection should be through grossly normal tissue planes uncontaminated by the tumor. If it is close to or displaces major vessels or nerves, these do not need to be resected if the adventitia or perineurium is removed and the underlying neurovascular structures are not involved with gross tumor. Radical excision or entire anatomic compartment resection is not routinely necessary. If resections with microscopically or grossly positive margins are anticipated, surgical clips should be left in place to identify high-risk areas for recurrence, particularly for retroperitoneal or intra-abdominal sarcomas, to help guide future RT. If closed suction drainage is used, the drains should exit the skin close to the surgical incision edge (in case re-resection or RT is indicated).

Limb-sparing surgery is recommended for most patients with extremity STS to achieve local tumor control with minimal morbidity. Evaluation for postoperative rehabilitation is recommended for all patients with extremity sarcoma. If indicated, rehabilitation should be continued until maximum function is achieved.

Resection Margins

Resection with appropriately negative margins is recommended, although negative but closer margins may be effective in patients undergoing RT.¹⁹ Close margins may be necessary to preserve uninvolved critical neurovascular structures. Microscopically positive surgical margins are associated with a higher rate of local recurrence and lower rate of disease-free survival in patients with extremity sarcomas.²⁰⁻²²

Both the surgeon and pathologist should document surgical margins in evaluating a resected specimen. If surgical margins are positive on final pathology, re-resection to obtain negative margins should strongly be considered if it will not have a significant impact on functionality.^{23,24} Adjuvant RT should be considered after resections with close soft tissue margins (< 1 cm) or a microscopically positive margin on bone, major blood vessels, or nerve.

Amputation for Extremity Sarcoma

Before considering amputation, patients should be evaluated by a surgeon with expertise in the treatment of STS. Amputation should be considered for patient preference, or if the gross total resection of the tumor is expected to render the limb nonfunctional.^{25–27}

Guidelines for RT

External-beam radiation therapy (XRT) can be administered as primary therapy, preoperatively, or postoperatively in STS. Advances in RT technology, such as brachytherapy, intensity-modulated radiation therapy (IMRT), and intraoperative radiation therapy (IORT), have led to improved treatment outcomes in patients with STS.²⁸ Brachytherapy involves the direct application of radioactive seeds into the tumor bed through catheters placed during surgery. The main advantage of IMRT is its ability to more closely contour the high-dose radiation volume to the tumor while minimizing the volume of high-dose radiation to the surrounding tissues.²⁹ IORT delivers radiation during surgery and is performed using different techniques, such as electron beam radiation or brachytherapy.

Preoperative RT

Preoperative RT has several advantages. First, the treatment volume is smaller because the need to cover the operative field is not present. Second, it may reduce seeding during surgical manipulation of the tumor. The tumor may or may not regress with preoperative RT, but the pseudocapsule may thicken and become acellular, easing resection and decreasing the risk for recurrence. However, the main disadvantage of preoperative RT is its effect on wound healing.³⁰ A higher acute wound healing complication rate has been observed when primary closure is used. Therefore, involvement of a plastic surgeon may be necessary to reduce wound complications when preoperative radiation is contemplated. After preoperative radiation, a 3- to 6-week interval is necessary before resection to allow acute radiation reactions to subside and decrease the risk for wound complications. Very long intervals between resection and postoperative radiation are not recommended because of the development of late fibrosis.

The usual dose of preoperative RT is 50 Gy. If wide margins are obtained, additional radiation may not be needed. Radiation boost with brachytherapy, IORT, or XRT is recommended for positive or close margins (see page 650).³¹ Often, margins are close because of their proximity to major neurovascular bundles or bone. Brachytherapy boosts should be delivered several days after surgery, through catheters placed at operation, with doses of 12 to 20 Gy based on margin status. Alternatively, a single intraoperative dose of 10 to 16 Gy, based on margin status, can be delivered immediately after resection with exposure

of the area at risk, avoiding uninvolved organs. XRT boosts may be an alternative to brachytherapy or IORT. Recommended doses are 10 to 14 Gy for close margins, 16 to 20 Gy for microscopically positive margins, and 20 to 26 Gy for grossly positive margins. Many institutions are no longer giving a boost after preoperative radiation to patients who have widely negative margins, based on local control rates that approach 95% with preoperative radiation at 50 Gy and negative margins.

Postoperative RT

Postoperative RT has been shown to improve local control in patients with high-grade extremity STS with positive surgical margins.³² In a recent report from Memorial Sloan-Kettering Cancer Center, in patients with extremity STS treated with limb-sparing surgery and a pathologically negative re-resection without RT, patients of elderly age and/or with stage III disease had a higher rate of local recurrence, even though the 5-year overall local recurrence rate was 9% with a median follow-up of 82 months.³³ Therefore, treatment decisions regarding the use of postoperative RT should be individualized and not solely based on the finding of margin-negative re-resection.

When surgical resection is the initial therapy, postoperative RT choices include brachytherapy, IORT, or XRT (see page 650). When XRT is used, sophisticated treatment planning with IMRT, tomotherapy, and/or proton therapy can be used to improve therapeutic effect. Most institutions include the entire operative bed within that radiation field. Total doses of RT should always be determined through normal tissue tolerance. RT is not a substitute for suboptimal surgical resection, and re-resection may be necessary. If the patient has not previously undergone RT, control of microscopic residual disease would be attempted with postoperative RT if re-resection is not feasible.

Brachytherapy alone has been used as an adjuvant treatment. Radiation delivered at 45 to 50 Gy at low-dose rate to the tumor bed has been shown to reduce recurrence without a significant effect on wound healing.³⁴ However, brachytherapy-alone techniques require special expertise and significant experience. The panel recommends 45 Gy low dose-rate brachytherapy for patients with negative margins. Low dose-rate brachytherapy (16–20 Gy) or a high dose-rate equivalent is recommended for patients with positive margins followed by XRT. XRT is delivered to the target volume to a total dose of 50 Gy (45 Gy for retroperitoneal or intra-abdominal sarcomas) after surgical healing is complete (3–8 weeks).

Recent reports from a retrospective study suggest that IORT provides excellent local control to STS of the extremity.³⁵ However, because IORT has not been proven superior, the guidelines recommend IORT (10–16 Gy) followed by a 50-Gy dose of XRT.

If no IORT or brachytherapy was used in the immediate operative or postoperative period, XRT is delivered to the target volume of a 50-Gy total dose (45 Gy for retroperitoneal or intra-abdominal sarcomas) after surgical healing is complete. An XRT boost should be used based on the margin status. For negative margins, an additional 10 to 16 Gy is recommended to the original tumor bed. For microscopically positive margins, an additional 16 to 20 Gy is recommended, and for grossly positive margins, an additional 20 to 26 Gy is suggested.

STS of the Extremities or Trunk

Surgery

Amputation was once considered the standard treatment to achieve local control in patients with extremity sarcomas.³⁶ In recent years, technical advances in reconstructive surgical procedures, implementation of multimodality therapy, and improved selection of patients for adjuvant therapy have minimized the functional deficits in patients who might otherwise require amputation.

In 1982, a randomized controlled trial (43 patients) showed that limb-sparing surgery with RT was an effective treatment in patients with high-grade STS of the extremities, with a local recurrence rate of 15% and no difference in overall and disease-free survival compared with amputation.³⁷ In another series of 77 patients treated with limb-sparing surgery without RT, the local recurrence rate was only 7% and resection margin status was a significant predictor of local recurrence.³⁸ The local recurrence rate was 13% when the resection margin was 1 cm or less compared with 0% when the resection margin was 1 cm or more. In a retrospective study of 115 patients with an STS of hand or foot, radical amputation as an initial treatment did not decrease the probability of regional metastasis and also did not improve the disease-specific survival.³⁹ These results suggest that limb-sparing surgery with or without adjuvant RT is an effective treatment option for extremity STS, and amputation should be reserved only for cases in which resection or re-resection with adequate margins cannot be performed without sacrificing the functional outcome.

RT

Randomized clinical trial data support the use adjunctive XRT in appropriately selected patients with STS of extremity.^{40–42} In a phase III randomized trial conducted by the Canadian Sarcoma Group,⁴⁰ local control and progression-free survival rates were similar in patients undergoing either pre- or postoperative XRT for localized primary or recurrent extremity sarcoma. However, preoperative RT was associated with a greater incidence of acute wound complications (35% vs. 17% for postoperative XRT), especially in lower extremity tumors (43% vs. 5% for upper extremity tumors). Late treatment-related side effects were more common in patients undergoing postoperative radiation, which is believed to be related to the higher postoperative XRT dose (66 vs. 50 Gy for preoperative) and the larger treatment volume. Therefore, the risk for local recurrence versus the toxicity of postoperative XRT should be assessed before making a decision regarding radiation.

The efficacy of postoperative XRT was shown in a prospective randomized trial comparing limb-sparing surgery alone and with adjuvant XRT. Postoperative XRT reduced the 10-year local recurrence rate in patients with high-grade sarcoma (none in patients who underwent surgery plus XRT vs. 22% in those who underwent surgery alone) and those with low-grade (5% for surgery plus XRT group vs. 32% for surgery alone).

In a prospective randomized trial, 164 patients with completely resected STS of the extremity or superficial trunk were randomized intraoperatively to receive either adjuvant brachytherapy or no brachytherapy.⁴³ With a median follow-up time of 76 months, the 5-year local control rates were 82% and 69% in the brachytherapy and no brachytherapy

groups, respectively. Patients with high-grade lesions who received brachytherapy had higher local control rates than those randomized to no brachytherapy (89% and 66%, respectively). However, brachytherapy had no impact on local control in patients with low-grade lesions. The 5-year freedom-from-distant-recurrence rates were 83% and 76%, respectively. Results of this trial showed that adjuvant brachytherapy improves local control after complete resection of STS in patients with high-grade lesions.

Postoperative IMRT after limb-sparing surgery is associated with excellent local control in selected patients with high-risk features. In a retrospective analysis, the 5-year local control rate was 94% in patients with negative and positive or close margins.⁴⁴ The risk for complications such as edema and joint stiffness were also favorable compared with conventional RT. Despite the excellent results of adjuvant IMRT in patients with extremity sarcomas, its efficacy must be confirmed in larger cohorts of patients with longer follow-up.

Definitive RT entails the delivery of maximal local dose compatible with known tissue tolerance, typically ranging from 70 to 80 Gy, using sophisticated instrument planning techniques. In a single-institution study (112 patients, 43% STS of extremity), tumor size and the dose of RT influenced local control and survival in patients with unresectable STS.⁴⁵ Local control rate was 51% for tumors less than 5 cm and 9% for tumors greater than 10 cm. Patients who received 63 Gy or more had better 5-year local control, disease-free survival, and overall survival rates (60%, 36%, and 52%, respectively) than patients treated with less than 63 Gy (22%, 10%, and 14%, respectively). Local control for patients receiving more than 63 Gy was 72% for lesions 5 cm or less, 42% for lesions 5 to 10 cm, and 25% for those greater than 10 cm.

Evaluation and Workup

All patients should be managed by a multidisciplinary team with expertise in STS.⁴⁶ The differential diagnosis of STS of the extremities includes ruling out desmoids and other malignant and benign lesions previously discussed. An essential element of the workup is a history and physical examination (H&P). Laboratory tests have a limited role. Adequate and high-quality imaging studies are crucial to good clinical management of patients, because the presence of metastatic disease may change the management of the primary lesion and the overall approach to the patient's disease management. Imaging studies should also provide details about tumor size and contiguity to nearby visceral structures and neurovascular landmarks. The propensities to spread to various locations vary among the subtypes of sarcoma. Therefore, imaging should be individualized based on the subtype of sarcoma.

MRI with or without CT is indicated for all lesions with a reasonable chance of being malignant (see page 632). MRI is preferred for extremity sarcomas, whereas CT is preferred for retroperitoneal sarcomas.⁴⁷⁻⁴⁹ CT angiogram may be useful in patients for whom MRI is not feasible. Plain radiograph of the primary lesion is optional. Given the risk for hematogenous spread from a high-grade sarcoma to the lungs, imaging of the chest is essential for accurate staging. Abdominal/pelvic CT should be considered for myxoid round cell liposarcoma, leiomyosarcoma, epithelioid sarcoma, or angiosarcoma, and MRI of the total spine should be considered for myxoid round cell liposarcomas because of the higher risk for metastasis to spine compared with other STS.⁵⁰⁻⁵² Central nervous system imaging

should be considered for patients with alveolar soft part sarcomas and angiosarcomas because alveolar soft part sarcomas have a relatively increased propensity to metastasize to the brain, especially in patients with stage IV disease in the presence of pulmonary metastases.⁵³

PET scan may be useful for prognostication and grading, and to assess response to chemotherapy.⁵⁴ Tumor metabolism data acquired by PET will be useful in accurate grading and prognostication in sarcoma.⁵⁵ Recent reports in literature have shown the value of PET in evaluating response to preoperative chemotherapy in patients with high-grade extremity STS and for predicting outcome in patients with liposarcoma.^{56,57} A large prospective study is underway to evaluate the value of PET scan combined with CT scan in predicting disease-free survival in patients undergoing preoperative chemotherapy for STS (www.cancer.gov/clinicaltrials/UMN-2005LS080).

Based on the initial workup, the patients are assigned to 1 of the following categories:

- Stage I
- Stage II–III
- Stage IV
- Recurrent disease

Stage I

Surgery is the primary treatment for low-grade stage I tumors and is considered definitive if margins are greater than 1 cm or the fascia plane is intact.^{58,59} Retrospective studies have shown a local control rate of 90% or more for surgery alone.⁶⁰ Long-term results of a prospective trial showed that selected patients with primary T1 STS of the extremity and trunk can be treated with surgery alone (R0 resection) with acceptable local control and excellent long-term survival.⁶¹ In the surgery alone arm, the cumulative incidence rates of local recurrence at 5 and 10 years were 7.9% and 10.6%, respectively, in patients who underwent R0 resection, and the 5- and 10-year sarcoma-specific death rates were 3.2%.

The panel recommends surgery alone as the primary treatment for low-grade stage I tumors (T1a–2b, N0, M0). If the final surgical margins are 1.0 cm or less, postoperative RT is included with a category 2B recommendation for T1a–b tumors and a category 1 recommendation for T2a–b tumors (see page 633). RT may not be necessary in patients with small lesions (< 5 cm), because these tumors are less frequently associated with local recurrence.

Stage II–III

Large high-grade extremity sarcomas (> 8–10 cm) at high risk for local recurrences and metastases should be considered for preoperative therapy. Preoperative chemotherapy or chemoradiation is used in many centers for downstaging large high-grade tumors to enable effective surgical resection, especially in the case of chemosensitive histologies.^{37,62–65} Concurrent chemoradiation with doxorubicin-based regimens has been shown to improve local control rates in patients with STS, although acute reactions must be considered.⁶⁶

Available evidence, although underpowered, suggests that anthracycline-based postoperative chemotherapy would improve disease-free survival in selected patients who are at high risk for recurrence but otherwise have good performance status.^{67,68}

The Sarcoma Meta-Analysis Collaboration performed a meta-analysis of 14 randomized trials (1568 patients) comparing adjuvant chemotherapy with follow-up, and in some cases RT after surgery, for treatment of various sarcomas.⁶⁹ The result of the meta-analysis showed that doxorubicin-based chemotherapy prolongs relapse-free survival in adults with localized, resectable STS of the extremity, and was associated with decreased recurrence rates. However, adjuvant chemotherapy does not seem to improve overall survival.⁷⁰ Another recent analysis of 674 patients with stage III STS (1984–1999) showed that clinical benefits from doxorubicin-based chemotherapy lasted for less than a year.⁷¹

In an Italian randomized cooperative trial, patients with high-grade or recurrent extremity sarcoma were randomized to undergo postoperative chemotherapy with epirubicin and ifosfamide or observation alone. After a median follow-up of 59 months, median disease-free (48 vs. 16 months) and overall survivals (75 vs. 46 months) were significantly better in the treatment group.^{72,73}

Remarkably little data have been generated in the adjuvant setting regarding the combination of aggressively dosed ifosfamide plus doxorubicin with growth factor support. EORTC-62931 is a completed phase III randomized study assessing the efficacy of adjuvant chemotherapy after definitive surgery in patients with excised high-grade STS at any site. Patients with macroscopically resected grade II and III tumors with no metastases were randomized to observation or chemotherapy with ifosfamide and doxorubicin with lenograstim. A planned interim analysis of this study showed no survival advantage for adjuvant chemotherapy with ifosfamide and doxorubicin in patients with resected high-grade STS.⁷⁴ The estimated relapse-free survival rate was 52% in both arms. Further analysis of this study is needed to make a detailed assessment of the role of adjuvant chemotherapy in resected STS.

Treatment options for stage II or III high-grade tumors should be decided by a multidisciplinary team, based on the performance status; comorbid factors, including age, tumor location, and histologic subtype of the tumor; and institutional experience.

Resectable Tumors—Surgery followed by RT with or without adjuvant chemotherapy or surgery alone (for small tumors that can be resected with wider surgical margins) is the primary treatment for resectable high-grade sarcomas with acceptable functional outcomes (see page 633).⁷⁵ The guidelines have also included preoperative RT, chemotherapy, or chemoradiation before surgery as alternative options for patients with resectable tumors with acceptable functional outcomes and for potentially resectable tumors with associated concerns for adverse functional outcomes. The panel included preoperative chemotherapy or chemoradiation for resectable disease with acceptable functional outcomes with a category 2B recommendation.

Postoperative RT boost for residual gross disease or microscopically positive margins or adjuvant chemotherapy alone can be considered for patients who have undergone preoperative RT or chemoradiation, whereas postoperative RT with or without adjuvant chemotherapy is recommended for those who underwent preoperative chemotherapy (see page 633). Because limited and conflicting data are available for adjuvant chemotherapy in patients with stage II or III disease, adjuvant chemotherapy for stage II or III tumors is included as a category 2B recommendation for all patients with resectable tumors, irrespective of the functional outcomes.

Unresectable Tumors—Unresectable tumors can be treated primarily with preoperative RT, chemoradiation, or chemotherapy. Tumors that become resectable after preoperative treatment can be treated with surgery (see page 634). Postoperative treatment options for these patients are similar to those described on page 633 of the algorithm for stage II or III resectable tumors.

Definitive RT (7000–8000 cGy) can be considered for select patients with unresectable tumors after preoperative treatment (see page 634). Observation is an option for asymptomatic patients whose tumors are not believed to be amenable to local control with definitive radiation. For symptomatic patients, the panel recommends moving directly to a palliative approach, defined broadly as chemotherapy, palliative surgery, or best supportive care.

Stage IV (Metastatic Disease)

Single agents (doxorubicin, ifosfamide, or dacarbazine) or anthracycline-based combination regimens (doxorubicin or epirubicin with ifosfamide and/or dacarbazine) have been widely used to treat metastatic disease.^{76–83} Liposomal anthracyclines were found to be active as first-line treatment for advanced sarcomas with a better toxicity profile than doxorubicin.^{84,85} Other chemotherapeutic agents have also been tested in clinical trials. Combined gemcitabine and docetaxel was found to be highly active in patients with predominantly uterine leiomyosarcomas who experienced no response to or for medical reasons could not tolerate ifosfamide plus doxorubicin.⁸⁶ In a randomized phase II study, progression-free survival (6.2 vs. 3.0 months, respectively) and overall survival (17.9 vs. 11.5 months, respectively) were superior to gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic STS.⁸⁷ In a separate report published after this study, this combination was found to be active in various histologic subtypes of sarcoma.⁸⁸

In a retrospective study conducted by the French Sarcoma Group in 133 patients with unresectable or metastatic STS, the gemcitabine and docetaxel combination was tolerable and showed better response and survival rates in patients with leiomyosarcoma.⁸⁹ Another phase II trial (MSKCC-99027) is evaluating the activity of gemcitabine, docetaxel, and filgrastim in patients with recurrent or persistent unresectable leiomyosarcoma or other STS that cannot be removed with surgery. In a phase II study, combination gemcitabine and vinorelbine was associated with clinically meaningful rates of disease control in patients with advanced STS.⁹⁰ Clinical benefit (complete response, partial response, or stable disease at 4 months) was seen in 25% of patients. Temozolomide as a single agent is also active in

patients with advanced pretreated STS, especially those with unresectable or metastatic leiomyosarcoma of both uterine and nonuterine origin.^{91,92}

Ecteinascidin 743 (ET-743, also known as trabectedin or Yondelis), is a marine-derived antitumor agent, which has shown objective responses in phase II trials of patients with progressive STS refractory to chemotherapy.^{93–97} NCT00210665 is an ongoing multicenter, open label, single-arm study providing access to treatment with trabectedin for patients with persistent or recurrent STS and who are not expected to benefit from currently available treatments.

Interim overall survival data are encouraging from an ongoing phase III trial (EORTC-62961) of regional hyperthermia (RHT) versus chemotherapy with EIA (etoposide, ifosfamide, and adriamycin) alone for patients with locally advanced high-risk STS, especially those with extremity sarcomas.⁹⁸ After a median follow-up of 24.9 months, disease-free survival (31.7 vs. 6.2 months, respectively), local progression-free survival (84% vs. 64%, respectively, for extremity sarcomas and 57% vs. 39%, respectively, for body wall and abdominal sarcomas), and overall response rate (28.7% vs. 12.6%, respectively) were significantly superior for patients treated with EIA plus RHT compared with those treated with EIA alone.⁹⁹

Isolated limb perfusion (ILP) has been used in Europe as a limb-sparing treatment for unresectable intermediate or high-grade extremity STS.¹⁰⁰ In European clinical trials, melphalan in combination with tumor necrosis factor- α (TNF- α) resulted in better response rates and limb-salvage rates than ILP with melphalan alone.¹⁰¹ Recombinant TNF- α -1A and melphalan has been approved in Europe for ILP in patients with locally advanced high-grade STS of the extremities.

Limited Metastases—Patients with limited metastasis confined to a single organ and limited tumor bulk or regional lymph node involvement should undergo primary tumor management as described for stage II or III tumors on page 633. Another option is to consider regional node dissection for nodal involvement with or without RT or metastasectomy with or without chemotherapy with or without RT (see page 635). The guidelines do not specify rules governing metastasectomy, which remains controversial for many cancers, including sarcoma. Several variables influence the decision to use metastasectomy, including the disease-free interval from original diagnosis to detection of the metastases, the patient's performance status, and the amount of prior therapy. Thoracotomy and video-assisted thoracic surgery should be used selectively depending on the clinical presentation of metastatic disease. In addition, patients can also undergo radiofrequency ablation or embolization procedures as an alternate method for control of metastatic lesions.

Disseminated Metastases—In the guidelines, a subsequent distinction is made between asymptomatic and symptomatic patients for those who present with disseminated disease (see page 635). One reasonable management option for asymptomatic patients is to offer close observation with a “watchful waiting” strategy, especially for patients who had a very long disease-free interval and have only a minimal burden of metastases (e.g., subcentimeter

pulmonary nodules). Alternatively, patients can also be treated with palliative approaches, such as palliative RT, chemotherapy, or palliative surgery. Palliative RT involves expedient treatment with sufficient dose to halt tumor growth or cause tumor regression. The outcome of this approach depends on the rapidity of growth and the status of systemic disease.

In addition, the guidelines have included ablation procedures (e.g., radiofrequency ablation or cryotherapy), embolization procedures, or stereotactic radiosurgery/radiotherapy as options for symptomatic patients with disseminated metastases. The guidelines are intentionally nonspecific about this group of options, because many different factors impact this decision (e.g., patient performance status, patient preferences, specific clinical problems from the metastases, treatment availability) and specific details are best left to clinical judgment.

Surveillance

Surveillance is deemed important to detect recurrences that might still be potentially curable. However, limited data are available in the literature on effective surveillance strategies.^{102–104} The guidelines outline a prudent follow-up schedule that avoids excessive testing. Higher-grade and larger tumors have a higher risk for dissemination; therefore, the surveillance recommendations for patients with these tumors are somewhat more intensive, particularly for the first 3 years after resection. Periodic imaging (MRI, CT, or ultrasound) of the primary site should be performed based on the estimated risk for locoregional recurrence. However, when the area can be easily followed by physical examination, imaging may not be required. After 10 years, the likelihood of developing a recurrence is small and follow-up should be individualized.

Stage I tumors are routinely followed with H&P every 3 to 6 months for 2 to 3 years, then annually (see page 633). Chest imaging should also be considered every 6 to 12 months. For stage II through IV disease, H&P and chest imaging should be performed every 3 to 6 months for 2 to 3 years, then every 6 months for the next 2 years, and then annually (see pages 633–635). Because these patients' risk never returns to zero, long-term follow-up is indicated, including consideration of MRI or CT scanning.¹⁰⁵ No study has ever proved that the use of more sensitive CT scans in routine surveillance would improve clinical outcomes. According to the reported data from MD Anderson Cancer Center, routine use of chest CT adds little clinical benefit when risk for pulmonary metastases is low.¹⁰⁶ However, in certain subsets of patients for whom chest radiographs are difficult to interpret because of anatomic considerations (e.g., scarring, emphysema), chest CT surveillance may be indicated.

Recurrent Disease

The management of recurrent disease encompasses a heterogeneous group of patients and clinical scenarios (see page 636). For a patient with a local recurrence, treatment decisions should be made using the same algorithm as for patients with a new primary lesion (see page 633).¹⁰⁷ For patients who present with metastatic recurrences, the guidelines distinguish between widely disseminated metastases and limited metastases confined to a single organ and the treatment options are similar to those described for stage IV disease at presentation (see page 635).

GISTs

GISTs are the most common mesenchymal neoplasms of the gastrointestinal tract, resulting from activating mutations in one of the receptor protein tyrosine kinases (KIT, also called CD117).¹²⁸ Most GISTs (95%) are KIT positive. Approximately 5% of GISTs have mutations in the platelet-derived growth factor-alpha (PDGFRA) genes and express little or no KIT.^{129,130} Therefore, the diagnosis of GIST for a tumor that is otherwise morphologically typical is not precluded by an absence of KIT staining.

GISTs can arise anywhere along the gastrointestinal tract, but the stomach (60%) and small intestine (30%) are the most common primary sites.^{131,132} Gastric GISTs have a more favorable prognosis than the intestinal ones. Patients with a suspected GIST may present with various symptoms, which may include early satiety, abdominal discomfort from pain or swelling, intraperitoneal hemorrhage, gastrointestinal bleeding, or anemia-related fatigue. Liver metastases and/or dissemination within the abdominal cavity are the most common clinical manifestations of malignancy. Lymph node metastases are extremely rare. Metastases in the lungs and other extra-abdominal locations are observed only in advanced cases.

Targeted Therapy for Patients With GIST

GIST tumors have been documented to be resistant to conventional chemotherapies. Because KIT activation occurs in most GIST cases, KIT-inhibition has emerged as the primary therapeutic treatment along with surgery.

Imatinib Mesylate—Imatinib mesylate, a selective inhibitor of the KIT protein tyrosine kinase, has produced durable clinical benefit and objective antitumor responses in most patients with GIST. Multiple clinical trials worldwide have consistently shown the efficacy of imatinib for patients with GIST. Phase II and III studies have shown high overall response rates, exceptionally good progression-free survival, and objective responses in more than 50% for patients with unresectable and/or metastatic GIST treated with imatinib.^{133–136} In February 2002, the FDA approved imatinib mesylate for the treatment of patients with KIT-positive unresectable and/or metastatic malignant GIST.¹³⁷

The presence and type of *KIT* or *PDGFRA* mutation status are predictive of response to imatinib therapy in patients with advanced or metastatic GISTs. *KIT* juxtamembrane domain (exon 11) mutations are the most common mutations in GISTs of all sites, whereas *KIT* extracellular domain (exon 9) mutations are specific for intestinal GISTs. *PDGFRA* mutations are common in gastric GISTs, with most affecting exon 18 in the tyrosine kinase domain 2.¹³⁸

In randomized clinical trials, patients with *KIT* exon 11 mutations had better response rates and longer progression-free and overall survival than those with *KIT* exon 9 mutations or no *KIT* or *PDGFRA* mutation. In the U.S.-Finnish B2222 phase II trial, the partial response rate was 83.5% for patients with exon 11 mutation compared with 47.8% for those with exon 9 mutations.¹³⁹ The EORTC-Italian Sarcoma Group-Australasian GI Trials Group phase III trial (EORTC-62005)¹⁴⁰ and the North American phase III study SWOG S0033/CALGB

150105¹⁴¹ also confirmed the findings from the B2222 study: that the *KIT* exon 11 genotype is associated with favorable outcome in patients with advanced GIST compared with *KIT* exon 9 genotype or wild-type (WT)-GIST.

Two separate phase III trials have assessed the efficacy of imatinib mesylate at 2 initial dose levels (400 mg daily vs. 800 mg daily, given as 400 mg twice a day) in patients with metastatic or unresectable GIST.^{135,136} Both studies showed equivalent response rates and overall survival for both dose levels; however, higher dose was associated with more side effects in both studies. The EORTC 62005 trial documented an earlier time-to-tumor progression for patients treated with 400 mg daily.¹³⁵ At a median follow-up of 760 days, 56% of patients assigned to imatinib once daily had experienced progression compared with 50% of those assigned to treatment twice daily. The S0033/CALGB 150105 study reported identical response rates (40% vs. 42%, respectively) at a median follow-up of 4.5 years, and no statistical differences were seen in progression-free survival (18 months for low-dose arm vs. 40 months for higher-dose arm) and median overall survival (55 and 51 months, respectively).¹³⁶ After progression on 400 mg daily, 33% of patients who crossed over to the higher dose showed objective response rates and stable disease. However, the small advantage in progression-free survival observed for high-dose imatinib in the EORTC 62005 trial was not corroborated by the S0033/CALGB 150105 trial.

Available data confirm the safety and efficacy of imatinib at 400 mg/d as the initial standard dose to achieve response induction. Dose escalation to 800 mg/d is a reasonable option for patients progressing on 400 mg/d. Recent data support the use of imatinib at 800 mg/d in patients with exon 9 mutations and advanced GIST.¹⁴² In a randomized EORTC phase III trial, patients whose tumors expressed an exon 9 *KIT* mutation treated with high-dose imatinib (800 mg/d) had a significantly superior progression-free survival ($P = .0013$), with a reduction of the relative risk of 61%.¹⁴³ In the North American Intergroup phase III trial (CALGB 150105), patients with exon 9 mutations treated with 800 mg of imatinib experienced improved response rates compared with those treated with 400 mg (67% vs. 17%, respectively).¹⁴¹ However, the progression-free survival advantage observed in EORTC-62005 among patients with exon 9 *KIT* mutations treated with high-dose imatinib was not confirmed in the S0033/CALGB 150105 study.

A meta-analysis of 1640 patients from both of these trials showed that treatment with high-dose imatinib (400 mg, twice daily) results in small but significant progression-free survival advantage compared with standard-dose imatinib (400 mg/d).¹⁴⁴ This meta-analysis also showed a progression-free survival benefit in patients with *KIT* exon 9 mutations treated with 800 mg of imatinib.

Preoperative Imatinib—Two randomized phase II studies evaluated the safety and efficacy of preoperative imatinib in patients with primary GISTs or resectable metastatic disease. The RTOG 0132/ACRIN 6665 trial evaluated the efficacy of preoperative imatinib (600 mg/d) in patients with potentially resectable primary disease (30 patients) or potentially resectable recurrent or metastatic disease (22 patients).¹⁴⁵ The response rates were 7% partial and 83% stable disease in patients with primary GIST, and 4.5% and 91%, respectively, in those with recurrent or metastatic disease. The estimated overall survival

rates for these patients were 93% and 91%, respectively, and the 2-year progression-free survival rates were 83% and 77%, respectively.

In a randomized trial conducted at the MD Anderson Cancer Center, 19 patients undergoing surgical resection were randomized to receive 3, 5, or 7 days of preoperative imatinib (600 mg/d).¹⁴⁶ The response rates assessed using FDG-PET and dynamic CT were 69% and 71%, respectively. Median disease-free survival of patients treated with surgery and imatinib was 46 months. Tumor size was a predictor of recurrence after postoperative imatinib.

Although the results of these 2 trials showed the safety and efficacy of preoperative imatinib in patients undergoing surgical resection, survival benefit could not be determined because all patients in both trials received imatinib postoperatively for 2 years. Currently, the decision to use preoperative therapy for patients with resectable primary or locally advanced GIST should be made on an individual basis.

Postoperative Imatinib—Surgery does not routinely cure GIST. Complete resection is possible in approximately 85% of patients with primary tumors. At least 50% of these patients will develop recurrence or metastasis after complete resection, and the 5-year survival rate is approximately 50%.^{147–149} Median time to recurrence after resection of primary high-risk GIST is approximately 2 years.

The American College of Surgeons Oncology Group (ACOSOG) first evaluated the efficacy of postoperative imatinib in a single-arm, multicenter, phase II intergroup trial involving 106 evaluable patients with primary GIST at high risk for recurrence based on clinicopathologic factors. Patients were treated with 1 year of imatinib at 400 mg/d. In this trial, postoperative imatinib prolonged relapse-free survival after complete resection and was also associated with improved overall survival compared with historical controls.¹⁵⁰ In 2002, ACOSOG undertook a phase III, double-blind, randomized trial (Z9001) of postoperative imatinib after resection of primary localized GISTs. In the recently published analysis, 713 patients from 230 sites were randomized either to 400 mg of imatinib (359 patients) or to placebo (354 patients) for 1 year after surgical resection. Median follow-up was 19.7 months, and 67% of patients completed 1 year of adjuvant imatinib treatment. Interim analysis showed that postoperative imatinib after resection of primary GIST improved relapse-free survival,¹⁵¹ which at 1 year was 98% in the imatinib arm vs. 83% in the placebo arm and was statistically different. Overall survival was not different in both arms.

Although the trial was not designed to assess patient subsets, subset analysis showed that relapse-free survival was statistically in favor of the imatinib arm (96% for imatinib vs. 67%–86% for placebo) in patients with high-risk tumors (> 6 cm). However, at this point, the trial results are not conclusive regarding the appropriate duration of treatment, and regarding the effect of imatinib resistance and genetic mutations on the outcome of adjuvant imatinib. Long-term follow-up is ongoing.

Based on the results of ACOSOG Z9001 trial, in December 2008, the FDA approved imatinib for postoperative treatment of adult patients after resection of KIT-positive GIST. Optimum duration of postoperative treatment has not yet been determined.

Management of Toxicities Caused by Imatinib Mesylate—The most common side effects of imatinib include fluid retention, diarrhea, nausea, fatigue, muscle cramps, abdominal pain, and rash. The side-effect profile may improve with prolonged therapy.¹⁵² Serious side effects (e.g., lung toxicity, liver function test [LFT] abnormalities, low blood counts, gastrointestinal bleeding) have been reported rarely and often improve after imatinib is withheld. LFT abnormalities are seen in fewer than 5% of patients. Leukopenia is rare and imatinib has been associated with neutropenic fever only rarely. The side-effect profile may improve with prolonged therapy and can be managed with appropriate supportive care measures. If life-threatening side effects occur with imatinib that cannot be managed with maximum supportive treatment, then sunitinib should be considered after imatinib is discontinued.

A recent report described congestive heart failure as a potential side effect of imatinib. However, in a retrospective analysis of 219 consecutive patients treated with imatinib, grade 3 or 4 cardiotoxic occurred in 8.2% of patients, were manageable with medical therapy, and infrequently required dose reduction or discontinuation of imatinib.¹⁵³ Arrhythmias, acute coronary syndromes, and heart failure were uncommon, occurring in fewer than 1% of treated patients. The authors concluded that imatinib is an uncommon cause of cardiotoxicity, and that the cardiovascular adverse events that occur are manageable when recognized and treated. However, patients on imatinib who present with significant fluid retention should be evaluated carefully.

Imatinib Mesylate Resistance—Imatinib benefits most patients with advanced GIST. However, some patients develop resistance to the drug. Primary resistance is defined as evidence of clinical progression developing during the first 6 months of imatinib therapy and is most commonly seen in patients with *KIT* exon 9, *PDGFRA* exon 18, or WT-GIST.¹⁵⁴ Secondary resistance seems to be related to the acquisition of new kinase mutations.¹⁵⁵ Patients who have been on imatinib for more than 6 months who experienced an initial response and then progression are categorized as having secondary resistance, which develops predominantly in patients who have secondary mutations in *KIT* exon 11.¹⁵⁶ Imatinib resistance can be managed either with dose escalation or switching to sunitinib.

Sunitinib Malate—Sunitinib malate (previously known as SU11248) is a multi-targeted tyrosine kinase inhibitor (TKI) that can induce objective responses and control progressive disease in patients with imatinib-resistant GIST.

In a recent randomized placebo-controlled phase III trial, sunitinib produced significant and sustained clinical benefit in patients with imatinib-resistant or -intolerant GIST.¹⁵⁷ In patients with imatinib-resistant GIST, sunitinib was associated with a significant improvement in median time to progression (27.3 vs. 6.4 weeks) and significantly greater estimated overall survival. Sunitinib treatment induced partial response in 14 patients (6.8%) and stable disease (> 22 weeks) in 36 patients (17.4%), compared with no partial responses and stable disease in 2 patients (1.9%) on placebo. In the imatinib-intolerant group, 4 of 9 patients randomized to sunitinib experienced partial response, with progressive disease in only one. In contrast, 3 of the 4 patients randomized to placebo had progressive disease at analysis and no partial response was observed. Sunitinib therapy was generally well

tolerated. In January 2006, sunitinib malate received FDA approval for the treatment of GIST in patients who experience disease progression on or are intolerant to imatinib mesylate.

The safety and efficacy of sunitinib on a continuous daily dosing schedule at 37.5 mg was evaluated in an open-label, multicenter, randomized phase II study in patients with advanced GIST after imatinib failure.¹⁵⁸ Patients were randomized (1:1) to receive continuous daily sunitinib (37.5 mg/d) in either the morning or evening for 28 days (1 cycle). The primary end point was the clinical benefit rate (CBR), defined as the percentage of patients with complete responses, partial responses, or stable disease for 24 weeks or more based on RECIST.

The overall CBR was 53% (13% had partial responses and 40% had stable disease). Median progression-free and overall survivals were 34 and 107 weeks, respectively. The most commonly reported treatment-related adverse events (diarrhea, fatigue, and nausea) were consistent with those known to be associated with intermittent dosing of sunitinib. Treatment-related hypertension and hypothyroidism experienced by 28% and 12% of patients, respectively, were successfully managed with appropriate supportive care measures. These adverse events have also been associated with long-term use of sunitinib at intermittent dosing. Results of this study suggest that continuous daily dosing seems to be an effective alternative dosing strategy with acceptable safety for patients with imatinib-resistant/intolerant GIST.

Management of Toxicities Caused by Sunitinib Malate—Sunitinib-related toxicities can often be managed with dose interruptions or reductions. Fatigue, nausea, and vomiting were dose-limiting toxicities for sunitinib in clinical trials. Other common toxicities include hematologic toxicities (anemia, neutropenia), diarrhea, abdominal pain, mucositis, anorexia, and skin discoloration. Sunitinib is associated with a significant risk for developing hand–foot skin reaction (HFSR).¹⁵⁹ Early detection and proper management of HFSR is vital during treatment with sunitinib. HFSR can be prevented with routine application of emollient lotions, but if significant, interruption of therapy is indicated, and if severe, dose reduction should be considered.

Hypertension is a common side effect reported in clinical trials, because sunitinib targets vascular endothelial growth factor receptor. However, the risk is higher in patients with renal cell carcinoma than in those with non–renal cell carcinoma.¹⁶⁰ Recent reports have shown that sunitinib is also associated with cardiotoxicity and hypothyroidism.^{161,162} In a retrospective analysis of the data from a phase I/II trial, 11% of patients experienced an adverse cardiovascular event, including congestive heart failure in 8% of patients and absolute reduction in the left ventricular ejection fraction in 28%.¹⁶¹ In a prospective, observational cohort study, abnormal serum thyroid stimulating hormone concentrations were documented in 62% of patients, and the risk for hypothyroidism increased with the duration of therapy.¹⁶²

Close monitoring for hypertension and left ventricular ejection fraction is essential in patients receiving sunitinib, especially those with a history of heart disease or cardiac risk

factors. Routine monitoring (every 3–6 months) of thyroid stimulating hormone concentration is indicated. If hypothyroidism is suggested, patients should receive thyroid hormone replacement therapy. Patients should monitor their blood pressure closely, and those who experience an increase in blood pressure should be treated with antihypertensives.

Principles of Biopsy and Pathologic Assessment

GISTs are soft and fragile, and biopsy may cause tumor hemorrhage and possibly increased risk for tumor dissemination. The decision to obtain a biopsy should be based on the extent of disease and the clinician's degree of suspicion of other malignancies. Biopsy may not be necessary if the tumor is easily resectable and preoperative therapy is not required. However, biopsy should be performed if preoperative therapy is being considered for unresectable or marginally resectable tumors (see page 643). Endoscopic ultrasound (EUS) biopsy is preferred over percutaneous. Recent reports have suggested that definitive diagnosis of GIST requires tissue acquisition through EUS-guided FNA.¹⁶³

Morphologic diagnosis based on careful microscopic examination of adequate tumor tissue is essential to confirm the diagnosis of GIST. The pathology report should include anatomic location, size, and an accurate assessment of the mitotic rate measured in the most proliferative area of the tumor and reported as the number of mitoses in 50 high power fields (see page 643). The differential diagnosis of GIST should be considered for any gastrointestinal sarcoma and for any other intra-abdominal sarcoma. The panel recommends referral to centers with expertise in sarcomas for cases with complex or unusual histopathologic features. Immunohistochemical staining for KIT and molecular genetic testing to identify mutations in the *KIT* or *PDGFRA* genes are useful in diagnosing GIST (page 643). However, 10% to 15% of GISTs have no detectable *KIT* or *PDGFRA* mutations (WT) GIST. The absence of mutations does not exclude the diagnosis of GIST. Results of a phase III study showed that patients with CD117-negative GIST have similar time-to-tumor progression but inferior overall survival compared with those with CD117-positive GIST, suggesting that patients with CD117-negative GIST may benefit from imatinib therapy.¹³⁹ Therefore, it is rational to offer patients with *KIT*-negative GIST a therapeutic trial of imatinib mesylate with close evaluation and follow-up.

Principles of Surgery for GIST

Surgery is the preferred primary treatment for patients with localized or potentially resectable GIST lesions. Although imatinib is the primary therapy for patients with metastatic GIST, surgery may be indicated for locally advanced or previously unresectable disease after a favorable response to preoperative imatinib and for limited disease progression on systemic therapy (see page 644).

GISTs are fragile and should be handled with care to avoid tumor rupture. The goal is to achieve complete gross resection of the tumor with an intact pseudocapsule. After removal of any suspected GIST, postoperative pathology assessment is essential to confirm the diagnosis. Segmented or wedge resection to obtain histologically negative margins is often appropriate (see page 644). Lymphadenectomy is usually not required given the low incidences of nodal metastases. Resection should be accomplished with minimal morbidity,

and complex multivisceral resection should be avoided. If the surgeon believes a complex surgical procedure is required, then a multidisciplinary consultation on the use of preoperative imatinib is recommended. Sphincter- and esophagus-sparing surgery should be considered for rectal and gastroesophageal junction GISTs, respectively. If abdominoperineal resection would be necessary to achieve a negative margin, then preoperative imatinib should be considered.

The role of laparoscopy in the resection of GISTs continues to expand. Although prospective trials are lacking, literature reports based on small series of patients and retrospective analyses have shown that laparoscopic or laparoscopic-assisted resections are not only possible, but are also associated with low recurrence rates, short hospital stay, and low morbidity. Laparoscopic approach may be considered for selected GISTs in favorable anatomic locations, such as anterior wall of the stomach, jejunum, and ileum. The same surgical principles of complete macroscopic resection, including preservation of the pseudocapsule and avoidance of tumor rupture, should be followed during laparoscopy (page 644). Resection specimen should be removed from the abdomen in a plastic bag to avoid spillage or seeding of port sites. Laparoscopic surgery could be feasible in other anatomic sites, such as smaller rectal GISTs. However, data on laparoscopic resection of GISTs at other sites are limited.

Initial Evaluation and Workup

All patients should be managed by a multidisciplinary team with expertise in sarcoma. Essential elements of the workup include the H&P, abdominal/pelvic CT scan with contrast and/or MRI, chest imaging, EUS in selected patients, endoscopy as indicated (if not performed previously), and surgical assessment (see page 637).

In patients with GIST, imaging is used for diagnosis, initial staging, restaging, monitoring response to therapy, and performing follow-up surveillance of possible recurrence. Imaging studies can include CT, MRI, and PET. Contrast-enhanced CT is the preferred imaging modality to characterize an abdominal mass and to evaluate its extent and the presence or absence of metastasis at the initial staging workup for biopsy-proven GIST. PET scan helps differentiate active tumor from necrotic or inactive scar tissue, malignant from benign tissue, and recurrent tumor from nondescript benign changes. PET provides significant value to the standard CT images, because changes in the metabolic activity of tumors often precede anatomic changes on CT. However, PET scan is not a substitute for CT. PET scans may be used to clarify ambiguous findings seen on CT or MRI. Many imaging centers are also equipped with combined PET-CT scanners, which may facilitate both anatomic and functional tumor evaluation in one step.¹⁶⁴ If clinicians consider using PET scan to monitor therapy, a baseline PET should be obtained before the start of therapy.

Resectable Disease

Surgery is the primary treatment for all patients with resectable GISTs of 2 cm or greater who have no significant risk for morbidity. However, the management of incidentally encountered small GISTs smaller than 2 cm remains controversial. Currently, data are insufficient to guide the management of very small GISTs (< 2 cm) discovered incidentally

on endoscopy, and the usefulness of regular EUS surveillance remains unestablished. Complete surgical resection is the mainstay of treatment in symptomatic patients. For a subset of patients with very small gastric GISTs (< 2 cm) with no high-risk EUS features (irregular extraluminal border, heterogeneous echo pattern, presence of cystic spaces, and echogenic foci), endoscopic surveillance at 6- to 12-month intervals may be considered (see page 638). The panel included this approach with a category 2B recommendation.

Patients with marginally resectable or resectable GIST with a significant risk for morbidity should be considered for preoperative imatinib before resection, if surgical morbidity would be improved by reducing the size of the tumor. However, close monitoring is essential, because some patients may become unresectable rapidly. Surgery is recommended if bleeding and/or symptoms are present. Baseline CT with or without MRI is recommended before the start of preoperative imatinib (see page 640). Because the optimal duration of preoperative therapy remains unknown, imatinib should be continued in patients experiencing response to therapy until maximal response (defined as no further improvement between 2 successive CT scans, which can take as long as 6–12 months). However, waiting for a maximal response before performing surgery is not always necessary. If no progression occurs, resection should be considered, if possible. If progression occurs, confirmed with CT scan, surgery is recommended after discontinuing imatinib (see page 640). Collaboration between the medical oncologist and surgeon is necessary to determine the appropriateness of surgery after major response or stable disease.

Metastatic, Unresectable, or Recurrent Disease

Advanced, unresectable, or metastatic GIST has a very high likelihood of clinical benefit and positive response after treatment with imatinib. Patients with a documented unresectable GIST, who would be at risk for severe functional deficit after resection, or who have widespread metastatic disease should be treated with imatinib mesylate in the preoperative setting (see page 640). Patients should be assessed within 3 months of initiating therapy to determine if their GIST has become resectable. In selected patients, imaging can be done before 3 months. If no progression occurs, resection can be considered after surgical consultation. Several studies have evaluated the impact of cytoreductive surgery on survival in patients with advanced GIST after treatment with imatinib. No definitive data exist to prove whether surgical resection improves clinical outcome in addition to TKI therapy for patients with resectable metastatic GIST. Prospective phase III trials are underway to assess whether resection changes outcome in patients with unresectable metastatic GIST responding to TKI therapy.

Imatinib therapy should be continued if resection is not feasible. Currently, continuous use of imatinib is recommended for metastatic GIST until progression. Patients should be maintained on the same dose, with no increase if they remain stable without objective progression of the disease. Termination of imatinib therapy in patients with GIST that is refractory to imatinib has been shown to result in a flare phenomenon, which in turn indicates that even in patients with progressive disease on imatinib therapy, imatinib may still be effective for some tumor cells.¹⁶⁵ Updated results from a randomized phase III trial by a French sarcoma group showed a significant increase in the rate of progressive disease

when imatinib therapy was interrupted in patients with advanced GIST that was stable or responding to treatment.¹⁶⁶

Recurrence after complete resection should be managed as described for unresectable or metastatic disease, because recurrent disease represents locoregional metastatic or infiltrative spread of the malignancy and has essentially the same prognosis as distant metastases overall.

Postoperative Treatment

In patients taking preoperative imatinib, dosing can be stopped immediately before surgery and resumed as soon as the patient is able to tolerate oral medications after surgery regardless of surgical margins. If persistent gross disease is present after resection, additional resection may be considered to remove residual disease. Imatinib treatment should be continued after re-resection regardless of surgical margins until progression occurs. Postoperative imatinib should be initiated after resection in patients who did not undergo prior imatinib therapy.

The panel has included postoperative imatinib as an alternative to observation for patients at significant risk for recurrence who have undergone complete resection for primary GIST (see page 641). Optimum duration of postoperative treatment has not yet been determined. Postoperative imatinib is recommended for at least 12 months in patients with intermediate- to high-risk GIST. Higher-risk patients may require longer treatment.

Risk stratification after surgical resection should be based on tumor mitotic rate, size, and location.¹⁶⁷ Gold et al.¹⁶⁸ developed a nomogram that takes into account tumor size, site, and mitotic index for predicting relapse-free survival after resection of localized primary GIST. This nomogram accurately predicts relapse-free survival after resection of localized primary GIST and might be useful for patient care, interpretation of trial results, and selection of patients for postoperative imatinib therapy.

Progressive Disease

Progression is defined as the appearance of a new lesion or an increase in tumor size. It may be determined using CT or MRI with clinical interpretation; PET may be used if the results are ambiguous (see page 642). For patients with limited progressive disease or with widespread systemic disease and good performance status (0–2), options include continuation of imatinib at the same dose, dose escalation as tolerated, or switching to sunitinib. Patients with limited progression should not be switched to sunitinib if most of the disease is still controlled by imatinib. Before dose escalation, all clinical and radiologic data, including lesion density on CT, should be taken into account. Patient compliance to imatinib therapy at standard dose should be assessed before altering the dose of imatinib or switching to sunitinib. For limited progressive disease that is potentially easily resectable, surgical resection should be considered.¹⁶⁹ Other treatment options include radiofrequency ablation or embolization (category 2B). RT (category 2B) for palliation can be considered for rare patients with bone metastases.

Options are limited for patients progressing on imatinib and sunitinib. Second-generation TKIs, such as sorafenib, dasatinib, and nilotinib, have shown activity in patients with imatinib- and sunitinib-resistant GIST. In a multicenter, ongoing phase II study involving patients with unresectable, KIT-positive GIST that had progressed on imatinib and sunitinib, 58% of patients who received sorafenib had stable disease.¹⁷⁰ Median progression-free survival was 5.3 months, and the estimated 1-year survival rate was 62%.

In another phase I trial, nilotinib alone and in combination with imatinib showed significant activity in patients with GIST resistant to prior treatment with TKIs.¹⁷¹ In a phase I dose-escalation study, 3 of 19 patients with refractory GIST had stable disease, which lasted more than 3 months in 1 patient.¹⁷² The Sarcoma Alliance for Research through Collaboration is completing a phase II multi-arm study of dasatinib in patients with imatinib- and sunitinib-refractory GIST. The efficacy and safety of nilotinib as a third-line therapy for GIST are being studied in an ongoing phase III trial.

The guidelines include sorafenib, dasatinib, or nilotinib as options for patients who are no longer experiencing clinical benefit from imatinib or sunitinib (see pages 651–653). Any patient who experiences progression of GIST despite prior therapy or who experiences a recurrence regardless of presentation should be considered for enrollment in a clinical trial, if an appropriate trial is available. Recent data reported by Fumagalli et al.¹⁷³ support rechallenging patients with imatinib after standard and investigational therapeutic options fail. In patients with progressive disease no longer receiving benefit from current TKI therapy, consider reintroduction of previously tolerated and effective TKI therapy for palliation of symptoms. The panel also feels that continuation of TKI therapy life-long for palliation of symptoms should be an essential component of best supportive care.

Surveillance

Every patient with a resected localized GIST should have a thorough H&P every 3 to 6 months; these patients should also have an abdominopelvic CT scan every 3 to 6 months. An identical schedule is used for patients who have persistent gross residual disease that is unresectable or for completely resected disease.

Guidelines Online

Information on retroperitoneal intra-abdominal soft tissue sarcomas and desmoid tumors (fibromatoses) can be found in the full soft tissue sarcoma guidelines, available online, at www.NCCN.org.

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At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in JNCCN and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Appendix

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

The full NCCN Clinical Practice Guidelines in Oncology: Soft Tissue Sarcoma are not printed in this issue of *JNCCN*, but can be accessed online at www.NCCN.org.

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Soft Tissue Sarcoma Guidelines Panel

Individual disclosures for the NCCN Soft Tissue Sarcoma Guidelines Panel members can be found on page 674. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, please visit www.NCCN.org.

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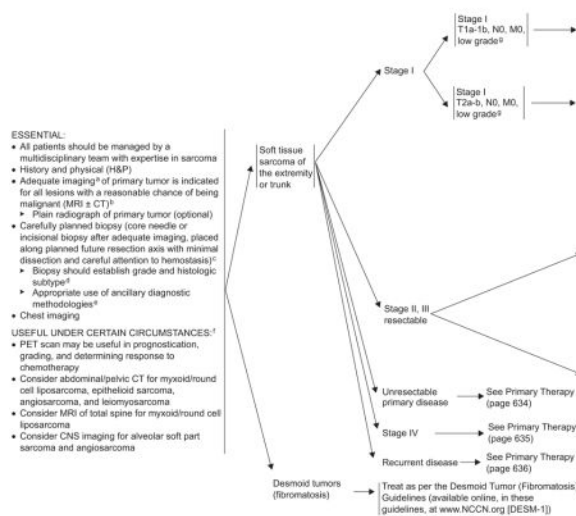
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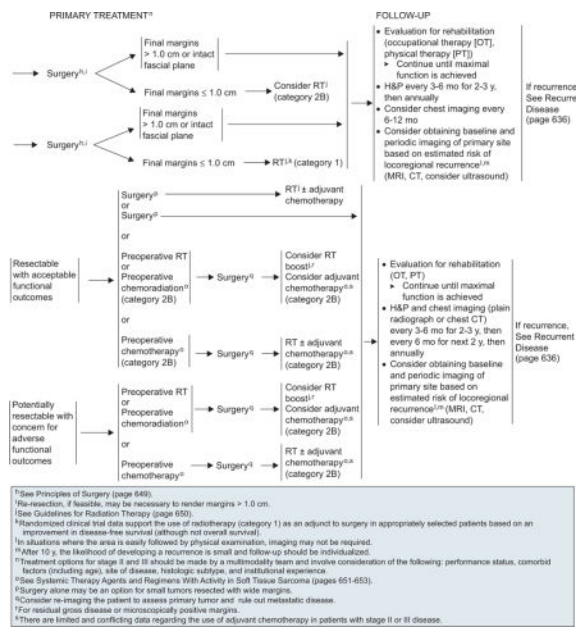
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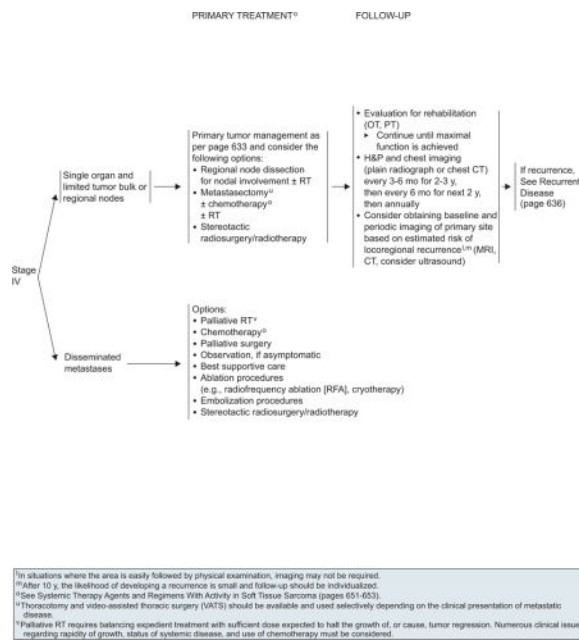
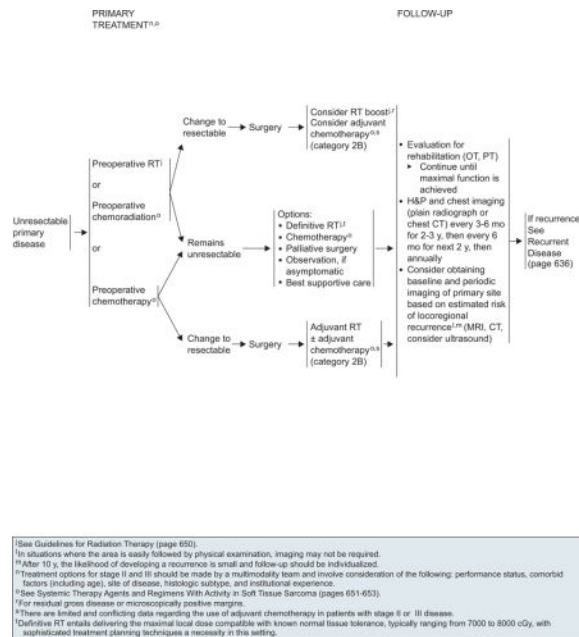
Specialties: †Medical Oncology; ¶Pathology; ¶Internal Medicine; ¶Surgery/Surgical Oncology; ¶Orthopedics/Orthopedic Oncology; §Radiotherapy/Radiation Oncology; ¶Pediatric Oncology; §Bone Marrow Transplantation

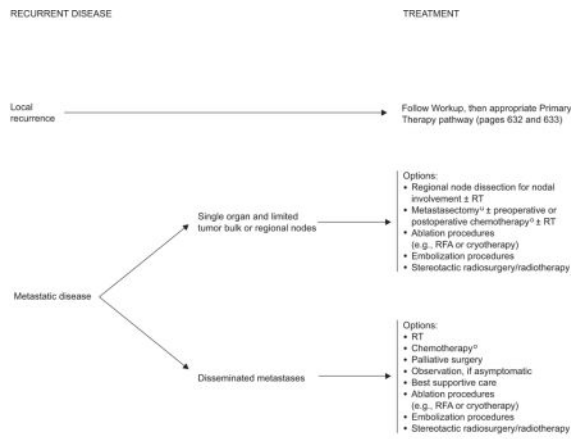
WORKUP



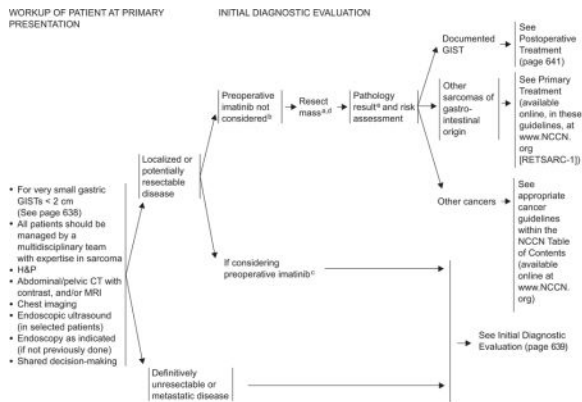
^aAdequate imaging should provide details about the size of tumor and contiguity to nearby visceral structures and neurovascular landmarks.
^bCT angiogram may be useful for patients in whom an MRI is not feasible.
^cIn selected institutions with clinical and pathologic expertise, an FNA may be acceptable.
^dSee Principles of Pathologic Assessment of Sarcoma Specimens (page 646).
^eSee Principles of Ancillary Techniques Useful in the Diagnosis of Sarcomas (pages 647 and 648).
^fDifferent subtypes have different propensities to spread to various locations, and imaging should be individualized based on subtypes.
^gSee American Joint Committee on Cancer (AJCC) Staging, 7th Edition (see staging table, available online, in these guidelines, at www.NCCN.org [ST-1]).





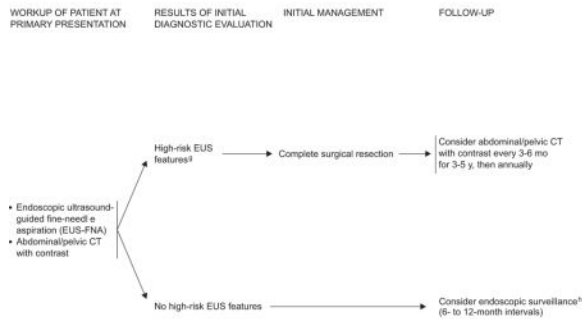


¹See Systemic Therapy Agents and Regimens With Activity in Soft Tissue Sarcoma (pages 661-663).
²Thoracotomy and video-assisted thoracic surgery (VATS) should be available and used selectively depending on the clinical presentation of metastatic disease.



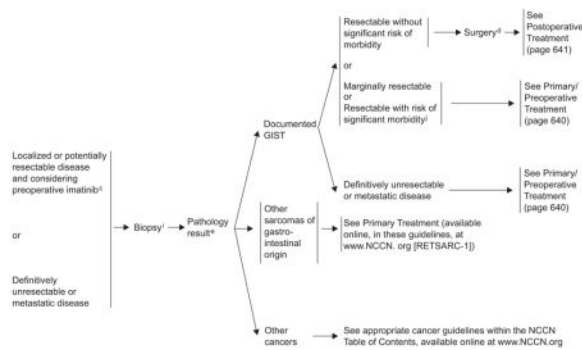
^aSurgery should induce minimal surgical morbidity; otherwise consider preoperative imatinib mesylate.
^bIf surgical morbidity would not improve by reducing the tumor size preoperatively.
^cIf surgical morbidity would be improved by reducing the tumor size preoperatively.
^dSee Principles of Surgery For GIST (page 644).
^ePathology report should include anatomic location, size, and an accurate assessment of the mitotic rate measured in the most proliferative area of the tumor. Mitotical analysis may predict response to therapy with kinase inhibitors (See Principles of Pathologic Assessment For GIST (page 643)).

APPROACH TO PATIENTS WITH VERY SMALL GASTRIC GISTS (< 2 CM)¹

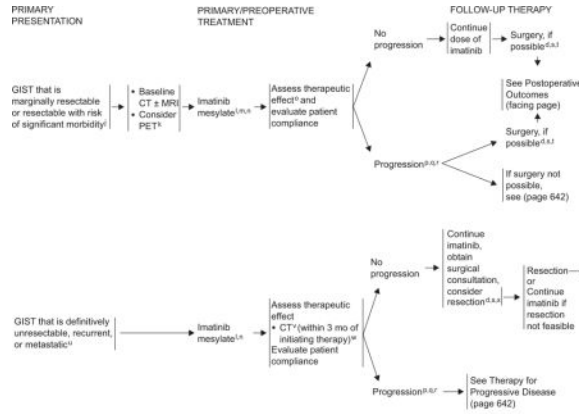


¹Adapted with permission from Sepe PS, Brugge WR. A guide for the diagnosis and management of gastrointestinal stromal cell tumors. *Nat Rev Gastroenterol Hepatol* 2008;6:363-371. All recommendations for this algorithm are category 2B.
²Possible high-risk EUS features include irregular border, cystic spaces, ulceration, echogenic foci, and heterogeneity.
³EUS surveillance should only be considered after a thorough discussion with the patient regarding the risks and benefits.

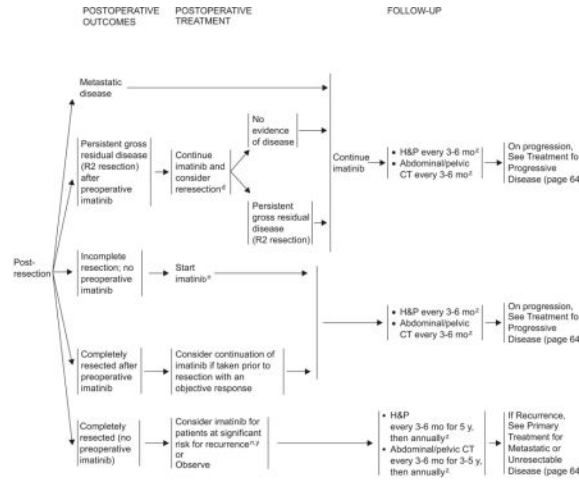
INITIAL DIAGNOSTIC EVALUATION



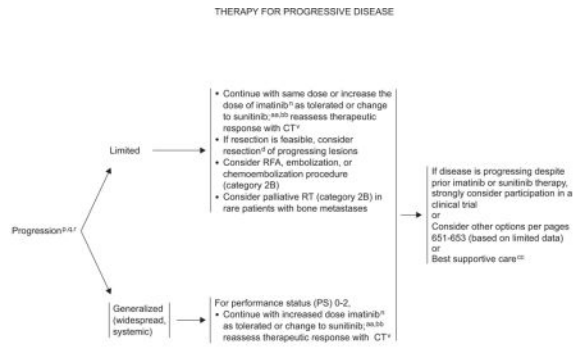
¹If surgical morbidity would be improved by reducing the tumor size preoperatively.
²See Principles of Surgery For GIST (page 644).
³Pathology report should include anatomic location, size, and accurate assessment of the mitotic rate measured in the most proliferative area of the tumor. Mutational analysis may predict response to therapy with kinase inhibitors (See Principles of Pathologic Assessment for GIST (page 643)).
⁴See Principles of Biopsy for GIST (page 643).
⁵Some patients may rapidly become unresectable; close monitoring is essential.



¹See Principles of Surgery For GIST (page 644).
²Some patients may rapidly become unresectable; dose monitoring is essential.
³PET is not a substitute for CT.
⁴If life-threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider surgery.
⁵Medical therapy is usual course of treatment; if patient is bleeding or symptomatic, may proceed to surgery.
⁶See Dosage and Administration of Imatinib (page 645).
⁷PET may give indication of imatinib activity after 2-4 wk of therapy when rapid resorption of activity is necessary; PET is not a substitute for diagnostic CT.
⁸Rarely, increase in tumor size may not indicate lack of drug efficacy; all clinical and radiographic data should be taken into account, including lesion density on CT.
⁹Progression may be determined by CT or MRI with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.
¹⁰Suggest referral to a sarcoma specialty center.
¹¹Collaboration between medical oncologist and surgeon is necessary to determine the appropriateness of surgery following major response or sustained stable disease.
¹²Dosing can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications.
¹³Consider baseline PET, if using PET during follow-up. PET is not a substitute for CT.
¹⁴Consider PET only if CT results are ambiguous.
¹⁵In some patients, it may be appropriate to image prior to 3 mo.
¹⁶No definitive data exist to prove whether surgical resection improves clinical outcomes in addition to TKI therapy alone in metastatic GIST. Prospective randomized trials are underway to assess whether resection changes outcomes in patients with metastatic GIST experiencing response to TKI therapy.



¹See Principles of Surgery For GIST (page 644).
²See Dosage and Administration of Imatinib (page 645).
³Adjuvant therapy for > 12 mo should be considered in patients with intermediate- to high-risk GIST (DeMatteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localized, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet 2009;373:1097-1104). The optimal duration has not yet been determined. Patients at significantly higher risk for disease recurrence may justify a longer course of therapy.
⁴Less surveillance may be acceptable for very small tumors (< 2 cm).



[§]See Principles of Surgery For GIST (page 644).
[¶]See Dosage and Administration of Imatinib (page 645).
^{¶¶}Rarely, increase in tumor size may not indicate lack of drug efficacy; all clinical and radiographic data should be taken into account, including lesion density on CT.
[†]Progression may be determined by CT or MRI with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.
^{¶¶¶}Suggest referral to a sarcoma specialty center.
^{¶¶¶¶}Consider PET only if CT results are ambiguous.
^{¶¶¶¶¶}See Dosage and Administration of Sunitinib (page 645).
^{¶¶¶¶¶¶}Clinical experience suggests that discontinuing kinase inhibitors, even in the setting of progressive disease, may accelerate the pace of disease progression and worsen symptoms.
^{¶¶¶¶¶¶¶}In patients with GIST progressing despite prior imatinib and sunitinib, consider reintroduction of a previously tolerated and effective tyrosine kinase inhibitor (TKI) for palliation of symptoms. Consider continuation of TKI therapy 96-week for palliation of symptoms as part of best supportive care.

PRINCIPLES OF BIOPSY FOR GIST

- GISTs are soft, fragile tumors. Biopsy may cause tumor hemorrhage and possibly increased risk for tumor dissemination.
- Consideration of biopsy should be based upon the extent of disease and suspicion of a given histologic subtype (e.g., lymphoma). EUS biopsy is preferred over percutaneous biopsy.
- Biopsy is generally necessary when planning preoperative therapy for primary GIST.
- Diagnosis is based on the Principles of Pathologic Assessment of Sarcoma Specimens (page 646); referrals to centers with expertise in sarcoma diagnosis is recommended for cases with complex or unusual histopathologic features.

PRINCIPLES OF PATHOLOGIC ASSESSMENT FOR GIST

- Pathologic assessment should follow the guidelines outlined on page 646.
- Morphologic diagnosis based on microscopic examination of histologic sections is the standard for GIST diagnosis. Several ancillary techniques are useful in support of GIST diagnosis, including immunohistochemistry (95% express CD117 and 80% express CD34) and molecular genetic testing (for mutations in *KIT* or *PDGFRA*). Referral to centers with expertise in sarcoma diagnosis is recommended for cases with complex or unusual histopathologic features.
- Tumor size and mitotic rate are used as guides to predict the malignant potential of GISTs, although it is notoriously difficult to predict the biologic potential of individual cases. The mitotic rate should be measured in the most proliferative

area of the tumor, and reported as the number of mitoses in 50 high power (400x total magnification) fields.

- Approximately 80% of GISTs have a mutation in the gene encoding the KIT receptor tyrosine kinase; another 5% to 10% of GISTs have a mutation in the gene encoding the related *PDGFRA* receptor tyrosine kinase. Because approximately 10% to 15% of GISTs have no detectable *KIT* or *PDGFRA* mutation, the absence of a mutation does not exclude the diagnosis of GIST. The presence and type of *KIT* and *PDGFRA* mutations are not strongly correlated with prognosis.
- The mutations in *KIT* and *PDGFRA* in GIST result in expression of mutant proteins with constitutive tyrosine kinase activity.

PRINCIPLES OF SURGERY FOR GIST

Primary (Resectable) GIST

The surgical procedure performed should aim to resect the tumor with histologically negative margins.

- Given the limited intramural extension, extended anatomic resections (such as total gastrectomy) are rarely indicated. Segmental or wedge resection to obtain negative margins is often appropriate.
- Lymphadenectomy is usually not required given the low incidence of nodal metastases.
- As GIST tends to be very friable, every effort should be made not to violate the pseudocapsule of the tumor.
- Re-resection is generally not indicated for microscopically positive margins on final pathology.

Resection should be accomplished with minimal morbidity and, in general, complex multi-visceral resection should be avoided. If the surgeon feels that a multi-visceral resection may be required, then multidisciplinary consultation is indicated regarding a course of preoperative imatinib therapy. Similarly, rectal GIST should be approached using a sphincter-sparing approach. If abdominoperineal resection (APR) would be necessary to achieve a negative margin resection, then preoperative imatinib therapy should be considered.

A laparoscopic approach may be considered for select GISTs in favorable anatomic locations (greater curvature or anterior wall of the stomach, jejunum, and ileum) by surgeons with appropriate laparoscopic experience.

- All oncologic principles of GIST resection must still be followed, including preservation of the pseudocapsule and avoidance of tumor spillage.
- Resection specimens should be removed from the abdomen in a plastic bag to prevent spillage or seeding of port sites.

Metastatic GIST

Imatinib is the primary therapy for metastatic GIST. Surgery may be indicated for:

- Limited disease progression refractory to systemic therapy.
- Locally advanced or previously unresectable tumors after a favorable response to preoperative imatinib.

If persistent metastatic or residual tumor remains after surgery, then imatinib should be continued as soon as the patient is able to tolerate oral intake.

DOSING AND ADMINISTRATION OF IMATINIB¹

Unresectable and/or Metastatic GIST

- Initiate dosing at 400 mg daily. Patients with documented mutations in *KIT* exon 9 may benefit from dose escalation up to 800 mg daily (given as 400 mg, twice daily), depending on tolerance.
- IF PROGRESSION OF DISEASE IS DOCUMENTED: Imatinib dose increase up to 800 mg daily (given as 400 mg, twice daily) may be considered, as clinically tolerated, in patients showing objective signs of disease progression at a lower dose and in the absence of severe adverse drug reactions.

Adjuvant Treatment After Complete Gross Resection of GIST

- 400 mg daily. In the randomized clinical study ACOSOG Z9001, imatinib was administered for 1 year, and patients at highest risk for recurrence showed increased rate of recurrence after discontinuation of drug dosing. The optimal duration of adjuvant treatment is not known.

DOSING AND ADMINISTRATION OF SUNITINIB¹

- The recommended dose of sunitinib is either:
 - 37.5 mg orally once daily without interruption or
 - 50 mg orally once daily on a schedule of 4 weeks on treatment followed by 2 weeks off (schedule 4/2).
- In patients receiving sunitinib, selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Sunitinib dose modification is recommended in patients who must receive concomitant CYP3A4 inhibitors or inducers.
 - A dose reduction for sunitinib to a minimum of 37.5 mg daily should be considered if sunitinib must be coadministered with a strong CYP3A4 inhibitor.

¹Information from the FDA label. For more detailed information, review the full content at www.fda.gov.

- A dose increase for sunitinib to a maximum of 87.5 mg daily should be considered if sunitinib must be co-administered with a CYP3A4 inducer. According to the package insert, in vitro studies indicate that sunitinib does not induce or inhibit major cytochrome enzymes.
- Sunitinib may be taken with or without food.

PRINCIPLES OF PATHOLOGIC ASSESSMENT OF SARCOMA SPECIMENS

- Pathologic assessment of biopsies and resection specimens should be carried out by an experienced sarcoma pathologist.
- Morphologic diagnosis based on microscopic examination of histologic sections remains the gold standard for sarcoma diagnosis. However, because several ancillary techniques are useful in support of morphologic diagnosis (including immunohistochemistry, classical cytogenetics, and molecular genetic testing), sarcoma diagnosis should be performed by pathologists who have access to these ancillary methods.¹
- The pathologic assessment should include evaluation of the following features, all of which should be specifically addressed in the pathology report:
 - Organ, site, and operative procedure
 - Primary diagnosis (using standardized nomenclature, such as provided in the World Health Organization Classification of Soft Tissue Tumors²).
 - Depth of tumor
 - Superficial (tumor does not involve the superficial fascia)
 - Deep
 - Size of tumor
 - Histologic grade (at the least, specify low or high grade, if applicable); ideally, grade using the French Federation of Cancer Centers Sarcoma Group or National Cancer Institute system
 - Necrosis
 - Present or absent
 - Microscopic or macroscopic
 - Approximate extent (percentage)
 - Status of margins of excision
 - Uninvolved

¹See Principles of Ancillary Techniques Useful in the Diagnosis of Sarcomas (page 647 and 648).

²Fletcher CD, Unni K, Mertens F, eds. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Soft Tissue and Bone. Lyon: IARC Press; 2002.

- Closer than 2 cm (state which margins and measured distance)
 - Involved (state which margins)
- Status of lymph nodes
 - Site
 - Number examined
 - Number positive
- Results of ancillary studies¹
 - Type of testing (electron microscopy, immunohistochemistry, molecular genetic analysis)
 - Where performed
- Additional tumor features
 - Mitotic rate
 - Presence or absence of vascular invasion
 - Character of tumor margin (well circumscribed or infiltrative)
 - Inflammatory infiltrate (type and extent)
- TNM Stage (see the staging table, available online, in these guidelines, at www.NCCN.org [ST-1])

PRINCIPLES OF ANCILLARY TECHNIQUES USEFUL IN THE DIAGNOSIS OF SARCOMAS

Morphologic diagnosis based on microscopic examination of histologic sections remains the gold standard for sarcoma diagnosis. However, several ancillary techniques are useful in support of morphologic diagnosis, including immunohistochemistry, classical cytogenetics, and molecular genetic testing. Molecular genetic testing has emerged as a particularly powerful ancillary testing approach because many sarcoma types harbor characteristic genetic aberrations, including single base-pair substitutions, deletions and amplifications, and translocations. Most molecular testing uses fluorescence in situ hybridization (FISH) approaches or polymerase chain reaction (PCR)-based methods.¹ Recurrent genetic aberrations in sarcoma² are listed below:

¹Molecular genetic analysis involves highly complex test methods. None of the methods are absolutely sensitive or provide results that are absolutely specific; test results must always be interpreted in the context of the clinical and pathologic features of the case. Testing should therefore be performed by a pathologist with expertise in sarcoma diagnosis and molecular diagnostic techniques.

²This table is not exhaustive for either sarcomas with characteristic genetic changes or the genes involved. Consultation with a pathologist who has expertise in sarcoma diagnosis and molecular diagnostic techniques should be obtained before testing.

TUMOR	ABERRATION	GENES INVOLVED
<u>Malignant Round Cell Tumors</u>		
Ewing's sarcoma/peripheral neuroectodermal tumor	t(11;22)(q24;q12) t(21;22)(q22;q12) other rare variants	<i>EWS-FLI1</i> <i>EWS-ERG</i> various
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	<i>EWS-WT1</i>
Embryonal rhabdomyosarcoma	Complex alterations	Unknown
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14) t(1;13)(p36;q14)	<i>PAX3-FKHR</i> <i>PAX7-FKHR</i>
<u>Lipomatous Tumors</u>		
Myxoid/round cell liposarcoma	t(12;16)(q13;p11)	TLS-CHOP
Atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLPS)	Supernumerary ring chromosomes; giant marker chromosomes	Amplification of region 12q14-15, including <i>MDM2</i> , <i>CDK4</i> , <i>HMG2</i> , <i>SAS</i> , <i>GLI</i>
Dedifferentiated liposarcoma	Same as for ALT/WDLPS	Same as for ALT/WDLPS
Pleomorphic liposarcoma	Complex alterations	Unknown
<u>Other Sarcomas</u>		
Alveolar soft part sarcoma	der(17)(X;17)(p11;q25)	<i>ASPL-TFE3</i>
Angiomatoid fibrous histiocytoma	t(2;22)(q33;q12) t(12;16)(q13;p11)	<i>EWS-CREB1</i> <i>TLS-ATF1</i>
Clear cell sarcoma	t(12;22)(q13;q12) t(2;22)(q33;q12)	<i>EWS-ATF1</i> <i>EWS-CREB1</i>
Congenital/infantile – fibrosarcoma	t(12;15)(p13;q25)	<i>ETV6-NTRK3</i>
Dermatofibrosarcoma protuberans	t(17;22)(q22;q13) and derivative ring chromosomes	<i>COL1A1-PDGFB</i>
Desmoid fibromatosis	Trisomy 8 or 20; loss of 5q	<i>CTNNB1</i> or <i>APC</i> mutations
Epithelioid sarcoma (proximal type)	Bi-allelic inactivation of 22q11.2	<i>INI1</i>
Extrarenal rhabdoid tumor	Bi-allelic inactivation of 22q11.2	<i>INI1</i>
Extraskeletal myxoid chondrosarcoma	Rearrangements of 9q22	<i>CHN</i>
Sporadic GIST Familial GIST (Carney-Stratakis syndrome)	Activating kinase mutations KREBS cycle mutation	<i>KIT</i> or <i>PDGFRA</i> <i>SDH</i> subunit mutations
Inflammatory myofibroblastic tumor	Rearrangements of 2p23	<i>ALK</i>
Leiomyosarcoma	Complex alterations	Unknown
Low-grade fibromyxoid sarcoma	t(7;16)(q34;p11)	<i>TLS-BBF2H7</i>
Malignant peripheral nerve sheath tumor	Complex alterations	Unknown
Synovial sarcoma	t(X;18)(p11;q11) t(X;18)(p11;q11)	<i>SYT-SSX1</i> <i>SYT-SSX2</i>
Tenosynovial giant cell tumor/pigmented villonodular synovitis (TGCT/PVNS)	t(1;2)(p13;q35)	<i>CSF1</i>

PRINCIPLES OF SURGERY

Biopsy of Sarcoma

- A pretreatment biopsy to diagnose and grade a sarcoma is highly preferred. Biopsy should be performed by an experienced surgeon (or radiologist) and may

be accomplished by open incisional or needle technique. Endoscopic or needle biopsy may be indicated for deep, thoracic, abdominal, or pelvic sarcomas.

Sarcoma Surgery

- The surgical procedure necessary to resect the tumor with appropriately negative margins should be used. Close margins may be necessary to preserve uninvolved critical neurovascular structures, bones, joints, etc. Ideally, the biopsy site should be excised en bloc with the definitive surgical specimen. Dissection should be through grossly normal tissue planes uncontaminated by tumor. If the tumor is close to or displaces major vessels or nerves, these need not be resected if the adventitia or perineurium is removed and the underlying neurovascular structures are not involved with gross tumor. Radical excision/entire anatomic compartment resection is not routinely necessary. Surgical clips should be placed to mark the periphery of the surgical field and other relevant structures to help guide potential future radiation therapy. If closed suction drainage is used, the drains should exit the skin close to the edge of the surgical incision (in case re-resection or radiation is indicated).

Resection Margins

- Surgical margins should be documented by both the surgeon and pathologist when evaluating a resected specimen. If surgical resection margins are positive on final pathology (other than bone, nerve, or major blood vessels), surgical re-resection to obtain negative margins should be strongly considered if it will not have a significant impact on functionality. Consideration for adjuvant radiation therapy should be given for a close (< 1 cm) soft tissue margin or a microscopically positive margin on bone, major blood vessels, or a major nerve.
 - R0 resection - No residual microscopic disease
 - R1 resection - Microscopic residual disease
 - R2 resection - Gross residual disease

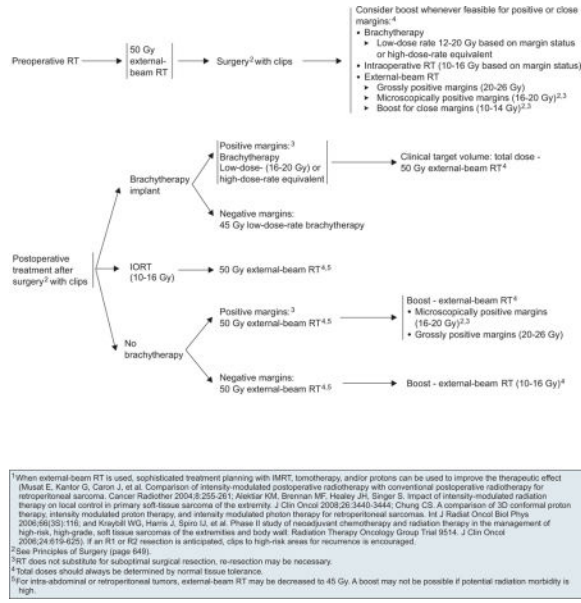
Limb Salvage Surgery

- For extremity sarcomas, the goal of surgery should be functional limb preservation, if possible, within the realm of an appropriate oncologic resection.

Amputation

- Before considering amputation, patients should be evaluated by a surgeon with expertise in the treatment of soft tissue sarcomas. Amputation to treat an extremity sarcoma should be considered based on patient preference or if gross total resection of the tumor is expected to render the limb nonfunctional.
- Evaluate postoperative rehabilitation (PT, OT) for patients with extremity sarcoma. Continue rehabilitation until maximal function is achieved.

GUIDELINES FOR RADIATION THERAPY¹



SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA^{a, b}

Extremity, Retroperitoneal, Intra-abdominal	Angiosarcoma	Desmoid Tumors (Fibromatosis)	GIST
<p><u>Combination regimens</u></p> <ul style="list-style-type: none"> • AD (doxorubicin, dacarbazine)^{1,2} • AIM (doxorubicin, ifosfamide, mesna)^{3,4} • MAID (mesna, doxorubicin, ifosfamide, dacarbazine)⁵ • Ifosfamide, epirubicin, mesna⁶ • Gemcitabine and docetaxel^{7,8} • Gemcitabine and vinorelbine⁹ 	<p><u>Single agents</u></p> <ul style="list-style-type: none"> • Doxorubicin¹⁰ • Ifosfamide^{6,11} • Epirubicin • Gemcitabine • Dacarbazine • Liposomal doxorubicin¹² • Temozolomide¹³ 	<ul style="list-style-type: none"> • Paclitaxel^{14,15} • Docetaxel • Vinorelbine • Sorafenib^{16,17} • Sunitinib¹⁸ • Bevacizumab¹⁹ • All other systemic therapy options as per extremity sarcoma 	<ul style="list-style-type: none"> • Sulindac²⁰ or other non-steroidal anti-inflammatory drugs (NSAIDs) including celecoxib^c • Tamoxifen²¹ • Toremifene²² • Methotrexate and vinblastine²³ • Low-dose interferon²⁴ • Doxorubicin-based regimens^{25,26} • Imatinib mesylate²⁷
<p><u>Solitary Fibrous Tumor/Hemangiopericytoma</u></p> <ul style="list-style-type: none"> • Bevacizumab and temozolomide³⁵ • Sunitinib^{36,37} 	<p><u>Pigmented Villonodular Synovitis/Tenosynovial Giant Cell Tumor (PVNS/TGCT)</u></p> <ul style="list-style-type: none"> • Imatinib³⁸ 		
<p><u>Alveolar Soft Part Sarcoma (ASPS)</u></p> <ul style="list-style-type: none"> • Sunitinib^{39,40} (category 2B) 	<p><u>PEComa, Recurrent Angiomyolipoma, Lymphangi leiomyomatosis</u></p> <ul style="list-style-type: none"> • Sirolimus⁴¹⁻⁴⁵ 		
<p>Chordoma (All recommendations are category 2B)</p>			
<p><u>Combination regimens</u></p> <ul style="list-style-type: none"> • Erlotinib and cetuximab • Imatinib and cisplatin⁴⁶ 	<p><u>Single agents</u></p> <ul style="list-style-type: none"> • Erlotinib⁴⁸ • Imatinib^{49,50} • Sunitinib³⁷ 		

• Imatinib and sirolimus^{4,7}

^a Alveolar soft part sarcoma and clear cell sarcomas are generally not sensitive to chemotherapy.

^b References for regimens, see pages 652 and 653.

^c The risk for cardiovascular events may be increased in patients receiving celecoxib. Physicians prescribing celecoxib should consider this emerging information when weighing the benefits against risks for individual patients (FDA Talk Paper T04-61, Dec 23, 2004).

¹ Zalupski M, Metch B, Balcerzak S, et al. Phase III comparison of doxorubicin and dacarbazine given by bolus versus infusion in patients with soft-tissue sarcomas: a Southwest Oncology Group study. *J Natl Cancer Inst* 1991;83:926-932.

² Antman K, Crowley J, Balcerzak SP, et al. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. *J Clin Oncol* 1993;11:1276-1285.

³ Grobmyer SR, Maki RG, Demetri GD, et al. Neo-adjuvant chemotherapy for primary high-grade extremity soft tissue sarcoma. *Ann Oncol* 2004;15:1667-1672.

⁴ Edmonson J, Ryan L, Blum R, et al. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. *J Clin Oncol* 1993;11:1269-1275.

⁵ Elias A, Ryan L, Sulkes A, et al. Response to mesna, doxorubicin, ifosfamide, and dacarbazine in 108 patients with metastatic or unresectable sarcoma and no prior chemotherapy. *J Clin Oncol* 1989;7:1208-1216.

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Individual Disclosure for the NCCN Soft Tissue Sarcoma Panel					
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Scott Antonia, MD, PhD	Novartis Pharmaceuticals Corporation; Ziopharm; and Pfizer Inc.	None	None	None	12/17/09
Robert S. Benjamin, MD	Novartis Pharmaceuticals Corporation	Novartis Pharmaceuticals Corporation	Johnson & Johnson; and Pfizer Inc.	None	12/29/09
Marilyn M. Bui, MD, PhD	None	None	None	None	8/13/09
Ephraim S. Casper, MD	None	Novartis Pharmaceuticals Corporation	None	None	9/29/09
Ernest U. Conrad III, MD	Stryker Corporation; and Zimmer Corporation	None	None	None	10/29/09
Thomas F. DeLaney, MD	None	None	None	None	7/3/09
George D. Demetri, MD	ARIAD Pharmaceuticals, Inc.; Daiichi-Sankyo Co.; Novartis Pharmaceuticals Corporation; Ziopharm; and Pfizer Inc.	ARIAD Pharmaceuticals, Inc.; Daiichi-Sankyo Co.; Johnson & Johnson; Novartis Pharmaceuticals Corporation; Koltan Pharmaceuticals; Ziopharm; and Pfizer Inc.	None	None	12/22/09
Kristen N. Ganjoo, MD	None	Genentech, Inc.; and GlaxoSmithKline	None	None	1/5/10
Martin J. Heslin, MD	None	None	None	None	1/7/10
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Sean V. McGarry, MD	None	None	None	Musculoskeletal Transplant Foundation	10/29/09
Richard J. O'Donnell, MD	None	None	None	None	10/29/09
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Raphael E. Pollock, MD, PhD	None	None	None	None	11/23/09
R. Lor Randall, MD	None	Musculoskeletal Tumor Society	None	None	11/4/09
Richard F. Riedel, MD	None	ARIAD Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	None	None	12/8/09
Karen D. Schupak, MD	None	None	None	None	7/2/09
Herbert S. Schwartz, MD	None	None	None	Musculoskeletal Transplant Foundation	7/1/09
Katherine Thornton, MD	Amgen Inc.; ARIAD Pharmaceuticals, Inc.; Celgene Corporation; and Genentech, Inc.	Pfizer Inc.	None	None	12/9/09
Margaret von Mehren, MD	Johnson & Johnson; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	ARIAD Pharmaceuticals, Inc.; Johnson & Johnson; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	None	None	2/26/10
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