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Soft Tissue Sarcoma, Version 2.2022

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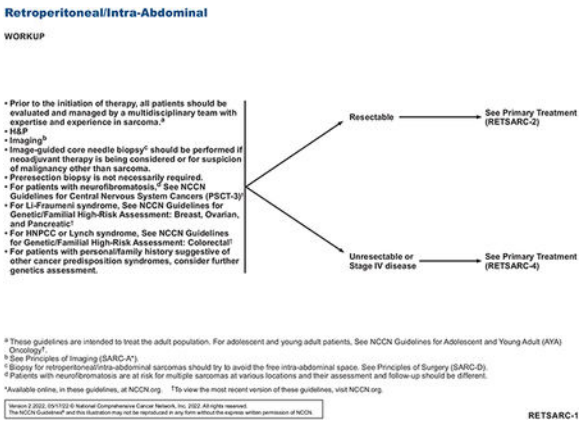
Abstract

Soft tissue sarcomas (STS) are rare malignancies of mesenchymal cell origin that display a heterogenous mix of clinical and pathologic characteristics. STS can develop from fat, muscle, nerves, blood vessels, and other connective tissues. The evaluation and treatment of patients with STS requires a multidisciplinary team with demonstrated expertise in the management of these tumors. The complete NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Soft Tissue Sarcoma provide recommendations for the diagnosis, evaluation, and treatment of extremity/superficial trunk/head and neck STS, as well as retroperitoneal/intra-abdominal STS, desmoid tumors, and rhabdomyosarcoma. This portion of the NCCN Guidelines discusses general principles for the diagnosis and treatment of retroperitoneal/intra-abdominal STS, outlines treatment recommendations, and reviews the evidence to support the guidelines recommendations.



Overview

Sarcomas are a rare and heterogeneous group of solid tumors of mesenchymal origin accounting for only 1% of all adult malignancies and 15% of childhood malignancies. They can be divided broadly into:

- Sarcomas of soft tissues (including fat, muscle, nerve and nerve sheath, blood vessels, and other connective tissues)
- Sarcomas of bone

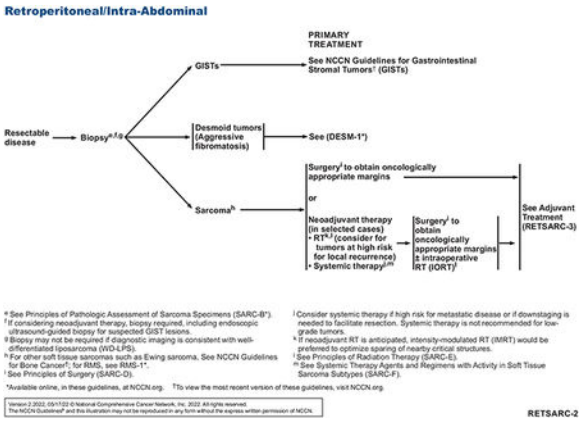
In 2022, an estimated 13,190 people will be diagnosed with soft tissue sarcoma (STS) in the United States, with approximately 5,130 deaths.[1] The true incidence of STS is underestimated, especially because a large proportion of patients with gastrointestinal stromal tumors (GISTs) may not have been included in tumor registry databases before 2001. Prior radiation therapy (RT) to the affected area is a risk factor for the development of STS.[2-4] Other risk factors that are associated with the development of STS include various chemicals (eg, herbicides, such as agent orange) and genetic syndromes (eg, Li-Fraumeni syndrome, neurofibromatosis).[5] More than 50 different histologic subtypes of STS have been identified. STS most commonly metastasizes to the lungs; tumors arising in the abdominal cavity more commonly metastasize to the liver and peritoneum.

The NCCN Guidelines for Soft Tissue Sarcoma address the management of STS in adult patients from the perspective of the following disease subtypes:

- STS of extremity, superficial/trunk, or head and neck
- Retroperitoneal or intra-abdominal STS
- Desmoid tumors (aggressive fibromatoses)
- Rhabdomyosarcoma

The anatomic site of the primary disease represents an important variable that influences treatment and outcome. Extremities (43%), the trunk (10%), viscera (19%), retroperitoneum (15%), or head and neck (9%) are the most common primary sites.[6] Desmoid tumors, or aggressive fibromatosis, are a unique soft tissue tumor subtype that is characterized by local infiltration rather than distant metastasis. Rhabdomyosarcoma is the most common STS of children and adolescents and is less common in adults.

Before start of treatment, all patients should be evaluated and managed by a multidisciplinary team with extensive expertise and experience in the treatment of STS.[7] Because STS is rare and often complex, adherence to evidence-based recommendations is particularly important. Analysis of data from 15,957 patients with STS in the National Cancer Database showed that NCCN Guidelines-adherent treatment was associated with improved survival outcomes.[8]



This portion of the NCCN Guidelines discusses general principles for the diagnosis and treatment of retroperitoneal/intra-abdominal STS. For the full NCCN Guidelines for STS, visit NCCN.org.

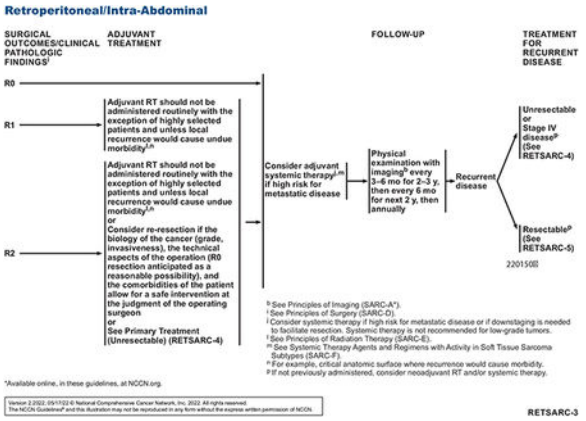
Retroperitoneal/Intra-abdominal Soft Tissue Sarcomas

Evaluation and Workup

The initial evaluation and workup for retroperitoneal/intra-abdominal STS (see RETSARC-1, page 816) are similar to those for the extremity sarcomas. This workup involves a thorough history and physical examination and appropriate imaging studies. CT is the preferred imaging modality, although MRI can also be used in certain situations. Chest imaging should be performed for histologies that have the potential for lung metastases. If possible, a multidisciplinary sarcoma panel should review the patient.

The differential diagnosis of retroperitoneal/intra-abdominal soft tissue mass includes malignant lesions (such as other sarcomas, GISTs, lymphomas, or germ cell tumors), desmoids, and benign lesions. Preresection biopsy is not necessary for all patients. However, confirmation of a sarcoma diagnosis (including histologic subtype) is required for patients being considered for neoadjuvant therapy. Image-guided (CT or ultrasound) core needle biopsy is preferred over open surgical biopsy, and should be performed if neoadjuvant therapy is being considered or for suspicion of malignancy other than sarcoma. The goal of this strategy is to avoid inappropriate major resection of another tumor, such as an intra-abdominal lymphoma or germ cell tumor. If a retroperitoneal STS is encountered unexpectedly when a laparotomy is performed for some other reason, a core needle biopsy should be done to establish the diagnosis as well as the histopathologic type and grade of tumor. Then, the optimal subsequent resection could be performed at a center with sarcoma expertise.

For additional information on the “Principles of Pathologic Assessment of Sarcoma Specimens,” see SARC-B (page 821).

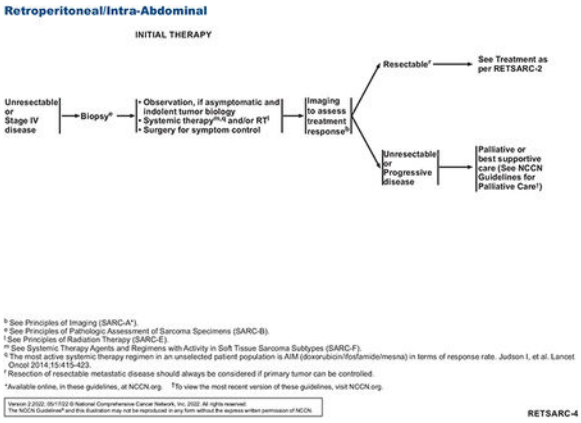


Radiation Therapy

RT can be administered either as neoadjuvant treatment of patients with resectable disease or as a primary treatment of those with unresectable disease. In general, the panel discourages adjuvant RT for retroperitoneal/intra-abdominal STS except for highly selected cases where local recurrence (LR) would cause undue morbidity. The panel emphasizes that RT is not a substitute for definitive surgical resection with oncologically appropriate margins and reresection may be necessary. If reresection is not feasible, adjuvant RT may be considered in highly selected patients, who have not received neoadjuvant RT, to attempt to control microscopic residual disease; however, this approach has not been validated in randomized trials and may be associated with toxicity, given the predilection for normal bowel to occupy the void left by resection of the sarcoma.

Newer RT techniques such as intensity-modulated RT (IMRT) and protons may allow tumor target coverage and acceptable clinical outcomes within normal tissue dose constraints to adjacent organs at risk.[9-13] When external beam RT (EBRT) is used, sophisticated treatment planning with IMRT, image-guided RT, and/or proton therapy can be used to improve therapeutic effect. However, the safety and efficacy of adjuvant RT techniques have yet to be evaluated in multicenter randomized controlled studies.

Neoadjuvant RT—If radiation is being considered for highly selected cases as part of multimodality therapy for retroperitoneal/intra-abdominal STS, a neoadjuvant approach is favored because there is a defined tumor target, displacement of the adjacent bowel, the potential to reduce the risk of tumor seeding at the time of surgery, and it may render tumors more amenable to resection.[14-16] Long-term results of 2 small nonrandomized prospective studies showed favorable 5-year local recurrence-free survival (RFS) (60%), disease-free survival (DFS) (46%), and overall survival (OS) rates (61%) following R0 or R1 resection after neoadjuvant RT in patients with intermediate or high-grade retroperitoneal STS.[17] Analysis of data from 11 studies of retroperitoneal STS in a recent systematic review and meta-analysis indicated lower rates of LR with neoadjuvant versus adjuvant RT (odds ratio [OR], 0.03; P=.02).[16]



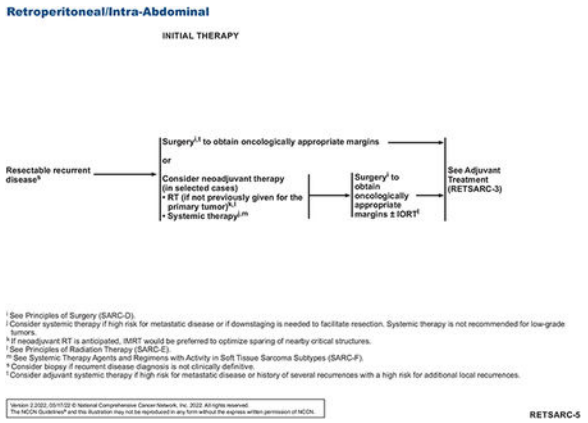
However, results from another study suggested that neoadjuvant RT may not be as effective for treating retroperitoneal/intra-abdominal STS as previously thought. EORTC-62092 (STRASS) was an open-label, randomized, phase III study that evaluated the efficacy and safety of neoadjuvant RT in 266 patients with primary localized retroperitoneal sarcoma.[18] The primary endpoint of the trial was not met, as the neoadjuvant RT + surgery group had a median abdominal RFS of 4.5 versus 5 years in the surgery only group (hazard ratio [HR], 1.01; log rank, *P*=.95). The most common grade 3 or 4 adverse events were lymphopenia (77%), anemia (12%), and hypoalbuminemia (12%) in the neoadjuvant RT + surgery group, and anemia (8%) and hypoalbuminemia (4%) in the surgery only group.

Although the authors stated that neoadjuvant RT should not be considered standard-of-care for retroperitoneal STS based on the STRASS data, this conclusion has drawn controversy.[18-21] Some have criticized the study design and interpretation of the data, including the use of a composite primary endpoint that defined a variety of events as abdominal recurrence. Additionally, information relevant to understanding the patient population, such as R0 versus R1 resection status, was not reported. The rate of grade 3 or 4 adverse events in the neoadjuvant RT group was also observed to be higher than that reported in another trial with a similar patient population, and could potentially be related to the rate of protocol compliance for RT reported in the STRASS trial (65%). Despite these limitations, it should be noted that the STRASS trial remains one of the few large randomized studies that has evaluated neoadjuvant RT for retroperitoneal STS.

Results from an exploratory post-hoc analysis of the STRASS data suggested that neoadjuvant RT may be favorable for certain patients with retroperitoneal sarcomas, such as those with liposarcoma (LPS).[18] Additional data from the trial also suggested that neoadjuvant RT may be effective in reducing the risk of LR.[18,20] Based on these observations, further investigation is needed to confirm which patients with retroperitoneal/intra-abdominal STS would benefit the most from neoadjuvant RT.

Based on the available evidence, the current guidelines recommend that neoadjuvant RT can be considered for selected patients with retroperitoneal/intra-abdominal STS who are at high risk for LR. If neoadjuvant RT is considered an appropriate treatment option, the guidelines recommend 50 Gy EBRT (in 1.8–2 Gy per fraction), followed by surgery with clips and consideration of intraoperative RT (IORT) boost for known or suspected positive margins at

the time of surgery (see SARC-E 3 of 4, page 823). Adjuvant EBRT boost is discouraged in this setting. An alternative approach to be considered in experienced centers only is 45–50 Gy in 25–28 fractions to the entire clinical target volume with dose-painted simultaneous integrated boost to total dose of 57.5 Gy in 25 fractions.[22,23] Since this approach is used in many NCCN Member Institutions, the guidelines have included this dosing schedule and recommend that higher-risk retroperitoneal margins should be jointly defined by the surgeon and the radiation oncologist, with no boost to be given after surgery.



Adjuvant RT—The panel discourages providing an adjuvant EBRT boost for retroperitoneal/intra-abdominal STS (see SARC-E 3 of 4, page 823). If RT is not given before surgical resection, consider follow-up with possible neoadjuvant EBRT at time of localized recurrence. If adjuvant RT is deemed necessary in highly selected cases, a coordinated effort by the surgeon and the radiation oncologist to displace bowel from the tumor bed with omentum or other tissue displacers is recommended to reduce the risk of RT-related bowel toxicity.

Intraoperative RT—The use of IORT for retroperitoneal STS is provocative, but interpretation of the results is limited by the nature of the small and heterogenous studies.[24-31] In a prospective single institution study of patients with retroperitoneal STS treated with a protocol involving maximal tumor resection, high-dose-rate IORT, and adjuvant EBRT, the overall 5-year local control rate for the whole group was 62%; local control rate was better for patients with primary tumors than for those with recurrent tumors (74% vs 54%; P=.40).[25] The overall 5-year distant metastasis-free survival rate was 82% (100% for those with low-grade tumors vs 70% for those with high-grade tumors; P=.05). The 5-year DFS and OS rates were 55% and 45%, respectively. IORT with or without EBRT has been effective in terms of local control and survival in patients with primary and recurrent retroperitoneal STS.[26-28,30] In a study that assessed the long-term outcome of patients with retroperitoneal STS treated by neoadjuvant RT, resection, and IORT with intraoperative electron beam RT, OS (74% and 30%, respectively) and local control (83% and 61%, respectively) were better in patients undergoing gross total resection and intraoperative electron beam RT compared with those who had only gross total resection.[26] An ongoing phase I/II study (ClinicalTrials.gov identifier: NCT01566123) is examining

neoadjuvant RT, followed by surgery with IORT in patients with high-risk retroperitoneal sarcoma. Preliminary results suggest promising local control and OS rates.[32]


PRINCIPLES OF PATHOLOGIC ASSESSMENT OF SARCOMA SPECIMENS

- Biopsy should establish malignancy, provide a specific diagnosis where possible, and provide a grade where appropriate or feasible, recognizing that limited biopsy material may underestimate grade.
- In patients without a definitive diagnosis following initial biopsy due to limited sampling size, repeat image-guided core needle biopsy should be considered to make a diagnosis.
- 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, since several ancillary techniques are useful in support of morphologic diagnosis (including immunohistochemistry [IHC], classical cytogenetics, and molecular genetic testing), sarcoma diagnosis should be carried out 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 the WHO Classification of Tumors of Soft Tissue and Bone[2])
- 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 (FNCLCC), NCI system, or appropriate diagnosis-specific grading system if applicable
- Necrosis
  - Present or absent
  - Microscopic or macroscopic
  - Approximate extent (percentage)
- Status of margins of excision
  - Uninvolved
  - Involved (state which margins)
  - Close (state which margins and measured distance)
- Quality of margin (a more limited fascial margin may be equivalent to a wider soft tissue margin)
- Status of lymph nodes
  - Site
  - Number examined
  - Number positive
- Results of ancillary studies[1]
  - Type of testing (ie, electron microscopy, IHC, molecular genetic analysis)
  - Where performed
- Additional tumor features of potential clinical value
  - Mitotic rate per 10 high-power fields (HPFs)
  - Presence or absence of vascular invasion
  - Character of tumor margin (well circumscribed or infiltrative)
  - Inflammatory infiltrate (type and extent)
- TNM Stage (See ST-5* through ST-8*)

[1] See Principles of Ancillary Techniques Useful in the Diagnosis of Sarcomas (SARC-C*).
[2] Fletcher CDM, Bridge JA, Hogendoorn P, Mertens F. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Soft Tissue and Bone, Fifth Edition. IARC, Lyon, 2020.

*Available online, in these guidelines, at NCCN.org.

SARC-B

Chemotherapy/Chemoradiation

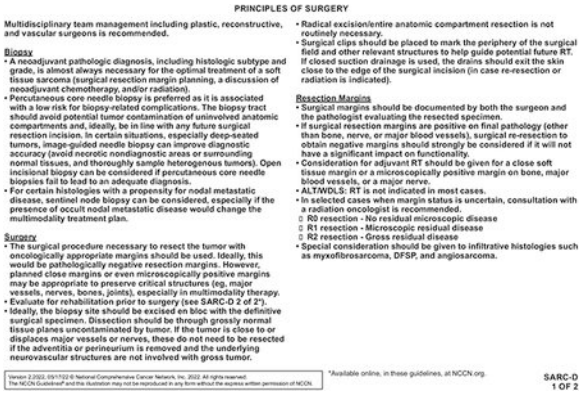
Resectable Disease

Neoadjuvant Therapy: Neoadjuvant chemotherapy[33-37] or chemoradiation[38-47] has been evaluated in single and multicenter studies in patients with high-grade tumors; however, much of the available randomized data speaks to the management of extremity sarcomas.

Studies that have evaluated neoadjuvant chemotherapy followed by surgery have reported inconsistent findings. The results of a randomized study that compared surgery alone versus neoadjuvant chemotherapy followed by surgery in 134 evaluable patients with high-risk tumors (tumors ≥8 cm of any grade, grade II/III tumors <8 cm, grade II/III locally recurrent tumors, or tumors with inadequate surgery) did not show a major survival benefit for patients receiving chemotherapy.[34] At a median follow-up of 7.3 years, the estimated 5-year DFS rate was 52% for the no chemotherapy arm and 56% for the chemotherapy arm (P=.3548). The corresponding 5-year OS rate for both arms was 64% and 65%, respectively (P=.2204). A cohort analysis of 674 patients with stage III STS of extremity treated at a single institution revealed that clinical benefits associated with neoadjuvant or adjuvant doxorubicin-based chemotherapy were not sustained beyond 1 year.[35] In another retrospective study, the benefit of neoadjuvant chemotherapy was only seen in patients with high-grade extremity tumors larger than 10 cm but not in patients with tumors 5 to 10 cm.[36]

In a single-institution study involving 48 patients with high-grade extremity STS (≥8 cm), the outcome of patients treated with neoadjuvant chemoradiation with the MAID (mesna, doxorubicin, ifosfamide, and dacarbazine) regimen followed by surgery and adjuvant chemotherapy with the same regimen was superior to that of historical controls.[40] The 5-year actuarial local control, freedom from distant metastasis, DFS, and OS rates were 92% and 86% (P=.1155), 75% and 44% (P=.0016), 70% and 42% (P=.0002), and 87% and 58% (P=.0003) for the MAID and control groups, respectively.[40] The same protocol was later evaluated in the RTOG 9514 study of 66 patients with large (≥8 cm), high-grade (stage II or III; grade 2 or 3 in a 3-tier grading system), primary or locally recurrent STS of the extremities or trunk.[42,43] The 5-year rates of locoregional failure (including amputation) and distant metastasis were 22% and 28%, respectively, with a median follow-

up of 7.7 years. The estimated 5-year DFS, distant DFS, and OS rates were 56%, 64%, and 71%, respectively.[43] Long-term follow-up data of these studies confirmed that neoadjuvant chemoradiation followed by resection and adjuvant chemotherapy with a doxorubicin-based regimen improves local control and OS and DFS rates in patients with high-grade STS of extremity and body wall; however, neoadjuvant chemoradiation was associated with significant short-term toxicities.[43,44]



PRINCIPLES OF SURGERY

Multidisciplinary team management including plastic, reconstructive, and vascular surgeons is recommended.

Biopsy

- A neoadjuvant pathologic diagnosis, including histologic subtype and grade, is almost always necessary for the optimal treatment of a soft tissue sarcoma (surgical resection margin planning, a discussion of neoadjuvant chemotherapy, and/or radiation).
- Percutaneous core needle biopsy is preferred as it is associated with a low risk for biopsy-related complications. The biopsy tract should avoid potential tumor contamination of uninvolved anatomic compartments and, ideally, be in line with any future surgical resection incision. In certain situations, especially deep-seated tumors, image-guided needle biopsy can improve diagnostic accuracy (avoid necrotic nondiagnostic areas or surrounding normal tissues, and thoroughly sample heterogenous tumors). Open incisional biopsy can be considered if percutaneous core needle biopsies fail to lead to an adequate diagnosis.
- For certain histologies with a propensity for nodal metastatic disease, sentinel node biopsy can be considered, especially if the presence of occult nodal metastatic disease would change the multimodality treatment plan.

Surgery

- The surgical procedure necessary to resect the tumor with oncologically appropriate margins should be used. Ideally, this would be pathologically negative resection margins. However, planned close margins or even microscopically positive margins may be appropriate to preserve critical structures (eg, major vessels, nerves, bones, joints), especially in multimodality therapy.
- Evaluate for rehabilitation prior to surgery (see SARC-D 2 of 2†).
- 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 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/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 RT. 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 the pathologist evaluating the 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 strongly be considered if it will not have a significant impact on functionality.
- Consideration for adjuvant RT should be given for a close soft tissue margin or a microscopically positive margin on bone, major blood vessels, or a major nerve.
- ALT/WDLS: RT is not indicated in most cases.
- In selected cases when margin status is uncertain, consultation with a radiation oncologist is recommended.
  - R0 resection - No residual microscopic disease
  - R1 resection - Microscopic residual disease
  - R2 resection - Gross residual disease
- Special consideration should be given to infiltrative histologies such as myxofibrosarcoma, DFSP, and angiosarcoma.

†Available online, in these guidelines, at NCCN.org.

SARC-D 1 OF 2

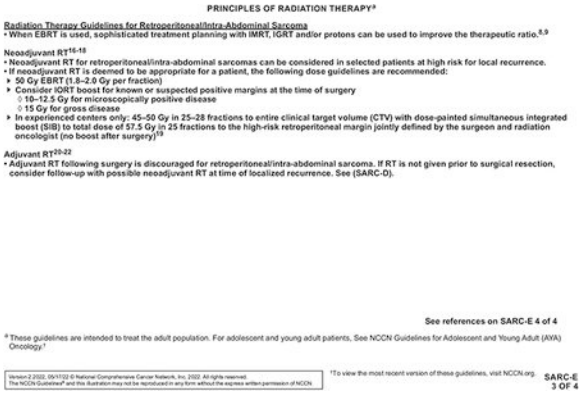
An ongoing prospective randomized trial, STRASS II (ClinicalTrials.gov identifier: NCT04031677), is evaluating the role of neoadjuvant chemotherapy in high-risk retroperitoneal STS.[48] Those randomized to chemotherapy will receive doxorubicin and ifosfamide, unless they have a diagnosis of leiomyosarcoma (LMS), in which case they will receive doxorubicin and dacarbazine. The study will randomize 250 patients and assess the difference in DFS with or without neoadjuvant chemotherapy.

Adjuvant Therapy: Available evidence from meta-analyses[49-53] and randomized clinical trials[54-59] suggests that adjuvant chemotherapy improves RFS in patients with STS of extremities. However, data regarding OS advantage are conflicting. It is not clear if the conclusions from these trials are applicable to retroperitoneal/intra-abdominal sarcomas, and thus care should be individualized.

The Sarcoma Meta-Analysis Collaboration performed a meta-analysis of 14 randomized studies (1,568 patients), which compared adjuvant chemotherapy to follow-up and in some cases RT after surgery with a variety of sarcomas.[50] The result of the meta-analysis showed that doxorubicin-based chemotherapy prolongs local and distant recurrence and overall RFS in adults with localized, resectable STS of the extremity and is associated with decreased recurrence rates. The OS advantage was not significant, although there was a trend in favor of adjuvant chemotherapy.

An updated meta-analysis also confirmed the marginal efficacy of adjuvant chemotherapy in terms of local, distant, and overall recurrence as well as OS (which is contrary to that reported in the Sarcoma Meta-Analysis Collaboration meta-analysis) in patients with localized STS (n=1,953).[52] A recent large, cohort-based analysis with a median follow-up of 9 years indicated that adjuvant chemotherapy may be associated with significantly improved 5-year metastasis-free survival (58% vs 49%; P=.01) and 5-year OS (58% vs 45%; P=.0002) in patients with French Federation of Cancer Centers Sarcoma Group (FNLCLCC) grade 3

STS, whereas it was not significantly different in those with FNCLCC grade 2 STS (5-year metastasis-free survival, 76% vs 73%; *P*=.27; 5-year OS, 75% vs 65%; *P*=.15).[53]


PRINCIPLES OF RADIATION THERAPY[a]

Radiation Therapy Guidelines for Retroperitoneal/Intra-Abdominal Sarcoma

- When EBRT is used, sophisticated treatment planning with IMRT, IGRT and/or protons can be used to improve the therapeutic ratio.[8,9]

Neoadjuvant RT[16-18]

- Neoadjuvant RT for retroperitoneal/intra-abdominal sarcomas can be considered in selected patients at high risk for local recurrence.
- If neoadjuvant RT is deemed to be appropriate for a patient, the following dose guidelines are recommended:
  - 50 Gy EBRT (1.8–2.0 Gy per fraction)
  - Consider IORT boost for known or suspected positive margins at the time of surgery
    - 10–12.5 Gy for microscopically positive disease
    - 15 Gy for gross disease
  - In experienced centers only: 45–50 Gy in 25–28 fractions to entire clinical target volume (CTV) with dose-painted simultaneous integrated boost (SIB) to total dose of 57.5 Gy in 25 fractions to the high-risk retroperitoneal margin jointly defined by the surgeon and radiation oncologist (no boost after surgery)[19]

Adjuvant RT[20-22]

- Adjuvant RT following surgery is discouraged for retroperitoneal/intra-abdominal sarcoma. If RT is not given prior to surgical resection, consider follow-up with possible neoadjuvant RT at time of localized recurrence. See (SARC-D).

See references on SARC-E 4 of 4

[a] These guidelines are intended to treat the adult population. For adolescent and young adult patients, See NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology.[1]

[†] To view the most recent version of these guidelines, visit NCCN.org.

SARC-E 3 OF 4

In the Italian cooperative study (n=104), which randomized patients with high-grade or recurrent extremity sarcoma to receive adjuvant chemotherapy with epirubicin and ifosfamide or observation alone, after a median follow-up of 59 months, median DFS (48 vs 16 months) and median OS (75 vs 46 months) were significantly better in the treatment group; the absolute benefit for OS from chemotherapy was 13% at 2 years. It increased to 19% at 4 years for patients receiving chemotherapy.[55] After a median follow-up of 90 months, the estimated 5-year OS rates were 66% and 46%, respectively (*P*=.04), for the treatment group and the control group; however, the difference was not statistically different in the intent-to-treat analysis.[60]

In another phase III study (EORTC-62931), 351 patients with macroscopically resected grade II–III tumors with no metastases were randomized to observation or adjuvant chemotherapy with ifosfamide and doxorubicin with lenograstim.[57] A planned interim analysis of this study showed no survival advantage for adjuvant chemotherapy in patients with resected high-grade STS. The estimated 5-year RFS was 52% in both arms and the corresponding OS rates were 64% and 69%, respectively, for patients assigned to adjuvant chemotherapy and observation. These findings are consistent with the results reported in an earlier EORTC study by Bramwell et ak.[54] In that study, adjuvant chemotherapy with CYVADIC (cyclophosphamide, vincristine, doxorubicin, and dacarbazine) was associated with higher RFS rates (56% vs 43% for the control group; *P*=.007) and significantly lower LR rates (17% vs 31% for the control group; *P*=.004). However, no differences were seen in distant metastases (32% and 36%, respectively, for CYVADIC and the control group; *P*=.42) and OS rates (63% and 56%, respectively, for CYVADIC and the control group; *P*=.64).

A pooled analysis of these 2 randomized EORTC studies (pooled, n=819) evaluated whether adjuvant doxorubicin-based chemotherapy provided survival benefits in any particular subset of patients with resected STS in these trials.[59] Adjuvant doxorubicin-based chemotherapy was associated with improved RFS in male patients and those older than 40 years, although female patients and those younger than 40 years who received adjuvant chemotherapy had marginally worse OS. However, RFS and OS were significantly improved in patients with R1 resection who received adjuvant chemotherapy compared with those who did not.


PRINCIPLES OF RADIATION THERAPY

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Long-term follow-up results of another prospective randomized study also showed that adjuvant chemotherapy with IFADIC (ifosfamide, doxorubicin, and dacarbazine) given every 14 days with growth factor support did not result in significant benefit in terms of RFS (39% for IFADIC and 44% for the control group; P=.87) as well as OS (P=.99) for patients with grade 2 or 3 STS.[58]

Advanced, Unresectable, or Metastatic Disease—Chemotherapy with single agents (dacarbazine, doxorubicin, epirubicin, or ifosfamide) or anthracycline-based combination regimens (doxorubicin or epirubicin with ifosfamide and/or dacarbazine) have been widely used for patients with advanced, unresectable, or metastatic disease.[61-73] Other chemotherapeutic agents such as gemcitabine, docetaxel, vinorelbine, pegylated liposomal doxorubicin, and temozolomide have also been evaluated in clinical trials. The METASARC observational study, which explored “real-world” outcomes among 2,225 patients with metastatic STS, found a positive association of OS with front-line combination chemotherapy, LMS histology, and locoregional treatment of metastases. However, with the exception of LMS, the benefits of systemic therapy beyond the second-line setting were very limited.[74]

Gemcitabine in combination with docetaxel, vinorelbine, or dacarbazine has been shown to be active in patients with unresectable or metastatic STS of various histologic subtypes.[75-79] In a randomized phase II study, the combination of gemcitabine and docetaxel was associated with superior progression-free survival (PFS) (6.2 and 3.0 months, respectively) and OS (17.9 and 11.5 months, respectively) compared with gemcitabine alone in patients with metastatic STS.[76] In another phase II study, the combination of gemcitabine and vinorelbine was also associated with clinically meaningful rates of disease control in patients with advanced STS.[77] Clinical benefit (complete response, partial response, or stable disease at 4 months or more) was seen in 25% of patients. The combination of gemcitabine and dacarbazine resulted in superior PFS (4.2 vs 2 months; P=.005), OS (16.8 vs 8.2 months; P=.014), and objective response rate (49% vs 25%; P=.009) compared with dacarbazine alone in patients with previously treated advanced STS.[78]

However, gemcitabine combination therapy was not superior to single-agent doxorubicin in the randomized phase III GeDDiS trial. Among patients with previously untreated advanced or metastatic disease (n=257), combination therapy with gemcitabine and docetaxel did not

result in superior PFS compared with doxorubicin (23.7 vs 23.3 weeks; P=.06).[79] It should be noted that this study used lower doses of gemcitabine and docetaxel as compared with other published studies.

SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA SUBTYPES[a,b,c,d]

Soft Tissue Sarcoma Subtypes with Non-Specific Histologies
(Regimens Appropriate for General Soft Tissue Sarcoma[a,f]; see other sections for histology-specific recommendations)

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Neoadjuvant/ Adjuvant Therapy	• AIM (doxorubicin, ifosfamide, mesna)[1-4] • Ifosfamide, epirubicin, mesna[5]	• AD LMS only (doxorubicin, dacarbazine)[1,2,6,7] if ifosfamide is not considered appropriate • Doxorubicin[1,2,6,8] • Gemcitabine and docetaxel[10,11]	• Ifosfamide[5,9,10-14] • Trabectedin (for myxoid liposarcoma)[15]
First-Line Therapy Advanced/Metastatic	• Anthracycline-based regimens: ▸ Doxorubicin[1,2,8,9] ▸ Epirubicin[16] ▸ Liposomal doxorubicin[17] ▸ AD (doxorubicin, dacarbazine)[1,2,6,7,18] ▸ AIM (doxorubicin, ifosfamide, mesna)[1-4,9] ▸ Ifosfamide, epirubicin, mesna[5] • *NTRK* gene fusion-positive sarcomas only ▸ Larotrectinib[g,19] ▸ Entrectinib[h,20]	• Gemcitabine-based regimens: ▸ Gemcitabine ▸ Gemcitabine and docetaxel[10,11] ▸ Gemcitabine and vinorelbine[13] ▸ Gemcitabine and dacarbazine[14]	• Pazopanib[i,21] (patients ineligible for IV systemic therapy or patients who are not candidates for anthracycline-based regimens) • MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[1,2,22,23]
Subsequent Lines of Therapy for Advanced/Metastatic Disease	• Pazopanib[i,2,21] • Eribulin[i,24] (category 1 recommendation for liposarcoma, category 2A for other subtypes • Trabectedin[i,25-27] (category 1 recommendation for liposarcoma and leiomyosarcoma, category 2A for other subtypes)	• Dacarbazine[14] • Ifosfamide[5,9,10-13,28] • Temozolomide[i,29] • Vinorelbine[i,30] • Regorafenib[i,31] • Gemcitabine-based regimens (if not given previously): ▸ Gemcitabine ▸ Gemcitabine and docetaxel[10,11] ▸ Gemcitabine and vinorelbine[13] ▸ Gemcitabine and dacarbazine[14] ▸ Gemcitabine and pazopanib (category 2B)[32]	• Pembrolizumab[k,33,70] (for myxofibrosarcoma, undifferentiated pleomorphic sarcoma [UPS], cutaneous angiosarcoma, and undifferentiated sarcomas) Footnotes and references see SARC-F, 7 of 11 AND SARC-F, 8 of 11

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Temozolomide,[80-82] pegylated liposomal doxorubicin,[83] and vinorelbine[84,85] have also shown activity as single agents in patients with advanced, metastatic, relapsed, or refractory disease. In a phase II study by the Spanish Group for Research on Sarcomas, temozolomide resulted in an overall response rate of 15.5% with a median OS of 8 months in patients with advanced pretreated STS.[82] The PFS rates at 3 and 6 months were 39.5% and 26%, respectively. In a prospective randomized phase II study, pegylated liposomal doxorubicin had equivalent activity and improved toxicity profile compared with doxorubicin; response rates were 9% and 10% for doxorubicin and pegylated liposomal doxorubicin, respectively, in patients with advanced or metastatic STS.[83] In a retrospective study of pretreated patients with metastatic STS, vinorelbine induced overall response in 6% of patients and 26% had stable disease.[84]

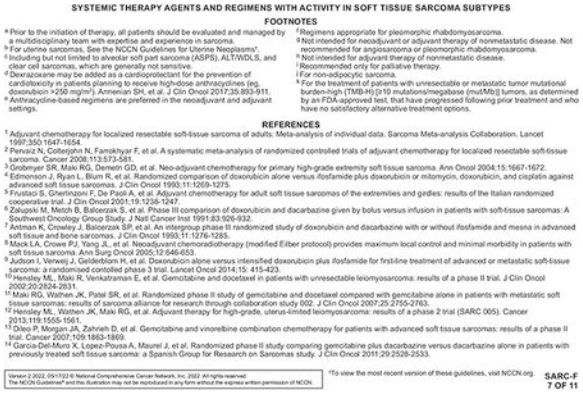
Trabectedin is a novel DNA-binding agent that has shown objective responses in phase II and III studies of patients with advanced STS.[86-94] Recent phase III data from a randomized, multicenter trial revealed a 2.7-month PFS benefit versus dacarbazine in metastatic LPS or LMS that progressed after anthracycline-based therapy.[92] However, the study failed to demonstrate an OS advantage for trabectedin over dacarbazine.[95]

Another study supported the efficacy of trabectedin in translocation-related sarcoma.[94] A phase III trial comparing trabectedin and doxorubicin-based chemotherapy revealed that neither arm showed superiority for PFS and OS; however, the trial was underpowered.[96] Preliminary results from the randomized phase III T-SAR trial revealed a PFS benefit for trabectedin over best supportive care in both “L-type” (LPS and LMS) and non–L-type pretreated advanced sarcoma.[97] However, trabectedin plus doxorubicin failed to show superiority over doxorubicin alone in a randomized phase II study of patients with advanced STS.[98] Trabectedin is included for palliative therapy as a category 1 recommendation for LPS and LMS (L-type) and as category 2A for non-L-type sarcomas.

Eribulin is a novel microtubule-inhibiting agent that has been evaluated as a single-agent therapy for STS, including LMS, adipocytic sarcoma, synovial sarcoma, and other tumor types.[99] Recent data from a phase III trial compared the survival benefit of eribulin

and dacarbazine in 452 patients with advanced LMS or LPS, revealing a median OS of 13.5 months and 11.5 months, respectively (HR, 0.77; 95% CI, 0.62–0.95; P=.017).[100] A subgroup analysis showed that the survival benefit was limited to LPS, and therefore eribulin is included for palliative therapy as a category 1 recommendation for LPS and as category 2A for other subtypes.

See SARC-F 1 of 11 (above) for a complete list of chemotherapy agents and regimens recommended for STS subtypes with nonspecific histologies.



SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA SUBTYPES

FOOTNOTES

[a] Prior to the initiation of therapy, all patients should be evaluated and managed by a multidisciplinary team with expertise and experience in sarcoma.
[b] For uterine sarcomas, See the NCCN Guidelines for Uterine Neoplasms®.
[c] Including but not limited to alveolar soft part sarcoma (ASPS), ALT/WDLS, and clear cell sarcomas, which are generally not sensitive.
[d] Dexrazoxane may be added as a cardioprotectant for the prevention of cardiotoxicity in patients planning to receive high-dose anthracyclines (eg, doxorubicin >250 mg/m²). Armenian SH, et al. J Clin Oncol 2017;35:893-911.
[e] Anthracycline-based regimens are preferred in the neoadjuvant and adjuvant settings.
[f] Regimens appropriate for pleomorphic rhabdomyosarcoma.
[g] Not intended for neoadjuvant or adjuvant therapy of nonmetastatic disease. Not recommended for angiosarcoma or pleomorphic rhabdomyosarcoma.
[h] Not intended for adjuvant therapy of nonmetastatic disease.
[i] Recommended only for palliative therapy.
[j] For non-adipocytic sarcoma.
[k] For the treatment of patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

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*To view the most recent version of these guidelines, visit NCCN.org.

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Targeted Therapy

More recently, a number of targeted therapies have shown promising results in patients with certain histologic types of advanced or metastatic STS.

Pazopanib, a multitargeted tyrosine kinase inhibitor, has demonstrated single-agent activity in patients with advanced STS subtypes except LPS.[101-107] In a phase III study (EORTC 62072), 369 patients with metastatic nonlipogenic STS for whom at least 1 anthracycline-based chemotherapy regimen had failed were randomized to either pazopanib or placebo.[103] Pazopanib significantly prolonged median PFS (4.6 vs 1.6 months for placebo; P<.0001) and there was also a trend toward improved OS (12.5 and 11 months, respectively; P=.25), although this was not statistically significant. Health-related quality-of-life measures did not improve or decline with the PFS benefit.[108] Pooled data from individuals who received pazopanib in phase II and III trials (n=344) revealed a subset of long-term responders/survivors presenting at baseline with good performance status, low-/intermediate-grade primary tumor, and normal hemoglobin level.[109] Results from the open-label phase II EPAZ study found that pazopanib demonstrated noninferior PFS compared with doxorubicin (4.4 vs 5.3 months, respectively) as a first-line treatment in elderly patients with advanced/metastatic STS.[110] The guidelines have included pazopanib as a first-line therapy option for those with advanced or metastatic disease who are ineligible for intravenous systemic therapy or are not candidates for anthracycline-based regimens, and as a subsequent-line treatment option for patients with advanced or metastatic nonlipogenic STS as palliative therapy (see SARC-F 1 of 11, page 825). Pazopanib in combination with gemcitabine is a category 2B subsequent-line treatment option for advanced/metastatic disease.[111]

The randomized, phase II REGOSARC trial examined regorafenib, a multitargeted tyrosine kinase inhibitor approved for treating GIST, in cohorts of patients with advanced LPS, LMS, synovial sarcoma, and other non-GIST STS subtypes (REGOSARC, n=182).[112,113] Compared with placebo, regorafenib significantly extended PFS in all but the LPS cohort. In patients with nonadipocytic STS, overall PFS for regorafenib and placebo-treated patients was 4 months versus 1 month (HR, 0.36; $P<.0001$). Regorafenib is included in the guidelines as a treatment option for advanced/metastatic nonadipocytic sarcomas, as well as angiosarcoma.[112,114]

Tropomyosin receptor kinase inhibitors larotrectinib and entrectinib have demonstrated efficacy in patients with neurotrophic receptor tyrosine kinase (*NTRK)* fusion-positive tumors, and are therefore recommended as first-line treatment options for patients with advanced or metastatic *NTRK* gene fusion-positive sarcomas in the guidelines.[115,116]

SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA SUBTYPES

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Programmed cell death protein 1 (PD-1) inhibitor pembrolizumab is approved by the United States FDA for unresectable or metastatic tumor mutational burden-high (≥10 mutations/megabases) tumors, as determined by an FDA-approved test, that have progressed after prior treatment and who have no satisfactory alternative options.[117] In the guidelines, pembrolizumab is included as a subsequent-line treatment option for patients with certain subtypes of advanced or metastatic STS, including myxofibrosarcoma, undifferentiated pleomorphic sarcoma, cutaneous angiosarcoma, and undifferentiated sarcomas.[118,119]

See SARC-F 1 of 11 (page 825) for a complete list of targeted therapies recommended for STS subtypes with nonspecific histologies.

Treatment Guidelines

Resectable Disease—Surgical wide resection with oncologically appropriate negative margins is a potentially curative treatment for nonmetastatic primary retroperitoneal/intra-abdominal sarcomas (see RETSARC-2, page 817). The margin status after surgery is an important factor associated with long-term DFS.[120-124] In a large single-institution series involving 500 patients, the median survival was 103 months for those who underwent complete resection with grossly negative margins in contrast to 18 months for those who underwent incomplete resection.[123]

Two recent retrospective analyses reported improved local control in patients with primary retroperitoneal sarcoma operated with more aggressive approaches such as complete compartmental resection and a more liberal visceral en bloc resection performed in high-volume centers.[125,126] Although the results are encouraging, this technique must be investigated in prospective clinical trials. For information on “Principles of Surgery,” see SARC-D 1 of 2 (page 822).

Given the close proximity of retroperitoneal/intra-abdominal sarcomas to critical structures, complete or macroscopic surgical resection is achieved in fewer than 70% of patients. LR and disease progression continue to be a significant cause of morbidity in many patients.[127-129] Multimodality treatment (surgery with RT and/or chemotherapy) is the subject of clinical investigation, given the inability to obtain negative surgical margins and high LR rates, as discussed previously.[130]

If RT is anticipated, neoadjuvant RT with an IMRT approach to optimize sparing of nearby critical structures is preferred because it reduces the risk of tumor seeding at surgery and may render tumors more amenable to resection.[14] Neoadjuvant RT can be considered in selected patients with retroperitoneal/intra-abdominal sarcomas who are at high risk for LR.[18] For patients treated with neoadjuvant EBRT (50 Gy; 1.8–2.0 Gy per fraction), the guidelines recommend consideration of IORT boost for patients with known or suspected positive margins at surgery, if this can be done within the constraints of adjacent normal tissue (see SARC-E 3 of 4, page 823). The guidelines recommend an IORT boost of 10–12.5 Gy for microscopic residual disease, and 15 Gy for gross disease.

An analysis involving 8,653 patients with resected retroperitoneal STS from the National Cancer Database revealed worse OS in the surgically resected cohort receiving chemotherapy (neoadjuvant and/or adjuvant) versus those who underwent surgery alone (40 vs 52 months; P=.002).[131] Neoadjuvant chemotherapy may have advantages over adjuvant chemotherapy. However, the role of neoadjuvant chemotherapy versus adjuvant chemotherapy has not yet been evaluated in randomized clinical trials.[132] Few data are available for the use of combined RT and chemotherapy. Decisions about adjuvant or neoadjuvant chemotherapy or RT are left to clinical judgment.[133-135] The regimens listed in the guidelines are based on the extrapolation of data derived from clinical trials on STS of the extremity that have included a small number of patients with retroperitoneal STS.[136]

The guidelines state that neoadjuvant systemic therapy can be considered as an option in selected cases; specifically, if there is a high risk for metastatic disease or if downstaging is needed to facilitate resection (see RETSARC-2, page 817). Systemic therapy is not recommended for low-grade tumors.

After surgery, adjuvant systemic therapy could be considered for all patients who are at high risk for metastatic disease based on surgical outcomes or clinical pathologic findings (see RETSARC-3, page 818). For R1 or R2 outcomes, adjuvant RT should not be administered routinely, with the exception of highly selected patients and unless LR would cause undue morbidity (eg, recurrence at a critical anatomic surface that would cause morbidity. For R2 outcomes, reresection can be considered if the cancer of the biology (grade, invasiveness),

the technical aspects of the surgery (R0 resection anticipated as a reasonable possibility), and the comorbidities of the patient allow for a safe intervention at the judgement of the operating surgeon. Additionally, the primary treatment options as described subsequently for unresectable disease are another alternative (see RETSARC-4, page 819).

Unresectable or Stage IV Disease—Unresectable tumors are defined as those that involve vital structures or tumors whose removal would cause unacceptable morbidity. Patients who are medically unresectable (ie, not medically fit to tolerate a major ret roperitoneal STS resection) are also included in this category.

Biopsy is recommended before any treatment of a patient with unresectable or metastatic disease (see RETSARC-4, page 819). Patients with unresectable or stage IV disease could be treated with systemic therapy and/or RT, or undergo surgery for symptom control. Observation is an option if the patient is asymptomatic and tumor growth is indolent. For patients undergoing definitive high-dose RT, favorable experience has been reported in the literature with the use of tissue displacement spacers to keep bowel out of the high-dose RT volume.[137] In terms of response rate, the most active chemotherapy regimen in an unselected patient population is AIM (doxorubicin/ifosfamide/mesna).[138]

For unresectable or stage IV disease, follow-up imaging is recommended to assess treatment response (see RETSARC-4, page 819). Options include CT (preferred) or MRI. Patients whose tumors become resectable after primary treatment should be managed as described previously for resectable disease (see RETSARC-2, page 817). Palliative or best supportive care are options if the tumor remains unresectable or if there is disease progression after primary treatment (see the NCCN Guidelines for Palliative Care at NCCN.org). In patients with stage IV disease, resection should always be considered for resectable metastatic disease if the primary tumor can be controlled.

Surveillance—Patients are recommended to undergo a follow-up physical examination with imaging (chest/abdominal/pelvic CT [preferred] or MRI) every 3 to 6 months for 2 to 3 years, then every 6 months for the next 2 years, and then annually, following management of primary disease (see RETSARC-3, page 818).

Recurrent Disease—For patients with resectable recurrent disease, biopsy should be considered if the recurrent disease diagnosis is not clinically definitive (see RETSARC-5, page 820). The guidelines recommend surgery to obtain oncologically appropriate margins; adjuvant systemic therapy can be considered if there is a high risk for metastatic disease or history of several recurrences with a high risk for additional local recurrences. In selected cases, neoadjuvant RT (if not previously given for the primary tumor) or neoadjuvant systemic therapy should be considered, followed by surgery with or without IORT. Adjuvant treatment may be considered for tumors at high risk for metastatic disease (see RETSARC-3, page 818). For patients with recurrent disease that is unresectable or stage IV, please refer to the management of unresectable or stage IV disease as described previously (RETSARC-4, page 819).

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NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1:

Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A:

Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B:

Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3:

Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials:

NCCN believes that the best management of any patient with cancer 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 evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN 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 representations or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

The complete NCCN Guidelines for Soft Tissue Sarcoma are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

Disclosures for the NCCN Soft Tissue Sarcoma Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Soft Tissue Sarcoma Panel members can be found on page 833. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.

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