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Soft Tissue Sarcoma, Version 2.2016

Clinical Practice Guidelines in Oncology

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Abstract

Soft tissue sarcomas (STS) are rare solid tumors 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 Guidelines for Soft Tissue Sarcoma (available at NCCN.org) provide recommendations for the diagnosis, evaluation, and treatment of extremity/superficial trunk/head and neck STS, as well as intra-abdominal/retroperitoneal STS, gastrointestinal stromal tumor, desmoid tumors, and rhabdomyosarcoma. This manuscript discusses guiding principles for the diagnosis and staging of STS and evidence for treatment modalities that include surgery, radiation, chemoradiation, chemotherapy, and targeted therapy.

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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 for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Sarcomas constitute a heterogeneous group of rare solid tumors of mesenchymal cell origin with distinct clinical and pathologic features; they 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.

Sarcomas collectively account for approximately 1% of all adult malignancies and 15% of pediatric

Please Note

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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 786. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

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

malignancies. In 2016, an estimated 12,310 people will be diagnosed with soft tissue sarcoma (STS) in the United States, and approximately 4,990 people will die of the disease.[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. In the United States, the incidence of GISTs is expected to be at least 5,000 new cases per year.[2,3] Prior radiation therapy (RT) to the affected area is a risk factor for the development of STS.[4–6] More than 50 different histologic subtypes of STS have been identified. The most common subtypes of STS are undifferentiated pleomorphic sarcoma, GIST, liposarcoma, leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumors.[7] The anatomic site of the primary disease represents an important variable that influences treatment and outcome. Extremities (43%), the trunk (10%), visceral (19%), retroperitoneum (15%), and head and neck (9%) are the most common primary sites.[8] STS most commonly metastasizes to the lungs; tumors arising in the abdominal cavity more commonly metastasize to the liver and peritoneum. Rhabdomyosarcoma (RMS) is the most common STS among children and adolescents and is less common in adults.

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

Text cont. on page 775.

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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, 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 World Health Organization Classification of Soft Tissue Tumors[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) or NCI system
  - 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)
  - Status of lymph nodes
    - Site
    - Number examined
    - Number positive
  - Results of ancillary studies[1]
    - Type of testing (electron microscopy, immunohistochemistry, molecular genetic analysis)
    - Where performed
  - Additional tumor features of potential clinical value
    - Mitotic rate
    - Presence or absence of vascular invasion
    - Character of tumor margin (well circumscribed or infiltrative)
    - Inflammatory infiltrate (type and extent)
  - TNM Stage (See ST-2*)

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

[1]See Principles of Ancillary Techniques Useful in the Diagnosis of Sarcomas (SARC-B*).

[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, Fourth Edition. IARC, Lyon, 2013.

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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, electron microscopy, and molecular genetic testing. Molecular genetic testing has emerged as a particularly powerful ancillary testing approach since many sarcoma types harbor characteristic genetic aberrations, including single base pair substitutions, deletions and amplifications, and translocations. Most molecular testing utilizes fluorescence in situ hybridization (FISH) approaches or polymerase chain reaction (PCR)-based methods.[1] Recurrent genetic aberrations in sarcoma[2] are listed below:

TUMOR	ABERRATION	GENE(S) INVOLVED
Malignant Round Cell Tumors		
Alveolar RMS	t(2;13)(q35;q14)	*PAX3-FOXO1*
	t(1;13)(p36;q14)	*PAX7-FOXO1*
	t(X;2)(q13;q35)	*PAX3-AFX*
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	*EWSR1-WT1*
Embryonal RMS	Complex alterations	Multiple, *MYOD1* mutation
Ewing sarcoma/peripheral neuroectodermal tumor	t(11;22)(q24;q12)	*EWSR1-FLI1*
	t(21;22)(q22;q12)	*EWSR1-ERG*
	t(2;22)(q33;q12)	*EWSR1-FEV*
	t(7;22)(p22;q12)	*EWSR1-ETV1*
	t(17;22)(q12;q12)	*EWSR1-E1AF*
	inv(22)(q12q;12)	*EWSR1-ZSG*
	t(16;21)(p11;q22)	*FUS-ERG*

[1]Molecular 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 carried out by a pathologist with expertise in sarcoma diagnosis and molecular diagnostic techniques.

[2]This table is not exhaustive for either sarcomas with characteristic genetic changes or the genes involved. For example, additional genetic aberrations found in alveolar RMS including *PAX3-NCOA1, PAX3-NCOA2*, and *PAX3-INO80D*. *CIC-DUX4* fusion is present in primitive round or short spindle cell sarcomas, resulting from translocation of t(4;19)(q35;q13) or t(10;19)(q26;q13). It is not clear if this is an entirely new subtype of sarcoma or a new subtype of Ewing sarcoma. *BCOR-CCNB3* fusion is considered Ewing-like sarcoma. *NCOA2* gene rearrangements and *MyoD* mutation have been identified in spindle cell RMS. *MIR143-NOTCH* fusion has recently been identified in glomus tumor. Receptor tyrosine kinase/RAS/PIK3CA aberrations are found in 93% of RMS cases. Loss of *TSC1* (9q34) or *TSC2* (16p13.3) (mTOR pathway) or gene fusions of the *TFE3* gene (microphthalmia-associated transcription factor family) have been identified in *PEComa*. *MPNST* is associated with loss of *SUZ12/EED* and alteration of *NF1* and *CDKN2A*. Consultation with a pathologist who has expertise in sarcoma diagnosis and molecular diagnostic techniques should be obtained prior to testing.

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PRINCIPLES OF ANCILLARY TECHNIQUES USEFUL IN THE DIAGNOSIS OF SARCOMAS

TUMOR	ABERRATION	GENE(S) INVOLVED
Lipomatous Tumors		
Atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLS)	Supernumerary ring chromosomes; giant marker chromosomes	Amplification of region 12q14-15, including *MDM2, CDK4, HMGA2, SAS, GL1*
Dedifferentiated liposarcoma	Same as for ALT/WDLS	Same as for ALT/WDLS
Myxoid/round cell liposarcoma	t(12;16)(q13;p11) t(12;22)(q13;q12)	*FUS-DD1T3* *EWSR1-DD1T3*
Pleomorphic liposarcoma	Complex alterations	Unknown
Other Sarcomas		
Alveolar soft part sarcoma	der(17)t(X;17)(p11;q25)	*ASPL-TFE3*
Angiomatoid fibrous histiocytoma	t(12;22) (q13;q12) t(2;22)(q33;q12) t(12;16)(q13;p11)	*EWSR1-ATF1* *EWSR1-CREB1* *FUS-ATF1*
Clear cell sarcoma	t(12;22)(q13;q12) t(2;22)(q33;q12)	*EWSR1-ATF1* *EWSR1-CREB1*
Congenital/infantile – fibrosarcoma	t(12;15)(p13;q25)	*ETV6-NTRK3*
Dermatofibrosarcoma protuberans	t(17;22)(q21;q13) and derivative ring chromosomes	*COLIA1-PDGFB*
Desmoid fibromatosis	Trisomy 8 or 20; loss of 5q21	*CTNNB1* or *APC* mutations
Epithelioid hemangioendothelioma	t(1;13)(p36;q25) t(X;11)(q22;p11.23)	*WWTR1-CAMTA1* *YAP1 - TFE3*
Epithelioid sarcoma	Inactivation, deletion, or mutation of *INI1 (SMARCB-1)*	*INI1 (SMARCB-1)*

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PRINCIPLES OF ANCILLARY TECHNIQUES USEFUL IN THE DIAGNOSIS OF SARCOMAS

TUMOR	ABERRATION	GENE(S) INVOLVED
Other Sarcomas—continued		
Extrarenal rhabdoid tumor	Inactivation of *INI1 (SMARCB-1)*	*INI1 (SMARCB-1)*
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12) t(9;17)(q22;q11) t(9;15)(q22;q21) t(3;9)(q11;q22)	*EWSR1-NR4A3* *TAF2N-NR4A3* *TCF12-NR4A3* *TFG-NR4A3*
Sporadic and familial GIST Carney-Stratakis syndrome (gastric GIST and paraganglioma)	Activating kinase mutations Krebs cycle mutation	*KIT* or *PDGFRA* *germline SDH* subunit mutations
Inflammatory myofibroblastic tumor (IMT)	t(1;2)(q22;p23) t(2;19)(p23;p13) t(2;17)(p23;q23) t(2;2)(p23;q13) t(2;11)(p23;p15) inv(2)(p23;q35)	*TPM3-ALK* *TPM4-ALK* *CLTC-ALK* *RANBP2-ALK* *CARS-ALK* *ATIC-ALK*
Leiomyosarcoma	Complex alterations	Unknown
Low-grade fibromyxoid sarcoma	t(7;16)(q33;p11) t(11;16)(p11;p11)	*FUS-CREB3L2* *FUS-CREB3L1*
Malignant peripheral nerve sheath tumor	Complex alterations	Unknown
Mesenchymal chondrosarcoma		*HEY1 - NCOA2*
Solitary fibrous tumor		*NAB2 - STAT6*
Synovial sarcoma	t(X;18)(p11;q11) t(X;18)(p11;q11) t(X;18)(p11;q11)	*SS18-SSX1* *SS18-SSX2* *SS18-SSX4*
Tenosynovial giant cell tumor/pigmented villonodular synovitis (TGCT/PVNS)	t(1;2)(p13;q35)	*CSF1*

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PRINCIPLES OF SURGERY

Biopsy

- A pretreatment biopsy to diagnose and grade a sarcoma is highly preferred. Biopsy should be carried out by an experienced surgeon (or radiologist) and may be accomplished by open incisional or needle technique. Core needle biopsy is preferred; however, an open incisional biopsy may be considered by an experienced surgeon. Endoscopic or image-guided needle biopsy may be indicated for deep, thoracic, abdominal, or pelvic sarcomas.

Surgery

- The surgical procedure necessary to resect the tumor with oncologically appropriate margins should be used. Close margins may be necessary to preserve 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 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 in evaluating a resected specimen.

Resection Margins (continued)

- 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 upon 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.

Limb Sparing Surgery

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

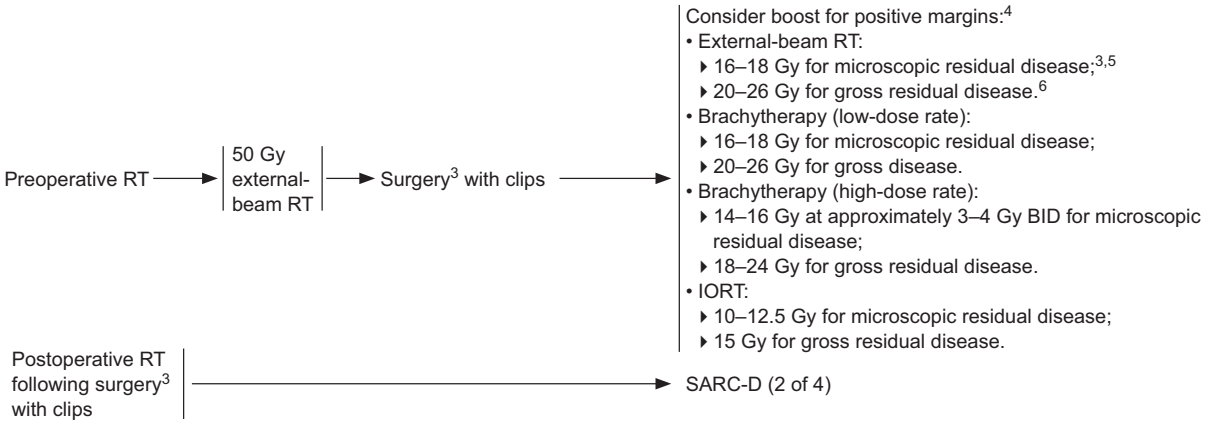
Amputation

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

SARC-C

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

RADIATION THERAPY GUIDELINES FOR SOFT TISSUE SARCOMA OF EXTREMITY/TRUNK/HEAD-NECK[1,2,*]



[*]These guidelines are intended to treat the adult population. For adolescent and young adult patients, refer to the Guidelines for Adolescent and Young Adult (AYA) Oncology (to view the most recent version of these guidelines, visit NCCN.org).

[1]If an R1 or R2 resection is anticipated, clips to high-risk areas for recurrence is encouraged. When external beam RT is used, sophisticated treatment planning with IMRT, tomotherapy, and/or protons can be used to improve the therapeutic ratio:

- Musat E, et al. Comparison of intensity-modulated postoperative radiotherapy with conventional postoperative radiotherapy for retroperitoneal sarcoma. Cancer Radiother 2004;8:255-261;
- Alektiar KM, et al. Impact of intensity-modulated radiation therapy on local control in primary soft-tissue sarcoma of the extremity. J Clin Oncol 2008;26:3440-3444;
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[2]Haas RL, DeLaney TF, O'Sullivan B, et al: Radiotherapy for management of extremity soft tissue sarcomas: why, when, and where? Int J Radiat Oncol Biol Phys 2012; 84:572-580.

[3]See Principles of Surgery (SARC-C).

[4]Total doses should always be determined by normal tissue tolerance. There are data to suggest that some patients with positive margins following preoperative RT such as those with low-grade, well-differentiated liposarcoma and a focally, "planned" positive margin on an anatomically fixed critical structure may do well without a boost. (Al Yami, et al, Int J Radiat Oncol Biol Phys 2010;77:1191-1197.)

[5]RT does not substitute for definitive surgery with negative margins; re-resection may be necessary.

[6]See Resection Margins (SARC-C).

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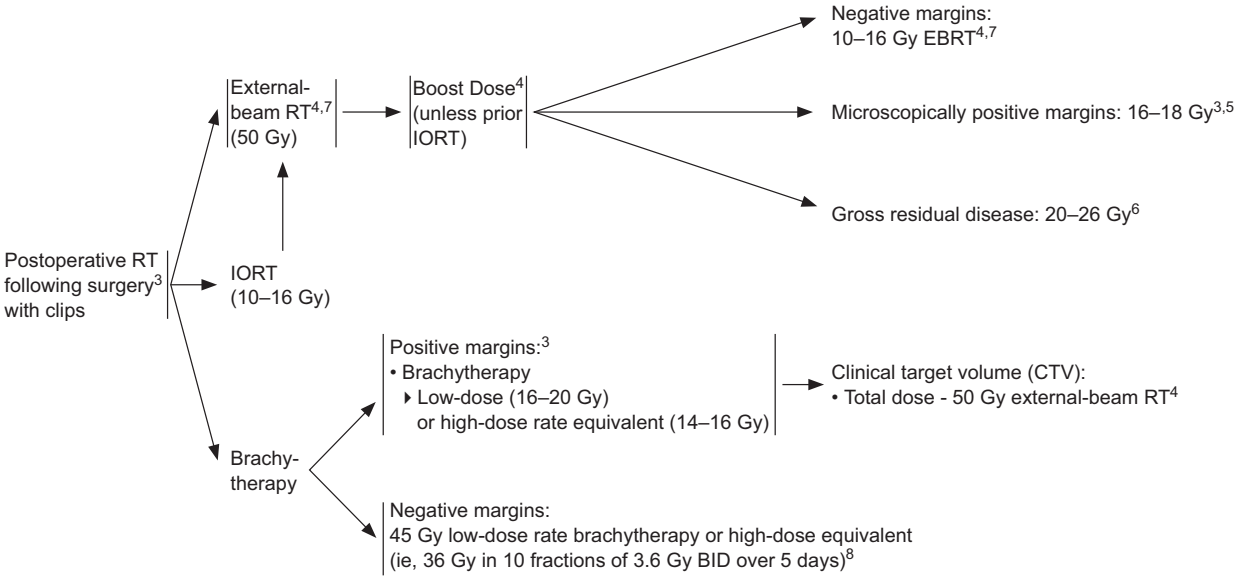
RADIATION THERAPY GUIDELINES FOR SOFT TISSUE SARCOMA OF EXTREMITY/TRUNK/HEAD-NECK[1,2]



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[5]RT does not substitute for definitive surgery with negative margins; re-resection may be necessary.

[6]See Resection Margins (SARC-C).

[7]For intra-abdominal or retroperitoneal tumors, external beam RT may be decreased to 45 Gy. A boost may not be possible if potential radiation morbidity is high.

[8]Data are still limited on the use of HDR brachytherapy for sarcomas. Until more data are available, HDR fraction sizes are recommended to be limited to 3–4 Gy. (Nag et al, Int J Radiat Onco Biol Phys 2001;49:1033-1043, 2001).

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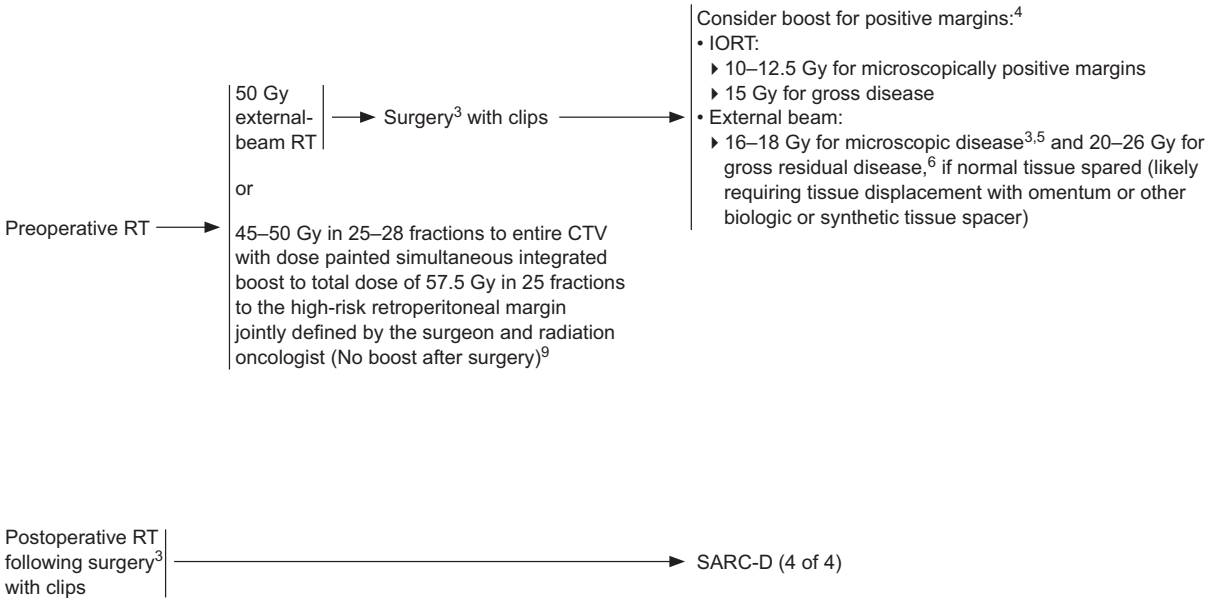
RADIATION THERAPY GUIDELINES FOR RETROPERITONEAL/INTRA-ABDOMINAL SARCOMA[1]



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[5]RT does not substitute for definitive surgery with negative margins; re-resection may be necessary.

[6]See Resection Margins (SARC-C).

[9]Tzeng CW, Fiveash JB, Popple, et al. Preoperative radiation therapy with selective dose escalation to the margin at risk for retroperitoneal sarcoma. Cancer 2006;107:371-379.

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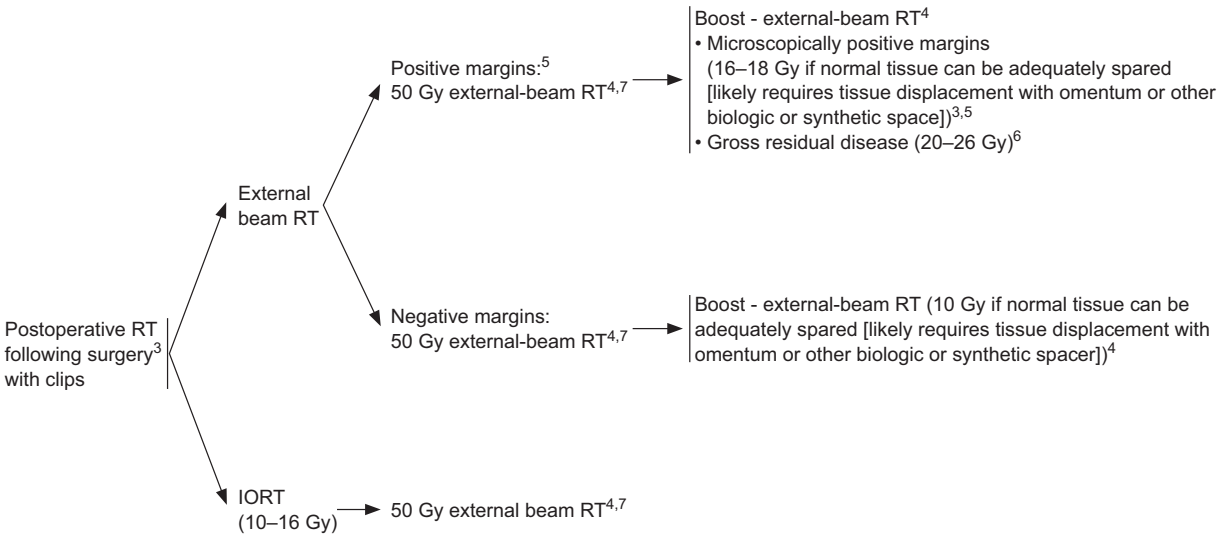
RADIATION THERAPY GUIDELINES FOR RETROPERITONEAL/INTRA-ABDOMINAL SARCOMA[10]



[3]See Principles of Surgery (SARC-C).

[4]Total doses should always be determined by normal tissue tolerance. There are data to suggest that some patients with positive margins following preoperative RT such as those with low-grade, well-differentiated liposarcoma and a focally, "planned" positive margin on an anatomically fixed critical structure may do well without a boost. (Al Yami, et al, Int J Radiat Oncol Biolo Phys 2010;77:1191-1197.)

[5]RT does not substitute for definitive surgery with negative margins; re-resection may be necessary.

[6]See Resection Margins (SARC-C).

[7]For intra-abdominal or retroperitoneal tumors, external beam RT may be decreased to 45 Gy. A boost may not be possible if potential radiation morbidity is high.

[10]If an R1 or R2 resection is anticipated, clips to high-risk areas for recurrence are encouraged. When external beam RT is used, sophisticated treatment planning with IMRT, tomotherapy, and/or protons can be used to improve the therapeutic ratio:

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- Yoon SS, Chen YL, Kirsch DG, Maduekwe UN, Rosenberg AE, Nielsen GP, Sahani DV, Choy E, Harmon DC, and DeLaney TF. Proton-beam, intensity-modulated, and/or intraoperative electron radiation therapy combined with aggressive anterior surgical resection for retroperitoneal sarcomas. Ann Surg Oncol 2010;17:1515-1529.

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA SUBTYPES (NON-SPECIFIC)[a,b,c]

Soft Tissue Sarcoma Subtypes with Non-Specific Histologies[d,e]		GIST[h]	Desmoid Tumors (Aggressive fibromatosis)
Combination regimens • AD (doxorubicin, dacarbazine)[1-4] • AIM (doxorubicin, ifosfamide, mesna)[3-6] • MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[3,4,7,8] • Ifosfamide, epirubicin, mesna[9] • Gemcitabine and docetaxel[10,11] • Gemcitabine and vinorelbine[f,12] • Gemcitabine and dacarbazine[13]	Single agents • Doxorubicin[3,4,14] • Ifosfamide[9,15] • Epirubicin[16] • Gemcitabine • Dacarbazine • Liposomal doxorubicin[17] • Temozolomide[f,18] • Vinorelbine[f,19] • Pazopanib[f,g,20] • Eribulin[f,21] • Trabectedin[f,22,23,24]	• Imatinib[25,26] • Sunitinib[27] • Regorafenib[28] Disease progression after imatinib, sunitinib, and regorafenib • Sorafenib[29-31] • Nilotinib[32,33] • Dasatinib[34] (for patients with D842V mutation) • Pazopanib[35]	• Sulindac[36]or other non-steroidal anti-inflammatory drugs (NSAIDs) including celecoxib • Tamoxifen ± Sulindac[37,38] • Toremifene[39] • Methotrexate and vinblastine[40] • Low-dose interferon[41] • Doxorubicin-based regimens[42-44] • Imatinib[45,46] • Sorafenib[47] • Methotrexate and vinorelbine[48] • Liposomal doxorubicin[49]

Non-Pleomorphic Rhabdomyosarcoma

Combination regimens
- Vincristine, dactinomycin, cyclophosphamide[50]
- Vincristine, doxorubicin, cyclophosphamide[51]
- Vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide[52]
- Vincristine, doxorubicin, ifosfamide[53]
- Cyclophosphamide and topotecan[54,55]
- Ifosfamide and doxorubicin[56]
- For Soft Tissue Ewings, see NCCN Guidelines for Bone Cancer (to view the most recent version of these guidelines, visit NCCN.org)
- Ifosfamide and etoposide[57]
- Irinotecan and vincristine[58,59]
- Vincristine and dactinomycin[60]
- Carboplatin and etoposide[61]
- Vinorelbine[f] and low-dose cyclophosphamide[62]
- Vincristine, irinotecan,temozolomide[63]

Single agents
- Doxorubicin[64]
- Irinotecan[55,65]
- Topotecan[66]
- Vinorelbine[f,67]
- High-dose methotrexate[i,68]
- Trabectedin[f,22,23,24]

[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 (to view the most recent version of these guidelines, visit NCCN.org).

[c]Alveolar soft part sarcoma (ASPS), well-differentiated liposarcoma/atypical lipomatous tumor, and clear cell sarcomas are generally not sensitive to cytotoxic chemotherapy.

[d]Anthracycline-based regimens are preferred in the neoadjuvant and adjuvant setting.

[e]Regimens appropriate for pleomorphic rhabdomyosarcoma.

[f]Recommended only for palliative therapy.

[g]Pazopanib should not be used for lipogenic sarcomas.

[h]Imatinib, sunitinib, and regorafenib are the three FDA agents approved for the treatment of GIST.

[i]High-dose methotrexate may be useful for select patients with CNS or leptomeningeal involvement when RT is not feasible.

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

<table>
<tr><td colspan="2">Pigmented Villonodular Synovitis/Tenosynovial Giant Cell Tumor (PVNS/TGCT)
• Imatinib[69]</td></tr>
<tr><td>Angiosarcoma
• Paclitaxel[70,71]
• Docetaxel
• Vinorelbine[f]
• Sorafenib[72]
• Sunitinib[73]
• Bevacizumab[74]
• All other systemic therapy options as per Soft Tissue Sarcoma Subtypes with Non-Specific Histologies (SARC-E 1 of 6)</td><td>Solitary Fibrous Tumor/Hemangiopericytoma
• Bevacizumab and temozolomide[75]
• Sunitinib[76,77]</td></tr>
<tr><td>Alveolar Soft Part Sarcoma (ASPS)
• Sunitinib[78,79] (category 2B)</td><td>PEComa, Recurrent Angiomyolipoma, Lymphangioleiomyomatosis
• Sirolimus[80-83]
• Everolimus[84]
• Temsirolimus[85,86]</td></tr>
<tr><td colspan="2">Inflammatory Myofibroblastic Tumor (IMT) with Anaplastic Lymphoma Kinase (ALK) Translocation
• Crizotinib[87]
• Ceritinib[88]</td></tr>
<tr><td colspan="2">Well-differentiated/Dedifferentiated Liposarcoma (WD-DDLS) for Retroperitoneal Sarcomas
• Palbociclib[89,90]</td></tr>
</table>

References on opposite page

[a]Prior to the initiation of therapy, all patients should be evaluated and managed by a multidisciplinary team with expertise and experience in sarcoma.

[c]Alveolar soft part sarcoma (ASPS), well-differentiated liposarcoma/atypical lipomatous tumor, and clear cell sarcomas are generally not sensitive to cytotoxic chemotherapy.

[f]Recommended only for palliative therapy.

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Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

Text cont. from page 759.

guidelines for the management of patients with sarcomas.

The complete NCCN Guidelines for STS (available at NCCN.org) address the management of STS in adult patients from the perspective of the following disease subtypes:

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

Before the start of treatment, all patients should be evaluated and managed by a multidisciplinary team with extensive expertise and experience in the treatment of STS.[9]

NOTE: This manuscript highlights only a portion of the NCCN Guidelines on STS. The guidelines in this issue discuss important general principles and evidence for diagnosis, staging, and treatment of STS in adult patients. For treatment recommendations specific to tumor location, stage, and subtype, please refer to the complete guidelines at NCCN.org.

Genetic Cancer Syndromes With Predisposition to STS

Genetic cancer syndromes caused by germline mutations in a number of different genes are also associated with an inherited predisposition for the development of STS.[5,10–14] Li-Fraumeni syndrome (resulting from germline mutations in the *TP53* tumor suppressor gene) is characterized by an increased risk of developing multiple primary malignancies, predominantly STS, osteosarcomas, breast cancer, leukemia, brain tumors, and adrenocortical carcinoma, before 45 years of age.[10,15–17] The incidence of STS ranges from 12% to 21% in individuals with *TP53* germline mutations.[18–20] In general, STS associated with Li-Fraumeni syndrome is diagnosed at significantly younger ages than sporadic STS. The mean age at diagnosis, however, varies with the histologic subtype. In an analysis of 475 tumors in 91 families with *TP53* germline mutations, Kleihues et al[18] reported RMS, fibrosarcomas, and undifferentiated pleomorphic sarcomas as the most frequent histologic subtypes, identified in 55%,13%, and 10% of patients, respectively. The mean age at diagnosis for RMS was younger than 6 years, and the mean age at diagnosis for undifferentiated pleomorphic sarcomas was older than 50 years.

Familial adenomatous polyposis (FAP) is an inherited autosomal-dominant colorectal cancer syndrome resulting from the germline mutations in the adenomatous polyposis coli [*APC*] gene on chromosome 5q21.[11,13] FAP is characterized by adenomatous colorectal polyps that progress to colorectal cancer at 35 to 40 years of age. Gardner syndrome is considered a variant of FAP with extracolonic manifestations such as osteomas, skin cysts, congenital hypertrophy of the retinal pigmented epithelium, and desmoid tumors (aggressive fibromatosis).[21] Desmoid tumors have been reported to occur in 7.5% to 16% of patients with FAP, and the relative risk of developing desmoid tumors is much higher in patients with FAP than in the general population.[22–25] In an International Dutch Cohort study involving 2,260 patients with FAP, positive family history for desmoid tumors, abdominal surgery, and the *APC* mutation site were identified as significant risk factors for the development of desmoid tumors.[25] The median age at diagnosis was 31 years, with most desmoid tumors arising in the intra-abdominal and abdominal wall locations (53% and 24%, respectively).

Carney-Stratakis syndrome is an autosomal-dominant familial syndrome characterized by a predisposition to GISTs and paragangliomas.[26] Germline loss-of-function mutations within the succinate dehydrogenase (*SDH*) gene subunits (*SDHB*, *SDHC*, and *SDHD*) have been identified in individuals with GISTs associated with Carney-Stratakis syndrome.[27] In an analysis of 11 patients from 9 families presenting with the GISTs and paragangliomas associated with Carney-Stratakis syndrome, Pasini et al[27] identified germline mutations in *SDHB*, *SDHC*, or *SDHD* genes in 8 patients (from 7 untreated families) with GISTs. The tumors also lacked activating *KIT* or platelet-derived growth factor receptor alpha (*PDGFRA*) mutations associated with sporadic GISTs. GISTs associated with Carney-Stratakis syndrome are also reported to be negative for SDHB protein expression by immunohistochemistry (IHC), in contrast to GIST with *KIT* or *PDGFRA* mutations or sporadic GIST.[28,29]

Hereditary retinoblastoma caused by a germline mutation in the retinoblastoma tumor suppressor gene (*RB1*) is also associated with an increased risk

for the development of STS.[12,30] Leiomyosarcoma is the most frequent STS subtype (with 78% of leiomyosarcomas diagnosed ≥30 years after the diagnosis of retinoblastoma). Although patients who underwent RT for retinoblastoma are at significantly increased risk of developing STS, the risks of developing STS are also increased in nonirradiated patients, indicating a genetic predisposition to STS that is independent of RT in patients with hereditary retinoblastoma.[12]

Neurofibromatoses are hereditary conditions caused by mutations in the neurofibromin 1 gene (*NF1*) or neurofibromin 2 gene (*NF2*).[31] Approximately 5% of patients with neurofibromatosis are thought to develop STS. Most commonly occurring are malignant peripheral nerve sheath tumors (MPNSTs), a type of sarcoma that can arise from previously benign neurofibromas.[32] For information on the treatment of MPNSTs, see the NCCN Guidelines for Central Nervous System Cancers (available at NCCN.org).

NCCN Recommendations for Genetic Testing and Counseling for Patients With Germline Mutations

- Patients (and their families) with a personal and/or family history suggestive of Li-Fraumeni syndrome should be considered for further genetic assessment, as outlined in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian (available at NCCN.org).
- *SDH* gene mutational analysis for the identification of germline mutations in the *SDH* gene subunits should be considered for patients with GIST lacking *KIT* or *PDGFRA* mutations. Loss of SDHB protein expression by IHC is a useful screen to identify patients who would be appropriate for germline mutation testing, but it is not diagnostic of a germline mutation.
- Evaluation for family history of FAP or Gardner syndrome is recommended for patients diagnosed with desmoid tumors (aggressive fibromatoses).

Pathology of STS

Biopsy

A pretreatment biopsy is highly preferred for the diagnosis and grading of STS and should be performed by an experienced surgeon or radiologist. Biopsy should establish the malignancy and provide a specific diagnosis where possible and a grade where appropriate or feasible, recognizing that limited biopsy material may underestimate grade. Biopsy may be accomplished via open incisional or core needle technique. Core needle biopsy is preferred; however, an open incisional biopsy may be considered by an experienced surgeon. In patients without a definitive diagnosis after initial biopsy due to limited sampling size, repeat image-guided core needle biopsy should be considered to make a diagnosis. Although fine-needle aspiration (FNA) is a convenient technique, it can be difficult to make an accurate primary diagnosis with FNA alone due to small specimen size; thus it is discouraged.[33] FNA may be acceptable in selected institutions with clinical and pathologic expertise. Endoscopic or needle biopsy may be indicated for deep thoracic, abdominal, or pelvic STS.

Principles of Pathologic Assessment

Pathologists with expertise in STS 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. The differential diagnosis of a soft tissue mass includes malignant lesions (such as primary or metastatic carcinoma, melanoma, or lymphoma), desmoids, and benign lesions (such as lipomas, lymphangiomas, leiomyomas, and neuromas). However, because identification of the histopathologic type of a sarcoma is often difficult, several ancillary techniques have been used as an adjunct to morphologic diagnosis. These techniques include conventional cytogenetics, IHC, electron microscopy, and molecular genetic testing. Pathologists should have access to optimal cytogenetic and molecular diagnostic techniques. The results of appropriate ancillary studies used as an adjunct to morphologic diagnosis should be included in the pathology report.

The pathology report should include specific details about the primary diagnosis (using standardized nomenclature according to the WHO Classification of Soft Tissue Tumors); the organ and site of sarcoma; depth, size, and histologic grade of the tumor; presence or absence of necrosis; status of excision margins and lymph nodes; TNM stage; and additional features, such as mitotic rate, presence or absence of vascular invasion, and the type and extent of inflammatory infiltration.

Molecular Diagnosis of STS

Molecular genetic testing has emerged as a particularly useful ancillary technique, because many subtypes of STS are associated with characteristic genetic aberrations, including single base-pair substitutions, deletions, amplifications, and translocations. STS can be divided into 2 major genetic groups: (1) sarcomas with specific genetic alterations (eg, chromosomal translocations or point mutations) and usually simple karyotypes; and (2) sarcomas with nonspecific genetic alterations and complex unbalanced karyotypes.[34]

STS with recurrent chromosomal translocations can be classified into subtypes depending on the presence of fusion gene transcripts (eg, *EWSR1-ATF1* in clear cell sarcoma, *TLS-CHOP* [also known as *FUS-DDIT3*] in myxoid or round cell liposarcoma, *SS18-SSX* [*SS18-SSX1* or *SS18-SSX2*] in synovial sarcoma, and *PAX-FOXO1* [*PAX3-FOXO1* or *PAX7-FOXO1*] in alveolar RMS). The fusion genes resulting from chromosomal translocations can provide useful diagnostic and prognostic information. See "Principles of Ancillary Techniques Useful in the Diagnosis of Sarcomas" for a list of recurrent genetic aberrations associated with other subtypes (SARC-B; pages 761–763).

Conventional cytogenetic analysis, fluorescence in situ hybridization, and polymerase chain reaction (PCR) are the most common techniques used in the molecular diagnosis of STS.[35] In a prospective study, Hill et al[36] concluded that PCR-based molecular analysis is more sensitive than conventional cytogenetics and is a useful adjunct for the diagnosis of alveolar RMS, synovial sarcoma, and myxoid liposarcoma that have variation in fusion gene partners.

The molecular heterogeneity of fusion gene transcripts has been suggested to predict prognosis in certain sarcoma subtypes. In patients with alveolar RMS presenting with metastatic disease, *PAX7-FOXO1* was associated with a favorable prognosis compared with *PAX3-FOXO1*.[37] In patients with synovial sarcoma, the prognostic impact of *SS18-SSX1* or *SS18-SSX2* is less clear, with 2 large studies showing conflicting results.[38,39] In myxoid liposarcoma, the variability of fusion gene transcript has no effect on clinical outcome.[40]

Although molecular genetic testing appears promising, it involves highly complex techniques and the methods are not absolutely sensitive or do not provide specific results. Molecular testing should be performed by a pathologist with expertise in the use of molecular diagnostic techniques for the diagnosis of STS. In addition, technical limitations associated with molecular testing suggest that molecular evaluation should be considered only as an ancillary technique. Molecular test results should therefore only be interpreted in the context of the clinical and pathologic features of a sarcoma.[35]

Staging

The AJCC staging system for STS has historically used a 4-grade system, but within the 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 the NCI system, are 3-tiered grading systems. The NCI system is based on the evaluation of tumor histology, location, and amount of tumor necrosis. The FNCLCC system is based on tumor differentiation, mitosis count, and tumor necrosis. In a comparative study of these systems in 410 adult patients with STS, the FNCLCC system showed a slightly increased ability to predict distant metastasis development and tumor mortality.[41] Riad et al[42] examined the impact of lymph node involvement on survival in patients with extremity sarcoma. Lymph node metastases developed in 3.7% of patients (39 of 1,066) who had surgery. The outcome of patients with isolated lymph node metastases was significantly better than with synchronous systemic and lymph node involvement (the estimated 4-year survival rates were 71% and 21%, respectively).[42] The outcome for patients with isolated lymph node involvement, treated with lymph node dissection, was also similar to that of patients with AJCC stage III extremity sarcomas.[42,43] The revised 2010 AJCC staging system incorporates a 3-tiered grading system, and lymph node disease has been reclassified as stage III rather than stage IV disease.[44] However, many clinicians prefer the 2-tiered system, which is also used in the algorithm.

Surgery

Surgical resection (with appropriately negative margins) is the standard primary treatment for most patients with STS, although close margins may be necessary to preserve uninvolved critical neurovascular

structures. RT and/or chemotherapy (in the case of chemosensitive histologies) are often used before surgery in many centers to downstage large, high-grade tumors to enable effective surgical resection, because the risk of failure in the surgical bed can be high. Postoperative RT should be considered after resections with close soft tissue margins (<1 cm) or a microscopically positive margin on bone, major blood vessels, or a nerve. In selected cases when margin status is uncertain, consultation with a radiation oncologist is recommended.

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 or entire anatomic compartment resection is not routinely necessary. If resections with microscopically positive 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 edge of the surgical incision (in case repeat resection or RT is indicated).

Both the surgeon and the pathologist should document surgical margins while evaluating a resected specimen. If surgical margins are positive on final pathology, reresection to obtain negative margins should strongly be considered if it will not have a significant impact on functionality.[45] In an analysis of 666 consecutive patients with localized STS treated with an apparent macroscopic total tumor resection, 295 patients underwent reresection of their tumor bed (residual tumor was found in 46% of patients, including macroscopic tumor in 28% of patients).[45] Reresection remained a significant predictor of local control. The local control rates at 5, 10, and 15 years were 85%, 85%, and 82%, respectively, for patients who underwent reresection. The corresponding local control rates were 78%, 73%, and 73%, respectively (P=.03), for patients who did not undergo reresection.

Radiation Therapy

RT can be administered as primary, preoperative, or postoperative treatment. Total RT doses are always determined based on the tissue tolerance. Newer RT techniques, such as brachytherapy, intraoperative RT (IORT), and intensity-modulated RT (IMRT), have led to the improvement of treatment outcomes in patients with STS. Brachytherapy involves the direct application of radioactive seeds into the tumor bed through catheters placed during surgery. Options include low-dose-rate (LDR) brachytherapy, fractionated high-dose-rate (HDR) brachytherapy, or intraoperative HDR brachytherapy. LDR and HDR brachytherapy are associated with similar rates of local control.[46] It has been suggested that HDR brachytherapy may be associated with lower incidences of severe toxicity; however, this has not been proven in randomized clinical trials.[46] The main advantage of IMRT is its ability to more closely contour the high-dose radiation volume, thereby minimizing the volume of high-dose radiation to the surrounding normal tissues.[47] Additionally, image-guided techniques may allow for reduced target volumes, further minimizing toxicity.[48] IORT is the delivery of radiation during surgery and can be performed using different techniques, such as electron beam RT or brachytherapy.[49]

Preoperative RT may reduce seeding during the 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 of recurrence.[50–52] Most institutions include the entire operative bed within the RT field. The main disadvantage of preoperative RT, however, is its effect on wound healing.[53,54] After preoperative RT, a 3- to 6-week interval is necessary before resection to allow acute reactions to subside and decrease the risk of wound complications. Involvement of a plastic surgeon in the team may be necessary to reduce wound complications when preoperative RT is contemplated.

Postoperative RT is associated with higher rates of long-term treatment-related side effects. In one retrospective analysis, although no evidence was seen for differences in disease outcome associated with the use of either preoperative or postoperative RT, a slight increase in late treatment-related side effects was seen with postoperative RT, mainly due to the higher doses used.[55] Positive surgical margins

are associated with higher rates of local recurrence.[56] Postoperative RT has been shown to improve local control in patients with positive surgical margins.[57] Of those with positive margins, RT doses greater than 64 Gy, microscopically positive margins, superficial location, and extremity site are associated with improved local control.

A postoperative RT boost of 16 Gy has been used in patients with positive surgical margins after the wound has healed. However, the results of a retrospective analysis showed that postoperative RT boost did not provide any advantage in preventing local recurrence in some patients with positive surgical margins (such as those with low-grade, well-differentiated liposarcoma and a focally, "planned" positive margin on an anatomically fixed critical structure).[58] Similarly, another retrospective matched cohort of patients with extremity STS found no added benefit of postoperative RT boost when evaluating local recurrence, distant metastasis, and mortality.[59]

The advantage of adding postoperative RT boost has not yet been evaluated in a randomized clinical trial. Intervals beyond 8 weeks between resection and postoperative RT are not recommended because of the development of late fibrosis and the proliferation of malignant cells. The risk of local recurrence versus the toxicity of postoperative RT should be assessed before making a decision regarding the use of postoperative RT.

Chemotherapy/Chemoradiation

Resectable Disease

Preoperative Therapy: Preoperative chemotherapy[60–63] or chemoradiation[64–71] has been evaluated in single and multicenter studies in patients with high-grade tumors.

Studies that have evaluated preoperative chemotherapy followed by surgery have reported inconsistent findings. The results of the only randomized study that compared surgery alone versus preoperative chemotherapy followed by surgery in 134 evaluable patients with high-risk tumors (tumors ≥8 cm of any grade, grade 2/3 tumors <8 cm, grade 2/3 locally recurrent tumors, or tumors with inadequate surgery) did not show a major survival benefit for patients receiving chemotherapy.[61] At a median follow-up of 7.3 years, the estimated 5-year disease-free survival (DFS) rate was 52% for the no-chemotherapy arm and 56% for the chemotherapy arm (*P*=.3548). The corresponding 5-year overall survival (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 preoperative or postoperative doxorubicin-based chemotherapy were not sustained beyond 1 year.[62] In another retrospective study, the benefit of preoperative 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.[63]

In a single-institution study involving 48 patients with high-grade extremity STS (≥8 cm), the outcome of patients treated with preoperative chemoradiation with the MAID (mesna, doxorubicin, ifosfamide, and dacarbazine) regimen followed by surgery and postoperative chemotherapy with the same regimen was superior to that of historical controls.[66] 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.[66] 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.[68,69] 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.[69] Long-term follow-up data of these studies confirmed that preoperative chemoradiation followed by resection and postoperative 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, preoperative chemoradiation was associated with significant short-term toxicities.[69,70]

Postoperative Therapy: Available evidence from meta-analyses[72–76] and randomized clinical trials [77–82] suggests that postoperative chemotherapy improves relapse-free survival (RFS) in patients with STS of extremities. However, data regarding OS advantage are conflicting.

The Sarcoma Meta-Analysis Collaboration (SMAC) performed a meta-analysis of 14 random-

ized studies (1,568 patients) that compared postoperative chemotherapy with follow-up and in some cases RT after surgery with a variety of sarcomas.[73] 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 postoperative chemotherapy.

An updated meta-analysis also confirmed the marginal efficacy of postoperative chemotherapy in terms of local, distant, and overall recurrence as well as OS (which is contrary to that reported in the SMAC meta-analysis) in patients with localized STS (n=1,953).[75] A recent large, cohort-based analysis with a median follow-up of 9 years indicated that postoperative 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 FNCLCC 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 and 5-year OS: 75% vs 65%; *P*=.15).[76]

In the Italian randomized cooperative study (n=104), which randomized patients with high-grade or recurrent extremity sarcoma to receive postoperative chemotherapy with epirubicin and ifosfamide or observation alone, median DFS (48 vs 16 months) and median OS (75 vs 46 months) were significantly better in the treatment group after a median follow-up of 59 months; the absolute benefit for OS from chemotherapy was 13% at 2 years. The benefit increased to 19% at 4 years for patients receiving chemotherapy.[78] After a median follow-up of 90 months, the estimated 5-year OS rate was 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.[83]

In another phase III randomized study (EORTC-62931), 351 patients with macroscopically resected grade 2/3 tumors with no metastases were randomized to observation or postoperative chemotherapy with ifosfamide and doxorubicin with lenograstim.[80] A planned interim analysis of this study showed no survival advantage for postoperative 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 postoperative chemotherapy and observation. These findings are consistent with the results reported in an earlier EORTC study by Bramwell et al.[77] In that study, postoperative 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 local recurrence rates (17% vs 31% for the control group; *P*=.004). However, no differences in distant metastases (32% and 36%, respectively, for CYVADIC and the control group; *P*=.42) or OS rates (63% and 56%, respectively, for CYVADIC and the control group; *P*=.64) were seen.

A recent 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.[82] Postoperative doxorubicin-based chemotherapy was associated with improved RFS in male patients and those older than 40 years, although female patients and those 40 years or younger 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.

Long-term follow-up results of another prospective randomized study also showed that postoperative chemotherapy with IFADIC (ifosfamide, dacarbazine, and doxorubicin 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.[81]

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.[84–96] Other chemotherapeutic agents such as gemcitabine, docetaxel, vinorelbine, pegylated liposomal doxorubicin, and temozolomide have also been evaluated in clinical trials.

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.[97–100] 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.[98] 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.[99] Clinical benefit (complete response [CR], partial response [PR], or stable disease at 4 months or more) was seen in 25% of patients.

In a more recent randomized study, 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.[100]

Temozolomide,[101–103] pegylated liposomal doxorubicin,[104] and vinorelbine[105,106] 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 of 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.[103] 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.[104] In a retrospective study of pretreated patients with metastatic STS, vinorelbine induced overall response in 6% of patients and 26% had stable disease.[105]

Trabectedin is a novel DNA-binding agent that has shown objective responses in phase II and III studies of patients with advanced STS.[107–115] Recent phase III data from a randomized, multicenter trial revealed a 2.7-month PFS benefit versus dacarbazine in metastatic liposarcoma or leiomyosarcoma that progressed after anthracycline-based therapy; the study is ongoing to determine OS.[113] Another recent study supported the efficacy of trabectedin in translocation-related sarcoma [115] 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.[116]

Eribulin is a novel microtubule inhibiting agent that has been evaluated as single-agent therapy for STS, including leiomyosarcoma, adipocytic sarcoma, synovial sarcoma, and other tumor types.[117] Recent data from a phase III trial compared the survival benefit of eribulin and dacarbazine in 452 patients with advanced leiomyosarcoma or liposarcoma, revealing a median OS of 13.5 and 11.5 months, respectively (hazard ratio [HR], 0.77; 95% CI, 0.62–0.95; *P*=.017).[118] In January 2016, the FDA approved eribulin for the treatment of liposarcomas only.

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 liposarcomas.[119] In a phase III study (EORTC 62072), 369 patients with metastatic nonlipogenic STS for whom at least one anthracycline-based chemotherapy regimen had failed were randomized to either pazopanib or placebo.[120] 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 it was not statistically significant. 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 tumors, and normal hemoglobin levels.[121] The guidelines have included pazopanib as an option for palliative therapy for patients with progressive, unresectable, or metastatic nonlipogenic STS.

Imatinib[122] and sunitinib[123,124] have also shown efficacy in patients with advanced and/or metastatic STS other than GIST. Crizotinib, an anaplastic lymphoma kinase (ALK) inhibitor, was active in inflammatory myofibroblastic tumor with ALK translocation.[125] The updated guidelines also include ceritinib, a next-generation ALK-inhibitor that has been successful in treating ALK-rearranged non–small cell lung cancer.[126]

mTOR inhibitors such as sirolimus, temsirolimus, and everolimus have also shown promising results in patients with metastatic perivascular epithelioid cell tumors and in those with recurrent lymphangi-

oleiomyomatosis or angiomyolipomas.[127–133] Additionally, sorafenib may be active in select subtypes of advanced and/or metastatic STS other than GIST (eg, leiomyosarcoma, desmoid tumors).[134,135]

Bevacizumab either alone or in combination with temozolomide was well tolerated and effective in patients with metastatic or locally advanced or recurrent epithelioid hemangiopericytoma and malignant solitary fibrous tumor.[136,137]

Palbociclib, an inhibitor of cyclin-dependent kinases 4 and 6, induced objective tumor response and a favorable PFS of 56% to 66% in patients with cyclin-dependent kinase-4–amplified, well-differentiated, or dedifferentiated liposarcoma.[138,139]

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Individual Disclosures of the NCCN Soft Tissue Sarcoma Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Date Completed
Robert S. Benjamin, MD[a]	Johnson & Johnson	Karyopharm Therapeutics Inc.; and Novartis Pharmaceuticals Corporation	None	9/24/15
Sarah Boles, MD	None	None	None	10/14/15
Marilyn M. Bui, MD, PhD	None	None	None	5/3/15
Ernest U. Conrad III, MD[b]	None	None	None	9/25/15
Kristen N. Ganjoo, MD	None	None	EMD Serono	5/1/15
Suzanne George, MD	ARIAD Pharmaceuticals, Inc.; Bayer HealthCare; Blueprint Medicines; Deciphera Pharmaceuticals, LLC; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	None	None	2/15/16
Ricardo J. Gonzalez, MD	None	None	Novartis Pharmaceuticals Corporation	4/30/15
Martin J. Heslin, MD	Genentech, Inc.	BestDoctors	None	5/12/15
John M. Kane III, MD	None	Rawle and Henderson	None	5/11/15
Henry Koon, MD	Bristol-Myers Squibb Company	Bristol-Myers Squibb Company	Bristol-Myers Squibb Company	9/24/15
Joel Mayerson, MD	None	Onkos Surgical	DePuy-Johnson & Johnson/Synthes	4/7/16
Martin McCarter, MD	None	Debbies Dream Foundation	None	5/19/16
Sean V. McGarry, MD	None	Musculoskeletal Transplant Foundation	None	2/20/16
Christian Meyer, MD, PhD	None	None	None	5/13/15
Richard J. O'Donnell, MD	None	None	None	2/22/16
Alberto S. Pappo, MD	None	None	ZIOPHARM Oncology, Inc.	1/6/16
I. Benjamin Paz, MD[b]	None	None	None	10/16/15
Ivy A. Petersen, MD	None	None	None	9/21/15
John D. Pfeifer, MD, PhD[b]	None	Agilent Technologies; Illumina, Inc.; PierianDx; and Strand Analytical Laboratories	None	5/6/15
R. Lor Randall, MD[b]	Children`s Oncology Group	Alan B. Slifka Foundation; Biomet, Inc.; International Society of Paediatric Oncology; Musculoskeletal Transplant Foundation; and Sarcoma Foundation of America	Biomet, Inc.; Musculoskeletal Transplant Foundation; and OncLive	4/7/16
Richard F. Riedel, MD	Astex Pharmaceuticals, Inc.; CytRx Corporation; Eisai Inc.; Morphotek Inc.; Novartis Pharmaceuticals Corporation; Plexxikon Inc.; Threshold Pharmaceuticals; and TRACON Pharmaceuticals, Inc.	CytRx Corporation; EMD Serono; Morphotek Inc.; and Novartis Pharmaceuticals Corporation	None	9/25/15
Scott Schuetze, MD, PhD	AB Science; Amgen Inc.; BioMed Valley Discoveries, Inc.; CytRx Corporation; Johnson & Johnson; SARC Threshold Pharmaceuticals	EMD Serono; and Oncos	None	6/12/15
Karen D. Schupak, MD	None	None	None	4/30/15
Herbert S. Schwartz, MD[b]	None	None	Musculoskeletal Transplant Foundation	5/18/16
William D. Tap, MD	Daiichi- Sankyo Co.; ImClone Systems Incorporated; Morphotek Inc.; and Threshold Pharmaceuticals	Advaxis, Inc.; ARIAD Pharmaceuticals, Inc.; EMD Serono; Novartis Pharmaceuticals Corporation; and Plexxikon Inc.	None	5/4/15
Margaret von Mehren, MD	AROG Pharmaceuticals LLC; ArQule, Inc.; Immune Design; Janssen Pharmaceutical Products, LP; Johnson & Johnson; Merck & Co., Inc.; Pfizer Inc.; SARC; and Synta Pharmaceuticals Corp.	AROG Pharmaceuticals LLC; Blueprint Medicines; and Janssen Pharmaceutical Products, LP	None	2/10/16
Jeffrey D. Wayne, MD	None	Novartis Pharmaceuticals Corporation	Novartis Pharmaceuticals Corporation	4/30/15

[a]The following individuals have disclosed that they have a spouse/domestic partner/dependent potential conflict:
Robert S. Benjamin, MD: Gilead Sciences, Inc.; Johnson & Johnson; Merck & Co., Inc.; and Pfizer Inc.
[b]The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty conflict:
Ernest U. Conrad III, MD: LifeNet Health Tissue Bank
I. Benjamin Paz, MD: LS BioPath
John D. Pfeifer, MD, PhD: PierianDX
R. Lor Randall, MD: Association of Bone and Joint Surgeons
Herbert S. Schwartz, MD: Musculoskeletal Transplant Foundation
The NCCN Guidelines staff have no conflicts to disclose.