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Soft Tissue Sarcoma, Version 2.2018

Clinical Practice Guidelines in Oncology

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Overview

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

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 STS 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 tumors, desmoid tumors, and rhabdomyosarcoma. This portion of the NCCN Guidelines discusses general principles for the diagnosis, staging, and treatment of STS of the extremities, superficial trunk, or head and neck; outlines treatment recommendations by disease stage; and reviews the evidence to support the guidelines recommendations.

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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.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult 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 representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full 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 563. (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.

Sarcomas collectively account for approximately 1% of all adult malignancies and 15% of pediatric malignancies. In 2018, an estimated 13,040 people will be diagnosed with soft tissue sarcoma (STS) in the United States, with approximately 5,150 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. A recent SEER database study calculated the annual incidence of GIST in the United States to be 0.78/100,000 in 2011.[2] Prior radiation therapy (RT) to the affected area is a risk factor for the development of STS.[3–5] More than 50 different histologic subtypes of STS have been identified. Common subtypes of STS include undifferentiated pleomorphic sarcoma (UPS), GIST, liposarcoma (LPS), and leiomyosarcoma (LMS).[6] 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.[7] 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 of children and adolescents and is less common in adults.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for STS 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

Text cont. on page 552.

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WORKUP

ESSENTIAL:
- Prior to the initiation of therapy, all patients should be evaluated and managed by a multidisciplinary team with expertise and experience in sarcoma
- H&P
- Adequate imaging of primary tumor[a,b] is indicated for all lesions with a reasonable chance of being malignant
- Carefully planned core needle [preferred] or incisional biopsy after adequate imaging (see SARC-D*)[c]
  - Place biopsy along future resection axis with minimal dissection and careful attention to hemostasis
  - Biopsy should establish grade and histologic subtype[d]
  - As appropriate, use ancillary diagnostic methodologies[e]
- Chest imaging[b]

USEFUL UNDER CERTAIN CIRCUMSTANCES:[f]
- Additional imaging as indicated see Principles of Imaging (SARC-A)
- Patients with personal/family history suggestive of Li-Fraumeni syndrome should be considered for further genetics assessment See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian†
- Patients with neurofibromatosis See NCCN Guidelines for Central Nervous System Cancers (PSCT-3)†

Special considerations for unique histologies[g]
- Desmoid tumors (Aggressive fibromatosis) → See DESM-1*
- Ewing sarcoma → See NCCN Guidelines for Bone Cancer†
- Rhabdomyosarcoma (RMS) → See RMS-1*

Other soft tissue sarcomas of the extremity/superficial trunk, head/neck[h]
- Stage I → See Primary (EXTSARC-2)
- Stage II, III resectable disease with acceptable functional outcomes → See Primary (EXTSARC-3)
- Stage II, III resectable disease with adverse functional outcomes or Unresectable primary disease → See Primary (EXTSARC-4)
- Synchronous Stage IV → See Primary (EXTSARC-5)
- Recurrent disease → See Primary (EXTSARC-6)

*Available online, in the complete version of these guidelines, at NCCN.org.
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[a]Imaging studies should include cross-sectional imaging (MRI with and without contrast +/- CT with contrast) to provide details about the size of tumor and contiguity to nearby visceral structures and neurovascular landmarks. Other imaging studies such as angiogram and plain radiograph may be warranted in selected circumstances.

[b]See Principles of Imaging (SARC-A).

[c]In selected institutions with clinical and pathologic expertise, an FNA may be acceptable.

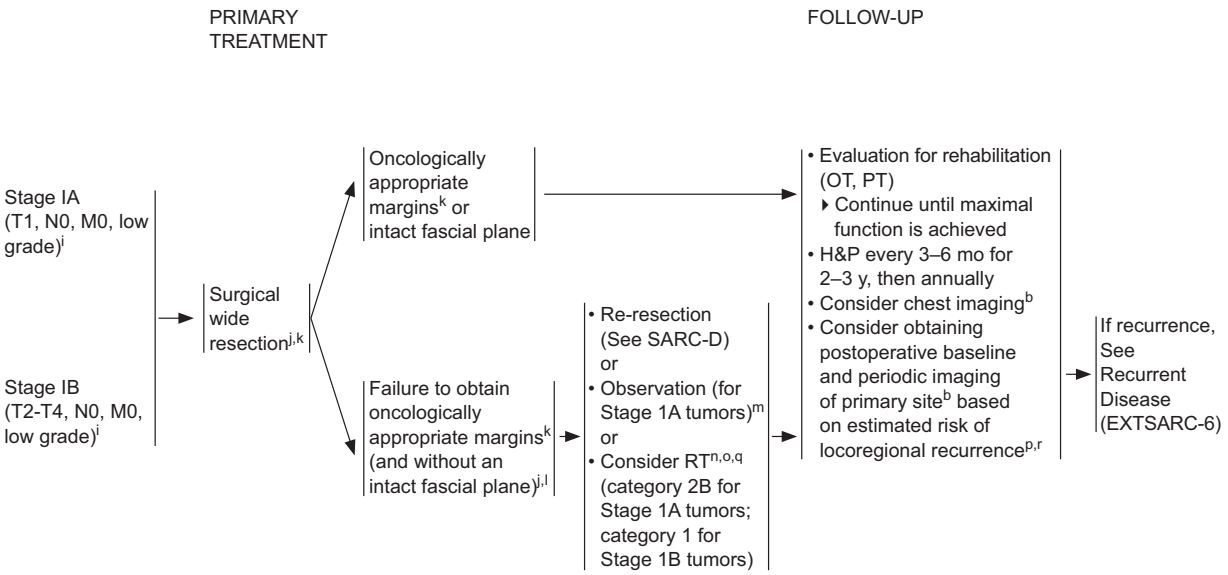
[d]See Principles of Pathologic Assessment of Sarcoma Specimens (SARC-B*).

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

[f]Different subtypes have different propensities to spread to various locations.

[g]Diagnoses that will impact the overall treatment plan.

[h]Patients with DFSP with fibrosarcomatous changes and/or malignant transformations can be treated according to this algorithm. For DFSP without fibrosarcomatous elements refer to treatment in the NCCN Guidelines for Dermatofibrosarcoma Protuberans†.



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[b]See Principles of Imaging (SARC-A).

[i]See American Joint Committee on Cancer (AJCC) Staging, 8th Edition (ST-3*).

[j]See Principles of Surgery (SARC-D*).

[k]Resection should be tailored to minimize surgical morbidity for patients with atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLS). En bloc resection with negative margins is generally sufficient to obtain long-term local control.

[l]In selected cases when margin status is uncertain, consultation with a radiation oncologist is recommended. Reresection, if feasible, may be necessary to render margins >1cm.

[m]Treatment options including revision surgery versus observation should be presented at an experienced multidisciplinary sarcoma tumor board to determine advantages and disadvantages of the decision.

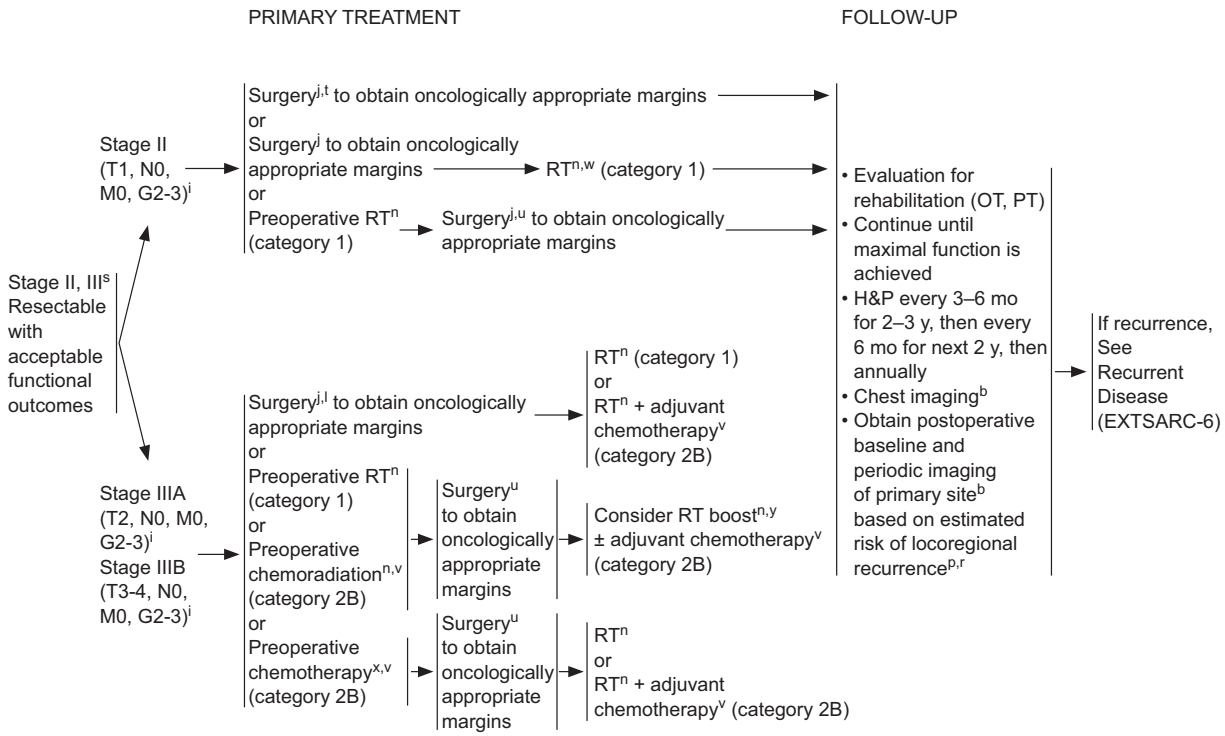
[n]Results of a randomized study showed a non-significant trend toward reduced late toxicities (fibrosis, edema, and joint stiffness) with preoperative compared to postoperative radiation and a significant association between these toxicities and increasing treatment field size. Because postoperative radiation fields are typically larger than preoperative fields, the panel has expressed a general preference for preoperative radiation, particularly when treatment volumes are large." (Davis AM, O'Sullivan B, Turcotte R, et al. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. Radiother Oncol 2005;75(1):48-53 and Nielsen OS, Cummings B, O'Sullivan B, et al. Preoperative and postoperative irradiation of soft tissue sarcomas: effect of radiation field size. Int J Radiat Oncol Biol Phys 1991;21(6):1595-1599. See Radiation Therapy Guidelines (SARC-E).

[o]Randomized clinical trial data support the use of radiation therapy as an adjunct to surgery in appropriately selected patients based on an improvement in disease-free survival (although not overall survival). (Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol 1998;16:197-203).

[p]In situations where the area is easily followed by physical examination, imaging may not be required.

[q]For patients with ALT/WDLS, observation is recommended for focally positive margins if re-resection, in the event of recurrence, would not be unduly morbid. RT is reserved for selected patients with recurrent or deeply infiltrative primary lesions with a risk of local recurrence, depending on the tumor location and patient's age.

[r]After 10 years, the likelihood of developing a recurrence is small and follow-up should be individualized.



*Available online, in the complete version of these guidelines, at NCCN.org.

[b]See Principles of Imaging (SARC-A).

[i]See American Joint Committee on Cancer (AJCC) Staging, 8th Edition (ST-3*).

[j]See Principles of Surgery (SARC-D*).

[l]In selected cases when margin status is uncertain, consultation with a radiation oncologist is recommended. Re-resection, if feasible, may be necessary to render margins >1.0 cm.

[n]Results of a randomized study showed a non-significant trend toward reduced late toxicities (fibrosis, edema, and joint stiffness) with preoperative compared to postoperative radiation and a significant association between these toxicities and increasing treatment field size. Because postoperative radiation fields are typically larger than preoperative fields, the panel has expressed a general preference for preoperative radiation, particularly when treatment volumes are large (Davis AM, O'Sullivan B, Turcotte R, et al. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. Radiother Oncol 2005;75(1):48-53 and Nielsen OS, Cummings B, O'Sullivan B, et al. Preoperative and postoperative irradiation of soft tissue sarcomas: effect of radiation field size. Int J Radiat Oncol Biol Phys 1991;21(6):1595-1599. See Radiation Therapy Guidelines (SARC-E).

[p]In situations where the area is easily followed by physical examination, imaging may not be required.

[r]After 10 years, the likelihood of developing a recurrence is small and follow-up should be individualized.

[s]Patients with stage III tumors with lymph node involvement should undergo regional lymph node dissection at the time of primary tumor resection ± RT.

[t]Surgery alone may be an option for small tumors resected with wide margins.

[u]Re-imaging using MRI with and without contrast (preferred for extremity imaging) or CT with contrast to assess primary tumor and rule out metastatic disease. See Principles of Imaging (SARC-A).

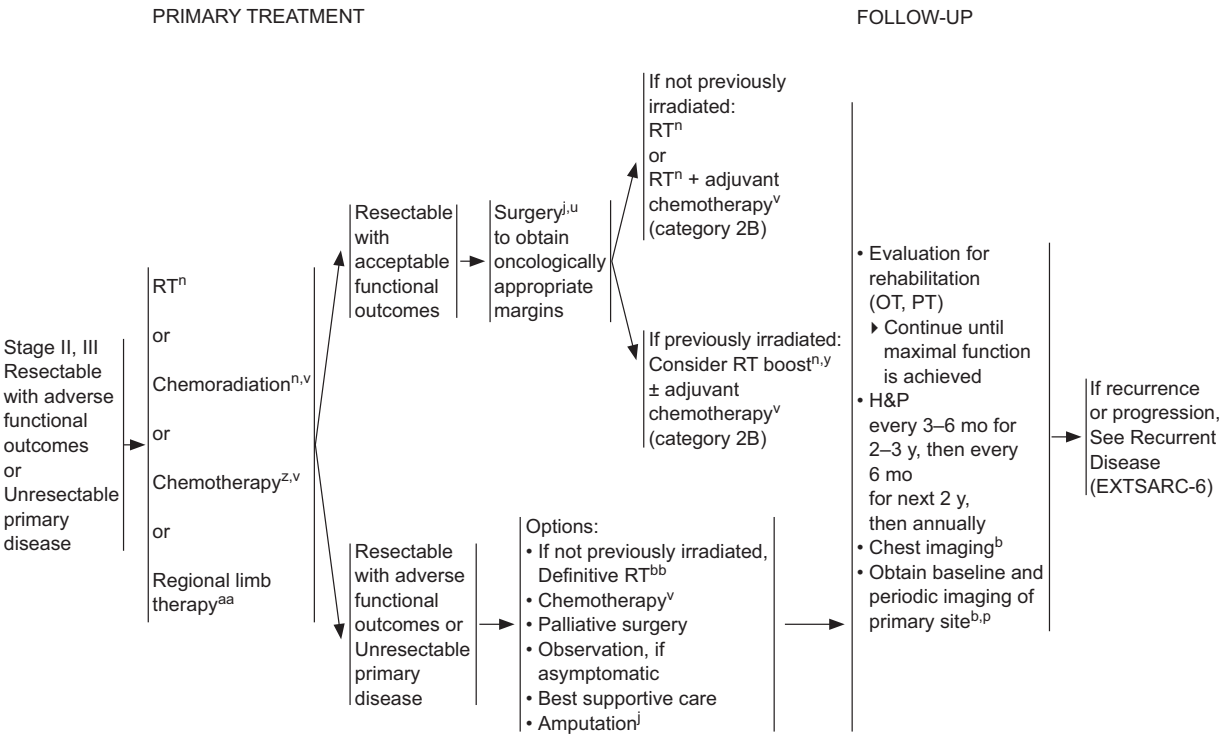
[v]See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F).

[w]RT may be used in select circumstances such as close or positive margins where re-excision is not feasible or for functional considerations.

[x]PET/CT may be useful in determining response to chemotherapy (Schuetze SM, Rubin BP, Vernon C, et al. Use of positron emission tomography in localized extremity soft tissue sarcoma treated with neoadjuvant chemotherapy. Cancer 2005;103:339-348).

[y]For residual gross disease or microscopically positive margins.

EXTSARC-3



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[b]See Principles of Imaging (SARC-A).

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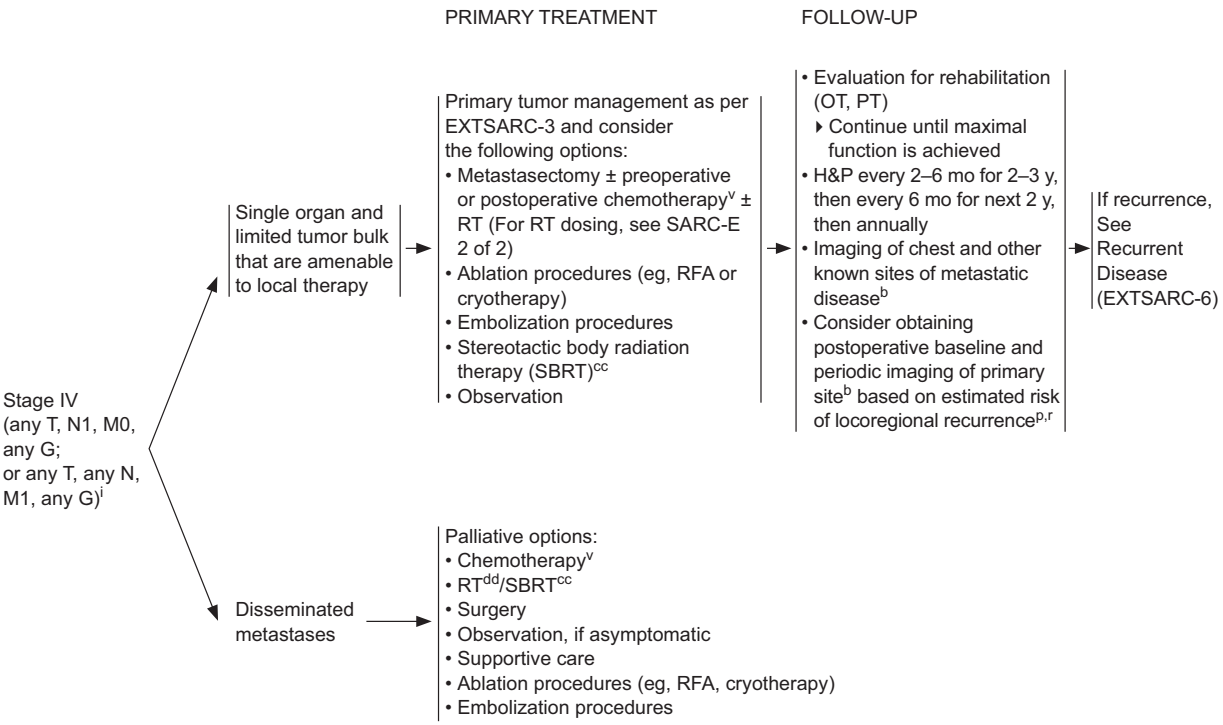
[v]See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F).

[y]For residual gross disease or microscopically positive margins.

[z]PET/CT may be useful in determining response to chemotherapy. (Schuetze SM, Rubin BP, Vernon C, et al. Use of positron emission tomography in localized extremity soft tissue sarcoma treated with neoadjuvant chemotherapy. Cancer 2005;103:339-348).

[aa]Should only be done at institutions with experience in regional limb therapy.

[bb]Definitive RT entails delivering the maximal local dose compatible with known normal tissue tolerance, typically in the range of 70–80 Gy with sophisticated treatment planning techniques being a necessity in this setting.



[b]See Principles of Imaging (SARC-A).

[i]See American Joint Committee on Cancer (AJCC) Staging, 8th Edition (ST-3), available online, in the complete version of these guidelines, at NCCN.org.

[p]In situations where the area is easily followed by physical examination, imaging may not be required.

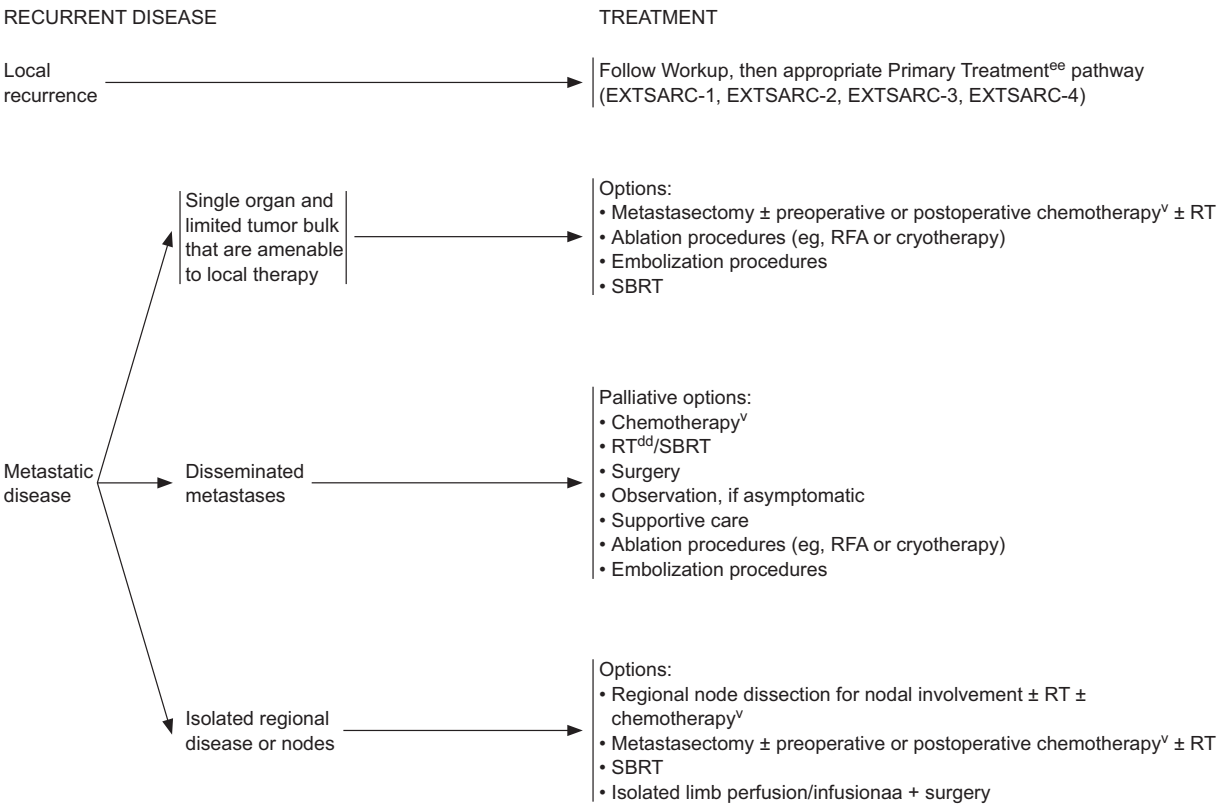
[r]After 10 years, the likelihood of developing a recurrence is small and follow-up should be individualized.

[v]See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F).

[cc]In retrospective studies, various SBRT dosing regimens have been reported to be effective for treatment of sarcoma metastases. Dose and fractionation should be determined by an experienced radiation oncologist based on normal tissue constraints. (Dhakal S, Corbin KS, Milano MT, et al. Stereotactic body radiotherapy for pulmonary metastases from soft-tissue sarcomas: excellent local lesion control and improved patient survival. Int J Radiat Oncol Biol Phys 2012;82(2):940-945. Navarria P, Ascolese AM, Cozzi L, et al. Stereotactic body radiation therapy for lung metastases from soft tissue sarcoma. Eur J Cancer 2015;51(5):668-674).

[dd]Palliative RT requires balancing expedient treatment with sufficient dose expected to halt the growth of or cause tumor regression. Numerous clinical issues regarding rapidity of growth, the status of systemic disease, and the use of chemotherapy must be considered. Recommended only for palliative therapy in patients with synchronous stage IV or recurrent disease with disseminated metastases.

EXTSARC-5



[v]See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F).

[aa]Should only be done at institutions with experience in regional limb therapy.

[dd]Palliative RT requires balancing expedient treatment with sufficient dose expected to halt the growth of, or cause tumor regression. Numerous clinical issues regarding rapidity of growth, the status of systemic disease, and the use of chemotherapy must be considered. Recommended only for palliative therapy in patients with synchronous stage IV or recurrent disease with disseminated metastases.

[ee]If local recurrence can be excised, a decision will need to be made on a case-by-case basis whether re-irradiation is possible. Some case series suggest benefit with re-irradiation [Catton C, Davis A, Bell R, et al. Soft tissue sarcoma of the extremity. Limb sparing after failure of combined conservative therapy. Radiother Oncol 41:209, 1996] while others do not [Torres MA, Ballo MT, Butler CE, et al. Management of locally recurrent soft-tissue sarcoma after prior surgery and radiation therapy. Int J Radiat Oncol Biol Phys 67:1124, 2007], likely reflecting differences in selection of patients for treatment with surgery and radiotherapy or surgery alone. Traditionally, the re-irradiation has been done with postoperative adjuvant brachytherapy but may now be able to be done as a combination of brachytherapy and IMRT to reduce the risks of morbidity with re-irradiation.

PRINCIPLES OF IMAGING

GENERAL

- CT and MRI performed with contrast is recommended throughout the guideline unless contraindicated or otherwise noted.
- As appropriate, abdominal/pelvic MRI with contrast can be substituted for abdominal/pelvic CT if contraindicated (ie, due to dye allergy).
- If obtaining abdominal/pelvic CT, chest CT may be performed without contrast unless simultaneously attained with contrast-enhanced abdominal/pelvic CT.
- Chest imaging without contrast preferred unless contrast is needed for mediastinal imaging.

EXTREMITY/SUPERIFICIAL TRUNK, HEAD/NECK

Workup

- Primary tumor imaging using MRI with and without contrast ± CT with contrast is recommended. Other imaging studies such as angiogram and plain radiograph may be warranted in certain circumstances.
- Chest imaging
  - X-ray or CT without contrast (preferred)
- Additional imaging studies as indicated:
  - PET/CT scan may be useful in staging, prognostication, and grading.
  - Consider abdominal/pelvic CT for myxoid/round cell liposarcoma, epithelioid sarcoma, angiosarcoma, and leiomyosarcoma.
  - Consider MRI of total spine for myxoid/round cell liposarcoma.
  - Consider CNS imaging with MRI (or CT if MRI is contraindicated) for alveolar soft part sarcoma and angiosarcoma.

Follow-up

Stage I

- Consider chest imaging every 6–12 months. X-ray or CT is preferred. Contrast may be used if also imaging abdomen/pelvis.
- Consider postoperative baseline and periodic imaging of primary site based on estimated risk of locoregional recurrence.
  - MRI with and without contrast and/or CT with contrast is recommended. Consider ultrasound for small lesions that are superficial. Ultrasound should be done by an ultrasonographer experienced in musculoskeletal disease.[1]

Stage II/III

- PET/CT may be useful in determining response to neoadjuvant chemotherapy for lesions that are larger than 3 cm, firm, and deep (not superficial).[2]
- Re-imaging is recommended after surgery using MRI with and without contrast (preferred for extremity imaging) or CT with contrast to assess primary tumor and rule out metastatic disease.
- Chest imaging using x-ray or CT is recommended every 3–6 months for 2–3 years, then every 6 months for next 2 years, then annually
- Resectable disease: postoperative baseline and periodic imaging of primary site based on estimated risk of locoregional recurrence
  - MRI with and without contrast and/or CT with contrast is recommended. Consider ultrasound for small lesions that are superficial. Ultrasound should be done by an ultrasonographer experienced in musculoskeletal disease.[1]
- Unresectable disease or resectable disease with adverse functional outcomes: Obtain postoperative baseline and periodic imaging of primary site based on estimated risk of locoregional recurrence.
  - MRI with and without contrast and/or CT with contrast is recommended. Consider ultrasound for small lesions that are superficial. Ultrasound should be done by an ultrasonographer experienced in musculoskeletal disease.[1]

Synchronous Stage IV

- Imaging of chest and other known sites of metastatic disease (x-ray or CT) is recommended every 2–6 months for 2–3 years, then every 6 months for next 2 years, then annually.
- Consider postoperative baseline and periodic imaging of the primary site based on estimated risk of locoregional recurrence.
  - MRI with and without contrast and/or CT with contrast is recommended. Consider ultrasound for small lesions that are superficial. Ultrasound should be done by an ultrasonographer experienced in musculoskeletal disease.[1]

Recurrent Disease

- Follow imaging recommendations for Workup, then use Follow-Up recommendations per appropriate primary treatment pathway.

[1]Choi H, Varma DGK, Fornage BD, et al. Soft-tissue sarcoma: MR imaging vs sonography for detection of local recurrence after surgery. AJR Am J Roentgenol 1991;157:353-358.

[2]Schuetze SM, Rubin BP, Vernon C, et al. Use of positron emission tomography in localized extremity soft tissue sarcoma treated with neoadjuvant chemotherapy. Cancer 2005;103:339-348.

SARC-A

1 AND 2 OF 3

Soft Tissue Sarcoma, Version 2.2018

RADIATION THERAPY GUIDELINES FOR SOFT TISSUE SARCOMA OF EXTREMITY/TRUNK/HEAD-NECK[1,2,3]

Preoperative RT → 50 Gy external-beam RT[4] → Surgery[5] with clips →

Consider observation in addition to boost for positive margins:[6,7]
- External-beam RT:
  - 16–18 Gy for microscopic residual disease;[5,8]
  - 20–26 Gy for gross residual disease.[5]
- Brachytherapy (low-dose rate):
  - 16–18 Gy for microscopic residual disease;
  - 20–26 Gy for gross disease.
- Brachytherapy (high-dose rate):
  - 14–16 Gy at approximately 3–4 Gy BID for microscopic residual disease;
  - 18–24 Gy for gross residual disease.
- IORT:
  - 10–12.5 Gy for microscopic residual disease;
  - 15 Gy for gross residual disease.

Postoperative RT following surgery[5] with clips → SARC-E (2 of 3)

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[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, and/or protons can be used to improve the therapeutic ratio:
- 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;
- Kraybill WG, Harris J, Spiro IJ, et al. Phase II study of neoadjuvant chemotherapy and radiation therapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group Trial 9514. J Clin Oncol 2006;24:619-625.

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

[4]External-beam RT in 1.8 to 2.0 Gy per fraction.

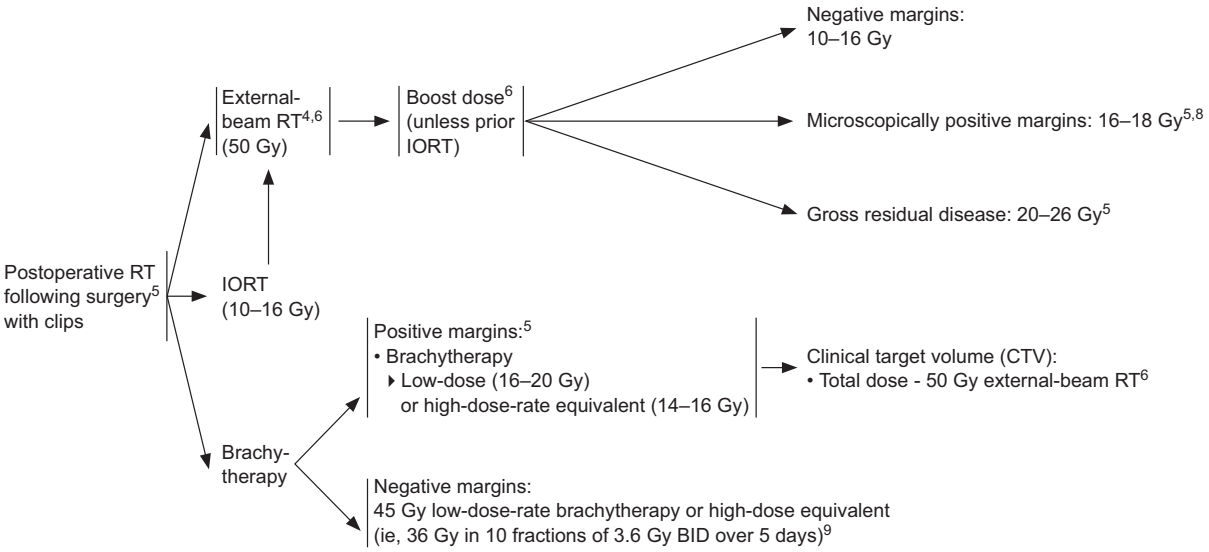
[5]See Resection Margins on Principles of Surgery (SARC-D*).

[6]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. (Gerrand et al. J Bone Joint Surg 2001;83-B:1149-1155.)

[7]There are also data to suggest that delivery of a boost for positive margins does not improve local control. Since delivery of a post-op boost does not clearly add benefit, the decision should be individualized and the potential toxicities should be carefully considered. (Al Yami, et al. Int J Radiat Oncol Biol Phys 2010;77:1191-1107; Pan, et al. J Surg Oncol 2014;110:817-822.)

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

RADIATION THERAPY GUIDELINES FOR SOFT TISSUE SARCOMA OF EXTREMITY/TRUNK/HEAD-NECK[1,2,3]



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- 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;
- Kraybill WG, Harris J, Spiro IJ, et al. Phase II study of neoadjuvant chemotherapy and radiation therapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group Trial 9514. J Clin Oncol 2006;24:619-625.

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

[4]External-beam RT in 1.8 to 2.0 Gy per fraction.

[5]See Resection Margins on Principles of Surgery (SARC-D*).

[6]Total doses should always be determined by normal tissue tolerance.

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

[9]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 Oncol Biol Phys 2001;49:1033-1043, 2001).

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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[k]	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] • Doxorubicin and olaratumab[g,14]	Single agents • Doxorubicin[3,4,15] • Ifosfamide[9,16] • Epirubicin[17] • Gemcitabine • Dacarbazine • Liposomal doxorubicin[18] • Temozolomide[f,19] • Vinorelbine[f,20] • Eribulin[f,h,21] • Trabectedin[f,i,22,23,24] • Pazopanib[f,j,25]	• Imatinib[26,27] • Sunitinib[28] • Regorafenib[29] Disease progression after imatinib, sunitinib, and regorafenib • Sorafenib[30-32] • Nilotinib[33,34] • Dasatinib[35] (for patients with D842V mutation) • Pazopanib[36] • Everolimus + TKI[l]	• Sulindac[37]or other non-steroidal anti-inflammatory drugs (NSAIDs), including celecoxib • Tamoxifen ± sulindac[38,39] • Toremifene[40] • Methotrexate and vinblastine[41] • Low-dose interferon[42] • Doxorubicin-based regimens[43-45] • Imatinib[46,47] • Sorafenib[48] • Methotrexate and vinorelbine[49] • Liposomal doxorubicin[50]

Non-Pleomorphic Rhabdomyosarcoma

Combination regimens
- Vincristine, dactinomycin, cyclophosphamide[51]
- Vincristine, doxorubicin, cyclophosphamide[52]
- Vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide[53]
- Vincristine, doxorubicin, ifosfamide[54]
- Cyclophosphamide and topotecan[55,56]
- Ifosfamide and doxorubicin[57]
- For Soft Tissue Ewing Sarcoma, see NCCN Guidelines for Bone Cancer[†]
- Ifosfamide and etoposide[58]
- Irinotecan and vincristine[59,60]
- Vincristine and dactinomycin[61]
- Carboplatin and etoposide[62]
- Vinorelbinef and low-dose cyclophosphamide[63]
- Vincristine, irinotecan, temozolomide[64]

Single agents
- Doxorubicin[65]
- Irinotecan[56,66]
- Topotecan[67]
- Vinorelbine[f,68]
- High-dose methotrexate[m,69]
- Trabectedin[f,23,24,25]

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

[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 uniterine sarcomas, see the NCCN Guidelines for Uterine Neoplasms[†].

[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]For use in STS histologies for which an anthracycline-containing regimen is appropriate.

[h]Category 1 recommendation for liposarcoma.

[i]Category 1 recommendation for liposarcoma and leiomyosarcoma (L-Types).

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

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

[l]TKIs to be considered for use in combination with everolimus include imatinib, sunitinib, or regorafenib.

[m]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[70]</td></tr>
<tr><td>Angiosarcoma
• Paclitaxel[71,72]
• Docetaxel
• Vinorelbinef
• Sorafenib[73]
• Sunitinib[74]
• Bevacizumab[75]
• All other systemic therapy options as per Soft Tissue Sarcoma Subtypes with Non-Specific Histologies (SARC-F 1 of 6)</td><td>Solitary Fibrous Tumor/Hemangiopericytoma
• Bevacizumab and temozolomide[76]
• Sunitinib[77,78]
• Sorafenib[79]</td></tr>
<tr><td>Alveolar Soft Part Sarcoma (ASPS)
• Sunitinib[80,81] (category 2B)</td><td>PEComa, Recurrent Angiomyolipoma, Lymphangioleiomyomatosis
• Sirolimus[82-8]5
• Everolimus[86]
• Temsirolimus[87,88]</td></tr>
<tr><td colspan="2">Inflammatory Myofibroblastic Tumor (IMT) with Anaplastic Lymphoma Kinase (ALK) Translocation
• Crizotinib[89]
• Ceritinib[90]</td></tr>
<tr><td colspan="2">Well-differentiated/Dedifferentiated Liposarcoma (WD-DDLS) for Retroperitoneal Sarcomas
• Palbociclib[91,92]</td></tr>
</table>

[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]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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SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA—References

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Cont. from page 537.

- GISTs
- Desmoid tumors (aggressive fibromatoses)
- RMS

Before treatment initiation, all patients should be evaluated and managed by a multidisciplinary team with extensive expertise and experience in the treatment of STS.[8] 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 (NCDB) showed that NCCN Guidelines–adherent treatment was associated with improved survival outcomes.[9]

This portion of the NCCN Guidelines discusses general principles and evidence for diagnosis and treatment of STS of the extremities, superficial trunk, or head and neck in adult patients. For treatment recommendations for intra-abdominal/retroperitoneal STS, GISTs, desmoid tumors, or RMS, please refer to the complete guidelines at NCCN.org.

STS of the Extremities, Superficial Trunk, or Head and Neck

Evaluation and Workup

The differential diagnosis of STS of the extremities includes ruling out desmoid tumors (aggressive fibromatosis), as well as the other malignant and benign lesions. An essential element of the workup is a history and physical (H&P) examination, imaging of the primary tumor and distant metastases, and a carefully planned biopsy (core needle or incisional biopsy). Adequate and high-quality imaging studies are crucial to good clinical management of patients, because the presence of metastatic disease may change the management of the primary lesion and the overall approach to the patient's disease management. The propensities to spread to various locations vary between the subtypes of sarcoma. Therefore, imaging should be individualized based on the subtype of sarcoma. Laboratory tests have a limited role.

Imaging studies should include cross-sectional imaging to provide details about tumor size and contiguity to nearby visceral structures and neurovascular landmarks. The panel recommends MRI with contrast, with or without CT with contrast. Other imaging studies such as CT angiogram and plain radiograph may be warranted in selected circumstances. Given the risk for hematogenous spread from a high-grade sarcoma to the lungs, imaging of the chest (CT without contrast [preferred] or radiograph) is essential for accurate staging. Abdominal/pelvic CT should be considered for angiosarcoma, LMS, myxoid/round cell LPS, or epithelioid sarcoma as well as STS without definitive pathology prior to final resection. MRI of the total spine should be considered for myxoid/round cell LPS due to the higher risk of metastasis to the spine compared to other STSs.[10–12] Alveolar soft part sarcoma has a relatively increased propensity to metastasize to the brain, especially in patients with stage IV disease in the presence of pulmonary metastases.[13] Central nervous system MRI (or CT if MRI is contraindicated) should be considered for patients with alveolar soft part sarcoma and angiosarcoma.

PET scans may be useful in staging, prognostication, grading, and determining histopathologic response to chemotherapy.[14–19] The maximum standardized uptake value (SUVmax) of F18-deoxyglucose has been shown to correlate with tumor grade and prognostication.[20,21] In a retrospective study, tumor SUVmax determined by PET was an independent predictor of survival and disease progression.[14] Schuetze et al[15] reported that the pretreatment SUVmax and change in SUVmax after preoperative chemotherapy independently identified patients with a high risk of recurrence. The value of combined PET/CT in predicting disease-free survival (DFS) in patients receiving preoperative chemotherapy for STS is being evaluated in an ongoing large prospective study.

Based on the initial workup, the patients are assigned to one of the following categories[22]:

- Stage I
- Stage II–III
- Unresectable disease
- Stage IV (synchronous metastatic disease)
- Recurrent disease

General Principles

Surgery

Positive surgical margin is a strong predictor of local recurrence (LR) for patients with extremity STS.[23–28] Microscopically positive margins are associated with a higher rate of LR and a lower rate of DFS in patients with extremity sarcomas.[23,24,26] In a large cohort study (1,668 patients) that exam-

ined the clinical significance of the main predictors of LR in patients with STS of the extremity and trunk, the 10-year cumulative possibility of LR was significantly higher for patients with positive surgical margins (23.9 vs 9.2 for those with negative margins; $P<.001$).[27] In a recent retrospective study that evaluated 278 patients with STS of the extremities treated between 2000 and 2006, patients with a positive margin were 3.76 times more likely to develop LR than those with negative margins (38% risk of LR after 6 years if the margins were positive vs 12% if the margins were negative).[28] Careful preoperative planning by an experienced sarcoma surgical team may enable anticipated planned positive margins in order to save critical structures without affording a worse oncologic outcome.[29]

Amputation was once considered the standard treatment to achieve local control in patients with extremity sarcomas.[30] Technical advances in reconstructive surgical procedures, implementation of multimodality therapy, and improved selection of patients for adjuvant therapy have minimized the functional deficits in patients who might otherwise require amputation. In 1982, a randomized control study of 43 patients showed that limb-sparing surgery with RT was an effective treatment in patients with high-grade STS of the extremities, with a LR rate of 15% and no difference in overall survival (OS) and DFS compared with amputation.[31] In another series of 77 patients treated with limb-sparing surgery without RT, the LR rate was only 7% and resection margin status was a significant predictor of LR.[32] The LR rate was 13% when the resection margin was ≤1 cm compared with 0% when the resection margin was ≥1 cm. In a retrospective study of 115 patients with an STS of hand or foot, radical amputation as an initial treatment did not decrease the probability of regional metastasis and also did not improve the disease-specific survival.[33]

Collectively, the data suggest that limb-sparing surgery with or without postoperative RT is an effective treatment option for extremity STS, and amputation should be reserved only for cases in which resection or reresection with adequate margins cannot be performed without sacrificing the functional outcome. The guidelines recommend that the goal of surgery for patients with STS of extremities should be functional limb preservation, if possible, within the realm of an appropriate oncologic resection. Limb-sparing surgery is recommended for most patients with STS of extremities to achieve local tumor control with minimal morbidity. Amputation may improve local control in patients who might not be candidates for limb-sparing surgery and should be considered with patient preference, or if the gross total resection of the tumor is expected to render the limb nonfunctional.[34–37] Before considering amputation, the patient should be evaluated by a surgeon with expertise in the treatment of STS. Evaluation for postoperative rehabilitation is recommended for all patients with extremity sarcoma. If indicated, rehabilitation should be continued until maximum function is achieved.

Radiation Therapy

Data from randomized studies[38–40] and retrospective analyses[41–45] support the use of preoperative or postoperative external-beam RT (EBRT) in appropriately selected patients. Brachytherapy (alone or in combination with EBRT)[42,46,47] and intensity-modulated RT (IMRT)[48,49] have also been evaluated as an adjunct to surgery.

Preoperative Versus Postoperative EBRT: Various studies have examined the benefits and risks for preoperative and postoperative RT in treating STS of the extremity, head and neck, or superficial trunk.

Recently, examination of data from 27,969 patients with extremity STS in the NCDB identified both preoperative and postoperative RT as factors associated with increased OS.[45] However, that data showed that preoperative RT was predictive of achieving R0 resection.[45] In a phase III randomized study conducted by the Canadian Sarcoma Group, local control and progression-free survival (PFS) rates were similar in patients receiving either preoperative or postoperative RT in patients with localized primary or recurrent disease.[40,50] However, preoperative RT was associated with a greater incidence of acute wound complications (35% vs 17% for postoperative RT), especially in lower-extremity tumors (43% vs 5% for upper extremity tumors). Late-treatment–related side effects were more common in patients receiving postoperative RT, which is believed to be related to the higher RT dose (66 vs 50 Gy for preoperative RT) and the larger treatment volume.[40,51]

The efficacy of postoperative EBRT following limb-sparing surgery was demonstrated in a prospec-

tive randomized study (91 patients with high-grade lesions and 51 patients with low-grade lesions).[39,52] Postoperative RT significantly reduced the 10-year LR rate among patients with high-grade lesions (no LRs in patients who underwent surgery plus RT vs 22% in those who underwent surgery alone; *P*=.0028). Among patients with low-grade lesions, the corresponding recurrence rates were 5% and 32%, respectively.[39] The probability of reduction in the LR rate in patients receiving EBRT was not significant in patients with low-grade lesions, suggesting postoperative RT after limb-sparing surgery may not be necessary for this group of patients. Outcomes at 20-year follow-up favored patients who received EBRT, but differences were not statistically significant. Ten-year OS was 82% and 77% for patients who received surgery alone versus surgery plus EBRT, and 20-year OS was 71% and 64% for these groups, respectively (*P*=.22).[52]

The French Sarcoma Group recently reported on a cohort of 283 patients with resectable atypical lipomatous tumor (ALT)/well-differentiated liposarcoma (WDLS) of the extremity or superficial trunk from the Conticabase database. In these patients, postoperative RT significantly improved 5-year local relapse-free survival (98.3% vs 80.3%, with and without adjuvant RT, respectively; *P*<.001).[53] Along with RT, tumor site and resection margin status were predictors of time to LR, but no difference in OS was seen.

In a report from the Memorial Sloan Kettering Cancer Center that reviewed the long-term outcomes of 200 patients treated with limb-sparing surgery, pathologically negative re-resection without RT was associated with a 5-year overall LR rate of 9%, at a median follow-up of 82 months.[54] Old age and/or stage III disease were associated with a higher rate of LR. Therefore, treatment decisions regarding the use of postoperative RT should be individualized and should not be solely based on the findings of margin-negative re-resection.

Brachytherapy: In a prospective randomized study, 164 patients with completely resected STS of the extremity or superficial trunk were randomized intraoperatively to receive either brachytherapy or no brachytherapy.[46] With a median follow-up time of 76 months, the 5-year local control rates were 82% and 69% in the brachytherapy and no brachytherapy groups, respectively. Patients with high-grade lesions who received brachytherapy had higher local control rates compared with those who received no brachytherapy (89% and 66%, respectively). However, brachytherapy had no impact on local control in patients with low-grade lesions. The 5-year freedom-from-distant-recurrence rates were 83% and 76%, respectively, in the 2 groups. In a retrospective analysis of 202 adult patients with primary high-grade STS of the extremity, brachytherapy after limb-sparing surgery resulted in lower rates of wound complications, favorable 5-year local control, and distant relapse-free survival and OS rates (84%, 63%, and 70%, respectively).[47]

IMRT: In a retrospective analysis of 41 patients with STS of extremity treated with limb-sparing surgery, postoperative IMRT resulted in a 5-year local control rate of 94% in patients with negative as well as positive or close margins, in selected patients with high-risk features.[48] The risk of complications such as edema and joint stiffness were also favorable when compared with conventional RT. In a more recent phase II study, O'Sullivan et al[55] reported that preoperative IMRT resulted in lower wound complication rates in patients with high-grade lesions (30.5% vs 43% reported in an earlier study using conventional EBRT). In a nonrandomized comparison of IMRT and brachytherapy in patients with high-grade, primary, nonmetastatic STS of extremity, local control was significantly better with IMRT than with brachytherapy (5-year local control rates were 92% and 81%, respectively; *P*=.04) despite higher rates of adverse features for IMRT.[49]

Intraoperative RT (IORT): Recent reports from a retrospective study suggest that IORT provides excellent local control for STS of the extremity.[56,57] Call et al[57] recently reported long-term outcomes for patients with STS of upper extremity treated with EBRT, surgery, and IORT. The 10-year local control and OS rates were 88% and 58%, respectively.[57] The 10-year local control rates were 89% and 86%, respectively, after margin-negative (R0) and margin-positive (R1 and R2) resections. IORT was also retrospectively examined in cohorts of patients with STS of the superficial trunk or extremity who received surgery, IORT, and EBRT at 3 Spanish institutions.[58,59] Five-year IORT in-field control was 86% and 70% for extremity and trunk wall STS, respectively. However, 5-year DFS was 62% in the ex-

tremity STS cohort and 45% in the trunk wall STS. Incomplete resection significantly impacted in-field control in both cohorts, and higher IORT dose was positively associated with in-field disease control in extremity STS.

Although the use of IMRT and IORT has resulted in excellent clinical outcomes, their efficacy needs to be confirmed in larger cohorts of patients with longer follow-up. Additionally, image guidance may continue to improve RT outcomes for patients with STS of the extremity. In a recent phase II trial (RTOG-0630; n=86), the use of preoperative image-guided RT to a reduced target volume resulted in significantly reduced late toxicity without any marginal field recurrences.[60] Additional studies will be required.

Panel Recommendations

When EBRT is used, sophisticated treatment planning with IMRT, tomotherapy, and/or proton therapy can be used to improve therapeutic effect. RT is not a substitute for definitive surgical resection with negative margins, and re-resection to negative margins is preferable.

The usual dose of preoperative RT is 50 Gy in 1.8 to 2.0 Gy per fraction. If the patient has not previously received RT, one could attempt to control microscopic residual disease with postoperative RT if re-resection is not feasible. If wide margins are obtained, postoperative RT may not be necessary. For patients treated with preoperative RT followed by surgery, the guidelines recommend consideration of observation in addition to postoperative RT boost for patients with positive margins. There are data to suggest that boost for positive margins does not improve local control.[61,62] Given no clear evidence to suggest added benefit, the panel recommends that the decision to provide boost be individualized with careful consideration of potential toxicities.

The recommended EBRT boost doses are 16 to 18 Gy for microscopic residual disease and 20 to 26 Gy for macroscopic residual disease. Brachytherapy boosts should be delivered several days after surgery, through catheters placed at surgery, with doses of 16 to 26 Gy for low dose-rate (LDR) brachytherapy and 14 to 24 Gy for high-dose rate (HDR) brachytherapy, based on the margin status. Alternatively, IORT (10–12.5 Gy for microscopic residual disease and 15 Gy for gross residual disease) can be delivered immediately after resection to the area at risk, avoiding the uninvolved organs.[56]

For patients who have not received preoperative RT, the postoperative choices include EBRT (50 Gy irrespective of surgical margins in 1.8–2.0 Gy per fraction), Intraoperative RT (IORT)w (10–16 Gy followed by 50 Gy EBRT), or brachytherapy. The guidelines recommend 45 Gy LDR brachytherapy or HDR equivalent for patients with negative margins. LDR brachytherapy (16–20 Gy) or HDR equivalent is recommended for patients with positive margins followed by EBRT. EBRT after IORT or brachytherapy is delivered to the target volume to a total dose of 50 Gy, after surgical healing is complete (3–8 weeks).

For patients treated with postoperative EBRT, the guidelines recommend an additional EBRT boost (unless prior IORT) to the original tumor bed based on the margin status (10–16 Gy for negative surgical margin; 16–18 Gy for microscopic residual disease; and 20–26 Gy for grossly positive margins). However, many institutions are no longer giving a boost after preoperative RT to patients who have widely negative margins, based on local control rates approaching 95% with preoperative RT at 50 Gy and negative margins. The panel also emphasizes that RT is not a substitute for suboptimal surgical resection and re-resection is preferred for patients with positive surgical margins.

Treatment Guidelines by Stage

Stage I: Surgical wide resection (with intent to obtain negative margins) is the primary treatment for stage IA (T1, N0, M0, G1) and IB (T2-4, N0, M0, G1) tumors and is considered definitive if margins are greater than 1 cm or the fascial plane is intact.[63,64] If the surgical margins are 1.0 cm or less and without an intact fascial plane, re-resection may be necessary.[54] Treatment options including revision surgery versus observation should be presented at an experienced multidisciplinary sarcoma tumor board to determine advantages and disadvantages of the decision.

Data from prospective studies support the use of RT as an adjunct to surgery in appropriately selected patients based on an improvement in DFS although not OS.[24,26,46] Postoperative RT is recommended for patients with final surgical margins of 1.0 cm or less and without an intact fascial plane (category 2B for stage IA tumors and category 1 for stage IB). RT may

not be necessary in patients with small low-grade lesions (5 cm or less), because these tumors are less frequently associated with LR.[39] Therefore, observation is included as an option for patients with stage IA disease with final surgical margins of 1.0 cm or less and with an intact fascial plane.

En bloc resection with negative margins is generally sufficient to obtain long-term local control in patients with ALT/WDLS; RT is not indicated in most cases.[65,66] In a report that reviewed information for 91 patients with ALT/WDLS of the extremity and trunk, positive surgical margins were associated with reduced local RFS, suggesting that function-preserving re-resection when possible or adjuvant RT could be considered for selected patients with positive surgical margins.[67] RT may also be an appropriate treatment option for selected patients with recurrent disease or deeply infiltrative primary lesions with a risk of LR, depending on tumor location and patient age.[68]

Stage II-III: Treatment options should be decided by a multidisciplinary team with extensive experience in the treatment of patients with STS, based on the patient's age, performance status, comorbidities, location, and histologic subtype of the tumor.

Preoperative chemotherapy has been shown to improve OS, DFS, and local control rates in patients with high-grade STS of extremity and trunk, although acute reactions must be considered.[69,70] An earlier randomized study showed that preoperative chemotherapy was not associated with a major survival benefit for patients with high-grade tumors.[71] Histotype-specific neoadjuvant chemotherapy was examined in a recent international randomized controlled trial of patients with high-risk STS (n=287; ISG-STS, 1001).[72] Standard neoadjuvant chemotherapy (epirubicin/ifosfamide) was compared with histotype-specific regimens for myxoid LPS (trabectedin), LMS (gemcitabine/dacarbazine), synovial sarcoma (high-dose ifosfamide), MPNST (etoposide/ifosfamide), and UPS (gemcitabine/docetaxel). At 46 months, DFS was 62% for standard chemotherapy versus 38% for the histotype-tailored regimens (hazard ratio, 2.00; 95% CI, 1.22–3.26; *P*=.006). Trial enrollment was closed due to futility.

Available evidence, although underpowered, suggests that anthracycline-based postoperative chemotherapy (now most commonly given as doxorubicin and ifosfamide or epirubicin and ifosfamide) would improve DFS in selected patients with good performance status who are at high risk of recurrence.[73–77] Preoperative or postoperative EBRT has been shown to improve local control in patients with high-grade lesions.[39,42,78]

Large stage II or III high-grade extremity resectable tumors (greater than 8–10 cm) that are at high risk for LR and metastases should be considered for preoperative and postoperative therapy. However, data are available supporting surgery alone as an adequate treatment option in selected patients with high-grade lesions. Long-term results of a prospective study showed that selected patients with high-grade T1 lesions can be treated using surgery alone (R0 resection) with acceptable local control and excellent long-term survival.[79] In the surgery alone arm, the cumulative incidence rates of LR at 5 and 10 years were 7.9% and 10.6%, respectively, in patients who underwent R0 resection, and the 5- and 10-year sarcoma-specific death rates were 3.2%. In an analysis of 242 patients with localized STS of the trunk and extremity treated with limb-sparing surgery, the 10-year local control rate was 87% to 93% for patients with resection margins of <1 cm compared with 100% for those with resection margins of ≥1 cm (*P*=.04).[32] Al-Refaie et al[80] also reported that the addition of RT did not result in any significant difference in OS or sarcoma-specific survival in patients with early-stage STS of the extremity.

Surgery preceded or followed by RT is recommended for patients with stage II tumors (T1, N0, M0, G2-3) that are resectable with acceptable functional outcomes (category 1 for preoperative or postoperative RT).[39,40,50] Surgery alone may be an option for patients with small tumors that can be resected with wider surgical margins.

Surgery followed by RT (category 1) with or without postoperative chemotherapy is the primary treatment for patients with stage IIIA (T2, N0, M0, G2-3) or IIIB (T3-4, N0, M0, G2-3) tumors that are resectable with acceptable functional outcomes. The impact of RT was analyzed in a SEER cohort of 2,606 patients with stage III soft-tissue extremity sarcoma. Similarly to smaller prospective studies and reviews, RT was associated with a significant 5-year survival benefit (65% vs 60%, *P*=.002). However, the timing of RT (ie, preoperative vs postoperative) was not a significant factor for survival.[81] Because only limited and conflicting data are available regarding the

potential benefits of postoperative chemotherapy for patients with stage II or III disease, postoperative chemotherapy is included as a category 2B recommendation.[73–77] Preoperative RT (category 1), preoperative chemotherapy (category 2B), or chemoradiation (category 2B) are also included as options for this group of patients.

Radical lymphadenectomy may provide long-term survival benefit for patients with isolated lymph node involvement. In a study that examined the natural history of lymph node metastasis in patients with STS, the median survival was 4.3 months for patients not treated with radical lymphadenectomy compared with 16.3 months for patients who underwent radical lymphadenectomy.[82] The 5-year survival rate for the latter group of patients was 46%. The guidelines recommend regional lymph node dissection at the time of primary surgery for patients with stage III tumors with lymph node involvement.

Patients with stage II or III tumors that are resectable with adverse functional outcomes should be managed as described in the subsequent section for unresectable disease.

Unresectable Disease: Patients with unresectable tumors can be treated primarily with RT, chemoradiation, chemotherapy, or regional limb therapy. Tumors that become resectable with acceptable functional outcomes after primary treatment can be treated with surgery followed by RT (if not previously irradiated) with or without postoperative chemotherapy. Because only limited and conflicting data exist regarding the potential benefits of postoperative chemotherapy, it is included as a category 2B recommendation. For patients whose tumors remain resectable with adverse functional outcomes or unresectable after primary treatment, a subsequent distinction is made between patients who are asymptomatic and those who are symptomatic. Observation is an option for patients who are asymptomatic. For patients who are symptomatic, the treatment options include chemotherapy, palliative surgery, amputation, or best supportive care.

A randomized phase III trial examining intensified doxorubicin plus ifosfamide versus doxorubicin alone did not find an OS benefit for combination therapy in patients with unresectable, advanced, or metastatic STS (14.3 vs 12.8 months; *P*=.076). However, response rates and PFS were improved for doxorubicin/ifosfamide compared with doxorubicin alone (26% vs 14%; *P*=.0006; 7.4 vs 4.6 months; *P*=.003).[83] However, subset analyses (n=310) indicated an OS benefit for doxorubicin/ifosfamide versus single-agent doxorubicin in patients with UPS.[84]

Definitive RT (70–80 Gy) can be considered for selected patients with unresectable tumors after primary treatment. In a single-institution study (112 patients, 43% extremity STS), tumor size and the dose of RT influenced local control and survival in patients with unresectable STS.[85] The local control rate was 51% for tumors <5 cm and 9% for tumors >10 cm. Patients who received 63 Gy or more had better 5-year local control, DFS, and OS rates (60%, 36%, and 52%, respectively) compared with patients who received <63 Gy (22%, 10%, and 14%, respectively). Local control for patients receiving >63 Gy was 72% for lesions ≤5 cm, 42% for lesions 5 to 10 cm, and 25% for lesions >10 cm.

Regional limb therapy (isolated limb perfusion [ILP] and isolated limb infusion [ILI]) has been evaluated as a limb-sparing treatment for unresectable intermediate or high-grade extremity STS. ILP requires the use of tumor necrosis factor-α (TNF-α) along with chemotherapy, which is not approved in the United States. ILI is a less invasive alternative to ILP for patients with unresectable STS of the extremities and can be used without TNF-α. Data from clinical trials suggest that ILP with melphalan or doxorubicin in combination with TNF-α[86–89] or ILI with doxorubicin or melphalan and dactinomycin[90–94] may be effective in the treatment of patients with unresectable STS of extremity.[95] Further prospective clinical trials are needed to better define the role for ILP or ILI in the management of patients with unresectable STS of the extremity.[95] The panel recommends that ILP for isolated regional or nodal disease be accompanied by surgical resection. ILP for recurrent disease should only be performed at institutions with experience in regional limb therapy.

Stage IV (Synchronous Metastatic Disease): Patients with metastatic stage IV disease (any T, N1, M0, any G; or any T, any N, M1, any G) have a poor prognosis with no disease-free interval.[96,97] Conflicting data exist on the potential survival benefit of metastasectomy. In a retrospective study of 48 patients with synchronous metastases, no improvement was seen in OS for patients treated with metastasectomy compared with those with unresectable disease.[96] In a more recent retrospective study involving 112 pa-

tients with metastatic disease at presentation, resection of metastatic disease, less than 4 pulmonary metastases, and the presence of lymph node metastases versus pulmonary metastases were identified as statistically significant variables for improved OS. The 5-year survival rate was 59% and 8%, respectively, for patients presenting with lymph node metastases and pulmonary metastases.[97] Pulmonary metastasectomy resulted in a median OS of 25.5 months in a retrospective analysis of 66 patients with sarcoma; however, recurrent metastasis was associated with poor prognosis.[98] Although recurrence is common after initial metastasectomy, data from a prospective review (n=539) suggested a potential survival benefit for repeat pulmonary metastasectomy in appropriately selected patients.[99]

Because no data are available to support the optimal management of patients presenting with metastatic disease, the guidelines are intentionally nonspecific about the treatment options for this group. Referral to a medical oncologist with extensive experience in the treatment of STS is recommended. Treatment options should be based on many factors, including performance status, patient preferences, specific clinical problems from the metastases, and treatment availability. In addition, clinical trial is the preferred treatment option for patients with metastatic disease.

Limited Metastases: Patients with limited metastasis confined to a single organ and limited tumor bulk who are amenable to local therapy should receive primary tumor management as described for stage II or III tumors. Another option is to consider metastasectomy with or without chemotherapy with or without RT. The guidelines do not specify rules governing metastasectomy, which remains controversial.[96,98,99] Several variables, including tumor resectability, number and location of metastases, and performance status, influence the decision to use metastasectomy.[97] In addition, patients can also receive stereotactic body RT (SBRT) or chemotherapy as an alternate method for control of metastatic lesions. Several recent reviews and case series support the use of SBRT for local control, with potential survival benefits in selected patients.[100–102]

Disseminated Metastases: For patients presenting with disseminated disease, a subsequent distinction is made between asymptomatic and symptomatic patients. Observation with a "watchful waiting" strategy is a reasonable management option for asymptomatic patients, especially if patients have only a minimal burden of metastases (eg, subcentimeter pulmonary nodules). Symptomatic patients can be treated with palliative RT, surgery, or chemotherapy. Palliative RT involves expedient treatment with sufficient dose to halt tumor growth or cause tumor regression. The outcome of this approach depends on the rapidity of growth and the status of systemic disease. In addition, the guidelines have included ablation procedures (eg, radiofrequency ablation [RFA] or cryotherapy) or SBRT as options for symptomatic patients.

Surveillance: Surveillance is deemed important to detect recurrences that might still be potentially curable. However, very limited data are available in the literature on effective surveillance strategies.[103–106] Because patient risk never returns to zero, long-term follow-up is indicated, including consideration of MRI or CT scan.[107] There has never been a study to prove that the use of more sensitive CT scans in routine surveillance would improve clinical outcomes. According to a report from MD Anderson Cancer Center, routine use of chest CT adds little clinical benefit when risk of pulmonary metastases is low.[108] However, in certain subsets of patients in whom chest radiographs are difficult to interpret because of anatomic considerations (eg, scarring, emphysema), chest CT may be indicated. A retrospective review examined surveillance imaging in 94 patients with intermediate or high-grade localized extremity/trunk STS who underwent radical resection and RT.[106] Thirty patients (32%) experienced recurrence after a median follow-up of 60 months (5 local, 26 distant). Surveillance imaging led to the detection of LR in 2 of 5 cases and distant recurrence (lung) in 22 of 26 cases. The authors concluded that surveillance chest imaging may be most useful for the detection of asymptomatic distant recurrence (ie, in the lung), while primary site imaging may only be useful for patients at high risk of LR.

Ultrasound has been used for the detection of early LRs and for the detection of micronodules >0.5 cm in diameter.[109–111] In a retrospective analysis that evaluated the value of MRI and ultrasound for the detection of LR after surgery in 21 patients with STS of extremities, the sensitivity of ultrasound was

slightly higher than that of MRI (100% vs 83%) and the specificity was slightly lower than that of MRI (79% vs 93%).[109] However, the differences were not statistically significant, suggesting that both MRI and ultrasound were equally useful in the detection of LR after surgery. In a subsequent report, Arya et al[110] also reported that ultrasound is associated with high sensitivity and specificity (92% and 94%, respectively) in the detection of early LR in patients with STS. These results confirm that ultrasound can be useful for the detection of LR. However, as reported by Choi et al,[109] ultrasound may be more difficult to interpret than MRI during the early postoperative period. Therefore, MRI should be used if ultrasound results are inconclusive.

The guidelines outline a prudent follow-up schedule by disease stage that avoids excessive testing. Higher grade and larger tumors have a higher risk of dissemination; therefore, the surveillance recommendations for patients with these tumors are somewhat more intensive, particularly for the first 3 years after resection. After 10 years, the likelihood of developing a recurrence is small and follow-up should be individualized.

Patients with stage I tumors are routinely followed up with H&P every 3 to 6 months for 2 to 3 years and then annually. Chest imaging is recommended every 6 to 12 months by CT (preferred) or radiograph. Postoperative baseline and periodic imaging of the primary tumor site is recommended based on estimated risk of locoregional recurrence. MRI with and without contrast and/or CT with contrast is recommended; ultrasound can be considered for the detection of LR in patients with smaller, superficial lesions and should be performed by an ultrasonographer with experience in musculoskeletal disease.[109,110] However, in situations in which the area is easily followed up using physical examination, imaging may not be required.[112]

For stage II-III and synchronous stage IV disease, postoperative re-imaging using MRI with and without contrast (preferred) or CT with contrast should be used to assess the primary tumor site and rule out metastatic disease. Baseline and periodic imaging of the primary site are recommended based on risk of locoregional recurrence; ultrasound can be considered for small, superficial lesions. H&P and imaging of the chest and other known sites of metastatic disease should be performed every 2 to 6 months for 2 to 3 years, then every 6 months for the next 2 years, and then annually.

Recurrent Disease: The management of recurrent disease encompasses a heterogeneous group of patients and clinical scenarios. In retrospective studies, isolated LR at sites other than the head and neck and deep trunk, resectability of recurrent and metastatic disease, disease-free interval, and number of metastases were identified as important predictive factors for long-term survival.[113–115]

For a patient with LR, treatment decisions should be made using the same algorithm as for patients with a new primary lesion.[116] In patients with LR, some case series suggest that combined conservative surgery and re-irradiation provide superior local control compared with local re-excision alone.[117] However, others have reported that conservative surgery alone results in local control in a minority of patients with locally recurrent disease after previous excision and EBRT,[118] likely reflecting differences in patient selection for surgery and RT or surgery alone. Therefore, the guidelines recommend that if LR can be excised, a decision regarding the use of re-irradiation will need to be made on a case-by-case basis. Traditionally, the re-irradiation has been done with postoperative brachytherapy, but now brachytherapy may be used in combination with IMRT to reduce the risks of morbidity with re-irradiation.

For patients with metastatic recurrences, the guidelines distinguish between limited metastases confined to a single organ, disseminated metastases, and isolated regional disease with nodal involvement. The treatment options for patients with limited metastases confined to a single organ or disseminated metastases are similar to that described for stage IV disease at presentation. In patients with isolated regional disease or nodal involvement, options include (1) regional node dissection with or without RT or chemotherapy; (2) metastasectomy with or without pre- or postoperative chemotherapy and/or RT; (3) SBRT; or (4) ILP/ILI with surgery. Limited data are available on the use of chemotherapy in patients undergoing metastasectomy. Results from a recent retrospective analysis suggest that chemotherapy has minimal impact on the survival of patients with metastatic extremity STS undergoing pulmonary metastasectomy.[119]

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Individual Disclosures for Soft Tissue Sarcoma Panel

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Robert S. Benjamin, MD[b]	Eli Lilly and Company, and Johnson & Johnson	Eli Lilly and Company, and Karyopharm Therapeutics, Inc.	None	3/15/17
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Ricardo J. Gonzalez, MD	None	None	None	1/10/17
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Henry Koon, MD	Bristol-Myers Squibb Company, and Merck & Co., Inc.	None	Bristol-Myers Squibb Company	4/14/17
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The NCCN Guidelines Staff have no conflicts to disclose.

[a]The following individuals have disclosed that they have an Employment/Governing Board, Patent, Equity, or Royalty:
I. Benjamin Paz MD: LS Biopath, Inc.
John Pfeifer, MD, PhD: PierianDX, an NGS software vendor that currently has no cash value
R. Lor Randall MD, FACS: Association of Bone and Joint Surgeons

[b]The following individuals have disclosed that they have a spouse/domestic partner/dependent potential conflict:
Robert Benjamin, MD: Gilead Sciences, Inc.; Johnson & Johnson; Merck & Co., Inc.; and Pfizer Inc.
Richard Riedel, MD: Limbguard, LLC