National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Soft Tissue Sarcoma

Version 2.2022 — May 17, 2022

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Continue

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Þ Internal medicine
† Medical oncology
т Orthopedics/Orthopedic oncology
≠ Pathology
¥ Patient advocacy
€ Pediatric oncology
§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical oncology
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- Extremity/Body Wall, Head/Neck (EXTSARC-1)
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- Desmoid Tumors (Aggressive Fibromatosis) (DESM-1)
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Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma Subtypes (SARC-F)
Principles of Cancer Risk Assessment and Counseling (SARC-G)

Staging and WHO Classification (ST-1)

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

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

Bone Sarcomas - See the NCCN Guidelines for Bone Cancer
Gastrointestinal Stromal Tumors - See the NCCN Guidelines for Gastrointestinal Stromal Tumors
Uterine Sarcomas - See the NCCN Guidelines for Uterine Neoplasms
Dermatofibrosarcoma Protuberans without Fibrosarcomatous Transformation - See the NCCN Guidelines for Dermatofibrosarcoma Protuberans

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Updates in Version 2.2022 of the NCCN Guidelines for Soft Tissue Sarcoma from Version 1.2022 include:

RETSARC-2
- RT modified: *(consider for tumors at high risk for local recurrence)* ~~(if not previously given for the primary tumor)~~.
- Footnote "j", modified: Consider systemic therapy if high risk for metastatic disease *or if downstaging is needed to facilitate resection*. ~~and/or high risk for local recurrence~~. Systemic therapy is not recommended for low-grade tumors. (Also for RETSARC-3 and RETSARC-5).

SARC-E (3 of 4)

Neoadjuvant RT, modified:
- *Neoadjuvant RT for retroperitoneal/intra-abdominal sarcomas can be considered in selected patients at high risk for local recurrence.*
- *If neoadjuvant RT is deemed to be appropriate for a patient, the following* ~~General~~ dose guidelines *are recommended*....
  - The following reference is new: *Bonvalot S, Gronchi A, Le Péchoux C, et al. Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC-62092: STRASS): a multicentre, open-label, randomised, phase 3 trial Lancet Oncol 2020;21:1366-1377.*

MS-1
- Sections of the Discussion have been updated to reflect the changes in the algorithm.

Updates in Version 1.2022 of the NCCN Guidelines for Soft Tissue Sarcoma from Version 3.2021 include:

Global change: "preoperative" changed to "*neoadjuvant" and* "postoperative" *to "adjuvant"*

EXTSARC-1
- Workup, Essential
  - Bullet 5, "Chest imaging" deleted; modified as follows: *Imaging of potential sites of metastatic disease*
  - Bullet 7, sub-bullet 3 modified as follows: For hereditary non-polyposis colorectal cancer (HNPCC or Lynch syndrome), See ~~NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic~~ NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (Also for RETSARC-1)
- Special considerations for unique histologies, new text added under "Rhabdomyosarcoma (RMS)": Dermatofibrosarcoma protuberans (DFSP) without fibrosarcomatous transformation.
- Footnotes
  - "b" modified MRI with and without contrast ± "and/or" CT with contrast.
  - "c" deleted: In selected institutions with clinical and pathologic expertise, a fine-needle aspiration biopsy (FNAB) may be acceptable.
  - "h" modified to include: *for other soft tissue sarcomas of the extremity/ body wall, head/neck (*EXTSARC-1 *and* EXTSARC-5*).* See SARC-F, 2 of 11.

EXTSARC-2
- Footnotes
  - Combined footnotes "m" and "n": *Neoadjuvant RT is preferred in these* ~~the rare~~ *selected circumstances (eg, wide resection to obtain negative margins would be technically challenging or result in significant morbidity or prior to re-resection following R2 resection).*
  - ~~m In the setting where wide surgical margins may be difficult or morbid, neoadjuvant radiation may be an option.~~
  - ~~n It may be appropriate to consider RT prior to re-resection for R2 resections.~~
  - "m" modified: Treatment options including *re-resection* ~~revision surgery~~

EXTSARC-3
- Follow-Up
  - Bullet 4 modified: Obtain *end-of-treatment* ~~adjuvant baseline~~
- Footnotes
  - Footnote "r" is new: *For management of a primary sarcoma with synchronous regional nodal metastatic disease, see above for treatment of the primary tumor and refer to* EXTSARC-6 *for management of nodal disease.* (Also for EXTSARC-4)
  - The text for footnote "s" was moved to SARC-E and the link remains directing the reader to the Principles of Radiation Therapy.

EXTSARC-5
- Primary Treatment
  - Bullet 3 modified: For lung metastases, resection ~~(preferred)~~ or stereotactic body radiation therapy (SBRT) combined text from bullet 4.
  - *Metastases* added to "embolization procedures (non-lung)" for upper and lower pathways. (Also for EXTSARC-6)
- Footnotes
  - "ee" modified to include: Baumann BC, et al. J Surg Oncol 2020;122:877-883. (Also for EXTSARC-6)
  - "gg" deleted: 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 systemic therapy must be considered. Recommended only for palliative therapy in patients with synchronous stage IV or recurrent disease with disseminated metastases. (Also for EXTSARC-6)

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Updates in Version 1.2022 of the NCCN Guidelines for Soft Tissue Sarcoma from Version 3.2021 include:

EXTSARC-6
- Isolated regional disease or nodes
  - Deleted the following under options:
    - ◊ Metastasectomy ± neoadjuvant or adjuvant systemic therapy ± RT
    - ◊ SBRT

Isolated limb perfusion/infusion ± surgery
- Footnotes
  - "aa" deleted: Should only be done at institutions with experience in isolated limb perfusion/infusion.

RETSARC-1
- Workup
  - Bullet 4 modified: Image-guided core needle biopsy should be performed if neoadjuvant therapy is being *considered* ~~given~~ or for suspicion of malignancy other than sarcoma.
  - Bullet 5 modified: Preresection biopsy is not necessarily required. ~~for well-differentiated liposarcoma.~~

RETSARC-2
- Primary Treatment
  - Sarcoma, Neoadjuvant therapy: *(in selected cases)* added. (Also for RETSARC-5)
- Primary Treatment First sub-bullet: *(if not previously given for the primary tumor)* added to RT (Also for RETSARC-5)
- Footnotes
  - "j" modified: Consider ~~post preoperative~~ systemic therapy ~~for histologies with~~ *if* high risk for metastatic disease and/or high risk for local recurrence. Systemic therapy is not recommended for low-grade tumors. (Also for RETSARC-3, RETSARC-5)

RETSARC-3
- Surgical Outcomes
  - RO: Consider adjuvant systemic therapy ~~for histologies with~~ *if* high risk for metastatic disease
  - Recommendations for R1 and R2 were separated into different branches.
  - R1: Adjuvant RT should not be administered routinely with the exception of highly selected patients and unless local recurrence would cause undue morbidity (Also for R2)
  - R2: ~~In highly selected cases, consider boost (10-16 Gy) if neoadjuvant RT was given~~.

RETSARC-4
- Bullet 1 modified: Observation, if asymptomatic *and indolent tumor biology*

RETSARC-5
- Added "Consider" before neoadjuvant therapy.
- Footnotes
  - "t" modified: Consider adjuvant systemic therapy ~~for histologies with~~ if high risk for metastatic disease or history of several recurrences with a high risk for additional local recurrences.
  - "u" deleted: If no prior RT for the treatment of the primary sarcoma.

DESM-1
- Workup
  - Bullet 3 modified: Consider evaluation for Gardner~~'s~~ syndrome/familial adenomatous polyposis (FAP) ~~if biopsy is diagnostic of desmoid~~
  - Bullet 4 modified: Appropriate imaging of primary site *with CT or MRI* as clinically indicated
- Footnotes
  - "b" deleted: See Principles of Imaging (SARC-A) (Also for DESM-2, DESM-3).
- Footnote "d," second sentence modified to include "initial" imaging every... (Also for DESM-3) .

DESM-2
- Column 2: Observation with imaging *with CT or MRI as indicated* and symptom management (Also for DESM-3)
- Column 4:
  - Stable/regression: Continue observation with imaging *with CT or MRI as indicated* (Also for DESM-3)
  - Progression: Consider ongoing observation with imaging *with CT or MRI as indicated*

DESM-4
- Title changed: *Treatment Based on Anatomic Location.* ~~Active Therapy for Progressive, Morbid, or Symptomatic Disease~~
- Significantly modified the page.

SARC-A
- Principles of Imaging
  - New table incorporates text from previous pages.

Continued

Updates in Version 1.2022 of the NCCN Guidelines for Soft Tissue Sarcoma from Version 3.2021 include:

SARC-C (1 of 3)

- **New statement added to page: Next-generation sequencing (NGS), including DNA and RNA sequencing, may be beneficial in selected patients. The timing of when to perform NGS and for which patients must be evaluated individually. NGS findings can help patients qualify for clinical trials and can identify actionable mutations that may not have been targeted by prior therapies. Thus, NGS may be appropriate for patients who may qualify for and who are interested in enrolling in a clinical trial or for patients with disease that is refractory who have failed or progressed on standard therapies or in certain histologies where NGS provides clinically actionable information. NGS should not replace expert pathology review, as NGS only rarely results in a diagnosis change following expert review. Technically successful NGS on bone biopsies requires use of decalcification agents, such as EDTA, that do not interfere with genomic testing.**

SARC-C (3 of 3)

- **The following genes are new for inflammatory myofibroblastic tumor: *ETV6-NTRK3 and TFG-ROS1***
- **The following references are new:**
  - ***Taylor MS, Chougule A, MacLeay AR, et al. Morphologic overlap between inflammatory myofibroblastic tumor and IgG4-related disease: Lessons from next-generation sequencing. Am J Surg Pathol 2019;43:314-324.***
  - ***Lopez-Nunez O, John I, Panasiti RN, et al. Infantile inflammatory myofibroblastic tumors: clinicopathological and molecular characterization of 12 cases. Mod Pathol 2020;33:576-590.***
  - ***Lovly CM, Gupta A, Lipson D, et al. Inflammatory myofibroblastic tumors harbor multiple potentially actionable kinase fusions. Cancer Discov 2014;4:889-895.***

SARC-D

- **Principles of Surgery**
  - **Biopsy**
    - **First bullet modified: A ~~*preoperative*~~ *neoadjuvant pathologic diagnosis, including histologic subtype and grade, is almost always necessary for the optimal treatment of a soft tissue sarcoma (surgical resection margin planning, a discussion of neoadjuvant chemotherapy, and/or radiation)***
    - **Second bullet modified: *Percutaneous core needle biopsy is preferred as it is associated with a low risk for biopsy-related complications. The biopsy tract should avoid potential tumor contamination of uninvolved anatomic compartments and, ideally, be in line with any future surgical resection incision. In certain situations, especially deep-seated tumors, image-guided needle biopsy can improve diagnostic accuracy (avoid necrotic nondiagnostic areas or surrounding normal tissues, and thoroughly sample heterogenous tumors). Open incisional biopsy can be considered if percutaneous core needle biopsies fail to lead to ~~make~~ an adequate diagnosis.~~ 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. Image-guided needle biopsy may be indicated for extremity/truncal sarcomas~~.**
  - **Surgery**
    - **Bullet 1 modified: The surgical procedure necessary to resect the tumor with oncologically appropriate margins should be used. *Ideally, this would be pathologically negative resection margins. However, planned close margins or even microscopically positive margins may be ~~necessary~~ appropriate* to preserve critical ~~*neurovascular*~~ structures (*eg, major vessels, nerves*, bones, joints), *especially in the setting of multimodality therapy*.**
    - **Bullet 2 modified: *Evaluate ~~neoadjuvantly~~ for rehabilitation prior to surgery* (see SARC-D 2 of 2).**

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Updates in Version 1.2022 of the NCCN Guidelines for Soft Tissue Sarcoma from Version 3.2021 include:

SARC-E (1 through 4)

- Principles of Radiation Therapy for Soft Tissue Sarcoma
  - This section of the guidelines has been significantly modified.

SARC-F (1 of 11)

- Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma
  - Footnotes corresponding to the title:
    - "c" modified: *Including but not limited to* alveolar soft part sarcoma (ASPS), ALT/WDLS, and clear cell sarcomas, which are generally not sensitive. ~~to cytotoxic systemic therapy~~
    - "d" is new: *Dexrazoxane may be added as a cardioprotectant for the prevention of cardiotoxicity in patients planning to receive high-dose anthracyclines (eg, doxorubicin >250 mg/m^2). Armenian SH, et al. J Clin Oncol 2017;35:893-911.*
  - Preferred, First-line Therapy Advanced/Metastatic
    - *NTRK* gene fusion-*positive* sarcomas *only* (moved from Useful in Certain Circumstances column)
      - Larotrectinib
      - Entrectinib
- Useful in Certain Circumstances
  - First-line Therapy Advanced/Metastatic
    - Pazopanib (patients ineligible for IV systemic therapy *or patients who are not candidates for anthracycline-based regimens*)
- Other Recommended Regimens
  - Neoadjuvant/Adjuvant Therapy
    - Bullet 1: AD *LMS only* (doxorubicin, dacarbazine) - if ifosfamide is not considered appropriate
- Other Recommended Regimens
  - Subsequent Lines of Therapy for Advanced/Metastatic Disease
    - Bullet 6: Gemcitabine-based regimens (*if not given previously*)
    - Sub-bullet 5: a new regimen, *Gemcitabine and pazopanib* is a category 2B recommendation
- Useful in Certain Circumstances
  - Subsequent Lines of Therapy for Advanced/Metastatic Disease
    - Pembrolizumab
      - Footnote "k": *For the treatment of patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.*

SARC-F (2 of 11)

- Desmoid Tumors (Aggressive Fibromatosis)
  - Deleted: Time to response "less" and "more" critical.
  - Footnote "l," *Optimal duration of TKI therapy has not been established. Discontinuation of TKI therapy can be considered (with careful monitoring) in patients with stable disease,* is new corresponding to the title.
- Non-Pleomorphic Rhabdomyosarcoma
  - Footnotes
    - "m": Removed from the header and placed next to all instances of VAC and VAI.
- Other Recommended Regimens
  - *Vinorelbine/cyclophosphamide/temsirolimus* added as a new regimen.

SARC-F (2 of 11) (continued)

    - New reference: Mascarenhas L, Chi YY, Hingorani P, et al. Randomized phase II trial of bevacizumab or temsirolimus in combination with chemotherapy for first relapse rhabdomyosarcoma: a report from the Children's Oncology Group. J Clin Oncol 2019;37:2866-2874.
- Useful in Certain Circumstances
  - *Maintenance chemotherapy (cyclophosphamide/vinorelbine) for patients with intermediate-risk RMS with CR following treatment with VAC or VAI regimen (please note: COG has an active prospective ongoing study, but considered a reasonable standard of care).*
    - New reference: *Bisogno G, DeSalvo GL, Bergeron C, et al.Vinorelbine and continuous low-dose cyclophosphamide as maintenance chemotherapy in patients with high-risk rhabdomyosarcoma (RMS 2005): a multicenter, open-label, randomised, phase 3 trial. Lancet Oncol 2019;20:1566-1575.*

SARC-F (3 of 11)

- Alveolar Soft Part Sarcoma (ASPS)
  - Preferred Regimens
    - *Pembrolizumab in combination with axitinib* added as a new regimen
    - New reference: *Wilky BA, Trucco MM, Subhawong TK, et al. Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a single-centre, single arm, phase 2 trial. Lancet Oncol 2019;20:837-848.*
- Angiosarcoma
  - Other Recommended Regimens
    - Moved sorafenib, sunitinib, and bevacizumab to Useful in certain circumstances

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Updates in Version 1.2022 of the NCCN Guidelines for Soft Tissue Sarcoma from Version 3.2021 include:

SARC-F (3 of 11) (continued)
- ◊ Deleted: ~~All other systemic therapy options recommended for Soft~~ Deleted: ~~All other systemic therapy options recommended for Soft Tissue Sarcoma Subtypes with Non-Specific Histologies~~

▸ Useful in Certain Circumstances
- ◊ *Regorafenib* added as a new regimen with the following reference: *Agulnik M, Schulte B, Robinson S, et al. An open-label single-arm phase II study of regorafenib for the treatment of angiosarcoma. Eur J Cancer 2021;154:201-208.*
- ◊ *Pembrolizumab* (for cutaneous angiosarcoma) added as a new regimen with the following reference: *Florou V, Rosenberg AE, Wieder E, et al. Angiosarcoma patients treated with immune checkpoint inhibitors: a case series of seven patients from a single institution. J Immunother Cancer 2019;7:285.*

SARC-F (4 of 11)
- Dermatofibrosarcoma Protuberans (DFSP) with Fibrosarcomatous Transformation

▸ Preferred Regimens
- ◊ *Imatinib* added as a new regimen with the following reference: *Rutkowski P, Klimczak A, Lugowski I, et al. Long-term results of treatment of advanced dermatofibrosarcoma protuberans (DFSP) with imatinib mesylate - The impact of fibrosarcomatous transformation. Eur J Surg Oncol 2017;43:1134-1141.*

SARC-F (4 of 11) (continued)
- Dermatofibrosarcoma Protuberans (DFSP) with Fibrosarcomatous Transformation

▸ Other Recommended Regimens
- ◊ ~~All other systemic therapy options recommended for Soft Tissue Sarcoma Subtypes with Non-Specific Histologies~~
  - – Anthracycline-based regimens:
    - ▪ *Doxorubicin*
    - ▪ *Epirubicin*
    - ▪ *Liposomal doxorubicin*
    - ▪ *AIM (doxorubicin, ifosfamide, mesna)*
    - ▪ *Ifosfamide, epirubicin, mesna*
    - ▪ *MAID (mesna, doxorubicin, ifosfamide, dacarbazine)*
  - – Gemcitabine-based regimens:
    - ▪ *Gemcitabine*
    - ▪ *Gemcitabine and docetaxel*
    - ▪ *Gemcitabine and vinorelbine*
    - ▪ *Gemcitabine and dacarbazine*
  - – *Pazopanib* (patients ineligible for IV systemic therapy *or patients who are not candidates for anthracycline-based regimens*)

SARC-F (5 of 11)
- Inflammatory Myofibroblastic Tumor (IMT) with Anaplastic Lymphoma Kinase (ALK) Translocation

▸ Preferred Regimens
- ◊ *Lorlatinib* added as a new regimen.

SARC-F (6 of 11)
- Solitary Fibrous Tumor

▸ Other Recommended Regimens
- ◊ ~~All other systemic therapy options recommended for Soft Tissue Sarcoma Subtypes with Non-Specific Histologies~~
- ◊ Anthracycline-based regimens:
  - – *Doxorubicin*
  - – *Epirubicin*
  - – *Liposomal doxorubicin*
  - – *AD (doxorubicin, dacarbazine)*
  - – *AIM (doxorubicin, ifosfamide, mesna)*
  - – *Ifosfamide, epirubicin, mesna*
  - – *MAID (mesna, doxorubicin,ifosfamide, dacarbazine)*
- ◊ Gemcitabine-based regimens:
  - – *Gemcitabine*
  - – *Gemcitabine and docetaxel*
  - – *Gemcitabine and vinorelbine*
  - – *Gemcitabine and dacarbazine*
- ◊ *Trabectedin*

- Tenosynovial Giant Cell Tumor/Pigmented Villonodular Synovitis

▸ Useful in Certain Circumstances
- ◊ *Nilotinib* added as a new regimen with the following reference: *Gelderblom H, Cropet C, Chevreau C, et. al. Nilotinib in locally advanced pigmented villonodular synovitis: a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol 2018;19:639-648.*

SARC-G
- Principles of Cancer Risk Assessment and Counseling

▸ This is a new page discussing when to consider genetic testing for inherited soft tissue sarcomas.

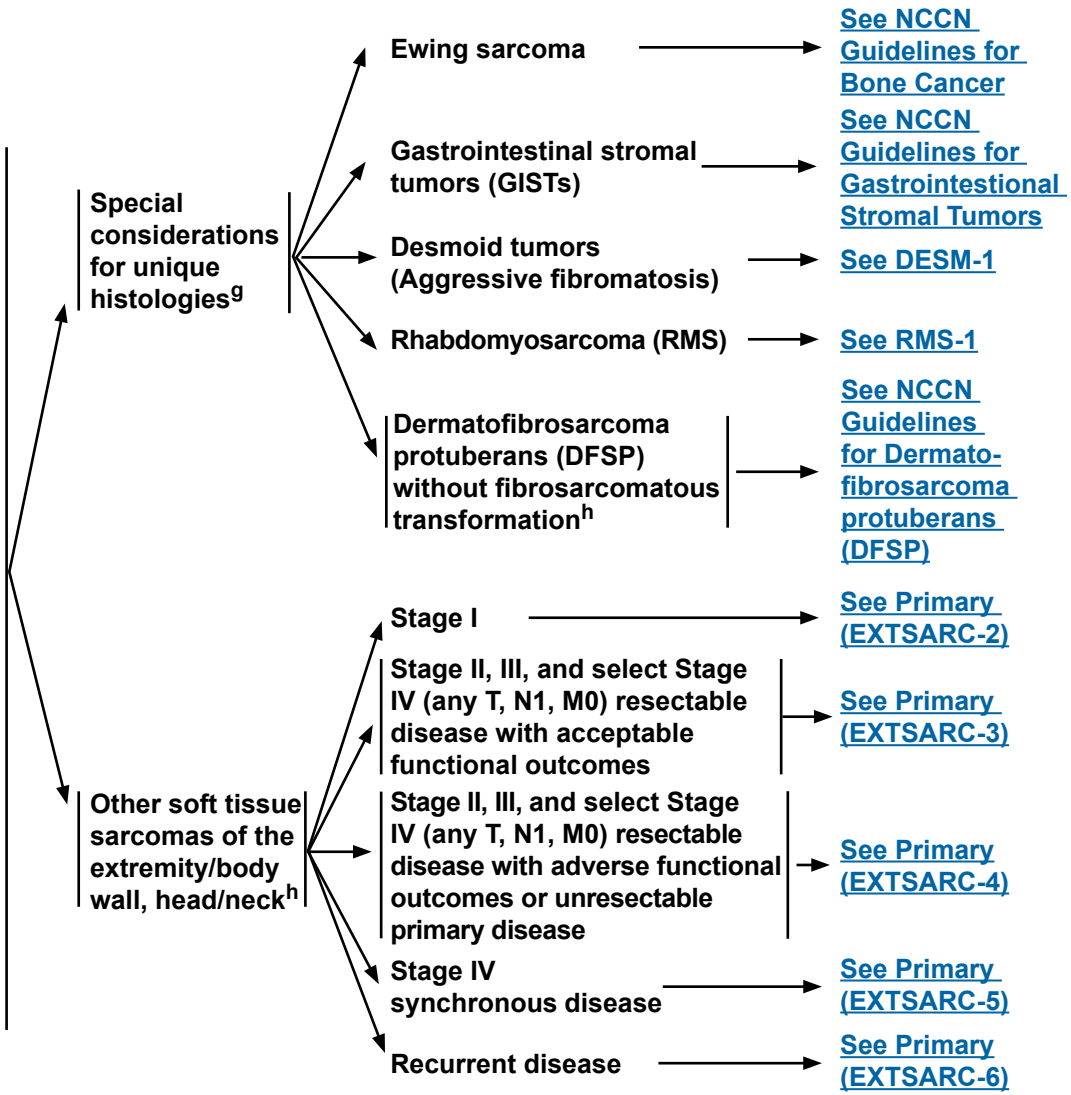
WORKUP

ESSENTIAL:

- Prior to the initiation of therapy, it is highly recommended that all patients be evaluated and managed by a multidisciplinary team with expertise and experience in sarcoma[a]
- H&P
- Adequate imaging of primary tumor[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)
  - Place biopsy along future resection axis with minimal dissection and careful attention to hemostasis
  - Biopsy should establish grade and histologic subtype[c]
  - As appropriate, use ancillary diagnostic methodologies[d]
- Imaging of potential sites of metastatic disease

USEFUL UNDER CERTAIN CIRCUMSTANCES[e]:

- Additional imaging as indicated; See Principles of Imaging (SARC-A)
- The following conditions are linked to increased incidence of sarcoma and other cancers:
  - For patients with neurofibromatosis,[f] See NCCN Guidelines for Central Nervous System Cancers (PSCT-3)
  - For Li-Fraumeni syndrome, See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic
  - For hereditary non-polyposis colorectal cancer (HNPCC or Lynch syndrome), See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
  - For patients with personal/family history suggestive of other cancer predisposition syndromes, consider further genetics assessment



See footnotes on EXTSARC-1A

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

FOOTNOTES

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

[b] Imaging studies should include cross-sectional imaging (MRI with and without contrast and/or 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. See Principles of Imaging (SARC-A).

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

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

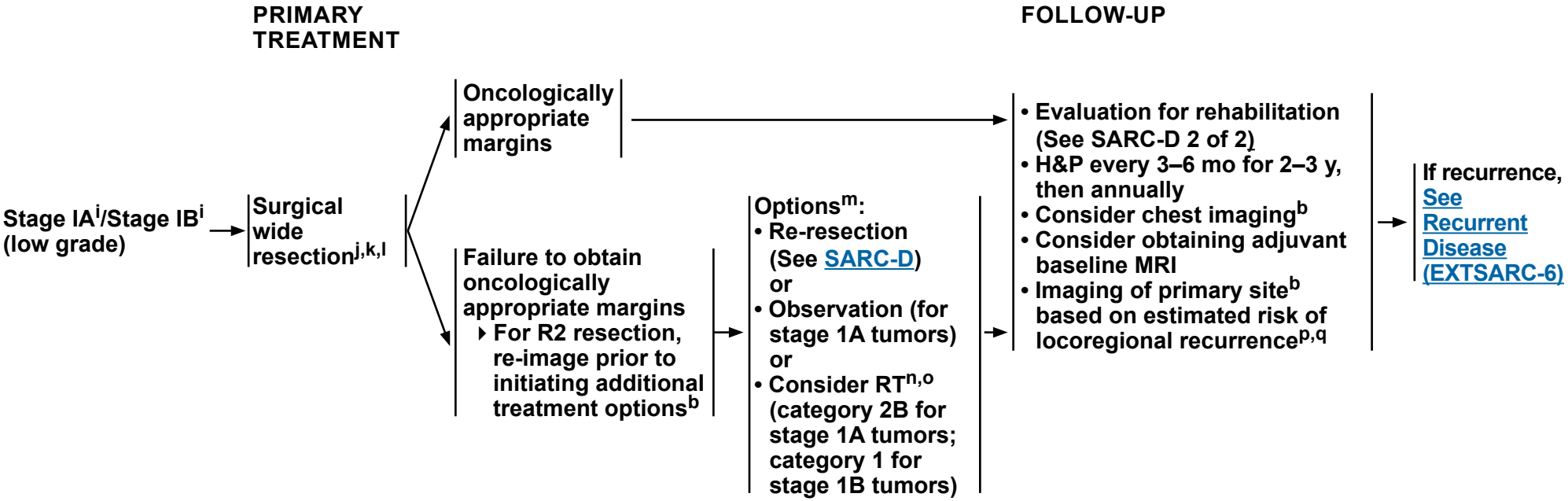
[e] Different subtypes have different propensities to spread to various locations.

[f] Patients with neurofibromatosis are at risk for multiple sarcomas at various locations and their assessment and follow-up should be different. (Reilly KM, et al. J Natl Cancer Inst 2017;109:djx124.

[g] Diagnoses that will impact the overall treatment plan. See SARC-F for special considerations for unique histologies.

[h] Patients with DFSP with fibrosarcomatous changes and/or malignant transformations should be treated according to the algorithms for other soft tissue sarcomas of the extremity/body wall, head/neck (EXTSARC-1 and EXTSARC-5). See SARC-F, 2 of 11.

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



[b] See Principles of Imaging (SARC-A).
[i] See American Joint Committee on Cancer (AJCC) Staging, 8th Edition (ST-5 and ST-6).
[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] Neoadjuvant RT is preferred in these selected circumstances (eg, wide resection to obtain negative margins would be technically challenging or result in significant morbidity or prior to re-resection following R2 resection).
[m] Treatment options including re-resection versus observation should be presented at an experienced multidisciplinary sarcoma tumor board to determine advantages and disadvantages of the decision.
[n] Randomized clinical trial data support the use of RT as an adjunct to surgery in appropriately selected patients based on an improvement in disease-free survival (although not overall survival). (Yang J, et al. J Clin Oncol 1998;16:197-203). See Principles of Radiation Therapy (SARC-E).
[o] 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.
[p] In situations where the area is easily followed by physical examination, imaging may not be required.
[q] After 10 years, the likelihood of developing a recurrence is small and follow-up should be individualized.

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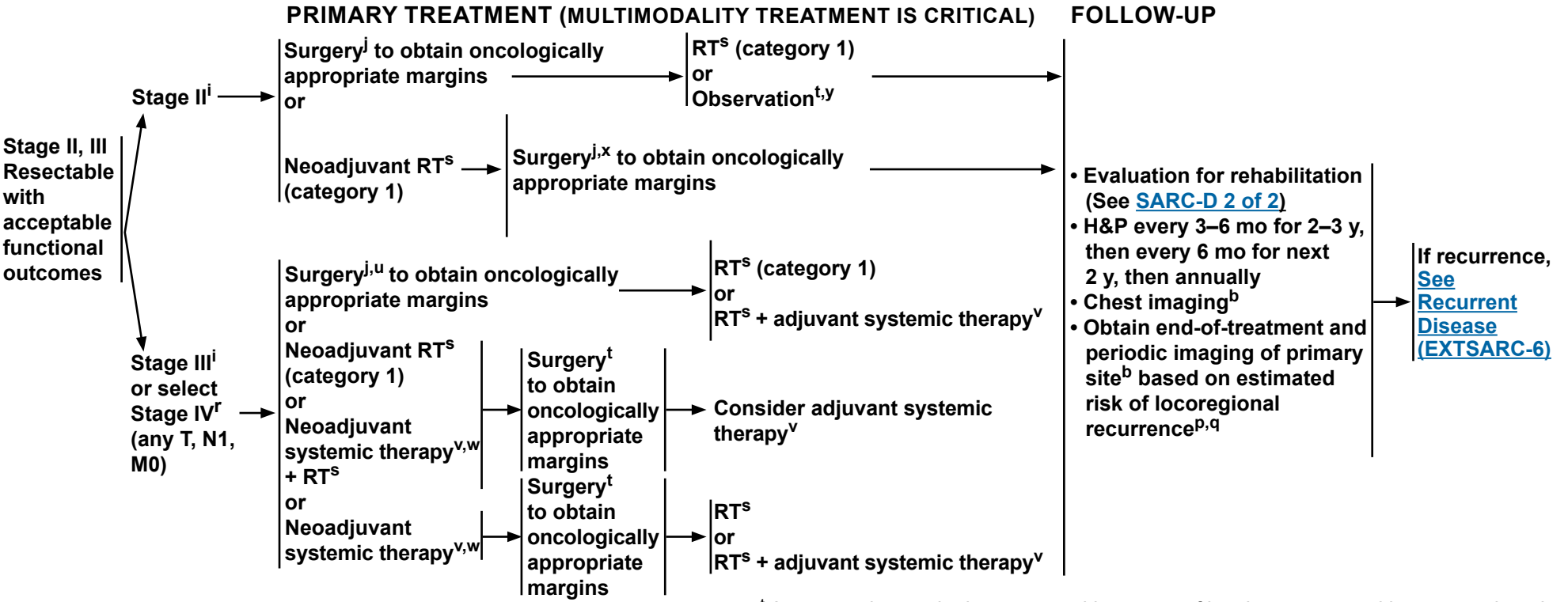

[b] See Principles of Imaging (SARC-A).
[i] See American Joint Committee on Cancer (AJCC) Staging, 8th Edition (ST-5 and ST-6).
[j] See Principles of Surgery (SARC-D).
[p] In situations where the area is easily followed by physical examination, imaging may not be required.
[q] After 10 years, the likelihood of developing a recurrence is small and follow-up should be individualized.
[r] For management of a primary sarcoma with synchronous regional nodal metastatic disease, see above for treatment of the primary tumor and refer to EXTSARC-6 for management of nodal disease.
[s] See Principles of Radiation Therapy (SARC-E) for discussion of adjuvant versus neoadjuvant therapy.
[t] A prospective study demonstrated low rates of local recurrence with surgery alone in carefully selected patients with high-grade tumors <5 cm (Pisters PW, et al. Ann Surg 2007;246:675-681). Consider omission of RT for tumors <5 cm resected with wide margins if a repeat resection would be feasible with low morbidity in the case of a recurrence.
[u] 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.
[v] See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma Subtypes (SARC-F).
[w] PET/CT may be useful in determining response to systemic therapy (Schuetze SM, et al. Cancer 2005;103:339-348).
[x] Re-image 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).
[y] Resections with wide negative margins may be considered for observation alone if the risk of radiation is unacceptable.

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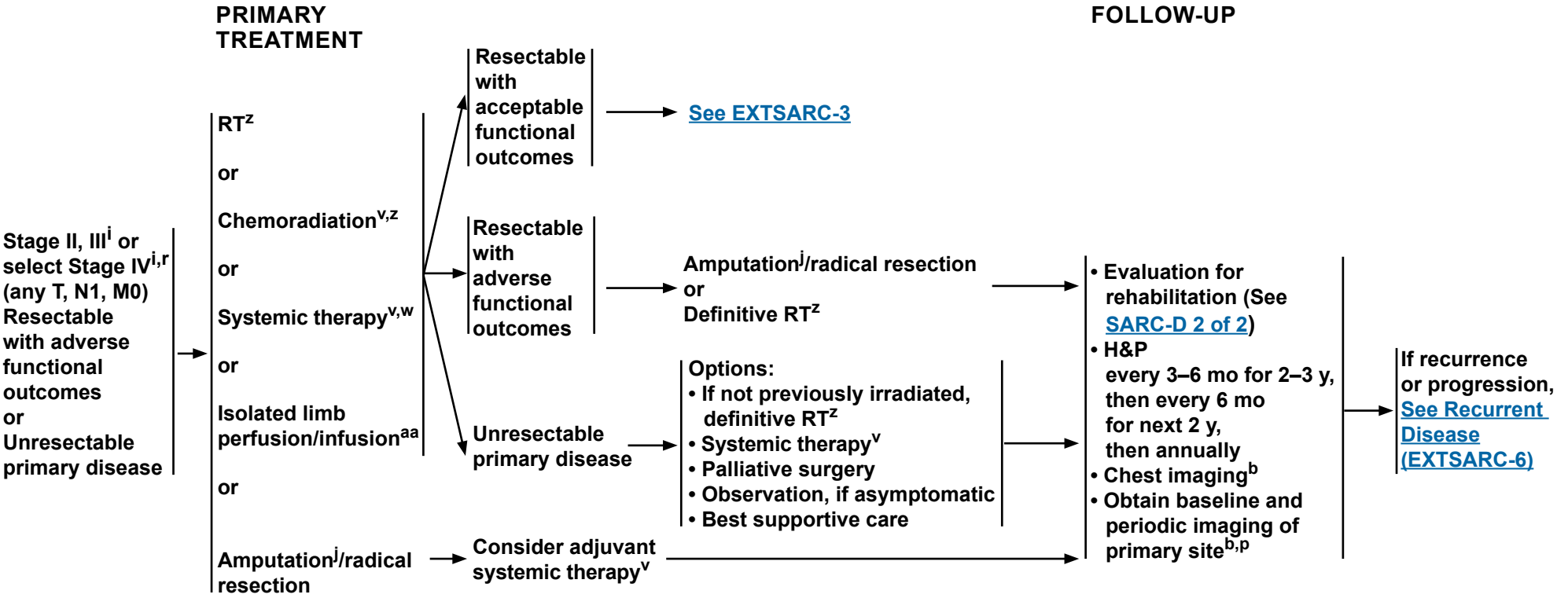

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[w] PET/CT may be useful in determining response to systemic therapy. (Schuetze SM, et al. Cancer 2005;103:339-348).
[z] See Principles of Radiation Therapy (SARC-E).
[aa] Should only be done at institutions with experience in isolated limb perfusion/infusion.

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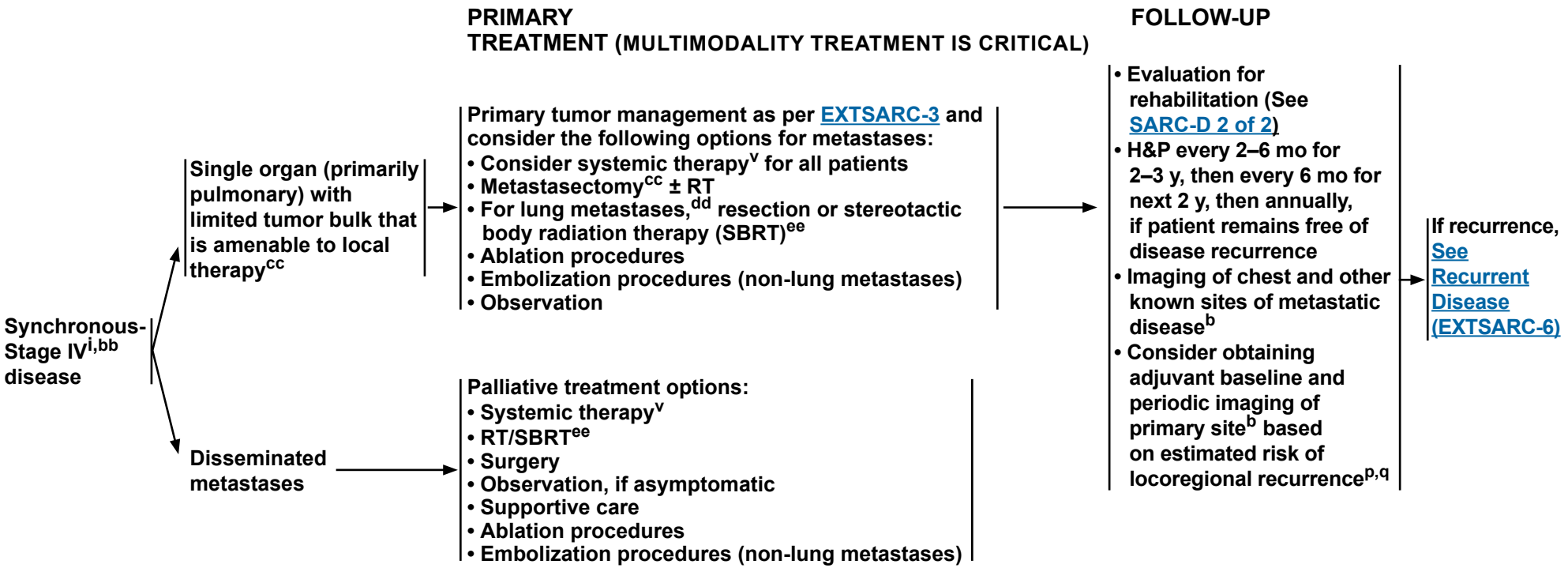

[b] See Principles of Imaging (SARC-A).
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[p] In situations where the area is easily followed by physical examination, imaging may not be required.
[q] After 10 years, the likelihood of developing a recurrence is small and follow-up should be individualized.
[v] See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma Subtypes (SARC-F).
[bb] For N1M0 patients, please refer to EXTSARC-3 or EXTSARC-4.
[cc] Patients with lymph node involvement (including isolated regional nodal metastatic disease) should undergo regional lymph node dissection ± RT.
[dd] Metastasectomy is the historical standard for patients with oligometastatic disease (primarily lung); the ultimate choice of local control modality may depend on factors such as performance status, patient preference, lesion location/accessibility, ability to preserve normal tissue function, and anticipated morbidity of a treatment modality.
[ee] 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, et al. Int J Radiat Oncol Biol Phys 2012;82:940-945; Navarria P, et al. Eur J Cancer 2015;51:668-674; Baumann BC, et al. J Surg Oncol 2020;122:877-883).

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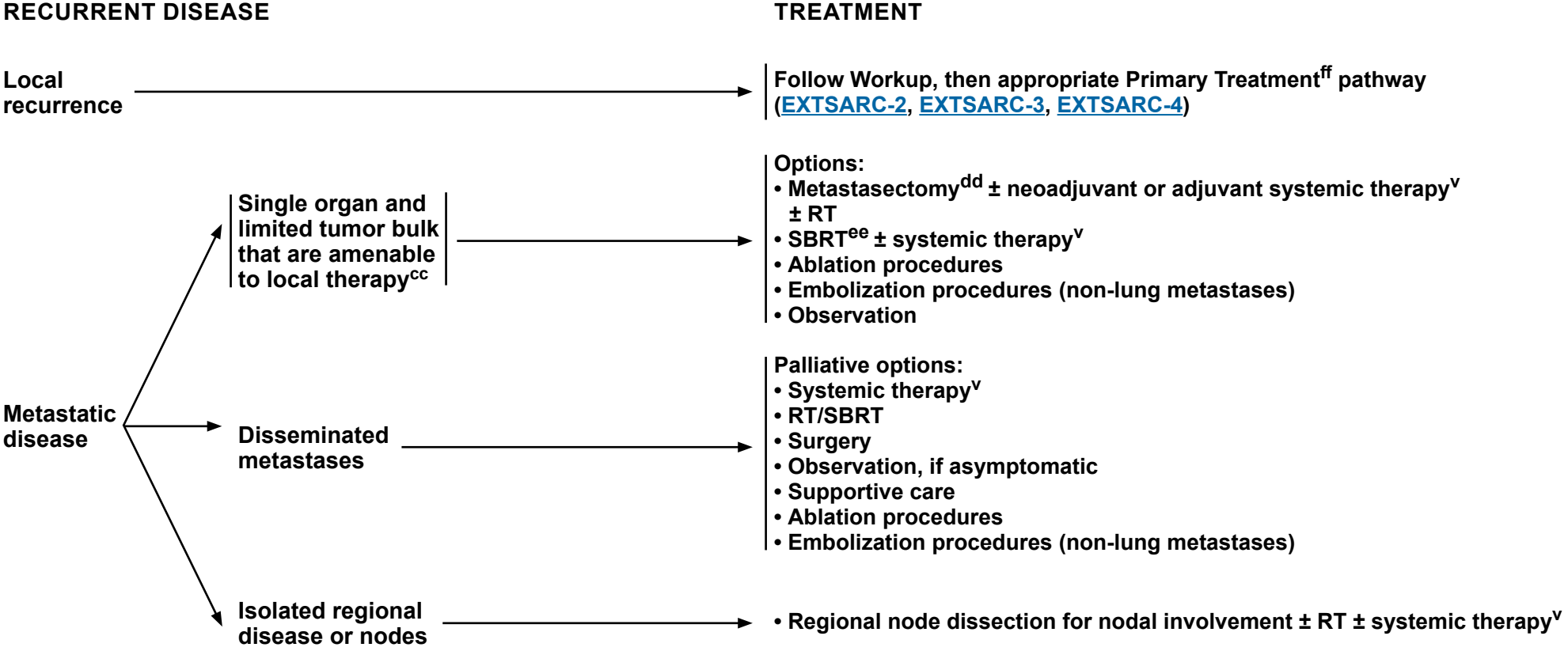

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[ff] If local recurrence can be excised, a decision will need to be made on a case-by-case basis whether re-irradiation is possible. Some case series suggest benefit with re-irradiation (Catton C, et al. Radiother Oncol 1996;41:209-214) while others do not (Torres MA, et al. Int J Radiat Oncol Biol Phys 2007;67:1124-1129), likely reflecting differences in selection of patients for treatment with surgery and radiotherapy or surgery alone. Brachytherapy, IMRT, and/or proton therapy may be utilized to reduce the morbidity of re-irradiation.

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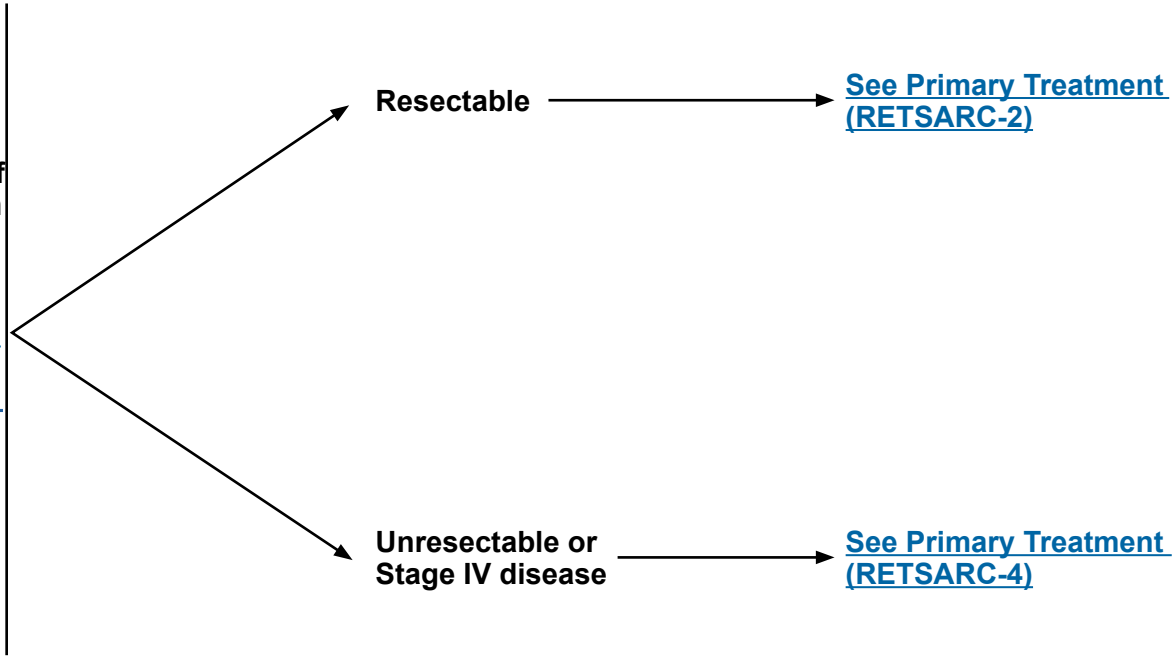
WORKUP

- **Prior to the initiation of therapy, all patients should be evaluated and managed by a multidisciplinary team with expertise and experience in sarcoma.[a]**
- **H&P**
- **Imaging[b]**
- **Image-guided core needle biopsy[c] should be performed if neoadjuvant therapy is being considered or for suspicion of malignancy other than sarcoma.**
- **Preresection biopsy is not necessarily required.**
- **For patients with neurofibromatosis,[d] See NCCN Guidelines for Central Nervous System Cancers (PSCT-3)**
- **For Li-Fraumeni syndrome, See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic**
- **For HNPCC or Lynch syndrome, See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal**
- **For patients with personal/family history suggestive of other cancer predisposition syndromes, consider further genetics assessment.**



[a] These guidelines are intended to treat the adult population. For adolescent and young adult patients, See NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology.
[b] See Principles of Imaging (SARC-A).
[c] Biopsy for retroperitoneal/intra-abdominal sarcomas should try to avoid the free intra-abdominal space. See Principles of Surgery (SARC-D).
[d] Patients with neurofibromatosis are at risk for multiple sarcomas at various locations and their assessment and follow-up should be different.

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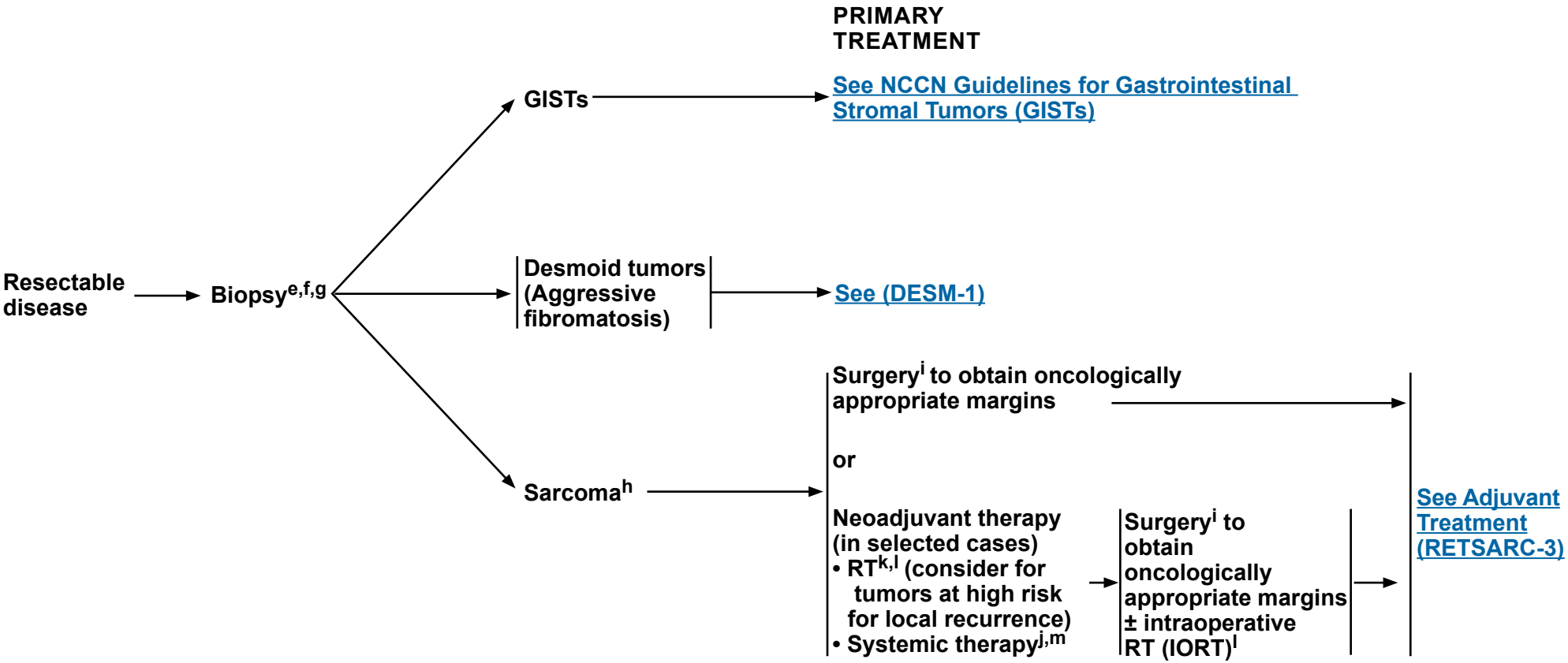

[e] See Principles of Pathologic Assessment of Sarcoma Specimens (SARC-B).
[f] If considering neoadjuvant therapy, biopsy required, including endoscopic ultrasound-guided biopsy for suspected GIST lesions.
[g] Biopsy may not be required if diagnostic imaging is consistent with well-differentiated liposarcoma (WD-LPS).
[h] For other soft tissue sarcomas such as Ewing sarcoma, See NCCN Guidelines for Bone Cancer; for RMS, see RMS-1.
[i] See Principles of Surgery (SARC-D).
[j] Consider systemic therapy if high risk for metastatic disease or if downstaging is needed to facilitate resection. Systemic therapy is not recommended for low-grade tumors.
[k] If neoadjuvant RT is anticipated, intensity-modulated RT (IMRT) would be preferred to optimize sparing of nearby critical structures.
[l] See Principles of Radiation Therapy (SARC-E).
[m] See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma Subtypes (SARC-F).

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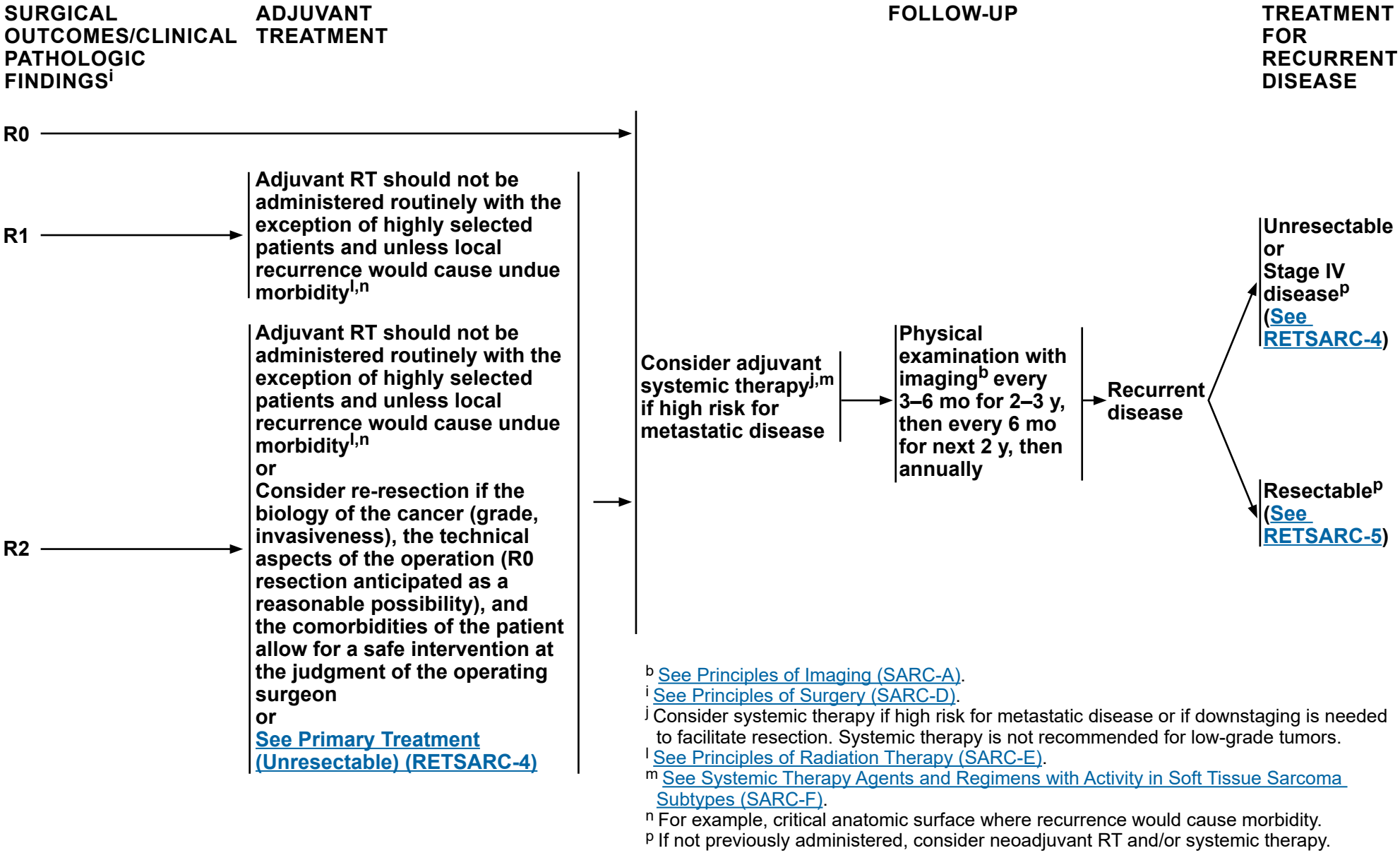

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[i] See Principles of Surgery (SARC-D).
[j] Consider systemic therapy if high risk for metastatic disease or if downstaging is needed to facilitate resection. Systemic therapy is not recommended for low-grade tumors.
[l] See Principles of Radiation Therapy (SARC-E).
[m] See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma Subtypes (SARC-F).
[n] For example, critical anatomic surface where recurrence would cause morbidity.
[p] If not previously administered, consider neoadjuvant RT and/or systemic therapy.

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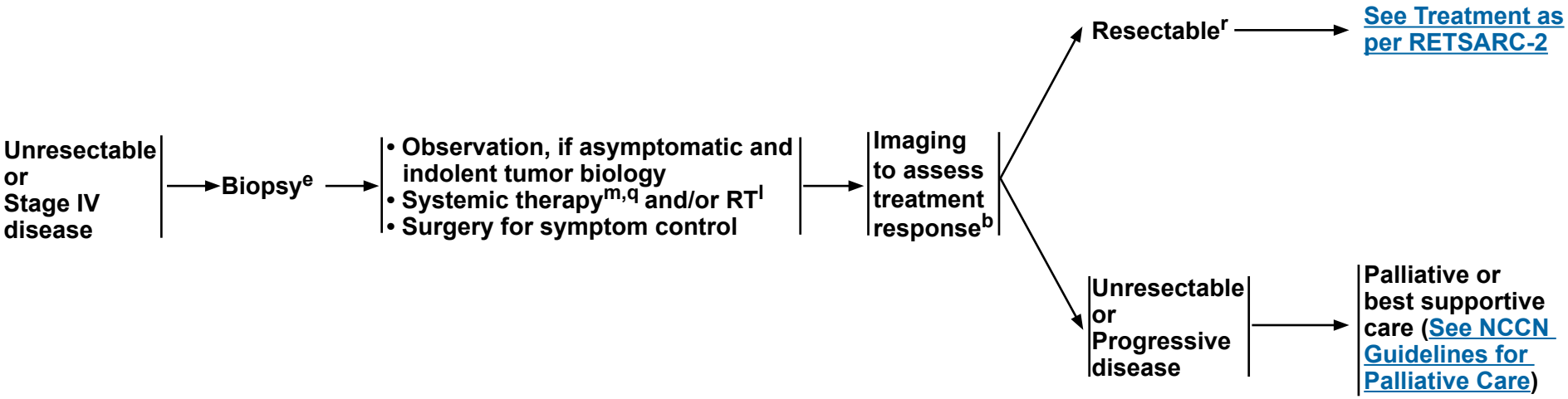
INITIAL THERAPY



[b] See Principles of Imaging (SARC-A).
[e] See Principles of Pathologic Assessment of Sarcoma Specimens (SARC-B).
[l] See Principles of Radiation Therapy (SARC-E).
[m] See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma Subtypes (SARC-F).
[q] The most active systemic therapy regimen in an unselected patient population is AIM (doxorubicin/ifosfamide/mesna) in terms of response rate. Judson I, et al. Lancet Oncol 2014;15:415-423.
[r] Resection of resectable metastatic disease should always be considered if primary tumor can be controlled.

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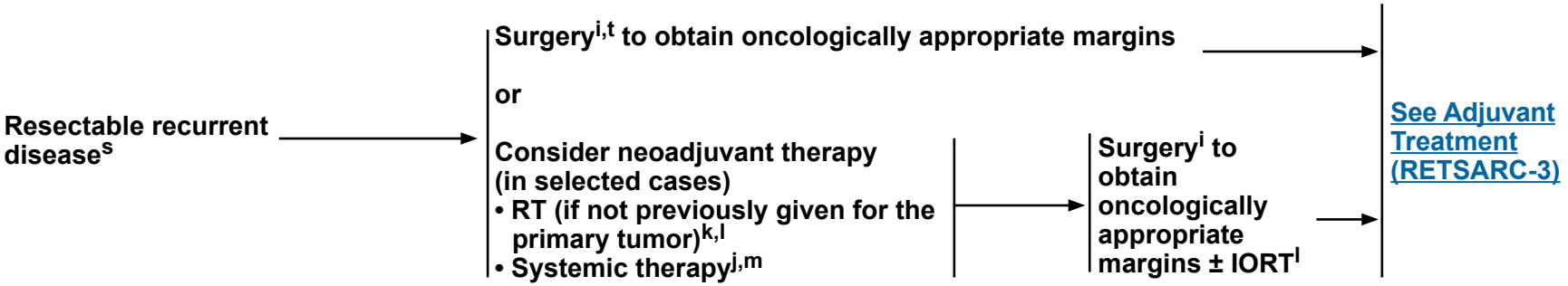

[i] See Principles of Surgery (SARC-D).
[j] Consider systemic therapy if high risk for metastatic disease or if downstaging is needed to facilitate resection. Systemic therapy is not recommended for low-grade tumors.
[k] If neoadjuvant RT is anticipated, IMRT would be preferred to optimize sparing of nearby critical structures.
[l] See Principles of Radiation Therapy (SARC-E).
[m] See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma Subtypes (SARC-F).
[s] Consider biopsy if recurrent disease diagnosis is not clinically definitive.
[t] Consider adjuvant systemic therapy if high risk for metastatic disease or history of several recurrences with a high risk for additional local recurrences.

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WORKUP

- 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
- Consider evaluation for Gardner syndrome[a]/familial adenomatous polyposis (FAP) (See NCCN Guidelines for Colorectal Cancer Screening)
- Appropriate imaging of primary site with CT or MRI as clinically indicated

→ Biopsy[b]

→ Anatomic location where progression would not be morbid → DESM-2

→ Anatomic location where progression would be morbid → DESM-3

[a] Gardner syndrome is an autosomal dominant disorder characterized by a triad of colonic polyposis, osteoma, and soft tissue tumors (Traill Z, et al. AJR Am J Roentgenol 1995;165:1460-1461).

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

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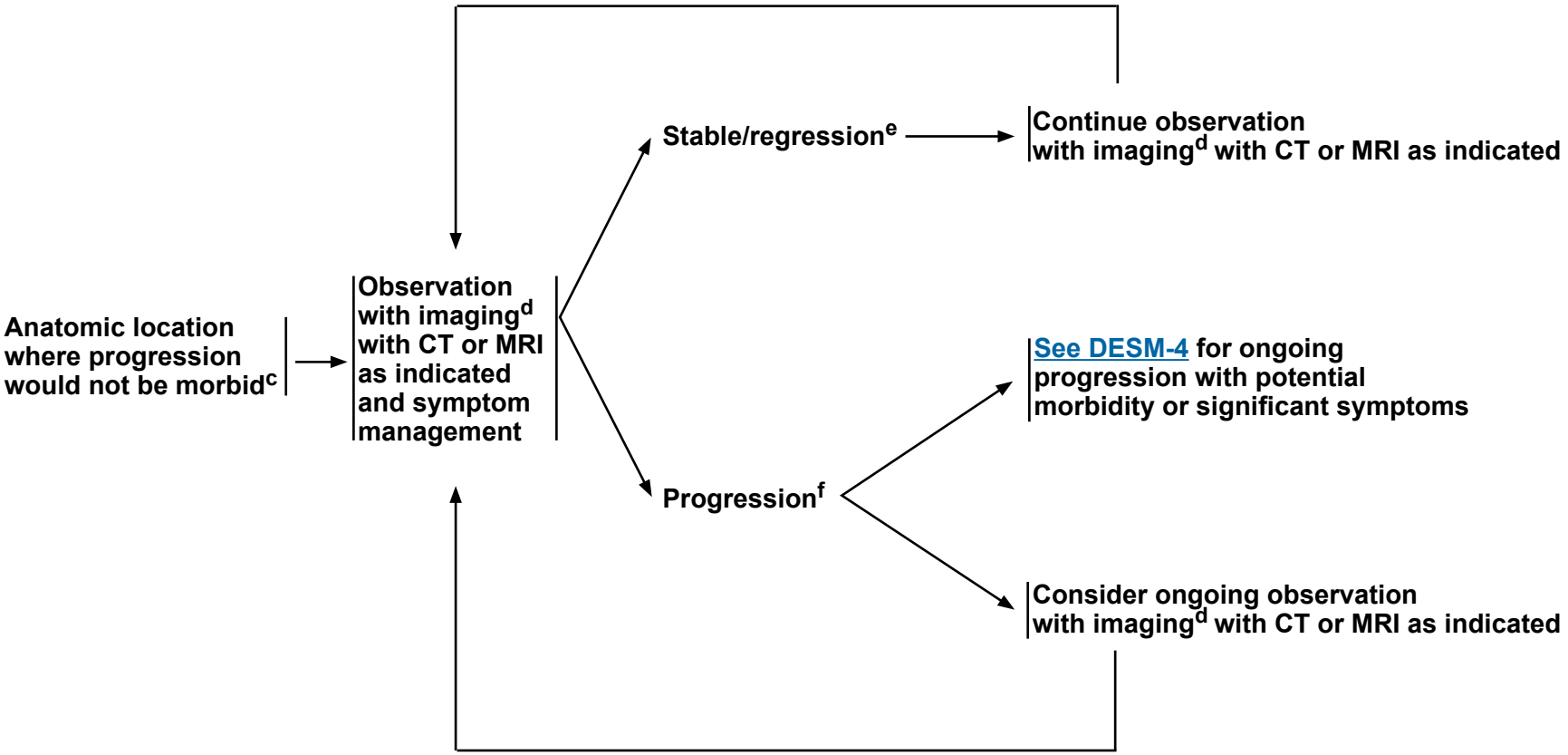

[c] For tumors that are symptomatic, or impairing or threatening in function, patients should be offered therapy with the decision based on the location of the tumor and potential morbidity of the therapeutic option.
[d] Optimal frequency for imaging depends on the anatomical location of tumor, risk of progression, and symptoms of disease progression. Initial imaging every 3 months is recommended. More frequent imaging may be indicated in symptomatic patients.
[e] Spontaneous regression has been reported in 20% of patients, supporting an initial period of observation in patients with newly diagnosed desmoid tumors (Gounder MM, et al. N Engl J Med 2018;379:2417-2428).
[f] A course of ongoing observation is an appropriate option even for patients with disease progression, if the patient is minimally symptomatic and the anatomical location of the tumor is not critical.

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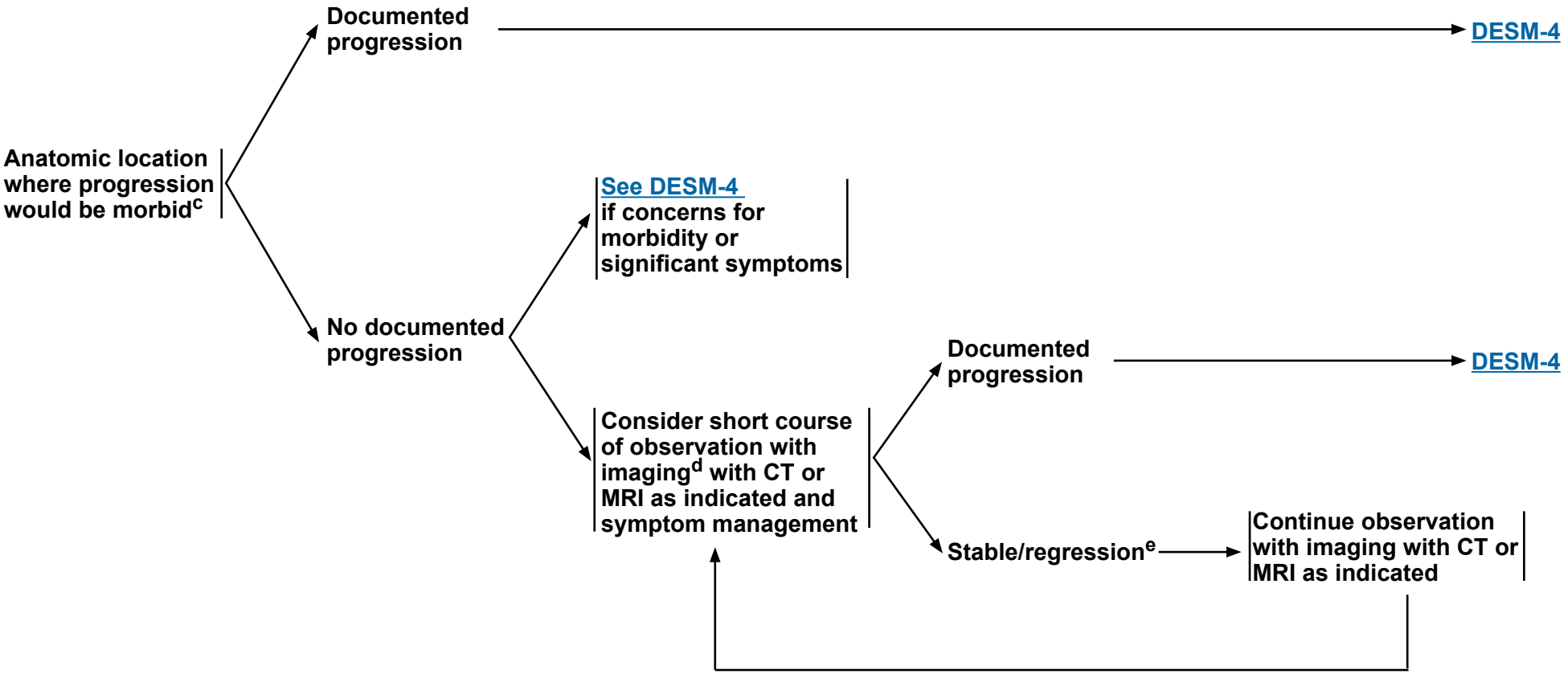

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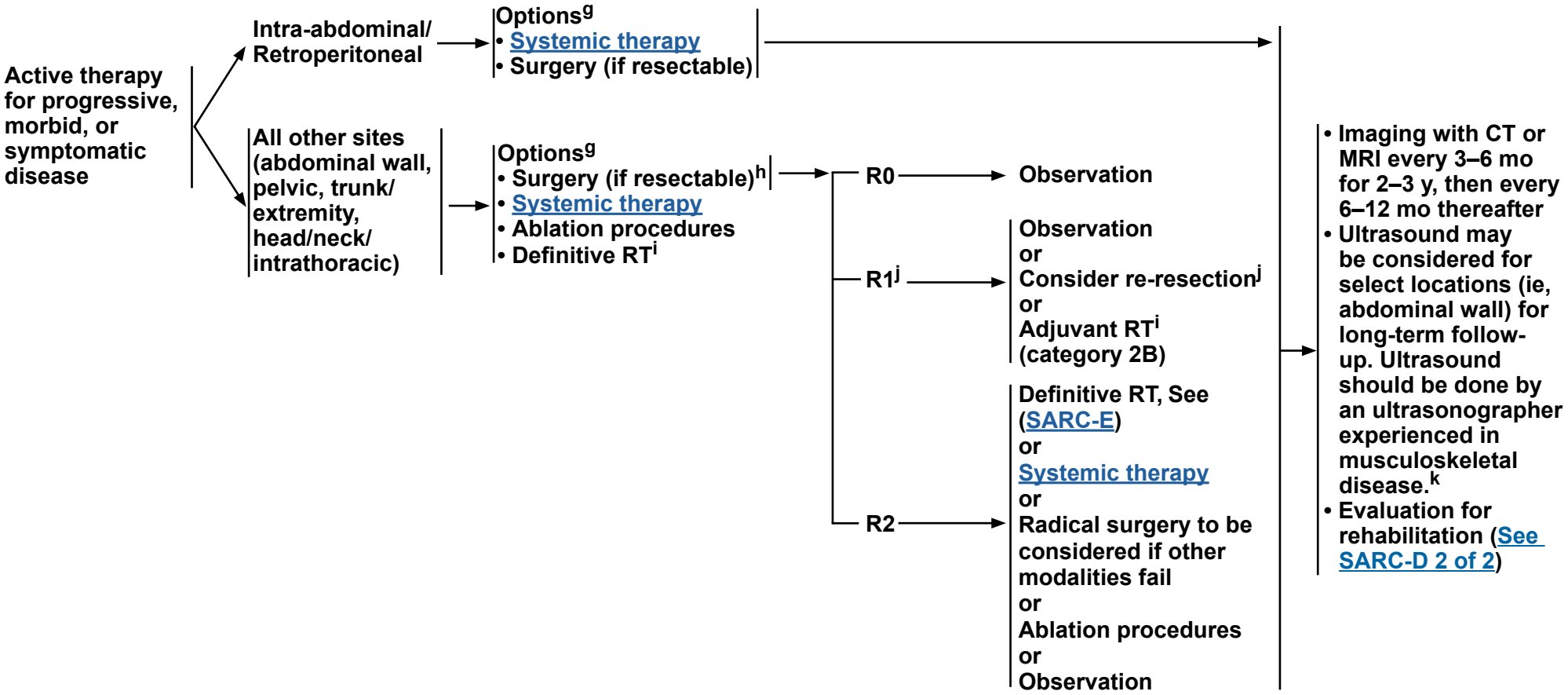
TREATMENT BASED ON ANATOMIC LOCATION

FOLLOW-UP



[g] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilities. Based on the situation, any of these treatment options may potentially be first- or second-line.

[h] Consider ± RT for head/neck/intrathoracic lesions where recurrence would be technically challenging to resect and would lead to significant morbidity.

[i] Consider RT for lesions where recurrence would be technically challenging to resect and would lead to significant morbidity.

[j] R1 margins are acceptable if achieving R0 margins would produce excessive morbidity (Cates JM, et al. Am J Surg Pathol 2014;38:1707-1714; Crago AM, et al. Ann Surg 2013;258:347-353; and Salas S, et al. J Clin Oncol 2011;29:3553-3558).

[k] Choi H, et al. AJR Am J Roentgenol 1991;157:353-358.

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NCCN Guidelines Version 2.2022
Rhabdomyosarcoma[a]

NCCN Guidelines Index
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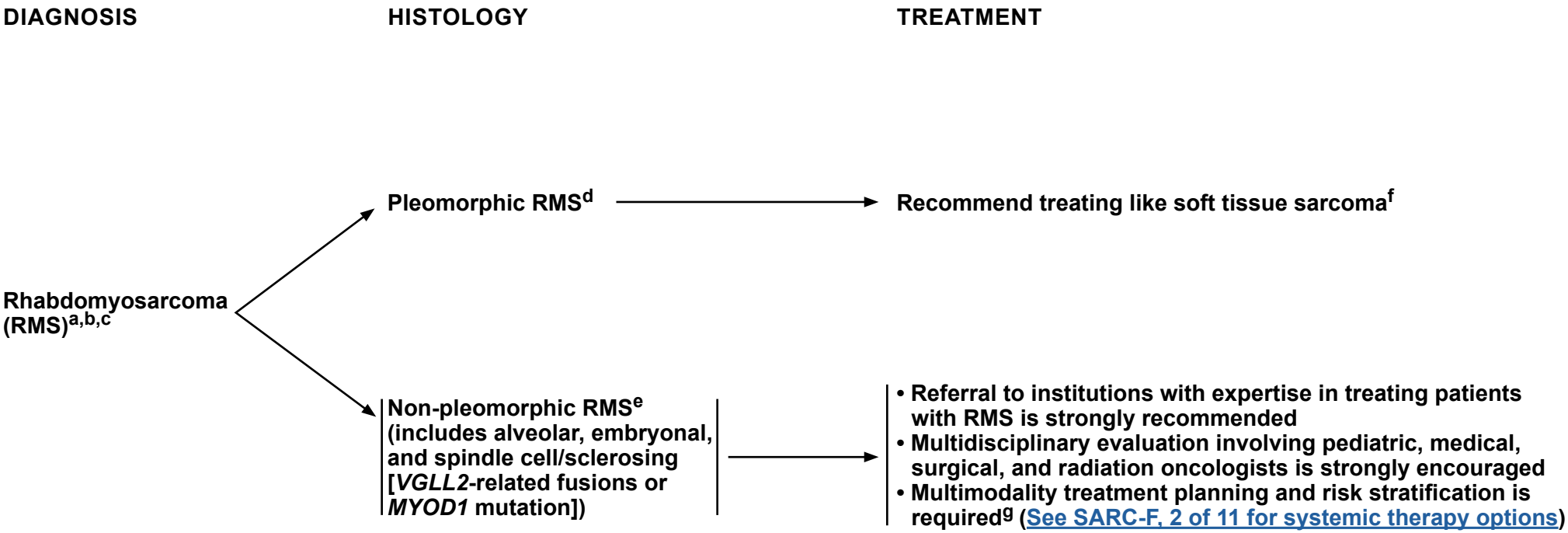
Discussion



[a] RMS that is identified within another histology should be treated as the original histology. This pathway refers to patients diagnosed with pure RMS after full slide review.
[b] PET or PET/CT scan may be useful for initial staging because of the possibility of nodal metastases and the appearance of unusual sites of initial metastatic disease in adult patients.
[c] Referral to centers with expertise in the management of pediatric cancers is recommended.
[d] Not to be confused with anaplastic variant in children.
[e] Up to 13% of RMS in younger patients may have anaplastic features and should not be confused with the high-grade tumors seen in adults designated as pleomorphic RMS.
[f] Pleomorphic RMS is usually excluded from RMS and soft tissue sarcoma randomized clinical trials. Consideration for treatment according to soft tissue sarcoma may be reasonable, including choices for systemic therapy. See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma Subtypes (SARC-F).
[g] Systemic therapy options for RMS may be different than those used with other soft tissue sarcoma histologies. See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma Subtypes (SARC-F).

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PRINCIPLES OF IMAGING[1]

Locations to Image	Imaging Modality[2]	Histologic Subtype(s)	Reason
Extremity/Chest wall/Head & neck	MRI (preferred) and/or CT	All (if primary site)	As part of initial workup and follow-up
Lungs	CT	All (with exception of well-differentiated [WD] liposarcoma)	As part of initial workup and follow-up
Retroperitoneal/Intra-abdominal	CT (preferred) or MRI Consider PET/CT	• All (if primary site) • WD/Dedifferentiated (DD) liposarcoma	• As part of initial workup and follow-up • To help differentiate between WD and DD liposarcoma and to help determine site for biopsy
Abdominal/Pelvic	CT or MRI	• Angiosarcoma • Epithelioid sarcoma • Myxoid/Round cell liposarcoma	As part of initial workup and follow-up given propensity for abdominal/pelvic metastases
CNS	MRI (preferred) or CT	• Angiosarcoma • Alveolar soft part sarcoma (ASPS) • Cardiac sarcoma (left sided)	As part of initial workup and follow-up given propensity for CNS metastases
Total spine	MRI	Myxoid/Round cell liposarcoma	As part of initial workup and follow-up given propensity for spine metastases
Regional lymph node basin[3]	CT or PET/CT	• Angiosarcoma • Clear cell sarcoma • Epithelioid sarcoma • Rhabdomyosarcoma • Synovial sarcoma	As part of initial workup and follow-up given propensity for nodal metastatic disease
Soft tissues	Consider screening whole body MRI	Myxoid/Round cell liposarcoma	Consider as part of initial workup and follow-up given propensity for soft tissue metastases (outside CT cap imaging field)
Any site	PET/CT	• Malignant peripheral nerve sheath tumor (MPNST) • Select histologies in which neoadjuvant therapy is being used	• Consider as part of initial workup to differentiate between neurofibroma(s) and MPNST • PET/CT scan may be useful in staging, prognostication, grading, and determining response to neoadjuvant therapy

[1] Anatomical definition for whole-body MRI:
• Considered vertex to toe tips; can modify from C1 to calves depending on the indication.
• The following contrast-enhanced scans should be considered to complete the whole-body MRI: anatomic, fluid-sensitive, and functional pulse sequences.
[2] Contrasted imaging preferred. Plain x-rays or MRI may be substituted for long-term survivors on surveillance to minimize radiation exposure from CT imaging.
[3] Basile G, Mattei JC, Alshaygy I, et al. Curability of patients with lymph node metastases from extremity soft-tissue sarcoma. Cancer 2020;126:5098-5108.

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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 [IHC], classical cytogenetics, and molecular genetic testing), sarcoma diagnosis should be carried out by pathologists who have access to these ancillary methods.[1]**
- **The pathologic assessment should include evaluation of the following features, all of which should be specifically addressed in the pathology report:**

- **Organ, site, and operative procedure**
- **Primary diagnosis (using standardized nomenclature, such as the WHO Classification of Tumors of Soft Tissue and Bone[2])**
- **Depth of tumor**
  - **Superficial (tumor does not involve the superficial fascia)**
  - **Deep**
- **Size of tumor**
- **Histologic grade (at the least, specify low or high grade if applicable); ideally, grade using the French Federation of Cancer Centers Sarcoma Group (FNCLCC), NCI system, or appropriate diagnosis-specific grading system if applicable**
- **Necrosis**
  - **Present or absent**
  - **Microscopic or macroscopic**
  - **Approximate extent (percentage)**
- **Status of margins of excision**
  - **Uninvolved**
  - **Involved (state which margins)**
  - **Close (state which margins and measured distance)**
- **Quality of margin (a more limited fascial margin may be equivalent to a wider soft tissue margin)**
- **Status of lymph nodes**
  - **Site**
  - **Number examined**
  - **Number positive**
- **Results of ancillary studies[1]**
  - **Type of testing (ie, electron microscopy, IHC, molecular genetic analysis)**
  - **Where performed**
- **Additional tumor features of potential clinical value**
  - **Mitotic rate per 10 high-power fields (HPFs)**
  - **Presence or absence of vascular invasion**
  - **Character of tumor margin (well circumscribed or infiltrative)**
  - **Inflammatory infiltrate (type and extent)**
- **TNM Stage (See ST-5 through ST-8)**

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

[2] Fletcher CDM, Bridge JA, Hogendoorn P, Mertens F. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Soft Tissue and Bone, Fifth Edition. IARC, Lyon, 2020.

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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 IHC, classical cytogenetics, electron microscopy, and molecular genetic testing. Molecular genetic testing has emerged as an 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 and next-generation sequencing (NGS)-based methods.[1] NGS, including DNA and RNA sequencing, may be beneficial in selected patients. The timing of when to perform NGS and for which patients must be evaluated individually. NGS findings can help patients qualify for clinical trials and can identify actionable mutations that may not have been targeted by prior therapies. Thus, NGS may be appropriate for patients who may qualify for and who are interested in enrolling in a clinical trial or for patients with disease that is refractory who have failed or progressed on standard therapies or in certain histologies where NGS provides clinically actionable information. NGS should not replace expert pathology review, as NGS only rarely results in a diagnosis change following expert review. Technically successful NGS on bone biopsies requires use of decalcification agents, such as EDTA, that do not interfere with genomic testing. 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)** **t(1;13)(p36;q14)** **t(X;2)(q13;q35)**	***PAX3-FOXO1*** ***PAX7-FOXO1*** ***PAX3-AFX***
Desmoplastic small round cell tumor	**t(11;22)(p13;q12)**	***EWSR1-WT1***
Embryonal RMS	**Complex alterations**	**Multiple,** ***MYOD1, KRAS, HRAS, TP53, NF1, NRAS, PIK3CA, FBXW7, FGFR4, BCOR***
Ewing sarcoma/peripheral neuroectodermal tumor	**t(11;22)(q24;q12)** **t(21;22)(q22;q12)** **t(2;22)(q33;q12)** **t(7;22)(p22;q12)** **t(17;22)(q12;q12)** **inv(22)(q12q;12)** **t(16;21)(p11;q22)**	***EWSR1-FLI1*** ***EWSR1-ERG*** ***EWSR1-FEV*** ***EWSR1-ETV1*** ***EWSR1-E1AF*** ***EWSR1-ZSG*** ***FUS-ERG***

[1] Molecular genetic analysis involves highly complex test methods. None of the methods is absolutely sensitive or provides 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 can be found in alveolar RMS, including *PAX3-NCOA1*, *PAX3-NCOA2*, and *PAX3-INO80D*. *NCOA2* gene rearrangements and *MyoD* mutation have been identified in spindle cell RMS. Receptor tyrosine kinase/*RAS*/*PIK3CA* aberrations are found in 93% of RMS cases. *MIR143-NOTCH* fusion has recently been identified in glomus tumor. 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.

Continued

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PRINCIPLES OF ANCILLARY TECHNIQUES USEFUL IN THE DIAGNOSIS OF SARCOMAS

TUMOR	ABERRATION	GENE(S) INVOLVED
Malignant Round Cell Tumors - continued		
Undifferentiated round cell sarcoma	t(4;19)(q35;q13) or t(10;19)(q26;q13) inv(X)(p11.4p11.22)	*CIC-DUX4*[3] *BCOR-CCNB3*[4]
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, GLI*
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-DDIT3* *EWSR1-DDIT3*
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*[5]
Dermatofibrosarcoma protuberans	t(17;22)(q21;q13) and derivative ring chromosomes	*COL1A1-PDGFB*
Desmoid fibromatosis	Trisomy 8 or 20; loss of 5q21	*CTNNB1* or *APC* mutations
High-grade endometrial stromal sarcoma	t(10;17)(q22;p13) t(x;22)(p11;q13)	*YWHAE-NUTM2* *ZC3H7B-BCOR*[6]

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Continued

PRINCIPLES OF ANCILLARY TECHNIQUES USEFUL IN THE DIAGNOSIS OF SARCOMAS

TUMOR	ABERRATION	GENE(S) INVOLVED
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)***
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*[5]** ***TPM4-ALK*[5]** ***CLTC-ALK*[5]** ***RANBP2-ALK*[5]** ***CARS-ALK*[5]** ***ATIC-ALK*[5]** ***ETV6-NTRK3*[5,7]** ***TFG-ROS1*[7,8,9]**
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		***NF1*, *CDKN2A* and *EED* or *SUZ12***
Mesenchymal chondrosarcoma	**t(8;8)(q13;q21)**	***HEY1 - NCOA2***
Solitary fibrous tumor	**inv(12)(q13q13)**	***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

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

Biopsy

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

Surgery

- The surgical procedure necessary to resect the tumor with oncologically appropriate margins should be used. Ideally, this would be pathologically negative resection margins. However, planned close margins or even microscopically positive margins may be appropriate to preserve critical structures (eg, major vessels, nerves, bones, joints), especially in multimodality therapy.
- Evaluate for rehabilitation prior to surgery (see SARC-D 2 of 2).
- Ideally, the biopsy site should be excised en bloc with the definitive surgical specimen. Dissection should be through grossly normal tissue planes uncontaminated by tumor. If the tumor is close to or displaces major vessels or nerves, these do not need to be resected if the adventitia or perineurium is removed and the underlying neurovascular structures are not involved with gross tumor.
- Radical excision/entire anatomic compartment resection is not routinely necessary.
- Surgical clips should be placed to mark the periphery of the surgical field and other relevant structures to help guide potential future RT. If closed suction drainage is used, the drains should exit the skin close to the edge of the surgical incision (in case re-resection or radiation is indicated).

Resection Margins

- Surgical margins should be documented by both the surgeon and the pathologist evaluating the resected specimen.
- If surgical resection margins are positive on final pathology (other than bone, nerve, or major blood vessels), surgical re-resection to obtain negative margins should strongly be considered if it will not have a significant impact on functionality.
- Consideration for adjuvant RT should be given for a close soft tissue margin or a microscopically positive margin on bone, major blood vessels, or a major nerve.
- ALT/WDLS: RT is not indicated in most cases.
- In selected cases when margin status is uncertain, consultation with a radiation oncologist is recommended.
  - R0 resection - No residual microscopic disease
  - R1 resection - Microscopic residual disease
  - R2 resection - Gross residual disease
- Special consideration should be given to infiltrative histologies such as myxofibrosarcoma, DFSP, and angiosarcoma.

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PRINCIPLES OF SURGERY

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

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 should be made for patient preference or if gross total resection of the tumor is expected to render the limb nonfunctional.**

Rehabilitation

Rehabilitation evaluation is recommended neoadjuvantly, adjuvantly, and in the outpatient setting to optimize functional outcomes and quality of life.

Prior to amputation or limb-sparing surgery, Physical Medicine and Rehabilitation (PM&R) physician consultation should be offered to provide education about functional outcomes of the planned surgery, set adjuvant goals, and establish care for longitudinal follow-up.

In the immediate adjuvant period, patients should receive a functional evaluation, typically by a physical therapist, to ensure that they are able to safely discharge home. If further rehabilitation is needed, a PM&R and occupational therapist should also evaluate the patient.

The oncology rehabilitation (ie, PM&R, physical/occupational therapy) team and the orthopedic/surgical oncology team should be well-coordinated to optimize patient care. This includes communicating the rehabilitation/surgical restrictions, precautions, and rehabilitation protocol prior to initiating therapy.

When possible, the rehabilitation plan of care should be overseen by a PM&R physician, who can prescribe medications, order and interpret diagnostic tests, and prescribe/oversee therapies. The plan should consider oncology treatment-related side effects and comorbidities such as lymphedema, systemic therapy-induced neuropathy and fatigue, radiation fibrosis, and impaired bone healing that may impact treatment.

Pain management should be integrated into the rehabilitation program to optimize outcomes. Phantom limb pain should be treated early. Interventions may include mirror therapy, motor imagery, massage, oral and topical analgesics, coping strategies, and patient education.

Special consideration should be given when progressing rehabilitation interventions for limb-sparing surgeries (ie, oncologic proximal humerus replacement, proximal tibia replacement, internal hemipelvectomy) that require adequate scar tissue formation essential for functional joint recovery.

The rehabilitation plan must address any psychological distress associated with the surgery, and include referrals to appropriate mental health providers when necessary. All patients should be connected to peer support groups.

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PRINCIPLES OF RADIATION THERAPY[a]

Radiation Therapy Guidelines for Soft Tissue Sarcoma of Extremity/Body Wall/Head and Neck[1]

Neoadjuvant RT

- **Potential benefits:**
  - **Lower total radiation dose**
  - **Shorter course of treatment**
  - **Treatment field size is frequently smaller**
  - **Associated with less late radiation toxicity and improved extremity function**
  - **The primary sarcoma is a defined target for radiation treatment planning**
  - **Treatment delivery not impacted by adjuvant wound healing issues**
  - **Potential downstaging of borderline resectable extremity sarcomas for possible limb salvage**
  - **Ability to restage patients after neoadjuvant radiation but before wide resection**
  - **Presence of distant metastases would prevent proceeding with a noncurative surgery**
- **Results of a randomized study showed a non-significant trend toward reduced late toxicities (fibrosis, edema, and joint stiffness) with neoadjuvant compared to adjuvant radiation and a significant association between these toxicities and increasing treatment field size.[2,3] Based on the pros and cons of neoadjuvant versus adjuvant radiation, the panel has expressed a general preference for neoadjuvant RT, because adjuvant radiation fields are typically larger than neoadjuvant radiation fields.**
- **General dose guidelines[4,5,6,7]:**
  - **50 Gy external beam RT (EBRT; 1.8–2.0 Gy per fraction)**
  - **If an R1 or R2 resection is anticipated, clips to high-risk areas for recurrence are encouraged. When EBRT is used, sophisticated treatment planning with intensity-modulated RT (IMRT) and/or protons can be used to improve the therapeutic ratio.[8,9]**
  - **Following neoadjuvant 50 Gy EBRT and surgery, for positive margins, consider observation or RT boost in select situations.**
    - ◊ **There are data to suggest that some patients with positive margins following neoadjuvant 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.[10]**
    - ◊ **There are also data to suggest that delivery of a boost for positive margins does not improve local control. Since delivery of an adjuvant RT boost does not clearly add benefit, the decision should be individualized and the potential toxicities should be carefully considered.[11,12]**
  - **If adjuvant boost radiation for a positive margin is felt to be appropriate, an additional 14–20 Gy can be considered with fractionated EBRT or brachytherapy.[13]**

See references on SARC-E 4 of 4

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

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PRINCIPLES OF RADIATION THERAPY[a]

Radiation Therapy Guidelines for Soft Tissue Sarcoma of Extremity/Body Wall/Head and Neck[1]

Adjuvant RT

- **Potential benefits:**
  - **Allow for definitive pathologic assessment, including margin status, where there was no definitive indication for neoadjuvant radiation.**
  - **Lower rate of adjuvant wound healing complications, especially in the lower extremity.**
- **Based on the pros and cons of neoadjuvant versus adjuvant radiation, the panel has expressed a general preference for neoadjuvant radiation, because adjuvant radiation fields are typically larger than neoadjuvant radiation fields.[2,3]**
- **Adjuvant RT following surgery with clips See Resection Margins on Principles of Surgery: (SARC-D).**
- **General dose guidelines (total doses should always be determined by normal tissue tolerance):**
  - **EBRT (50 Gy; 1.8–2.0 Gy per fraction) to larger volume followed by a boost to the tumor bed (10–20 Gy depending on surgical margins).**
  - **Brachytherapy ± EBRT**
    - ◊ **Positive margins: Low dose-rate (16–20 Gy) or high dose-rate equivalent brachytherapy (14–16 Gy) + 50 Gy EBRT**
    - ◊ **Negative margins: Low dose-rate (45 Gy) or high dose-rate equivalent brachytherapy (36 Gy in 3.6 Gy BID over 10 fractions in 5 days)**

Definitive RT for Unresectable Disease[14]

- **If definitive RT is planned for patients who are not surgical candidates, RT should be given to an initial larger volume, akin to what is used for neoadjuvant radiation followed by a boost to the gross tumor with more limited margin.**
- **Doses to the initial volume should be 50 Gy with a boost of at least 63 Gy; however, higher doses of 70–80 Gy can be considered, limited by tolerance of normal structures.**

Radiation Therapy for Desmoid Tumors

- **Definitive RT is an appropriate treatment option for patients with desmoid tumors. Treatment is often reserved for patients who cannot tolerate or progress through systemic therapy and where surgery would be too morbid or would result in positive margins.**
  - **The recommended dose of definitive RT is 56 Gy in 28 fractions.[15]**
- **Neoadjuvant radiation to a dose of 50 Gy in 25 fractions can be considered in select cases.**

See references on SARC-E 4 of 4

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PRINCIPLES OF RADIATION THERAPY[a]

Radiation Therapy Guidelines for Retroperitoneal/Intra-Abdominal Sarcoma

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

Neoadjuvant RT[16-18]

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

Adjuvant RT[20-22]

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

See references on SARC-E 4 of 4

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PRINCIPLES OF RADIATION THERAPY

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

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

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

Footnotes and references see SARC-F, 7 of 11

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

Desmoid Tumors (Aggressive Fibromatosis)[l]	Non-Pleomorphic Rhabdomyosarcoma
Preferred regimens • Sorafenib (category 1)[34] • Methotrexate and vinorelbine[35] • Methotrexate and vinblastine[36] • Imatinib[37,38] • Liposomal doxorubicin[39] • Doxorubicin ± dacarbazine[40-42] • Pazopanib[43] **Useful in certain circumstances** • Sulindac[44] or other nonsteroidal anti-inflammatory drugs (NSAIDs), including celecoxib (for pain)	**Preferred regimens** • Vincristine, dactinomycin, cyclophosphamide (VAC)[m,45] • Vincristine, dactinomycin, ifosfamide (VAI-Europe)[m] **Other recommended regimens** • Vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide[46] • Vincristine, doxorubicin, cyclophosphamide[47] • Vincristine, doxorubicin, ifosfamide[48] • Cyclophosphamide and topotecan[49] • Ifosfamide and doxorubicin[50] • Ifosfamide and etoposide[51] • Irinotecan and vincristine[52,53] • Carboplatin and etoposide[54] • Vinorelbine and low-dose cyclophosphamide[i,55] • Vincristine, irinotecan, temozolomide[56] • Irinotecan[52,53,57] • Topotecan[58] • Vinorelbine[i,59] • Vinorelbine/cyclophosphamide/temsirolimus[60] **Useful in certain circumstances** • Maintenance chemotherapy (cyclophosphamide/vinorelbine) for patients with intermediate-risk RMS with CR following treatment with VAC or VAI regimen (please note: COG has an active prospective ongoing study, but considered a reasonable standard of care)[61]

Footnotes and references see SARC-F, 7 of 11

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

Alveolar Soft Part Sarcoma (ASPS)	Angiosarcoma
Preferred regimens • Sunitinib[62,63] • Pazopanib[64] • Pembrolizumab[65] • Pembrolizumab in combination with axitinib[66]	**Preferred regimens** • Paclitaxel[67,68] • Anthracycline- or gemcitabine-based regimens recommended for Soft Tissue Sarcoma Subtypes with Non-Specific Histologies (See SARC-F, 1 of 11) **Other recommended regimens** • Docetaxel[69] • Vinorelbine[i] • Pazopanib **Useful in certain circumstances** • Pembrolizumab[70] (for cutaneous angiosarcoma) • Regorafenib[71] • Sorafenib[72] • Sunitinib[73] • Bevacizumab[n,74]

Footnotes and references see SARC-F, 7 of 11

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

Dermatofibrosarcoma Protuberans (DFSP) with Fibrosarcomatous Transformation	Epithelioid Sarcoma	Extraskeletal Osteosarcoma
Preferred regimens • Imatinib[75] **Other recommended regimens** • Anthracycline-based regimens: ▸ Doxorubicin[1,2,8,9] ▸ Epirubicin[16] ▸ Liposomal doxorubicin[17] ▸ AIM (doxorubicin, ifosfamide, mesna)[1-4,8] ▸ Ifosfamide, epirubicin, mesna[5] ▸ MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[1,2,22,23] • Gemcitabine-based regimens: ▸ Gemcitabine ▸ Gemcitabine and docetaxel[10,11] ▸ Gemcitabine and vinorelbine[13] ▸ Gemcitabine and dacarbazine[14] • Pazopanib[j,21] (patients ineligible for IV systemic therapy or patients who are not candidates for anthracycline-based regimens)	**Preferred regimens** • Tazemetostat[o,76]	**Preferred regimens** • Usually treated as soft tissue sarcoma with the following: ▸ Ifosfamide or platinum-based therapy (cisplatin/doxorubicin)[77]

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

Inflammatory Myofibroblastic Tumor (IMT) with Anaplastic Lymphoma Kinase (ALK) Translocation	Malignant Perivascular Epithelioid Cell Tumor (PEComa) (for locally advanced unresectable or metastatic disease)	Recurrent Angiomyolipoma, Lymphangioleiomyomatosis
Preferred regimens • ALK inhibitors ▸ Crizotinib[78] ▸ Ceritinib[79] ▸ Brigatinib[80,81] ▸ Lorlatinib	**Preferred regimens** • Albumin-bound sirolimus[82,83] **Other recommended regimens** • Sirolimus[84-87] • Everolimus[88] • Temsirolimus[89,90]	**Preferred regimens** • Sirolimus[84-87] • Everolimus[88] • Temsirolimus[89,90]

Footnotes and references see SARC-F, 7 of 11

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

Solitary Fibrous Tumor	Tenosynovial Giant Cell Tumor/Pigmented Villonodular Synovitis	Well-Differentiated/Dedifferentiated Liposarcoma (WD-DDLS) for Retroperitoneal Sarcomas
Preferred regimens • Bevacizumab[n] and temozolomide[91] • Sunitinib[73,92] • Sorafenib[93] • Pazopanib[94] **Other recommended regimens** • Anthracycline-based regimens: ▸ Doxorubicin[1,2,8,9] ▸ Epirubicin[16] ▸ Liposomal doxorubicin[17] ▸ AD (doxorubicin, dacarbazine)[1,2,6,7,18] ▸ AIM (doxorubicin, ifosfamide, mesna)[1-4,8] ▸ Ifosfamide, epirubicin, mesna[5] ▸ MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[1,2,22,23] • Gemcitabine-based regimens: ▸ Gemcitabine ▸ Gemcitabine and docetaxel[10,11] ▸ Gemcitabine and vinorelbine[13] ▸ Gemcitabine and dacarbazine[14] • Trabectedin[i]	**Preferred regimens** • Pexidartinib (category 1)[95] **Useful in certain circumstances** • Imatinib[96] • Nilotinib[97]	**Useful in certain circumstances** • Palbociclib[p,98]

Footnotes and references see SARC-F, 7 of 11

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

FOOTNOTES

[a] Prior to the initiation of therapy, all patients should be evaluated and managed by a multidisciplinary team with expertise and experience in sarcoma.
[b] For uterine sarcomas, See the NCCN Guidelines for Uterine Neoplasms.
[c] Including but not limited to alveolar soft part sarcoma (ASPS), ALT/WDLS, and clear cell sarcomas, which are generally not sensitive.
[d] Dexrazoxane may be added as a cardioprotectant for the prevention of cardiotoxicity in patients planning to receive high-dose anthracyclines (eg, doxorubicin >250 mg/m^2). Armenian SH, et al. J Clin Oncol 2017;35:893-911.
[e] Anthracycline-based regimens are preferred in the neoadjuvant and adjuvant settings.
[f] Regimens appropriate for pleomorphic rhabdomyosarcoma.
[g] Not intended for neoadjuvant or adjuvant therapy of nonmetastatic disease. Not recommended for angiosarcoma or pleomorphic rhabdomyosarcoma.
[h] Not intended for adjuvant therapy of nonmetastatic disease.
[i] Recommended only for palliative therapy.
[j] For non-adipocytic sarcoma.
[k] For the treatment of patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.
[l] Optimal duration of TKI therapy has not been established. Discontinuation of TKI therapy can be considered (with careful monitoring) in patients with stable disease.
[m] For patients with intermediate-risk disease, consider maintenance therapy with vinorelbine and cyclophosphamide for 6 months.
[n] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[o] Single-agent therapy for the treatment of metastatic or locally advanced epithelioid sarcoma not eligible for complete resection.
[p] Single-agent therapy for the treatment of unresectable WD-DDLS.

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

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

- **See the following for a thorough discussion of how and when to consider testing, important elements of pre-test counseling, points to consider when using multi-gene testing, how tumor testing can inform germline testing, important elements in post-test counseling, and the importance of family communication:**
  - **Principles of Cancer Risk Assessment and Counseling (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic [EVAL-A])**
- **For pedigree development, see Pedigree: First-, Second-, and Third-Degree Relatives of Proband (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic [EVAL-B])**

- **When to consider genetic testing for inherited soft tissue sarcomas:**
  - **For Li-Fraumeni syndrome, See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic**
  - **For hereditary non-polyposis colorectal cancer (HNPCC or Lynch syndrome) and FAP/attenuated FAP (AFAP) (for desmoid tumors), See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal**
  - **For patients with personal/family history suggestive of other cancer predisposition syndromes, consider further genetics assessment.**

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

Table 1
Histopathologic Type
Tumors included in the soft tissue category are listed below as per the 2020 World Health Organization classification of tumors:

Adipocytic Tumors
Benign
- Lipoma NOS
  - Intramuscular lipoma
  - Chondrolipoma
- Lipomatosis
  - Diffuse lipomatosis
  - Multiple symmetrical lipomatosis
  - Pelvic lipomatosis
  - Steroid lipomatosis
  - HIV lipodystrophy
- Lipomatosis of nerve
  - Lipoblastomatosis
  - Localized (lipoblastoma)
  - Diffuse (lipoblastomatosis)
- Angiolipoma NOS
  - Cellular angiolipoma
- Myolipoma
- Chondroid lipoma
- Spindle cell lipoma
- Atypical spindle cell/pleomorphic lipomatous tumor
- Hibernoma

Intermediate (locally aggressive)
- Atypical lipomatous tumor

Malignant
- Liposarcoma, well-differentiated, NOS
  - Lipoma-like liposarcoma
  - Inflammatory liposarcoma
  - Sclerosing liposarcoma
- Dedifferentiated liposarcoma
- Myxoid liposarcoma
- Pleomorphic liposarcoma
  - Epithelioid liposarcoma
- Myxoid pleomorphic liposarcoma

Fibroblastic/Myofibroblastic Tumors
Benign
- Nodular fasciitis
  - Intravascular fasciitis
  - Cranial fasciitis
- Proliferative fasciitis
- Proliferative myositis
- Myositis ossificans and fibro-osseous pseudotumor to digits
- Ischemic fasciitis
- Elastofibroma
- Fibrous hamartoma of infancy
- Fibromatosis colli
- Juvenile hyaline fibromatosis
- Inclusion body fibromatosis
- Fibroma of tendon sheath
- Desmoplastic fibroblastoma
- Myofibroblastoma
- Calcifying aponeurotic fibroma
- *EWSR1-SMAD3*-positive fibroblastic tumor (emerging)
- Angiomyofibroblastoma
- Cellular angiofibroma
- Angiofibroma NOS
- Nuchal fibroma
- Acral fibromyxoma
- Gardner fibroma

Intermediate (locally aggressive)
- Solitary fibrous tumor, benign
- Palmar/plantar-type fibromatosis
- Desmoid-type fibromatosis
  - Extra-abdominal desmoid
  - Abdominal fibromatosis
  - Lipofibromatosis
  - Giant cell fibroblastoma

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Continued

Table 1
Histopathologic Type
Tumors included in the soft tissue category are listed below as per the 2020 World Health Organization classification of tumors:

Fibroblastic/Myofibroblastic Tumors (continued)
Intermediate (rarely metastasizing)
- Dermatofibrosarcoma protuberans NOS
  - Pigmented dermatofibrosarcoma protuberans
  - Dermatofibrosarcoma protuberans, fibrosarcomatous
  - Myxoid dermatofibrosarcoma protuberans
    - ◊ Dermatofibrosarcoma protuberans with myoid differentiation
  - Plaque-like dermatofibrosarcoma protuberans
- Solitary fibrous tumor, NOS
  - Fat-forming (lipomatous) solitary fibrous tumor
  - Giant cell-rich solitary fibrous tumor
- Inflammatory myofibroblastic tumor
  - Epithelioid inflammatory myofibroblastic sarcoma
- Myofibroblastic sarcoma
- Superficial CD34-positive fibroblastic tumor
- Myxoinflammatory fibroblastic sarcoma
- Infantile fibrosarcoma

Malignant
- Solitary fibrous tumor, malignant
- Fibrosarcoma NOS
- Myxofibrosarcoma
  - Epithelioid myxofibrosarcoma
- Low-grade fibromyxoid sarcoma
- Sclerosing epithelioid fibrosarcoma

So-called Fibrohistiocytic Tumors
Benign
- Tenosynovial giant cell tumor NOS
  - Tenosynovial giant cell tumor, diffuse
- Deep benign fibrous histiocytoma

Intermediate (rarely metastasizing)
- Plexiform fibrohistiocytic tumor
- Giant cell tumor of soft parts NOS

Malignant
- Malignant tenosynovial giant cell tumor

Vascular Tumors
Benign
- Haemangioma NOS
- Intramuscular haemangioma
- Arteriovenous haemangioma
- Venous haemangioma
- Epithelioid haemangioma
  - Cellular epithelioid haemangioma
  - Atypical epithelioid haemangioma
- Lymphangioma NOS
  - Lymphangiomatosis
- Cystic lymphangioma
- Acquired tufted haemangioma

Intermediate (locally aggressive)
- Kaposiform haemangioendothelioma

Intermediate (rarely metastasizing)
- Retiform haemangioendothelioma
- Papillary intralymphatic angioendothelioma
- Composite haemangioendothelioma
  - Neuroendocrine composite haemangioendothelioma
- Kaposi sarcoma
  - Classic indolent Kaposi sarcoma
  - Endemic African Kaposi sarcoma
  - AIDS-associated Kaposi sarcoma
  - Latrogenic Kaposi sarcoma
- Pseudomyogenic (epithelioid sarcoma-like)
  - Haemangioendothelioma

Malignant
- Epithelioid haemangioendothelioma NOS
  - Epithelioid haemangioendothelioma with *WWTR1-CAMTA1* fusion
- Epithelioid haemangioendothelioma with *YAP1-TFE3* fusion
- Angiosarcoma

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Continued

Table 1
Histopathologic Type
Tumors included in the soft tissue category are listed below as per the 2020 World Health Organization classification of tumors:

Pericytic (perivascular) tumors
Benign and intermediate
- Glomus tumor NOS
  - Glomangioma
  - Glomangiomyoma
  - Glomangiomatosis
  - Glomus tumor of uncertain malignant potential
- Myopericytoma
  - Myofibromatosis
  - Myofibroma

Benign and intermediate
  - Infantile myofibromatosis
- Angioleiomyoma

Malignant
- Glomus tumor, malignant

Smooth muscle tumors
Benign and intermediate
- Leiomyoma NOS
- Smooth muscle tumor of uncertain malignant potential

Malignant
- Leiomyosarcoma NOS

Skeletal muscle tumors
Benign
- Rhabdomyoma NOS
  - Fetal rhabdomyoma
  - Adult rhabdomyoma
  - Genital rhabdomyoma

Malignant
- Embryonal rhabdomyosarcoma NOS
  - Embryonal rhabdomyosarcoma, pleomorphic
  - Alveolar rhabdomyosarcoma
  - Pleomorphic rhabdomyosarcoma NOS
  - Spindle cell rhabdomyosarcoma
  - Congenital spindle cell rhabdomyosarcoma with *VGLL2/NCOA2/CITED2* rearrangements
  - *MYOD1*-mutant spindle cell/sclerosing rhabdomyosarcoma
  - Intraosseous spindle cell rhabdomyosarcoma with *TFCP2/NCOA2* Intraosseous spindle cell rhabdomyosarcoma with *TFCP2/NCOA2* rearrangements
- Ectomesenchymoma

Chondro-osseous tumors
Benign
- Chondroma NOS
  - Chondroblastoma-like soft tissue chondroma

Malignant
- Osteosarcoma, extraskeletal

Peripheral nerve sheath tumors
Benign
- Schwannoma NOS
  - Ancient schwannoma
  - Cellular schwannoma
  - Plexiform schwannoma
  - Epithelioid schwannoma
  - Microcystic/reticular schwannoma
- Neurofibroma NOS
  - Ancient neurofibroma
  - Cellular neurofibroma
  - Atypical neurofibroma
  - Plexiform neurofibroma
- Perineurioma NOS
  - Reticular perineurioma
  - Sclerosing perineurioma
- Granular cell tumor NOS
- Nerve sheath myxoma
- Solitary circumscribed neuroma
  - Plexiform solitary circumscribed neuroma
  - Reticular perineurioma
  - Sclerosing perineurioma

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Continued

Table 1
Histopathologic Type
Tumors included in the soft tissue category are listed below as per the 2020 World Health Organization classification of tumors:

Peripheral nerve sheath tumors (continued)
- Granular cell tumor NOS
- Nerve sheath myxoma
- Solitary circumscribed neuroma
  - Plexiform solitary circumscribed neuroma
- Meningioma NOS
- Benign triton tumor/neuromuscular choristoma
- Hybrid nerve sheath tumor
  - Perineurioma/schwannoma
  - Schwannoma/neurofibroma
  - Perineuroma/neurofibroma

Malignant
- Malignant peripheral nerve sheath tumor NOS
  - Malignant peripheral nerve sheath tumor, epithelioid
- Melanotic malignant peripheral malignant triton tumor
- Malignant granular cell tumor
- Perineurioma, malignant

Tumors of Uncertain Differentiation
Benign
- Myxoma NOS
  - Cellular myxoma
- Aggressive angiomyxoma

Tumors of Uncertain Differentiation
- Aggressive angiomyxoma
- Pleomorphic hyalinizing angiectatic tumor
- Phosphaturic mesenchymal tumor NOS
- Perivascular epithelioid tumor, benign
- Angiomyolipoma

Tumors of Uncertain Differentiation (continued)
Intermediate (locally aggressive)
- Haemosiderotic fibrolipomatous tumor
- Angiomyolipoma, epithelioid *intermediate (rarely metastasizing)*
- Atypical fibroxanthoma
- Angiomatoid fibrous histiocytoma
- Ossifying fibromyxoid tumor, NOS
- Mixed tumor NOS
- Mixed tumor, malignant, NOS
- Myoepithelioma NOS

Malignant
- Phosphaturic mesenchymal tumor, malignant
- *NTRK*-rearranged spindle cell neoplasm (emerging)
- Synovial sarcoma NOS
  - Synovial sarcoma, spindle cell
  - Synovial sarcoma, biphasic
  - Synovial sarcoma, poorly differentiated
- Epithelioid sarcoma
  - Proximal or large cell epithelioid sarcoma
- Classic epithelioid sarcoma alveolar soft part sarcoma
- Clear cell sarcoma NOS
- Extraskeletal myxoid chondrosarcoma
- Desmoplastic small round cell tumor
- Rhabdoid tumor NOS
- Perivascular epithelioid tumor, malignant
- Intimal sarcoma
- Ossifying fibromyxoid tumor, malignant
- Myoepithelial carcinoma
- Undifferentiated sarcoma
- Spindle cell sarcoma, undifferentiated
- Pleomorphic sarcoma, undifferentiated
- Round cell sarcoma, undifferentiated

Used with permission, Fletcher CDM, Bridge JA, Hogendoorn P, Mertens F, eds. World Health Organization Classification of Tumours of Soft Tissue and Bone. Fifth Edition. Lyon: IARC;2020.

Continued

American Joint Committee on Cancer (AJCC) Staging System for Soft Tissue Sarcoma of the Head and Neck (8th ed, 2017)

Table 2. Definitions for T, N, M

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T1	Tumor ≤2 cm
T2	Tumor >2 cm to ≤4 cm
T3	Tumor >4 cm
T4	Tumor with invasion of adjoining structures
T4a	Tumor with orbital invasion, skull base/dural invasion, invasion of central compartment viscera, involvement of facial skeleton, or invasion of pterygoid muscles
T4b	Tumor with brain parenchymal invasion, carotid artery encasement, prevertebral muscle invasion, or central nervous system involvement via perineural spread
N	**Regional Lymph Nodes**
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastasis
M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis
G	**Definition of Grade** **FNCLCC Histologic Grade - see Histologic Grade (G)**
GX	Grade cannot be assessed
G1	Total differentiation, mitotic count and necrosis score of 2 or 3
G2	Total differentiation, mitotic count and necrosis score of 4 or 5
G3	Total differentiation, mitotic count and necrosis score of 6, 7, or 8

Anatomic Stage/Prognostic Groups
This is a new classification that needs data collection before defining a stage grouping for head and neck sarcomas.

Histologic Grade (G)
The FNCLCC grade is determined by three parameters: differentiation, mitotic activity, and extent of necrosis. Each parameter is scored as follows: differentiation (1-3), mitotic activity (1-3), and necrosis (0-2). The scores are added to determine the grade.

Tumor Differentiation

1 Sarcomas closely resembling normal adult mesenchymal tissue (e.g., low-grade leiomyosarcoma)

2 Sarcomas for which histologic typing is certain (e.g., myxoid/round cell liposarcoma)

3 Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, soft tissue osteosarcoma, Ewing sarcoma/primitive neuroectodermal tumor (PNET) of soft tissue

Mitotic Count

In the most mitotically active area of the sarcoma, 10 successive high-power fields (HPF; one HPF at 400× magnification= 0.1734 mm^2) are assessed using a 40× objective.

1 0-9 mitoses per 10 HPF

2 10-19 mitoses per 10 HPF

3 ≥20 mitoses per 10 HPF

Tumor Necrosis

Evaluated on gross examination and validated with histologic sections.

0 No necrosis

1 <50% tumor necrosis

2 ≥50% tumor necrosis

Histopathologic Type
Please see the WHO Classification of Tumors (ST-1)

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Continued

American Joint Committee on Cancer (AJCC) Staging System for Soft Tissue Sarcoma of the Trunk and Extremities (8th ed, 2017)

Table 3. **Definitions for T, N, M**

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence for primary tumor
T1	Tumor 5 cm or less in greatest dimension
T2	Tumor more than 5 cm and less than or equal to 10 cm in greatest dimension
T3	Tumor more than 10 cm and less than or equal to 15 cm in greatest dimension
T4	Tumor more than 15 cm in greatest dimension
N	**Regional Lymph Nodes**
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastasis
M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis
G	**Definition of Grade** **FNCLCC Histologic Grade - See Histologic Grade (G)**
GX	Grade cannot be assessed
G1	Total differentiation, mitotic count and necrosis score of 2 or 3
G2	Total differentiation, mitotic count and necrosis score of 4 or 5
G3	Total differentiation, mitotic count and necrosis score of 6, 7, or 8

Table 4. **AJCC Anatomic Stage/Prognostic Groups**

	T	N	M	G
Stage IA	T1	N0	M0	G1, GX
Stage IB	T2	N0	M0	G1, GX
	T3	N0	M0	G1, GX
	T4	N0	M0	G1, GX
Stage II	T1	N0	M0	G2, G3
Stage IIIA	T2	N0	M0	G2, G3
Stage IIIB	T3	N0	M0	G2, G3
	T4	N0	M0	G2, G3
Stage IV	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

Histologic Grade (G)

The FNCLCC grade is determined by three parameters: differentiation, mitotic activity, and extent of necrosis. Each parameter is scored as follows: differentiation (1-3), mitotic activity (1-3), and necrosis (0-2). The scores are added to determine the grade.

Tumor Differentiation

1 Sarcomas closely resembling normal adult mesenchymal tissue (e.g., low-grade leiomyosarcoma)

2 Sarcomas for which histologic typing is certain (e.g., myxoid/round cell liposarcoma)

3 Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, soft tissue osteosarcoma, Ewing sarcoma/primitive neuroectodermal tumor (PNET) of soft tissue

Mitotic Count

In the most mitotically active area of the sarcoma, 10 successive high-power fields (HPF; one HPF at 400× magnification= 0.1734 mm^2) are assessed using a 40× objective.

1 0-9 mitoses per 10 HPF

2 10-19 mitoses per 10 HPF

3 ≥20 mitoses per 10 HPF

Tumor Necrosis

Evaluated on gross examination and validated with histologic sections.

0 No necrosis

1 <50% tumor necrosis

2 ≥50% tumor necrosis

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Continued

American Joint Committee on Cancer (AJCC) Staging System for Soft Tissue Sarcoma of the Abdomen and Thoracic Visceral Organs (8th ed, 2017)

Table 5. **Definitions for T, N, M**

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T1	Organ confined
T2	Tumor extension into tissue beyond organ
T2a	Invades serosa or visceral peritoneum
T2b	Extension beyond serosa (mesentery)
T3	Invades another organ
T4	Multifocal involvement
T4a	Multifocal (2 sites)
T4b	Multifocal (3-5 sites)
T4c	Multifocal (>5 sites)
N	**Regional Lymph Nodes**
N0	No regional lymph node involvement or unknown lymph node status
N1	Lymph node involvement present
M	**Distant Metastasis**
M0	No metastasis
M1	Metastases present
G	**Definition of Grade** **FNCLCC Histologic Grade - See Histologic Grade (G)**
GX	Grade cannot be assessed
G1	Total differentiation, mitotic count and necrosis score of 2 or 3
G2	Total differentiation, mitotic count and necrosis score of 4 or 5
G3	Total differentiation, mitotic count and necrosis score of 6, 7, or 8

Anatomic Stage/Prognostic Groups

There is no recommended prognostic stage grouping at this time.

Histologic Grade (G)

The FNCLCC grade is determined by three parameters: differentiation, mitotic activity, and extent of necrosis. Each parameter is scored as follows: differentiation (1-3), mitotic activity (1-3), and necrosis (0-2). The scores are added to determine the grade.

Tumor Differentiation

1	Sarcomas closely resembling normal adult mesenchymal tissue (e.g., low-grade leiomyosarcoma)
2	Sarcomas for which histologic typing is certain (e.g., myxoid/round cell liposarcoma)
3	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, soft tissue osteosarcoma, Ewing sarcoma/primitive neuroectodermal tumor (PNET) of soft tissue

Mitotic Count

In the most mitotically active area of the sarcoma, 10 successive high-power fields (HPF; one HPF at 400× magnification= 0.1734 mm^2) are assessed using a 40× objective.

1	0-9 mitoses per 10 HPF
2	10-19 mitoses per 10 HPF
3	≥20 mitoses per 10 HPF

Tumor Necrosis

Evaluated on gross examination and validated with histologic sections.

0	No necrosis
1	<50% tumor necrosis
2	≥50% tumor necrosis

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Continued

American Joint Committee on Cancer (AJCC) Staging System for Soft Tissue Sarcoma of the Retroperitoneum (8th ed, 2017)

Table 8. **Definitions for T, N, M**

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 5 cm or less in greatest dimension
T2	Tumor more than 5 cm and less than or equal to 10 cm in greatest dimension
T3	Tumor more than 10 cm and less than or equal to 15 cm in greatest dimension
T4	Tumor more than 15 cm in greatest dimension
N	**Regional Lymph Nodes**
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastases
M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastases

G	**Definition of Grade** **FNCLCC Histologic Grade - See Histologic Grade (G)**
GX	Grade cannot be assessed
G1	Total differentiation, mitotic count and necrosis score of 2 or 3
G2	Total differentiation, mitotic count and necrosis score of 4 or 5
G3	Total differentiation, mitotic count and necrosis score of 6, 7, or 8

Table 9. **AJCC Anatomic Stage/Prognostic Groups**

	T	N	M	G
Stage IA	T1	N0	M0	G1, GX
Stage IB	T2	N0	M0	G1, GX
	T3	N0	M0	G1, GX
	T4	N0	M0	G1, GX
Stage II	T1	N0	M0	G2, G3
Stage IIIA	T2	N0	M0	G2, G3
Stage IIIB	T3	N0	M0	G2, G3
	T4	N0	M0	G2, G3
	Any T	N1	M0	Any G
Stage IV	Any T	Any N	M1	Any G

Histologic Grade (G)

The FNCLCC grade is determined by three parameters: differentiation, mitotic activity, and extent of necrosis. Each parameter is scored as follows: differentiation (1-3), mitotic activity (1-3), and necrosis (0-2). The scores are added to determine the grade.

Tumor Differentiation

1	Sarcomas closely resembling normal adult mesenchymal tissue (e.g., low-grade leiomyosarcoma)
2	Sarcomas for which histologic typing is certain (e.g., myxoid/round cell liposarcoma)
3	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, soft tissue osteosarcoma, Ewing sarcoma/primitive neuroectodermal tumor (PNET) of soft tissue

Mitotic Count

In the most mitotically active area of the sarcoma, 10 successive high-power fields (HPF; one HPF at 400× magnification= 0.1734 mm^2) are assessed using a 40× objective.

1	0-9 mitoses per 10 HPF
2	10-19 mitoses per 10 HPF
3	≥20 mitoses per 10 HPF

Tumor Necrosis

Evaluated on gross examination and validated with histologic sections.

0	No necrosis
1	<50% tumor necrosis
2	≥50% tumor necrosis

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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 indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Discussion

This discussion corresponds to the NCCN Guidelines for Soft Tissue Sarcoma. Sections of this discussion were updated on May 16, 2022 to correspond with the latest algorithm. The remainder of the discussion was last updated on March 27, 2018.

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Overview

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

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

In 2022, an estimated 13,190 people will be diagnosed with soft tissue sarcoma (STS) in the United States, with approximately 5130 deaths.[1] The true incidence of STS is underestimated, especially because a large proportion of patients with gastrointestinal stromal tumors (GISTs) may not have been included in tumor registry databases before 2001. Prior radiation therapy (RT) to the affected area is a risk factor for the development of STS.[2-4] Other risk factors that are associated with the development of STS include various chemicals (eg, herbicides, such as agent orange) as well as genetic syndromes (eg, Li-Fraumeni syndrome, neurofibromatosis).[5] More than 50 different histologic subtypes of STS have been identified. STS most commonly metastasizes to the lungs; tumors arising in the abdominal cavity more commonly metastasize to the liver and peritoneum.

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

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

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%), or head and neck (9%) are the most common primary sites.[6] Desmoid tumors, or aggressive fibromatosis (AF), are a unique soft tissue tumor subtype that is characterized by local infiltration rather than distant metastasis. RMS is the most common STS of children and adolescents, and is less common in adults.

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

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Soft Tissue Sarcoma, an electronic search of the PubMed database was performed to obtain key literature in STS, using the following search terms: soft tissue sarcoma OR desmoid OR aggressive fibromatosis OR rhabdomyosarcoma OR *sarcoma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Study; Clinical Trial; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 50 citations and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Genetic Cancer Syndromes with Predisposition to Soft Tissue Sarcoma

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.[3,9-13]

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.[9,14-16] The incidence of STS ranges from 12% to 21% in individuals with *TP53* germline mutations.[17-19] 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 and colleagues reported RMS, fibrosarcomas, and UPS as the most frequent histologic subtypes identified in 55%,13%, and 10% of patients, respectively.[17] The mean age at diagnosis for RMS was younger than 6 years, and the mean age at diagnosis for UPS 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.[10,12] FAP is characterized by adenomatous colorectal polyps that progress to colorectal cancer at 35 to 40 years of age. Gardner's 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).[20] 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 the general population.[21-24] In an International Dutch Cohort study involving 2260 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.[24] The median age at diagnosis was 31 years, with the majority of 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.[25] 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.[26] In an analysis of 11 patients from 9 families presenting with GIST and paragangliomas associated with Carney-Stratakis syndrome, Pasini and colleagues identified germline mutations in *SDHB*, *SDHC,* or *SDHD* genes in 8 patients (from 7 untreated families) with GISTs.[26] 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.[27,28]

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.[11,29] LMS is the most frequent STS subtype (with 78% of LMS diagnosed 30 or more years after the diagnosis of retinoblastoma). Although patients with RT for retinoblastoma are at significantly increased risk of developing STS, the risks of developing STS are also increased in non-irradiated patients as well, indicating a genetic predisposition to STS that is independent of RT in patients with hereditary retinoblastoma.[11]

Neurofibromatoses are hereditary conditions caused by mutations in the neurofibromin 1 gene (NF1) or neurofibromin 2 gene (NF2).[30] 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.[31] For information on the treatment of MPNSTs, see the NCCN Guidelines for Central Nervous System Cancers at www.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 genetics assessment as outlined in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.
- *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's syndrome is recommended for patients diagnosed with desmoid tumors (aggressive fibromatoses).

Pathology of Soft Tissue Sarcomas

Biopsy

A pretreatment biopsy is highly preferred for the diagnosis and grading of STS. Biopsy should be performed by an experienced surgeon or radiologist, placed along the future resection axis with minimal dissection and careful attention to hemostasis. The goal of biopsy is to 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. It may be accomplished by 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 following 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 and is thus discouraged.[32] FNA may be acceptable in select institutions with clinical and pathologic expertise. Endoscopic or needle biopsy may be indicated for deep thoracic, abdominal, or pelvic 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, since the 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 STS tumor); 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; tumor, node, and metastasis (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 Soft Tissue Sarcomas

Molecular genetic testing has emerged as a particularly useful ancillary technique since many subtypes of STS are associated with characteristic genetic aberrations including single base-pair substitutions, deletions, amplifications, and translocations. STS can be divided into two major genetic groups: 1) sarcomas with specific genetic alterations (eg, chromosomal translocations or point mutations) and usually simple karyotypes; and 2) sarcomas with non-specific genetic alterations and complex unbalanced karyotypes.[33]

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 LPS, *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* in the guidelines for a list of recurrent genetic aberrations associated with other subtypes.

Conventional cytogenetic analysis, fluorescence in situ hybridization (FISH), and polymerase chain reaction (PCR) are the most common techniques used in the molecular diagnosis of STS.[34] In a prospective study, Hill and colleagues 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 LPS that have variation in fusion gene partners.[35] Molecular genetic testing was analyzed in a prospective, multicenter study (GENSARC) that enrolled 395

patients with histologic diagnoses of various sarcoma subtypes.[36] Molecular classification of samples from these patients was performed using FISH, comparative genomic hybridization, and PCR, resulting in modified diagnoses in 53 cases. The modified molecular diagnosis reportedly shifted prognosis and primary management in 45 of these cases.

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 to *PAX3-FOXO1*.[37] In patients with synovial sarcoma, the prognostic impact of *SS18-SSX1* or *SS18-SSX2* is less clear with two large studies showing conflicting results.[38,39] In myxoid LPS, the variability of fusion gene transcript has no effect on clinical outcome.[40]

While molecular genetic testing appears promising, it involves highly complex techniques and the methods are not absolutely sensitive or they 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.[34]

Staging

The revised AJCC Cancer Staging Manual, Eighth Edition (2017), effective January 2018, is based on TNM and tumor grade. AJCC follows the grading system of the French Federation of Cancer Centers Sarcoma Group (FNCLCC), a 3-tiered system based on tumor cell differentiation, mitotic activity, and extent of necrosis.[41] The panel recommends determination of histologic grade using the FNCLCC or AJCC/National Cancer Institute (NCI) system or appropriate diagnosis-specific grading system if applicable.

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 prior to 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 following 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 re-resection or RT is indicated).

Both the surgeon and the pathologist should document surgical margins while evaluating a resected specimen. Complete tumor resection is a primary prognostic factor for local recurrence (LR). If surgical margins are positive on final pathology, re-resection to obtain negative margins should be strongly considered if it will not have a significant impact on functionality.[42,43] In an analysis of 666 consecutive patients with localized STS treated with an apparent macroscopic total tumor resection, residual tumor was found in 46% of patients, including macroscopic tumor in 28%. A total of 295 patients underwent reresection of their tumor bed. Local control rates at 5, 10, and 15 years were 85%, 85%, and 82%, respectively, for patients who underwent reresection, versus 78%, 73%, and 73%, respectively (P = .03) for patients who did not undergo reresection. Recent studies of tumor margin classification systems provide insight into LR risk assessment and may help to guide surgical planning and decisions regarding re-resection.[44,45]

The implications of lymph node evaluation were recently examined based on data from 2993 patients with resected STS in the NCDB (5.9% nodal metastasis rate).[46] Omission of nodal evaluation was associated with risk of death, and pathologic identification of nodal disease was related to lower median OS in histologic subtypes such as epithelioid and clear cell sarcomas.

Radiation Therapy

RT can be administered either 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.[47] LDR and HDR brachytherapy are associated with similar rates of local control.[48] 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.[48] 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.[49] Additionally, image-guided techniques may allow for reduced target volumes, further minimizing toxicity.[50,51] IORT is the delivery of radiation during surgery and it can be performed using different techniques such as electron beam RT or brachytherapy.[52]

A recent systematic review and meta-analysis examined the effects of external beam RT (EBRT) (vs. no EBRT) on LR and OS, also comparing preoperative to postoperative approaches for STS.[53] Data analysis from 16 studies (n = 3958) indicated that EBRT reduced LR and improved OS for retroperitoneal STS, and reduced LR for STS of the extremity, head and neck, or trunk wall (OR, 0.49; 95% CI, 0.31–0.77; P = .002). Based on a subset of 11 studies, LR rates were lower with preoperative RT than for postoperative RT for retroperitoneal STS (OR, 0.03; P = .02) and other tumor locations (OR, 0.67; P =.01). 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.[54,55]

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.[56-58] Most institutions include the

entire operative bed within the RT field. The main disadvantage of preoperative RT, however, is its effect on wound healing.[59,60] Wound complications in patients with sarcoma are more frequently associated with pre- vs. postoperative RT.[53] 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.[61] Involvement of a plastic surgeon on 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 there was no evidence for differences in disease outcome associated with the use of either preoperative or postoperative RT, there was a slight increase in late treatment-related side effects with postoperative RT, mainly due to the higher doses used.[62] Positive surgical margins are associated with higher rates of LR.[63] Postoperative RT has been shown to improve local control in patients with positive surgical margins.[64] Of those with positive margins, RT doses >64 Gy, microscopically positive margins, superficial location, and extremity site are associated with improved local control.

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 LR in some patients with positive surgical margins (such as those with low-grade, well-differentiated LPS [WDLS] and a focally “planned” positive margin on an anatomically fixed critical structure).[65] Similarly, another retrospective matched cohort of patients with extremity STS found no added benefit of postoperative RT boost when evaluating LR, distant metastasis, and mortality.[66]

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 LR 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[67-71] or chemoradiation[72-81] 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 a randomized study that compared surgery alone vs. preoperative chemotherapy followed by surgery in 134 evaluable patients with high-risk tumors (tumors ≥8 cm of any grade, grade II/III tumors <8 cm, grade II/III locally recurrent tumors, or tumors with inadequate surgery) did not show a major survival benefit for patients receiving chemotherapy.[68] 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 one year.[69] 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.[70]

In a single-institution study involving 48 patients with high-grade extremity STS (8 cm or larger), 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.[74] 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.[74] The same protocol was later evaluated in the RTOG 9514 study of 66 patients with large (8 cm or larger), 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.[76,77] 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.[77] 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.[77,78]

Postoperative Therapy

Available evidence from meta-analyses[82-86] and randomized clinical trials[87-92] 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 randomized studies (1568 patients), which compared postoperative chemotherapy to follow-up and in some cases RT after surgery with a variety of sarcomas.[83] 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 = 1953).[85] 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; 5-year OS: 75% vs. 65%, *P* = .15).[86]

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, after a median follow-up of 59 months, median DFS (48 vs. 16 months) and median OS (75 months vs. 46 months) were significantly better in the treatment group; the absolute benefit for OS from chemotherapy was 13% at 2 years and increased to 19% at 4 years for patients receiving chemotherapy.[88] 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.[93]

In another phase III randomized study (EORTC-62931), 351 patients with macroscopically resected grade II-III tumors with no metastases were randomized to observation or postoperative chemotherapy with ifosfamide and doxorubicin with lenograstim.[90] 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 and colleagues.[87] 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 LR rates (17% vs. 31% for the control group; *P* = .004). However, there were no differences in distant metastases (32% and 36%, respectively, for CYVADIC and the control group; *P* = .42) and OS rates (63% and 56%, respectively, for CYVADIC and the control group; *P* = .64).

A recent pooled analysis of these two 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.[92] Postoperative doxorubicin-based chemotherapy was associated with improved RFS in male patients and those aged >40 years, although female patients and those aged <40 years who received adjuvant chemotherapy had marginally worse OS. However, RFS and OS were significantly improved in patients with R1 resection who received adjuvant chemotherapy compared with those who did not.

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.[91]

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.[94-106] Other chemotherapeutic agents such as gemcitabine, docetaxel, vinorelbine, pegylated liposomal doxorubicin, and temozolomide have also been evaluated in clinical trials. The recently published METASARC observational study, which explored “real-world” outcomes among 2225 patients with metastatic STS, found a positive association of OS with front-line combination chemotherapy, LMS histology, and locoregional treatment of metastases. However, with the exception of LMS, the benefits of systemic therapy beyond the second-line setting were very limited.[107]

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.[108-112] In a randomized phase II study, the combination of gemcitabine and docetaxel was associated with superior progression-free survival (PFS) (6.2 months and 3.0 months, respectively) and OS (17.9 months and 11.5 months, respectively) compared to gemcitabine alone in patients with metastatic STS.[109] 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.[110] Clinical benefit (complete response [CR], partial response [PR], or stable disease at 4 months or more) was seen in 25% of patients. The combination of gemcitabine and dacarbazine resulted in superior PFS (4.2 months vs. 2 months; *P* = .005), OS (16.8 months vs. 8.2 months; *P* = .014), and objective response rate (49% vs. 25%; *P* = .009) compared to dacarbazine alone in patients with previously treated advanced STS.[111]

However, gemcitabine combination therapy was not superior to single-agent doxorubicin in the randomized phase III GeDDiS trial. Among patients with previously untreated advanced or metastatic disease (n = 257), combination therapy with gemcitabine and docetaxel did not result in superior PFS compared with doxorubicin (23.7 weeks vs. 23.3 weeks, *P* = .06).[112]

Temozolomide,[113-115] pegylated liposomal doxorubicin,[116] and vinorelbine[117,118] have also shown activity as single agents in patients with advanced, metastatic, relapsed, or refractory disease. In a phase II study by the Spanish Group for Research on Sarcomas, temozolomide resulted in an overall response rate of 15.5% with a median OS of 8 months in patients with advanced pretreated STS.[115] The PFS rates at 3 months 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 to doxorubicin; response rates were 9% and 10% for doxorubicin and pegylated liposomal doxorubicin, respectively, in patients with advanced or metastatic STS.[116] In a retrospective study of pretreated patients with metastatic STS, vinorelbine induced overall response in 6% of patients and 26% had stable disease.[117]

Trabectedin is a novel DNA-binding agent that has shown objective responses in phase II and III studies of patients with advanced STS.[119-127] Recent phase III data from a randomized, multicenter trial revealed a 2.7-month PFS benefit versus dacarbazine in metastatic LPS or LMS that progressed after anthracycline-based therapy; the study is ongoing to determine OS.[125] Another recent study supported the efficacy of trabectedin in translocation-related sarcoma.[127] 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.[128] Preliminary results from the randomized phase III T-SAR trial revealed a PFS benefit for trabectedin over best supportive care in both “L-type” (LPS and LMS) and non–L-type pretreated advanced sarcoma.[129] However, trabectedin plus doxorubicin failed to demonstrate superiority over doxorubicin alone in a randomized phase II study of patients with advanced STS.[130] Trabectedin is included for palliative therapy as a category 1 recommendation for LPS and LMS (L-type) and as category 2A for non–L-type sarcomas.

Eribulin is a novel microtubule-inhibiting agent that has been evaluated as a single-agent therapy for STS, including LMS, adipocytic sarcoma, synovial sarcoma, and other tumor types.[131] Recent data from a phase III trial compared the survival benefit of eribulin and dacarbazine in 452 patients with advanced LMS or LPS, revealing a median OS of 13.5 months and 11.5 months, respectively (HR, 0.77; 95% CI, 0.62–0.95; *P* = .017).[132] Eribulin is included for palliative therapy as a category 1 recommendation for LPS.

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 (TKI), has demonstrated single-agent activity in patients with advanced STS subtypes except LPS.[133-136] In a phase III study (EORTC 62072), 369 patients with metastatic non-lipogenic STS who had failed at least one anthracycline-based chemotherapy regimen were randomized to either pazopanib or placebo.[135] Pazopanib significantly prolonged median PFS (4.6 months vs.1.6 months for placebo; *P* < .0001) and there was also a trend toward improved OS (12.5 months and 11 months, respectively; *P* = .25), although it was not statistically significant. Health-related quality-of-life measures did not improve or decline with the PFS benefit.[137] Pooled data from individuals who received pazopanib in phase II and III trials (n =

344) revealed a subset of long-term responders/survivors presenting at baseline with good performance status, low-/intermediate-grade primary tumor, and normal hemoglobin level.[138] The guidelines have included pazopanib as an option for palliative therapy for patients with progressive, unresectable, or metastatic non-lipogenic STS.

Imatinib[139] and sunitinib[140,141] have also shown efficacy in patients with advanced and/or metastatic STS other than GIST. Sorafenib appeared to be active in a small cohort of patients with solitary fibrous tumor.[142] Crizotinib, an anaplastic lymphoma kinase (ALK) inhibitor, was active in inflammatory myofibroblastic tumor (IMT) with ALK translocation.[143] The updated guidelines also include ceritinib, a next-generation ALK inhibitor that has been successful in treating ALK-rearranged non-small cell lung cancer.[144]

mTOR inhibitors such as sirolimus, temsirolimus, and everolimus have also shown promising results in patients with metastatic perivascular epithelioid cell tumors (PEComas) and in patients with recurrent lymphangioleiomyomatosis or angiomyolipomas.[145-151] Additionally, sorafenib may be active in select subtypes of advanced and/or metastatic STS other than GIST (eg, LMS, desmoid tumors).[152,153]

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.[154,155]

Palbociclib, an inhibitor of cyclin-dependent kinases (CDKs) 4 and 6, induced objective tumor response and a favorable PFS of 56% to 66% in patients with CDK-4–amplified, well-differentiated or dedifferentiated liposarcoma (WD/DDLS).[156,157]

The randomized, phase II REGOSARC trial examined regorafenib, an agent approved for treating GIST, in cohorts of patients with advanced LPS, LMS, synovial sarcoma, and other non-GIST STS subtypes (REGOSARC, n = 182).[158,159] Compared to placebo, regorafenib significantly extended PFS in all but the LPS cohort. In patients with nonadipocytic STS, overall PFS for regorafenib and placebo-treated patients was 4 months vs. 1 month (HR 0.36, $P < .0001$).

Soft Tissue Sarcomas 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 x-ray) 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.[160-162] 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.[163] 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.[164-169] The maximum standardized uptake value (SUVmax) of F18-deoxyglucose has been shown to correlate with tumor grade and prognostication.[170,171] In a retrospective study, tumor SUVmax determined by PET was an independent predictor of survival and disease progression.[164] Schuetze and colleagues reported that the pretreatment SUVmax and change in SUVmax after preoperative chemotherapy independently identified patients with a high risk of recurrence.[165] Patients with a change in the SUVmax of 40% or more in response to chemotherapy were at a significantly lower risk of recurrence and death after complete resection and postoperative RT; the projected 5-year RFS rate for this group of patients was 80% compared to 40% for those with a less than 40% reduction in SUVmax.[165] PET was useful in the early assessment of response to preoperative chemotherapy and was also significantly more accurate than the RECIST criteria in the assessment of histopathologic response to preoperative chemotherapy.[167,168] In a prospective study of 50 patients with resectable, high-grade STS, a 35% reduction in the SUV after first cycle of chemotherapy was a sensitive predictor of histopathologic response.[168] The value of combined PET/CT in predicting 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:

- Stage I
- Stage II-III
- Unresectable disease
- Stage IV (Synchronous Metastatic Disease)
- Recurrent disease

General Principles of Treatment

Surgery

Positive surgical margin is a strong predictor of LR for patients with extremity STS.[172-177] Microscopically positive margins are associated with a higher rate of LR and a lower rate of DFS in patients with extremity sarcomas.[172,173,175] In a large cohort study (1668 patients) that examined the clinical significance of the main predictors of LR in patients with STS of 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; $P < .001$).[176] 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 compared to 12% if the margins were negative).[177] 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.[43]

Amputation was once considered the standard treatment to achieve local control in patients with extremity sarcomas.[178] 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 OS and DFS as compared to amputation.[179] 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.[180] The LR rate was 13% when the resection margin was 1 cm or less as compared to 0% when the resection margin was 1 cm or more. In a retrospective study of 115 patients with an STS of hand or foot, radical amputation as an initial treatment did not decrease the probability of regional metastasis and also did not improve the disease-specific survival.[181]

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 where 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 it should be considered with patient preference, or if the gross total resection of the tumor is expected to render the limb nonfunctional.[182-185] Prior to 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[63,186,187] and retrospective analyses[59,188-191] support the use of preoperative or postoperative EBRT in appropriately selected patients. Brachytherapy (alone or in combination with EBRT)[188,192,193] and IMRT[194,195] have also been evaluated as an adjunct to surgery.

Preoperative vs. Postoperative EBRT

Various studies have examined the benefits and risks for preoperative and postoperative RT approached for 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.[191] However, that data showed that preoperative RT was predictive of achieving R0 resection.[191] In a phase III randomized study conducted by the Canadian Sarcoma Group, local control and PFS rates were similar in patients receiving either preoperative or postoperative RT in patients with localized primary or recurrent disease.[187,196] 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 Gy vs. 50 Gy for preoperative RT) and the larger treatment volume.[54,187]

The efficacy of postoperative EBRT following limb-sparing surgery was demonstrated in a prospective randomized study (91 patients with high-grade lesions and 51 patients with low-grade lesions).[186,197] 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.[186] 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).[197]

The French Sarcoma Group recently reported on a cohort of 283 patients with resectable atypical lipomatous tumor (ALT)/WDLS of the extremity or superficial trunk from the Conticabase database. In these patients, postoperative RT significantly improved 5-year local RFS (98.3% vs. 80.3%, with and without adjuvant RT, respectively; *P* < .001).[198] Along with RT, tumor site and resection margin status were predictors of time to LR, but no difference in OS was observed.

In a report from the Memorial Sloan Kettering Cancer Center (MSKCC) 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.[199] 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.[192] 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 to 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 two groups. In a retrospective analysis of 202 adult patients with primary high-grade STS of the extremity, brachytherapy following limb-sparing surgery resulted in lower rates of wound complications, favorable 5-year local control, and distant RFS and OS rates (84%, 63%, and 70%, respectively).[193]

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.[194] 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 and colleagues reported that preoperative IMRT resulted in lower wound complication rate in patients with high-grade lesions (30.5% vs. 43% reported in earlier study using conventional EBRT).[200] 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 brachytherapy (5-year local control rates were 92% and 81%, respectively; *P* = .04) despite higher rates of adverse features for IMRT.[195]

IORT

Recent reports from a retrospective study suggest that IORT provides excellent local control to STS of the extremity.[201,202] Call and colleagues recently reported long-term outcome of 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.[202] The 10-year local control rates were 89% and 86%, respectively, following 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.[203,204] 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 extremity 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.[51] 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.[65,205] 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 operation, with doses of 16 to 26 Gy for LDR brachytherapy and 14 to 24 Gy for 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.[201]

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), IORT (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 following 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, low grade) and IB (T2-4, N0, M0, low grade) tumors and is considered definitive if margins are greater than 1 cm or the fascial plane is intact.[206,207] If the surgical margins are 1.0 cm or less and without an intact fascial plane, re-resection may be necessary.[199] 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.[173,175,192] 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.[186] 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.[208,209] In one report that reviewed 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.[210] 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 the tumor location and patient's age.[211]

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 chemoradiation 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.[77,78] An earlier randomized study showed that preoperative chemotherapy was not associated with a major survival benefit for patients with high-grade tumors.[68] Histotype-specific neoadjuvant chemotherapy was examined in a recent international RCT of patients with high-risk STS (n = 287; ISG-STS 1001).[71] 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 (HR, 2.00; 95% CI, 1.22–3.26; *P* = .006). Trial enrollment was closed due to futility.

The results of a recent phase III randomized study (EORTC 62961) showed that regional hyperthermia (RHT) increases the benefit of preoperative chemotherapy in patients with localized high-risk STS.[212] In this study, 341 patients were randomized to receive either preoperative chemotherapy with etoposide, ifosfamide, and doxorubicin (EIA) alone, or

combined with RHT (EIA plus RHT). After a median follow-up of 34 months, among 149 patients with STS of the extremity, the 2-year DFS and local PFS rates were 70% and 92%, respectively, for patients treated with EIA plus RHT. The corresponding survival rates were 57% and 80% for those treated with EIA alone. However, these results need to be confirmed in large cohort studies and the use of RHT with preoperative chemotherapy is not recommended in the guidelines.

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.[87-91] Preoperative or postoperative EBRT has been shown to improve local control in patients with high-grade lesions.[53,186,188]

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, there are data supporting that surgery alone is an adequate treatment option in selected patients with high-grade lesions. Long-term results of a prospective study demonstrated that selected patients with high-grade T1 lesions can be treated by surgery alone (R0 resection) with acceptable local control and excellent long-term survival.[213] 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 less than 1 cm compared with 100% for those with resection margins of 1 cm or more (P = .04).[180] Al-Refaie and colleagues 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.[214]

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).[186,187,196] 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 2606 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.[215] Since there are only limited and conflicting data regarding the potential benefits of postoperative chemotherapy for stage II or III patients, postoperative chemotherapy is included as a category 2B recommendation.[87-91] 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 to 16.3 months in patients who underwent radical lymphadenectomy.[216] 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 below 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 following primary treatment can be treated with surgery followed by RT (if not previously irradiated) with or without postoperative chemotherapy. Since there are only limited and conflicting data 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 following primary treatment, a subsequent distinction is made between asymptomatic and symptomatic patients. Observation is an option for asymptomatic patients. For symptomatic patients, 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 months 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 months vs. 4.6 months, *P* = .003).[217] However, subset analyses (n = 310) indicated an OS benefit for doxorubicin/ifosfamide versus single-agent doxorubicin in patients with UPS.[218]

Definitive RT (70–80 Gy) can be considered for selected patients with unresectable tumors following 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.[219] The local control rate was 51% for tumors less than 5 cm and 9% for tumors greater than 10 cm. Patients who received 63 Gy or more had better 5-year local control, DFS, and OS rates (60%, 36%, and 52%, respectively) compared to patients who received less than 63 Gy (22%, 10%, and 14%, respectively). Local control for patients receiving more than 63 Gy was 72% for lesions 5 cm or less, 42% for lesions 5 to 10 cm, and 25% for lesions more than 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[220-223] or ILI with doxorubicin or melphalan and dactinomycin[224-228] may be effective in the treatment of patients with unresectable STS of extremity.[229] 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.[229] 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.[230,231] Conflicting data exist on the potential survival benefit of metastasectomy. In a retrospective study of 48 patients with synchronous metastases, there was no improvement in OS for patients treated with metastasectomy compared to those with unresectable disease.[230] In a more recent retrospective study involving 112 patients with metastatic

disease at presentation, resection of metastatic disease, less than 4 pulmonary metastases, and the presence of lymph node metastases vs. 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.[231] 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.[232] 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.[233]

Since there are no data to support the optimal management of patients presenting with metastatic disease, the guidelines are intentionally nonspecific about the treatment options for this group of patients. 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 that 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.[230,232,233] Several variables, including tumor resectability, number and location of metastases, and performance status influence the decision to use metastasectomy.[231] 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.[234-236]

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, sub-centimeter 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.[237-240] Because patient risk never returns to zero, long-term follow-up is indicated, including consideration of MRI or CT scan.[241] 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 the report from MD Anderson Cancer Center, routine use of chest CT adds little clinical benefit when risk of pulmonary metastases is low.[242] 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.[240] Thirty patients (32%) recurred after a median follow-up of 60 months (5 local, 26 distant). Surveillance imaging led to the detection of LR in 2 out of 5 cases and distant recurrence (lung) in 22 out 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 less than 0.5 cm in diameter.[243-245] 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%).[243] 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 and colleagues 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.[244] These results confirm that ultrasound can be useful for the detection of LR. However, as reported by Choi and colleagues, ultrasound may be more difficult to interpret than MRI during the early postoperative period.[243] 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.

Stage I tumors are routinely followed 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 x-ray. 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.[243,244] However, in situations where the area is easily followed by physical examination, imaging may not be required.[246]

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.[247-249]

For a patient with a LR, treatment decisions should be made using the same algorithm as for patients with a new primary lesion.[250] In patients with LR, some case series suggest that combined conservative surgery and re-irradiation provide superior local control compared to local

re-excision alone.[251] 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,[252] 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.[253]

Retroperitoneal/Intra-abdominal Soft Tissue Sarcomas

Evaluation and Workup

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

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

For additional information on the *Principles of Pathologic Assessment of Sarcoma Specimens*, please refer to SARC-B.

Radiation Therapy

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

Newer RT techniques such as intensity-modulated RT (IMRT) and protons may allow tumor target coverage and acceptable clinical outcomes within normal tissue dose constraints to adjacent organs at risk.[190,254-257] When external beam RT (EBRT) is used, sophisticated treatment planning with IMRT, image-guided RT (IGRT), and/or proton therapy can be used to improve therapeutic effect. However, the safety and efficacy of adjuvant RT techniques have yet to be evaluated in multicenter randomized controlled studies.

Neoadjuvant RT

If radiation is being considered for highly selected cases as part of the multimodality therapy for retroperitoneal/intra-abdominal STS, a neoadjuvant approach is favored as there is a defined tumor target, displacement of the adjacent bowel, the potential to reduce the risk of tumor seeding at the time of surgery, and may render tumors more amenable to resection.[53,258,259] Long-term results of two small non-randomized prospective studies showed favorable 5-year local recurrence-

free survival (RFS) (60%), disease-free survival (DFS) (46%), and overall survival (OS) rates (61%) following R0 or R1 resection after neoadjuvant RT in patients with intermediate or high-grade retroperitoneal STS.[260] Analysis of data from 11 studies of retroperitoneal STS in a recent systematic review and meta-analysis indicated lower rates of LR with neoadjuvant versus adjuvant RT (odds ratio [OR], 0.03; *P* = .02).[53]

However, results from another study suggested that neoadjuvant RT may not be as effective for treating retroperitoneal/intra-abdominal STS as previously thought. EORTC-62092 (STRASS) was an open-label, randomized, phase 3 study that evaluated the efficacy and safety of neoadjuvant RT in 266 patients with primary localized retroperitoneal sarcoma.[261] The primary endpoint of the trial was not met, as the neoadjuvant RT + surgery group had a median abdominal recurrence-free survival of 4.5 versus 5 years in the surgery only group (hazard ratio [HR], 1.01; log rank *P* = .95). The most common grade 3 or 4 adverse events were lymphopenia (77%), anemia (12%), and hypoalbuminemia (12%) in the neoadjuvant RT + surgery group, and anemia (8%) and hypoalbuminemia (4%) in the surgery only group.

Although the authors stated that neoadjuvant RT should not be considered standard-of-care for retroperitoneal STS based on the STRASS data, this conclusion has drawn controversy.[261-264] Some have criticized the study design and interpretation of the data, including the use of a composite primary endpoint that defined a variety of events as abdominal recurrence. Additionally, information relevant to understanding the patient population, such as R0 versus R1 resection status, was not reported. The rate of grade 3 or 4 adverse events in the neoadjuvant RT group was also observed to be higher than that reported in another trial with a similar patient population, and could potentially be related to the rate of protocol compliance for RT reported in the STRASS trial (65%). Despite these limitations, it should be noted that the STRASS trial remains one of the few large randomized studies that has evaluated neoadjuvant RT for retroperitoneal STS.

Results from an exploratory post-hoc analysis of the STRASS data suggested that neoadjuvant RT may be favorable for certain patients with retroperitoneal sarcomas, such as those with liposarcoma.[261] Additional data from the trial also suggested that neoadjuvant RT may be effective in reducing the risk of LR.[261,263] Based on these observations, further investigation is needed to confirm which patients with retroperitoneal/intra-abdominal STS would benefit the most from neoadjuvant RT.

Based on the available evidence, the current guidelines recommend that neoadjuvant RT can be considered for selected patients with retroperitoneal/intra-abdominal STS who are at high risk for LR. If neoadjuvant RT is considered an appropriate treatment option, the guidelines recommend 50 Gy external beam radiation therapy (EBRT) (in 1.8–2 Gy per fraction), followed by surgery with clips and consideration of intraoperative RT (IORT) boost for known or suspected positive margins at the time of surgery (SARC-E 3 of 4). Adjuvant EBRT boost is discouraged in this setting. An alternative approach to be considered in experienced centers only is 45–50 Gy in 25–28 fractions to the entire clinical target volume (CTV) with dose-painted simultaneous integrated boost to total dose of 57.5 Gy in 25 fractions.[265,266] Since this approach is used in many NCCN Member Institutions, the guidelines have included this dosing schedule and recommend that higher-risk retroperitoneal margins should be jointly defined by the surgeon and the radiation oncologist, with no boost to be given after surgery.

Adjuvant RT

The panel discourages providing an adjuvant EBRT boost for retroperitoneal/intra-abdominal STS (SARC-E 3 of 4). If RT is not given prior to surgical resection, consider follow-up with possible neoadjuvant EBRT at time of localized recurrence. If adjuvant RT is deemed necessary

in highly selected cases, a coordinated effort by the surgeon and the radiation oncologist to displace bowel from the tumor bed with omentum or other tissue displacers is recommended to reduce the risk of RT-related bowel toxicity.

Intraoperative RT

The use of IORT for retroperitoneal STS is provocative, but interpretation of the results is limited by the nature of the small and heterogenous studies.[267-274] In a prospective single institution study of patients with retroperitoneal STS treated with a protocol involving maximal tumor resection, high-dose-rate (HDR) IORT, and adjuvant EBRT, the overall 5-year local control rate for the whole group was 62%; local control rate was better for patients with primary tumors than for those with recurrent tumors (74% vs. 54%; *P* = .40).[268] The overall 5-year distant metastasis-free survival rate was 82% (100% for those with low-grade tumors vs. 70% for those with high-grade tumors; *P* = .05). The 5-year DFS and OS rates were 55% and 45%, respectively. IORT with or without EBRT has been effective in terms of local control and survival in patients with primary and recurrent retroperitoneal STS.[269-271,273] In a study that assessed the long-term outcome of patients with retroperitoneal STS treated by neoadjuvant RT, resection, and IORT with intraoperative electron beam RT (IOERT), OS (74% and 30%, respectively) and local control (83% and 61%, respectively) were better in patients undergoing gross total resection and IOERT compared to those who had only gross total resection.[269] An ongoing phase I/II study (NCT01566123) is examining neoadjuvant RT, followed by surgery with IORT in patients with high-risk retroperitoneal sarcoma. Preliminary results suggest promising local control and OS rates.[275]

Chemotherapy/Chemoradiation

Resectable Disease

Neoadjuvant Therapy

Neoadjuvant chemotherapy[67-71] or chemoradiation[72-81] has been evaluated in single and multicenter studies in patients with high-grade tumors; however, much of the available randomized data speaks to the management of extremity sarcomas.

Studies that have evaluated neoadjuvant chemotherapy followed by surgery have reported inconsistent findings. The results of a randomized study that compared surgery alone versus neoadjuvant chemotherapy followed by surgery in 134 evaluable patients with high-risk tumors (tumors ≥8 cm of any grade, grade II/III tumors <8 cm, grade II/III locally recurrent tumors, or tumors with inadequate surgery) did not show a major survival benefit for patients receiving chemotherapy.[68] 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 OS rate for both arms was 64% and 65%, respectively (*P* = .2204). A cohort analysis of 674 patients with stage III STS of extremity treated at a single institution revealed that clinical benefits associated with neoadjuvant or adjuvant doxorubicin-based chemotherapy were not sustained beyond 1 year.[69] In another retrospective study, the benefit of neoadjuvant chemotherapy was only seen in patients with high-grade extremity tumors larger than 10 cm but not in patients with tumors 5 to 10 cm.[70]

In a single-institution study involving 48 patients with high-grade extremity STS (≥8 cm), the outcome of patients treated with neoadjuvant chemoradiation with the MAID (mesna, doxorubicin, ifosfamide, and dacarbazine) regimen followed by surgery and adjuvant chemotherapy with the same regimen was superior to that of historical controls.[74] 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.[74] 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.[76,77] 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.[77] Long-term follow-up data of these studies confirmed that neoadjuvant chemoradiation followed by resection and adjuvant chemotherapy with a doxorubicin-based regimen improves local control and OS and DFS rates in patients with high-grade STS of extremity and body wall; however, neoadjuvant chemoradiation was associated with significant short-term toxicities.[77,78]

An ongoing prospective randomized trial, STRASS II (NCT04031677), is evaluating the role of neoadjuvant chemotherapy in high-risk retroperitoneal STS.[276] Those randomized to chemotherapy will receive doxorubicin and ifosfamide, unless they have a diagnosis of leiomyosarcoma (LMS), in which case they will receive doxorubicin and dacarbazine. The study will randomize 250 patients and assess the difference in DFS with or without neoadjuvant chemotherapy.

Adjuvant Therapy

Available evidence from meta-analyses[82-86] and randomized clinical trials[87-92] suggests that adjuvant chemotherapy improves RFS in patients with STS of extremities. However, data regarding OS advantage are conflicting. It is not clear if the conclusions from these trials are applicable to retroperitoneal/intra-abdominal sarcomas, and thus care should be individualized.

The Sarcoma Meta-Analysis Collaboration (SMAC) performed a meta-analysis of 14 randomized studies (1568 patients), which compared adjuvant chemotherapy to follow-up and in some cases RT after surgery with a variety of sarcomas.[83] The result of the meta-analysis showed that doxorubicin-based chemotherapy prolongs local and distant recurrence and overall RFS in adults with localized, resectable STS of the extremity and is associated with decreased recurrence rates. The OS advantage was not significant, although there was a trend in favor of adjuvant chemotherapy.

An updated meta-analysis also confirmed the marginal efficacy of adjuvant chemotherapy in terms of local, distant, and overall recurrence as well as OS (which is contrary to that reported in the SMAC meta-analysis) in patients with localized STS (n = 1953).[85] A recent large, cohort-based analysis with a median follow-up of 9 years indicated that adjuvant chemotherapy may be associated with significantly improved 5-year metastasis-free survival (58% vs. 49%; *P* = .01) and 5-year OS (58% vs. 45%; *P* = .0002) in patients with 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; 5-year OS, 75% vs. 65%; *P* = .15).[86]

In the Italian cooperative study (n = 104), which randomized patients with high-grade or recurrent extremity sarcoma to receive adjuvant chemotherapy with epirubicin and ifosfamide or observation alone, after a median follow-up of 59 months, median DFS (48 vs. 16 months) and median OS (75 vs. 46 months) were significantly better in the treatment group; the absolute benefit for OS from chemotherapy was 13% at 2 years and increased to 19% at 4 years for patients receiving chemotherapy.[88] 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.[93]

In another phase III study (EORTC-62931), 351 patients with macroscopically resected grade II–III tumors with no metastases were randomized to observation or adjuvant chemotherapy with ifosfamide and doxorubicin with lenograstim.[90] A planned interim analysis of this study showed no survival advantage for adjuvant chemotherapy in patients with resected high-grade STS. The estimated 5-year RFS was 52% in both arms and the corresponding OS rates were 64% and 69%, respectively, for patients assigned to adjuvant chemotherapy and observation. These findings are consistent with the results reported in an earlier EORTC study by Bramwell and colleagues.[87] In that study, adjuvant chemotherapy with CYVADIC (cyclophosphamide, vincristine, doxorubicin, and dacarbazine) was associated with higher RFS rates (56% vs. 43% for the control group; P = .007) and significantly lower LR rates (17% vs. 31% for the control group; P = .004). However, there were no differences in distant metastases (32% and 36%, respectively, for CYVADIC and the control group; P = .42) and OS rates (63% and 56%, respectively, for CYVADIC and the control group; P = .64).

A pooled analysis of these two 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.[92] Adjuvant doxorubicin-based chemotherapy was associated with improved RFS in male patients and those older than 40 years, although female patients and those younger than 40 years who received adjuvant chemotherapy had marginally worse OS. However, RFS and OS were significantly improved in patients with R1 resection who received adjuvant chemotherapy compared with those who did not.

Long-term follow-up results of another prospective randomized study also showed that adjuvant chemotherapy with IFADIC (ifosfamide, doxorubicin, and dacarbazine) given every 14 days with growth factor support did not result in significant benefit in terms of RFS (39% for IFADIC and 44% for the control group; P = .87) as well as OS (P = .99) for patients with grade 2 or 3 STS.[91]

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.[94-106] Other chemotherapeutic agents such as gemcitabine, docetaxel, vinorelbine, pegylated liposomal doxorubicin, and temozolomide have also been evaluated in clinical trials. The METASARC observational study, which explored “real-world” outcomes among 2225 patients with metastatic STS, found a positive association of OS with front-line combination chemotherapy, LMS histology, and locoregional treatment of metastases. However, with the exception of LMS, the benefits of systemic therapy beyond the second-line setting were very limited.[107]

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.[108-112] 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 to gemcitabine alone in patients with metastatic STS.[109] 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.[110] Clinical benefit (complete response [CR], partial response [PR], or stable disease at 4 months or more) was seen in 25% of patients. The combination of gemcitabine and dacarbazine resulted in superior PFS (4.2 vs. 2 months; P = .005), OS (16.8 vs. 8.2 months; P =

.014), and objective response rate (49% vs. 25%; *P* = .009) compared to dacarbazine alone in patients with previously treated advanced STS.[111]

However, gemcitabine combination therapy was not superior to single-agent doxorubicin in the randomized phase III GeDDiS trial. Among patients with previously untreated advanced or metastatic disease (n = 257), combination therapy with gemcitabine and docetaxel did not result in superior PFS compared with doxorubicin (23.7 vs. 23.3 weeks; *P* = .06).[112] It should be noted that this study utilized lower doses of gemcitabine and docetaxel as compared to other published studies.

Temozolomide,[113-115] pegylated liposomal doxorubicin,[116] and vinorelbine[117,118] have also shown activity as single agents in patients with advanced, metastatic, relapsed, or refractory disease. In a phase II study by the Spanish Group for Research on Sarcomas, temozolomide resulted in an overall response rate of 15.5% with a median OS of 8 months in patients with advanced pretreated STS.[115] 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 to doxorubicin; response rates were 9% and 10% for doxorubicin and pegylated liposomal doxorubicin, respectively, in patients with advanced or metastatic STS.[116] In a retrospective study of pretreated patients with metastatic STS, vinorelbine induced overall response in 6% of patients and 26% had stable disease.[117]

Trabectedin is a novel DNA-binding agent that has shown objective responses in phase II and III studies of patients with advanced STS.[119-127] Recent phase III data from a randomized, multicenter trial revealed a 2.7-month PFS benefit versus dacarbazine in metastatic liposarcoma (LPS) or LMS that progressed after anthracycline-based therapy.[125] However, the study failed to demonstrate an overall survival advantage for trabectedin over dacarbazine.[277]

Another study supported the efficacy of trabectedin in translocation-related sarcoma.[127] 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.[128] Preliminary results from the randomized phase III T-SAR trial revealed a PFS benefit for trabectedin over best supportive care in both “L-type” (LPS and LMS) and non–L-type pretreated advanced sarcoma.[129] However, trabectedin plus doxorubicin failed to demonstrate superiority over doxorubicin alone in a randomized phase II study of patients with advanced STS.[130] Trabectedin is included for palliative therapy as a category 1 recommendation for LPS and LMS (L-type) and as category 2A for non–L-type sarcomas.

Eribulin is a novel microtubule-inhibiting agent that has been evaluated as a single-agent therapy for STS, including LMS, adipocytic sarcoma, synovial sarcoma, and other tumor types.[131] Recent data from a phase III trial compared the survival benefit of eribulin and dacarbazine in 452 patients with advanced LMS or LPS, revealing a median OS of 13.5 months and 11.5 months, respectively (HR, 0.77; 95% CI, 0.62–0.95; *P* = .017).[132] A subgroup analysis demonstrated that the survival benefit was limited to LPS, and therefore eribulin is included for palliative therapy as a category 1 recommendation for LPS and as category 2A for other subtypes.

Please refer to SARC-F 1 of 11 for a complete list of chemotherapy agents and regimens recommended for STS subtypes with non-specific histologies.

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 (TKI), has demonstrated single-agent activity in patients with advanced STS subtypes except LPS.[133-136,278-280] In a phase III study (EORTC 62072), 369 patients with metastatic non-lipogenic STS who had failed at least one anthracycline-based chemotherapy regimen were randomized to either pazopanib or placebo.[135] Pazopanib significantly prolonged median PFS (4.6 vs.1.6 months for placebo; $P < .0001$) and there was also a trend toward improved OS (12.5 and 11 months, respectively; $P = .25$), although this was not statistically significant. Health-related quality-of-life measures did not improve or decline with the PFS benefit.[137] Pooled data from individuals who received pazopanib in phase II and III trials (n = 344) revealed a subset of long-term responders/survivors presenting at baseline with good performance status, low-/intermediate-grade primary tumor, and normal hemoglobin level.[138] Results from the open-label phase II EPAZ study found that pazopanib demonstrated non-inferior PFS compared with doxorubicin (4.4 vs. 5.3 months, respectively) as a first-line treatment in elderly patients with advanced/metastatic STS.[281] The guidelines have included pazopanib as a first-line therapy option for those with advanced or metastatic disease who are ineligible for intravenous (IV) systemic therapy or are not candidates for anthracycline-based regimens, and as a subsequent-line treatment option for patients with advanced or metastatic non-lipogenic STS as palliative therapy (SARC-F 1 of 11). Pazopanib in combination with gemcitabine is a category 2B subsequent-line treatment option for advanced/metastatic disease.[282]

The randomized, phase II REGOSARC trial examined regorafenib, a multi-targeted tyrosine kinase inhibitor approved for treating GIST, in cohorts of patients with advanced LPS, LMS, synovial sarcoma, and other non-GIST STS subtypes (REGOSARC, n = 182).[158,159] Compared to placebo, regorafenib significantly extended PFS in all but the LPS cohort. In patients with nonadipocytic STS, overall PFS for regorafenib and placebo-treated patients was 4 months versus 1 month (HR, 0.36; $P < .0001$). Regorafenib is included in the guidelines as a treatment option for advanced/metastatic non-adipocytic sarcomas, as well as angiosarcoma.[158,283]

Tropomyosin receptor kinase (TRK) inhibitors larotrectinib and entrectinib have demonstrated efficacy in patients with neurotrophic receptor tyrosine kinase (*NTRK)* fusion-positive tumors, and are therefore recommended as first-line treatment options for patients with advanced or metastatic *NTRK* gene fusion-positive sarcomas in the guidelines.[284,285]

Programmed cell death protein 1 (PD-1) inhibitor pembrolizumab is approved by the U.S. Food and Drug Administration (FDA) for unresectable or metastatic tumor mutational burden-high (TMB-H) (≥10 mutations/megabases [mut/Mb]) tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative options.[286] In the guidelines, pembrolizumab is included as a subsequent-line treatment option for patients with certain subtypes of advanced or metastatic STS, including myxofibrosarcoma, undifferentiated pleomorphic sarcoma (UPS), cutaneous angiosarcoma, and undifferentiated sarcomas.[287,288]

Please refer to SARC-F 1 of 11 for a complete list of targeted therapies recommended for STS subtypes with non-specific histologies.

Treatment Guidelines

Resectable Disease

Surgical wide resection with oncologically appropriate negative margins is a potentially curative treatment for nonmetastatic primary retroperitoneal/intra-abdominal sarcomas (RETSARC-2). The margin status after surgery is an important factor associated with long-term DFS.[289-293] In a large single-institution series involving 500 patients, the median survival was 103 months for those who underwent complete

resection with grossly negative margins in contrast to 18 months for those who underwent incomplete resection.[292]

Two recent retrospective analyses reported improved local control in patients with primary retroperitoneal sarcoma operated with more aggressive approaches such as complete compartmental resection and a more liberal visceral en bloc resection performed in high-volume centers.[294,295] While the results are encouraging, this technique needs to be investigated in prospective clinical trials. For information on the *Principles of Surgery*, please refer to SARC-D 1 of 2.

Given the close proximity of retroperitoneal/intra-abdominal sarcomas to critical structures, complete or macroscopic surgical resection is achieved in less than 70% of patients. LR and disease progression continue to be a significant cause of morbidity in many patients.[296-298] Multimodality treatment (surgery with RT and/or chemotherapy) is the subject of clinical investigation, given the inability to obtain negative surgical margins and high LR rates, as discussed above.[299]

If RT is anticipated, neoadjuvant RT with an IMRT approach to optimize sparing of nearby critical structures is preferred because it reduces the risk of tumor seeding at the time of surgery and may render tumors more amenable to resection.[258] Neoadjuvant RT can be considered in selected patients with retroperitoneal/intra-abdominal sarcomas who are at high risk for local recurrence.[261] For patients treated with neoadjuvant EBRT (50 Gy; 1.8–2.0 Gy per fraction), the guidelines recommend consideration of IORT boost for patients with known or suspected positive margins at the time of surgery, if this can be done within the constraints of adjacent normal tissue (SARC-E 3 of 4). The guidelines recommend an IORT boost of 10–12.5 Gy for microscopic residual disease, and 15 Gy for gross disease.

An analysis of 8653 patients with resected retroperitoneal STS from the NCDB revealed worse OS in the surgically resected cohort receiving chemotherapy (neoadjuvant and/or adjuvant) versus those who underwent surgery alone (40 vs. 52 months; P = .002).[300] Neoadjuvant chemotherapy may have advantages over adjuvant chemotherapy. However, the role of neoadjuvant chemotherapy versus adjuvant chemotherapy has not yet been evaluated in randomized clinical trials.[301] Little data are available for the use of combined RT and chemotherapy. Decisions about adjuvant or neoadjuvant chemotherapy or RT are left to clinical judgment.[302-304] The regimens listed in the guidelines are based on the extrapolation of data derived from clinical trials on STS of the extremity that have included a small number of patients with retroperitoneal STS.[305]

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

Following surgery, adjuvant systemic therapy could be considered for all patients who are at high risk for metastatic disease based on surgical outcomes or clinical pathologic findings (RETSARC-3). For R1 or R2 outcomes, adjuvant RT should not be administered routinely, with the exception of highly selected patients and unless local recurrence would cause undue morbidity. For example, recurrence at a critical anatomic surface that would cause morbidity. For R2 outcomes, re-resection can be considered if the cancer of the biology (grade, invasiveness), the technical aspects of the operation (R0 resection anticipated as a reasonable possibility), and the comorbidities of the patient allow for a safe intervention at the judgement of the operating surgeon. Additionally, the primary treatment options as described below for unresectable disease are another alternative (RETSARC-4).

Unresectable or Stage IV Disease

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

Biopsy is recommended before any treatment for a patient with unresectable or metastatic disease (RETSARC-4). Patients with unresectable or stage IV disease could be treated with systemic therapy and/or RT, or undergo surgery for symptom control. Observation is an option if the patient is asymptomatic and there is indolent tumor growth. For patients undergoing definitive high-dose RT, there has been favorable experience reported in the literature with the use of tissue displacement spacers to keep bowel out of the high-dose RT volume.[306] In terms of response rate, the most active chemotherapy regimen in an unselected patient population is AIM (doxorubicin/ifosfamide/mesna).[217]

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

Surveillance

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

Recurrent Disease

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

Desmoid Tumors (Aggressive Fibromatoses)

Desmoid tumors, also known as aggressive fibromatoses, are unique mesenchymal neoplasms that are often considered to be locally malignant but nonmetastasizing neoplasms. Specifically, these tumors are an aggressive fibroblastic proliferation of well-circumscribed, locally invasive, and differentiated fibrous tissue. Desmoid tumors can cause functional morbidity and are often locally invasive, but they rarely metastasize. The location and presentation of desmoids vary, from the abdominal wall of young pregnant females, to intra-abdominal mesenteric masses, and to large extremity masses in older men and women.

Desmoid tumors often pose difficult decisions for patients because of the extent of surgery required for optimal control, their high recurrence rate, and their long natural history. Although they do not exhibit the histopathologic features to classify them as sarcomas, desmoid tumors are often categorized as low-grade sarcomas because of their high tendency to recur locally after excision.

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.[21-24] Abdominal desmoids may be a component of FAP and may also arise through elective surgical intervention (eg, colectomy) in susceptible patients.[21,307,308] In patients who have been treated with prophylactic colectomy, desmoids now represent a more significant cause of morbidity than carcinoma of the colon.[309]

Mutations in the *CTNNB1* gene encoding the β-catenin pathway have been identified in sporadic desmoid tumors, although the correlation of *CTNNB1* mutation status with the clinical outcome remains uncertain.[310-314] Lazar and colleagues identified mutations in the *CTNNB1* gene in 85% of patients with desmoid tumors.[310] Three distinct mutations, 41A, 45F, and 45P, were identified in 59%, 33%, and 8% of cases, respectively. Mutation 45F was associated with a high risk of recurrence; 5-year RFS rate was 23% for patients harboring 45F mutation compared to 57% for those with 41A and 68% for those with no mutations.[310] In a retrospective study of patients with extra-abdominal desmoid tumors, Domont and colleagues reported *CTNNB1* mutations in 87% of patients, and the 5-year RFS rate was significantly worse in patients with β-catenin mutations, regardless of the genotype, compared with wild-type tumors (49% vs. 75%, respectively).[311] Columbo and colleagues also reported that mutation 45F was associated with higher rates of LR among patients with primary, completely resected, sporadic desmoid tumors and mutation 45F was more prevalent in extra-abdominal desmoid tumors compared to other sites.[313] In contrast to these findings, Mullen and colleagues reported that *CTNNB1* mutation status or the specific *CTNNB1* mutation was not associated with any statistically significant difference in recurrence risk in a subset of 115 patients with desmoid tumors who underwent macroscopically complete surgical resection.[314] At a median follow-up of 31 months, the 5-year RFS rates were 58% and 74%, respectively, for patients with *CTNNB1* mutations and for those with wild-type tumors. Additional prospective studies are needed to confirm whether genotyping of *CTNNB1* may provide important information regarding the risk of recurrence and the selection of patients for adjuvant treatment options.

Evaluation and Workup

The workup for desmoid tumors includes H&P (with evaluation for Gardner's syndrome/FAP) and appropriate imaging of the primary site with CT or MRI as clinically indicated. All patients should be managed by a multidisciplinary team. Biopsy should be performed for suspicious masses to confirm the diagnosis, and may not be necessary if complete resection is planned. The differential diagnosis for desmoids depends on location; it includes other sarcomas, other malignant carcinomas, and benign lesions.

Desmoid tumors of the breast are difficult to differentiate from carcinomas, because they resemble carcinomas clinically and radiologically.[315-318]

Treatment Guidelines

Resectable Tumors

Surgery is the primary treatment for patients with resectable desmoid tumors.[319-323] Tumor location and size, patients' age, and margin status have been identified as factors associated with recurrence following resection. Extra-abdominal tumors have a higher risk of recurrence than abdominal tumors. In an analysis of 203 patients with desmoid tumors treated with surgery, Gronchi and colleagues reported significantly higher DFS rates for patients with abdominal wall tumors than those with extremity tumors. The 10-year DFS rates were 88% and 62%, respectively ($P < .01$).[324] In a more recent report involving 211 patients with desmoid tumors treated with surgery, Peng and colleagues also reported similar findings.[325] The median RFS was not reached following resection for patients with either abdominal wall or intra-abdominal tumors, whereas the median RFS was 29.4 months for patients with extra-abdominal tumors ($P < .001$).

The impact of positive resection margins on local control and risk of recurrence remains controversial.[326] Some studies have reported margin status as an independent prognostic factor of recurrence.[325,327-330] Other studies have failed to demonstrate any clear association between resection margins and risk of recurrence.[324,331] Recent data suggest no difference in outcomes between patients with R0 or R1 resection margins who undergo careful observation.[332-334] Therefore, R1 margins are acceptable if achieving R0 margins would produce excessive morbidity. However, a recent meta-analysis of 16 studies, including data from 1295 patients, found that R1 resections were associated with an almost 2-fold higher risk of recurrence (risk ratio, 1.78; 95% CI, 1.40–2.26).[330]

Several retrospective series have reported that postoperative RT significantly improves local control and PFS compared to surgery alone, suggesting that postoperative RT could be considered for patients who are at high risk of LR.[330,331,335-340] However, in another series of patients with desmoid tumors of the chest wall, postoperative RT did not reduce the risk of recurrence.[323]

The results of recent retrospective analyses suggest that observation may be appropriate for selected patients with resectable tumors (small size, asymptomatic, and tumors located at sites where increase in size will not alter the outcome of surgery or lead to functional limitation).[341,342] In a retrospective analysis of 142 patients with desmoid fibromatoses (74 with primary tumor and 68 with recurrence) reported by Fiore and colleagues, the 5-year PFS rates for patients with primary tumors were 47% for those who were treated with a "wait and see" approach (no surgery or RT) and 54% for those who received medical therapy (chemotherapy or hormonal therapy; $P = .70$).[342] The corresponding survival rates were 54% and 61% ($P = .48$) for patients with recurrence. Large tumors (greater than 10 cm in size) and tumors located on the trunk were associated with a high risk of recurrence.

Based on these results, the panel concluded that patients with desmoid fibromatoses can be managed appropriately with a careful "wait and see" approach if their tumors are asymptomatic and are not located in an area that could lead to functional limitations if the tumor increases in size. The guidelines have included observation as an option for selected patients with resectable tumors. Stable tumors can be followed with continued observation using H&P exam with appropriate imaging. If there is progression, patients can be treated with surgery and/or RT and/or systemic therapy.

For symptomatic patients with large tumors causing morbidity, pain, or functional limitation, treatment choices should be based on the location of

the tumor and potential morbidity of the treatment. Options include surgery and/or RT and/or systemic therapy. Patients with resectable tumors should be treated with complete surgical resection when feasible. Microscopically positive margins may be acceptable if achieving negative margins would produce excessive morbidity. If surgical margins are negative after resection (R0 resection) or if there is complete radiographic response, patients may only be observed. For microscopically positive margins or minimal residual disease (R1 resection), observation or re-resection can be considered. Postoperative RT reduces the risk of recurrence in patients with positive margins and should be considered only if a subsequent relapse might lead to increased morbidity. Patients with macroscopic surgical margins (R2 resection) are treated as described below for unresectable disease.

For treating progressive or recurrent desmoid tumors, options include: systemic therapy; resection; resection plus RT (50 Gy, if not previously irradiated); or RT alone (50–56 Gy, if not previously irradiated).

Unresectable Tumors

In the case of unresectable desmoid tumors, amputation should almost never be considered. Functional outcomes are important, and alternatives to amputation may be open to patients who have unresectable desmoid tumors.[324,343] RT is a reasonable treatment option for patients with unresectable tumors, depending on the possible morbidity of treatment.[331,344-347]

In a retrospective analysis of 23 patients with extra-mesenteric desmoid tumors treated with RT for gross residual unresectable disease, 7 patients sustained LR, yielding a 5-year actuarial local control rate of 69%. In another retrospective analysis that included 13 patients with unresectable tumors treated with RT alone as a definitive local therapy, the actuarial 3-year freedom-from-recurrence rate was 92.3%.[331] In a multicenter, prospective phase II study of 44 patients with inoperable desmoid tumors of trunk and extremities treated with RT (56 Gy in 28 fractions), Keus and colleagues reported a 3-year local control rate of 81.5%, at a median follow-up of 4.8 years.[347] During the first 3 years, CR, PR, and stable disease were observed in 13.6%, 36.4%, and 40.9% of patients, respectively. Response to RT was slow, with continuing regression seen even after 3 years.[347]

Definitive RT (50–56 Gy in the absence of any prior RT only for desmoid tumors of the extremity head and neck or superficial trunk), systemic therapy, and observation are some of the options for patients with unresectable tumors. Radical surgery should be considered only if other treatment modalities fail. RT is not generally recommended for retroperitoneal/intra-abdominal desmoid tumors.

Systemic therapy using non-steroidal anti-inflammatory drugs (NSAIDs), hormonal or biological agents, or cytotoxic drugs have shown promising results in patients with desmoid tumors.[348,349] In a prospective study, tamoxifen in combination with sulindac resulted in disease stabilization in patients with progressive or recurrent tumors following surgery.[350] The results of a retrospective, non-randomized study showed that interferon alfa with or without tretinoin may be effective in prolonging the disease-free interval after intralesional or marginal surgery in patients with extra-abdominal desmoid tumors.[351] In case reports, toremifene has been effective in disease stabilization following surgery.[352-355] Doxorubicin-based chemotherapy has been effective in patients with recurrent or unresectable tumors.[356-359] The combination of methotrexate and vinorelbine or vinblastine has also been associated with prolonged stable disease in patients with unresectable or recurrent tumors.[358,360-362]

Imatinib and sorafenib have also been evaluated in patients with unresectable, progressive, or recurrent aggressive fibromatosis.[153,363-365] In a phase II multicenter study, imatinib resulted in an objective response rate of 6% and the 1-year PFS rate was 66% in patients with unresectable

tumors.[364] Long-term follow-up results of the phase II study by the French Sarcoma Group also showed that imatinib resulted in objective responses and stable disease in a large proportion of patients with recurrent or progressive aggressive fibromatosis.[365] At a median follow-up of 34 months, the 2-year PFS and OS rates were 55% and 95%, respectively. The non-progression rates at 3, 6, and 12 months were 91%, 80%, and 67%, respectively. In a study of 26 patients (11 patients received sorafenib as first-line therapy and the remaining 15 patients had received a median of 2 prior systemic therapies), sorafenib induced PR in 25% of patients and 70% of patients had stable disease, with a median follow-up of 6 months.[153]

The guidelines have included NSAIDs (sulindac or celecoxib), hormonal or biological agents (tamoxifen, toremifene, or low-dose interferon), chemotherapy (methotrexate and vinblastine, doxorubicin-based regimens), and TKIs (imatinib and sorafenib) as options for systemic therapy for patients with advanced or unresectable desmoid tumors. The risk of cardiovascular events may be increased in patients receiving celecoxib, and patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. Physicians prescribing celecoxib should consider this information when weighing the benefits against risks for individual patients.

Surveillance

Every patient should have an H&P with CT or MRI every 3 to 6 months for 2 to 3 years and then every 6 to 12 months thereafter. Disease progression or recurrence should be managed as described under primary treatment for resectable or unresectable disease.

Rhabdomyosarcoma

RMS is more common among children and adolescents but is less common in adults accounting for 2% to 5% of all STSs.[366] RMS has three histologic subtypes: embryonal (including botryoid and spindle cell variants), alveolar (including a solid variant), and pleomorphic histologies.[367,368] Embryonal and alveolar variants occur mainly in children and adolescents. Although pleomorphic RMS occurs predominantly in adults, embryonal and alveolar variants are also well represented.[366,368-373]

The incidence of pleomorphic RMS increases with age and the overall prognosis of RMS in adults is poor.[374] In a study of 39 adult patients treated at a single institution, the incidence of pleomorphic RMS increased with age (0%, 27%, and 60%, respectively, for ages 16–19, 20–49, and 50 or older) and the median survival was 2.25 years after diagnosis.[374] Extremities, trunk wall, and genitourinary organs are the most common primary sites for pleomorphic RMS in adults.[375-377] In a recent SEER database analysis of 1071 adults (older than 19 years) with RMS, the most common primary sites included extremities (26%) and trunk (23%) followed by genitourinary tract (17%) and head and neck (9%).[372] Pleomorphic histologies (19% vs. 1% in children; $P < .0001$) and unfavorable sites (65% vs. 55% in children; $P < .0001$) were more common in adults; the estimated 5-year OS rates were 27% for adults compared to 63% for pediatric patients.[372]

Given the rarity of the clinical situation, there are very limited data (mostly from single-institution retrospective studies) available on the management of adults with RMS. Multimodality treatment (surgery, RT, and chemotherapy) has been used in all of these studies. In the largest retrospective single-institution study that evaluated 180 patients diagnosed with RMS (18 years or older; 143 patients with embryonal, alveolar, or RMS not otherwise specified; and 37 patients with pleomorphic histology), Ferrari and colleagues reported 5-year EFS and OS rates of 28% and 40%, respectively.[366] The overall response rate was 85% in patients with embryonal and alveolar RMS treated with chemotherapy according to the pediatric protocol. Surgery was the main treatment in patients with

pleomorphic RMS (74% compared to 34% with non-pleomorphic histologies), and the EFS rate was 37% for patients who underwent complete resection compared to 0% in patients with unresectable tumors.[366]

Other retrospective studies from MD Anderson Cancer Center (82 adults) and Dana Farber Cancer Institute (39 patients) have also reported high overall response rates to chemotherapy (75% and 82%, respectively).[370,378] Survival was significantly better for patients with disease responding to chemotherapy than those with disease that did not. In the MD Anderson Cancer Center study, the 10-year metastasis-free survival was 72% for patients with disease that responded to chemotherapy compared to 19% for those with disease that failed to respond.[370]

In the series from Dana Farber Cancer Institute, metastatic disease at presentation and poor response to chemotherapy were independent predictors of poor prognosis; the 5-year survival rate was 57% for patients with a CR to chemotherapy compared to only 7% for those with poor response.[378] In this study, 5-year survival rates were also higher for patients who underwent complete resection than for those who did not (63% vs. 29% and 46% for those who underwent compromised or incomplete resections, respectively).[378] Hawkins and colleagues also reported that margin status after resection was predictive of disease-specific survival in adult patients (105 months for patients who underwent complete resection compared to 9 months for those with positive margins).[369]

Chemotherapy regimens used in adults with RMS are usually derived from the pediatric clinical trials on RMS conducted by international cooperative groups.[379] Vincristine, dactinomycin, and cyclophosphamide (VAC) has been the standard chemotherapy for pediatric nonmetastatic RMS (intermediate or high risk).[380] In a randomized study (D9803) from the Children's Oncology Group (COG), there was no significant survival benefit of adding topotecan to standard VAC regimen in children with intermediate-risk RMS. In this study, at a median follow-up of 4.3 years, the 4-year failure-free-survival (FFS) rate was 73% and 68%, respectively, for patients treated with VAC and VAC alternating with vincristine, topotecan, and cyclophosphamide (P = .30).[380] RT resulted in good local control for patients with alveolar RMS who underwent primary tumor resection before initiation of chemotherapy. [381]

The results of the Intergroup RMS Study (D9602) showed that newly diagnosed patients with low-risk RMS treated with vincristine and dactinomycin had similar 5-year FFS rates compared to those patients treated with vincristine, dactinomycin, and cyclophosphamide (89% and 85%, respectively), suggesting that vincristine and dactinomycin could be an appropriate option for patients with newly diagnosed, low-risk RMS.[382] Vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide (VAC-IE) was found to be effective for patients with intermediate-risk RMS.[383] A recent study from COG in primarily pediatric patients with metastatic RMS investigated intensive multiagent therapy with radiation that included blocks of vincristine/irinotecan, interval compression with VAC-IE, and vincristine/dactinomycin/cyclophosphamide. For patients with zero to one Oberlin risk factor, the 3-year EFS of 69% (95% CI, 52%–82%) was improved compared with historical controls, whereas high-risk disease had a 3-year EFS of 20% (95% CI, 11%–30%).[384]

Newer agents such as carboplatin,[385] irinotecan,[386-389] topotecan,[390-392] and vinorelbine[393,394] have also shown activity in the treatment of pediatric patients with metastatic, relapsed, or refractory RMS. A phase II study recently provided preliminary evidence for efficacy and tolerability of RT with concurrent irinotecan/carboplatin regimens for patients with intermediate or high-risk RMS.[395]

Retrospective studies on adults with RMS have used a variety of multidrug chemotherapy regimens, including cyclophosphamide or ifosfamide, doxorubicin, and/or dactinomycin with or without vincristine or other drugs such as cisplatin, carboplatin, and etoposide.[366,370,374,378,396] In the MD Anderson Cancer Center study, the 10-year overall, disease-free, and metastasis-free survival rates were 47%, 45%, and 59%, respectively, for adult patients treated with chemotherapy regimens containing vincristine and cyclophosphamide with dactinomycin or doxorubicin.[370] Esnaola and colleagues reported an overall response rate of 82%, with a CR rate of 45% in adults with RMS treated with vincristine, doxorubicin, and cyclophosphamide or other doxorubicin-based chemotherapy regimens.[378] Ogilvie and colleagues also reported that chemotherapy with vincristine, doxorubicin, and ifosfamide resulted in an overall response rate of 86% in 11 adult patients with pleomorphic RMS; the 2-year OS and DFS rates were 55% and 64%, respectively.[396] Additionally, a recent review suggested that vincristine, irinotecan, and temozolomide in combination with local therapy may provide some degree of disease control for relapsed RMS.[397]

These guidelines strongly recommend that all patients should be referred to institutions with expertise in treating patients with RMS. Evaluation by a multidisciplinary team involving pediatric, medical, surgical, and radiation oncologists is strongly encouraged. Multimodality treatment (surgery, RT, and chemotherapy) planning and risk stratification is required for all patients.[379] PET imaging may be useful for initial staging because of the possibility of nodal metastases and the appearance of unusual sites of initial metastatic disease in adult patients.[398]

Systemic chemotherapy options for RMS may be different than those used with other STS histologies. Pleomorphic RMS is usually excluded from RMS randomized clinical trials. Consideration to treat according to STS guidelines may be warranted for this group of patients. In the absence of data from prospective clinical trials, there are no definitive, optimal regimens for the management of adult RMS. See *Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma* in the algorithm for a list of chemotherapy regimens that are recommended for the management of adults with RMS.

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