



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Soft Tissue Sarcoma

Version 2.2017 — February 8, 2017

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Soft Tissue Sarcoma

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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.

To find clinical trials online at NCCN Member Institutions, [click here: nccn.org/clinical_trials/physician.html](#).

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

See [NCCN Categories of Evidence and Consensus](#).

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NCCN Guidelines Version 2.2017 Updates

Soft Tissue Sarcoma

Updates in Version 2.2017 of the NCCN Guidelines for Soft Tissue Sarcoma from Version 1.2017 include:

[MS-1](#) - The discussion section was updated to reflect the changes in the algorithm.

Updates in Version 1.2017 of the NCCN Guidelines for Soft Tissue Sarcoma from Version 2.2016 include:

Global changes

- A new section for "*Principles of Imaging*" that includes recommendations for "Workup" and "Follow-up" was added to the Guidelines to clarify recommended modalities wherever imaging is mentioned. Recommendations for specific imaging modalities (eg, CT, PET, MRI) were removed from the algorithms and described in greater detail in the new imaging section. ([SARC-A](#))

[EXTSARC-1](#)

Footnotes

- "a" modified: "Imaging studies should include cross-sectional imaging (*MRI with and without contrast +/- CT with contrast*) to provide details about the size of tumor and contiguity to nearby visceral structures and neurovascular landmarks. Other imaging studies such as angiogram and plain radiograph may be warranted in selected circumstances.
- "b": "*See Principles of Imaging (SARC-A)*" is new to the page.
- "g" modified: "*PET/CT may be useful in determining response to chemotherapy for lesions that are larger than 3 cm, firm, and deep, not superficial...*"

[EXTSARC-3](#)

Staging

- Stage IIB modified: "*T2a-2b, N0, M0, G2*"
 - ▶ Stage III modified: "*T2a-2b, N0, M0, G3 or Any T, N1, M0, Any G*"
- Footnote "v" modified: "*Re-imaging using MRI with and without contrast (preferred for extremity imaging) or CT with contrast to assess primary tumor and rule out metastatic disease. See Principles of Imaging (SARC-A)*" (Also for [EXTSARC-4](#)).

[EXTSARC-5](#)

Follow-up

- Bullet 3: "*Imaging of chest and other known sites of metastatic disease*" is new to the page

[EXTSARC-6](#)

Treatment

- Bullet 1: Removed "category 2B for chemotherapy and RT"
- Bullet 12: Removed "category 2B for chemotherapy"
- Bullet 13: Removed "category 2B for chemotherapy and RT"

[RETSARC-1](#)

Workup

- Bullet 3: "*Imaging*" is new to the page.
- Bullet 8: "*Patients with neurofibromatosis*" is new to the page.

[RETSARC-3](#)

Follow-up

- 2nd bullet modified: "~~Consider Obtain~~ chest imaging"

[RETSARC-4](#)

Primary Treatment

5th column: "*Imaging to assess treatment response*" is new to the page.

[GIST-1](#)

Workup at Primary Presentation

- Deleted "Endoscopy ± ultrasound as indicated in selected patients."

[GIST-4](#)

- 2nd column: "*Baseline Imaging*" is new to the page. (Also applies to [GIST-5](#))

Footnotes

- "r" modified: "PET may give indication of imatinib activity after 2–4 weeks of therapy when rapid readout of activity is necessary. Diagnostic abdominal/pelvic CT or MRI with contrast is indicated every 8–12 weeks; routine long-term PET follow-up is rarely indicated. Frequency of response assessment imaging may be decreased if patient is responding to treatment." (Also applies to [GIST-5](#) and [GIST-6](#))
- "t" modified: "Progression may be determined by abdominal/pelvic CT or MRI with contrast with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous." (Also applies to [GIST-5](#), [GIST-6](#), [GIST-7](#))

[GIST-6](#)

Postoperative treatment

- "*(low-risk disease)*" has been added to Observe
- The following statement has been modified: "Consider continuation of imatinib if taken prior to resection ~~with an objective response~~"

[GIST-A](#) (2 of 3 and 3 of 3)

- Tables have been modified to reflect the data from Miettinen.

NCCN Guidelines Version 2.2017 Updates

Soft Tissue Sarcoma

GIST-B

Principles of Pathologic Assessment for GIST

- 2nd bullet, 2nd sentence modified: "Several ancillary techniques are useful in support of GIST diagnosis, including immunohistochemistry (95% 97% expression CD117, 99% expression DOG1, and 80% 81% CD34 expression) and molecular genetic testing (for mutations in *KIT* or *PDGFRA*)."

DESM-1

Workup

- 3rd bullet modified: "Appropriate imaging of primary site with CT or MRI with contrast as clinically indicated."

DESM-3

Follow-up

- 2nd bullet modified: "H&P with appropriate imaging (CT or MRI with contrast) every 3–6 mo for 2–3 y, then annually"

SARC-E (1 of 3)

Radiation Therapy for STS of Extremity/Trunk/Head-Neck

- Column 4: "Consider *observation in addition to* boost for positive margins." Corresponding reference: Al Yami, et al. *Int J Radiat Oncol Biol Phys* 2010;77:1191-1107; Pan et al. *J Surg Oncol* 2014;110:817-822.

References

- "3" is new to the title of the page: "*These guidelines are intended to treat the adult population. For adolescent and young adult patients, refer to the Guidelines for Adolescent and Young Adult (AYA) Oncology.*"
- "4" is new the the page: "*External-beam RT in 1.8 to 2.0 Gy per fraction*" (Also for SARC-E (2 of 3) and SARC-E (3 of 3).)
- "6" includes a new reference: "Total doses should always be determined by normal tissue tolerance. There are data to suggest that some patients with positive margins following preoperative RT such as those with low-grade, well-differentiated liposarcoma and a focally, "planned" positive margin on an anatomically fixed critical structure may do well without a boost. (Al Yami, et al, *Int J Radiat Oncol Biol Phys* 2010;77:1191-1197.) Gerrand et al. *J Bone Joint Surg* 2001;83-B:1149-1155."

SARC-E (3 of 3)

Radiation Therapy Guidelines for Retroperitoneal/Intra-abdominal Sarcoma

- A new reference corresponds to the page title, Baldini et al. *Int J Radiat Oncol Biol Phys* 2015;92:602-612.
- Column 2:
 - ▶ "*In experienced centers only*" was added to "45–50 Gy in 25–28 fractions to entire CTV..."

Column 3:

- ▶ "Consider *IORT* boost for positive margins;"
- ▶ "*A postoperative EBRT boost is discouraged*: If deemed necessary:16–18 Gy for microscopic disease and 20–26 Gy for gross residual disease,if normal tissue spared (likely requiring tissue displacement with omentum or other biologic or synthetic tissue spacer)."

References

- "1" removed: "Alektiar KM, et al. Impact of intensity-modulated radiation therapy on local control in primary soft-tissue sarcoma of the extremity. *J Clin Oncol* 2008;26:3440-3444; Kraybill WG, Harris J, Spiro JJ, et al. Phase II study of neoadjuvant chemotherapy and radiation therapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group Trial 9514. *J Clin Oncol*. 2006;24:619-625."
- "4" removed: Total doses should always be determined by normal tissue tolerance. There are data to suggest that some patients with positive margins following preoperative RT such as those with low-grade, well-differentiated liposarcoma and a focally, "planned" positive margin on an anatomically fixed critical structure may do well without a boost. (Al Yami, et al, *Int J Radiat Oncol Biol Phys* 2010;77:1191-1197).
- "11" is new to the page: "Baldini et al. *Ann Surg Oncol* 2015;22:2846-2852. Postoperative RT following surgery with clips is discouraged. If RT is not given prior to surgical resection, consider follow up with possible pre-operative EBRT at time of localized recurrence. See (SARC-D). Trans-Atlantic RPS Working Group. Management of Primary Retroperitoneal Sarcoma (RPS) in the Adult: A Consensus Approach from the Trans-Atlantic RPS Working Group. *Ann Surg Oncol* 2015;22:256-263."

SARC-E (4 of 4)

- Page deleted

SARC-F

Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma Subtypes (Non-Specific)

- Included *olatumab* in combination with doxorubicin for treating histologic subtypes of STS for which an anthracycline-containing regimen is appropriate.
- "Category 1 recommendation for liposarcoma and leiomyosarcoma (L-Types), non L-Types (Category 2A)" is a new footnote corresponding to eribulin and trabectedin.



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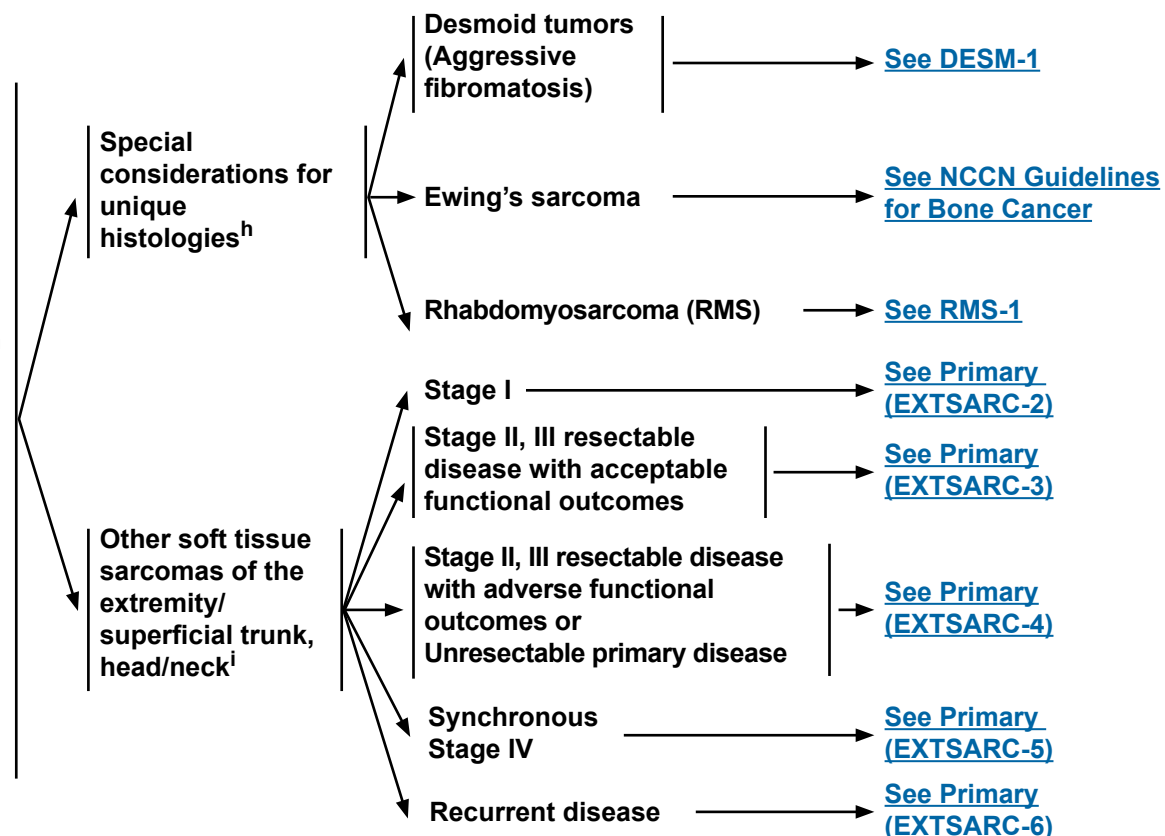
Extremity/Superficial Trunk, Head/Neck

WORKUP

ESSENTIAL:

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

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



^aImaging studies should include cross-sectional imaging (MRI with and without contrast +/- CT with contrast) to provide details about the size of tumor and contiguity to nearby visceral structures and neurovascular landmarks. Other imaging studies such as angiogram and plain radiograph may be warranted in selected circumstances.

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

^cIn selected institutions with clinical and pathologic expertise, an FNA may be acceptable.

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

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

^fDifferent subtypes have different propensities to spread to various locations.

^gPET/CT may be useful in determining response to chemotherapy for lesions that are larger than 3 cm, firm, and deep, not superficial (Schuetze SM, Rubin BP, Vernon C, et al. Use of positron emission tomography in localized extremity soft tissue sarcoma treated with neoadjuvant chemotherapy. *Cancer* 2005;103:339-348).

^hDiagnoses that will impact the overall treatment plan.

ⁱPatients with DFSP with fibrosarcomatous changes and/or malignant transformations can be treated according to this algorithm. For DFSP without fibrosarcomatous elements refer to treatment in [NCCN Guidelines for Dermatofibrosarcoma Protuberans](#).

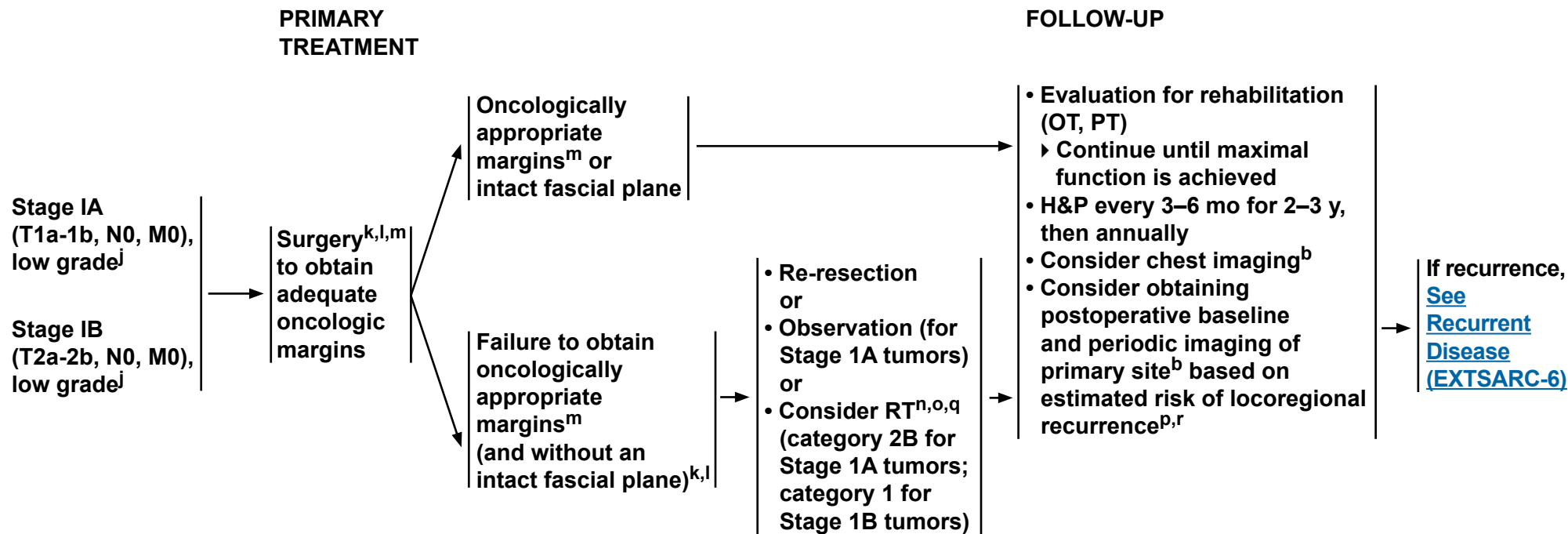
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Extremity/Superficial Trunk, Head/Neck



^bSee [Principles of Imaging \(SARC-A\)](#).

^jSee American Joint Committee on Cancer (AJCC) Staging, 7th Edition ([ST-2](#)).

^kSee [Principles of Surgery \(SARC-D\)](#).

^lIn selected cases when margin status is uncertain, consultation with a radiation oncologist is recommended. Reresection, if feasible, may be necessary to render margins >1.0 cm.

^mResection 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.

ⁿSee [Radiation Therapy Guidelines \(SARC-E\)](#).

^oRandomized clinical trial data support the use of radiation therapy as an adjunct to surgery in appropriately selected patients based on an improvement in

disease-free survival (although not overall survival). (Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *J Clin Oncol* 1998;16:197-203).

^pIn situations where the area is easily followed by physical examination, imaging may not be required.

^qFor 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.

^rAfter 10 y, the likelihood of developing a recurrence is small and follow-up should be individualized.

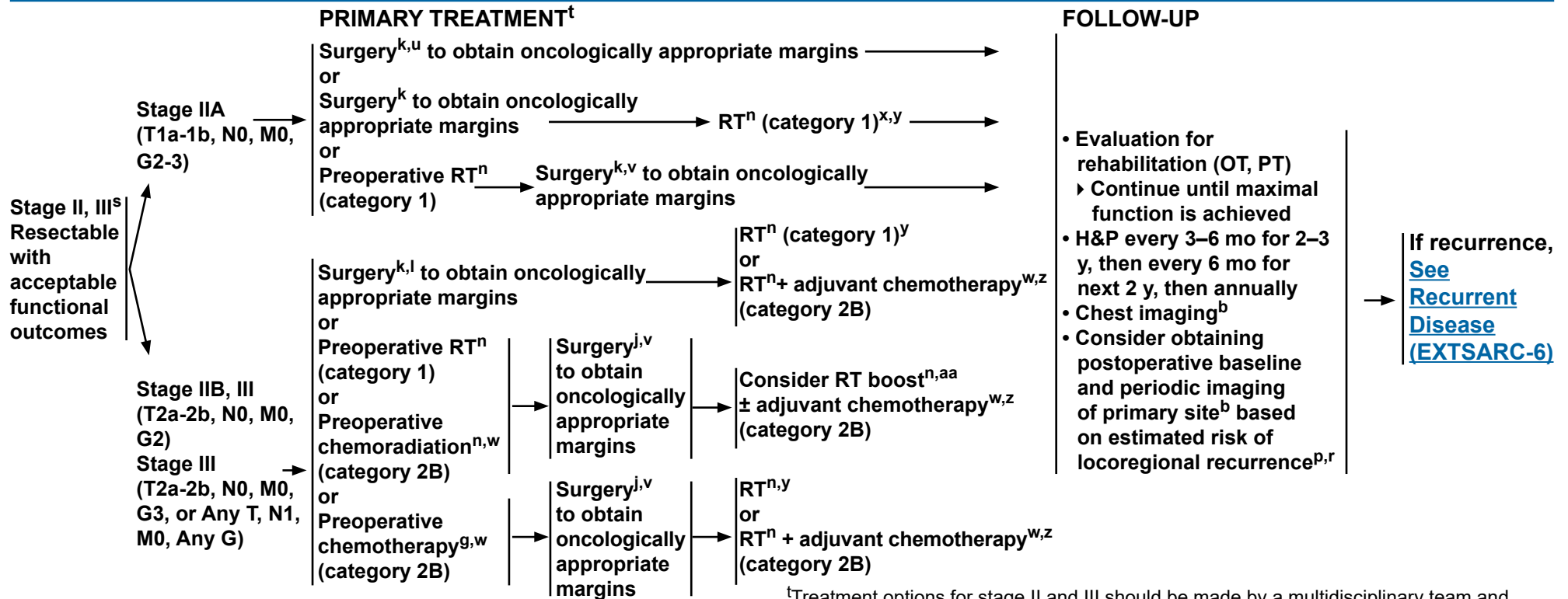
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Extremity/Superficial Trunk, Head/Neck



^bSee Principles of Imaging (SARC-A).

^gPET/CT may be useful in determining response to chemotherapy for lesions that are larger than 3 cm, firm, and deep, not superficial (Schuetze SM, Rubin BP, Vernon C, et al. Use of positron emission tomography in localized extremity soft tissue sarcoma treated with neoadjuvant chemotherapy. Cancer 2005;103:339-348).

^kSee Principles of Surgery (SARC-D).

^lIn selected cases when margin status is uncertain, consultation with a radiation oncologist is recommended. Reresection, if feasible, may be necessary to render margins >1.0 cm.

ⁿSee Radiation Therapy Guidelines (SARC-E).

^pIn situations where the area is easily followed by physical examination, imaging may not be required.

^rAfter 10 y, the likelihood of developing a recurrence is small and follow-up should be individualized.

^sPatients with stage III tumors with lymph node involvement should undergo regional lymph node dissection at the time of primary tumor resection ± RT.

[†]Treatment options for stage II and III should be made by a multidisciplinary team and involve consideration of the following: performance status, comorbid factors (including age), site of disease, histologic subtype, and institutional experience.

^uSurgery alone may be an option for small tumors resected with wide margins.

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

^wSee Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F).

^xRT may be used in select circumstances such as close or positive margins where re-excision is not feasible or for functional considerations.

^yYang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol 1998;16:197-203.

^zThere are limited and conflicting data regarding the potential benefits of adjuvant chemotherapy in stage II or stage III patients.

^{aa}For residual gross disease or microscopically positive margins.

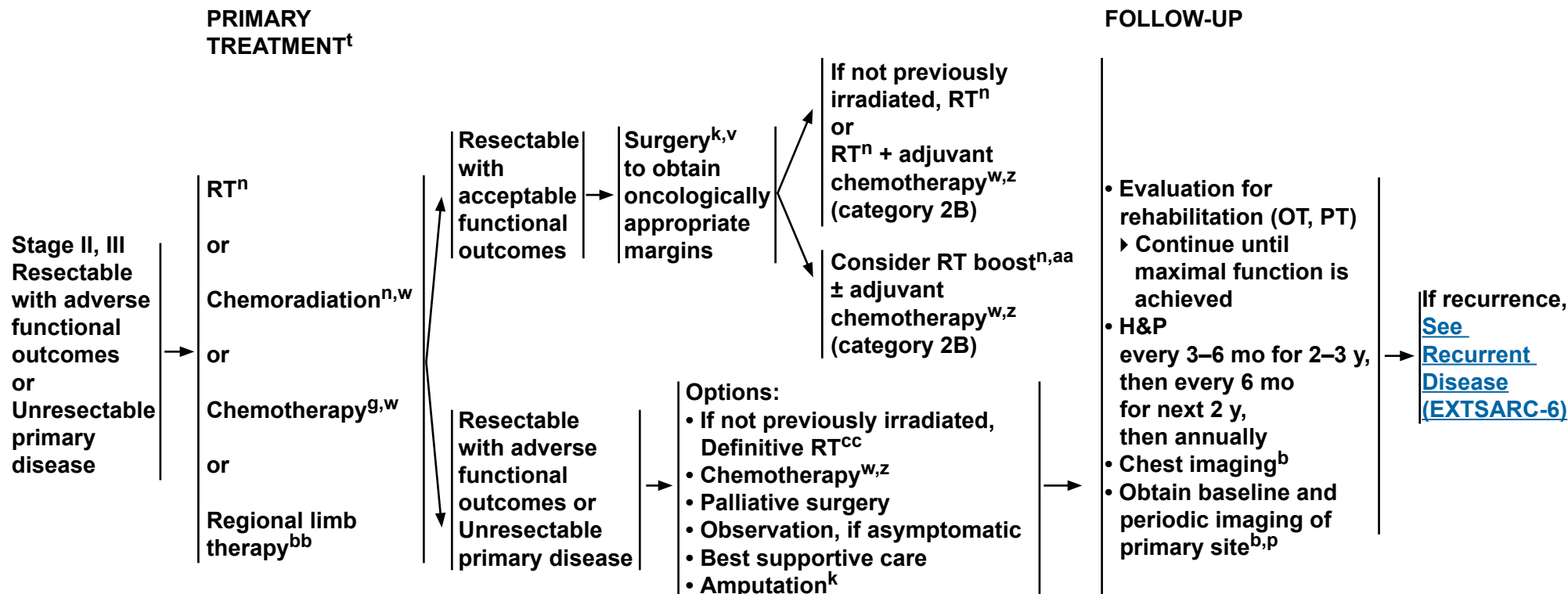
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Extremity/Superficial Trunk, Head/Neck



^bSee Principles of Imaging (SARC-A).

^gPET/CT may be useful in determining response to chemotherapy for lesions that are larger than 3 cm, firm, and deep, not superficial (Schuetze SM, Rubin BP, Vernon C, et al. Use of positron emission tomography in localized extremity soft tissue sarcoma treated with neoadjuvant chemotherapy. Cancer 2005;103:339-348).

^kSee Principles of Surgery (SARC-D).

ⁿSee Radiation Therapy Guidelines (SARC-E).

^pIn situations where the area is easily followed by physical examination, imaging may not be required.

^tTreatment options for stage II and III should be made by a multidisciplinary team and involve consideration of the following: performance status, comorbid factors (including age), site of disease, histologic subtype, and institutional experience.

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

^wSee Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F).

^zThere are limited and conflicting data regarding the potential benefits of adjuvant chemotherapy in stage II or stage III patients.

^{aa}For residual gross disease or microscopically positive margins.

^{bb}Should only be done at institutions with experience in regional limb therapy.

^{cc}Definitive RT entails delivering the maximal local dose compatible with known normal tissue tolerance, typically in the range of 7000–8000 cGy with sophisticated treatment planning techniques being a necessity in this setting.

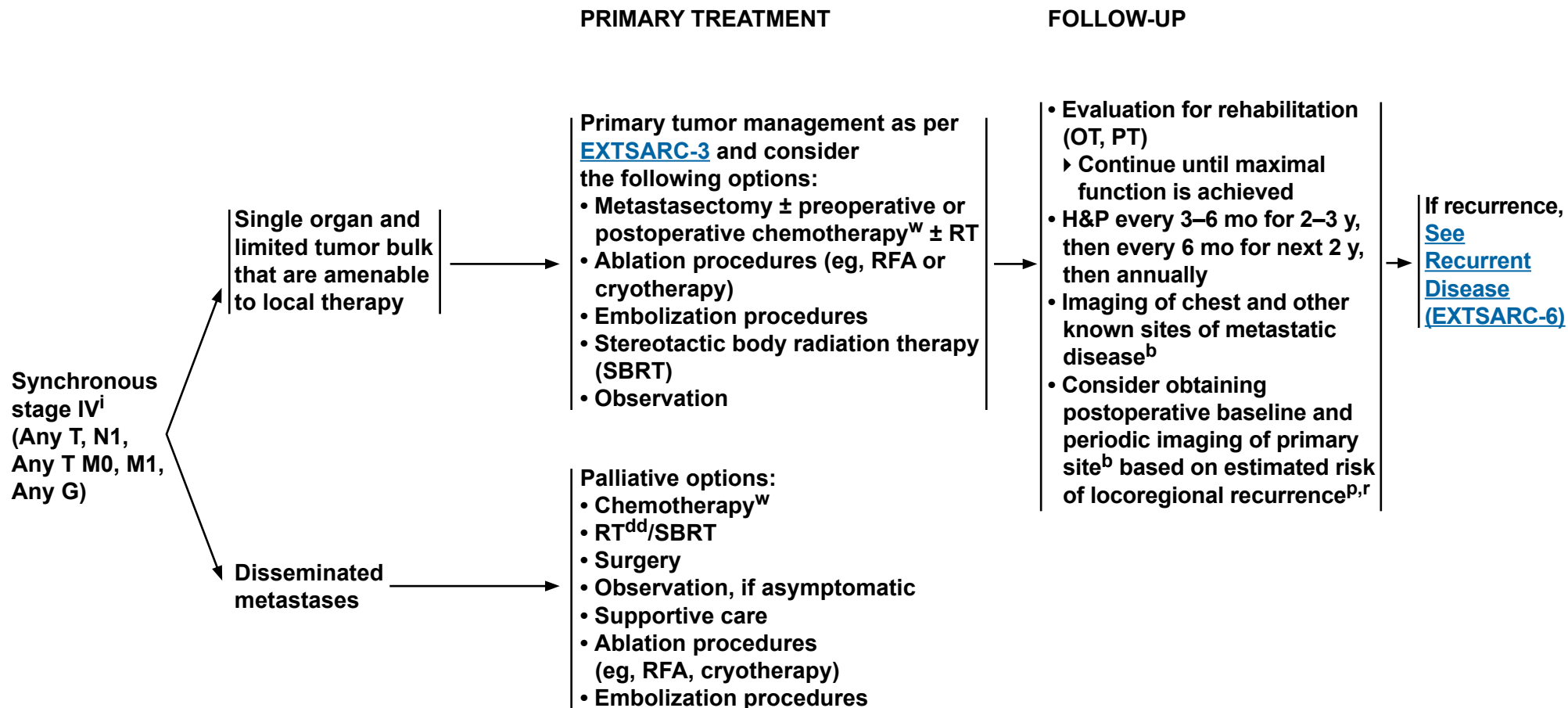
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Extremity/Superficial Trunk, Head/Neck



^bSee [Principles of Imaging \(SARC-A\)](#).

ⁱPatients with DFSP with fibrosarcomatous changes and/or malignant transformations can be treated according to this algorithm.

^pIn situations where the area is easily followed by physical examination, imaging may not be required.

^rAfter 10 y, the likelihood of developing a recurrence is small and follow-up should be individualized.

^wSee [Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma \(SARC-F\)](#).

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

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Extremity/Superficial Trunk, Head/Neck

RECURRENT DISEASE

TREATMENT

Local
recurrence

Follow Workup, then appropriate Primary Treatment^{ee} pathway
([EXTSARC-1](#), [EXTSARC-2](#), [EXTSARC-3](#), [EXTSARC-4](#))

Metastatic
disease

Single organ and
limited tumor bulk
that are amenable
to local therapy

Options:

- Metastasectomy ± preoperative or postoperative chemotherapy^w ± RT
- Ablation procedures (eg, RFA or cryotherapy)
- Embolization procedures
- SBRT

Disseminated
metastases

Palliative options:

- Chemotherapy^w
- RT^{dd}/SBRT
- Surgery
- Observation, if asymptomatic
- Supportive care
- Ablation procedures (eg, RFA or cryotherapy)
- Embolization procedures

Isolated regional
disease or nodes

Options:

- Regional node dissection for nodal involvement ± RT ± chemotherapy^w
- Metastasectomy ± preoperative or postoperative chemotherapy^w ± RT
- SBRT
- Isolated limb perfusion/infusion

^wSee [Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma \(SARC-E\)](#)

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

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

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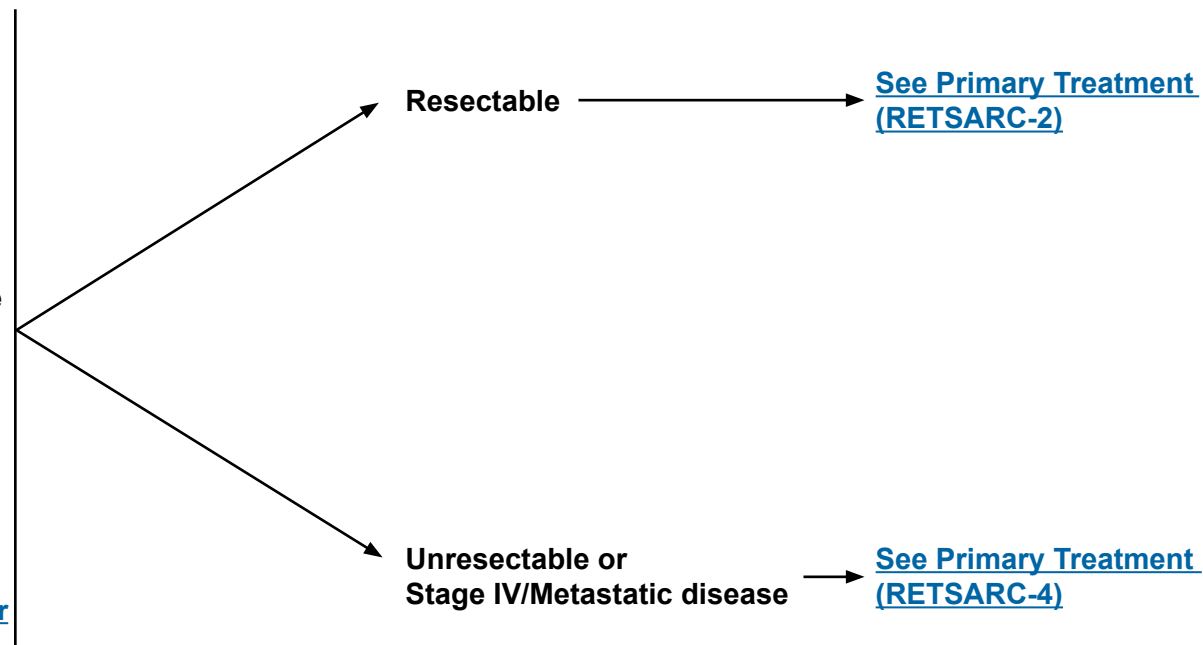


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Retroperitoneal/Intra-Abdominal

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
- Imaging^a
- Preresection biopsy not necessarily required; consider biopsy if there is suspicion of malignancies other than sarcoma
- Biopsy is necessary for patients receiving preoperative RT or chemotherapy
- Image-guided^a core needle biopsy is preferred over open surgical biopsy^b
- Patients with personal/family history suggestive of Li-Fraumeni syndrome should be considered for further genetics assessment. [See NCCN Guidelines for Genetic/Familial High Risk Assessment: Breast and Ovarian](#)
- Patients with neurofibromatosis: [See NCCN Guidelines for Central Nervous System Cancers \(PSCT-3\)](#)



^a[See Principles of Imaging \(SARC-A\).](#)

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

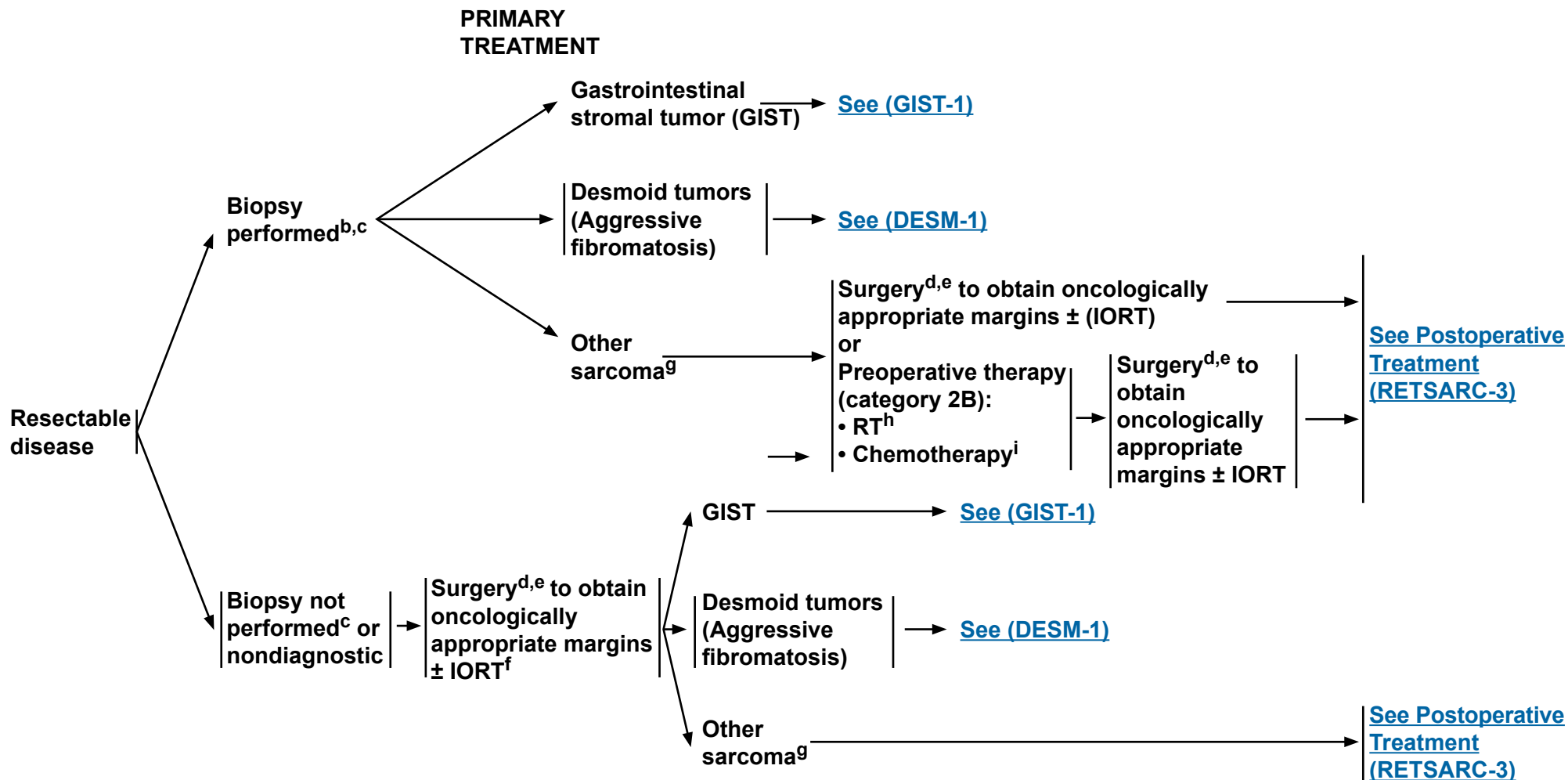
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Retroperitoneal/Intra-Abdominal



^bSee Principles of Pathologic Assessment of Sarcoma Specimens (SARC-B).

^cBiopsy required if considering preoperative therapy, including endoscopic biopsy for suspected GIST lesions.

^dSee Principles of Surgery (SARC-D).

^eIf RT is anticipated, preferred approach would be preoperative RT with an IMRT approach to optimize sparing of nearby critical structures.

^fIORT may be considered provided frozen section pathology can confidently demonstrate a

non-GIST/non-desmoid histology.

^gFor other soft tissue sarcomas such as Ewing's sarcoma, see NCCN Guidelines for Bone Cancer; for RMS, see RMS-1; for Desmoid tumors (aggressive fibromatosis), see DESM-1.

^hSee Radiation Therapy Guidelines (SARC-E).

ⁱSee Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F).

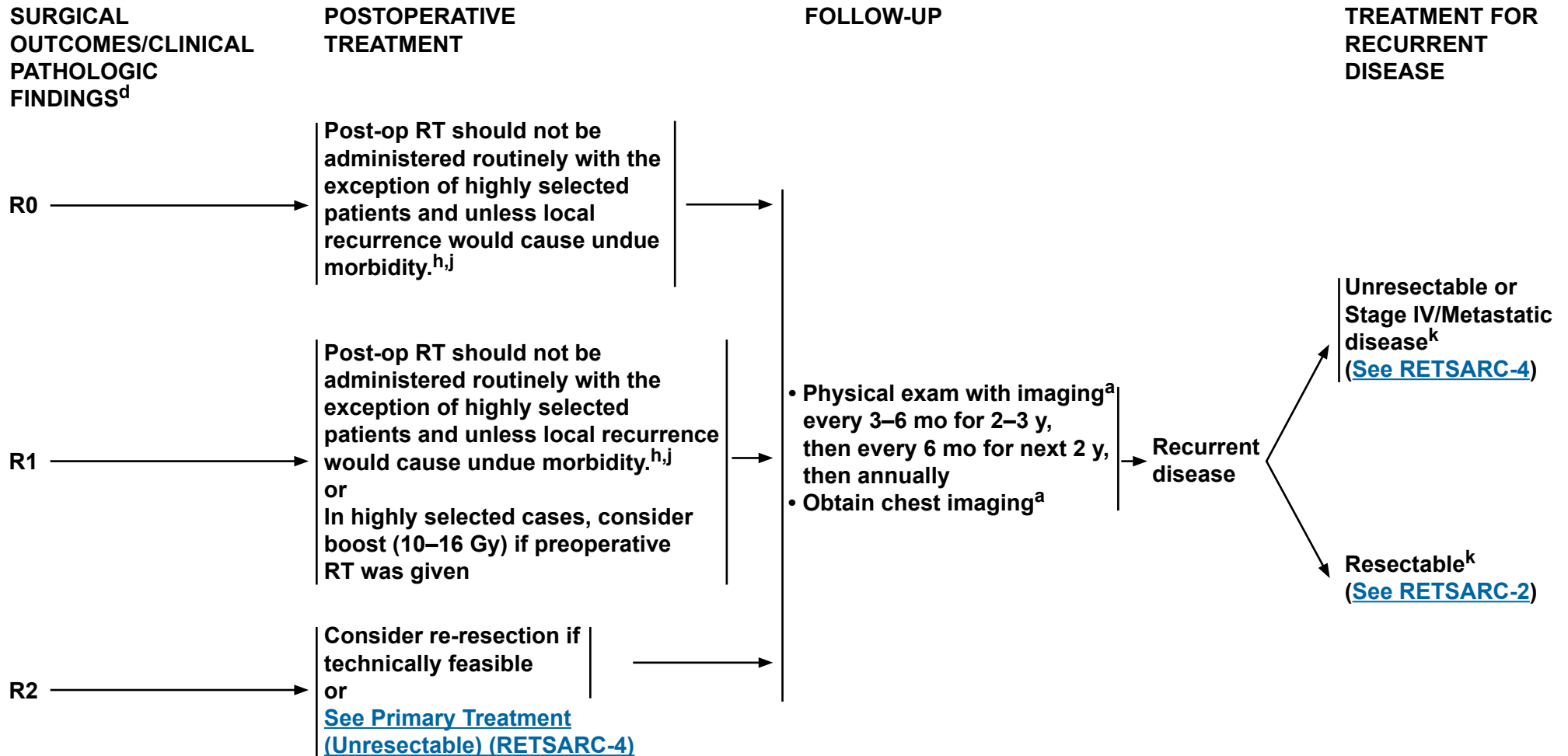
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Retroperitoneal/Intra-Abdominal



^aSee Principles of Imaging (SARC-A).

^dSee Principles of Surgery (SARC-D).

^hSee Radiation Therapy Guidelines (SARC-E).

^jFor example, critical anatomic surface where recurrence would cause morbidity.

^kIf not previously administered, consider preoperative RT and/or chemotherapy.

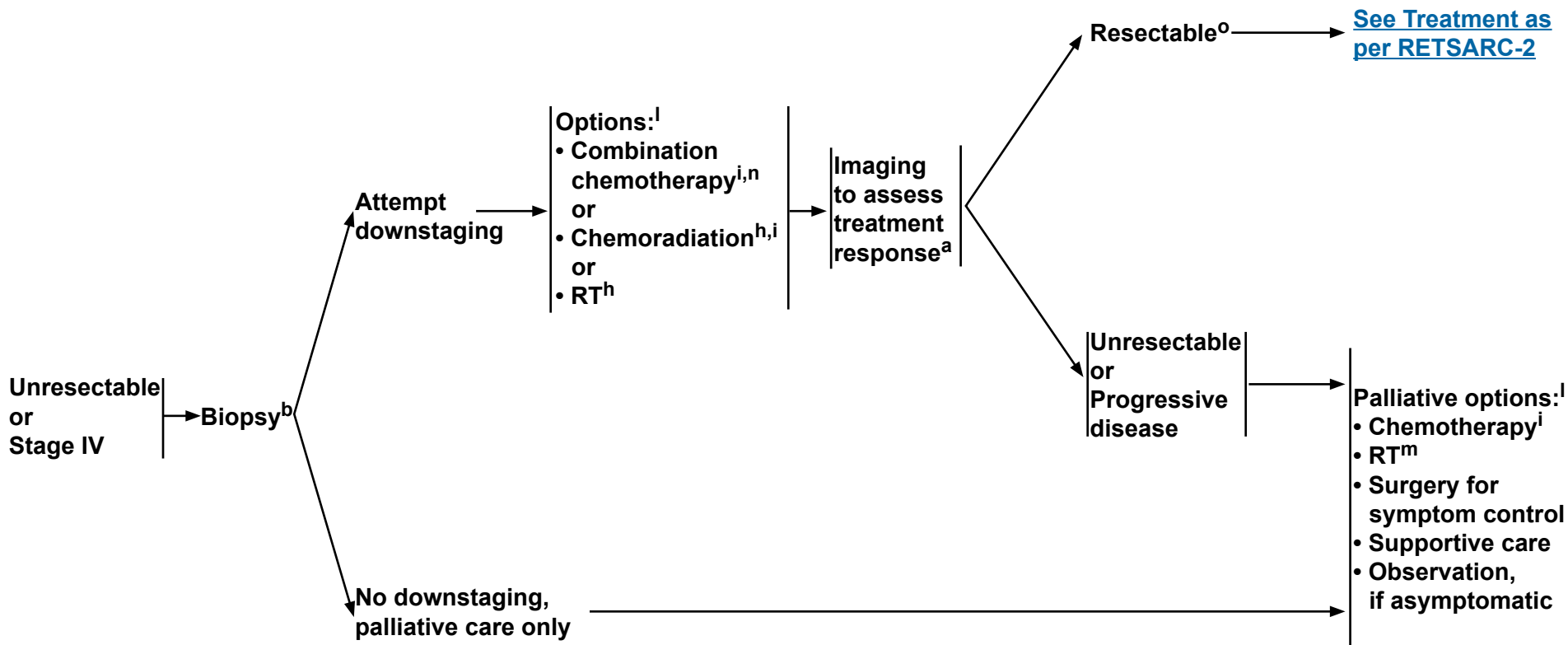
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Retroperitoneal/Intra-Abdominal

PRIMARY TREATMENT



^aSee Principles of Imaging (SARC-A).

^bSee Principles of Pathologic Assessment of Sarcoma Specimens (SARC-B).

^hSee Radiation Therapy Guidelines (SARC-E).

ⁱSee Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F).

^lBalance risks of treatment, likelihood of rendering patient resectable, and performance status of patient with potential clinical benefits. The options listed may be used either alone, sequentially, or in combination.

^mPalliative RT requires balancing expedient treatment with sufficient dose expected to halt the growth of or cause tumor regression. Numerous clinical issues regarding rapidity of growth, the status of systemic disease, and the use of chemotherapy must be considered. Recommended only for patients with unresectable or progressive disease.

ⁿThe most active chemotherapy regimen in an unselected patient population is AIM (doxorubicin/ifosfamide/mesna). Judson I, Verweij J, Gelderblom H, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. *Lancet Oncol* 2014; 15(4):415-23.

^oResection of resectable metastatic disease should always be considered if primary tumor can be controlled.

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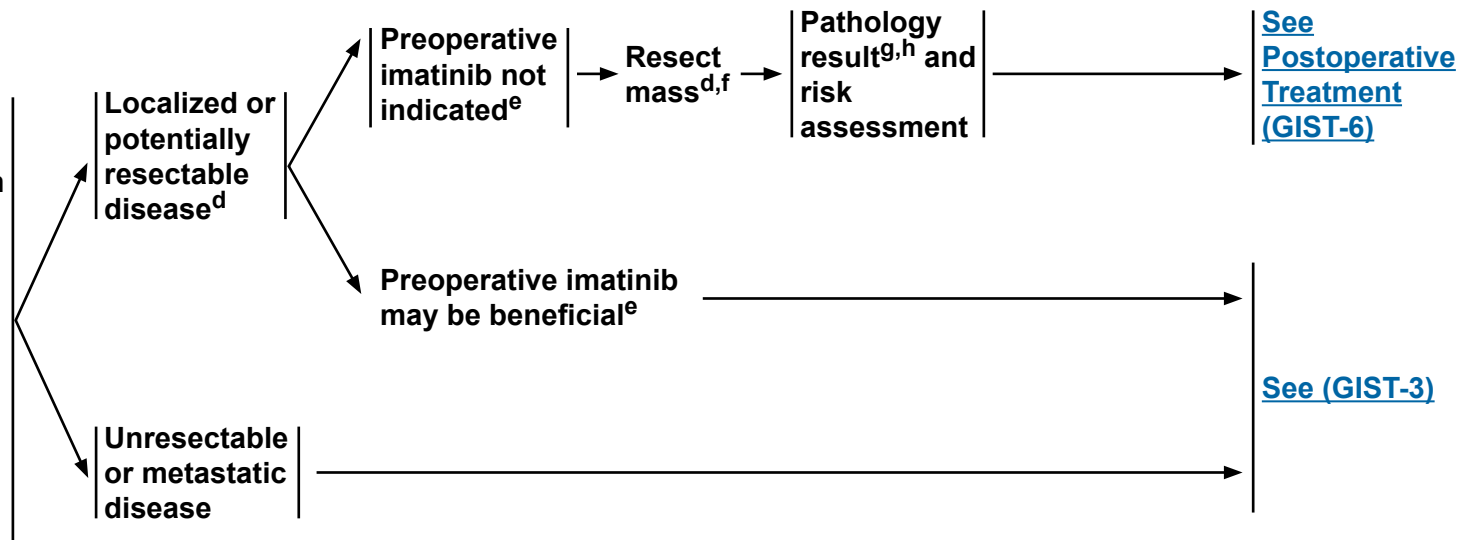
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Gastrointestinal Stromal Tumors (GIST)

WORKUP AT PRIMARY PRESENTATION^a

- Prior to the initiation of therapy, all patients should be evaluated and managed by a multidisciplinary team with expertise and experience in sarcoma
- For very small gastric GISTs <2 cm ([See GIST-2](#))
- Imaging^b
- Consider chest imaging^b
- Testing for mutations in *KIT* and *PDGFRA* is strongly recommended^c
- Genotyping should be performed when medical therapy is planned

RESULTS OF INITIAL DIAGNOSTIC EVALUATION



^aSee American Joint Committee on Cancer (AJCC) Staging, 7th Edition ([ST-3/GIST](#)).

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

^cFor tumors lacking mutation in *KIT* or *PDGFRA*, recommend testing the tumor for SDHB by immunohistochemistry and if deficient (SDH deficient GIST) recommend referral for germ line testing.

^dSurgery should induce minimal surgical morbidity; consider preoperative imatinib if surgery would induce significant morbidity.

^ePreoperative imatinib may prohibit accurate assessment of recurrence risk. Consider preoperative imatinib only if surgical morbidity could be reduced

by downstaging the tumor preoperatively. Testing tumor for mutation is recommended prior to starting preoperative imatinib to ensure tumor has a genotype that is likely to respond to treatment.

^f[See Principles of Surgery for GIST \(GIST-C\)](#).

^gPathology report should include anatomic location, size, and an accurate assessment of the mitotic rate measured in the most proliferative area of the tumor. Mutational analysis may predict response to therapy with tyrosine kinase inhibitors. ([See Principles of Pathologic Assessment for GIST \[GIST-B\]](#)).

^h[See RETSARC-1](#) if the pathology results indicate sarcomas of GI origin other than GIST.

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Gastrointestinal Stromal Tumors (GIST)

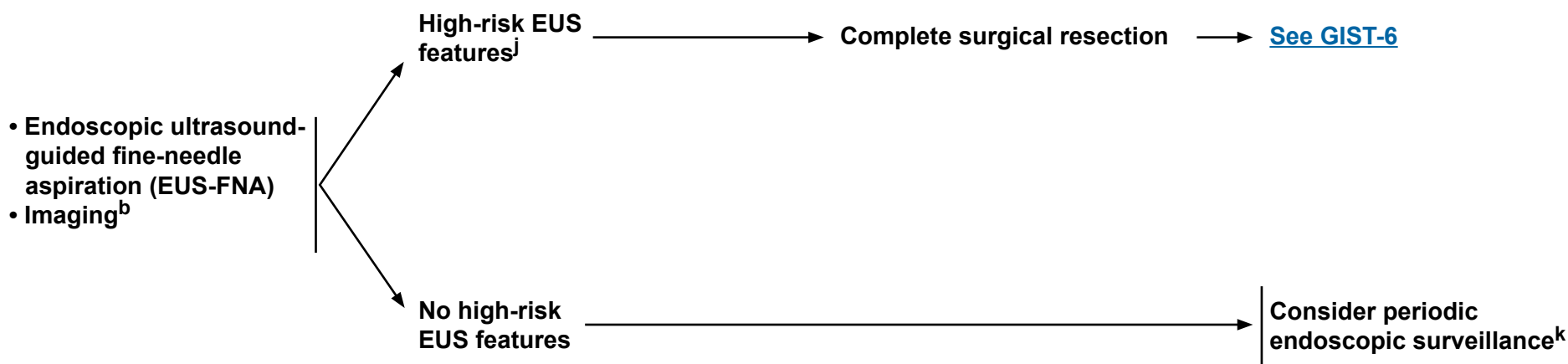
APPROACH TO PATIENTS WITH VERY SMALL GASTRIC GISTS (<2 CM)ⁱ

**WORKUP AT
PRIMARY PRESENTATION**

**RESULTS OF INITIAL
DIAGNOSTIC EVALUATION**

INITIAL MANAGEMENT

FOLLOW-UP



^bSee Principles of Imaging (SARC-A).

ⁱAdapted with permission from Sepe PS, Brugge WR. A guide for the diagnosis and management of gastrointestinal stromal cell tumors. *Nat Rev Gastroenterol Hepatol* 2009;6:363-371. All recommendations for this algorithm are category 2B.

^jPossible high-risk EUS features include irregular border, cystic spaces, ulceration, echogenic foci, and heterogeneity.

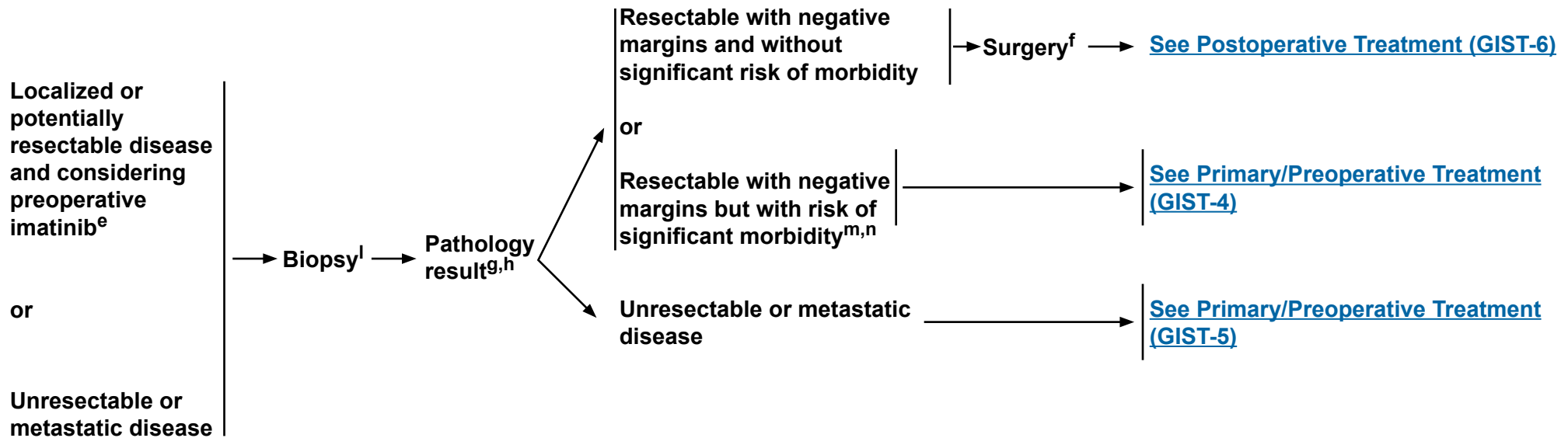
^kEndoscopic ultrasonography surveillance should only be considered after a thorough discussion with the patient regarding the risks and benefits. Evans J, Chandrasekhara V, Chatahadi, KV, et al. The role of endoscopy in the management of premalignant and malignant conditions of the stomach. *Gastrointest Endosc*. 2015;82(1):1-8.

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INITIAL DIAGNOSTIC EVALUATION



^ePreoperative imatinib may prohibit accurate assessment of recurrence risk. Consider preoperative imatinib only if surgical morbidity could be reduced by downstaging the tumor preoperatively. Testing tumor for mutation is recommended prior to starting preoperative imatinib to ensure tumor has a genotype that is likely to respond to treatment.

^f[See Principles of Surgery for GIST \(GIST-C\).](#)

^gPathology report should include anatomic location, size, and an accurate assessment of the mitotic rate measured in the most proliferative area of the tumor. Mutational analysis may predict response to therapy with tyrosine kinase inhibitors. ([See Principles of Pathologic Assessment for GIST \(GIST-B\)](#)).

^h[See RETSARC-1](#), if the pathology results indicate sarcomas of GI origin other than GIST.

^l[See Principles of Biopsy for GIST \(GIST-A\).](#)

^mSome patients may rapidly become unresectable; close monitoring is essential.

ⁿFor SDH-deficient GIST extensive surgery with significant morbidity (ie, total gastrectomy) is not recommended.

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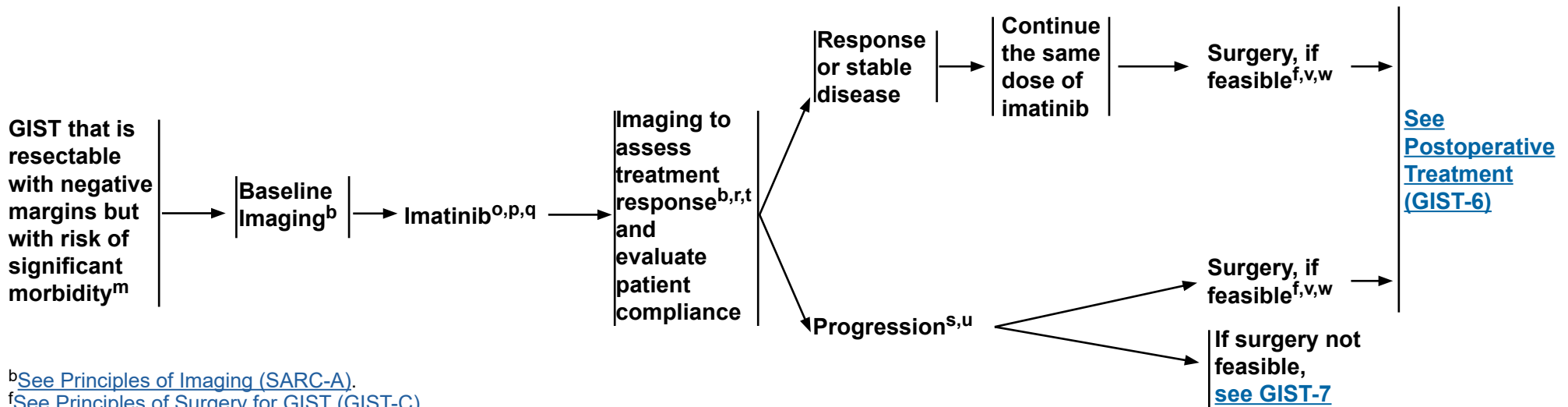
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Gastrointestinal Stromal Tumors (GIST)

PRIMARY PRESENTATION

PRIMARY/PREOPERATIVE TREATMENT

FOLLOW-UP THERAPY



^bSee Principles of Imaging (SARC-A).

^fSee Principles of Surgery for GIST (GIST-C).

^mSome patients may rapidly become unresectable; close monitoring is essential.

^oIf life-threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider sunitinib.

^pMedical therapy is the usual course of treatment. However, patient may proceed to surgery if bleeding or symptomatic.

^qBecause patients with advanced GISTs have different responses to imatinib, mutational testing should be performed; approximately 90% of patients have disease that respond to imatinib when their tumors have a *KIT* exon 11 mutation; approximately 50% of patients have disease that respond when their tumors harbor a *KIT* exon 9 mutation, and the likelihood of response improves with the use of 800 mg imatinib rather than the standard 400 mg dose. Most mutations in the *PDGFRA* gene are associated with a response to imatinib, with the notable exception of D842V. In the absence of *KIT* and *PDGFRA* mutations, advanced GISTs have a 0%–45% likelihood of responding to imatinib. Metastatic disease with acquired drug resistance is usually the result of secondary, imatinib-resistant mutations in *KIT* or *PDGFRA*. *SDH*-deficient GIST may have a higher probability of response to sunitinib.

^rPET may give indication of imatinib activity after 2–4 weeks of therapy when rapid readout of activity is necessary. Diagnostic abdominal/pelvic CT or MRI with contrast is indicated every 8–12 weeks; routine long-term PET follow-up is rarely indicated. Frequency of response assessment imaging may be decreased if patient is responding to treatment.

^sRarely, increase in tumor size may not indicate lack of drug efficacy; all clinical and radiographic data should be taken into account, including lesion density on CT.

^tProgression may be determined by abdominal/pelvic CT or MRI with contrast with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.

^uSuggest referral to a sarcoma specialty center.

^vCollaboration between medical oncologist and surgeon is necessary to determine the appropriateness of surgery, following major response or sustained stable disease.

^wImatinib can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications. If other TKIs, such as sunitinib or regorafenib, are being used, therapy should be stopped at least one week prior to surgery and can be restarted based on clinical judgment or recovery from surgery.

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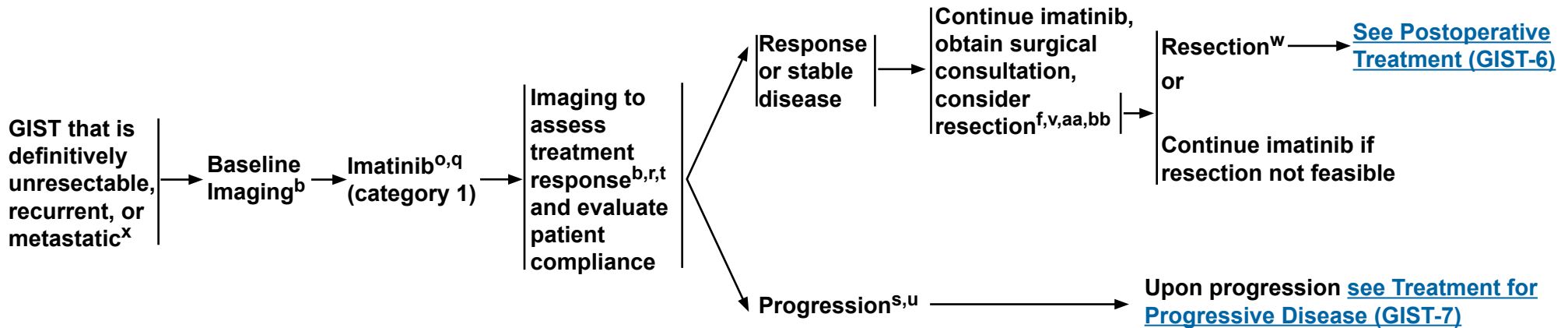
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Gastrointestinal Stromal Tumors (GIST)

PRIMARY PRESENTATION

PRIMARY/PREOPERATIVE TREATMENT

FOLLOW-UP THERAPY



^bSee Principles of Imaging (SARC-A).

^fSee Principles of Surgery for GIST (GIST-C).

^oIf life-threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider sunitinib.

^qBecause patients with advanced GISTs have different responses to imatinib, mutational testing should be performed, approximately 90% of patients have disease that respond to imatinib when their tumors have a *KIT* exon 11 mutation; approximately 50% of patients have disease that respond when their tumors harbor a *KIT* exon 9 mutation, and the likelihood of response improves with the use of 800 mg imatinib rather than the standard 400 mg dose. Most mutations in the *PDGFRA* gene are associated with a response to imatinib, with the notable exception of D842V. In the absence of *KIT* and *PDGFRA* mutations, advanced GISTs have a 0%–45% likelihood of responding to imatinib. Metastatic disease with acquired drug resistance is usually the result of secondary, imatinib-resistant mutations in *KIT* or *PDGFRA*. SDH deficient GIST may have a higher probability of response to sunitinib.

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^vCollaboration between medical oncologist and surgeon is necessary to determine the appropriateness of surgery following major response or sustained stable disease.

^wImatinib can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications. If other TKIs, such as sunitinib or regorafenib, are being used, therapy should be stopped at least one week prior to surgery and can be restarted based on clinical judgment or recovery from surgery.

^xConsider baseline PET, if using PET during follow-up. PET is not a substitute for CT.

^{aa}No definitive data exist to prove whether surgical resection improves clinical outcomes in addition to TKI therapy alone in metastatic GIST. Prospective randomized trials are underway to assess whether or not resection changes outcomes in patients with metastatic GIST responding to TKI therapy.

^{bb}Consider resection if complete resection can be obtained in primary metastatic disease.

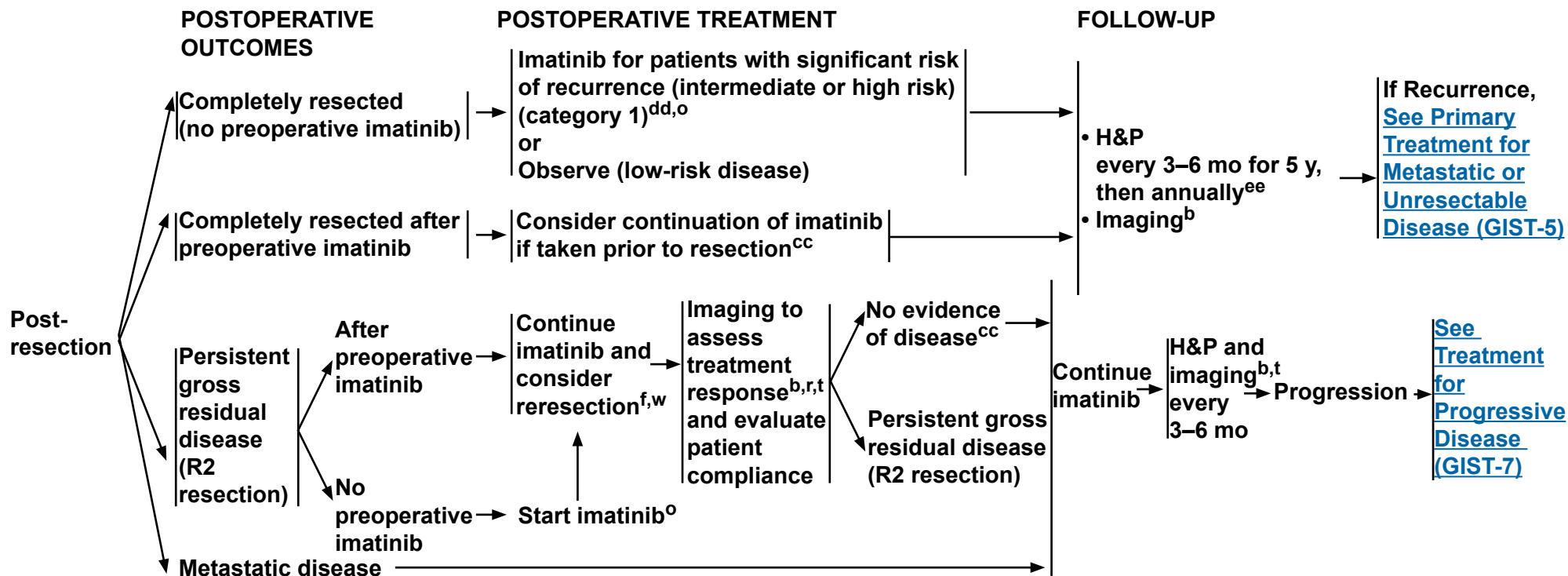
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Gastrointestinal Stromal Tumors (GIST)



^bSee Principles of Imaging (SARC-A).

^fSee Principles of Surgery for GIST (GIST-C).

^oIf life-threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider sunitinib.

^rPET may give indication of imatinib activity after 2–4 weeks of therapy when rapid readout of activity is necessary. Diagnostic abdominal/pelvic CT or MRI with contrast is indicated every 8–12 weeks; routine long-term PET follow-up is rarely indicated. Frequency of response assessment imaging may be decreased if patient is responding to treatment.

^tProgression may be determined by abdominal/pelvic CT or MRI with contrast with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.

^wImatinib can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications. If other TKIs, such as sunitinib or regorafenib, are being used, therapy should be stopped at least one week prior to surgery and can be restarted based on clinical judgment or recovery from surgery.

^{cc}For patients with complete resections following preoperative imatinib, continuation of imatinib should be considered. The duration of postoperative imatinib has not been studied in randomized trials; there are single and multi-institutional trials supporting the benefit for continuation of imatinib for two years following surgery.

^{dd}Postoperative imatinib for at least 36 months should be considered for high-risk tumors. The results of a randomized trial (SSGXVIII/AIO) suggest that postoperative imatinib administered for 36 months improves relapse-free survival and overall survival compared to 12 months for patients with a high estimated risk of recurrence (tumor greater than 5 cm in size with high mitotic rate [>5 mitoses/50 HPF], tumor rupture, or a risk of recurrence of greater than 50% after surgery). The results of the ACOSOG trial Z9001 showed that postoperative imatinib improved RFS in patients with GIST ≥ 3 cm in size with the greatest benefit noted in tumors at higher risk of recurrence (intermediate and high risk). This trial did not demonstrate overall survival benefit.

^{ee}Less frequent surveillance may be acceptable for very small tumors (<2 cm).

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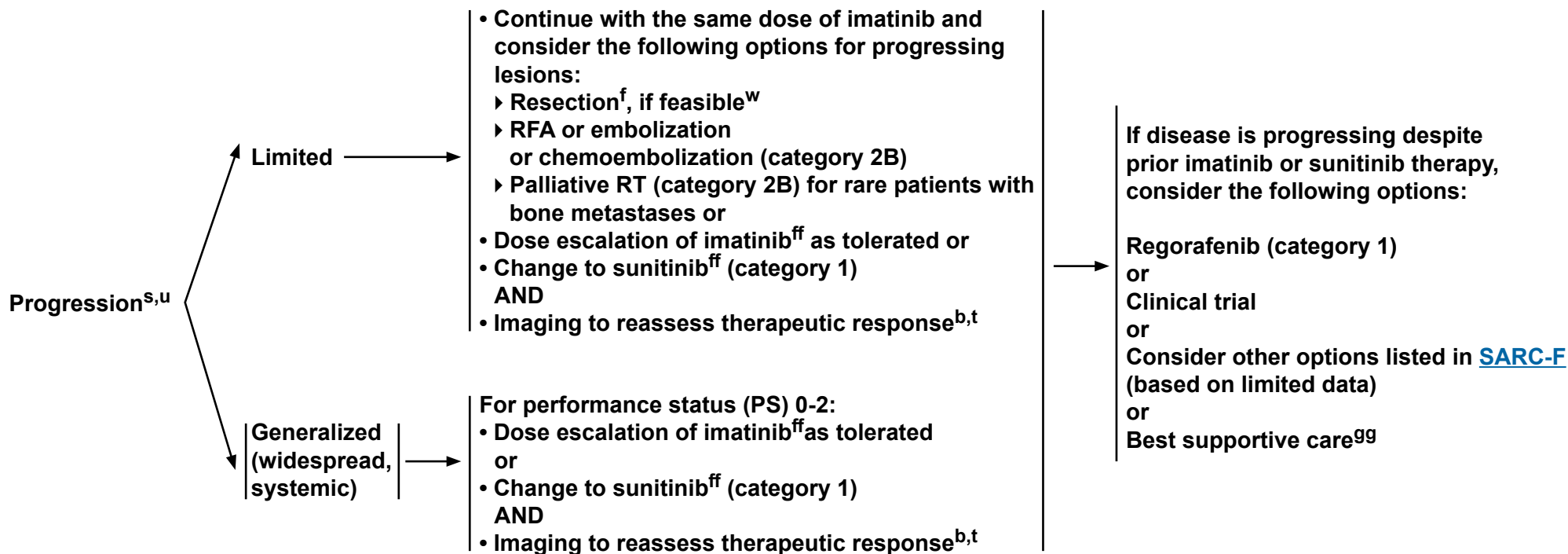
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Gastrointestinal Stromal Tumors (GIST)

TREATMENT FOR PROGRESSIVE DISEASE



^bSee Principles of Imaging (SARC-A).

^fSee Principles of Surgery For GIST (GIST-C).

^sRarely, increase in tumor size may not indicate lack of drug efficacy; all clinical and radiographic data should be taken into account, including lesion density on CT.

^tProgression may be determined by abdominal/pelvic CT or MRI with contrast with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.

^uSuggest referral to a sarcoma specialty center.

^wImatinib can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications. If other TKIs, such as sunitinib or regorafenib, are being used, therapy should be stopped at least one week prior to surgery and can be restarted based on clinical judgment or recovery from surgery.

^{ff}Clinical experience suggests that discontinuing tyrosine kinase inhibitor (TKI) therapy, even in the setting of progressive disease, may accelerate the pace of disease progression and worsen symptoms.

⁹⁹In patients with GIST progressing despite prior imatinib, sunitinib, and regorafenib consider other options listed in [SARC-F](#) (based on limited data) or reintroduction of a previously tolerated and effective TKI for palliation of symptoms. Consider continuation of TKI therapy life-long for palliation of symptoms as part of best supportive care.

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PRINCIPLES OF BIOPSY FOR GIST

- GISTs are soft and fragile tumors. EUS-FNA biopsy of primary site is preferred over percutaneous biopsy (due to the risk for hemorrhage and intra-abdominal tumor dissemination).
- Consideration of biopsy should be based on the suspected tumor type and extent of disease.
- Biopsy is necessary to confirm the diagnosis of primary GIST prior to the initiation of preoperative therapy.
- Percutaneous image-guided biopsy may be appropriate for confirmation of metastatic disease.
- Diagnosis is based on the Principles of Pathologic Assessment ([See SARC-B](#)); referral to centers with expertise in sarcoma diagnosis is recommended for cases with complex or unusual histopathologic features.
- Testing for mutations in *KIT* and *PDGFRA* is strongly recommended.
- Testing for germline mutations in the *SDH* genes should be considered for patients with wild-type GIST (lacking *KIT* or *PDGFRA* mutations).
- Risk stratification:
 - ▶ While tumor size and mitotic rate are used to assess the risk of metastasis of GIST, it is notoriously difficult to predict the biologic behavior of GIST based on pathologic features alone; thus, guidelines for risk stratification by tumor site have been developed.
 - ▶ Most gastric GISTs behave in an overall indolent manner and those smaller than 2 cm are almost universally benign. See Table 1: Gastric GISTs: Proposed Guidelines for Assessing the Malignant Potential ([GIST-A 2 of 3](#)).
 - ▶ GIST of the small intestine tends to be more aggressive than its gastric counterpart. See Table 2: Small Intestinal GISTs: Proposed Guidelines for Assessing Malignant Potential ([GIST-A 3 of 3](#)).
 - ▶ GIST of the colon is most commonly seen in the rectum; colonic GIST tends to have an aggressive biological behavior, and tumors with mitotic activity can recur and metastasize despite a small size of <2 cm.
 - ▶ Specific mutations in *KIT* or *PDGFRA* show some correlation with tumor phenotype, but mutations are not strongly correlated with the biologic potential of individual tumors. The accumulated data show that *KIT* mutations are not preferentially present in high-grade tumors, and can also be found in small incidental tumors as well as tumors that have a benign course. Similarly, mutational analysis of *PDGFRA* cannot be used to predict the behavior of individual tumors.

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Gastrointestinal Stromal Tumors (GIST)

PREDICTORS OF GIST BIOLOGIC BEHAVIOR

Table 1: Gastric GISTs: Proposed Guidelines for Assessing the Malignant Potential^{1,2}

<u>Tumor Size</u>	<u>Mitotic Rate</u>	<u>Predicted Biologic Behavior</u>
≤2 cm	≤5 mitoses/50 HPFs	Metastasis rate: 0%
	>5 mitoses/50 HPFs	Metastasis rate: 0%*
>2 cm ≤5 cm	≤5 mitoses/50 HPFs	Metastasis rate: 1.9%
	>5 mitoses/50 HPFs	Metastasis rate: 16%
>5 cm ≤10 cm	≤5 mitoses/50 HPFs	Metastasis rate: 3.6%
	>5 mitoses/50 HPFs	Metastasis rate: 55%
>10 cm	≤5 mitoses/50 HPFs	Metastasis rate: 12%
	>5 mitoses/50 HPFs	Metastasis rate: 86%

GISTs: Gastrointestinal stromal tumors; HPFs: High-power fields; *predicted rate based on tumor category with very small numbers

¹Data from Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Sem Diag Path* 2006;23:70-83.

²Per 50 HPF is a total of 5 mm². For most modern microscopes, 20 HPF 40 x lenses/fields encompasses 5 mm². (Rubin BP, Blanke CD, Demetri G, et al. CAP: Protocol for the examination of specimens from patients with gastrointestinal stromal tumor (GIST) checklist for GIST. June 2012.)

Available at: http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2012/GIST_12protocol_3021.pdf.

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Gastrointestinal Stromal Tumors (GIST)**PREDICTORS OF GIST BIOLOGIC BEHAVIOR****Table 2: Small Intestinal GISTs: Proposed Guidelines for Assessing the Malignant Potential^{1,2}**

<u>Tumor Size</u>	<u>Mitotic Rate</u>	<u>Predicted Biologic Behavior</u>
≤2 cm	≤5 mitoses/50 HPFs	Metastasis rate: 0%
	>5 mitoses/50 HPFs	Metastasis rate: 50%*
>2 cm ≤5 cm	≤5 mitoses/50 HPFs	Metastasis rate: 4.3%–8.3%
	>5 mitoses/50 HPFs	Metastasis rate: 50%–73%
>5 cm ≤10 cm	≤5 mitoses/50 HPFs	Metastasis rate: 24%
	>5 mitoses/50 HPFs	Metastasis rate: 85%
>10 cm	≤5 mitoses/50 HPFs	Metastasis rate: 34%–52%
	>5 mitoses/50 HPFs	Metastasis rate: 86%–90%
GISTs: Gastrointestinal stromal tumors; HPFs: High-power fields; *predicted rate based on tumor category with very small numbers		

¹Data from Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Sem Diag Path* 2006;23:70-83.²Per 50 HPF is a total of 5 mm². For most modern microscopes, 20 HPF 40 x lenses/fields encompasses 5 mm². Rubin BP, Blanke CD, Demetri, GD, et al. CAP: Protocol for the Examination of Specimens From Patients With Gastrointestinal Stromal Tumor (GIST). Version 3.1.0.0, December 2014.<http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution%20Folders/WebContent/pdf/cp-gist-14protocol.pdf>**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.**



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Gastrointestinal Stromal Tumors (GIST)

PRINCIPLES OF PATHOLOGIC ASSESSMENT FOR GIST

- Pathologic assessment should follow the guidelines outlined in [SARC-B](#).
- Morphologic diagnosis based on microscopic examination of histologic sections is the standard for GIST diagnosis. Several ancillary techniques are useful in support of GIST diagnosis, including immunohistochemistry (97% expression CD117, 99% expression DOG1, and 81% CD34 expression) and molecular genetic testing (for mutations in *KIT* or *PDGFRA*). DOG1 immunostaining may be useful for cases that cannot be categorized as GIST based on CD117 immunostaining. Referral to centers with expertise in sarcoma diagnosis is recommended for cases with complex or unusual histopathologic features.
- Tumors lacking *KIT* or *PDGFRA* mutations should be considered for further evaluations such as staining for SDHB by immunohistochemistry, *BRAF* mutation analysis, and *SDH* gene mutation analysis.
- Tumor size and mitotic rate are used as guides to predict the malignant potential of GISTs, although it is notoriously difficult to predict the biologic potential of individual cases. The mitotic rate should be measured in the most proliferative area of the tumor, and reported as the number of mitoses per 5 mm² of tissue.
- Approximately 80% of GISTs have a mutation in the gene encoding the *KIT* receptor tyrosine kinase; another 5%–10% of GISTs have a mutation in the gene encoding the related *PDGFRA* receptor tyrosine kinase. The presence and type of *KIT* and *PDGFRA* mutations are not strongly correlated with prognosis. About 10%–15% of GISTs lack mutation in *KIT* or *PDGFRA*. The vast majority of these GISTs have functional inactivation of the succinate dehydrogenase complex (SDH), which can be detected by lack of expression of SDHB on immunohistochemistry. Inactivation of the SDH complex may result from a mutation or from epigenetic silencing. A small minority of GISTs that retain SDH expression have inactivating mutations of *NF1* or activating mutations in *BRAF*.
- The mutations in *KIT* and *PDGFRA* in GIST result in expression of mutant proteins with constitutive tyrosine kinase activity. If tyrosine kinase inhibitors are considered as part of the treatment plan, genetic analysis of the tumor should be considered since the presence of mutations (or absence of mutations) in specific regions of the *KIT* and *PDGFRA* genes are correlated with response (or lack of a response) to specific tyrosine kinase inhibitors. However, the type of mutation cannot be accurately predicted based on the anatomic site of origin or histopathologic features.
- GISTs with *SDH* mutation arise in the stomach in younger individuals, frequently metastasize, may involve lymph nodes, and usually grow slowly. They are usually resistant to imatinib.
- In patients with advanced GISTs, approximately 90% of patients benefit from imatinib when their tumors have a *KIT* exon 11 mutation; approximately 50% of patients benefit from imatinib when their tumors harbor a *KIT* exon 9 mutation, and the likelihood of response improves with the use of 800 mg imatinib rather than the standard 400 mg dose. Most mutations in the *PDGFRA* gene are associated with a response to imatinib, with the notable exception of D842V. In the absence of *KIT* and *PDGFRA* mutations, only a subset of patients with advanced GISTs benefit from imatinib. Metastatic disease with acquired drug resistance is usually the result of secondary, imatinib-resistant mutations in *KIT* or *PDGFRA*. Sunitinib treatment is indicated for patients with imatinib-resistant tumors or imatinib intolerance. Regorafenib is indicated for patients with disease progression on imatinib and sunitinib.

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PRINCIPLES OF SURGERY FOR GIST

Primary (Resectable) GIST

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

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

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

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

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

Unresectable or Metastatic GIST

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

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

Imatinib can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications. If other TKIs, such as sunitinib or regorafenib, are being used, therapy should be stopped at least one week prior to surgery and can be restarted based on clinical judgment or recovery from surgery.

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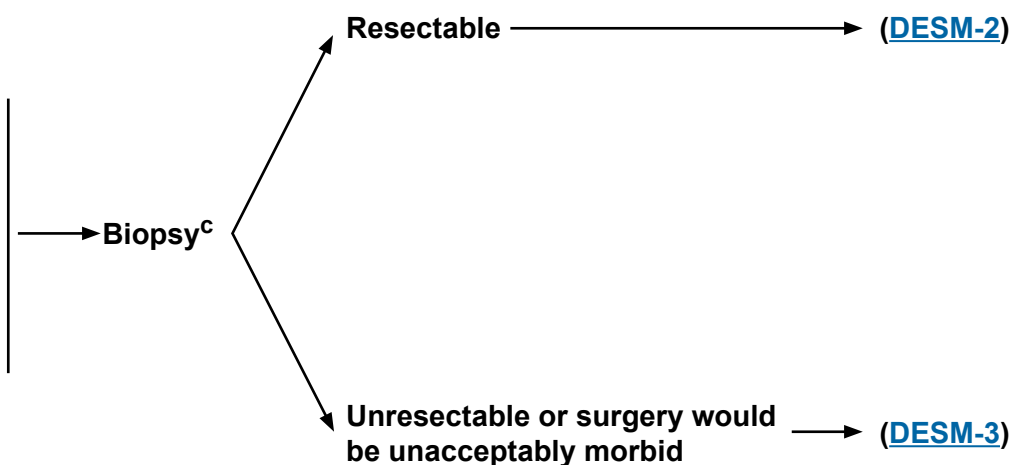


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Desmoid Tumors (Aggressive Fibromatosis)

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 including evaluation for Gardner's syndrome^a/familial adenomatous polyposis (FAP) ([See NCCN Guidelines for Colorectal Cancer Screening](#))
- Appropriate imaging^b of primary site as clinically indicated



^aGardner's syndrome is an autosomal dominant disorder characterized by a triad of colonic polyposis, osteoma, and soft tissue tumors. (Traill Z, Tuson J, Woodham C. Adrenal carcinoma in a patient with Gardner's syndrome: imaging findings. *AJR Am J Roentgenol* 1995;165:1460-1461).

^bSee [Principles of Imaging \(SARC-A\)](#).

^cSee [Principles of Pathologic Assessment of Sarcoma Specimens \(SARC-B\)](#).

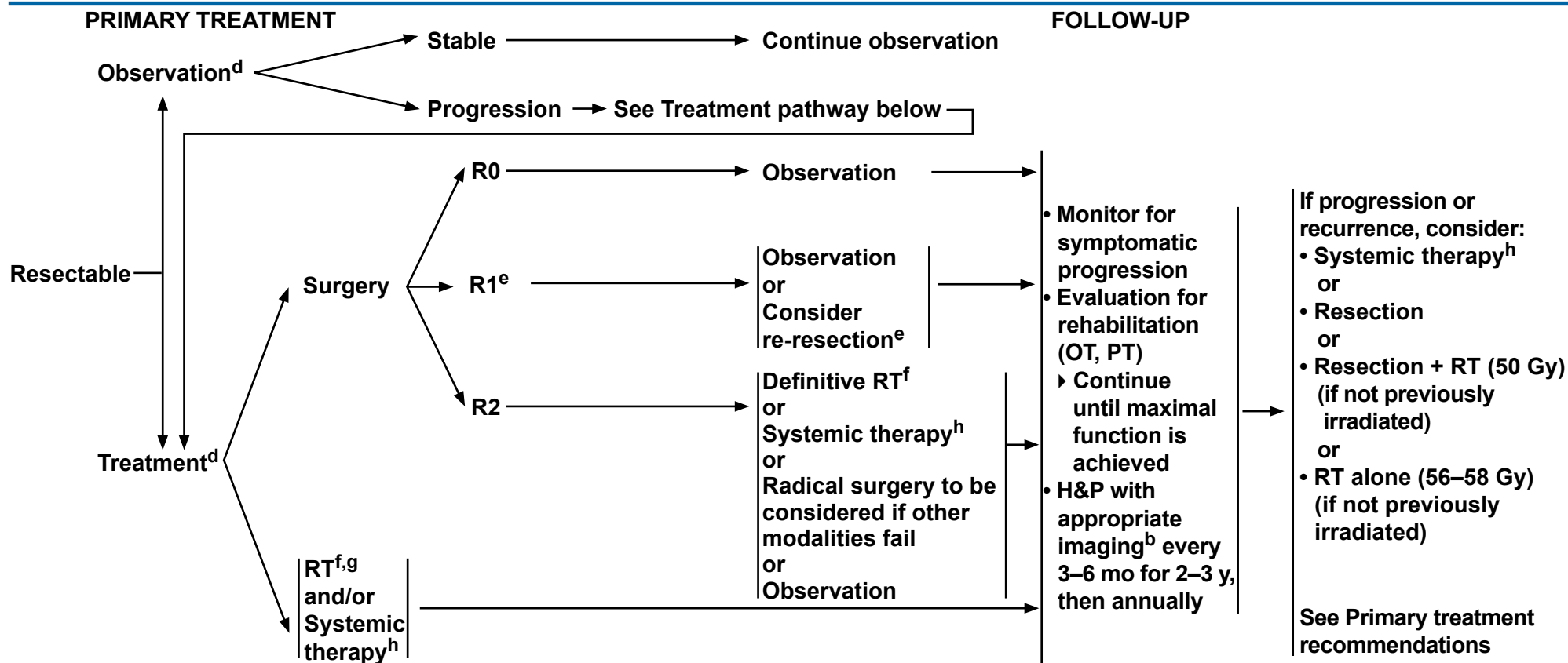
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Desmoid Tumors (Aggressive Fibromatosis)



^bSee Principles of Imaging (SARC-A).

^dFor tumors that are symptomatic, or impairing or threatening function, patients should be offered therapy with the decision based on the location of the tumor and potential morbidity of the therapeutic option.

^eR1 margins are acceptable if achieving R0 margins would produce excessive morbidity. (Cates JM, Stricker TP. Surgical resection margins in desmoid-type fibromatosis: a critical reassessment. *Am J Surg Pathol* 2014;38(12):1707-14). Crago AM, Denton D, Salas S, et al. A prognostic nomogram for prediction of recurrence in desmoid fibromatosis. *Ann Surg* 2013; 258(2): 347-53; and Salas S, Dufresne A, Bui B, et al. Prognostic factors influencing progression-free survival determined from a series of sporadic desmoid tumors: a wait-and-see policy according to tumor presentation. *J Clin Oncol* 2011; 29(26):3553-8).

^fRT is not generally recommended for desmoid tumors that are retroperitoneal/intra-abdominal. RT is generally only recommended for desmoid tumors that are in the extremity, superficial trunk, or head and neck.

^gDose of definitive RT without surgery: 56–58 Gy in the absence of any prior radiation therapy.

^hSee Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F).

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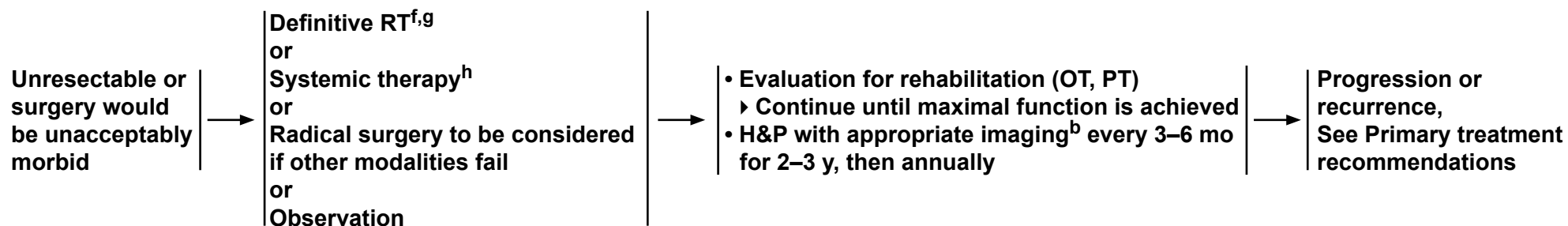


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Desmoid Tumors (Aggressive Fibromatosis)

PRIMARY TREATMENT

FOLLOW-UP



^bSee [Principles of Imaging \(SARC-A\)](#).

^fRT is not generally recommended for desmoid tumors that are retroperitoneal/intra-abdominal. RT is generally only recommended for desmoid tumors that are in the extremity, superficial trunk, or head and neck.

^gDose of definitive RT without surgery: 54–58 Gy in the absence of any prior radiation therapy.

^hSee [Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma \(SARC-F\)](#).

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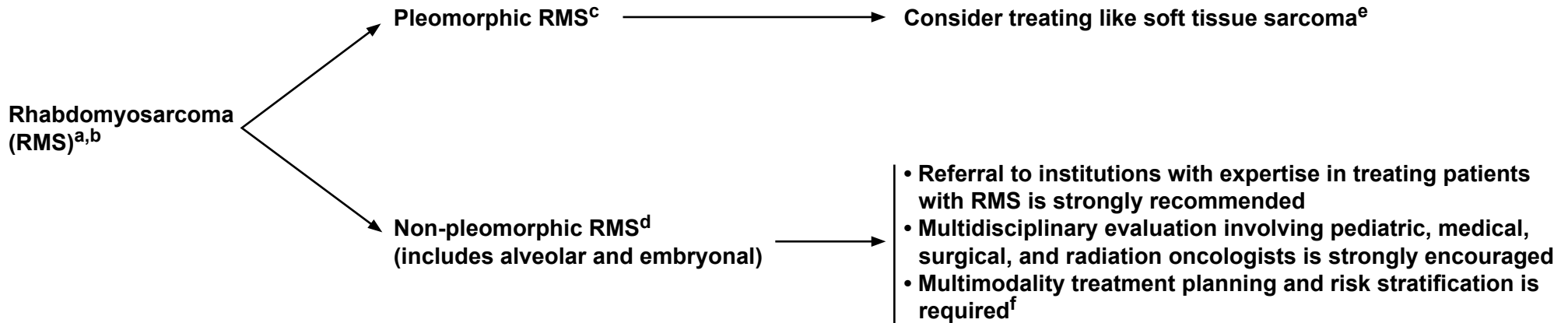
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DIAGNOSIS

HISTOLOGY

TREATMENT



^aRMS 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.

^bPET 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.

^cNot to be confused with anaplastic variant in children.

^dUp to 13% of rhabdomyosarcomas in younger patients may have anaplastic features and should not be confused with the high-grade tumors seen in adults designated as pleomorphic rhabdomyosarcomas.

^ePleomorphic 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 \(SARC-F\).](#)

^fSystemic chemotherapy 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 \(SARC-F\).](#)

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PRINCIPLES OF IMAGING

GENERAL

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

EXTREMITY/SUPERFICIAL TRUNK, HEAD/NECK

Workup

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

Follow-up

Stage I

- Consider chest imaging every 6–12 mo, x-ray or CT (preferred), contrast may be used if also imaging abdomen/pelvis
- Consider postoperative baseline and periodic imaging of primary site based on estimated risk of locoregional recurrence
 - ▶ MRI with and without contrast and/or CT with contrast, and consider ultrasound for small lesions that are superficial. Ultrasound should be done by an ultrasonographer experienced in musculoskeletal disease.²

Stage II/III

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

¹Schuetze SM, Rubin BP, Vernon C, et al. Use of positron emission tomography in localized extremity soft tissue sarcoma treated with neoadjuvant chemotherapy. *Cancer* 2005;103:339-348

²Choi H, Varma DGK, Fornage BD, Kim EE, et al. Soft-tissue sarcoma: MR imaging vs sonography for detection of local recurrence after surgery. *AJR* 1991;157:353-358.

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PRINCIPLES OF IMAGING

Follow-up

Stage II/III

- **Unresectable disease or resectable with adverse functional outcomes: obtain postoperative baseline and periodic imaging of primary site based on estimated risk of locoregional recurrence**
 - ▶ **MRI with and without and/or CT with contrast, and consider ultrasound for small lesions that are superficial. Ultrasound should be done by an ultrasonographer experienced in musculoskeletal disease.²**

Synchronous Stage IV

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

Recurrent Disease

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

RETROPERITONEAL/INTRA-ABDOMINAL

Workup

- **Chest/abdomen/pelvic CT ± abdominal/pelvic MRI**

Follow-up

Resectable disease

- **Postoperative imaging with abdominal/pelvic CT or MRI every 3–6 mo for 2–3 y, then every 6 mo for next 2 y, then annually**
- **Obtain chest imaging, x-ray or CT (preferred)**

Unresectable or Stage IV disease

- **Imaging to assess treatment response**
 - ▶ **Chest/abdominal/pelvic CT, or chest CT without contrast and abdominal/pelvic MRI with contrast**

GIST

Initial Workup

- **For very small GIST <2 cm: perform abdominal/pelvic CT**
- **For all other GIST:**
 - ▶ **Abdominal/pelvic CT and/or abdominal/pelvic MRI**
 - ▶ **Consider chest imaging using x-ray or CT**

¹Schuetze SM, Rubin BP, Vernon C, et al. Use of positron emission tomography in localized extremity soft tissue sarcoma treated with neoadjuvant chemotherapy. *Cancer* 2005;103:339-348

²Choi H, Varma DGK, Fornage BD, Kim EE, et al. Soft-tissue sarcoma: MR imaging vs sonography for detection of local recurrence after surgery. *AJR* 1991;157:353-358.

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GIST - Response Assessment

PRINCIPLES OF IMAGING

Resectable disease with negative margins but risk of significant morbidity

- Obtain baseline abdominal/pelvic CT and/or MRI
- Consider PET/CT
 - ▶ Obtain baseline PET/CT if using PET/CT during follow-up, PET is not a substitute for CT
- Imaging to assess preoperative imatinib response
 - ▶ Abdominal/pelvic CT or MRI is indicated every 8–12 weeks
 - ▶ PET may give indication of imatinib activity after 2–4 weeks of therapy when rapid readout of activity is necessary
- Progression may be determined by abdominal/pelvic CT or MRI with clinical interpretation; PET/CT may be used to clarify if CT or MRI are ambiguous
- For R2 resection or discovery of metastatic disease, assess postoperative imatinib response using abdominal/pelvic CT or MRI every 8–12 weeks

Definitively unresectable, recurrent, or metastatic disease

- Obtain baseline abdominal/pelvic CT and/or MRI
- Consider PET/CT
 - ▶ Obtain baseline PET/CT if using PET/CT during follow-up, PET is not a substitute for CT
- Imaging to assess imatinib response
 - ▶ Abdominal/pelvic CT or MRI every 8–12 weeks of initiating therapy; in some patients, it may be appropriate to image before 3 mo
- Progression may be determined by abdominal/pelvic CT or MRI with clinical interpretation; PET/CT may be used to clarify if CT or MRI are ambiguous

Follow-up

- For completely resected disease, perform abdominal/pelvic CT every 3–6 months for 3–5 y, then annually
 - ▶ Less frequent surveillance may be acceptable for very small tumors (<2 cm)
- For incompletely resected disease or discovery of metastatic disease during surgery, perform abdominal/pelvic CT every 3–6 months
- Progression may be determined by CT or MRI with clinical interpretation; PET/CT may be used to clarify if CT or MRI are ambiguous
- After treatment for progressive disease, reassess therapeutic response with abdominal/pelvic CT or MRI
 - ▶ Consider PET/CT only if CT results are ambiguous

DESMOID (Aggressive Fibromatosis)

Initial Workup

- Primary site imaging with CT or MRI as indicated

Follow-up

- Imaging with CT or MRI every 3–6 mo for 2–3 y, then annually

¹Schuetze SM, Rubin BP, Vernon C, et al. Use of positron emission tomography in localized extremity soft tissue sarcoma treated with neoadjuvant chemotherapy. *Cancer* 2005;103:339-348

²Choi H, Varma DGK, Fornage BD, Kim EE, et al. Soft-tissue sarcoma: MR imaging vs sonography for detection of local recurrence after surgery. *AJR* 1991;157:353-358.

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**PRINCIPLES OF PATHOLOGIC ASSESSMENT OF SARCOMA SPECIMENS**

- **Biopsy should establish malignancy, provide a specific diagnosis where possible, and provide a grade where appropriate or feasible, recognizing that limited biopsy material may underestimate grade.**
- **In patients without a definitive diagnosis following initial biopsy due to limited sampling size, repeat image-guided core needle biopsy should be considered to make a diagnosis.**
- **Pathologic assessment of biopsies and resection specimens should be carried out by an experienced sarcoma pathologist.**
- **Morphologic diagnosis based on microscopic examination of histologic sections remains the gold standard for sarcoma diagnosis. However, since several ancillary techniques are useful in support of morphologic diagnosis (including immunohistochemistry, classical cytogenetics, and molecular genetic testing), sarcoma diagnosis should be carried out by pathologists who have access to these ancillary methods.¹**
- **The pathologic assessment should include evaluation of the following features, all of which should be specifically addressed in the pathology report:**
 - ▶ **Organ, site, and operative procedure**
 - ▶ **Primary diagnosis (using standardized nomenclature, such as the World Health Organization Classification of Soft Tissue Tumors²)**
 - ▶ **Depth of tumor**
 - ◊ **Superficial (tumor does not involve the superficial fascia)**
 - ◊ **Deep**
 - ▶ **Size of tumor**
 - ▶ **Histologic grade (at the least, specify low or high grade if applicable); ideally, grade using the French Federation of Cancer Centers Sarcoma Group (FNCLCC) or NCI system**
 - ▶ **Necrosis**
 - ◊ **Present or absent**
 - ◊ **Microscopic or macroscopic**
 - ◊ **Approximate extent (percentage)**
 - ▶ **Status of margins of excision**
 - ◊ **Uninvolved**
 - ◊ **Involved (state which margins)**
 - ◊ **Close (state which margins and measured distance)**
 - ▶ **Status of lymph nodes**
 - ◊ **Site**
 - ◊ **Number examined**
 - ◊ **Number positive**
 - ▶ **Results of ancillary studies¹**
 - ◊ **Type of testing (electron microscopy, immunohistochemistry, molecular genetic analysis)**
 - ◊ **Where performed**
 - ▶ **Additional tumor features of potential clinical value**
 - ◊ **Mitotic rate**
 - ◊ **Presence or absence of vascular invasion**
 - ◊ **Character of tumor margin (well circumscribed or infiltrative)**
 - ◊ **Inflammatory infiltrate (type and extent)**
 - ▶ **TNM Stage ([See ST-2](#))**

¹[See Principles of Ancillary Techniques Useful in the Diagnosis of Sarcomas \(SARC-C\).](#)²Fletcher CDM, Bridge JA, Hogendoorn P, Mertens F. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Soft Tissue and Bone, Fourth Edition. IARC, Lyon, 2013.**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 ANCILLARY TECHNIQUES USEFUL IN THE DIAGNOSIS OF SARCOMAS

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

TUMOR	ABERRATION	GENE(S) INVOLVED
<u>Malignant Round Cell Tumors</u>		
Alveolar RMS	t(2;13)(q35;q14) t(1;13)(p36;q14) t(X;2)(q13;q35)	<i>PAX3-FOXO1</i> <i>PAX7-FOXO1</i> <i>PAX3-AFX</i>
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	<i>EWSR1-WT1</i>
Embryonal RMS	Complex alterations	Multiple, <i>MYOD1</i> mutation
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)	<i>EWSR1-FLI1</i> <i>EWSR1-ERG</i> <i>EWSR1-FEV</i> <i>EWSR1-ETV1</i> <i>EWSR1-E1AF</i> <i>EWSR1-ZSG</i> <i>FUS-ERG</i>

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

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

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NCCN Guidelines Version 2.2017
Soft Tissue Sarcoma**PRINCIPLES OF ANCILLARY TECHNIQUES USEFUL IN THE DIAGNOSIS OF SARCOMAS**

TUMOR	ABERRATION	GENE(S) INVOLVED
<u>Lipomatous Tumors</u>		
Atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLS)	Supernumerary ring chromosomes; giant marker chromosomes	Amplification of region 12q14-15, including <i>MDM2</i>, <i>CDK4</i>, <i>HMG2</i>, <i>SAS</i>, <i>GL1</i>
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)	<i>FUS-DD1T3</i> <i>EWSR1-DD1T3</i>
Pleomorphic liposarcoma	Complex alterations	Unknown
<u>Other Sarcomas</u>		
Alveolar soft part sarcoma	der(17)t(X;17)(p11;q25)	<i>ASPL-TFE3</i>
Angiomatoid fibrous histiocyoma	t(12;22)(q13;q12) t(2;22)(q33;q12) t(12;16)(q13;p11)	<i>EWSR1-ATF1</i> <i>EWSR1-CREB1</i> <i>FUS-ATF1</i>
Clear cell sarcoma	t(12;22)(q13;q12) t(2;22)(q33;q12)	<i>EWSR1-ATF1</i> <i>EWSR1-CREB1</i>
Congenital/infantile fibrosarcoma	t(12;15)(p13;q25)	<i>ETV6-NTRK3</i>
Dermatofibrosarcoma protuberans	t(17;22)(q21;q13) and derivative ring chromosomes	<i>COL1A1-PDGFB</i>
Desmoid fibromatosis	Trisomy 8 or 20; loss of 5q21	<i>CTNNB1</i> or <i>APC</i> mutations
Epithelioid hemangioendothelioma	t(1;13)(p36;q25) t(X;11)(q22;p11.23)	<i>WWTR1-CAMTA1</i> <i>YAP1 - TFE3</i>
Epithelioid sarcoma	Inactivation, deletion, or mutation of <i>INI1 (SMARCB-1)</i>	<i>INI1 (SMARCB-1)</i>

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PRINCIPLES OF ANCILLARY TECHNIQUES USEFUL IN THE DIAGNOSIS OF SARCOMAS

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

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PRINCIPLES OF SURGERY**Biopsy**

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

Surgery

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

Resection Margins

- Surgical margins should be documented by both the surgeon and

Resection Margins (continued)

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

Limb Sparing Surgery

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

Amputation

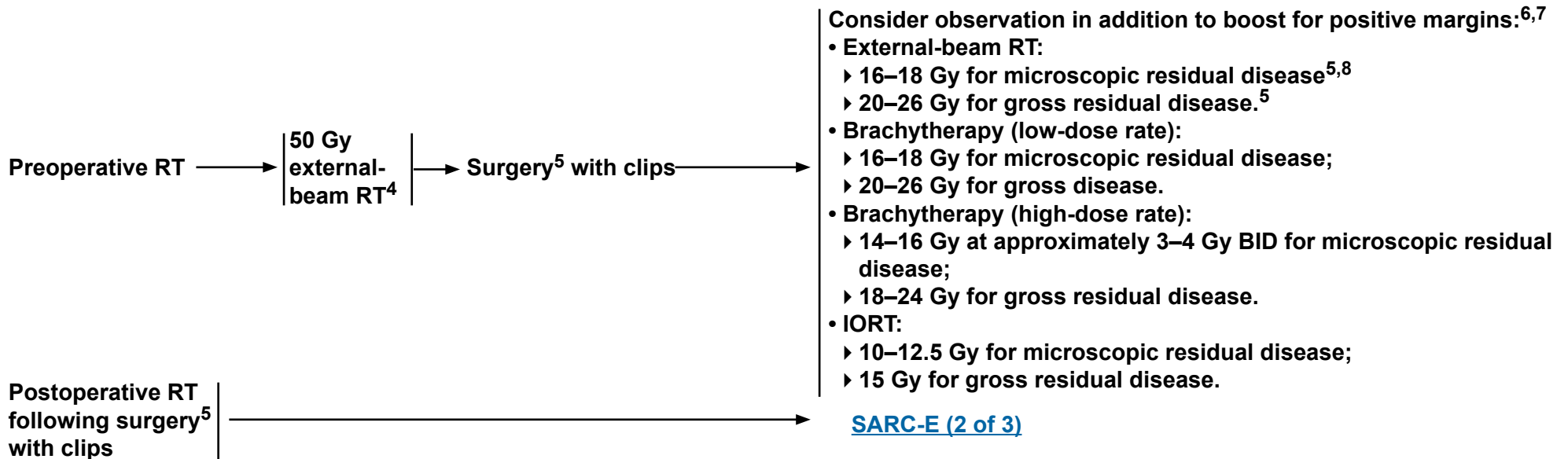
- Prior to considering amputation, patients should be evaluated by a surgeon with expertise in the treatment of soft tissue sarcomas.
- Consideration for amputation to treat an extremity sarcoma should be made for patient preference or if gross total resection of the tumor is expected to render the limb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

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RADIATION THERAPY GUIDELINES FOR SOFT TISSUE SARCOMA OF EXTREMITY/TRUNK/HEAD-NECK^{1,2,3}



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

- Musat E, et al. Comparison of intensity-modulated postoperative radiotherapy with conventional postoperative radiotherapy for retroperitoneal sarcoma. *Cancer Radiother* 2004;8:255-261;
- Alektiar KM, et al. Impact of intensity-modulated radiation therapy on local control in primary soft-tissue sarcoma of the extremity. *J Clin Oncol* 2008;26:3440-3444;
- Chung CS, et al. A comparison of 3D conformal proton therapy, intensity modulated proton therapy, and intensity modulated photon therapy for retroperitoneal sarcomas. *Int J Radiat Oncol Biol Phys* 2006;66(3S):116;
- Kraybill WG, Harris J, Spiro IJ, et al. Phase II study of neoadjuvant chemotherapy and radiation therapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group Trial 9514. *J Clin Oncol* 2006;24:619-625.

²Haas RL, DeLaney TF, O'Sullivan B, et al: Radiotherapy for management of extremity soft tissue sarcomas: why, when, and where? *Int J Radiat Oncol Biol*

Phys 2012; 84:572-580.

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

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

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

⁶Total doses should always be determined by normal tissue tolerance. There are data to suggest that some patients with positive margins following preoperative RT such as those with low-grade, well-differentiated liposarcoma and a focally, "planned" positive margin on an anatomically fixed critical structure may do well without a boost. (Gerrand et al. *J Bone Joint Surg* 2001;83-B:1149-1155.)

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

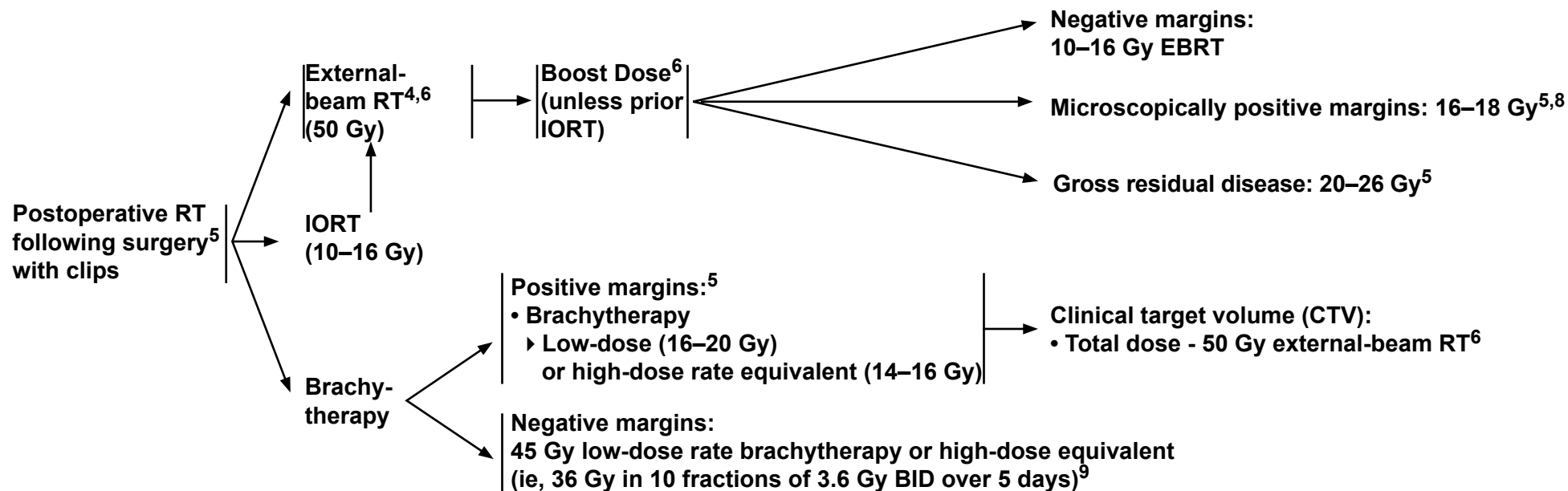
⁸RT does not substitute for definitive surgery with negative margins; re-resection may be necessary.

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

- Musat E, et al. Comparison of intensity-modulated postoperative radiotherapy with conventional postoperative radiotherapy for retroperitoneal sarcoma. *Cancer Radiother* 2004;8:255-261;
- Alektiar KM, et al. Impact of intensity-modulated radiation therapy on local control in primary soft-tissue sarcoma of the extremity. *J Clin Oncol* 2008;26:3440-3444;
- Chung CS, et al. A comparison of 3D conformal proton therapy, intensity modulated proton therapy, and intensity modulated photon therapy for retroperitoneal sarcomas. *Int J Radiat Oncol Biol Phys* 2006;66(3S):116;
- Kraybill WG, Harris J, Spiro IJ, et al. Phase II study of neoadjuvant chemotherapy and radiation therapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group Trial 9514. *J Clin Oncol* 2006;24:619-625.

²Haas RL, DeLaney TF, O'Sullivan B, et al: Radiotherapy for management of extremity soft tissue sarcomas: why, when, and where? *Int J Radiat Oncol Biol Phys*, 2012; 84:572-580.

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

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

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

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

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

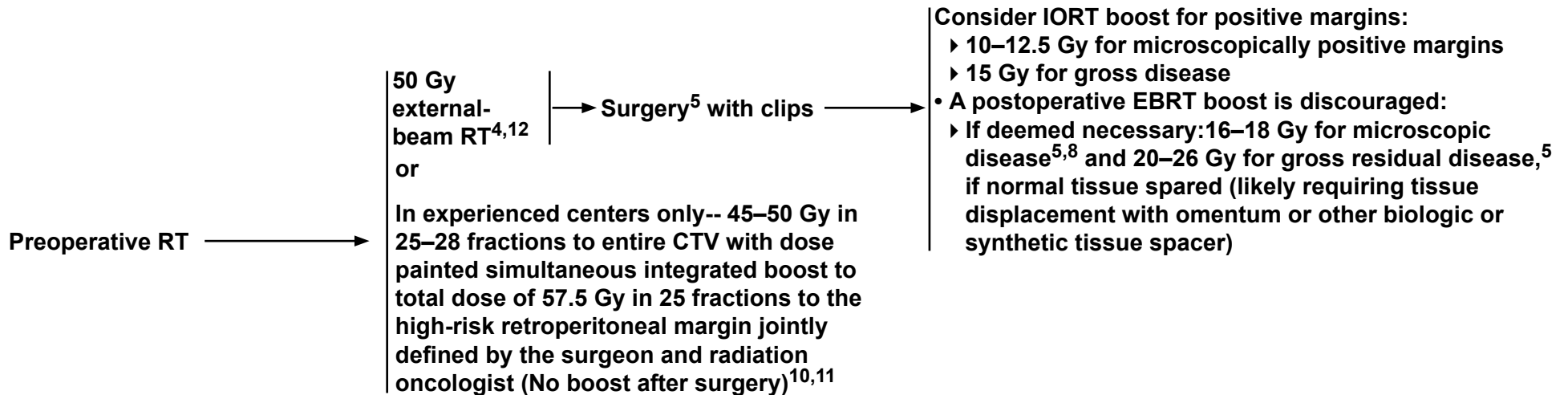
⁹Data are still limited on the use of HDR brachytherapy for sarcomas. Until more data are available, HDR fraction sizes are recommended to be limited to 3–4 Gy. (Nag et al, *Int J Radiat Onco Biol Phys* 2001;49:1033-1043, 2001).

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RADIATION THERAPY GUIDELINES FOR RETROPERITONEAL/INTRA-ABDOMINAL SARCOMA^{1,12}



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

- Musat E, et al. Comparison of intensity-modulated postoperative radiotherapy with conventional postoperative radiotherapy for retroperitoneal sarcoma. *Cancer Radiother* 2004;8:255-261.
- Chung CS, et al. A comparison of 3D conformal proton therapy, intensity modulated proton therapy, and intensity modulated photon therapy for retroperitoneal sarcomas. *Int J Radiat Oncol Biol Phys* 2006;66(3S):116.

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

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

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

¹⁰Tzeng CW, Fiveash JB, Popple, et al. Preoperative radiation therapy with selective dose escalation to the margin at risk for retroperitoneal sarcoma. *Cancer* 2006;107:371-379.

¹¹Baldini et al. *Ann Surg Oncol* 2015;22:2846-2852.

- Postoperative RT following surgery with clips is discouraged. If RT is not given prior to surgical resection, consider follow-up with possible preoperative EBRT at time of localized recurrence. [See \(SARC-D\)](#). Trans-Atlantic RPS Working Group. Management of Primary Retroperitoneal Sarcoma (RPS) in the Adult: A Consensus Approach from the Trans-Atlantic RPS Working Group. *Ann Surg Oncol* 2015;22:256-263.

¹²Baldini et al. *Int J Radiat Oncol Biol Phys* 2015;92:602-612.

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NCCN Guidelines Version 2.2017

Soft Tissue Sarcoma

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

Soft Tissue Sarcoma Subtypes with Non-Specific Histologies ^{d,e}	GIST ^j	Desmoid Tumors (Aggressive fibromatosis)
<p>Combination regimens</p> <ul style="list-style-type: none"> • AD (doxorubicin, dacarbazine)¹⁻⁴ • AIM (doxorubicin, ifosfamide, mesna)³⁻⁶ • MAID (mesna, doxorubicin, ifosfamide, dacarbazine)^{3,4,7,8} • Ifosfamide, epirubicin, mesna⁹ • Gemcitabine and docetaxel^{10,11} • Gemcitabine and vinorelbine^{f,12} • Gemcitabine and dacarbazine¹³ • Doxorubicin and olaratumab^{9,14} <p>Single agents</p> <ul style="list-style-type: none"> • Doxorubicin^{3,4,15} • Ifosfamide^{9,16} • Epirubicin¹⁷ • Gemcitabine • Dacarbazine • Liposomal doxorubicin¹⁸ • Temozolomide^{f,19} • Vinorelbine^{f,20} • Eribulin^{f,h,21} • Trabectedin^{f,h,22,23,24} • Pazopanib^{f,i,25} 	<ul style="list-style-type: none"> • Imatinib^{26,27} • Sunitinib²⁸ • Regorafenib²⁹ <p>Disease progression after imatinib, sunitinib, and regorafenib</p> <ul style="list-style-type: none"> • Sorafenib³⁰⁻³² • Nilotinib^{33,34} • Dasatinib³⁵ (for patients with D842V mutation) • Pazopanib³⁶ 	<ul style="list-style-type: none"> • Sulindac³⁷ or other non-steroidal anti-inflammatory drugs (NSAIDs) including celecoxib • Tamoxifen ± Sulindac^{38,39} • Toremifene⁴⁰ • Methotrexate and vinblastine⁴¹ • Low-dose interferon⁴² • Doxorubicin-based regimens⁴³⁻⁴⁵ • Imatinib^{46,47} • Sorafenib⁴⁸ • Methotrexate and vinorelbine⁴⁹ • Liposomal doxorubicin⁵⁰

Non-Pleomorphic Rhabdomyosarcoma

Combination regimens

- Vincristine, dactinomycin, cyclophosphamide⁵¹
- Vincristine, doxorubicin, cyclophosphamide⁵²
- Vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide⁵³
- Vincristine, doxorubicin, ifosfamide⁵⁴
- Cyclophosphamide and topotecan^{55,56}
- Ifosfamide and doxorubicin⁵⁷
- For Soft Tissue Ewings, [see NCCN Guidelines for Bone Cancer](#)

- Ifosfamide and etoposide⁵⁸
- Irinotecan and vincristine^{59,60}
- Vincristine and dactinomycin⁶¹
- Carboplatin and etoposide⁶²
- Vinorelbine^f and low-dose cyclophosphamide⁶³
- Vincristine, irinotecan, temozolomide⁶⁴

Single agents

- Doxorubicin⁶⁵
- Irinotecan^{56,66}
- Topotecan⁶⁷
- Vinorelbine^{f,68}
- High-dose methotrexate^{k,69}
- Trabectedin^{f,23,24,25}

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

^bFor uterine sarcomas, see the [NCCN Guidelines for Uterine Neoplasms](#).

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

^dAnthracycline-based regimens are preferred in the neoadjuvant and adjuvant setting.

^eRegimens appropriate for pleomorphic rhabdomyosarcoma.

^fRecommended only for palliative therapy.

^gFor use in STS histologies for which an anthracycline-containing regimen is appropriate.

^hCategory 1 recommendation for liposarcoma and leiomyosarcoma (L-Types), non L-Types (Category 2A).

ⁱPazopanib should not be used for lipogenic sarcomas.

^jImatinib, sunitinib, and regorafenib are the three FDA agents approved for the treatment of GIST.

^kHigh-dose methotrexate may be useful for select patients with CNS or leptomeningeal involvement when RT is not feasible.

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

<p><u>Pigmented Villonodular Synovitis/Tenosynovial Giant Cell Tumor (PVNS/TGCT)</u></p> <ul style="list-style-type: none"> • Imatinib⁷⁰ 	
<p><u>Angiosarcoma</u></p> <ul style="list-style-type: none"> • Paclitaxel^{71,72} • Docetaxel • Vinorelbine^f • Sorafenib⁷³ • Sunitinib⁷⁴ • Bevacizumab⁷⁵ • All other systemic therapy options as per Soft Tissue Sarcoma Subtypes with Non-Specific Histologies (SARC-F 1 of 6) 	<p><u>Solitary Fibrous Tumor/Hemangiopericytoma</u></p> <ul style="list-style-type: none"> • Bevacizumab and temozolomide⁷⁶ • Sunitinib^{77,78}
<p><u>Alveolar Soft Part Sarcoma (ASPS)</u></p> <ul style="list-style-type: none"> • Sunitinib^{79,80} (category 2B) 	<p><u>PEComa, Recurrent Angiomyolipoma, Lymphangiomyomatosis</u></p> <ul style="list-style-type: none"> • Sirolimus⁸¹⁻⁸⁴ • Everolimus⁸⁵ • Temsirolimus^{86,87}
<p><u>Inflammatory Myofibroblastic Tumor (IMT) with Anaplastic Lymphoma Kinase (ALK) Translocation</u></p> <ul style="list-style-type: none"> • Crizotinib⁸⁸ • Ceritinib⁸⁹ 	
<p><u>Well-differentiated/Dedifferentiated Liposarcoma (WD-DDLS) for Retroperitoneal Sarcomas</u></p> <ul style="list-style-type: none"> • Palbociclib^{90,91} 	

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

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

^fRecommended only for palliative therapy.

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**SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA--References**

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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.

**Table 1
Histopathologic Type**

Tumors included in the soft tissue category are listed below as per the 2002 World Health Organization classification of tumors:

Adipocytic Tumors

- Dedifferentiated liposarcoma*
- Myxoid/round cell liposarcoma
- Pleomorphic liposarcoma

Fibroblastic/Myofibroblastic Tumors

- Fibrosarcoma**
- Myxofibrosarcoma, low grade
- Low-grade fibromyxoid sarcoma
- Sclerosing epithelioid fibrosarcoma

So-called Fibrohistiocytic Tumors

- Undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma (MFH) (including pleomorphic, giant cell, myxoid/high-grade myxofibrosarcoma and inflammatory forms)

Smooth Muscle Tumors

- Leiomyosarcoma

Skeletal Muscle Tumors

- Rhabdomyosarcoma (embryonal, alveolar, and pleomorphic forms)

Vascular Tumors

- Epithelioid hemangioendothelioma
- Angiosarcoma, deep***

Tumors of Peripheral Nerves

- Malignant peripheral nerve sheath tumor

Chondro-osseous Tumors

- Extraskeletal chondrosarcoma (mesenchymal and other variants)
- Extraskeletal osteosarcoma

Tumors of Uncertain Differentiation

- Synovial sarcoma
- Epithelioid sarcoma
- Alveolar soft-part sarcoma
- Clear cell sarcoma of soft tissue
- Extraskeletal myxoid chondrosarcoma
- Primitive neuroectodermal tumor (PNET)/extraskeletal Ewing tumor
- Desmoplastic small round cell tumor
- Extrarenal rhabdoid tumor
- Undifferentiated sarcoma; sarcoma, not otherwise specified (NOS)

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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.



NCCN Guidelines Version 2.2017 Staging Soft Tissue Sarcoma

Table 1

**American Joint Committee On Cancer (AJCC) Staging System For
Soft Tissue Sarcoma
(7th ed, 2010)**

Primary Tumor (T)

- TX** Primary tumor cannot be assessed
- T0** No evidence of primary tumor
- T1** Tumor 5 cm or less in greatest dimension*
 - T1a** Superficial tumor
 - T1b** Deep tumor*
- T2** Tumor more than 5 cm in greatest dimension*
 - T2a** Superficial tumor
 - T2b** Deep tumor

*Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor is located either exclusively beneath the superficial fascia, superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia.

Regional Lymph Nodes (N)

- NX** Regional lymph nodes cannot be assessed
- N0** No regional lymph node metastasis
- N1†** Regional lymph node metastasis

†Presence of positive nodes (N1) in M0 tumors is considered Stage III.

Distant Metastases (M)

- M0** No distant metastasis
- M1** Distant metastasis

Histologic Grade

- GX** Grade cannot be assessed
- G1** Grade 1
- G2** Grade 2
- G3** Grade 3

Anatomic Stage/Prognostic Groups

Stage IA	T1a	N0	M0	G1, GX
	T1b	N0	M0	G1, GX
Stage IB	T2a	N0	M0	G1, GX
	T2b	N0	M0	G1, GX
Stage IIA	T1a	N0	M0	G2, G3
	T1b	N0	M0	G2, G3
Stage IIB	T2a	N0	M0	G2
	T2b	N0	M0	G2
Stage III	T2a,T2b	N0	M0	G3
	Any T	N1	M0	Any G
Stage IV	Any T	Any N	M1	Any G

[Continued...](#)

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NCCN Guidelines Version 2.2017 Staging Soft Tissue Sarcoma

American Joint Committee On Cancer (AJCC) Staging System For Gastrointestinal Stromal Tumor (7th ed, 2010)

Primary Tumor (T)

- TX** Primary tumor cannot be assessed
- T0** No evidence for primary tumor
- T1** Tumor 2 cm or less
- T2** Tumor more than 2 cm but not more than 5 cm
- T3** Tumor more than 5 cm but not more than 10 cm
- T4** Tumor more than 10 cm in greatest dimension

Regional Lymph Nodes (N)

- N0** No regional lymph node metastasis or*
- N1** Regional lymph node metastasis

*If regional node status is unknown, use N0, not NX.

Distant Metastasis (M)

- M0** No distant metastasis
- M1** Distant metastasis

Histologic Grade (G)

- GX** Grade cannot be assessed
- G1** Low grade; mitotic rate ≤5/50 HPF
- G2** High grade; mitotic rate >5/50 HPF

Anatomic Stage/Prognostic Groups

*Gastric GIST**

Group	T	N	M	Mitotic rate
Stage IA	T1 or T2	N0	M0	Low
Stage IB	T3	N0	M0	Low

Anatomic Stage/Prognostic Groups (Continued)

Stage II	T1	N0	M0	High
	T2	N0	M0	High
	T4	N0	M0	Low
Stage IIIA	T3	N0	M0	High
Stage IIIB	T4	N0	M0	High
Stage IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate

*Small Intestinal GIST***

Group	T	N	M	Mitotic rate
Stage IA	T1 or T2	N0	M0	Low
Stage II	T3	N0	M0	Low
Stage IIIA	T1	N0	M0	High
	T4	N0	M0	Low
Stage IIIB	T2	N0	M0	High
	T3	N0	M0	High
	T4	N0	M0	High
Stage IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate

*Note: Also to be used for omentum.

**Note: Also to be used for esophagus, colorectal, mesentery, and peritoneum.

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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Soft Tissue Sarcoma

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Overview

Sarcomas constitute a heterogeneous group of rare solid tumors of mesenchymal cell origin with distinct clinical and pathologic features; they are usually divided into two broad categories:

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

Sarcomas collectively account for approximately 1% of all adult malignancies and 15% of pediatric malignancies. In 2017, an estimated 12,390 people will be diagnosed with soft tissue sarcoma (STS) in the United States, with approximately 4,990 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. In the United States, the incidence of GISTs is expected to be at least 5000 new cases per year.^{2,3} Prior radiation therapy (RT) to the affected area is a risk factor for the development of STS.⁴⁻⁶ More than 50 different histologic subtypes of STS have been identified. The most common subtypes of STS are undifferentiated pleomorphic sarcoma, GISTs, liposarcoma, leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumors (MPNSTs).⁷ The anatomic site of the primary disease represents an important variable that influences treatment and outcome. Extremities (43%), the trunk (10%), visceral (19%), retroperitoneum (15%), or head and neck (9%) are the most common primary sites.⁸ STS most commonly metastasizes to the lungs; tumors arising in the abdominal cavity more commonly metastasize to the liver and peritoneum. Rhabdomyosarcoma (RMS) is the most common STS of children and adolescents and is less common in adults.

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

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

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.⁹

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 published between 08/01/2015 to 07/06/2016, using the following search terms: soft tissue sarcoma OR gastrointestinal stromal tumor 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 62 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.^{5,10-14}

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

Familial adenomatous polyposis (FAP) is an inherited autosomal-dominant colorectal cancer syndrome resulting from the germline mutations in the adenomatous polyposis coli [*APC*] gene on chromosome 5q21.^{11,13} FAP is characterized by adenomatous colorectal polyps that progress to colorectal cancer at 35 to 40 years of age. Gardner'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).²¹ Desmoid tumors have been reported to occur in 7.5% to 16% of patients with FAP, and the relative risk of developing desmoid tumors is much higher in patients with FAP than the general population.²²⁻²⁵ 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.²⁵ 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.²⁶ Germline loss-of-function mutations within the succinate dehydrogenase (*SDH*) gene subunits (*SDHB*, *SDHC*, and *SDHD*) have been identified in individuals with GISTs associated with Carney-Stratakis syndrome.²⁷ In an analysis of 11 patients from 9 families presenting with the 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.²⁷ The tumors also lacked activating *KIT* or platelet-derived growth factor receptor alpha (*PDGFRA*) mutations associated with sporadic GISTs. GISTs associated with Carney-

Stratakis syndrome are also reported to be negative for SDHB protein expression by immunohistochemistry (IHC), in contrast to GIST with *KIT* or *PDGFRA* mutations or sporadic GIST.^{28,29}

Hereditary retinoblastoma caused by a germline mutation in the retinoblastoma tumor suppressor gene (*RB1*) is also associated with an increased risk for the development of STS.^{12,30} Leiomyosarcoma is the most frequent STS subtype (with 78% of leiomyosarcomas diagnosed 30 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.¹²

Neurofibromatoses are hereditary conditions caused by mutations in the neurofibromin 1 gene (*NF1*) or neurofibromin 2 gene (*NF2*).³¹ Approximately 5% of patients with neurofibromatosis are thought to develop STS. Most commonly occurring are MPNSTs, a type of sarcoma that can arise from previously benign neurofibromas.³² For information on the treatment of MPNSTs, see the NCCN Guidelines for Central Nervous System Cancers 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, and should be performed by an experienced surgeon or radiologist. Biopsy should establish the malignancy and provide a specific diagnosis where possible and a grade where appropriate or feasible, recognizing that limited biopsy material may underestimate grade. Biopsy may be accomplished 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.³³ FNA may be acceptable in selected institutions with clinical and pathologic expertise. Endoscopic or needle biopsy may be indicated for deep thoracic, abdominal, or pelvic STS.

Principles of Pathologic Assessment

Pathologists with expertise in STS should review the pathologic assessment of biopsies and resected specimens, especially for initial

histopathologic classification. Margins must be thoroughly evaluated in these specimens. Morphologic assessment based on microscopic examination of histologic sections remains the gold standard of sarcoma diagnosis. The differential diagnosis of a soft tissue mass includes malignant lesions (such as primary or metastatic carcinoma, melanoma, or lymphoma), desmoids, and benign lesions (such as lipomas, lymphangiomas, leiomyomas, and neuromas). However, 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.³⁴

STS with recurrent chromosomal translocations can be classified into subtypes depending on the presence of fusion gene transcripts (eg, *EWSR1-ATF1* in clear cell sarcoma, *TLS-CHOP* [also known as *FUS-DDIT3*] in myxoid or round cell liposarcoma, *SS18-SSX* [*SS18-SSX1* or *SS18-SSX2*] in synovial sarcoma, and *PAX-FOXO1* [*PAX3-FOXO1* or *PAX7-FOXO1*] in alveolar RMS). The fusion genes resulting from chromosomal translocations can provide useful diagnostic and prognostic information. See *Principles of Ancillary Techniques Useful in the Diagnosis of Sarcomas* 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.³⁵ 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 liposarcoma that have variation in fusion gene partners.³⁶

Molecular genetic testing was analyzed in a prospective, multicenter study (GENSARC) that enrolled 395 patients with histologic diagnoses of various sarcoma subtypes.³⁷ 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*.³⁸ In patients with synovial sarcoma, the prognostic impact of *SS18-SSX1* or *SS18-SSX2* is less clear with two large studies showing conflicting results.^{39,40} In myxoid liposarcoma, the variability of fusion gene transcript has no effect on clinical outcome.⁴¹

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.³⁵

Staging

The AJCC staging system for STS has historically used a four-grade system, but within the staging groups this effectively functioned as a 2-tiered system (G1/G2 [low] and G3/G4 [high]). The two most widely employed systems, the French Federation of Cancer Centers Sarcoma Group (FNCLCC) and the National Cancer Institute (NCI) system, are three-tiered grading systems. The NCI system is based on the evaluation of tumor histology, location, and amount of tumor necrosis. The FNCLCC system is based on tumor differentiation, mitosis count, and tumor necrosis. In a comparative study of these two systems in 410 adult patients with STS, the FNCLCC system showed a slightly increased ability to predict distant metastasis development and tumor mortality.⁴² Riad and colleagues examined the impact of lymph node involvement on survival in patients with extremity sarcoma.⁴³ Lymph

node metastases developed in 3.7% (39 out of 1066) of patients who had surgery. The outcome of patients with isolated lymph node metastases was significantly better than with synchronous systemic and lymph node involvement (the estimated 4-year survival rates were 71% and 21%, respectively).⁴³ The outcome for patients with isolated lymph node involvement, treated with lymph node dissection, was also similar to that of patients with AJCC stage III extremity sarcomas.^{43,44} The revised 2010 AJCC staging system incorporates a 3-tiered grading system, and lymph node disease has been reclassified as stage III rather than stage IV disease.⁴⁵ However, many clinicians prefer the 2-tiered system, which is also used in the algorithm.

Surgery

Surgical resection (with appropriately negative margins) is the standard primary treatment for most patients with STS, although close margins may be necessary to preserve uninvolved critical neurovascular structures. RT and/or chemotherapy (in the case of chemosensitive histologies) are often used 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 (less than 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. If surgical margins are positive on final pathology, re-resection to obtain negative margins should strongly be considered if it will not have a significant impact upon functionality.⁴⁶ In an analysis of 666 consecutive patients with localized STS treated with an apparent macroscopic total tumor resection, 295 patients underwent re-resection of their tumor bed (residual tumor was found in 46% of patients, including macroscopic tumor in 28% of patients).⁴⁶ Reresection remained a significant predictor of local control. The local control rates at 5, 10, and 15 years were 85%, 85%, and 82%, respectively, for patients who underwent re-resection. The corresponding local control rates were 78%, 73%, and 73%, respectively ($P = .03$), for patients who did not undergo re-resection.

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

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.⁵¹⁻⁵³ Most institutions include the entire operative bed within the RT field. The main disadvantage of preoperative RT, however, is its effect on wound healing.^{54,55} 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.⁵⁶ Involvement of a plastic surgeon in the team may be necessary to reduce wound complications when preoperative RT is contemplated.

Postoperative RT is associated with higher rates of long-term treatment-related side effects. In one retrospective analysis, although 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.⁵⁷ Positive surgical margins

are associated with higher rates of local recurrence.⁵⁸ Postoperative RT has been shown to improve local control in patients with positive surgical margins.⁵⁹ 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 local recurrence in some patients with positive surgical margins (such as those with low-grade, well-differentiated liposarcoma (WDLs) and a focally, “planned” positive margin on an anatomically fixed critical structure).⁶⁰ Similarly, another retrospective matched cohort of patients with extremity STS found no added benefit of postoperative RT boost when evaluating local recurrence, distant metastasis, and mortality.⁶¹

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

Chemotherapy/Chemoradiation

Resectable Disease

Preoperative Therapy

Preoperative chemotherapy⁶²⁻⁶⁵ or chemoradiation⁶⁶⁻⁷⁵ has been evaluated in single and multicenter studies in patients with high-grade tumors.

Studies that have evaluated preoperative chemotherapy followed by surgery have reported inconsistent findings. The results of the only randomized study that compared surgery alone 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.⁶³ 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.⁶⁴ 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.⁶⁵

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.⁶⁸ 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.⁶⁸ 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 three-tier grading system), primary, or locally recurrent STS of the extremities or trunk.^{70,71} 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.⁷¹ 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.^{71,72}

Postoperative Therapy

Available evidence from meta-analyses⁷⁶⁻⁸⁰ and randomized clinical trials⁸¹⁻⁸⁶ 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 (1,568 patients), which compared postoperative chemotherapy to follow-up and in some cases RT after surgery with a variety of sarcomas.⁷⁷ 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).⁷⁹ 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%, $P = .15$).⁸⁰

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.⁸² 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.⁸⁷

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.⁸⁴ 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.⁸¹ In that study, postoperative chemotherapy with CYVADIC

(cyclophosphamide, vincristine, doxorubicin, and dacarbazine) was associated with higher RFS rates (56% vs. 43% for the control group; $P = .007$) and significantly lower local recurrence rates (17% vs. 31% for the control group; $P = .004$). However, 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.⁸⁶ 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.⁸⁵

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.⁸⁸⁻¹⁰⁰ Other chemotherapeutic agents such as

gemcitabine, docetaxel, vinorelbine, pegylated liposomal doxorubicin, and temozolomide have also been evaluated in clinical trials.

Gemcitabine in combination with docetaxel, vinorelbine, or dacarbazine has been shown to be active in patients with unresectable or metastatic STS of various histologic subtypes.¹⁰¹⁻¹⁰⁴ In a randomized phase II study, the combination of gemcitabine and docetaxel was associated with superior 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.¹⁰² 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.¹⁰³ Clinical benefit (complete response [CR], partial response [PR], or stable disease at 4 months or more) was seen in 25% of patients. In a more recent randomized study, the combination of gemcitabine and dacarbazine resulted in superior progression-free survival (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%; $P = .009$) than dacarbazine alone in patients with previously treated advanced STS.¹⁰⁴

Temozolomide,¹⁰⁵⁻¹⁰⁷ pegylated liposomal doxorubicin,¹⁰⁸ and vinorelbine^{109,110} have also shown activity as single agents in patients with advanced, metastatic, relapsed, or refractory disease. In a phase II study by the Spanish Group of Research on Sarcomas, temozolomide resulted in an overall response rate of 15.5% with a median OS of 8 months in patients with advanced pretreated STS.¹⁰⁷ 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.¹⁰⁸ In a retrospective study of



pretreated patients with metastatic STS, vinorelbine induced overall response in 6% of patients and 26% had stable disease.¹⁰⁹

Trabectedin is a novel DNA-binding agent that has shown objective responses in phase II and III studies of patients with advanced STS.¹¹¹⁻¹¹⁹ Recent phase III data from a randomized, multicenter trial revealed a 2.7-month PFS benefit versus dacarbazine in metastatic liposarcoma or leiomyosarcoma that progressed after anthracycline-based therapy; the study is ongoing to determine OS.¹¹⁷ Another recent study supported the efficacy of trabectedin in translocation-related sarcoma.¹¹⁹ 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.¹²⁰ Preliminary results from the randomized phase III T-SAR trial revealed a PFS benefit for trabectedin over best supportive care in both “L-type” (liposarcoma and leiomyosarcoma) and non-L-type pretreated advanced sarcoma.¹²¹ Trabectedin is included for palliative therapy as a category 1 recommendation for liposarcoma and leiomyosarcoma (“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 leiomyosarcoma, adipocytic sarcoma, synovial sarcoma, and other tumor types.¹²² Recent data from a phase III trial compared the survival benefit of eribulin and dacarbazine in 452 patients with advanced leiomyosarcoma or liposarcoma, revealing a median OS of 13.5 months and 11.5 months, respectively (HR, 0.77; 95% CI, 0.62–0.95; $P = .017$).¹²³ Eribulin is included for palliative therapy as a category 1 recommendation for L-type sarcomas and as category 2A for non-L-type sarcomas.

Targeted Therapy

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

Olaratumab is a novel monoclonal antibody that blocks PDGFR- α . Phase II data from 133 patients with anthracycline-naïve, unresectable, or advanced/metastatic STS showed improved survival for olaratumab plus doxorubicin versus doxorubicin alone. When comparing olaratumab plus doxorubicin versus doxorubicin alone, median PFS was 6.6 months versus 4.1 months, respectively ($P = .0615$). Median OS was 26.5 months versus 14.7 months, respectively ($P = .0003$).¹²⁴ The guidelines recommend combination therapy with doxorubicin and olaratumab for use in STS histologies for which an anthracycline-containing regimen is appropriate.

Pazopanib, a multitargeted tyrosine kinase inhibitor (TKI), has demonstrated single-agent activity in patients with advanced STS subtypes except liposarcomas.¹²⁵⁻¹²⁸ 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.¹²⁷ 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.¹²⁹ 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.¹³⁰ The guidelines have included pazopanib as an

option for palliative therapy for patients with progressive, unresectable, or metastatic non-lipogenic STS.

Imatinib¹³¹ and sunitinib^{132,133} have also shown efficacy in patients with advanced and/or metastatic STS other than GIST. Crizotinib, an anaplastic lymphoma kinase (ALK) inhibitor, was active in inflammatory myofibroblastic tumor (IMT) with ALK translocation.¹³⁴ The updated guidelines also include ceritinib, a next-generation ALK inhibitor that has been successful in treating ALK-rearranged non-small cell lung cancer.¹³⁵

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 lymphangiomyomatosis or angiomyolipomas.¹³⁶⁻¹⁴² Additionally, sorafenib may be active in select subtypes of advanced and/or metastatic STS other than GIST (eg, leiomyosarcoma, desmoid tumors).^{143,144}

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.^{145,146}

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).^{147,148}

Soft Tissue Sarcomas of the Extremities, Superficial Trunk, or Head and Neck

General Principles

Surgery

Positive surgical margin is a strong predictor of local recurrence for patients with extremity STS.¹⁴⁹⁻¹⁵⁴ Microscopically positive margins are associated with a higher rate of local recurrence and a lower rate of DFS in patients with extremity sarcomas.^{149,150,152} In a large cohort study (1668 patients) that examined the clinical significance of the main predictors of local recurrence in patients with STS of extremity and trunk, the 10-year cumulative possibility of local recurrence was significantly higher for patients with positive surgical margins (23.9 vs. 9.2 for those with negative margins; $P < .001$).¹⁵³ In a recent retrospective study that evaluated 278 patients with STS of the extremities treated between 2000 and 2006, the risk of patients with a positive margin were 3.76 times more likely to develop local recurrence than those with negative margins (38% risk of local recurrence after 6 years if the margins are positive compared to 12% if the margins are negative).¹⁵⁴ 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.¹⁵⁵

Amputation was once considered as the standard treatment to achieve local control in patients with extremity sarcomas.¹⁵⁶ In recent years, technical advances in reconstructive surgical procedures, implementation of multimodality therapy, and improved selection of patients for adjuvant therapy have minimized the functional deficits in patients who might otherwise require amputation. Nevertheless, amputation in certain circumstances is an acceptable procedure in

terms of optimizing function and oncologic control, as well as minimizing overall morbidity.

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 local recurrence rate of 15% and no difference in OS and DFS as compared to amputation.¹⁵⁷ In another series of 77 patients treated with limb-sparing surgery without RT, the local recurrence rate was only 7% and resection margin status was a significant predictor of local recurrence.¹⁵⁸ The local recurrence 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.¹⁵⁹ These results 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.¹⁶⁰⁻¹⁶³

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^{58,164,165} and retrospective analyses^{54,166-168} support the use of preoperative or postoperative external beam RT (EBRT) in appropriately selected patients. Brachytherapy (alone or in combination with EBRT)^{166,169,170} and IMRT^{171,172} has also been evaluated as an adjunct to surgery.

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.^{165,173} 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), and 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.^{165,174} 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).¹⁷⁵

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).^{164,176} Postoperative RT significantly reduced the 10-year local recurrence

rate among patients with high-grade lesions (no local recurrences 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.¹⁶⁴ The probability of reduction in the local recurrence 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 ($P = .22$).¹⁷⁶

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 local recurrence rate of 9%, at a median follow-up of 82 months.¹⁷⁷ Old age and/or stage III disease were associated with a higher rate of local recurrence. 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.

The French Sarcoma Group recently reported on a cohort of 283 patients with resectable atypical lipomatous tumor/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; $P < .001$).¹⁷⁸ Along with RT, tumor site and resection margin status were predictors of time to local recurrence, but no difference in OS was observed.

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.¹⁶⁹ 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).¹⁷⁰

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.¹⁷¹ The risk of complications such as edema and joint stiffness were also favorable when compared with conventional RT. 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.¹⁷²

The impact of radiotherapy 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

radiotherapy (ie, preoperative vs. postoperative) was not a significant factor for survival.¹⁷⁹

Recent reports from a retrospective study suggest that IORT provides excellent local control to STS of the extremity.^{180,181} 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.¹⁸¹ 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.^{182,183} 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.⁴⁹ 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.

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. The usual dose of preoperative RT is 50 Gy in 1.8 to 2.0 Gy per fraction. Postoperative RT is recommended for all patients with positive margins.¹⁸⁴ 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.^{60,185} 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.¹⁸⁰

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 does not substitute for suboptimal surgical resection and re-resection is preferred for patients with positive surgical margins.

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, leiomyosarcoma, myxoid round cell liposarcoma, 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 liposarcomas due to the higher risk of metastasis to the spine compared to other STSs.¹⁸⁶⁻¹⁸⁸ 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.¹⁸⁹ 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 for firm and deep (not superficial) lesions larger than 3 cm in patients with high-grade extremity STS.¹⁹⁰⁻¹⁹⁵ The maximum standardized uptake value (SUVmax) of F18-deoxyglucose has been shown to correlate with tumor grade and prognostication.^{196,197} In a retrospective study, tumor SUVmax determined by PET was an independent predictor of survival and disease progression.¹⁹⁰ Schuetze and colleagues reported that the pretreatment SUVmax and change in SUVmax after preoperative chemotherapy independently identified patients with a high risk of recurrence.¹⁹¹ 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.¹⁹¹ 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.^{193,194} 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.¹⁹⁴ 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

Treatment Guidelines by Stage

Stage I

Surgery (with intent to obtain negative margins) is the primary treatment for T1a-2b, N0, M0 tumors and is considered definitive if margins are greater than 1 cm or the fascial plane is intact.^{198,199} If the surgical margins are 1.0 cm or less and without an intact fascial plane, re-resection may be necessary.¹⁷⁷

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.^{150,152,169} 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 T1a-1b tumors and category 1 for T2a-2b tumors). RT may not be necessary in patients with small low-grade lesions (5 cm or less), because these tumors are less frequently associated with local recurrence.¹⁶⁴ Therefore, observation is included as an option for patients with T1a-1b tumors 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 atypical lipomatous tumor (ALT)/WDLS; RT is not indicated in most cases.^{200,201} 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.²⁰² RT may also be an appropriate treatment option for selected patients with recurrent disease or deeply infiltrative primary lesions with a risk of local recurrence, depending on the tumor location and patient's age.²⁰³

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.^{71,72} The results of the only completed randomized study showed that preoperative chemotherapy is not associated with a major survival benefit for patients with high-grade tumors.⁶³ An ongoing randomized study from

the Italian Sarcoma Group is examining preoperative chemotherapy in 287 patients with localized high-grade sarcoma of the extremity or trunk wall. Preliminary results suggest that anthracycline/ifosfamide combination regimens were associated with an average RFS and OS benefit of 20% over other histology-driven regimens.²⁰⁴

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.²⁰⁵ 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.⁸¹⁻⁸⁵ Postoperative EBRT has been shown to improve local control in patients with high-grade lesions.^{164,166}

Large stage II or III high-grade extremity resectable tumors (greater than 8–10 cm) that are at high risk for local recurrences 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.²⁰⁶ In the surgery alone arm, the cumulative incidence rates of local recurrence at 5 and 10 years were 7.9% and 10.6%, respectively, in patients who underwent R0 resection, and the 5- and 10-year sarcoma-specific death rates were 3.2%. 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 ($P = .04$).¹⁵⁸ Recently, 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.²⁰⁷

Surgery followed by RT is recommended for patients with stage IIA tumors (T1a-b, N0, M0, G2-3) that are resectable with acceptable functional outcomes.¹⁶⁴ Since preoperative RT has been shown to decrease the risk of recurrence following surgery (albeit with wound complications),^{165,173} the panel has included preoperative RT (category 1) followed by surgery as one of the treatment options. Surgery alone may be an option for patients with small tumors that can be resected with wider surgical margins.

Surgery followed by RT with or without postoperative chemotherapy is the primary treatment for patients with stage IIB (T2a-b, N0, M0, G2) or III (T2a-2b, N0, M0; or any T, N1, M0, any G) tumors that are resectable with acceptable functional outcomes. 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.⁸¹⁻⁸⁵ Preoperative RT (category 1), 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.²⁰⁸ 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, or chemotherapy. 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 recent 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, $P = .003$).²⁰⁹

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.²¹⁰ 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 . Preliminary data from clinical trials suggest that ILP with melphalan or doxorubicin in combination with TNF- α ²¹¹⁻²¹⁴ or ILI with doxorubicin or melphalan and dactinomycin²¹⁵⁻²¹⁸ may be effective in the treatment of patients with unresectable STS of extremity. 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. The guidelines have included regional limb therapy as a primary treatment option for patients with unresectable tumors treated at institutions with experience in regional limb therapy.

Stage IV (Synchronous Metastatic Disease)

Patients who present with metastatic disease have a poor prognosis with no disease-free interval.^{219,220} 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.²¹⁹ 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.²²⁰ 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 extremely poor prognosis.²²¹

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.^{219,221} Several variables, including tumor resectability, number and location of metastases, and performance status influence the decision to use metastasectomy.²²⁰ In addition, patients can also receive stereotactic body RT (SBRT) or chemotherapy as an alternate method for control of metastatic lesions.

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.²²²⁻²²⁵ Because patient risk never returns to zero, long-term follow-up is indicated, including

consideration of MRI or CT scan.²²⁶ 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.²²⁷ 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.²²⁵ Thirty patients (32%) recurred after a median follow-up of 60 months (5 local, 26 distant). Surveillance imaging led to the detection of local recurrence 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 local recurrence.

Ultrasound has been used for the detection of early local recurrences and for the detection of micronodules less than 0.5 cm in diameter.²²⁸⁻²³⁰ In a retrospective analysis that evaluated the value of MRI and ultrasound for the detection of local recurrence 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%).²²⁸ However, the differences were not statistically significant, suggesting that both MRI and ultrasound were equally useful in the detection of local recurrences 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 local recurrences in patients with STS.²²⁹ These results confirm that

ultrasound can be useful for the detection of local recurrences. However, as reported by Choi and colleagues, ultrasound may be more difficult to interpret than MRI during the early postoperative period.²²⁸ 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 local recurrences in patients with smaller, superficial lesions and should be performed by an ultrasonographer with experience in musculoskeletal disease.^{228,229} However, in situations where the area is easily followed by physical examination, imaging may not be required.²³¹

For stage II/III and synchronous stage IV disease, PET/CT may be useful for determining response to neoadjuvant chemotherapy in patients with at least 3 cm lesions that are firm and deep. 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 should be considered 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 3 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 local recurrence 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.²³²⁻²³⁴

For a patient with a local recurrence, treatment decisions should be made using the same algorithm as for patients with a new primary lesion.²³⁵ In patients with local recurrence, some case series suggest that combined conservative surgery and re-irradiation provide superior local control compared to local re-excision alone.²³⁶ 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,²³⁷ likely reflecting differences in patient selection for surgery and RT or surgery alone. Therefore, the guidelines recommend that if local recurrence 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. 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.²³⁸

Retroperitoneal/Intra-abdominal Soft Tissue Sarcomas

General Principles

Surgery

Surgical resection of a localized tumor with negative margins remains the standard, potentially curative treatment for patients with retroperitoneal/intra-abdominal STS. Postoperative margin status is the most important factor contributing to long-term DFS.²³⁹⁻²⁴³ In the largest 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.²⁴²

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.^{244,245} While the results are encouraging, this technique needs to be investigated in prospective clinical trials.

Radiation Therapy

RT can be administered either as preoperative or postoperative treatment for patients with resectable disease and as a primary treatment for those with unresectable disease. 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, postoperative RT may be considered in highly selected patients, who have not received preoperative RT, to attempt to control microscopic residual disease, although this approach has not been validated in randomized trials.

Newer RT techniques such as IMRT and 3D conformal RT using protons or photons may allow tumor target coverage and acceptable clinical outcomes within normal tissue dose constraints to adjacent organs at risk.^{168,246-248} When EBRT is used, sophisticated treatment planning with IMRT, tomotherapy, 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.

Preoperative RT

Preoperative RT is often preferred, because it reduces the risk of tumor seeding at the time of surgery and may render tumors more amenable to resection.^{249,250} Long-term results of two prospective studies showed favorable 5-year local RFS (60%), DFS (46%), and OS rates (61%) following R0 or R1 resection after preoperative RT in patients with intermediate or high-grade retroperitoneal STS.²⁵¹ The usual dose of preoperative RT is 50 Gy. In a single-institution study, Tzeng and colleagues demonstrated that preoperative RT with selective dose escalation (45 Gy in 25 fractions to the entire tumor plus margin and a boost dose of 57.5 Gy to the posterior retroperitoneal tumor margin determined by the surgeon and the radiation oncologist to be at highest

risk) was tolerable and allowed for the use of higher RT doses to the high-risk clinical target volume (high-risk CTV) judged to be at greatest risk for local tumor recurrence.²⁵² In this study, which included 16 patients with biopsy-proven retroperitoneal STS, 14 patients (88%) had undergone macroscopic resection. With a median follow-up of 28 months, there were only 2 local recurrences, with the actuarial 2-year local control rate of 80%.

NCCN recommends 50 Gy preoperative RT (in 1.8–2 Gy per fraction), followed by surgery with clips and consideration of IORT boost for positive margins. Postoperative EBRT boost is discouraged in this setting. An alternative approach to be considered in experienced centers only is 45 to 50 Gy to the entire CTV with dose-painted simultaneous integrated boost to total dose of 57.5 Gy.^{252,253} 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. An ongoing phase III, randomized, multi-center EORTC trial is evaluating preoperative RT for previously untreated, nonmetastatic retroperitoneal STS (NCT01344018).

Postoperative RT

Postoperative RT has been associated with improved RFS in retrospective nonrandomized studies with no improvement in OS.^{241,254} In one study, the combined use of preoperative RT and postoperative brachytherapy resulted in significantly better DFS and OS in patients with low-grade tumors.²⁵⁵ In a recent retrospective study, the use of conformal postoperative RT along with aggressive surgical resection was associated with a trend towards decreased local recurrence rate and improved RFS compared to surgery alone.²⁵⁶ At the 5-year follow-up, the RFS rate was 60% and 47%, respectively ($P = .02$);

however, there was no significant difference in OS between the two groups.

The panel discourages providing a postoperative EBRT boost. If postoperative RT is deemed necessary, 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 Radiation Therapy

The use of IORT has provided encouraging results in patients with retroperitoneal STS.²⁵⁷⁻²⁶⁴ In patients with retroperitoneal STS prospectively treated at a single institution with a protocol involving maximal tumor resection, high-dose-rate IORT and postoperative 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%; $P = .40$).²⁵⁸ 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.^{259-261,263} In a study that assessed the long-term outcome of patients with retroperitoneal STS treated by preoperative 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.²⁵⁹ An ongoing study (NCT01566123) is examining preoperative RT, followed by surgery with IORT in patients with high-risk retroperitoneal sarcoma. Preliminary results suggest promising local control and OS rates.²⁶⁵

Evaluation and Workup

The initial evaluation and workup for retroperitoneal abdominal STS are similar to that for the extremity sarcomas. This workup involves a thorough H&P and appropriate imaging studies, including chest, abdominal, and pelvic CT with contrast with or without an abdominal/pelvic MRI. Chest imaging should be done, especially for patients whose tumors warrant preoperative or postoperative chemotherapy. If possible, a multidisciplinary sarcoma panel should review the patient. Note that for staging, all retroperitoneal lesions are considered deep lesions.

The differential diagnosis of retroperitoneal abdominal soft tissue mass includes malignant lesions (such as other sarcomas, GISTs, lymphomas, or germ cell tumors), desmoids, and benign lesions. Proof of the histologic subtype by biopsy is necessary for patients before receiving preoperative chemotherapy or RT. Biopsy should be considered if there is suspicion of malignancies other than STS. Image-guided (CT or ultrasound) core needle biopsy is preferred over open surgical biopsy. 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.

Treatment Guidelines by Resectability/Stage

Resectable Disease

Surgery (to obtain oncologically appropriate margins) with or without IORT is the primary treatment for most patients with resectable disease. However, complete or macroscopic surgical resection is



achieved in less than 70% of patients with primary tumors, due to their close proximity to vital structures. Local recurrence and disease progression continue to be associated with a significant cause of morbidity in the majority of patients.²⁶⁶⁻²⁶⁸ Multimodality treatment (surgery with RT and/or chemotherapy) is therefore favored due to the inability to obtain negative surgical margins and high local recurrence rates.²⁶⁹

If RT is anticipated, preoperative RT with an IMRT approach to optimize sparing of 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.²⁴⁹

Analysis of 8653 patients with resected retroperitoneal STS from the National Cancer Database revealed worse OS in the surgically resected cohort receiving chemotherapy versus those who underwent surgery alone (40 months vs. 52 months, $P = .002$).²⁷⁰ Preoperative chemotherapy may have advantages over postoperative chemotherapy. However, the role of preoperative chemotherapy vs. postoperative chemotherapy has not yet been evaluated in randomized clinical trials.²⁷¹ Little data are available for the use of combined RT and chemotherapy. Decisions about postoperative or preoperative chemotherapy or RT are left to clinical judgment.²⁷²⁻²⁷⁴ 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.²⁷⁵

In the phase III randomized study (EORTC 62961), the addition of RHT to preoperative chemotherapy with EIA was associated with a significant survival benefit.²⁰⁵ At 5-year follow-up, among 149 patients with non-extremity STS, patients treated with EIA plus RHT had superior DFS (34% vs. 27%, $P = .040$) and local PFS (56% vs. 45%

after 5 years, $P = .044$) compared with those receiving EIA alone.²⁷⁶ As is the case with STS of extremities, these results need to be confirmed in large cohort studies and the use of RHT with preoperative chemotherapy is not recommended in the guidelines for the treatment of patients with retroperitoneal or abdominal STS.

Preoperative RT or chemotherapy could be considered prior to surgery in patients whose diagnosis has been confirmed by biopsy. For patients treated with preoperative EBRT (50 Gy) followed by surgery, the guidelines recommend consideration of postoperative RT boost for patients with positive margins, if this can be done within the constraints of adjacent normal tissue. The guidelines recommend an EBRT boost of 16 to 18 Gy for microscopic residual disease, and 20 to 26 Gy for grossly positive margins. 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.

Postoperative treatment options are dependent on surgical outcomes and clinical or pathologic findings following surgery. Due to risk of morbidity, postoperative RT should not be administered routinely to patients with negative margin resection (R0) or microscopically positive margins (R1 resection). Highly selected candidates for postoperative RT may include patients with pathologic findings of high-grade disease, extremely large tumors, close surgical margins, or high risk of recurrence. For highly selected patients with R1 resections, RT boost (10–16 Gy) can be considered. Re-resection, if feasible, should be considered for patients with macroscopically positive margins (R2 resection). Alternatively, these patients could also be managed as described below for unresectable disease. The options for postoperative RT include EBRT (50 Gy irrespective of surgical margins) or IORT (10 Gy followed by EBRT). For patients treated with

postoperative EBRT, the guidelines recommend postoperative RT boost to the original tumor bed based on the margin status (10 Gy for negative surgical margin if normal tissue can be adequately spared by tissue displacement with omentum or other biologic or synthetic spacer; 16–18 Gy for microscopic residual disease; and 20–26 Gy for gross residual disease). The dose recommendations above must be balanced and considered in the context of the adjacent normal tissue tolerance to RT.

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. Patients with unresectable or stage IV disease could be treated with chemotherapy, chemoradiation, or RT in an attempt to downstage tumors. 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.²⁷⁷ The most active chemotherapy regimen in an unselected patient population is AIM (doxorubicin/ifosfamide/mesna).²⁰⁹

For unresectable or stage IV disease, follow-up imaging is recommended to assess treatment response. Options include chest/abdominal/pelvic CT or chest CT without contrast and abdominal/pelvic MRI with contrast. Patients whose tumors become resectable following primary treatment should be managed as described above for resectable disease. If the tumor remains

unresectable or if there is disease progression following primary treatment, management decisions depend on whether patients are symptomatic or asymptomatic. Asymptomatic patients can be observed, whereas symptomatic patients can be treated with palliative therapy (chemotherapy, RT, or surgery) for symptom control or best supportive care. In patients with stage IV disease, resection should always be considered for resectable metastatic disease. 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.

Surveillance

Patients should have a follow-up physical examination with imaging (chest/abdominal/pelvic CT or MRI) every 3 to 6 months for 2 to 3 years, then every 6 months for the next 2 years, and then annually. Chest imaging should be obtained preferably CT over conventional radiography.

Recurrent Disease

For patients with resectable, unresectable, or disseminated recurrences, the guidelines recommend the same management after biopsy, as outlined for primary disease. Preoperative RT and/or chemotherapy should be considered for recurrent disease, if not administered previously. Palliative treatment for symptom control (RT, chemotherapy, or surgery) and best supportive care are potential options that oncologists should discuss with symptomatic patients. Enrollment in a clinical trial is preferred and should be considered if an appropriate trial is available.

Gastrointestinal Stromal Tumors

GISTs are the most common STS of the gastrointestinal (GI) tract, resulting most commonly from *KIT* or *PDGFRA* activating mutations.²⁷⁸

GISTs can arise anywhere along the GI tract, but stomach (60%) and small intestine (30%) are the most common primary sites.²⁷⁹ Duodenum (4%–5%) and rectum (4%) are the less common primary sites, and only a small number of cases have been reported in the esophagus (<1%) and colon and appendix (1%–2%).²⁷⁹ Patients with a suspected GIST may present with a variety of symptoms, which may include early satiety, abdominal discomfort due to pain or swelling, intraperitoneal hemorrhage, GI bleeding, or fatigue related to anemia. Some patients may present with an acute abdomen (as a result of tumor rupture, GI obstruction, or appendicitis-like pain), which requires immediate medical attention.²⁸⁰ Liver metastases and/or dissemination within the abdominal cavity are the most common clinical manifestations of malignancy. Lymph node metastases are extremely rare. Metastases in the lungs and other extra-abdominal locations are observed only in advanced cases.

General Principles

Biopsy and Pathologic Assessment

GISTs are soft and fragile tumors. The decision to obtain a biopsy should be based on the suspected tumor type and the extent of disease. Biopsy is necessary to confirm the diagnosis of primary GIST prior to the initiation of preoperative therapy.²⁸⁰ Recent reports have suggested that definitive diagnosis of GIST requires tissue acquisition via endoscopic ultrasound (EUS)-guided FNA.²⁸¹ EUS-guided FNA (EUS-FNA) biopsy of primary site is preferred over percutaneous biopsy due to the risk of tumor hemorrhage and intra-abdominal tumor dissemination. Percutaneous image-guided biopsy may be appropriate for confirmation of metastatic disease.

Morphologic diagnosis based on careful microscopic examination of adequate tumor tissue is essential to confirm the diagnosis of GIST. Pathology report should include anatomic location, size, and an

accurate assessment of the mitotic rate measured in the most proliferative area of the tumor and reported as the number of mitoses in 50 high-power fields (HPFs) (equivalent to 5 mm² of tissue). The differential diagnosis of GIST should be considered for any GI sarcoma, as well as for any other intra-abdominal sarcoma. The panel recommends referral to centers with expertise in sarcomas for cases with complex or unusual histopathologic features.

Most GISTs (95%) express *KIT* (CD117). Approximately 80% of GISTs have a mutation in the gene encoding the *KIT* receptor tyrosine kinase; another 5% to 10% of GISTs have a mutation in the gene encoding the related *PDGFRA* receptor tyrosine kinase.^{3,282,283} About 10% to 15% of GISTs have no detectable *KIT* or *PDGFRA* mutations (wild-type GIST). Other commonly expressed markers include CD34 antigen (70%), smooth muscle actin (25%), and desmin (less than 5%).²⁸⁴

Most of the *KIT* mutations occur in the juxtamembrane domain encoded by *KIT* exon 11 and some are detected in the extracellular domain encoded by exon 9.²⁸⁵ *KIT* mutations have also been identified in the tyrosine kinase domain (exon 13 and exon 17), although they are very rare.²⁸⁶ The majority of the *PDGFRA* mutations affect exon 18 in the tyrosine kinase domain.²⁸⁵ Few mutations also occur in exon 12 (juxtamembrane domain) and exon 14 (tyrosine kinase domain 1), although they are rare.²⁸⁷ *KIT* exon 11 mutations are most common in GISTs of all sites, whereas *KIT* exon 9 mutations are specific for intestinal GISTs and *PDGFRA* exon 18 mutations are common in gastric GISTs.²⁸⁵

Immunohistochemical staining for CD117, DOG1, and/or CD-34 and molecular genetic testing to identify *KIT* and/or *PDGFRA* mutations are useful in the diagnosis of GIST. However, *KIT* positivity alone may not be sufficient to confirm the diagnosis and, conversely, the absence of

KIT and/or *PDGFRA* mutations does not exclude the diagnosis of GIST. In GISTs with *PDGFRA* mutations, immunostaining with *PDGFRA* has been shown to be helpful in discriminating between *KIT*-negative GIST and other gastrointestinal mesenchymal lesions.

Loss-of-function mutations in the *SDH* gene subunits or loss of SDHB protein expression by IHC have been identified in a majority of wild-type GISTs lacking *KIT* and *PDGFRA* mutations; these findings have led to the use of the term SDH-deficient GIST, which is preferred over the older term, wild-type GIST, for this subset of GISTs.²⁸⁸⁻²⁹² SDHB IHC can be useful for the diagnosis of SDH-deficient GIST. *BRAF* exon 15 mutation (V600E) has also been reported in a small subset of patients with intestinal high-risk GISTs lacking *KIT*/*PDGFRA* mutations.^{293,294} DOG1 is a calcium-dependent, receptor-activated chloride channel protein and it is expressed in GISTs independent of mutation type. DOG1 expression was not different between the *KIT*/*PDGFRA* mutant or wild-type GIST, but there was a clear distinction between tumors with *PDGFRA* and *KIT* mutations. GISTs with *PDGFRA* mutations had a low *KIT* expression and high DOG1 expression, which can be used in the diagnosis of *KIT*-negative tumors.²⁹⁵ DOG1 immunostaining may be useful for cases that cannot be categorized as GIST based on CD117 immunostaining and mutation testing for *KIT* and *PDGFRA*. DOG1 and *KIT* could be used together in difficult cases exhibiting unexpected *KIT* negativity or positivity.²⁸⁰

Tumors lacking *KIT* and *PDGFRA* mutations should be considered for further evaluations such as SDHB immunostaining. If the tumor is SDH-deficient, germline testing for *SDH* mutations would be indicated. Inactivating *NF1* mutations or activating *BRAF* mutations are present in a small minority of tumors that lack *KIT* and *PDGFRA* mutations but retain SDH expression.

Prognostic Factors

Tumor size and the mitotic rate are the most widely used pathologic features for the risk stratification of GIST. However, it is difficult to predict the malignant potential of GIST based on these features alone. In a long-term follow-up of 1765 patients with gastric GISTs, Miettinen and colleagues reported that the metastatic rate was 86% for tumors >10 cm with a mitotic index of >5 mitoses/50 HPFs, whereas tumors of the same size with a mitotic index of <5 mitoses/50 HPFs have a relatively low metastatic rate of 11%.²⁹⁶ In a subsequent report involving 906 patients with small intestinal GIST, tumors >10 cm with a mitotic index of ≤5 mitoses/50 HPF had a metastatic rate of 50%, which is a contrast to that reported for gastric GIST with similar tumor parameters.²⁹⁷ Therefore, in addition to the tumor size and mitotic rate, tumor site has also been included in the guidelines developed by Miettinen and colleagues for the risk stratification of primary GIST.²⁷⁹ According to these guidelines, gastric GISTs have an overall indolent behavior and those that are ≤2 cm (irrespective of the mitotic index) are essentially benign, whereas small intestinal GISTs tend to be more aggressive than gastric GISTs. Rectal GISTs are also very aggressive and tumors <2 cm with a mitotic index of >5 mitoses/50 HPFs have a higher risk of recurrence and malignant potential.

Mutations can be found in high-grade tumors as well as in small incidental GISTs and tumors that have a benign course. Therefore, *KIT* mutational status is not used to determine the malignant potential of a primary GIST. Tumor genotype has been shown to be an independent prognostic factor based on review of 1056 patients with localized GIST in the ConticaGIST database. Factors associated with poorer DFS were *KIT* exon 9 duplication, *KIT* exon 11 deletions, nongastric site, larger tumor size, and high mitotic index, whereas *PDGFRA* exon 18 mutations were associated with better prognosis.²⁹⁸ Long-term follow-up (median 73 months) from the BFR14 trial by the French Sarcoma

Group identified female sex as an independent prognostic factor for higher PFS and OS in patients treated with standard-dose imatinib.²⁹⁹

The presence and the type of *KIT* or *PDGFRA* mutation status are predictive of response to TKI therapy in patients with advanced or metastatic GIST. GISTs with *SDH* mutations are also less sensitive to TKIs. They typically arise in the stomach and are observed in younger individuals, frequently metastasize, may feature lymph node involvement, and tend to grow slowly. See *Impact of Mutational Status on Response to Imatinib or Sunitinib in Patients with Advanced or Metastatic GIST* in this Discussion.

Imaging

In patients with GIST, imaging is used for diagnosis, initial staging, restaging, monitoring response to therapy, and performing follow-up surveillance of possible recurrence. Contrast-enhanced CT is the imaging modality of choice to characterize an abdominal mass, as well as to evaluate its extent and the presence or absence of metastasis at the initial staging workup for biopsy-proven GIST. PET scan helps to differentiate active tumor from necrotic or inactive scar tissue, malignant from benign tissue, and recurrent tumor from nondescript benign changes. PET provides significant value to the standard CT images, because changes in the metabolic activity of tumors often precede anatomic changes on CT. However, PET scan is not a substitute for CT. PET/CT scans may be used to clarify ambiguous findings seen on CT or MRI or to assess complex metastatic disease in patients who are being considered for surgery. Even in this clinical setting there is no clear evidence that PET provides significant information that cannot be obtained using IV contrast-enhanced CT. PET may be of benefit in patients with IV contrast allergy, particularly for peritoneal disease; MRI with or without contrast usually yields excellent anatomical definition of liver metastases.²⁸⁰ If clinicians

consider using PET scan to monitor therapy, a baseline PET should be obtained prior to the start of therapy.

Response Assessment

To assess response to TKI therapy, abdominal/pelvic CT or MRI is indicated every 8 to 12 weeks. PET may give an indication of imatinib activity after 2 to 4 weeks if rapid read-out is necessary.³⁰⁰ Various CT response criteria have been investigated and compared in patients with GIST, including iterations of RECIST, Choi, and WHO criteria.^{225,301-306}

Experts have advocated that the CT response criteria proposed by Choi are much better than RECIST criteria to assess the response of GIST to TKI therapy. Choi criteria have been validated in one center in patients with GIST who had not previously received TKI therapy.³⁰¹ However, these criteria are not universally accepted, they have not been validated for patients who have received several targeted therapies, and the ease of use outside specialized centers is unknown. Some recent studies have supported the use of RECIST, WHO, or volumetric criteria for sunitinib or regorafenib response assessment following progression on imatinib.³⁰³⁻³⁰⁵

The EORTC developed metabolic response criteria for tumors evaluated with PET that provide definitions for complete metabolic response, partial metabolic response, stable metabolic disease, or disease metabolic progression.³⁰⁷ However, since there is a 95% correlation between the information from regular contrast-enhanced CT and PET/CT scans, CT scans with IV contrast are the preferred routine imaging modality for patients with GIST on TKI therapy.

Early assessment of treatment response to sunitinib has been shown to be a predictor of clinical outcome. However, the preliminary findings from this study need to be confirmed in larger prospective studies.³⁰⁰

Surgery

Surgery is the primary treatment of choice for patients with localized or potentially resectable GIST lesions. While imatinib is the primary therapy for patients with metastatic GIST, surgery may be indicated for locally advanced or previously unresectable disease after a favorable response to preoperative imatinib and for limited disease progression on systemic therapy. If persistent metastatic or residual tumor remains after surgery, then imatinib should be continued as soon as the patient is able to tolerate oral intake.

GISTs are fragile and should be handled with care to avoid tumor rupture. The goal is to achieve complete gross resection of the tumor with an intact pseudocapsule. After removal of any suspected GIST, postoperative pathology assessment is essential to confirm the diagnosis. Segmented or wedge resection to obtain negative margins is often appropriate. Lymphadenectomy is usually not required given the low incidences of nodal metastases, but resection of pathologically enlarged nodes should be considered in patients with SDH-deficient GIST. Resection should be accomplished with minimal morbidity and complex multivisceral resection should be avoided. Re-resection is generally not indicated for microscopically positive margins on final pathology. If abdominoperineal resection would be necessary to achieve a negative margin, then preoperative imatinib should be considered. If the surgeon feels that a complex surgical procedure is required, then a multidisciplinary consultation regarding the use of preoperative imatinib is recommended.

Sphincter-sparing surgery and esophagus-sparing surgery should be considered for rectal and gastroesophageal junction GISTs, respectively. Several case reports have demonstrated that the use of preoperative imatinib enables organ-sparing surgery and improves surgical outcomes in patients with rectal GISTs.²⁸⁰

The role for laparoscopy in the resection of GISTs continues to expand. Although prospective studies are lacking, literature reports based on a small series of patients and retrospective analyses have demonstrated that not only are laparoscopic or laparoscopic-assisted resections possible, but they are also associated with low recurrence rates, short hospital stay duration, and low morbidity.²⁸⁰ A meta-analysis of 19 studies (n = 1060 GIST cases) revealed no difference in long-term outcomes of GIST resections using laparotomy and laparoscopy, but laparoscopic approaches were associated with less blood loss, lower complication rates, and shorter hospital stays.³⁰⁸

Laparoscopic approach may be considered for selected GISTs in favorable anatomic locations such as anterior wall of the stomach, jejunum, and ileum. The same surgical principles of complete macroscopic resection including the preservation of the pseudocapsule and avoidance of tumor rupture should be followed during laparoscopy. Resection specimen should be removed from the abdomen in a plastic bag to avoid spillage or seeding of port sites. Laparoscopic surgery could be feasible in other anatomic sites, such as smaller rectal GISTs. However, data on laparoscopic resection of GISTs at other sites are limited.

Targeted Therapy

GISTs have previously been documented to be resistant to conventional chemotherapies. Since *KIT* activation occurs in the majority of cases of GISTs, *KIT*-inhibition has emerged as the primary therapeutic modality along with surgery for the treatment of GISTs.

Imatinib

Imatinib, a selective inhibitor of the *KIT* protein tyrosine kinase, has produced durable clinical benefit and objective responses in most patients with GIST. In phase II and III studies, imatinib has resulted in

high overall response rates and exceptionally good PFS in patients with unresectable and/or metastatic GIST, inducing objective responses in more than 50% of the patients.³⁰⁹⁻³¹³ In February 2002, the FDA approved use of imatinib for the treatment of patients with *KIT*-positive unresectable and/or metastatic malignant GIST. Long-term follow-up results of the B2222 study (n = 147, randomly assigned to receive 400 or 600 mg of imatinib daily) confirmed that imatinib induces durable disease control in patients with advanced GIST.³¹⁴ The estimated 9-year OS rate was 35% for all patients, 38% for those with CR or PR, and 49% for those with stable disease. Low tumor bulk at baseline predicted for longer TTP and improved OS.

Two separate phase III studies (EORTC 62005 study and the S0033/CALGB 150105 study) have assessed the efficacy of imatinib at two initial dose levels (400 mg daily vs. 800 mg daily, given as 400 mg twice a day) in patients with metastatic or unresectable GIST.^{310,311,313} Both studies showed equivalent response rates and OS for both dose levels. Higher dose of imatinib was associated with more side effects than the lower dose in both studies. The EORTC 62005 study (n = 946) documented an earlier TTP for patients receiving 400 mg daily.³¹⁰ At a median follow-up of 760 days, 56% of patients allocated to imatinib once a day had progressed compared with 50% of those who were assigned to treatment twice a day. The S0033/CALGB 150105 study (n = 746) reported identical response rates (40% vs. 42%, respectively) at a median follow-up of 4.5 years and there were no statistical differences in PFS (18 months for low-dose arm vs. 40 months for higher dose arm) and median OS (55 and 51 months, respectively).³¹³ Following progression on 400 mg daily, 33% of patients who crossed over to the higher dose achieved objective response rates and stable disease. This finding is consistent with that of the EORTC 62005 study, in which 133 (55%) patients who progressed on low-dose imatinib

crossed over to high-dose imatinib; subsequently, 2% of patients had PR and 27% had stable disease.³¹¹ However, the small advantage in PFS observed for high-dose imatinib in the EORTC 62005 study was not corroborated by the S0033/CALGB 150105 study.

Available data confirm the safety and efficacy of imatinib at 400 mg/d as the initial standard dose to achieve response induction.^{310,313} Dose escalation to 800 mg/d is a reasonable option for patients progressing on 400 mg/d.³¹¹

Preoperative Imatinib

The RTOG 0132/ACRIN 6665 is the first prospective study that evaluated the efficacy of preoperative imatinib (600 mg/d) in patients with potentially resectable primary disease (30 patients) or potentially resectable recurrent or metastatic disease (22 patients).³¹⁵ Among patients with primary GIST, PR and stable disease were observed in 7% and 83% of patients, respectively. In patients with recurrent or metastatic GIST, PR and stable disease were observed in 4.5% and 91% of patients, respectively. The estimated 2-year OS rate was 93% and 91% for patients with primary GIST and those with recurrent or metastatic GIST, respectively. The estimated 2-year PFS rate was 83% and 77%, respectively.

In a study conducted at MD Anderson Cancer Center, 19 patients undergoing surgical resection for primary GIST (with or without metastases) or recurrent disease (local or metastatic) were randomized to receive 3, 5, or 7 days of preoperative imatinib (600 mg daily).³¹⁶ The response rate assessed by FDG-PET and dynamic CT was 69% and 71%, respectively. Median DFS of patients treated with surgery and imatinib was 46 months. Tumor size was a predictor of recurrence after postoperative imatinib. However, in this study, there was no histologic evidence of cytoreduction within 3 to 7 days of preoperative imatinib.

In another prospective study, Fiore and colleagues reported that preoperative imatinib improved resectability and reduced surgical morbidity in patients with primary GISTs, unresectable or resectable through a major surgical procedure with significant surgical morbidity. Median size reduction was 34% and the estimated 3-year PFS rate was 77%.³¹⁷ Imatinib was continued postoperatively for 2 years in all patients.

In the subgroup analysis of patients with non-metastatic, locally advanced, primary GIST treated with imatinib within the prospective BFR14 phase III study, preoperative imatinib was associated with a PR rate of 60% (15 of 25 patients), and 36% (9 of 25 patients) of patients underwent surgical resection of primary tumor after a median of 7.3 months of imatinib treatment.³¹⁸ All patients who underwent resection were treated with postoperative imatinib. The 3-year PFS and OS rates were 67% and 89%, respectively, for patients who underwent resection. All patients who underwent resection were treated with postoperative imatinib.

While the results of these prospective studies have demonstrated the safety and efficacy of preoperative imatinib in patients undergoing surgical resection, survival benefit could not be determined since all patients included in 3 of these studies also received postoperative imatinib postoperatively for 2 years.^{315,316,318} At the present time, the decision to use preoperative imatinib for patients with resectable primary or locally advanced or recurrent GIST should be made on an individual basis.

Postoperative Imatinib

Surgery does not routinely cure GIST. Complete resection is possible in approximately 85% of patients with primary tumors. At least 50% of these patients will develop recurrence or metastasis following complete

resection and the 5-year survival rate is about 50%.³¹⁹⁻³²¹ Median time to recurrence after resection of primary high-risk GIST is about 2 years. A retrospective review of 506 patients with completely resected GIST revealed the potential for underestimating risk of recurrence, particularly in the case of intermediate size, intermediate level mitotic count, and non-gastric tumors.³²² The data suggested that at least 3 years of adjuvant treatment was associated with higher RFS for patients with higher-risk disease. Multiple randomized studies have investigated the optimal duration of adjuvant therapy for resected GIST.

Imatinib therapy was investigated in a phase III, double-blind study (ACOSOG Z9001), which randomized patients with primary localized GISTs (3 cm or greater in size) to postoperative imatinib 400 mg (317 patients) or placebo (328 patients) for one year after complete resection.³²³ At a median follow-up of 74 months, the RFS rate was significantly higher in the imatinib arm compared to placebo (HR, 0.6; 95% CI, 0.43–0.75; Cox model adjusted $P < .001$). OS was not significantly different between the imatinib and placebo arms.³²⁴ Further analyses revealed that imatinib therapy was associated with higher RFS in patients with *KIT* exon 11 deletions (but not *KIT* exon 11 insertion or point mutation, *KIT* exon 9 mutation, *PDGFRA* mutation, or wild-type tumor). Tumor genotype was not associated with RFS in the placebo arm.

An intergroup randomized trial (EORTC-62024: [NCT00103168](#)) compared observation with 2 years of adjuvant imatinib following R0/R1 resection in 908 patients with localized, intermediate, or high-risk GIST.³²⁵ RFS for imatinib versus observation was 84% versus 66% at 3 years and 69% versus 63% at 5 years ($P < .001$). However, the endpoint of 5-year imatinib failure-free survival (IFFS) did not reach significance at 87% versus 84% (HR, 0.79; 98.5% CI, 0.50–1.25; $P = .21$).

The results of another randomized phase III study from the Scandinavian Sarcoma Group (SSG XVIII/AIO) suggest that postoperative imatinib administered for 36 months improves RFS and OS compared to 12 months for patients with a high estimated risk of recurrence after surgery.^{326,327} In this study, patients with a high risk for GIST recurrence after surgery (tumor greater than 10 cm in size with a mitotic rate of >10 mitoses/50 HPF or tumor greater than 5 cm in size with a mitotic rate of >5 mitoses/50 HPF or a risk of recurrence of greater than 50%) were randomized to 12 months (n = 200) or 36 months (n = 200) of postoperative imatinib. The median follow-up was 90 months. The RFS and OS were significantly longer in the 36-month group compared to the 12-month group (5-year RFS: 71.1% vs. 52.3%, respectively; $P < .001$; 5-year OS: 91.9% vs. 85.3% respectively; $P = .036$). Follow-up analyses were designed to elucidate risk factors for recurrence following postoperative imatinib therapy, revealing the highest risk for recurrence among patients with non-gastric GIST and tumors with high mitotic count.³²⁸

Management of Toxicities

The most common side effects of imatinib include fluid retention, diarrhea, nausea, fatigue, muscle cramps, abdominal pain, and rash. The side effect profile may improve with prolonged therapy.³²⁹ Serious side effects (such as liver function test [LFT] abnormalities, lung toxicity, low blood counts, and GI bleeding) have rarely been reported and often improve after imatinib is withheld. LFT abnormalities are seen in fewer than 5% of patients. Leukopenia is quite rare and imatinib has only rarely been associated with neutropenic fever. The side effect profile may improve with prolonged therapy and can be managed with appropriate supportive care measures. If life-threatening side effects occur with imatinib that cannot be managed by maximum supportive

treatment, then sunitinib should be considered, after discontinuing imatinib.

A recent report described congestive heart failure (CHF) as a potential side effect of imatinib. However, in a retrospective analysis of 219 consecutive patients treated with imatinib, grade 3 or 4 cardiotoxicity occurred in 8.2% of patients, who were manageable with medical therapy, and infrequently required dose reduction or discontinuation of imatinib.³³⁰ Arrhythmias, acute coronary syndromes, or heart failure were uncommon, occurring in less than 1% of treated patients. The authors concluded that imatinib is an uncommon cause of cardiotoxicity, and that the cardiovascular adverse events that occur are manageable when recognized and treated. However, patients on imatinib who present with significant fluid retention should be evaluated carefully.

Sunitinib

Sunitinib is a multi-targeted TKI that can induce objective responses and control progressive disease in patients with imatinib-resistant GIST. SDH-deficient GIST may have a higher probability of response to sunitinib.

In a randomized phase III placebo-controlled study, sunitinib produced significant, sustained clinical benefit in patients with imatinib-resistant or imatinib-intolerant GIST.³³¹ In patients with imatinib-resistant GIST, sunitinib resulted in a significant improvement in median time to progression (27.3 vs. 6.4 weeks) and significantly greater estimated OS. Sunitinib treatment induced PR in 14 patients (6.8%) and stable disease (22 weeks or more) in 36 patients (17.4%) versus no PRs and stable disease in 2 patients (1.9%) on placebo. In the imatinib-intolerant group, 4 out of 9 patients randomized to sunitinib achieved PR and one patient had progressive disease. In contrast, three of the four patients

randomized to placebo had progressive disease at the time of analysis and no PR was observed. Sunitinib was generally well tolerated. In January 2006, sunitinib received FDA approval for the treatment of GIST, after disease progression on or intolerance to imatinib.

The safety and efficacy of sunitinib on a continuous daily dosing schedule at 37.5 mg was evaluated in an open-label, multicenter, randomized phase II study in patients with advanced GIST after imatinib failure.³³² Patients were randomized (1:1) to receive continuous daily sunitinib (37.5 mg/d) either in the morning or in the evening for 28 days (one cycle). The primary endpoint was the clinical benefit rate (CBR) defined as the percentage of patients with CRs, PRs, or stable disease for 24 weeks or more based on RECIST. The overall CBR was 53% (13% of patients had PRs and 40% had stable disease). Median PFS and OS were 34 weeks and 107 weeks, respectively. The most commonly reported treatment-related adverse events (diarrhea, fatigue, and nausea) were consistent with those known to be associated with sunitinib intermittent dosing. Treatment-related hypertension and hypothyroidism (experienced by 28% and 12% of patients, respectively) were successfully managed with appropriate supportive care measures. Both of these adverse events have also been associated with the long-term use of sunitinib on intermittent dosing. The results of this study suggest that continuous daily dosing appears to be an effective alternative dosing strategy with acceptable safety for patients with imatinib-resistant/-intolerant GIST.

Results were recently reported from an international study of sunitinib safety and efficacy in patients with imatinib resistant/intolerant advanced GIST (n = 1124).³³³ The median PFS was 8.3 months (95% CI, 8.0–9.4 months) and median OS was 16.6 months (95% CI, 14.9–18.0 months); safety findings were in line with previous studies. In a follow-up retrospective analysis of a subset of this trial population (n =

230), PFS was significantly better for patients with a primary mutation in *KIT* exon 9 compared to those with a primary mutation in exon 11 (12.3 months vs. 7 months; HR, 0.59; 95% CI, 0.39–0.89; *P* = .011).³³⁴

Management of Toxicities

Sunitinib-related toxicities can often be managed with dose interruptions or reductions. Fatigue, nausea, and vomiting were dose-limiting toxicities for sunitinib in clinical trials. Other common toxicities include hematologic toxicities (ie, anemia, neutropenia), diarrhea, abdominal pain, mucositis, anorexia, and skin discoloration. Sunitinib is associated with a significant risk of developing hand-foot skin reaction (HFSR).³³⁵ Early detection and proper management of HFSR is vital during treatment with sunitinib. HFSR can be prevented with routine application of emollient lotions. If it is significant, interruption of therapy is indicated; if it is severe, dose reduction should be considered.

Hypertension is a common side effect reported in clinical trials, since sunitinib targets vascular endothelial growth factor receptor (VEGFR). However, the risk is higher in patients with renal cell carcinoma (RCC) compared to those with non-RCC.³³⁶ Recent reports have shown that sunitinib is also associated with cardiotoxicity and hypothyroidism.^{337,338} In a retrospective analysis of the data from phase I-II studies, 11% of patients had an adverse cardiovascular event including CHF in 8% of patients and absolute reduction in the left ventricular ejection fraction (LVEF) in 28% of patients.³³⁷ In a prospective, observational cohort study, abnormal serum thyroid-stimulating hormone (TSH) concentrations were documented in 62% of patients and the risk for hypothyroidism increased with the duration of therapy.³³⁸

Close monitoring for hypertension and LVEF is essential in patients receiving sunitinib, especially in patients with a history of heart disease

or cardiac risk factors. Routine monitoring (every 3–6 months) of TSH is indicated. If hypothyroidism is suggested, patients should receive thyroid hormone replacement therapy. Patients should monitor their blood pressure closely and those who experience an increase in blood pressure should be treated with antihypertensives.²⁸⁰

Impact of Mutational Status on Response to Imatinib or Sunitinib in Patients with Advanced or Metastatic GIST

The presence and type of *KIT* or *PDGFRA* mutation has been identified as the predictor of response to imatinib. In randomized clinical trials, the presence of a *KIT* exon 11 mutation was associated with better response rates, PFS, and OS compared to *KIT* exon 9 mutations or wild-type GIST.^{299,339-342}

Long term follow-up (median 73 months) from the prospective, multicenter, randomized phase III BFR14 trial by the French Sarcoma Group identified *KIT* exon 11 mutations as an independent prognostic factor for higher PFS and OS in patients treated with standard-dose imatinib when compared with patients who had wild-type GIST or *KIT* exon 9 mutations.²⁹⁹

In the US-Finnish B2222 phase II study, PR rates, event-free survival (EFS), and OS rates were better for patients with *KIT* exon 11 mutations than those with *KIT* exon 9 mutations or had no detectable kinase mutations.³³⁹ The PR rates for patients with *KIT* exon 11 mutations, *KIT* exon 9 mutations, or no detectable kinase mutations were 83.5%, 48%, and no responses, respectively. The presence of *KIT* exon 11 mutations was the strongest prognostic factor reducing the risk of death by more than 95%.

In a randomized EORTC-62005 study, the presence of *KIT* exon 9 mutations was the strongest adverse prognostic factor for risk of

progression and death.³⁴⁰ In this trial, treatment with high-dose imatinib (800 mg/d) resulted in a significantly superior PFS with a reduction of the relative risk of 61% ($P = .0013$), in patients whose tumors expressed a *KIT* exon 9 mutation.³⁴¹ In addition, the response rate after crossover from 400 mg daily to 400 mg twice daily imatinib was much higher among patients with *KIT* exon 9 mutations (57%) than among patients with *KIT* exon 11 mutations (7%).

The North American Intergroup phase III trial (SWOG S0033/CALGB 150105) also confirmed the findings from B2222 and EORTC-62005 studies. Patients with *KIT* exon 9 mutation treated with 800 mg imatinib had improved response rates compared to those treated with 400 mg imatinib (67% vs.17%, respectively).³⁴² However, the PFS advantage observed in the EORTC-62005 study in patients with *KIT* exon 9 mutations treated with high-dose imatinib was not confirmed in the S0033/CALGB 150105 study. The results of the North American Intergroup phase III trial also showed that patients with CD117-negative GIST have similar time to tumor progression but inferior OS compared to those with CD117-positive GIST, suggesting that patients with CD117-negative GIST may benefit from imatinib therapy.³⁴² Therefore, it is rational to offer *KIT*-negative GIST patients a therapeutic trial of imatinib with close evaluation and follow-up.

A meta-analysis of EORTC-62005 and SWOG S0033/CALGB 150105 phase III trials that randomized 1,640 patients with advanced GIST to standard-dose imatinib (400 mg daily) or high-dose imatinib (800 mg daily) showed a benefit in PFS for patients with *KIT* exon 9 mutations treated with 800 mg of imatinib.³⁴³ In a recent international survey that reported the outcome of GIST patients with *PDGFRA* mutations, none of 31 evaluable patients with D842V mutation had a response, whereas 21 of 31 (68%) had disease progression.³⁴⁴ Median PFS was 2.8 months for patients with D842V substitution and 28.5 months for



patients with other *PDGFRA* mutations. With 46 months of follow-up, median OS was 14.7 months for patients with D842V substitutions and was not reached for patients with other *PDGFRA* mutations.

Heinrich and colleagues reported that sunitinib induced higher response rates in patients with primary *KIT* exon 9 mutations than those with *KIT* exon 11 mutations (58% vs. 34%, respectively). PFS and OS were significantly longer for patients with *KIT* exon 9 mutations or with wild-type GIST compared to those with *KIT* exon 11 mutations. There were only 4 patients with *PDGFRA* mutations; of these 2 had a primary and one had a secondary D842V mutation and did not respond to treatment. In patients with *KIT* exon 11 mutations, PFS and OS were longer for those with secondary exon 13 or 14 mutations compared to those with exon 17 or 18 mutations. Additional studies are needed to confirm these findings. SDH-deficient GIST may have a higher probability of response to sunitinib compared with imatinib in patients with unresectable, recurrent, or metastatic GIST.

Resistance to Imatinib and Sunitinib

While imatinib benefits most patients with advanced GIST, some patients develop resistance to the drug. Primary resistance is defined as the evidence of clinical progression developing during the first 6 months of imatinib therapy and it is most commonly seen in patients with *KIT* exon 9 mutations treated with imatinib at 400 mg daily, *PDGFRA* exon 18 D842V mutations, or those with tumors that lack identifiable activating mutations in *KIT* or *PDGFRA*, the majority of which are SDH-deficient GIST.^{339,340,342,345} Secondary resistance is seen in patients who have been on imatinib for more than 6 months with an initial response or disease stabilization followed by progression, most commonly because of the outgrowth of tumor clones with secondary mutations in *KIT*.³⁴⁶⁻³⁴⁹ Dose escalation to 800 mg/d or switching to

sunitinib is a reasonable option for patients progressing on imatinib 400 mg/d.^{311,331,332}

Comprehensive molecular studies investigating the mechanisms of resistance to sunitinib are limited by the small number of patients who are surgical candidates after their disease failed to respond to two different TKI therapies. Nevertheless, available evidence (both clinical and preclinical) indicates that while sunitinib is very sensitive to ATP-binding pocket mutations that confer resistance to imatinib, it has little activity against other imatinib-resistant mutations in the *KIT* activation loop.³⁵⁰⁻³⁵²

Management of Resistance to Imatinib and Sunitinib

Regorafenib, a multikinase inhibitor with activity against *KIT*, PDGFR, and VEGFR, was recently approved by the FDA for the treatment of patients with locally advanced, unresectable, or metastatic GIST previously treated with imatinib and sunitinib. In the phase III randomized GRID trial, 199 patients with metastatic and/or unresectable GIST progressing on prior therapy with imatinib and sunitinib were randomized to regorafenib (n = 133) or placebo (n = 66).³⁵³ The median PFS (4.8 months vs. 0.9 months; $P < .0001$) and the disease control rate (DCR; 53% vs. 9%) were significantly higher for regorafenib compared to placebo. The PFS rates at 3 and 6 months were 60% and 38%, respectively, for regorafenib compared to 11% and 0%, respectively, for placebo. The HR for OS was 0.77 with 85% of patients in the placebo arm crossing over to regorafenib due to disease progression. The most common treatment-related adverse events (grade 3 or higher) were hypertension (23%), HFSR (20%), and diarrhea (5%).

Sorafenib,³⁵⁴⁻³⁵⁷ nilotinib,³⁵⁸⁻³⁶² dasatinib,^{363,364} and pazopanib³⁶⁵ have also shown activity in patients with GIST resistant to imatinib and sunitinib.

Much of the data on these TKIs comes from phase II studies and retrospective analyses involving a small number of patients.

In a prospective, multicenter, phase II study of 38 patients with unresectable, KIT-positive GIST that had progressed on imatinib and sunitinib, sorafenib resulted in a DCR of 68% (55% of patients who had stable disease and 13% who had PR).³⁵⁴ Median PFS and OS were 5.2 months and 11.6 months, respectively; 1-year and 2-year survival rates were 50% and 29%, respectively. In a retrospective analysis of 124 patients with metastatic GIST resistant to imatinib and sunitinib, sorafenib also demonstrated activity resulting in median PFS and OS of 6.4 months and 13.5 months, respectively.³⁵⁶ It should be noted that patients included in this study had not been treated with regorafenib, and the efficacy of sorafenib following regorafenib therapy in patients with metastatic GIST resistant to imatinib and sunitinib has not been studied.

In a retrospective analysis of 52 patients with advanced GIST resistant to imatinib and sunitinib, nilotinib resulted in a 10% response rate and 37% DCR.³⁵⁹ Median PFS and OS were 12 weeks and 34 weeks, respectively. In a randomized phase III study of nilotinib as third-line therapy and best supportive care (with or without a TKI) in patients with GIST resistant or intolerant to imatinib and sunitinib (248 patients), the PFS on nilotinib was not found to be superior to best supportive care (109 days vs. 111 days; $P = .56$). In a post hoc subset analysis, patients progressing on both imatinib and sunitinib who had not received any other therapy had an improved OS (>4 months) with nilotinib compared to best supportive care (405 vs. 280 days; $P = .02$). The clinical benefit associated with nilotinib may be specific to subsets of patients with *KIT* exon 17 mutations, previously treated with imatinib and sunitinib.³⁶² A recent phase III study investigating nilotinib

as an alternative front-line agent to imatinib for unresectable or metastatic GIST was terminated early due to futility.³⁶⁶

Dasatinib has demonstrated activity against *PDGFRA* D842V mutation that confers the highest resistance to imatinib, and it could be an effective treatment option for this group of patients with imatinib-resistant GIST.³⁶³ In the phase II study of 50 patients with advanced GIST resistant to imatinib, dasatinib was associated with a median PFS and OS of 2 and 19 months, respectively, with response assessment by Choi criteria.³⁶⁴ Median PFS for patients with wild-type GIST was 8.4 months.

Pazopanib has also shown marginal activity in unselected, heavily pretreated patients with advanced GIST. In a multicenter phase II study of patients with advanced GIST following failure of at least imatinib and sunitinib ($n = 25$), pazopanib was well tolerated resulting in stable disease in 48% of patients, with a 24-week non-progression (CR + PR + stable disease) rate of 17%.³⁶⁵ The median PFS and OS were 1.9 months and 10.7 months, respectively.

Initial Evaluation and Workup

All patients should be managed by a multidisciplinary team with expertise in sarcoma. Essential elements of the workup include the H&P, primary site and chest imaging, EUS in selected patients, endoscopy as indicated (if not previously done), and surgical assessment. Genotyping is recommended for cases in which medical therapy is anticipated. For very small GIST (<2 cm), abdominal/pelvic CT is sufficient. For all other GISTs, workup includes baseline abdominal/pelvic CT and/or abdominal/pelvic MRI, along with chest imaging using CT or x-ray. PET/CT can be considered. Baseline PET/CT should be performed if PET/CT will be used during follow-up.

Treatment Guidelines

Resectable Disease

Primary/Preoperative Treatment

Surgery is the primary treatment for all patients with GISTs (2 cm or greater) that are resectable without significant risk of morbidity. Preoperative imatinib may be beneficial as primary treatment for patients with GIST that is resectable with negative margins but with a significant risk of morbidity.^{315,317} The use of preoperative imatinib may, however, prohibit the accurate assessment of recurrence risk. Preoperative imatinib should be considered only if surgical morbidity could be reduced by downstaging the tumor prior to resection. Close monitoring is essential, because some patients may rapidly become unresectable. In prospective studies, preoperative imatinib has been tested at a daily dose of either 400 mg^{317,318} or 600 mg.^{315,316} The guidelines recommend an initial dose of 400 mg daily. Patients with documented *KIT* exon 9 mutations may benefit from dose escalation up to 800 mg daily (given as 400 mg twice daily), as tolerated.

Baseline imaging is recommended prior to the start of preoperative imatinib. To assess response to TKI therapy, abdominal/pelvic CT or MRI is indicated every 8 to 12 weeks. PET may give an indication of imatinib activity after 2 to 4 weeks if rapid read-out is necessary. Since the optimal duration of preoperative therapy remains unknown, in patients with disease that is responding to therapy, imatinib should be continued until maximal response (defined as no further improvement between 2 successive CT scans, which can take as long as 6–12 months). However, it is not always necessary to wait for a maximal response to perform surgery. Surgery is recommended if bleeding and/or symptoms are present. For patients with disease that is responding to treatment, response assessment imaging can be performed less frequently. Progression may be determined by

abdominal/pelvic CT or MRI with clinical interpretation with PET/CT used as needed to clarify ambiguous results. If there is no progression, continuation of the same dose of imatinib is recommended and resection should be considered, if possible. If there is progression, surgery is recommended after discontinuing imatinib. In patients taking preoperative imatinib, dosing can be stopped right before surgery and resumed as soon as the patient is able to tolerate oral medications following surgery regardless of surgical margins. Collaboration between the medical oncologist and the surgeon is necessary to determine the appropriateness of surgery following major response or stable disease.

However, the management of incidentally encountered small GISTs less than 2 cm remains controversial.²⁸⁰ At present, there are insufficient data to guide the management of very small GISTs (less than 2 cm) discovered incidentally on endoscopy and the usefulness of regular EUS surveillance has not been established. Complete surgical resection is the mainstay of treatment in symptomatic patients. For a subset of patients with very small gastric GISTs (less than 2 cm) with no high-risk EUS features (ie, irregular extra-luminal border, heterogeneous echo pattern, presence of cystic spaces, echogenic foci), periodic endoscopic surveillance may be considered.^{281,367} The panel has included this approach with a category 2B recommendation.

Postoperative Treatment

Based on results of the ACOSOG Z9001 study and the randomized phase III study (SSGXVIII/AIO, [NCT00116935](#)), the guidelines recommend postoperative imatinib following complete resection for primary GIST with no preoperative imatinib for patients at intermediate or high risk of recurrence (category 1).^{323,326} The panel recommends that postoperative imatinib for at least 36 months should be considered for patients with high-risk GIST.^{326,327}

Estimation of risk of recurrence is important in selecting patients who would benefit from postoperative therapy following complete resection. In the ACOSOG Z9001 study, risk stratification was based only on tumor size and postoperative imatinib improved RFS in patients with GIST 3 cm or larger; however, it was statistically significant in patients with intermediate (6 cm or greater and less than 10 cm) and high risk (greater than 10 cm) of recurrence.^{323,324} In the SSGXVIII/AIO study, risk stratification was based on tumor size, site, mitotic count, and rupture; survival benefit was seen in patients with high risk of recurrence (mitotic index of >5 mitoses/50 HPF, size >5 cm, non-gastric location, and tumor rupture).³²⁶

Risk stratification after surgical resection should be based on tumor mitotic rate, size, and location.³⁶⁸ Gold and colleagues have developed a nomogram, taking into account tumor size, site, and mitotic index, to predict RFS after resection of localized primary GIST.³⁶⁹ This nomogram accurately predicts RFS after resection of localized primary GIST and might be useful for patient care, interpretation of study results, and selection of patients for postoperative imatinib therapy.

For patients with complete resection following preoperative imatinib, the panel agreed that continuation of imatinib (at the same dose that induced objective response) is warranted. The panel acknowledged that while data from single and multi-institutional studies support the continuation of postoperative imatinib for two years following surgery, the exact duration of postoperative imatinib in this group of patients has not been studied in randomized studies.³¹⁵⁻³¹⁸ The long-term analysis of the RTOG 0132 study suggested that a high percentage of patients progressed after discontinuation of 2-year postoperative imatinib therapy.³⁷⁰

For patients with completely resected disease who did not receive preoperative imatinib, postoperative imatinib is recommended for patients with intermediate or high-risk disease (category 1). Observation can be considered for completely resected, low-risk disease.

In patients with persistent gross disease following resection (R2 resection) who received preoperative imatinib, additional resection may be considered to remove residual disease. Imatinib treatment should be continued following re-resection regardless of surgical margins until progression. Postoperative imatinib should be initiated following resection, if the patient had not received prior imatinib therapy.

Unresectable, Metastatic, or Recurrent Disease

Baseline imaging is recommended prior to initiation of treatment. Imatinib (category 1) is the primary treatment for patients with advanced, unresectable, or metastatic GIST. Imatinib has been shown to improve resectability and reduce surgical morbidity in patients with documented unresectable GIST or in patients for whom resection would carry the risk of severe postoperative functional deficit.^{317,318} Several retrospective studies have demonstrated survival benefit of cytoreductive surgery following preoperative imatinib in patients with advanced or metastatic GIST responding to preoperative imatinib.³⁷¹⁻³⁷⁸ No definitive data exist to prove whether surgical resection improves clinical outcome in addition to TKI therapy for patients with resectable metastatic GIST. Prospective phase III studies are underway to assess whether or not resection changes outcome in patients with unresectable metastatic GIST responding to TKI therapy.

Providers should consider resection if complete resection can be obtained in primary metastatic disease. To assess response to TKI therapy, abdominal/pelvic CT or MRI is indicated every 8 to 12 weeks.

PET may give an indication of imatinib activity after 2 to 4 weeks if rapid read-out is necessary. If there is no progression, resection can be considered following surgical consultation. Imatinib should be continued if resection is not feasible. At this time, continuous use of imatinib is recommended for metastatic GIST until progression. The patient should be maintained on the same dose, and the dose of imatinib should not be increased if patients remain stable without objective progression of the disease. Termination of imatinib in patients with GIST that is refractory to imatinib has been shown to result in a flare phenomenon, which in turn indicates that even in patients with progressive disease on imatinib therapy, there are some tumor cells for which imatinib may still be effective.³⁷⁹

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

Progressive Disease

Progression is defined as the appearance of a new lesion or an increase in tumor size and may be determined by abdominal/pelvic CT or MRI with clinical interpretation, using PET/CT as needed to clarify ambiguous results.

Dose escalation of imatinib up to 800 mg daily (given as 400 mg twice daily) as tolerated or switching to sunitinib (category 1) are included as options for patients with progressive disease (limited disease or widespread systemic disease in patients with good performance status) on standard-dose imatinib.^{311,331,332} All clinical and radiological data, including lesion density on CT and patient compliance to treatment with

standard-dose imatinib, should be assessed prior to dose escalation of imatinib or switching to sunitinib.

For patients with limited progressive disease on standard-dose imatinib, second-line therapy with sunitinib should be initiated only if the majority of disease is no longer controlled by imatinib; consideration of other therapeutic interventions for progressing lesion(s) is warranted. Surgical resection should be considered in carefully selected patients with limited progressive disease that is potentially easily resectable.^{371,376,380} However, incomplete resections are frequent with high complication rates. The guidelines have included, only for patients with limited progressive disease, continuation of imatinib at the same initial dose and treatment of progressing lesions with resection, RFA, chemoembolization (category 2B), or palliative RT (category 2B) for rare patients with bone metastases.²⁸⁰

Regorafenib (category 1) is recommended for patients with disease progression on imatinib and sunitinib.³⁵³ Based on limited data,³⁵⁴⁻³⁶⁴ the guidelines have also included sorafenib, dasatinib, or nilotinib as additional options for patients who are no longer receiving clinical benefit from imatinib, sunitinib, or regorafenib, although all data regarding the potential benefit of these agents are in the pre-regorafenib era.

In patients with progressive disease no longer receiving benefit from current TKI therapy, re-introduction of previously tolerated and effective TKI therapy for palliation of symptoms can be considered.^{381,382} The results of a recent randomized study demonstrated that imatinib rechallenge significantly improved PFS and DCR in patients with advanced GIST after failure of at least



imatinib and sunitinib.³⁸² However, the duration of survival benefit was brief due to continued progression of TKI-resistant clones.

Any patient who has disease progression despite prior therapy or who has a recurrence, regardless of presentation, should be considered for enrollment in a clinical trial, if an appropriate trial is available.

Continuation of TKI Therapy

The optimal duration of TKI therapy in patients with responding or stable disease is not known. The results of a prospective, multicenter, randomized phase III study (BFR14) show that there was a significant increase in the rate of progressive disease when imatinib therapy was interrupted in patients with advanced disease that was stable or responding to imatinib therapy.^{383,384} A recent report from this study confirmed that patients with rapid disease progression after interruption of imatinib had a poorer prognosis.³⁸⁵ More importantly, the quality of response upon reintroduction of imatinib did not reach the tumor status observed at randomization.

The panel strongly recommends that TKI therapy at the prescribed daily dose should be continued as long as patients are receiving clinical benefit (response or stable disease). The panel also feels that continuation of TKI therapy life-long for palliation of symptoms should be an essential component of best supportive care. However, short interruptions for one to two weeks, when medically necessary, have not been shown to negatively impact disease control or other outcomes.

Surveillance

Patients with completely resected, incompletely resected, or metastatic GIST should have a thorough H&P every 3 to 6 months; abdominal/pelvic CT scan should be performed every 3 to 6 months for

3 to 5 years, then annually. Less frequent surveillance may be acceptable for very small tumors (>2 cm). Progression may be determined by CT or MRI with clinical interpretation; PET/CT can be considered to clarify ambiguous CT results.

Desmoid Tumors (Aggressive Fibromatoses)

Desmoid tumors, also known as aggressive fibromatoses, are unique mesenchymal neoplasms, which are often considered 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 the general population.²²⁻²⁵ Abdominal desmoids may be a component of FAP and may also arise through elective surgical intervention (eg, colectomy) in susceptible patients.^{22,386,387} In patients who have been treated with prophylactic colectomy, desmoids now represent a more significant cause of morbidity than carcinoma of the colon.³⁸⁸



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.³⁸⁹⁻³⁹³ Lazar and colleagues identified mutations in the *CTNNB1* gene in 85% of patients with desmoid tumors.³⁸⁹ 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.³⁸⁹ 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).³⁹⁰ Columbo and colleagues also reported that mutation 45F was associated with higher rates of local recurrence among patients with primary, completely resected, sporadic desmoid tumors and mutation 45F was more prevalent in extra-abdominal desmoid tumors compared to other sites.³⁹² 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.³⁹³ 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.³⁹⁴⁻³⁹⁷

Treatment Guidelines

Resectable Tumors

Surgery is the primary treatment for patients with resectable desmoid tumors.³⁹⁸⁻⁴⁰² 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 ($P < .01$).⁴⁰³ In a more recent report involving 211 patients with desmoid tumors treated with surgery, Peng and colleagues also reported similar findings.⁴⁰⁴ 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 ($P < .001$). However, the impact of positive resection margins on local control and risk of recurrence remains controversial.⁴⁰⁵ Some studies have reported margin status as an independent prognostic factor of recurrence.^{404,406-408} Other studies

have failed to demonstrate any clear association between resection margins and risk of recurrence.^{403,409} Recent data suggest no difference in outcomes between patients with R0 or R1 resection margins who undergo careful observation.⁴¹⁰⁻⁴¹² Therefore, R1 margins are acceptable if achieving R0 margins would produce excessive morbidity.

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 local recurrence.^{409,413-418} However, in another series of patients with desmoid tumors of the chest wall, postoperative RT did not reduce the risk of recurrence.⁴⁰²

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).^{419,420} 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; $P = .70$).⁴²⁰ 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 “watch and wait” 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. If there is progression, they 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 (56–58 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.^{403,421} RT is a reasonable treatment option for patients with unresectable tumors, depending on the possible morbidity of treatment.^{409,422-425}

In a retrospective analysis of 23 patients with extra-mesenteric desmoid tumors treated with RT for gross residual unresectable disease, 7 patients sustained local recurrence, 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%.⁴⁰⁹ 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.⁴²⁵ 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.⁴²⁵

Definitive RT (54–58 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.^{426,427} In a prospective study, tamoxifen in combination with sulindac resulted in disease stabilization in patients with progressive or recurrent tumors following surgery.⁴²⁸ 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.⁴²⁹ In case reports, toremifene has been effective in disease stabilization following surgery.⁴³⁰⁻⁴³³ Doxorubicin-based chemotherapy has been

effective in patients with recurrent or unresectable tumors.⁴³⁴⁻⁴³⁷ The combination of methotrexate and vinorelbine or vinblastine has also been associated with prolonged stable disease in patients with unresectable or recurrent tumors.^{436,438-440}

Imatinib and sorafenib have also been evaluated in patients with unresectable, progressive, or recurrent aggressive fibromatosis.^{144,441-443} 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.⁴⁴² 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.⁴⁴³ 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.¹⁴⁴

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 annually. 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.⁴⁴⁴ RMS has three histologic subtypes: embryonal (including botryoid and spindle cell variants), alveolar (including a solid variant), and pleomorphic histologies.^{445,446} 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.^{444,446-451}

The incidence of pleomorphic RMS increases with age and the overall prognosis of RMS in adults is poor.⁴⁵² 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.⁴⁵² Extremities, trunk wall, and genitourinary organs are the most common primary sites for pleomorphic RMS in adults.⁴⁵³⁻⁴⁵⁵ In a recent SEER database analysis of 1,071 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%).⁴⁵⁰ 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.⁴⁵⁰

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.⁴⁴⁴ 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.⁴⁴⁴

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).^{448,456} 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.⁴⁴⁸

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.⁴⁵⁶ 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).⁴⁵⁶ 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).⁴⁴⁷

Chemotherapy regimens used in adults with RMS are usually derived from the pediatric clinical trials on RMS conducted by international cooperative groups.⁴⁵⁷ Vincristine, dactinomycin, and cyclophosphamide (VAC) has been the standard chemotherapy for pediatric nonmetastatic RMS (intermediate or high risk).⁴⁵⁸ 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 ($P = .30$).⁴⁵⁸ RT resulted in good local control for patients with alveolar RMS who underwent primary tumor resection before initiation of chemotherapy.⁴⁵⁹

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.⁴⁶⁰ Vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide (VAC-IE) was found to be effective for patients with intermediate-risk RMS.⁴⁶¹ 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 factors, 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%).⁴⁶²

Newer agents such as carboplatin,⁴⁶³ irinotecan,^{464–467} topotecan,^{468–470} and vinorelbine^{471,472} have also shown activity in the treatment of pediatric patients with metastatic, relapsed, or refractory RMS. Additionally, 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.⁴⁷³

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.^{444,448,452,456,474} 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.⁴⁴⁸ 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.⁴⁵⁶ Recently, 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.⁴⁷⁴



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.⁴⁵⁷ 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.⁴⁷⁵

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 is no optimal chemotherapy for the management of adults with RMS. In the guidelines, vincristine and dactinomycin (with or without cyclophosphamide);^{458,460} vincristine, doxorubicin, and cyclophosphamide (alone or alternating with ifosfamide and etoposide);⁴⁶¹ and vincristine, doxorubicin, and ifosfamide⁴⁷⁴ are included as options for systemic chemotherapy. High-dose methotrexate may be useful for selected patients with CNS or leptomeningeal involvement when RT is not feasible.⁴⁷⁶ See *Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma* in the guidelines for a list of other chemotherapy regimens that are recommended for the management of adults with RMS.

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