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þ Internal medicine
† Orthopedics/orthopedic oncology
€ Pediatric oncology

**NCCN Guidelines Panel Disclosures**

**NCCN Guidelines Index**

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**Discussion**

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NCCN Guidelines Panel Disclosures

NCCN Guidelines Version 3.2012 Sub-Committees
Soft Tissue Sarcoma

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Summary of the Guidelines Updates

Soft Tissue Sarcoma

- Soft-Tissue Extremity/Trunk, Head/Neck (EXTSARC-1)
- Retroperitoneal/Intra-abdominal (RETSARC-1)
- Gastrointestinal Stromal Tumors (GIST-1)
  - Principles of Biopsy for GIST (GIST-A)
  - Principles of Pathologic Assessment for GIST (GIST-B)
  - Principles of Surgery for GIST (GIST-C)
  - Dosing and Administration of Imatinib (GIST-D)
  - Dosing and Administration of Sunitinib (GIST-E)
- Desmoid Tumors (Aggressive fibromatosis) (DESM-1)
- Rhabdomyosarcoma (RMS-1)
- Principles of Pathologic Assessment of Sarcoma Specimens (SARC-A)
- Principles of Ancillary Techniques Useful in the Diagnosis of Sarcomas (SARC-B)
- Principles of Surgery (SARC-C)
- Guidelines for Radiation Therapy (SARC-D)
- Systemic Therapy Agents and Regimens (SARC-E)
- Staging (ST-1)

Bone Sarcomas - See the NCCN Guidelines for Bone Cancer
Uterine Sarcomas - See the NCCN Guidelines for Uterine Neoplasms
Dermatofibrosarcoma Protub erans - See the NCCN Guidelines for Dermatofibrosarcoma Protub erans

Clinical Trials: The NCCN believes that the best management for any cancer patient 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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Updates in version 3.2012 of the NCCN Guidelines for Soft Tissue Sarcoma from version 2.2012 include:

Gastrointestinal Stromal Tumors (GIST)

GIST-7 and SARC-E Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma

- Regorafenib was added as a treatment option for GIST patients with disease progression after imatinib and sunitinib.

MS-1

- The Discussion text was updated to correspond to the changes in the algorithm.

Updates in version 2.2012 of the NCCN Guidelines for Soft Tissue Sarcoma from version 1.2012 include:

Global Changes

- A section on recommendations, including systemic therapy options, for the management of patients with Rhabdomyosarcoma was added (RMS-1).

- The algorithm entitled “Extremity/Trunk” changed to “Extremity/Trunk, Head/Neck” (EXTSARC-1).

- The Discussion text was updated to correspond to the changes in the algorithm (MS-1).

Extremity/Trunk, Head/Neck

EXTSARC-1

- After “Workup”, a new pathway called “Special considerations for unique histologies” was added with corresponding footnote “i” that states, “Diagnosis of a specific histology that will impact the overall treatment plan.”

- Footnote “a” was revised as follows, “All patients, especially those with rhabdomyosarcoma, should be evaluated by institutions with expertise and experience in treating soft tissue sarcoma”.

SARC-E Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma

- 1 of 5:
  - Under Extremity/Trunk, Head/Neck a new footnote “b” was added for “Temozolomide” and “Pazopanib”, that states, “Recommended only for palliative therapy.”
  - A new section was added that lists systemic therapy regimens for rhabdomyosarcoma.
Updates in version 1.2012 of the NCCN Guidelines for Soft Tissue Sarcoma from version 2.2011 include:

**Global Changes**
- The algorithm entitled “Desmoid Tumors (Fibromatosis)” changed to “Desmoid Tumors (Aggressive fibromatosis)”.
- Footnote “a” that states, “All patients, especially those with rhabdomyosarcoma, should be evaluated by institutions with expertise and experience in treating soft tissue sarcoma” is new to the algorithm.
- Third column: “Final margins ≤ 1.0 cm” changed to “Final margins ≤ 1.0 cm (and without an intact fascial plane)”.
- Footnote “j”: The following sentence was added “In selected cases when margin status is uncertain, consultation with a radiation oncologist is recommended”.
- Footnote “p” that states, “Consider ultrasound for smaller lesions that are superficial. Ultrasound should be done by an ultrasonographer experienced in musculoskeletal disease,” is new to the algorithm.
- Stage II, III; Potentially resectable with concern for adverse functional outcomes; Primary Treatment: The recommendation “Preoperative chemotherapy” changed from category 2A to 2B.
- Primary Treatment for Unresectable primary disease: The recommendation “Limb perfusion” changed to “Isolated regional limb therapy”. A similar change was also made in footnote “x”.
- “Stage IV” changed to “Synchronous stage IV”.
- After Metastatic disease:
  - A new pathway for “Isolated regional disease or nodes” was added.
  - Single organ and limited tumor bulk: The recommendation “Metastasectomy ± preoperative or postoperative chemotherapy ± RT” was clarified as “(category 2B for chemotherapy and RT)”.
  - Footnote “aa” that states, “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, while others do not, likely reflecting differences in selection of patients for treatment with surgery and radiotherapy or surgery alone. Traditionally, the re-irradiation has been done with post-operative 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,” is new to the algorithm.

**Retroperitoneal/Intra-abdominal**
- R1 pathway; Postoperative Therapy: The recommendation “Consider boost (10-16 Gy)” was changed to “Consider boost (10-16 Gy) if preoperative RT was given”.

**Footnote Changes**
- Footnote “aa” that states, “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, while others do not, likely reflecting differences in selection of patients for treatment with surgery and radiotherapy or surgery alone. Traditionally, the re-irradiation has been done with post-operative 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,” is new to the algorithm.

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- After Metastatic disease:
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Gastrointestinal Stromal Tumors (GIST)

GIST-1
- **Workup**
  - Fifth bullet: The recommendation “Chest imaging” changed to “Consider chest imaging”.
  - The recommendation “Shared decision making” was removed.
- **Footnote “b”** was revised to read, “Preoperative imatinib should not be considered if surgical morbidity would not improve by reducing the size of the tumor preoperatively”.
- **Footnote “c”** was revised to read, “Consider preoperative imatinib if surgical morbidity would be improved by reducing the size of the tumor preoperatively. Preoperative imatinib may prohibit accurate assessment of recurrence risk”.

GIST-3
- After Documented GIST: “Marginally resectable or resectable with negative margins but with risk of significant morbidity” changed to “Resectable with negative margins but with risk of significant morbidity.”

GIST-4
- **Footnote “m”** was revised as follows: “Medical therapy is the usual course of treatment. However, patient may proceed to surgery if bleeding or symptomatic.”

GIST-6
- **Postoperative Outcomes:** “Incomplete resection; no preoperative imatinib” changed to “Persistent gross residual disease (R2 resection); no preoperative imatinib”.
- After “Completely resected (no preoperative imatinib): The recommendation “Consider imatinib for patients at significant risk of recurrence (intermediate or high risk) (category 1).”
- New footnote “y” was added that states, “For patients with complete resections following preoperative therapy, continued imatinib is warranted. The length 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 post-surgery”.
- **Footnote “z”** was revised as follows: “Adjuvant imatinib for at least 36 months should be considered for high risk tumors. The results of a recently completed randomized trial (SSGXVIII/AIO) suggest that adjuvant imatinib administered for 36 months improves relapse free survival (RFS) and overall survival (OS) compared to 12 months of adjuvant imatinib for patients with a high estimated risk of recurrence (tumor greater than 5 cm in size with high mitotic rate (> 5 mitoses/50 HPF) or a risk of recurrence of greater than 50%) after surgery. The results of ACOSOG trial Z9001 showed that adjuvant imatinib improved relapse free survival in patients with GIST ≥ 3 cm in size with the greatest benefit noted in tumors at higher risk of recurrence (intermediate and high-risk).”
NCCN Guidelines Version 3.2012 Updates
Soft Tissue Sarcoma

Gastrointestinal Stromal Tumors (GIST)---continued

GIST-A--Principles of Biopsy for GIST
- This page was revised extensively, including the addition of the following statement, “Percutaneous image guided biopsy may be appropriate for confirmation of metastatic disease.”

GIST-B--Principles of Pathologic Assessment for GIST
- Third bullet: The number of mitoses in 50 high power was additionally defined as “equivalent to 5mm² of tissue”.

GIST-D--Dosing and Administration of Imatinib
- This page was revised extensively, including the addition of the statement, “Imatinib should be taken with a low fat meal and a large glass of water.

GIST-E--Dosing and Administration of Sunitinib
- This page was revised extensively.

Desmoid Tumors (Aggressive Fibromatosis)

DESM-1
- Footnote “a” defining Gardner’s syndrome is new to the algorithm.

DESM-2
- Footnote “f”: The second sentence was revised as follows, “RT is generally only recommended for desmoid tumors that are in the extremity, superficial trunk or head and neck.”
- Footnote “g” was clarified as “Dose of definitive RT without surgery: 54-58 Gy in the absence of any prior radiation therapy.”
- Footnote “h” that states “Dose of adjuvant/post-operative RT is 50 Gy” is new to the algorithm.

SARC-B Principles of Ancillary Techniques Useful in the Diagnosis of Sarcomas
- This page was revised to reflect current nomenclature.

SARC-C Principles of Surgery
- Under Resection Margins: a new bullet was added that states, “In selected cases where margin status is uncertain, consultation with a radiation oncologist is recommended”.

SARC-D Guidelines for Radiation Therapy
- Preoperative RT pathway; After “Surgery with clips”: The recommendation “Consider boost whenever feasible for positive or close margins” changed to “Consider boost for positive or close margins.”
- The following statement was added to footnote 5: “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.”

SARC-E Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma
- Extremity, Retroperitoneal, Intra-abdominal: Vinorelbine and Pazopanib were added as single agents with category 2A recommendation. For pazopanib, footnote “c” was added that states, “Pazopanib should not be used for lipogenic sarcomas.”
- Desmoid Tumors (Aggressive fibromatosis): Sorafenib was added as a single agent with a category 2A recommendation.
- Chordoma: Erlotinib, alone or in combination with cetuximab was removed.
- Inflammatory Myofibroblastic Tumor (IMT) with ALK Translocation is a new subtype that was added to the page. Crizotinib was added as a single agent for the treatment of IMT with a category 2A recommendation.
WORKUP

ESSENTIAL:
- All patients should be managed by a multidisciplinary team with expertise in sarcoma.\(^a\)
- H&P
- Adequate imaging\(^b\) of primary tumor is indicated for all lesions with a reasonable chance of being malignant (MRI ± CT)\(^c\)
  - Plain radiograph of primary tumor (optional)
- 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)\(^d\)
  - Biopsy should establish grade and histologic subtype\(^e\)
  - Appropriate use of ancillary diagnostic methodologies\(^f\)
- Chest imaging

USEFUL UNDER CERTAIN CIRCUMSTANCES:\(^g\)
- PET scan may be useful in prognostication, grading and determining response to chemotherapy
- Consider abdominal/pelvic CT for myxoid/round cell liposarcoma, epithelioid sarcoma, angiosarcoma, and leiomyosarcoma
- Consider MRI of total spine for myxoid/round cell liposarcoma
- Consider CNS imaging for alveolar soft part sarcoma and angiosarcoma
- Adequate imaging should provide details about the size of tumor and contiguity to nearby visceral structures and neurovascular landmarks.
- CT angiogram may be useful for patients in whom an MRI is not feasible.
- In selected institutions with clinical and pathologic expertise, an FNA may be acceptable.

\(^{a}\)All patients should be evaluated by institutions with expertise and experience in treating soft tissue sarcoma.

\(^{b}\)Adequate imaging should provide details about the size of tumor and contiguity to nearby visceral structures and neurovascular landmarks.

\(^{c}\)CT angiogram may be useful for patients in whom an MRI is not feasible.

\(^{d}\)In selected institutions with clinical and pathologic expertise, an FNA may be acceptable.

\(^{e}\)See Principles of Pathologic Assessment of Sarcoma Specimens (SARC-A).

\(^{f}\)See Principles of Ancillary Techniques Useful in the Diagnosis of Sarcomas (SARC-B).

\(^{g}\)Different sub-types have different propensities to spread to various locations and imaging should be individualized based upon sub-types.

\(^{h}\)May be useful 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).

\(^{i}\)Diagnosis of a specific histology that will impact the overall treatment plan.
### PRIMARY TREATMENT

#### Stage IA

- **T1a-1b, N0, M0, low grade**
  - Final margins > 1.0 cm or intact fascial plane
    - Surgery
  - Final margins ≤ 1.0 cm (and without an intact fascial plane)
    - Consider RT (category 2B) or Observation

#### Stage IB

- **T2a-b, N0, M0, low grade**
  - Final margins > 1.0 cm or intact fascial plane
    - Surgery
  - Final margins ≤ 1.0 cm (and without an intact fascial plane)
    - Consider RT (category 1)

### FOLLOW-UP

- Evaluation for rehabilitation (occupational therapy (OT), physical therapy (PT))
  - Continue until maximal function is achieved
- H&P every 3-6 mo for 2-3 y, then annually
- Consider chest imaging every 6-12 mo
- Consider obtaining postoperative baseline and periodic imaging of primary site based on estimated risk of locoregional recurrence (MRI, CT, consider ultrasound)

#### If recurrence, See Recurrent Disease (EXTSARC-6)

---

1. See American Joint Committee on Cancer (AJCC) Staging, 7th Edition (ST-1).
2. See Principles of Surgery (SARC-C). In selected cases when margin status is uncertain, consultation with a radiation oncologist is recommended.
3. Resection, if feasible, may be necessary to render margins > 1.0 cm.
4. See Guidelines for Radiation Therapy (SARC-D).
5. Randomized clinical trial data support the use of radiation therapy (category 1) as an adjunct to surgery in appropriately selected patients based on an improvement in disease-free survival (although not overall survival).
6. In situations where the area is easily followed by physical examination, imaging may not be required.
7. After 10 y, the likelihood of developing a recurrence is small and follow-up should be individualized.

---

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Extremity/Trunk, Head/Neck

**Discussion**

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**PRIMARY TREATMENT**

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<th>Stage II, III† Resectable disease</th>
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<td>Resectable with acceptable functional outcomes</td>
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<td>Surgery**</td>
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<tr>
<td>Surgery+</td>
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<td>or</td>
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<tr>
<td>Preoperative RT+</td>
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<td>or</td>
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<tr>
<td>Preoperative chemoradiation (category 2B)</td>
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<td>Preoperative chemotherapy (category 2B)</td>
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<th>FOLLOW-UP</th>
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<td>RT± adjuvant chemotherapy (category 2B for adjuvant chemotherapy)</td>
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<tr>
<td>Consider RT boost</td>
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<td>Consider adjuvant chemotherapy (category 2B)</td>
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- Evaluation for rehabilitation (OT, PT)
  - Continue until maximal function is achieved
- H&P and chest imaging (plain radiograph or chest CT) every 3-6 mo for 2-3 y, then every 6 mo for next 2 y, then annually
- Consider obtaining postoperative baseline and periodic imaging of primary site based on estimated risk of locoregional recurrence (MRI, CT, consider ultrasound)

If recurrence, See Recurrent Disease (EXTSARC-6)

---

**k** See Principles of Surgery (SARC-C).

**m** See Guidelines for Radiation Therapy (SARC-D).

**n** See Principles of Systemic Therapy (SARC-E).

**o** In situations where the area is easily followed by physical examination, imaging may not be required.

**p** After 10 y, the likelihood of developing a recurrence is small and follow-up should be individualized.


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

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

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

**u** See Principles of Systemic Therapy (SARC-E).

**v** Consider re-imaging to assess primary tumor and to rule out metastatic disease.

**w** For residual gross disease or microscopically positive margins.

**x** There are limited and conflicting data regarding the potential benefits of adjuvant chemotherapy in stage II or stage III patients.
Unresectable primary disease

### PRIMARY TREATMENT

- **RT**
  - or
  - Chemoradiation
  - or
  - Chemotherapy
  - or
  - Isolated regional limb therapy

---

### FOLLOW-UP

- **Evaluation for rehabilitation (OT, PT)**
  - Continue until maximal function is achieved
- **H&P and chest imaging**
  - (plain radiograph or chest CT)
  - every 3-6 mo for 2-3 y, then every 6 mo for next 2 y, then annually
- **Consider obtaining baseline and periodic imaging of primary site**
  - (MRI, CT, consider ultrasound)

---

**Changes to resectable**

- **See EXTSARC-3**

---

**Remains unresectable**

- Options:
  - Definitive RT
  - Chemotherapy
  - Palliative surgery
  - Observation, if asymptomatic
  - Best supportive care

---

**If recurrence, see Recurrent Disease (EXTSARC-6)**

---

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**PRIMARY TREATMENT**

- **Single organ and limited tumor bulk that are amenable to complete resection**

  - **Synchronous stage IV**
  - **Disseminated metastases**

  - Primary tumor management as per **EXTSARC-3** and consider the following options:
    - Metastasectomy
    - Chemotherapy
    - Stereotactic radiosurgery/RT
    - Chemotherapy
    - Observation

  - **Options:**
    - Palliative RT
    - Palliative chemotherapy
    - Palliative surgery
    - Observation, if asymptomatic
    - Best supportive care
    - Ablation procedures
      - (eg, radiofrequency ablation (RFA), cryotherapy)
    - Embolization procedures
    - Stereotactic radiosurgery/RT

---

**FOLLOW-UP**

- **Evaluation for rehabilitation (OT, PT)**
  - Continue until maximal function is achieved
- **H&P and chest imaging** (plain radiograph or chest CT) every 3-6 mo for 2-3 y, then every 6 mo for next 2 y, then annually
- **Consider obtaining postoperative baseline and periodic imaging of primary site based on estimated risk of locoregional recurrence** 
  - (MRI, CT, consider ultrasound)

---

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

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


3 See Principles of Systemic Therapy (SARC-E).

4 Thoracotomy and video-assisted thoracic surgery (VATS) should be available and used selectively depending on the clinical presentation of metastatic disease.

5 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.
RECURRENT DISEASE

Local recurrence

Single organ and limited tumor bulk

Metastatic disease

Disseminated metastases

Isolated regional disease or nodes

TREATMENT

Follow Workup, then appropriate Primary Therapy (category 2A unless otherwise indicated) (

EXTSARC-1, EXTSARC-2, and EXTSARC-3)

Options:
- Metastasectomy ± preoperative or postoperative chemotherapy ± RT (category 2B for chemotherapy and RT)
- Ablation procedures (eg, RFA or cryotherapy)
- Embolization procedures
- Stereotactic radiosurgery/RT

Options:
- Palliative chemotherapy
- Palliative surgery
- Observation, if asymptomatic
- Best supportive care
- Ablation procedures (eg, RFA or cryotherapy)
- Embolization procedures
- Stereotactic radiosurgery/RT

Options:
- Regional node dissection for nodal involvement ± RT ± chemotherapy (category 2B for chemotherapy)
- Metastasectomy ± preoperative or postoperative chemotherapy ± RT (category 2B for chemotherapy and RT)
- Stereotactic radiosurgery/RT

Note: All recommendations are category 2A unless otherwise indicated.

Thoracotomy and video-assisted thoracic surgery (VATS) should be available and used selectively depending on the clinical presentation of metastatic disease.

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.

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 salvage 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 post-operative 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.
WORKUP

- All patients should be managed by a multidisciplinary team with expertise in sarcoma
- H&P
- Chest/abdominal/pelvic CT with contrast ± MRI
- Preresection biopsy not necessarily required, based on degree of suspicion of other malignancies
- Biopsy is necessary for patients receiving preoperative radiotherapy or chemotherapy (CT-guided core biopsy is preferred)\(^a\)

\(^a\)See Principles of Pathologic Assessment of Sarcoma Specimens (SARC-A).

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Biopsy performed\(^a,\)\(^b\):

- Gastrointestinal stromal tumor (GIST) → See (GIST-1)
- Desmoid tumors (Aggressive fibromatosis) → See (DESM-1)
- Other sarcoma

Biopsy not performed\(^b\) or nondiagnostic:

- Surgery \(\pm\) IORT\(^d\)
- Desmoid tumors (Aggressive fibromatosis) → See (DESM-1)
- Other sarcoma

Surgery \(\pm\) IORT or Preoperative therapy (category 2B):

- RT\(^e\)
- Chemotherapy\(^f\)
- Surgery\(^c\) \(\pm\) IORT → See Postoperative Treatment (RETSARC-3)

\(^a\) See Principles of Pathologic Assessment of Sarcoma Specimens (SARC-A).
\(^b\) Biopsy required if considering preoperative therapy, including endoscopic biopsy for suspected GIST lesions.
\(^c\) See Principles of Surgery (SARC-C).
\(^d\) IORT may be considered provided frozen section pathology can confidently demonstrate a non-GIST/non-desmoid histology.
\(^e\) See Guidelines for Radiation Therapy (SARC-D).
\(^f\) See Principles of Systemic Therapy (SARC-E).
### Surgical Outcomes/ Clinical Pathological Findings

| R0 | Consider postoperative RT<sup>e</sup>,<sup>g</sup> in highly selected patients<sup>h</sup> (category 2B) | • Physical exam with imaging (abdominal/pelvic CT) every 3-6 mo for 2-3 y, then annually  
• Consider chest imaging  
→ **Recurrent Disease** (see RETSARC-5) |
| R1 | Consider postoperative RT<sup>e</sup> (category 2B) if no preoperative RT  
Consider boost (10-16 Gy) if preoperative RT was given | • Physical exam with imaging (abdominal/pelvic CT) every 3-6 mo for 2-3 y, then every 6 mo for next 2 y, then annually  
• Consider chest imaging  
→ **See Primary Treatment (Unresectable)** (RETSARC-4) |

<sup>c</sup>See Principles of Surgery (SARC-C).  
<sup>e</sup>See Guidelines for Radiation Therapy (SARC-D).  
<sup>g</sup>Patients who receive preoperative RT should not receive any additional therapy.  
<sup>h</sup>For example, patients with high grade tumors, an extremely large tumor, critical anatomic surface where recurrence would cause morbidity, or close margins.

**Note:** All recommendations are category 2A unless otherwise indicated.  
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**NCCN Guidelines Version 3.2012**  
Retroperitoneal/Intra Abdominal

**PRIMARY TREATMENT**

---

**Unresectable or Stage IV**  
→ Biopsy

**Options:**
- Chemotherapy
- RT
- Palliative surgery for symptom control
- Best supportive care
- Observation, if asymptomatic
- Resection of resectable metastatic disease should always be considered if primary tumor can be controlled

---

**Down-staging following response**

**Resectable**  
→ See Treatment as per RETSARC-2

**Unresectable**

---

**No down-staging**

**Unresectable or progressive disease**  
→ Biopsy

**Options:**
- Palliative chemotherapy
- Palliative RT
- Palliative surgery for symptom control
- Best supportive care
- Observation, if asymptomatic

---

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

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See Principles of Pathologic Assessment of Sarcoma Specimens (SARC-A).  
See Guidelines for Radiation Therapy (SARC-D).  
See Principles of Systemic Therapy (SARC-E).  
Balance risks of treatment, likelihood of rendering patient resectable, performance status of patient, with potential clinical benefits. The options listed may be used either alone, sequentially, or in combination.
Recurrent disease

Resectable

See Primary Treatment (Resectable) (RETSARC-2)

Unresectable or Stage IV

See Primary Treatment (Unresectable) (RETSARC-4)

\[ j \text{Consider preoperative RT and/or chemotherapy if not previously administered.} \]

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**WORKUP AT PRIMARY PRESENTATION**

- For very small gastric GISTs < 2 cm (See GIST-2)
- All patients should be evaluated by a multidisciplinary team with expertise in sarcoma
- H&P
- Abdominal/pelvic CT with contrast, and/or MRI
- Consider chest imaging
- Endoscopic ultrasound (in selected patients)
- Endoscopy as indicated (if not previously done)

**RESULTS OF INITIAL DIAGNOSTIC EVALUATION**

- Preoperative imatinib not considered
  - If considering preoperative imatinib
    - Definitively unresectable or metastatic disease
  - Localized or potentially resectable disease
    - Resect mass
    - Pathology result and risk assessment

**Definitively unresectable or metastatic disease**

- Pathology result and risk assessment
- Other sarcomas of GI origin
- Other cancers

**Localized or potentially resectable disease**

- Preoperative imatinib not considered
- Resect mass

**Note:** All recommendations are category 2A unless otherwise indicated.

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

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**a** Surgery should induce minimal surgical morbidity, otherwise consider preoperative imatinib.

**b** Preoperative imatinib should not be considered if surgical morbidity would not improve by reducing the size of the tumor preoperatively.

**c** Consider preoperative imatinib if surgical morbidity would be improved by reducing the size of the tumor preoperatively. Preoperative imatinib may prohibit accurate assessment of recurrence risk.

**d** See Principles of Surgery For GIST (GIST-C).

**e** Pathology 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]).
### Approach to Patients with Very Small Gastrointestinal Stromal Tumors (< 2 cm)

<table>
<thead>
<tr>
<th>Workup at Primary Presentation</th>
<th>Results of Initial Diagnostic Evaluation</th>
<th>Initial Management</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk EUS features*</td>
<td>Complete surgical resection</td>
<td>Consider abdominal/pelvic CT with contrast every 3-6 months for 3-5 years, then annually</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider endoscopic surveillance** (6-12 month intervals)</td>
<td></td>
</tr>
<tr>
<td>No High-risk EUS features</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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*Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA)

**Adapted 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.

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

**Endoscopic ultrasonography surveillance should only be considered after a thorough discussion with the patient regarding the risks and benefits.
INITIAL DIAGNOSTIC EVALUATION

Localized or potentially resectable disease and considering preoperative imatinib

<table>
<thead>
<tr>
<th>Documented GIST</th>
<th>Definitively unresectable or metastatic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy</td>
<td>See Postoperative Treatment (GIST-6)</td>
</tr>
<tr>
<td>Pathology result</td>
<td>See Primary/Preoperative Treatment (GIST-4)</td>
</tr>
<tr>
<td>Other sarcomas of GI origin</td>
<td>See Primary Treatment (RETSARC-1)</td>
</tr>
<tr>
<td>Other cancers</td>
<td>See appropriate cancer guidelines within the NCCN Table of Contents</td>
</tr>
</tbody>
</table>

Definitively unresectable or metastatic disease

Resectable without significant risk of morbidity

<table>
<thead>
<tr>
<th>Surgery</th>
</tr>
</thead>
</table>

or

Resectable with negative margins but with risk of significant morbidity

See Primary/Preoperative Treatment (GIST-5)

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

Consider preoperative imatinib if surgical morbidity would be improved by reducing the size of the tumor preoperatively. Preoperative imatinib may prohibit accurate assessment of recurrence risk.

See Principles of Surgery For GIST (GIST-C).

Pathology 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])

See Principles of Biopsy for GIST (GIST-A).

Some patients may rapidly become unresectable; close monitoring is essential.
GIST that is resectable with negative margins but with risk of significant morbidity:

- Baseline CT ± MRI
- Consider PET

→ Imatinib

Assess therapeutic effect and evaluate patient compliance

No progression → Continue dose of imatinib → Surgery, if possible

Progression → If surgery not possible, see GIST-7

See Postoperative Treatment (GIST-6)

---

dSee Principles of Surgery For GIST (GIST-C).

iSome patients may rapidly become unresectable; close monitoring is essential.

kPET is not a substitute for a CT.

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

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

nSee Dosage and Administration of Imatinib (GIST-D).

qPET may give indication of imatinib activity after 2-4 wks of therapy when rapid readout of activity is necessary; PET is not a substitute for diagnostic CT.

pRarely, 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.

qProgression may be determined by CT or MRI with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.

rSuggest referral to a sarcoma specialty center.

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

tImatinib can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications.

Note: All recommendations are category 2A unless otherwise indicated.

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

Note: All recommendations are category 2A unless otherwise indicated.

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

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### GIST-5

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

Rarely, 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.

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

PET is not a substitute for CT. Consider PET only if CT results are ambiguous.

Progression may be determined by CT or MRI with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.

Suggest referral to a sarcoma specialty center.

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

In some patients, it may be appropriate to image prior to 3 months.

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.

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**GIST-6**

Resection or Continue imatinib if resection not feasible

---

**GIST-7**

See Therapy for Progressive Disease (GIST-7)
**NCCN Guidelines Version 3.2012**

**Gastrointestinal Stromal Tumors (GIST)**

### POSTOPERATIVE OUTCOMES

- **Metastatic disease**
- **Persistent gross residual disease (R2 resection) after preoperative imatinib**
  - Continue imatinib
  - and consider resection

### POSTOPERATIVE TREATMENT

- **Persistent gross residual disease (R2 resection)**
  - Continue imatinib
  - and consider resection

### FOLLOW-UP

- **No evidence of disease**
  - • H&P every 3-6 mo
  - • Abdominal/pelvic CT every 3-6 mo

- **Persistent gross residual disease (R2 resection)**
  - Continue imatinib

- **Completely resected (no preoperative imatinib)**
  - Start imatinib

- **Completely resected after preoperative imatinib**
  - Consider continuation of imatinib if taken prior to resection with an objective response
  - Imatinib for patients with significant risk of recurrence (intermediate or high risk) (category 1)
  - or Observe

- **No evidence of disease**
  - • H&P every 3-6 mo for 5 y
  - then annually

- **Persistent gross residual disease (R2 resection)**
  - Continue imatinib

- **Completely resected after preoperative imatinib**
  - Consider continuation of imatinib if taken prior to resection with an objective response

- **Imatinib for patients with significant risk of recurrence (intermediate or high risk)**
  - (category 1)

- **Completely resected after preoperative imatinib**
  - Consider continuation of imatinib if taken prior to resection with an objective response

- **Imatinib for patients with significant risk of recurrence (intermediate or high risk)**
  - (category 1)

**Discussion**

- All recommendations are category 2A unless otherwise indicated.
- Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
- Post-resection: Consider at least 2 years of adjuvant imatinib for high-risk patients, as evidence suggests a survival benefit associated with prolonged imatinib therapy.
- Follow-up: Maintain close post-surgical surveillance for patients with high-risk tumors.
- Post-operative outcomes: Persistent gross residual disease or metastatic disease require specific treatment strategies.
- **Note:** All recommendations are category 2A unless otherwise indicated.
- Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
TREATMENT FOR PROGRESSIVE DISEASE

- For performance status (PS) 0-2,
  - Continue with increased dose imatinib\(^n,cc\) as tolerated or change to sunitinib;\(^bb,cc\) reassess therapeutic response with CT\(^v\)
  - If resection is feasible, consider resection\(^d\) of progressing lesion(s)
  - Consider radiofrequency ablation (RFA) or embolization or chemoembolization procedure (category 2B)
  - Consider palliative RT (category 2B) in rare patients with bone metastases

If disease is progressing despite prior imatinib or sunitinib therapy, consider the following options:
- Regorafenib
- Clinical trial
- Consider other options listed in SARC-E (based on limited data)
- Best supportive care\(^dd\)

Rarely, 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.
Progression may be determined by CT or MRI with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.
Suggest referral to a sarcoma specialty center.

See Principles of Surgery For GIST (GIST-C).
See Dosage and Administration of Imatinib (GIST-D).
See Dosage and Administration of Sunitinib (GIST-E).

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

• GISTs are soft and fragile tumors. Endoscopic ultrasound guided fine-needle aspiration (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 upon 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 noted below;¹ referral to centers with expertise in sarcoma diagnosis is recommended for cases with complex or unusual histopathologic features.

¹ See Principles of Pathologic Assessment of Sarcoma Specimens (SARC-A).

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PRINCIPLES OF PATHOLOGIC ASSESSMENT FOR GIST

- Pathologic assessment should follow the guidelines outlined in SARC-A.

- 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 (95% express CD117 and 80% express CD34) and molecular genetic testing (for mutations in KIT or PDGFRA). Referral to centers with expertise in sarcoma diagnosis is recommended for cases with complex or unusual histopathologic features.

- 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 in 50 high power (400× total magnification, equivalent to 5mm² of tissue) fields.

- 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. Since about 10-15% of GISTs have no detectable KIT or PDGFRA mutation, the absence of a mutation does not exclude the diagnosis of GIST. The presence and type of KIT and PDGFRA mutations are not strongly correlated with prognosis.

- The mutations in KIT and PDGFRA in GIST result in expression of mutant proteins with constitutive tyrosine kinase activity.

Note: All recommendations are category 2A unless otherwise indicated.

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

Metastatic GIST
Imatinib is the primary therapy for metastatic GIST. Surgery may be indicated for:
- Limited disease progression refractory to systemic therapy.
- Locally advanced or previously unresectable tumors after a favorable response to preoperative imatinib.

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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Preoperative imatinib for GIST that is resectable with negative margins but with risk of significant morbidity:

- Initiate dosing at 400 mg daily. Patients with documented mutations in KIT exon 9 may benefit from dose escalation up to 800 mg daily (given as 400 mg twice daily), depending upon tolerance.\(^1,2,3\)

Unresectable and/or metastatic GIST:

- Initiate dosing at 400 mg daily.\(^4\) Patients with documented mutations in KIT exon 9 may benefit from dose escalation up to 800 mg daily (given as 400 mg twice daily), depending upon tolerance.\(^1,2,3\)
- **IF PROGRESSION OF DISEASE IS DOCUMENTED:** Imatinib dose increase up to 800 mg daily (given as 400 mg twice daily) may be considered, as clinically tolerated, in patients showing objective signs of disease progression at a lower dose and in the absence of severe adverse drug reactions.\(^4\)

Post operative imatinib:

- 400 mg daily following complete gross resection of GIST.\(^4\)

Imatinib should be taken with a low fat meal and a large glass of water.

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\(^4\) Information from the FDA label. For more detailed information review the full content at: www.fda.gov.
The recommended dose of sunitinib is either:

- 50 mg orally once daily on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2).\(^1\)  
- 37.5 mg orally once daily without interruption.\(^2\)

In patients receiving sunitinib, selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Sunitinib dose modification is recommended in patients who must receive concomitant CYP3A4 inhibitors or inducers.

A dose reduction for sunitinib:

- For a starting dose of 50 mg (schedule 4/2) decrease to a minimum of 37.5 mg daily should be considered if sunitinib must be coadministered with a strong CYP3A4 inhibitor.
- For a starting dose of 37.5 mg orally once daily without interruption decrease to a minimum dose of 25 mg daily should be considered if sunitinib must be coadministered with a strong CYP3A4 inhibitor.

A dose increase for sunitinib:

- For a starting dose of 50 mg (schedule 4/2) increase to a maximum of 87.5 mg daily should be considered if sunitinib must be coadministered with a CYP3A4 inducer. According to the package insert, in vitro studies indicate that sunitinib does not induce or inhibit major cytochrome enzymes.
- For a starting dose of 37.5 mg orally once daily without interruption increase to a maximum of 62.5 mg daily should be considered if sunitinib must be co-administered with a CYP3A4 inducer. According to the package insert, in vitro studies indicate that sunitinib does not induce or inhibit major cytochrome enzymes.

Sunitinib may be taken with or without food.

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1 Information from the FDA label. For more detailed information review the full content at: [www.fda.gov](http://www.fda.gov).
WORKUP

- All patients should be managed by a multidisciplinary team with expertise in sarcoma
- H&P including evaluation for Gardner's Syndrome^a
  (See NCCN Guidelines for Colorectal Cancer Screening)
- Appropriate imaging of primary site with CT or MRI as clinically indicated

Resectable

Unresectable or surgery would be unacceptably morbid


^bMay not be necessary if complete resection planned.

^cSee Principles of Pathologic Assessment of Sarcoma Specimens (SARC-A).
**Discussion**

Note: All recommendations are category 2A unless otherwise indicated.

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

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**PRIMARY TREATMENT**

**Observation**

- Stable → Continue observation

- Progression → See Treatment pathway below

**Resectable**

- Surgery\(^e\) and/or RT\(^f,g,h\) and/or Systemic therapy\(^i\)

- Treatment\(^d\)

  - R0 or Complete radiographic response → Observation or Consider postoperative RT\(^h\) if large tumor

  - R1 or Minimal residual disease → Consider resection or RT\(^h\), if no prior RT or Observation

  - R2 or Gross residual disease → Definitive RT\(^f,g\) or Systemic therapy\(^i\) or Radical surgery to be considered if other modalities fail or Observation

**FOLLOW-UP**

- Evaluation for rehabilitation (OT, PT)
  - Continue until maximal function is achieved

- H&P with appropriate imaging every 3-6 mo for 2-3 y, then annually

- Progression or Recurrence, See Primary treatment recommendations

---

\(^d\) For 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.

\(^e\) For desmoids, microscopic positive margins are acceptable if achieving negative margins would produce excessive morbidity.

\(^f\) See Principles of Systemic Therapy (SARC-E).

\(^g\) RT 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.

\(^h\) Dose of definitive RT without surgery: 54-58 Gy in the absence of any prior radiation therapy.

Desmoid Tumors (Aggressive Fibromatosis)

PRIMAR Y TREATMENT  

Unresectable or surgery would be unacceptably morbid

Definitive RT\textsuperscript{f,g} or Systemic therapy\textsuperscript{i} or Radical surgery to be considered if other modalities fail or Observation

FOLLOW-UP

\begin{itemize}
  \item Evaluation for rehabilitation (OT, PT)
  \begin{itemize}
    \item Continue until maximal function is achieved
  \end{itemize}
  \item H&P with appropriate imaging every 3-6 mo for 2-3 y, then annually
\end{itemize}

Progression or Recurrence, See Primary treatment recommendations

\textsuperscript{f}RT is generally only recommended for desmoid tumors that are in the extremity, superficial trunk or head and neck.

\textsuperscript{g}Dose of definitive RT without surgery: 54-58 Gy in the absence of any prior radiation therapy.

\textsuperscript{i}See Principles of Systemic Therapy (SARC-E).

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

Consider treating like soft tissue sarcoma

Rhabdomyosarcoma (RMS)\textsuperscript{a,b}

Non-pleomorphic RMS
(includes alveolar and embryonal)

- Referral to institutions with expertise in treating patients with rhabdomyosarcoma is strongly recommended
- Multidisciplinary evaluation involving pediatric oncologists, medical, surgical, and radiation oncologists is strongly encouraged
- Multimodality treatment planning and risk stratification is required

\textsuperscript{a}RMS that is identified within another histology should be treated as the original histology. This pathway refers to patients diagnosed with pure RMS after full slide review.

\textsuperscript{b}PET 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.

\textsuperscript{c}Pleomorphic RMS is usually excluded from RMS and soft tissue sarcoma randomized clinical trials. Consideration to treatment according to soft tissue sarcoma may be warranted. \textit{See Principles of Systemic Therapy (SARC-E)}.

\textsuperscript{d}Systemic chemotherapy options for RMS may be different than those used with other soft tissue sarcoma histologies. \textit{See Principles of Systemic Therapy (SARC-E)}.
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.
• 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, for example, the World Health Organization Classification of Soft Tissue Tumors).²
- Depth of tumor
  - Superficial (tumor does not involve the superficial fascia)
  - Deep
- Size of tumor
- Histologic grade (at the least, specify low or high grade, if applicable); ideally, grade using the French Federation of Cancer Centers Sarcoma Group (FNCLCC) or National Cancer Institute (NCI) system
- Necrosis
  - Present or absent
  - Microscopic or macroscopic
  - Approximate extent (percentage)
- Status of margins of excision
  - Uninvolved
  - Closer than 2 cm (state which margins and measured distance)
  - Involved (state which margins)
- 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
  - 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-1)

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

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
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. Recurrent genetic aberrations in sarcoma are listed below:

<table>
<thead>
<tr>
<th>TUMOR</th>
<th>ABERRATION</th>
<th>GENE(S) INVOLVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant Round Cell Tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ewing sarcoma / peripheral</td>
<td>t(11;22)(q24;q12)</td>
<td>EWS1-FLI1</td>
</tr>
<tr>
<td>neuroectodermal tumor</td>
<td>t(21;22)(q22;q12)</td>
<td>EWS1-ERG</td>
</tr>
<tr>
<td></td>
<td>t(2;22)(q33;q12)</td>
<td>EWSR1-FEV</td>
</tr>
<tr>
<td></td>
<td>t(7;22)(p22;q12)</td>
<td>EWSR1-ETV1</td>
</tr>
<tr>
<td></td>
<td>t(17;22)(q12;q12)</td>
<td>EWSR1-E1AF</td>
</tr>
<tr>
<td></td>
<td>inv(22)(q12;q12)</td>
<td>EWSR1-ZSG</td>
</tr>
<tr>
<td></td>
<td>t(16;21)(p11;q22)</td>
<td>FUS-ERG</td>
</tr>
<tr>
<td>Desmoplastic small round cell tumor</td>
<td>t(11;22)(p13;q12)</td>
<td>EWS-WT1</td>
</tr>
<tr>
<td>Embryonal rhabdomyosarcoma</td>
<td>Complex alterations</td>
<td>Unknown</td>
</tr>
<tr>
<td>Alveolar rhabdomyosarcoma</td>
<td>t(2;13)(q35;q14)</td>
<td>PAX3-FOXO1</td>
</tr>
<tr>
<td></td>
<td>t(1;13)(p36;q14)</td>
<td>PAX7-FOXO1</td>
</tr>
<tr>
<td></td>
<td>t(X;2)(q13;q35)</td>
<td>PAX3-AFX</td>
</tr>
</tbody>
</table>

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. Consultation with a pathologist who has expertise in sarcoma diagnosis and molecular diagnostic techniques should be obtained prior to testing.

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### PRINCIPLES OF ANCILLARY TECHNIQUES USEFUL IN THE DIAGNOSIS OF SARCOMAS

<table>
<thead>
<tr>
<th>TUMOR</th>
<th>ABERRATION</th>
<th>GENE(S) INVOLVED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lipomatous Tumors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myxoid/round cell liposarcoma</td>
<td>t(12;16)(q13;p11) t(12;22)(q13;q12)</td>
<td><em>FUS-DD1T3</em>, <em>EWSR1-DD1T3</em></td>
</tr>
<tr>
<td>Atypical lipomatous tumor/well differentiated liposarcoma (ALT/WDLPS)</td>
<td>Supernumerary ring chromosomes; giant marker chromosomes</td>
<td>Amplification of region 12q14-15, including <em>MDM2</em>, <em>CDK4</em>, <em>HMG2</em>, <em>SAS</em>, <em>GL1</em></td>
</tr>
<tr>
<td>Dedifferentiated liposarcoma</td>
<td>Same as for ALT/WDLPS</td>
<td>Same as for ALT/WDLPS</td>
</tr>
<tr>
<td>Pleomorphic liposarcoma</td>
<td>Complex alterations</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Other Sarcomas</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alveolar soft part sarcoma</td>
<td>der(17)t(X;17)(p11;q25)</td>
<td><em>ASPL-TFE3</em></td>
</tr>
<tr>
<td>Angiomyloid fibrous histiocytoima</td>
<td>t(12;22)(q13;q12) t(2;22)(q33;q12) t(12;16)(q13;p11)</td>
<td><em>EWSR1-ATF1</em>, <em>EWSR1-CREB1</em>, <em>FUS-ATF1</em></td>
</tr>
<tr>
<td>Clear cell sarcoma</td>
<td>t(12;22)(q13;q12) t(2;22)(q33;q12)</td>
<td><em>EWSR1-ATF1</em>, <em>EWSR1-CREB1</em></td>
</tr>
<tr>
<td>Congenital/infantile – fibrosarcoma</td>
<td>t(12;15)(p13;q25)</td>
<td><em>ETV6-NTRK3</em></td>
</tr>
<tr>
<td>Dermatofibrosarcoma protuberans</td>
<td>t(17;22)(q21;q13) and derivative ring chromosomes</td>
<td><em>COLIA1-PDGFB</em></td>
</tr>
<tr>
<td>Desmoid fibromatosis</td>
<td>Trisomy 8 or 20; loss of 5q21</td>
<td><em>CTNNB1</em> or <em>APC</em> mutations</td>
</tr>
<tr>
<td>Epithelioid sarcoma (proximal type)</td>
<td>Inactivation of <em>INI1</em></td>
<td><em>INI1</em></td>
</tr>
<tr>
<td>Extrarenal rhabdoid tumor</td>
<td>Inactivation of <em>INI1</em></td>
<td><em>INI1</em></td>
</tr>
</tbody>
</table>

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### PRINCIPLES OF ANCILLARY TECHNIQUES USEFUL IN THE DIAGNOSIS OF SARCOMAS

<table>
<thead>
<tr>
<th>TUMOR</th>
<th>ABERRATION</th>
<th>GENE(S) INVOLVED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other Sarcomas</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extraskeletal myxoid chondrosarcoma</td>
<td>t(9;22)(q22;q12), t(9;17)(q22;q11), t(9;15)(q22;q21), t(3;9)(q11;q22)</td>
<td>EWSR1-NR4A3, TAF2-NR4A3, TCF12-NR4A3, TFG-NR4A3</td>
</tr>
<tr>
<td>Sporadic and familial GIST</td>
<td>Activating kinase mutations</td>
<td>KIT or PDGFR A</td>
</tr>
<tr>
<td>Carney-Stratakis syndrome (gastric GIST and paragaglioma)</td>
<td>Krebs cycle mutation</td>
<td>germline SDH subunit mutations</td>
</tr>
<tr>
<td>Inflammatory myofibroblastic tumor</td>
<td>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)</td>
<td>TPM3-ALK, TPM4-ALK, CLTC-ALK, RANBP2-ALK, CARS-ALK, ATIC-ALK</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>Complex alterations</td>
<td>Unknown</td>
</tr>
<tr>
<td>Low grade fibromyxoid sarcoma</td>
<td>t(7;16)(q33;p11), t(11;16)(p11;p11)</td>
<td>FUS-CREB3L2, FUS-CREB3L1</td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath tumor</td>
<td>Complex alterations</td>
<td>Unknown</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>t(X;18)(p11;q11), t(X;18)(p11;q11), t(X;18)(p11;q11)</td>
<td>SS18-SSX1, SS18-SSX2, SS18-SSX4</td>
</tr>
<tr>
<td>Tenosynovial giant cell tumor/pigmented villonodular synovitis (TGCT/PVNS)</td>
<td>t(1;2)(p13;q35)</td>
<td>CSF1</td>
</tr>
</tbody>
</table>

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PRINCIPLES OF SURGERY

Biopsy of Sarcoma

- 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. Endoscopic or needle biopsy may be indicated for deep, thoracic, abdominal or pelvic sarcomas.

Sarcoma Surgery

- The surgical procedure necessary to resect the tumor with appropriately negative margins should be used. Close margins may be necessary to preserve uninvolved 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 radiation therapy. If closed suction drainage is used, the drains should exit the skin close to the edge of the surgical incision (in case re-resection or radiation is indicated).

Resection Margins

- Surgical margins should be documented by both the surgeon and the pathologist in evaluating a resected specimen. 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 radiation therapy should be given for a close soft tissue margin or a microscopically positive margin on bone, major blood vessels, or a major nerve.
- 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

Limb Salvage 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 postoperative rehabilitation (PT, OT) for patients with extremity sarcoma. Continue rehabilitation until maximal function is achieved.

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**GUIDELINES FOR RADIATION THERAPY**

**Preoperative RT**
- **50 Gy external-beam RT**

**Surgery**
- **2** with clips

**Postoperative treatment following surgery**
- **50 Gy external beam RT**

**IORT**
- **(10-16 Gy)**

**Brachytherapy implant**
- **Positive margins:**
  - Brachytherapy (16-20 Gy)
  - Low dose (16-20 Gy) or high dose rate equivalent

**Negative margins:**
- 45 Gy low dose rate brachytherapy or high dose equivalent

**No brachytherapy**
- **Positive margins:**
  - 50 Gy external-beam RT

**Negative margins:**
- 50 Gy external-beam RT

Consider boost for positive or close margins:
- **5**
  - Brachytherapy
  - Low-dose rate 12-20 Gy based on margin status or high dose rate equivalent

**Clinical target volume:** total dose - 50 Gy external-beam RT

**Intraoperative RT**
- **(10-16 Gy based on margin status)**

**External-beam RT**
- **Grossly positive margins (20-26 Gy)**
- **Microscopically positive margins (16-20 Gy)**
- **Boost for close margins (10-14 Gy)**

**Data**
- **2**
- **3**
- **4**
- **5**
- **6**


2. **See Principles of Surgery (SARC-B)**

3. **RT does not substitute for suboptimal surgical resection, re-resection may be necessary.**

4. **Data are still limited on the use of HDR brachytherapy for sarcomas. Until more data is available, HDR fraction sizes are recommended to be limited to 3-4 Gy. (Nag et al, Int J Radiat Oncol Biol Phys, Vol. 49, No. 4, pp 1033-1043, 2001).**

5. **Total doses should always be determined by normal tissue tolerance. There are data to suggest that some patients with positive margins following pre-operative 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.)**

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

7. **See Resection Margins (SARC-C).**
### SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA

#### Extremity/Trunk, Head/Neck, Retroperitoneal, Intra-abdominal

<table>
<thead>
<tr>
<th>Combination regimens</th>
<th>Single agents</th>
<th>GIST</th>
<th>Desmoid Tumors (Aggressive fibromatosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD (doxorubicin, dacarbazin)</td>
<td>Doxorubicin&lt;sup&gt;10, 11&lt;/sup&gt;</td>
<td>Imatinib&lt;sup&gt;18, 19&lt;/sup&gt;</td>
<td>Sulindac&lt;sup&gt;30&lt;/sup&gt; or other non-steroidal anti-inflammatory drugs (NSAIDs) including celecoxib&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>AIM (doxorubicin, ifosfamide, mesna)</td>
<td>Ifosfamide&lt;sup&gt;6, 12&lt;/sup&gt;</td>
<td>Sunitinib&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Tamoxifen&lt;sup&gt;31&lt;/sup&gt;</td>
</tr>
<tr>
<td>MAID (mesna, doxorubicin, ifosfamide, dacarbazin)</td>
<td>Epirubicin</td>
<td>Disease progression after imatinib and sunitinib</td>
<td>Toremifene&lt;sup&gt;32&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ifosfamide, epirubicin, mesna</td>
<td>Gemcitabine</td>
<td>Regorafenib&lt;sup&gt;21, 22&lt;/sup&gt;</td>
<td>Methotrexate and vinblastine&lt;sup&gt;33&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gemcitabine and docetaxel</td>
<td>Dacarbazine</td>
<td>Sorafenib&lt;sup&gt;23-25&lt;/sup&gt;</td>
<td>Low-dose interferon&lt;sup&gt;34&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gemcitabine and vinorelbine</td>
<td>Liposomal doxorubicin&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Nilotinib&lt;sup&gt;26-28&lt;/sup&gt;</td>
<td>Doxorubicin-based regimens&lt;sup&gt;35-37&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Temozolomide&lt;sup&gt;b, 14&lt;/sup&gt;</td>
<td>Dasatinib&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Imatinib&lt;sup&gt;38, 39&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Vinorelbine&lt;sup&gt;15&lt;/sup&gt;</td>
<td></td>
<td>Sorafenib&lt;sup&gt;40&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Pazopanib&lt;sup&gt;b, c, 16, 17&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Rhabdomyosarcoma

<table>
<thead>
<tr>
<th>Combination regimens</th>
<th>Single agents</th>
<th>Desmoid Tumors (Aggressive fibromatosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine, dactinomycin, cyclophosphamide&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Ifosfamide and etoposide&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Sulindac&lt;sup&gt;30&lt;/sup&gt; or other non-steroidal anti-inflammatory drugs (NSAIDs) including celecoxib&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vincristine, doxorubicin, cyclophosphamide&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Irinotecan and vincristine&lt;sup&gt;49, 50&lt;/sup&gt;</td>
<td>Tamoxifen&lt;sup&gt;31&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vincristine, doxorubicin and cyclophosphamide alternating with Ifosfamide and etoposide&lt;sup&gt;43&lt;/sup&gt;</td>
<td>Vincristine and dactinomycin&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Toremifene&lt;sup&gt;32&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vincristine, doxorubicin, ifosfamide&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Carboplatin and etoposide&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Methotrexate and vinblastine&lt;sup&gt;33&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cyclophosphamide and topotecan&lt;sup&gt;45, 46&lt;/sup&gt;</td>
<td>Vinorelbine and low-dose cyclophosphamide&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Low-dose interferon&lt;sup&gt;34&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ifosfamide and doxorubicin&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Vincristine, irinotecan, temozolomide&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Doxorubicin-based regimens&lt;sup&gt;35-37&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imatinib&lt;sup&gt;38, 39&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sorafenib&lt;sup&gt;40&lt;/sup&gt;</td>
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<td></td>
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</tbody>
</table>

<sup>a</sup>Alveolar soft part sarcoma and clear cell sarcomas are generally not sensitive to chemotherapy.

<sup>b</sup>Recommended only for palliative therapy.

<sup>c</sup>Pazopanib should not be used for lipogenic sarcomas.

<sup>d</sup>The risk of cardiovascular events may be increased in patients receiving celecoxib. Physicians prescribing celecoxib should consider this emerging information when weighing the benefits against risks for individual patients. (FDA Talk Paper T04-61, Dec 23, 2004)

<sup>e</sup>High-dose methotrexate may be useful for select patients with CNS or leptomeningeal involvement when RT is not feasible.

---

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

#### Pigmented Villonodular Synovitis/Tenosynovial Giant Cell Tumor (PVNS/TGCT)
- **Imatinib**[^60]

#### Angiosarcoma
- Paclitaxel[^61,62]
- Docetaxel
- Vinorelbine
- Sorafenib[^63]
- Sunitinib[^64]
- Bevacizumab[^65]
- All other systemic therapy options as per extremity sarcoma[^SARC-E 1 of 5]

#### Alveolar soft part sarcoma (ASPS)
- **Sunitinib**[^69,70] (category 2B)

#### Chordoma (All recommendations are category 2B)
- **Combination regimens**
  - Imatinib and cisplatin[^75]
  - Imatinib and sirolimus[^76]
- **Single agents**
  - Imatinib[^77,78]
  - Sunitinib[^68]

#### Solitary Fibrous Tumor/Hemangiopericytoma
- Bevacizumab and temozolomide[^66]
- Sunitinib[^67,68]

#### PEComa, Recurrent Angiomyolipoma, Lymphangioleiomyomatosis
- **Sirolimus**[^71-74]

#### Inflammatory Myofibroblastic Tumor (IMT) with ALK Translocation
- **Crizotinib**[^79]

[^SARC-E 1 of 5]: Alveolar soft part sarcoma and clear cell sarcomas are generally not sensitive to chemotherapy.

---

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---

[^60]: Imatinib
[^61,62]: Paclitaxel
[^63]: Sorafenib
[^64]: Sunitinib
[^65]: Bevacizumab
[^SARC-E 1 of 5]: SARC-E of 5
[^75]: Imatinib and cisplatin
[^76]: Imatinib and sirolimus
[^77,78]: Imatinib
[^68]: Sunitinib
[^69,70]: Sunitinib
[^66]: Bevacizumab and temozolomide
[^67,68]: Sunitivinib
[^71-74]: Sirolimus
[^79]: Crizotinib


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


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### Table 1

**American Joint Committee On Cancer (AJCC) Staging System For Soft Tissue Sarcoma**

(7th ed, 2010)

<table>
<thead>
<tr>
<th>Staging Group</th>
<th>T Stage</th>
<th>N Stage</th>
<th>M Stage</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage IA</strong></td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
<td>G1, GX</td>
</tr>
<tr>
<td></td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
<td>G1, GX</td>
</tr>
<tr>
<td><strong>Stage IB</strong></td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
<td>G1, GX</td>
</tr>
<tr>
<td></td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
<td>G1, GX</td>
</tr>
<tr>
<td><strong>Stage IIA</strong></td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
<td>G2, G3</td>
</tr>
<tr>
<td></td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
<td>G2, G3</td>
</tr>
<tr>
<td><strong>Stage IIB</strong></td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
<td>G2</td>
</tr>
<tr>
<td></td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
<td>G2</td>
</tr>
<tr>
<td><strong>Stage III</strong></td>
<td>T2a, T2b</td>
<td>N0</td>
<td>M0</td>
<td>G3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N1</td>
<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td><strong>Stage IV</strong></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>Any G</td>
</tr>
</tbody>
</table>

*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)**

<table>
<thead>
<tr>
<th>N Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1†</td>
<td>Regional lymph node metastasis</td>
</tr>
</tbody>
</table>

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

**Distant Metastases (M)**

<table>
<thead>
<tr>
<th>M Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

**Histologic Grade**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GX</td>
<td>Grade cannot be assessed</td>
</tr>
<tr>
<td>G1</td>
<td>Grade 1</td>
</tr>
<tr>
<td>G2</td>
<td>Grade 2</td>
</tr>
<tr>
<td>G3</td>
<td>Grade 3</td>
</tr>
</tbody>
</table>

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### Table 1 - Continued

#### Histopathologic Type

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adipocytic Tumors</strong></td>
<td></td>
</tr>
<tr>
<td>Dedifferentiated liposarcoma*</td>
<td></td>
</tr>
<tr>
<td>Myxoid/round cell liposarcoma</td>
<td></td>
</tr>
<tr>
<td>Pleomorphic liposarcoma</td>
<td></td>
</tr>
<tr>
<td><strong>Fibroblastic/Myofibroblastic Tumors</strong></td>
<td></td>
</tr>
<tr>
<td>Fibrosarcoma**</td>
<td></td>
</tr>
<tr>
<td>Myxofibrosarcoma, low grade</td>
<td></td>
</tr>
<tr>
<td>Low-grade fibromyxoid sarcoma</td>
<td></td>
</tr>
<tr>
<td>Sclerosing epithelioid fibrosarcoma</td>
<td></td>
</tr>
<tr>
<td><strong>So-called Fibrohistiocytic Tumors</strong></td>
<td></td>
</tr>
<tr>
<td>Undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma (MFH) (including pleomorphic, giant cell, myxoid/high-grade myxofibrosarcoma and inflammatory forms)</td>
<td></td>
</tr>
<tr>
<td><strong>Smooth Muscle Tumors</strong></td>
<td></td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td></td>
</tr>
<tr>
<td><strong>Skeletal Muscle Tumors</strong></td>
<td></td>
</tr>
<tr>
<td>Rhabdomyosarcoma (embryonal, alveolar, and pleomorphic forms)</td>
<td></td>
</tr>
<tr>
<td><strong>Vascular Tumors</strong></td>
<td></td>
</tr>
<tr>
<td>Epithelioid hemangioendothelioma</td>
<td></td>
</tr>
<tr>
<td>Angiosarcoma, deep***</td>
<td></td>
</tr>
<tr>
<td><strong>Tumors of Uncertain Differentiation</strong></td>
<td></td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td></td>
</tr>
<tr>
<td>Epithelioid sarcoma</td>
<td></td>
</tr>
<tr>
<td>Alveolar soft-part sarcoma</td>
<td></td>
</tr>
<tr>
<td>Clear cell sarcoma of soft tissue</td>
<td></td>
</tr>
<tr>
<td>Extraskeletal myxoid chondrosarcoma</td>
<td></td>
</tr>
<tr>
<td>Primitive neuroectodermal tumor (PNET)/extraskeletal Ewing tumor</td>
<td></td>
</tr>
<tr>
<td>Desmoplastic small round cell tumor</td>
<td></td>
</tr>
<tr>
<td>Extrarenal rhabdoid tumor</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated sarcoma; sarcoma, not otherwise specified (NOS)</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:** *It is recognized that dedifferentiated liposarcoma primarily arises in the context of deep atypical lipomatous tumor/well-differentiated liposarcoma, a sarcoma of intermediate malignancy due to lack of metastatic capacity.

**The category of fibrosarcoma can be considered to be inclusive of fibrosarcomatous differentiation in dermatofibrosarcoma protuberans.

***Cutaneous angiosarcoma may be difficult to stage using the AJCC system.

The following histologic types are not included: inflammatory myofibroblastic tumor, fibromatosis (desmoid tumor), mesothelioma, sarcomas arising in tissues apart from soft tissue (e.g., parenchymal organs).
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.

Overview

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

In the United States, the annual incidence of soft tissue sarcoma (STS) for 2012 is estimated to be about 11,280 cases, with an overall mortality rate of approximately 3,900 cases per year, which includes adults and children. Sarcomas collectively account for approximately 1% of all adult malignancies and 15% of pediatric malignancies. The true incidence of sarcomas 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. Prior radiation therapy (RT) to the affected area, generally some years prior to the development of the sarcoma, is a risk factor for STS.

More than 50 different histological subtypes of STS have been identified. The most common subtypes of STS are pleomorphic sarcoma [also known as malignant fibrous histiocytoma (MFH)], GISTs, liposarcoma, leiomyosarcoma, synovial sarcoma, malignant peripheral nerve sheath tumors. The anatomic site of the primary disease represents an important variable that influences treatment and outcome. Extremities (60%), the trunk (19%), retroperitoneum (15%) or head and neck (9%) are the most common primary sites. STS most commonly metastasize 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 childhood and is less common in adults.

The NCCN Guidelines for STS are based on evidence and consensus. The guidelines address the management of STS in adult patients from the perspective of the following disease subtypes:

- STS of extremity, trunk or head and neck
- Retroperitoneal or intra-abdominal STS
- GISTs
- Desmoid tumors (Aggressive Fibromatoses)
- Rhabdomyosarcoma
The guidelines recommend that all patients with STS should be evaluated and managed by a multidisciplinary team with expertise and experience in the treatment of STS.\(^7\)

**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, provide a specific diagnosis where possible and a grade where appropriate or feasible, recognizing that limited biopsy material may underestimate grade. Biopsy can be accomplished by either core needle or open incisional techniques. 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.\(^8\) FNA may be acceptable in selected institutions with clinical and pathological expertise. Endoscopic or needle biopsy may be indicated for deep thoracic, abdominal or pelvic STS.

**Principles of Pathological Assessment**

Pathologists with expertise in STS should review pathological assessment of biopsies and resected specimens, especially for initial histopathological classification. Margins must be thoroughly evaluated in these specimens. Morphologic assessment based on microscopic examination of histological 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 histopathological type of a sarcoma is often difficult, several ancillary techniques have been used as an adjunct to morphologic diagnosis. These techniques include conventional cytogenetics, immunohistochemistry, electron microscopy and molecular genetic testing. The 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 World Health Organization Classification of STS tumor), organ and the site of sarcoma, depth, size and histological 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. The size at presentation depends on the location: tumors in the proximal extremities and retroperitoneum are often quite large, whereas distal extremity tumors are often small.

**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: (i) sarcomas with specific genetic alterations (eg, chromosomal translocations or point mutations) and usually simple karyotypes; and (ii) sarcomas with non-specific genetic alterations and complex unbalanced karyotypes.\(^9\)

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*]
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. In a prospective study, Hill and colleagues concluded that PCR-based molecular analysis is more sensitive than conventional cytogenetics and is an useful adjunct for the diagnosis of alveolar RMS, synovial sarcoma and myxoid liposarcoma that have variation in fusion gene partners.

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

While molecular genetic testing looks promising, it involves highly complex techniques and the methods are not absolutely sensitive or provide specific results. 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. Molecular testing should be performed by a pathologist with expertise in the use molecular diagnostic techniques for the diagnosis of STS.

## Staging

The American Joint Committee on Cancer (AJCC) STS staging system has historically used a four-grade system, but within the STS 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) or 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. Riad et al examined the impact of lymph node involvement on survival in patients with extremity sarcoma. Lymph node metastases developed in 3.7% (39 out of 1066 patients) who had surgery. The outcome of patients with isolated lymph node metastases was significantly better than with synchronous systemic and lymph node involvement (estimated 4-year survival rates were 71% and 21% respectively). 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. 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. However, many clinicians prefer the 2-tiered system, which is also used in the algorithm.
Principles of Surgery

The panel has included a separate section on the principles of sarcoma surgery because surgery is the standard primary treatment for most patients with STS. If surgery cannot be performed in accordance with these principles, preoperative RT or chemotherapy should be considered as alternative treatment options. Many clinicians choose to augment surgery with RT and chemotherapy, either preoperatively or postoperatively, because the risk of failure in the surgical bed can be high.\textsuperscript{20,21} When appropriate, the guidelines have incorporated these treatment options that are supported by clinical trial data or extensive clinical experience.

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).

Limb sparing surgery is recommended for most patients with STS of extremities to achieve local tumor control with minimal morbidity. Evaluation for postoperative rehabilitation is recommended for all patients with extremity sarcoma. If indicated, rehabilitation should be continued until maximum function is achieved.

Resection margins

Resection with appropriately negative margins is recommended, although negative but closer margins may be effective in those patients undergoing RT.\textsuperscript{22} Close margins may be necessary to preserve uninvolved critical neurovascular structures. Microscopically positive surgical margins are associated with a higher rate of local recurrence and lower rate of disease-free survival (DFS) in patients with extremity sarcomas.\textsuperscript{23-25}

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.\textsuperscript{26,27} Adjuvant 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.

Amputation for Extremity Sarcoma

Prior to considering amputation, the patient should be evaluated by a surgeon with expertise in the treatment of STS. Amputation should be considered for patient preference, or if the gross total resection of the tumor is expected to render the limb nonfunctional.\textsuperscript{28-30}

Guidelines for Radiation Therapy

RT can be administered either as primary therapy, preoperatively or postoperatively in STS. Advances in RT technology such as brachytherapy, intensity-modulated radiation therapy (IMRT) and intraoperative radiation therapy (IORT) have led to the improvement of treatment outcomes in patients with STS.\textsuperscript{31}
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.\(^{32}\) 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.\(^{32}\) The guidelines recommend that HDR brachytherapy fraction sizes should be limited to 3-4 Gy until more data are available.\(^{33}\) 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.\(^{34}\) IORT is the delivery of radiation during surgery and it can be performed using different techniques such as electron beam RT or brachytherapy.

**Preoperative RT**

Preoperative RT has several advantages. First, the treatment volume is smaller, because there is no need to cover the operative field. Second, 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. However, the main disadvantage of preoperative RT is its effect on wound healing.\(^{35}\) A higher acute wound healing complication rate has been observed when primary closure is used. Therefore, involvement of a plastic surgeon in the team may be necessary to reduce wound complications when preoperative RT is contemplated. After preoperative RT, a 3-6 week interval is necessary before resection to allow acute reactions to subside and decrease the risk of wound complications. Very long intervals between resection and postoperative RT are not recommended, because of the development of late fibrosis.

The usual dose of preoperative RT is 50 Gy. If wide margins are obtained, additional RT may not be needed. RT boost with brachytherapy, IORT or external beam RT is recommended for positive or close margins.\(^{36}\) Often, close margins are essential because of the proximity of many of these tumors to major neurovascular bundles or bone. Brachytherapy boosts should be delivered several days after surgery, through catheters placed at operation, with doses of 12-20 Gy based on margin status. Alternatively, a single IORT dose of 10-16 Gy, based on margin status, can be delivered immediately after resection to the area at risk, avoiding the uninvolved organs. External beam RT boosts may be an alternative to brachytherapy or IORT. The guidelines recommend RT doses of 10-14 Gy for close margins, 16-20 Gy for microscopically positive margins, and 20-26 Gy for grossly positive margins. 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.

**Postoperative RT**

Postoperative RT has been shown to improve local control in patients with high-grade extremity STS with positive surgical margins.\(^{37}\) In a recent report from Memorial Sloan-Kettering Cancer Center (MSKCC), among patients with extremity STS treated with limb-sparing surgery and a pathologically negative re-resection without RT, the 5-year overall local recurrence rate was 9% with a median follow-up of 82 months.\(^{38}\) Old age and/or stage III disease were identified as factors associated with a higher rate of local recurrence. Therefore, treatment decisions regarding the use of postoperative RT should be individualized and not be solely based on the finding of margin negative re-resection.
When surgical resection is the initial therapy, postoperative RT choices include brachytherapy, IORT or external beam RT. When external beam RT is used, sophisticated treatment planning with IMRT, tomotherapy and/or proton therapy can be used to improve therapeutic effect. Most institutions include the entire operative bed within that radiation field. Total doses of RT should always be determined by normal tissue tolerance. RT is not a substitute for suboptimal surgical resection, and re-resection may be necessary. 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. There are data to suggest that some patients (such as those with low-grade, well-differentiated liposarcoma and a focally, "planned" positive margin on an anatomically fixed critical structure) with positive margins following preoperative RT and surgery may do well without a boost.  

Brachytherapy alone has been used as an adjuvant treatment. LDR brachytherapy (45-50 Gy) to the tumor bed has been shown to reduce recurrence without a significant effect on wound healing. However, brachytherapy techniques require special expertise and significant experience. The panel recommends 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 external beam RT. External beam RT is delivered to the target volume to a total dose of 50 Gy (45 Gy for retroperitoneal or intra-abdominal sarcomas), after surgical healing is complete (3-8 weeks).

Recent reports from a retrospective study suggest that IORT provides excellent local control to STS of the extremity. However, since IORT has not been proven superior, the guidelines recommend IORT (10-16 Gy) followed by an external beam RT dose of 50 Gy.

If no IORT or brachytherapy was used in the immediate operative or postoperative period, external beam RT is delivered to the target volume to a total dose of 50 Gy (45 Gy for retroperitoneal or intra-abdominal sarcomas), after surgical healing is complete. An additional external beam RT boost to the original tumor bed should be used based on the margin status (10-16 Gy for negative margins; 16-20 Gy for microscopically positive margins; and 20-26 Gy for grossly positive margins).

**Chemotherapy/Chemoradiation**

**Resectable disease**

Chemotherapy or chemoradiation is used as an adjunct to surgery in many centers to downstage large high-grade tumors to enable effective surgical resection, especially in the case of chemo-sensitive histologies.

**Preoperative therapy**

Preoperative chemoradiation or chemotherapy has been evaluated in single and multicenter trials in patients with high-grade tumors.

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 MAID (mesna, doxorubicin, ifosfamide and dacarbazine) regimen followed by surgery and postoperative chemotherapy with the same regimen were superior to that of historical control patients. The 5-year actuarial local control, freedom from distant metastasis, disease-free and overall survival rates were 92% and 86% (p = 0.1155), 75% and 44% (p = 0.0016), 70% and 42% (p = 0.0002) and 87% and 58% (p = 0.0003) for the MAID and control patient groups respectively. The same protocol was later evaluated in the RTOG 9514 trial in 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 STSs of the extremities or trunk. 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 overall survival (OS) rates were 56%, 64% and 71%, respectively. Long-term follow-up data of both these studies confirmed that preoperative chemoradiation followed by resection and postoperative chemotherapy with doxorubicin-based regimens improve local control, OS and DFS rates in patients with high-grade STS of extremity and body wall, although preoperative chemoradiation was associated with significant short-term toxicities.

Studies that have evaluated preoperative chemotherapy followed by surgery have reported inconsistent findings. In one retrospective study, the benefit of preoperative chemotherapy was only seen in patients with high-grade tumors larger than 10 cm but not in patients with tumors 5-10 cm. Another cohort analysis of 674 patients with stage III STS treated at a single institution revealed that clinical benefits associated with pre- or postoperative doxorubicin-based chemotherapy were not sustained beyond year. The results of the only randomized study that compared surgery alone vs. preoperative chemotherapy followed by surgery in patients with high-grade tumors did not show a major survival benefit for patients receiving chemotherapy. At a median follow-up of 7.3 years, the estimated 5-year DFS rate was 52% for the no chemotherapy arm and 56% for the chemotherapy arm (p = 0.3548). The corresponding 5-year overall survival rate for both arms was 64% and 65%, respectively (p = 0.2204).

**Postoperative therapy**

Available evidence from meta-analyses and randomized clinical trials suggest 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 trials (1,568 patients) which compared adjuvant chemotherapy to follow-up and in some cases RT after surgery with a variety of sarcomas. 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 was 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. 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 = 0.01) and 5-year OS (58% vs.45%, p = 0.0002) 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 = 0.27; 5-year OS: 75% vs. 65%, p = 0.15).

In the Italian randomized cooperative trial, 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
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. Other chemotherapeutic agents such as gemcitabine, docetaxel, vinorelbine, pegylated liposomal doxorubicin and temozolomide have also been evaluated in clinical trials.

Gemcitabine, alone or in combination with docetaxel or vinorelbine has been evaluated in phase II studies. While gemcitabine as a single agent showed only modest activity in patients with unresectable or metastatic STS, the combination of gemcitabine and docetaxel was highly active in patients with unresectable leiomyosarcoma (LMS) or in those with LMS that has progressed after doxorubicin-based therapy. In a separate report that was published following this study, this combination was found to be active in a variety of histological subtypes of sarcoma.

In a subsequent 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. In a retrospective study conducted by the French Sarcoma group in 133 patients with unresectable or metastatic STS, the combination of gemcitabine and docetaxel was tolerable, demonstrating better response and survival for patients with leiomyosarcoma. In a phase II study, the combination of gemcitabine and vinorelbine was also associated with clinically meaningful rates of disease control in patients with advanced STS. Clinical benefit (complete response, partial response or stable disease at 4 months or more) was seen in 25% of patients.
Temozolomide, pegylated liposomal doxorubicin, and vinorelbine 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 Sarcomas, temozolomide resulted in an overall response rate of 15.5% with a median OS of 8 months in patients with advanced pretreated STS. 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 advanced or metastatic STS. In a retrospective study of pretreated patients with metastatic STS, vinorelbine induced overall response in 6% of patients and 26% had stable disease.

Trabectedin is a novel DNA-binding agent that has shown objective responses in phase II trials of patients with advanced STS. An ongoing multicenter study is evaluating the efficacy of trabectedin in patients with advanced or metastatic STS (excluding leiomyosarcoma and liposarcoma) that has relapsed or refractory to standard treatment options. (http://clinicaltrials.gov/ct2/show/NCT00210665).

Targeted therapy

More recently, a number of targeted therapies have shown promising results in patients with certain histological types of advanced or metastatic STS. Pazopanib, a multitargeted tyrosine kinase inhibitor has demonstrated single-agent activity in patients with advanced STS subtypes except liposarcomas. In a phase III trial (EORTC 62072), 369 patients with metastatic STS who had failed at least one anthracycline-based chemotherapy regimen were randomized to either pazopanib or placebo. Pazopanib significantly prolonged median PFS (20 weeks vs. 7 weeks for placebo; p < 0.0001) and there was also a trend toward improved OS (11.9 months and 10.4 months respectively) although it was not statistically significant. The guidelines have included pazopanib as an option for palliative therapy for patients with progressive, unresectable or metastatic non-lipogenic sarcomas.

Imatinib and sunitinib have shown efficacy in patients with advanced and/or metastatic STS other than GISTs [alveolar soft part sarcoma (ASPS), chordoma, pigmented villonodular synovitis/tenosynovial giant cell tumor (PVNS/TGCT) and solitary fibrous tumor/hemangiopericytoma]. Crizotinib, an anaplastic lymphoma kinase (ALK) inhibitor was active in inflammatory myofibroblastic tumor with ALK translocation. Sirolimus has shown promising results in patients with metastatic perivascular epithelioid cell tumors (PEComas) and in patients with recurrent lymphangioleiomyomatosis or angiomyolipomas. Bevacizumab in combination with temozolomide was well tolerated and effective in patients with locally advanced, recurrent, and metastatic hemangiopericytoma and malignant solitary fibrous tumor.

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

Surgery

Amputation was once considered as the standard treatment to achieve local control in patients with extremity sarcomas. 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.

In 1982, a randomized control trial (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. 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. 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 a 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. These results suggest that limb-sparing surgery with or without adjuvant RT is an effective treatment option for extremity STS and amputation should be reserved only for cases where resection or re-resection with adequate margins cannot be performed without sacrificing the functional outcome.

**Radiation Therapy**

Data from randomized trials and retrospective analyses support the use of preoperative or postoperative external beam RT in appropriately selected patients with STS of extremity. In a phase III randomized trial 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 extremity sarcoma. 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. Therefore, the risk of local recurrence versus the toxicity of postoperative RT should be assessed before making a decision regarding RT.

The efficacy of postoperative RT was demonstrated in a prospective randomized trial comparing limb-sparing surgery and limb-sparing surgery with postoperative RT. Postoperative RT reduced 10-year local recurrence rate in patients with high-grade sarcoma (no local recurrences in patients who underwent surgery plus RT vs. 22% in those who underwent surgery alone) as well as low-grade sarcoma (5% for surgery plus RT group vs. 32% for those who underwent surgery alone).

Adjuvant brachytherapy has been shown to improve local control after complete resection of STS in patients with high-grade lesions. In a prospective randomized trial, 164 patients with completely resected STS of the extremity or superficial trunk were randomized intraoperatively to receive either adjuvant brachytherapy or no brachytherapy. 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 were randomized to no brachytherapy (89% and 66% respectively). However, brachytherapy had no impact on local control in patients with low-grade. The 5-year freedom-from-distant-recurrence rates were 83% and 76% respectively in the two groups.

Postoperative IMRT following limb-sparing surgery is associated with excellent local control in selected patients with high risk features. In a retrospective analysis, the 5-year local control rate was 94% in patients with negative as well as positive or close margins. The risk of complications such as edema and joint stiffness were also favorable when compared with conventional RT. In a nonrandomized comparison...
of local control by IMRT versus 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 = 0.04) despite higher rates of adverse features for IMRT.\textsuperscript{128} Despite the excellent results of adjuvant IMRT in patients with extremity sarcomas, its efficacy needs to be confirmed in larger cohorts of patients with longer follow-up.

Definitive RT entails the delivery of maximal local dose compatible with known tissue tolerance, typically in the range of 70-80 Gy with sophisticated instrument planning techniques. 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.\textsuperscript{129} 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 that are 5 to 10 cm, and 25% for lesions that are more than 10 cm.

**Evaluation and Workup**

The differential diagnosis of STS of the extremities includes ruling out desmoids, as well as the other malignant and benign lesions previously discussed. An essential element of the workup is a history and physical examination. Laboratory tests have a limited role.

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. Imaging studies should also provide details about tumor size and contiguity to nearby visceral structures and neurovascular landmarks. The propensities to spread to various locations vary between the subtypes of sarcoma. Therefore imaging should be individualized based on the subtype of sarcoma.

Magnetic resonance imaging (MRI) with or without computed tomography (CT) is indicated for all lesions with a reasonable chance of being malignant. MRI is preferred for extremity sarcomas, whereas CT is preferred for retroperitoneal sarcomas.\textsuperscript{130-132} CT angiogram may be useful for patients in whom MRI is not feasible. Plain radiograph of the primary lesion is optional. Given the risk for hematogenous spread from a high-grade sarcoma to the lungs, imaging of the chest is essential for accurate staging. Abdominal/pelvic CT should be considered for angiosarcoma, leiomyosarcoma, myxoid round cell liposarcoma or epithelioid sarcoma. 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 STS.\textsuperscript{133-135} ASPS has a relatively increased propensity to metastasize to the brain, especially in patients with stage IV disease in the presence of pulmonary metastases.\textsuperscript{136} Central nervous system (CNS) imaging should be considered for patients with ASPS and angiosarcomas.

Positron emission tomography (PET) scans may be useful in prognostication, grading and determining histopathological response to chemotherapy for firm, and deep (not superficial) lesions larger than 3 cm in patients with high-grade extremity STS.\textsuperscript{137-142} The maximum standardized uptake (SUVmax) value of F18-deoxyglucose (FDG) has been shown to correlate with tumor grade and prognostication.\textsuperscript{143,144} In a retrospective study, tumor SUVmax determined by PET was an independent predictor of survival and disease progression.\textsuperscript{137} Schuetze et al reported that the pretreatment SUVmax and change in SUVmax after preoperative chemotherapy independently identified patients at...
high risk of recurrence.\textsuperscript{138} 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.\textsuperscript{138} 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.\textsuperscript{141,140} 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.\textsuperscript{141} 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 (www.cancer.gov/clinicaltrials/UMN-2005LS080).

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

- **Stage I**
- **Stage II-III**
- **Stage IV**
- **Recurrent disease**

### Stage I

Surgery is the primary treatment for low grade stage I tumors and is considered definitive if margins are greater than 1 cm or the fascia plane is intact.\textsuperscript{145,146} Retrospective studies have demonstrated a local control of 90\% or more for surgery alone.\textsuperscript{147} Data from randomized clinical trials support the use of RT as an adjunct to surgery in appropriately selected patients based on an improvement in DFS although not OS.\textsuperscript{116,126} Long-term results of a prospective trial demonstrated that selected patients with primary T1 STS of the extremity and trunk can be treated by surgery alone (R0 resection) with acceptable local control and excellent long-term survival.\textsuperscript{147} 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\%.

The panel recommends surgery alone as the primary treatment for low grade stage I tumors (T1a-2b, N0, M0). If the final surgical margins are 1.0 cm or less and without an intact fascial plane, postoperative RT is included with a category 2B recommendation for T1a-b tumors and category 1 recommendation for T2a-b tumors. RT may not be necessary in patients with small lesions (5 cm or less), because these tumors are less frequently associated with local recurrence.

### Stage II-III

Treatment options should be decided by a multidisciplinary team, based on the performance status, comorbid factors including age, location and histological subtype of the tumor and institutional experience.

#### Resectable Tumors

Surgery followed by RT with or without adjuvant chemotherapy is the primary treatment for resectable high-grade sarcomas with acceptable functional outcomes.\textsuperscript{148} There is data suggesting that surgery alone is an adequate treatment option for selected patients treated with limb-sparing surgery with wider surgical margins.\textsuperscript{113,149} In an analysis of 242 patients with localized STS of the trunk and extremity, the 10-year local control rate was 87-93\% 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).\textsuperscript{113} Recently, Al-Refaie et al also reported that the
addition of RT to did not result in any significant difference in OS or sarcoma-specific survival in patients with early stage STS of the extremity. In the guidelines, surgery alone is included as an option for patients with small tumors that can be resected with wider surgical margins.

Radical lymphadenectomy may provide long-term survival in patients with isolated lymph node involvement. In a study that examined the natural history of lymph node metastasis in patients with sarcomas, 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. 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.

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. The results of the only randomized study showed that preoperative chemotherapy is not associated with a major survival benefit for patients with high-grade tumors. The results of a recent phase III randomized trial (EORTC 62961) showed that regional hyperthermia (RHT) increases the benefit of neoadjuvant chemotherapy in patients with localized high-risk STS. In this study, 341 patients were randomized to receive either neoadjuvant 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 extremity sarcoma, 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 would improve DFS in selected patients with good performance status who are at high-risk of recurrence.

Large stage II or III high-grade extremity resectable sarcomas (greater than 8-10 cm) at high risk for local recurrences and metastases should be considered for preoperative and postoperative therapy. The panel has included preoperative RT, chemotherapy (category 2B for all patients with resectable tumors irrespective of the functional outcomes) or chemoradiation (category 2B for patients with resectable tumors with acceptable functional outcomes) prior to surgery as options for all patients with resectable tumors. Postoperative chemotherapy alone can be considered for patients who have received preoperative RT or chemoradiation, whereas postoperative RT with or without postoperative chemotherapy is recommended for those who received preoperative chemotherapy. 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 for all patients with resectable tumors irrespective of the functional outcomes.

Postoperative RT boost of 16 Gy has been used in patients with positive surgical margins after the wound has healed, since positive margins are associated with higher rates of local recurrence. However, the results of a recent retrospective analysis showed that postoperative RT boost did not provide any advantage in preventing local recurrence in patients with positive surgical margins. The advantage of adding postoperative RT boost has not yet been evaluated in a randomized clinical trial. The guidelines recommend consideration of postoperative RT boost for patients with residual gross
disease or microscopically positive margins after surgery. The panel also emphasizes that RT does not substitute for suboptimal surgical resection and re-resection may be necessary in patients with positive surgical margins.

**Unresectable Tumors**

Unresectable tumors can be treated primarily with RT, chemoradiation or chemotherapy. Isolated limb regional therapy (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 or ILI with doxorubicin or melphalan and dactinomycin 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 extremity sarcomas. The guidelines have included isolated regional limb therapy as an option for patients with unresectable tumors treated at institutions with experience in limb perfusion therapy.

Tumors that become resectable following preoperative treatment can be treated with surgery. Postoperative treatment options for this group of patients are similar to that described for patients with stage II or III resectable tumors. Definitive RT (7000-8000 cGy) can be considered for selected patients with unresectable tumors following preoperative treatment. Observation is an option for patients whose tumors are not felt to be amenable to local control with definitive RT if the patients are asymptomatic. For symptomatic patients the panel recommends moving directly to a palliative approach, defined broadly as chemotherapy, palliative surgery or best supportive care.

**Stage IV (synchronous metastatic Disease)**

Patients who present with metastatic disease represent a group with no disease-free interval and have a poor prognosis despite aggressive surgical resection of primary tumor and metastases. In a retrospective study of 48 patients with STS and synchronous metastases, there was no improvement in OS for patients treated with metastasectomy compared to those with unresectable disease. 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 lymph node metastases and pulmonary metastases.

Since there is 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. Treatment options should be based on many factors including performance status, patient preferences, specific clinical problems from the metastases and treatment availability.

**Limited Metastases**

Patients with limited metastasis confined to a single organ and limited tumor bulk that are amenable to complete resection 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 for many
cancers, including sarcoma. Several variables including tumor resectability, number of metastases and performance status influence the decision to use metastasectomy. Thoracotomy and video-assisted thoracic surgery (VATS) should be used selectively depending on the clinical presentation of metastatic disease.\textsuperscript{161,162} In addition, patients can also receive stereotactic radiosurgery or chemotherapy as an alternate method for control of metastatic lesions.

**Disseminated Metastases**

In the guidelines, a subsequent distinction is made between asymptomatic and symptomatic patients for those who present with disseminated disease. One reasonable management option for asymptomatic patients is to offer close observation with a "watchful waiting" strategy; this is especially true if patients have only a minimal burden of metastases (eg, sub-centimeter pulmonary nodules). Alternatively, patients can also be treated with palliative approaches such as 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 radiofrequency ablation (RFA) or cryotherapy, embolization procedures or stereotactic radiosurgery/RT as options for symptomatic patients with disseminated metastases.

**Surveillance**

Surveillance is deemed important to detect recurrences that might still be potentially curable. However, very limited data is available in the literature on effective surveillance strategies.\textsuperscript{163-165} Because these patients’ risk never returns to zero, long-term follow-up is indicated, including consideration of MRI or CT scan.\textsuperscript{166} 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.\textsuperscript{167} However, in certain subsets of patients in whom chest radiographs are difficult to interpret because of anatomic considerations (scarring, emphysema, etc.), chest CT may be indicated.

Ultrasound has been used for the detection of early local recurrences and for the detection of micronodules less than 0.5 cm in diameter.\textsuperscript{168-170} 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\%).\textsuperscript{168} 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 et al 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.\textsuperscript{169} These results confirm that ultrasound can be useful for the detection of local recurrences. However, as reported by Choi et al., ultrasound may be more difficult to interpret than MRI during the early postoperative period.\textsuperscript{168} Therefore, MRI should be used if ultrasound results are inconclusive.

The guidelines outline a prudent follow-up schedule 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. Periodic imaging (MRI, CT, or ultrasound) of the primary site should be done based on the estimated risk of locoregional recurrence. The guidelines recommend that ultrasound can be considered for the detection of local recurrences in patients with smaller
lesions that are superficial and should be performed by an ultrasonographer with experience in musculoskeletal disease. However, in situations where the area is easily followed by physical examination, imaging may not be required. 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 3-6 months for 2-3 years and then annually. Chest imaging should also be considered every 6 to 12 months. For stage II-IV disease, H&P and chest imaging should be done every 3-6 months for 2-3 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.

For a patient with a local recurrence, treatment decisions should be made using the same algorithm as for patients with a new primary lesion. 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 whereas others have reported that conservative surgery alone results in local control in a minority of patients who have failed locally after previous excision and external beam RT, likely reflecting differences in patient selection for treatment with 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 adjuvant 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 widely disseminated metastases, limited metastases confined to a single organ and isolated regional disease with nodal involvement. The treatment options for patients with disseminated metastases or limited metastases confined to a single organ are similar to that described for Stage IV disease at presentation. In patients with isolated regional disease or nodal involvement, options include regional node dissection with or without RT or chemotherapy (category 2B for chemotherapy), metastasectomy or stereotactic radiosurgery. Limited data are available on the use of chemotherapy in patients undergoing metastasectomy. Results from a recent retrospective analyses suggest that chemotherapy has minimal impact on the survival of patients with metastatic extremity STS undergoing pulmonary metastasectomy.

The guidelines have included the use of chemotherapy and RT (before or after metastasectomy) with a category 2B recommendation.

**Retroperitoneal/Intra-abdominal Soft Tissue Sarcomas**

Surgical resection of a localized tumor with grossly negative margins remains the standard, potentially curative treatment for retroperitoneal STS. Postoperative margin status is the most important factor contributing to long-term DFS. 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.
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 resections performed in high-volume centers. While the results are encouraging, this new surgical technique needs to be investigated in prospective clinical trials.

**Radiation Therapy**

The role of adjuvant RT has not been evaluated in randomized trials in patients with retroperitoneal STS. Long-term results of two prospective trials showed favorable 5-year local RFS (60%), DFS (46%) and OS rates (61%) among patients who had R0 or R1 resection after preoperative RT for intermediate or high grade retroperitoneal STS. Postoperative RT has been associated with improved RFS in retrospective nonrandomized studies, although there was no improvement in OS. In one trial, combined use of preoperative RT and postoperative brachytherapy resulted in significantly better DFS and OS in patients with primary retroperitoneal STS and in those with low-grade tumors. Preoperative RT is often preferred, because the primary tumor acts to displace some of the abdominal organs out of the RT fields and it may render unresectable tumors more amenable to resection.

The use of IORT with or without external beam RT has provided encouraging results in patients with retroperitoneal sarcomas. IORT has been used with electron beam RT (IOERT) or HDR brachytherapy (HDR-IORT). In patients with retroperitoneal STS treated with a protocol involving maximal tumor resection, HDR-IORT at the MSKCC, patients with primary disease and those with low-grade tumors had significantly better local control rate (74% for patients with primary disease vs. 54% for those with recurrent disease) and overall distant metastasis-free survival rate (100% for those with low-grade tumors vs. 70% for those with high-grade tumors). IOERT has also been effective in terms of local control and survival in patients with primary and recurrent retroperitoneal STS. In a trial that assessed the long-term outcome of patients with retroperitoneal sarcoma treated by preoperative RT, resection, and 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. The feasibility and safety of preoperative concurrent chemoradiation followed by surgical resection and IOERT has also been demonstrated in a phase I trial.

Postoperative RT using newer techniques such as IMRT, 3D conformal proton therapy, and intensity modulated proton therapy (IMPT) may allow tumor target coverage and acceptable clinical outcomes within normal tissue dose constraints to adjacent organs at risk in some patients with retroperitoneal STS who did not receive pre-operative radiotherapy. Multicenter randomized controlled trials are needed to address the toxicities and therapeutic benefits of adjuvant RT techniques in patients with retroperitoneal STS.

**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 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, GIST, lymphomas, or germ cell tumors), desmoids, and benign lesions. The need for a biopsy remains somewhat controversial, and this decision should be based on the clinician’s degree of suspicion that another malignancy is possible. Proof of the histological subtype by biopsy is necessary for patients before receiving preoperative chemotherapy or RT; a CT-guided core biopsy is preferred. 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 sarcoma is encountered unexpectedly at the time of laparotomy is performed for some other reason, a core biopsy should be done to establish the diagnosis as well as the histopathological type and grade of tumor. Then, the optimal subsequent resection could be performed.

**Resectable Disease**

Although surgery is the standard treatment for retroperitoneal abdominal sarcomas, complete surgical resection or macroscopic surgical resection is only achieved in less than 70% of patients with primary retroperitoneal sarcomas, because they often are near vital structures. Local recurrence and disease progression continue to be associated with a significant cause of morbidity in the majority of patients. Multimodality treatment is usually favored for retroperitoneal sarcomas due to the inability to obtain negative margin resections and high local recurrence rates. 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. Little data are available for use of combined RT and chemotherapy. Decisions about adjuvant or neoadjuvant chemotherapy or RT are left to clinical judgment. 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 small number of patients with retroperitoneal sarcomas. In the phase III randomized trial (EORTC 62961), the addition of RHT to neoadjuvant chemotherapy with EIA was associated with a significant survival benefit. After a median follow-up of 34 months, among 192 patients with non-extremity sarcomas, the 2-year DFS and local PFS rates were 50% and 64% respectively for patients treated with EIA plus RHT. The corresponding survival rates were 33% and 45% for those treated with EIA alone. As is the case with STS of extremities, these results need to be confirmed in large cohort studies and the use RHT with neoadjuvant chemotherapy is not recommended in the guidelines for the treatment of patients with retroperitoneal or abdominal STS.

Biopsy is performed only if preoperative therapy is considered. Endoscopic biopsy is recommended for suspected GIST lesions. In patients with diagnostic biopsy, surgery with or without IORT is the primary treatment option for non-GIST or non-desmoid resectable lesions. Alternatively, preoperative therapy (RT or chemotherapy) could be considered followed by surgery with or without IORT. Surgery is the primary treatment if biopsy is not performed or it is non-diagnostic. IORT can be considered provided the frozen section pathology can confidently demonstrate non-GIST or non-desmoid histology. Although most patients with retroperitoneal sarcomas (which are often liposarcomas) could be managed with surgical resection with or without IORT, the options for other therapy should be discussed, especially if incomplete resection is a reasonable probability.

Postoperative treatment options are dependent on surgical outcomes and clinical or pathological findings following surgery. Postoperative RT
Soft Tissue Sarcoma (category 2B) could be considered (if not received preoperatively) for all patients with microscopic positive margins (R1 resection) and in highly selected patients (e.g., patients with pathological findings of high grade disease, extremely large tumors, close surgical margins or high risk of recurrence) following negative margin resection (R0 resection). Alternatively, postoperative RT boost (10-16 Gy) can be considered in patients with microscopic positive margins (R1 resection) who received preoperative RT. Macroscopic positive margins (R2 resection) should be managed as unresectable disease.

Unresectable or Stage IV Disease

Unresectable retroperitoneal STS are defined as tumors that involve unresectable vital structures or tumors whose removal would cause unacceptable morbidity. Biopsy is recommended before any treatment for a patient with unresectable or metastatic retroperitoneal sarcoma. Patients with unresectable or stage IV disease have several options for primary treatment including chemotherapy or RT to downstage tumors prior to resection. Observation is considered for asymptomatic patients. Symptomatic patients can be treated with palliative surgery for symptom control or best supportive care. In patients with stage IV disease, resection should always be considered for resectable metastatic disease.

Unresectable tumors that become resectable following primary chemotherapy or RT should be managed as described under resectable disease. Following primary treatment, if patients have progressive disease or remain unresectable with no downstaging of tumor, management decisions depend on whether patients are symptomatic or asymptomatic. Observation is considered for asymptomatic patients, whereas for symptomatic patients, can be treated with palliative RT or chemotherapy, palliative surgery for symptom control or best supportive care.

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 should be considered if an appropriate trial is available.

Surveillance

Patients with low-grade tumors that have been successfully resected should have a follow-up physical examination with imaging (chest/abdominal/pelvic CT) every 3-6 months for 2-3 years and then annually. Patients with high-grade tumors that have been successfully resected need more frequent surveillance. They should have a follow-up physical examination with imaging (chest/abdominal/pelvic CT) every 3-6 months for 2-3 years, then every 6 months for the next 2 years, and then annually.

Gastrointestinal Stromal Tumors

GISTs are the most common mesenchymal neoplasms of the gastrointestinal tract, resulting from activating mutations in one of the receptor protein tyrosine kinases (KIT, also called CD117). Most GISTs (95%) are KIT positive. About 5% of GISTs are truly negative for detectable KIT expression, the so-called “KIT-negative GISTS”. A portion of these KIT-negative GISTs have mutations in the platelet derived growth factor-alpha (PDGFRA) genes and express little or no
Therefore, the diagnosis of GIST for a tumor that is otherwise morphologically typical is not precluded by an absence of KIT staining.

GISTs can arise anywhere along the gastrointestinal tract, but stomach (60%) and small intestine (30%) are the most common primary sites. Gastric GISTs have a more favorable prognosis than the intestinal ones. Miettinen et al. have suggested (based on the long-term follow-up of more than 1600 patients) guidelines for the risk stratification of primary GISTs based on mitotic index, size and site. According to these guidelines, gastric GISTs that are 2 cm or less with a mitotic index of 5 or less per 50 HPF can be regarded as essentially benign, but lesions larger than 2 cm with the same mitotic index have a risk of recurrence. Patients with a suspected GIST may present with a variety of symptoms which may include early satiety, abdominal discomfort due to pain or swelling, intra-peritoneal hemorrhage, GI bleeding, or fatigue related to anemia. 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.

**Principles of 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. Recent reports have suggested that definitive diagnosis of GIST requires tissue acquisition via EUS-guided fine-needle aspiration (FNA). Endoscopic ultrasound (EUS)-guided fine needle aspiration (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 (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 histopathological features. Immunohistochemical staining for KIT and molecular genetic testing to identify mutations in the KIT or PDGFRA genes are useful in the diagnosis of GIST.

About 10-15% of GISTs have no detectable KIT or PDGFRA mutations [wild-type GIST (WT-GIST)]. The absence of mutations does not exclude the diagnosis of GIST. DOG1 is calcium dependent, receptor activated chloride channel protein and it seems to be expressed in GIST independent of mutation type. DOG1 expression was not different between the KIT/PDGFRA mutant or WT-GISTs, but there was a clear distinction between PDGFRA- and KIT- mutant tumors; PDGFRA mutant GISTs had a low KIT expression and high DOG1 expression, which can be used in the diagnosis of KIT-negative tumors. 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.
Principles of 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 histologically negative margins is often appropriate. Lymphadenectomy is usually not required given the low incidences of nodal metastases. Resection should be accomplished with minimal morbidity and complex multi-visceral 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 (GE) 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.212

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 mesylate

Imatinib mesylate, a selective inhibitor of the KIT protein tyrosine kinase, has produced durable clinical benefit and objective antitumor responses in most patients with GIST. Multiple clinical trials worldwide have consistently shown the efficacy of imatinib for patients with GIST. Phase II and III studies have demonstrated high overall response rates and exceptionally good PFS for patients with unresectable and/or metastatic GIST, as well as showing objective responses in more than 50% of the patients.213-216 In February 2002, the FDA approved of imatinib mesylate for the treatment of patients with KIT-positive
unresectable and/or metastatic malignant GIST. Long-term follow-up results of the B2222 trial (n = 147, randomly assigned to received 400 or 600 mg of imatinib daily) confirmed that imatinib induces durable disease control in pts with advanced GIST. The estimated 9-year OS rate for all pts was 35%; 38% for those with complete or partial response and 49% for those with stable disease. Low tumor bulk at baseline predicted for longer TTP and improved OS.

The presence and the type of KIT or PDGFRA mutation status are predictive of response to imatinib therapy in patients with advanced or metastatic GISTs. Mutations in KIT juxtamembrane domain (exon11) mutations are the most common in GISTs of all sites, whereas KIT extracellular domain (exon 9) mutations are specific for intestinal GISTs. PDGFRA mutations are common in gastric GISTs and a majority of the mutations affect exon 18 in tyrosine kinase domain 2.

In randomized clinical trials, patients with KIT exon 11 mutations had better response rates, longer PFS and OS compared to those with KIT exon 9 mutations or no KIT or PDGFRA mutation. In the U.S. Finnish B2222 phase II trial, partial response rate was 83.5% for those with exon 11 mutation compared to 47.8% for those with exon 9 mutations. The EORTC (European Organization for Research and Treatment of Cancer)-Italian Sarcoma Group (ISG)-Australasian GI Trials Group (AGITG)-phase III trial (EORTC-62005) and the North American phase III study SWOG (Southwest Oncology Group) S0033/CALGB 150105 also confirmed the findings from B2222 study, that the KIT exon 11 genotype is associated with favorable outcome in patients with advanced GIST compared to KIT exon 9 genotype or WT-GIST. The results of the S0033/CALGB 15010 study 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. Therefore, it is rational to offer KIT-negative GIST patients a therapeutic trial of imatinib mesylate with close evaluation and follow-up.

Two separate phase III trials have assessed the efficacy of imatinib mesylate 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. 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 trial documented an earlier TTP for patients receiving 400 mg daily. 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 reported identical response rates (40% vs. 42% respectively) at a median follow-up of 4.5 years and there was 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). Following progression on 400 mg daily, 33% of patients that crossed over to the higher dose achieved objective response rates and stable disease. However, the small advantage in PFS observed for high-dose imatinib in the EORTC 62005 trial was not corroborated by the S0033/CALGB 150105 trial.

Available data confirm the safety and efficacy of imatinib at 400 mg/day as the initial standard dose to achieve response induction. In a randomized EORTC phase III trial, treatment with the high-dose imatinib (800 mg/day) resulted in a significantly superior PFS with a reduction of the relative risk of 61% (p = 0.0013), in patients whose tumors expressed an exon 9 KIT. In the North American Intergroup phase III trial (CALGB 150105), patients with exon-9 mutations treated with 800 mg imatinib had improved response rates compared to those
treated with 400 mg imatinib (67% vs. 17% respectively). 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 trial. The results of the meta-analysis of 1,640 patients from both these trials showed that treatment with high-dose imatinib (400 mg twice daily) results in small but significant PFS advantage compared to standard dose imatinib (400 mg daily). This meta-analysis also showed a benefit in PFS for patients with KIT exon 9 mutations treated with 800 mg of imatinib. Dose escalation to 800 mg/day is a reasonable option for patients progressing on 400 mg/day. Recent data support the use of imatinib at 800 mg/day in patients with exon 9 mutations and advanced GIST.

Preoperative Imatinib
The RTOG 0132/ACRIN 6665 is the first prospective study that evaluated the efficacy of preoperative imatinib (600 mg/day) in patients with potentially resectable primary disease (30 patients) or potentially resectable recurrent or metastatic disease (22 patients). Among patients with primary GIST, partial response and stable disease were observed in 7% and 83% of patients respectively. The corresponding response rates in patients with recurrent or metastatic disease were 4.5% and 91% respectively. The estimated 2-year overall survival (OS) rate was 93% and 91% for patients with primary GIST and those with recurrent or metastatic GIST respectively. The estimated 2-year progression-free survival (PFS) rate was 83% and 77% respectively.

In a trial conducted at the M.D. Andersen 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). 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 3-7 days of preoperative imatinib.

In another prospective study, Fiore et al 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%. 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 trial, preoperative imatinib was associates with in partial response 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. 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. At the present time, the decision to use preoperative therapy 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%. Median time to recurrence after resection of primary high-risk GIST is about 2 years.

In the single arm multicenter phase II intergroup trial conducted by the American College of Surgeons Oncology Group (ACOSOG), postoperative imatinib (400 mg/day) for one year following complete resection prolonged RFS and improved OS compared to historical controls in patients (n = 106) with primary GIST at high-risk of recurrence based on clinicopathological factors. These findings were confirmed in a subsequent phase III, double-blind randomized trial (ACOSOG Z9001), which randomized patients with primary localized GISTs (3 cm or greater in size) to postoperative imatinib 400 mg (359 patients) or placebo (354 patients) for one year after complete resection. At a median follow-up of 19.7 months, the RFS rate at one year was significantly higher in the imatinib arm compared to placebo (98% and 83% respectively, p < 0.001). OS was not different in both arms (99.2% vs. 99.7% respectively; p = 0.47). In the subset analysis, relapse-free survival (RFS) was statistically in favor of the imatinib arm in patients with intermediate-risk (6 cm or greater and less than 10 cm; 98% vs. 76% for placebo; p = 0.05) and high-risk tumors (10 cm or greater; 77% vs. 41% for placebo; p < 0.0001). Long-term follow-up is ongoing to determine the appropriate duration of treatment and the impact of mutational status on the outcome of patients treated with postoperative imatinib.

The results of a recently completed Scandinavian Sarcoma Group XVIII trial (SSGXVIII/AIO) suggest that adjuvant imatinib administered for 36 months improves RFS and OS compared to 12 months for patients with a high estimated risk of recurrence after surgery. In this trial, 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 adjuvant imatinib. The median follow-up was 54 months. The RFS and OS were longer in the 36-month group compared to the 12-month group (5-year RFS: 66% vs. 48%, respectively; p <.0001; 5-year OS: 92 % vs. 82% respectively; p =.019).

Management of Toxicities Caused by Imatinib Mesylate

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. Serious side effects (such as liver function test (LFT) abnormalities, lung toxicity, low blood counts, 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 cardiotoxic occurred in 8.2% of patients, were manageable with medical therapy, and infrequently required dose reduction or discontinuation of
imatinib. 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.

**Imatinib Mesylate Resistance**
Imatinib benefits most patients with advanced GIST. However, some patients develop resistance to the drug. Primary resistance is defined as 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, PDGFRA exon 18 or those with WT-GIST. Secondary resistance appears to be related to the acquisition of new kinase mutations. Patients who have been on imatinib for more than 6 months with an initial response and then experience progression are categorized as having secondary resistance, which develops predominantly in patients who have secondary mutations in KIT exon 11. Imatinib resistance can be managed either by dose escalation or by switching to sunitinib.

**Sunitinib malate**
Sunitinib malate (previously known as SU11248) is a multi-targeted tyrosine kinase inhibitor that can induce objective responses and control progressive disease in patients with imatinib-resistant GIST.

In a recent randomized phase III placebo-controlled trial, sunitinib produced significant, sustained clinical benefit in patients with imatinib-resistant or imatinib-intolerant GIST. In patients with imatinib-resistant GIST, sunitinib was associated with a significant improvement in median time to progression (27.3 vs. 6.4 weeks) and significantly greater estimated OS. Sunitinib treatment induced partial response in 14 patients (6.8%) and stable disease (22 weeks or more) in 36 patients (17.4%) vs. no partial responses and stable disease in 2 patients (1.9%) on placebo. In the imatinib-intolerant group, 4 out of 9 patients randomized to sunitinib achieved partial response, with progressive disease in only one. In contrast, three of the four patients randomized to placebo had progressive disease at the time of analysis and no partial response was observed. Sunitinib therapy was generally well tolerated. In January 2006, sunitinib malate received FDA approval for the treatment of GIST, after disease progression on or intolerance to imatinib mesylate.

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. Patients were randomized (1:1) to receive continuous daily sunitinib (37.5 mg/day) either in the morning or in the evening for 28 days (one cycle). The primary end-point was the clinical benefit rate (CBR) defined as the percentage of patients with complete responses, partial responses or stable disease for 24 weeks or more based on RECIST. The overall CBR was 53% [13% had partial responses 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.

Heinrich et al. recently reported that the clinical activity of sunitinib in imatinib-resistant GISTs is significantly influenced by both primary and secondary mutations in the KIT kinase domain.\textsuperscript{243} 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 WT-GIST compared to those with KIT exon 11 mutations. There was no clinical benefit for those with PDGFR\textsubscript{A} mutations (exon 12 and exon 18). 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.

\textit{Management of Toxicities Caused by Sunitinib Malate}

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 (anemia, neutropenia), diarrhea, abdominal pain, mucositis, anorexia, and skin discoloration. Sunitinib is associated with a significant risk of developing hand-foot skin reaction (HFSR).\textsuperscript{244} 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 VEGFR. However, the risk is higher in patients with renal cell carcinoma (RCC) compared to those with non-RCC.\textsuperscript{245} Recent reports have shown that sunitinib is also associated with cardiotoxicity and hypothyroidism.\textsuperscript{246,247} In a retrospective analysis of the data from phase I-II trials, 11\% of the patients had adverse cardiovascular event including CHF in 8\% of patients and absolute reduction in the left ventricular ejection fraction (LVEF) in 28\% of patients.\textsuperscript{246} In a prospective, observational cohort study, abnormal serum TSH concentrations were documented in 62\% of patients and the risk for hypothyroidism increased with the duration of therapy.\textsuperscript{247}

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.\textsuperscript{212}

\textit{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, abdominal/pelvic CT scan with contrast and/or MRI, chest imaging, endoscopic ultrasound in selected patients, endoscopy as indicated (if not previously done) and surgical assessment.

\textit{Imaging of GISTs}

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 scans may be used to clarify ambiguous findings seen on CT or MRI. PET may also be useful 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, in particular for peritoneal disease; MRI with or without contrast usually yields excellent anatomical definition of liver metastases. Many imaging centers are also equipped with combined PET-CT scanners, which may facilitate both anatomic and functional tumor evaluation in one step. If clinicians consider using PET scan to monitor therapy, a baseline PET should be obtained prior to start of therapy.

**Response Assessment**

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. However, these criteria have not yet been universally accepted, have not been validated for patients that have receive several targeted therapies, and the ease of use outside specialized centers is unknown. The EORTC has 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. 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 needs to be confirmed in larger prospective studies.

**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 should be considered if it would improve surgical morbidity by reducing the size of the tumor prior to resection. Preoperative imatinib is recommended as primary treatment for patients with GIST that is resectable with negative margins but with a significant risk of morbidity. The use of preoperative imatinib may however prohibit the accurate assessment of recurrence risk. Close monitoring is essential, because some patients may rapidly become unresectable. Surgery is recommended if bleeding and/or symptoms are present. Baseline CT with or without MRI is recommended prior to the start of preoperative imatinib. Since the optimal duration of preoperative therapy remains unknown, in patients 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.

In prospective studies, preoperative imatinib has been tested at a daily dose of either 400 mg or 600 mg. The guidelines recommend an initial dose of 400 mg daily. Patients with documented mutations in KIT exon 9 may benefit from dose escalation up to 800 mg daily (given as 400 mg twice daily), as tolerated. If there is no progression, continuation of same dose of imatinib is recommended...
and resection should be considered, if possible. If there is progression, as confirmed with CT scan, 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. 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 remains unestablished. 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 (irregular extra-luminal border, heterogeneous echo pattern, presence of cystic spaces and echogenic foci), endoscopic surveillance at 6 to 12 months intervals may be considered. The panel has included this approach with a category 2B recommendation.

**Postoperative treatment**
Based on results of the the ACOSOG Z9001 trial and the recently completed randomized trial (SSGXVIII/AIO), 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). The panel recommends that postoperative imatinib for at least 36 months should be considered for patients with high-risk GIST.

Estimation of risk of recurrence is important in selecting patients who would benefit from postoperative therapy following complete resection. In the ACOSOG Z9001 trial, risk stratification was based only on the tumor size and postoperative imatinib improved RFS in patients with GIST 3 cm or larger in size but 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. In the SSGXVIII/AIO trial, risk stratification was based on tumour size, site, mitotic count and rupture; survival benefit was seen in patients with high-risk of recurrence (mitotic count >5/50 HPF, size >5 cm, non-gastric location and tumour rupture).

Risk stratification after surgical resection should be based on tumor mitotic rate, size and location. Gold et al. have developed a nomogram, taking into account tumor size, site and mitotic index, to predict RFS after resection of localized primary GIST. This nomogram accurately predicts RFS after resection of localized primary GIST and might be useful for patient care, interpretation of trial 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 trials support the benefit for 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 trials. The long-term analysis of RTOG 0132 study suggested that a high percentage of patients progressed after discontinuation of 2-year postoperative imatinib therapy.
In patients who have received preoperative imatinib, if there is persistent gross disease following resection (R2 resection), 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**

Advanced, unresectable, or metastatic GIST has a very high likelihood of clinical benefit and positive response after treatment with imatinib. Patients with a documented unresectable GIST or patients for whom resection would carry the risk of severe postoperative functional deficit or those with widespread metastatic disease should be treated with imatinib mesylate in the preoperative setting. Patients should be assessed within 3 months of initiating therapy to determine if their GIST has become resectable. In selected patients, imaging can be done prior to 3 months. If there is no progression, resection can be considered following surgical consultation. Several retrospective studies have demonstrated survival benefit of cytoreductive surgery following preoperative imatinib in patients with advanced or metastatic GIST responding to preoperative imatinib. 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 trials are underway to assess whether or not resection changes outcome in patients with unresectable metastatic GIST responding to TKI therapy.

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 therapy 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.

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 appearance of a new lesion or an increase in tumor size. It may be determined using CT or MRI with clinical interpretation; PET may be used if the results are ambiguous. For patients with limited progressive disease or for those with widespread systemic disease and good performance status (0-2), options include continuation of imatinib at the same dose, dose escalation, or switching to sunitinib. Patients with limited progression should not be switched to sunitinib if most of the disease is still controlled by imatinib. In patients showing objective signs of disease progression on standard dose imatinib and in the absence of severe adverse drug reactions, dose escalation up to 800 mg daily (given as 400 mg twice daily) may be considered, as clinically tolerated. Prior to dose escalation, all clinical and radiological data, including lesion density on CT should be taken into account. Patient compliance to imatinib therapy at standard dose should be assessed before altering the dose of imatinib or switching to sunitinib.
For limited progressive disease that is potentially easily resectable, surgical resection should be considered.\textsuperscript{255,260} Recent data from a relatively large study has shown that cytoreductive surgery on sunitinib in heavily pretreated patients is feasible and carefully selected patients may experience durable control of previously progressive disease than that expected for sunitinib treatment alone.\textsuperscript{264} However, incomplete resections were frequent and complication rates were high. Other treatment options include RFA or embolization (category 2B),\textsuperscript{212} RT (category 2B) for palliation can be considered in rare patients with bone metastases.

Options are limited for patients progressing on imatinib and sunitinib. Second-generation TKIs such as sorafenib,\textsuperscript{265-267} nilotinib,\textsuperscript{268-270} dasatinib\textsuperscript{271,272} and regorafenib\textsuperscript{273-275} have shown activity in patients with GIST resistant to imatinib and sunitinib.

In retrospective analysis (32 patients), sorafenib was significantly active in patients with metastatic GIST resistant to imatinib and sunitinib.\textsuperscript{265} In a prospective multicenter phase II study involving patients with unresectable, KIT-positive GIST that had progressed on imatinib and sunitinib, 55% of patients who received sorafenib had stable disease and 13% had partial response.\textsuperscript{266} 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 phase I trial, nilotinib, alone and in combination with imatinib showed significant activity in patients with advanced imatinib-resistant GIST; 38 patients had stable disease and two patients achieved partial response with a median PFS of 134 days for the entire group.\textsuperscript{268} In a retrospective analysis, nilotinib resulted in 10% response rate and 37% disease control rates in patients who had failed prior imatinib and sunitinib.\textsuperscript{269} Median PFS and OS were 12 weeks and 34 weeks respectively. The efficacy and safety of nilotinib as third-line therapy for GIST are being studied in an ongoing phase III trial.

In a phase I dose escalation study, 3 of the 19 patients with refractory GIST treated with dasatinib had stable disease, which lasted for more than 3 months in one of these patients.\textsuperscript{271} In the phase II study conducted by Sarcoma Alliance for Research through Collaboration (SARC), dasatinib demonstrated significant activity by ORR in patients with imatinib and sunitinib refractory GIST.\textsuperscript{272} The PR rate was 32% (15/47) of by Choi criteria and 21% evaluable patients (10/47) were progression-free for more than 6 months. Median PFS and OS were 2 and 19 months respectively. Median PFS for patients with WT-GIST was 8.4 months.

Regorafenib is a multikinase inhibitor with activity against KIT, PDGFR and VEGFR. In a phase II trial, regorafenib demonstrated significant activity in patients with advanced GIST after failure of both imatinib and sunitinib.\textsuperscript{273} In the subsequent phase III randomized trial (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). The primary endpoint was PFS and the secondary endpoints included OS and disease control rate (DCR).\textsuperscript{274,275} The median PFS (4.8 months vs. 0.9 months; P < .0001) and the DCR (53% vs 9%) were significantly higher for regorafenib compared to placebo.\textsuperscript{274,275} The PFS rates at 3 and 6 months were 60% and 38% respectively for regorafenib compared to 11% and 0% respectively for placebo.\textsuperscript{274} The HR for OS was 0.77 with 85% of patients in placebo arm crossing over to regorafenib due to disease progression.

Regorafenib was also well tolerated with hypertension (23%), hand-foot skin reaction (20%) and diarrhea (5%) being the most common treatment-related adverse events (grade 3 or higher).\textsuperscript{275}
Any patient who has disease progression despite prior therapy or who has a recurrence, regardless of presentation, should be considered a candidate for enrollment in a clinical trial, if an appropriate trial is available. Based on the results of the phase III GRID trial discussed above, the panel has included regorafenib as an option for patients with disease progression on imatinib and sunitinib. Regorafenib is currently under review at the FDA for approval in patients with advanced GIST progressing on standard therapies. The guidelines have also included sorafenib, dasatinib or nilotinib as additional options for patients who are no longer receiving clinical benefit from imatinib or sunitinib, based on the limited data (as discussed above).

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. Recent data reported by Fumagalli et al. support rechallenging patients with imatinib after failing standard and investigational therapeutic options. The panel also feels that continuation of TKI therapy life-long for palliation of symptoms should be an essential component of best supportive care.

**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 is significant increase in the rate of progressive disease when imatinib therapy was interrupted in patients with advanced disease who were stable or responding to imatinib therapy. In this study, patients with non-progressive disease after 3 years of imatinib treatment were randomly assigned to continuation or interruption of their treatment. After a median follow-up of 35 months after randomization, 2-year PFS was 80% in the continuation group and 16% in the interruption group. The panel strongly recommends that patients should continue taking TKI therapy as long as they are receiving clinical benefit (response or stable disease). It is important to maintain the prescribed daily dosing of TKI therapy to achieve optimal clinical outcome. However, short interruptions for one to two weeks, when medically necessary have not been shown to impact negatively on the control of disease or other outcomes.

**Surveillance**

Every patient with a resected localized GIST should have a thorough H&P every 3-6 months; these patients should also have an abdominopelvic CT scan every 3-6 months. An identical schedule is used for patients who have persistent gross residual disease that is unresectable or for completely resected disease.

**Desmoid Tumors (Aggressive Fibromatoses)**

Desmoid tumors, also known as aggressive fibromatoses, are unique mesenchymal neoplasms, which are often considered “benign malignancies.” Specifically, these tumors are an aggressive fibroblastic proliferation of well-circumscribed, locally invasive, differentiated fibrous tissue. 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. Abdominal desmoids may be a component of the familial adenomatous polyposis (FAP) and may also arise through elective surgical intervention (eg, colectomy) in susceptible patients. In patients who have been treated with prophylactic colectomy, desmoids now represent a more significant cause of morbidity than carcinoma of the colon. Although they do not exhibit the histopathological features to classify them as sarcomas, 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.\(^{281}\) Desmoid tumors are often categorized as low-grade
sarcomas because of their high tendency to recur locally after excision.
They can be locally destructive and infiltrative; in one series from,
approximately 10% of patients died of progressive disease.\(^{282}\) Although
desmoid tumors are often locally invasive, they rarely metastasize.
Most patients do not die of their tumors.\(^{283}\) Desmoids can cause
functional morbidity.

Dysregulation of β-catenin pathway has been commonly identified in
sporadic desmoids although the incidence of \(CTNNB1\) (the gene
encoding β-catenin) mutations is uncertain. Lazar et al recently
reported that mutations in exon 3 of \(CTNNB1\) gene are identified in
85% of desmoids.\(^{284}\) 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.\(^{284}\) Domont et al also
reported β-catenin mutations in 87% of patients with extra-abdominal
desmoid fibromatosis.\(^{285}\) This retrospective study was restricted to
patients with extra-abdominal tumors and the 5-year RFS rate was
significantly worse in β-catenin mutated tumors, regardless of the
genotype, compared with wild-type tumors (49% vs. 75%,
respectively).\(^{285}\) These findings are in contrast to that reported by
Lazar et al.\(^{284}\) Additional prospective studies are needed to confirm
whether genotyping of \(CTNNB1\) may provide important prognostic
information regarding the risk of recurrence and may be helpful in 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), chest imaging, 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. Desmoids of the breast are
difficult to differentiate from carcinomas, because desmoids resemble
carcinomas clinically and radiologically.\(^{286-289}\)

**Resectable Tumors**

Surgery is the primary treatment for patients with resectable desmoid
tumors.\(^{290-293}\) Preoperative RT or chemoradiation has been associated
with local control.\(^{294,295}\) 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).\(^{296-298}\) In a retrospective analysis of 142 patients
with desmoid fibromatoses (74 with primary tumor and 68 with
recurrence) reported by Fiore et al, 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 = 0.70)).\(^{297}\) The
corresponding survival rates were 54% and 61% (p = 0.48) for patients
with recurrence. Large tumors (greater than 10 cm in size) and tumors
located on the trunk were associated with 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. However, the impact of positive resection margins on local control and risk of recurrence remains controversial.299 Microscopic 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. Large tumors can be treated with postoperative RT. For microscopic positive margins or minimal residual disease (R1 resection), additional resection or high-dose RT (if not received prior to surgery) can be considered. Several retrospective series have reported that postoperative RT significantly improves local control and PFS compared to surgery alone.300-304 Postoperative RT reduces the risk of recurrence in patients with positive margins and should be considered if a subsequent relapse might lead to increased morbidity. Patients with macroscopic surgical margins (R2 resection) are treated as described below for unresectable disease.

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.305,306 Desmoid tumors respond slowly to RT; often 2 years may be required for desmoid tumors to fully respond to RT. Irradiation of an unresectable tumor is a reasonable consideration, depending on the possible morbidity of treatment.307,308 For example, 23 patients received RT for gross disease, because it was not resectable; 7 sustained local recurrence, yielding a 69% actuarial control rate at 5 years. Kiel and Suit reported even higher control; thus, 8 of 10 patients treated primarily with RT achieved a complete response without resection (5 patients) or achieved stabilization (3 patients) of their disease after some regression.309 In a more recent retrospective analysis of 95 patients with desmoid tumors who underwent definitive local therapy (surgery, RT or a combination of both), with a median follow-up of 38 months, the actuarial 3-year local control rate was not significantly different among the three treatment groups (84.6%, 92.3% and 69.0% respectively; p = 0.3).310

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.311,312 In a prospective study, tamoxifen in combination with sulindac resulted in disease stabilization in patients with progressive or recurrent tumors following surgery.313 The results of a retrospective, non-randomized study showed that interferon alpha 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.314 In case reports, toremifene has been effective in disease stabilization following surgery.315-318 Doxorubicin-based chemotherapy has been effective in patients with recurrent or unresectable tumors.319-321 The combination of
methotrexate and vinblastine has also been associated with prolonged stable disease in patients with unresectable or recurrent tumors.\textsuperscript{321,322}

Imatinib has also been active in patients with unresectable, progressive or recurrent aggressive fibromatosis.\textsuperscript{323} In a phase II multicenter trial (SARC trial), imatinib resulted in an objective response rate of 6\% and the 1-year PFS rate was 66\% in patients with unresectable DF.\textsuperscript{324} Long-term follow-up results of the phase II trial 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 DF.\textsuperscript{325} 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. Sorafenib has also shown activity in patients with progressive disease on chemotherapy. In a study of 26 patients, sorafenib induced partial response in 25\% of patients and 70\% of patients had stable disease, with a median follow-up of 6 months.\textsuperscript{326}

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 tyrosine kinase inhibitors (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. In 2005, FDA issued a black box warning for celecoxib regarding an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. 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 appropriate imaging every 3-6 months for 2-3 years and then annually. Disease progression or recurrence should be managed as described under primary treatment for resectable or unresectable disease.

### Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is more common among children and adolescents but it is less common in adults accounting for 2\%-5\% of all soft tissue sarcomas.\textsuperscript{327} RMS has three histologic subtypes: embryonal (including botryoid, and spindle cell variants), alveolar (including a solid variant) and pleomorphic rhabdomyosarcoma.\textsuperscript{328,329} 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.\textsuperscript{327,329-334} The incidence of pleomorphic RMS increases with age and the overall prognosis of RMS in adults is poor.\textsuperscript{335} 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.\textsuperscript{335} Extremities, trunk wall and genitourinary organs are the most common primary sites for pleomorphic RMS in adults.\textsuperscript{336-338} 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\%).\textsuperscript{333} Pleomorphic histologies (19\% vs. 1\% in children; p < 0.0001) and unfavorable sites (65\% vs. 55\% in children; p < 0.0001) were more common in adults; the estimated 5-year overall survival rates were 27\% for adults compared to 63\% for pediatric patients.\textsuperscript{333}
Given the rarity of the clinical situation, there is 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 et al reported a 5-year event-free and overall survival rates of 28% and 40% respectively. 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 event-free survival rate was 37% for patients who underwent complete resection compared to 0% in patients with unresectable tumors. Other retrospective studies from MD Andersen Cancer Center (82 adults) and Dana Farber Cancer Institute (39 patients) have also reported high overall response rates to chemotherapy (75% and 82% respectively). Survival was significantly better for patients responding to chemotherapy than those who did not. In the MD Andersen Cancer Center study, the 10-year metastasis-free survival was 72% for patients responding to chemotherapy compared to 19% for those who failed to respond. 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 complete response to chemotherapy compared to only 7% for those with poor response. In this study, 5-year survival rates were also higher for patients who underwent complete resection than those who did not (63% vs. 29% and 46% for those who underwent compromised or incomplete resections, respectively). Hawkins et al 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).

Chemotherapy regimens used in adults with RMS are usually derived from the pediatric clinical trials on RMS conducted by international cooperative groups. Vincristine, dactinomycin and cyclophosphamide (VAC) has been the standard chemotherapy for pediatric nonmetastatic RMS (intermediate- or high-risk). In a randomized study (D9803) from the Children’s Oncology Group, there was no significant survival benefit of adding topotecan to standard VAC regimen in children with intermediate-risk RMS. In this trial, at a median follow-up of 4.3 years, 4-year FFS rate was 73% and 68% respectively for patients treated with VAC and VAC alternating with vincristine, topotecan and cyclophosphamide (p = 0.3). The results of the Intergroup Rhabdomyosarcoma Study (D9602) showed that newly diagnosed patients with low-risk RMS treated with vincristine and dactinomycin has similar 5-year failure-free survival rates compared to those patients treated with vincristine, dactinomycin and cyclophosphamide (89% and 85% respectively), suggesting that vincristine and actinomycin could be an appropriate option for patients with newly diagnosed low-risk RMS. Vincristine, doxorubicin and cyclophosphamide alternating with ifosfamide and etoposide was found to be effective for patients with newly diagnosed low-risk RMS. Newer agents such as carboplatin, irinotecan, topotecan and vinorelbine have also shown activity in the treatment of patients with metastatic, relapsed or refractory RMS.

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.
In the MD Andersen 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. Esnaola et al reported overall response rate of 82%, with a complete response rate of 45% in adults with RMS treated with vincristine, doxorubicin and cyclophosphamide or other doxorubicin-based chemotherapy regimens. Recently, Ogilvie et al also reported that chemotherapy with vincristine, doxorubicin and ifosfamide resulted in an overall response rate of 86% in eleven adult patients with pleomorphic RMS; the 2-year overall and disease-free survival rates were 55% and 64% respectively.

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 oncologists, medical, surgical, and radiation oncologists is strongly encouraged. Multimodality treatment (surgery, RT and chemotherapy) planning and risk stratification is required for all patients. 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.

Systemic chemotherapy options for RMS may be different than those used with other soft tissue sarcoma histologies. Pleomorphic RMS is usually excluded from RMS randomized clinical trials. Consideration to treat according to soft tissue sarcoma 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), vincristine, doxorubicin and cyclophosphamide (alone or alternating with ifosfamide and etoposide) and vincristine, doxorubicin and ifosfamide 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. 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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