Soft Tissue Sarcoma Clinical Pathway

The following pathway was developed through multidisciplinary efforts with physicians from the Mary Bird Perkins – Our Lady of the Lake Cancer Center. These pathways should be used as a supplemental guide for treatment for physicians at the Mary Bird Perkins – Our Lady of the Lake Cancer Center, and are not intended to replace the independent medical or professional judgment of physicians or other health care providers.

*Approved by the Sarcoma Specialty Treatment Team November 2017
**Multidisciplinary Sarcoma Team consult**

**H&P**

**Adequate Imaging for the primary**

**Planned Core needle biopsy (preferred), 14 gauge coaxial needle set or incisional biopsy after adequate imaging**

**Chest CT Scan without contrast**

**Histology specific Imaging * (as clinically indicated)**

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**Diagnostic Work Up**

1. Multidisciplinary Sarcoma Team consult
2. **H&P**
3. Adequate Imaging for the primary
4. Planned Core needle biopsy (preferred), 14 gauge coaxial needle set or incisional biopsy after adequate imaging
5. Chest CT Scan without contrast
6. Histology specific Imaging * (as clinically indicated)

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**Soft Tissue Sarcoma Clinical Pathway**

**Staging**

- **Stage 1**
- **Stage II, III resectable (with acceptable functional outcomes)**
- **Stage II, III resectable (with adverse functional outcomes or unresectable primary)**
- Recurrent disease
- Sub-optimal Surgical Resection
- Synchronous Stage IV

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

* Principles of imaging (SARC-A)

* In selected institutions with clinical and pathological expertise, an FNA may be acceptable

* See principles of Pathologic Assessment of Sarcoma Specimens (SARC-B)

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

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

* Different subtypes have different propensities to spread to various locations.

* Diagnoses that will impact the overall treatment plan

* Certain histology has a propensity to metastasize to CNS and or abdomen/pelvis.


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**See next page for staging breakdown:**

1. Stage IA (T1a-1b,N0,M0, low grade, smaller size <5cm)
2. Stage IB (T2a-2b,N0,M0, low grade, smaller size <5cm)
Soft Tissue Sarcoma Clinical Pathway

Stage

**Stage IA** (T1a-1b,N0,M0, low grade, smaller size, 5cm or less in size)
- Surgical wide resection k,j
  - Appropriate margins k
  - Or intact fascial plane
  - Failure to obtain appropriate margins k (and without an intact fascial plane)

**Stage IB** (T2a-2b,N0,M0, low grade, smaller size, more than 5cm)
- Surgical wide resection j,k
  - Appropriate margins k
  - Or intact fascial plane
  - Failure to obtain appropriate margins k (and without an intact fascial plane)

Follow-Up

**Stage IA**
- Eval. for Rehabilitation (PT, OT)
- H&P q 3-6months for 2-3 y, then annually
- Consider obtaining postop baseline & local imaging of primary site k based on estimated risk of locoregional recurrence p,r
- Re-resection
- Observation
- Consider RT n,o,q (category 2B for Stage 1A tumors. Category 1 for Stage 1B tumors)

**Stage IB**
- Lung imaging
- Eval. for Rehabilitation (PT, OT)
- H&P q 3-6months for 2-3 y, then annually
- Consider obtaining postop baseline & local imaging of primary site k based on estimated risk of locoregional recurrence p,r
- Re-resection
- Observation
- Consider RT n,o,q (category 2B for Stage 1A tumors. Category 1 for Stage 1B tumors)

Follow-Up

- Lung imaging
- Eval. for Rehabilitation (PT, OT)
- H&P q 3-6months for 2-3 y, then annually
- Consider obtaining postop baseline & local imaging of primary site k based on estimated risk of locoregional recurrence p,r

Notes:
- See Principal of Imaging (SARC-A).
- See American Joint Committee on Cancer (AJCC) Staging, 8th edition.
- See Principles of Surgery (SARC-D)
- Resection should be tailored to minimize surgical morbidity for patients with atypical lipomatous tumor/well-differentiated liposarcoma (ALT/DWS). En bloc resection with negative margins is generally sufficient to obtain long-term local control.
- In selected cases when margin status is uncertain, consultation with a radiation oncologist is recommended. Resection, if feasible, may be necessary to render >1cm.
- Treatment options including revision surgery vs. observation should be presented at an experienced multidisciplinary sarcoma tumor board to determine advantages and disadvantages of the decision.
- Results of a randomized study showed a non-significant trend toward reduced late toxicities (fibrosis, edema, and joint stiffness) with preoperative compared to postoperative radiation and a significant association between these toxicities and increasing treatment field size. Because postoperative radiation fields are typically larger than preoperative fields, the panel has expressed a general preference for preoperative radiation, particularly when treatment volumes are large.
- Randomized clinical trial data support the use of radiation therapy as an adjunct to surgery in appropriately selected patients based on an improvement in disease-free survival (although not overall survival).
- In situations where the area is easily followed by physical examination, imaging may not be required.
- For patients with ALT/WDLS, observation is recommended for locally positive margins if re-resection, in the event of recurrence, would not be unduly morbid. RT is reserved for selected patients with recurrent or deeply infiltrative primary lesions with a risk of local recurrence, depending on the tumor location and patient age.
- After 10y, the likelihood of developing a recurrence is small and follow-up should be individualized.
- Certain histology has a propensity to metastasize to CNS and or abdomin/pelvis.
### Stage II

*Includes:*
- $T1a-1b, N0, M0, G2-3$
- $T2a-2b, N0, M0, G2$

#### Primary Treatment

Preoperative XRT, surgery then +/- Adjuvant chemo

#### Follow-up

- Eval. for Rehabilitation (PT, OT)
  - Continue until maximal function is achieved

- H&P q 3-6 months for 2-3 years, then q 6 months for next 2 years then annually

- Consider obtaining postop baseline & local imaging of primary site based on estimated risk of locoregional recurrence

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*Principles of Imaging (SARC-A).*

*See American Joint Committee on Cancer (AJCC) Staging, 8th edition.*

*See Principles of Surgery (SARC-A).*

*Results of a randomized study showed a non-significant trend toward reduced late toxicities (fibrosis, edema, and joint stiffness) with preoperative compared to postoperative radiation and a significant association between these toxicities and increasing treatment field size. Because postoperative radiation fields are typically larger than preoperative fields, the panel has expressed a general preference for preoperative radiation, particularly when treatment volumes are large.*

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

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

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

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

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

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

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

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

*PET/CT may be useful in determining response to chemotherapy.*

*For residual gross disease or microscopically positive margins.*

*If both risk of DM and LR is high & tumor is chemo-sensitive, then my preference is: pre-op chemo then pre-op XRT (only 5 more weeks of treatment anyway) then surgery.*

*For select intermediate grade, smaller tumors, can consider surgery alone or postoperative radiation and warrant multidisciplinary evaluation.*
**Stage III** resectable with acceptable functional outcomes

(T2a-b, N0, M0, G3, or Any T, N1, M0, Any G)

**Primary Treatment**

1. Preoperative RT<sup>n</sup> (category 1)
   - or
2. Preoperative chemotherapy <sup>1, v</sup> (category 2B)
   - Surgery <sup>y</sup> to obtain appropriate margins
   - Consider RT boost <sup>5, v</sup> + or – Adjuvant chemotherapy (category 2B)
   - Or
   - RT<sup>n</sup>
   - Or
   - RT<sup>n</sup> + adjuvant chemotherapy <sup>v</sup> (category 2B)

**Follow-up**

- Eval. for Rehabilitation (PT, OT)
- Continue until maximal function is achieved
- H&P q 3-6 months for 2-3 years, then q 6 months for next 2 years then annually
- Consider obtaining postop baseline & local imaging of primary site<sup>b</sup> based on estimated risk of locoregional recurrence<sup>b, r</sup>

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<sup>b</sup>Principles of Imaging (SARC-A).
<sup>i</sup>See American Joint Committee on Cancer (AJCC) Staging, 8<sup>th</sup> edition.
<sup>1</sup>See Principles of Surgery (SARC-A).
<sup>2</sup>Results of a randomised study showed a non-significant trend toward reduced late toxicities (fibrosis, edema, and joint stiffness) with preoperative compared to postoperative radiation and a significant association between these toxicities and increasing treatment field size. Because postoperative radiation fields are typically larger than preoperative fields, the panel has expressed a general preference for preoperative radiation, particularly when treatment volumes are large.
<sup>3</sup>In selected cases when margin status is uncertain, consultation with a radiation oncologist is recommended, re-resection if feasible, may be necessary to render margins > 1.0 cm.
<sup>4</sup>In situations where the area is easily followed by physical examination, imaging may not be required.
<sup>5</sup>After 10y, the likelihood of developing a recurrence is small and follow-up should be individualized.
<sup>6</sup>Patients with stage III tumors with lymph node involvement should undergo regional lymph node dissection at the time of primary tumor resection + or- RT.
<sup>7</sup>Surgery alone may be an option for small tumors resected with wide margins.
<sup>8</sup>RT may be used in selected circumstances such as close or positive margins where re-excision is not feasible or for functional considerations.
<sup>9</sup>For residual gross disease or microscopically positive margins
<sup>10</sup>See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F).
<sup>11</sup>RT may be used in select circumstances such as close or positive margins where re-excision is not feasible or for functional considerations.
<sup>12</sup>PET/CT may be useful in determining response to chemotherapy
# Soft Tissue Sarcoma Clinical Pathway

## Primary Treatment

1. **Stage II, III resectable with adverse functional outcomes**
   - RT
   - Chemoradiation \(^n,v\)
   - Chemotherapy \(^z,v\)
   - Regional Limb Therapy\(^b\)

   Resectable with acceptable functional outcomes

2. **Unresectable primary disease**

<table>
<thead>
<tr>
<th>Resectable with adverse functional outcomes or Unresectable disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery (^j) to obtain appropriate margins</td>
</tr>
<tr>
<td>If not previously irradiated, RT (^n) Or</td>
</tr>
<tr>
<td>RT(^n) + adjuvant chemotherapy(^v) (category 2B)</td>
</tr>
<tr>
<td>If previously irradiated: Consider RT boost (^n,v) + or-</td>
</tr>
<tr>
<td>adjuvant chemotherapy(^v) (category 2B)</td>
</tr>
<tr>
<td>Options:</td>
</tr>
<tr>
<td>1. Definitive RT(^n), if not previously irradiated</td>
</tr>
<tr>
<td>2. Chemotherapy(^v)</td>
</tr>
<tr>
<td>3. Palliative surgery</td>
</tr>
<tr>
<td>4. Observation, if asymptomatic</td>
</tr>
<tr>
<td>5. Best Supportive Care</td>
</tr>
<tr>
<td>6. Amputation (^j)</td>
</tr>
</tbody>
</table>

## Treatment Options

- Eval. for Rehabilitation (PT, OT)
  - Continue until maximal function is achieved
- H&P q 3-6 months for 2-3 years, then q 6 months for next 2 years, then annually
- Consider obtaining postop baseline & local imaging of primary site\(^b\) based on estimated risk of locoregional recurrence\(^j\)

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\(^a\) Principles of Imaging (SARC-A)

\(^b\) See Principles of Surgery (SARC-A)

\(^c\) Results of a randomized study showed a non-significant trend toward reduced late toxicities (fibrosis, edema, and joint stiffness) with preoperative compared to postoperative radiation and a significant association between these toxicities and increasing treatment field size. Because postoperative radiation fields are typically larger than preoperative fields, the panel has expressed a general preference for preoperative radiation, particularly when treatment volumes are large.

\(^d\) In situations where the area is easily followed by physical examination, imaging may not be required.

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

\(^f\) See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F)

\(^g\) For residual gross disease or microscopically positive margins.

\(^h\) PET/CT may be useful in determining response to chemotherapy

\(^i\) Should only be done at institutions with experience with regional limb therapy.

\(^j\) Definitive RT entails delivering the maximal local dose compatible with known normal tissue tolerance, typically in the range of 70-80 Gy with sophisticated treatment planning techniques being a necessity in this setting.
Synchronous Stage IV (Any T/N/G, M1)

Primary Treatment

1. Primary Tumor Management as per Page 3-4 and consider the following options:
   - Metastectomy + or - preop or postop chemotherapy + or - RT (For RT dosing, see SARC E, 2nd Ed)
   - Ablation (RFA, cryotherapy)
   - Embolization procedures
   - SBRT \(^{cc}\)
   - Observation

Palliative Options

- Chemotherapy\(^{a}\)
- RT\(^{dd}/\)SBRT \(^{cc}\)
- Surgery
- Observation, if asymptomatic
- Supportive Care
- Ablation procedures (RFA, Cryotherapy)
- Embolization procedures

Follow-up

- Eval. for Rehabilitation (PT, OT)
  - Continue until maximal function is achieved
- H&P q 3-6 months for 2-3 years, then q 6 months for next 2 years, then annually
- Imaging of chest and other sites of metastatic disease\(^{b}\)
- Consider obtaining postop baseline & local imaging of primary site\(^{a}\) based on estimated risk of locoregional recurrence\(^{dd}\)

\(^{a}\)Principles of Imaging (SARC-A).
\(^{b}\)In situations where the area is easily followed by physical examination, imaging may not be required.
\(^{c}\)After 10y, the likelihood of developing a recurrence is small and follow-up should be individualized.
\(^{d}\)See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F).

\(^{cc}\)In retrospective studies, various SBRT dosing regimens have been reported to be effective for treatment of sarcoma metastases. Dose and fractionation should be determined by an experienced radiation oncologist based on normal tissue constraints.

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

**Metastatic Disease**

- Local Recurrence
- Single organ and limited tumor bulk that are amenable to local therapy
- Disseminated metastases
- Isolated regional disease or nodes

**Primary Treatment**

Follow Diagnostic Workup, then appropriate Primary Treatment**

*Pages 1-4*

**Options:**
- Metastasectomy + or - preoperative or postoperatively chemotherapy** +or- RT
- Ablation procedures (eg, RFA or cryotherapy)
- Embolization procedures
- SBRT

**Palliative Options:**
- Chemotherapy**
- RT** or SBRT
- Surgery
- Observation, *if asymptomatic*
- Supportive Care
- Ablation procedures (RFA, Cryotherapy)
- Embolization procedures

**Options:**
- Regional node dissection for nodal involvement +or- RT +or- chemotherapy**
- SBRT
- Metastasectomy +or- preop or postop chemotherapyw +or- RT
- Isolated limb perfusion/infusion ** + surgery

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**Recurrent Disease**

- Follow Diagnostic Workup, then appropriate Primary Treatment**

*Pages 1-4*

**Isolated regional disease or nodes**

**Options:**
- Chemotherapy**
- RT** or SBRT
- Surgery
- Observation, *if asymptomatic*
- Supportive Care
- Ablation procedures (RFA, Cryotherapy)
- Embolization procedures

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**Notes:**

- **See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F)**
- **Should only be done at institution with experience in regional limb therapy.**
- **Palliative RT requires balancing expedient treatment with sufficient does expected to halt the growth of or cause tumor regression. Numerous clinical issues regarding rapidity of growth, the status of systemic disease, and the use of chemotherapy must be considered. Recommended only for palliative therapy in patients with synchronous stage IV or recurrent disease with disseminated metastases.**
- **If local recurrence can be excised, a decision will need to be made on a case-by-case basis where 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 postoperative adjuvant brachytherapy but may now be able to be done as a combination of brachytherapy and IMRT to reduce the risks of morbidity with re-irradiation.**
Soft Tissue Sarcoma Clinical Pathway

Retroperitoneal/ Intra-Abdominal
Work Up

1. Multidisciplinary Sarcoma Team consult
2. H&P
3. Imaging
4. Pre-resection biopsy not necessarily required; consider biopsy if there is suspicion of malignancies other than sarcoma
5. Biopsy is necessary for patients receiving preoperative RT or chemotherapy
6. Image-guided® Core needle biopsy is preferred over open surgical biopsy®
7. Patients with personal/family history suggestive of Li-Fraumeni syndrome should be considered for further genetics assessment.
8. Patients with neurofibromatosis

Biopsy performed®\(^{c,d}\)

Gastrointestinal stromal tumor (GIST)

Other Sarcoma®

Surgery\(^{d,e}\) to obtain appropriate margins
Or
Preoperative therapy (category 2B):
• RT
• Chemotherapy

Surgery\(^{d,e}\) to obtain appropriate margins

(GIST)

Other Sarcoma®

See Next Page

\(^a\) See Principles of Imaging (SARC-A).
\(^b\) See Principles of Pathologic Assessment of Sarcoma Specimens (SARC-B)
\(^{c}\) Biopsy required if considering preoperative therapy, including endoscopic biopsy for suspected GIST.
\(^d\) See principles of Surgery (SARC-D).
\(^e\) If RT is anticipated, preferred approach would be preoperative RT with an IMRT approach to optimize sparing of nearby critical structures.
\(^f\) IORT may be considered provided frozen section pathology can confidently demonstrate a non-GIST/non-desmoid histology.
\(^g\) For other soft tissue sarcomas such as Ewing’s sarcoma, See NCCN Guidelines for Bone Cancer.
\(^h\) See Radiation Therapy Guidelines (SARC-E).
\(^i\) See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F)
### Surgical Outcomes/Clinical Pathologic Findings

<table>
<thead>
<tr>
<th>Pathologic Findings</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
<td>Post-op RT should not be administered routinely with the exception of highly selected patients and unless local recurrence would cause undue morbidity.</td>
</tr>
<tr>
<td>R1</td>
<td>Post-op RT should not be administered routinely with the exception of highly selected patients and unless local recurrence would cause undue morbidity. Or In highly selected cases, consider boost (10-16 Gy) if preoperative RT was given</td>
</tr>
<tr>
<td>R2</td>
<td>Consider re-resection if technically feasible or <a href="#">See Primary Treatment Unresectable (Next Page)</a></td>
</tr>
</tbody>
</table>

### Treatment for Recurrent Disease

- Unresectable or Stage IV/Metastatic disease:
  - Physical exam with imaging q 3-6 months for 2-3 years, then q 6 months for next 2 years, then annually
  - Obtain chest imaging

- Resectable:
  - [See page 8](#)

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- See Principles of Imaging (SARC-A)
- See Principles of Surgery (SARC-D)
- See Radiation Therapy Guidelines (SARC-E)

*For example, critical anatomic surface where recurrence would cause morbidity.*

*If not previously administered, consider preoperative RT and/or chemotherapy.*
Soft Tissue Sarcoma Clinical Pathway
Retroperitoneal/Intra-Abdominal

Primary Treatment

Options:
- Combination chemotherapy
- Chemoradiation
- RT

Imaging to assess treatment response

Resectable

Unresectable or progressive disease

Palliative Care Options:
- Chemotherapy
- RT
- Surgery for symptom control
- Observation, if asymptomatic
- Supportive Care
- Observation, if symptomatic

Unresectable or Stage IV

Biopsy

No downstaging, palliative care only

Attempt downstaging

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

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

The most active chemotherapy in an unselected patient population is AIM (doxorubicin/ifosfamide/mesna) in terms of response rate.

Resection of resectable metastatic disease should always be considered if primary tumor can be controlled.
Soft Tissue Sarcoma Clinical Pathway

Gastrointestinal Stromal Tumors (GIST)
**Soft Tissue Sarcoma Clinical Pathway**

**GIST**

### Work Up At Primary Presentation

1. Prior to the initiation of therapy, all patients should be evaluated and managed by a multidisciplinary team with expertise and experience in sarcoma.
2. For every small gastric GISTs <2cm (See page 12)
3. Local Imaging
4. Consider mutation testing
   - KIT
   - PDGFRA
5. Consider genotyping

### Results of Initial Diagnostic Evaluation

<table>
<thead>
<tr>
<th>Localized or potentially resectable disease</th>
<th>Preoperative imatinib not indicated</th>
<th>Resect mass</th>
<th>Pathology result and risk assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unresectable or metastatic disease</td>
<td>Consider preoperative imatinib to decrease surgical morbidity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*See American Joint Committee on Cancer (AJCC) Staging, 8th edition.*

*See Principles of Imaging (SARC-A).*

*For tumors lacking mutation in KIT and PDGFRA, recommend testing the tumor for SDHB by immunohistochemistry and if deficient (SDH-deficient GIST) recommend referral to germline testing.*

*Surgery should induce minimal surgical morbidity consider preoperative imatinib if surgery would indicate significant morbidity.*

*Preoperative imatinib may prohibit accurate assessment of recurrence risk. Consider neoadjuvant imatinib only if surgical morbidity could be reduced by downstaging the tumor preoperatively. Maximal response may require treatment for 6 months or more to achieve. Testing tumor for mutation is recommended prior to starting preoperative imatinib to ensure tumor has a genotype that is likely to respond.*

*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 RETSARC-1 if the pathology results indicate sarcomas of GI origin other than GIST.*
**Results of Initial Diagnostic Evaluation**

1. Endoscopic Ultrasound-guided fine-needle aspiration (EUS-FNA)
2. Imaging

**Initial Management**

- High-risk EUS features:
  - Complete surgical resection

- No high-risk EUS features:
  - Consider periodic endoscopic surveillance

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- **Work Up At Primary Presentation**
- **Initial Management**
- **Follow-Up**

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a See Principles of Imaging (SARC-A).

b Adapted with permission from Sepe PS, Brugge WR. A guide for the diagnosis and management of gastrointestinal stromal cell tumors. All recommendations for this algorithm are category 2B.

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

d Endoscopic ultrasonography surveillance should only be considered after a thorough discussion with the patient regarding the risks and benefits.

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Preoperative imatinib may prohibit accurate assessment of recurrence risk. Consider neoadjuvant imatinib only if surgical morbidity could be reduced by downstaging the tumor preoperatively. Maximal response may require treatment for 6 months or more to achieve. Testing tumor for mutation is recommended prior to starting preoperative imatinib to ensure tumor has a genotype that is likely to respond to treatment.

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))

Some patients may rapidly become unresectable, close monitoring is essential.

For SDH-deficient GIST extensive surgery with significant morbidity (i.e. total gastrectomy) is not recommended.
Soft Tissue Sarcoma Clinical Pathway

**Primary Presentation**

GIST that is resectable with negative margins but with risk of significant morbidity

**Primary Treatment**

1. **Baseline Imaging**
2. **Imatinib**
3. Imaging to assess treatment response

**Follow-up Therapy**

1. Response or stable disease
2. Continue the same dose of imatinib
3. Surgery if feasible

**Secondary Treatment**

See Postoperative Treatment (Page 16 & 17)

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1. See Principles of Imaging (SARC-A).
2. See principles of Surgery for GIST (GIST-C).
3. Some patients may rapidly become unresectable, close monitoring is essential.
4. If life-threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider sunitinib.
5. Medical therapy is the usual course of treatment. However, patient may proceed to surgery if bleeding or symptomatic.
6. Because patients with advanced GISTs have different responses to imatinib, mutational testing should be performed. Approximately, 90% of patients have disease that responds to imatinib when their tumors have a KIT exon 11 mutation; approximately 50% of patients have disease that responds when their tumors harbor a KIT exon 9 mutation, and the likelihood of response improves the use of 800 mg imatinib rather than the standard 400 mg dose. Most mutations in the PDGFRA gene are associated with a response to imatinib, with the notable exception of D842V. In the absence of KIT and PDGFRA mutations, advanced GISTs have a 0%-45% likelihood of responding to imatinib, although tumors known to be SDH deficient or having alternative drivers (i.e., NF1, BRAF) are unlikely to benefit. Metastatic disease with acquired drug resistance is usually the result of secondary, imatinib-resistant mutations in KIT or PDGFRA. SDH-deficient GIST may have a higher probability of response to sunitinib.
7. PET may give indication of imatinib activity after 2-4 weeks of therapy when rapid readout of activity is necessary. Diagnostic abdominal/pelvic CT or MRI with contrast is indicated every 8-12 weeks; routine long-term PET follow-up is rarely indicated. Frequency of response assessment imaging may be decreased if patient is responding to treatment.
8. 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.
9. Progression may be determined by abdominal/pelvic CT or MRI with contrast with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.
10. Suggest referral to a sarcoma specialty center.
11. Assess medication adherence before determining that therapy was ineffective.
12. Collaboration between medical oncologist and surgeon is necessary to determine the appropriateness of surgery, following major response or sustained stable disease. Maximal response may require treatment for 6 months or more to achieve.
13. Imatinib can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications. If other TKIs, such as sunitinib or regorafenib, are being used, therapy should be stopped at least one week prior to surgery and can be restarted based on clinical judgment or recovery from surgery.

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**Primary Presentation**

**Primary Treatment**

**Follow-up Therapy**

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**See Postoperative Treatment (Page 16 & 17)**
GIST that is definitively unresectable, recurrent, or metastatic

*See Principles of Imaging (SARC-A).

- Imatinib is the usual course of treatment. However, patient may proceed to surgery if bleeding or symptomatic.
- Because patients with advanced GISTs have different responses to imatinib, mutational testing should be performed. Approximately, 90% of patients have disease that responds to imatinib when their tumors have a KIT exon 11 mutation; approximately 50% of patients have disease that respond when their tumors harbor a KIT exon 9 mutation, and the likelihood of response improves the use of 800 mg imatinib rather than the standard 400 mg dose. Most mutations in the PDGFRA gene are associated with a response to imatinib, with the notable exception of D842V. In the absence of KIT and PDGFRA mutations, advanced GISTs have a 0%-45% likelihood of responding to imatinib, although tumors known to be SDH deficient or having alternative drivers (i.e. NF1, BRAF) are unlikely to benefit. Metastatic disease with acquired drug resistance is usually the result of secondary, imatinib-resistant mutations in KIT or PDGFRA. SDH-deficient GIST may have a higher probability of response to sunitinib.
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- Progression may be determined by abdominal/pelvic CT or MRI with contrast with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.
- Suggest referral to a sarcoma specialty center.
- Assess medication adherence before determining that therapy was ineffective.
- Collaboration between medical oncologist and surgeon is necessary to determine the appropriateness of surgery, following major response or sustained stable disease. Maximal response may require treatment for 6 months or more to achieve.
- Imatinib can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications. If other TKIs, such as sunitinib or regorafenib, are being used, therapy should be stopped at least one week prior to surgery and can be restarted based on clinical judgment or recovery from surgery.
- 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.
- Consider resection if complete resection can be obtained in primary metastatic disease.

# Soft Tissue Sarcoma Clinical Pathway

**GIST**

### Primary Presentation

- Baseline Imaging
- Imatinib
- Imaging to assess treatment response

### Primary Treatment

- Response or stable disease
  - Continue imatinib, obtain surgical consultation, consider resection
- Progression (evaluate treatment adherence)
  - Or
  - Continue imatinib if resection not feasible

### Follow-up Therapy

- Resection
- Upon progression, see treatment for Progressive Disease

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*See Postoperative Treatment (Page 16 & 17)*
Soft Tissue Sarcoma Clinical Pathway
GIST

**Postoperative Outcomes**

- Completely resected (no preoperative imatinib)
- Completely resected after preoperative imatinib

**Postoperative Treatment**

- Imatinib \(^5\) for patients with significant risk of recurrence (intermediate or high risk) (category 1) \(^6\).

Or

- Observe (low-risk disease)
  - Consider continuation of imatinib if taken prior to resection \(^{40}\)

**Postoperative Treatment**

- H&P q 3-6 months for 5 years, then annually \(^{46}\)
- Imaging

**Follow-up**

- If recurrence, See Primary Treatment for Metastatic Unresectable Disease (Page 15)

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\(^1\)See Principles of Imaging (SARC-A).

\(^2\)See principles of Surgery for GIST (GIST-C).

\(^3\)If life-threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider sunitinib.

\(^4\)Because patients with advanced GISTs have different responses to imatinib, mutational testing should be performed. Approximately, 90% of patients have disease that responds to imatinib when their tumors have a KIT exon 11 mutation; approximately 50% of patients have disease that responds when their tumors harbor a KIT exon 9 mutation, and the likelihood of response improves the use of 800 mg imatinib rather than the standard 400 mg dose. Most mutations in the PDGFRA gene are associated with a response to imatinib, with the notable exception of D842V. In the absence of KIT and PDGFRA mutations, advanced GISTs have a 0%-45% likelihood of responding to imatinib, although tumors known to be SDH deficient or having alternative drivers (i.e. NF1, BRAF) are unlikely to benefit. Metastatic disease with acquired drug resistance is usually the result of secondary, imatinib-resistant mutations in KIT or PDGFRA. SDH-deficient GIST may have a higher probability of response to sunitinib.

\(^5\)PET may give indication of imatinib activity after 2-4 weeks of therapy when rapid readout of activity is necessary. Diagnostic abdominal/pelvic CT or MRI with contrast is indicated every 8-12 weeks; routine long-term PET follow-up is rarely indicated. Frequency of response assessment imaging may be decreased if patient is responding to treatment.

\(^6\)Progression may be determined by abdominal/pelvic CT or MRI with contrast with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.

\(^{40}\)Collaboration between medical oncologist and surgeon is necessary to determine the appropriateness of surgery, following major response or sustained stable disease. Maximal response may require treatment for 6 months or more to achieve.

\(^{46}\)For patients with complete resections following preoperative imatinib, continuation of imatinib should be considered. The duration of postoperative imatinib has not been studied in randomized trials; there are single and multi-institutional trials supporting the benefit for continuation of imatinib for two years following surgery.

\(^{41}\)Postoperative imatinib for at least 36 months should be considered for high-risk tumors. The results of a randomized trial (SSGXXVIII/AIO) suggest that postoperative imatinib administered for 36 months improves relapse-free survival and overall survival compared to 12 months for patients with a high estimated risk of recurrence (tumor greater than 5cm in size with a high mitotic rate (>5 mitoses/50HPF), tumor rupture, or a risk of recurrence of greater than 50% after surgery). The results of the ACOSOG trial Z9001 showed that postoperative imatinib improved RFS in patients with GIST greater than or equal to 3cm in size with the greatest benefit noted in tumors at higher risk of recurrence (intermediate and high risk). This trial did not demonstrate overall survival benefit.

\(^{42}\)Less frequent may be acceptable for very small tumors (<2cm).
**Postoperative Outcomes**

- **Persistent gross residual disease** (R2 resection) after preoperative imatinib.
- No preoperative imatinib.

**Postoperative Treatment**

- **Continue imatinib** and consider resection.
- Imaging to assess treatment response and evaluate patient adherence.
- Persistent gross residual disease (R2 resection).

**Follow-up**

- H&P and imaging if progression.

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1. See Principles of Imaging (SARC-A).
2. See principles of Surgery for GIST (GIST-C).
3. If life-threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider sunitinib.
4. Because patients with advanced GISTs have different responses to imatinib, mutational testing should be performed. Approximately, 90% of patients have disease that responds to imatinib when their tumors have a KIT exon 11 mutation; approximately 50% of patients have disease that responds when their tumors harbor a KIT exon 9 mutation, and the likelihood of response improves the use of 800 mg imatinib rather than the standard 400 mg dose. Most mutations in the PDGFRA gene are associated with a response to imatinib, with the notable exception of D842V. In the absence of KIT and PDGFRA mutations, advanced GISTs have a 0%-45% likelihood of responding to imatinib, although tumors known to be SDH deficient or having alternative drivers (i.e. NF1, BRAF) are unlikely to benefit. Metastatic disease with acquired drug resistance is usually the result of secondary, imatinib-resistant mutations in KIT or PDGFRA. SDH-deficient GIST may have a higher probability of response to sunitinib.
5. PET may give indication of imatinib activity after 2-4 weeks of therapy when rapid readout of activity is necessary. Diagnostic abdominal/pelvic CT or MRI with contrast is indicated every 8-12 weeks; routine long-term PET follow-up is rarely indicated. Frequency of response assessment imaging may be decreased if patient is responding to treatment.
6. Progression may be determined by abdominal/pelvic CT or MRI with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.
7. Collaboration between medical oncologist and surgeon is necessary to determine the appropriateness of surgery, following major response or sustained stable disease. Maximal response may require treatment for 6 months or more to achieve.
8. For patients with complete resections following preoperative imatinib, continuation of imatinib should be considered. The duration of postoperative imatinib has not been studied in randomized trials; there are single and multi-institutional trials supporting the benefit for continuation of imatinib for two years following surgery.
9. Postoperative imatinib for at least 36 months should be considered for high-risk tumors. The results of a randomized trial (SSGK/VIII/AIO) suggest that postoperative imatinib administered for 36 months improves relapse-free survival and overall survival compared to 12 months for patients with a high estimated risk of recurrence (tumor greater than 5cm in size with a high mitotic rate [>5 mitoses/50HPF], tumor rupture, or a risk of recurrence of greater than 50% after surgery). The results of the ACOSOG trial Z9001 showed that postoperative imatinib improved RFS in patients with GIST greater than or equal to 3cm in size with the greatest benefit noted in tumors at higher risk of recurrence (intermediate and high risk). This trial did not demonstrate overall survival benefit.
10. Less frequent may be acceptable for very small tumors (<2cm).
Soft Tissue Sarcoma Clinical Pathway
GIST

Treatment for Progressive Disease

• Continue with the same dose of imatinib and consider the following options for progression lesions:
  • Resection, if feasible
  • RFA of embolization or chemoembolization (category 2B)
  • Palliative RT (category 2B) for rare patients with bone metastases
• Dose escalation of imatinib as tolerated
• Change to sunitinib (category 1)
• Imaging to reassess therapeutic response

If disease is progressing despite prior imatinib or sunitinib therapy, consider the following options:
• Regorafenib (category 1)
  Or
• Clinical Trial
  Or
• Consider other options listed in SARC-F (based on limited data)
  Or
• Supportive Care

For performance status (PS) 0-2:
• Dose escalation of imatinib
• Change to sunitinib (category 1)
• Imaging to reassess therapeutic response

Limited

Generalized (widespread, systemic)

1See Principles of Imaging (SARC-A).
2See principles of Surgery for GIST (GIST-C).
3Rarely, 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.
4Progression may be determined by abdominal/pelvic CT or MRI with contrast with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.
5Suggest referral to a sarcoma specialty center.
6Collaboration between medical oncologist and surgeon is necessary to determine the appropriateness of surgery, following major response or sustained stable disease. Maximal response may require treatment for 6 months or more to achieve.
7Clinical experience suggest that discontinuing tyrosine kinase inhibitor (TKI) therapy, even in the setting of progressive disease, may accelerate the pace of disease progression and worsen symptoms.
8In patients with GIST progressing despite prior imatinib, sunitinib, and regorafenib consider other options listed in SARC-F (based on limited data) or reintroduction of a previously tolerated and effective TKI for palliation of symptoms. Consider continuation of TKI therapy life-long for palliation of symptoms as part of best supportive care.
The following pathway was developed through multidisciplinary efforts with physicians from the Mary Bird Perkins – Our Lady of the Lake Cancer Center. These pathways should be used as a supplemental guide for treatment for physicians at the Mary Bird Perkins – Our Lady of the Lake Cancer Center, and are not intended to replace the independent medical or professional judgment of physicians or other health care providers.

The pathway does not include principles or practices for therapy. Review the following pages within the NCCN Guidelines as an additional resource:

- Principles of Imaging (SARC-A)
- Principles of Pathologic Assessment of Sarcoma Specimens (SARC-B)
- Principles of Ancillary Techniques Useful in the Diagnosis of Sarcomas (SARC-C)
- Principles of Surgery (SARC-D)
- Review Radiation Therapy Guidelines for Soft Tissue Sarcoma of Extremity/Trunk/Head-Neck (SARC-E)
- Review Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma Subtypes (Non-specific) (SARC-F)
- Principles of Biopsy for GIST (GIST – A)
- Principles of Pathologic Assessment for GIST (GIST-B)
- Principles of Surgery (GIST- C)
References


7. Sylvie Bonvalot, MD, PhD, Antonin Levy, MD, Philippe Terrier, MD, Dimitri Tzanis, MD, PhD, Sara Bellefqih, MD, Axel Le Cesne, MD, and Ce´cile Le Pe´choux, MD. 2017. Primary Extremity Soft Tissue Sarcomas: Does Local Control Impact Survival?. *Annals of Surgical Oncology.*