# 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

MARY BIRD PERKINS
OUR LADY OF THE LAKE
CANCER CENTER

*Approved by the Sarcoma Specialty Treatment Team November 2017

## Diagnostic Work Up

1. Multidisciplinary Sarcoma Team consult
2. H&P
3. Adequate Imaging for the primary [ab]
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)*

Soft tissue sarcoma of the Extremity/Superficial trunk, head/neck

## 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

**See next page for staging breakdown:**

1. Stage IA (T1a-1b,N0,M0, low grade, smaller size <5cm[j])
2. Stage IB (T2a-2b,N0,M0, low grade, smaller size <5cm[j])

[a]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.

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

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

[d] See principles of Pathologic Assessment of Sarcoma Specimens (SARC-B)

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

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

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

[g] Diagnoses that will impact the overall treatment plan

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

* 14 gauge needle recommendation. Henshaw, Robert M., Jelinek, James, Malawer, Martin M., Shmookler Barry M., Welker, James A. The Percutaneous Needle Biopsy is Safe and Recommended in the Diagnosis of Musculoskeletal Masses. 2000. American Cancer Society. http://onlinelibrary.wiley.com/doi/10.1002/1097-0142(20001215)89:12%3C2677::AID-CNCR22%3E3.0.CO;2-L/pdf

# Soft Tissue Sarcoma Clinical Pathway

## Stage

**Stage IA** *(T1a-1b,N0,M0, low grade, smaller size, 5cm[j] or less in size)*

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

- Eval. for Rehabilitation (PT, OT)
  - Continue until maximal function is achieved
- H&P q 3-6months for 2-3 y, then annually
- Consider obtaining postop baseline & local imaging of primary site[b] 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 Stage1B tumors)*

## Stage

**Stage IB** *(T2a-2b,N0,M0, low grade, smaller size, more than 5cm[j])*

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

- Lung imaging
- Eval. for Rehabilitation (PT, OT)
  - Continue until maximal function is achieved
- H&P q 3-6months for 2-3 y, then annually
- Consider obtaining postop baseline & local imaging of primary site[b] based on estimated risk of locoregional recurrence[p,r]

[b] See Principal of Imaging (SARC-A).
[i] See American Joint Committee on Cancer (AJCC) Staging, 8th edition.
[J] See Principles of Surgery (SARC-D)
[k] Resection should be tailored to minimize surgical morbidity for patients with atypical lipomatous tumor/well-differentiated liposarcoma (ALT/DWS) . En bloc resection with negative margins is generally sufficient to obtain long-term local control.
[l] In selected cases when margin status is uncertain, consultation with a radiation oncologists is recommended. Reresection, if feasible, may be necessary to render >1cm.
[m] 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.
[n] Results of a randomized study showed a non-significant trend toward reduced late toxicities (fibrosis, edema, and joint stiffness) with preoperative compared to postoperative radiation and a significant association between these toxicities and increasing treatment field size. Because postoperative radiation fields are typically larger than preoperative fields, the panel has expressed a general preference for preoperative radiation, particularly when treatment volumes are large.
[O] Randomized clinical trial data support the use of radiation therapy as an adjunct to surgery in appropriately selected patients based on an improvement in disease-free survival (although not overall survival).
[P] In situations where the area is easily followed by physical examination, imaging may not be required.
[q] For patients with ALT/WDLS, observation is recommended for 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.
[r] 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 abdomen/pelvis.

# Soft Tissue Sarcoma Clinical Pathway

## Stage

### 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[b] based on estimated risk of locoregional recurrence[p,r]

[b] Principles of Imaging (SARC-A).
[i] See American Joint Committee on Cancer (AJCC) Staging, 8th edition.
[j] See Principles of Surgery (SARC-A)
[n] Results of a randomized study showed a non-significant trend toward reduced late toxicities (fibrosis, edema, and joint stiffness) with preoperative compared to postoperative radiation and a significant association between these toxicities and increasing treatment field size. Because postoperative radiation fields are typically larger than preoperative fields, the panel has expressed a general preference for preoperative radiation, particularly when treatment volumes are large
[l] In selected cases when margin status is uncertain, consultation with a radiation oncologist is recommended, re-resection if feasible, may be necessary to render margins > 1.0 cm.
[P] In situations where the area is easily followed by physical examination, imaging may not be required.
[R] After 10y, the likelihood of developing a recurrence is small and follow-up should be individualized.
[S] Patients with stage III tumors with lymph node involvement should undergo regionals lymph node dissection at the time of primary tumor resection + or- RT.
[t] Surgery alone may be an option for small tumors resected with wide margins
[U] Re-imaging using MRI with and without contrast (preferred for extremity imaging) or CT with contrast to assess primary tumor and rule out metastatic disease. See Principles of Imaging (SARC-A).
[v] See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F)
[w] RT may be used in select circumstances such as close or positive margins where re-excision is not feasible or for functional considerations.
[x] PET/CT may be useful in determining response to chemotherapy
[y] 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

# Soft Tissue Sarcoma Clinical Pathway

## Stage

Stage III[s] resectable with acceptable functional outcomes

**Stage III**

*(T2a-2b, N0, M0, G3, or Any T, N1, M0, Any G)*

## Primary Treatment

1. Preoperative RT[n] *(category 1)*

or

2. Preoperative chemotherapy [x,v] *(category 2B)*

→ Surgery [u] to obtain appropriate margins

→ Consider RT boost [n,y] + or – Adjuvant chemotherapy *(category 2B)*

Or

RT[n]

Or

RT[n] + adjuvant chemotherapy [v] *(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[b] based on estimated risk of locoregional recurrence[p,r]

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

[i] See American Joint Committee on Cancer (AJCC) Staging, 8th edition.

[J] See Principles of Surgery (SARC-A)

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

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

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

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

[s] Patients with stage III tumors with lymph node involvement should undergo regionals lymph node dissection at the time of primary tumor resection + or- RT.

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

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

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

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

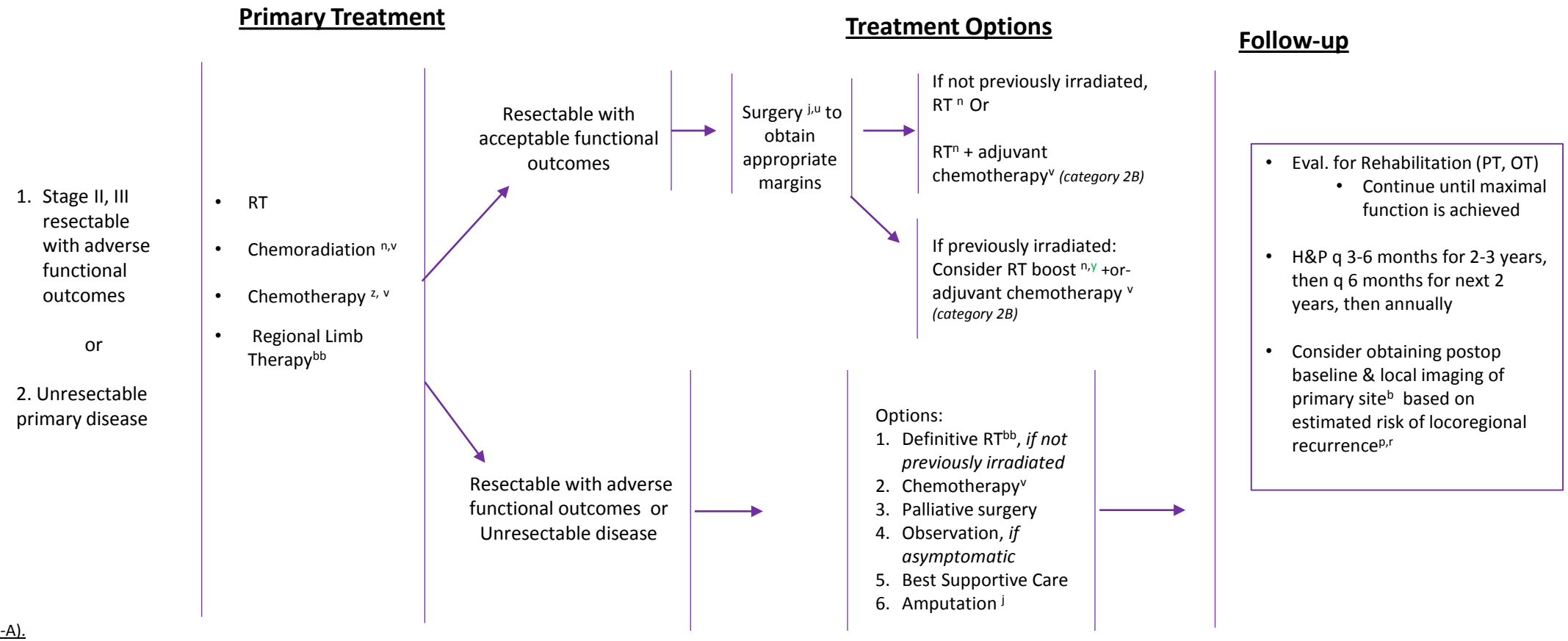
[x] PET/CT may be useful in determining response to chemotherapy

[y] 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 and warrant multidisciplinary evaluation

# Soft Tissue Sarcoma Clinical Pathway




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

[j] See Principles of Surgery (SARC-A)

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

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

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

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

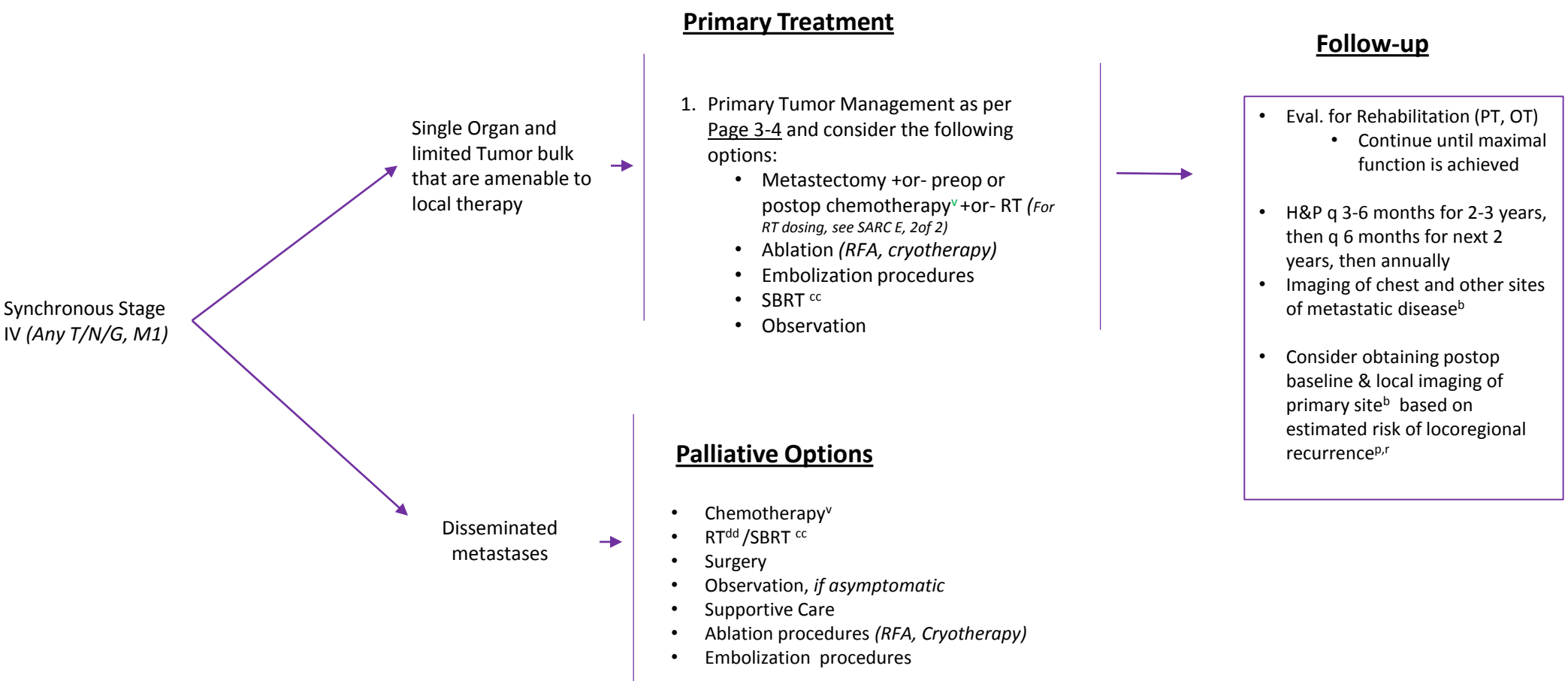
[y] For residual gross disease or microscopically positive margins.

[z] PET/CT may be useful in determining response to chemotherapy

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

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

# Soft Tissue Sarcoma Clinical Pathway




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

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

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

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

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

[dd] 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.

# Soft Tissue Sarcoma Clinical Pathway

## Recurrent Disease

## Primary Treatment

Local Recurrence → Follow Diagnostic Workup, then appropriate Primary Treatment[ee] **(Pages 1- 4)**

Metastatic Disease

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

**Options:**

- Metastasectomy + or – preoperative or postoperatively chemotherapy[v] +or- RT
- Ablation procedures (eg, RFA or cryotherapy)
- Embolization procedures
- SBRT

- Disseminated metastases →

**Palliative Options:**

- Chemotherapy[v]
- RT[dd] /SBRT
- Surgery
- Observation, *if asymptomatic*
- Supportive Care
- Ablation procedures *(RFA, Cryotherapy)*
- Embolization procedures

- Isolated regional disease or nodes →

**Options:**

- Regional node dissection for nodal involvement +or- RT +or- chemotherapy[v]
- SBRT
- Metastasectomy +or- preop or postop chemotherapyw +or- RT
- Isolated limb perfusion/infusion [aa] + surgery

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

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

[dd] 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.

[ee] If local recurrence can be excised, a decision will ned 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.

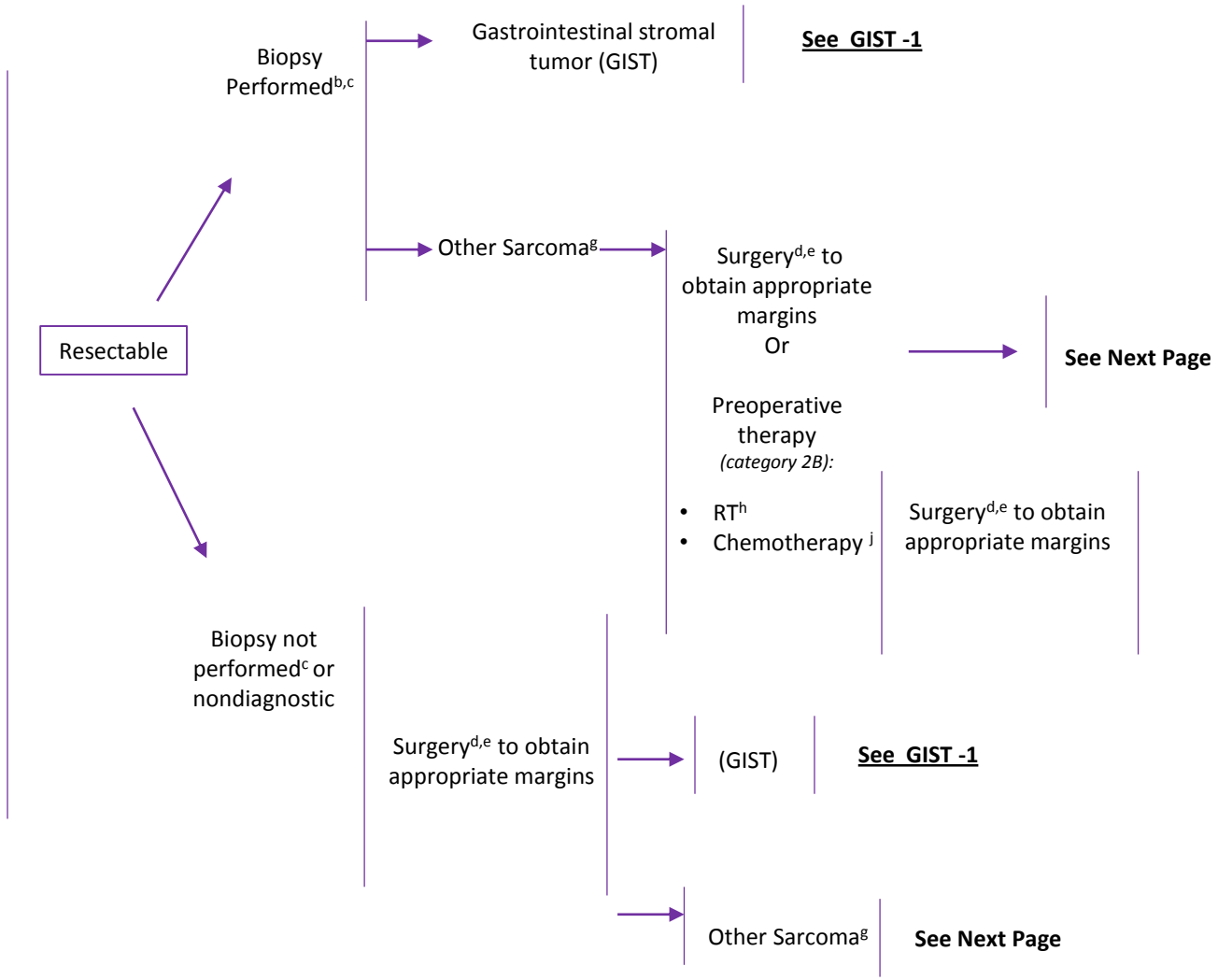
# Soft Tissue Sarcoma Clinical Pathway

## Retroperitoneal/ Intra-Abdominal

# Soft Tissue Sarcoma Clinical Pathway
# Retroperitoneal/ Intra-Abdominal

## Work Up

1. Multidisciplinary Sarcoma Team consult
2. H&P
3. Imaging [a]
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[a] Core needle biopsy is preferred over open surgical biopsy[b]
7. Patients with personal/family history suggestive of Li-Fraumeni syndrome should be considered for further genetics assessment.
8. Patients with neurofibromatosis




[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)

# Soft Tissue Sarcoma Clinical Pathway
# Retroperitoneal/ Intra-Abdominal

## Surgical Outcomes/Clinical Pathologic Findings

**R0**

Post-op RT should not be administered routinely with the exception of highly selected patients and unless local recurrence would cause undue morbidity[h,j]

**R1**

Post-op RT should not be administered routinely with the exception of highly selected patients and unless local recurrence would cause undue morbidity[h,j]

Or

In highly selected cases, consider boost (10-16 Gy) if preoperative RT was given

**R2**

Consider re-resection if technically feasible or
**See Primary Treatment Unresectable (Next Page))**

## Follow-up

- Physical exam with imaging[a] q 3-6months for 2-3 years, then q 6 months for next 2 years, then annually
- Obtain chest imaging[a]

## Treatment for Recurrent Disease

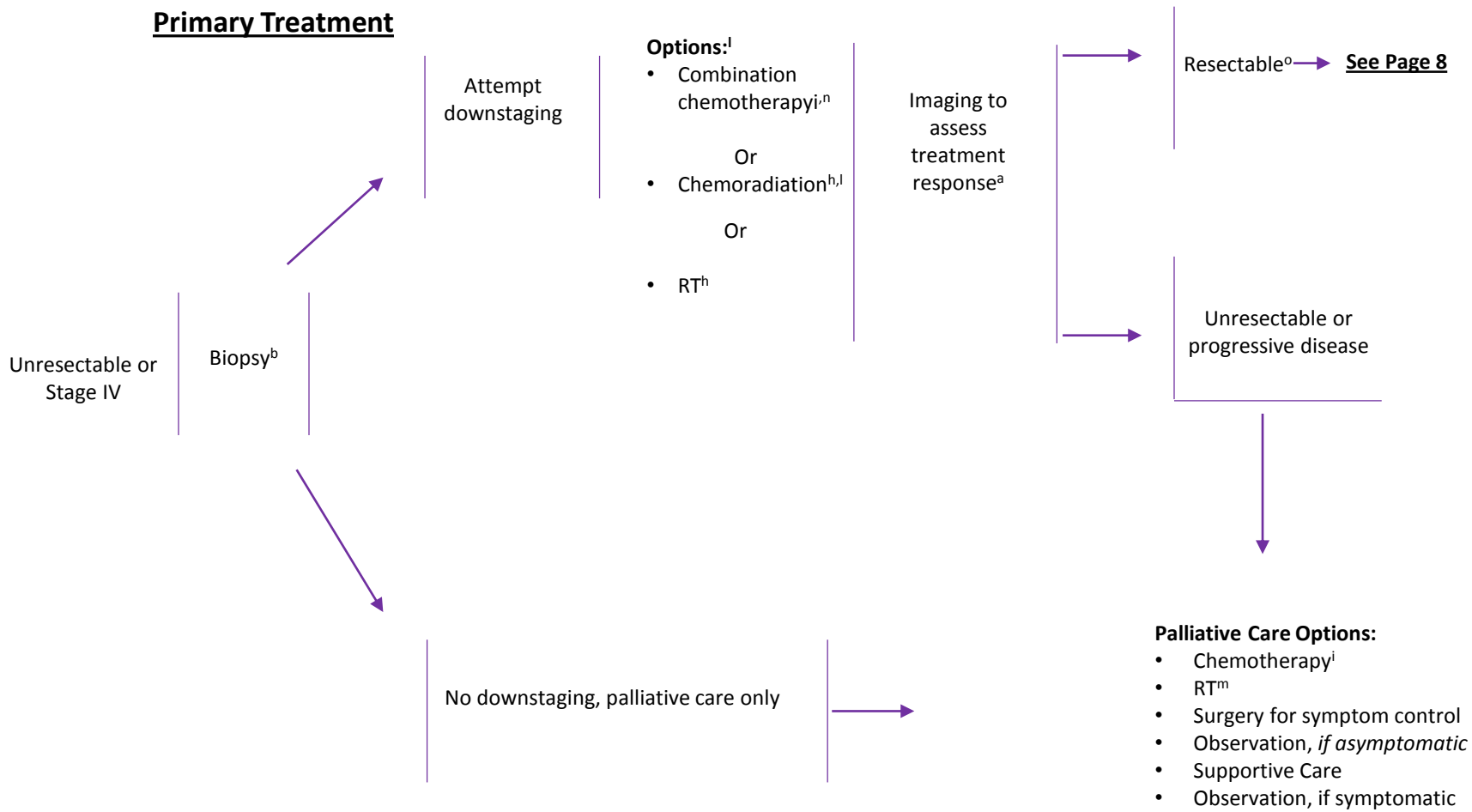
Recurrent Disease

Uresectable or Stage IV/Metastatic disease[k]
**See Next Page**

Resectable[k]
**See page 8**

[a]See Principles of Imaging (SARC-A)
[d]See Principles of Surgery (SARC-D)
[h]See Radiation Therapy Guidelines (SARC-E)
[j] For example, critical anatomic surface where recurrence would cause morbidity.
[k] If not previously administered, consider preoperative RT and/or chemotherapy.

# Soft Tissue Sarcoma Clinical Pathway
# Retroperitoneal/ Intra-Abdominal




[a]See Principles of Imaging (SARC-A)
[b]See Principles of Pathologic Assessment of Sarcoma Specimens (SARC-B)
[h]See Radiation Therapy Guidelines (SARC-E)
[l]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.
[m] 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 patients with unresectable or progressive disease.
[n]The most active chemotherapy in an unselected patient population is AIM (doxorubicin/ifosfamide/mesna) in terms of response rate.
[o] Resection of resectable metastatic disease should always be considered if primary tumor can be controlled.

# Soft Tissue Sarcoma Clinical Pathway

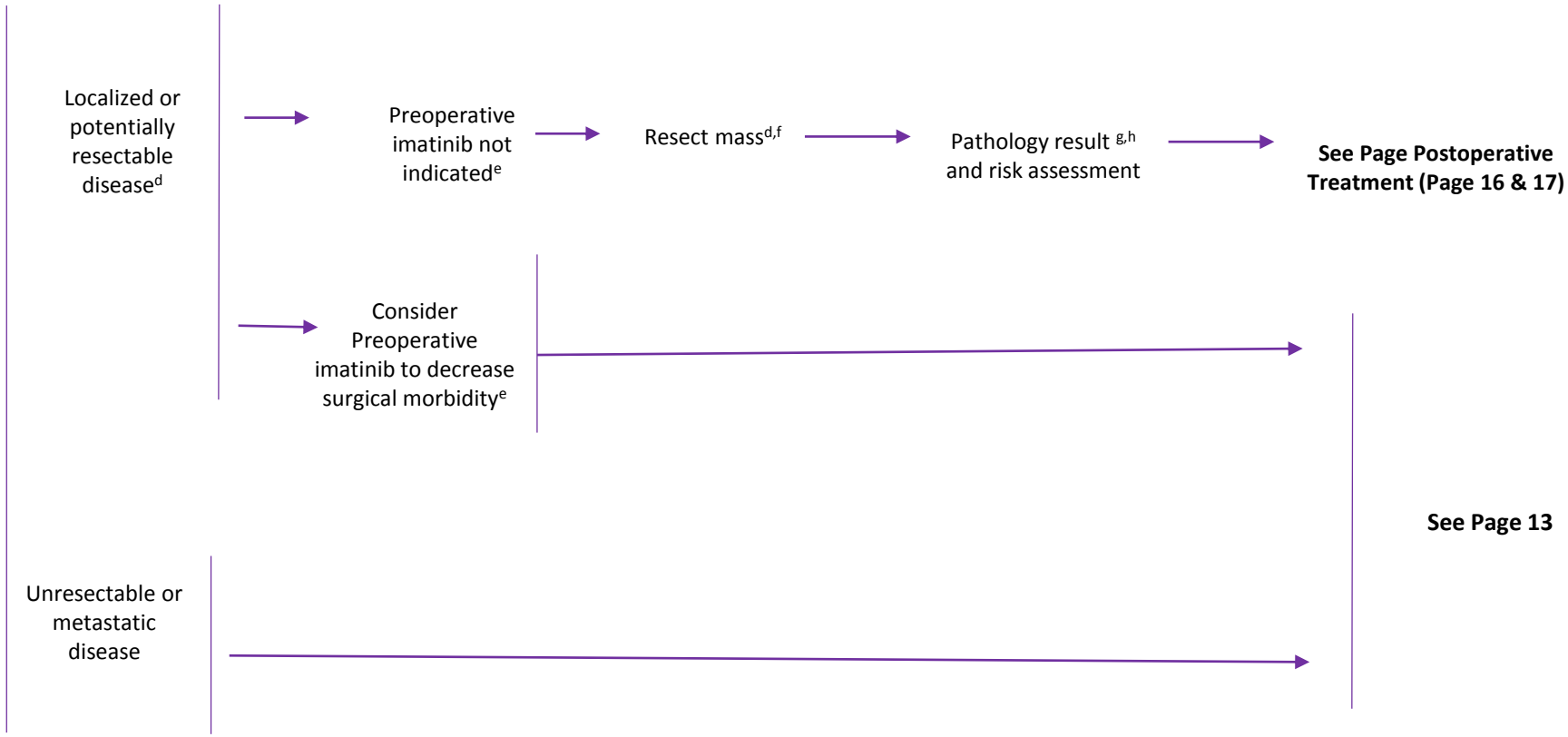
## Gastrointestinal Stromal Tumors (GIST)

# 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[b]
4. Consider mutation testing
   - KIT
   - PDGFRA
5. Consider genotyping

## Results of Initial Diagnostic Evaluation




[aa]See American Joint Committee on Cancer (AJCC) Staging, 8th edition.
[a]See Principles of Imaging (SARC-A).
[C] 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.
[d]Surgery should induce minimal surgical morbidity consider preoperative imatinib if surgery would induce significant morbidity
[e] 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.
[f] See principles of surgery for GIST (GIST-C)
[g]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])
[h]See RETSARC-1 if the pathology results indicate sarcomas of GI origin other than GIST.

# Soft Tissue Sarcoma Clinical Pathway
# GIST

## Work Up At Primary Presentation

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

## Results of Initial Diagnostic Evaluation

- High-risk EUS features[j]
- No high-risk EUS features

## Initial Management

- Complete surgical resection

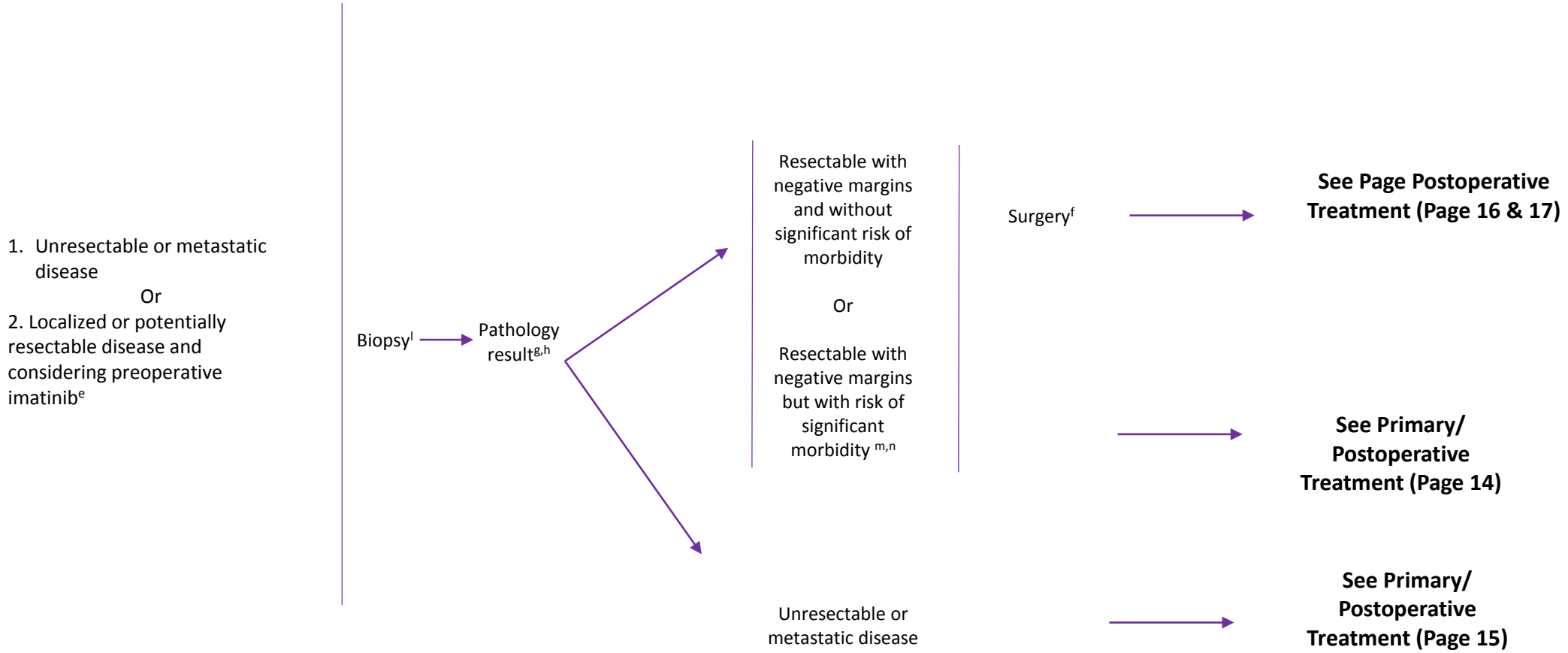
## Follow-Up

- **See Page Postoperative Treatment (Page 16 & 17)**
- **Consider periodic endoscopic surveillance[k]**

[a] See Principles of Imaging (SARC-A).
[i] 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.
[j] Possible high-risk EUC features include irregular border, cystic spaces, ulceration, echogenic foci, and heterogeneity.
[k] Endoscopic ultrasonography surveillance should only be considered after a thorough discussion with the patient regarding the risks and benefits.

# Soft Tissue Sarcoma Clinical Pathway
# GIST

## Initial Diagnostic Evaluation




[e] 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.

[f] See principles of Surgery for GIST (GIST-C)

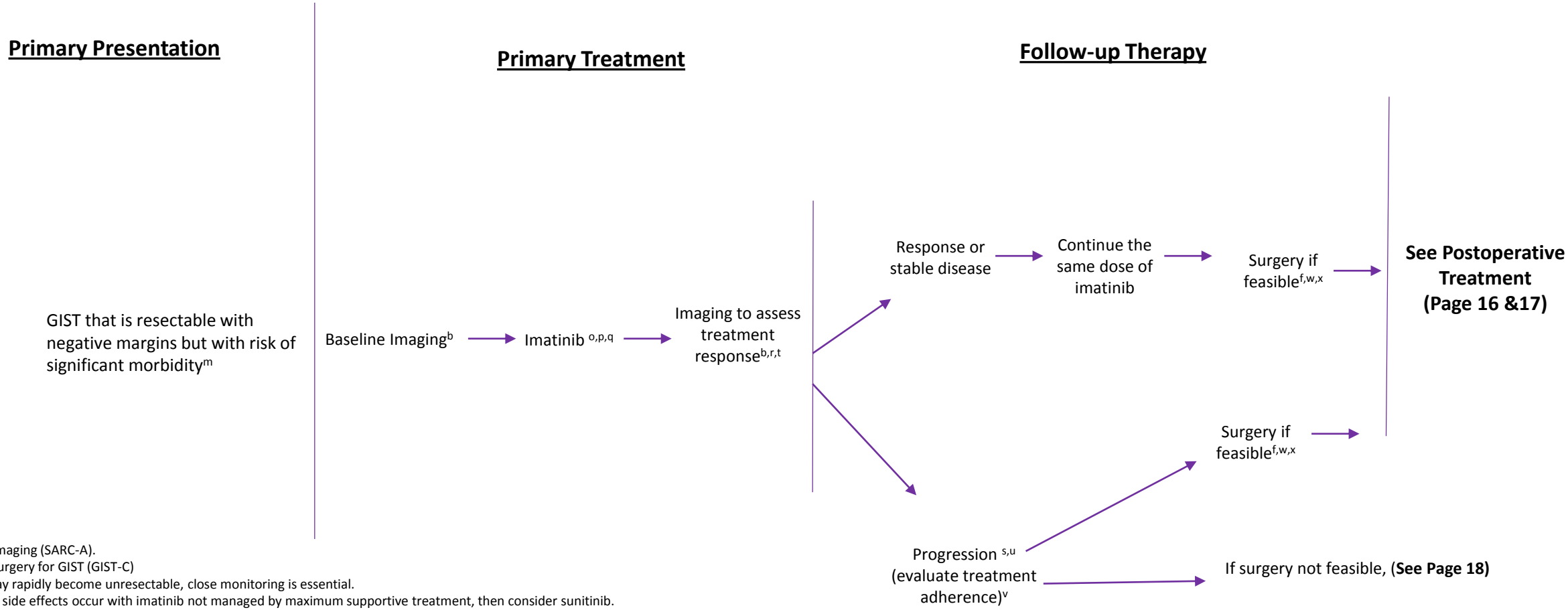
[g] Pathology report should include anatomic location, size, and an accurate assessment of the mitotic rate measured in the most proliferative area of the tumor. Mutational analysis may predict response to therapy with tyrosine kinase inhibitors. (See principles of Pathologic Assessment for GIST [GIST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

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

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

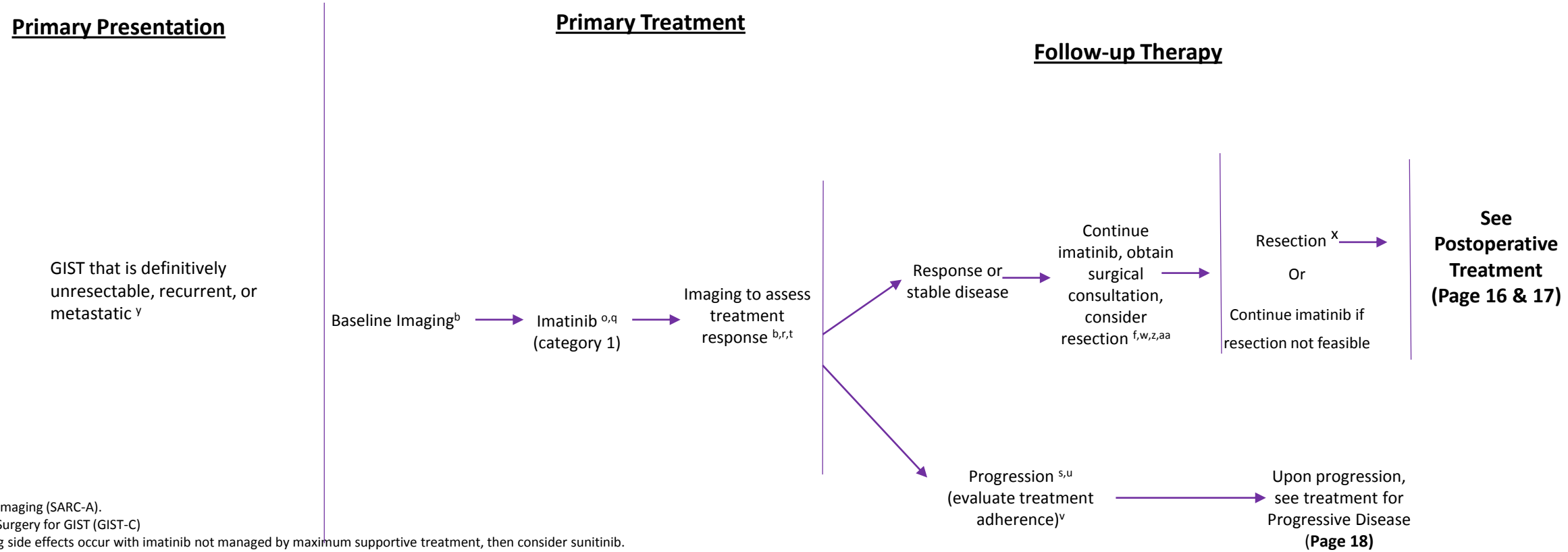
[n] For SDH-deficient GIST extensive surgery with significant morbidity (i.e. total gastrectomy) is not recommended.

# Soft Tissue Sarcoma Clinical Pathway
# GIST



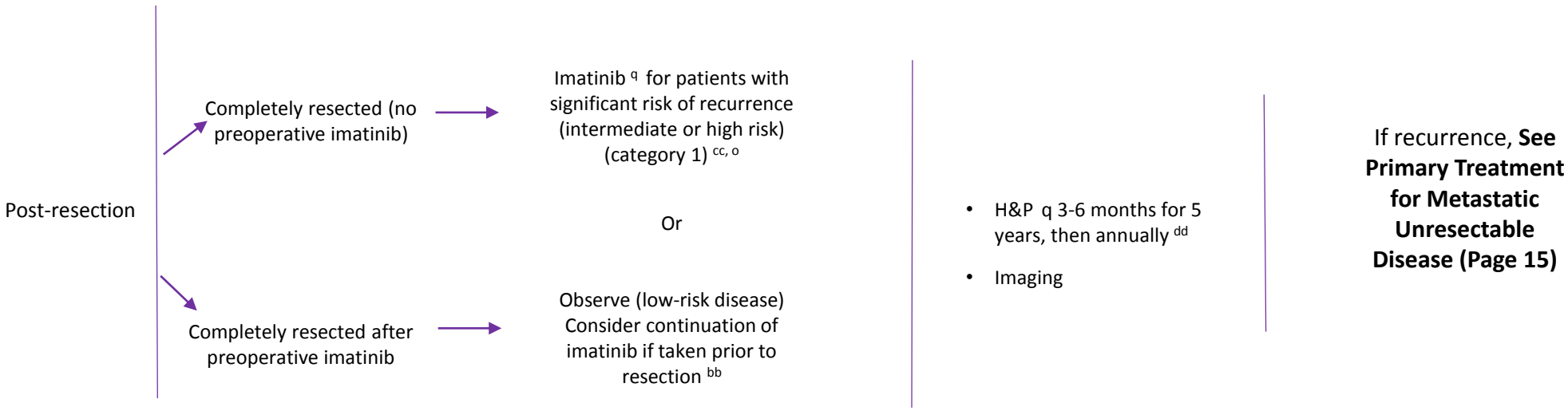

[b]See Principles of Imaging (SARC-A).
[c]See principles of Surgery for GIST (GIST-C)
[m] Some patients may rapidly become unresectable, close monitoring is essential.
[o] If life-threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider sunitinib.
[p] Medical therapy is the usual course of treatment. However, patient may proceed to surgery if bleeding or symptomatic.
[q]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 sunitib.
[F] 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.
[s] 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.
[t] 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 ambigious.
[u] Suggest referral to a sarcoma specialty center.
[v] Assess medication adherence before determining that therapy was ineffective.
[w]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.
[x]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 sunitib 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.

# Soft Tissue Sarcoma Clinical Pathway
# GIST



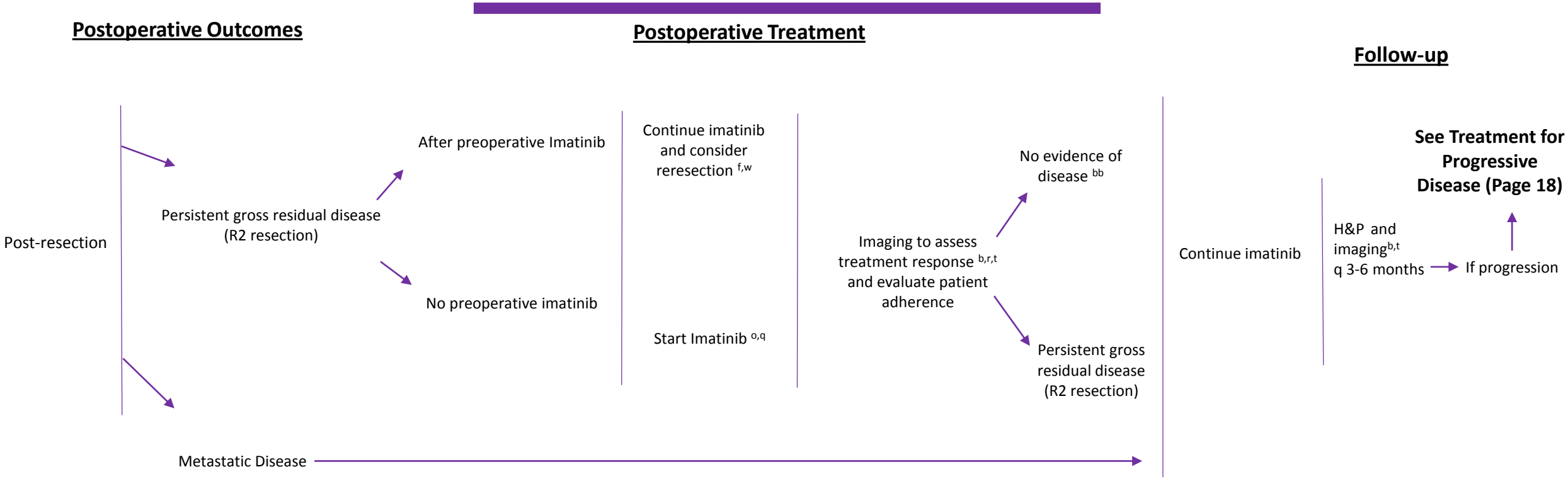

[b] See Principles of Imaging (SARC-A).
[c] See principles of Surgery for GIST (GIST-C)
[O] If life-threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider sunitinib.
[P] Medical therapy is the usual course of treatment. However, patient may proceed to surgery if bleeding or symptomatic.
[q] 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 sunitib.
[F] 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.
[S] 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.
[t] 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 ambigious.
[U] Suggest referral to a sarcoma specialty center.
[V] Assess medication adherence before determining that therapy was ineffective.
[W] 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.
[X] 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 sunitib 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.
[Z] 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.
[aa] Consider resection if complete resection can be obtained in primary metastatic disease.

# Soft Tissue Sarcoma Clinical Pathway
# GIST




[b]See Principles of Imaging (SARC-A).
[f]See principles of Surgery for GIST (GIST-C)
[O] If life-threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider sunitinib.
[q] 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 sunitib.
[r] 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.
[t] 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.
[w] 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.
[bb] 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.
[cc] Postoperative imatinib for at least 36 months should be considered for high-risk tumors. The results of a randomized trial (SSGXVIII/AIO) suggest that postoperative imatinib administered for 36 months improves relapse-free survival and overall survival compared to 12 months for patients with a high estimated risk of recurrence (tumor greater than 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.
[dd] Less frequent may be acceptable for very small tumors (<2cm).

# Soft Tissue Sarcoma Clinical Pathway
# GIST




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

[f] See principles of Surgery for GIST (GIST-C)

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

[q] 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 sunitib.

[r] 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.

[t] 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.

[w] 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.

[bb] 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.

[cc] Postoperative imatinib for at least 36 months should be considered for high-risk tumors. The results of a randomized trial (SSGXVIII/AIO) suggest that postoperative imatinib administered for 36 months improves relapse-free survival and overall survival compared to 12 months for patients with a high estimated risk of recurrence (tumor greater than 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.

[dd] Less frequent may be acceptable for very small tumors (<2cm).

# Soft Tissue Sarcoma Clinical Pathway
# GIST

## Treatment for Progressive Disease

Progression

→ Limited

- Continue with the same does of imatinib and consider the following options for progression lesions:
  - Resection [f], if feasible [w]
  - RFA of embolization or chemoembolization *(category 2B)*
  - Palliative RT *(category 2B)* for rare patients with bone metastases
- Dose escalation of imatinib [ee] as tolerated
- Change to sunitinib [ee]
- Imaging to reassess therapeutic response [b,t]

→ Generalized (widespread, systemic)

For performance status (PS) 0-2:

- Dose Escalation of imatinib [ee] as tolerated
- Change to sunitinib [ee] (category 1)
- Imaging to reassess therapeutic response [b,t]

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

[b]See Principles of Imaging (SARC-A).
[f]See principles of Surgery for GIST (GIST-C)
[s] 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.
[t] 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.
[u] Suggest referral to a sarcoma specialty center.
[w] 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.
[ee] Clinical 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.
[ff] In 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


1. Kelly K Curtis , Jonathan B Ashman , Christopher P Beauchamp, Adam J Schwartz, Matthew D Callister, Amylou C Dueck, Leonard L Gunderson and Tom R Fitch. 2011. Neoadjuvant chemoradiation compared to neoadjuvant radiation alone and surgery alone for Stage II and III soft tissue sarcoma of the extremities. *Radiation Oncology.*
2. Sandro Pasquall, Alessandro Gronchi. 2017. Neoadjuvant chemotherapy in soft tissue sarcomas: latest evidence and clinical implications. *Therapeutic Advances in Medical Oncology.*
3. Adam Dangoor, Beatrice Seddon, Craig Gerrand, Robert Grimer, Jeremy Whelan and Ian Judson. 2016. UK guidelines for the management of soft tissue sarcomas. *Clinical Sarcoma Research.*
4. NCCN Guidelines. October 2017 Version. Soft Tissue Sarcoma.
5. A. Lo´pez-Pousa, J. Martin Broto, J. Martinez Trufero, I. Sevilla, C. Valverde, R. Alvarez, J. A. Carrasco Alvarez, J. Cruz Jurado, N. Hindi, X. Garcia del Muro. 2016. SEOM Clinical Guideline of management of soft-tissue sarcoma .*Clinical Guides in Oncology.*
6. The ESMO/Europeran Sarcoma Network Working Group. 2014. Soft tissue and visceral sarcomas. ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *ESMO.*
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.*
8. Thomas F. Delaney, M.D., Ira J. Spiro, M.D., PH.D., Herman D. Suit, M.D., D. Phil.,Mark C. Gebhardt, M.D.,Franci J. Hornicek, M.D., PH.D., Henry J. Mankin, M.D., Andrew L. Rosenberg, M.D., Daniel I. Rosenthal, M.D.,Fariba Miryousefi, M.D.,Marcus Ancukiewicz, PH.D., and David C. Harmon, M.D. 2003. Neoadjuvant chemotherapy and Radiotherapy for Large Extremity Soft-tissue Sarcomas. *International Journal Radiation Oncology Biology Physics.*