

**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)**

# **Soft Tissue Sarcoma**

Version 2.2011

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## Soft Tissue Sarcoma

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**Bone Sarcomas** - [See the NCCN Bone Cancer Guidelines](#)

**Uterine Sarcomas** - [See the NCCN Uterine Cancer Guidelines](#)

**Dermatofibrosarcoma Protuberans** - [See the NCCN Dermatofibrosarcoma Protuberans Guidelines](#)

**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 2.2011 of the NCCN Guidelines™ for Soft Tissue Sarcoma from version 1.2011 include:

### Gastrointestinal Stromal Tumors (GIST)

#### GIST-6

- Previously footnote “y” recommended adjuvant therapy with imatinib for at least 12 months for intermediate to high risk GIST patients. Based on the results of the recently completed randomized trial (SSGXVIII/AIO), footnote “y” was revised as follows: “Adjuvant imatinib for at least **36 months** should be considered for patients with high risk GIST. 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 (Joensuu H, Eriksson M, Hatrman J, et al. Twelve versus 36 months of adjuvant imatinib (IM) as treatment of operable GIST with a high risk of recurrence: Final results of a randomized trial (SSGXVIII/AIO). ASCO Meeting Abstracts 2011;29:LBA1)”.

#### MS-1

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

Updates in version 1.2011 of the NCCN Guidelines™ for Soft Tissue Sarcoma from version 2.2010 include:

### Extremity/Trunk

#### EXTSARC-1

- Workup; PET recommendation: New footnote “g” was added that states, “May be useful for lesions that are larger than 3 cm, firm, and deep, not superficial”.

#### EXTSARC-2

- For Stage IA; Final margins  $\leq$  1.0 cm pathway: Observation was added as an option.
- For Stage IB; Final margins  $\leq$  1.0 cm pathway: “RT (category 1)” changed to “**Consider** RT (category 1)”.
- Follow-up; Fourth bullet: Changed to “Consider obtaining **postoperative** baseline...” (Also for [EXTSARC-3](#), [EXTSARC-5](#))

#### EXTSARC-3

- Resectable with acceptable functional outcomes pathway: After surgery, the treatment recommendation “RT  $\pm$  adjuvant chemotherapy” was clarified as “category 2B for adjuvant chemotherapy”.
- Footnote “o” that states, “Stage III tumors with lymph node involvement should undergo regional lymph node dissection at the time of primary tumor resection  $\pm$  RT” is new to the algorithm.

### Extremity/Trunk---continued

#### EXTSARC-4

- Algorithm was revised extensively, including deletion of pathways.
- Unresectable primary disease; Primary treatment: Limb perfusion was added as a treatment option with corresponding footnote “v” that states, “Should only be done at institutions with experience in limb perfusion therapy.
- Follow-up; Last bullet: After “Consider obtaining baseline and periodic imaging of primary site,” the following recommendation was removed “based on estimated risk of locoregional recurrence”.

#### EXTSARC-5

- Single organ and limited tumor bulk were clarified as “that are amenable to complete resection”.
  - ▶ Primary treatment: Chemotherapy and Observation were added as options. “Regional node dissection for nodal involvement  $\pm$  RT” was removed as an option.



### Retroperitoneal/Intra-abdominal

#### RETSARC-1

- **Workup:** “Chest imaging” was removed as a separate bullet, but is now included as part of the third bullet. “Endoscopy as indicated” was removed as an option.

#### RETSARC-2

- **Biopsy performed; Other sarcoma:** Treatment option changed to “Surgery ± IORT or Preoperative therapy...”.
- **Footnote “d”** that states, “IORT may be considered provided frozen section pathology can confidently demonstrate a non-GIST/non-desmoid histology,” is new to the algorithm.

#### RETSARC-3

- **After R0,** the Low grade and High grade pathways were removed.
- **R1; Postoperative therapy:** Recommendations changed to “Consider postoperative RT (category 2B), if no preoperative RT or Consider boost (10-16 Gy)”.
- **Footnote “g”** is new to the algorithm.
- **Footnote “h”** was revised to include high grade tumors.

### Gastrointestinal Stromal Tumors (GIST)

#### GIST-1

- **Workup; Second bullet:** “All patients should be managed by a multidisciplinary team...” changed to “All patients should be evaluated by a multidisciplinary team...”

#### GIST-6

- **Footnote y:** The first sentence was clarified as “Adjuvant therapy for at least 12 months should be considered in patients with intermediate to high risk GIST to decrease the risk of recurrence”. The following statement was added “Studies are ongoing to assess the impact on overall survival from adjuvant therapy”.

### Desmoid Tumors (Fibromatosis) (DESM-1, DESM-2, DESM-3)

- This algorithm was extensively revised. After “Resectable” two pathways were added for “Observation” and “Treatment”.
- Footnotes “c” and “g” are new to the algorithm.

### SARC-B Principles of Ancillary Techniques Useful in the Diagnosis of Sarcomas

- Page was revised to update gene names and translocations.

### SARC-C Principles of Surgery

- **Resection Margins:** “1 < cm” was removed from the statement, “Consideration for adjuvant radiation therapy should be given for a close (< 1 cm) soft tissue margin...”

### SARC-D Guidelines for Radiation Therapy

- **Brachytherapy implant pathway; Negative margins:** “or high dose equivalent” with corresponding footnote “4” was added as an option.
- **Footnote “7”** is new to the algorithm.



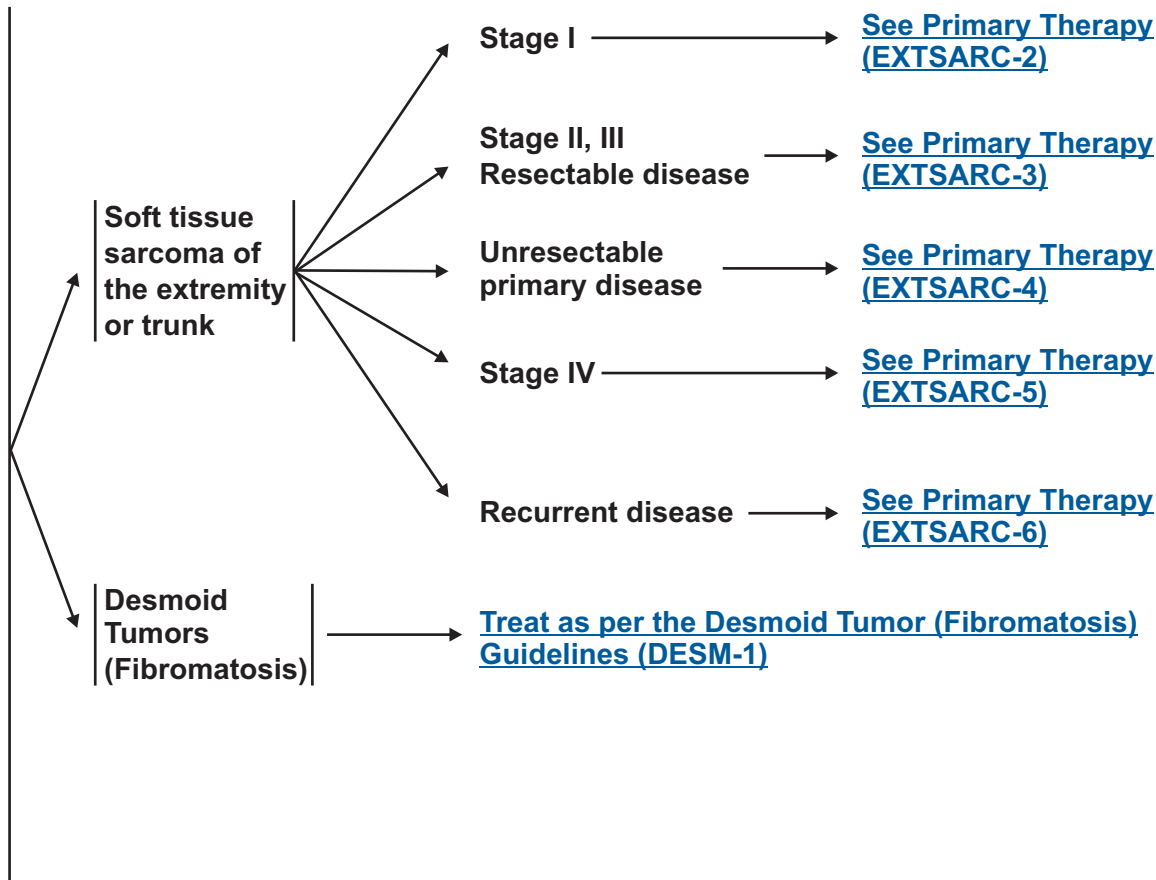
**WORKUP**

**ESSENTIAL:**

- All patients should be managed by a multidisciplinary team with expertise in sarcoma
- H&P
- Adequate imaging<sup>a</sup> of primary tumor is indicated for all lesions with a reasonable chance of being malignant (MRI ± CT)<sup>b</sup>
  - ▶ 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)<sup>c</sup>
  - ▶ Biopsy should establish grade and histologic subtype<sup>d</sup>
  - ▶ Appropriate use of ancillary diagnostic methodologies<sup>e</sup>
- Chest imaging

**USEFUL UNDER CERTAIN CIRCUMSTANCES:<sup>f</sup>**

- PET scan may be useful in prognostication, grading and determining response to chemotherapy<sup>g</sup>
- 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



<sup>a</sup>Adequate imaging should provide details about the size of tumor and contiguity to nearby visceral structures and neurovascular landmarks.

<sup>b</sup>CT angiogram may be useful for patients in whom an MRI is not feasible.

<sup>c</sup>In selected institutions with clinical and pathologic expertise, an FNA may be acceptable.

<sup>d</sup>[See Principles of Pathologic Assessment of Sarcoma Specimens \(SARC-A\).](#)

<sup>e</sup>[See Principles of Ancillary Techniques Useful in the Diagnosis of Sarcomas \(SARC-B\).](#)

<sup>f</sup>Different sub-types have different propensities to spread to various locations and imaging should be individualized based upon sub-types.

<sup>g</sup>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).

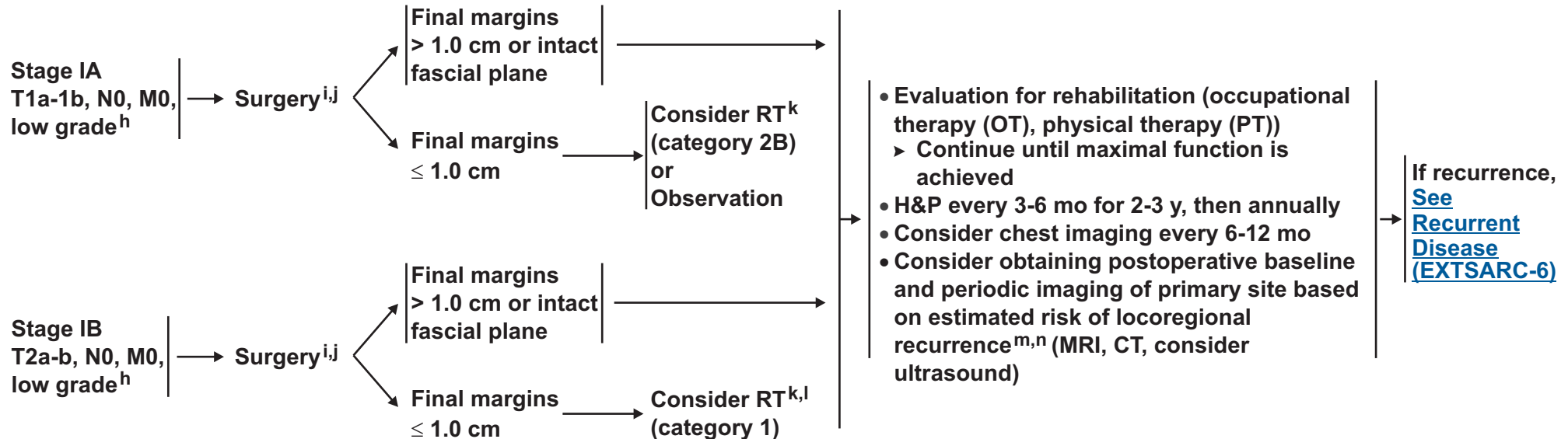
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**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



**PRIMARY  
TREATMENT**

**FOLLOW-UP**



<sup>h</sup>See American Joint Committee on Cancer (AJCC) Staging, 7th Edition ([ST-1](#)).

<sup>i</sup>See [Principles of Surgery \(SARC-C\)](#).

<sup>j</sup>Reresection, if feasible, may be necessary to render margins > 1.0 cm.

<sup>k</sup>See [Guidelines for Radiation Therapy \(SARC-D\)](#).

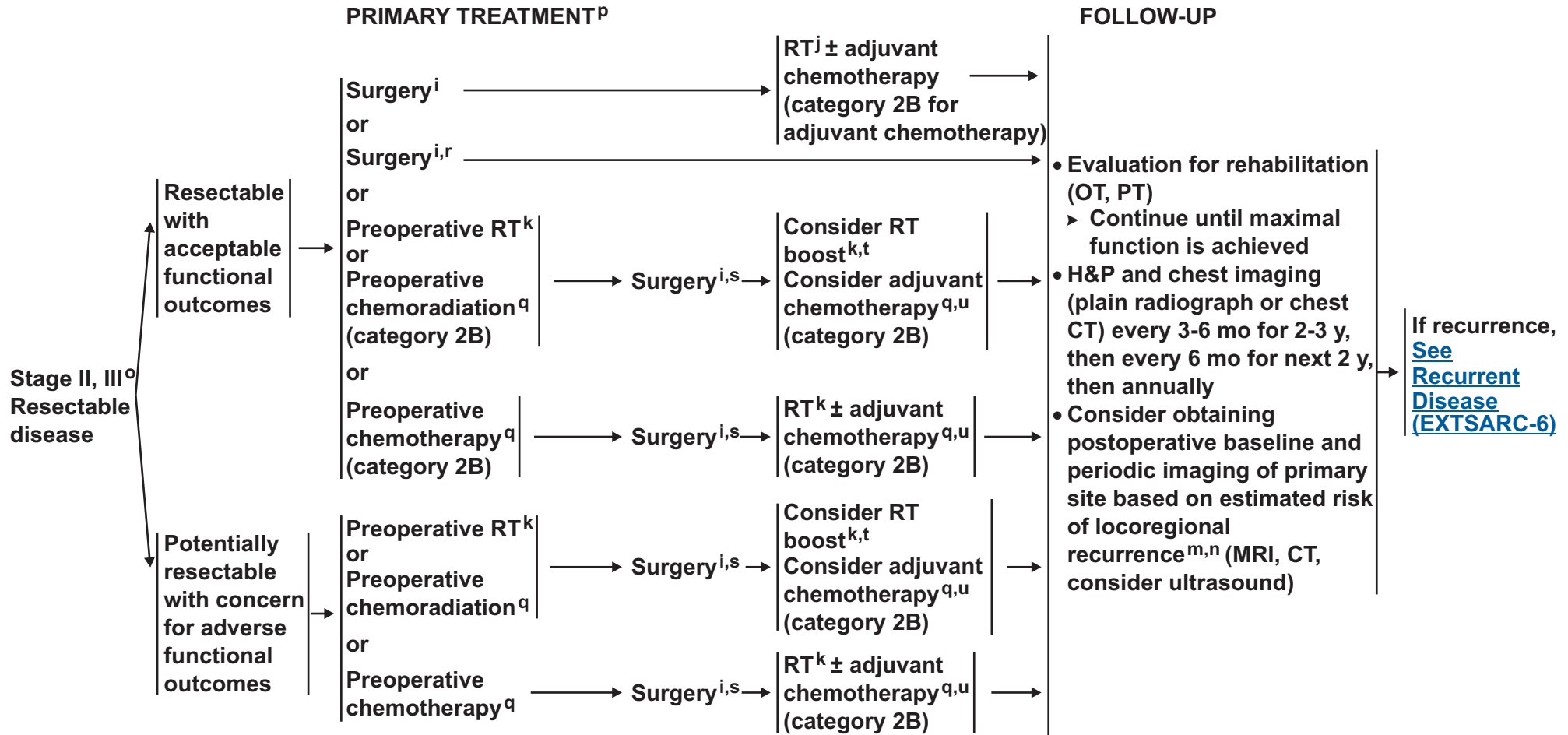
<sup>l</sup>Randomized clinical trial data support the use of radiation therapy (category 1) as an adjunct to surgery in appropriately selected patients based on an improvement in disease-free survival (although not overall survival).

<sup>m</sup>In situations where the area is easily followed by physical examination, imaging may not be required.

<sup>n</sup>After 10 y, the likelihood of developing a recurrence is small and follow-up should be individualized.

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<sup>i</sup>See Principles of Surgery (SARC-C).

<sup>k</sup>See Principles of Radiation Therapy (SARC-D).

<sup>m</sup>In situations where the area is easily followed by physical examination, imaging may not be required.

<sup>n</sup>After 10 y, the likelihood of developing a recurrence is small and follow-up should be individualized.

<sup>o</sup>Stage III tumors with lymph node involvement should undergo regional lymph node dissection at the time of primary tumor resection ± RT.

<sup>P</sup>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.

<sup>q</sup>See Principles of Systemic Therapy (SARC-E).

<sup>r</sup>Surgery alone may be an option for small tumors resected with wide margins.

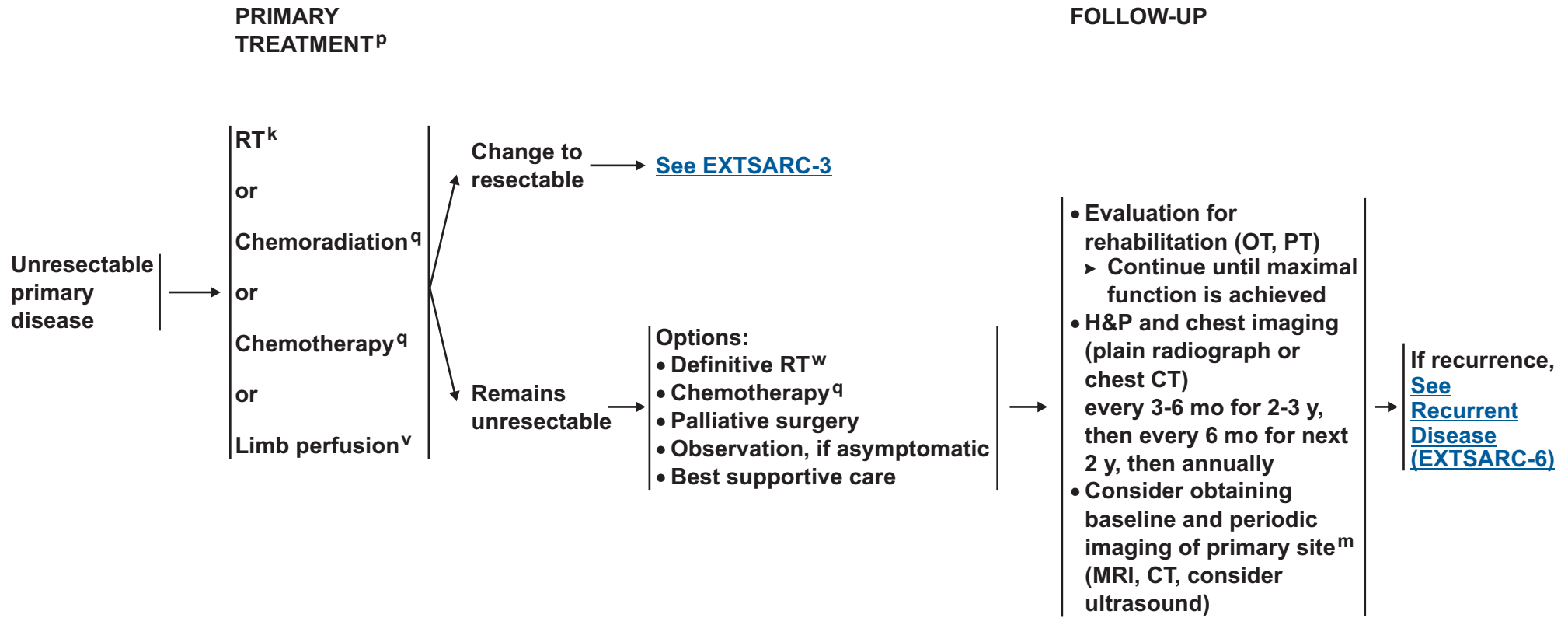
<sup>s</sup>Consider re-imaging to assess primary tumor and to rule out metastatic disease.

<sup>t</sup>For residual gross disease or microscopically positive margins.

<sup>u</sup>There are limited and conflicting data regarding the potential benefits of adjuvant chemotherapy in stage II or stage III patients.

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<sup>k</sup>See [Principles of Radiation Therapy \(SARC-D\)](#).

<sup>m</sup>In situations where the area is easily followed by physical examination, imaging may not be required.

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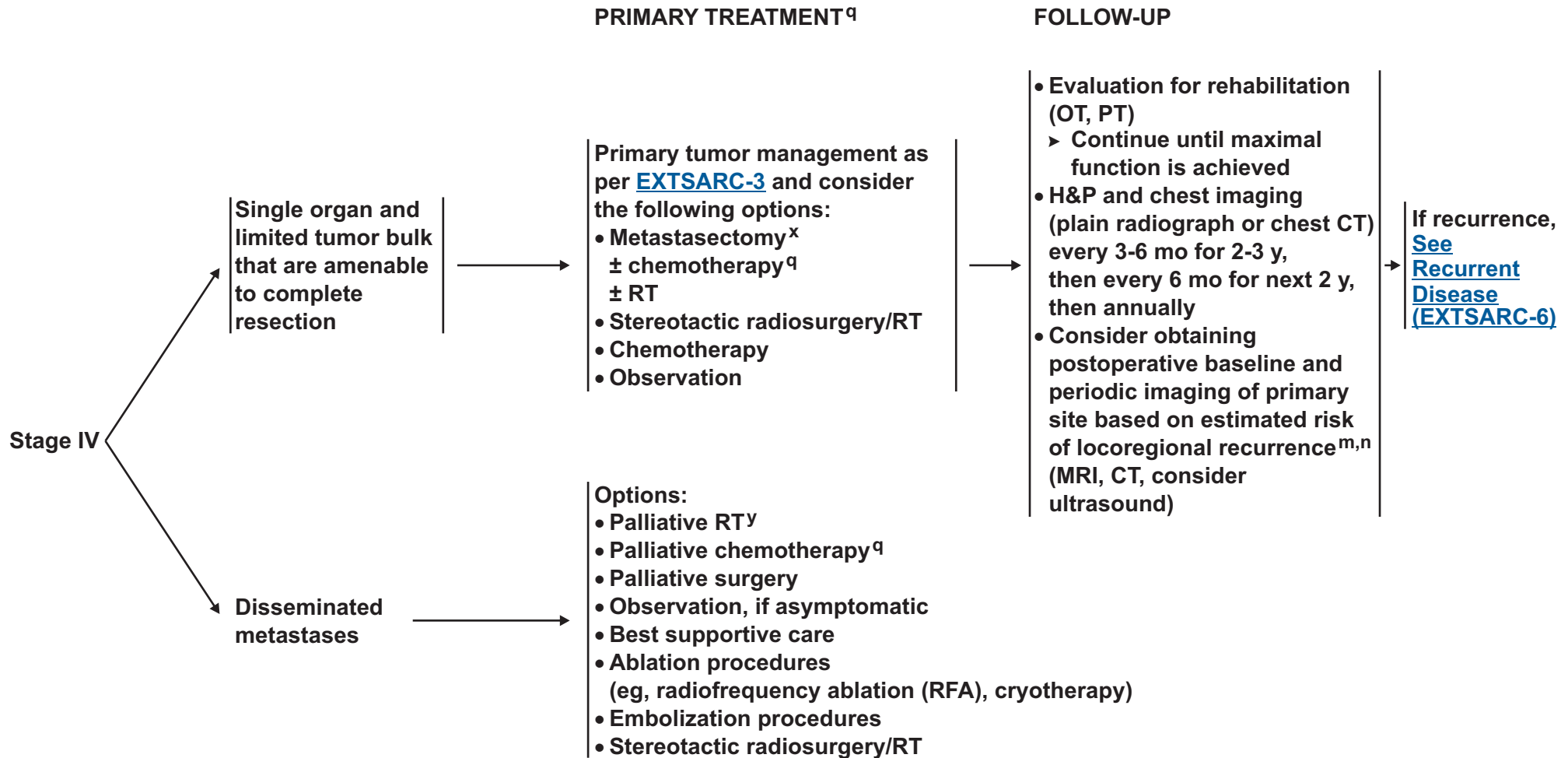
<sup>q</sup>See [Principles of Systemic Therapy \(SARC-E\)](#).

<sup>v</sup>Should only be done at institutions with experience in limb perfusion therapy.

<sup>w</sup>Definitive RT entails delivering the maximal local dose compatible with known normal tissue tolerance, typically in the range of 7000-8000cGy with sophisticated treatment planning techniques being a necessity in this setting.

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<sup>m</sup>In situations where the area is easily followed by physical examination, imaging may not be required.

<sup>n</sup>After 10 y, the likelihood of developing a recurrence is small and follow-up should be individualized.

<sup>q</sup>[See Principles of Systemic Therapy \(SARC-E\).](#)

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

<sup>y</sup>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.

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### RECURRENT DISEASE

### TREATMENT

Local  
recurrence

Follow Workup, then  
appropriate Primary Therapy  
pathway ([EXTSARC-1](#),  
[EXTSARC-2](#), and [EXTSARC-3](#))

Metastatic  
disease

Single organ and  
limited tumor bulk  
or regional nodes

Options:

- Regional node dissection for nodal involvement ± RT
- Metastasectomy<sup>x</sup> ± preoperative or postoperative chemotherapy<sup>q</sup> ± RT
- Ablation procedures (eg, RFA or cryotherapy)
- Embolization procedures
- Stereotactic radiosurgery/RT

Disseminated  
metastases

Options:

- Palliative RT<sup>y</sup>
- Palliative chemotherapy<sup>q</sup>
- Palliative surgery
- Observation, if asymptomatic
- Best supportive care
- Ablation procedures (eg, RFA or cryotherapy)
- Embolization procedures
- Stereotactic radiosurgery/RT

<sup>q</sup>See [Principles of Systemic Therapy \(SARC-E\)](#).

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

<sup>y</sup>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.

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### 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)<sup>a</sup>

Resectable

[See Primary Treatment \(RETSARC-2\)](#)

Unresectable  
or  
Stage IV

[See Primary Treatment \(RETSARC-4\)](#)

<sup>a</sup>[See Principles of Pathologic Assessment of Sarcoma Specimens \(SARC-A\).](#)

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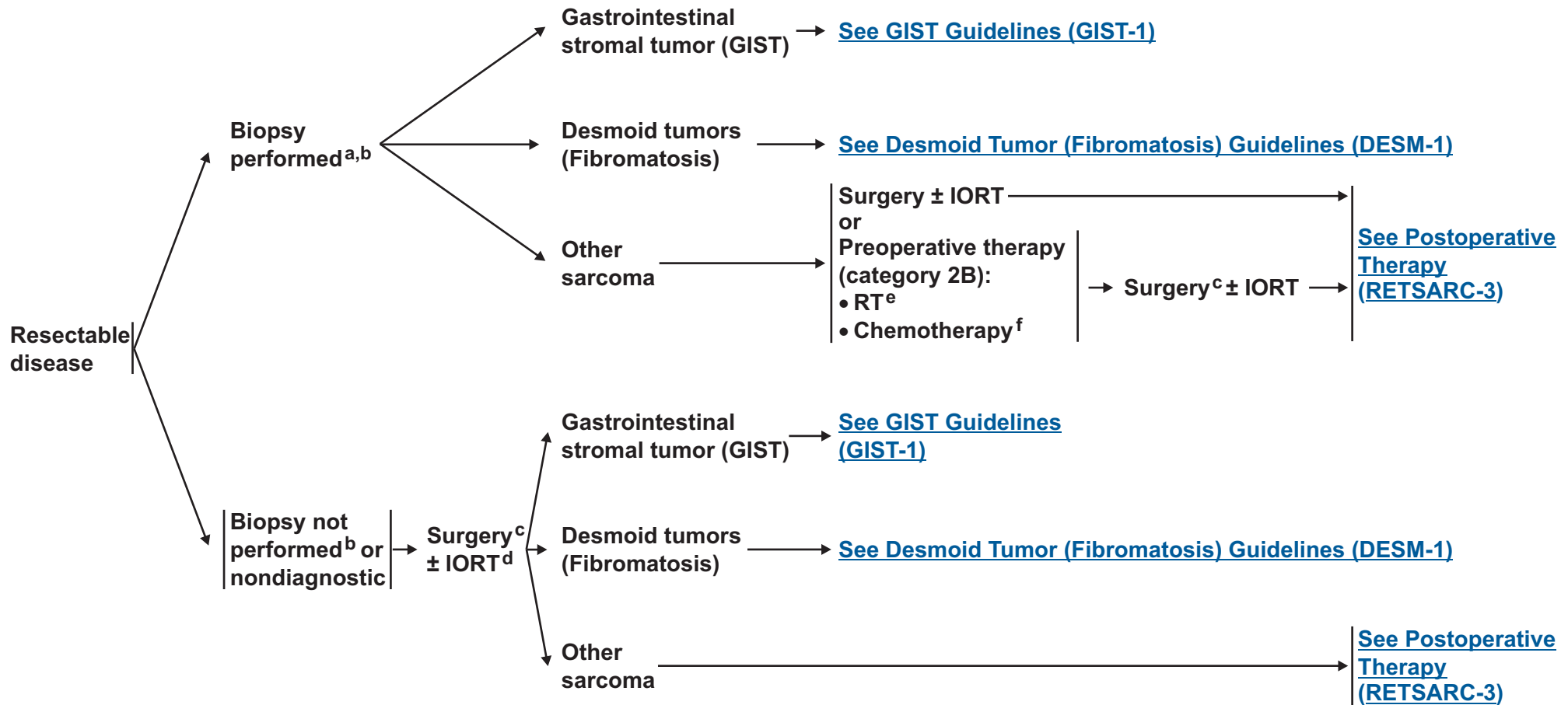
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# NCCN Guidelines™ Version 2.2011

## Retroperitoneal/Intra Abdominal

### PRIMARY TREATMENT



<sup>a</sup>See [Principles of Pathologic Assessment of Sarcoma Specimens \(SARC-A\)](#).

<sup>b</sup>Biopsy required if considering preoperative therapy, including endoscopic biopsy for suspected GIST lesions.

<sup>c</sup>See [Principles of Surgery \(SARC-C\)](#).

<sup>d</sup>IORT may be considered provided frozen section pathology can confidently demonstrate a non-GIST/non-desmoid histology.

<sup>e</sup>See [Guidelines for Radiation Therapy \(SARC-D\)](#).

<sup>f</sup>See [Principles of Systemic Therapy \(SARC-E\)](#).

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SURGICAL OUTCOMES/CLINICAL PATHOLOGICAL FINDINGS <sup>c</sup>	POSTOPERATIVE THERAPY	FOLLOW-UP
R0	Consider postoperative RT <sup>e,g</sup> in highly selected patients <sup>h</sup> (category 2B)	<ul style="list-style-type: none"> <li>Physical exam with imaging (abdominal/pelvic CT) every 3-6 mo for 2-3 y, then annually</li> <li>Consider chest imaging</li> </ul>
R1	Consider postoperative RT <sup>e</sup> (category 2B) if no preoperative RT or Consider boost (10-16 Gy)	<ul style="list-style-type: none"> <li>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</li> <li>Consider chest imaging</li> </ul>
R2	<a href="#">See Primary Treatment (Unresectable) (RETSARC-4)</a>	

[Recurrent Disease \(see RETSARC-5\)](#)

<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.

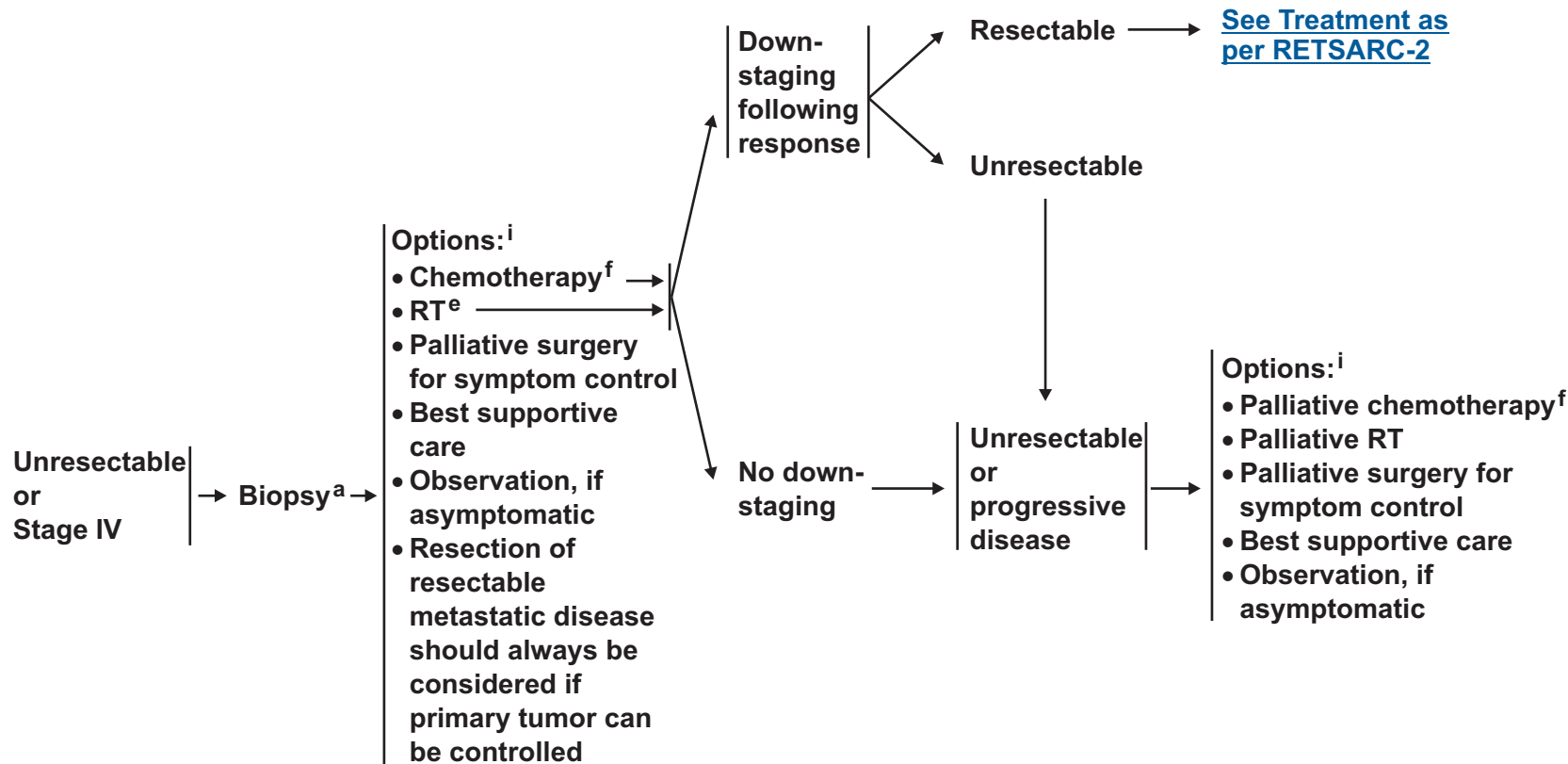
<sup>h</sup>For example, patients with high grade tumors, an extremely large tumor, critical anatomic surface where recurrence would cause morbidity, or close margins.

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**PRIMARY TREATMENT**



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<sup>e</sup>See [Guidelines for Radiation Therapy \(SARC-D\)](#).

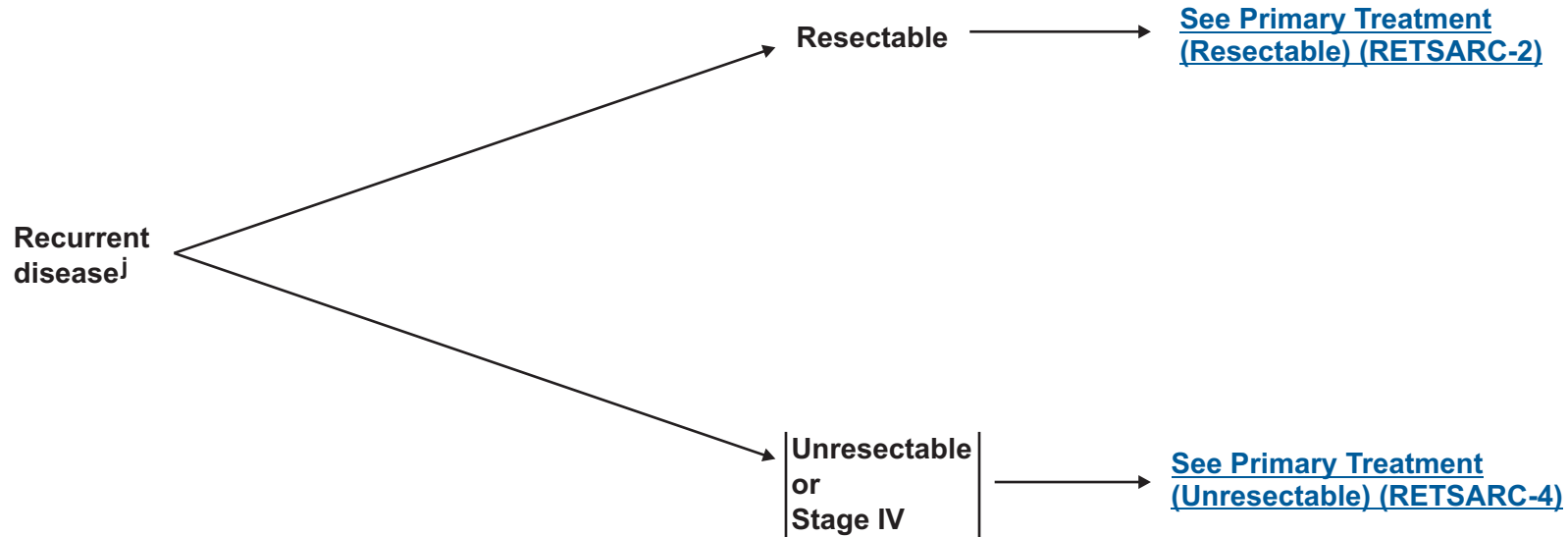
<sup>f</sup>See [Principles of Systemic Therapy \(SARC-E\)](#).

<sup>i</sup>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.

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### RECURRENT DISEASE



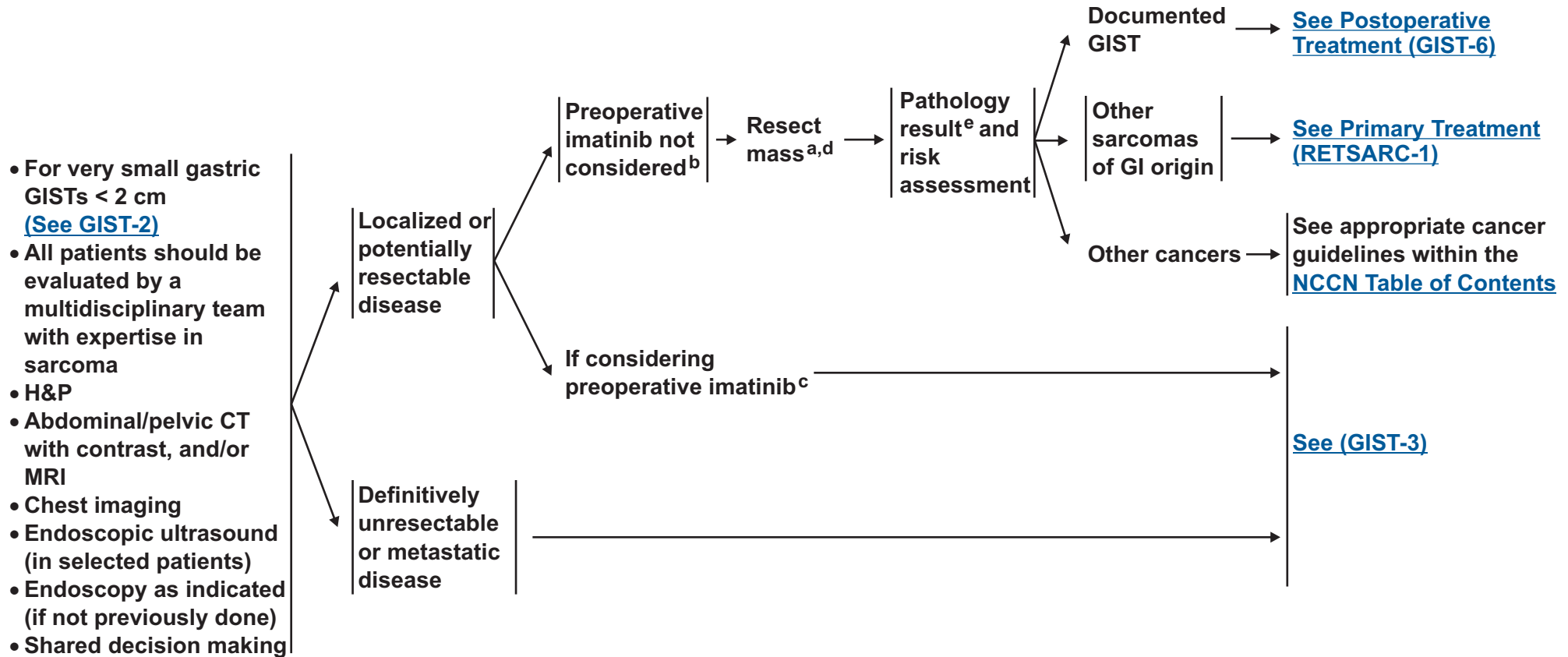
<sup>j</sup>Consider preoperative RT and/or chemotherapy if not previously administered.

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**WORKUP OF PATIENT AT  
PRIMARY PRESENTATION**

**INITIAL DIAGNOSTIC EVALUATION**



<sup>a</sup>Surgery should induce minimal surgical morbidity, otherwise consider preoperative imatinib.

<sup>b</sup>If surgical morbidity would not improve by reducing the size of the tumor preoperatively.

<sup>c</sup>If surgical morbidity would be improved by reducing the size of the tumor preoperatively.

<sup>d</sup>[See Principles of Surgery For GIST \(GIST-C\)](#).

<sup>e</sup>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 kinase inhibitors. ([See Principles of Pathologic Assessment For GIST \[GIST-B\]](#))

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**APPROACH TO PATIENTS WITH VERY SMALL GASTRIC GISTS (< 2 CM)<sup>f</sup>**

**WORKUP OF PATIENT AT  
PRIMARY PRESENTATION**

**RESULTS OF INITIAL  
DIAGNOSTIC EVALUATION**

**INITIAL MANAGEMENT**

**FOLLOW-UP**

- Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA)
- Abdominal/pelvic CT with contrast

**High-risk EUS features<sup>g</sup>**

**Complete surgical resection**

**Consider abdominal/pelvic CT with contrast every 3-6 months for 3-5 years, then annually**

**No High-risk EUS features**

**Consider endoscopic surveillance<sup>h</sup> (6 -12 month intervals)**

<sup>f</sup>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.

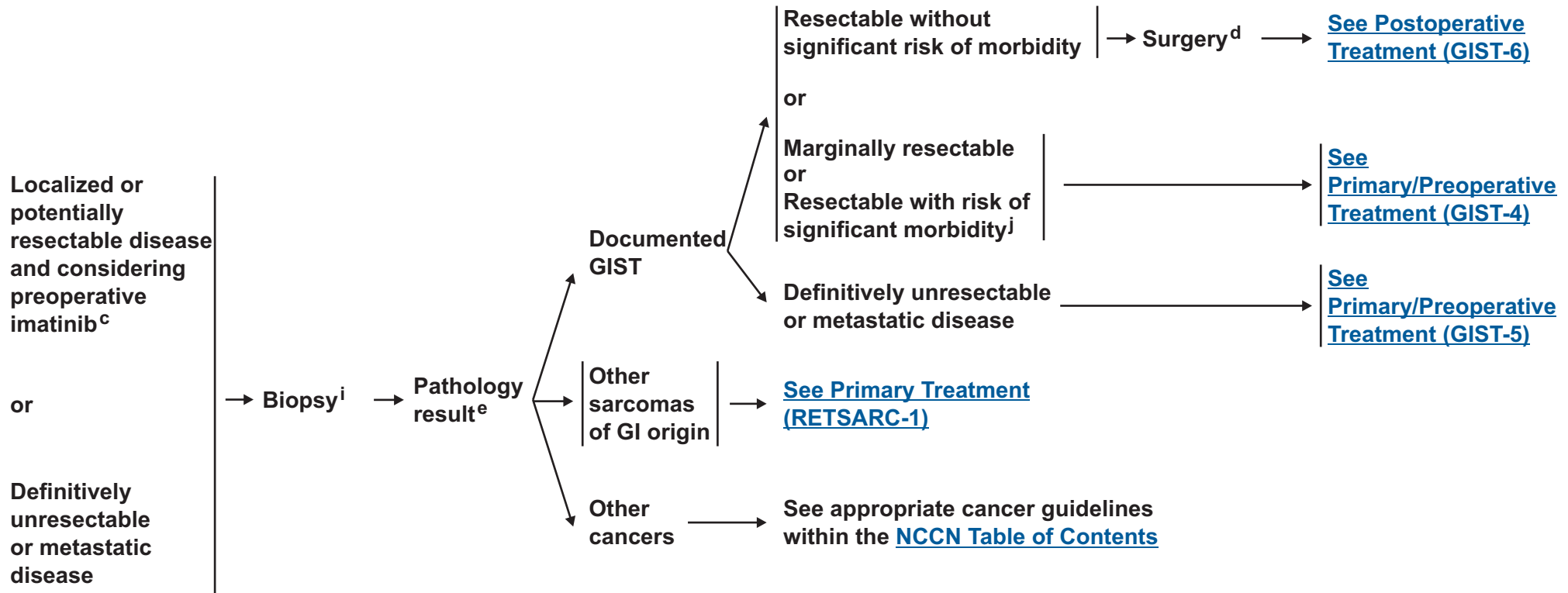
<sup>g</sup>Possible high-risk EUS features include irregular border, cystic spaces, ulceration, echogenic foci, and heterogeneity.

<sup>h</sup>Endoscopic ultrasonography surveillance should only be considered after a thorough discussion with the patient regarding the risks and benefits.

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**INITIAL DIAGNOSTIC EVALUATION**



<sup>c</sup>If surgical morbidity would be improved by reducing the size of the tumor preoperatively.

<sup>d</sup>[See Principles of Surgery For GIST \(GIST-C\).](#)

<sup>e</sup>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 kinase inhibitors. [\(See Principles of Pathologic Assessment for GIST \[GIST-B\]\)](#)

<sup>i</sup>[See Principles of Biopsy for GIST \(GIST-A\).](#)

<sup>j</sup>Some patients may rapidly become unresectable; close monitoring is essential.

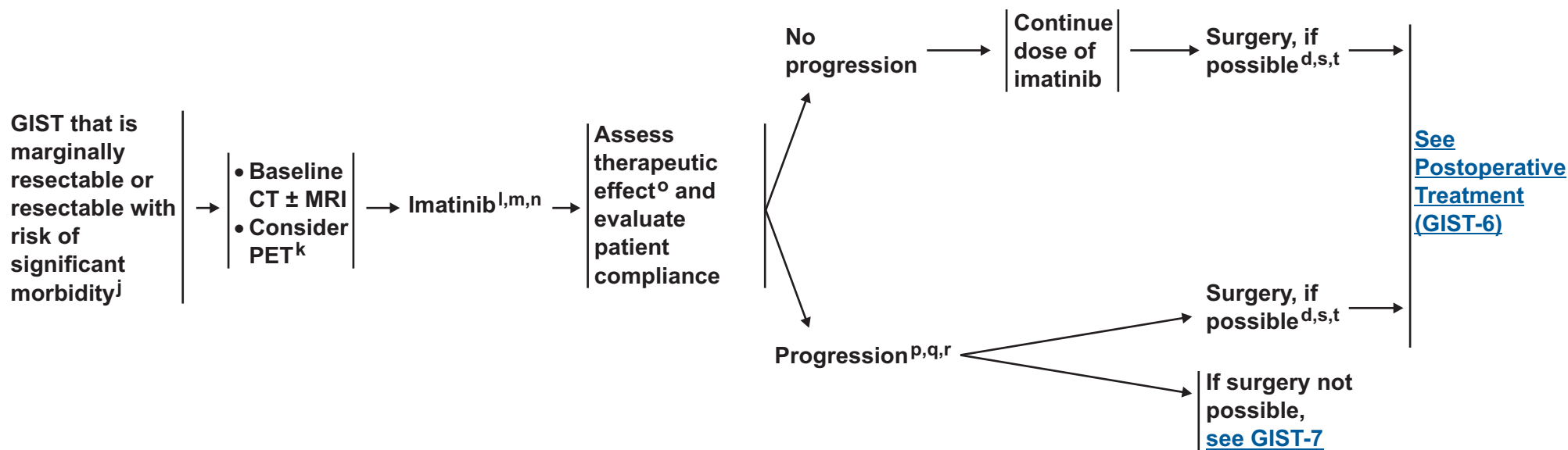
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**PRIMARY  
PRESENTATION**

**PRIMARY/PREOPERATIVE  
TREATMENT**

**FOLLOW-UP THERAPY**



<sup>d</sup> [See Principles of Surgery For GIST \(GIST-C\).](#)

<sup>j</sup> Some patients may rapidly become unresectable; close monitoring is essential.

<sup>k</sup> PET is not a substitute for a CT.

<sup>l</sup> If life threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider sunitinib.

<sup>m</sup> Medical therapy is usual course of treatment, if patient bleeding or symptomatic, may proceed to surgery.

<sup>n</sup> [See Dosage and Administration of Imatinib \(GIST-D\).](#)

<sup>o</sup> PET 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.

<sup>p</sup> 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.

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

<sup>r</sup> Suggest referral to a sarcoma specialty center.

<sup>s</sup> Collaboration between medical oncologist and surgeon necessary to determine appropriateness of surgery, following major response or sustained stable disease.

<sup>t</sup> Dosing can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications.

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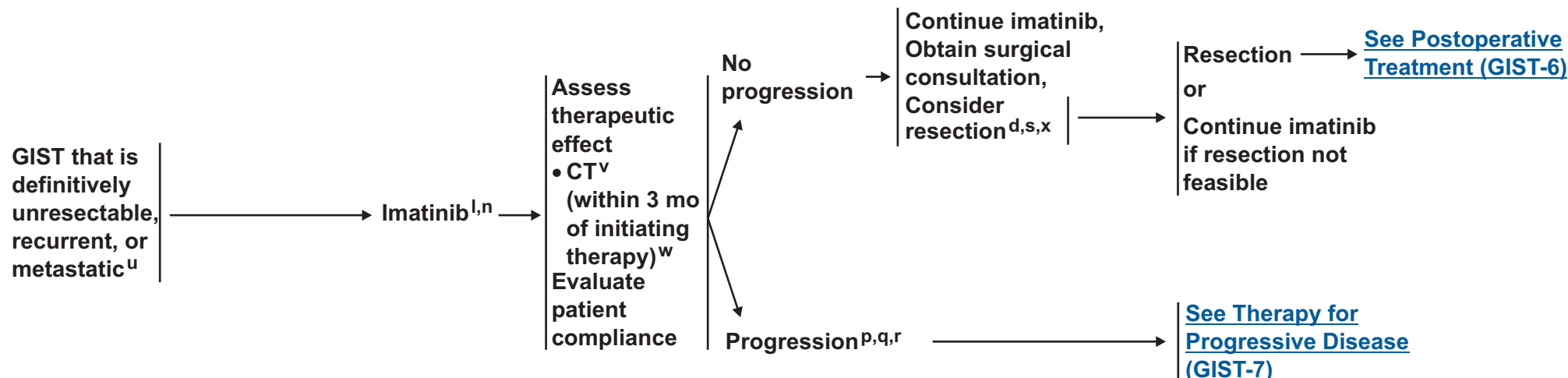
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**PRIMARY  
PRESENTATION**

**PRIMARY/PREOPERATIVE  
TREATMENT**

**FOLLOW-UP THERAPY**



<sup>d</sup>See Principles of Surgery For GIST (GIST-C).

<sup>l</sup>If life threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider sunitinib.

<sup>n</sup>See Dosage and Administration of Imatinib (GIST-D).

<sup>p</sup>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.

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

<sup>r</sup>Suggest referral to a sarcoma specialty center.

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

<sup>u</sup>Consider baseline PET, if using PET during follow-up. PET is not a substitute for CT.

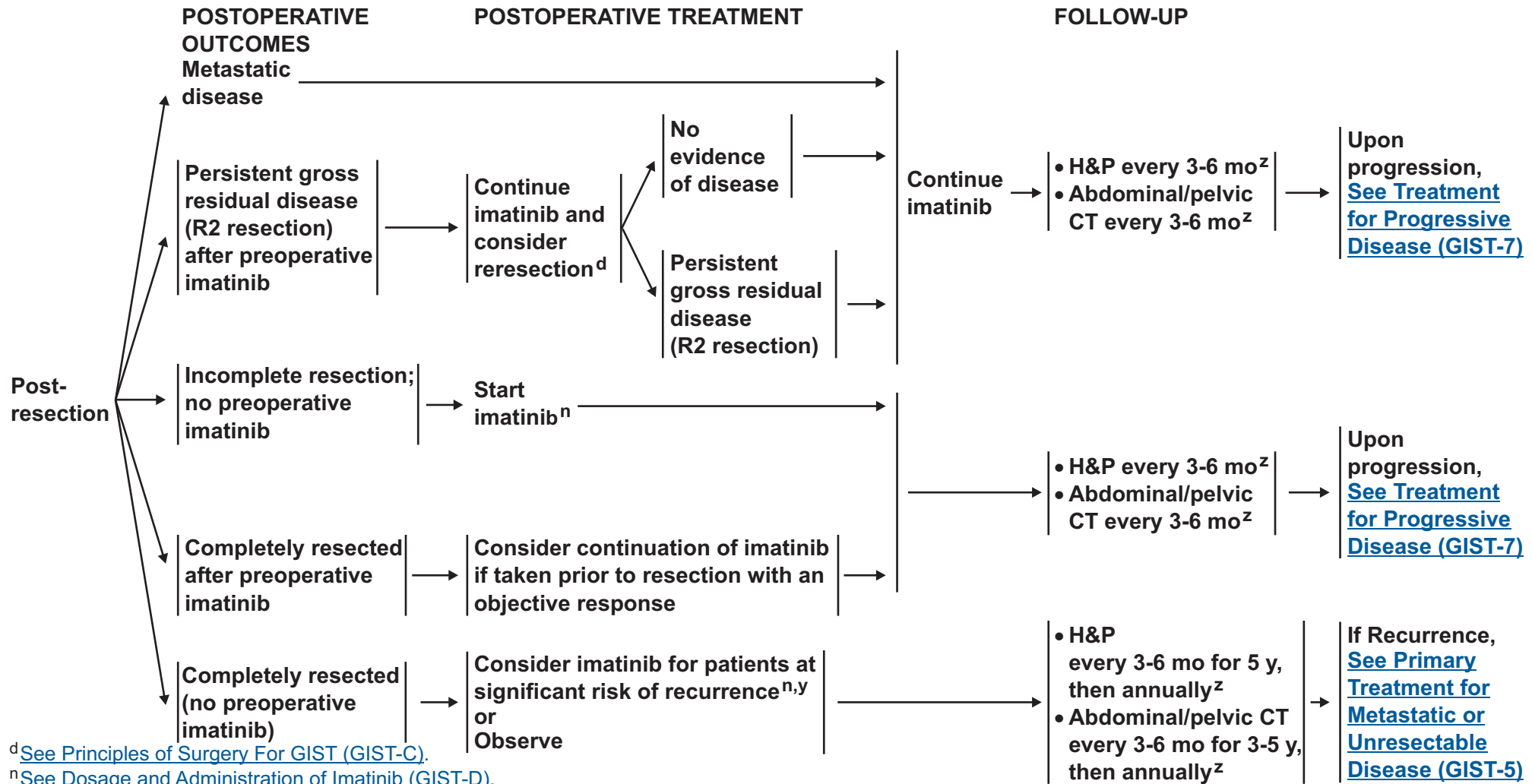
<sup>v</sup>Consider PET only if CT results are ambiguous.

<sup>w</sup>In some patients, it may be appropriate to image prior to 3 months.

<sup>x</sup>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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<sup>d</sup>See Principles of Surgery For GIST (GIST-C).

<sup>n</sup>See Dosage and Administration of Imatinib (GIST-D).

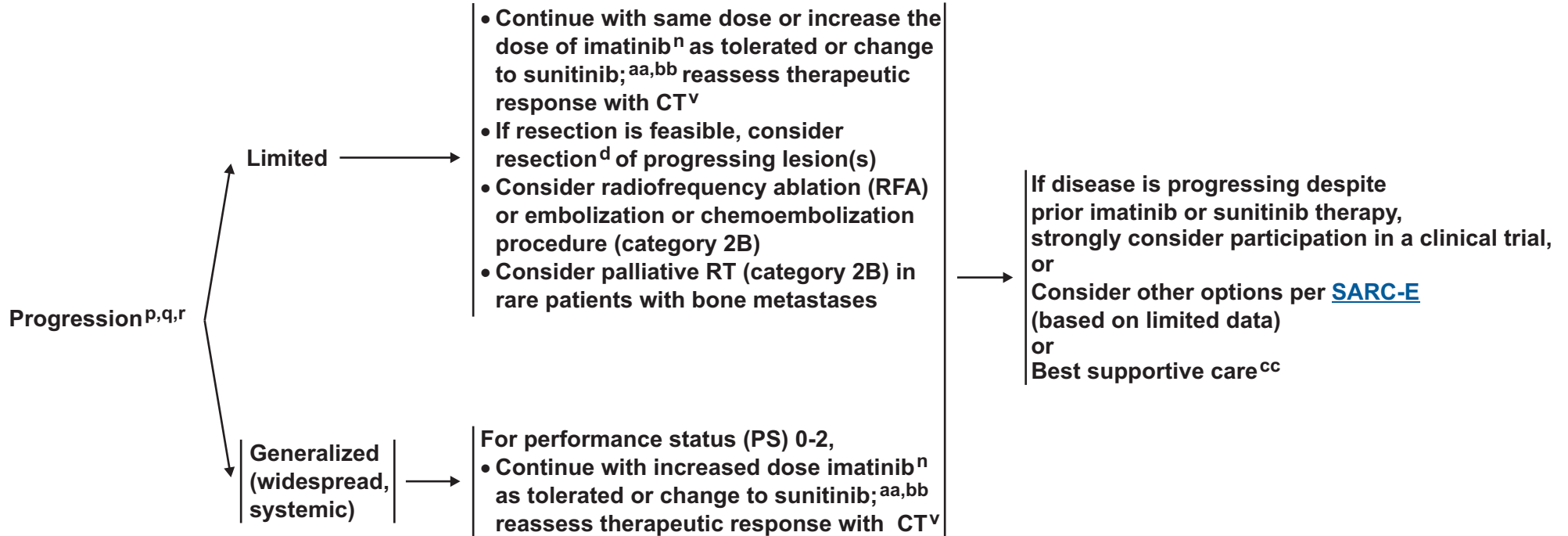
<sup>y</sup>Adjuvant imatinib for at least 36 months should be considered for patients with high risk GIST. The results of a recently completed randomized trial (SSGXVIII/AIO) suggest that adjuvant imatinib administered for 36 months improves relapse free survival (RFS) and overall survival (OS) compared 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 (Joensuu H, Eriksson M, Hatmann J, et al. Twelve versus 36 months of adjuvant imatinib (IM) as treatment of operable GIST with a high risk of recurrence: Final results of a randomized trial (SSGXVIII/AIO). ASCO Meeting Abstracts 2011;29:LBA1)

<sup>z</sup>Less frequent surveillance may be acceptable for very small tumors (< 2 cm).

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**TREATMENT FOR PROGRESSIVE DISEASE**



<sup>d</sup>See [Principles of Surgery For GIST \(GIST-C\)](#).

<sup>n</sup>See [Dosage and Administration of Imatinib \(GIST-D\)](#).

<sup>P</sup>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.

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

<sup>r</sup>Suggest referral to a sarcoma specialty center.

<sup>v</sup>Consider PET only if CT results are ambiguous.

<sup>aa</sup>See [Dosage and Administration of Sunitinib \(GIST-E\)](#).

<sup>bb</sup>Clinical experience suggests that discontinuing kinase inhibitors, even in the setting of progressive disease, may accelerate the pace of disease progression and worsen symptoms.

<sup>cc</sup>In patients with GIST progressing despite prior imatinib and sunitinib, consider reintroduction of a previously tolerated and effective tyrosine kinase inhibitor (TKI), for palliation of symptoms. Consider continuation of TKI therapy life-long for palliation of symptoms as part of best supportive care.

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### PRINCIPLES OF BIOPSY FOR GIST

- **GISTs are soft and fragile tumors and biopsy may cause tumor hemorrhage and possibly increased risk for tumor dissemination.**
- **Consideration of biopsy should be based upon the extent of disease and suspicion of a given histologic subtype (eg, lymphoma). Endoscopic ultrasound (EUS) biopsy is preferred over percutaneous biopsy.**
- **Biopsy is generally necessary when planning preoperative therapy for primary GIST.**
- **Diagnosis is based on the Principles of Pathologic Assessment noted below;<sup>1</sup> referral to centers with expertise in sarcoma diagnosis is recommended for cases with complex or unusual histopathologic features.**

<sup>1</sup> [See Principles of Pathologic Assessment of Sarcoma Specimens \(SARC-A\).](#)

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**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 (400X total magnification) 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.

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## PRINCIPLES OF SURGERY FOR GIST

### Primary (Resectable) GIST

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

- Given the limited intramural extension, extended anatomic resections (such as total gastrectomy) are rarely indicated. Segmental or wedge resection to obtain negative margins is often appropriate.
- Lymphadenectomy is usually not required given the low incidence of nodal metastases.
- 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.

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## DOSING AND ADMINISTRATION OF IMATINIB<sup>1</sup>

### Unresectable and/or metastatic GIST:

- 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.
- **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.

### Adjuvant treatment following complete gross resection of GIST:

- 400 mg daily. In the randomized clinical study ACOSOG Z9001, imatinib was administered for one year, and patients at highest risk of recurrence demonstrated increased rate of recurrence following discontinuation of drug dosing. The optimal duration of adjuvant treatment is not known.

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

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### DOSING AND ADMINISTRATION OF SUNITINIB<sup>1</sup>

- **The recommended dose of sunitinib is either:**
  - **37.5 mg orally once daily without interruption**
  - or
  - **50 mg orally once daily on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2).**
- **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 to a minimum of 37.5 mg daily should be considered if sunitinib must be coadministered with a strong CYP3A4 inhibitor.**
  - **A dose increase for sunitinib to a maximum of 87.5 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.**

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

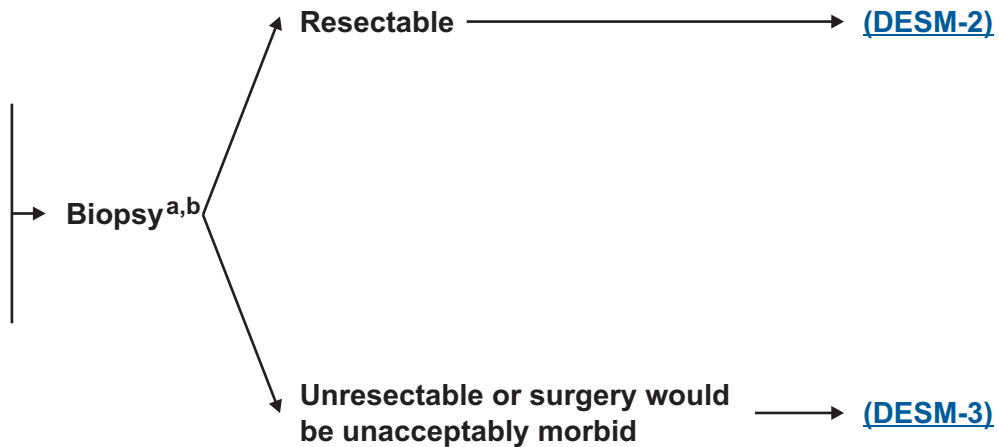
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### WORKUP

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



<sup>a</sup>May not be necessary if complete resection planned.

<sup>b</sup>[See Principles of Pathologic Assessment of Sarcoma Specimens \(SARC-A\).](#)

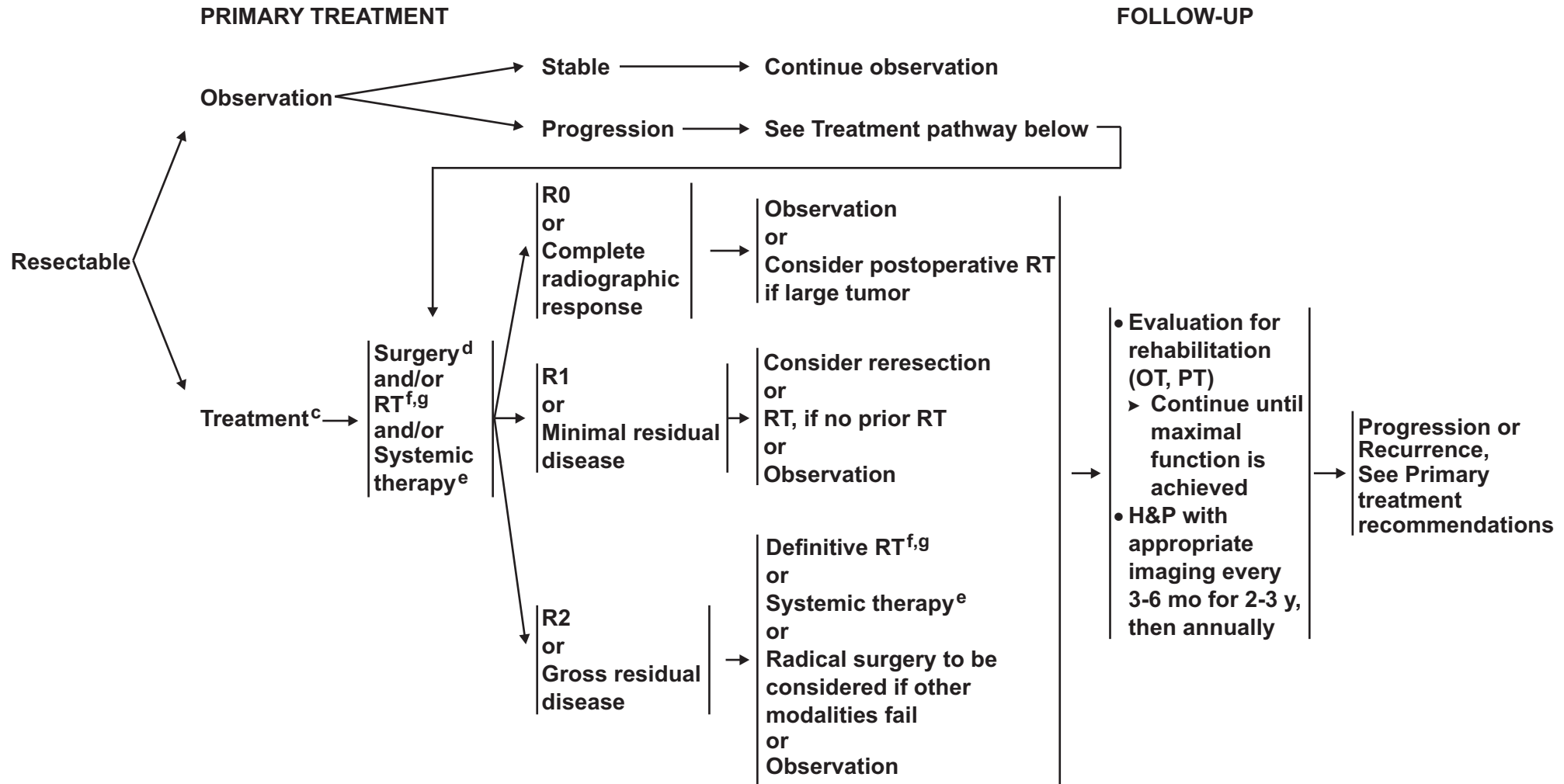
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# NCCN Guidelines™ Version 2.2011

## Desmoid Tumors (Fibromatosis)



<sup>c</sup>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.

<sup>d</sup>For desmoids, microscopic positive margins are acceptable if achieving negative margins would produce excessive morbidity.

<sup>e</sup>[See Principles of Systemic Therapy \(SARC-E\).](#)

<sup>f</sup>RT is not generally recommended for desmoid tumors that are retroperitoneal/intra-abdominal. RT is only recommended for desmoid tumors that are in the extremity.

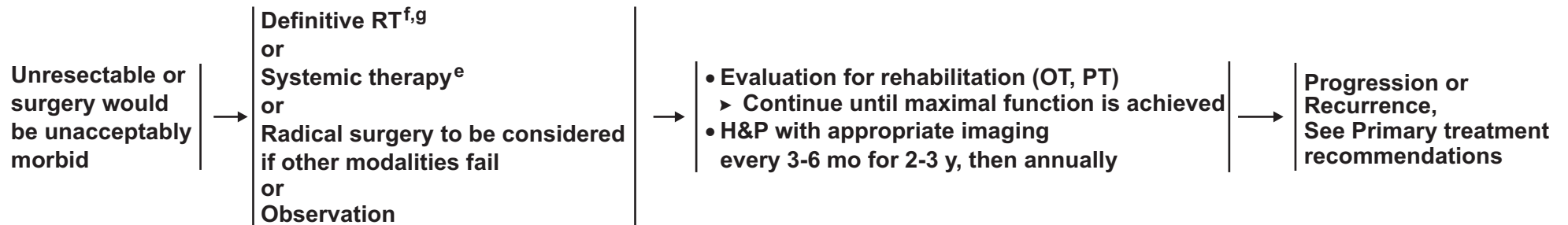
<sup>g</sup>Dose of definitive RT: 54-58 Gy in the absence of any prior radiation therapy.

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**PRIMARY TREATMENT**

**FOLLOW-UP**



<sup>e</sup>See [Principles of Systemic Therapy \(SARC-E\)](#).

<sup>f</sup>RT is not generally recommended for desmoid tumors that are retroperitoneal/intra-abdominal. RT is only recommended for desmoid tumors that are in the extremity.

<sup>g</sup>Dose of definitive RT: 54-58 Gy in the absence of any prior radiation therapy.

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## PRINCIPLES OF PATHOLOGIC ASSESSMENT OF SARCOMA SPECIMENS

- **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.<sup>1</sup>**
- **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<sup>2</sup>).**
  - ▶ **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 studies<sup>1</sup>**
    - ◊ **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](#))**

<sup>1</sup>[See Principles of Ancillary Techniques Useful in the Diagnosis of Sarcomas \(SARC-B\).](#)

<sup>2</sup>World Health Organization Classification of Tumours. Pathology and Genetics. Tumours of Soft Tissue and Bone. Lyon: IARC Press; 2002.

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

Morphologic diagnosis based on microscopic examination of histologic sections remains the gold standard for sarcoma diagnosis. However, several ancillary techniques are useful in support of morphologic diagnosis, including 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.<sup>1</sup> Recurrent genetic aberrations in sarcoma<sup>2</sup> are listed below:

TUMOR	ABERRATION	GENE(S) INVOLVED
<b><u>Malignant Round Cell Tumors</u></b>		
Ewing sarcoma / peripheral neuroectodermal tumor	t(11;22)(q24;q12) t(21;22)(q22;q12) t(2;22)(q33;q12) t(7;22)(p22;q12) t(17;22)(q12;q12) inv(22)(q12q;12) t(16;21)(p11;q22)	<i>EWS1-FLI1</i> <i>EWS1-ERG</i> <i>EWSR1-FEV</i> <i>EWSR1-ETV1</i> <i>EWSR1-E1AF</i> <i>EWSR1-ZSG</i> <i>FUS-ERG</i>
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	<i>EWS-WT1</i>
Embryonal rhabdomyosarcoma	Complex alterations	Unknown
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14) t(1;13)(p36;q14) t(X;2)(q13;q35)	<i>PAX3-FKHR</i> <i>PAX7-FKHR</i> <i>PAX3-AFX</i>

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

<sup>2</sup>This 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

TUMOR	ABERRATION	GENE(S) INVOLVED
<b><u>Lipomatous Tumors</u></b>		
Myxoid/round cell liposarcoma	t(12;16)(q13;p11) t(12;22)(q13;q12)	<i>FUS-DD1T3</i> <i>EWSR1-DD1T3</i>
Atypical lipomatous tumor/well differentiated liposarcoma (ALT/WDLPS)	Supernumerary ring chromosomes; giant marker chromosomes	Amplification of region 12q14-15, including <i>MDM2</i> , <i>CDK4</i> , <i>HMGA2</i> , <i>SAS</i> , <i>GL1</i>
Dedifferentiated liposarcoma	Same as for ALT/WDLPS	Same as for ALT/WDLPS
Pleomorphic liposarcoma	Complex alterations	Unknown
<b><u>Other Sarcomas</u></b>		
Alveolar soft part sarcoma	der(17)t(X;17)(p11;q25)	<i>ASPL-TFE3</i>
Angiomatoid fibrous histiocytoma	t(12;22)(q13;q12) t(2;22)(q33;q12) t(12;16)(q13;p11)	<i>EWSR1-ATF1</i> <i>EWSR1-CREB1</i> <i>FUS-ATF1</i>
Clear cell sarcoma	t(12;22)(q13;q12) t(2;22)(q33;q12)	<i>EWSR1-ATF1</i> <i>EWSR1-CREB1</i>
Congenital/infantile – fibrosarcoma	t(12;15)(p13;q25)	<i>ETV6-NTRK3</i>
Dermatofibrosarcoma protuberans	t(17;22)(q21;q13) and derivative ring chromosomes	<i>COLIA1-PDGFB</i>
Desmoid fibromatosis	Trisomy 8 or 20; loss of 5q21	<i>CTNNB1</i> or <i>APC</i> mutations
Epithelioid sarcoma (proximal type)	Bi-allelic inactivation of 22q11.2	<i>INI1</i>
Extrarenal rhabdoid tumor	Bi-allelic inactivation of 22q11.2	<i>INI1</i>

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

TUMOR	ABERRATION	GENE(S) INVOLVED
<b>Other Sarcomas--(continued)</b>		
Extraskeletal myxoid chondrosarcoma	Rearrangements of 9q22 t(9;22)(q22;q12) t(9;17)(q22;q11) t(9;15)(q22;q21) t(3;9)(q11;q22)	<i>CHN</i> <i>EWSR1-NR4A3</i> <i>TAF2N-NR4A3</i> <i>TCF12-NR4A3</i> <i>TFG-NR4A3</i>
Sporadic GIST Familial GIST (Carney-Stratakis syndrome)	Activating kinase mutations Krebs cycle mutation	<i>KIT</i> or <i>PDGFRA</i> <i>SDH</i> subunit mutations
Inflammatory myofibroblastic tumor	t(1;2)(q22;p23) t(2;19)(p23;p13) t(2;17)(p23;q23) t(2;2)(p23;q13) t(2;11)(p23;p15) inv(2)(p23;q35)	<i>TPM3-ALK</i> <i>TPM4-ALK</i> <i>CLTC-ALK</i> <i>RANB2-ALK</i> <i>CARS-ALK</i> <i>ATIC-ALK</i>
Leiomyosarcoma	Complex alterations	Unknown
Low grade fibromyxoid sarcoma	t(7;16)(q33;p11) t(11;16)(p11;p11)	<i>FUS-CREB3L2</i> <i>FUS-CREB3L1</i>
Malignant peripheral nerve sheath tumor	Complex alterations	Unknown
Synovial sarcoma	t(X;18)(p11;q11) t(X;18)(p11;q11) t(X;18)(p11;q11)	<i>SS18-SSX1</i> <i>SS18-SSX2</i> <i>SS18-SSX4</i>
Tenosynovial giant cell tumor/pigmented villonodular synovitis (TGCT/PVNS)	t(1;2)(p13;q35)	<i>CSF1</i>

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## PRINCIPLES OF SURGERY

### Biopsy 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.
  - ▶ 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

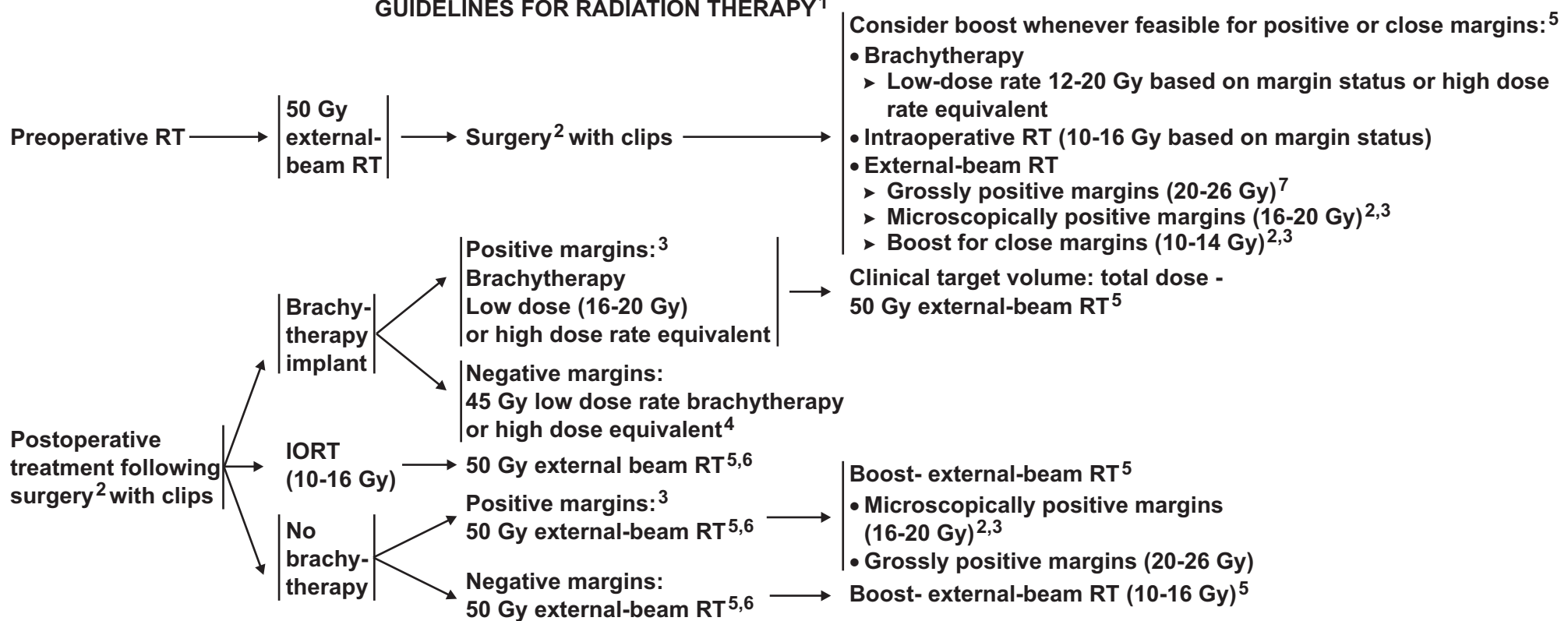
- Prior to considering amputation, patients should be evaluated by a surgeon with expertise in the treatment of soft tissue sarcomas.
- Consideration for amputation to treat an extremity sarcoma should be made for patient preference or if gross total resection of the tumor is expected to render the limb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

**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.



### GUIDELINES FOR RADIATION THERAPY<sup>1</sup>



<sup>1</sup>When external beam RT is used, sophisticated treatment planning with IMRT, tomotherapy, and/or protons can be used to improve the therapeutic ratio (1. Musat E et al. Comparison of intensity -modulated postoperative radiotherapy with conventional postoperative radiotherapy for retroperitoneal sarcoma. Cancer Radiother 2004; 8(4): 255-261; 2.) Alektiar KM et al. Impact of intensity-modulated radiation therapy on local control in primary soft-tissue sarcoma of the extremity. J Clin Oncol 2008; 26(20):3440-3444; 3.) Chung CS et al. A comparison of 3D conformal proton therapy, intensity modulated proton therapy, and intensity modulated photon therapy for retroperitoneal sarcomas. Int J Radiat Oncol Biol Phys 2006;66(3S):116; and 4.) Kraybill WG, Harris J, Spiro IJ, et al. Phase II Study of Neoadjuvant Chemotherapy and Radiation Therapy in the Management of High-Risk, High-Grade, Soft Tissue Sarcomas of the Extremities and Body Wall: Radiation Therapy Oncology Group Trial 9514. J Clin Oncol. 2006;24(4):619-625). If an R1 or R2 resection is anticipated, clips to high risk areas for recurrence is encouraged.

<sup>2</sup>[See Principles of Surgery \(SARC-B\).](#)

<sup>3</sup>RT does not substitute for suboptimal surgical resection, re-resection may be necessary.

<sup>4</sup>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 Onco Biol Phys, Vol. 49, No. 4, pp 1033-1043, 2001).

<sup>5</sup>Total doses should always be determined by normal tissue tolerance.

<sup>6</sup>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.

<sup>7</sup>[See Resection Margins \(SARC-C\).](#)

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

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**SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA<sup>a,b</sup>**

<p><b><u>Extremity, Retroperitoneal, Intra-abdominal</u></b></p> <p><b><u>Combination regimens</u></b></p> <ul style="list-style-type: none"> <li>• AD (doxorubicin, dacarbazine)<sup>1,2</sup></li> <li>• AIM (doxorubicin, ifosfamide, mesna)<sup>3,4</sup></li> <li>• MAID (mesna, doxorubicin, ifosfamide, dacarbazine)<sup>5</sup></li> <li>• Ifosfamide, epirubicin, mesna<sup>6</sup></li> <li>• Gemcitabine and docetaxel<sup>7,8</sup></li> <li>• Gemcitabine and vinorelbine<sup>9</sup></li> </ul> <p><b><u>Single agents</u></b></p> <ul style="list-style-type: none"> <li>• Doxorubicin<sup>10</sup></li> <li>• Ifosfamide<sup>6,11</sup></li> <li>• Epirubicin</li> <li>• Gemcitabine</li> <li>• Dacarbazine</li> <li>• Liposomal doxorubicin<sup>12</sup></li> <li>• Temozolomide<sup>13</sup></li> </ul>	<p><b><u>Angiosarcoma</u></b></p> <ul style="list-style-type: none"> <li>• Paclitaxel<sup>14,15</sup></li> <li>• Docetaxel</li> <li>• Vinorelbine</li> <li>• Sorafenib<sup>16,17</sup></li> <li>• Sunitinib<sup>18</sup></li> <li>• Bevacizumab<sup>19</sup></li> <li>• All other systemic therapy options as per extremity sarcoma</li> </ul>	<p><b><u>Desmoid Tumors (Fibromatosis)</u></b></p> <ul style="list-style-type: none"> <li>• Sulindac<sup>20</sup> or other non-steroidal anti-inflammatory drugs (NSAIDs) including celecoxib<sup>c</sup></li> <li>• Tamoxifen<sup>21</sup></li> <li>• Toremifene<sup>22</sup></li> <li>• Methotrexate and vinblastine<sup>23</sup></li> <li>• Low-dose interferon<sup>24</sup></li> <li>• Doxorubicin-based regimens<sup>25,26,27</sup></li> <li>• Imatinib<sup>28,29</sup></li> </ul>	<p><b><u>GIST</u></b></p> <ul style="list-style-type: none"> <li>• Imatinib<sup>30,31</sup></li> <li>• Sunitinib<sup>32</sup></li> </ul> <p><b><u>Disease progression after imatinib and sunitinib</u></b></p> <ul style="list-style-type: none"> <li>• Sorafenib<sup>33,34,35</sup></li> <li>• Nilotinib<sup>36,37</sup></li> <li>• Dasatanib<sup>38</sup></li> </ul>
<p><b><u>Solitary Fibrous Tumor/Hemangiopericytoma</u></b></p> <ul style="list-style-type: none"> <li>• Bevacizumab and temozolomide<sup>39</sup></li> <li>• Sunitinib<sup>40,41</sup></li> </ul>	<p><b><u>Pigmented Villonodular Synovitis/Tenosynovial Giant Cell Tumor (PVNS/TGCT)</u></b></p> <ul style="list-style-type: none"> <li>• Imatinib<sup>42</sup></li> </ul>		
<p><b><u>Alveolar soft part sarcoma (ASPS)</u></b></p> <ul style="list-style-type: none"> <li>• Sunitinib<sup>43,44</sup> (category 2B)</li> </ul>	<p><b><u>PEComa, Recurrent Angiomyolipoma, Lymphangiomyomatosis</u></b></p> <ul style="list-style-type: none"> <li>• Sirolimus<sup>45-49</sup></li> </ul>		
<p><b><u>Chordoma (All recommendations are category 2B)</u></b></p> <p><b><u>Combination regimens</u></b></p> <ul style="list-style-type: none"> <li>• Erlotinib and cetuximab</li> <li>• Imatinib and cisplatin<sup>50</sup></li> <li>• Imatinib and sirolimus<sup>51</sup></li> </ul> <p><b><u>Single agents</u></b></p> <ul style="list-style-type: none"> <li>• Erlotinib<sup>52</sup></li> <li>• Imatinib<sup>53,54</sup></li> <li>• Sunitinib<sup>41</sup></li> </ul>			

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

<sup>b</sup>References for regimens, see [SARC-E 2 of 3](#).

<sup>c</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)

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

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



**Table 1**  
**American Joint Committee On Cancer (AJCC) Staging System**  
**For Soft Tissue Sarcoma**  
**(7th ed, 2010)**

**Primary Tumor (T)**

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

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

**Regional Lymph Nodes (N)**

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

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

**Distant Metastases (M)**

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

**Histologic Grade**

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

**Anatomic Stage/Prognostic Groups**

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

[Continued...](#)

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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:

**Adipocytic Tumors**

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

**Fibroblastic/Myofibroblastic Tumors**

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

**So-called Fibrohistiocytic Tumors**

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

**Smooth Muscle Tumors**

- Leiomyosarcoma

**Skeletal Muscle Tumors**

- Rhabdomyosarcoma (embryonal, alveolar, and pleomorphic forms)

**Vascular Tumors**

- Epithelioid hemangioendothelioma
- Angiosarcoma, deep\*\*\*

**Tumors of Peripheral Nerves**

- Malignant peripheral nerve sheath tumor

**Chondro-osseous Tumors**

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

**Tumors of Uncertain Differentiation**

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

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 (eg, parenchymal organs).

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## Discussion

### NCCN Categories of Evidence and Consensus

**Category 1:** The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

**Category 2A:** The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

**Category 2B:** The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

**Category 3:** The recommendation is based on any level of evidence but reflects major disagreement.

**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.

Soft tissue sarcomas (STS) are the most frequent sarcomas. The annual incidence of STS in the United States for 2010 is estimated to be about 10,520 cases, with an overall mortality rate of approximately 3,920 cases per year, which includes adults and children.<sup>1</sup> The true

incidence of sarcomas is underestimated, especially because a large proportion of patients with gastrointestinal stromal tumors (GIST) may not have been counted in tumor registry databases before 2001. GIST is expected to have an incidence of at least 5000 new cases per year in the United States.<sup>2,3</sup> Collectively, sarcomas account for approximately 1% of all adult malignancies and 15% of pediatric malignancies. Prior radiation therapy (RT) to the affected area, generally some years prior to the development of the sarcoma, is a risk factor for STS.<sup>4</sup>

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)], GIST, liposarcoma, leiomyosarcoma, synovial sarcoma, malignant peripheral nerve sheath tumors.<sup>5</sup> Rhabdomyosarcoma is the most common STS of childhood. Extremities (60%), the trunk (19%), retroperitoneum (15%) or head and neck (9%) are the most common primary sites.<sup>6</sup> The anatomic site of the primary disease represents an important variable that influences treatment and outcome. STS most commonly metastasize to the lungs; tumors arising in the abdominal cavity more commonly metastasize to the liver and peritoneum.

The NCCN encompasses institutions with extensive experience in the management of sarcomas using primary multidisciplinary care and functioning as referral centers for consultative support of community-based practitioners. NCCN Guidelines for STS are based on evidence and consensus. The guidelines address the management of STS in adult patients from the perspective of four disease subtypes:

- STS of extremity/trunk
- Retroperitoneal or intra-abdominal STS
- GIST
- Desmoid tumors (Fibromatosis)



## Pathology of Soft Tissue Sarcomas

### Biopsy

A pretreatment biopsy is highly preferred for the diagnosis and grading of sarcomas, and should be performed by an experienced surgeon or radiologist. Biopsy can be accomplished by 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.<sup>7</sup> 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 sarcomas.

### Principles of Pathological Assessment

Pathologists with sarcoma expertise 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 such as conventional cytogenetics, immunohistochemistry, electron microscopy and molecular genetic testing are useful to support the morphologic diagnosis. 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, TNM stage and additional features of the tumor 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 testing since many STS subtypes 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 such as chromosomal translocations or point mutations and usually simple karyotypes and (ii) sarcomas with non-specific genetic alterations and complex unbalanced karyotypes.<sup>8</sup>

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 (SYT)-SSX (SS18-SSX1 or SS18-SSX2)* in synovial sarcoma, and *PAX-FKHR (PAX3-FKHR or PAX7-FKHR)* in alveolar rhabdomyosarcoma]. 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.

Most common techniques used in the molecular diagnosis include conventional cytogenetic analysis, fluorescence in-situ hybridization (FISH) and polymerase chain reaction (PCR)-based methods.<sup>9</sup> In a prospective study, Hill and colleagues concluded that PCR-based molecular analysis is a useful adjunct and more sensitive than conventional cytogenetics for the diagnosis of certain subtypes of STS including alveolar rhabdomyosarcoma, synovial sarcoma and myxoid liposarcoma that have variation in fusion gene partners.<sup>10</sup>

The molecular heterogeneity of fusion transcripts has been suggested to predict prognosis in certain sarcoma subtypes. In patients with alveolar rhabdomyosarcoma presenting with metastatic disease, *PAX7-FKHR* was associated with a favorable prognosis compared to *PAX3-FKHR*.<sup>11</sup> In patients with synovial sarcoma, the prognostic impact of fusion gene transcripts *SS18-SSX1* or *SS18-SSX2* is less clear with two large studies showing conflicting results.<sup>12, 13</sup> In myxoid liposarcoma, the variability of fusion transcript has no effect on clinical outcome.<sup>14</sup>

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.<sup>9</sup> Molecular testing should be performed by a pathologist with expertise in sarcoma diagnosis and molecular diagnostic techniques.

## 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 two-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.<sup>15</sup> Riad et al examined the impact of lymph node involvement on survival in patients with extremity sarcoma.<sup>16</sup> 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).<sup>16</sup> 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.<sup>16, 17</sup> The revised 2010 AJCC staging system incorporates a three-tiered grading system and lymph node disease has been reclassified as Stage III rather than Stage IV disease.<sup>18</sup> However, many clinicians prefer the two-tiered system; therefore, this system is also used in the algorithm.

## Principles of Surgery

Because surgery is the standard primary treatment for most sarcomas, the panel has included a separate section on principles of sarcoma surgery. If a patient cannot be surgically treated in accordance with



these principles of sarcoma surgery, preoperative RT or chemotherapy should be considered as alternate treatment options. Because the risk of failure in the surgical bed can be high, many clinicians choose to augment surgery with RT and chemotherapy, either preoperatively or postoperatively.<sup>19, 20</sup> When appropriate, the guidelines incorporate these therapies that are supported by clinical trial data or extensive clinical experience.<sup>21</sup>

### **Sarcoma Surgery**

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 extremity STS 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.<sup>22</sup> 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.<sup>23-25</sup>

Both the surgeon and the pathologist should document surgical margins, in 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.<sup>26, 27</sup> 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.

### **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.<sup>28-30</sup>

### **Guidelines for Radiation Therapy**

External beam radiation therapy (XRT) 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.<sup>31</sup>

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 high dose rate therapy. LDR and HDR



brachytherapy are associated with similar rates of local control.<sup>32</sup> It has been suggested that HDR technique may be associated with lower incidences of severe toxicity; however, this has not been proven in randomized clinical trials.<sup>32</sup> The guidelines recommend that HDR fraction sizes should be limited to 3-4 Gy until more data are available.<sup>33</sup> The main advantage of IMRT is its ability to more closely contour the high dose radiation volume to the tumor and in doing so minimize the volume of high dose radiation to surrounding normal tissues.<sup>34</sup> IORT is the delivery of radiation during surgery and it can be performed using different techniques such as electron beam radiation or brachytherapy.

### **Preoperative RT**

Preoperative RT has several advantages. First, the treatment volume is smaller, because the need to cover the operative field is not present. Second, preoperative radiation may reduce seeding during 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.<sup>35</sup> 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 radiation is contemplated. After preoperative radiation, a 3-6 week interval is necessary before resection to allow acute radiation reactions to subside and decrease the risk of wound complications. Very long intervals between resection and postoperative radiation 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 XRT is recommended for positive or close margins.<sup>36</sup> Often, margins are close 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 intraoperative dose of 10-16 Gy, based on margin status, can be delivered immediately after resection with exposure of the area at risk, avoiding uninvolved organs. XRT boosts may be an alternative to brachytherapy or IORT. Recommended doses are 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 that approach 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.<sup>37</sup> In a recent report from Memorial Sloan-Kettering Cancer Center (MSKCC), in patients with extremity STS treated with limb-sparing surgery and a pathologically negative re-resection without radiation therapy, patients with old age and/or stage III disease had a higher rate of local recurrence, even though the 5-year overall local recurrence rate was 9% with a median follow-up of 82 months.<sup>38</sup> 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 XRT. When XRT 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.

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.<sup>39</sup> However, brachytherapy-alone techniques require special expertise and significant experience. The panel recommends 45 Gy LDR brachytherapy or high dose rate equivalent for patients with negative margins. LDR brachytherapy (16-20 Gy) or high dose rate equivalent is recommended for patients with positive margins followed by XRT. XRT 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.<sup>40</sup> However, since IORT has not been proven superior, the guidelines recommend IORT (10-16 Gy) followed by a dose of 50 Gy XRT.

If no IORT or brachytherapy was used in the immediate operative or postoperative period, XRT 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 XRT boost should be used based

on the margin status. For negative margins, an additional 10-16 Gy is recommended to the original tumor bed. For microscopically positive margins, an additional 16-20 Gy is recommended; for grossly positive margins, an additional 20-26 Gy is suggested.

### Soft Tissue Sarcomas of the Extremities or Trunk

#### Surgery

Amputation was once considered as the standard treatment to achieve local control in patients with extremity sarcomas.<sup>41</sup> 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 overall survival (OS) and DFS as compared to amputation.<sup>42</sup> 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.<sup>43</sup> 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.<sup>44</sup> 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

Randomized clinical trial data support the use adjunctive XRT in appropriately selected patients with STS of extremity.<sup>45-47</sup> In a phase III randomized trial conducted by the Canadian Sarcoma group, local control and progression-free survival (PFS) rates were similar in patients receiving either preoperative or postoperative XRT in patients with localized primary or recurrent extremity sarcoma.<sup>45,48</sup> However, preoperative RT was associated with a greater incidence of acute wound complications (35% vs. 17% for postoperative XRT), 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 radiation, which is believed to be related to the higher postoperative XRT dose (66 Gy vs. 50 Gy for preoperative XRT) and the larger treatment volume.<sup>45</sup> Therefore, the risk of local recurrence versus the toxicity of postoperative XRT should be assessed before making a decision regarding radiation.

The efficacy of postoperative XRT was demonstrated in a prospective randomized trial comparing limb-sparing surgery and limb-sparing surgery with adjuvant XRT.<sup>46</sup> Postoperative XRT reduced 10-year local recurrence rate in patients with high-grade sarcoma (no local recurrences in patients who underwent surgery plus XRT vs. 22% in those who underwent surgery alone) as well as low-grade sarcoma (5% for surgery plus XRT group vs. 32% for those who underwent surgery alone).<sup>46</sup>

Adjuvant brachytherapy has been shown to improve local control after complete resection of STS in patients with high-grade lesions.<sup>49</sup> 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.<sup>49</sup> 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.<sup>50</sup> 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.<sup>51</sup> 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.<sup>52</sup> 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

All patients should be managed by a multidisciplinary team with expertise in soft tissue sarcoma.<sup>53</sup> 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 (H&P). 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 sub-types of sarcoma. Therefore imaging should be individualized based on the sub-type of sarcoma.

PET scans may be useful in prognostication, grading and determining response to chemotherapy, for lesions that are larger than 3 cm, firm, and deep, not superficial.<sup>54</sup> 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.<sup>55-57</sup> 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.<sup>58-60</sup> Alveolar soft part sarcomas (ASPS) have a relatively increased propensity to metastasize to the brain, especially in patients with stage IV disease in the presence of pulmonary metastases.<sup>61</sup> CNS imaging should be considered for patients with ASPS and angiosarcomas

Positron emission tomography (PET) scan may be useful for prognostication, grading and to assess response to chemotherapy.<sup>62, 63</sup> The standardized uptake values (SUV) of F18-deoxyglucose have been shown to correlate with tumor grade and prognostication in patients with soft tissue sarcomas.<sup>64, 65</sup> Recent reports in literature have demonstrated the value of PET scan in evaluating histopathological response to preoperative chemotherapy and predicting outcomes in patients with high-grade extremity STS.<sup>54, 66-68</sup> PET was significantly more accurate than the RECIST criteria in assessing histopathologic response to neoadjuvant therapy.<sup>66</sup> Schuetze et al reported that the pretreatment SUVmax and change in SUVmax after neoadjuvant chemotherapy independently identified patients at high risk of tumor recurrence.<sup>54</sup> Patients whose tumors had 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 adjuvant RT; the projected 5-year recurrence survival rate for this group of patients was 80% compared with 40% for patients with a less than 40% reduction in SUVmax.<sup>54</sup> PET was also useful in the early assessment of response to neoadjuvant chemotherapy.<sup>67</sup> In a prospective study of 50 patients with resectable high-grade STS, a 35% reduction in tumor FDG uptake after first cycle of chemotherapy was a sensitive predictor of histopathologic tumor response.<sup>67</sup> In a retrospective study, tumor



SUV(max) value determined by PET was an independent predictor of survival and disease progression.<sup>68</sup> A large prospective study is underway to evaluate PET combined with CT in predicting DFS in patients receiving preoperative chemotherapy for STS ([www.cancer.gov/clinicaltrials/UMN-2005LS080](http://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.<sup>69, 70</sup> Retrospective studies have demonstrated a local control of 90% or more for surgery alone.<sup>71</sup> Data from randomized clinical trials support the use of RT as an adjunct to surgery in appropriately selected patients based on an improvement in disease-free survival although not overall survival.<sup>46, 49, 72</sup> 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.<sup>71</sup> 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, 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

Large high-grade extremity sarcomas (greater than 8-10 cm) at high risk for local recurrences and metastases and should be considered for preoperative therapy. Preoperative chemotherapy or chemoradiation is used in many centers for high-grade tumors to downstage a large tumor to enable effective surgical resection, especially in the case of chemosensitive histologies.<sup>42, 73-78</sup>

Concurrent chemoradiation with doxorubicin-based regimens has been shown to improve local control rates in patients with STS, although acute reactions must be considered.<sup>79</sup> A phase III randomized trial (EORTC 62961) showed that regional hyperthermia (RHT) increases the benefit of neoadjuvant chemotherapy in patients with localized high-risk STS.<sup>80</sup> In this study, 341 patients (149 patients with extremity STS; 189 patients with non-extremity STS) 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, 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.

The Sarcoma Meta Analysis Collaboration 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.<sup>81</sup> The result of the meta-analysis showed that



doxorubicin-based chemotherapy prolongs relapse-free survival (RFS) in adults with localized, resectable STS of the extremity and was associated with decreased recurrence rates. However, adjuvant chemotherapy does not appear to improve OS.<sup>82</sup> Another recent analysis of 674 patients with stage III STS (1984-1999) revealed that clinical benefits from doxorubicin-based chemotherapy lasted for less than a year.<sup>83</sup>

In an Italian randomized cooperative trial, patients with high-grade or recurrent extremity sarcoma were randomized to receive postoperative chemotherapy with epirubicin and ifosfamide or observation alone.<sup>84</sup> After a median follow-up of 59 months, median DFS (48 vs. 16 months) and median OS (75 months vs. 46 months) were significantly better in the treatment group. The absolute benefit for OS from chemotherapy was 13% at 2 years and increased to 19% at 4 years for patients receiving chemotherapy.<sup>84</sup> After a median follow-up of 90 months, the estimated 5-year OS rate was 66% for the treatment group compared with 46% for the control group ( $P = 0.04$ ).<sup>85</sup>

Remarkably little data have been generated in the adjuvant setting regarding the combination of aggressively dosed ifosfamide plus doxorubicin with growth factor support. The efficacy of adjuvant chemotherapy after definitive surgery in patients with excised high-grade STS at any site was assessed in a phase III randomized study (EORTC-62931).<sup>86</sup> In this study, 351 Patients with macroscopically resected grade II-III tumors with no metastases were randomized to observation or chemotherapy with ifosfamide and doxorubicin with lenograstim. A planned interim analysis of this study showed that there is no survival advantage for adjuvant chemotherapy with ifosfamide and doxorubicin in patients with resected high grade STS.<sup>86</sup> The estimated 5-year RFS was 52% in both arms and the corresponding OS rates were 64% and 69% respective for patients

assigned to chemotherapy and observation. Further analysis of this study is needed to make a detailed assessment of the role of adjuvant chemotherapy in resected STS.

A recent large cohort-based analysis with a median follow-up of 9 years indicated that patients with FNCLCC grade 3 non-metastatic STS may benefit from adjuvant chemotherapy.<sup>87</sup> Adjuvant chemotherapy was significantly associated with improved 5-year metastasis-free survival (58% vs. 49%,  $P = 0.01$ ) and 5-year OS (58% vs. 45%,  $P = 0.0002$ ) in grade 3 patients, whereas it was not significantly different in grade 2 patients (5-year metastasis-free survival: 76% vs. 73%,  $P = 0.27$ ; 5-year OS: 75% vs. 65%,  $P = 0.15$ ).<sup>87</sup>

Available evidence, although underpowered, suggests that anthracycline-based postoperative chemotherapy would improve DFS in selected patients who are at high risk of recurrence but otherwise are in good performance status.<sup>88-90</sup> Treatment options for stage II or III high-grade tumors 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 or surgery alone (for small tumors that can be resected with wider surgical margins) is the primary treatment for resectable high-grade sarcomas with acceptable functional outcomes.<sup>91</sup> The guidelines have also included preoperative RT, chemotherapy or chemoradiation prior to surgery as alternative options for patients with resectable tumors with acceptable functional outcomes and for potentially resectable tumors with concerns for adverse functional outcomes. The panel has included preoperative chemotherapy or chemoradiation for resectable disease



with acceptable functional outcomes with a category 2B recommendation. 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.<sup>92</sup> 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.

Adjuvant chemotherapy alone can be considered for patients who have received preoperative RT or chemoradiation, whereas postoperative RT with or without adjuvant chemotherapy is recommended for those who received preoperative chemotherapy. Since there are only limited and conflicting data regarding the potential benefits of adjuvant chemotherapy for stage II or III patients, adjuvant 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.<sup>47</sup> 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.<sup>93</sup> 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 perfusion (ILP) has been evaluated as a limb sparing treatment for unresectable intermediate or high-grade extremity STS. Preliminary data from clinical trials suggest that ILP with melphalan or doxorubicin in combination with tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) may be effective in the treatment of patients with unresectable STS of extremity.<sup>94-96</sup> Further prospective clinical trials are needed to identify the role for ILP in patients with unresectable extremity sarcomas. The guidelines have included ILP 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 radiation 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 (Metastatic Disease)**

Single agents (doxorubicin, ifosfamide or dacarbazine) or anthracycline-based combination regimens (doxorubicin or epirubicin with ifosfamide and/or dacarbazine) have been widely used for metastatic disease.<sup>97-104</sup> Other chemotherapeutic agents have also



been evaluated in clinical trials. In a randomized phase II study, pegylated liposomal doxorubicin had equivalent activity and improved toxicity profile in patients advanced or metastatic STS.<sup>105</sup> Gemcitabine and docetaxel was found to be highly active in patients with predominantly uterine leiomyosarcomas, who had failed ifosfamide plus doxorubicin or cannot tolerate this regimen for medical reasons.<sup>106</sup> In a randomized phase II study, PFS (6.2 months vs. 3.0 months respectively) and OS (17.9 months vs. 11.5 months respectively) were superior to gemcitabine and docetaxel compared to gemcitabine alone in patients with metastatic STS.<sup>107</sup> 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.<sup>108</sup> In a retrospective study conducted by the French Sarcoma group in 133 patients with unresectable or metastatic soft-tissue sarcoma, gemcitabine and docetaxel combination was tolerable and demonstrated better response and survival for leiomyosarcoma.<sup>109</sup> Another phase II trial (MSKCC-99027) is evaluating the activity of gemcitabine, docetaxel and filgrastim in patients with recurrent or persistent unresectable leiomyosarcoma or other STS that cannot be removed by surgery. In a phase II study, the combination of gemcitabine and vinorelbine was associated with clinically meaningful rates of disease control in patients with advanced soft-tissue sarcoma.<sup>110</sup> Clinical benefit (complete response, partial response or stable disease at 4 months or more) was seen in 25% of patients. Temozolomide as a single agent also is active in patients with advanced pretreated STS, especially among patients with unresectable or metastatic leiomyosarcoma of both uterine and non-uterine origin.<sup>111, 112</sup>

Ecteinascidin 743 (ET-743, also known as trabectedin), is a marine-derived anti-tumor agent, which has shown objective responses in phase II trials of patients with advanced STS.<sup>113-118</sup> NCT00210665 is

an ongoing multicenter, open label single arm study, to provide access to treatment with trabectedin for patients with persistent or recurrent STS and who are not expected to benefit from currently available treatments (<http://clinicaltrials.gov/ct2/show/NCT00210665>).

#### **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 influence the decision to use metastasectomy, including the disease-free interval from original diagnosis to detection of the metastases, the patient's performance status, and the amount of prior therapy. Thoracotomy and video-assisted thoracic surgery (VATS) should be used selectively depending on the clinical presentation of metastatic disease. 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 had a very long disease-free interval and 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 ablation procedures (eg, radiofrequency ablation or cryotherapy), embolization procedures or stereotactic radiosurgery/RT as options for symptomatic patients with disseminated metastases. The guidelines are intentionally nonspecific about this group of options, because many different issues are factored into this decision (eg, patient performance status, patient preferences, specific clinical problems from the metastases, treatment availability), and specific details are best left to clinical judgment.

### 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.<sup>119-121</sup> 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. 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. Because these patients' risk

never returns to zero, long-term follow-up is indicated, including consideration of MRI or CT scanning.<sup>122</sup> 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.<sup>123</sup> 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.

### Recurrent Disease

The management of recurrent disease encompasses a heterogeneous group of patients and clinical scenarios. For a patient with a local recurrence, treatment decisions should be made using the same algorithm as for patients with a new primary lesion.<sup>124</sup> For patients who present with metastatic recurrences the guidelines distinguish between widely disseminated metastases and limited metastases confined to a single organ and the treatment options are similar to that described for Stage IV disease at presentation.

### Retroperitoneal/Intra-Abdominal Soft Tissue Sarcomas

#### Surgery

Surgical resection of a localized tumor with grossly negative margins remains the standard, potentially curative treatment for retroperitoneal STS. Post-operative margin status is the most important factor contributing to long-term DFS.<sup>125-128</sup> 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.<sup>128</sup>



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.<sup>129, 130</sup> 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.<sup>131</sup> Postoperative XRT has been associated with improved RFS in retrospective nonrandomized studies, although there was no improvement in OS.<sup>127, 132</sup> In one trial, combined use of preoperative XRT and postoperative brachytherapy resulted in significantly better DFS and OS in patients with primary retroperitoneal STS and in those with low-grade tumors.<sup>133</sup> 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.<sup>134</sup>

The use of IORT with or without XRT 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).<sup>135</sup> IOERT has also been effective in terms of local control and survival in patients with primary and recurrent retroperitoneal STS.<sup>136-139</sup> In a trial that assessed the long-term outcome of patients with retroperitoneal sarcoma treated by preoperative XRT, 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.<sup>136</sup> The feasibility and safety of preoperative concurrent chemoradiation followed by surgical resection and IOERT has also been demonstrated in a phase I trial.<sup>140</sup>

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.<sup>22, 141, 142</sup> 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.<sup>143-145</sup> Multimodality treatment is usually favored for retroperitoneal sarcomas due to the inability to obtain negative margin resections and high local recurrence rates.<sup>146</sup> In a phase III randomized trial (EORTC 62961), the addition of RHT to neoadjuvant chemotherapy with EIA was associated with a significant survival benefit.<sup>80</sup> After a median follow-up of 34 months, 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. 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.<sup>147</sup> Little data are available for use of combined RT and chemotherapy. Decisions about adjuvant or neoadjuvant chemotherapy or RT are left to clinical judgment.<sup>148-150</sup>

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 a 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 (category 2B) could be considered (if not received preoperatively) for all patients with microscopic positive margins (R1 resection) and in highly selected patients (eg. 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). 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, 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, treatment options are similar to those listed under primary treatment for unresectable or metastases.

### 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).<sup>151</sup> 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 KIT.<sup>152, 153</sup> 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.<sup>154</sup> 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.<sup>155</sup> 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.<sup>155</sup> 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, and biopsy may cause tumor hemorrhage and possibly increased risk for tumor dissemination. The decision to obtain a biopsy should be based on the extent of disease and the clinician's degree of suspicion of other malignancies. Biopsy may not be necessary if the tumor is easily resectable and preoperative therapy is not required. However, biopsy should be done if preoperative therapy is being considered for unresectable or marginally resectable tumors. Endoscopic ultrasound (EUS) biopsy is preferred over percutaneous. Recent reports have suggested that definitive diagnosis of GIST requires tissue acquisition via EUS-guided fine-needle aspiration (FNA).<sup>156</sup>

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. 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.<sup>157</sup> 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.<sup>158</sup>

### 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.

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. If the surgeon feels that a complex surgical procedure is required then a multidisciplinary consultation regarding the use of preoperative imatinib is recommended. Sphincter-sparing surgery and esophagus-sparing surgery should be considered for rectal and gastroesophageal junction GISTs respectively. If abdominoperineal resection would be necessary to achieve a negative margin, then preoperative imatinib should be considered.

The role for laparoscopy in the resection of GISTs continues to expand. Although prospective trials are lacking, literature reports based on small series of patients and retrospective analyses have demonstrated that not only are laparoscopic or laparoscopic-assisted resections possible, but they are also associated with low recurrence rates, short hospital stay duration and low morbidity. Laparoscopic approach may be considered for selected GISTs in favorable anatomic locations such as anterior wall of the stomach, jejunum and ileum. The same surgical principles of complete macroscopic resection including the preservation of the pseudocapsule and avoidance of tumor rupture should be followed during laparoscopy. Resection specimen should be removed from the abdomen in a plastic bag to avoid spillage or seeding of port sites. Laparoscopic surgery could be feasible in other anatomic sites, such as smaller rectal GISTs. However, data on laparoscopic resection of GISTs at other sites are limited.

### Targeted Therapy

GIST tumors 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.<sup>159-162</sup> In February 2002, the FDA approved of imatinib mesylate for the treatment of patients with KIT-positive unresectable and/or metastatic malignant GIST.<sup>163</sup> 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.<sup>164</sup> 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.<sup>165</sup>



In randomized clinical trials, patients with *KIT* exon 11 mutations had better response rates, longer progression-free survival (PFS) and overall survival (OS) compared to those with *KIT* exon 9 mutations or no *KIT* or *PDGFRA* mutation.<sup>166-168</sup> 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.<sup>166</sup> The EORTC (European Organization for Research and Treatment of Cancer)-Italian Sarcoma Group (ISG)-Australasian GI Trials Group (AGITG)-phase III trial (EORTC-62005)<sup>167</sup> and the North American phase III study SWOG (Southwest Oncology Group) S0033/CALGB 150105<sup>168</sup> 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.<sup>168</sup> 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.<sup>161, 162</sup> 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.<sup>161</sup> 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).<sup>162</sup> 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.<sup>168-170</sup> 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*.<sup>169</sup> 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).<sup>168</sup> 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).<sup>170</sup> 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.<sup>171</sup>



### *Preoperative Imatinib*

The safety and efficacy of preoperative imatinib in patients with primary GISTs or preoperative imatinib in patients with resectable metastatic disease was evaluated in two randomized phase II studies.<sup>172, 173</sup> The RTOG 0132/ACRIN 6665 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).<sup>172</sup> The response rates in patients with primary GIST were 7% partial and 83% stable disease. The corresponding response rates in patients with recurrent or metastatic disease were 4.5% and 91% respectively. The estimated OS was 93% and 91% for patients with primary GIST and those with recurrent or metastatic GIST respectively. Two year PFS was 83% and 77% respectively. In a randomized trial conducted at the M.D. Andersen Cancer Center, 19 patients undergoing surgical resection were randomized to receive 3, 5, or 7 days of preoperative imatinib (600 mg daily).<sup>173</sup> 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.

While the results of these two trials showed the safety and efficacy of preoperative imatinib in patients undergoing surgical resection, survival benefit could not be determined since all patients in both trials received imatinib postoperatively for 2 years. This long-term analysis of RTOG 0132 study suggested that a high percentage of patients progressed after discontinuation of 2-year postoperative imatinib therapy.<sup>174</sup> At the present time, the decision to use preoperative therapy for patients with resectable primary or locally advanced 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%.<sup>175-177</sup> Median time to recurrence after resection of primary high-risk GIST is about 2 years.

The American College of Surgeons Oncology Group (ACOSOG) first evaluated the efficacy of postoperative imatinib in a single arm multicenter phase II intergroup trial in 106 evaluable patients with primary GIST at high risk of recurrence based on clinicopathological factors. Patients were treated with 1 year of imatinib at 400 mg/day.<sup>178</sup> In this trial, postoperative imatinib prolonged RFS following complete resection and was also associated with improved OS compared to historical controls.

In 2002, ACOSOG undertook a phase III, double-blind randomized trial (Z9001) of postoperative imatinib (400 mg/day vs. placebo) after resection of primary localized GISTs. Patients were randomized to imatinib 400 mg (359 patients) or placebo (354 patients) for one year after surgical resection. The interim analysis showed that the use of postoperative imatinib following resection of primary GIST improved RFS.<sup>179</sup> Analysis of 713 patients from 230 sites with a median follow-up of 19.7 months was recently published. Sixty seven percent of patients completed one year of adjuvant imatinib. RFS at one year was 98% in the imatinib arm vs. 83% in the placebo arm, which was statistically different. OS was not different in both arms. Although the trial was not designed to assess patient subsets, subset analysis showed that RFS was statistically in favor of the imatinib arm (96% for imatinib vs. 67-86% for placebo) in patients with high-risk tumors (greater than 6 cm).<sup>179</sup> However, at this point, the trial results are not conclusive regarding the appropriate duration of treatment, and regarding the



effect of imatinib resistance and genetic mutations on the outcome of adjuvant imatinib. Long-term follow-up is ongoing. Based on the results of ACOSOG Z9001 trial, in December 2008, the FDA approved imatinib for postoperative treatment of adult patients following resection of KIT-positive GIST.

The results of a recently completed randomized 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.<sup>180</sup> In this trial, patients with a high-risk for GIST recurrence after surgery (tumor greater than 5 cm in size with high mitotic rate (> 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.<sup>181</sup> 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.<sup>182</sup> 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.<sup>183</sup> Secondary resistance appears to be related to the acquisition of new kinase mutations.<sup>184</sup> 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.<sup>185</sup> 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.<sup>186</sup> 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.<sup>187</sup> 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.<sup>188</sup> 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 *PDGFRA* 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.

#### *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).<sup>189</sup> 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.<sup>190</sup>

Recent reports have shown that sunitinib is also associated with cardiotoxicity and hypothyroidism.<sup>191, 192</sup> 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.<sup>191</sup> 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.<sup>192</sup>

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.<sup>158</sup>

### 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.

### 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.<sup>158</sup> Many imaging centers are also equipped with combined PET-CT scanners, which may facilitate both anatomic and functional tumor evaluation in one step.<sup>193</sup> 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.<sup>194</sup> 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.<sup>195</sup> 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.<sup>196</sup>

### Resectable Disease

Surgery is the primary treatment for all patients with resectable GISTs that are 2 cm or greater without significant risk of morbidity. However, the management of incidentally encountered small GISTs less than 2 cm remains controversial.<sup>158</sup> 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.<sup>156</sup> The panel has included this approach with a category 2B recommendation.

Patients with marginally resectable or resectable GIST with a significant risk of morbidity should be considered for preoperative imatinib prior to resection, if surgical morbidity would be improved by reducing the size of the tumor. However, 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. If there is no progression, resection should be considered, if possible. If there is progression, as confirmed with CT scan, surgery is recommended after discontinuing imatinib. Collaboration between the medical oncologist and the surgeon is necessary to determine the appropriateness of surgery following major response or stable disease.

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. If there is persistent gross disease following 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. The panel has included postoperative imatinib as an alternative to observation, for patients at significant risk of recurrence who have undergone complete resection for primary GIST.<sup>179, 180</sup> Based on the results of the recently completed randomized trial (SSGXVIII/AIO), the panel recommends that postoperative imatinib for at least 36 months should be considered for patients with high-risk GIST (tumor greater than 5 cm in size with high mitotic rate (> 5 mitoses/ 50 HPF)).<sup>180</sup> Risk stratification after surgical resection should be based on tumor mitotic rate, size and location.<sup>197</sup> Gold et al. have developed a nomogram, taking into account tumor size, site and mitotic index, to predict relapse-free survival (RFS) after



resection of localized primary GIST.<sup>198</sup> 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.

### **Metastatic, Unresectable 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 studies have evaluated the impact of cytoreductive surgery on survival in patients with advanced GIST after treatment with 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.<sup>199</sup>

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 as tolerated or switching to sunitinib. Patients with limited progression should not be switched to sunitinib if most of the disease is still controlled by imatinib. 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.<sup>200</sup> Other treatment options include radiofrequency ablation or embolization (category 2B). 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,<sup>201-203</sup> nilotinib<sup>204, 205</sup> and dasatinib,<sup>206, 207</sup> have shown activity in patients with imatinib and sunitinib resistant GIST. In retrospective analysis (32 patients), sorafenib was significantly active in patients with metastatic GIST



resistant to imatinib and sunitinib.<sup>201</sup> 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.<sup>202</sup> 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.<sup>204</sup> In a retrospective analysis, nilotinib resulted in 10% response rate and 37% disease control rates in patients who had failed prior imatinib and sunitinib.<sup>205</sup> 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.<sup>206</sup> 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.<sup>207</sup> 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.

Any patient who has progression of GIST 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 limited data (as discussed above), the guidelines have included sorafenib, dasatinib or nilotinib as options for patients who are no longer receiving clinical benefit from imatinib or

sunitinib. 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.<sup>208</sup> 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.<sup>209, 210</sup> 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.<sup>210</sup>

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 (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)<sup>211</sup> and may also arise through elective surgical intervention (eg, colectomy) in susceptible patients.<sup>212</sup> 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.<sup>213</sup> 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.<sup>214</sup> Although desmoid tumors are often locally invasive, they rarely metastasize. Most patients do not die of their tumors.<sup>215</sup> Desmoids can cause functional morbidity.

Dysregulation of  $\beta$ -catenin pathway has been commonly identified in sporadic desmoids although the incidence of *CTNNB1* (the gene

encoding  $\beta$ -catenin) mutations is uncertain. Lazar et al recently reported that mutations in exon 3 of *CTNNB1* gene are identified in 85% of desmoids.<sup>216</sup> 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.<sup>216</sup> Domont et al also reported  $\beta$ -catenin mutations in 87% of patients with extra-abdominal desmoid fibromatosis.<sup>217</sup> This retrospective study was restricted to patients with extra-abdominal tumors and the 5-year RFS rate was significantly worse in  $\beta$ -catenin mutated tumors, regardless of the genotype, compared with wild-type tumors (49% vs. 75%, respectively).<sup>217</sup> These findings are in contrast to that reported by Lazar et al.<sup>216</sup> 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.<sup>218-220</sup>



## Resectable Tumors

Complete macroscopic surgical resection is the primary treatment for resectable desmoid tumors.<sup>221-224</sup> The results of recent retrospective analyses suggest that observation may be appropriate for selected patients with resectable tumors.<sup>225-227</sup> 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 ( $p = 0.70$ )).<sup>226</sup> 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. Preoperative RT or chemoradiation has been associated with local control.<sup>228, 229</sup>

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. 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.<sup>230</sup> 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.<sup>231, 232</sup> Desmoid tumors respond slowly to radiation; often 2 years may be required for desmoid tumors to fully respond to radiation. Irradiation of an unresectable tumor is a reasonable consideration, depending on the possible morbidity of treatment.<sup>233, 234</sup> For example, 23 patients received radiation 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 radiation achieved a complete response without resection (5 patients) or achieved stabilization (3 patients) of their disease after some regression.<sup>235</sup>

Definitive RT (only for desmoid tumors of the extremity), systemic therapy or observation are some of the options for patients with unresectable tumors. Radical surgery should be considered only if other treatment modalities fail.

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.<sup>236, 237</sup> In a prospective study, tamoxifen in combination with sulindac resulted in disease stabilization in patients with progressive or recurrent tumors following surgery.<sup>238</sup> The results of a retrospective, non-randomized study showed that interferon alfa with or without tretinoin may be effective in prolonging the disease-free interval after intralesional or marginal surgery in patients with extra-abdominal desmoid tumors.<sup>239</sup> In case reports, toremifene has been effective in disease stabilization following surgery.<sup>240-243</sup> Doxorubicin-based chemotherapy has been effective in patients with unresectable tumors.<sup>244-246</sup> In a phase II study, the combination of methotrexate and vinblastine was associated with prolonged stable disease in a substantial subset of patients with unresectable aggressive fibromatosis.<sup>247</sup>

Imatinib has also been active in patients with unresectable, progressive or recurrent aggressive fibromatosis.<sup>248</sup> In a phase II multicenter trial (SARC trial), imatinib resulted in an objective response rate of 6% and the 1-year progression-free survival was 66% in patients with unresectable DF.<sup>249</sup> 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.<sup>250</sup> At a median follow-up of 34 months, the 2-year progression-free and overall survival rates were 55% and 95%, respectively. The non-progression rates at 3, 6 and 12 months were 91%, 80% and 67% respectively.

The guidelines have included sulindac or other NSAIDs (including celecoxib), tamoxifen, toremifene, low-dose interferon, methotrexate and vinblastine, doxorubicin-based regimens and imatinib 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. Physicians prescribing celecoxib should consider

this emerging information when weighing the benefits against risks for individual patients. In December 2004, FDA issued a public health advisory recommending limited use of Cox-2 inhibitors (FDA Talk Paper No. T04-61; December 23, 2004).

### 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.

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