National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Soft Tissue Sarcoma

V.2.2007

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ξ Bone Marrow Transplantation
≠ Pathology
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To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Consensus

Summary of Guidelines Updates

The NCCN Soft Tissue Sarcoma Guidelines do not include the management of Rhabdomyosarcoma, Ewing's Sarcoma, or Desmoplastic small round cell tumors.

These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations nor warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2007.

Summary of the Guidelines updates

The 1.2007 version of the Soft Tissue Sarcoma Guidelines was changed to a 2.2007 version due to the update of the GIST section based upon the GIST Task Force Meeting. Summary of changes include:

- **"Shared decision making" was added under workup (GIST-1).**
- **"Risk assessment" was added to "pathology review" after resect mass (GIST-1).**
- **Footnotes "e" and "f" are new to the page (GIST-1).**
- **Footnote "j" was modified (GIST-2 and GIST-3).**
- **Footnotes "l" and "n" are new to the page (GIST-2).**
- **"Incomplete resection; no previous imatinib" and "Completely resected after neoadjuvant therapy" were added as postresection categories (GIST-4).**
- **Footnote "t" is new to the page (GIST-5).**

Continued...

Summary of the Guidelines updates (continued)

Summary of changes in the 1.2007 version of the Soft Tissue Sarcoma Guidelines from the 3.2006 version include:

Global Changes

- A note was added to the Table of Contents that the Sarcoma Guidelines do not include the management of Rhabdomyosarcoma, Ewing's sarcoma, or Desmoplastic small round cell tumors.
- The Principles of Surgery section was revised (SARC-A).
- The Guidelines for Radiation Therapy are now applicable to all sites (SARC-B)
- Generally Accepted Systemic Therapy (SARC-C) - epirubicin (single agent) and the combination of epirubicin, ifosfamide and mesna were added. Imatinib was added as an option for desmoid tumors.

Extremity

- The chest x-ray recommendation was changed to chest imaging (EXTSARC-1).
- PET scan recommendation was modified to it "may be useful in prognostication, grading and determining response to chemotherapy" (EXTSARC-1).
- The indications for abdominal/pelvic CT were expanded to epithelioid, angiosarcoma, and leiomyosarcoma (EXTSARC-1).
- Chemotherapy was removed as an additional treatment option with surgery or surgery + RT (EXTSARC-2).
- The treatment recommendations for Stage II and III were revised based upon resectability and the treatment options expanded. Footnotes k, l, and m are new to the page (EXTSARC-3).
- The category "regional nodes" was added with treatment recommendations (EXTSARC-4).
- The statement that Thoracotomy was preferred over VATs was removed from footnote o (EXTSARC-4).

Retroperitoneal/Abdominal

- The category of marginally resectable was removed (RETSARC-1).
- Footnote a is new to the page. Intraoperative Radiation Therapy (IORT) was added as a treatment option with surgery. After surgery, the treatment recommendations are now based upon the R resection (R0, R1, R2) (RETSARC-2).
- Postoperative RT was changed to a category 2B designation for R0 high grade and R1 resections (RETSARC-2).
- Footnote f is new to the page (RETSARC-4).

Gastrointestinal Stromal Tumors (GIST)

- Endoscopic ultrasound was added to the workup (GIST-1).
- The recommendation for baseline PET was changed to consider and a MRI was added. Response was changed to therapeutic effect with the result of "no progression" or "progression". If the patient progresses, the recommendation is to confirm with CT and then surgery (GIST-2).
- The recommendation for baseline PET is now only if PET will be used in follow-up assessment. Footnote l is new to the page (GIST-3).
- For limited progression, palliative RT was added with a category 2B designation for rare patients with bone metastases. Clarification was added to only consider discontinuation of imatinib or sunitinib if the patient no longer is receiving clinical benefit (GIST-5).

Intra-abdominal sarcomas other than GIST

- The option for IORT was added to surgery. Postoperative RT was removed and patients with a total resection proceed to follow-up (GISARC-1).

Desmoid Tumors

- RT was removed as a treatment option. Therapy options are based upon R resection after surgery (DESMSARC-1).

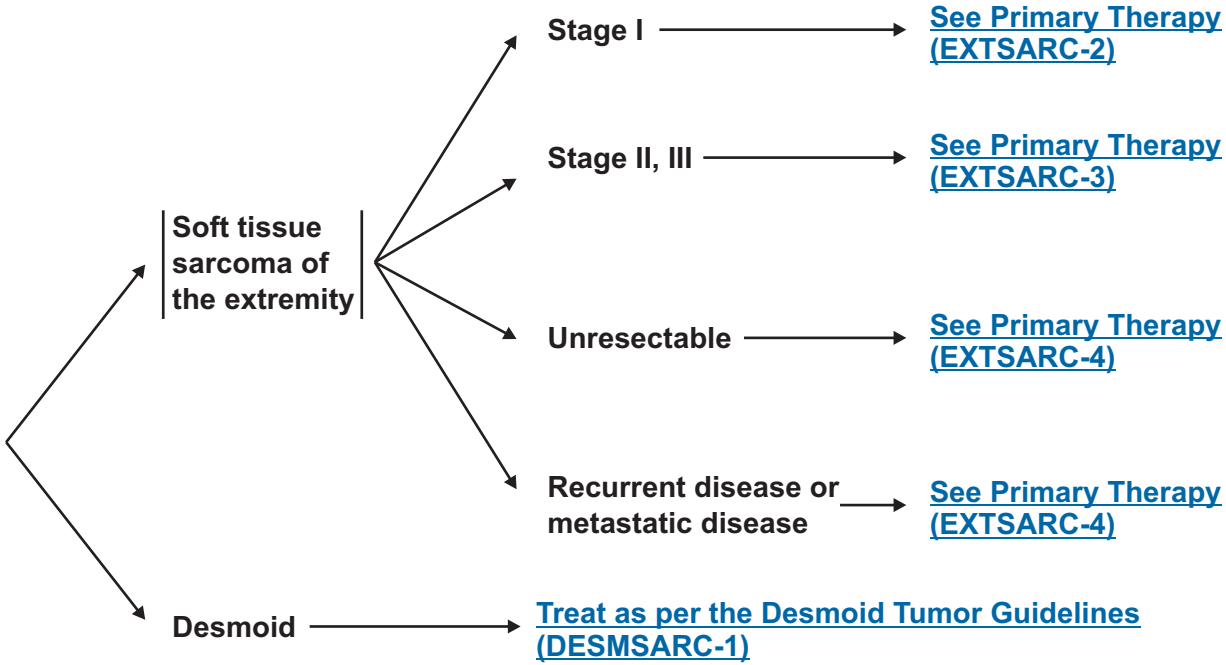
WORKUP

ESSENTIAL:

- All patients should be managed by a multidisciplinary team with expertise in sarcoma
- H&P
- Adequate imaging[a] of primary tumor is indicated for all lesions with a reasonable chance of being malignant (MRI ± CT)
  - Plain radiograph of primary tumor (optional)
- Carefully planned biopsy (core needle or incisional biopsy after adequate imaging, placed along longitudinal axis, with minimal dissection and careful attention to hemostasis)[b]
  - Biopsy should establish grade and histologic subtype
  - Appropriate use of expert molecular and cytogenetic analysis[c]
- Chest imaging

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- PET scan may be useful in prognostication, grading and determining response to chemotherapy
- Consider abdominal/pelvic CT for myxoid liposarcoma, epithelioid sarcoma, angiosarcoma, and leiomyosarcoma.



[a] Adequate imaging should provide details about the size of tumor and contiguity to nearby visceral structures and neurovascular landmarks.
[b] In selected institutions with clinical and pathologic expertise, an FNA may be acceptable.
[c] Molecular diagnostic techniques can be useful in establishing the diagnosis of synovial sarcoma, clear cell sarcoma, and liposarcoma.

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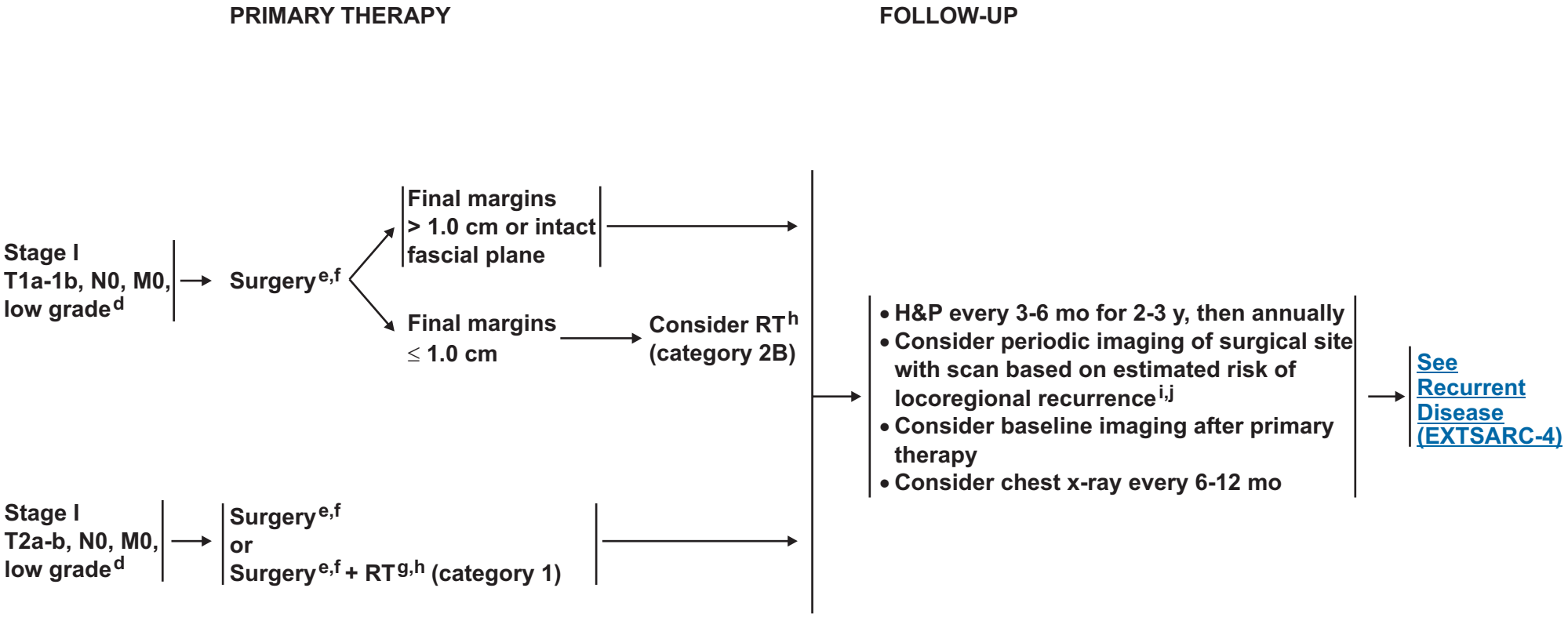

[d] See the American Joint Committee on Cancer (AJCC) Staging Manual, 6th Edition for conversion to a three or four tiered grading system.

[e] See Principles of Surgery (SARC-A).

[f] Reresection, if feasible, may be necessary to render margins > 1.0 cm.

[g] Randomized clinical trial data support the use of radiotherapy (category 1) as an adjunct to surgery in appropriately selected patients based on an improvement in disease-free survival (although not overall survival). The preferred timing of treatment (preoperative vs postoperative) has not been defined.

[h] See Guidelines for Radiation Therapy (SARC-B).

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

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

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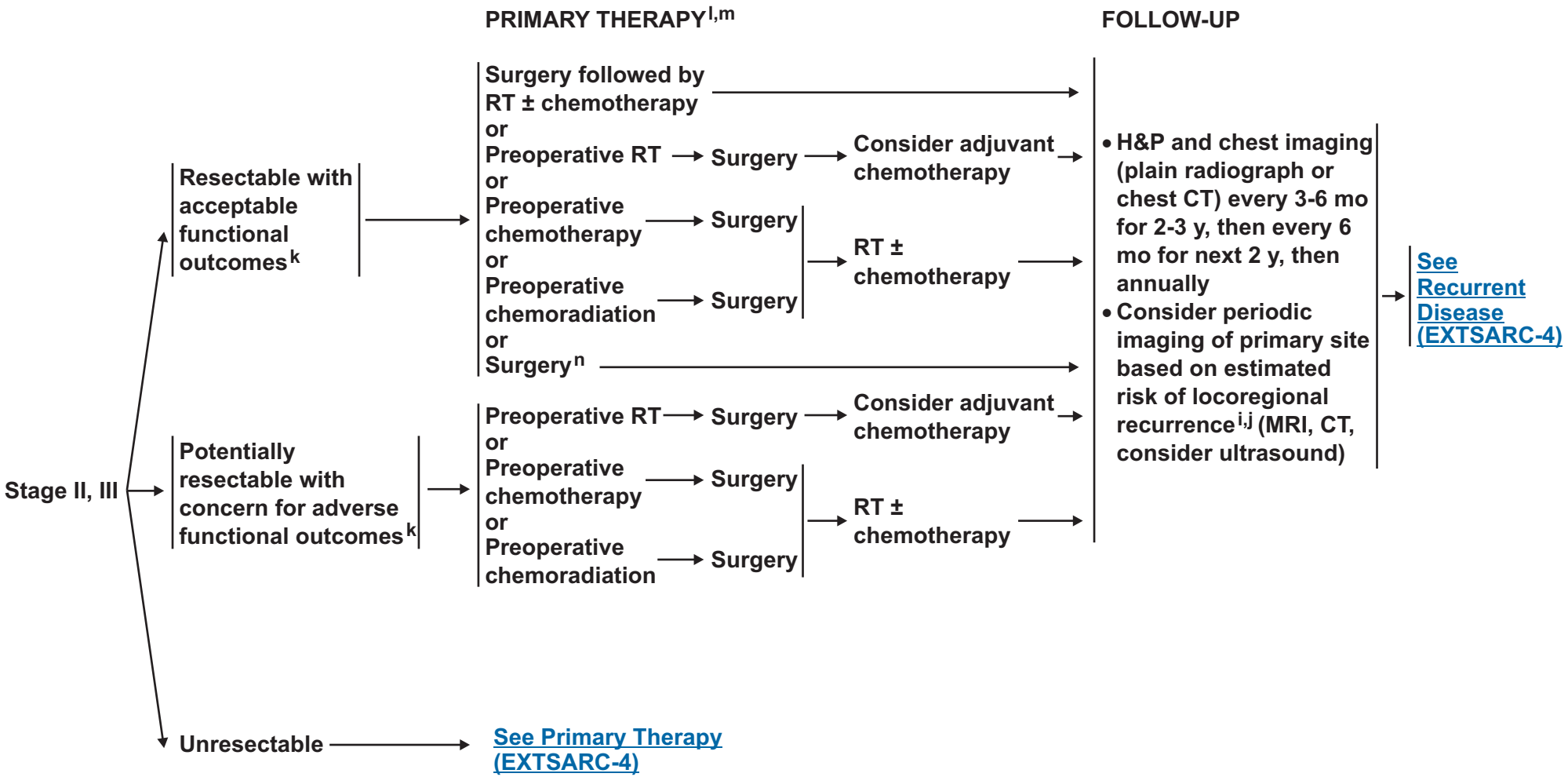

[i] In situations where the area is easily followed by physical examination, imaging may not be required.

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

[k] Large (> 10 cm), high grade sarcomas are at a higher risk for local recurrence and metastases and should be considered for preoperative therapy (chemotherapy and/or radiation therapy) prior to resection.

[l] 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.

[m] See Principles of Systemic Therapy (SARC-C).

[n] Surgery may be an option for small tumors resected with wide margins.

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RECURRENT DISEASE OR PRIMARY PRESENTATION WITH METASTATIC OR UNRESECTABLE DISEASE

PRIMARY THERAPY

Local recurrence → **Follow Workup, then appropriate Primary Therapy pathway (EXTSARC-1, EXTSARC-2, and EXTSARC-3)**

Metastatic or unresectable disease

→ **Single organ and limited tumor bulk, regional nodes** →

Primary tumor management as per EXTSARC-1
- **Consider regional node dissection for nodal involvement**
- **Consider metastasectomy[o] ± preoperative or postoperative chemotherapy[m] ± RT**
- **Ablation (radiofrequency ablation [RFA])**
- **Embolization procedures**

→ **Disseminated metastases or unresectable** →

Options:
- **Observation, if asymptomatic**
- **Chemotherapy[m]**
- **RT**
- **Palliative surgery**
- **Best supportive care**
- **Ablation procedures (eg, RFA or cryotherapy)**
- **Embolization procedures**

[m] See Principles of Systemic Therapy (SARC-C).

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

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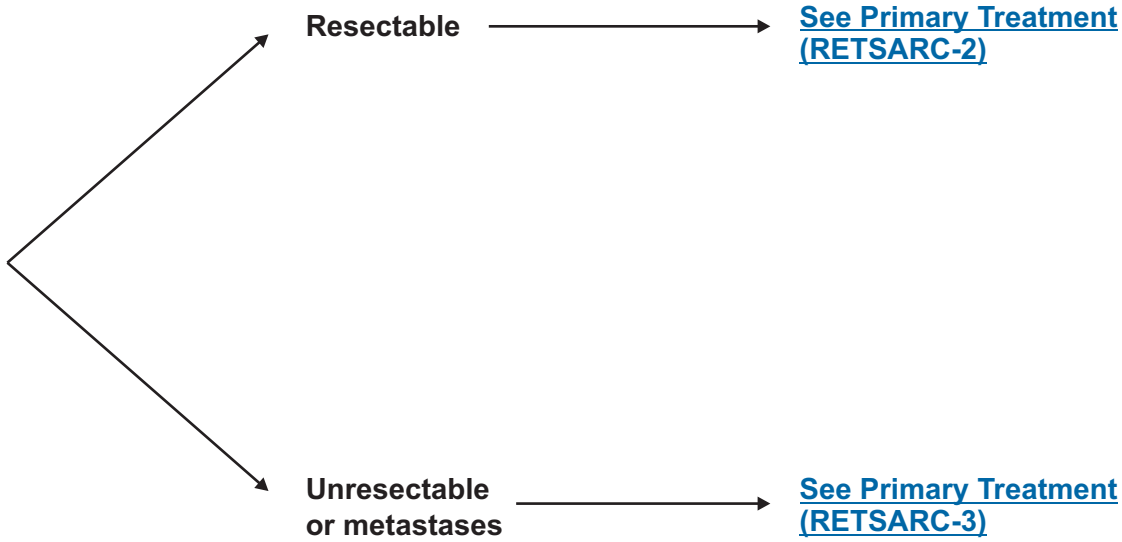
WORKUP

- All patients should be managed by a multidisciplinary team with expertise in sarcoma
- H&P
- 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)
- Chest imaging
- Endoscopy as indicated



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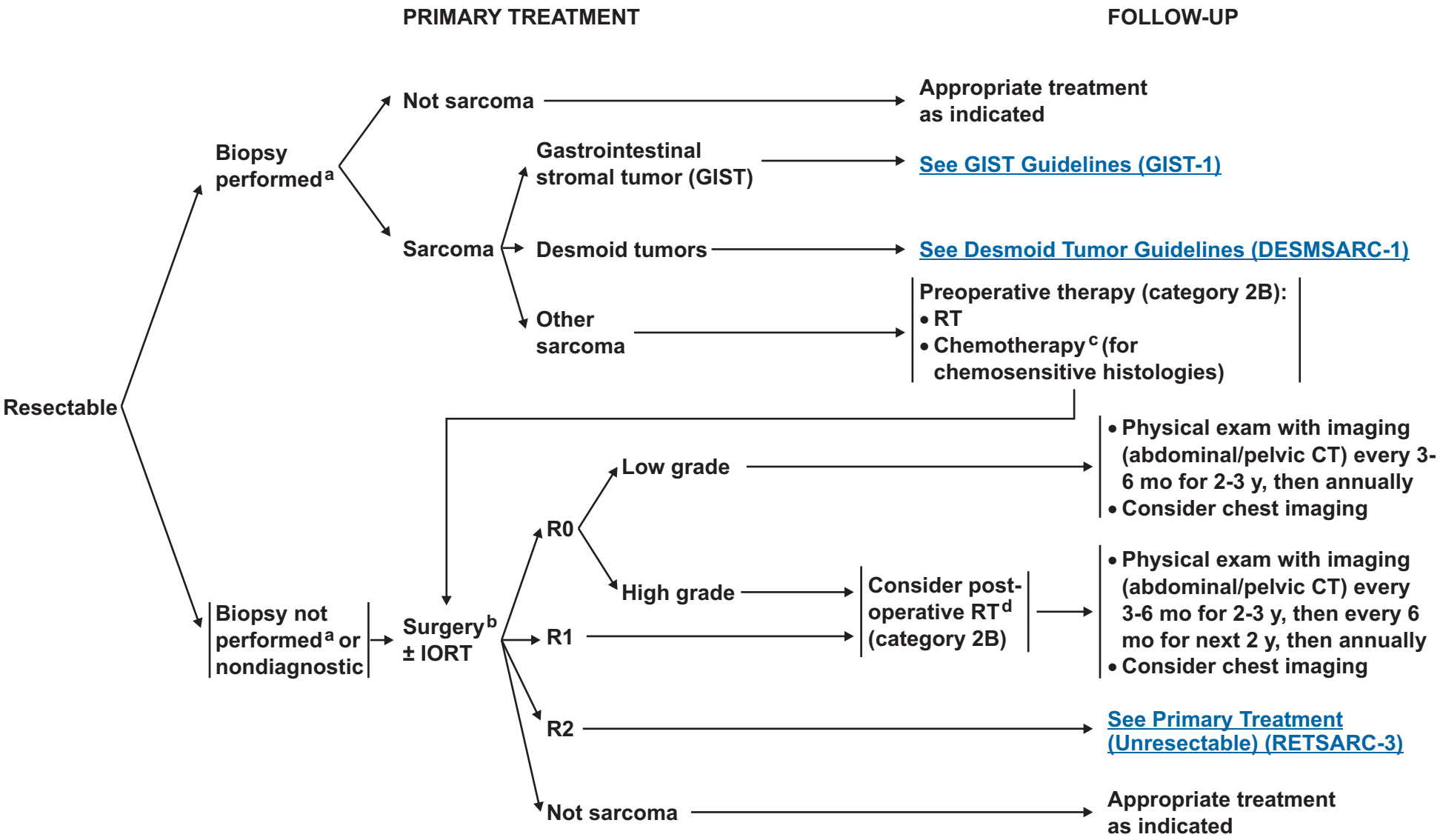

[a] Biopsy required if considering preoperative therapy.
[b] See Principles of Surgery (SARC-A).
[c] See Principles of Systemic Therapy (SARC-C).
[d] See Guidelines for Radiation Therapy (SARC-B).

Recurrent Disease (see RETSARC-4)

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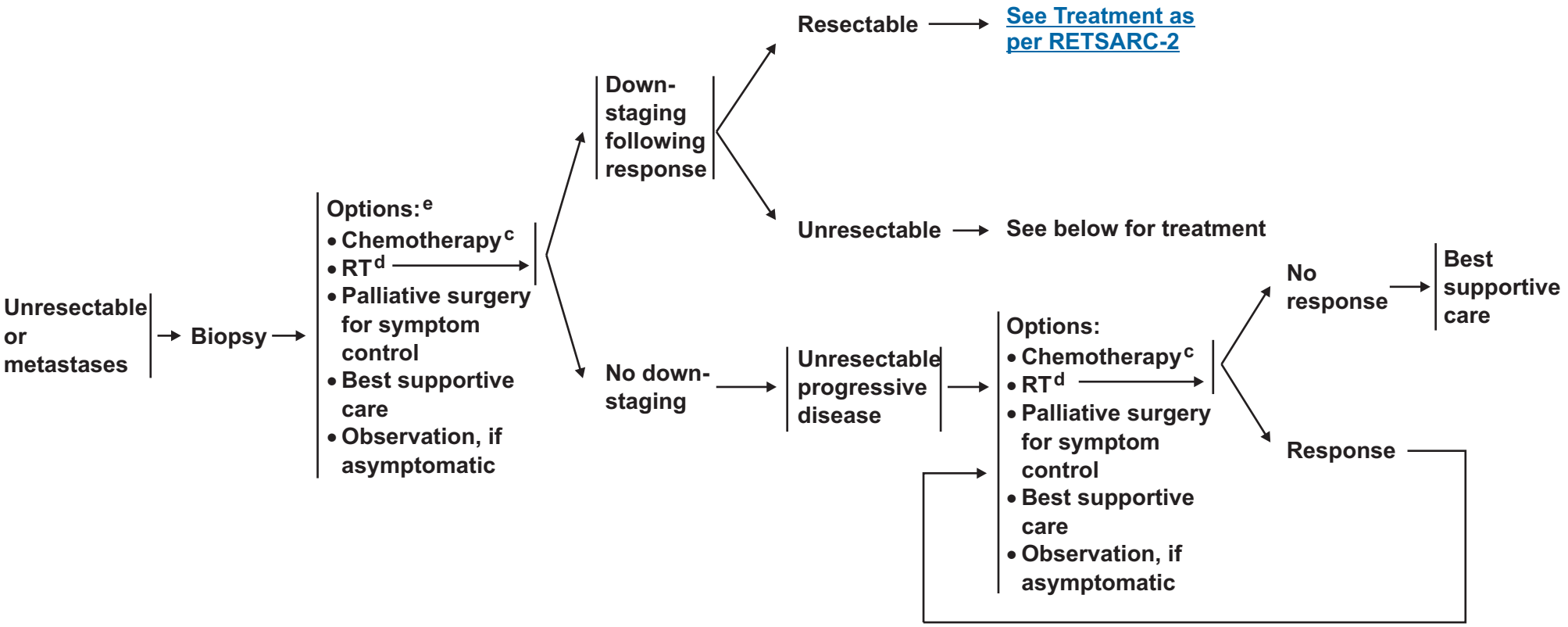
PRIMARY TREATMENT



Recurrent Disease (see RETSARC-4)

[c] See Principles of Systemic Therapy (SARC-C).
[d] See Guidelines for Radiation Therapy (SARC-B).
[e] Balance risks of treatment, likelihood of rendering patient resectable, performance status of patient, with potential clinical benefits.

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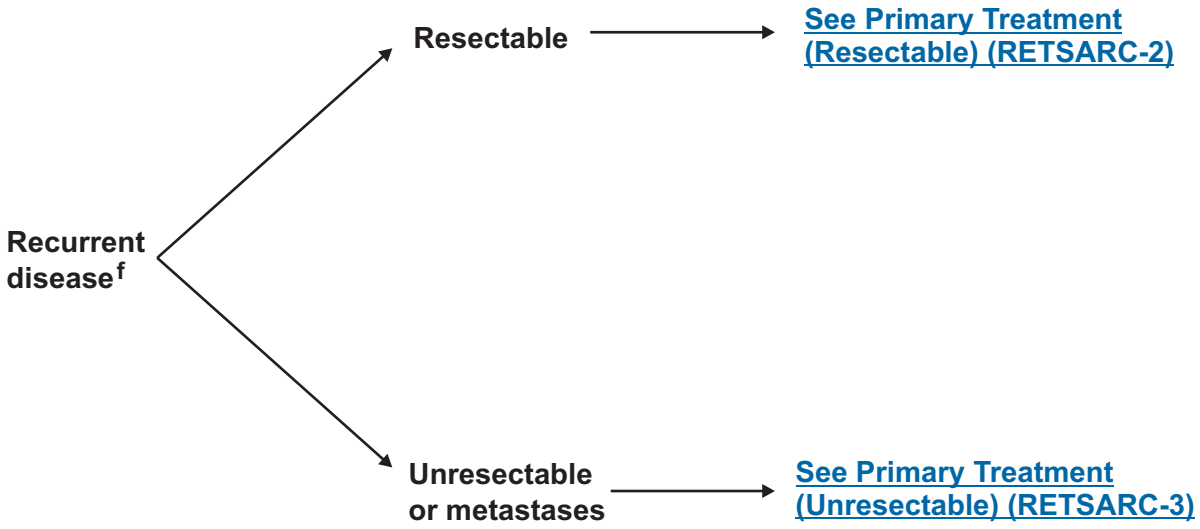
RECURRENT DISEASE



[f]Consider preoperative RT and/or chemotherapy if not previously administered.

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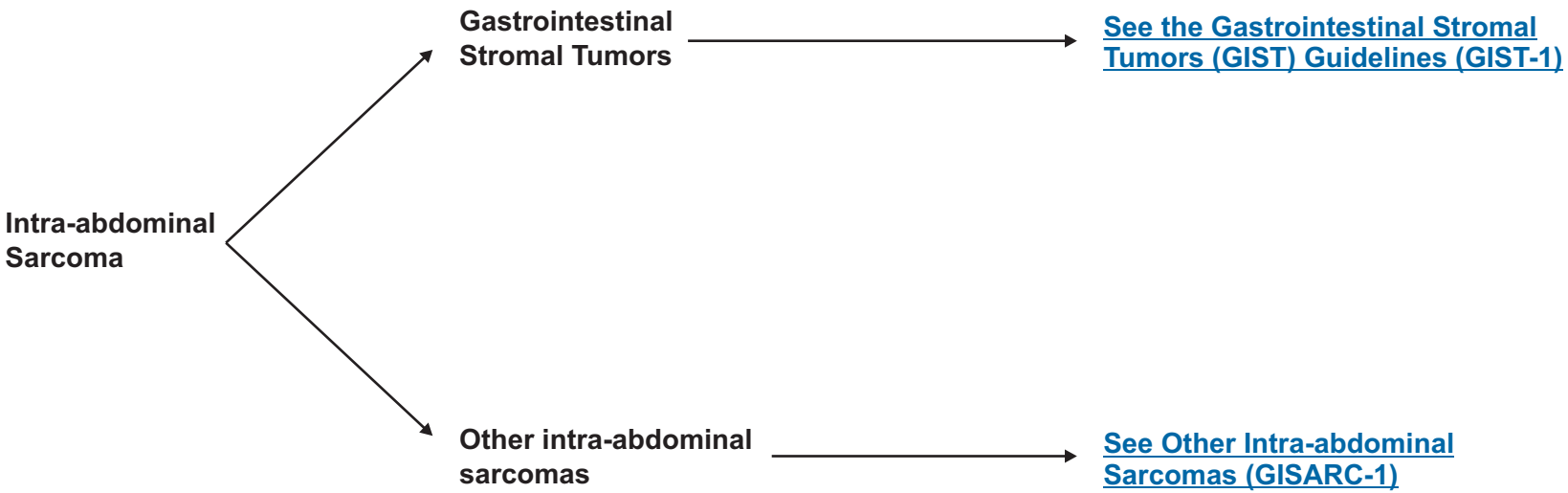
Intra-abdominal Sarcoma



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WORKUP OF PATIENT AT PRIMARY PRESENTATION

- All patients should be managed by a multidisciplinary team with expertise in sarcoma
- H&P
- Abdominal/pelvic CT with contrast, and/or MRI
- Chest imaging
- Endoscopic ultrasound
- Endoscopy as indicated (if not previously done)
- Shared decision making

INITIAL DIAGNOSTIC EVALUATION

Localized or potentially resectable disease[a]

- **Neoadjuvant therapy not considered[b]** → **Resect mass** → **Pathology result[e,f] and risk assessment**
  - **Documented GIST** → See Postsurgical Therapy (GIST-4)
  - **Other sarcomas of GI origin** → See GISARC-1
  - **Other cancers** → See appropriate cancer guidelines within the NCCN Table of Contents
- **If considering neoadjuvant therapy[c]** → **Biopsy[d]** → **Pathology result[e,f]**
  - **Documented GIST**
    - **Marginally resectable or Resectable with risk of significant morbidity[g]** → See Primary Treatment (GIST-2)
    - **Definitively unresectable or metastatic disease** → See Primary Treatment (GIST-3)
  - **Other sarcomas of GI origin** → See Primary Treatment (GISARC-1)
  - **Other cancers** → See appropriate cancer guidelines within the NCCN Table of Contents

Definitively unresectable or metastatic disease → **Biopsy[d]** → **Pathology result[e,f]**

[a] Surgery should induce minimal surgical morbidity, otherwise consider preoperative imatinib mesylate.
[b] If surgical morbidity would not improve by reducing the size of the tumor preoperatively.
[c] If surgical morbidity would be improved by reducing the size of the tumor preoperatively.
[d] See Principles of Biopsy (GIST-A).
[e] Report should include size and mitotic rate, fields should be in the most mitotic area.
[f] Mutational analysis may have predictive value and is currently being investigated. Consider molecular analysis if available.
[g] Some patients may rapidly become unresectable; close monitoring is essential.

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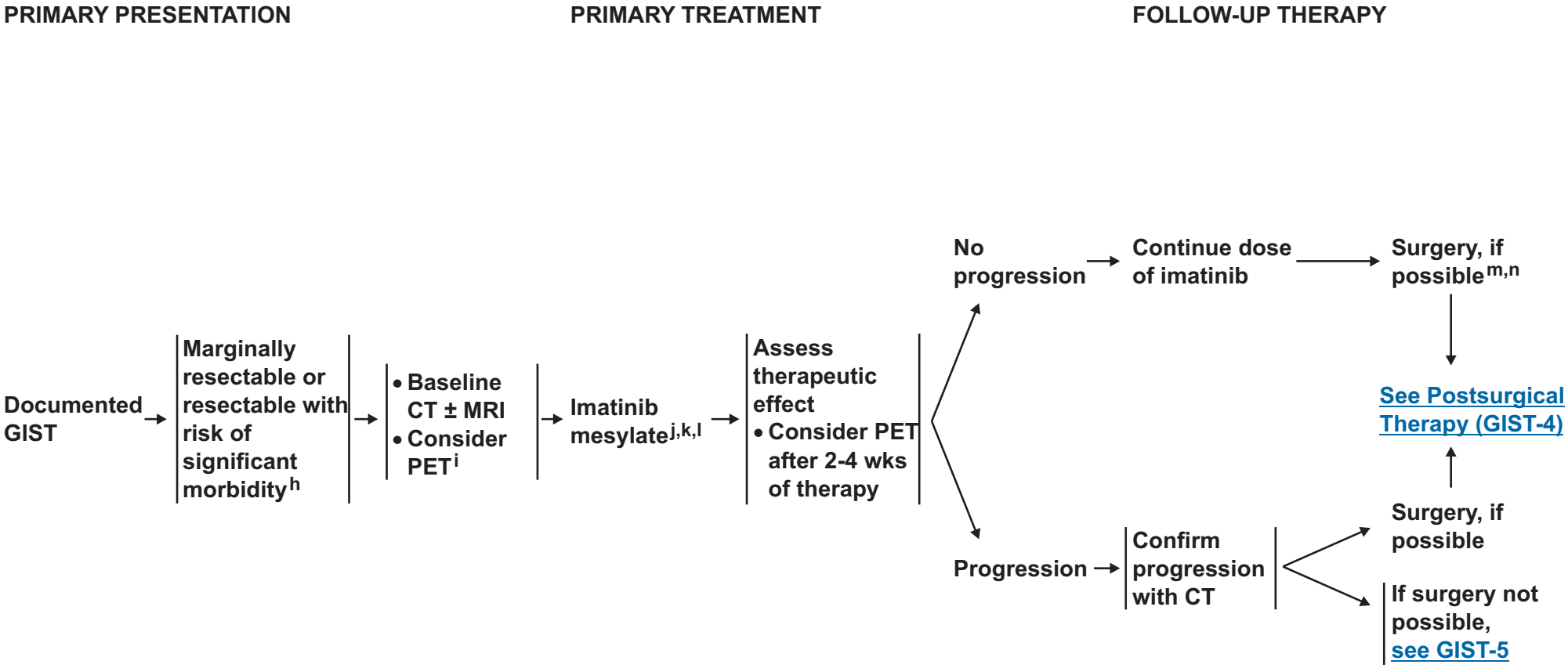

[h]Some patients may rapidly become unresectable; close monitoring is essential.
[i]PET is not a substitute for a CT.
[j]Suggested starting dose is 400 mg/day. If molecular diagnosis available and exon 9 positive, recent data support the use of imatinib at 800 mg/day (category 2B).
[k]If life threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider sunitinib.
[l]Medical therapy is usual course of treatment, if patient bleeding or symptomatic, may proceed to surgery.
[m]Collaboration between medical oncologist and surgeon necessary to determine appropriateness of surgery, following major response or sustained stable disease.
[n]Dosing can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications.

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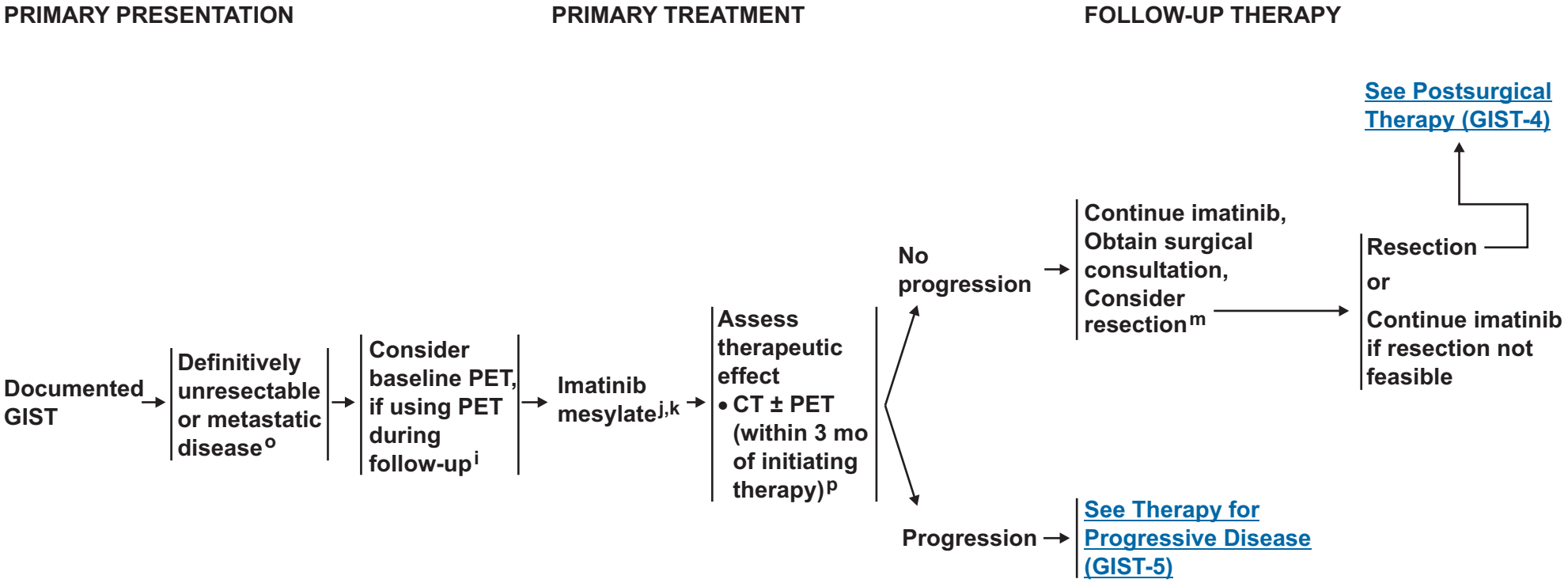

[i]PET is not a substitute for CT.
[j]Suggested starting dose is 400 mg/day. If molecular diagnosis available and exon 9 positive, recent data support the use of imatinib at 800 mg/day (category 2B).
[k]If life threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider sunitinib.
[m]Collaboration between medical oncologist and surgeon necessary to determine appropriateness of surgery, following major response or sustained stable disease.
[o]May observe low-volume asymptomatic metastases.
[p]In some patients, it may be appropriate to image prior to 3 months.

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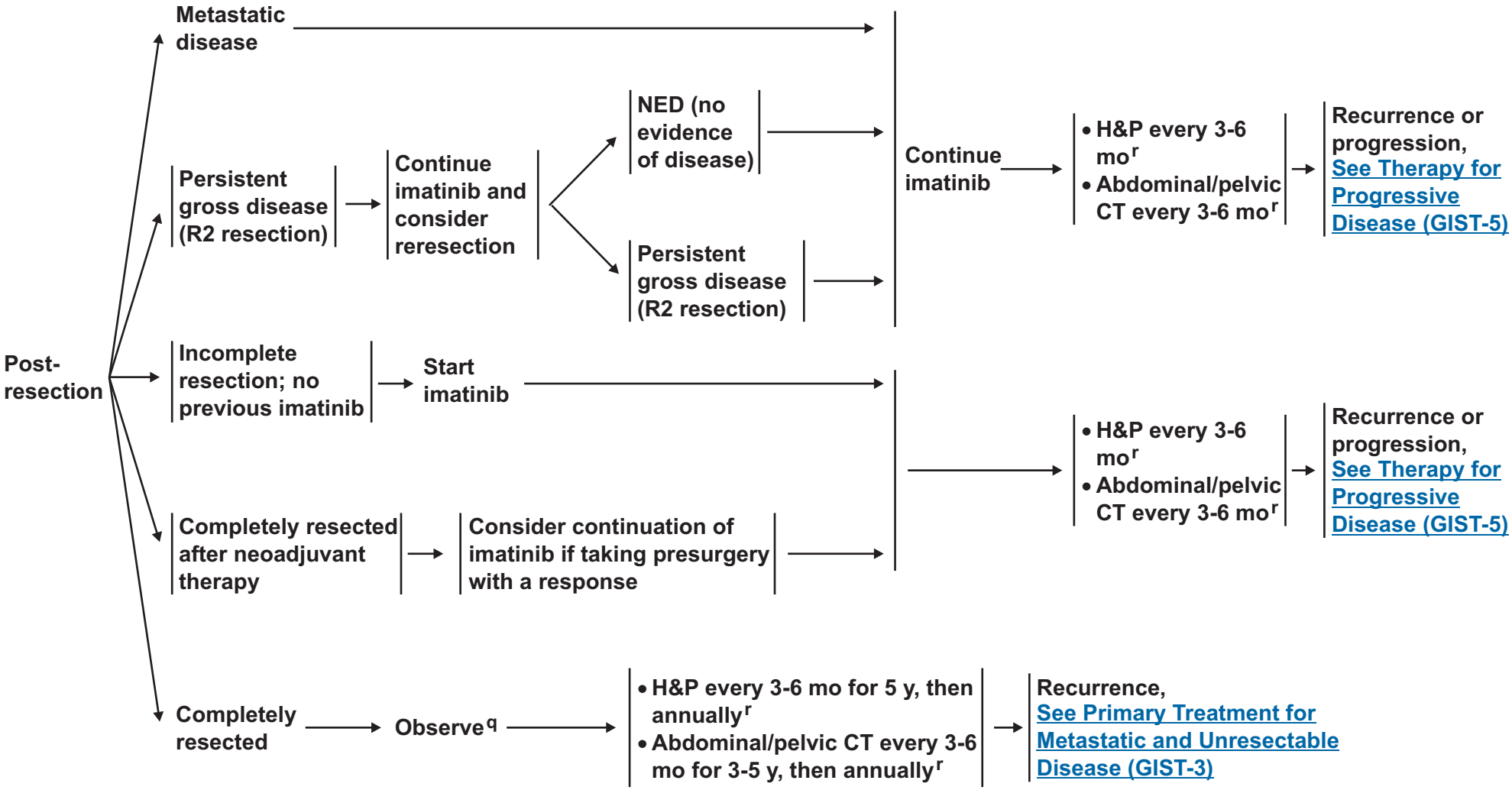
Gastrointestinal Stromal Tumors (GIST)

POSTSURGICAL THERAPY



[q]Some physicians choose to administer adjuvant imatinib for high risk patients, even though there are no data to support this off trial. National cooperative group trials are ongoing to address this question and patients should be encouraged to enroll.

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

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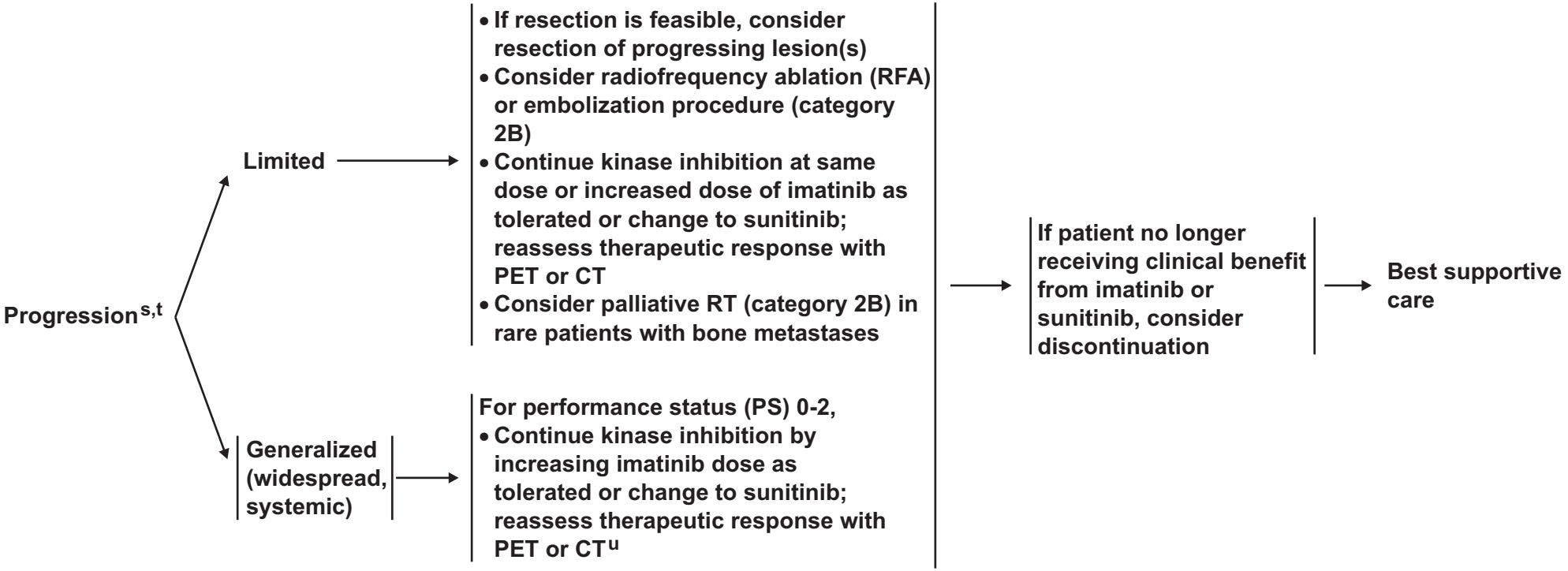
THERAPY FOR PROGRESSIVE DISEASE



[s]Progression may be determined by CT or MRI with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.
[t]Suggest referral to a sarcoma specialty center.
[u]Clinical experience recommends continuing imatinib, especially if progression is slow.

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Gastrointestinal Stromal Tumors (GIST)

PRINCIPLES OF BIOPSY

- 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 necessary when planning neoadjuvant therapy.
- Specialized pathology, referral to specialist centers for sarcomas with complex or unusual features.
- CD 117 immunostain if GIST in differential.
- Consider investigational mutation assay for CD 117 (KIT) negative tumors.
- GISTs should be handled with care to avoid tumor rupture. The goal is to achieve complete gross resection with an intact pseudo-capsule.

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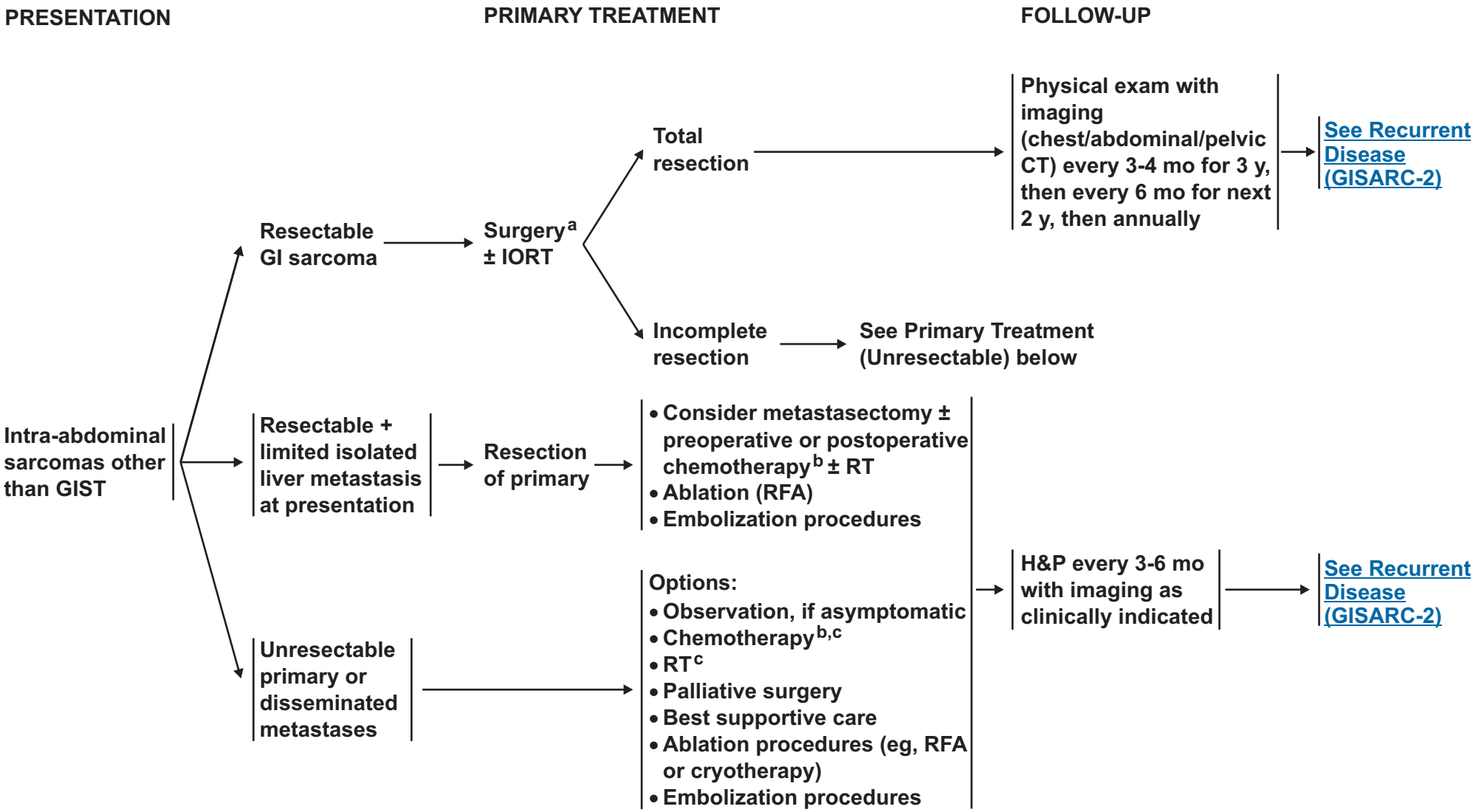
Intra-abdominal Sarcomas other than GIST



[a] See Principles of Surgery (SARC-A).
[b] See Principles of Systemic Therapy (SARC-C).
[c] If response, follow the resectable pathway.

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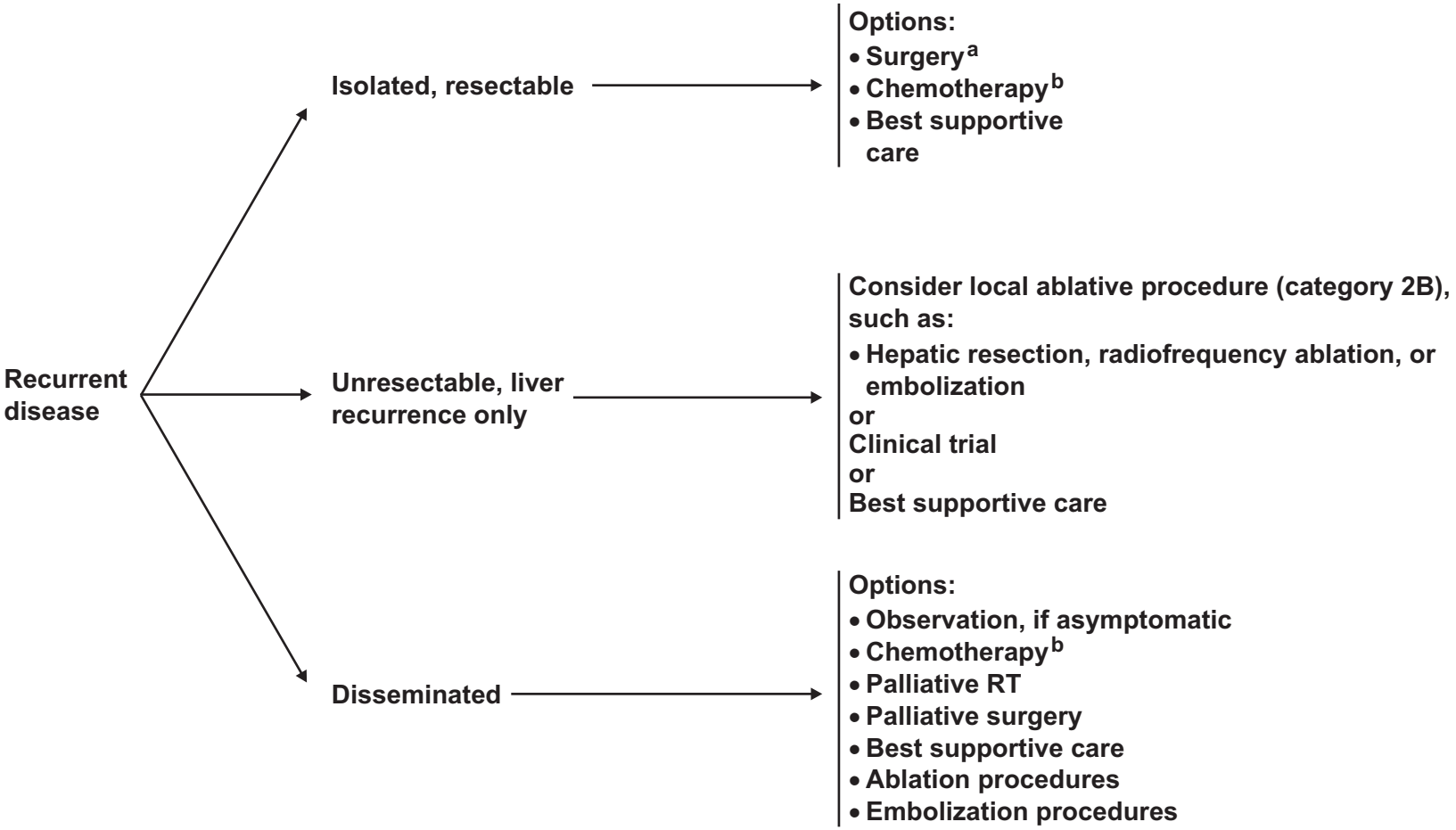
Intra-abdominal Sarcomas other than GIST

RECURRENT DISEASE



[a] See Principles of Surgery (SARC-A).
[b] See Principles of Systemic Therapy (SARC-C).

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Soft Tissue Sarcoma

Desmoid Tumors

Guidelines Index
Sarcoma Table of Contents
Staging, MS, References

WORKUP

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

→ Biopsy[a]

PRIMARY TREATMENT

Resectable → Surgery[b]

- R0 → Observation or Consider postoperative RT if large tumor
- R1 → Consider reresection or RT, if no prior RT or Observation
- R2 → RT or Systemic therapy[c] or Radical surgery to be considered if other modalities fail or Observation

Unresectable or surgery would be unacceptably morbid → RT or Systemic therapy[c] or Radical surgery to be considered if other modalities fail or Observation

→ H&P with appropriate imaging every 3-6 mo for 2-3 y, then annually → Recurrence, treat like primary disease

[a] May not be necessary if complete resection planned.
[b] For desmoids, microscopic positive margins are acceptable if achieving negative margins would produce excessive morbidity.
[c] See Principles of Systemic Therapy (SARC-C).

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PRINCIPLES OF SURGERY

- **Biopsy of Sarcoma**
  Biopsy is preferred to diagnose and grade sarcomas. 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.
- **Resection Margins**
  Surgical margins should be documented by both the surgeon and the pathologist in evaluating a resected specimen. Margins less than 1.0 cm should be evaluated carefully for postoperative adjuvant therapy and if possible identified intraoperatively by the surgeon.
  R0 resection - No residual microscopic disease
  R1 resection - Microscopic residual disease
  R2 resection - Gross residual disease
- **Pathology**
  Pathologic assessment of biopsies and resected specimens should be carried out by an experienced sarcoma pathologist with access to cytogenetic and molecular diagnostics.
- **Amputation**
  Consideration of amputation to treat extremity sarcoma should be made for patient preference or if one or more of the following tumor characteristics occur:
  - Extensive soft tissue mass and/or skin involvement
  - Involvement of a major artery or nerve
  - Extensive bony involvement necessitating whole bone resection
  - Failure of preoperative chemotherapy or radiation therapy
  - Tumor recurrence after prior adjuvant radiation
- **Limb Salvage Surgery**
  Limb salvage surgery is generally preferred to achieve local tumor control with minimal morbidity.
- **Consider postoperative rehabilitation (PT, OT) for patients with extremity sarcoma.**

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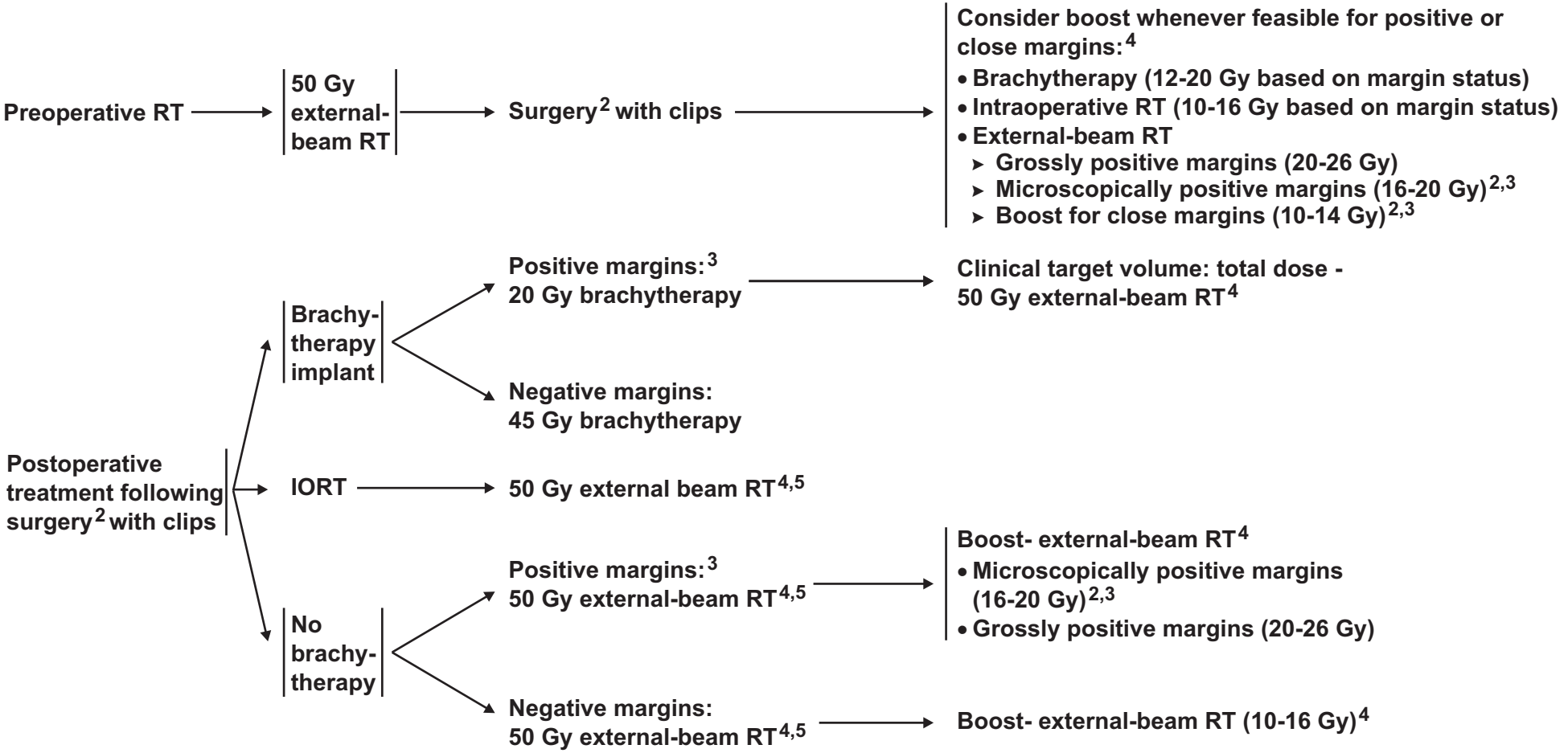
Soft Tissue Sarcoma

GUIDELINES FOR RADIATION THERAPY[1]



[1] Sophisticated treatment planning with IMRT and protons can be used to improve the therapeutic effect. If an R1 or R2 resection is anticipated, clips to high risk areas for recurrence is encouraged particularly for retroperitoneal or intra-abdominal tumors.

[2] See Principles of Surgery (SARC-A).

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

[4] Total doses should always be determined by normal tissue tolerance.

[5] 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.

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.

Soft Tissue Sarcoma

GENERALLY ACCEPTED SYSTEMIC THERAPY AGENTS AND REGIMENS[a,b]

Combination regimens
- AD (doxorubicin, dacarbazine)[1,2]
- AIM (doxorubicin, ifosfamide, mesna)[3,4]
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[5]
- Ifosfamide, epirubicin, mesna[6]
- Gemcitabine and docetaxel[7,8]

Single agents
- Doxorubicin[9]
- Ifosfamide[6,10]
- Epirubicin
- Gemcitabine
- Dacarbazine
- Liposomal doxorubicin[11]

Special situations:

Desmoid Tumors
- Sulindac[12] or other non-steroidal anti-inflammatory drugs (NSAIDS) including celecoxib*
- Tamoxifen[13]
- Toremifene[14]
- Methotrexate and vinblastine[15]
- Low-dose interferon[16]
- Doxorubicin-based regimens[17,18]
- Imatinib mesylate[19]

Angiosarcoma
- Paclitaxel
- Docetaxel
- Vinorelbine

GIST
- Imatinib mesylate[20,21]
- Sunitinib malate[22]

*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)

[a] Alveolar soft part sarcoma and clear cell sarcomas are generally not sensitive to chemotherapy.
[b] References for regimens, see SARC-C 2 of 2.

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.

GENERALLY ACCEPTED SYSTEMIC THERAPY AGENTS AND REGIMENS
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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.

Staging (2002 AJCC 6th Edition)

Table 1

2002 American Joint Committee On Cancer (AJCC) Staging System For Soft Tissue Sarcoma

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. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumors

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) is considered stage IV.

Distant Metastases (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastases

Histologic Grade

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Poorly differentiated or undifferentiated (four-tiered systems only)

Stage Grouping

Stage I	T1a, 1b, 2a, 2b	N0	M0	G1--2	G1	Low
Stage II	T1a, 1b, 2a	N0	M0	G3--4	G2--3	High
Stage III	T2b	N0	M0	G3--4	G2--3	High
Stage IV	Any T	N1	M0	Any G	Any G	High or Low
	Any T	N0	M1	Any G	Any G	High or Low

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Histopathologic Type

Tumors included in the soft tissues category are listed below:

- Alveolar soft-part sarcoma
- Desmoplastic small round cell tumor
- Epithelioid sarcoma
- Clear cell sarcoma
- Chondrosarcoma, extraskeletal
- Osteosarcoma, extraskeletal
- Gastrointestinal stromal tumor
- Ewing's sarcoma/primitive neuroectodermal tumor
- Fibrosarcoma
- Leiomyosarcoma
- Liposarcoma
- Malignant fibrous histiocytoma
- Malignant hemangiopericytoma
- Malignant peripheral nerve sheath tumor
- Rhabdomyosarcoma
- Synovial sarcoma
- Sarcoma, NOS

Manuscript

NCCN Categories of Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Sarcomas constitute a heterogeneous group of rare solid tumors of mesenchymal cell origin with distinct clinical and pathological features; they are usually divided into two broad categories: (1) sarcomas of soft tissues (including fat, muscle, nerve and nerve sheath, blood vessels, and other connective tissues); and (2) sarcomas of bone. NCCN Soft Tissue Sarcoma guidelines do not include the management of Rhabdomyosarcoma, Ewing's sarcoma, and Desmoplastic Small Round Cell Tumor (DSCRT).

Soft tissue sarcomas are the most frequent sarcomas.[1,2] The annual incidence of soft tissue sarcomas in the United States for 2007 is estimated to be about 9,220 cases, with an overall mortality rate of approximately 3,560 cases per year, which includes adults and children.[3] The 5-year survival rate of soft tissue sarcomas is 50-60%.[4]

The true incidence of sarcomas may be underestimated, especially, because a large proportion of patients with the sarcoma known as gastrointestinal stromal tumor (GIST) may not have been counted in tumor registry databases before 2001. GIST alone is expected to have an incidence of at least 5000 new cases per year in the United States.[5,6]

Collectively, sarcomas account for approximately 1% of all adult malignancies and 15% of pediatric malignancies; adult soft tissue sarcomas are discussed in this guideline. External radiation therapy (RT) is a risk factor for soft tissue sarcoma.[7] Most commonly, a soft tissue sarcoma presents as an asymptomatic mass. 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). 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. The anatomic site of the primary disease represents an important variable that influences treatment and outcome. Soft tissue sarcomas of the extremities account for about 50% of all sarcomas, gastrointestinal (GI) sarcomas for 25%, retroperitoneal sarcomas for 15-20%, and head and neck for 9%. The most common subtypes of soft tissue sarcomas are malignant fibrous histiocytoma, liposarcoma, leiomyosarcoma, unclassified sarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumors;[8] however, more than 50 different histologic subtypes of soft tissue sarcoma have been identified.[1] Soft tissue sarcomas 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 oncology care

and functioning as referral centers for consultative support of community-based practitioners. The expertise of the NCCN institutions allows this group to use their extensive experience in defining these consensus practice guidelines for the management of patients with sarcomas. These practice guidelines address sarcoma management from the perspective of four disease subtypes: soft tissue extremity sarcomas, retroperitoneal (including nongastrointestinal visceral) sarcomas, GIST and other intra-abdominal sarcomas, and the unique mesenchymal neoplasm known as desmoid tumor (also known as desmoid aggressive fibromatosis). Current staging groups and nomenclature for classifying soft tissue sarcomas are given in Table 1. The American Joint Committee on Cancer (AJCC) revised this staging system in 2002, and these guidelines reflect the new staging.[9]

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 (SARC-A). 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 (neoadjuvant) or postoperatively (adjuvant).[10,11,12] When appropriate, these guidelines incorporate those adjuvant therapies that are supported by clinical trial data or extensive clinical experience.[13,14]

Biopsy

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

Resection margins

Both the surgeon and the pathologist should document surgical margins, in evaluating a resected specimen. Margins less than 1 cm should be evaluated carefully for postoperative therapy and if possible identified intraoperatively. Re-resection, if feasible may be required to achieve optimal margins (greater than1 cm), primarily for non-intra abdominal tumors.

Limb sparing surgery is generally preferred to achieve local tumor control with minimal morbidity.[15] Postoperative rehabilitation should be considered for patients with extremity sarcoma.

Amputation for Extremity Sarcoma

Amputation should be considered for patient preference or if the tumor has the following characteristics: extensive soft tissue mass and/or skin involvement, major arterial or nerve involvement, extensive bony involvement that requires whole bone resection, failure of preoperative therapy or recurrence following prior adjuvant radiation.[16,17]

Pathology

Pathologists with sarcoma expertise should review pathology assessment of biopsies and resected specimens, especially for initial histopathologic classification. Margins must be thoroughly evaluated in these specimens. Because identification of the histopathologic type of a sarcoma is often difficult, pathologists should have access to optimal cytogenetic and molecular diagnostic techniques. Molecular and cytogenetic analysis can be useful for establishing the diagnosis of synovial sarcoma, clear cell sarcoma and liposarcoma.

Guidelines for Radiation Therapy

Sophisticated treatments with intensity-modulated radiation therapy (IMRT) and proton-beam should be considered to improve therapeutic effect.[18] 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 (SARC-B). Total doses of RT should be determined by normal tissue tolerance.

Preoperative RT

The usual dose of preoperative RT is 50 Gy. An intraoperative boost or a postoperative boost with brachytherapy or an external-beam RT is recommended for positive or close margins.[19] 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.[20] A higher 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 to 6 weeks interval before resection is necessary to decrease the risk of wound complications. Very long intervals between resection and postoperative radiation are not recommended.

If wide margins are obtained, additional radiation may not be needed. Often, margins are close because of the proximity of many of these tumors to major neurovascular bundles or bone. At the time of resection, surgical clips should outline the area of recurrence risk. Brachytherapy boosts should be delivered several days after surgery, through catheters placed at operation, with doses of 12 to 20 Gy based on margin status. Alternatively, a single intraoperative dose to the tumor bed of 10 to16 Gy, based on margin status, can be delivered immediately after resection with exposure of the area at risk, avoiding uninvolved organs. External-beam RT boosts may be an alternative to brachytherapy or intraoperative radiation: 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 radiation to patients who have widely negative margins, based on local control rates that approach 95% with preoperative radiation at 50 Gy and negative margins.[19]

Postoperative RT

Postoperative RT has been to improve local control in patients with high-grade extremity soft tissue sarcomas with positive surgical margins.[21] When surgical resection is the initial therapy, postoperative RT choices include intraoperative radiation therapy (IORT), brachytherapy or external beam RT. 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 reresection is not feasible.

External-beam RT is delivered to large fields after surgical healing is complete (at 3-8 weeks) to doses of 50 Gy. Most institutions include the entire operative bed within that radiation field. Total doses of RT should always be determined by normal tissue tolerance. For intraabdominal or retroperitoneal tumors, this dose may be decreased to 45 Gy. An intraoperative boost may not be possible if radiation morbidity is high.

If no intraoperative radiation or brachytherapy was used in the immediate operative or postoperative period, an external-beam RT boost should be added. For negative margins, an additional 10-16 Gy is recommended to a reduced field that includes the original tumor bed, based on grade and width of margins. For microscopically positive

margins, an additional 16-20 Gy is recommended; for grossly positive margins, an additional 20-26 Gy is suggested.

Brachytherapy alone has been used as an adjuvant in patients with negative margins. 45-50 Gy to the tumor bed has been shown to reduce recurrence without a significant effect on wound healing.[22] However, brachytherapy-alone techniques require special expertise and significant experience. If brachytherapy is used as a boost, doses of 10-20 Gy based on margin are recommended; a boost dose of 10-16 Gy for close margins or 20 Gy for positive margins is recommended.

Recent reports from a retrospective study suggest that IORT provides excellent local control to soft tissue sarcoma of the extremity, when used as a boost to external beam RT.[23] However, since IORT has not been proven to be superior, the guidelines recommend IORT followed by a dose of 50 Gy external beam RT.

Soft Tissue Sarcomas of the Extremities

Evaluation and Workup

All patients should be managed by a multidisciplinary team with expertise in soft-tissue sarcoma.[24] The differential diagnosis of soft tissue sarcomas 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. 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.[25-27] 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 myxoid liposarcoma, leiomyosarcoma, epithelioid sarcoma or angiosarcoma.

^{18}Fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET) scan may be useful for prognostication, grading and to assess response to chemotherapy.[28] Tumor metabolism data acquired by FDG-PET will be useful in accurate grading and prognostication in sarcoma.[29] Recent reports in literature have demonstrated the value of FDG-PET scan in evaluating response to neoadjuvant chemotherapy in patients with high-grade extremity soft tissue sarcomas, prediction of outcome in liposarcoma.[30,31,32]

A large prospective study is underway to study the value of FDG-PET scan combined with CT scan in predicting disease-free survival in patients receiving neoadjuvant chemotherapy for soft tissue sarcoma (www.cancer.gov/clinicaltrials/UMN-2005LS080).

Staging

The 2002 AJCC staging system accommodates some of the three- and four-tiered systems for establishing grade.[9] However, many clinicians prefer the two-tiered system (ie, low versus high grade); therefore, this system is also used in the algorithm (EXTSARC-2). Recommendations for translating the three- and four-tiered systems into a two-tiered system are shown in Table 1.

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

- Low Grade tumors (Stage I)
- High-Grade Tumors (Stage II or III)

- Unresectable disease
- Recurrent Disease or Primary presentation of Metastatic disease

Low Grade Tumors (Stage I)

Surgery is the primary treatment for stage I (T1a-1b, N0, M0) low-grade tumors and is considered definitive if margins are greater than 1 cm or the fascia plane is intact. Postoperative RT is considered at some NCCN institutions when final margins are 1 cm or less (category 2B).

Surgical resection alone or in combination with RT (category 1) is recommended for stage I (T2a-b, N0, M0) low-grade tumors (EXTSARC-2). RT may not be necessary in patients with small lesions (5 cm or less), because these tumors are less frequently associated with local recurrence.[33,34] There are data from two randomized trials and three large single-institution studies that support using adjunctive RT in appropriately selected patients.[35-40] Patients receiving either preoperative or postoperative RT have similar rates of local control and progression-free survival.[41] However, preoperative RT is associated with a greater incidence of wound complications, especially in lower extremity tumors.[20] Therefore, the risk of local recurrence versus the toxicity of adjuvant RT should be assessed before making a decision regarding radiation.

High-Grade Tumors (Stage II or III)

Large high-grade extremity sarcomas (greater than 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.[42- 45,46,47] Concurrent chemoradiation with doxorubicin-based regimens has been shown to improve local control rates in patients with soft tissue sarcoma.[48] Available evidence although underpowered, suggests that anthracycline-based postoperative chemotherapy would improve disease-free survival in selected patients who are at high risk of recurrence but otherwise are in good performance status.[49,50,51]

Sarcoma Meta Analysis Corporation performed a meta-analysis of 14 randomized trials (1,568 patients) which compared adjuvant chemotherapy to follow-up and in some cases radiation therapy after surgery with a variety of sarcomas.[49] The result of the meta-analysis showed that doxorubicin-based chemotherapy prolongs relapse-free survival in adults with localized, resectable soft tissue sarcoma of the extremity and was associated with decreased recurrence rates. However, adjuvant chemotherapy does not appear to improve overall survival.[52] Another recent analysis of 674 patients with stage III soft-tissue sarcoma (1984-1999) revealed that clinical benefits from doxorubicin-based chemotherapy lasted for less than a year.[53]

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. After a median follow-up of 59 months, median disease-free survival (48 months vs.16 months) and median overall survival (75 months vs. 46 months) were significantly better in the treatment group.[54,55]

Remarkably little data have been generated in the adjuvant setting regarding the combination of aggressively dosed ifosfamide plus doxorubicin supported by hematopoietic cytokine therapy. Phase III randomized study (EORTC-62931) is ongoing to assess the efficacy of adjuvant chemotherapy after definitive surgery in patients with high-grade primary or recurrent soft tissue sarcoma at any site. Interim overall survival data are encouraging from an ongoing phase III trial (EORTC-62961) of regional hyperthermia versus chemotherapy (etoposide, ifosfamide, adriamycin) alone for patients with high-risk soft tissue sarcomas, especially for extremity sarcomas.[56]

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 histologic subtype of the tumor and institutional experience.

Surgery followed by RT with or without chemotherapy is the primary treatment for resectable high-grade sarcomas. The guidelines recommend various neoadjuvant approaches including preoperative RT or chemotherapy or chemoradiation prior to surgery, followed by postoperative radiation with or without chemotherapy for resectable tumors with acceptable functional outcomes and for potentially resectable tumors with concerns for adverse functional outcomes. Adjuvant chemotherapy alone can be considered in the case of patients who have received preoperative radiation alone (EXTSARC-3). Surgery alone is an option for small tumors that can be resected with wider surgical margins.[57]

Recurrent Disease

The management of recurrent disease or primary presentation with metastases (EXTSARC-4) 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 (EXTSARC-1 and EXTSARC-2).[58] For patients who present with metastases or unresectable disease following primary treatment, the guidelines distinguish between widely disseminated metastases and limited metastases confined to a single organ.

Metastatic or Unresectable Disease

It has not been shown that locally advanced soft tissue sarcoma in an extremity can be reduced in size sufficiently by induction chemotherapy to permit function-preserving limb-sparing surgery.[59] 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.[60-66] Liposomal anthracyclines were found to be active as first-line treatment for advanced sarcomas with better toxicity profile than doxorubicin.[67,68] Other chemotherapeutic agents have also been tested in clinical trials.[11]

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.[69] In a separate report that was published following this study, this combination was found to be active in a variety of histologic subtypes of sarcoma.[70] 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.[71] A phase II trial (MSKCC-99027) is evaluating the activity of gemcitabine plus docetaxel administered with filgrastim in patients with recurrent or persistent unresectable leiomyosarcoma or other soft tissue sarcoma that cannot be removed by surgery. Another phase III trial is comparing gemcitabine and the combination of gemcitabine and docetaxel in patients with unresectable soft tissue sarcoma (NCT00142571).

Ecteinascidin 743 (ET-743, also known as trabectedin or Yondelis®), a marine-derived anti-tumor agent, has shown objective responses in phase II trials of patients with progressive soft tissue sarcomas that are refractory to chemotherapy.[72-74] A multicenter, open-label single-arm study of trabectedin is an ongoing study, to provide access to treatment with trabectedin for patients who previously received treatment for soft tissue sarcoma, who have relapsed or refractory to or intolerant of standard therapies for treatment of soft tissue sarcoma, but who may benefit from treatment with trabectedin.

Isolated limb perfusion (ILP) has been employed in Europe as a limb sparing treatment for unresectable intermediate or high-grade extremity soft tissue sarcomas.[75] In European clinical trials, melphalan in combination with tumor necrosis factor-α (TNF- α) resulted in better response rates and limb-salvage rates compared to ILP with melphalan alone.[76] Recombinant TNFα-1A and melphalan has been approved in Europe for ILP in patients with locally advanced high grade soft tissue sarcoma of the extremities.

In the guidelines, a subsequent distinction is made between asymptomatic and symptomatic patients for those who present with unresectable or widely 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). Another equally reasonable alternative is to offer such patients palliative therapy, even "preemptive" palliation that might involve aggressive chemotherapy and/or metastasectomy before symptoms develop. For symptomatic patients most panel members would recommend moving directly to a palliative approach, defined broadly as chemotherapy, RT, palliative surgery, ablation procedures (eg, radiofrequency ablation or cryotherapy), embolization procedures or best supportive care. 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.

In contrast, a patient who presents with limited metastasis confined to a single organ and limited tumor bulk or regional lymph node involvement should receive management as per primary tumors (EXTSARC-1) and consideration should be given to management of the regional or distant disease. Another option is to consider regional node dissection for nodal involvement or metastasectomy with or without preoperative or postoperative 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 radiofrequency ablation or embolization procedures as an alternate method for control of metastatic lesions.

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.[77,78,79] 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 consider 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 to 6 months for 2 to 3 years and then annually (EXTSARC-2). Baseline imaging should be considered after primary therapy. Chest x-ray should also be

considered every 6 to 12 months. For stage II and stage III tumors, H&P and chest imaging (plain radiograph or chest CT) should be done every 3 to 6 months for 2-3 years, then every 6 months for the next 2 years, and then annually (EXTSARC-3). Because these patients' risk never returns to zero, long-term follow-up is indicated, including consideration of MRI or CT scanning.[80] Chest imaging (plain radiograph or chest CT) is performed every 3 to 6 months for 5 years and then annually, given the risk of metastatic disease in these high-grade lesions. 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 reported data from M. D. Anderson Cancer Center, routine use of chest CT adds little clinical benefit, when risk of pulmonary metastases is low.[81] However, in certain subsets of patients in whom chest radiographs are difficult to interpret because of anatomic considerations (scarring, emphysema, etc), chest CT surveillance may be indicated.[77]

Retroperitoneal Abdominal Soft Tissue Sarcomas

Evaluation and Workup

The initial evaluation and workup for retroperitoneal abdominal soft tissue sarcomas are similar to that for the extremity sarcomas. This workup involves a thorough H&P and appropriate imaging studies, including an abdominal and pelvic CT with contrast with or without an MRI. Chest imaging with a plain radiograph or CT should be done, especially for patients whose tumors warrant preoperative or postoperative chemotherapy. If possible, the patient should be reviewed by a multidisciplinary sarcoma panel. Note that for staging, all retroperitoneal lesions are considered to be 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 histologic 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 performed for some other reason, a core biopsy should be done to establish the diagnosis as well as the histopathologic type and grade of tumor. Then, the optimal subsequent resection could be performed.

Primary Treatment

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 occurs in approximately half of the patients who have undergone complete resection. Multimodality treatment is usually favored for retroperitoneal sarcomas due to the inability to obtain negative margin resections and high local recurrence rates.[82] Preoperative RT is often preferred, because the volume of abdominal organs in the RT fields is smaller and it may render unresectable tumors more amenable to resection. Preoperative chemotherapy may have advantages over postoperative chemotherapy. However, the role of adjuvant RT or preoperative chemotherapy vs. postoperative chemotherapy has not yet been evaluated in randomized clinical trials.

Multi-institutional prospective randomized phase III trial (ACOSOG-Z9031) assessing the value of preoperative RT in patients with primary retroperitoneal soft tissue sarcoma is ongoing. Primary objective of this study is to find out if preoperative radiation therapy will prolong survival without disease relapse. Little data are available for

use of combined RT and chemotherapy. Decisions about adjuvant or neoadjuvant chemotherapy or RT are left to clinical judgment.[83,84,85]

Primary treatment depends on the resectability of the sarcoma (RETSARC-2). Biopsy is performed only if preoperative therapy (category 2B) is considered. CT-guided core biopsy is preferred. Preoperative RT or preoperative chemotherapy (for chemo sensitive histologies) could be considered. Although most patients with retroperitoneal sarcomas (which are often liposarcomas) could be managed with surgical resection with or without intraoperative RT (IORT), the options for other therapy should be discussed, especially if incomplete resection is a reasonable probability. Long-term results of two prospective trials showed favorable 5-year local recurrence-free (60%), disease-free (46%) and overall survival rates (61%) among patients who had R0 or R1 resection after preoperative RT for intermediate or high grade retroperitoneal sarcoma.[86] Postoperative RT (category 2B) could be considered in patients with pathologic findings of high grade disease following negative margin resection or for microscopic positive margins (R1 resection). Macroscopic positive margins (R2 resection) should be managed as unresectable disease.

Unresectable retroperitoneal sarcomas 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 (RETSARC-3). Patients with unresectable or metastatic disease have several options for primary treatment after biopsy including chemotherapy or RT to downstage tumors prior to resection.[61,65] In asymptomatic patients, palliative surgery for symptom control, best supportive care, or observation are additional options. Unresectable tumors that become resectable following primary chemotherapy or RT should be managed as described under resectable disease (RETSARC-2).

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 (RETSARC-3).

Recurrent Disease

For patients with resectable, unresectable or disseminated recurrences, the guidelines recommend the same management after biopsy, as outlined for primary disease (RETSARC-4). 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 to 6 months for 2 to 3 years, then every 6 months for the next 2 years, and then annually. Chest imaging should be considered in both cases.

Intra-abdominal Soft Tissue Sarcoma

Patients whose lesions are suspected of being gastrointestinal (GI) or intra-abdominal sarcomas should be presented to a multidisciplinary

tumor board for evaluation, ideally before primary surgery. Suspicious GI or intra-abdominal lesion(s) are divided into the following groups: (1) gastrointestinal stromal tumors (GIST) and (2) other intra-abdominal sarcomas. The NCCN guideline now provides separate pathways for GIST and other sarcomas of the intra-abdominal region.

Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumor (GIST) is one of the many subsets of different types of histologies of soft tissue sarcomas, resulting from a mutation in one of the receptor protein tyrosine kinases (KIT, also called CD117). [87,88] GISTs are the most common mesenchymal neoplasms of the gastrointestinal tract. Most GISTs (85-95%) are KIT positive. A few GISTS (about 5%) may be CD117 (KIT) negative; therefore, the diagnosis of GIST for a tumor that is otherwise morphologically typical is not precluded by an absence of KIT staining.[89] GISTs can arise anywhere along the GI tract but are most common in the stomach (50%) and small bowel (25%).[90] In patients with a clinically significant GIST(s), symptoms may include early satiety, bloating, 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.

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, abdominopelvic CT scan with contrast and/or MRI, chest imaging, endoscopic ultrasound, endoscopy as indicated (if not previously done) and surgical assessment.

Principles of Biopsy

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. Endoscopic ultrasound (EUS) biopsy is preferred over percutaneous. Preoperative biopsy may not be appropriate if the tumor is easily resectable. Biopsy is necessary when planning neoadjuvant therapy for suspicious GIST. Optimal pathology of a sufficient amount of tumor tissue is necessary to make the diagnosis of GIST with certainty. 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 specialized centers for sarcomas with complex or unusual features and expert pathology evaluation of the biopsy or resected mass with the staining of the pathologic specimen for the CD117 antigen (reflecting the KIT receptor tyrosine kinase). Consider using investigational mutational analysis for KIT-negative tumors (GIST-A).

Targeted Therapy for GIST

GIST tumor had previously been documented to be resistant to conventional chemotherapies. Since KIT activation occurs in the majority of cases of GISTs, in recent years KIT-inhibition has emerged as a promising new treatment for GISTs that are resistant to chemotherapy.

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 progression free survival for patients with unresectable and/or metastatic GIST, as well as showing objective responses in more than 50% of the patients.[91,92,93,94] In February 2002

FDA approved of imatinib mesylate for the treatment of patients with KIT (CD117) positive unresectable and/or metastatic malignant GIST. Suggested starting dose of imatinib mesylate is 400 mg/day to achieve response induction. However, increase in progression free survival was observed in patients randomized to higher dose (800 mg/day).[95]

Some patients develop primary resistance to imatinib and in others resistance becomes evident after several months, as the disease progresses during treatment with imatinib. Sunitinib malate (Sutent®, 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.[96,97]

In a recent randomized phase III placebo-controlled trial, sunitinib produced significant, sustained clinical benefit in patients with imatinib-resistant or imatinib-intolerant GIST.[98,99] 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 overall survival. 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 pts 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.

Primary Treatment

Surgery is the primary treatment of choice for localized or potentially resectable GIST lesions. Surgery should produce minimal surgical morbidity. If surgical morbidity would be improved by reducing the size of the tumor, preoperative treatment with imatinib should be considered. GISTs should be handled with care to avoid tumor rupture. The goal is to achieve complete gross resection with an intact pseudocapsule, which is not always possible. GISTs should be handled with care to avoid tumor rupture. If the pseudocapsule is torn, bleeding and tumor rupture may ensue. GISTs often project from the stomach or intestine and tend to displace adjacent structures. Consequently, GISTs can often be lifted away from surrounding organs. After removal of any suspected GIST, postoperative pathology assessment is essential to confirm the diagnosis.

Patients with marginally resectable or resectable GIST lesions with risk of significant morbidity should be treated with imatinib. PET scans allow rapid assessment of imatinib therapy. Baseline CT with or without MRI followed by subsequent PET scans about 2 to 4 weeks after therapy should be considered to assess therapeutic effect. If there is no progression, resection should be considered, if possible (GIST-2). In stable and responding patients, imatinib therapy should be continued until maximal response, which may take 3-6 months. Collaboration between the medical oncologist and the surgeon is necessary to determine the appropriateness of surgery following major response or stable disease. If there is progression, as confirmed with CT scan, surgery is recommended after discontinuing imatinib (GIST-2). However, close monitoring is essential, because some patients may rapidly become unresectable.

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 lesion(s) 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 (GIST-3). 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. CT with or without ^{18}FDG-PET can be used to assess the therapeutic effect. Both CT and PET can identify an abnormal mass and can detect changes in the mass (eg, response or progression).[100] If there is no progression, resection can be considered following surgical consultation. Imatinib therapy should be continued if resection is not feasible. Surgery can be considered if bleeding is present or if there is a limited solitary metastasis.

For patients who experience life threatening side effects with imatinib therapy, that are not managed by supportive treatment, the panel recommends sunitinib therapy prior to surgery, after discontinuing imatinib (GIST-2 and GIST-3). Few GISTS may be CD117 (KIT) negative, but they may also be sensitive to imatinib. Therefore, it is rational to offer CD117-negative GIST patients a therapeutic trial of imatinib mesylate with close evaluation and follow-up.[101]

Post Surgical Treatment

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%.[102,103,104] National and European cooperative group clinical trials are currently ongoing to evaluate the benefit of adjuvant imatinib and patients should be encouraged to enroll in these trials.

Patients who have undergone complete resection should be observed. Some physicians choose to administer adjuvant imatinib off clinical trial for high-risk patients following complete resection, even though there is no data to support this (GIST-4). The median time to recurrence after resection of primary high-risk GIST is about 2 years. Recurrence of GIST following complete resection should be managed as described for unresectable or metastatic disease (GIST-3), because recurrent disease represents locoregional metastatic or infiltrative spread of the malignancy and carries essentially the same prognosis as distant metastases overall.

Postoperative imatinib should be continued following a grossly margin positive resection (R2). Additional resection may be considered to remove any persistent gross residual disease. Imatinib treatment should be continued following reresection regardless of surgical margins until progression. At this time, continuous use of imatinib is recommended for metastatic GIST until progression (GIST-4). 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,[105] which in turn indicates that even in patients with progressive disease on imatinib therapy, there may be a few tumor cells for which imatinib may still be effective. Updated results from a randomized phase III trial by French sarcoma group show that there is significant increase in the rate of progressive disease when imatinib therapy was interrupted in GIST patients with advanced disease.[106]

Progressive Disease

Progression is defined as appearance of a new lesion or as increase in tumor size. It may be determined using CT or MRI with clinical interpretation; PET may be used if the results are ambiguous (GIST-5). For limited progressive disease that is potentially easily resectable, surgical resection should be considered.[107] Other treatment options include radiofrequency ablation or embolization (category 2B). Radiation therapy (category 2B) for palliation can be considered in rare patients with bone metastases. Treatment with imatinib should be continued at the same dose or at increased dose as tolerated in

patients with limited progressive disease. In patients with widespread systemic disease and good performance status (0-2), imatinib dose should be increased as tolerated. Alternatively, sunitinib can also be considered for both of these indications. In a randomized, multicenter international trial, sunitinib produced significant clinical benefit (disease control and superior survival) compared with placebo in patients with advanced GIST after failure and discontinuation of imatinib.[108]

Best supportive care should be provided following discontinuation of treatment for patients who are no longer receiving clinical benefit from imatinib or sunitinib. 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.

Surveillance

Every patient with localized or potentially resectable GIST should have a thorough H&P every 3 to 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 (GIST-4).

Intra-Abdominal Soft Tissue Sarcomas Other Than GIST

Primary Treatment

Definitive surgery with intraoperative RT is the primary therapeutic modality for patients with resectable intra-abdominal GI sarcomas other than GIST or those that occur in the abdomen or pelvis without evidence of metastasis (GISARC-1). For patients who have resectable primary disease and limited isolated liver metastasis, definitive surgery should be performed for the primary disease. Several options exist for isolated liver lesions, including metastasectomy (with or without preoperative or postoperative chemotherapy with or without RT), radiofrequency ablation or embolization procedures.

Unresectable primary or disseminated metastatic GI sarcomas have a poor prognosis overall (GISARC-1). Asymptomatic patients can be observed or they can also be treated with chemotherapy, RT, palliative surgery, best supportive care, embolization or ablation procedures. If there is response to either chemotherapy or RT, then the tumors should be treated as described above for resectable tumors. Patients can also be enrolled in an appropriate clinical trial.

Surveillance

Every patient, regardless of initial status at presentation or type of primary therapy, should have a thorough H&P with imaging (chest/abdomen/pelvis CT) as clinically indicated. The surveillance schedule varies depending on the type of disease (eg, low versus high grade; resectable versus metastatic) (GISARC-1).

Recurrent Disease

Regardless of presentation, any patient who has progression of disease despite prior therapy, or who has a recurrence, should be considered a candidate for enrollment in a clinical trial, if an appropriate trial is available. The treatment options depend on the nature and location of the recurrence. If the recurrence is isolated and potentially easily resectable, surgical resection or chemotherapy may be considered; best supportive care is also an option. For unresectable with only a liver recurrence, consider a local ablative procedure (category 2B) such as hepatic resection, radiofrequency ablation, chemoembolization, or other local therapy. Several options are available for patients with disseminated disease as outlined in GISARC-2.

Desmoid Tumors

Desmoid tumors, also known as aggressive fibromatoses, 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) syndrome[109] and may also arise through elective surgical intervention (eg, colectomy) in susceptible patients.[110] 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 histopathologic 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.[111] 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 Memorial Sloan-Kettering Cancer Center, approximately 10% of patients died of progressive disease.[112] Although desmoid tumors are often locally invasive, they rarely metastasize. Most patients do not die of their tumors.[113] Desmoids can cause functional morbidity.

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 (DESMSARC-1). All patients should be managed by a multidisciplinary team. Biopsy should be performed for suspicious masses to confirm the diagnosis, and may not be necessary if complete resection is planned. The differential diagnosis for desmoids depends on location; it includes other sarcomas, other malignant carcinomas, and benign lesions. Desmoid tumors of the breast are difficult to differentiate from carcinomas, because desmoids resemble carcinomas clinically and radiologically.[114-116]

Primary Treatment

The algorithm has two main branches that depend on whether a patient presents with resectable or unresectable disease (DESMSARC-1). Primary treatment for desmoid tumors is surgery to obtain very wide margins.[117-120] Microscopically positive margins may be acceptable if achieving negative margins would produce excessive morbidity. If surgical margins are negative after resection, patients may only be observed. Large tumors can be treated with postoperative RT. For microscopic positive margins, additional resection or high-dose radiation can be considered. RT reduces the risk of recurrence in patients with positive margins and should be considered if a subsequent relapse might lead to increased morbidity.

In the case of unresectable disease, amputation should almost never be considered. Functional outcomes are important, and alternatives to amputation may be open to patients who have unresectable desmoid tumors.[121,122] Desmoids respond slowly to radiation; often 2 years may be required for desmoids to fully respond to radiation. Irradiation of an unresectable desmoid is a reasonable consideration, depending on the possible morbidity of treatment.[119,123,124] 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 achieved 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.[125]

For patients with macroscopic surgical margins, unresectable disease or if surgery would be unacceptably morbid the following options are available: RT, systemic therapy (SARC-B), radical surgery (if other modalities fail) or observation (DESMSARC-1). Recurrent disease is managed in the same manner as primary disease

Promising data exist for the use of cytostatic (especially hormonal agents) or cytotoxic systemic therapy.[126] Cytostatic options include tamoxifen, interferon-alpha and other low-toxicity interventions, such as sulindac and other nonsteroidal anti-inflammatory agents (including celecoxib), which have been reported to halt progression of these tumors.[127-135] 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). If cytostatic agents fail, cytotoxic therapy with low-toxicity regimens could be considered. Regimens include methotrexate with vinblastine[136,137] or a doxorubicin-based regimen.[138-141]

Imatinib mesylate has also shown some activity against desmoid tumors.[142,143] Early results from SARC (Sarcoma Alliance for Research through Collaboration) phase II multicenter trial indicate that imatinib has activity in unresectable or difficult-to-resect desmoids tumors.[144] This is the largest reported phase II trial of desmoid tumors. The panel has now included imatinib mesylate for the treatment of desmoid tumors.

Surveillance

Postsurgical baseline imaging should be performed after sufficient time has elapsed to allow scarring to be completed after the surgery. Every patient should have an H&P with appropriate imaging every 3 to 6 months (depending on the risk from the resected disease, anatomic location, etc) for 2 to 3 years and then annually.

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