National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Soft Tissue Sarcoma

V.2.2010

Continue

www.nccn.org

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

NCCN Soft Tissue Sarcoma Panel Members

*George D. Demetri, MD/Chair †
Dana-Farber Cancer Institute|
Harvard Cancer Center

Scott Antonia, PhD, MD †
H. Lee Moffitt Cancer Center
& Research Institute

Robert S. Benjamin, MD †
The University of Texas
M. D. Anderson Cancer Center

Marilyn M. Bui, MD, PhD ≠
H. Lee Moffitt Cancer Center
& Research Institute

Ephraim S. Casper, MD † Þ
Memorial Sloan-Kettering Cancer Center

Ernest U. Conrad, III, MD ¶ τ
Fred Hutchinson Cancer Research
Center/Seattle Cancer Care Alliance

Thomas F. DeLaney, MD §
Massachusetts General Hospital
Cancer Center

Kristen N. Ganjoo, MD †
Stanford Comprehensive Cancer Center

Robert Heck, Jr., MD ¶
University of Tennessee Cancer Institute

Martin J. Heslin, MD ¶
University of Alabama at Birmingham
Comprehensive Cancer Center

Raymond J. Hutchinson, MD € ξ
University of Michigan
Comprehensive Cancer Center

John M. Kane III, MD ¶
Roswell Park Cancer Institute

G. Douglas Letson, MD ¶
H. Lee Moffitt Cancer Center
& Research Institute

Sean V. McGarry, MD
UNMC Eppley Cancer Center at
The Nebraska Medical Center

Richard J. O'Donnell, MD ¶
UCSF Helen Diller Family
Comprehensive Cancer Center

I. Benjamin Paz, MD ¶
City of Hope
Comprehensive Cancer Center

John D. Pfeifer, MD, PhD ≠
Siteman Cancer Center at Barnes-Jewish
Hospital and Washington University
School of Medicine

Raphael E. Pollock, MD ¶
The University of Texas
M. D. Anderson Cancer Center

R. Lor Randall, MD ¶
Huntsman Cancer Institute at
the University of Utah

Richard F. Riedel, MD †
Duke Comprehensive Cancer Center

Karen D. Schupak, MD §
Memorial Sloan-Kettering Cancer Center

Herbert S. Schwartz, MD ¶
Vanderbilt-Ingram Cancer Center

Katherine Thornton, MD †
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

*Margaret von Mehren, MD †
Fox Chase Cancer Center

Jeffrey Wayne, MD ¶
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

† Medical Oncology
¶ Surgery/Surgical oncology
Þ Internal medicine
τ Orthopedics/orthopedic oncology
§ Radiotherapy/Radiation oncology
€ Pediatric oncology
ξ Bone Marrow Transplantation
≠ Pathology
*Writing Committee Member

Continue

NCCN Guidelines Panel Disclosures

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Table of Contents

NCCN Soft Tissue Sarcoma Panel Members
Summary of Guidelines Updates

Soft Tissue Sarcoma
- Soft-Tissue Extremity/Trunk (EXTSARC-1)
- Retroperitoneal/Abdominal (RETSARC-1)
- Gastrointestinal Stromal Tumors (GIST-1)
  - Principles of Biopsy for GIST (GIST-A)
  - Principles of Pathologic Assessment for GIST (GIST-B)
  - Principles of Surgery for GIST (GIST-C)
  - Dosing and Administration of Imatinib (GIST-D)
  - Dosing and Administration of Sunitinib (GIST-E)
- Desmoid Tumors (Fibromatosis) (DESM-1)

Principles of Pathologic Assessment of Sarcoma Specimens (SARC-A)
Principles of Ancillary Techniques Useful in the Diagnosis of Sarcomas (SARC-B)
Principles of Surgery (SARC-C)
Guidelines for Radiation Therapy (SARC-D)
Systemic Therapy Agents and Regimens (SARC-E)
Bone Sarcomas - See the NCCN Bone Cancer Guidelines
Uterine Sarcomas - See the NCCN Uterine Cancer Guidelines
Dermatofibrosarcoma Protuberans - See the NCCN Dermatofibrosarcoma Protuberans Guidelines

Guidelines Index
Print the Sarcoma Guideline

For help using these documents, please click here

Staging
Discussion
References

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

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 evidence and 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. ©2010.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Summary of the Guidelines updates

Summary of the changes in the 2.2010 version of the Soft Tissue Sarcoma Guidelines from the 1.2010 version include:

- **The Soft Tissue Sarcoma Discussion section was updated correspondent to the changes in the algorithm (MS-1).**

Summary of the changes in the 1.2010 version of the Soft Tissue Sarcoma Guidelines from the 2.2009 version include:

Global Changes:

- **The algorithm title "Soft-Tissue Extremity" changed to "Soft-Tissue Extremity/Trunk".**
- **The algorithm title "Desmoid Tumors" changed to "Desmoid Tumors (Fibromatosis)".**
- **The phrase "neoadjuvant" changed to "preoperative" throughout the guidelines.**
- **The Staging tables were updated to reflect the 7th edition (2010) of the AJCC Staging Manual (ST-1) and (ST-2).**

Extremity/Trunk

EXTSARC-1

- **Workup**
  - **Essential; Fourth bullet: "...placed along longitudinal axis with minimal dissection..." changed to "placed along planned future resection axis with minimal dissection..."**
  - **Useful Under Certain Circumstances:**
    - **Third bullet: Changed to "Consider MRI of total spine for myxoid/round cell liposarcoma.**
    - **A new bullet was added that states, "Consider CNS imaging for alveolar soft part sarcoma and angiosarcoma".**
- **"Stage II, III Unresectable" changed to "Unresectable primary disease".**
- **Footnote "f" that states, "Different sub-types have different propensities to spread to various locations and imaging should be individualized based sub-types" is new to the page.**

EXTSARC-2

- **Follow-up: A new bullet was added that states, "Consider obtaining baseline and periodic imaging of primary site based on estimated risk of locoregional recurrence (MRI, CT, consider ultrasound).**

EXTSARC-3

- **The recommendations for primary treatment for both "Stage II,III Resectable" pathways were reorganized for clarity.**

EXTSARC-3---continued

- **Resectable and Potentially resectable pathways: For patients receiving preoperative RT or preoperative chemoradiation, then surgery, "Consider RT boost" was added as an adjuvant treatment option.**
- **"The RT ± chemotherapy" recommendations were clarified as "RT ± adjuvant chemotherapy".**
- **Footnote "q" that states, "Consider re-imaging patient to assess primary tumor and to rule out metastatic disease" is new to the page.**
- **Footnote "r" regarding the use of RT boost for residual gross disease or microscopically positive margins is new to the page.**
- **Footnotes "p" and "s" were revised.**

EXTSARC-4

- **The pathway "Unresectable" changed to "Unresectable primary disease".**
- **Preoperative RT or Preoperative chemoradiation; Change to resectable; Surgery pathway: The adjuvant treatment recommendations "RT ± chemotherapy or Chemotherapy" changed to "Consider RT boost, Consider adjuvant chemotherapy (category 2B)".**
- **Under Primary Treatment: "Preoperative chemotherapy" now has a separate pathway.**

EXTSARC-5

- **Follow-up; Last bullet: "Consider periodic imaging of primary site..." changed to "Consider obtaining baseline and periodic imaging..."**

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.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Summary of the Guidelines updates---continued

Retroperitoneal/Intra-abdominal

- No changes to the guidelines.

Gastrointestinal Stromal Tumors (GIST)

Note: The GIST algorithm was revised extensively including the addition/deletion of pages and footnotes.

GIST-1

- Footnote "e" regarding the pathology report was revised.

GIST-2

- This is a new page that provides recommendations for managing patients with very small gastric GISTs (< 2 cm).

GIST-3

- This page now covers "Localized or potentially resectable disease and considering preoperative imatinib" or Definitively unresectable or metastatic disease".

GIST-4

- "Assess therapeutic effect" changed to "Assess therapeutic effect and evaluate patient compliance".
- The recommendation "Consider PET after 2-4 wks of therapy" was removed from the algorithm and placed in footnote "o".
- Footnote "p" is new to the page.
- After "Progression", the recommendation "Confirm progression with CT" was removed and included as part of the new footnote "q".

GIST-5

- Primary Presentation; After "GIST that is definitively unresectable, recurrent, or metastatic": The recommendation "Consider baseline PET, if using PET during follow-up" was removed from the algorithm and included in footnote "u".
- Primary/Preoperative Treatment:
  - "CT ± PET (within 3 mo of initiating therapy" changed to "CT (within 3 mo...)" with corresponding footnote "v" that states, "Consider PET only if CT results are ambiguous".
  - Evaluate patient compliance was added.
- Footnote "x" regarding surgical resection and metastatic GIST.

GIST-6

- Footnote "y" was revised.

GIST-7

- For both the "Limited" and "Generalized progression" pathways, the recommendation "...reassess therapeutic response with PET or CT" changed to "...reassess therapeutic response with CT" and new footnote "v" was added..
- Last column: The recommendations were revised for clarity.
- Footnote "bb" was revised "Clinical experience recommends continuing imatinib even if progression is low" was revised to state, "Clinical experience suggests that discontinuing kinase inhibitors, even in the setting of progressive disease, may accelerate the pace of disease progression and worsen symptoms."
- Footnote "cc" that states, "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" is new to the page.

GIST-A Principles of Biopsy

- This page was revised extensively.

GIST-B Principles of Pathologic Assessment

- This is a new page that provides recommendations for the pathologic assessment of GIST.

GIST-C Principles of Surgery for GIST

- This is a new page that provides surgical recommendations for patients with primary (resectable) GIST or metastatic GIST.

GIST-D Dosing and Administration of Imatinib

- The potential drug interactions with imatinib table was removed and now this page refers to the FDA website to review the full content of the FDA label.

GIST-E Dosing and Administration of Sunitinib

- The potential drug interactions with sunitinib table was removed and now this page refers to the FDA website to review the full content of the FDA label.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Summary of the Guidelines updates---continued

Desmoid Tumors

- No changes to the guidelines.

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

- The heading "Spindle cell tumors" changed to "Other Sarcomas".
- "Malignant fibrous histiocytoma" was added.
- After "Low grade fibromyxoid sarcoma": For clarity, the "Gastrointestinal Stromal Tumors" listing changed to "Sporadic GIST" and "Familial GIST (Carney-Stratakis syndrome)".

SARC-C Principles of Surgery

- Sarcoma Surgery: "The surgical procedure necessary to resect the tumor with 2-3cm negative margins should be used. Ideally, the biopsy site should be..." changed to "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..."
- Amputation: First bullet: Second sentence was revised to read "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".

SARC-D Guidelines for Radiation Therapy

- "Postoperative treatment following surgery with clips" pathway: "IORT" changed to "IORT (10-16 Gy)".

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

- The following systemic therapy agents were added:
  - Extremity, Retroperitoneal, Intra-abdominal:
    - Combination Regimens: Gemcitabine and vinorelbine
    - Single agents: Temozolomide
  - All Other systemic Therapy Options as per Extremity Sarcoma: Bevacizumab
  - GIST: Dasatanib
- The following soft tissue sarcoma sub-types and systemic therapy agents are new to this version of the Guidelines:
  - Solitary Fibrous Tumor/Hemangiopericytoma: Bevacizumab and temozolomide; Sunitinib
  - Alveolar soft part sarcoma (ASPS): Sunitinib (category 2B)
  - Chordoma (all recomendations are category 2B)
    - Combination regimens: Erlotinib and cetuximab; Imatinib and cisplatin; Imatinib and sirolimus
    - Single agents: Erlotinib, Imatinib, Sunitinib
- Pigmented Villonodular Synovitis/Tenosynovial Giant Cell Tumor (PVNS/TGCT): Imatinib
- PEComa, Recurrent Angiomyolipoma, Lymphangioleiomyomatosis: Sirolimus

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

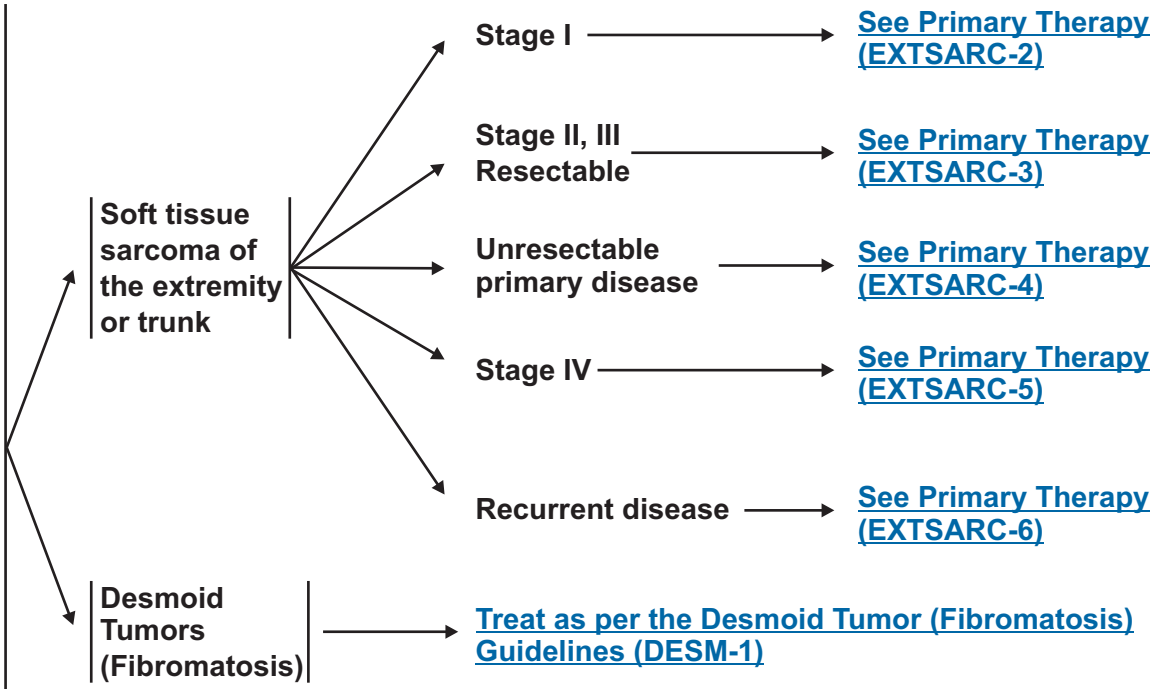
WORKUP

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)[b]
  - 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)[c]
  - Biopsy should establish grade and histologic subtype[d]
  - Appropriate use of ancillary diagnostic methodologies[e]
- Chest imaging

USEFUL UNDER CERTAIN CIRCUMSTANCES:[f]

- PET scan may be useful in prognostication, grading and determining response to chemotherapy
- Consider abdominal/pelvic CT for myxoid/round cell liposarcoma, epithelioid sarcoma, angiosarcoma, and leiomyosarcoma
- Consider MRI of total spine for myxoid/round cell liposarcoma
- Consider CNS imaging for alveolar soft part sarcoma and angiosarcoma

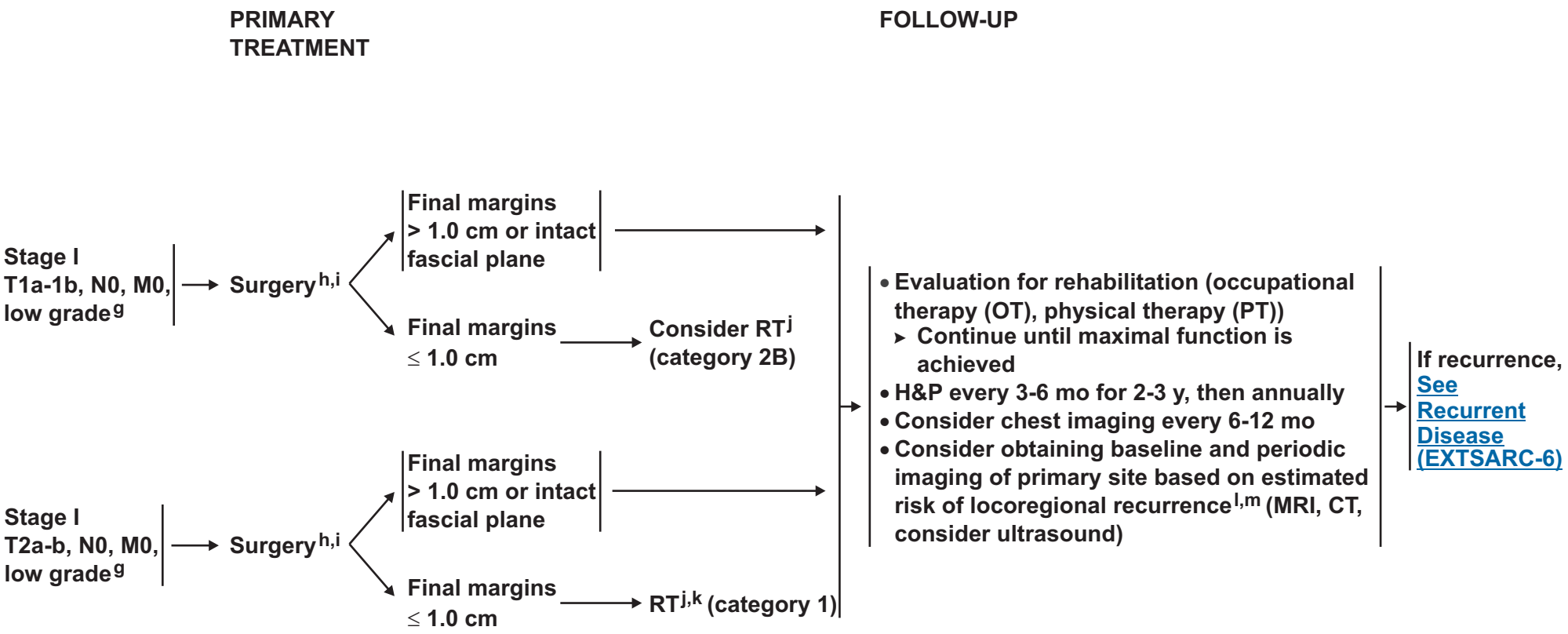


[a] Adequate imaging should provide details about the size of tumor and contiguity to nearby visceral structures and neurovascular landmarks.
[b] CT angiogram may be useful for patients in whom an MRI is not feasible.
[c] In selected institutions with clinical and pathologic expertise, an FNA may be acceptable.
[d] See Principles of Pathologic Assessment of Sarcoma Specimens (SARC-A).
[e] See Principles of Ancillary Techniques Useful in the Diagnosis of Sarcomas (SARC-B).
[f] Different sub-types have different propensities to spread to various locations and imaging should be individualized based upon sub-types.

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.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

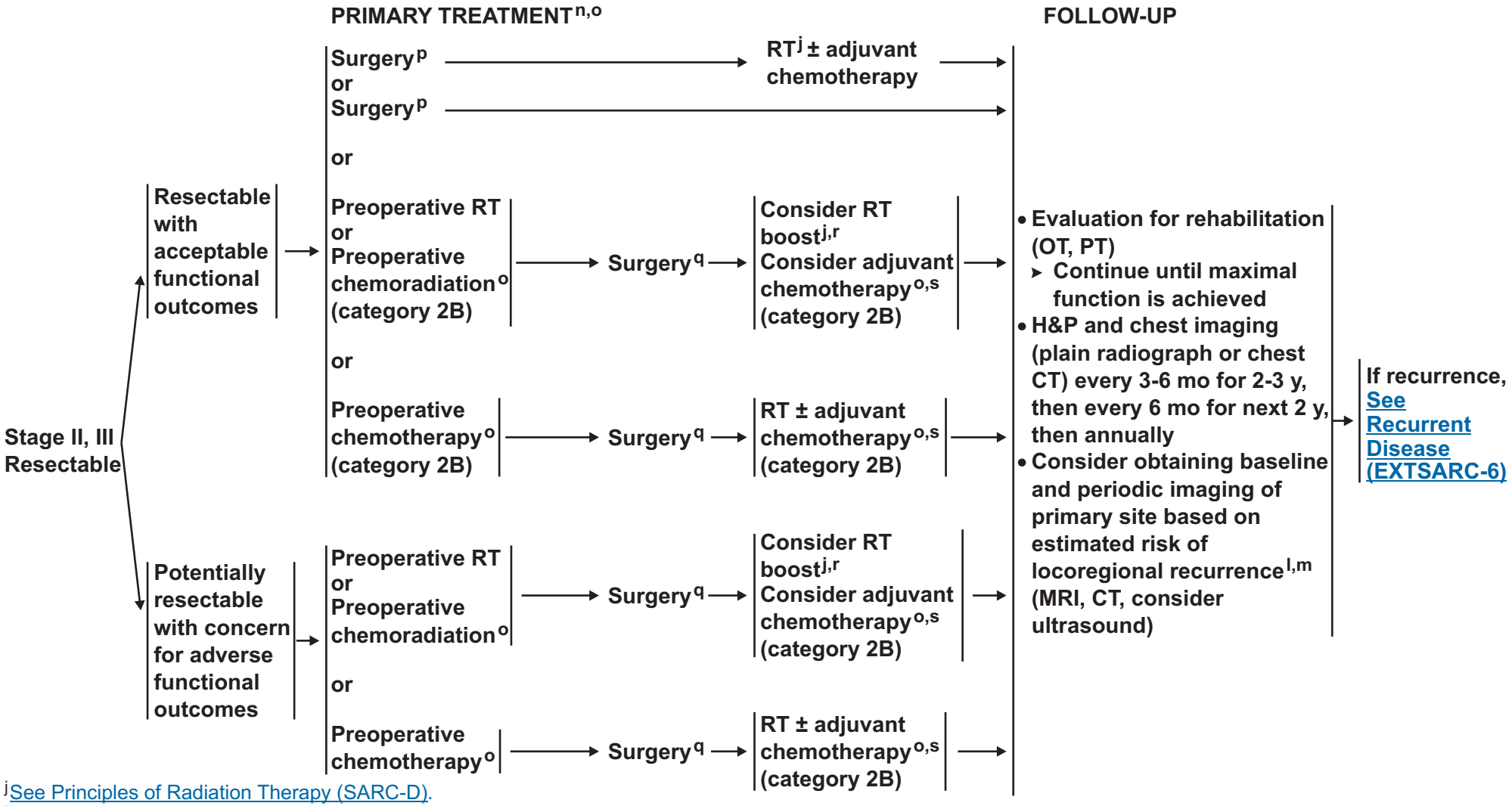
Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.



[g] See American Joint Committee on Cancer (AJCC) Staging, 7th Edition (ST-1).
[h] See Principles of Surgery (SARC-C).
[i] Reresection, if feasible, may be necessary to render margins > 1.0 cm.
[j] See Guidelines for Radiation Therapy (SARC-D).
[k] 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).
[l] In situations where the area is easily followed by physical examination, imaging may not be required.
[m] After 10 y, the likelihood of developing a recurrence is small and follow-up should be individualized.

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

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.



[j] See Principles of Radiation Therapy (SARC-D).

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

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

[n] 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.

[o] See Principles of Systemic Therapy (SARC-E).

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

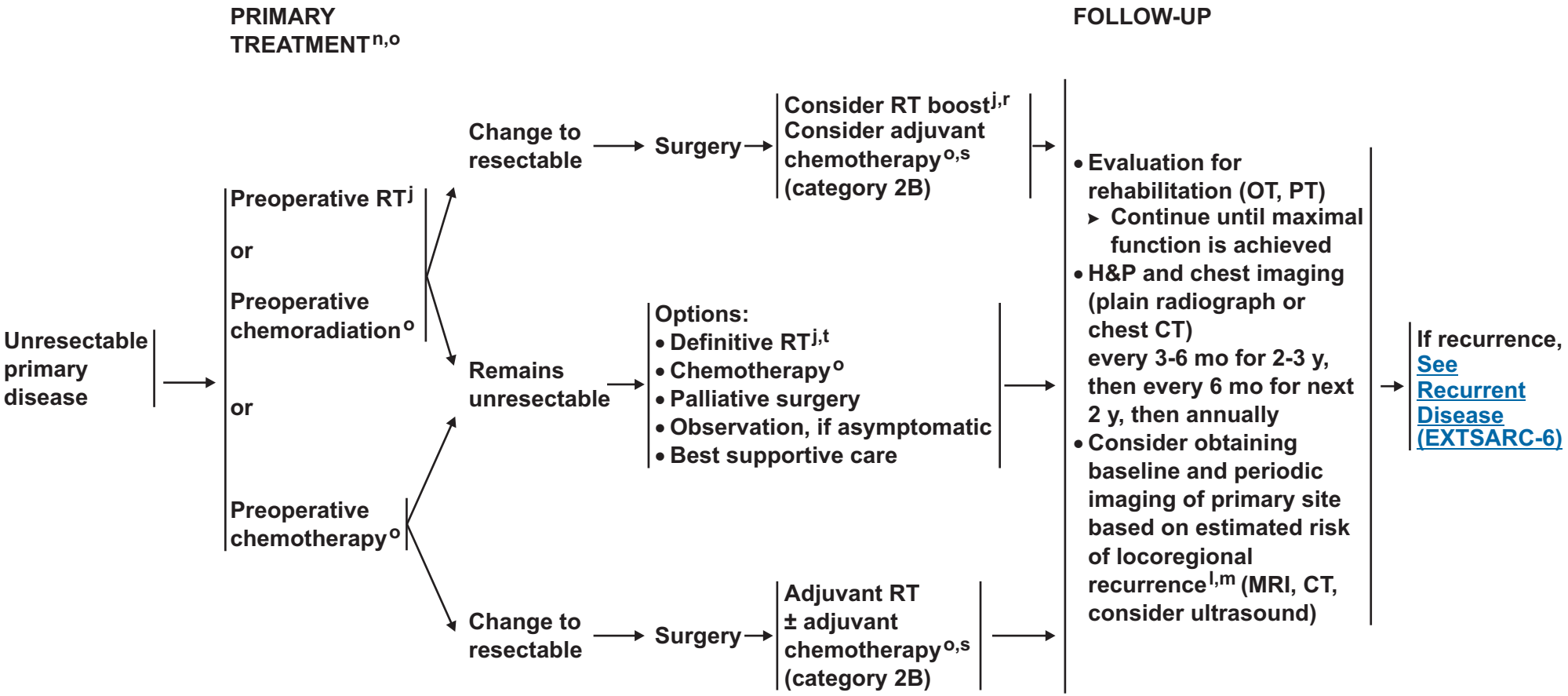
[q] Consider re-imaging patient to assess primary tumor and to rule out metastatic disease.

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

[s] There are limited and conflicting data regarding the use of adjuvant chemotherapy in stage II or stage III patients.

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.

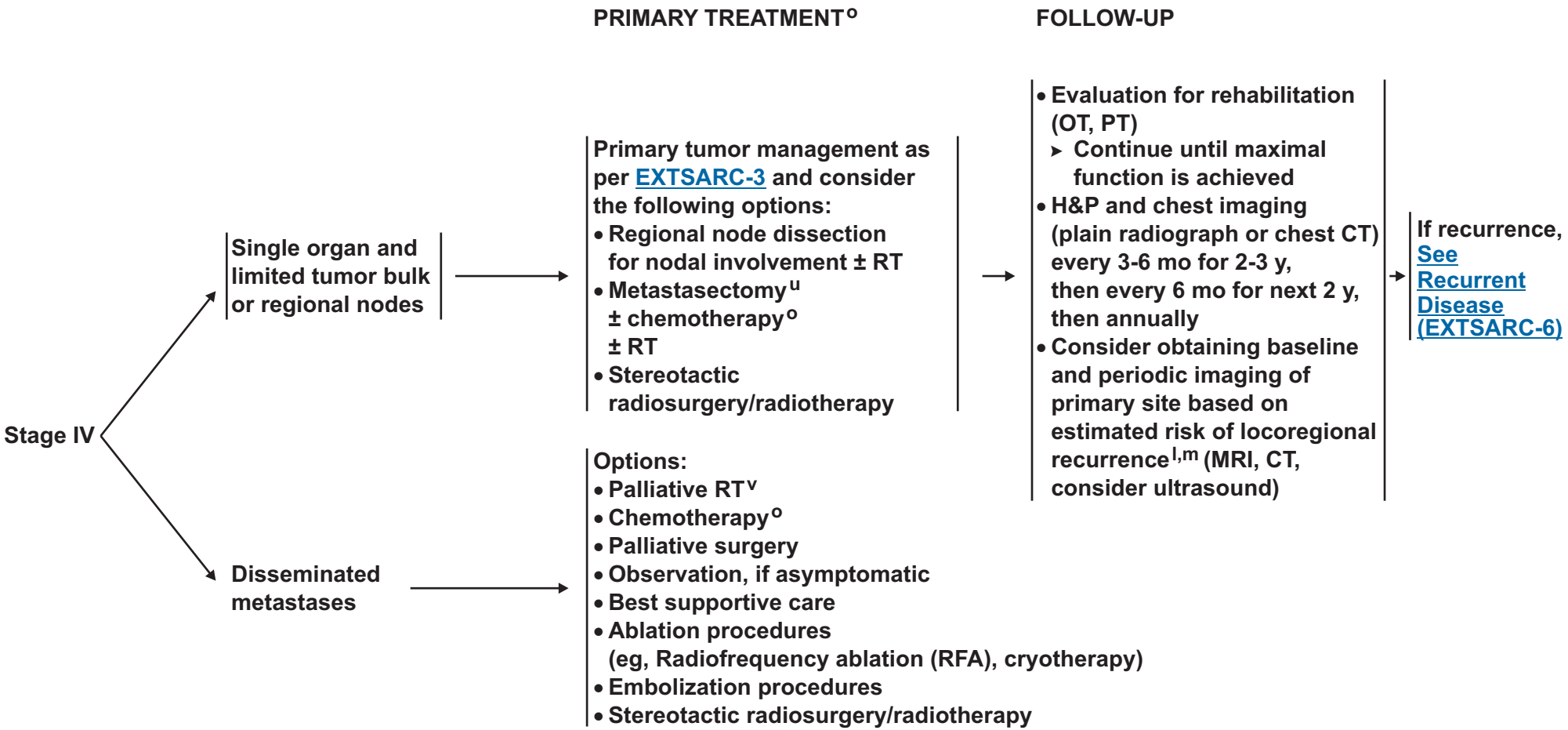
Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.



[j] See Principles of Radiation Therapy (SARC-D).
[l] In situations where the area is easily followed by physical examination, imaging may not be required.
[m] After 10 y, the likelihood of developing a recurrence is small and follow-up should be individualized.
[n] 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.
[o] See Principles of Systemic Therapy (SARC-E).
[r] For residual gross disease or microscopically positive margins.
[s] There are limited and conflicting data regarding the use of adjuvant chemotherapy in stage II or stage III patients.
[t] 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.

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.

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

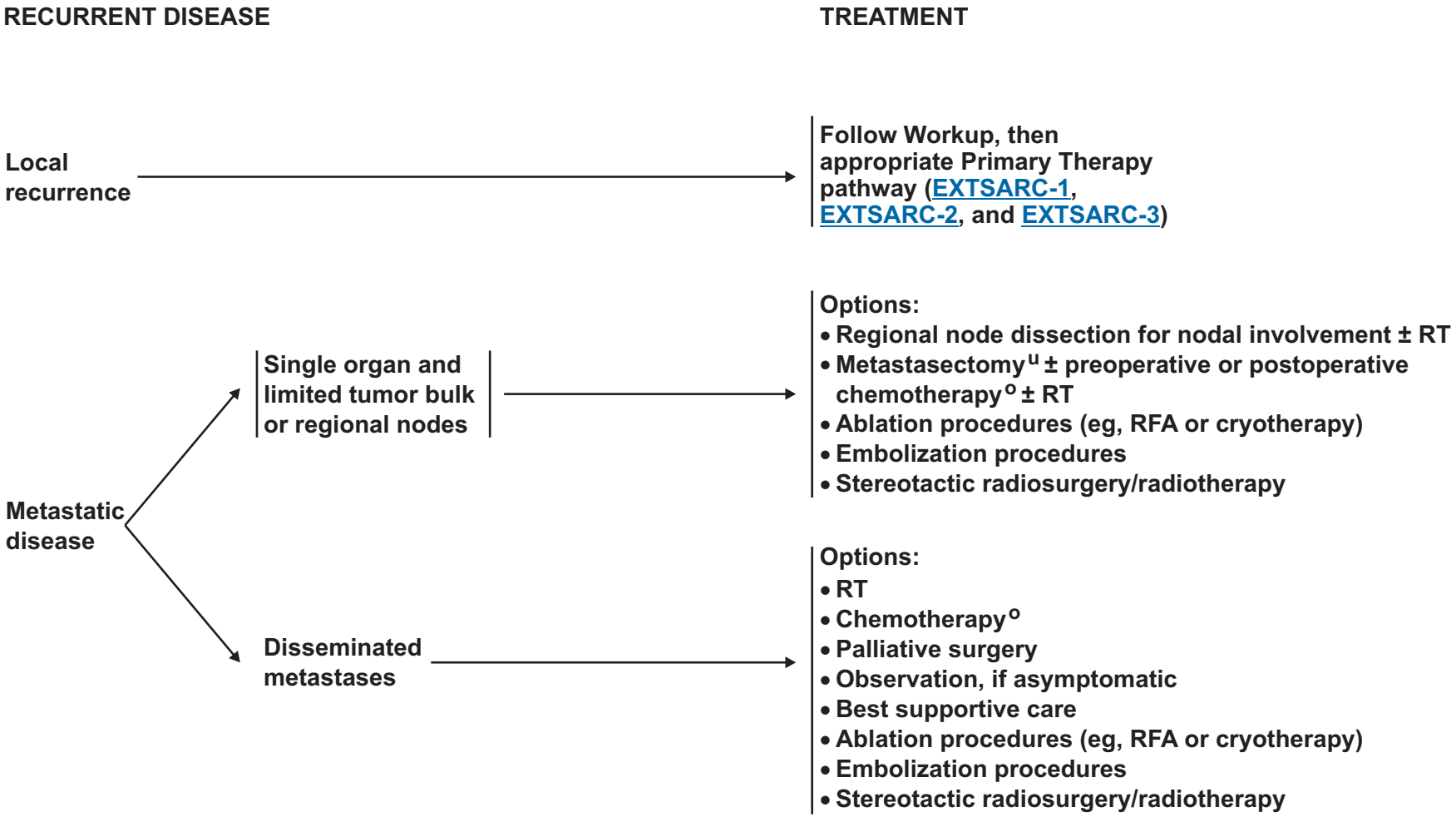


[l] In situations where the area is easily followed by physical examination, imaging may not be required.
[m] After 10 y, the likelihood of developing a recurrence is small and follow-up should be individualized.
[o] See Principles of Systemic Therapy (SARC-E).
[u] Thoracotomy and video-assisted thoracic surgery (VATS) should be available and used selectively depending on the clinical presentation of metastatic disease.
[v] 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.

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.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.



[o] See Principles of Systemic Therapy (SARC-E).

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

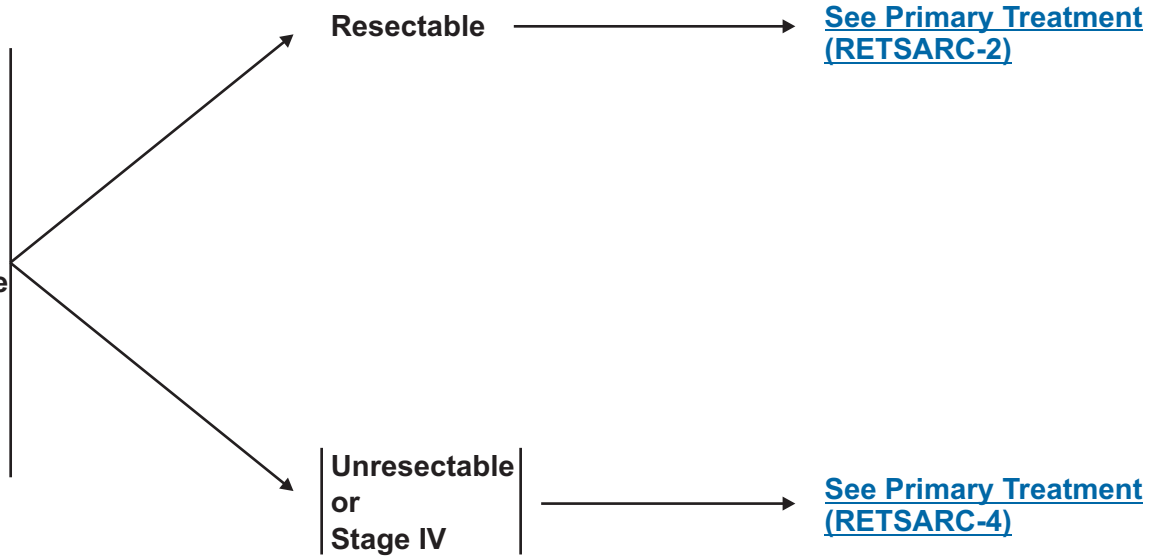
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

WORKUP

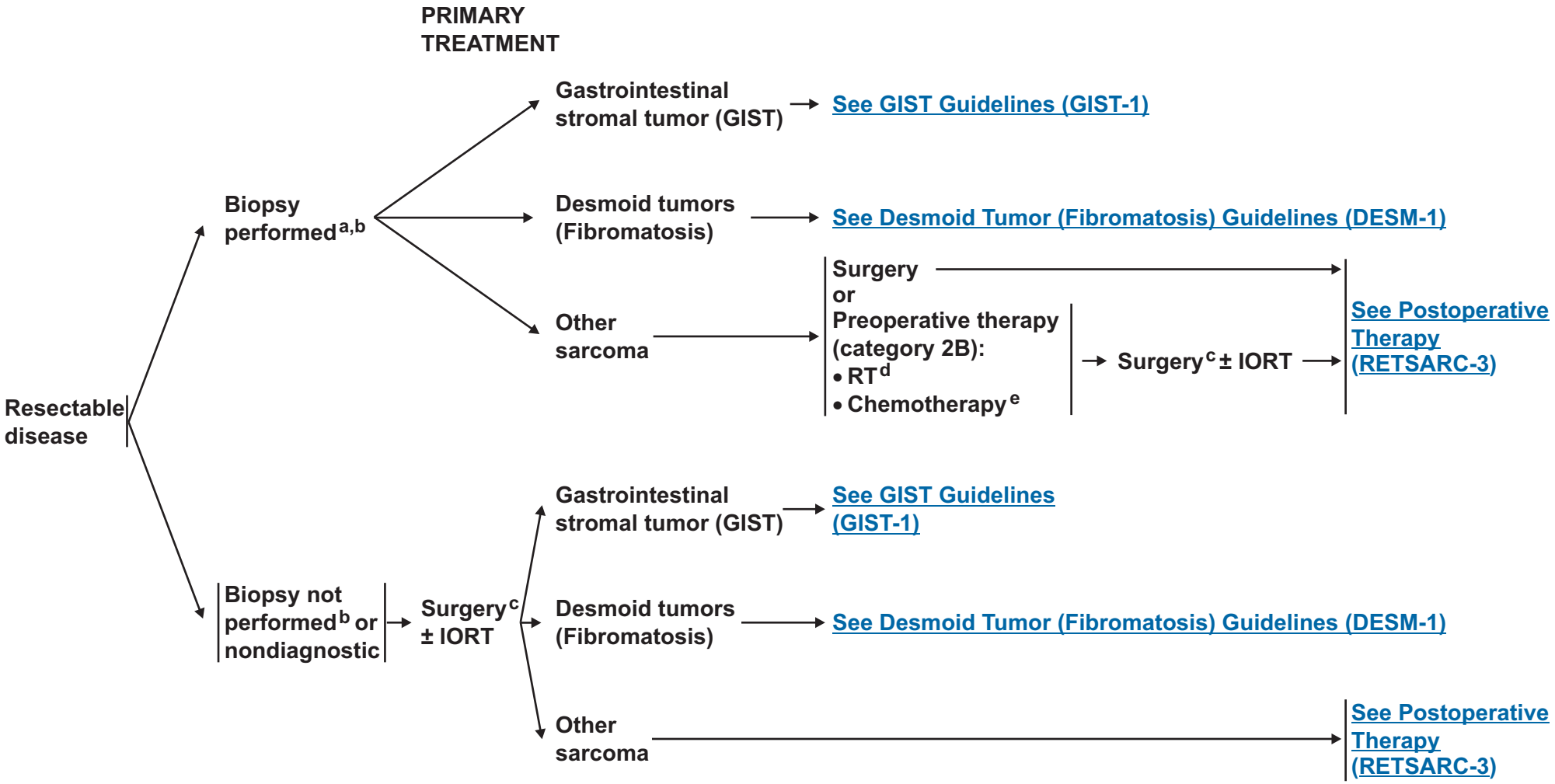
- All patients should be managed by a multidisciplinary team with expertise in sarcoma
- H&P
- Abdominal/pelvic CT with contrast ± MRI
- Preresection biopsy not necessarily required, based on degree of suspicion of other malignancies
- Biopsy is necessary for patients receiving preoperative radiotherapy or chemotherapy (CT-guided core biopsy is preferred)[a]
- Chest imaging
- Endoscopy as indicated
- If clinical suspicion of GIST, see GIST-1



[a] See Principles of Pathologic Assessment of Sarcoma Specimens (SARC-A).

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

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

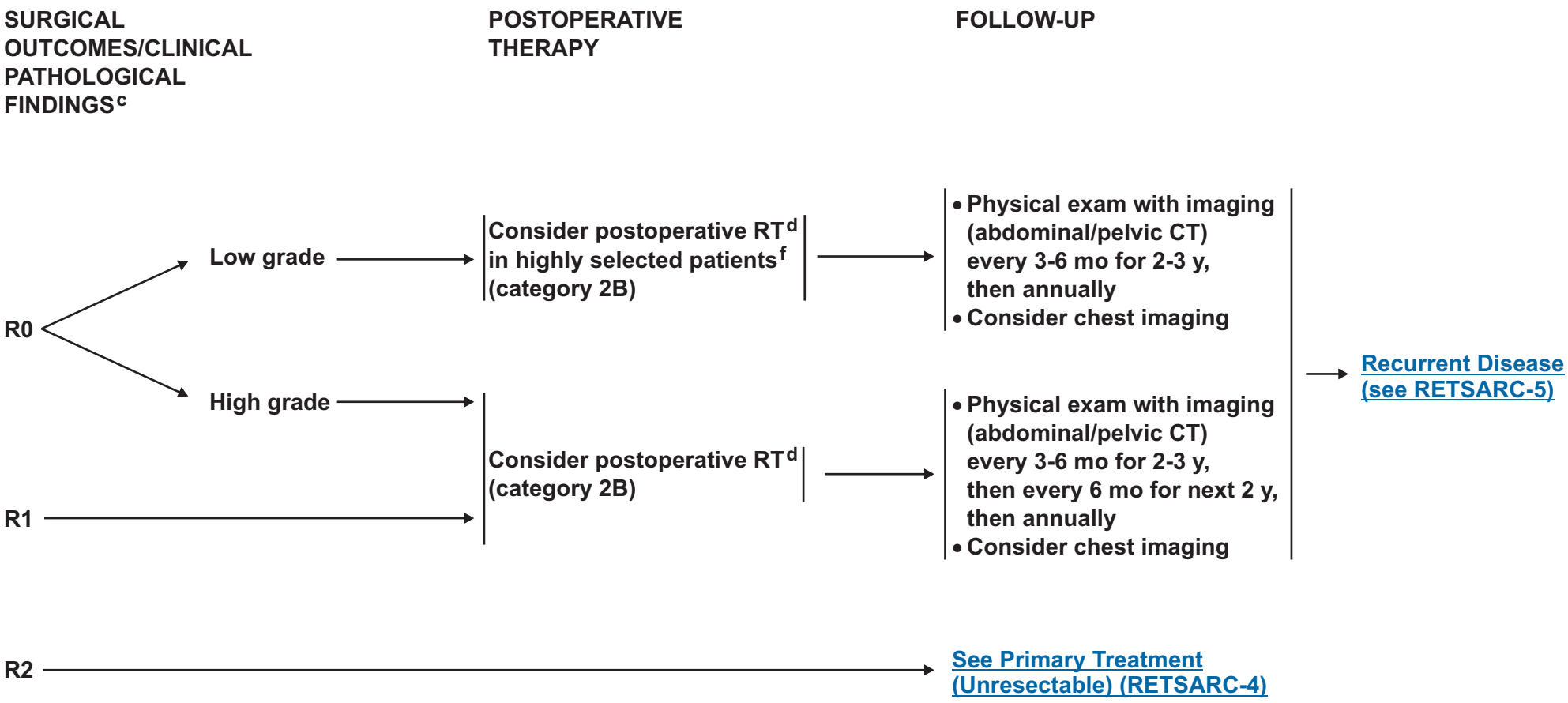


[a] See Principles of Pathologic Assessment of Sarcoma Specimens (SARC-A).
[b] Biopsy required if considering preoperative therapy, including endoscopic biopsy for suspected GIST lesions.
[c] See Principles of Surgery (SARC-C).
[d] See Guidelines for Radiation Therapy (SARC-D).
[e] See Principles of Systemic Therapy (SARC-E).

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

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

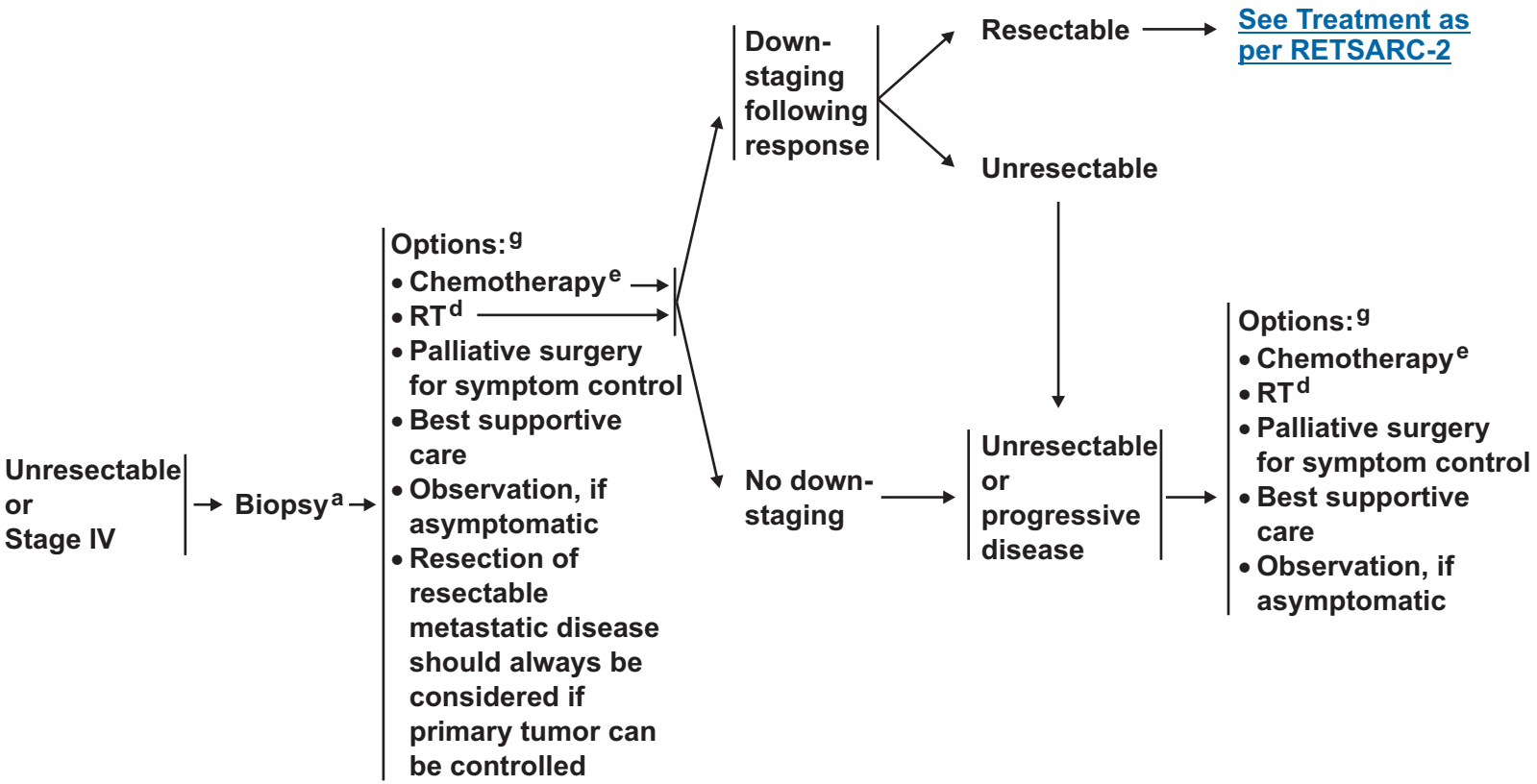


[c] See Principles of Surgery (SARC-C).
[d] See Guidelines for Radiation Therapy (SARC-D).
[f] For example, patients with an extremely large tumor, critical anatomic surface where recurrence would cause morbidity, or close margins.

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

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRIMARY TREATMENT



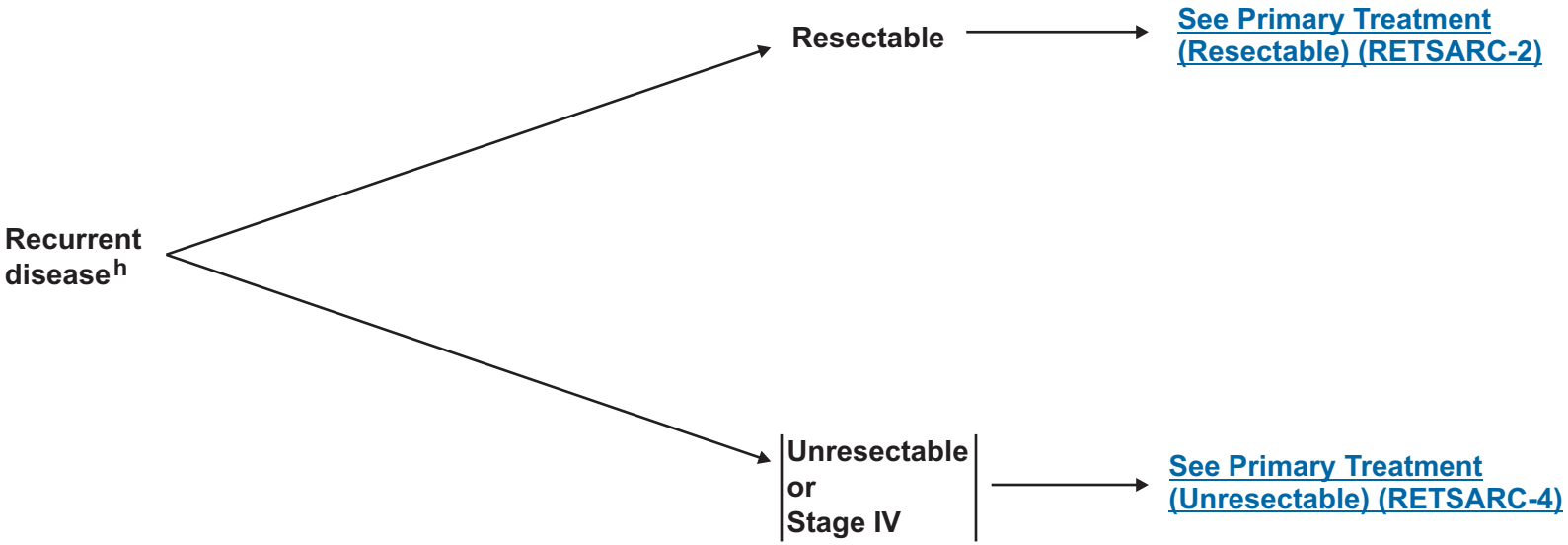
[a] See Principles of Pathologic Assessment of Sarcoma Specimens (SARC-A).
[d] See Guidelines for Radiation Therapy (SARC-D).
[e] See Principles of Systemic Therapy (SARC-E).
[g] Balance risks of treatment, likelihood of rendering patient resectable, performance status of patient, with potential clinical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

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.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

RECURRENT DISEASE



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

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

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

WORKUP OF PATIENT AT PRIMARY PRESENTATION

INITIAL DIAGNOSTIC EVALUATION

- For very small gastric GISTs < 2 cm (See GIST-2)
- 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 (in selected patients)
- Endoscopy as indicated (if not previously done)
- Shared decision making

Localized or potentially resectable disease

- **Preoperative imatinib not considered**[b] → **Resect mass**[a,d] → **Pathology result**[e] **and risk assessment**
  - **Documented GIST** → See Postoperative Treatment (GIST-6)
  - **Other sarcomas of GI origin** → See Primary Treatment (RETSARC-1)
  - **Other cancers** → See appropriate cancer guidelines within the NCCN Table of Contents
- **If considering preoperative imatinib**[c] → See (GIST-3)

Definitively unresectable or metastatic disease → See (GIST-3)

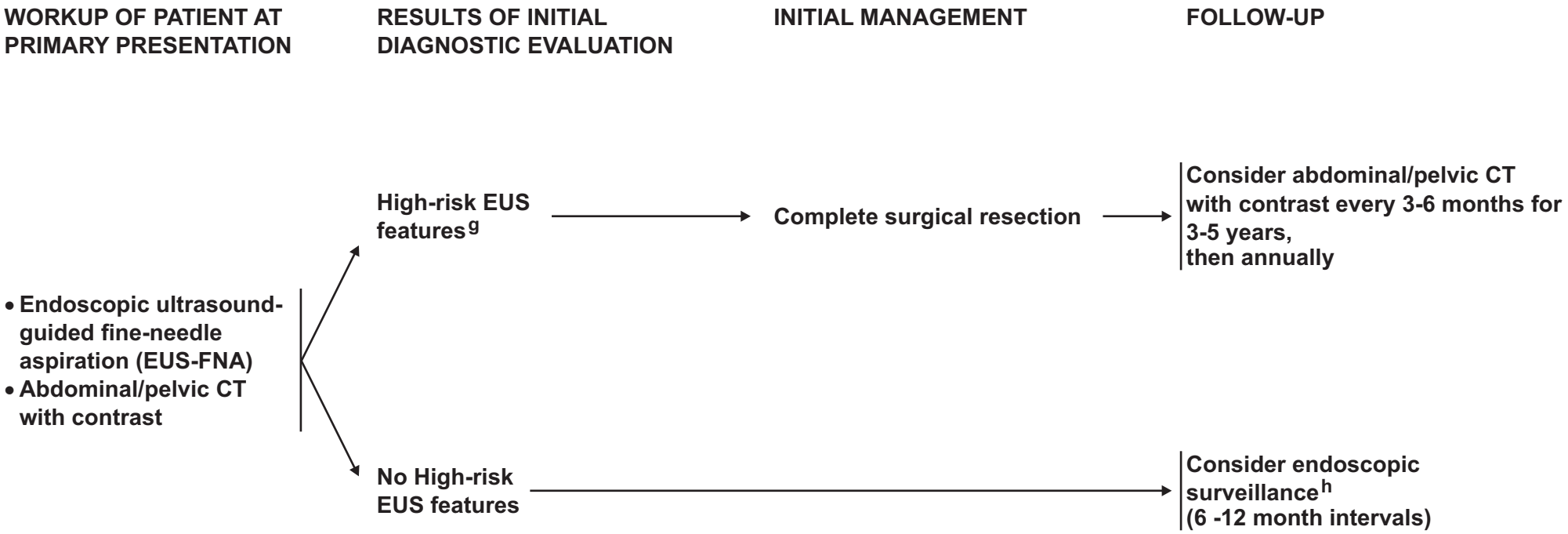
[a] Surgery should induce minimal surgical morbidity, otherwise consider preoperative imatinib mesylate.
[b] If surgical morbidity would not improve by reducing the size of the tumor preoperatively.
[c] If surgical morbidity would be improved by reducing the size of the tumor preoperatively.
[d] See Principles of Surgery For GIST (GIST-C).
[e] Pathology report should include anatomic location, size, and an accurate assessment of the mitotic rate measured in the most proliferative area of the tumor. Mutational analysis may predict response to therapy with kinase inhibitors. (See Principles of Pathologic Assessment For GIST [GIST-B])

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.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

APPROACH TO PATIENTS WITH VERY SMALL GASTRIC GISTS (< 2 CM)[f]



[f]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.

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

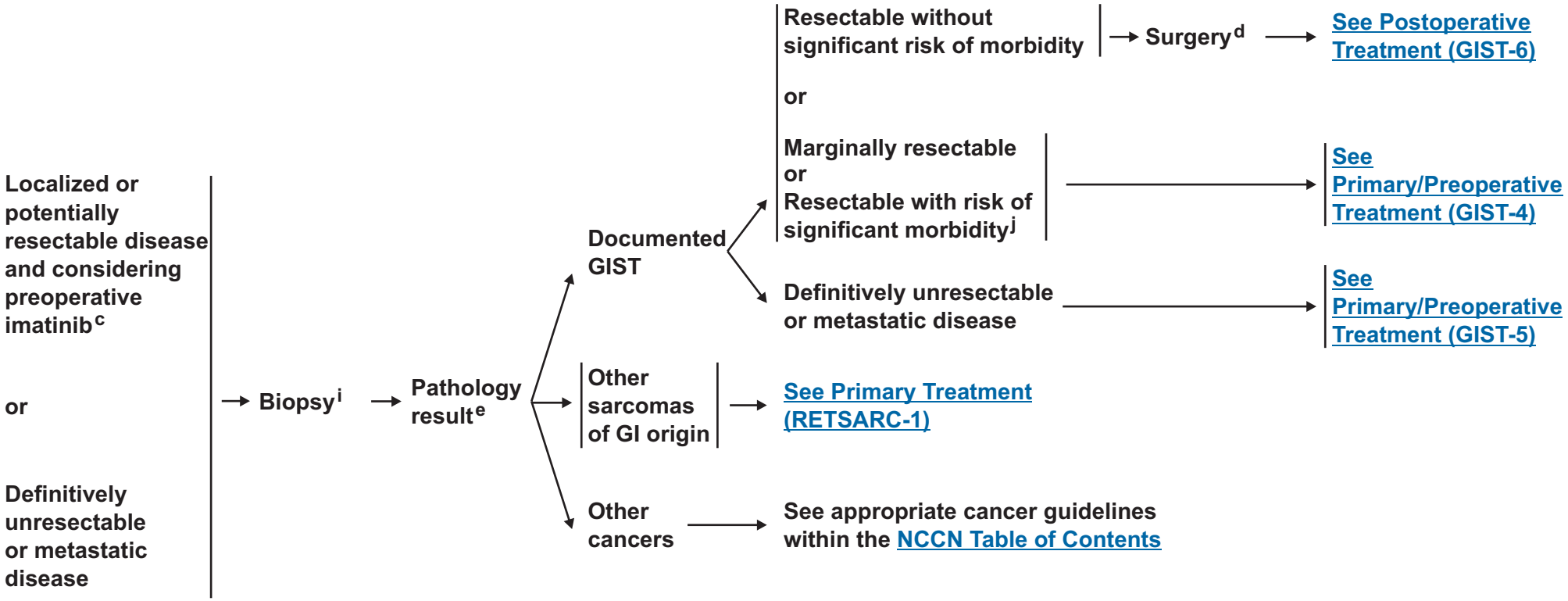
[h]Endoscopic ultrasonography surveillance should only be considered after a thorough discussion with the patient regarding the risks and benefits.

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.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

INITIAL DIAGNOSTIC EVALUATION



[c] If surgical morbidity would be improved by reducing the size of the tumor preoperatively.

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

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

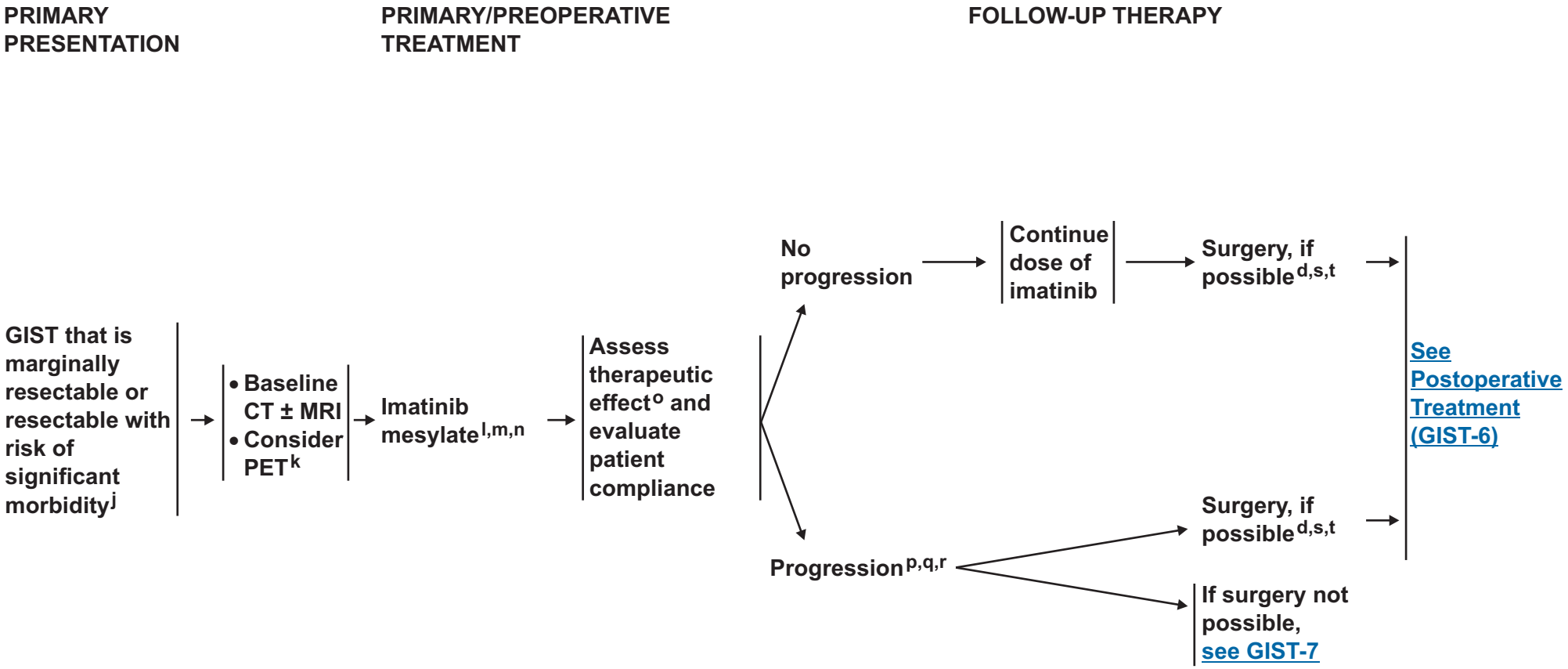
[i] See Principles of Biopsy for GIST (GIST-A).

[j] Some patients may rapidly become unresectable; close monitoring is essential.

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.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

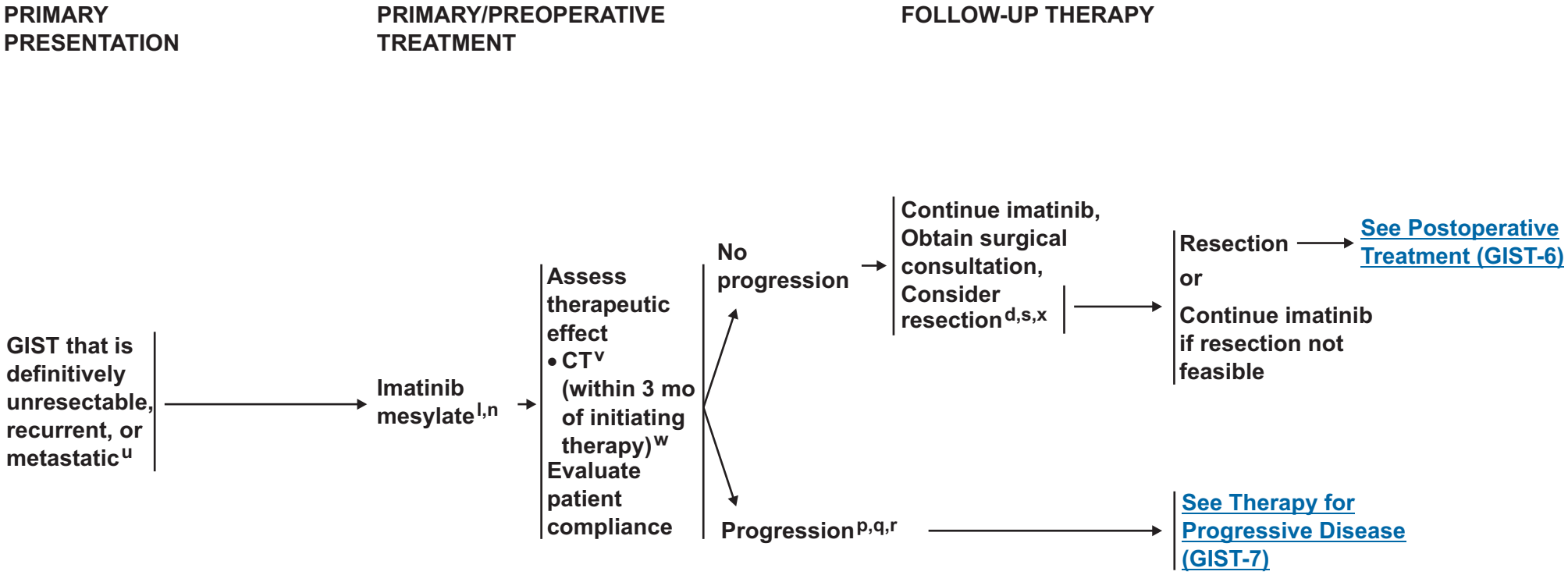


[d] See Principles of Surgery For GIST (GIST-C).
[j] Some patients may rapidly become unresectable; close monitoring is essential.
[k] PET is not a substitute for a CT.
[l] If life threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider sunitinib.
[m] Medical therapy is usual course of treatment, if patient bleeding or symptomatic, may proceed to surgery.
[n] See Dosage and Administration of Imatinib (GIST-D).
[o] 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.
[p] 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.
[q] Progression may be determined by CT or MRI with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.
[r] Suggest referral to a sarcoma specialty center.
[s] Collaboration between medical oncologist and surgeon necessary to determine appropriateness of surgery, following major response or sustained stable disease.
[t] Dosing can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications.

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

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

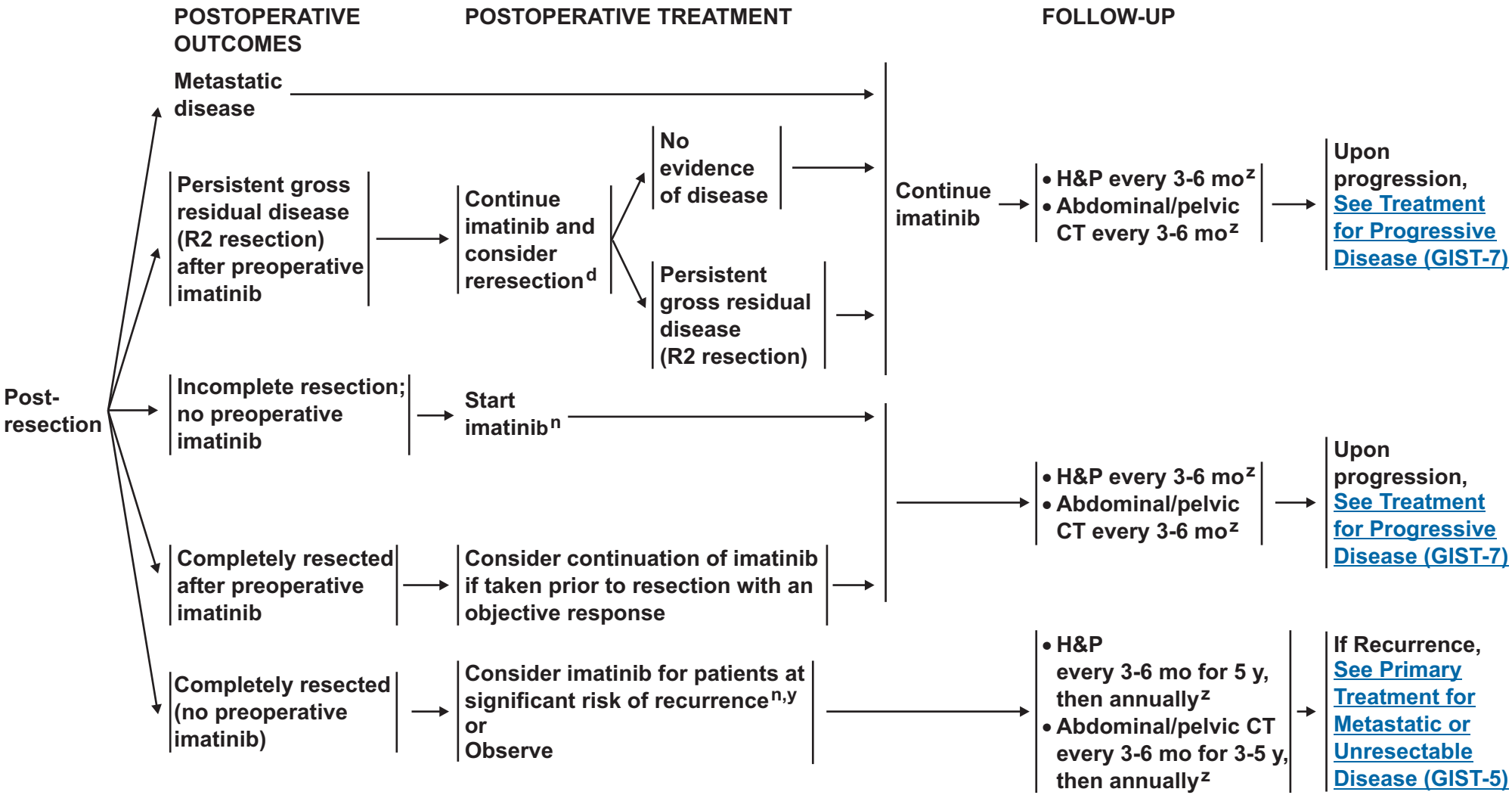


[d] See Principles of Surgery For GIST (GIST-C).
[l] If life threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider sunitinib.
[n] See Dosage and Administration of Imatinib (GIST-D).
[p] Rarely, increase in tumor size may not indicate lack of drug efficacy; all clinical and radiographic data should be taken into account, including lesion density on CT.
[q] Progression may be determined by CT or MRI with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.
[r] Suggest referral to a sarcoma specialty center.
[s] Collaboration between medical oncologist and surgeon is necessary to determine the appropriateness of surgery, following major response or sustained stable disease.
[u] Consider baseline PET, if using PET during follow-up. PET is not a substitute for CT.
[v] Consider PET only if CT results are ambiguous.
[w] In some patients, it may be appropriate to image prior to 3 months.
[x] 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.

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.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.



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

[n] See Dosage and Administration of Imatinib (GIST-D).

[y] Adjuvant therapy for at least 12 months should be considered in patients with intermediate to high risk GIST (DeMatteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet. 2009;373(9669):1097-1104). The optimal duration has not yet been determined. Patients at significantly higher risk for disease recurrence may justify a longer course of therapy.

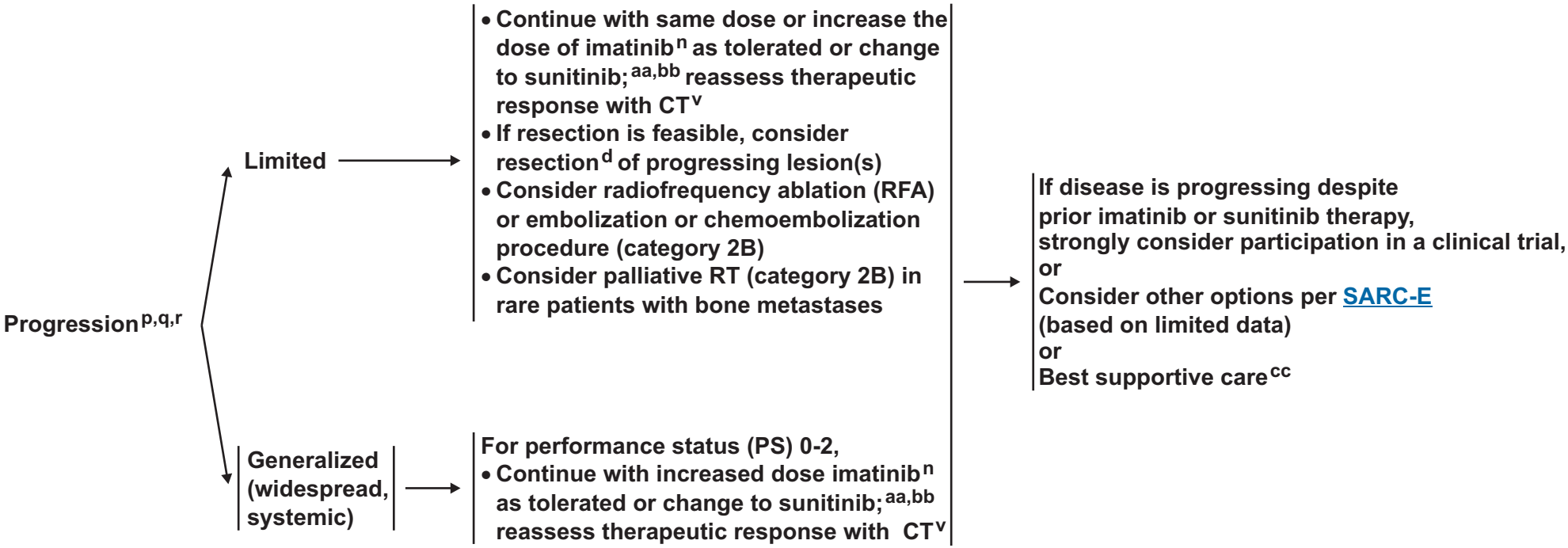
[z] Less surveillance may be acceptable for very small tumors (< 2 cm).

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.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

TREATMENT FOR PROGRESSIVE DISEASE



[d] See Principles of Surgery For GIST (GIST-C).
[n] See Dosage and Administration of Imatinib (GIST-D).
[p] 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.
[q] Progression may be determined by CT or MRI with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.
[r] Suggest referral to a sarcoma specialty center.
[v] Consider PET only if CT results are ambiguous.
[aa] See Dosage and Administration of Sunitinib (GIST-E).
[bb] Clinical experience suggests that discontinuing kinase inhibitors, even in the setting of progressive disease, may accelerate the pace of disease progression and worsen symptoms.
[cc] 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.

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.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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;[1] referral to centers with expertise in sarcoma diagnosis is recommended for cases with complex or unusual histopathologic features.**

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

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

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.

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.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF SURGERY FOR GIST

Primary (Resectable) GIST

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

- **Given the limited intramural extension, extended anatomic resections (such as total gastrectomy) are rarely indicated. Segmental or wedge resection to obtain negative margins is often appropriate.**
- **Lymphadenectomy is usually not required given the low incidence of nodal metastases.**
- **As GIST tends to be very friable, every effort should be made not to violate the pseudocapsule of the tumor.**
- **Re-resection is generally not indicated for microscopically positive margins on final pathology.**

Resection should be accomplished with minimal morbidity and, in general, complex multi-visceral resection should be avoided. If the surgeon feels that a multi-visceral resection may be required, then multidisciplinary consultation is indicated regarding a course of preoperative imatinib therapy. Similarly, rectal GIST should be approached via a sphincter-sparing approach. If abdominoperineal resection (APR) would be necessary to achieve a negative margin resection, then preoperative imatinib therapy should be considered.

A laparoscopic approach may be considered for select GISTs in favorable anatomic locations (greater curvature or anterior wall of the stomach, jejunum, and ileum) by surgeons with appropriate laparoscopic experience.

- **All oncologic principles of GIST resection must still be followed, including preservation of the pseudocapsule and avoidance of tumor spillage.**
- **Resection specimens should be removed from the abdomen in a plastic bag to prevent spillage or seeding of port sites.**

Metastatic GIST

Imatinib is the primary therapy for metastatic GIST. Surgery may be indicated for:

- **Limited disease progression refractory to systemic therapy.**
- **Locally advanced or previously unresectable tumors after a favorable response to preoperative imatinib.**

If persistent metastatic or residual tumor remains after surgery, then imatinib should be continued as soon as the patient is able to tolerate oral intake.

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

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

DOSING AND ADMINISTRATION OF IMATINIB[1]

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.**

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

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.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

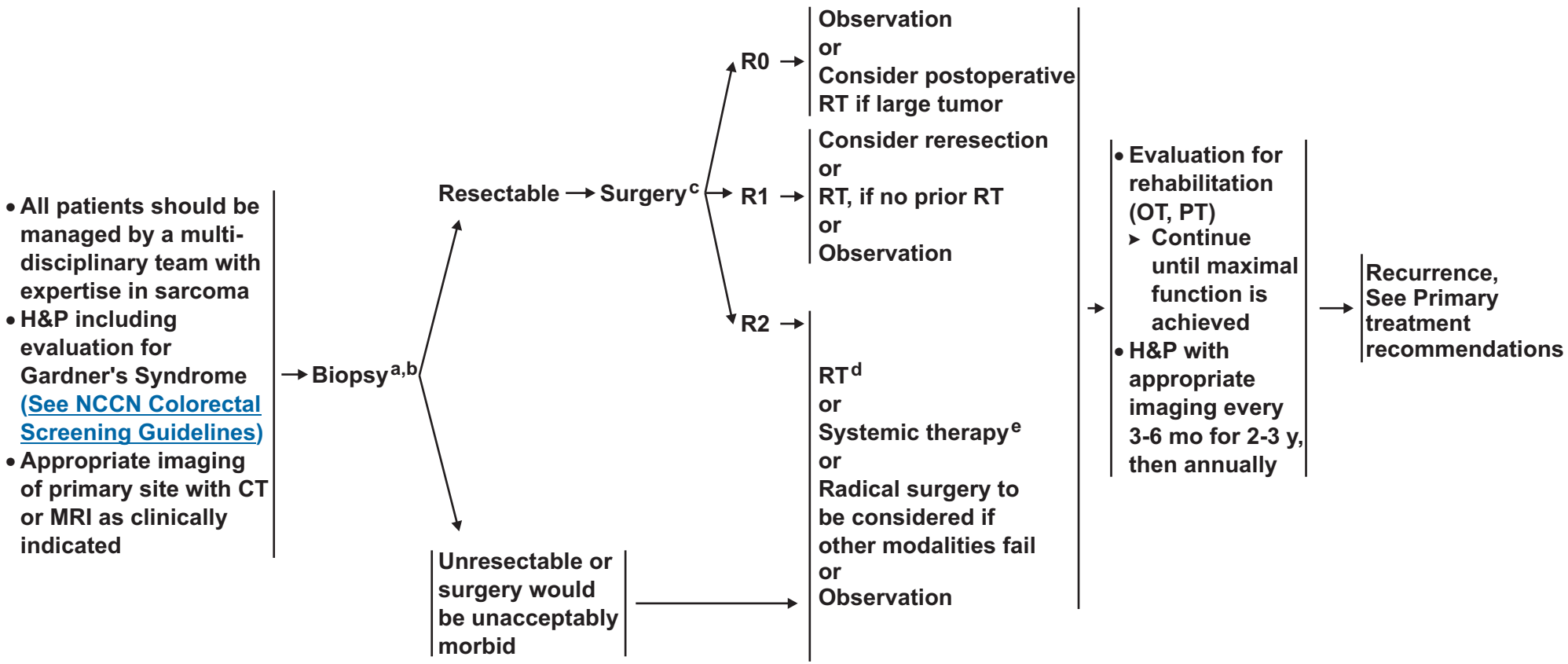
DOSING AND ADMINISTRATION OF SUNITINIB[1]

- **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.**

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

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.

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.



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

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

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[1]**
- **The pathologic assessment should include evaluation of the following features, all of which should be specifically addressed in the pathology report:**

- **Organ, site, and operative procedure**
- **Primary diagnosis (using standardized nomenclature, for example, the World Health Organization Classification of Soft Tissue Tumors[2]).**
- **Depth of tumor**
  - **Superficial (tumor does not involve the superficial fascia)**
  - **Deep**
- **Size of tumor**
- **Histologic grade (at the least, specify low or high grade, if applicable); ideally, grade using the French Federation of Cancer Centers Sarcoma Group (FNCLCC) or National Cancer Institute (NCI) system**
- **Necrosis**
  - **Present or absent**
  - **Microscopic or macroscopic**
  - **Approximate extent (percentage)**
- **Status of margins of excision**
  - **Uninvolved**
  - **Closer than 2 cm (state which margins and measured distance)**
  - **Involved (state which margins)**
- **Status of lymph nodes**
  - **Site**
  - **Number examined**
  - **Number positive**
- **Results of ancillary studies[1]**
  - **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)**

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

[2] World Health Organization Classification of Tumours. Pathology and Genetics. Tumours of Soft Tissue and Bone. Lyon: IARC Press; 2002.

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.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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, 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.[1] Recurrent genetic aberrations in sarcoma[2] are listed below:

TUMOR	ABERRATION	GENE(S) INVOLVED
Malignant Round Cell Tumors		
Ewing sarcoma / peripheral neuroectodermal tumor	t(11;22)(q24;q12) t(21;22)(q22;q12) other rare variants	*EWS-FLI1* *EWS-ERG* various
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	*EWS-WT1*
Embryonal rhabdomyosarcoma	Complex alterations	Unknown
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14) t(1;13)(p36;q14)	*PAX3-FKHR* *PAX7-FKHR*
Lipomatous Tumors		
Myxoid/round cell liposarcoma	t(12;16)(q13;p11)	*TLS-CHOP*
Atypical lipomatous tumor/well differentiated liposarcoma (ALT/WDLPS)	Supernumerary ring chromosomes; giant marker chromosomes	Amplification of region 12q14-15, including *MDM2, CDK4, HMGA2, SAS, GL1*
Dedifferentiated liposarcoma	Same as for ALT/WDLPS	Same as for ALT/WDLPS
Pleomorphic liposarcoma	Complex alterations	Unknown

[1] 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.

[2] 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.

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.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF ANCILLARY TECHNIQUES USEFUL IN THE DIAGNOSIS OF SARCOMAS

TUMOR	ABERRATION	GENE(S) INVOLVED
Other Sarcomas		
Alveolar soft part sarcoma	der(17)(X;17)(p11;q25)	*ASPL-TFE3*
Angiomatoid fibrous histiocytoma	t(2;22)(q33;q12) t(12;16)(q13;p11)	*EWS-CREB1* *TLS-ATF1*
Clear cell sarcoma	t(12;22)(q13;q12) t(2;22)(q33;q12)	*EWS-ATF1* *EWS-CREB1*
Congenital/infantile – fibrosarcoma	t(12;15)(p13;q25)	*ETV6-NTRK3*
Dermatofibrosarcoma protuberans	t(17;22)(q22;q13) and derivative ring chromosomes	*COL1A1-PDGFB*
Desmoid fibromatosis	Trisomy 8 or 20; loss of 5q	*CTNNB1* or *APC* mutations
Epithelioid sarcoma (proximal type)	Bi-allelic inactivation of 22q11.2	*INI1*
Extrarenal rhabdoid tumor	Bi-allelic inactivation of 22q11.2	*INI1*
Extraskeletal myxoid chondrosarcoma	Rearrangements of 9q22	*CHN*
Sporadic GIST Familial GIST (Carney-Stratakis syndrome)	Activating kinase mutations KREBS cycle mutation	*KIT or PDGFRA* *SDH* subunit mutations
Inflammatory myofibroblastic tumor	Rearrangements of 2p23	*ALK*
Leiomyosarcoma	Complex alterations	Unknown
Low grade fibromyxoid sarcoma	t(7;16)(q34;p11)	*TLS-BBF2H7*
Malignant peripheral nerve sheath tumor	Complex alterations	Unknown
Synovial sarcoma	t(X;18)(p11;q11) t(X;18)(p11;q11)	*SYT-SSX1* *SYT-SSX2*
Tenosynovial giant cell tumor/pigmented villonodular synovitis (TGCT/PVNS)	t(1;2)(p13;q35)	*CSF1*

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.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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 (< 1 cm) 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

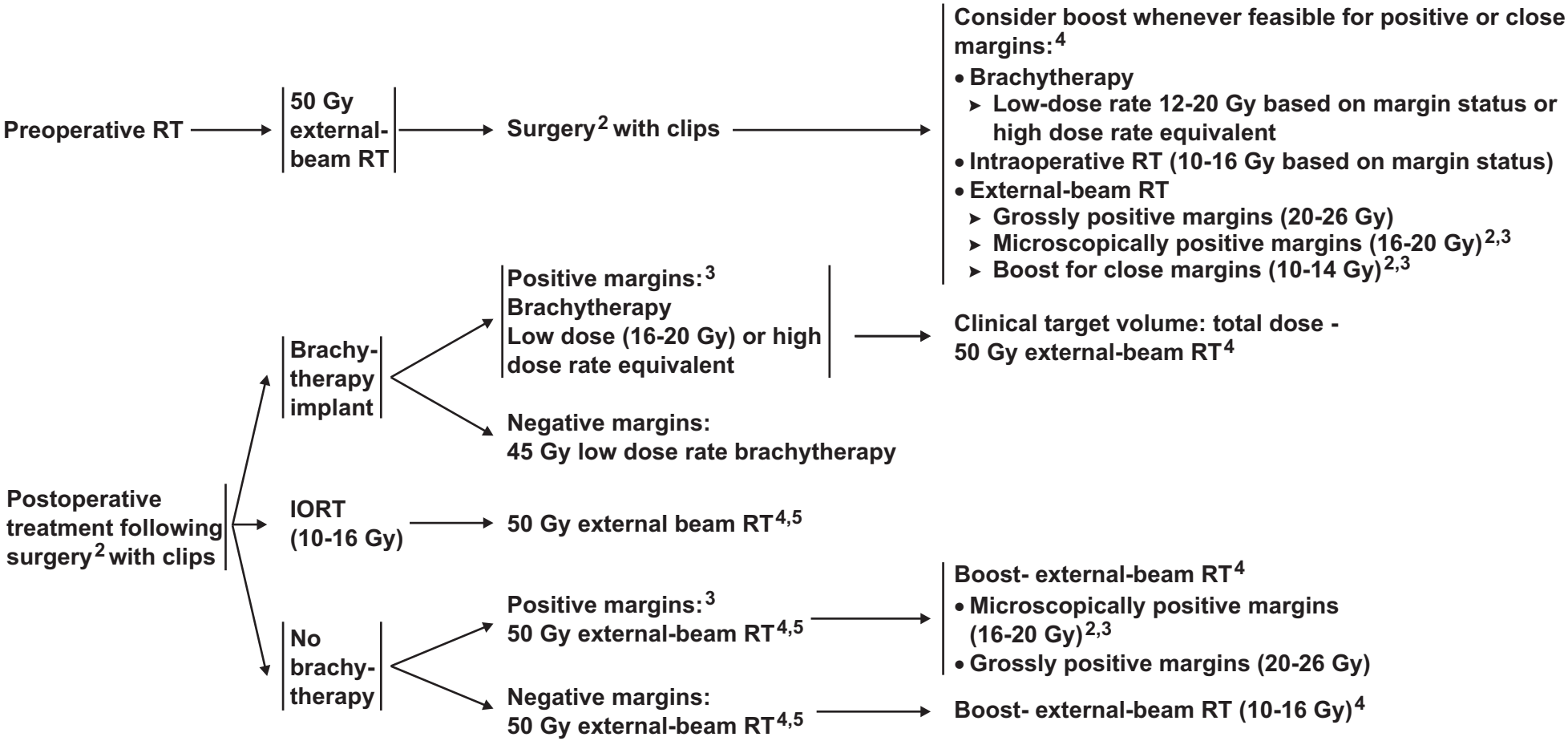
- Prior to considering amputation, patients should be evaluated by a surgeon with expertise in the treatment of soft tissue sarcomas. Consideration for amputation to treat an extremity sarcoma should be made for patient preference or if gross total resection of the tumor is expected to render the limb 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.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

GUIDELINES FOR RADIATION THERAPY[1]



[1] When external beam RT is used, sophisticated treatment planning with IMRT, tomotherapy, and/or protons can be used to improve the therapeutic effect (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.

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

[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.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA[a,b]

Extremity, Retroperitoneal, Intra-abdominal

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]
- Gemcitabine and vinorelbine[9]

Single agents
- Doxorubicin[10]
- Ifosfamide[6,11]
- Epirubicin
- Gemcitabine
- Dacarbazine
- Liposomal doxorubicin[12]
- Temozolomide[13]

Angiosarcoma
- Paclitaxel[14,15]
- Docetaxel
- Vinorelbine
- Sorafenib[16,17]
- Sunitinib[18]
- Bevacizumab[19]
- All other systemic therapy options as per extremity sarcoma

Desmoid Tumors (Fibromatosis)
- Sulindac[20] or other non-steroidal anti-inflammatory drugs (NSAIDS) including celecoxib[c]
- Tamoxifen[21]
- Toremifene[22]
- Methotrexate and vinblastine[23]
- Low-dose interferon[24]
- Doxorubicin-based regimens[25,26]
- Imatinib mesylate[27]

GIST
- Imatinib[28,29]
- Sunitinib[30]
- Sorafenib[31]
- Nilotinib[32,33]
- Dasatanib[34]

Solitary Fibrous Tumor/Hemangiopericytoma
- Bevacizumab and temozolomide[35]
- Sunitinib[36,37]

Pigmented Villonodular Synovitis/Tenosynovial Giant Cell Tumor (PVNS/TGCT)
- Imatinib[38]

Alveolar soft part sarcoma (ASPS)
- Sunitinib[39,40] (category 2B)

PEComa, Recurrent Angiomyolipoma, Lymphangioleiomyomatosis
- Sirolimus[41-45]

Chordoma (All recommendations are category 2B)

Combination regimens
- Erlotinib and cetuximab
- Imatinib and cisplatin[46]
- Imatinib and sirolimus[47]

Single agents
- Erlotinib[48]
- Imatinib[49,50]
- Sunitinib[37]

[a] Alveolar soft part sarcoma and clear cell sarcomas are generally not sensitive to chemotherapy.
[b] References for regimens, see SARC-E 2 of 3.
[c] 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)

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.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

[1] Zalupski M, Metch B, Balcerzak S, et al. Phase III comparison of doxorubicin and dacarbazine given by bolus versus infusion in patients with soft-tissue sarcomas: A Southwest Oncology Group Study. J Natl Cancer Inst. 1991;83(13):926-932.

[2] Antman K, Crowley J, Balcerzak SP et al. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. J Clin Oncol 1993;11(7):1276-1285.

[3] Grobmyer SR, Maki RG, Demetri GD, et al. Neo-adjuvant chemotherapy for primary high-grade extremity soft tissue sarcoma. Ann Oncol. 2004;15(11):1667-1672.

[4] Edmonson J, Ryan L, Blum R, et al. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. J Clin Oncol. 1993;11(7):1269-1275.

[5] Elias A, Ryan L, Sulkes A, et al. Response to mesna, doxorubicin, ifosfamide, and dacarbazine in 108 patients with metastatic or unresectable sarcoma and no prior chemotherapy. J Clin Oncol 1989;7(9): 1208-1216.

[6] Frustaci S, Gherlinzoni F, De Paoli A, et al. Adjuvant Chemotherapy for Soft Tissue Sarcomas of the Extremities and Girdles: Results of the Italian Randomized Cooperative Trial. J Clin Oncol. 2001;19(5):1238-1247.

[7] Hensley ML, Maki R, Venkatraman E et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. J Clin Oncol 2002;20(1 2):2824-2831.

[8] Leu KM, Ostruszka U, Schewach D, et al. Laboratory and clinical evidence of synergistic cytotoxicity of sequential treatment with gemcitabine followed by docetaxel in the treatment of sarcoma. J Clin Oncol 2004;22(9):1706-1712.

[9] Dileo P, Morgan JA, Zahrieh D, et al. Gemcitabine and vinorelbine combination chemotherapy for patients with advanced soft tissue sarcomas: results of a phase II trial. Cancer. 2007;109:1863-1869.

[10] Tierney JF. Adjuvant chemotherapy for localized resectable soft-tissue sarcoma of adults: Meta-analysis of individual data. Lancet 1997;350:1647-1654.

[11] Antman KH et al. Dana-Farber Cancer Institute studies in advanced sarcoma. Semin Oncol. 1990;1(Suppl 2):7-15.

[12] Judson I, Radford J, Harris M, et al. Randomized phase II trial of pegylated liposomal doxorubicin versus doxorubicin in the treatment of advanced or metastatic soft tissue sarcoma: a study by the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer 2001 ;37(7):870-877.

[13] Talbot SM, Keohan ML, Hesdorffer M, et al. A Phase II trial of temozolomide in patients with unresectable or metastatic soft tissue sarcoma. Cancer 2003; 98(9):1942-1946.

[14] Penel N, Bui BN, Bay J-O, et al. Phase II Trial of Weekly Paclitaxel for Unresectable Angiosarcoma: The ANGIOTAX Study. J Clin Oncol. 2008;26(32):5269-5274.

[15] Schlemmer M, Reichardt P, Verweij J, et al. Paclitaxel in patients with advanced angiosarcomas of soft tissue: a retrospective study of the EORTC soft tissue and bone sarcoma group. Eur J Cancer. 2008;44(16):2433-2436.

[16] Maki RG, Keohan ML, Undevia SD, et al. Updated results of a phase II study of oral multi-kinase inhibitor sorafenib in sarcomas, CTEP study #7060. J Clin Oncol (Meeting Abstracts). 2008;26(15_suppl):10531.

[17] Maki RG, D'Adamo DR, Keohan ML, et al. Phase II study of sorafenib in patients with metastatic or recurrent sarcomas. J Clin Oncol. 2009;27:3133-3140.

[18] Keohan ML, Morgan JA, D'Adamo DR, et al. Continuous daily dosing (CDD) of sunitinib (SU) in patients with metastatic soft tissue sarcomas (STS) other than GIST: Results of a phase II trial. J Clin Oncol (Meeting Abstracts). 2008;26(15_suppl):10533.

[19] Agulnik M, Okuno SH, Von Mehren M, et al. An open-label multicenter phase II study of bevacizumab for the treatment of angiosarcoma. J Clin Oncol (Meeting Abstracts) 2009;27(15S):10522-.

[20] Hansmann A, Adolph C, Vogel T, et al. High-dose tamoxifen and sulindac as first-line treatment for desmoid tumors. Cancer 2004;100:612-620.

[21] Chao AS, Lai CH, Hsueh S, et al. Successful treatment of recurrent pelvic desmoid tumor with tamoxifen: case report. Hum Reprod 2000;15:311-313.

[22] Benson JR MK, Baum M. Management of desmoid tumours including a case report of toremifene. Ann Oncol. 1994;5(2):173-177.

[23] Azzarelli A, Gronchi A, Bertulli R, et al. Low-dose chemotherapy with methotrexate and vinblastine for patients with advanced aggressive fibromatosis. Cancer. 2001;92(5):1259-1264.

[24] Leithner A, Schnack B, Katterschafka T, et al. Treatment of extra-abdominal desmoid tumors with interferon-alpha with or without tretinoin. J Surg Oncol 2000;73:21-25.

[25] Seiter K, Kemeny N. Successful treatment of a desmoid tumor with doxorubicin. Cancer 1993;71:2242-2244.

[26] Patel SR, Evans HL, Benjamin RS. Combination chemotherapy in adult desmoid tumors. Cancer 1993;72:3244-3247.

[27] Chugh R, Maki RG, Thomas DG, et al. A SARC phase II multicenter trial of imatinib mesylate (IM) in patients with aggressive fibromatosis. J Clin Oncol (Meeting Abstracts). 2006;24(18_suppl):9515.

[28] Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347(7):472-480.

[29] Verweij J, Casali PG, Zalcberg J, etal. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomized trial. Lancet 2004;364(9440):1127-1134.

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.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

[30] Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumor after failure of imatinib: a randomized controlled trial. Lancet. 2006;368:1329-1338.

[31] Wiebe L, Kasza KE, Maki RG, et al. Activity of sorafenib (SOR) in patients (pts) with imatinib (IM) and sunitinib (SU)-resistant (RES) gastrointestinal stromal tumors (GIST): A phase II trial of the University of Chicago Phase II Consortium. J Clin Oncol (Meeting Abstracts). 2008;26(15_suppl):10502.

[32] Blay JY, Casali PG, Reichardt P, et al. A phase I study of nilotinib alone and in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors (GIST): Study update. J Clin Oncol (Meeting Abstracts). 2008;26(15_suppl):10553.

[33] Montemurro M, Schoffski P, Reichardt P, et al. Nilotinib in advanced GIST: A retrospective analysis of nilotinib in compassionate use. J Clin Oncol (Meeting Abstracts). 2008;26(15_suppl):10523.

[34] Demetri G, Lo Russo P, MacPherson RJ, et al. Phase I Dose-Escalation and Pharmacokinetic Study of Dasatinib in Patients with Advanced Solid Tumors. Clinical Cancer Research 2009; 15:6232-6240.

[35] Park MS, Patel SR, Ludwig JA, et al. Combination therapy with temozolomide and bevacizumab in the treatment of hemangiopericytoma/malignant solitary fibrous tumor. J Clin Oncol (Meeting Abstracts) 2008;26(15_suppl):10512-.

[36] Casali PG, Stacchiotti S, Palassini E, et al. Evaluation of the antitumor activity of sunitinib malate (SM) in solitary fibrous tumor (SFT). J Clin Oncol (Meeting Abstracts) 2009;27(15S):10571-.

[37] George S, Merriam P, Maki RG, et al. Multicenter Phase II Trial of Sunitinib in the Treatment of Nongastrointestinal Stromal Tumor Sarcomas. J Clin Oncol. 2009;27:3154-3160.

[38] Blay JY, El Sayadi H, Thiesse P, Garret J, Ray-Coquard I. Complete response to imatinib in relapsing pigmented villonodular synovitis/tenosynovial giant cell tumor (PVNS/TGCT). Ann Oncol. 2008;19:821-822.

[39] Stacchiotti S, Tamborini E, Bertulli R, et al. Response to sunitinib malate (SM) in alveolar soft part sarcoma (ASPS). J Clin Oncol (Meeting Abstracts). 2008;26:10592-.

[40] Stacchiotti S, Tamborini E, Marrari A, et al. Response to sunitinib malate in advanced alveolar soft part sarcoma. Clin Cancer Res 2009;15:1096-1104.

[41] Bissler JJ, McCormack FX, Young LR, et al. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. N Engl J Med 2008;358:140-151.

[42] Chen F, Omasa M, Kondo N, et al. Sirolimus treatment for recurrent lymphangioleiomyomatosis after lung transplantation. Ann Thorac Surg. 2009;87:6-7.

[43] Davies DM, Johnson SR, Tattersfield AE, et al. Sirolimus therapy in tuberous sclerosis or sporadic lymphangioleiomyomatosis. N Engl J Med 2008;358:200-203.

[44] Wagner AJ, Malinowska-Kolodziej I, Morgan JA, et al. Clinical Activity of mTOR Inhibition With Sirolimus in Malignant Perivascular Epithelioid Cell Tumors: Targeting the Pathogenic Activation of mTORC1 in Tumors. J Clin Oncol 2010;28(5):835-840.

[45] Taille C, Debray MP, Crestani B. Sirolimus treatment for pulmonary lymphangioleiomyomatosis. Ann Intern Med. 2007;146:687-688.

[46] Casali PG, Stacchiotti S, Grosso F, et al. Adding cisplatin (CDDP) to imatinib (IM) re-establishes tumor response following secondary resistance to IM in advanced chordoma. J Clin Oncol (Meeting Abstracts) 2007;25(18_suppl):10038-.

[47] Stacchiotti S, Marrari A, Tamborini E, et al. Response to imatinib plus sirolimus in advanced chordoma. Ann Oncol. 2009;20:1886-1894.

[48] Singhal N, Kotasek D, Parnis FX. Response to erlotinib in a patient with treatment refractory chordoma. Anticancer Drugs 2009;20(10):953-955.

[49] Geoerger B, Morland B, Ndiaye A, et al. Target-driven exploratory study of imatinib mesylate in children with solid malignancies by the Innovative Therapies for Children with Cancer (ITCC) European Consortium. Eur J Cancer. 2009; 45:2342-2351.

[50] Casali PG, Messina A, Stacchiotti S, et al. Imatinib mesylate in chordoma. Cancer. 2004;101:2086-2097.

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.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Staging

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

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

Continued...

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC (SBM). (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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).

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC (SBM). (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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 2009 is estimated to be about 10,660 cases, with an overall mortality rate of approximately 3,820 cases per year, which includes adults and children.[1] 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.[2,3] 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.[4] 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.[5] 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.[6] 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 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. NCCN STS guidelines address sarcoma management in adult patients from the perspective of four disease subtypes:

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

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

The guidelines do not include the management of rhabdomyosarcoma, Ewing's sarcoma, and desmoplastic small round cell tumor (DSCRT).

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.[7] 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 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 addition features of the tumor such as mitotic rate, presence or absence of vascular invasion and the type and extent of inflammatory infiltration (SARC-A). 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 (SARC-B). 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.[8]

STS with recurrent chromosomal translocations can be classified into subtypes depending on the presence of fusion gene transcripts [eg. *EWS-ATF1* in clear cell sarcoma, *TLS-CHOP* in myxoid or round cell liposarcoma, *SYT-SSX (SYT-SSX1 or SYT-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.

Most common techniques used in the molecular diagnosis include conventional cytogenetic analysis, fluorescence in-situ hybridization (FISH) and polymerase chain reaction (PCR)-based methods.[9] In a prospective study, Hill and colleagues concluded that PCR-based

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[10]

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*.[11] In patients with synovial sarcoma, the prognostic impact of fusion gene transcripts *SYT-SSX1* and *SYT-SSX2* is less clear with two large studies showing conflicting results.[12,13] In myxoid liposarcoma, the variability of fusion transcript has no effect on clinical outcome.[14]

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 morphologic features of a sarcoma.[9]

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.[15] The 2002 AJCC staging system accommodated some of the three- and four-tiered systems for establishing the grade. The revised 2010 AJCC staging system incorporates a three-tiered grading system (ST-1). However, many clinicians prefer the two-tiered system; therefore, this system is also used in the algorithm (EXTSARC-2).

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-C). 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.[16,17] When appropriate, the guidelines incorporate these therapies that are supported by clinical trial data or extensive clinical experience.[18]

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

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[19] 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.[20-22]

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.[23,24] 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. [25-27]

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.[28] Brachytherapy involves the direct application of radioactive seeds into the tumor bed through catheters placed during surgery. 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.[29] 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.[30] A higher acute would 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.

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

The usual dose of preoperative RT is 50 Gy. If wide margins are obtained, additional radiation may not be needed. Radiation boost with brachytherapy, IORT or an XRT is recommended for positive or close margins (SARC-D).[31] 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 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.

Postoperative RT

Postoperative RT has been shown to improve local control in patients with high-grade extremity STS with positive surgical margins.[32] 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.[33] 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 (SARC-D). 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. 45-50 Gy at low-dose rate to the tumor bed has been shown to reduce recurrence without a significant effect on wound healing.[34]However, brachytherapy-alone techniques require special expertise and significant experience. The panel recommends 45 Gy low dose rate brachytherapy for patients with negative margins. Low dose rate 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.[35] 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.

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[36] 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.[37] 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.[38]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.[39] 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.[40-42] 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. 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). 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. 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. 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).

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 (BRT) or no BRT).[43] With a median follow-up time of 76 months, the 5-year local control rates were 82% and 69% in the BRT and no BRT groups respectively. Patients with high-grade lesions who received BRT had higher local control rates compared to those who were randomized to no BRT (89% and 66% respectively). However, BRT 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. Results of this trial showed that adjuvant brachytherapy improves local control after complete resection of STS in patients with high-grade lesions.

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[44] The risk of complications such as edema and joint stiffness were also favorable when compared with conventional RT. 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.[45] 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 to10 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.[46] 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.

Magnetic resonance imaging (MRI) with or without computed tomography (CT) is indicated for all lesions with a reasonable chance of being malignant (EXTSARC-1). MRI is preferred for extremity sarcomas, whereas CT is preferred for retroperitoneal sarcomas.[47-49] 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 myxoid round cell liposarcoma, leiomyosarcoma, epithelioid sarcoma or angiosarcoma and MRI of the total spine should be considered for myxoid round cell liposarcomas due to the higher risk of metastasis to spine compared to other STS.[50-52] CNS imaging should be considered for patients with alveolar soft part sarcomas (ASPS) and angiosarcomas since ASPS have a relatively increased propensity to metastasize to the brain, especially in patients with stage IV disease in the presence of pulmonary metastases.[53]

Positron emission tomography (PET) scan may be useful for prognostication, grading and to assess response to chemotherapy.[54] Tumor metabolism data acquired by PET will be useful in accurate grading and prognostication in sarcoma.[55] Recent reports in literature have demonstrated the value of PET scan in evaluating response to preoperative chemotherapy in patients with high-grade extremity STS, prediction of outcome in liposarcoma.[56,57] A large prospective study is underway to study the value of PET scan combined with CT scan in predicting DFS in patients receiving preoperative chemotherapy for STS (www.cancer.gov/clinicaltrials/UMN-2005LS080).

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[58,59] Retrospective studies have demonstrated a local control of 90% or more for surgery alone.[60] 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.[61] 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 (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.

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.[37,62-65] Concurrent chemoradiation with doxorubicin-based regimens has been shown to improve local control rates in patients with STS, although acute reactions must be considered.[66] 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.[67,68]

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.[69] 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).[70] 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.[71]

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 DFS (48 vs.16 months) and median OS (75 months vs. 46 months) were significantly better in the treatment group.[72,73]

Remarkably little data have been generated in the adjuvant setting regarding the combination of aggressively dosed ifosfamide plus doxorubicin with growth factor support. EORTC-62931 is a completed phase III randomized study to assess the efficacy of adjuvant chemotherapy after definitive surgery in patients with excised

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

high-grade STS at any site. 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.[74] The estimated RFS was 52% in both arms. Further analysis of this study is needed to make a detailed assessment of the role of adjuvant chemotherapy in resected STS.

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 (EXTSARC-3).[75] 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.

Postoperative RT boost for residual gross disease or microscopically positive margins or 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 (EXTSARC-3). Since limited and conflicting data are available for adjuvant chemotherapy for stage II or III patients, adjuvant chemotherapy for stage II or III tumors is included as a category 2B recommendation for all patients with resectable tumors irrespective of the functional outcomes.

Unresectable Tumors

Unresectable tumors can be treated primarily with preoperative RT, chemoradiation or chemotherapy. Tumors that become resectable following preoperative treatment can be treated with surgery (EXTSARC-4). Postoperative treatment options for this group of patients are similar to that described in EXTSARC-3 for stage II or III resectable tumors.

Definitive RT (7000-8000 cGy) can be considered for selected patients with unresectable tumors following preoperative treatment (EXTSARC-4). 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. [76-83] Liposomal anthracyclines were found to be active as first-line treatment for advanced sarcomas with better toxicity profile than doxorubicin.[84,85] Other chemotherapeutic agents have also been tested in clinical trials. 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.[86] In a randomized phase II study, PFS (6.2 months vs. 3.0 months respectively) and OS (17.9

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

months vs.11.5 months respectively) were superior to gemcitabine and docetaxel compared to gemcitabine alone in patients with metastatic STS.[87] 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.[88] 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.[89] 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.[90] 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.[91,92]

Ecteinascidin 743 (ET-743, also known as trabectedin or Yondelis®), is a marine-derived anti-tumor agent, which has shown objective responses in phase II trials of patients with progressive STS that are refractory to chemotherapy.[93-97] 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.

Interim OS data are encouraging from an ongoing phase III trial (EORTC-62961) of regional hyperthermia (RHT) versus chemotherapy with EIA (etoposide, ifosfamide and adriamycin) alone for patients with locally advanced high-risk STS, especially for extremity sarcomas.[98] After a median follow-up of 24.9 months, DFS (31.7 months vs. 6.2 months respectively), local PFS (84% vs. 64% respectively for extremity sarcomas and 57% vs. 39% respectively for body wall and abdominal sarcomas) and overall response rate 28.7% vs. 12.6% respectively) were significantly superior for patients treated with EIA plus RHT compared to those treated with EIA alone.[99]

Isolated limb perfusion (ILP) has been employed in Europe as a limb sparing treatment for unresectable intermediate or high-grade extremity STS.[100] 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.[101] Recombinant TNFα-1A and melphalan has been approved in Europe for ILP in patients with locally advanced high grade STS of the extremities.

Limited Metastases

Patients with limited metastasis confined to a single organ and limited tumor bulk or regional lymph node involvement should receive primary tumor management as described for stage II or III tumors in EXTSARC-3. Another option is to consider regional node dissection for nodal involvement with or without RT or metastasectomy with or without chemotherapy with or without RT (EXTSARC-5). 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.

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Disseminated Metastases

In the guidelines, a subsequent distinction is made between asymptomatic and symptomatic patients for those who present with disseminated disease (EXTSARC-5). 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, chemotherapy or palliative surgery. 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/radiotherapy 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.[102-104] 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 (EXTSARC-2). 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 (EXTSARC-3 EXTSARC-4 and EXTSARC-5). Because these patients' risk never returns to zero, long-term follow-up is indicated, including consideration of MRI or CT scanning.[105] 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.[106] 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.

Recurrent Disease

The management of recurrent disease encompasses a heterogeneous group of patients and clinical scenarios (EXTSARC-6). 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-2 and EXTSARC-3).[107] 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 (EXTSARC-5).

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[108-111] 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.[111]

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.[112,113] 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.[114] Postoperative XRT has been associated with improved RFS in retrospective nonrandomized studies, although there was no improvement in OS.[110,115] 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.[116] 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.[117]

The use of IORT with or without XRT has provided encouraging results in single institution studies. In patients with retroperitoneal STS treated with a protocol involving maximal tumor resection, high-dose rate IORT (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).[32] Long-term results of another trial also demonstrated the efficacy of IORT using electron beam RT (IOERT). OS (74% and 30% respectively) and local control (83% and 61% respectively) were better in patients undergoing gross total resection and IOERT compared to those who had only gross total resection. The feasibility and safety of preoperative concurrent chemoradiation followed by surgical resection and IOERT has also been demonstrated in a phase I trial.[118]

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.[119,120] 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 an abdominal and pelvic CT with contrast with or without an MRI (RETSARC-1). Chest imaging with a plain radiograph or CT should be done, especially for patients whose tumors warrant preoperative or postoperative chemotherapy. If possible, a multidisciplinary sarcoma panel should

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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 significant cause of morbidity in majority of the patients.[121-123] Multimodality treatment is usually favored for retroperitoneal sarcomas due to the inability to obtain negative margin resections and high local recurrence rates.[124] 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.[125] Little data are available for use of combined RT and chemotherapy. Decisions about adjuvant or neoadjuvant chemotherapy or RT are left to clinical judgment.[117,126,127]

Biopsy is performed only if preoperative therapy (category 2B) is considered (RETSARC-2). Endoscopic biopsy is recommended for suspected GIST lesions. CT-guided core biopsy is preferred. In patients with diagnostic biopsy, surgery alone is the primary treatment option for resectable lesions. Alternatively, preoperative RT or preoperative chemotherapy could be considered followed by surgery with or without IORT. Surgery with or without IORT is the primary treatment if biopsy is not performed or it is non-diagnostic. 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 (RETSARC-3). Postoperative RT (category 2B) could be considered in patients with pathological findings of high grade disease following negative margin resection (R0) or for microscopic positive margins (R1 resection). In patients with extremely large tumors, close surgical margins or high risk of recurrence, postoperative RT can be considered following negative R0 resection for low grade tumors. 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 (RETSARC-4). Patients with unresectable or stage IV disease have several options for primary treatment including chemotherapy or RT to

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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 (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-4).

Recurrent Disease

For patients with resectable, unresectable or disseminated recurrences, the guidelines recommend the same management after biopsy, as outlined for primary disease (RETSARC-5). 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 (RETSARC-3). 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).[128] Most GISTs (95%) are KIT positive. About 5% of GISTs have mutations in the platelet derived growth factor-alpha (PDGFRA) genes and express little or no KIT.[129,130] 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 GI tract, but stomach (60%) and small intestine (30%) are the most common primary sites.[131,132] Gastric GISTs have a more favorable prognosis than the intestinal ones. 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.

Targeted Therapy for GIST Patients

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.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[133-136] In February 2002, the FDA approved of imatinib mesylate for the treatment of patients with KIT positive unresectable and/or metastatic malignant GIST.[137]

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 the tyrosine kinase domain 2.[138]

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. 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.[139] The EORTC (European Organization for Research and Treatment of Cancer)-Italian Sarcoma Group (ISG)-Australasian GI Trials Group (AGITG)-phase III trial (EORTC-62005)[140] and the North American phase III study SWOG (Southwest Oncology Group) S0033/CALGB 150105[141] 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.

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.[135,136] 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.[135] 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).[136] 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. 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.[142] 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.[143] In the North American Intergroup phase III trial (CALGB 150105), patients with exon-9 mutations treated

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

with 800 mg imatinib had improved response rates compared to those treated with 400 mg imatinib (67% vs.17% respectively).[141] 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).[144] This meta-analysis also showed a benefit in PFS for patients with *KIT* exon 9 mutations treated with 800 mg of imatinib.

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. 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).[145] 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).[146] 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. 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%.[147-149] 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. In this trial, postoperative imatinib prolonged RFS following complete resection and was also associated with improved OS compared to historical controls.[150] 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.[151] 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

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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). 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. Optimum duration of postoperative treatment has not yet been determined.

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.[152] Serious side effects (such as lung toxicity, LFT abnormalities, 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.[153] 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.[154] Secondary resistance appears to be related to the acquisition of new kinase mutations.[155] 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.[156] 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.[157] 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

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[158] 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.

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 HFS.[159] Early detection and proper management of HFS is vital during treatment with sunitinib. HFS 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.[160] Recent reports have shown that sunitinib is also associated with cardiotoxicity and hypothyroidism.[161,162] In a retrospective analysis of the data from phase I-II trials, 11% of the patients had adverse cardiovascular event including congestive heart failure (CHF) in 8% of patients and absolute reduction in the left ventricular ejection fraction (LVEF) in 28% of patients.[161] 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.[162]

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.

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

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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 (GIST-A). 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).[163]

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 (GIST-B). 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 GIST diagnosis (GIST-B). However, 10-15% of GISTs have no detectable KIT or PDGFRA mutations (wild-type) GIST. The absence of mutations does not exclude the diagnosis of GIST. The results of a phase III study 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.[139] Therefore, it is rational to offer KIT-negative GIST patients a therapeutic trial of imatinib mesylate with close evaluation and follow-up.

Principles of Surgery for GIST

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 (GIST-C).

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 (GIST-C). 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, them 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 (GIST-C). Resection specimen should be

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.

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 (GIST-1).

In patients with GIST, imaging is used for diagnosis, initial staging, restaging, monitoring response to therapy, and performing follow-up surveillance of possible recurrence. Imaging studies can include CT, MRI and PET. 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. Many imaging centers are also equipped with combined PET-CT scanners, which may facilitate both anatomic and functional tumor evaluation in one step.[164] If clinicians consider using PET scan to monitor therapy, a baseline PET should be obtained prior to start of therapy.

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. 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 (GIST-2). 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 (GIST-4). 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 (GIST-4). Collaboration between the medical oncologist and the surgeon is necessary to determine the appropriateness of surgery following major response or stable disease.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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 (GIST-5). 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 therapy 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.[165] 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 who were stable or responding to imatinib therapy.[166]

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.

Postoperative Treatment

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 (GIST-6). Optimum duration of postoperative treatment has not yet been determined at this time. Postoperative imatinib is recommended for at least 12 months in patients with intermediate to high-risk GIST patients. Higher risk patients may require longer duration of treatment. Risk stratification after surgical resection should be based on tumor mitotic rate, size and location.[167] 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.[168] 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.

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

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

interpretation; PET may be used if the results are ambiguous (GIST-7). 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.[169] 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, dasatinib, and nilotinib have shown activity in patients with imatinib and sunitinib resistant GIST. In a multicenter ongoing phase II study involving patients with unresectable, KIT-positive GIST that had progressed on imatinib and sunitinib, 58% of patients who received sorafenib had stable disease.[170] Median PFS was 5.3 months and with an estimated 1-year survival rate of 62%. In another phase I trial, nilotinib, alone and in combination with imatinib showed significant activity in patients with GIST who are resistant to prior TKIs.[171] In a phase I dose escalation study, 3 of the 19 patients with refractory GIST had stable disease, which lasted for more than 3 months in one of these patients.[172] Sarcoma Alliance for Research through Collaboration (SARC) is completing a phase II multi-arm study of dasatinib in imatinib and sunitinib refractory GIST. The efficacy and safety of nilotinib as third- line therapy for GIST are being studied in an ongoing phase III trial.

The guidelines have included sorafenib, dasatinib or nilotinib as options for patients who are no longer receiving clinical benefit from imatinib or sunitinib (SARC-E). 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. Recent data reported by Fumagalli et al. support rechallenging patients with imatinib after failing standard and investigational therapeutic options.[173] In patients with progressive disease no longer receiving benefit from current TKI therapy, consider re-introduction of previously tolerated and effective TKI therapy for palliation of symptoms. The panel also feels that continuation of TKI therapy life-long for palliation of symptoms should be an essential component of best supportive care.

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) syndrome[174] and may also arise through elective surgical intervention (eg, colectomy) in susceptible patients.[175] In patients who have been treated with prophylactic colectomy,

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[176] 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.[177] Although desmoid tumors are often locally invasive, they rarely metastasize. Most patients do not die of their tumors.[178] 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 (DESM-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. Desmoids of the breast are difficult to differentiate from carcinomas, because desmoids resemble carcinomas clinically and radiologically.[179-181]

Resectable Tumors

Surgery is the primary treatment for resectable desmoid tumors.[182-185] Microscopic 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 (DESM-1). Large tumors can be treated with postoperative RT. For microscopic positive margins, additional resection or high-dose RT 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. Patients with macroscopic surgical margins 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.[186,187] 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.[188,189] 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.[190]

Promising data exist for the use of cytostatic or cytotoxic systemic therapy.[191] 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.[192-199] 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). Imatinib mesylate has also been active in patients with unresectable, progressive or recurrent aggressive fibromatosis.[200,201]

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

RT, systemic therapy or observation are some of the options for patients with unresectable desmoid tumors (DESM-1). Radical surgery should be considered only if other treatment modalities fail.

Surveillance

Every patient should have an H&P with appropriate imaging every 3-6 months for 2-3 years and then annually.

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009;59:225-249.

2. D'Amato G, Steinert DM, McAuliffe JC, Trent JC. Update on the biology and therapy of gastrointestinal stromal tumors. Cancer Control. 2005;12:44-56.

3. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol. 2002;33:459-465.

4. Zahm S, Fraumeni JJ. The epidemiology of soft tissue sarcoma. Semin Oncol. 1997;24:504-514.

5. Coindre J, Terrier P, Guillou L, et al. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. Cancer. 2001;91:1914-1926.

6. Cormier JN, Pollock RE. Soft tissue sarcomas. CA Cancer J Clin. 2004;54:94-109.

7. Domanski HA. Fine-needle aspiration cytology of soft tissue lesions: diagnostic challenges. Diagn Cytopathol. 2007;35:768-773.

8. Antonescu CR. The role of genetic testing in soft tissue sarcoma. Histopathology. 2006;48:13-21.

9. Pfeifer JD, Hill DA, O'Sullivan MJ, Dehner LP. Diagnostic gold standard for soft tissue tumours: morphology or molecular genetics? Histopathology. 2000;37:485-500.

10. Hill DA, O'Sullivan MJ, Zhu X, et al. Practical application of molecular genetic testing as an aid to the surgical pathologic diagnosis of sarcomas: a prospective study. Am J Surg Pathol. 2002;26:965-977.

11. Sorensen PHB, Lynch JC, Qualman SJ, et al. PAX3-FKHR and PAX7-FKHR Gene Fusions Are Prognostic Indicators in Alveolar Rhabdomyosarcoma: A Report From the Children's Oncology Group. J Clin Oncol. 2002;20:2672-2679.

12. Guillou L, Benhattar J, Bonichon F, et al. Histologic Grade, But Not SYT-SSX Fusion Type, Is an Important Prognostic Factor in Patients With Synovial Sarcoma: A Multicenter, Retrospective Analysis. J Clin Oncol. 2004;22:4040-4050.

13. Ladanyi M, Antonescu CR, Leung DH, et al. Impact of SYT-SSX Fusion Type on the Clinical Behavior of Synovial Sarcoma: A Multi-Institutional Retrospective Study of 243 Patients. Cancer Res. 2002;62:135-140.

14. Antonescu CR, Tschernyavsky SJ, Decuseara R, et al. Prognostic Impact of P53 Status, TLS-CHOP Fusion Transcript Structure, and Histological Grade in Myxoid Liposarcoma: A Molecular and Clinicopathologic Study of 82 Cases. Clin Cancer Res. 2001;7:3977-3987.

15. Guillou L, Coindre J, Bonichon F, et al. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. J Clin Oncol. 1997;15:350-362.

16. Dileo P, Demetri GD. Update on new diagnostic and therapeutic approaches for sarcomas. Clin Adv Hematol Oncol. 2005;3:781-791.

17. Mocellin S, Rossi C, Brandes A, Nitti D. Adult soft tissue sarcomas: conventional therapies and molecularly targeted approaches. Cancer Treat Rev. 2006;32:9-27.

18. Brennan MF, Casper ES, Harrison LB, Shiu MH, Gaynor J, Hajdu SI. The role of multimodality therapy in soft-tissue sarcoma. Ann Surg. 1991;214:328-336; discussion 336-328.

19. Kim B, Chen YL, Kirsch DG, et al. An Effective Preoperative Three-Dimensional Radiotherapy Target Volume for Extremity Soft Tissue Sarcoma and the Effect of Margin Width on Local Control. Int J Radiat Oncol Biol Phys. 2009.

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

20. Fleming JB, Berman RS, Cheng SC, et al. Long-term outcome of patients with American Joint Committee on Cancer stage IIB extremity soft tissue sarcomas. J Clin Oncol. 1999;17:2772-2780.

21. Gerrand CH, Wunder JS, Kandel RA, et al. Classification of positive margins after resection of soft-tissue sarcoma of the limb predicts the risk of local recurrence. J Bone Joint Surg Br. 2001;83:1149-1155.

22. Pisters PW, Leung DH, Woodruff J, Shi W, Brennan MF. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol. 1996;14:1679-1689.

23. Lewis JJ, Leung D, Espat J, Woodruff JM, Brennan MF. Effect of reresection in extremity soft tissue sarcoma. Annals of Surgery. 2000;231:655-663.

24. Zagars GK, Ballo MT, Pisters PW, Pollock RE, Patel SR, RS. B. Surgical margins and reresection in the management of patients with soft tissue sarcoma using conservative surgery and radiation therapy. Cancer. 2003;97:2544-2553.

25. Ghert MA, Abudu A, Driver N, et al. The indications for and the prognostic significance of amputation as the primary surgical procedure for localized soft tissue sarcoma of the extremity. Annals of Surgical Oncology. 2005;12:10-17.

26. Stojadinovic A, Jaques DP, Leung DH, Healey JH, Brennan MF. Amputation for recurrent soft tissue sarcoma of the extremity: indications and outcome. Ann Surg Oncol. 2001;8:509-518.

27. Williard WC, Hajdu SI, Casper ES, Brennan MF. Comparison of amputation with limb-sparing operations for adult soft tissue sarcoma of the extremity. Annals of Surgery. 1992;215:269-275.

28. DeLaney TF, Trofimov AV, Engelsman M, HD. S. Advanced-technology radiation therapy in the management of bone and soft tissue sarcomas. Cancer Control. 2005;12:27-35.

29. Leibel SA, Fuks Z, Zelefsky MJ, et al. Intensity-modulated radiotherapy. Cancer J. 2002;8:164-176.

30. Davis A, O'Sullivan B, Bell R, et al. Function and health status outcomes in a randomized trial comparing preoperative and postoperative radiotherapy in extremity soft tissue sarcoma. J Clin Oncol. 2002;20:4472-4477.

31. Sadoski C, Suit H, Rosenberg A, Mankin H, Efird J. Preoperative radiation, surgical margins, and local control of extremity sarcomas of soft tissues. J Surg Oncol. 1993;52:223-230.

32. Alektiar KM, Velasco J, Zelefsky MJ, Woodruff JM, Lewis JJ, Brennan MF. Adjuvant radiotherapy for margin-positive high-grade soft tissue sarcoma of the extremity. Int J Radiat Oncol Biol Phys. 2000;48:1051-1058.

33. Cahlon O, Spierer M, Brennan MF, Singer S, Alektiar KM. Long-term outcomes in extremity soft tissue sarcoma after a pathologically negative re-resection and without radiotherapy. Cancer. 2008;112:2774-2779.

34. Alektiar KM, Leung D, Zelefsky MJ, Healey JH, Brennan MF. Adjuvant brachytherapy for primary high-grade soft tissue sarcoma of the extremity. Ann Surg Oncol. 2002;9:48-56.

35. Tran QN, Kim AC, Gottschalk AR, et al. Clinical outcomes of intraoperative radiation therapy for extremity sarcomas. Sarcoma. 2006;2006:91671.

36. Clark MA, Thomas JM. Amputation for soft-tissue sarcoma. Lancet Oncol. 2003;4:335-342.

37. Rosenberg SA, Tepper J, Glatstein E, et al. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Ann Surg. 1982;196:305-315.

38. Baldini EH, Goldberg J, Jenner C, et al. Long-Term Outcomes After Function-Sparing Surgery Without Radiotherapy for Soft Tissue Sarcoma of the Extremities and Trunk. J Clin Oncol. 1999;17:3252-3259.

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

39. Lin PP, Guzel VB, Pisters PW, et al. Surgical management of soft tissue sarcomas of the hand and foot. Cancer. 2002;95:852-861.

40. O'Sullivan B, Davis A, Turcotte R, et al. Five-year results of a randomized phase III trial of pre-operative vs post-operative radiotherapy in extremity soft tissue sarcoma. J Clin Oncol (Meeting Abstracts). 2004;22:9007.

41. Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol. 1998;16:197-203.

42. Wilson AN, Davis A, Bell RS, et al. Local control of soft tissue sarcoma of the extremity: the experience of a multidisciplinary sarcoma group with definitive surgery and radiotherapy. Eur J Cancer. 1994;30A:746-751.

43. Pisters PW, Harrison LB, Leung DH, Woodruff JM, Casper ES, Brennan MF. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. J Clin Oncol. 1996;14:859-868.

44. Alektiar KM, Brennan MF, Healey JH, Singer S. Impact of intensity-modulated radiation therapy on local control in primary soft-tissue sarcoma of the extremity. J Clin Oncol. 2008;26:3440-3444.

45. Kepka L, DeLaney TF, Suit HD, Goldberg SI. Results of radiation therapy for unresected soft-tissue sarcomas. Int J Radiat Oncol Biol Phys. 2005;63:852-859.

46. Clasby R, Tilling K, Smith MA, Fletcher CD. Variable management of soft tissue sarcoma: regional audit with implications for specialist care. Br J Surg. 1997;84:1692-1696.

47. Demas BE, Heelan RT, Lane J, Marcove R, Hajdu S, Brennan MF. Soft-tissue sarcomas of the extremities: comparison of MR and CT in determining the extent of disease. AJR Am J Roentgenol. 1988;150:615-620.

48. Hanna SL, Fletcher BD. MR imaging of malignant soft-tissue tumors. Magn Reson Imaging Clin N Am. 1995;3:629-650.

49. Heslin MJ, Smith JK. Imaging of soft tissue sarcomas. Surg Oncol Clin N Am. 1999;8:91-9107.

50. Schwab JH, Boland P, Guo T, et al. Skeletal metastases in myxoid liposarcoma: an unusual pattern of distant spread. Ann Surg Oncol. 2007;14:1507-1514.

51. Schwab JH, Boland PJ, Antonescu C, Bilsky MH, Healey JH. Spinal metastases from myxoid liposarcoma warrant screening with magnetic resonance imaging. Cancer. 2007;110:1815-1822.

52. Tateishi U, Hasegawa T, Beppu Y, Kawai A, Satake M, Moriyama N. Prognostic significance of MRI findings in patients with myxoid-round cell liposarcoma. AJR Am J Roentgenol. 2004;182:725-731.

53. Portera CA, Jr., Ho V, Patel SR, et al. Alveolar soft part sarcoma: clinical course and patterns of metastasis in 70 patients treated at a single institution. Cancer. 2001;91:585-591.

54. Schuetze SM. Utility of positron emission tomography in sarcomas. Current Opinion in Oncology. 2006;18:369-373.

55. Folpe AL, Lyles RH, Sprouse JT, Conrad EU, 3rd, Eary JF. (F-18) fluorodeoxyglucose positron emission tomography as a predictor of pathologic grade and other prognostic variables in bone and soft tissue sarcoma. Clin Cancer Res. 2000;6:1279-1287.

56. 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.

57. Eary JF, O'Sullivan F, Powitan Y, et al. Sarcoma tumor FDG uptake measured by PET and patient outcome: a retrospective analysis. Eur J Nucl Med Mol Imaging. 2002;29:1149-1154.

58. Geer RJ, Woodruff J, Casper ES, Brennan MF. Management of small soft-tissue sarcoma of the extremity in adults. Arch Surg. 1992;127:1285-1289.

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

59. Karakousis CP, Emrich LJ, Rao U, Khalil M. Limb salvage in soft tissue sarcomas with selective combination of modalities. Eur J Surg Oncol. 1991;17:71-80.

60. Pisters PWT, O'Sullivan B, Maki RG. Evidence-Based Recommendations for Local Therapy for Soft Tissue Sarcomas. J Clin Oncol. 2007;25:1003-1008.

61. Pisters PW, Pollock RE, Lewis VO, et al. Long-term results of prospective trial of surgery alone with selective use of radiation for patients with T1 extremity and trunk soft tissue sarcomas. Ann Surg. 2007;246:675-681; discussion 681-682.

62. 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;24:619-625.

63. Grobmyer SR, Maki RG, Demetri GD, et al. Neo-adjuvant chemotherapy for primary high-grade extremity soft tissue sarcoma. Ann Oncol. 2004;15:1667-1672.

64. DeLaney TF SI, Suit HD, Gebhardt MC, Hornicek FJ, Mankin HJ, Rosenberg AL, Rosenthal DI, Miryousefi F, Ancukiewicz M, Harmon DC. Neoadjuvant chemotherapy and radiotherapy for large extremity soft-tissue sarcomas. Int J Radiat Oncol Biol Phys. 2003;56:1117-1127.

65. Pisters PW, Patel SR, Varma DG, et al. Preoperative chemotherapy for stage IIIB extremity soft tissue sarcoma: long-term results from a single institution. J Clin Oncol. 1997;15:3481-3487.

66. Pisters PWT, Ballo MT, Patel SR. Preoperative Chemoradiation Treatment Strategies for Localized Sarcoma. Ann Surg Oncol. 2002;9:535-542.

67. Maki RG. Role of chemotherapy in patients with soft tissue sarcomas. Expert Review of Anticancer Therapy. 2004;4:229-236.

68. Tierney JF, Mosseri V, Stewart LA, Souhami RL, Parmar MK. Adjuvant chemotherapy for soft-tissue sarcoma: review and meta-analysis of the published results of randomised clinical trials. Br J Cancer. 1995;72:469-475.

69. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Sarcoma Meta-analysis Collaboration. Lancet. 1997;350:1647-1654.

70. Bramwell V, Rouesse J, Steward W, et al. Adjuvant CYVADIC chemotherapy for adult soft tissue sarcoma--reduced local recurrence but no improvement in survival: a study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol. 1994;12:1137-1149.

71. Cormier JN, Huang X, Xing Y, et al. Cohort Analysis of Patients With Localized, High-Risk, Extremity Soft Tissue Sarcoma Treated at Two Cancer Centers: Chemotherapy-Associated Outcomes. J Clin Oncol. 2004;22:4567-4574.

72. Frustaci S, De Paoli A, Bidoli E, et al. Ifosfamide in the Adjuvant Therapy of Soft Tissue Sarcomas. Oncology. 2003;65:80-84.

73. Frustaci S, Gherlinzoni F, De Paoli A, et al. Adjuvant Chemotherapy for Adult Soft Tissue Sarcomas of the Extremities and Girdles: Results of the Italian Randomized Cooperative Trial. J Clin Oncol. 2001;19:1238-1247.

74. Woll PJ, van Glabbeke M, Hohenberger P, et al. Adjuvant chemotherapy (CT) with doxorubicin and ifosfamide in resected soft tissue sarcoma (STS): Interim analysis of a randomised phase III trial. J Clin Oncol (Meeting Abstracts). 2007;25:10008-.

75. Alektiar KM, Leung D, Zelefsky MJ, Brennan MF. Adjuvant Radiation for Stage II-B Soft Tissue Sarcoma of the Extremity. J Clin Oncol. 2002;20:1643-1650.

76. Antman K, Crowley J, Balcerzak S, et al. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. J Clin Oncol. 1993;11:1276-1285.

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

77. Antman KH, Judson EAI. Dana-Farber Cancer Institute studies in advanced sarcoma. Semin Oncol. 1990;1:7-15.

78. Bramwell VH, Anderson D, Charette ML. Doxorubicin-based chemotherapy for the palliative treatment of adult patients with locally advanced or metastatic soft tissue sarcoma. Cochrane Database Syst Rev. 2003:CD003293.

79. Edmonson J, Ryan L, Blum R, et al. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. J Clin Oncol. 1993;11:1269-1275.

80. Elias A, Ryan L, Sulkes A, Collins J, Aisner J, Antman KH. Response to mesna, doxorubicin, ifosfamide, and dacarbazine in 108 patients with metastatic or unresectable sarcoma and no prior chemotherapy. J Clin Oncol. 1989;7:1208-1216.

81. Lorigan P, Verweij J, Papai Z, et al. Phase III trial of two investigational schedules of ifosfamide compared with standard-dose doxorubicin in advanced or metastatic soft tissue sarcoma: a European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. J Clin Oncol. 2007;25:3144-3150.

82. Santoro A, Tursz T, Mouridsen H, et al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first- line treatment of advanced soft tissue sarcomas: a randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol. 1995;13:1537-1545.

83. Zalupski M, Metch B, Balcerzak S, et al. Phase III Comparison of Doxorubicin and Dacarbazine Given by Bolus Versus Infusion in Patients With Soft-Tissue Sarcomas: A Southwest Oncology Group Study. J Natl Cancer Inst. 1991;83:926-932.

84. Siehl JM, Thiel E, Schmittel A, Hutter G, Keilholz U. Liposomal anthracyclines and ifosfamide in the first line treatment of advanced soft tissue sarcomas: A two cohort phase II study. J Clin Oncol (Meeting Abstracts). 2006;24:9563.

85. Siehl JM, Thiel E, Schmittel A, et al. Ifosfamide/liposomal daunorubicin is a well tolerated and active first-line chemotherapy regimen in advanced soft tissue sarcoma: results of a phase II study. Cancer. 2005;104:611-617.

86. Hensley ML, Maki R, Venkatraman E, et al. Gemcitabine and Docetaxel in Patients With Unresectable Leiomyosarcoma: Results of a Phase II Trial. J Clin Oncol. 2002;20:2824-2831.

87. Maki RG, Wathen JK, Patel SR, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002. J Clin Oncol. 2007;25:2755-2763.

88. Leu KM, Ostruszka LJ, Shewach D, et al. Laboratory and Clinical Evidence of Synergistic Cytotoxicity of Sequential Treament With Gemcitabine Followed by Docetaxel in the Treatment of Sarcoma. J Clin Oncol. 2004;22:1706-1712.

89. Bay JO, Ray-Coquard I, Fayette J, et al. Docetaxel and gemcitabine combination in 133 advanced soft-tissue sarcomas: A retrospective analysis. International Journal of Cancer. 2006;119:706-711.

90. Dileo P, Morgan JA, Zahrieh D, et al. Gemcitabine and vinorelbine combination chemotherapy for patients with advanced soft tissue sarcomas: results of a phase II trial. Cancer. 2007;109:1863-1869.

91. Garcia del Muro X, Lopez-Pousa A, Martin J, et al. A phase II trial of temozolomide as a 6-week, continuous, oral schedule in patients with advanced soft tissue sarcoma: a study by the Spanish Group for Research on Sarcomas. Cancer. 2005;104:1706-1712.

92. Talbot SM, Keohan ML, Hesdorffer M, et al. A phase II trial of temozolomide in patients with unresectable or metastatic soft tissue sarcoma. Cancer. 2003;98:1942-1946.

93. Le Cesne A, Blay JY, Judson I, et al. Phase II Study of ET-743 in Advanced Soft Tissue Sarcomas: A European Organisation for the

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group Trial. J Clin Oncol. 2005;23:576-584.

94. Garcia-Carbonero R, Supko JG, Manola J, et al. Phase II and Pharmacokinetic Study of Ecteinascidin 743 in Patients With Progressive Sarcomas of Soft Tissues Refractory to Chemotherapy. J Clin Oncol. 2004;22:1480-1490.

95. Garcia-Carbonero R, Supko JG, Maki RG, et al. Ecteinascidin-743 (ET-743) for Chemotherapy-Naive Patients With Advanced Soft Tissue Sarcomas: Multicenter Phase II and Pharmacokinetic Study. J Clin Oncol. 2005;23:5484-5492.

96. Yovine A, Riofrio M, Blay JY, et al. Phase II Study of Ecteinascidin-743 in Advanced Pretreated Soft Tissue Sarcoma Patients. J Clin Oncol. 2004;22:890-899.

97. Laverdiere C, Kolb EA, Supko JG, et al. Phase II study of ecteinascidin 743 in heavily pretreated patients with recurrent osteosarcoma. Cancer. 2003;98:832-840.

98. Issels RD, Lindner LH, Wust P, et al. Regional hyperthermia (RHT) improves response and survival when combined with systemic chemotherapy in the management of locally advanced, high grade soft tissue sarcomas (STS) of the extremities, the body wall and the abdomen: A phase III randomised pros. J Clin Oncol (Meeting Abstracts). 2007;25:10009.

99. Issels R, Schlemmer M. Current trials and new aspects in soft tissue sarcoma of adults. Cancer Chemotherapy and Pharmacology. 2002;49:4-8.

100. Grunhagen DJ, Brunstein F, ten Hagen TL, van Geel AN, de Wilt JH, Eggermont AM. TNF-based isolated limb perfusion: a decade of experience with antivascular therapy in the management of locally advanced extremity soft tissue sarcomas. Cancer Treat Res. 2004;120:65-79.

101. Grunhagen DJ, de Wilt JH, Graveland WJ, Verhoef C, van Geel AN, Eggermont AM. Outcome and prognostic factor analysis of 217 consecutive isolated limb perfusions with tumor necrosis factor-? and melphalan for limb-threatening soft tissue sarcoma. Cancer. 2006;106:1776-1784.

102. Whooley BP, Mooney MM, Gibbs JF, Kraybill WG. Effective follow-up strategies in soft tissue sarcoma. Seminars in Surgical Oncology. 1999;17:83-87.

103. Whooley BP, Gibbs JF, Mooney MM, McGrath BE, Kraybill WG. Primary extremity sarcoma: what is the appropriate follow-up? Ann Surg Oncol. 2000;7:9-14.

104. Kane III JM. Surveillance strategies for patients following surgical resection of soft tissue sarcomas. Curr Opin Oncol. 2004;16:328-332.

105. Lewis JJ, Leung D, Casper ES, Woodruff J, Hajdu SI, Brennan MF. Multifactorial analysis of long-term follow-up (more than 5 years) of primary extremity sarcoma. Arch Surg. 1999;134:190-194.

106. Fleming JB, Cantor SB, Varma DG, et al. Utility of chest computed tomography for staging in patients with T1 extremity soft tissue sarcomas. Cancer. 2001;92:863-868.

107. Singer S, Antman K, Corson JM, Eberlein TJ. Long-term salvageability for patients with locally recurrent soft-tissue sarcomas. Arch Surg. 1992;127:548-553; discussion 553-544.

108. Anaya DA, Lev DC, Pollock RE. The role of surgical margin status in retroperitoneal sarcoma. J Surg Oncol. 2008;98:607-610.

109. Bevilacqua RG, Rogatko A, Hajdu SI, Brennan MF. Prognostic factors in primary retroperitoneal soft-tissue sarcomas. Arch Surg. 1991;126:328-334.

110. Heslin MJ, Lewis JJ, Nadler E, et al. Prognostic factors associated with long-term survival for retroperitoneal sarcoma: implications for management. J Clin Oncol. 1997;15:2832-2839.

111. Lewis JJ, Leung D, Woodruff JM, Brennan MF. Retroperitoneal soft-tissue sarcoma: analysis of 500 patients treated and followed at a single institution. Ann Surg. 1998;228:355-365.

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

112. Bonvalot S, Rivoire M, Castaing M, et al. Primary Retroperitoneal Sarcomas: A Multivariate Analysis of Surgical Factors Associated With Local Control. J Clin Oncol. 2009;27:31-37.

113. Gronchi A, Lo Vullo S, Fiore M, et al. Aggressive surgical policies in a retrospectively reviewed single-institution case series of retroperitoneal soft tissue sarcoma patients. J Clin Oncol. 2009;27:24-30.

114. Pawlik TM, Pisters PW, Mikula L, et al. Long-term results of two prospective trials of preoperative external beam radiotherapy for localized intermediate- or high-grade retroperitoneal soft tissue sarcoma. Ann Surg Oncol. 2006;13:508-517.

115. Catton CN, O'Sullivan B, Kotwall C, Cummings B, Hao Y, Fornasier V. Outcome and prognosis in retroperitoneal soft tissue sarcoma. Int J Radiat Oncol Biol Phys. 1994;29:1005-1010.

116. Jones JJ, Catton CN, O'Sullivan B, et al. Initial Results of a Trial of Preoperative External-Beam Radiation Therapy and Postoperative Brachytherapy for Retroperitoneal Sarcoma. Ann Surg Oncol. 2002;9:346-354.

117. Mendenhall WM, Zlotecki RA, Hochwald SN, Hemming AW, Grobmyer SR, Cance WG. Retroperitoneal soft tissue sarcoma. Cancer. 2005;104:669-675.

118. Pisters PWT, Ballo MT, Fenstermacher MJ, et al. Phase I Trial of Preoperative Concurrent Doxorubicin and Radiation Therapy, Surgical Resection, and Intraoperative Electron-Beam Radiation Therapy for Patients With Localized Retroperitoneal Sarcoma. J Clin Oncol. 2003;21:3092-3097.

119. Musat E, Kantor G, Caron J, et al. Comparison of intensity-modulated postoperative radiotherapy with conventional postoperative conformal radiotherapy for retroperitoneal sarcoma. Cancer Radiother. 2004;8:255-261.

120. Yoon S, Chen Y-L, Kirsch D, et al. Proton-Beam, Intensity-Modulated, and/or Intraoperative Electron Radiation Therapy Combined with Aggressive Anterior Surgical Resection for Retroperitoneal Sarcomas. Annals of Surgical Oncology.

121. Ballo MT, Zagars GK, Pollock RE, et al. Retroperitoneal soft tissue sarcoma: an analysis of radiation and surgical treatment. Int J Radiat Oncol Biol Phys. 2007;67:158-163.

122. Gronchi A, Casali PG, Fiore M, et al. Retroperitoneal soft tissue sarcomas: patterns of recurrence in 167 patients treated at a single institution. Cancer. 2004;100:2448-2455.

123. Stoeckle E, Coindre JM, Bonvalot S, et al. Prognostic factors in retroperitoneal sarcoma: a multivariate analysis of a series of 165 patients of the French Cancer Center Federation Sarcoma Group. Cancer. 2001;92:359-368.

124. Raut C, Pisters PWT. Retroperitoneal sarcomas: Combined-modality treatment approaches. Journal of Surgical Oncology. 2006;94:81-87.

125. Thomas DM, O'Sullivan B, Gronchi A. Current concepts and future perspectives in retroperitoneal soft-tissue sarcoma management. Expert Rev Anticancer Ther. 2009;9:1145-1157.

126. Windham CT, Pisters PWT. Retroperitoneal Sarcomas. Cancer Control. 2005;12:36-43.

127. Singer S, Corson JM, Demetri GD, Healey EA, Marcus K, Eberlein TJ. Prognostic factors predictive of survival for truncal and retroperitoneal soft-tissue sarcoma. Ann Surg. 1995;221:185-195.

128. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science. 1998;279:577-580.

129. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. Science. 2003;299:708-710.

Version 2.2010, 04/15/10 © 2010 National Comprehensive Cancer Network, Inc. All rights reserved. **These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.**

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

130. Hirota S, Ohashi A, Nishida T, et al. Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. Gastroenterology. 2003;125:660-667.

131. Miettinen M, Lasota J. Gastrointestinal stromal tumors: Pathology and prognosis at different sites. Seminars in Diagnostic Pathology. 2006;23:70-83.

132. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med. 2006;130:1466-1478.

133. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med. 2002;347:472-480.

134. Blanke CD, Demetri GD, von Mehren M, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol. 2008;26:620-625.

135. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet. 2004;364:1127-1134.

136. Blanke CD, Rankin C, Demetri GD, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. J Clin Oncol. 2008;26:626-632.

137. Dagher R, Cohen M, Williams G, et al. Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. Clin Cancer Res. 2002;8:3034-3038.

138. Lasota J, Miettinen M. Clinical significance of oncogenic KIT and PDGFRA mutations in gastrointestinal stromal tumours. Histopathology. 2008;53:245-266.

139. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol. 2003;21:4342-4349.

140. Debiec-Rychter M, Dumez H, Judson I, et al. Use of c-KIT/PDGFRA mutational analysis to predict the clinical response to imatinib in patients with advanced gastrointestinal stromal tumours entered on phase I and II studies of the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer. 2004;40:689-695.

141. Heinrich MC, Owzar K, Corless CL, et al. Correlation of Kinase Genotype and Clinical Outcome in the North American Intergroup Phase III Trial of Imatinib Mesylate for Treatment of Advanced Gastrointestinal Stromal Tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. J Clin Oncol. 2008;26:5360-5367.

142. Zalcberg JR, Verweij J, Casali PG, et al. Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg. European journal of cancer. 2005;41:1751-1757.

143. Debiec-Rychter M, Sciot R, Le Cesne A, et al. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. Eur J Cancer. 2006;42:1093-1103.

144. Gastrointestinal Stromal Tumor Meta-Analysis Group Comparison of Two Doses of Imatinib for the Treatment of Unresectable or Metastatic Gastrointestinal Stromal Tumors: A Meta-Analysis of 1,640 Patients. J Clin Oncol. 2010;28:1247-1253.

145. Eisenberg BL, Harris J, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. J Surg Oncol. 2009;99:42-47.

146. McAuliffe JC, Hunt KK, Lazar AJ, et al. A randomized, phase II study of preoperative plus postoperative imatinib in GIST: evidence of rapid radiographic response and temporal induction of tumor cell apoptosis. Ann Surg Oncol. 2009;16:910-919.

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

147. Eisenberg BL, Judson I. Surgery and Imatinib in the Management of GIST: Emerging Approaches to Adjuvant and Neoadjuvant Therapy

Ann Surg Oncol. 2004;11:465-475.

148. Gold JS, Dematteo RP. Combined surgical and molecular therapy: the gastrointestinal stromal tumor model. Ann Surg. 2006;244:176-184.

149. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg. 2000;231:51-58.

150. Dematteo RP, Antonescu CR, Chadaram V, et al. Adjuvant imatinib mesylate in patients with primary high risk gastrointestinal stromal tumor (GIST) following complete resection: Safety results from the U.S. Intergroup Phase II trial ACOSOG Z9000. J Clin Oncol (Meeting Abstracts). 2005;23:9009-.

151. Dematteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet. 2009;373:1097-1104.

152. Guilhot F. Indications for Imatinib Mesylate Therapy and Clinical Management. Oncologist. 2004;9:271-281.

153. Trent JC, Patel SS, Zhang J, et al. Rare incidence of congestive heart failure in gastrointestinal stromal tumor and other sarcoma patients receiving imatinib mesylate. Cancer. 2010;116:184-192.

154. Benjamin RS, Debiec-Rychter M, Le Cesne A, et al. Gastrointestinal stromal tumors II: medical oncology and tumor response assessment. Semin Oncol. 2009;36:302-311.

155. Maleddu A, Pantaleo MA, Nannini M, et al. Mechanisms of secondary resistance to tyrosine kinase inhibitors in gastrointestinal stromal tumours (Review). Oncol Rep. 2009;21:1359-1366.

156. Heinrich MC, McArthur GA, Demetri GD, et al. Clinical and Molecular Studies of the Effect of Imatinib on Advanced Aggressive Fibromatosis (desmoid tumor). J Clin Oncol. 2006;24:1195-1203.

157. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet. 2006;368:1329-1338.

158. George S, Blay JY, Casali PG, et al. Clinical evaluation of continuous daily dosing of sunitinib malate in patients with advanced gastrointestinal stromal tumour after imatinib failure. Eur J Cancer. 2009;45:1959-1968.

159. Chu D, Lacouture ME, Weiner E, Wu S. Risk of hand-foot skin reaction with the multitargeted kinase inhibitor sunitinib in patients with renal cell and non-renal cell carcinoma: a meta-analysis. Clin Genitourin Cancer. 2009;7:11-19.

160. Zhu X, Stergiopoulos K, Wu S. Risk of hypertension and renal dysfunction with an angiogenesis inhibitor sunitinib: systematic review and meta-analysis. Acta Oncol. 2009;48:9-17.

161. Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet. 2007;370:2011-2019.

162. Torino F, Corsello SM, Longo R, Barnabei A, Gasparini G. Hypothyroidism related to tyrosine kinase inhibitors: an emerging toxic effect of targeted therapy. Nat Rev Clin Oncol. 2009;6:219-228.

163. Sepe PS, Moparty B, Pitman MB, Saltzman JR, Brugge WR. EUS-guided FNA for the diagnosis of GI stromal cell tumors: sensitivity and cytologic yield. Gastrointest Endosc. 2009;70:254-261.

164. Van den Abbeele AD. The lessons of GIST--PET and PET/CT: a new paradigm for imaging. Oncologist. 2008;13 Suppl 2:8-13.

165. Van Den Abbeele AD, Badawi RD, Manola J, et al. Effects of cessation of imatinib mesylate (IM) therapy in patients (pts) with IM-refractory gastrointestinal stromal tumors (GIST) as visualized by FDG-PET scanning. J Clin Oncol (Meeting Abstracts). 2004;22:3012-.

166. Blay J-Y, Le Cesne A, Ray-Coquard I, et al. Prospective Multicentric Randomized Phase III Study of Imatinib in Patients With Advanced Gastrointestinal Stromal Tumors Comparing Interruption

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Versus Continuation of Treatment Beyond 1 Year: The French Sarcoma Group. J Clin Oncol. 2007;25:1107-1113.

167. Dematteo RP, Gold JS, Saran L, et al. Tumor mitotic rate, size, and location independently predict recurrence after resection of primary gastrointestinal stromal tumor (GIST). Cancer. 2008;112:608-615.

168. Gold JS, Gonen M, Gutierrez A, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. Lancet Oncol. 2009;10:1045-1052.

169. Raut CP, Posner M, Desai J, et al. Surgical Management of Advanced Gastrointestinal Stromal Tumors After Treatment With Targeted Systemic Therapy Using Kinase Inhibitors. J Clin Oncol. 2006;24:2325-2331.

170. Wiebe L, Kasza KE, Maki RG, et al. Activity of sorafenib (SOR) in patients (pts) with imatinib (IM) and sunitinib (SU)-resistant (RES) gastrointestinal stromal tumors (GIST): A phase II trial of the University of Chicago Phase II Consortium. ASCO Meeting Abstracts. 2008;26:10502.

171. Blay JY, Casali PG, Reichardt P, et al. A phase I study of nilotinib alone and in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors (GIST): Study update. ASCO Meeting Abstracts. 2008;26:10553.

172. Demetri GD, Lo Russo P, MacPherson IR, et al. Phase I dose-escalation and pharmacokinetic study of dasatinib in patients with advanced solid tumors. Clin Cancer Res. 2009;15:6232-6240.

173. Fumagalli E, Coco P, Morosi C, et al. Rechallenge with Imatinib in GIST patients resistant to second or third line therapy 2009 Connective Tissue Oncology Society (CTOS) 15th Annual Meeting:Abstract 39404.

174. Scott RJ, Froggatt NJ, Trembath RC, Evans DG, Hodgson SV, Maher ER. Familial infiltrative fibromatosis (desmoid tumours) (MIM135290) caused by a recurrent 3' APC gene mutation. Hum Mol Genet. 1996;5:1921-1924.

175. Friedl W, Caspari R, Sengteller M, et al. Can APC mutation analysis contribute to therapeutic decisions in familial adenomatous polyposis? Experience from 680 FAP families. Gut. 2001;48:515-521.

176. Pignatti G, Barbanti-Brodano G, Ferrari D, et al. Extraabdominal desmoid tumor. A study of 83 cases. Clin Orthop Relat Res. 2000:207-213.

177. Posner MC, Shiu MH, Newsome JL, Hajdu SI, Gaynor JJ, Brennan MF. The desmoid tumor. Not a benign disease. Arch Surg. 1989;124:191-196.

178. Sorensen A, Keller J, Nielsen OS, Jensen OM. Treatment of aggressive fibromatosis: a retrospective study of 72 patients followed for 1-27 years. Acta Orthop Scand. 2002;73:213-219.

179. Godwin Y, McCulloch TA, Sully L. Extra-abdominal desmoid tumour of the breast: review of the primary management and the implications for breast reconstruction. Br J Plast Surg. 2001;54:268-271.

180. Yamaguchi H, Sakakibara T, Hino M, et al. A case of fibromatosis of the breast. Breast Cancer. 2002;9:175-178.

181. Kouriefs C, Leris ACA, Mokbel K, WellsC W, Carpenter R. Infiltrating fibromatosis of the breast: a potential pitfall. Int J Clin Pract. 2002;56:401-402.

182. Lev D, Kotilingam D, Wei C, et al. Optimizing treatment of desmoid tumors. J Clin Oncol. 2007;25:1785-1791.

183. Pritchard DJ, Nascimento AG, Petersen IA. Local control of extra-abdominal desmoid tumors. J Bone Joint Surg Am. 1996;78:848-854.

184. Ballo MT, Zagars GK, Pollack A, Pisters PW, Pollack RA. Desmoid tumor: prognostic factors and outcome after surgery, radiation therapy, or combined surgery and radiation therapy. J Clin Oncol. 1999;17:158-167.

Printed by Jorge Garc?a on 12/30/2010 8:37:12 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

185. Stojadinovic A, Hoos A, Karpoff HM, et al. Soft tissue tumors of the abdominal wall: analysis of disease patterns and treatment. Arch Surg. 2001;136:70-79.

186. Gronchi A, Casali PG, Mariani L, et al. Quality of surgery and outcome in extra-abdominal aggressive fibromatosis: a series of patients surgically treated at a single institution. J Clin Oncol. 2003;21:1390-1397.

187. Lewis JJ, Boland PJ, Leung DH, Woodruff JM, Brennan MF. The enigma of desmoid tumors. Ann Surg. 1999;229:866-872.

188. Ballo MT, Zagars GK, Pollack A. Radiation therapy in the management of desmoid tumors. Int J Radiat Oncol Biol Phys. 1998;42:1007-1014.

189. Schulz-Ertner D, Zierhut D, Mende U, Harms W, Branitzki P, Wannenmacher M. The role of radiation therapy in the management of desmoid tumors. Strahlenther Onkol. 2002;178:78-83.

190. Kiel KD, Suit HD. Radiation therapy in the treatment of aggressive fibromatoses (desmoid tumors). Cancer. 1984;54:2051-2055.

191. Janinis J, Patriki M, Vini L, Aravantinos G, Whelan JS. The pharmacological treatment of aggressive fibromatosis: a systematic review. Ann Oncol. 2003;14:181-190.

192. Chao AS, Lai CH, Hsueh S, Chen CS, Yang YC, Soong YK. Successful treatment of recurrent pelvic desmoid tumour with tamoxifen: case report. Hum Reprod. 2000;15:311-313.

193. Hansmann A, Adolph C, Vogel T, Unger A, Moeslein G. High-dose tamoxifen and sulindac as first-line treatment for desmoid tumors. Cancer. 2004;100:612-620.

194. Izes JK, Zinman LN, Larsen CR. Regression of large pelvic desmoid tumor by tamoxifen and sulindac. Urology. 1996;47:756-759.

195. Lackner H, Urban C, Kerbl R, Schwinger W, Beham A. Noncytotoxic drug therapy in children with unresectable desmoid tumors. Cancer. 1997;80:334-340.

196. Leithner A, Schnack B, Katterschafka T, et al. Treatment of extra-abdominal desmoid tumors with interferon-alpha with or without tretinoin. J Surg Oncol. 2000;73:21-25.

197. Thomas S, Datta-Gupta S, Kapur BM. Treatment of recurrent desmoid tumour with tamoxifen. Aust N Z J Surg. 1990;60:919-921.

198. Waddell WR, Gerner RE, Reich MP. Nonsteroid antiinflammatory drugs and tamoxifen for desmoid tumors and carcinoma of the stomach. J Surg Oncol. 1983;22:197-211.

199. Wilcken N, Tattersall MH. Endocrine therapy for desmoid tumors. Cancer. 1991;68:1384-1388.

200. Chugh R, Maki RG, Thomas DG, et al. A SARC phase II multicenter trial of imatinib mesylate (IM) in patients with aggressive fibromatosis. J Clin Oncol (Meeting Abstracts). 2006;24:9515.

201. Dufresne A, Penel N, Salas S, et al. Updated outcome with long-term follow-up of imatinib for the treatment of progressive or recurrent aggressive fibromatosis (desmoid tumor): A FNCLCC/ French Sarcoma Group phase II trial. ASCO Meeting Abstracts. 2009;27:10518-.