National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Soft Tissue Sarcoma

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‡ Hematology/ Hematologic oncology
Þ Internal medicine
† Medical oncology
т Orthopedics/Orthopedic oncology
≠ Pathology
¥ Patient advocacy
€ Pediatric oncology
§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical oncology
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Continue

Bone Sarcomas - See the NCCN Guidelines for Bone Cancer
Uterine Sarcomas - See the NCCN Guidelines for Uterine Neoplasms
Dermatofibrosarcoma Protuberans - See the NCCN Guidelines for Dermatofibrosarcoma Protuberans and the NCCN Guidelines for Soft Tissue Sarcoma (Extremity/Body Wall, Head/Neck, EXTSARC-1 and EXTSARC-5)

Clinical Trials: NCCN believes that the best management for any patient with cancer 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/member_institutions.aspx.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

Updates in Version 2.2020 of the NCCN Guidelines for Soft Tissue Sarcoma from Version 1.2020 include:

GIST-D (1 of 2)
- Ripretinib has been added as a 4L treatment option for patients with unresectable or metastatic GIST (progressive after imatinib, sunitinib, and regorafenib) with the corresponding reference, von Mehren M, Serrano C, Bauer S, et al: INVICTUS: A phase III, interventional, double-blind, placebo-controlled study to assess the safety and efficacy of ripretinib as fourth-line therapy in advanced GIST. 2019 ESMO Congress. Abstract LBA87.

Updates in Version 1.2020 of the NCCN Guidelines for Soft Tissue Sarcoma from Version 6.2019 include:

Global Changes:
- The NCCN Categories of Preference has been applied to all of the systemic therapy regimens.
- Interferon alfa-2b, and peginterferon alfa-2b have been removed from the algorithm due to product discontinuation.

Gastrointestinal Stromal Tumors (GIST) and Desmoid Tumors:
- *These two sections were extensively revised, rearranged, reformatted, and condensed.*

EXTSARC-1
- The title of the page has been modified: Extremity/*Body Wall*, ~~Superficial Trunk~~, Head/Neck (Also for all pages in the extremity section).

Workup Essential
- 1st bullet, modified: Prior to the initiation of therapy, *it is highly recommended that* all patients should be evaluated and managed by a multidisciplinary team with expertise and experience in sarcoma ~~See NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology~~
- 7th bullet is new: The following conditions are linked to increased incidence of sarcoma and other cancers:
  - Patients with hereditary non-polyposis colorectal cancer (HNPCC or Lynch syndrome) should be considered for further assessment. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic
  - Patients with neurofibromatosis type 1 have an increased risk for developing both malignant peripheral nerve sheath tumors (MPNSTs) and gastrointestinal stromal tumors (GISTs). ~~In addition to routine cancer surveillance for the treated index sarcoma, consideration should be given to surveillance strategies, such as whole body MRI, to assess for second primary sarcoma development.~~

Footnote
- "a", new: *These guidelines are intended to treat the adult population. For adolescent and young adult patients,* refer to the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology.
- "b", modified as follows for this page only: Imaging studies should include cross-sectional imaging (MRI with and without contrast +/- CT with contrast) to provide details about the size of tumor and contiguity to nearby visceral structures and neurovascular landmarks. Other imaging studies such as angiogram and plain radiograph may be warranted in selected circumstances.
- "i", modified: Patients with DFSP with fibrosarcomatous changes and/or malignant transformations *should* ~~can~~ be treated according to this algorithm. For DFSP without fibrosarcomatous elements refer to treatment in the NCCN Guidelines for Dermatofibrosarcoma Protuberans.

EXTSARC-2

Primary Treatment
- 3rd column, lower pathway: *For R2 resection, re-image prior to initiating treatment options.*

Follow-Up
- 4th bullet, modified: Consider obtaining postoperative baseline *MRI*

Footnotes
- "j", modified: See American Joint Committee on Cancer (AJCC) Staging, 8th Edition (ST-2 and ST-3) (Also for EXTSARC-3, EXTSARC-5)
- "n"deleted: ~~Results of a randomized study showed a non-significant trend toward reduced late toxicities (fibrosis, edema, and joint stiffness) with preoperative compared to postoperative radiation and a significant association between these toxicities and increasing treatment field size. Because postoperative radiation fields are typically larger than preoperative fields, the panel has expressed a general preference for preoperative radiation, particularly when treatment volumes are large. [Davis AM, O'Sullivan B, Turcotte R, et al. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. Radiother Oncol 2005;75(1):48-53 and Nielsen OS, Cummings B, O'Sullivan B, et al. Preoperative and postoperative irradiation of soft tissue sarcomas: effect of radiation field size. Int J Radiat Oncol Biol Phys 1991;21(6):1595-1599.] See Principles of Radiation Therapy (SARC-E).~~ Corresponding to the 4th column, 3rd bullet, Consider RT.

EXTSARC-3

Primary Treatment
- 2nd column, bottom pathway: Stage IIIA Stage III B modified to Stage III
- *Multimodality treatment critical*, is new to the page. (Also for EXTSARC-5)
- Preoperative RT (category 1) ~~and~~/or ~~Preoperative chemoradiation (category 2B) and/~~ or Preoperative chemotherapy
- ~~Category 2B~~ is now category 2A throughout the page.
- *Preoperative chemotherapy + RT,* is new.

Follow-up
- 1st bullet, modified: Evaluation for rehabilitation ~~(OT/PT)~~ (Also for EXTSARC-5)

Footnote
- "s", modified: A prospective study demonstrated low rates of local recurrence with surgery alone in carefully selected patients with high-grade tumors less than 5 cm (Ann Surg 2007;246(4):675-81). Consider omission of RT for tumors <5 cm resected with wide margins and a repeat resection would be feasible with low morbidity in the case of a recurrence. ~~Surgery alone may be an option for small tumors resected with wide margins.~~

Continued

Updates in Version 1.2020 of the NCCN Guidelines for Soft Tissue Sarcoma from Version 6.2019 include:

EXTSARC-4

3rd column, bottom pathway, modified: *Consider adjuvant chemotherapy,* is new coming off of amputation.

Footnote
- "z", modified: Definitive RT entails delivering the maximal local dose compatible with known normal tissue tolerance, typically in the range of 70–80 Gy with sophisticated treatment planning techniques being a necessity in this setting. *Conduct early assessment to determine if patient can be resected.*

EXTSARC-5
- 2nd column, modified: Single organ *(primarily pulmonary)* and limited tumor bulk that are amenable to local therapy

Primary Treatment
- Primary tumor management as per EXTSARC-3 and consider the following options *for metastases*:
  - *Consider chemotherapy for all patients, is new to the page.*
  - Metastasectomy ~~± preoperative or postoperative chemotherapy~~ ± RT
  - *For lung metastases, resection (preferred) or SBRT*
  - Stereotactic body radiation therapy (SBRT) ~~± chemotherapy~~
  - Ablation procedures ~~(eg, RFA or cryo)~~ (Also for EXTSARC-6)
  - Embolization procedures *(non-lung)*
- Palliative *treatment* options

Footnotes
- 2nd bullet modified: H&P..., then anually, *if it remains free of disease recurrence*

Footnotes
- "aa", modified: Patients with lymph node involvement (including isolated regional nodal metastastic disease) should undergo regional lymph node dissection ~~at the time of primary tumor resection~~ ± RT.
- "bb", modified: Metastasectomy is the historical standard for patients with oligometastatic disease *(primarily lung)* and is preferred if feasible; the choice of local control modality may depend on factors such as performance status, patient preference, lesion location/accessibility, ability to preserve normal tissue function, and anticipated morbidity of a treatment modality.

EXTSARC-6
- Removed ~~EXTSARC-1~~ from workup for local recurrence
- "±" surgery was added to isolated limb perfusion/infusion

RETSARC-1

Work-Up
- 2nd column, bottom pathway: Unresectable or Stage IV/~~Metastatic~~ disease

Footnotes
- "b", is new to the page: *Biopsy for retroperitoneal/intra-abdominal sarcomas should try to avoid the free intra-abdominal space. See Principles of Surgery (SARC-D).*

RETSARC-2
- Removed ~~performed~~ from biopsy in the 2nd column

Primary Treatment
- 3rd column, middle pathway, modified: ~~Other~~ Sarcoma
- Surgery to obtain oncologically appropriate margins ~~± IORT~~
- Preoperative therapy is a (category 2A) from a ~~category 2B~~
- ~~Bottom pathway deleted~~

Footnotes
- "e", modified: ~~Biopsy required~~ If considering preoperative therapy, *biopsy required*, including *endoscopic ultrasound-guided biopsy for suspected GIST lesions.*
- "f" is new to the page: *Biopsy may not be required if diagnostic imaging is consistent with WD-LPS.*
  - ~~IORT may be considered provided frozen section pathology can confidently demonstrate a non-GIST/non-desmoid histology.~~
- "g", modified: For other soft tissue sarcomas such as Ewing sarcoma, see NCCN Guidelines for Bone Cancer; for RMS, see RMS-1; ~~for Desmoid tumors (aggressive fibromatosis), see DESM-1.~~
- "i", modified: *If preoperative RT is anticipated, IMRT would be preferred* to optimize sparing of nearby critical structures.

RETSARC-3

Postoperative Treatment
- *Consider postoperative chemotherapy for histologies with high risk for metastatic disease,* is new to the page, coming off R0, R1 and R2.

Treatment for Recurrent Disease
- Stage IV ~~metastatic~~ disease

Footnotes
- "l", is new to the page: *Chemotherapy not recommended for low-grade tumors.*

RETSARC-4
- 1st column: Unresectable or Stage IV *disease*
- ~~Attempt downstaging~~ and ~~No downstaging, palliative care only~~ coming off unresectable or Stage IV disease have been deleted.

Primary Treatment
- Modified as follows:
  - Observation, if asymptomatic
  - Systemic therapy and/or RT
  - Surgery for symptom control
- 6th column, Palliative options deleted

Continued

Updates in Version 1.2020 of the NCCN Guidelines for Soft Tissue Sarcoma from Version 6.2019 include:

SARC-A (1 through 3)
Principles of Imaging
- This section was extensively revised, rearranged, reformatted, and condensed.

SARC-C (1 of 3)
Principles of Ancillary Techniques Useful in the Diagnosis of Sarcomas
- *Undifferentiated round cell sarcoma* is new to the page, as well as the following aberrations, genes, and references:
  - t(4;19)(q35;q13) or t(10;19)(q26;q13) / Gene(s):*CIC-DUX4*
  - inv(X),(p11.4p11.22) / Gene(s):*BCOR-CCNB3*
    - ◊ *Yoshimoto T, Tanaka M, Homme M, et al. CIC-DUX4 induces small round cell sarcomas distinct from Ewing sarcoma. Cancer Res 2017;77(11):2927-2937.*
    - ◊ *Kao YC, Owosho AA, Sung YS, et al. BCOR-CCNB3-fusion positive sarcomas: A clinicopathologic and molecular analysis of 36 cases with comparison to morphologic spectrum and clinical behavior of other round cell sarcomas. Am J Surg Path 2018;42(5):604-615.*

References
- The following sentences have been removed from reference 2 (the aberration and gene(s) and have been moved to the algorithm:
  - CIC-DUX4 fusion is present in primitive round or short spindle cell sarcomas, resulting from translocation of t(4;19)(q35;q13) or t(10;19)(q26;q13). It is not clear if this is an entirely new subtype of sarcoma or a new subtype of Ewing sarcoma. BCOR-CCNB3 fusion is considered Ewing-like sarcoma. (See SARC-C, 1 of 3)
  - MPNST is associated with loss of SUZ12/EED and alteration of NF1 and CDKN2A. Consultation with a pathologist who has expertise in sarcoma diagnosis and molecular diagnostic techniques should be obtained prior to testing. (See SARC-C 3 of 3).

SARC-C (2 of 3)
- The following aberrations have been added to High-grade endometrial stromal sarcoma
  - *t(10;17)(q22;p13) / Gene(s):YWHAE-NUTM2* ~~FAM22A/B~~
  - *t(x;11)(q22;p11.23) / Gene(s):ZC3H7B-BCOR*
    - ◊ *Lewis N, Soslow RA, Delair DF, et al. ZC3H7B-BCOR high-grade endometrial stromal sarcomas: a report of 17 cases of a newly defined entity. Mod Pathol 2018;31:674-684.*
    - ◊ *Yamamoto H, Yoshida A, Taguchi K, et al. ALK, ROS1 and NTRK3 gene rearrangements in inflammatory myofibroblastic tumours. Histopathology 2016;69:72-83 corresponding to NTRK3 on* SARC-C (2 of 3) *and ALK on* SARC-C (3 of 3).

SARC-C (3 of 3)
- Mesenchymal chondrosarcoma has been modified to include:
  - *t(8;8)(q13;q21)*
- Solitary fibrous tumor has been modified to include: *inv(12)(q13q13)*

SARC-D (1 through 2)
Principles of Surgery
- This section was extensively revised, rearranged, reformatted, and condensed.

SARC-E (1 of 4)
Principles of Radiation Therapy for Soft Tissue Sarcoma
- First bullet, last sub-sub-bullet, modified: *Presence of* distant metastases would prevent *proceeding with* a noncurative surgery.
- 3rd bullet, 2nd sub-bullet: Following preoperative 50 Gy EBRT and surgery, for positive margins, consider observation or RT boost *in select situations*
- *4th sub, sub-bullet: deleted "*IORT (intraoperative RT)*"*

SARC-E (2 of 4)
- 3rd bullet, 1st sub-bullet: deleted "EBRT boost"
- 4th sub-bullet, deleted "IORT (10-16Gy) + EBRT (50 GY)"

SARC-E (3 of 4)
- 1st sub-sub-bullet, modified: Consider IORT boost for *known or suspected positive* margins *at the time of surgery*

SARC-E (4 of 4)
References
- *Li XA, et al. Pract Radiat Oncol 2016 Jul-Aug;6(4):e135-40.*
- *Wang D, et al. RTOG-0630 Trial J Clin Oncol. 2015 Jul 10;33(20):2231-8.*
- *Bahig H, et al. Int J Radiat Oncol Biol Phys 2013 Jun 1;86(2):298-303.*
- *Wang D, et al. Int J Radiat Oncol Biol Phys 2011 Nov 15;81(4):e525-8.*
- *Baldini EH, et al. Int J Radiat Oncol Biol Phys 2015 Jul 1;92(3):602-12.*
- *Baldini EH, et al. Ann Surg Oncol 2015 Sep;22(9):2846-52.*

SARC-F (3 of 9)
Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma
- Solitary Fibrous Tumor/~~Hemangiopericytoma~~

SARC-F (4 of 9)
- Alveolar Soft Part Sarcoma (ASPS)
  - Sunitinib and pembrolizumab are now listed with a category 2A recommendation.
- Undifferentiated Pleomorphic Sarcoma (UPS)
  - Pembrolizumab is now listed with a category 2A recommendation.

SARC-F (6 of 9)
- Footnotes and references corresponding to regimens listed for GIST and Desmoids are now listed on GIST-D and DESM-5A, respectively.

WORKUP

ESSENTIAL:
- Prior to the initiation of therapy, it is highly recommended that all patients be evaluated and managed by a multidisciplinary team with expertise and experience in sarcoma[a]
- H&P
- Adequate imaging of primary tumor[b] is indicated for all lesions with a reasonable chance of being malignant
- Carefully planned core needle [preferred] or incisional biopsy after adequate imaging (See SARC-D)[c]
  - Place biopsy along future resection axis with minimal dissection and careful attention to hemostasis
  - Biopsy should establish grade and histologic subtype[d]
  - As appropriate, use ancillary diagnostic methodologies[e]
- Chest imaging[b]

USEFUL UNDER CERTAIN CIRCUMSTANCES:[f]
- Additional imaging as indicated; see Principles of Imaging (SARC-A)
- The following conditions are linked to increased incidence of sarcoma and other cancers:
  - Patients with personal/family history suggestive of Li-Fraumeni syndrome should be considered for further genetics assessment. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic
  - Patients with hereditary non-polyposis colorectal cancer (HNPCC or Lynch syndrome) should be considered for further assessment See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
  - Patients with neurofibromatosis[g] type 1 have an increased risk for developing both malignant peripheral nerve sheath tumors (MPNSTs) and gastrointestinal stromal tumors (GISTs).

Special considerations for unique histologies[h]
- Gastrointestinal stromal tumors (GIST) → See (GIST-1)
- Desmoid tumors (Aggressive fibromatosis) → See DESM-1
- Ewing sarcoma → See NCCN Guidelines for Bone Cancer
- Rhabdomyosarcoma (RMS) → See RMS-1

Other soft tissue sarcomas of the extremity/body wall, head/neck[i]
- Stage I → See Primary (EXTSARC-2)
- Stage II, III resectable disease with acceptable functional outcomes → See Primary (EXTSARC-3)
- Stage II, III resectable disease with adverse functional outcomes or Unresectable primary disease → See Primary (EXTSARC-4)
- Stage IV synchronous disease → See Primary (EXTSARC-5)
- Recurrent disease → See Primary (EXTSARC-6)

See footnotes on EXTSARC-1A

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

FOOTNOTES

[a] These guidelines are intended to treat the adult population. For adolescent and young adult patients, refer to the See NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology.

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

[c] In selected institutions with clinical and pathologic expertise, a fine-needle aspiration biopsy (FNAB) may be acceptable.

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

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

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

[g] Patients with neurofibromatosis are at risk for multiple sarcomas at various locations and their assessment and follow-up should be different. (Reilly KM, et al. J Natl Cancer Inst 2017;109(8).

[h] Diagnoses that will impact the overall treatment plan. See SARC-F for special considerations for unique histologies.

[i] Patients with DFSP with fibrosarcomatous changes and/or malignant transformations should be treated according to this algorithm. For DFSP without fibrosarcomatous elements refer to treatment in the NCCN Guidelines for Dermatofibrosarcoma Protuberans.

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PRIMARY TREATMENT

FOLLOW-UP

Stage IA[j] / Stage IB[j] (low grade) → **Surgical wide resection[k,l]**

- → **Oncologically appropriate margins** → Follow-up
- → **Failure to obtain oncologically appropriate margins**
  - ▸ For R2 resection, re-image prior to initiating additional treatment options[b]
  - → • Re-resection (See SARC-D)
    or
    • Observation (for stage 1A tumors)[m]
    or
    • Consider RT[n,o] (category 2B for stage 1A tumors; category 1 for stage 1B tumors)
    → Follow-up

Follow-up:
- Evaluation for rehabilitation (See SARC-D 2 of 2)
- H&P every 3–6 mo for 2–3 y, then annually
- Consider chest imaging[b]
- Consider obtaining postoperative baseline MRI
- Imaging of primary site[b] based on estimated risk of locoregional recurrence[p,q]

→ **If recurrence, See Recurrent Disease (EXTSARC-6)**

[b]See Principles of Imaging (SARC-A).
[j]See American Joint Committee on Cancer (AJCC) Staging, 8th Edition (ST-2 and ST-3).
[k]See Principles of Surgery (SARC-D).
[l]Resection should be tailored to minimize surgical morbidity for patients with atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLS). En bloc resection with negative margins is generally sufficient to obtain long-term local control.
[m]Treatment options including revision surgery versus observation should be presented at an experienced multidisciplinary sarcoma tumor board to determine advantages and disadvantages of the decision.
[n]Randomized clinical trial data support the use of radiation therapy as an adjunct to surgery in appropriately selected patients based on an improvement in disease-free survival (although not overall survival). (Yang J,et al. J Clin Oncol 1998;16:197-203). See Principles of Radiation Therapy (SARC-E).
[o]For patients with ALT/WDLS, observation is recommended for focally positive margins if re-resection, in the event of recurrence, would not be unduly morbid. RT is reserved for selected patients with recurrent or deeply infiltrative primary lesions with a risk of local recurrence, depending on the tumor location and patient's age.
[p]In situations where the area is easily followed by physical examination, imaging may not be required.
[q]After 10 years, the likelihood of developing a recurrence is small and follow-up should be individualized.

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PRIMARY TREATMENT (MULTIMODALITY TREATMENT IS CRITICAL) | **FOLLOW-UP**

Stage II, III Resectable with acceptable functional outcomes

- **Stage II[j]** →
  - Surgery[k] to obtain oncologically appropriate margins → RT[r,x] (category 1) → Follow-up
  - or Preoperative RT[r] (category 1) → Surgery[k,w] to obtain oncologically appropriate margins → Follow-up
  - Surgery[k,s] to obtain oncologically appropriate margins → Follow-up
- **Stage III[j]** →
  - Surgery[k,t] to obtain oncologically appropriate margins → RT[r] (category 1) or RT[r] + adjuvant chemotherapy[u] → Follow-up
  - or Preoperative RT[r] (category 1) or Preoperative chemotherapy[u,v] + RT[r] → Surgery[w] to obtain oncologically appropriate margins → Consider adjuvant chemotherapy[u]
  - or Preoperative chemotherapy[u,v] → Surgery[w] to obtain oncologically appropriate margins → RT[r] or RT[r] + adjuvant chemotherapy[u]

FOLLOW-UP

- Evaluation for rehabilitation (See SARC-D 2 of 2)
- H&P every 3–6 mo for 2–3 y, then every 6 mo for next 2 y, then annually
- Chest imaging[b]
- Obtain postoperative baseline and periodic imaging of primary site[b] based on estimated risk of locoregional recurrence[p,q]

→ **If recurrence,** See Recurrent Disease (EXTSARC-6)

[b] See Principles of Imaging (SARC-A).
[j] See American Joint Committee on Cancer (AJCC) Staging, 8th Edition (ST-2 and ST-3).
[k] See Principles of Surgery (SARC-D).
[p] In situations where the area is easily followed by physical examination, imaging may not be required.
[q] After 10 years, the likelihood of developing a recurrence is small and follow-up should be individualized.
[r] Results of a randomized study showed a non-significant trend toward reduced late toxicities (fibrosis, edema, and joint stiffness) with preoperative compared to postoperative radiation and a significant association between these toxicities and increasing treatment field size. Because postoperative radiation fields are typically larger than preoperative fields, the panel has expressed a general preference for preoperative radiation, particularly when treatment volumes are large. [Davis AM, et al. Radiother Oncol 2005;75(1):48-53 and Nielsen OS, et al. Int J Radiat Oncol Biol Phys 1991;21(6):1595-1599.] See Principles of Radiation Therapy (SARC-E).
[s] A prospective study demonstrated low rates of local recurrence with surgery alone in carefully selected patients with high-grade tumors less than 5 cm (Pisters PW, Ann Surg 2007;246(4):675-81). Consider omission of RT for tumors <5 cm resected with wide margins; a repeat resection would be feasible with low morbidity in the case of a recurrence.
[t] In selected cases when margin status is uncertain, consultation with a radiation oncologist is recommended. Re-resection, if feasible, may be necessary to render margins >1.0 cm.
[u] See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F).
[v] PET/CT may be useful in determining response to chemotherapy (Schuetze SM, et al. Cancer 2005;103:339-348).
[w] Re-imaging using MRI with and without contrast (preferred for extremity imaging) or CT with contrast to assess primary tumor and rule out metastatic disease. See Principles of Imaging (SARC-A).
[x] RT may be used in select circumstances such as close or positive margins where re-excision is not feasible or for functional considerations.

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PRIMARY TREATMENT | **FOLLOW-UP**

Stage II, III Resectable with adverse functional outcomes or Unresectable primary disease →

- **RT[n]** or **Chemoradiation[r,u]** or **Chemotherapy[u,v]** or **Regional limb therapy[y]** →
  - **Resectable with acceptable functional outcomes** → See EXTSARC-3
  - **Resectable with adverse functional outcomes** → **Amputation[k] or Definitive RT** → Follow-up
  - **Unresectable primary disease** → **Options:**
    - If not previously irradiated, Definitive RT[z]
    - Chemotherapy[u]
    - Palliative surgery
    - Observation, if asymptomatic
    - Best supportive care

    → Follow-up
- or **Amputation[k]** → **Consider adjuvant chemotherapy[u]** → Follow-up

Follow-up:
- Evaluation for rehabilitation (See SARC-D 2 of 2)
- H&P every 3–6 mo for 2–3 y, then every 6 mo for next 2 y, then annually
- Chest imaging[b]
- Obtain baseline and periodic imaging of primary site[b,p]

→ **If recurrence or progression,** See Recurrent Disease (EXTSARC-6)

[b]See Principles of Imaging (SARC-A).
[k]See Principles of Surgery (SARC-D).
[p]In situations where the area is easily followed by physical examination, imaging may not be required.
[r]Results of a randomized study showed a non-significant trend toward reduced late toxicities (fibrosis, edema, and joint stiffness) with preoperative compared to postoperative radiation and a significant association between these toxicities and increasing treatment field size. Because postoperative radiation fields are typically larger than preoperative fields, the panel has expressed a general preference for preoperative radiation, particularly when treatment volumes are large. [Davis AM, et al. Radiother Oncol 2005;75(1):48-53 and Nielsen OS, et al. Int J Radiat Oncol Biol Phys 1991;21(6):1595-1599.] See Principles of Radiation Therapy (SARC-E).
[u]See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F).
[v]PET/CT may be useful in determining response to chemotherapy. (Schuetze SM, et al. Cancer 2005;103:339-348).
[y]Should only be done at institutions with experience in regional limb therapy.
[z]Definitive RT entails delivering the maximal local dose compatible with known normal tissue tolerance, typically in the range of 70–80 Gy with sophisticated treatment planning techniques being a necessity in this setting. Conduct early assessment to determine if the disease can be resected.

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PRIMARY TREATMENT (MULTIMODALITY TREATMENT IS CRITICAL) | **FOLLOW-UP**

Synchronous-Stage IV[j] disease

→ **Single organ (primarily pulmonary) with limited tumor bulk that is amenable to local therapy[aa]**
→ **Primary tumor management as per EXTSARC-3 and consider the following options for metastases:**
- **Consider chemotherapy[u] for all patients**
- **Metastasectomy[aa,bb] ± RT**
- **For lung metastases, resection (preferred) or SBRT**
- **Stereotactic body radiation therapy (SBRT)[cc]**
- **Ablation procedures**
- **Embolization procedures (non-lung)**
- **Observation**

→ **Disseminated metastases**
→ **Palliative treatment options:**
- **Chemotherapy[u]**
- **RT[dd]/SBRT[cc]**
- **Surgery**
- **Observation, if asymptomatic**
- **Supportive care**
- **Ablation procedures**
- **Embolization procedures (non-lung)**

FOLLOW-UP:
- **Evaluation for rehabilitation (See SARC-D 2 of 2)**
- **H&P every 2–6 mo for 2–3 y, then every 6 mo for next 2 y, then annually, if it remains free of disease recurrence**
- **Imaging of chest and other known sites of metastatic disease[b]**
- **Consider obtaining postoperative baseline and periodic imaging of primary site[b] based on estimated risk of locoregional recurrence[p,q]**

→ **If recurrence, See Recurrent Disease (EXTSARC-6)**

[b]See Principles of Imaging (SARC-A).
[j]See American Joint Committee on Cancer (AJCC) Staging, 8th Edition (ST-2 and ST-3).
[p]In situations where the area is easily followed by physical examination, imaging may not be required.
[q]After 10 years, the likelihood of developing a recurrence is small and follow-up should be individualized.
[u]See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F).
[aa]Patients with lymph node involvement (including isolated regional nodal metastastic disease) should undergo regional lymph node dissection ± RT.
[bb]Metastasectomy is the historical standard for patients with oligometastatic disease (primarily lung) and is preferred if feasible; the choice of local control modality may depend on factors such as performance status, patient preference, lesion location/accessibility, ability to preserve normal tissue function, and anticipated morbidity of a treatment modality.
[cc]In retrospective studies, various SBRT dosing regimens have been reported to be effective for treatment of sarcoma metastases. Dose and fractionation should be determined by an experienced radiation oncologist based on normal tissue constraints. [Dhakal S, et al. Int J Radiat Oncol Biol Phys 2012;82(2):940-945 and Navarria P, et al. Eur J Cancer 2015;51(5):668-674].
[dd]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. Recommended only for palliative therapy in patients with synchronous stage IV or recurrent disease with disseminated metastases.

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RECURRENT DISEASE / TREATMENT

Local recurrence → Follow Workup, then appropriate Primary Treatment[ee] pathway (EXTSARC-2, EXTSARC-3, EXTSARC-4)

Metastatic disease

- **Single organ and limited tumor bulk that are amenable to local therapy[aa]** → Options:
  - Metastasectomy[aa,bb] ± preoperative or postoperative chemotherapy[u] ± RT
  - SBRT[cc] ± chemotherapy[u]
  - Ablation procedures
  - Embolization procedures
  - Observation
- **Disseminated metastases** → Palliative options:
  - Chemotherapy[u]
  - RT[dd]/SBRT
  - Surgery
  - Observation, if asymptomatic
  - Supportive care
  - Ablation procedures
  - Embolization procedures
- **Isolated regional disease or nodes** → Options:
  - Regional node dissection for nodal involvement ± RT ± chemotherapy[u]
  - Metastasectomy[aa,bb] ± preoperative or postoperative chemotherapy[u] ± RT
  - SBRT
  - Isolated limb perfusion/infusion[ff] ± surgery

See footnotes on EXTSARC-6A

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FOOTNOTES

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

[aa]Patients with lymph node involvement (including isolated regional nodal metastastic disease) should undergo regional lymph node dissection ± RT.

[bb]Metastasectomy is the historical standard for patients with oligometastatic disease (primarily lung) and is preferred if feasible; the choice of local control modality may depend on factors such as performance status, patient preference, lesion location/accessibility, ability to preserve normal tissue function, and anticipated morbidity of a treatment modality.

[cc]In retrospective studies, various SBRT dosing regimens have been reported to be effective for treatment of sarcoma metastases. Dose and fractionation should be determined by an experienced radiation oncologist based on normal tissue constraints. [Dhakal S, et al. Int J Radiat Oncol Biol Phys 2012;82(2):940-945 and Navarria P, et al. Eur J Cancer 2015;51(5):668-674].

[dd]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. Recommended only for palliative therapy in patients with synchronous stage IV or recurrent disease with disseminated metastases.

[ee]If local recurrence can be excised, a decision will need to be made on a case-by-case basis whether re-irradiation is possible. Some case series suggest benefit with re-irradiation (Catton C, et al. Radiother Oncol 1996;41:209-214) while others do not (Torres MA, et al. Management of locally recurrent soft-tissue sarcoma after prior surgery and radiation therapy. Int J Radiat Oncol Biol Phys 67:1124, 2007), likely reflecting differences in selection of patients for treatment with surgery and radiotherapy or surgery alone. Traditionally, the re-irradiation has been done with postoperative adjuvant brachytherapy but may now be able to be done as a combination of brachytherapy and IMRT to reduce the risks of morbidity with re-irradiation.

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

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WORKUP

- Prior to the initiation of therapy, all patients should be evaluated and managed by a multidisciplinary team with expertise and experience in sarcoma.
- H&P
- Imaging[a]
- Image-guided core needle biopsy[b] should be performed if preoperative therapy is being given or for suspicion of malignancy other than sarcoma.
- Preresection biopsy is not necessarily required for well-differentiated liposarcoma.
- Patients with personal/family history suggestive of Li-Fraumeni syndrome should be considered for further genetics assessment. See NCCN Guidelines for Genetic/Familial High Risk Assessment: Breast, Ovarian, and Pancreatic
- For patients with neurofibromatosis,[c] see NCCN Guidelines for Central Nervous System Cancers (PSCT-3)

→ Resectable → See Primary Treatment (RETSARC-2)

→ Unresectable or Stage IV disease → See Primary Treatment (RETSARC-4)

[a]See Principles of Imaging (SARC-A).
[b]Biopsy for retroperitoneal/intra-abdominal sarcomas should try to avoid the free intra-abdominal space. See Principles of Surgery (SARC-D).
[c]Patients with neurofibromatosis are at risk for multiple sarcomas at various locations and their assessment and follow-up should be different.

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PRIMARY TREATMENT

Resectable disease → **Biopsy[d,e,f]** →

- **Gastrointestinal stromal tumors (GIST)** → **See (GIST-1)**
- **Desmoid tumors (Aggressive fibromatosis)** → **See (DESM-1)**
- **Sarcoma[g]** →
  - **Surgery[h] to obtain oncologically appropriate margins** → **See Postoperative Treatment (RETSARC-3)**
  - **or**
  - **Preoperative therapy**
    - **RT[i,j]**
    - **Chemotherapy[k]**

    → **Surgery[h] to obtain oncologically appropriate margins ± IORT[j]** → **See Postoperative Treatment (RETSARC-3)**

[d]See Principles of Pathologic Assessment of Sarcoma Specimens (SARC-B).
[e]If considering preoperative therapy, biopsy required, including endoscopic ultrasound-guided biopsy for suspected GIST lesions.
[f]Biopsy may not be required if diagnostic imaging is consistent with WD-LPS.
[g]For other soft tissue sarcomas such as Ewing sarcoma, see NCCN Guidelines for Bone Cancer; for RMS, see RMS-1.
[h]See Principles of Surgery (SARC-D).
[i]If preoperative RT is anticipated, IMRT would be preferred to optimize sparing of nearby critical structures.
[j]See Principles of Radiation Therapy (SARC-E).
[k]See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F).

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SURGICAL OUTCOMES/CLINICAL PATHOLOGIC FINDINGS[h]	POSTOPERATIVE TREATMENT		FOLLOW-UP		TREATMENT FOR RECURRENT DISEASE
R0 →	Post-op RT should not be administered routinely with the exception of highly selected patients and unless local recurrence would cause undue morbidity[j,l]	→ Consider postoperative chemotherapy for histologies with high risk for metastatic disease[m]	→ Physical exam with imaging[a] every 3–6 mo for 2–3 y, then every 6 mo for next 2 y, then annually	→ Recurrent disease	→ Unresectable or Stage IV disease[n] (See RETSARC-4)
R1 →	Post-op RT should not be administered routinely with the exception of highly selected patients and unless local recurrence would cause undue morbidity[j,l] or In highly selected cases, consider boost (10–16 Gy) if preoperative RT was given				→ Resectable[n] (See RETSARC-2)
R2 →	Consider re-resection if technically feasible for low-grade disease or well-differentiated liposarcoma or See Primary Treatment (Unresectable) (RETSARC-4)				

[a]See Principles of Imaging (SARC-A).
[h]See Principles of Surgery (SARC-D).
[j]See Principles of Radiation Therapy (SARC-E).
[l]For example, critical anatomic surface where recurrence would cause morbidity.
[m]Chemotherapy not recommended for low-grade tumors.
[n]If not previously administered, consider preoperative RT and/or chemotherapy.

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PRIMARY TREATMENT

Unresectable or Stage IV disease → **Biopsy[d]** →
- **Observation, if asymptomatic**
- **Systemic therapy[k,q] and/or RT[j,k]**
- **Surgery for symptom control**

→ **Imaging to assess treatment response[a]**

- **Resectable[r]** → **See Treatment as per RETSARC-2**
- **Unresectable or Progressive disease** → **Palliative or best supportive care (See NCCN Guidelines for Palliative Care)**

[a]See Principles of Imaging (SARC-A).
[d]See Principles of Pathologic Assessment of Sarcoma Specimens (SARC-B).
[j]See Principles of Radiation Therapy (SARC-E).
[k]See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F).
[o]Balance risks of treatment, likelihood of rendering patient resectable, and performance status of patient with potential clinical benefits. The options listed may be used either alone, sequentially, or in combination.
[p]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. Recommended only for patients with unresectable or progressive disease.
[q]The most active chemotherapy regimen in an unselected patient population is AIM (doxorubicin/ifosfamide/mesna) in terms of response rate. Judson I, et al. Lancet Oncol 2014;15(4):415-23.
[r]Resection of resectable metastatic disease should always be considered if primary tumor can be controlled.

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WORKUP AT PRIMARY PRESENTATION

- **All patients should be evaluated and managed by a multidisciplinary team with expertise and experience in GIST/sarcoma**

- **For very small gastric GISTs <2 cm[a]**
  - **Endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB)[b]**
  - **Imaging[c]**

- **Mass known to be or clinically suspicious for GIST[d]**
  - **Imaging[c]**
  - **Consider chest imaging[c]**
  - **Genotyping should be performed when medical therapy is being considered[e]**

MANAGEMENT BASED ON THE RESULTS OF INITIAL DIAGNOSTIC EVALUATION

For very small gastric GISTs <2 cm:

- **No high-risk EUS features** → **Consider periodic endoscopic or radiographic surveillance[c,j]**
- **High-risk EUS features[f]** → **Complete surgical resection[k]** → **See (GIST-3) for Postoperative Outcomes and Treatment**

Mass known to be or clinically suspicious for GIST:

- **Resectable with minimal morbidity** → **Complete surgical resection[k]** → **See (GIST-3) for Postoperative Outcomes and Treatment**
- **Resectable with significant morbidity[h,i]** → **Consider neoadjuvant imatinib to decrease surgical morbidity[g,l]** → **Biopsy[b,m] and risk assessment** → **See (GIST-2)**
- **Unresectable or metastatic disease** → **See (GIST-4)**

[a]Sepe PS, Nat Rev Gastroenterol Hepatol 2009;6:363-371.
[b]Pathology report should include anatomic location, size, and an accurate assessment of the mitotic rate measured in the most proliferative area of the tumor (See GIST-A).
[c]See Principles of Imaging (SARC-A).
[d]See American Joint Committee on Cancer (AJCC) Staging, 8th Edition (ST-5/GIST).
[e]Mutational analysis may predict response to therapy with tyrosine kinase inhibitors (TKIs) (See GIST-B).
[f]Possible high-risk EUS features include irregular border, cystic spaces, ulceration, echogenic foci, and heterogeneity.
[g]Some patients may rapidly become unresectable; close monitoring is essential.
[h]Extensive surgery associated with significant morbidity (ie, total gastrectomy to reduce risk of recurrence in stomach) is generally not recommended for SDH-deficient GIST with multifocal disease.
[i]Neoadjuvant therapy should be considered for locally advanced GIST in certain anatomical locations (eg, rectum, esophageal and esophagogastric junction, and duodenum) or if a multivisceral resection would be required to resect all gross tumor.
[j]Endoscopic ultrasonography surveillance should only be considered after a thorough discussion with the patient regarding the risks and benefits. Evans J, et al. Gastrointest Endosc 2015;82(1):1-8.
[k]See Principles of Surgery for GIST (GIST-C).
[l]Neoadjuvant imatinib may prohibit accurate assessment of recurrence risk following resection. Consider neoadjuvant imatinib only if surgical morbidity could be reduced by downsizing the tumor preoperatively. Maximal response may require treatment for 6 months or more to achieve. Testing tumor for mutation is recommended prior to starting preoperative imatinib to ensure tumor has a genotype that is likely to respond to treatment.
[m]See RETSARC-1 if the pathology results indicate sarcomas of GI origin other than GIST.

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PRIMARY PRESENTATION | **PRIMARY TREATMENT** | **FOLLOW-UP THERAPY**

- **Resectable GIST with significant morbidity[g]** → **Baseline Imaging[c,n]** → **Imatinib[e,o,p] (category 1)** → **Imaging to assess treatment response[c,q,r] and evaluate patient adherence**
  - **Response or stable disease** → **Continue the same dose of imatinib** → **Surgery, if feasible[k,s,t]** → **See (GIST-3) for Postoperative Outcomes and Treatment**
  - **Progression[r]**
    - → **Surgery, if feasible[k,s,t]** → **See (GIST-3) for Postoperative Outcomes and Treatment**
    - → **If surgery not feasible, see GIST-5**

[c]See Principles of Imaging (SARC-A).
[e]Mutational analysis may predict response to therapy with TKIs (See GIST-B).
[g]Some patients may rapidly become unresectable; close monitoring is essential.
[k]See Principles of Surgery for GIST (GIST-C).
[n]Consider baseline PET/CT, if using PET/CT during follow-up. PET/CT is not a substitute for CT.
[o]If life-threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider sunitinib.
[p]Medical therapy is the usual course of treatment. However, patient may proceed to surgery if bleeding or symptomatic tumor or poor treatment tolerance.
[q]PET/CT may give indication of imatinib efficacy after 2–4 weeks of therapy when rapid readout of activity is necessary. Diagnostic abdominal/pelvic CT or MRI with contrast is indicated every 8–12 weeks; routine long-term PET/CT follow-up is rarely indicated. Frequency of response assessment imaging may be decreased if patient is responding to treatment.
[r]Progression may be determined by abdominal/pelvic CT or MRI with contrast with clinical interpretation; increase in tumor size in the presence of decrease in tumor density is consistent with drug efficacy or benefit. PET/CT scan may be used to clarify if CT or MRI are ambiguous.
[s]Collaboration between medical oncologist and surgeon is necessary to determine the appropriateness and timing of surgery, following major response or sustained stable disease. Maximal response may require treatment for 6 months or more to achieve.
[t]Imatinib can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications. If sunitinib is being used, therapy should be stopped at least one week prior to surgery and can be restarted based on clinical judgment of recovery from surgery.

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POSTOPERATIVE OUTCOMES	ADJUVANT TREATMENT	FOLLOW-UP	
Completely resected (no preoperative imatinib) →	**Observe (low-risk disease)** or **Adjuvant imatinib[e] for patients with significant risk of recurrence (intermediate or high risk) (category 1)[o,u] (See GIST-A)** →	• **H&P every 3 mo for high risk, every 3–6 mo for 5 y (every 3 months if high risk), then annually[v]** • **Imaging[c]** →	**If Recurrence, See (GIST-4)**
Completely resected after preoperative imatinib →	**Consider continuation of adjuvant imatinib if taken prior to resection[u]** →	(same follow-up as above)	
Persistent microscopic residual disease (R1 resection) or gross residual disease (R2 resection) →			**See (GIST-4)**

[c]See Principles of Imaging (SARC-A).
[e]Mutational analysis may predict response to therapy with TKIs (See GIST-B).
[o]If life-threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider sunitinib.
[u]The PERSIST study has shown the feasibility of 5-year adjuvant imatinib with no evidence of recurrence in patients with imatinib-sensitive GIST [Raut CP, et al. JAMA Oncol 2018;4(12):e184060].
[v]Less frequent surveillance may be acceptable for very small tumors (<2 cm), unless they are associated with high mitotic rate.

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PRIMARY PRESENTATION | **PRIMARY TREATMENT** | **FOLLOW-UP THERAPY**

Unresectable, recurrent, or metastatic GIST → **Baseline Imaging[c,n]** → **TKI[e,o] (see GIST-D)** → **Imaging to assess treatment response[c,q,r] and evaluate patient adherence**

- **Response or stable disease** → **Continue TKI (see GIST-D) obtain surgical consultation, consider resection[k,s,w,x]** →
  - **Resection[t]** → **See (GIST-3) for Postoperative Outcomes and Treatment**
  - or
  - **Continue TKI (see GIST-D) if resection not feasible** → **H&P and imaging[c,r] every 3–6 mo**
- **Progression[r]** → **See (GIST-5)**

[c]See Principles of Imaging (SARC-A).
[e]Mutational analysis may predict response to therapy with TKIs (See GIST-B).
[k]See Principles of Surgery for GIST (GIST-C).
[n]Consider baseline PET/CT, if using PET/CT during follow-up. PET/CT is not a substitute for CT.
[o]If life-threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider sunitinib.
[q]PET/CT may give indication of imatinib efficacy after 2–4 weeks of therapy when rapid readout of activity is necessary. Diagnostic abdominal/pelvic CT or MRI with contrast is indicated every 8–12 weeks; routine long-term PET/CT follow-up is rarely indicated. Frequency of response assessment imaging may be decreased if patient is responding to treatment.
[r]Progression may be determined by abdominal/pelvic CT or MRI with contrast with clinical interpretation; increase in tumor size in the presence of decrease in tumor density is consistent with drug efficacy or benefit. PET/CT scan may be used to clarify if CT or MRI are ambiguous.
[s]Collaboration between medical oncologist and surgeon is necessary to determine the appropriateness and timing of surgery, following major response or sustained stable disease. Maximal response may require treatment for 6 months or more to achieve.
[t]Imatinib can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications. If other TKIs, such as sunitinib or avapritinib are being used, therapy should be stopped at least one week prior to surgery and can be restarted based on clinical judgment or recovery from surgery.
[w]Consider resection or ablation/liver directed therapy for hepatic metastatic disease.
[x]Resection of metastatic disease, especially if complete resection can be achieved, has been associated with improved outcomes in patients on imatinib or sunitinib who have evidence of radiographic response, or limited disease progression.

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TREATMENT FOR PROGRESSIVE DISEASE

Progression[r]

- **Limited[aa]** →
  - Continue with the same dose of TKI[y,aa] and consider the following options for lesions progressing on imatinib:
    - Resection,[k] if feasible[t]
    - Ablation procedures or embolization or chemoembolization (category 2B)
    - Palliative RT (category 2B) for rare patients with bone metastases or
  - Dose escalation of imatinib[y] as tolerated or
  - Change to sunitinib[y] (category 1)

    AND
  - Imaging to reassess therapeutic response[c,r]

- **Generalized (widespread, systemic)[aa]** →
  - For performance status (PS) 0–2: and progression on imatinib:
  - Dose escalation of imatinib[y] as tolerated

    OR

    Change to sunitinib[y] (category 1)
  - If progression on sunitinib, then regorafenib (category 1)

    AND
  - Imaging to reassess therapeutic response[c,r]

→ If disease is progressing despite prior imatinib/sunitinib/regorafenib/ therapy, consider the following options:

Clinical trial
or
Consider other options listed in GIST-D (based on limited data)
or
Consider repeat tumor biopsy to potentially identify uncommon mutations that may have a corresponding targeted therapy
or
Best supportive care[z]

[c]See Principles of Imaging (SARC-A).
[k]See Principles of Surgery for GIST (GIST-C).
[r]Progression may be determined by abdominal/pelvic CT or MRI with contrast with clinical interpretation; increase in tumor size in the presence of decrease in tumor density is consistent with drug efficacy or benefit. PET/CT scan may be used to clarify if CT or MRI are ambiguous.
[t]Imatinib can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications. If other TKIs, such as sunitinib or avapritinib, are being used, therapy should be stopped at least one week prior to surgery and can be restarted based on clinical judgment or recovery from surgery.
[y]Clinical experience suggests that discontinuing TKI therapy, even in the setting of progressive disease, may accelerate the pace of disease progression and worsen symptoms.
[z]Reintroduction of a previously tolerated and effective TKI can be considered for palliation of symptoms. Consider continuation of TKI therapy life-long for palliation of symptoms as part of best supportive care.
[aa]Treatment with avapritinib can be continued for limited progression. There are no other appropriate treatment options for GIST progressing on avapritinib. Clinical trial is recommended.

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PRINCIPLES OF BIOPSY AND RISK STRATIFICATION FOR GIST

- **An endoscopic transmural biopsy would be favored over a percutaneous transperitoneal biopsy, if the risk for peritoneal seeding by the tumor is low. However, percutaneous image-guided biopsy may be appropriate for the confirmation of locally advanced or metastatic disease. Consideration of biopsy should be based on the suspected tumor type and extent of disease. Biopsy is necessary to confirm the diagnosis of primary GIST prior to the initiation of preoperative therapy.**

- **Morphologic diagnosis based on microscopic examination of histologic sections is the standard for GIST diagnosis. Several ancillary techniques are recommended in support of GIST diagnosis, including immunohistochemistry (IHC) for CD117, DOG1, and CD34 and molecular genetic testing for *KIT* and *PDGFRA* mutations.**

- **Diagnosis is based on the Principles of Pathologic Assessment (See SARC-B); referral to centers with expertise and experience in the diagnosis and management of GIST/sarcoma is recommended for cases with complex or unusual histopathologic features.**

- **Risk stratification:**
  - **Tumor size and mitotic rate are used to predict the malignant potential of GIST, although notoriously difficult to predict the biologic behavior of GIST based on pathologic features alone; thus, guidelines for risk stratification by tumor site have been developed.**
  - **Most gastric GISTs behave in an indolent manner, especially when less than 2 cm. See Table 1: Gastric GISTs: Proposed Guidelines for Assessing the Malignant Potential (GIST-A 2 of 3).**
  - **GIST of the small intestine tends to be more aggressive than its gastric counterpart. See Table 2: Non-Gastric GISTs: Proposed Guidelines for Assessing Malignant Potential (GIST-A 3 of 3).**
  - **GIST of the colon is most commonly seen in the rectum; colorectal GIST tends to have an aggressive biological behavior, and tumors with mitotic activity can recur and metastasize despite a small size of <2 cm.**

Continued

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PREDICTORS OF GIST BIOLOGIC BEHAVIOR

Table 1: Gastric GISTs: Proposed Guidelines for Assessing the Malignant Potential[1]

Tumor Size	Mitotic Rate[2]	Predicted Biologic Behavior
≤2 cm	≤5 mitoses/50 HPFs	Metastasis rate: 0%
	>5 mitoses/50 HPFs	Metastasis rate: 0%*
>2 cm to ≤5 cm	≤5 mitoses/50 HPFs	Metastasis rate: 1.9%
	>5 mitoses/50 HPFs	Metastasis rate: 16%
>5 cm to ≤10 cm	≤5 mitoses/50 HPFs	Metastasis rate: 3.6%
	>5 mitoses/50 HPFs	Metastasis rate: 55%
>10 cm	≤5 mitoses/50 HPFs	Metastasis rate: 12%
	>5 mitoses/50 HPFs	Metastasis rate: 86%

GISTs: Gastrointestinal stromal tumors; HPFs: High-power fields; *predicted rate based on tumor category with very small numbers

[1]Data from Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Sem Diag Path 2006;23:70-83.
[2]The mitotic rate should be measured in the most proliferative area of the tumor, and reported as the number of mitoses per 50 HPF of tissue· Per 50 HPF is a total of 5mm². For most modern microscopes, 20 to 25 HPF 40 x lenses/fields encompasses 5 mm². Laurini JA, Blanke CD, Cooper K, et al. Protocol for the Examination of Specimens From Patients With Gastrointestinal Stromal Tumor (GIST). Version 4.0.1.0, June 2017. Available at: https://cap.objects.frb.io/protocols/cp-gisofttissue-gist-17protocol-4010.pdf.

Continued

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PREDICTORS OF GIST BIOLOGIC BEHAVIOR

Table 2: Non-Gastric GISTs: Proposed Guidelines for Assessing the Malignant Potential[1]

Tumor Size	Mitotic Rate[2]	Predicted Biologic Behavior
≤2 cm	≤5 mitoses/50 HPFs	Metastasis rate: 0%
	>5 mitoses/50 HPFs	Metastasis rate: 50%–54%
>2 cm to ≤5 cm	≤5 mitoses/50 HPFs	Metastasis rate: 1.9%–8.5%
	>5 mitoses/50 HPFs	Metastasis rate: 50%–73%
>5 cm to ≤10 cm	≤5 mitoses/50 HPFs	Metastasis rate: 24%
	>5 mitoses/50 HPFs	Metastasis rate: 85%
>10 cm	≤5 mitoses/50 HPFs	Metastasis rate: 34%–52%
	>5 mitoses/50 HPFs	Metastasis rate: 71%–90%

GISTs: Gastrointestinal stromal tumors; HPFs: High-power fields

[1]Data from Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Sem Diag Path 2006;23:70-83.
[2]The mitotic rate should be measured in the most proliferative area of the tumor, and reported as the number of mitoses per 50 HPF of tissue· Per 50 HPF is a total of 5mm^2. For most modern microscopes, 20 to 25 HPF 40 x lenses/fields encompasses 5 mm^2. Laurini JA, Blanke CD, Cooper K, et al. Protocol for the Examination of Specimens From Patients With Gastrointestinal Stromal Tumor (GIST). Version 4.0.1.0, June 2017. Available at: https://cap.objects.frb.io/protocols/cp-gisofttissue-gist-17protocol-4010.pdf.

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PRINCIPLES OF MUTATION TESTING

- 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. 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. Testing for *KIT* and *PDGFRA* mutations is strongly recommended if TKIs are considered as part of the treatment plan since the presence of mutations (or absence of mutations) in specific regions of the *KIT* and *PDGFRA* genes are correlated with response (or lack of a response) to specific TKIs.

- Specific mutations in *KIT* or *PDGFRA* show some correlation with tumor phenotype, but mutations are not strongly correlated wih the biologic potential of individual tumors. The accumulated data show that *KIT* mutations are not preferentially present in high-grade tumors, and can also be found in small incidental tumors as well as tumors that have an indolent course. Similary, mutational analysis of *PDGFRA* cannot be used to predict the behavior of individual tumors.

- GIST tumors have different response rates to imatinib based upon the tumor mutation status: 90% for tumors that have a *KIT* exon 11 mutation, 50% for tumors that have a *KIT* exon 9 mutation and the likelihood of response improves with the use of imatinib 400 mg BID. Most *PDGFRA* mutations are associated with a response to imatinib, with the exception of D842V, which is unlikely to respond to imatinib and most other approved TKIs for GIST except avapritinib.

- Metastatic disease with acquired drug resistance is usually the result of secondary, imatinib-resistant mutations in *KIT* or *PDGFRA*. Sunitinib treatment is indicated for patients with imatinib-resistant tumors or imatinib intolerance. Regorafenib is indicated for patients with disease progression on imatinib and sunitinib. Referral to clinical trial is strongly recommended for patients with mutations resistant to imatinib, sunitinib, regorafenib, and avapritinib.

- About 10%–15% of GISTs lack mutation in *KIT* or *PDGFRA*. The vast majority of these GISTs have functional inactivation of the succinate dehydrogenase (SDH) complex, which can be detected by lack of expression of SDHB on IHC. Inactivation of the SDH complex may result from a mutation or from epigenetic silencing. A small minority of GISTs that retain SDH expression have alternative driver mutations.

- Testing for alternative driver mutations is indicated for tumors that are negative for *KIT* or *PDGFRA* mutations. Testing includes assessment for SDHB deficiency by IHC for gastric tumors and *SDH* mutation testing for SDHB-deficient tumors by IHC. In addition, next-generation sequencing (NGS) testing for alternative driver mutations (eg, *BRAF*, *NF1*, *NTRK*, and *FGFR* fusions) should be performed for non-gastric tumors or SDHB-positive tumors.

- GISTs with *SDH* mutation typically arise in the stomach in younger individuals, frequently metastasize, may involve lymph nodes, and usually grow slowly. They are usually resistant to imatinib. In the absence of *KIT* and *PDGFRA* mutations, only a subset of patients with advanced GISTs benefit from imatinib, although tumors known to be SDH deficient or having alternative drivers (eg, *NF1, BRAF*) are unlikely to benefit from imatinib. SDH-deficient tumors may benefit from therapy with sunitinib or regorafenib. Referral to a genetic counselor for germline testing assessment is recommended for all patients with SDH-deficient GISTs and those with GISTs that have *NF1 or SDH* mutations. Patients with SDH mutations are at risk of paraganglioma; 24-hour urine testing is recommended prior to surgery (See GIST-C).

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GENERAL 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; however, resection of pathologically enlarged nodes should be considered in patients with SDH-deficient GIST.
- As GIST tends to be very friable, every effort should be made not to violate the pseudocapsule of the tumor (ie, avoid tumor rupture – any tumor spillage or fracture, laceration of the tumor capsule with or without macroscopic spillage, piecemeal resection, and incisional biopsy occurring either before or at the time of the operation).
- 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. 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 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.

Unresectable or Metastatic GIST

Imatinib is the primary therapy for metastatic GIST. Surgery may be indicated for:
- Limited disease progression refractory to imatinib.
- Locally advanced or previously unresectable tumors or low-volume stage IV disease after a favorable response to systemic imatinib therapy.
- Management of symptomatic bleeding or obstruction.

Considerations Prior to Surgery
- Imatinib can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications. If other TKIs, such as sunitinib, regorafenib, or avapritinib, are being used, therapy should be stopped at least one week prior to surgery and can be restarted based on clinical judgment or recovery from surgery.
- Patients with SDH mutations are at risk of paraganglioma and therefore serum/urine catecholamine/metanephrine testing should be considered before an operation.

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SYSTEMIC THERAPY AGENTS AND REGIMENS FOR UNRESECTABLE OR METASTATIC GIST

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
First-line therapy for unresectable recurrent or metastatic disease	• Imatinib[a,1,2] (category 1) • Avapritinib[a,b,3] (for GIST with *PDGFRA* exon 18 mutation, including *PDGFRA* D842V mutations)		
Second-line therapy for unresectable or metastatic disease (progressive disease after imatinib)	• Sunitinib[a,4] (category 1)		
Third-line therapy for unresectable or metastatic disease (progressive disease after imatinib and sunitinib)	• Regorafenib[a,5] (category 1)		
Fourth-line therapy for unresectable or metastatic disease (progressive disease after imatinib, sunitinib, and regorafenib)	• Ripretinib[a,6]		• Sorafenib[7-9] • Nilotinib[10-11] • Dasatinib[12] (for patients with *PDGFRA* D842V mutation) • Pazopanib[13] • Everolimus + TKI[c,14] • Avapritinib[a,b,3]

[a]FDA-approved TKIs for the treatment of GIST.
[b]Indicated for GIST with *PDGFRA* exon 18 mutation, including *PDGFRA* D842V mutations.
[c]TKIs to be considered for use in combination with everolimus include imatinib, sunitinib, or regorafenib.

See references, on GIST-D (2 of 2)

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SYSTEMIC THERAPY AGENTS AND REGIMENS FOR UNRESECTABLE OR METASTATIC GIST

REFERENCES

[1]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.
[2]Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomized trial. Lancet 2004;364(9440):1127-1134.
[3]Heinrich M, Jones RL, von Mehren M, et al. Clinical response to avapritinib by RECIST and Choi Criteria in ≥4th line and PDGFRA exon 18 gastrointestinal stromal tumors (GIST). Connective Tissue Oncology Society Annual Meeting, Tokyo, Japan, November 15, 2019.
[4]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.
[5]Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:295-302.
[6]von Mehren M, Serrano C, Bauer S, et al: INVICTUS: A phase III, interventional, double-blind, placebo-controlled study to assess the safety and efficacy of ripretinib as fourth-line therapy in advanced GIST. 2019 ESMO Congress. Abstract LBA87.
[7]Montemurro M, Gelderblom H, Bitz U, et al. Sorafenib as third- or fourth-line treatment of advanced gastrointestinal stromal tumour and pretreatment including both imatinib and sunitinib, and nilotinib: A retrospective analysis. Eur J Cancer 2013;49:1027-1031.
[8]Kindler HL, Campbell NP, Wroblewski K, et al. Sorafenib (SOR) in patients (pts) with imatinib (IM) and sunitinib (SU)-resistant (RES) gastrointestinal stromal tumors (GIST): Final results of a University of Chicago Phase II Consortium trial. J Clin Oncol 2011;29:Abstract 10009.
[9]Park SH, Ryu MH, Ryoo BY, et al. Sorafenib in patients with metastatic gastrointestinal stromal tumors who failed two or more prior tyrosine kinase inhibitors: a phase II study of Korean gastrointestinal stromal tumors study group. Invest New Drugs 2012;30:2377-2383.
[10]Montemurro M, Schoffski P, Reichardt P, et al. Nilotinib in the treatment of advanced gastrointestinal stromal tumours resistant to both imatinib and sunitinib. Eur J Cancer 2009;45:2293-2297.
[11]Sawaki A, Nishida T, Doi T, et al. Phase 2 study of nilotinib as third-line therapy for patients with gastrointestinal stromal tumor. Cancer 2011;117:4633-4641.
[12]Trent JC, Wathen K, von Mehren M, et al. A phase II study of dasatinib for patients with imatinib-resistant gastrointestinal stromal tumor (GIST). J Clin Oncol 2011;29:Abstract 10006.
[13]Ganjoo KN, Villalobos VM, Kamaya A., et al. A multicenter phase II study of pazopanib in patients with advanced gastrointestinal stromal tumors (GIST) following failure of at least imatinib and sunitinib. Ann Oncol 2014;25(1):236-40.
[14]choffski P, Reichardt P, Blay JY, et al. A phase I-II study of everolimus (RAD001) in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors. Ann Oncol 2010;21(10):1990-1998.

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WORKUP

- Prior to the initiation of therapy, all patients should be evaluated and managed by a multidisciplinary team with expertise and experience in sarcoma
- H&P
- Consider evaluation for Gardner's syndrome[a]/familial adenomatous polyposis (FAP) if biopsy is diagnostic of desmoid (See NCCN Guidelines for Colorectal Cancer Screening)
- Appropriate imaging[b] of primary site as clinically indicated

→ Biopsy[c]

- → Anatomic location where progression would not be morbid → DESM-2
- → Anatomic location where progression would be morbid → DESM-3

[a]Gardner's syndrome is an autosomal dominant disorder characterized by a triad of colonic polyposis, osteoma, and soft tissue tumors. (Traill Z, et al. AJR Am J Roentgenol 1995;165:1460-1461).

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

[c]See Principles of Pathologic Assessment of Sarcoma Specimens (SARC-B).

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PRIMARY TREATMENT[d]

Anatomic location where progression would not be morbid → **Observation with imaging[b,e] and symptom management**

- **Stable/regression[f]** → **Continue observation with imaging[b,e]** (→ back to Observation with imaging and symptom management)
- **Progression[g]**
  - → **See DESM-4 for ongoing progression with potential morbidity or significant symptoms**
  - → **Consider ongoing observation with imaging[b,e]** (→ back to Observation with imaging and symptom management)

[b]See Principles of Imaging (SARC-A).
[d]For tumors that are symptomatic, or impairing or threatening in function, patients should be offered therapy with the decision based on the location of the tumor and potential morbidity of the therapeutic option.
[e]Optimal frequency for imaging depends on the anatomical location of tumor, risk of progression, and symptoms of disease progression. Imaging every 3 months is recommended. More frequent imaging may be indicated in symptomatic patients.
[f]Spontaneous regression has been reported in 20% of patients, supporting an initial period of observation in patients with newly diagnosed desmoid tumors (Gounder et al. N Engl J Med 2018;379:2417-2428).
[g]A course of ongoing observation is an appropriate option even for patients with disease progression, if the patient is minimally symptomatic and the anatomical location of the tumor is not critical.

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PRIMARY TREATMENT[d]

Anatomic location where progression would be morbid
- **Documented progression** → **DESM-4**
- **No documented progression**
  - **See DESM-4 if concerns for morbidity or significant symptoms**
  - **Consider short course of observation with imaging[b,e] and symptom management**
    - **Documented progression** → **DESM-4**
    - **Stable/regression[f]** → **Continue observation with imaging[b]** → (return to Consider short course of observation with imaging and symptom management)

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

[d]For tumors that are symptomatic, or impairing or threatening in function, patients should be offered therapy with the decision based on the location of the tumor and potential morbidity of the therapeutic option.

[e]Optimal frequency for imaging depends on the anatomical location of tumor, risk of progression, and symptoms of disease progression. Imaging every 3 months is recommended. More frequent imaging may be indicated in symptomatic patients.

[f]Spontaneous regression has been reported in 20% of patients, supporting an initial period of observation in patients with newly diagnosed desmoid tumors (Gounder et al. N Engl J Med 2018;379:2417-2428).

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PRIMARY TREATMENT

Anatomic location[h]

- **Truncal/extremity** →
  - **Surgery (if resectable)**[i]
    - **R0** → **Observation**
    - **R1**[j] → **Observation** or **Consider re-resection**[j] or **Adjuvant RT**[k] **(category 2B)**
    - **R2** → **Definitive RT** or **Systemic therapy** See (DESM-5) or **Radical surgery to be considered if other modalities fail** or **Ablation procedures** or **Observation**
  - **OR**
  - **Ablation procedures**[i]
  - **OR**
  - **Definitive RT**[i]
  - **OR**
  - **Systemic therapy**[i] See (DESM-5)
- **Intra-abdominal/ mesenteric** →
  - **Surgery (if resectable)**
  - **OR**
  - **Systemic therapy** See (DESM-5)

[h] RT is not generally recommended for desmoid tumors that are retroperitoneal/intra-abdominal. RT is generally only recommended for desmoid tumors that are in the extremity, superficial trunk, or head and neck.
[i] Based on the situation, any of these treatment options may potentially be first- or second-line.
[j] R1 margins are acceptable if achieving R0 margins would produce excessive morbidity. [Cates JM, et al. Am J Surg Pathol 2014;38(12):1707-1714; Crago AM, et al. Ann Surg 2013; 258(2):347-353; and Salas S, et al. J Clin Oncol 2011;29(26):3553-3558.]
[k] Consider RT for lesions where recurrence would be technically challenging to resect and would lead to significant morbidity.

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Timeframe for treatment response

- **Time to response less critical** → **PRIMARY TREATMENT (SYSTEMIC THERAPY)[l]**
  - **Preferred regimen:** Tamoxifen ± sulindac
  - **Other recommended regimens:** Sulindac[3] (or other nonsteroidal anti-inflammatory drugs [NSAIDs] including celecoxib) or Methotrexate/vinblastine or Methotrexate/vinorelbine or Toremifene or Imatinib

- **Time to response more critical** → **PRIMARY TREATMENT (SYSTEMIC THERAPY)[l]**
  - **Preferred regimen:** Sorafenib (category 1)
  - **Other recommended regimen:** Liposomal doxorubicin
  - **Useful in certain circumstances:** Doxorubicin ± dacarbazine

→ **FOLLOW-UP**
- H&P with appropriate imaging[b] every 3–6 mo for 2–3 y, then every 6–12 mo thereafter

→ **If progression consider:**
- Alternative Systemic Therapy not used for primary treatment
  OR
- Resection[j]
  OR
- Resection[j] + RT[h] (50 Gy) (if not previously irradiated)
  OR
- Definitive RT[h] (50–56 Gy) (if not previously irradiated)

[b]See Principles of Imaging (SARC-A).
[h]RT is not generally recommended for desmoid tumors that are retroperitoneal/intra-abdominal. RT is generally only recommended for desmoid tumors that are in the extremity, superficial trunk, or head and neck.
[j]R1 margins are acceptable if achieving R0 margins would produce excessive morbidity. [Cates JM, et al. Am J Surg Pathol 2014;38(12):1707-1714; Crago AM, et al. Ann Surg 2013;258(2):347-353; and Salas S, et al. J Clin Oncol 2011;29(26):3553-3558).
[l]See DESM-5A for references for regimens.

See references, DESM-5A

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REFERENCES

Tamoxifen ± sulindac

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.

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.

Sulindac

Tsukada K, Church JM, Jagelman DJ, et al. Noncytotoxic therapy for intra-abdominal desmoid tumor in patients with familial adenomatous polyposis. Dis Colon Rectum 1992;35:29-33.

Methotrexate + vinblastine

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.

Methotrexate + vinorelbine

Weiss AJ, Horowitz S, Lackman RD. Therapy of desmoid tumors and fibromatosis using vinorelbine. Am J Clin Oncol 1999;22:193-195.

Toremifine

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

Imatinib

Chugh R, Wathen JK, Patel SR, et al. Efficacy of imatinib in aggressive fibromatosis: Results of a phase II multicenter Sarcoma Alliance for Research through Collaboration (SARC) trial. Clin Cancer Res 2010;16:4884-4891.

Penel N, Le Cesne A, Bui BN, et al. Imatinib for progressive and recurrent aggressive fibromatosis (desmoid tumors): an FNCLCC/French Sarcoma Group phase II trial with a long-term follow-up. Ann Oncol 2011;22:452-457.

Sorafenib

Gounder MM, Lefkowitz RA, Keohan ML, et al. Activity of sorafenib against desmoid tumor/deep fibromatosis. Clin Cancer Res 2011;17:4082-4090.

Liposomal doxorubicin

Constantinidou A, Jones RL, Scurr M, et al. Pegylated liposomal doxorubicin, an effective, well-tolerated treatment for refractory aggressive fibromatosis. Eur J Cancer 2009;45:2930-2934.

Doxorubicin ± dacarbazine

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

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

de Camargo VP, Keohan ML, D'Adamo DR, et al. Clinical outcomes of systemic therapy for patients with deep fibromatosis (desmoid tumor). Cancer 2010;116:2258-2265.

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DIAGNOSIS	HISTOLOGY	TREATMENT
Rhabdomyosarcoma (RMS)[a,b]	Pleomorphic RMS[c] →	Recommend treating like soft tissue sarcoma[e]
	Non-pleomorphic RMS[d] (includes alveolar and embryonal) →	• Referral to institutions with expertise in treating patients with RMS is strongly recommended • Multidisciplinary evaluation involving pediatric, medical, surgical, and radiation oncologists is strongly encouraged • Multimodality treatment planning and risk stratification is required[f]

[a]RMS that is identified within another histology should be treated as the original histology. This pathway refers to patients diagnosed with pure RMS after full slide review.
[b]PET or PET/CT scan may be useful for initial staging because of the possibility of nodal metastases and the appearance of unusual sites of initial metastatic disease in adult patients.
[c]Not to be confused with anaplastic variant in children.
[d]Up to 13% of RMS in younger patients may have anaplastic features and should not be confused with the high-grade tumors seen in adults designated as pleomorphic RMS.
[e]Pleomorphic RMS is usually excluded from RMS and soft tissue sarcoma randomized clinical trials. Consideration for treatment according to soft tissue sarcoma may be reasonable, including choices for systemic therapy. See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F).
[f]Systemic chemotherapy options for RMS may be different than those used with other soft tissue sarcoma histologies. See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-F).

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PRINCIPLES OF IMAGING

GENERAL

- CT and MRI performed with contrast is recommended throughout the guideline unless contraindicated or otherwise noted.
- As appropriate, abdominal/pelvic MRI with contrast can be substituted for abdominal/pelvic CT if contraindicated (ie, due to dye allergy).
- If obtaining abdominal/pelvic CT, chest CT may be performed without contrast unless simultaneously attained with contrast-enhanced abdominal/pelvic CT.
- Chest imaging without contrast preferred unless contrast is needed for mediastinal imaging.
- If recurrent disease, follow imaging recommendations for Workup, then use Follow-up recommendations per appropriate primary treatment pathway.
- PET/CT scan may be useful in staging, prognostication, grading, and determining response to neoadjuvant therapy.
- In addition to recommendations below, additional imaging studies to consider as part of the workup and follow-up, based on histologic subtype, are indicated as follows:
  - Abdominal/pelvic CT for myxoid/round cell liposarcoma, epithelioid sarcoma, angiosarcoma, and leiomyosarcoma
  - MRI of total spine for myxoid/round cell liposarcoma
  - CNS imaging with MRI (or CT if MRI is contraindicated) for alveolar soft part sarcoma and angiosarcoma, and left sided cardiac sarcoma
  - Pelvic CT imaging for lower-extremity well-differentiated liposarcoma

EXTREMITY/BODY WALL, HEAD/NECK

Workup

- Primary tumor imaging using MRI with and without contrast ± CT with contrast is recommended.
  - Other imaging studies such as angiogram and plain radiograph may be warranted in certain circumstances.
- Chest imaging
  - X-ray or CT without contrast (preferred)

Follow-up

- General considerations for assessing primary tumor site in follow-up
  - Obtain imaging of the primary site after neoadjuvant therapy, postoperatively and periodically based on estimated risk of locoregional recurrence.
  - MRI with and without contrast and/or CT with contrast is recommended.
  - In patients with no radiographic evidence of disease, imaging of primary site, chest, and other sites at risk of metastatic disease is recommended every 3–6 months for 2–3 years, then every 6 months for the next 2 years, then annually.
  - For patients with known radiographic evidence of disease, imaging of known sites of metastatic disease is recommended every 2–3 months.
  - Consider ultrasound for small lesions that are superficial. Ultrasound should be performed by an ultrasonographer experienced in musculoskeletal disease.[1]
- Low risk for distant recurrence
  - Consider chest imaging every 6–12 months. X-ray or CT is preferred. Contrast may be used if also imaging abdomen/pelvis.
- Intermediate/high risk for distant recurrence
  - Chest imaging using x-ray or CT is recommended every 3–6 months for 2–3 years, then every 6 months for the next 2 years, then annually.

[1] Choi H, Varma DGK, Fornage BD, et al. Soft-tissue sarcoma: MR imaging vs sonography for detection of local recurrence after surgery. AJR Am J Roentgenol 1991;157:353-358.

Continued

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PRINCIPLES OF IMAGING

RETROPERITONEAL/INTRA-ABDOMINAL

Workup
- Primary tumor imaging with chest/abdominal/pelvic CT ± abdominal/pelvic MRI is recommended.[a]

Follow-up
- Obtain chest imaging, x-ray, or CT (preferred).[a]
- Obtain imaging of the primary site after neoadjuvant therapy, postoperatively and periodically based on estimated risk of locoregional recurrence.
- In patients with no radiographic evidence of disease, imaging of primary site, chest, and other sites at risk of metastatic disease is recommended every 3–6 months for 2–3 years, then every 6 months for the next 2 years, then annually.
- For patients with known radiographic evidence of disease, imaging of known sites of metastatic disease is recommended every 2–3 months.
- Imaging may include chest/abdominal/pelvic CT, or chest CT without contrast and abdominal/pelvic MRI with contrast.

GIST

Workup
- For very small GIST <2 cm: Perform abdominal/pelvic CT with contrast and/or abdominal/pelvic MRI with contrast.
- For all other GIST:
  - Abdominal/pelvic CT with contrast and/or abdominal/pelvic MRI with contrast
  - Chest imaging using x-ray or CT

Response Assessment

Resectable disease with significant morbidity
- Obtain baseline abdominal/pelvic CT and/or MRI.
- Consider PET/CT
  - Obtain baseline PET/CT if using PET/CT during follow-up; PET is not a substitute for CT.

Response Assessment (continued)
- Imaging to assess response to preoperative TKI
  - Abdominal/pelvic CT or MRI is indicated every 8–12 weeks
  - PET may give indication of TKI activity after 2–4 weeks of therapy when rapid readout of activity is necessary
- Progression may be determined by abdominal/pelvic CT or MRI with clinical interpretation; PET/CT may be used to clarify if CT or MRI is ambiguous.
- For R2 resection or discovery of metastatic disease, assess response to postoperative TKI using abdominal/pelvic CT or MRI every 8–12 weeks .

Definitively unresectable, recurrent, or metastatic disease
- Obtain baseline abdominal/pelvic CT and/or MRI
- Consider imaging of chest intermittently
- Consider PET/CT
  - Obtain baseline PET/CT if using PET/CT during follow-up; PET is not a substitute for CT.
- Imaging to assess response to TKI
- Abdominal/pelvic CT or MRI every 8–12 weeks of initiating therapy; in some patients, it may be appropriate to image before 3 months.
- Progression may be determined by abdominal/pelvic CT or MRI with clinical interpretation; PET/CT may be used to clarify if CT or MRI is ambiguous.

Follow-up
- For completely resected primary disease, perform abdominal/pelvic CT every 3–6 months for 3–5 years, then annually.
  - Less frequent imaging surveillance may be acceptable for low-risk or very small tumors (<2 cm).
  - More frequent imaging surveillance may be required for patients with high-risk disease who discontinue TKI therapy.
- For incompletely resected disease or discovery of metastatic disease during surgery, perform abdominal/pelvic CT every 3–6 months.

[a]Well-differentiated liposarcoma does not require chest imaging.

Continued

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PRINCIPLES OF IMAGING

Follow-up (continued)
- **Progression may be determined by CT or MRI with clinical interpretation; PET/CT may be used to clarify if CT or MRI are ambiguous.**
- **After treatment for progressive disease, reassess therapeutic response with abdominal/pelvic CT or MRI.**
  - **Consider PET/CT only if CT results are ambiguous.**

DESMOID TUMORS (Aggressive Fibromatosis)
Workup
- **Primary site imaging with CT or MRI as indicated**

Follow-up
- **Imaging with CT or MRI every 3–6 months for 2–3 years, then every 6–12 months thereafter**
- **Ultrasound may be considered for select locations (ie, abdominal wall) for long-term follow-up. Ultrasound should be done by an ultrasonographer experienced in musculoskeletal disease.[1]**

[1]Choi H, Varma DGK, Fornage BD, et al. Soft-tissue sarcoma: MR imaging vs sonography for detection of local recurrence after surgery. AJR Am J Roentgenol 1991;157:353-358.

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PRINCIPLES OF PATHOLOGIC ASSESSMENT OF SARCOMA SPECIMENS

- **Biopsy should establish malignancy, provide a specific diagnosis where possible, and provide a grade where appropriate or feasible, recognizing that limited biopsy material may underestimate grade.**
- **In patients without a definitive diagnosis following initial biopsy due to limited sampling size, repeat image-guided core needle biopsy should be considered to make a diagnosis.**
- **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 IHC, 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, such as the WHO Classification of Tumours of Soft Tissue and Bone[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), NCI system, or appropriate diagnosis-specific grading system if applicable**
  - **Necrosis**
    - **Present or absent**
    - **Microscopic or macroscopic**
    - **Approximate extent (percentage)**
  - **Status of margins of excision**
    - **Uninvolved**
    - **Involved (state which margins)**
    - **Close (state which margins and measured distance)**
  - **Status of lymph nodes**
    - **Site**
    - **Number examined**
    - **Number positive**
  - **Results of ancillary studies[1]**
    - **Type of testing (ie, electron microscopy, IHC, molecular genetic analysis)**
    - **Where performed**
  - **Additional tumor features of potential clinical value**
    - **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-2 through ST-6)**

[1] See Principles of Ancillary Techniques Useful in the Diagnosis of Sarcomas (SARC-C).
[2] Fletcher CDM, Bridge JA, Hogendoorn P, Mertens F. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Soft Tissue and Bone, Fourth Edition. IARC, Lyon, 2013.

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PRINCIPLES OF ANCILLARY TECHNIQUES USEFUL IN THE DIAGNOSIS OF SARCOMAS

Morphologic diagnosis based on microscopic examination of histologic sections remains the gold standard for sarcoma diagnosis. However, several ancillary techniques are useful in support of morphologic diagnosis, including IHC, classical cytogenetics, electron microscopy, and molecular genetic testing. Molecular genetic testing has emerged as a particularly powerful ancillary testing approach since many sarcoma types harbor characteristic genetic aberrations, including single base pair substitutions, deletions and amplifications, and translocations. Most molecular testing utilizes fluorescence in situ hybridization (FISH) approaches or polymerase chain reaction (PCR)-based methods and next-generation sequencing (NGS)-based methods.[1] Recurrent genetic aberrations in sarcoma[2] are listed below:

TUMOR	ABERRATION	GENE(S) INVOLVED
Malignant Round Cell Tumors		
Alveolar RMS	t(2;13)(q35;q14) t(1;13)(p36;q14) t(X;2)(q13;q35)	*PAX3-FOXO1* *PAX7-FOXO1* *PAX3-AFX*
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	*EWSR1-WT1*
Embryonal RMS	Complex alterations	Multiple, *MYOD1* mutation
Ewing sarcoma/peripheral neuroectodermal tumor	t(11;22)(q24;q12) t(21;22)(q22;q12) t(2;22)(q33;q12) t(7;22)(p22;q12) t(17;22)(q12;q12) inv(22)(q12q;12) t(16;21)(p11;q22)	*EWSR1-FLI1* *EWSR1-ERG* *EWSR1-FEV* *EWSR1-ETV1* *EWSR1-E1AF* *EWSR1-ZSG* *FUS-ERG*
Undifferentiated round cell sarcoma	t(4;19)(q35;q13) or t(10;19)(q26;q13) inv(X)(p11.4p11.22)	*CIC-DUX4*[3] *BCOR-CCNB3*[4]

[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. For example, additional genetic aberrations can be found in alveolar RMS, including *PAX3-NCOA1*, *PAX3-NCOA2*, and *PAX3-INO80D*. *NCOA2* gene rearrangements and *MyoD* mutation have been identified in spindle cell RMS. Receptor tyrosine kinase/*RAS*/*PIK3CA* aberrations are found in 93% of RMS cases. *MIR143-NOTCH* fusion has recently been identified in glomus tumor. Loss of *TSC1* (9q34) or *TSC2* (16p13.3) (mTOR pathway) or gene fusions of the *TFE3* gene (microphthalmia-associated transcription factor family) have been identified in PEComa.

[3]Yoshimoto T, Tanaka M, Homme M, et al. *CIC-DUX4* induces small round cell sarcomas distinct from Ewing sarcoma. Cancer Res 2017;77(11):2927-2937.

[4]Kao YC, Owosho AA, Sung YS, et al. BCOR-CCNB3-fusion positive sarcomas: A clinicopathologic and molecular analysis of 36 cases with comparison to morphologic spectrum and clinical behavior of other round cell sarcomas. Am J Surg Path 2018;42(5):604-615.

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PRINCIPLES OF ANCILLARY TECHNIQUES USEFUL IN THE DIAGNOSIS OF SARCOMAS

TUMOR	ABERRATION	GENE(S) INVOLVED
Lipomatous Tumors		
Atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLS)	Supernumerary ring chromosomes; giant marker chromosomes	Amplification of region 12q14-15, including *MDM2, CDK4, HMGA2, SAS, GLI*
Dedifferentiated liposarcoma	Same as for ALT/WDLS	Same as for ALT/WDLS
Myxoid/round cell liposarcoma	t(12;16)(q13;p11) t(12;22)(q13;q12)	*FUS-DDIT3* *EWSR1-DDIT3*
Pleomorphic liposarcoma	Complex alterations	Unknown
Other Sarcomas		
Alveolar soft part sarcoma	der(17)t(X;17)(p11;q25)	*ASPL-TFE3*
Angiomatoid fibrous histiocytoma	t(12;22)(q13;q12) t(2;22)(q33;q12) t(12;16)(q13;p11)	*EWSR1-ATF1* *EWSR1-CREB1* *FUS-ATF1*
Clear cell sarcoma	t(12;22)(q13;q12) t(2;22)(q33;q12)	*EWSR1-ATF1* *EWSR1-CREB1*
Congenital/infantile fibrosarcoma	t(12;15)(p13;q25)	*ETV6-NTRK3*[5]
Dermatofibrosarcoma protuberans	t(17;22)(q21;q13) and derivative ring chromosomes	*COL1A1-PDGFB*
Desmoid fibromatosis	Trisomy 8 or 20; loss of 5q21	*CTNNB1* or *APC* mutations
High-grade endometrial stromal sarcoma	t(10;17)(q22;p13) t(x;22)(p11;q13)	*YWHAE-NUTM2* *ZC3H7B-BCOR*[6]
Epithelioid hemangioendothelioma	t(1;13)(p36;q25) t(X;11)(q22;p11.23)	*WWTR1-CAMTA1* *YAP1 - TFE3*

[5]Yamamoto H, Yoshida A, Taguchi K, et al. ALK, ROS1 and NTRK3 gene rearrangements in inflammatory myofibroblastic tumours. Histopathology 2016;69:72-83.
[6]Lewis N, Soslow RA, Delair DF, et al. ZC3H7B-BCOR high-grade endometrial stromal sarcomas: a report of 17 cases of a newly defined entity. Mod Pathol 2018;31:674-684.

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PRINCIPLES OF ANCILLARY TECHNIQUES USEFUL IN THE DIAGNOSIS OF SARCOMAS

TUMOR	ABERRATION	GENE(S) INVOLVED
Other Sarcomas - continued		
Epithelioid sarcoma	Inactivation, deletion, or mutation of *INI1 (SMARCB-1)*	*INI1 (SMARCB-1)*
Extrarenal rhabdoid tumor	Inactivation of *INI1 (SMARCB-1)*	*INI1 (SMARCB-1)*
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12) t(9;17)(q22;q11) t(9;15)(q22;q21) t(3;9)(q11;q22)	*EWSR1-NR4A3* *TAF2N-NR4A3* *TCF12-NR4A3* *TFG-NR4A3*
Sporadic and familial GIST Carney-Stratakis syndrome (gastric GIST and paraganglioma)	Activating kinase mutations Krebs cycle mutation	*KIT* or *PDGFRA* *Germline SDH* subunit mutations
Inflammatory myofibroblastic tumor (IMT)	t(1;2)(q22;p23) t(2;19)(p23;p13) t(2;17)(p23;q23) t(2;2)(p23;q13) t(2;11)(p23;p15) inv(2)(p23;q35)	*TPM3-ALK*[5] *TPM4-ALK*[5] *CLTC-ALK*[5] *RANBP2-ALK*[5] *CARS-ALK*[5] *ATIC-ALK*[5]
Leiomyosarcoma	Complex alterations	Unknown
Low-grade fibromyxoid sarcoma	t(7;16)(q33;p11) t(11;16)(p11;p11)	*FUS-CREB3L2* *FUS-CREB3L1*
Malignant peripheral nerve sheath tumor		*NF1, CDKN2A* and *EED* or *SUZ12*
Mesenchymal chondrosarcoma	t(8;8)(q13;q21)	*HEY1 - NCOA2*
Solitary fibrous tumor	inv(12)(q13q13)	*NAB2 - STAT6*
Synovial sarcoma	t(X;18)(p11;q11) t(X;18)(p11;q11) t(X;18)(p11;q11)	*SS18-SSX1* *SS18-SSX2* *SS18-SSX4*
Tenosynovial giant cell tumor/pigmented villonodular synovitis (TGCT/PVNS)	t(1;2)(p13;q35)	*CSF1*

[5]Yamamoto H, Yoshida A, Taguchi K, et al. ALK, ROS1 and NTRK3 gene rearrangements in inflammatory myofibroblastic tumours. Histopathology 2016;69:72-83.

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PRINCIPLES OF SURGERY

Multidisciplinary team management including plastic, reconstructive, and vascular surgeons is recommended.

Biopsy

- 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. Core needle biopsy is preferred; however, an open incisional biopsy may be considered by an experienced surgeon. Image-guided needle biopsy may be indicated for extremity/truncal sarcomas.

Surgery

- The surgical procedure necessary to resect the tumor with oncologically appropriate margins should be used. Close margins may be necessary to preserve critical neurovascular structures, bones, joints, etc.
- Evaluate preoperatively for rehabilitation (see SARC-D 2 of 2)
- 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 do not need to 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 RT.

  If closed suction drainage is used, the drains should exit the skin close to the edge of the surgical incision (in case re-resection or radiation is indicated).

Resection Margins

- Surgical margins should be documented by both the surgeon and the pathologist evaluating the 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 RT should be given for a close soft tissue margin or a microscopically positive margin on bone, major blood vessels, or a major nerve.
- ALT/WDLS: RT is not indicated in most cases.
- In selected cases when margin status is uncertain, consultation with a radiation oncologist is recommended.
  - R0 resection - No residual microscopic disease
  - R1 resection - Microscopic residual disease
  - R2 resection - Gross residual disease
- Special consideration should be given to infiltrative histologies such as myxofibrosarcoma, dermatofibrosarcoma protuberans (DFSP), and angiosarcoma.

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PRINCIPLES OF SURGERY

Multidisciplinary team management including plastic, reconstructive, and vascular surgeons is recommended.

Limb-Sparing 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 should be made for patient preference or if gross total resection of the tumor is expected to render the limb nonfunctional.

Rehabilitation
Rehabilitation evaluation is recommended preoperatively, postoperatively, and in the outpatient setting in order to optimize functional outcomes and quality of life.

Prior to amputation or limb-sparing surgery, rehabilitation Physical Medicine and Rehabilitation (PM&R) physician consultation should be offered to provide education about functional outcomes of the planned surgery, set postoperative goals, and establish care for longitudinal follow-up.

In the immediate postoperative period, patients should receive a functional evaluation, typically by a physical therapist, to ensure that they are able to safely discharge home. If further rehabilitation is needed, PM&R and occupational therapist should also evaluate the patient.

The oncology rehabilitation (PM&R, physical/occupational therapy) team and the orthopedic/surgical oncology team should be well-coordinated to optimize patient care. This includes communicating the rehabilitation/surgical restrictions, precautions, and rehabilitation protocol prior to initiating therapy.

When possible, the rehabilitation plan of care should be overseen by a PM&R physician, who can prescribe medications, order and interpret diagnostic tests, and prescribe/oversee therapies. The plan should consider oncology treatment-related side effects and comorbidities such as lymphedema, chemotherapy-induced neuropathy and fatigue, radiation fibrosis, and impaired bone healing that may impact treatment.

Pain management should be integrated into the rehabilitation program to optimize outcomes. Phantom limb pain should be treated early. Interventions may include mirror therapy, motor imagery, massage, oral and topical analgesics, coping strategies, and patient education.

Special consideration should be given when progressing rehabilitation interventions for limb-sparing surgeries (ie, oncologic proximal humerus replacement, proximal tibia replacement, internal hemipelvectomy) that require adequate scar tissue formation essential for functional joint recovery.

The rehabilitation plan must address any psychological distress associated with the surgery, and include referrals to appropriate mental health providers when necessary. All patients should be connected to peer support groups.

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PRINCIPLES OF RADIATION THERAPY FOR SOFT TISSUE SARCOMA

Radiation Therapy Guidelines for Soft Tissue Sarcoma of Extremity/Body Wall/Head and Neck[1,2,3]

- Potential benefits of preoperative radiation therapy:
  - Lower total radiation dose
  - Shorter course of treatment
  - Treatment field size is frequently smaller
    - Associated with less late radiation toxicity and improved extremity function
  - The primary sarcoma is a defined target for radiation treatment planning
  - Treatment delivery not impacted by postoperative wound healing issues
  - Potential downstaging of borderline resectable extremity sarcomas for possible limb salvage
  - Ability to restage patients after preoperative radiation but before wide resection
    - Presence of distant metastases would prevent proceeding with a noncurative surgery

- Based on the pros and cons of preoperative versus postoperative radiation, the panel has expressed a general preference for preoperative radiation.

- Preoperative RT[4,5,6,7]
  - 50 Gy external beam RT (EBRT)[8] (surgery with clips to follow)
  - Following preoperative 50 Gy EBRT and surgery, for positive margins, consider observation or RT boost in select situations[9]
  - If using RT boost, consider:[9,10]
    - EBRT:
      - 16–18 Gy for microscopic residual disease[11,12]
      - 20–26 Gy for gross residual disease[11]
    - Brachytherapy (low dose-rate):
      - 16–18 Gy for microscopic residual disease
      - 20–26 Gy for gross disease
    - Brachytherapy (high dose-rate):
      - 14–16 Gy at approximately 3–4 Gy BID for microscopic residual disease
      - 18–24 Gy for gross residual disease

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PRINCIPLES OF RADIATION THERAPY FOR SOFT TISSUE SARCOMA

Radiation Therapy Guidelines for Soft Tissue Sarcoma of Extremity/Body Wall/Head and Neck[1,2,3]

- **Potential benefits of postoperative radiation therapy:**
  - **Allow for definitive pathologic assessment, including margin status, where there was not a definitive indication for preoperative radiation.**
  - **Lower rate of postoperative wound healing complications, especially in the lower extremity.**

- **Based on the pros and cons of preoperative versus postoperative radiation, the panel has expressed a general preference for preoperative radiation.**

- **Postoperative RT following surgery[11] with clips**
  - **EBRT (50 Gy)[8,10]**
    - **Boost dose:**
      - **Negative margins: 10–16 Gy**
      - **Microscopically positive margins: 16–18 Gy[11,12]**
      - **Gross residual disease: 20–26 Gy[11]**
  - **Brachytherapy ± EBRT**
    - **Positive margins:[11]**
      - **Low dose-rate (16–20 Gy) or high dose-rate equivalent (14–16 Gy) brachytherapy + 50 Gy EBRT[10]**
    - **Negative margins:[11]**
      - **45 Gy low dose-rate or high dose-rate equivalent (ie, 36 Gy in 3.6 Gy BID over 10 fractions in 5 days)[10] brachytherapy**

See references on SARC-E 4 of 4

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PRINCIPLES OF RADIATION THERAPY FOR SOFT TISSUE SARCOMA

Radiation Therapy Guidelines for Retroperitoneal/Intra-Abdominal Sarcoma[13,14]

- **Preoperative RT (surgery with clips to follow)[15,16]**
  - **50 Gy EBRT[8,16]**
    - ◊ **Consider IORT boost for known or suspected positive margins at the time of surgery**
      - **– 10–12.5 Gy for microscopically positive disease**
      - **– 15 Gy for gross disease**
    - ◊ **A postoperative EBRT boost is discouraged. If deemed necessary in highly selected cases, consider the following doses:**
      - **– 16–18 Gy for microscopic disease[11,12]**
      - **– 20–26 Gy for gross residual disease,[11] if normal tissue spared (likely requiring tissue displacement with omentum or other biologic or synthetic tissue spacer)**

      OR
    - ◊ **In experienced centers only – 45–50 Gy in 25–28 fractions to entire CTV with dose-painted simultaneous integrated boost (SIB) to total dose of 57.5 Gy in 25 fractions to the high-risk retroperitoneal margin jointly defined by the surgeon and radiation oncologist (no boost after surgery)[17,18]**

See references on SARC-E 4 of 4

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PRINCIPLES OF RADIATION THERAPY FOR SOFT TISSUE SARCOMA

[1]If an R1 or R2 resection is anticipated, clips to high-risk areas for recurrence are encouraged. When EBRT is used, sophisticated treatment planning with IMRT and/or protons can be used to improve the therapeutic ratio:
- 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;
- 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.

[2]Haas RL, DeLaney TF, O'Sullivan B, et al. Radiotherapy for management of extremity soft tissue sarcomas: why, when, and where? Int J Radiat Oncol Biol Phys, 2012; 84:572-580.

[3]These guidelines are intended to treat the adult population. For adolescent and young adult patients, refer to the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology.

[4]Li XA, Chen X, Zhang Q, et al. Margin reduction from image guided radiation therapy for soft tissue sarcoma: Secondary analysis of Radiation Therapy Oncology Group 0630 results. Pract Radiat Oncol 2016 Jul-Aug;6(4):e135-40.

[5]Wang D, Zhang Q, Eisenberg BL, et al. Significant reduction of late toxicities in patients with extremity sarcoma treated with image-guided radiation therapy to a reduced target volume: Results of Radiation Therapy Oncology Group RTOG-0630 Trial. J Clin Oncol 2015 Jul 10;33(20):2231-2238.

[6]Bahig H, Roberge D, Bosch W, et al. Agreement among RTOG sarcoma radiation oncologists in contouring suspicious peritumoral edema for preoperative radiation therapy of soft tissue sarcoma of the extremity. Int J Radiat Oncol Biol Phys 2013 Jun 1;86(2):298-303.

[7]Wang D, Bosch W, Roberge D, et al. RTOG sarcoma radiation oncologists reach consensus on gross tumor volume and clinical target volume on computed tomographic images for preoperative radiotherapy of primary soft tissue sarcoma of extremity in Radiation Therapy Oncology Group studies. Int J Radiat Oncol Biol Phys 2011 Nov 15;81(4):e525-e528.

[8]EBRT in 1.8 to 2.0 Gy per fraction.

[9]There are data to suggest that some patients with positive margins following preoperative RT such as those with low-grade, well-differentiated liposarcoma and a focally,"planned" positive margin on an anatomically fixed critical structure may do well without a boost. (Gerrand CH, et al. J Bone Joint Surg Br 2001;83:1149-1155). There are also data to suggest that delivery of a boost for positive margins does not improve local control. Since delivery of a post-op boost does not clearly add benefit, the decision should be individualized and the potential toxicities should be carefully considered. (Al Yami, et al. Int J Radiat Oncol Biol Phys 2010;77:1191-1107; Pan, et al. J Surg Oncol 2014;110:817-822).

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

[11]See Resection Margins on Principles of Surgery (SARC-D).

[12]RT does not substitute for definitive surgery with negative margins; re-resection may be necessary.

[13]Baldini EH, Wang D, Haas RL, et al. Treatment guidelines for preoperative radiation therapy for retroperitoneal sarcoma: Preliminary consensus of an international expert panel. Int J Radiat Oncol Biol Phys 2015;92:602-612.

[14]Postoperative RT following surgery is discouraged for retroperitoneal/intra-abdominal sarcoma. If RT is not given prior to surgical resection, consider follow-up with possible preoperative EBRT at time of localized recurrence. See (SARC-D). In highly select cases where a postoperative EBRT boost is considered, intraoperative placement of clips at areas of high risk for recurrence or anticipated R1/R2 resection is encouraged. When EBRT is used in these rare situations, sophisticated treatment planning with IMRT, IGRT, and/or protons can be used to improve the therapeutic ratio.
- Trans-Atlantic RPS Working Group. Management of primary retroperitoneal sarcoma (RPS) in the adult: a consensus approach from the Trans-Atlantic RPS Working Group. Ann Surg Oncol 2015;22:256-263.
- Musat E, Kantor G, Caron J, et al. Comparison of intensity-modulated postoperative radiotherapy with conventional postoperative radiotherapy for retroperitoneal sarcoma. Cancer Radiother 2004;8:255-261.
- Swanson EL, Indelicato DJ, Louis D, et al. Comparison of three-dimensional (3D) conformal proton radiotherapy (RT), 3D conformal photon RT, and intensity-modulated RT for retroperitoneal and intra-abdominal sarcomas. Int J Radiat Oncol Biol Phys 2012 Aug 1;83(5):1549-57.

[15]Baldini EH, Wang D, Haas RL, et al. Treatment guidelines for preoperative radiation therapy for retroperitoneal sarcoma: Preliminary consensus of an international expert panel. Int J Radiat Oncol Biol Phys 2015 Jul 1;92(3):602-612.

[16]Baldini EH, Bosch W, Kane JM, et al. Retroperitoneal sarcoma (RPS) high risk gross tumor volume boost (HR GTV boost) contour delineation agreement among NRG sarcoma radiation and surgical oncologists. Ann Surg Oncol 2015 Sep;22(9):2846-2852.

[17]Data are still limited on the use of HDR brachytherapy for sarcomas. Until more data are available, HDR fraction sizes are recommended to be limited to 3–4 Gy Nag S, et al. Int J Radiat Oncol Biol Phys 2001;49:1033-1043.

[18]Tzeng CW, Fiveash JB, Popple RA, et al. Preoperative radiation therapy with selective dose escalation to the margin at risk for retroperitoneal sarcoma. Cancer 2006;107:371-379.

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

Soft Tissue Sarcoma Subtypes with Non-Specific Histologies
(Regimens Appropriate for General STS;[d,e] see other sections for histology-specific recommendations)

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Neoadjuvant/Adjuvant Therapy	• AIM (doxorubicin, ifosfamide, mesna)[1-4] • Ifosfamide, epirubicin, mesna[5]	• AD (doxorubicin, dacarbazine)[1,2,6,7]- if ifosfamide is not considered appropriate • Doxorubicin[1,2,8] • Gemcitabine and docetaxel[9,10]	• Ifosfamide[5,8,9-13]
First-Line Therapy Advanced/ Metastatic	• Anthracycline-based regimens: ▸ Doxorubicin[1,2,8] ▸ Epirubicin[14] ▸ Liposomal doxorubicin[15] ▸ AD (doxorubicin, dacarbazine)[1,2,6,7] ▸ AIM (doxorubicin, ifosfamide, mesna)[1-4] ▸ MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[1,2,16,17] ▸ Ifosfamide, epirubicin, mesna[5]	• Gemcitabine-based regimens: ▸ Gemcitabine ▸ Gemcitabine and docetaxel[9,10] ▸ Gemcitabine and vinorelbine[11] ▸ Gemcitabine and dacarbazine[12]	• Pazopanib[18] (patients ineligible for IV chemotherapy) • Larotrectinib[j,19] (for *NTRK* gene-fusion sarcomas) • Entrectinib[k,20] (for *NTRK* gene-fusion sarcomas
Subsequent Lines of Therapy for Advanced/Metastatic Disease	• Eribulin[f,g,21] (category 1 recommendation for liposarcoma, category 2A for other subtypes) • Pazopanib[f,18] (for non-adipocytic sarcoma) • Trabectedin[f,h, 22-24] (category 1 recommendation for liposarcoma and leiomyosarcoma)	• Dacarbazine • Ifosfamide[5,8,9-13] • Temozolomide[f,25] • Vinorelbine[f,26] • Regorafenib[i,27]	

Footnotes see SARC-F, 5 of 9

Note: All recommendations are category 2A unless otherwise indicated.
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SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA SUBTYPES

Non-Pleomorphic Rhabdomyosarcoma

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Vincristine, dactinomycin, cyclophosphamide[28] • Vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide[29]	• Vincristine, doxorubicin, cyclophosphamide[30] • Vincristine, doxorubicin, ifosfamide[31] • Cyclophosphamide and topotecan[32,33] • Ifosfamide and doxorubicin[34] • Ifosfamide and etoposide[35] • Irinotecan and vincristine[36,37] • Vincristine and dactinomycin[38] • Carboplatin and etoposide[39] • Vinorelbine and low-dose cyclophosphamide[f,40] • Vincristine, irinotecan, temozolomide[41] • Doxorubicin[42] • Irinotecan[33,43] • Topotecan[44] • Vinorelbine[f,45] • High-dose methotrexate[l,46] • Trabectedin[f,22-24]	

Footnotes see SARC-F, 5 of 9

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SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA SUBTYPES

Angiosarcoma

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Paclitaxel[45,47,48] • Anthracycline- or gemcitabine-based regimens recommended for Soft Tissue Sarcoma Subtypes with Non-Specific Histologies (See SARC-F, 1 of 9).	• Docetaxel[49] • Vinorelbine[f] • Sorafenib[50] • Sunitinib[51] • Bevacizumab[52] • Pazopanib • All other systemic therapy options recommended for Soft Tissue Sarcoma Subtypes with Non-Specific Histologies (See SARC-F, 1 of 9)	

Solitary Fibrous Tumor

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Bevacizumab and temozolomide[53] • Sunitinib[51,54] • Sorafenib[55] • Pazopanib[54]	All other systemic therapy options recommended for Soft Tissue Sarcoma Subtypes with Non-Specific Histologies (See SARC-F, 1 of 9)	

Footnotes see SARC-F, 5 of 9

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SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA SUBTYPES

Tenosynovial Giant Cell Tumor/Pigmented Villonodular Synovitis

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Pexidartinib (category 1)[57] • Imatinib[58]		

Alveolar Soft Part Sarcoma (ASPS)

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Sunitinib[59,60] • Pazopanib[61] • Pembrolizumab[62]		

PEComa, Recurrent Angiomyolipoma, Lymphangioleiomyomatosis

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Sirolimus[63-66] • Everolimus[67] • Temsirolimus[68,69]		

Inflammatory Myofibroblastic Tumor (IMT) with Anaplastic Lymphoma Kinase (ALK) Translocation

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• ALK inhibitors ‣ Crizotinib[70] ‣ Ceritinib[71]		

Footnotes see SARC-F, 5 of 9

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SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA SUBTYPES

Well-Differentiated/Dedifferentiated Liposarcoma (WD-DDLS) for Retroperitoneal Sarcomas

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
		• Palbociclib[m,72-73]

Undifferentiated Pleomorphic Sarcoma (UPS)

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
All other systemic therapy options recommended for Soft Tissue Sarcoma Subtypes with Non-Specific Histologies (See SARC-F, 1 of 9)	• Pembrolizumab[n,74-75]	

Epithelioid Sarcoma

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Tazemetostat[o,76]		

FOOTNOTES

[a]Prior to the initiation of therapy, all patients should be evaluated and managed by a multidisciplinary team with expertise and experience in sarcoma.
[b]For uterine sarcomas, see the NCCN Guidelines for Uterine Neoplasms.
[c]Alveolar soft part sarcoma (ASPS), ALT/WDLS, and clear cell sarcomas are generally not sensitive to cytotoxic chemotherapy.
[d]Anthracycline-based regimens are preferred in the neoadjuvant and adjuvant settings.
[e]Regimens appropriate for pleomorphic rhabdomyosarcoma.
[f]Recommended only for palliative therapy.
[g]Category 1 recommendation for liposarcoma, category 2A for other subtypes.
[h]Category 1 recommendation for liposarcoma and leiomyosarcoma (L-Types).
[i]For non-adipocytic sarcoma.
[j]Not intended for preoperative or adjuvant therapy of nonmetastatic disease. Not recommended for angiosarcoma or pleomorphic rhabdomyosarcoma.
[k]Not intended for adjuvant therapy of nonmetastatic disease.
[l]High-dose methotrexate may be useful for select patients with CNS or leptomeningeal involvement when RT is not feasible.
[m]Single-agent therapy for the treatment of unresectable well-differentiated/dedifferentiated liposarcoma (WD-DDLS).
[n]Single-agent for the treatment of metastatic undifferentiated pleomorphic sarcoma.
[o]Since agent for the treatment of metastatic or locally advanced epithelioid sarcoma not eligible for complete resection.

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

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

[2]Pervaiz N, Colterjohn N, Farrokhyar F, et al. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer 2008;113:573-581.

[3]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.

[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;11:1269-1275.

[5]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;19:1238-1247.

[6]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.

[7]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;11:1276-1285.

[8]Mack LA, Crowe PJ, Yang JL, et al. Preoperative chemoradiotherapy (modified Eilber protocol) provides maximum local control and minimal morbidity in patients with soft tissue sarcoma. Ann Surg Oncol 2005;12:646-653.

[9]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.

[10]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.

[11]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.

[12]Garcia-Del-Muro X, Lopez-Pousa A, Maurel J, et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. J Clin Oncol 2011;29:2528-2533.

[13]Antman KH, Elias A. Dana-Farber Cancer Institute studies in advanced sarcoma. Semin Oncol 1990;1(Suppl 2):7-15.

[14]Petrioli R, Coratti A, Correale P, et al. Adjuvant epirubicin with or without Ifosfamide for adult soft-tissue sarcoma. Am J Clin Oncol 2002;25:468-473.

[15]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; 37:870-877.

[16]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;7:1208-1216.

[17]Kraybill WG, Harris J, Spiro IJ, et al. Long-term results of a phase 2 study of neoadjuvant chemotherapy and radiotherapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group Trial 9514. Cancer 2010;116:4613-4621.

[18]van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012;379:1879-1886.

[19]Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adult and children. N Engl J Med 2018 378(8):731-739.

[20]Demetri GD, Paz-Ares L, Farago AF, et al. Efficacy and safety of entrectinib in patients with NTRK fusion-positive tumours: pooled analysis of STARTRK-2, STARTRK-1 and ALKA-372-001. Presented at the European Society for Medical Oncology Meeting in Munich, Germany; October12-23, 2018. Oral Presentation.

[21]Schöffski P, Ray-Coquard IL, Cioffi A, et al. Activity of eribulin mesylate in patients with soft-tissue sarcoma: a phase 2 study in four independent histological subtypes. Lancet Oncol 2011;12(11):1045-1052.

[22]Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. J Clin Oncol 2015;33:1-8.

[23]Kawai A, Araki N, Sugiura H, et al. Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: a randomised, open-label, phase 2 study. Lancet Oncol 2015;16(4):406-416.

Continued

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SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA
REFERENCES

[24]Samuels BL, Chawla S, Patel S, et al. Clinical outcomes and safety with trabectedin therapy in patients with advanced soft tissue sarcomas following failure of prior chemotherapy: results of a worldwide expanded access program study. Ann Oncol 2013;24(6):1703-1709.

[25]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.

[26]Kuttesch JF Jr, Krailo MD, Madden T, et al. Phase II evaluation of intravenous vinorelbine (Navelbine) in recurrent or refractory pediatric malignancies: a Children's Oncology Group study. Pediatr Blood Cancer 2009; 53:590-593.

[27]Berry V, Basson L, Bogart E, et al. REGOSARC: Regorafenib vesus placebo in doxorubicin-refractory soft-tissue sarcoma-A quality-adjusted time without symptoms of progression or toxicity analysis. Cancer 2017;123:2294-2302.

[28]Arndt CAS, Stoner JA, Hawkins DS, et al. Vincristine, actinomycin, and cyclophosphamide compared with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan, and cyclophosphamidefor intermediate-risk rhabdomyosarcoma: children's oncology group study D9803. J Clin Oncol 2009;27:5182-5188.

[29]Arndt CAS, Hawkins DS, Meyer WH, et al. Comparison of results of a pilot study of alternating vincristine/doxorubicin/cyclophosphamide and etoposide/ifosfamide with IRS-IV in intermediate risk rhabdomyosarcoma: a report from the Children's Oncology Group. Pediatr Blood Cancer 2008;50:33-36.

[30]Little DJ, Ballo MT, Zagars GK, et al. Adult rhabdomyosarcoma: outcome following multimodality treatment. Cancer 2002;95:377-388.

[31]Ogilvie CM, Crawford EA, Slotcavage RL, et al. Treatment of adult rhabdomyosarcoma. Am J Clin Oncol 2010;33:128-131.

[32]Saylors RL, Stine KC, Sullivan J, et al. Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumors: a Pediatric Oncology Group phase II study. J Clin Oncol 2001;19:3463-3469.

[33]Walterhouse DO, Lyden ER, Breitfeld PP, et al. Efficacy of topotecan and cyclophosphamide given in a phase II window trial in children with newly diagnosed metastatic rhabdomyosarcoma: a Children's Oncology Group study. J Clin Oncol 2004;22:1398-1403.

[34]Sandler E, Lyden E, Ruymann F, et al. Efficacy of ifosfamide and doxorubicin given as a phase II "window" in children with newly diagnosed metastatic rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study Group. Med Pediatr Oncol 2001;37:442-448.

[35]Breitfeld PP, Lyden E, Raney RB, et al. Ifosfamide and etoposide are superior to vincristine and melphalan for pediatric metastatic rhabdomyosarcoma when administered with irradiation and combination chemotherapy: a report from the Intergroup Rhabdomyosarcoma Study Group. J Pediatr Hematol Oncol 2001;23:225-233.

[36]Pappo AS, Lyden E, Breitfeld P, et al. Two consecutive phase II window trials of irinotecan alone or in combination with vincristine for the treatment of metastatic rhabdomyosarcoma: the Children's Oncology Group. J Clin Oncol 2007;25:362-369.

[37]Mascarenhas L, Lyden ER, Breitfeld PP, et al. Randomized phase II window trial of two schedules of irinotecan with vincristine in patients with first relapse or progression of rhabdomyosarcoma: a report from the Children's Oncology Group. J Clin Oncol 2010;28:4658-4663. Erratum in J Clin Oncol 2011;4629(4610):1394.

[38]Raney RB, Walterhouse DO, Meza JL, et al. Results of the Intergroup Rhabdomyosarcoma Study Group D9602 protocol, using vincristine and dactinomycin with or without cyclophosphamide and radiation therapy, for newly diagnosed patients with low-risk embryonal rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. J Clin Oncol 2011;29:1312-1318.

[39]Klingebiel T, Pertl U, Hess CF, et al. Treatment of children with relapsed soft tissue sarcoma: report of the German CESS/CWS REZ 91 trial. Med Pediatr Oncol 1998;30:269-275.

[40]Casanova M, Ferrari A, Bisogno G, et al. Vinorelbine and low-dose cyclophosphamide in the treatment of pediatric sarcomas: pilot study for the upcoming European Rhabdomyosarcoma Protocol. Cancer 2004;101:1664-1671.

[41]McNall-Knapp RY, Williams CN, Reeves EN, et al. Extended phase I evaluation of vincristine, irinotecan, temozolomide, and antibiotic in children with refractory solid tumors. Pediatr Blood Cancer 2010;54:909-915.

[42]Bergeron C, Thiesse P, Rey A, et al Revisiting the role of doxorubicin in the treatment of rhabdomyosarcoma: An up-front window study in newly diagnosed children with high-risk metastatic disease. Eur J Cancer 2008; 44:427-431.

[43]Vassal G, Couanet D, Stockdale E, et al. Phase II trial of irinotecan in children with relapsed or refractory rhabdomyosarcoma: a joint study of the French Society of Pediatric Oncology and the United Kingdom Children's Cancer Study Group. J Clin Oncol 2007;25:356-361.

Continued

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SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA

REFERENCES

[44]Pappo AS, Lyden E, Breneman J, et al. Up-front window trial of topotecan in previously untreated children and adolescents with metastatic rhabdomyosarcoma: an intergroup rhabdomyosarcoma study. J Clin Oncol 2001;19:213-219.

[45]Casanova M, Ferrari A, Spreafico F, et al. Vinorelbine in previously treated advanced childhood sarcomas: evidence of activity in rhabdomyosarcoma. Cancer 2002;94:3263-3268.

[46]Pappo AS, Bowman LC, Furman WL, et al. A phase II trial of high-dose methotrexate in previously untreated children and adolescents with high-risk unresectable or metastatic rhabdomyosarcoma. J Pediatr Hematol Oncol 1997;19:438-442.

[47]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;26:5269-5274.

[48]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;44:2433-2436.

[49]Van Hoesel QG, Verweij J, Catimel G, et al. Phase II study with docetaxel (Taxotere) in advanced soft tissue sarcomas of the adult. EORTC Soft Tissue and Bone Sarcoma Group. Ann Oncol 1994;5(6):539-542.

[50]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.

[51]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.

[52]Agulnik M, Yarber JL, Okuno SH, et al. An open-label, multicenter, phase II study of bevacizumab for the treatment of angiosarcoma and epithelioid hemangioendotheliomas. Ann Oncol 2013;24:257-263.

[53]Park MS, Patel SR, Ludwig JA, et al. Activity of temozolomide and bevacizumab in the treatment of locally advanced, recurrent, and metastatic hemangiopericytoma and malignant solitary fibrous tumor. Cancer 2011;117:4939-4947.

[54]Stacchiotti S, Negri T, Libertini M, et al. Sunitinib malate in solitary fibrous tumor (SFT). Ann Oncol 2012;23:3171-3179.

[55]Valentin T, Fournier C, Penel N, et al. Sorafenib in patients with progressive malignant solitary fibrous tumors: a subgroup analysis from a phase II study of the French Sarcoma Group (GSF/GETO). Invest New Drugs 2013;31(6):1626-1627.

[56]Ebata T, Shimoi T, Bun S, et al. Efficacy and safety of pazopanib for recurrent or metastatic solitary fibrous tumor. Oncology 2018;94:340-344.

[57]Tap WD, Gelderblom H, Palmerini E, et al. Pexidartinib versus placebo for advanced tenosynovial giant cell tumor (ENLIVEN): a randomized phase 3 trial Lancet 2019 Aug 10;394:478-487.

[58]Cassier PA, Gelderblom H, Stacchiotti S, et al. Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. Cancer 2012;118:1649-1655.

[59]Stacchiotti S, Negri T, Zaffaroni N, et al. Sunitinib in advanced alveolar soft part sarcoma: evidence of a direct antitumor effect. Ann Oncol 2011;22:1682-1690.

[60]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.

[61]Stacchiotti S, Mir O, Le Cesne A, et al. Activity of pazopanib and trabectedin in advanced alveolar soft part sarcoma. Oncologist 2018; 23(1):62-70.

[62]Groisberg R, Hong DS, Behrang A, et al. Characteristics and outcomes of patients with advanced sarcoma enrolled in early phase immunotherapy trials. J Immunother Cancer 2017;5(1):100.

[63]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.

[64]Davies DM, de Vries PJ, Johnson SR, et al. Sirolimus therapy for angiomyolipoma in tuberous sclerosis and sporadic lymphangioleiomyomatosis: a phase 2 trial. Clin Cancer Res 2011;17:4071-4081.

[65]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;28:835-840.

[66]McCormack FX, Inoue Y, Moss J, et al. Efficacy and safety of sirolimus in lymphangioleiomyomatosis. N Engl J Med 2011;364:1595-1606.

[67]Gennatas C, Michalaki V, Kairi PV, et al. Successful treatment with the mTOR inhibitor everolimus in a patient with perivascular epithelioid cell tumor. World J Surg Oncol 2012;10:181.

[68]Benson C, Vitfell-Rasmussen J, Maruzzo M, et al. A retrospective study of patients with malignant PEComa receiving treatment with sirolimus or temsirolimus: the Royal Marsden Hospital experience. Anticancer Res 2014 Jul;34(7):3663-3668.

[69]Italiano A, Delcambre C, Hostein I, et al. Treatment with the mTOR inhibitor temsirolimus in patients with malignant PEComa. Ann Oncol 2010;21(5):1135-1137.

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Continued

SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA

REFERENCES

[70]Butrynski JE, D'Adamo DR, Hornick JL, et al. Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. N Engl J Med 2010;363:1727-1733.

[71]Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med 2014;370(13):1189-97.

[72]Dickson MA, Tap WD, Keohan ML, et al. Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified well differentiated or dedifferentiated liposarcoma. J Clin Oncol 2013;31(16):2024-2028.

[73]Dickson MA, Tap WD, Keohan ML, et al. Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified liposarcoma. J Clin Oncol 2013;27:31(15) (May 20 Supplement) Abstract 10512.

[74]Burgess MA, Bolejack V, Van Tine BA, et al. Multicenter phase II study of pembrolizumab (P) in advanced soft tissue sarcoma(STS) and bone sarcomas (BS): Final results of SARC028 and biomarker analyses. J Clin Oncol 2017;35 (Supplement; Abstract 11008).

[75]Burgess MA, Bolejack V, Van Tine BA, et al. Multicenter phase II study of pembrolizumab (P) in advanced soft tissue sarcoma(STS) and bone sarcomas (BS): Final results of SARC028 and biomarker analyses. J Clin Oncol 2017;35 (Supplement; Abstract 11008).

[76]Stacchiotti S, Schoffski P, Jones R, et al. Safety and efficacy of tazemetostat, a first-in-class EZH2 inhibitor, in patients with epithelioid sarcoma (NCT0261950). J Clin Oncol 2019;37:11003.

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Table 1

Histopathologic Type

Tumors included in the soft tissue category are listed below as per the 2013 World Health Organization classification of tumors:

Adipocytic Tumors
- Atypical lipomatous tumor
- Well-differentiated liposarcoma
- Liposarcoma, NOS
- Dedifferentiated liposarcoma
- Myxoid/round cell liposarcoma
- Pleomorphic liposarcoma

Fibroblastic/Myofibroblastic Tumors
- Dermatofibrosarcoma protuberans
- Fibrosarcomatous dermatofibrosarcoma protuberans
- Pigmented dermatofibrosarcoma protuberans
- Solitary fibrous tumor, malignant
- Inflammatory myofibroblastic tumor
- Low-grade myofibroblastic sarcoma
- Adult fibrosarcoma
- Myxofibrosarcoma (formerly myxoid malignant fibrous histiocytoma [myxoid MFH])
- Low-grade fibromyxoid sarcoma
- Sclerosing epithelioid fibrosarcoma

So-called Fibrohistiocytic Tumors
- Giant cell tumor of soft tissues

Smooth Muscle Tumors
- Leiomyosarcoma (excluding skin)

Pericytic (Perivascular) Tumors
- Malignant glomus tumor

Skeletal Muscle Tumors
- Embryonal rhabdomyosarcoma (including botryoid, anaplastic)
- Alveolar rhabdomyosarcoma (including solid, anaplastic)
- Pleomorphic rhabdomyosarcoma
- Spindle cell/sclerosing rhabdomyosarcoma

Vascular Tumors
- Retiform hemangioendothelioma
- Pseudomyogenic (epithelioid sarcoma-like) hemangioendothelioma
- Epithelioid hemangioendothelioma
- Angiosarcoma of soft tissue

Chondro-osseous Tumors
- Extraskeletal osteosarcoma

Gastrointestinal Stromal Tumors
- Gastrointestinal stromal tumor, malignant

Nerve Sheath Tumors
- Malignant peripheral nerve sheath tumor
- Epithelioid malignant peripheral nerve sheath tumor
- Malignant triton tumor
- Malignant granular cell tumor

Tumors of Uncertain Differentiation
- Ossifying fibromyxoid tumor, malignant
- Stromal sarcoma, NOS
- Myoepithelial carcinoma
- Phosphaturic mesenchymal tumor, malignant
- Synovial sarcoma (NOS, spindle cell, biphasic)
- Epithelioid sarcoma
- Alveolar soft part sarcoma
- Clear cell sarcoma of soft tissue
- Extraskeletal myxoid chondrosarcoma
- Extraskeletal Ewing sarcoma
- Desmoplastic small round cell tumor
- Extrarenal rhabdoid tumor
- Perivascular epithelioid cell tumor (PEComa), NOS
- Intimal sarcoma

Undifferentiated/Unclassified Sarcoma
- Undifferentiated (spindle cell sarcoma, pleomorphic sarcoma, round cell sarcoma, epithelioid sarcoma, NOS)

Used with permission, Fletcher CDM, Bridge JA, Hogendoorn P, Mertens F, eds. World Health Organization Classification of Tumours of Soft Tissue and Bone. Fourth Edition. Lyon: IARC;2013.

Continued

American Joint Committee On Cancer (AJCC) Staging System for Soft Tissue Sarcoma of the Head and Neck (8th ed, 2017)

Table 2. Definitions for T, N, M

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T1	Tumor ≤2 cm
T2	Tumor >2 cm to ≤4 cm
T3	Tumor >4 cm
T4	Tumor with invasion of adjoining structures
T4a	Tumor with orbital invasion, skull base/dural invasion, invasion of central compartment viscera, involement of facial skeleton, or invasion of pterygoid muscles
T4b	Tumor with brain parenchymal invasion, carotid artery encasement, prevertebral muscle invasion, or central nervous system involvement via perineural spread

N	**Regional Lymph Nodes**
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastasis

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis

G	**Definition of Grade** **FNCLCC Histologic Grade - see Histologic Grade (G)**
GX	Grade cannot be assessed
G1	Total differentiation, mitotic count and necrosis score of 2 or 3
G2	Total differentiation, mitotic count and necrosis score of 4 or 5
G3	Total differentiation, mitotic count and necrosis score of 6, 7, or 8

Anatomic Stage/Prognostic Groups
This is a new classification that needs data collection before defining a stage grouping for head and neck sarcomas

Histologic Grade (G)

The FNCLCC grade is determined by three parameters: differentiation, mitotic activity, and extent of necrosis. Each parameter is scored as follows: differentiation (1-3), mitotic activity (1-3), and necrosis (0-2). The scores are added to determine the grade

Tumor Differentiation

1	Sarcomas closely resembling normal adult mesenchymal tissue (e.g., low-grade leiomyosarcoma)
2	Sarcomas for which histologic typing is certain (e.g., myxoid/round cell liposarcoma)
3	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, soft tissue osteosarcoma, Ewing Sarcoma/primitive neuroectodermal tumor (PNET) of soft tissue

Mitotic Count

In the most mitotically active area of the sarcoma, 10 successive high-power fields (HPF; one HPF at 400× magnification= 0.1734 mm^2) are assessed using a 40× objective.

1	0-9 mitoses per 10 HPF
2	10-19 mitoses per 10 HPF
3	≥20 mitoses per 10 HPF

Tumor Necrosis

Evaluated on gross examination and validated with histologic sections.

0	No necrosis
1	<50% tumor necrosis
2	≥50% tumor necrosis

Histopathologic Type

Please see the WHO Classification of Tumors (ST-1)

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Continued

American Joint Committee On Cancer (AJCC) Staging System for Soft Tissue Sarcoma of the Trunk and Extremities (8th ed, 2017)

Table 3. **Definitions for T, N, M**

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence for primary tumor
T1	Tumor 5 cm or less in greatest dimension
T2	Tumor more than 5 cm and less than or equal to10 cm in greatest dimension
T3	Tumor more than 10cm and less than or equal to 15 cm in greatest dimension
T4	Tumor more than 15 cm in greatest dimension

N	**Regional Lymph Nodes**
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastasis

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis

G	**Definition of Grade** **FNCLCC Histologix Grade - See Histologic Grade (G)**
GX	Grade cannot be assessed
G1	Total differentiation, mitotic count and necrosis score of 2 or 3
G2	Total differentiation, mitotic count and necrosis score of 4 or 5
G3	Total differentiation, mitotic count and necrosis score of 6, 7, or 8

Table 4. **AJCC Anatomic Stage/Prognostic Groups**

	T	**N**	**M**	**G**
Stage IA	T1	N0	M0	G1, GX
Stage IB	T2	N0	M0	G1, GX
	T3	N0	M0	G1, GX
	T4	N0	M0	G1, GX
Stage II	T1	N0	M0	G2, G3
Stage IIIA	T2	N0	M0	G2, G3
Stage IIIB	T3	N0	M0	G2, G3
	T4	N0	M0	G2, G3
Stage IV	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

Histologic Grade (G)

The FNCLCC grade is determined by three parameters: differentiation, mitotic activity, and extent of necrosis. Each parameter is scored as follows: differentiation (1-3), mitotic activity (1-3), and necrosis (0-2). The scores are added to determine the grade

Tumor Differentiation

1	Sarcomas closely resembling normal adult mesenchymal tissue (e.g., low-grade leiomyosarcoma)
2	Sarcomas for which histologic typing is certain (e.g., myxoid/round cell liposarcoma)
3	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, soft tissue osteosarcoma, Ewing Sarcoma/primitive neuroectodermal tumor (PNET) of soft tissue

Mitotic Count

In the most mitotically active area of the sarcoma, 10 successive high-power fields (HPF; one HPF at 400× magnification= 0.1734 mm^2) are assessed using a 40× objective.

1	0-9 mitoses per 10 HPF
2	10-19 mitoses per 10 HPF
3	≥20 mitoses per 10 HPF

Tumor Necrosis

Evaluated on gross examination and validated with histologic sections.

0	No necrosis
1	<50% tumor necrosis
2	≥50% tumor necrosis

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Continued

American Joint Committee On Cancer (AJCC) Staging System for Soft Tissue Sarcoma of the Abdomen and Thoracic Visceral Organs (8th ed, 2017)

Table 5. Definitions for T, N, M

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T1	Organ confined
T2	Tumor extension into tissue beyond organ
T2a	Invades serosa or visceral peritoneum
T2b	Extension beyond serosa (mesentery)
T3	Invades another organ
T4	Multifocal involvement
T4a	Multifocal (2 sites)
T4b	Multifocal (3-5 sites)
T4c	Multifocal (>5 sites)

N	**Regional Lymph Nodes**
N0	No regional lymph node involvement or unknown lymph node status
N1	Lymph node involvement present

M	**Distant Metastasis**
M0	No metastasis
M1	Metastases present

G	**Definition of Grade** **FNCLCC Histologix Grade - See Histologic Grade (G)**
GX	Grade cannot be assessed
G1	Total differentiation, mitotic count and necrosis score of 2 or 3
G2	Total differentiation, mitotic count and necrosis score of 4 or 5
G3	Total differentiation, mitotic count and necrosis score of 6, 7, or 8

Anatomic Stage/Prognostic Groups

There is no recommended prognostic stage grouping at this time.

Histologic Grade (G)

The FNCLCC grade is determined by three parameters: differentiation, mitotic activity, and extent of necrosis. Each parameter is scored as follows: differentiation (1-3), mitotic activity (1-3), and necrosis (0-2). The scores are added to determine the grade

Tumor Differentiation

1	Sarcomas closely resembling normal adult mesenchymal tissue (e.g., low-grade leiomyosarcoma)
2	Sarcomas for which histologic typing is certain (e.g., myxoid/round cell liposarcoma)
3	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, soft tissue osteosarcoma, Ewing Sarcoma/primitive neuroectodermal tumor (PNET) of soft tissue

Mitotic Count

In the most mitotically active area of the sarcoma, 10 successive high-power fields (HPF; one HPF at 400× magnification= 0.1734 mm^2) are assessed using a 40× objective.

1	0-9 mitoses per 10 HPF
2	10-19 mitoses per 10 HPF
3	≥20 mitoses per 10 HPF

Tumor Necrosis

Evaluated on gross examination and validated with histologic sections.

0	No necrosis
1	<50% tumor necrosis
2	≥50% tumor necrosis

Continued

American Joint Committee On Cancer (AJCC) Staging System for Gastrointestinal Stromal Tumor (8th ed, 2017)

Table 6. Definitions for T, N, M

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less
T2	Tumor more than 2 cm but not more than 5 cm
T3	Tumor more than 5 cm but not more than 10 cm
T4	Tumor more than 10 cm in greatest dimension

N	Regional Lymph Nodes
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastasis

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis

Grading for GIST is dependent on mitotic rate

Low	5 or fewer mitoses per 5 mm^2, or per 50 HPF
High	Over 5 mitoses per 5 mm^2, or per 50 HPF

Table 7. AJCC Anatomic Stage/Prognostic Groups

*Gastric GIST**

	T	N	M	Mitotic Rate
Stage IA	T1 or T2	N0	M0	Low
Stage IB	T3	N0	M0	Low
Stage II	T1	N0	M0	High
	T2	N0	M0	High
	T4	N0	M0	Low
Stage IIIA	T3	N0	M0	High
Stage IIIB	T4	N0	M0	High
Stage IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate

*Small Intestinal GIST***

	T	N	M	Mitotic Rate
Stage I	T1 or T2	N0	M0	Low
Stage II	T3	N0	M0	Low
Stage IIIA	T1	N0	M0	High
	T4	N0	M0	Low
Stage IIIB	T2	N0	M0	High
	T3	N0	M0	High
	T4	N0	M0	High
Stage IV	Any T	N1	M0	Any rate
	Any T	Any N	M1	Any rate

*Note: Also to be used for omentum.
**Note: Also to be used for esophagus, colorectal, mesenteric, and peritoneal.

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Continued

American Joint Committee On Cancer (AJCC) Staging System for Soft Tissue Sarcoma of the Retroperitoneum (8th ed, 2017)

***Table 8.* Definitions for T, N, M**

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 5 cm or less in greatest dimension
T2	Tumor more than 5 cm and less than or equal to 10 cm in greatest dimension
T3	Tumor more than 10 cm and less than or equal to 15 cm in greatest dimension
T4	Tumor more than 15 cm in greatest dimension

N	**Regional Lymph Nodes**
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastases

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastases

G	**Definition of Grade** **FNCLCC Histologic Grade - See Histologic Grade (G)**
GX	Grade cannot be assessed
G1	Total differentiation, mitotic count and necrosis score of 2 or 3
G2	Total differentiation, mitotic count and necrosis score of 4 or 5
G3	Total differentiation, mitotic count and necrosis score of 6, 7, or 8

***Table 9.* AJCC Anatomic Stage/Prognostic Groups**

	T	**N**	**M**	**G**
Stage IA	T1	N0	M0	G1, GX
Stage IB	T2	N0	M0	G1, GX
	T3	N0	M0	G1, GX
	T4	N0	M0	G1, GX
Stage II	T1	N0	M0	G2, G3
Stage IIIA	T2	N0	M0	G2, G3
Stage IIIB	T3	N0	M0	G2, G3
	T4	N0	M0	G2, G3
	Any T	N1	M0	Any G
Stage IV	Any T	Any N	M1	Any G

Histologic Grade (G)

The FNCLCC grade is determined by three parameters: differentiation, mitotic activity, and extent of necrosis. Each parameter is scored as follows: differentiation (1-3), mitotic activity (1-3), and necrosis (0-2). The scores are added to determine the grade.

Tumor Differentiation

1	Sarcomas closely resembling normal adult mesenchymal tissue (e.g., low-grade leiomyosarcoma)
2	Sarcomas for which histologic typing is certain (e.g., myxoid/round cell liposarcoma)
3	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, soft tissue osteosarcoma, Ewing Sarcoma/primitive neuroectodermal tumor (PNET) of soft tissue

Mitotic Count

In the most mitotically active area of the sarcoma, 10 successive high-power fields (HPF; one HPF at 400× magnification= 0.1734 mm^2) are assessed using a 40× objective.

1	0-9 mitoses per 10 HPF
2	10-19 mitoses per 10 HPF
3	≥20 mitoses per 10 HPF

Tumor Necrosis

Evaluated on gross examination and validated with histologic sections.

0	No necrosis
1	<50% tumor necrosis
2	≥50% tumor necrosis

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Discussion

This discussion corresponds to the NCCN Guidelines for Soft Tissue Sarcoma. Last updated on 03/27/18.

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Table of Contents

Overview

Sarcomas constitute a heterogeneous group of rare solid tumors of mesenchymal cell origin with distinct clinical and pathologic 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.

Sarcomas collectively account for approximately 1% of all adult malignancies and 15% of pediatric malignancies. In 2018, an estimated 13,040 people will be diagnosed with soft tissue sarcoma (STS) in the United States, with approximately 5150 deaths.[1] The true incidence of STS is underestimated, especially because a large proportion of patients with gastrointestinal stromal tumors (GISTs) may not have been included in tumor registry databases before 2001. A recent SEER database study calculated the annual incidence of GIST in the United States to be 0.78/100,000 in 2011.[2] Prior radiation therapy (RT) to the affected area is a risk factor for the development of STS.[3-5] More than 50 different histologic subtypes of STS have been identified. Common subtypes of STS include undifferentiated pleomorphic sarcoma (UPS), GIST, liposarcoma (LPS), and leiomyosarcoma (LMS).[6] The anatomic site of the primary disease represents an important variable that influences treatment and outcome. Extremities (43%), the trunk (10%), visceral (19%), retroperitoneum (15%), or head and neck (9%) are the most common primary sites.[7] STS most commonly metastasizes to the lungs; tumors arising in the abdominal cavity more commonly metastasize to the liver and peritoneum. Rhabdomyosarcoma (RMS) is the most common STS of children and adolescents and is less common in adults.

The NCCN Guidelines® for Soft Tissue Sarcoma address the management of STS in adult patients from the perspective of the following disease subtypes:

- STS of extremity, superficial/trunk, or head and neck
- Retroperitoneal or intra-abdominal STS
- GISTs
- Desmoid tumors (aggressive fibromatoses)
- RMS

Prior to initiation of treatment, all patients should be evaluated and managed by a multidisciplinary team with extensive expertise and experience in the treatment of STS.[8] Because STS is rare and often complex, adherence to evidence-based recommendations is particularly important. Analysis of data from 15,957 patients with STS in the National Cancer Database (NCDB) showed that NCCN Guidelines-adherent treatment was associated with improved survival outcomes.[9]

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Soft Tissue Sarcoma, an electronic search of the PubMed database was performed to obtain key literature in STS, using the following search terms: soft tissue sarcoma OR gastrointestinal stromal tumor OR desmoid OR aggressive fibromatosis OR rhabdomyosarcoma OR *sarcoma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Study; Clinical Trial; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 50 citations and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Genetic Cancer Syndromes with Predisposition to Soft Tissue Sarcoma

Genetic cancer syndromes caused by germline mutations in a number of different genes are also associated with an inherited predisposition for the development of STS.[4,10-14]

Li-Fraumeni syndrome (resulting from germline mutations in the *TP53* tumor suppressor gene) is characterized by an increased risk of developing multiple primary malignancies, predominantly STS, osteosarcomas, breast cancer, leukemia, brain tumors, and adrenocortical carcinoma before 45 years of age.[10,15-17] The incidence of STS ranges from 12% to 21% in individuals with *TP53* germline mutations.[18-20] In general, STS associated with Li-Fraumeni syndrome is diagnosed at significantly younger ages than sporadic STS. The mean age at diagnosis, however, varies with the histologic subtype. In an analysis of 475 tumors in 91 families with *TP53* germline mutations, Kleihues and colleagues reported RMS, fibrosarcomas, and UPS as the most frequent histologic subtypes identified in 55%,13%, and 10% of patients, respectively.[18] The mean age at diagnosis for RMS was younger than 6 years, and the mean age at diagnosis for UPS was older than 50 years.

Familial adenomatous polyposis (FAP) is an inherited autosomal-dominant colorectal cancer syndrome resulting from the germline mutations in the adenomatous polyposis coli [*APC*] gene on chromosome 5q21.[11,13] FAP is characterized by adenomatous colorectal polyps that progress to colorectal cancer at 35 to 40 years of age. Gardner's syndrome is considered a variant of FAP with extracolonic manifestations such as osteomas, skin cysts, congenital hypertrophy of the retinal pigmented epithelium, and desmoid tumors (aggressive fibromatosis).[21] Desmoid tumors have been reported to occur in 7.5% to 16% of patients with FAP, and the relative risk of developing desmoid tumors is much higher in patients with FAP than the general population.[22-25] In an International Dutch Cohort study involving 2260 patients with FAP, positive family history for desmoid tumors, abdominal surgery, and the *APC* mutation site were identified as significant risk factors for the development of desmoid tumors.[25] The median age at diagnosis was 31 years, with the majority of desmoid tumors arising in the intra-abdominal and abdominal wall locations (53% and 24%, respectively).

Carney-Stratakis syndrome is an autosomal-dominant familial syndrome characterized by a predisposition to GISTs and paragangliomas.[26] Germline loss-of-function mutations within the succinate dehydrogenase (*SDH*) gene subunits (*SDHB*, *SDHC,* and *SDHD*) have been identified in individuals with GISTs associated with Carney-Stratakis syndrome.[27] In an analysis of 11 patients from 9 families presenting with GIST and paragangliomas associated with Carney-Stratakis syndrome, Pasini and colleagues identified germline mutations in *SDHB*, *SDHC,* or *SDHD* genes in 8 patients (from 7 untreated families) with GISTs.[27] The tumors also lacked activating *KIT* or platelet-derived growth factor receptor alpha (*PDGFRA*) mutations associated with sporadic GISTs. GISTs associated with Carney-Stratakis syndrome are also reported to be negative for SDHB protein expression by immunohistochemistry (IHC), in contrast to GIST with *KIT* or *PDGFRA* mutations or sporadic GIST.[28,29]

Hereditary retinoblastoma caused by a germline mutation in the retinoblastoma tumor suppressor gene (*RB1*) is also associated with an increased risk for the development of STS.[12,30] LMS is the most frequent STS subtype (with 78% of LMS diagnosed 30 or more years after the diagnosis of retinoblastoma). Although patients with RT for retinoblastoma are at significantly increased risk of developing STS, the risks of developing STS are also increased in non-irradiated patients as well, indicating a genetic predisposition to STS that is independent of RT in patients with hereditary retinoblastoma.[12]

Neurofibromatoses are hereditary conditions caused by mutations in the neurofibromin 1 gene (NF1) or neurofibromin 2 gene (NF2).31 Approximately 5% of patients with neurofibromatosis are thought to develop STS. Most commonly occurring are malignant peripheral nerve sheath tumors (MPNSTs), a type of sarcoma that can arise from previously benign neurofibromas.32 For information on the treatment of MPNSTs, see the NCCN Guidelines for Central Nervous System Cancers at www.NCCN.org.

NCCN Recommendations for Genetic Testing and Counseling for Patients with Germline Mutations

- Patients (and their families) with a personal and/or family history suggestive of Li-Fraumeni syndrome should be considered for further genetics assessment as outlined in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.
- *SDH* gene mutational analysis for the identification of germline mutations in the *SDH* gene subunits should be considered for patients with GIST lacking KIT or PDGFRA mutations. Loss of SDHB protein expression by IHC is a useful screen to identify patients who would be appropriate for germline mutation testing, but it is not diagnostic of a germline mutation.
- Evaluation for family history of FAP or Gardner's syndrome is recommended for patients diagnosed with desmoid tumors (aggressive fibromatoses).

Pathology of Soft Tissue Sarcomas

Biopsy

A pretreatment biopsy is highly preferred for the diagnosis and grading of STS. Biopsy should be performed by an experienced surgeon or radiologist, placed along the future resection axis with minimal dissection and careful attention to hemostasis. The goal of biopsy is to establish the malignancy and provide a specific diagnosis where possible and a grade where appropriate or feasible, recognizing that limited biopsy material may underestimate grade. It may be accomplished by open incisional or core needle technique. Core needle biopsy is preferred; however, an open incisional biopsy may be considered by an experienced surgeon. In patients without a definitive diagnosis following initial biopsy due to limited sampling size, repeat image-guided core needle biopsy should be considered to make a diagnosis. Although fine-needle aspiration (FNA) is a convenient technique, it can be difficult to make an accurate primary diagnosis with FNA alone due to small specimen size and is thus discouraged.[33] FNA may be acceptable in select institutions with clinical and pathologic expertise. Endoscopic or needle biopsy may be indicated for deep thoracic, abdominal, or pelvic STS.

Principles of Pathologic Assessment

Pathologists with expertise in STS should review the pathologic assessment of biopsies and resected specimens, especially for initial histopathologic classification. Margins must be thoroughly evaluated in these specimens. Morphologic assessment based on microscopic examination of histologic 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 histopathologic type of a sarcoma is often difficult, several ancillary techniques have been used as an adjunct to morphologic diagnosis. These techniques include conventional cytogenetics, IHC, electron microscopy, and molecular genetic testing. 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 WHO Classification of STS tumor); the organ and site of sarcoma; depth, size, and histologic grade of the tumor; presence or absence of necrosis; status of excision margins and lymph nodes; tumor, node, and metastasis (TNM) stage; and additional features such as mitotic rate, presence or absence of vascular invasion, and the type and extent of inflammatory infiltration.

Molecular Diagnosis of Soft Tissue Sarcomas

Molecular genetic testing has emerged as a particularly useful ancillary technique since many subtypes of STS are associated with characteristic genetic aberrations including single base-pair substitutions, deletions, amplifications, and translocations. STS can be divided into two major genetic groups: 1) sarcomas with specific genetic alterations (eg, chromosomal translocations or point mutations) and usually simple karyotypes; and 2) sarcomas with non-specific genetic alterations and complex unbalanced karyotypes.[34]

STS with recurrent chromosomal translocations can be classified into subtypes depending on the presence of fusion gene transcripts (eg, *EWSR1-ATF1* in clear cell sarcoma, *TLS-CHOP* [also known as *FUS-DDIT3*] in myxoid or round cell LPS, *SS18-SSX* [*SS18-SSX1 or SS18-SSX2*] in synovial sarcoma, and *PAX-FOXO1* [*PAX3-FOXO1 or PAX7-FOXO1*] in alveolar RMS). The fusion genes resulting from chromosomal translocations can provide useful diagnostic and prognostic information. See *Principles of Ancillary Techniques Useful in the Diagnosis of Sarcomas* in the guidelines for a list of recurrent genetic aberrations associated with other subtypes.

Conventional cytogenetic analysis, fluorescence in situ hybridization (FISH), and polymerase chain reaction (PCR) are the most common techniques used in the molecular diagnosis of STS.[35] In a prospective study, Hill and colleagues concluded that PCR-based molecular analysis is more sensitive than conventional cytogenetics and is a useful adjunct for the diagnosis of alveolar RMS, synovial sarcoma, and myxoid LPS that have variation in fusion gene partners.[36] Molecular genetic testing was analyzed in a prospective, multicenter study (GENSARC) that enrolled 395 patients with histologic diagnoses of various sarcoma subtypes.[37] Molecular classification of samples from these patients was performed using FISH, comparative genomic hybridization, and PCR, resulting in modified diagnoses in 53 cases. The modified molecular diagnosis reportedly shifted prognosis and primary management in 45 of these cases.

The molecular heterogeneity of fusion gene transcripts has been suggested to predict prognosis in certain sarcoma subtypes. In patients with alveolar RMS presenting with metastatic disease, *PAX7-FOXO1* was associated with a favorable prognosis compared to *PAX3-FOXO1*.[38] In patients with synovial sarcoma, the prognostic impact of *SS18-SSX1* or *SS18-SSX2* is less clear with two large studies showing conflicting results.[39,40] In myxoid LPS, the variability of fusion gene transcript has no effect on clinical outcome.[41]

While molecular genetic testing appears promising, it involves highly complex techniques and the methods are not absolutely sensitive or they do not provide specific results. Molecular testing should be performed by a pathologist with expertise in the use of molecular diagnostic techniques for the diagnosis of STS. In addition, technical limitations associated with molecular testing suggest that molecular evaluation should be considered only as an ancillary technique. Molecular test results should therefore only be interpreted in the context of the clinical and pathologic features of a sarcoma.[35]

Staging

The revised AJCC Cancer Staging Manual, Eighth Edition (2017), effective January 2018, is based on TNM and tumor grade. AJCC follows the grading system of the French Federation of Cancer Centers Sarcoma Group (FNCLCC), a 3-tiered system based on tumor cell differentiation, mitotic activity, and extent of necrosis.[42] The panel recommends determination of histologic grade using the FNCLCC or AJCC/National Cancer Institute (NCI) system or appropriate diagnosis-specific grading system if applicable.

Surgery

Surgical resection (with appropriately negative margins) is the standard primary treatment for most patients with STS, although close margins may be necessary to preserve uninvolved critical neurovascular structures. RT and/or chemotherapy (in the case of chemosensitive histologies) are often used prior to surgery in many centers to downstage large high-grade tumors to enable effective surgical resection, because the risk of failure in the surgical bed can be high. Postoperative RT should be considered following resections with close soft tissue margins (<1 cm) or a microscopically positive margin on bone, major blood vessels, or a nerve. In selected cases when margin status is uncertain, consultation with a radiation oncologist is recommended.

The biopsy site should be excised en bloc with the definitive surgical specimen. Dissection should be through grossly normal tissue planes uncontaminated by tumor. If the tumor is close to or displaces major vessels or nerves, these need not be resected if the adventitia or perineurium is removed and the underlying neurovascular structures are not involved with gross tumor. Radical excision or entire anatomic compartment resection is not routinely necessary. If resections with microscopically positive or grossly positive margins are anticipated, surgical clips should be left in place to identify high-risk areas for recurrence, particularly for retroperitoneal or intra-abdominal sarcomas to help guide future RT. If closed suction drainage is used, the drains should exit the skin close to the edge of the surgical incision (in case re-resection or RT is indicated).

Both the surgeon and the pathologist should document surgical margins while evaluating a resected specimen. Complete tumor resection is a primary prognostic factor for local recurrence (LR). If surgical margins are positive on final pathology, re-resection to obtain negative margins should be strongly considered if it will not have a significant impact on functionality.[43,44] In an analysis of 666 consecutive patients with localized STS treated with an apparent macroscopic total tumor resection, residual tumor was found in 46% of patients, including macroscopic tumor in 28%. A total of 295 patients underwent reresection of their tumor bed. Local control rates at 5, 10, and 15 years were 85%, 85%, and 82%, respectively, for patients who underwent reresection, versus 78%, 73%, and 73%, respectively (P = .03) for patients who did not undergo reresection. Recent studies of tumor margin classification systems provide insight into LR risk assessment and may help to guide surgical planning and decisions regarding re-resection.[45,46]

The implications of lymph node evaluation were recently examined based on data from 2993 patients with resected STS in the NCDB (5.9% nodal metastasis rate).[47] Omission of nodal evaluation was associated with risk of death, and pathologic identification of nodal disease was related to lower median OS in histologic subtypes such as epithelioid and clear cell sarcomas.

Radiation Therapy

RT can be administered either as primary, preoperative, or postoperative treatment. Total RT doses are always determined based on the tissue tolerance. Newer RT techniques such as brachytherapy, intraoperative RT (IORT), and intensity-modulated RT (IMRT) have led to the improvement of treatment outcomes in patients with STS. Brachytherapy involves the direct application of radioactive seeds into the tumor bed through catheters placed during surgery. Options include low dose-rate (LDR) brachytherapy, fractionated high dose-rate (HDR) brachytherapy, or intraoperative HDR brachytherapy.[48] LDR and HDR brachytherapy are associated with similar rates of local control.[49] It has been suggested that HDR brachytherapy may be associated with lower incidences of severe toxicity; however, this has not been proven in randomized clinical trials.[49] The main advantage of IMRT is its ability to more closely contour the high-dose radiation volume thereby minimizing the volume of high-dose radiation to the surrounding normal tissues.[50] Additionally, image-guided techniques may allow for reduced target volumes, further minimizing toxicity.[51,52] IORT is the delivery of radiation during surgery and it can be performed using different techniques such as electron beam RT or brachytherapy.[53]

A recent systematic review and meta-analysis examined the effects of external beam RT (EBRT) (vs. no EBRT) on LR and OS, also comparing preoperative to postoperative approaches for STS.[54] Data analysis from 16 studies (n = 3958) indicated that EBRT reduced LR and improved OS for retroperitoneal STS, and reduced LR for STS of the extremity, head and neck, or trunk wall (OR, 0.49; 95% CI, 0.31–0.77; *P* = .002). Based on a subset of 11 studies, LR rates were lower with preoperative RT than for postoperative RT for retroperitoneal STS (OR, 0.03; *P* = .02) and other tumor locations (OR, 0.67; *P* =.01). Results of a randomized study showed a non-significant trend toward reduced late toxicities (fibrosis, edema, and joint stiffness) with preoperative compared to postoperative radiation and a significant association between these toxicities and increasing treatment field size. Because postoperative radiation fields are typically larger than preoperative fields, the panel has expressed a general preference for preoperative radiation, particularly when treatment volumes are large.[55,56]

Preoperative RT may reduce seeding during the 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.[57-59] Most institutions include the entire operative bed within the RT field. The main disadvantage of preoperative RT, however, is its effect on wound healing.[60,61] Wound complications in patients with sarcoma are more frequently associated with pre- vs. postoperative RT.[54] After preoperative RT, a 3- to 6-week interval is necessary before resection to allow acute reactions to subside and decrease the risk of wound complications.[62] Involvement of a plastic surgeon on the team may be necessary to reduce wound complications when preoperative RT is contemplated.

Postoperative RT is associated with higher rates of long-term treatment-related side effects. In one retrospective analysis, although there was no evidence for differences in disease outcome associated with the use of either preoperative or postoperative RT, there was a slight increase in late treatment-related side effects with postoperative RT, mainly due to the higher doses used.63 Positive surgical margins are associated with higher rates of LR.64 Postoperative RT has been shown to improve local control in patients with positive surgical margins.65 Of those with positive margins, RT doses >64 Gy, microscopically positive margins, superficial location, and extremity site are associated with improved local control.

Postoperative RT boost of 16 Gy has been used in patients with positive surgical margins after the wound has healed. However, the results of a retrospective analysis showed that postoperative RT boost did not provide any advantage in preventing LR in some patients with positive surgical margins (such as those with low-grade, well-differentiated LPS [WDLS] and a focally "planned" positive margin on an anatomically fixed critical structure).[66] Similarly, another retrospective matched cohort of patients with extremity STS found no added benefit of postoperative RT boost when evaluating LR, distant metastasis, and mortality.[67]

The advantage of adding postoperative RT boost has not yet been evaluated in a randomized clinical trial. Intervals beyond 8 weeks between resection and postoperative RT are not recommended because of the development of late fibrosis and the proliferation of malignant cells. The risk of LR versus the toxicity of postoperative RT should be assessed before making a decision regarding the use of postoperative RT.

Chemotherapy/Chemoradiation

Resectable Disease

Preoperative Therapy

Preoperative chemotherapy[68-72] or chemoradiation[73-82] has been evaluated in single and multicenter studies in patients with high-grade tumors.

Studies that have evaluated preoperative chemotherapy followed by surgery have reported inconsistent findings. The results of a randomized study that compared surgery alone vs. preoperative chemotherapy followed by surgery in 134 evaluable patients with high-risk tumors (tumors ≥8 cm of any grade, grade II/III tumors <8 cm, grade II/III locally recurrent tumors, or tumors with inadequate surgery) did not show a major survival benefit for patients receiving chemotherapy.[69] At a median follow-up of 7.3 years, the estimated 5-year disease-free survival (DFS) rate was 52% for the no chemotherapy arm and 56% for the chemotherapy arm (P = .3548). The corresponding 5-year overall survival (OS) rate for both arms was 64% and 65%, respectively (P = .2204). A cohort analysis of 674 patients with stage III STS of extremity treated at a single institution revealed that clinical benefits associated with preoperative or postoperative doxorubicin-based chemotherapy were not sustained beyond one year.[70] In another retrospective study, the benefit of preoperative chemotherapy was only seen in patients with high-grade extremity tumors larger than 10 cm but not in patients with tumors 5 to 10 cm.[71]

In a single-institution study involving 48 patients with high-grade extremity STS (8 cm or larger), the outcome of patients treated with preoperative chemoradiation with the MAID (mesna, doxorubicin, ifosfamide, and dacarbazine) regimen followed by surgery and postoperative chemotherapy with the same regimen was superior to that of historical controls.[75] The 5-year actuarial local control, freedom from distant metastasis, DFS, and OS rates were 92% and 86% (P = .1155), 75% and 44% (P = .0016), 70% and 42% (P = .0002), and 87% and 58% (P = .0003) for the MAID and control groups, respectively.[75] The same protocol was later evaluated in the RTOG 9514 study of 66 patients with large (8 cm or larger), high-grade (stage II or III; grade 2 or 3 in a 3-tier grading system), primary, or locally recurrent STS of the extremities or trunk.[77,78] The 5-year rates of locoregional failure (including amputation) and distant metastasis were 22% and 28%, respectively, with a median follow-up of 7.7 years. The estimated 5-year DFS, distant DFS, and OS rates were 56%, 64%, and 71%, respectively.[78] Long-term follow-up data of these studies confirmed that preoperative chemoradiation followed by resection and postoperative chemotherapy with a doxorubicin-based regimen improves local control and OS and DFS rates in patients with high-grade STS of extremity and body wall; however, preoperative chemoradiation was associated with significant short-term toxicities.[78,79]

Postoperative Therapy

Available evidence from meta-analyses[83-87] and randomized clinical trials [88-93] suggests that postoperative chemotherapy improves relapse-free survival (RFS) in patients with STS of extremities. However, data regarding OS advantage are conflicting.

The Sarcoma Meta-Analysis Collaboration (SMAC) performed a meta-analysis of 14 randomized studies (1568 patients), which compared postoperative chemotherapy to follow-up and in some cases RT after surgery with a variety of sarcomas.[84] The result of the meta-analysis showed that doxorubicin-based chemotherapy prolongs local and distant recurrence and overall RFS in adults with localized, resectable STS of the extremity and is associated with decreased recurrence rates. The OS advantage was not significant, although there was a trend in favor of postoperative chemotherapy.

An updated meta-analysis also confirmed the marginal efficacy of postoperative chemotherapy in terms of local, distant, and overall recurrence as well as OS (which is contrary to that reported in the SMAC meta-analysis) in patients with localized STS (n = 1953).[86] A recent large, cohort-based analysis with a median follow-up of 9 years indicated that postoperative chemotherapy may be associated with significantly improved 5-year metastasis-free survival (58% vs. 49%, *P* = .01) and 5-year OS (58% vs. 45%, *P* = .0002) in patients with FNCLCC grade 3 STS, whereas it was not significantly different in those with FNCLCC grade 2 STS (5-year metastasis-free survival: 76% vs. 73%, *P* = .27; 5-year OS: 75% vs. 65%, *P* = .15).[87]

In the Italian randomized cooperative study (n = 104), which randomized patients with high-grade or recurrent extremity sarcoma 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; the absolute benefit for OS from chemotherapy was 13% at 2 years and increased to 19% at 4 years for patients receiving chemotherapy.[89] After a median follow-up of 90 months, the estimated 5-year OS rate was 66% and 46%, respectively (*P* = .04), for the treatment group and the control group; however, the difference was not statistically different in the intent-to-treat analysis.[94]

In another phase III randomized study (EORTC-62931), 351 patients with macroscopically resected grade II-III tumors with no metastases were randomized to observation or postoperative chemotherapy with ifosfamide and doxorubicin with lenograstim.[91] A planned interim analysis of this study showed no survival advantage for postoperative chemotherapy in patients with resected high-grade STS. The estimated 5-year RFS was 52% in both arms and the corresponding OS rates were 64% and 69%, respectively, for patients assigned to postoperative chemotherapy and observation. These findings are consistent with the results reported in an earlier EORTC study by Bramwell and colleagues.[88] In that study, postoperative chemotherapy with CYVADIC (cyclophosphamide, vincristine, doxorubicin, and dacarbazine) was associated with higher RFS rates (56% vs. 43% for the control group; *P* = .007) and significantly lower LR rates (17% vs. 31% for the control group; *P* = .004). However, there were no differences in distant metastases (32% and 36%, respectively, for CYVADIC and the control group; *P* = .42) and OS rates (63% and 56%, respectively, for CYVADIC and the control group; *P* = .64).

A recent pooled analysis of these two randomized EORTC studies (pooled n = 819) evaluated whether adjuvant doxorubicin-based chemotherapy provided survival benefits in any particular subset of patients with resected STS in these trials.[93] Postoperative doxorubicin-based chemotherapy was associated with improved RFS in male patients and those aged >40 years, although female patients and those aged <40 years who received adjuvant chemotherapy had marginally worse OS. However, RFS and OS were significantly improved in patients with R1 resection who received adjuvant chemotherapy compared with those who did not.

Long-term follow-up results of another prospective randomized study also showed that postoperative chemotherapy with IFADIC (ifosfamide, dacarbazine, and doxorubicin) given every 14 days with growth factor support did not result in significant benefit in terms of RFS (39% for IFADIC and 44% for the control group; *P* = .87) as well as OS (*P* = .99) for patients with grade 2 or 3 STS.[92]

Advanced, Unresectable, or Metastatic Disease

Chemotherapy with single agents (dacarbazine, doxorubicin, epirubicin, or ifosfamide) or anthracycline-based combination regimens (doxorubicin or epirubicin with ifosfamide and/or dacarbazine) have been widely used for patients with advanced, unresectable, or metastatic disease.[95-107] Other chemotherapeutic agents such as gemcitabine, docetaxel, vinorelbine, pegylated liposomal doxorubicin, and temozolomide have also been evaluated in clinical trials. The recently published METASARC observational study, which explored "real-world" outcomes among 2225 patients with metastatic STS, found a positive association of OS with front-line combination chemotherapy, LMS histology, and locoregional treatment of metastases. However, with the exception of LMS, the benefits of systemic therapy beyond the second-line setting were very limited.[108]

Gemcitabine in combination with docetaxel, vinorelbine, or dacarbazine has been shown to be active in patients with unresectable or metastatic STS of various histologic subtypes.[109-113] In a randomized phase II study, the combination of gemcitabine and docetaxel was associated with superior progression-free survival (PFS) (6.2 months and 3.0 months, respectively) and OS (17.9 months and 11.5 months, respectively) compared to gemcitabine alone in patients with metastatic STS.[110] In another phase II study, the combination of gemcitabine and vinorelbine was also associated with clinically meaningful rates of disease control in patients with advanced STS.[111] Clinical benefit (complete response [CR], partial response [PR], or stable disease at 4 months or more) was seen in 25% of patients. The combination of gemcitabine and dacarbazine resulted in superior PFS (4.2 months vs. 2 months; *P* = .005), OS (16.8 months vs. 8.2 months; *P* = .014), and objective response rate (49% vs. 25%; *P* = .009) compared to dacarbazine alone in patients with previously treated advanced STS.[112]

However, gemcitabine combination therapy was not superior to single-agent doxorubicin in the randomized phase III GeDDiS trial. Among patients with previously untreated advanced or metastatic disease (n = 257), combination therapy with gemcitabine and docetaxel did not result in superior PFS compared with doxorubicin (23.7 weeks vs. 23.3 weeks, *P* = .06).[113]

Temozolomide,[114-116] pegylated liposomal doxorubicin,[117] and vinorelbine[118,119] have also shown activity as single agents in patients with advanced, metastatic, relapsed, or refractory disease. In a phase II study by the Spanish Group for Research on Sarcomas, temozolomide resulted in an overall response rate of 15.5% with a median OS of 8 months in patients with advanced pretreated STS.[116] The PFS rates at 3 months and 6 months were 39.5% and 26%, respectively. In a prospective randomized phase II study, pegylated liposomal doxorubicin had equivalent activity and improved toxicity profile compared to doxorubicin; response rates were 9% and 10% for doxorubicin and pegylated liposomal doxorubicin, respectively, in patients with advanced or metastatic STS.[117] In a retrospective study of pretreated patients with metastatic STS, vinorelbine induced overall response in 6% of patients and 26% had stable disease.[118]

Trabectedin is a novel DNA-binding agent that has shown objective responses in phase II and III studies of patients with advanced STS.[120-128] Recent phase III data from a randomized, multicenter trial revealed a 2.7-month PFS benefit versus dacarbazine in metastatic LPS or LMS that progressed after anthracycline-based therapy; the study is ongoing to determine OS.[126] Another recent study supported the efficacy of trabectedin in translocation-related sarcoma.[128] A phase III trial comparing trabectedin and doxorubicin-based chemotherapy revealed that neither arm showed superiority for PFS and OS; however, the trial was underpowered.[129] Preliminary results from the randomized phase III T-SAR trial revealed a PFS benefit for trabectedin over best supportive care in both "L-type" (LPS and LMS) and non–L-type pretreated advanced sarcoma.[130] However, trabectedin plus doxorubicin failed to demonstrate superiority over doxorubicin alone in a randomized phase II study of patients with advanced STS.[131] Trabectedin is included for palliative therapy as a category 1 recommendation for LPS and LMS (L-type) and as category 2A for non–L-type sarcomas.

Eribulin is a novel microtubule-inhibiting agent that has been evaluated as a single-agent therapy for STS, including LMS, adipocytic sarcoma, synovial sarcoma, and other tumor types.[132] Recent data from a phase III trial compared the survival benefit of eribulin and dacarbazine in 452 patients with advanced LMS or LPS, revealing a median OS of 13.5 months and 11.5 months, respectively (HR, 0.77; 95% CI, 0.62–0.95; P = .017).[133] Eribulin is included for palliative therapy as a category 1 recommendation for LPS.

Targeted Therapy

More recently, a number of targeted therapies have shown promising results in patients with certain histologic types of advanced or metastatic STS.

Pazopanib, a multitargeted tyrosine kinase inhibitor (TKI), has demonstrated single-agent activity in patients with advanced STS subtypes except LPS.[135-138] In a phase III study (EORTC 62072), 369 patients with metastatic non-lipogenic STS who had failed at least one anthracycline-based chemotherapy regimen were randomized to either pazopanib or placebo.[137] Pazopanib significantly prolonged median PFS (4.6 months vs.1.6 months for placebo; $P < .0001$) and there was also a trend toward improved OS (12.5 months and 11 months, respectively; P = .25), although it was not statistically significant. Health-related quality-of-life measures did not improve or decline with the PFS benefit.[139] Pooled data from individuals who received pazopanib in phase II and III trials (n = 344) revealed a subset of long-term responders/survivors presenting at baseline with good performance status, low-/intermediate-grade primary tumor, and normal hemoglobin level.[140] The guidelines have included pazopanib as an option for palliative therapy for patients with progressive, unresectable, or metastatic non-lipogenic STS.

Imatinib[141] and sunitinib[142,143] have also shown efficacy in patients with advanced and/or metastatic STS other than GIST. Sorafenib appeared to be active in a small cohort of patients with solitary fibrous tumor.[144] Crizotinib, an anaplastic lymphoma kinase (ALK) inhibitor, was active in inflammatory myofibroblastic tumor (IMT) with ALK translocation.[145] The updated guidelines also include ceritinib, a next-generation ALK inhibitor that has been successful in treating ALK-rearranged non-small cell lung cancer.[146]

mTOR inhibitors such as sirolimus, temsirolimus, and everolimus have also shown promising results in patients with metastatic perivascular epithelioid cell tumors (PEComas) and in patients with recurrent lymphangioleiomyomatosis or angiomyolipomas.[147-153] Additionally, sorafenib may be active in select subtypes of advanced and/or metastatic STS other than GIST (eg, LMS, desmoid tumors).[154,155]

Bevacizumab either alone or in combination with temozolomide was well tolerated and effective in patients with metastatic or locally advanced or recurrent epithelioid hemangiopericytoma and malignant solitary fibrous tumor.[156,157]

Palbociclib, an inhibitor of cyclin-dependent kinases (CDKs) 4 and 6, induced objective tumor response and a favorable PFS of 56% to 66% in patients with CDK-4–amplified, well-differentiated or dedifferentiated liposarcoma (WD/DDLS).[158,159]

The randomized, phase II REGOSARC trial examined regorafenib, an agent approved for treating GIST, in cohorts of patients with advanced LPS, LMS, synovial sarcoma, and other non-GIST STS subtypes (REGOSARC, n = 182).[160,161] Compared to placebo, regorafenib significantly extended PFS in all but the LPS cohort. In patients with nonadipocytic STS, overall PFS for regorafenib and placebo-treated patients was 4 months vs. 1 month (HR 0.36, $P < .0001$).

Soft Tissue Sarcomas of the Extremities, Superficial Trunk, or Head and Neck

Evaluation and Workup

The differential diagnosis of STS of the extremities includes ruling out desmoid tumors (aggressive fibromatosis), as well as the other malignant and benign lesions. An essential element of the workup is a history and physical (H&P) examination, imaging of the primary tumor and distant metastases, and a carefully planned biopsy (core needle or incisional biopsy). 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. The propensities to spread to various locations vary between the subtypes of sarcoma. Therefore, imaging should be individualized based on the subtype of sarcoma. Laboratory tests have a limited role.

Imaging studies should include cross-sectional imaging to provide details about tumor size and contiguity to nearby visceral structures and neurovascular landmarks. The panel recommends MRI with contrast, with or without CT with contrast. Other imaging studies such as CT angiogram and plain radiograph may be warranted in selected circumstances. Given the risk for hematogenous spread from a high-grade sarcoma to the lungs, imaging of the chest (CT without contrast [preferred] or x-ray) is essential for accurate staging. Abdominal/pelvic CT should be considered for angiosarcoma, LMS, myxoid/round cell LPS, or epithelioid sarcoma as well as STS without definitive pathology prior to final resection. MRI of the total spine should be considered for myxoid/round cell LPS due to the higher risk of metastasis to the spine compared to other STSs.[162-164] Alveolar soft part sarcoma has a relatively increased propensity to metastasize to the brain, especially in patients with stage IV disease in the presence of pulmonary metastases.[165] Central nervous system MRI (or CT if MRI is contraindicated) should be considered for patients with alveolar soft part sarcoma and angiosarcoma.

PET scans may be useful in staging, prognostication, grading, and determining histopathologic response to chemotherapy.[166-171] The maximum standardized uptake value (SUVmax) of F18-deoxyglucose has been shown to correlate with tumor grade and prognostication.[172,173] In a retrospective study, tumor SUVmax determined by PET was an independent predictor of survival and disease progression.[166] Schuetze and colleagues reported that the pretreatment SUVmax and change in SUVmax after preoperative chemotherapy independently identified patients with a high risk of recurrence.[167] Patients with a change in the SUVmax of 40% or more in response to chemotherapy were at a significantly lower risk of recurrence and death after complete resection and postoperative RT; the projected 5-year RFS rate for this group of patients was 80% compared to 40% for those with a less than 40% reduction in SUVmax.[167] PET was useful in the early assessment of response to preoperative chemotherapy and was also significantly more accurate than the RECIST criteria in the assessment of histopathologic response to preoperative chemotherapy.[169,170] In a prospective study of 50 patients with resectable, high-grade STS, a 35% reduction in the SUV after first cycle of chemotherapy was a sensitive predictor of histopathologic response.[170] The value of combined PET/CT in predicting DFS in patients receiving preoperative chemotherapy for STS is being evaluated in an ongoing large prospective study.

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

- Stage I
- Stage II-III
- Unresectable disease
- Stage IV (Synchronous Metastatic Disease)
- Recurrent disease

General Principles of Treatment

Surgery

Positive surgical margin is a strong predictor of LR for patients with extremity STS.[174-179] Microscopically positive margins are associated with a higher rate of LR and a lower rate of DFS in patients with extremity sarcomas.[174,175,177] In a large cohort study (1668 patients) that examined the clinical significance of the main predictors of LR in patients with STS of extremity and trunk, the 10-year cumulative possibility of LR was significantly higher for patients with positive surgical margins (23.9 vs. 9.2 for those with negative margins; $P < .001$).[178] In a recent retrospective study that evaluated 278 patients with STS of the extremities treated between 2000 and 2006, patients with a positive margin were 3.76 times more likely to develop LR than those with negative margins (38% risk of LR after 6 years if the margins were positive compared to 12% if the margins were negative).[179] Careful preoperative planning by an experienced sarcoma surgical team may enable anticipated planned positive margins in order to save critical structures without affording a worse oncologic outcome.[44]

Amputation was once considered the standard treatment to achieve local control in patients with extremity sarcomas.[180] 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 study of 43 patients showed that limb-sparing surgery with RT was an effective treatment in patients with high-grade STS of the extremities, with a LR rate of 15% and no difference in OS and DFS as compared to amputation.[181] In another series of 77 patients treated with limb-sparing surgery without RT, the LR rate was only 7% and resection margin status was a significant predictor of LR.[182] The LR 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 an 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.[183]

Collectively, the data suggest that limb-sparing surgery with or without postoperative RT is an effective treatment option for extremity STS and amputation should be reserved only for cases where resection or reresection with adequate margins cannot be performed without sacrificing the functional outcome. The guidelines recommend that the goal of surgery for patients with STS of extremities should be functional limb preservation, if possible, within the realm of an appropriate oncologic resection. Limb-sparing surgery is recommended for most patients with STS of extremities to achieve local tumor control with minimal morbidity. Amputation may improve local control in patients who might not be candidates for limb-sparing surgery and it should be considered with patient preference, or if the gross total resection of the tumor is expected to render the limb nonfunctional.[184-187] Prior to considering amputation, the patient should be evaluated by a surgeon with expertise in the treatment of STS. Evaluation for postoperative rehabilitation is recommended for all patients with extremity sarcoma. If indicated, rehabilitation should be continued until maximum function is achieved.

Radiation Therapy

Data from randomized studies[64,188,189] and retrospective analyses[60,190-193] support the use of preoperative or postoperative EBRT in appropriately selected patients. Brachytherapy (alone or in combination with EBRT)[190,194,195] and IMRT[196,197] have also been evaluated as an adjunct to surgery.

Preoperative vs. Postoperative EBRT

Various studies have examined the benefits and risks for preoperative and postoperative RT approached for treating STS of the extremity, head and neck, or superficial trunk.

Recently, examination of data from 27,969 patients with extremity STS in the NCDB identified both preoperative and postoperative RT as factors associated with increased OS.[193] However, that data showed that preoperative RT was predictive of achieving R0 resection.[193] In a phase III randomized study conducted by the Canadian Sarcoma Group, local control and PFS rates were similar in patients receiving either preoperative or postoperative RT in patients with localized primary or recurrent disease.[189,198] However, preoperative RT was associated with a greater incidence of acute wound complications (35% vs.17% for postoperative RT), especially in lower extremity tumors (43% vs. 5% for upper extremity tumors). Late-treatment–related side effects were more common in patients receiving postoperative RT, which is believed to be related to the higher RT dose (66 Gy vs. 50 Gy for preoperative RT) and the larger treatment volume.[55,189]

The efficacy of postoperative EBRT following limb-sparing surgery was demonstrated in a prospective randomized study (91 patients with high-grade lesions and 51 patients with low-grade lesions).[188,199] Postoperative RT significantly reduced the 10-year LR rate among patients with high-grade lesions (no LRs in patients who underwent surgery plus RT vs. 22% in those who underwent surgery alone; P = .0028). Among patients with low-grade lesions, the corresponding recurrence rates were 5% and 32%, respectively.[188] The probability of reduction in the LR rate in patients receiving EBRT was not significant in patients with low-grade lesions, suggesting postoperative RT after limb-sparing surgery may not be necessary for this group of patients. Outcomes at 20-year follow-up favored patients who received EBRT, but differences were not statistically significant. Ten-year OS was 82% and 77% for patients who received surgery alone versus surgery plus EBRT, and 20-year OS was 71% and 64% for these groups, respectively (P = .22).[199]

The French Sarcoma Group recently reported on a cohort of 283 patients with resectable atypical lipomatous tumor (ALT)/WDLS of the extremity or superficial trunk from the Conticabase database. In these patients, postoperative RT significantly improved 5-year local RFS (98.3% vs. 80.3%, with and without adjuvant RT, respectively; $P < .001$).[200] Along with RT, tumor site and resection margin status were predictors of time to LR, but no difference in OS was observed.

In a report from the Memorial Sloan Kettering Cancer Center (MSKCC) that reviewed the long-term outcomes of 200 patients treated with limb-sparing surgery, pathologically negative re-resection without RT was associated with a 5-year overall LR rate of 9%, at a median follow-up of 82 months.[201] Old age and/or stage III disease were associated with a higher rate of LR. Therefore, treatment decisions regarding the use of postoperative RT should be individualized and should not be solely based on the findings of margin-negative re-resection.

Brachytherapy

In a prospective randomized study, 164 patients with completely resected STS of the extremity or superficial trunk were randomized intraoperatively to receive either brachytherapy or no brachytherapy.[194] With a median follow-up time of 76 months, the 5-year local control rates were 82% and 69% in the brachytherapy and no brachytherapy groups, respectively. Patients with high-grade lesions who received brachytherapy had higher local control rates compared to those who received no brachytherapy (89% and 66%, respectively). However, brachytherapy had no impact on local control in patients with low-grade lesions. The 5-year freedom-from-distant-recurrence rates were 83% and 76%, respectively, in the two groups. In a retrospective analysis of 202 adult patients with primary high-grade STS of the extremity, brachytherapy following limb-sparing surgery resulted in lower rates of wound complications, favorable 5-year local control, and distant RFS and OS rates (84%, 63%, and 70%, respectively).[195]

IMRT

In a retrospective analysis of 41 patients with STS of extremity treated with limb-sparing surgery, postoperative IMRT resulted in a 5-year local control rate of 94% in patients with negative as well as positive or close margins, in selected patients with high-risk features.[196] The risk of complications such as edema and joint stiffness were also favorable when compared with conventional RT. In a more recent phase II study, O'Sullivan and colleagues reported that preoperative IMRT resulted in lower wound complication rate in patients with high-grade lesions (30.5% vs. 43% reported in earlier study using conventional EBRT).[202] In a nonrandomized comparison of IMRT and brachytherapy in patients with high-grade, primary, nonmetastatic STS of extremity, local control was significantly better with IMRT than brachytherapy (5-year local control rates were 92% and 81%, respectively; *P* = .04) despite higher rates of adverse features for IMRT.[197]

IORT

Recent reports from a retrospective study suggest that IORT provides excellent local control to STS of the extremity.[203,204] Call and colleagues recently reported long-term outcome of patients with STS of upper extremity treated with EBRT, surgery, and IORT. The 10-year local control and OS rates were 88% and 58%, respectively.[204] The 10-year local control rates were 89% and 86%, respectively, following margin-negative (R0) and margin-positive (R1 and R2) resections. IORT was also retrospectively examined in cohorts of patients with STS of the superficial trunk or extremity who received surgery, IORT, and EBRT at 3 Spanish institutions.[205,206] Five-year IORT in-field control was 86% and 70% for extremity and trunk wall STS, respectively. However, 5-year DFS was 62% in the extremity STS cohort and 45% in the trunk wall STS. Incomplete resection significantly impacted in-field control in both cohorts, and higher IORT dose was positively associated with in-field disease control in extremity STS.

Although the use of IMRT and IORT has resulted in excellent clinical outcomes, their efficacy needs to be confirmed in larger cohorts of patients with longer follow-up. Additionally, image guidance may continue to improve RT outcomes for patients with STS of the extremity. In a recent phase II trial (RTOG-0630; n = 86), the use of preoperative image-guided RT to a reduced target volume resulted in significantly reduced late toxicity without any marginal field recurrences.[52] Additional studies will be required.

Panel Recommendations

When EBRT is used, sophisticated treatment planning with IMRT, tomotherapy, and/or proton therapy can be used to improve therapeutic effect. RT is not a substitute for definitive surgical resection with negative margins, and re-resection to negative margins is preferable.

The usual dose of preoperative RT is 50 Gy in 1.8 to 2.0 Gy per fraction. 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. If wide margins are obtained, postoperative RT may not be necessary. For patients treated with preoperative RT followed by surgery, the guidelines recommend consideration of observation in addition to postoperative RT boost for patients with positive margins. There are data to suggest that boost for positive margins does not improve local control.[66,207] Given no clear evidence to suggest added benefit, the panel recommends that the decision to provide boost be individualized with careful consideration of potential toxicities.

The recommended EBRT boost doses are 16 to 18 Gy for microscopic residual disease, and 20 to 26 Gy for macroscopic residual disease. Brachytherapy boosts should be delivered several days after surgery, through catheters placed at operation, with doses of 16 to 26 Gy for LDR brachytherapy and 14 to 24 Gy for HDR brachytherapy, based on the margin status. Alternatively, IORT (10–12.5 Gy for microscopic residual disease and 15 Gy for gross residual disease) can be delivered immediately after resection to the area at risk, avoiding the uninvolved organs.[203]

For patients who have not received preoperative RT, the postoperative choices include EBRT (50 Gy irrespective of surgical margins in 1.8–2.0 Gy per fraction), IORT (10–16 Gy followed by 50 Gy EBRT), or brachytherapy. The guidelines recommend 45 Gy LDR brachytherapy or HDR equivalent for patients with negative margins. LDR brachytherapy (16–20 Gy) or HDR equivalent is recommended for patients with positive margins followed by EBRT. EBRT following IORT or brachytherapy is delivered to the target volume to a total dose of 50 Gy, after surgical healing is complete (3–8 weeks).

For patients treated with postoperative EBRT, the guidelines recommend an additional EBRT boost (unless prior IORT) to the original tumor bed based on the margin status (10–16 Gy for negative surgical margin; 16–18 Gy for microscopic residual disease; and 20–26 Gy for grossly positive margins). However, many institutions are no longer giving a boost after preoperative RT to patients who have widely negative margins, based on local control rates approaching 95% with preoperative RT at 50 Gy and negative margins. The panel also emphasizes that RT is not a substitute for suboptimal surgical resection and re-resection is preferred for patients with positive surgical margins.

Treatment Guidelines by Stage

Stage I

Surgical wide resection (with intent to obtain negative margins) is the primary treatment for stage IA (T1, N0, M0, low grade) and IB (T2-4, N0, M0, low grade) tumors and is considered definitive if margins are greater than 1 cm or the fascial plane is intact.[208,209] If the surgical margins are 1.0 cm or less and without an intact fascial plane, re-resection may be necessary.[201] Treatment options including revision surgery versus observation should be presented at an experienced multidisciplinary sarcoma tumor board to determine advantages and disadvantages of the decision.

Data from prospective studies support the use of RT as an adjunct to surgery in appropriately selected patients based on an improvement in DFS although not OS.[175,177,194] Postoperative RT is recommended for patients with final surgical margins of 1.0 cm or less and without an intact fascial plane (category 2B for stage IA tumors and category 1 for stage IB). RT may not be necessary in patients with small low-grade lesions (5 cm or less), because these tumors are less frequently associated with LR.[188] Therefore, observation is included as an option for patients with stage IA disease with final surgical margins of 1.0 cm or less and with an intact fascial plane.

En bloc resection with negative margins is generally sufficient to obtain long-term local control in patients with ALT/WDLS; RT is not indicated in most cases.[210,211] In one report that reviewed 91 patients with ALT/WDLS of the extremity and trunk, positive surgical margins were associated with reduced local RFS, suggesting that function-preserving re-resection when possible or adjuvant RT could be considered for selected patients with positive surgical margins.[212] RT may also be an appropriate treatment option for selected patients with recurrent disease or deeply infiltrative primary lesions with a risk of LR, depending on the tumor location and patient's age.[213]

Stage II-III

Treatment options should be decided by a multidisciplinary team with extensive experience in the treatment of patients with STS, based on the patient's age, performance status, comorbidities, location, and histologic subtype of the tumor.

Preoperative chemoradiation has been shown to improve OS, DFS, and local control rates in patients with high-grade STS of extremity and trunk, although acute reactions must be considered.[78,79] An earlier randomized study showed that preoperative chemotherapy was not associated with a major survival benefit for patients with high-grade tumors.[69] Histotype-specific neoadjuvant chemotherapy was examined in a recent international RCT of patients with high-risk STS (n = 287; ISG-STS 1001).[72] Standard neoadjuvant chemotherapy (epirubicin/ifosfamide) was compared with histotype-specific regimens for myxoid LPS (trabectedin), LMS (gemcitabine/dacarbazine), synovial sarcoma (high-dose ifosfamide), MPNST (etoposide/ifosfamide), and UPS (gemcitabine/docetaxel). At 46 months, DFS was 62% for standard chemotherapy versus 38% for the histotype-tailored regimens (HR, 2.00; 95% CI, 1.22–3.26; *P* = .006). Trial enrollment was closed due to futility.

The results of a recent phase III randomized study (EORTC 62961) showed that regional hyperthermia (RHT) increases the benefit of preoperative chemotherapy in patients with localized high-risk STS.[214] In this study, 341 patients were randomized to receive either preoperative chemotherapy with etoposide, ifosfamide, and doxorubicin (EIA) alone, or combined with RHT (EIA plus RHT). After a median follow-up of 34 months, among 149 patients with STS of the extremity, the 2-year DFS and local PFS rates were 70% and 92%, respectively, for patients treated with EIA plus RHT. The corresponding survival rates were 57% and 80% for those treated with EIA alone. However, these results need to be confirmed in large cohort studies and the use of RHT with preoperative chemotherapy is not recommended in the guidelines.

Available evidence, although underpowered, suggests that anthracycline-based postoperative chemotherapy (now most commonly given as doxorubicin and ifosfamide or epirubicin and ifosfamide) would improve DFS in selected patients with good performance status who are at high risk of recurrence.[88-92] Preoperative or postoperative EBRT has been shown to improve local control in patients with high-grade lesions.[54,188,190]

Large stage II or III high-grade extremity resectable tumors (greater than 8–10 cm) that are at high risk for LR and metastases should be considered for preoperative and postoperative therapy. However, there are data supporting that surgery alone is an adequate treatment option in selected patients with high-grade lesions. Long-term results of a prospective study demonstrated that selected patients with high-grade T1 lesions can be treated by surgery alone (R0 resection) with acceptable local control and excellent long-term survival.[215] In the surgery alone arm, the cumulative incidence rates of LR 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%. In an analysis of 242 patients with localized STS of the trunk and extremity treated with limb-sparing surgery, the 10-year local control rate was 87% to 93% for patients with resection margins of less than 1 cm compared with 100% for those with resection margins of 1 cm or more (P = .04).[182] Al-Refaie and colleagues also reported that the addition of RT did not result in any significant difference in OS or sarcoma-specific survival in patients with early-stage STS of the extremity.[216]

Surgery preceded or followed by RT is recommended for patients with stage II tumors (T1, N0, M0, G2-3) that are resectable with acceptable functional outcomes (category 1 for preoperative or postoperative RT).[188,189,198] Surgery alone may be an option for patients with small tumors that can be resected with wider surgical margins.

Surgery followed by RT (category 1) with or without postoperative chemotherapy is the primary treatment for patients with stage IIIA (T2, N0, M0, G2-3) or IIIB (T3-4, N0, M0, G2-3) tumors that are resectable with acceptable functional outcomes. The impact of RT was analyzed in a SEER cohort of 2606 patients with stage III soft-tissue extremity sarcoma. Similarly to smaller prospective studies and reviews, RT was associated with a significant 5-year survival benefit (65% vs. 60%, P = .002). However, the timing of RT (ie, preoperative vs. postoperative) was not a significant factor for survival.[217] Since there are only limited and conflicting data regarding the potential benefits of postoperative chemotherapy for stage II or III patients, postoperative chemotherapy is included as a category 2B recommendation.[88-92] Preoperative RT (category 1), preoperative chemotherapy (category 2B), or chemoradiation (category 2B) are also included as options for this group of patients.

Radical lymphadenectomy may provide long-term survival benefit for patients with isolated lymph node involvement. In a study that examined the natural history of lymph node metastasis in patients with STS, the median survival was 4.3 months for patients not treated with radical lymphadenectomy compared to 16.3 months in patients who underwent radical lymphadenectomy.[218] The 5-year survival rate for the latter group of patients was 46%. The guidelines recommend regional lymph node dissection at the time of primary surgery for patients with stage III tumors with lymph node involvement.

Patients with stage II or III tumors that are resectable with adverse functional outcomes should be managed as described below for unresectable disease.

Unresectable Disease

Patients with unresectable tumors can be treated primarily with RT, chemoradiation, chemotherapy, or regional limb therapy. Tumors that become resectable with acceptable functional outcomes following primary treatment can be treated with surgery followed by RT (if not previously irradiated) with or without postoperative chemotherapy. Since there are only limited and conflicting data regarding the potential benefits of postoperative chemotherapy, it is included as a category 2B recommendation. For patients whose tumors remain resectable with adverse functional outcomes or unresectable following primary treatment, a subsequent distinction is made between asymptomatic and symptomatic patients. Observation is an option for asymptomatic patients. For symptomatic patients, the treatment options include chemotherapy, palliative surgery, amputation, or best supportive care.

A randomized phase III trial examining intensified doxorubicin plus ifosfamide versus doxorubicin alone did not find an OS benefit for combination therapy in patients with unresectable, advanced, or metastatic STS (14.3 months vs. 12.8 months; P = .076). However, response rates and PFS were improved for doxorubicin/ifosfamide compared with doxorubicin alone (26% vs. 14%, *P* = .0006; 7.4 months vs. 4.6 months, *P* = .003).[219] However, subset analyses (n = 310) indicated an OS benefit for doxorubicin/ifosfamide versus single-agent doxorubicin in patients with UPS.[220]

Definitive RT (70–80 Gy) can be considered for selected patients with unresectable tumors following primary treatment. 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.[221] The local control rate was 51% for tumors less than 5 cm and 9% for tumors greater than 10 cm. Patients who received 63 Gy or more had better 5-year local control, DFS, and OS rates (60%, 36%, and 52%, respectively) compared to patients who received less than 63 Gy (22%, 10%, and 14%, respectively). Local control for patients receiving more than 63 Gy was 72% for lesions 5 cm or less, 42% for lesions 5 to 10 cm, and 25% for lesions more than 10 cm.

Regional limb therapy (isolated limb perfusion [ILP] and isolated limb infusion [ILI]) has been evaluated as a limb-sparing treatment for unresectable intermediate or high-grade extremity STS. ILP requires the use of tumor necrosis factor-α (TNF-α) along with chemotherapy, which is not approved in the United States. ILI is a less invasive alternative to ILP for patients with unresectable STS of the extremities and can be used without TNF-α. Data from clinical trials suggest that ILP with melphalan or doxorubicin in combination with TNF-α[222-225] or ILI with doxorubicin or melphalan and dactinomycin[226-230] may be effective in the treatment of patients with unresectable STS of extremity.[231] Further prospective clinical trials are needed to better define the role for ILP or ILI in the management of patients with unresectable STS of the extremity.[231] The panel recommends that ILP for isolated regional or nodal disease be accompanied by surgical resection. ILP for recurrent disease should only be performed at institutions with experience in regional limb therapy.

Stage IV (Synchronous Metastatic Disease)

Patients with metastatic stage IV disease (any T, N1, M0, any G; or any T, any N, M1, any G) have a poor prognosis with no disease-free interval.[232,233] Conflicting data exist on the potential survival benefit of metastasectomy. In a retrospective study of 48 patients with synchronous metastases, there was no improvement in OS for patients treated with metastasectomy compared to those with unresectable disease.[232] In a more recent retrospective study involving 112 patients with metastatic disease at presentation, resection of metastatic disease, less than 4 pulmonary metastases, and the presence of lymph node metastases vs. pulmonary metastases were identified as statistically significant variables for improved OS. The 5-year survival rate was 59% and 8%, respectively, for patients presenting with lymph node metastases and pulmonary metastases.[233] Pulmonary metastasectomy resulted in a median OS of 25.5 months in a retrospective analysis of 66 patients with sarcoma; however, recurrent metastasis was associated with poor prognosis.[234] Although recurrence is common after initial metastasectomy, data from a prospective review (n = 539) suggested a potential survival benefit for repeat pulmonary metastasectomy in appropriately selected patients.[235]

Since there are no data to support the optimal management of patients presenting with metastatic disease, the guidelines are intentionally nonspecific about the treatment options for this group of patients. Referral to a medical oncologist with extensive experience in the treatment of STS is recommended. Treatment options should be based on many factors, including performance status, patient preferences, specific clinical problems from the metastases, and treatment availability. In addition, clinical trial is the preferred treatment option for patients with metastatic disease.

Limited Metastases

Patients with limited metastasis confined to a single organ and limited tumor bulk that are amenable to local therapy should receive primary tumor management as described for stage II or III tumors. Another option is to consider metastasectomy with or without chemotherapy with or without RT. The guidelines do not specify rules governing metastasectomy, which remains controversial.[232,234,235] Several variables, including tumor resectability, number and location of metastases, and performance status influence the decision to use metastasectomy.[233] In addition, patients can also receive stereotactic body RT (SBRT) or chemotherapy as an alternate method for control of metastatic lesions. Several recent reviews and case series support the use of SBRT for local control, with potential survival benefits in selected patients.[236-238]

Disseminated Metastases

For patients presenting with disseminated disease, a subsequent distinction is made between asymptomatic and symptomatic patients. Observation with a "watchful waiting" strategy is a reasonable management option for asymptomatic patients, especially if patients have only a minimal burden of metastases (eg, sub-centimeter pulmonary nodules). Symptomatic patients can be treated with palliative RT, surgery, or chemotherapy. Palliative RT involves expedient treatment with sufficient dose to halt tumor growth or cause tumor regression. The outcome of this approach depends on the rapidity of growth and the status of systemic disease. In addition, the guidelines have included ablation procedures (eg, radiofrequency ablation [RFA] or cryotherapy) or SBRT as options for symptomatic patients.

Surveillance

Surveillance is deemed important to detect recurrences that might still be potentially curable. However, very limited data are available in the literature on effective surveillance strategies.[239-242] Because patient risk never returns to zero, long-term follow-up is indicated, including consideration of MRI or CT scan.[243] There has never been a study to prove that the use of more sensitive CT scans in routine surveillance would improve clinical outcomes. According to the report from MD Anderson Cancer Center, routine use of chest CT adds little clinical benefit when risk of pulmonary metastases is low.[244] However, in certain subsets of patients in whom chest radiographs are difficult to interpret because of anatomic considerations (eg, scarring, emphysema), chest CT may be indicated. A retrospective review examined surveillance imaging in 94 patients with intermediate or high-grade localized extremity/trunk STS who underwent radical resection and RT.[242] Thirty patients (32%) recurred after a median follow-up of 60 months (5 local, 26 distant). Surveillance imaging led to the detection of LR in 2 out of 5 cases and distant recurrence (lung) in 22 out of 26 cases. The authors concluded that surveillance chest imaging may be most useful for the detection of asymptomatic distant recurrence (ie, in the lung), while primary site imaging may only be useful for patients at high risk of LR.

Ultrasound has been used for the detection of early LRs and for the detection of micronodules less than 0.5 cm in diameter.[245-247] In a retrospective analysis that evaluated the value of MRI and ultrasound for the detection of LR after surgery in 21 patients with STS of extremities, the sensitivity of ultrasound was slightly higher than that of MRI (100% vs. 83%) and the specificity was slightly lower than that of MRI (79% vs. 93%).[245] However, the differences were not statistically significant, suggesting that both MRI and ultrasound were equally useful in the detection of LR after surgery. In a subsequent report, Arya and colleagues also reported that ultrasound is associated with high sensitivity and specificity (92% and 94%, respectively) in the detection of early LR in patients with STS.[246] These results confirm that ultrasound can be useful for the detection of LR. However, as reported by Choi and colleagues, ultrasound may be more difficult to interpret than MRI during the early postoperative period.[245] Therefore, MRI should be used if ultrasound results are inconclusive.

The guidelines outline a prudent follow-up schedule by disease stage 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. After 10 years, the likelihood of developing a recurrence is small and follow-up should be individualized.

Stage I tumors are routinely followed with H&P every 3 to 6 months for 2 to 3 years and then annually. Chest imaging is recommended every 6 to 12 months by CT [preferred] or x-ray. Postoperative baseline and periodic imaging of the primary tumor site is recommended based on estimated risk of locoregional recurrence. MRI with and without contrast and/or CT with contrast is recommended; ultrasound can be considered for the detection of LR in patients with smaller, superficial lesions and should be performed by an ultrasonographer with experience in musculoskeletal disease.[245,246] However, in situations where the area is easily followed by physical examination, imaging may not be required.[248]

For stage II/III and synchronous stage IV disease, postoperative re-imaging using MRI with and without contrast (preferred) or CT with contrast should be used to assess the primary tumor site and rule out metastatic disease. Baseline and periodic imaging of the primary site are recommended based on risk of locoregional recurrence; ultrasound can be considered for small, superficial lesions. H&P and imaging of the chest and other known sites of metastatic disease should be performed every 2 to 6 months for 2 to 3 years, then every 6 months for the next 2 years, and then annually.

Recurrent Disease

The management of recurrent disease encompasses a heterogeneous group of patients and clinical scenarios. In retrospective studies, isolated LR at sites other than the head and neck and deep trunk, resectability of recurrent and metastatic disease, disease-free interval, and number of metastases were identified as important predictive factors for long-term survival.[249-251]

For a patient with a LR, treatment decisions should be made using the same algorithm as for patients with a new primary lesion.[252] In patients with LR, some case series suggest that combined conservative surgery and re-irradiation provide superior local control compared to local re-excision alone.[253] However, others have reported that conservative surgery alone results in local control in a minority of patients with locally recurrent disease after previous excision and EBRT,[254] likely reflecting differences in patient selection for surgery and RT or surgery alone. Therefore, the guidelines recommend that if LR can be excised, a decision regarding the use of re-irradiation will need to be made on a case-by-case basis. Traditionally, the re-irradiation has been done with postoperative brachytherapy, but now brachytherapy may be used in combination with IMRT to reduce the risks of morbidity with re-irradiation.

For patients with metastatic recurrences the guidelines distinguish between limited metastases confined to a single organ, disseminated metastases, and isolated regional disease with nodal involvement. The treatment options for patients with limited metastases confined to a single organ or disseminated metastases are similar to that described for stage IV disease at presentation. In patients with isolated regional disease or nodal involvement, options include: 1) regional node dissection with or without RT or chemotherapy; 2) metastasectomy with or without pre- or postoperative chemotherapy and/or RT; 3) SBRT; or 4) ILP/ILI with surgery. Limited data are available on the use of chemotherapy in patients undergoing metastasectomy. Results from a recent retrospective analysis suggest that chemotherapy has minimal impact on the survival of patients with metastatic extremity STS undergoing pulmonary metastasectomy.[255]

Retroperitoneal/Intra-abdominal Soft Tissue Sarcomas

General Principles

Surgery

Surgical resection of a localized tumor with negative margins remains the standard, potentially curative treatment for patients with retroperitoneal/intra-abdominal STS. Postoperative margin status is the most important factor contributing to long-term DFS.[256-260] In a large 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.[259]

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 resection performed in high-volume centers.[261,262] While the results are encouraging, this technique needs to be investigated in prospective clinical trials.

Radiation Therapy

RT can be administered either as preoperative treatment for patients with resectable disease or as a primary treatment for those with unresectable disease. The panel discourages postoperative RT with the exception of highly selected cases or if LR would cause undue morbidity. The panel emphasizes that RT is not a substitute for definitive surgical resection with oncologically appropriate margins and re-resection may be necessary. If re-resection is not feasible, postoperative RT may be considered in highly selected patients, who have not received preoperative RT, to attempt to control microscopic residual disease; however, this approach has not been validated in randomized trials.

A recent case-controlled, propensity score-matched study of the NCDB examined preoperative RT (n = 563) and postoperative RT (n = 2215) versus no RT/surgery alone (n = 6290) in retroperitoneal STS.[263] Both preoperative and postoperative RT were associated with OS when compared with surgery alone (preoperative RT: HR, 0.70; 95% CI, 0.59–0.82; $P < .0001$; postoperative RT: HR, 0.78; 95% CI, 0.71–0.85; $P < .0001$); however, preoperative and postoperative approaches were not directly compared.[263]

Newer RT techniques such as IMRT and 3D conformal RT using protons or photons may allow tumor target coverage and acceptable clinical outcomes within normal tissue dose constraints to adjacent organs at risk.[192,264-267] When EBRT is used, sophisticated treatment planning with IMRT, tomotherapy, and/or proton therapy can be used to improve therapeutic effect. However, the safety and efficacy of adjuvant RT techniques have yet to be evaluated in multicenter randomized controlled studies.

Preoperative RT

Preoperative RT is often preferred, because it reduces the risk of tumor seeding at the time of surgery and may render tumors more amenable to resection.[54,268,269] Long-term results of two prospective studies showed favorable 5-year local RFS (60%), DFS (46%), and OS rates (61%) following R0 or R1 resection after preoperative RT in patients with intermediate or high-grade retroperitoneal STS.[270] Analysis of data from 11 studies of retroperitoneal STS in a recent systematic review and meta-analysis indicated lower rates of LR with preoperative vs. postoperative RT (OR, 0.03; $P = .02$).[54] The usual dose of preoperative RT is 50 Gy. In a single-institution study, Tzeng and colleagues demonstrated that preoperative RT with selective dose escalation (45 Gy in 25 fractions to the entire tumor plus margin and a boost dose of 57.5 Gy to the posterior retroperitoneal tumor margin determined by the surgeon and the radiation oncologist to be at highest risk) was tolerable and allowed for the use of higher RT doses to the high-risk clinical target volume (high-risk CTV) judged to be at greatest risk for local tumor recurrence.[271] In this study, which included 16 patients with biopsy-proven retroperitoneal STS, 14 patients (88%) had undergone macroscopic resection. With a median follow-up of 28 months, there were only 2 LR, with the actuarial 2-year local control rate of 80%.

NCCN recommends 50 Gy preoperative RT (in 1.8–2 Gy per fraction), followed by surgery with clips and consideration of IORT boost for positive margins. Postoperative EBRT boost is discouraged in this setting. An alternative approach to be considered in experienced centers only is 45 to 50 Gy to the entire CTV with dose-painted simultaneous integrated boost to total dose of 57.5 Gy in 25 fractions.[271,272] Since this approach is used in many NCCN Member Institutions, the guidelines have included this dosing schedule and recommend that higher-risk retroperitoneal margins should be jointly defined by the surgeon and the radiation oncologist, with no boost to be given after surgery. An ongoing phase III, randomized, multicenter EORTC trial is evaluating preoperative RT for previously untreated, nonmetastatic retroperitoneal STS (NCT01344018).

Postoperative RT

The data regarding the survival benefits of postoperative RT are conflicting. Postoperative RT has been associated with improved RFS in retrospective nonrandomized studies with no improvement in OS.[258,273,274] In a recent retrospective study, the use of conformal postoperative RT along with aggressive surgical resection was associated with a trend towards decreased LR rate and improved RFS compared to surgery alone.[274] At the 5-year follow-up, the RFS rate was 60% and 47%, respectively (*P* = .02); however, there was no significant difference in OS between the two groups. In one study, the combined use of preoperative RT and postoperative brachytherapy resulted in significantly better DFS and OS in patients with low-grade tumors.[275]

The panel discourages providing a postoperative EBRT boost for retroperitoneal/intra-abdominal sarcoma. If RT is not given prior to surgical resection, consider follow-up with possible preoperative EBRT at time of localized recurrence. If postoperative RT is deemed necessary in highly selected cases, a coordinated effort by the surgeon and the radiation oncologist to displace bowel from the tumor bed with omentum or other tissue displacers is recommended to reduce the risk of RT-related bowel toxicity.

Intraoperative Radiation Therapy

The use of IORT has provided encouraging results in patients with retroperitoneal STS.[276-283] In patients with retroperitoneal STS prospectively treated at a single institution with a protocol involving maximal tumor resection, HDR IORT, and postoperative EBRT, the overall 5-year local control rate for the whole group was 62%; local control rate was better for patients with primary tumors than for those with recurrent tumors (74% vs. 54%; *P* = .40).[277] The overall 5-year distant metastasis-free survival rate was 82% (100% for those with low-grade tumors vs. 70% for those with high-grade tumors; *P* = .05). The 5-year DFS and OS rates were 55% and 45%, respectively. IORT with or without EBRT has been effective in terms of local control and survival in patients with primary and recurrent retroperitoneal STS.[278-280,282] In a study that assessed the long-term outcome of patients with retroperitoneal STS treated by preoperative RT, resection, and IORT with intraoperative 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.[278] An ongoing study (NCT01566123) is examining preoperative RT, followed by surgery with IORT in patients with high-risk retroperitoneal sarcoma. Preliminary results suggest promising local control and OS rates.[284]

Evaluation and Workup

The initial evaluation and workup for retroperitoneal abdominal STS are similar to that for the extremity sarcomas. This workup involves a thorough H&P and appropriate imaging studies, including chest, abdominal, and pelvic CT with contrast with or without an abdominal/pelvic MRI. Chest imaging should be done, especially for patients whose tumors warrant preoperative or postoperative chemotherapy. If possible, a multidisciplinary sarcoma panel should review the patient. Note that for staging, all retroperitoneal lesions are considered deep lesions.

The differential diagnosis of retroperitoneal abdominal soft tissue mass includes malignant lesions (such as other sarcomas, GISTs, lymphomas, or germ cell tumors), desmoids, and benign lesions. Proof of the histologic subtype by biopsy is necessary for patients before receiving preoperative chemotherapy or RT. Biopsy should be considered if there is suspicion of malignancies other than STS. Image-guided (CT or ultrasound) core needle biopsy is preferred over open surgical biopsy. 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 STS is encountered unexpectedly when a laparotomy is performed for some other reason, a core needle biopsy should be done to establish the diagnosis as well as the histopathologic type and grade of tumor. Then, the optimal subsequent resection could be performed.

Treatment Guidelines by Resectability/Stage

Resectable Disease

Surgery (to obtain oncologically appropriate margins) with or without IORT is the primary treatment for most patients with resectable disease. However, complete or macroscopic surgical resection is achieved in less than 70% of patients with primary tumors due to their close proximity to vital structures. LR and disease progression continue to be associated with a significant cause of morbidity in the majority of patients.[285-287] Multimodality treatment (surgery with RT and/or chemotherapy) is therefore favored due to the inability to obtain negative surgical margins and high LR rates.[288]

If RT is anticipated, preoperative RT with an IMRT approach to optimize sparing of critical structures is preferred because it reduces the risk of tumor seeding at the time of surgery and may render tumors more amenable to resection.[268]

Analysis of 8653 patients with resected retroperitoneal STS from the NCDB revealed worse OS in the surgically resected cohort receiving chemotherapy versus those who underwent surgery alone (40 months vs. 52 months, *P* = .002).[289] 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.[290] Little data are available for the use of combined RT and chemotherapy. Decisions about postoperative or preoperative chemotherapy or RT are left to clinical judgment.[291-293] The regimens listed in the guidelines are based on the extrapolation of data derived from clinical trials on STS of the extremity that have included a small number of patients with retroperitoneal STS.[294]

In the phase III randomized study (EORTC 62961), the addition of RHT to preoperative chemotherapy with EIA was associated with a significant survival benefit.[214] At 5-year follow-up, among 149 patients with non-extremity STS, patients treated with EIA plus RHT had superior DFS (34% vs. 27%, *P* = .040) and local PFS (56% vs. 45% after 5 years, *P* = .044) compared with those receiving EIA alone.[295] As is the case with STS of extremities, these results need to be confirmed in large cohort studies and the use of RHT with preoperative chemotherapy is not recommended in the guidelines for the treatment of patients with retroperitoneal or abdominal STS.

Preoperative RT or chemotherapy could be considered prior to surgery in patients whose diagnosis has been confirmed by biopsy. For patients treated with preoperative EBRT (50 Gy) followed by surgery, the guidelines recommend consideration of postoperative RT boost for patients with positive margins, if this can be done within the constraints of adjacent normal tissue. The guidelines recommend an EBRT boost of 16 to 18 Gy for microscopic residual disease, and 20 to 26 Gy for grossly positive margins. Alternatively, IORT (10–12.5 Gy for microscopic residual disease and 15 Gy for gross residual disease) can be delivered immediately after resection to the area at risk, avoiding the uninvolved organs.

Postoperative treatment options are dependent on surgical outcomes and clinical or pathologic findings following surgery. Due to risk of morbidity, postoperative RT should not be administered routinely to patients with negative margin resection (R0) or microscopically positive margins (R1 resection). Highly selected candidates for postoperative RT may include patients with pathologic findings of high-grade disease, extremely large tumors, close surgical margins, or high risk of recurrence. For highly selected patients with R1 resections, RT boost (10–16 Gy) can be considered. Re-resection, if feasible, should be considered for patients with macroscopically positive margins (R2 resection). Alternatively, these patients could also be managed as described below for unresectable disease. The options for postoperative RT include EBRT (50 Gy irrespective of surgical margins) or IORT (10–16 Gy followed by EBRT). For patients treated with postoperative EBRT, the guidelines recommend postoperative RT boost to the original tumor bed based on the margin status (10–16 Gy for negative surgical margin if normal tissue can be adequately spared by tissue displacement with omentum or other biologic or synthetic spacer; 16–18 Gy for microscopic residual disease; and 20–26 Gy for gross residual disease). The dose recommendations above must be balanced and considered in the context of the adjacent normal tissue tolerance to RT.

Unresectable or Stage IV Disease

Unresectable tumors are defined as those that involve vital structures or tumors whose removal would cause unacceptable morbidity. Patients who are medically unresectable (ie, not medically fit to tolerate a major retroperitoneal STS resection) are also included in this category.

Biopsy is recommended before any treatment for a patient with unresectable or metastatic disease. Patients with unresectable or stage IV disease could be treated with chemotherapy, chemoradiation, or RT in an attempt to downstage tumors. For patients undergoing definitive high-dose RT, there has been favorable experience reported in the literature with the use of tissue displacement spacers to keep bowel out of the high-dose RT volume.[296] In terms of response rate, the most active chemotherapy regimen in an unselected patient population is AIM (doxorubicin/ifosfamide/mesna).[219]

For unresectable or stage IV disease, follow-up imaging is recommended to assess treatment response. Options include chest/abdominal/pelvic CT or chest CT without contrast and abdominal/pelvic MRI with contrast. Patients whose tumors become resectable following primary treatment should be managed as described above for resectable disease. If the tumor remains unresectable or if there is disease progression following primary treatment, management decisions depend on whether patients are symptomatic or asymptomatic. Asymptomatic patients can be observed, whereas symptomatic patients can be treated with palliative therapy (chemotherapy, RT, or surgery) for symptom control or best supportive care. In patients with stage IV disease, resection should always be considered for resectable metastatic disease. 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.

Surveillance

Patients should have a follow-up physical examination with imaging (chest/abdominal/pelvic CT or MRI) every 3 to 6 months for 2 to 3 years, then every 6 months for the next 2 years, and then annually.

Recurrent Disease

For patients with resectable, unresectable, or disseminated recurrences, the guidelines recommend the same management after biopsy, as outlined for primary disease.[297] 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 is preferred and should be considered if an appropriate trial is available.

Gastrointestinal Stromal Tumors

GISTs are the most common STS of the gastrointestinal (GI) tract, resulting most commonly from *KIT* or *PDGFRA* activating mutations.[298] GISTs can arise anywhere along the GI tract, but stomach (60%) and small intestine (30%) are the most common primary sites.[299] Duodenum (4%–5%) and rectum (4%) are the less common primary sites, and only a small number of cases have been reported in the esophagus (<1%) and colon and appendix (1%–2%).[299] Patients with a suspected GIST may present with a variety of symptoms, which may include early satiety, abdominal discomfort due to pain or swelling, intraperitoneal hemorrhage, GI bleeding, or fatigue related to anemia. Some patients may present with an acute abdomen (as a result of tumor rupture, GI obstruction, or appendicitis-like pain), which requires immediate medical attention.[300] 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.

General Principles

Biopsy and Pathologic Assessment

GISTs are soft and fragile tumors. The decision to obtain a biopsy should be based on the suspected tumor type and the extent of disease. Biopsy is necessary to confirm the diagnosis of primary GIST prior to the initiation of preoperative therapy.[300] Recent reports have suggested that definitive diagnosis of GIST requires tissue acquisition via endoscopic ultrasound (EUS)-guided FNA.[301] EUS-guided FNA (EUS-FNA) biopsy of primary site is preferred over percutaneous biopsy due to the risk of tumor hemorrhage and intra-abdominal tumor dissemination. Percutaneous image-guided biopsy may be appropriate for confirmation of metastatic disease.

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 (HPFs) (equivalent to 5 mm^2 of tissue). 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 histopathologic features.

Most GISTs (95%) express *KIT* (CD117). Approximately 80% of GISTs have a mutation in the gene encoding the *KIT* receptor tyrosine kinase; another 5% to 10% of GISTs have a mutation in the gene encoding the related *PDGFRA* receptor tyrosine kinase.[302-304] About 10% to 15% of GISTs have no detectable *KIT* or *PDGFRA* mutations (wild-type GIST). Other commonly expressed markers include CD34 antigen (70%), smooth muscle actin (25%), and desmin (less than 5%).[305]

Most of the *KIT* mutations occur in the juxtamembrane domain encoded by KIT exon 11 and some are detected in the extracellular domain encoded by exon 9.[306] KIT mutations have also been identified in the tyrosine kinase domain (exon 13 and exon 17), although they are very rare.[307] The majority of the *PDGFRA* mutations affect exon 18 in the tyrosine kinase domain 2.[306] Few mutations also occur in exon 12 (juxtamembrane domain) and exon 14 (tyrosine kinase domain 1), although they are rare.[308] *KIT* exon 11 mutations are most common in GISTs of all sites, whereas *KIT* exon 9 mutations are specific for intestinal GISTs and *PDGFRA* exon 18 mutations are common in gastric GISTs.[306]

Immunohistochemical staining for CD117, DOG1, and/or CD34 and molecular genetic testing to identify *KIT* and/or *PDGFRA* mutations are useful in the diagnosis of GIST. However, *KIT* positivity alone may not be sufficient to confirm the diagnosis and, conversely, the absence of *KIT* and/or *PDFGRA* mutations does not exclude the diagnosis of GIST. In GISTs with *PDGFRA* mutations, immunostaining with *PDGFRA* has been shown to be helpful in discriminating between *KIT*-negative GIST and other GI mesenchymal lesions.

Loss-of-function mutations in the *SDH* gene subunits or loss of SDHB protein expression by IHC have been identified in a majority of wild-type GISTs lacking *KIT* and *PDGFRA* mutations; these findings have led to the use of the term SDH-deficient GIST, which is preferred over the older term, wild-type GIST, for this subset of GIST.[309-313] SDHB IHC can be useful for the diagnosis of *SDH*-deficient GIST. *BRAF* exon 15 mutation (V600E) has also been reported in a small subset of patients with intestinal high-risk GISTs lacking *KIT/PDGFRA* mutations.[314,315] DOG1 is a calcium-dependent, receptor-activated chloride channel protein and it is expressed in GISTs independent of mutation type. DOG1 expression was not different between the *KIT/PDGFRA* mutant or wild-type GIST, but there was a clear distinction between tumors with *PDGFRA* and *KIT* mutations. GISTs with *PDGFRA* mutations had a low *KIT* expression and high DOG1 expression, which can be used in the diagnosis of *KIT*-negative tumors.[316] DOG1 immunostaining may be useful for cases that cannot be categorized as GIST based on CD117 immunostaining and mutation testing for *KIT* and *PDGFRA*. DOG1 and *KIT* could be used together in difficult cases exhibiting unexpected *KIT* negativity or positivity.[300]

Tumors lacking *KIT* and *PDGFRA* mutations should be considered for further evaluations such as SDHB immunostaining. If the tumor is *SDH*-deficient, germline testing for *SDH* mutations would be indicated. Inactivating *NF1* mutations or activating *BRAF* mutations are present in a small minority of tumors that lack *KIT* and *PDGFRA* mutations but retain *SDH* expression.

Prognostic Factors

Tumor size and the mitotic rate are the most widely used pathologic features for the risk stratification of GIST. However, it is difficult to predict the malignant potential of GIST based on these features alone. In a long-term follow-up of 1765 patients with gastric GISTs, Miettinen and colleagues reported that the metastatic rate was 86% for tumors >10 cm with a mitotic index of >5 mitoses/50 HPFs, whereas tumors of the same size with a mitotic index of <5 mitoses/50 HPFs have a relatively low metastatic rate of 11%.[317] In a subsequent report involving 906 patients with small intestinal GIST, tumors >10 cm with a mitotic index of ≤5 mitoses/50 HPF had a metastatic rate of 50%, which is a contrast to that reported for gastric GIST with similar tumor parameters.[318] Therefore, in addition to the tumor size and mitotic rate, tumor site has also been included in the guidelines developed by Miettinen and colleagues for the risk stratification of primary GIST.[299] According to these guidelines, gastric GISTs have an overall indolent behavior and those that are ≤2 cm (irrespective of the mitotic index) are essentially benign, whereas small intestinal GISTs tend to be more aggressive. Rectal GISTs are also very aggressive, and tumors <2 cm with a mitotic index of >5 mitoses/50 HPFs have a higher risk of recurrence and malignant potential.

Mutations can be found in high-grade tumors as well as in small incidental GISTs and tumors that have a benign course. Therefore, *KIT* mutational status is not used to determine the malignant potential of a primary GIST. Tumor genotype has been shown to be an independent prognostic factor based on review of 1056 patients with localized GIST in the ConticaGIST database. Factors associated with poorer DFS were *KIT* exon 9 duplication, *KIT* exon 11 deletions, nongastric site, larger tumor size, and high mitotic index, whereas *PDGFRA* exon 18 mutations were associated with better prognosis.[319] Long-term follow-up (median 73 months) from the BFR14 trial by the French Sarcoma Group identified female sex as an independent prognostic factor for higher PFS and OS in patients treated with standard-dose imatinib.[320]

The presence and the type of *KIT* or *PDGFRA* mutation status are predictive of response to TKI therapy in patients with advanced or metastatic GIST. GISTs with *SDH* mutations are also less sensitive to TKIs. They typically arise in the stomach and are observed in younger individuals, frequently metastasize, may feature lymph node involvement, and tend to grow slowly. See *Impact of Mutational Status on Response to Imatinib or Sunitinib in Patients with Advanced or Metastatic GIST* in this Discussion.

Imaging

In patients with GIST, imaging is used for diagnosis, initial staging, restaging, monitoring response to therapy, and performing follow-up surveillance of possible recurrence. Contrast-enhanced CT is the imaging modality of choice to characterize an abdominal mass, as well as to evaluate its extent and the presence or absence of metastasis at the initial staging workup for biopsy-proven GIST. PET 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 is not a substitute for CT. PET/CT may be used to clarify ambiguous findings seen on CT or MRI or to assess complex metastatic disease in patients who are being considered for surgery. Even in this clinical setting there is no clear evidence that PET provides significant information that cannot be obtained using IV contrast-enhanced CT. PET may be of benefit in patients with IV contrast allergy, particularly for peritoneal disease; MRI with or without contrast usually yields excellent anatomical definition of liver metastases.[300] If clinicians consider using PET to monitor therapy, a baseline PET should be obtained prior to the start of therapy.

Response Assessment

To assess response to TKI therapy, abdominal/pelvic CT or MRI is indicated every 8 to 12 weeks. PET may give an indication of imatinib activity after 2 to 4 weeks if rapid read-out is necessary.[321] Various CT response criteria have been investigated and compared in patients with GIST, including iterations of RECIST, Choi, and WHO criteria.[242,322-327]

Experts have advocated that the CT response criteria proposed by Choi are much better than RECIST criteria to assess the response of GIST to TKI therapy. Choi criteria have been validated in one center in patients with GIST who had not previously received TKI therapy.[322] However, these criteria are not universally accepted, they have not been validated for patients who have received several targeted therapies, and the ease of use outside specialized centers is unknown. Some recent studies have supported the use of RECIST, WHO, or volumetric criteria for sunitinib or regorafenib response assessment following progression on imatinib.[324-326]

The EORTC developed metabolic response criteria for tumors evaluated with PET that provide definitions for complete metabolic response, partial metabolic response, stable metabolic disease, or disease metabolic progression.[328] However, since there is a 95% correlation between the information from regular contrast-enhanced CT and PET/CT, CT with IV contrast is the preferred routine imaging modality for patients with GIST on TKI therapy.

Surgery

Surgery is the primary treatment of choice for patients with localized or potentially resectable GIST lesions. Preoperative imatinib can be considered to decrease surgical morbidity. 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.

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 negative margins is often appropriate. Lymphadenectomy is usually not required given the low incidences of nodal metastases, but resection of pathologically enlarged nodes should be considered in patients with *SDH*-deficient GIST. Resection should be accomplished with minimal morbidity and complex multivisceral resection should be avoided. Re-resection is generally not indicated for microscopically positive margins on final pathology. If abdominoperineal resection would be necessary to achieve a negative margin, then preoperative imatinib should be considered. 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. Several case reports have demonstrated that the use of preoperative imatinib enables organ-sparing surgery and improves surgical outcomes in patients with rectal GISTs.[300]

The role for laparoscopy in the resection of GISTs continues to expand. Although prospective studies are lacking, literature reports based on a 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.[300] A meta-analysis of 19 studies (n = 1060 GIST cases) revealed no difference in long-term outcomes of GIST resections using laparotomy and laparoscopy, but laparoscopic approaches were associated with less blood loss, lower complication rates, and shorter hospital stays.[329]

Laparoscopic approach may be considered for selected GISTs in favorable anatomic locations such as anterior wall of the stomach, jejunum, and ileum. The same surgical principles of complete macroscopic resection, including the preservation of the pseudocapsule and avoidance of tumor rupture, should be followed during laparoscopy. Resection specimen should be removed from the abdomen in a plastic bag to avoid spillage or seeding of port sites. Laparoscopic surgery could be feasible in other anatomic sites, such as smaller rectal GISTs. However, data on laparoscopic resection of GISTs at other sites are limited.

Targeted Therapy

GISTs have previously been documented to be resistant to conventional chemotherapies. Since *KIT* activation occurs in the majority of cases of

GIST, KIT inhibition has emerged as the primary therapeutic modality along with surgery for the treatment of GIST.

Imatinib

Imatinib, a selective inhibitor of the KIT protein tyrosine kinase, has produced durable clinical benefit and objective responses in most patients with GIST. In phase II and III studies, imatinib has resulted in high overall response rates and exceptionally good PFS in patients with unresectable and/or metastatic GIST, inducing objective responses in more than 50% of the patients.[330-334] In February 2002, the FDA approved use of imatinib for the treatment of patients with *KIT*-positive unresectable and/or metastatic malignant GIST. Long-term follow-up results of the B2222 study (n = 147, randomly assigned to receive 400 or 600 mg of imatinib daily) confirmed that imatinib induces durable disease control in patients with advanced GIST.[335] The estimated 9-year OS rate was 35% for all patients, 38% for those with CR or PR, and 49% for those with stable disease. Low tumor bulk at baseline predicted for longer TTP and improved OS.

Two separate phase III studies (EORTC 62005 study and the S0033/CALGB 150105 study) have assessed the efficacy of imatinib 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.[331,332,334] 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. Although initial findings from the EORTC 62005 study (n = 946) suggested an earlier TTP for patients receiving 400 mg daily,[331] at a median follow-up of 10.9 years, no significant differences in survival were observed based on imatinib dose level.[336] In the 400-mg daily vs. 800-mg daily cohort, 10-year PFS rates were 9.5% versus 9.2% (HR, 0.91; 95% CI, 0.79–1.04; *P* = .18) and 10-year OS rates were 19.4% and 21.5%, respectively (HR, 0.93; 95% CI, 0.80–1.07; *P* = .31). Similarly, the S0033/CALGB 150105 study (n = 746) reported identical response rates (40% vs. 42%, respectively) at a median follow-up of 4.5 years and there were 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).[334] Following progression on 400 mg daily, 33% of patients who crossed over to the higher dose achieved objective response rates and stable disease. Among the patients who crossed over to the 800-mg daily dose after progression in EORTC 62005 study (n= 196, 47%), median PFS was 2.76 months.[336]

Available data confirm the safety and efficacy of imatinib at 400 mg/d as the initial standard dose to achieve response induction.[331,334] Dose escalation to 800 mg/d is a reasonable option for patients progressing on 400 mg/d.[332]

Preoperative Imatinib

The RTOG 0132/ACRIN 6665 is the first prospective study that evaluated the efficacy of preoperative imatinib (600 mg/d) in patients with potentially resectable primary disease (30 patients) or potentially resectable recurrent or metastatic disease (22 patients).[337] Among patients with primary GIST, PR and stable disease were observed in 7% and 83% of patients, respectively. In patients with recurrent or metastatic GIST, PR and stable disease were observed in 4.5% and 91% of patients, respectively. The estimated 2-year OS rate was 93% and 91% for patients with primary GIST and those with recurrent or metastatic GIST, respectively. The estimated 2-year PFS rate was 83% and 77%, respectively.

In a study conducted at MD Anderson Cancer Center, 19 patients undergoing surgical resection for primary GIST (with or without metastases) or recurrent disease (local or metastatic) were randomized to receive 3, 5, or 7 days of preoperative imatinib (600 mg daily).[338] 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. However, in this study, there was no histologic evidence of cytoreduction within 3 to 7 days of preoperative imatinib.

In another prospective study, Fiore and colleagues reported that preoperative imatinib improved resectability and reduced surgical morbidity in patients with primary GIST, unresectable or resectable through a major surgical procedure with significant surgical morbidity. Median size reduction was 34% and the estimated 3-year PFS rate was 77%.[339] Imatinib was continued postoperatively for 2 years in all patients.

In the subgroup analysis of patients with non-metastatic, locally advanced, primary GIST treated with imatinib within the prospective BFR14 phase III study, preoperative imatinib was associated with a PR rate of 60% (15 of 25 patients), and 36% (9 of 25 patients) of patients underwent surgical resection of primary tumor after a median of 7.3 months of imatinib treatment.[340] All patients who underwent resection were treated with postoperative imatinib. The 3-year PFS and OS rates were 67% and 89%, respectively, for patients who underwent resection. All patients who underwent resection were treated with postoperative imatinib.

While the results of these prospective studies have demonstrated the safety and efficacy of preoperative imatinib in patients undergoing surgical resection, survival benefit could not be determined since all patients included in 3 of these studies also received postoperative imatinib postoperatively for 2 years.[337,338,340] Maximal response may require treatment for ≥6 months. Preoperative imatinib may prohibit accurate assessment of recurrence risk and should be considered only if surgical morbidity could be reduced by downstaging the tumor preoperatively. At the present time, the decision to use preoperative imatinib for patients with resectable primary or locally advanced or recurrent 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%.[341-343] Median time to recurrence after resection of primary high-risk GIST is about 2 years. A retrospective review of 506 patients with completely resected GIST revealed the potential for underestimating risk of recurrence, particularly in the case of intermediate size, intermediate-level mitotic count, and non-gastric tumors.[344] The data suggested that at least 3 years of adjuvant treatment was associated with higher RFS for patients with higher-risk disease. Multiple randomized studies have investigated the optimal duration of adjuvant therapy for resected GIST.

Imatinib therapy was investigated in a phase III, double-blind study (ACOSOG Z9001) that randomized patients with primary localized GIST (≥3 cm in size) to postoperative imatinib 400 mg (317 patients) or placebo (328 patients) for one year after complete resection.[345] At a median follow-up of 74 months, the RFS rate was significantly higher in the imatinib arm compared to placebo (HR, 0.6; 95% CI, 0.43–0.75; Cox model adjusted *P* < .001). OS was not significantly different between the imatinib and placebo arms.[346] Further analyses revealed that imatinib therapy was associated with higher RFS in patients with *KIT* exon 11 deletions (but not *KIT* exon 11 insertion or point mutation, *KIT* exon 9 mutation, *PDGFRA* mutation, or wild-type tumor). Tumor genotype was not associated with RFS in the placebo arm.

An intergroup randomized trial (EORTC-62024: NCT00103168) compared observation with 2 years of adjuvant imatinib following R0/R1 resection in 908 patients with localized, intermediate, or high-risk GIST. [347] RFS for imatinib versus observation was 84% versus 66% at 3 years and 69% versus 63% at 5 years (*P* < .001). However, the endpoint of 5-year imatinib failure-free survival (IFFS) did not reach significance at 87% versus 84% (HR, 0.79; 98.5% CI, 0.50–1.25; *P* = .21).

The results of another randomized phase III study from the Scandinavian Sarcoma Group (SSG XVIII/AIO) suggest that a longer duration of postoperative imatinib improves RFS and OS for patients with a high estimated risk of recurrence after surgery.[348,349] In this study, patients with a high risk for GIST recurrence after surgery were randomized to 12 months (n = 200) or 36 months (n = 200) of postoperative imatinib. After a median follow-up of 90 months, RFS and OS were significantly longer in the 36-month group compared to the 12-month group (5-year RFS: 71.1% vs. 52.3%, respectively; *P* < .001; 5-year OS: 91.9 % vs. 85.3% respectively; *P* = .036). The highest risk for recurrence was observed among patients with non-gastric GIST and tumors with high mitotic count.[350]

Management of Toxicities

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.[351] Serious side effects (such as liver function test [LFT] abnormalities, lung toxicity, low blood counts, and GI bleeding) have rarely been reported and often improve after imatinib has been 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. In a retrospective analysis of 219 consecutive patients treated with imatinib, grade 3 or 4 cardiotoxicity occurred in 8.2% of patients who were manageable with medical therapy, and infrequently required dose reduction or discontinuation of imatinib.[352] 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.

Sunitinib

Sunitinib is a multitargeted TKI that can induce objective responses and control progressive disease in patients with imatinib-resistant GIST. SDH-deficient GIST may have a higher probability of response to sunitinib.

In a randomized, phase III, placebo-controlled study, sunitinib produced significant, sustained clinical benefit in patients with imatinib-resistant or imatinib-intolerant GIST.[353] In patients with imatinib-resistant GIST, sunitinib resulted in a significant improvement in median time to progression (27.3 vs. 6.4 weeks) and significantly greater estimated OS. Sunitinib treatment induced PR in 14 patients (6.8%) and stable disease (≥22 weeks) in 36 patients (17.4%) versus no PRs and stable disease in 2 patients (1.9%) on placebo. In the imatinib-intolerant group, 4 out of 9 patients randomized to sunitinib achieved PR and one patient had progressive disease. In contrast, 3 of the 4 patients randomized to placebo had progressive disease at the time of analysis and no PR was observed. Sunitinib was generally well tolerated. In January 2006, sunitinib received FDA approval for the treatment of GIST after disease progression on or intolerance to imatinib.

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.[354] Patients were randomized (1:1) to receive continuous daily sunitinib (37.5 mg/d) either in the morning or in the evening for 28 days (one cycle). The primary endpoint was the clinical benefit rate (CBR) defined as the percentage of patients with CRs, PRs, or stable disease for 24 weeks or more based on RECIST criteria. The overall CBR was 53% (13% of patients had a PR 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.

Results were recently reported from an international study of sunitinib safety and efficacy in patients with imatinib-resistant/-intolerant advanced GIST (n = 1124).[355] The median PFS was 8.3 months (95% CI, 8.0–9.4 months) and the median OS was 16.6 months (95% CI, 14.9–18.0 months); safety findings were in line with previous studies. In a follow-up retrospective analysis of a subset of this trial population (n = 230), PFS was significantly better for patients with a primary mutation in *KIT* exon 9 compared to those with a primary mutation in exon 11 (12.3 months vs. 7 months; HR, 0.59; 95% CI, 0.39–0.89; *P* = .011).[356]

Management of Toxicities

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 (ie, anemia, neutropenia), diarrhea, abdominal pain, mucositis, anorexia, and skin discoloration. Sunitinib is associated with a significant risk of developing hand-foot skin reaction (HFSR).[357] Early detection and proper management of HFSR is vital during treatment with sunitinib. HFSR can be prevented with routine application of emollient lotions. If it is significant, interruption of therapy is indicated; if it is severe, dose reduction should be considered.

Hypertension is a common side effect reported in clinical trials, since sunitinib targets vascular endothelial growth factor receptor (VEGFR). However, the risk is higher in patients with renal cell carcinoma (RCC) compared to those with non-RCC.[358] Recent reports have shown that sunitinib is also associated with cardiotoxicity and hypothyroidism.[359,360] In a retrospective analysis of the data from phase I-II studies, 11% of patients had an adverse cardiovascular event including CHF in 8% of patients and absolute reduction in the left ventricular ejection fraction (LVEF) in 28% of patients.[359] In a prospective, observational cohort study, abnormal serum thyroid-stimulating hormone (TSH) concentrations were documented in 62% of patients and the risk for hypothyroidism increased with the duration of therapy.[360]

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.[300]

Impact of Mutational Status on Response to Imatinib or Sunitinib in Patients with Advanced or Metastatic GIST

The presence and type of *KIT* or *PDGFRA* mutation has been identified as the predictor of response to imatinib. In randomized clinical trials, the presence of a *KIT* exon 11 mutation was associated with better response rates, PFS, and OS compared to *KIT* exon 9 mutations or wild-type GIST.[320,361-364]

Long-term follow-up (median 73 months) from the prospective, multicenter, randomized, phase III BFR14 trial by the French Sarcoma Group identified *KIT* exon 11 mutations as an independent prognostic factor for higher PFS and OS in patients treated with standard-dose imatinib when compared with patients who had wild-type GIST or *KIT* exon 9 mutations.[320]

In the US-Finnish B2222 phase II study, PR rates, event-free survival (EFS), and OS rates were better for patients with *KIT* exon 11 mutations than those with *KIT* exon 9 mutations or who had no detectable kinase mutations.[361] The PR rates for patients with *KIT* exon 11 mutations, *KIT* exon 9 mutations, or no detectable kinase mutations were 83.5%, 48%, and no responses, respectively. The presence of *KIT* exon 11 mutations was the strongest prognostic factor reducing the risk of death by more than 95%.

In a randomized EORTC 62005 study, the presence of *KIT* exon 9 mutations was the strongest adverse prognostic factor for risk of progression and death.[362] In this trial, treatment with high-dose imatinib (800 mg/d) resulted in a significantly superior PFS with a reduction of the relative risk of 61% (P = .0013) in patients whose tumors expressed a *KIT* exon 9 mutation.[363] In addition, the response rate after crossover from 400 mg daily to 400 mg twice-daily imatinib was much higher among patients with *KIT* exon 9 mutations (57%) than among patients with *KIT* exon 11 mutations (7%).

The North American Intergroup phase III trial (SWOG S0033/CALGB 150105) also confirmed the findings from B2222 and EORTC 62005 studies. Patients with a *KIT* exon 9 mutation treated with 800 mg imatinib had improved response rates compared to those treated with 400 mg imatinib (67% vs. 17%, respectively).[364] 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 study. The results of the North American Intergroup phase III trial also showed that patients with CD117-negative GIST have similar time to tumor progression but inferior OS compared to those with CD117-positive GIST, suggesting that patients with CD117-negative GIST may benefit from imatinib therapy.[364] Therefore, it is rational to offer *KIT*-negative GIST patients a therapeutic trial of imatinib with close evaluation and follow-up.

A meta-analysis of EORTC 62005 and SWOG S0033/CALGB 150105 phase III trials that randomized 1640 patients with advanced GIST to standard-dose imatinib (400 mg daily) or high-dose imatinib (800 mg daily) showed a benefit in PFS for patients with *KIT* exon 9 mutations treated with 800 mg of imatinib.[365] In a recent international survey that reported the outcome of GIST patients with *PDGFRA* mutations, none of 31 evaluable patients with a *D842V* mutation had a response, whereas 21 of 31 (68%) had disease progression.[366] Median PFS was 2.8 months for patients with a D842V substitution and 28.5 months for patients with other *PDGFRA* mutations. With 46 months of follow-up, median OS was 14.7 months for patients with D842V substitutions and was not reached for patients with other *PDGFRA* mutations.

Follow-up analysis of the randomized phase III study from the Scandinavian Sarcoma Group (SSG XVIII/AIO) revealed that patients with GIST harboring a *KIT* exon 11 deletion appear to benefit most from longer-duration imatinib, showing higher RFS when allocated to the 3-year versus 1-year imatinib group.[367] A similar pattern related to duration of treatment was not observed for GISTs harboring other mutations.

Heinrich and colleagues reported that sunitinib induced higher response rates in patients with primary *KIT* exon 9 mutations than those with *KIT* exon 11 mutations (58% vs. 34%, respectively).[368] PFS and OS were significantly longer for patients with *KIT* exon 9 mutations or with wild-type GIST compared to those with *KIT* exon 11 mutations. There were only 4 patients with *PDGFRA* mutations; of these 2 had a primary and one had a secondary *D842V* mutation and did not respond to treatment. In patients with *KIT* exon 11 mutations, PFS and OS were longer for those with secondary exon 13 or 14 mutations compared to those with exon 17 or 18 mutations. Additional studies are needed to confirm these findings. SDH-deficient GIST may have a higher probability of response to sunitinib compared with imatinib in patients with unresectable, recurrent, or metastatic GIST.

Resistance to Imatinib and Sunitinib

While imatinib benefits most patients with advanced GIST, some patients develop resistance to the drug. Primary imatinib resistance is defined as the 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 mutations treated with imatinib at 400 mg daily, *PDGFRA* exon 18 *D842V* mutations, or those with tumors that lack identifiable activating mutations in *KIT* or *PDGFRA,* the majority of which are *SDH*-deficient GIST.[361,362,364,368] Secondary resistance is seen in patients who have been on imatinib for more than 6 months with an initial response or disease stabilization followed by progression, most commonly because of the outgrowth of tumor clones with secondary mutations in *KIT*.[369-372] Dose escalation to 800 mg/d or switching to sunitinib is a reasonable option for patients progressing on imatinib 400 mg/d.[332,353,354]

Comprehensive molecular studies investigating the mechanisms of resistance to sunitinib are limited by the small number of patients who are surgical candidates after their disease failed to respond to two different TKI therapies. Nevertheless, available evidence (both clinical and preclinical) indicates that while sunitinib is very sensitive to adenosine triphosphate (ATP)-binding pocket mutations that confer resistance to imatinib, it has little activity against other imatinib-resistant mutations in the *KIT* activation loop.[373-375]

Management of Resistance to Imatinib and Sunitinib

Regorafenib, a multikinase inhibitor with activity against *KIT*, PDGFR, and VEGFR, was approved by the FDA for the treatment of patients with locally advanced, unresectable, or metastatic GIST previously treated with imatinib and sunitinib. In the phase III randomized GRID trial, 199 patients with metastatic and/or unresectable GIST progressing on prior therapy with imatinib and sunitinib were randomized to regorafenib (n = 133) or placebo (n = 66).[376] The median PFS (4.8 months vs. 0.9 months; $P < .0001$) and the disease control rate (DCR; 53% vs. 9%) were significantly higher for regorafenib compared to placebo. The PFS rates at 3 and 6 months were 60% and 38%, respectively, for regorafenib compared to 11% and 0%, respectively, for placebo. The HR for OS was 0.77 with 85% of patients in the placebo arm crossing over to regorafenib due to disease progression. The most common treatment-related adverse events (grade 3 or higher) were hypertension (23%), HFSR (20%), and diarrhea (5%). Long-term follow-up (median 41 months) from a separate phase II study of regorafenib in unresectable or metastatic GIST (n = 33) suggested that patients with *KIT* exon 11 mutations or *SDH*-deficient GIST may derive a greater PFS benefit than patients with *KIT/PDGFRA* wild-type, non-*SDH*-deficient tumors.[377]

Sorafenib,[378-381] nilotinib,[382-386] dasatinib,[387,388] and pazopanib[389,390] have also shown activity in patients with GIST resistant to imatinib and sunitinib. Much of the data on these TKIs comes from phase II studies and retrospective analyses involving a small number of patients.

In a prospective, multicenter, phase II study of 38 patients with unresectable, KIT-positive GIST that had progressed on imatinib and sunitinib, sorafenib resulted in a DCR of 68% (55% of patients who had stable disease and 13% who had PR).[378] Median PFS and OS were 5.2 months and 11.6 months, respectively; 1-year and 2-year survival rates were 50% and 29%, respectively. In a retrospective analysis of 124 patients with metastatic GIST resistant to imatinib and sunitinib, sorafenib also demonstrated activity resulting in median PFS and OS of 6.4 months and 13.5 months, respectively.[380] It should be noted that patients included in this study had not been treated with regorafenib, and the efficacy of sorafenib following regorafenib therapy in patients with metastatic GIST resistant to imatinib and sunitinib has not been studied.

Nilotinib resulted in a 10% response rate and 37% DCR in a retrospective analysis of 52 patients with advanced GIST resistant to imatinib and sunitinib.[383] Median PFS and OS were 12 weeks and 34 weeks, respectively. In a randomized phase III study of nilotinib as third-line therapy and best supportive care (with or without a TKI) in patients with GIST resistant or intolerant to imatinib and sunitinib (248 patients), the PFS on nilotinib was not found to be superior to best supportive care (109 days vs. 111 days; *P* = .56).[385] In a post hoc subset analysis, patients progressing on both imatinib and sunitinib who had not received any other therapy had an improved OS (>4 months) with nilotinib compared to best supportive care (405 vs. 280 days; *P* = .02). The clinical benefit associated with nilotinib may be specific to subsets of patients with *KIT* exon 17 mutations who were previously treated with imatinib and sunitinib.[386] Additionally, a recent phase III study investigating nilotinib as an alternative front-line agent to imatinib for unresectable or metastatic GIST was terminated early due to futility.[391]

Dasatinib has demonstrated activity against *PDGFRA* D842V mutation, which confers the highest resistance to imatinib, and it could be an effective treatment option for this group of patients with imatinib-resistant GIST.[387] In the phase II study of 50 patients with advanced GIST resistant to imatinib, dasatinib was associated with a median PFS and OS of 2 and 19 months, respectively, with response assessment by Choi criteria.[388] Median PFS for patients with wild-type GIST was 8.4 months.

Pazopanib has also shown modest activity in unselected, heavily pretreated patients with advanced GIST.[389,390] In a recent randomized, phase II trial comparing pazopanib to best supportive care in patients with imatinib- and sunitinib-resistant GIST (n = 81), median PFS was 3.4 months versus 2.3 months, respectively (HR, 0.59; 95% CI, 0.37–0.96; *P* = .03).[390]

Everolimus in combination with a TKI (ie, imatinib, sunitinib, regorafenib) may also be active in imatinib-resistant GIST.[390,392]

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, primary site and chest imaging, EUS in selected patients, endoscopy as indicated (if not previously done), and surgical assessment. Genotyping is recommended for cases in which medical therapy is anticipated. For very small GISTs (<2 cm), abdominal/pelvic CT and/or MRI is sufficient. For all other GISTs, workup includes baseline abdominal/pelvic CT and/or abdominal/pelvic MRI, along with chest imaging using CT or x-ray. PET/CT can be considered. Baseline PET/CT should be performed if PET/CT will be used during follow-up.

Treatment Guidelines

Resectable Disease

Primary/Preoperative Treatment

Surgery is the primary treatment for all patients with GIST (2 cm or greater) that are resectable without significant risk of morbidity. Preoperative imatinib may be beneficial as primary treatment for patients with GIST that is resectable with negative margins but with a significant risk of morbidity.[337,339] The use of preoperative imatinib may, however, prohibit the accurate assessment of recurrence risk. Preoperative imatinib should be considered only if surgical morbidity could be reduced by downstaging the tumor prior to resection. Close monitoring is essential, because some patients may rapidly become unresectable. In prospective studies, preoperative imatinib has been tested at a daily dose of either 400 mg[339,340] or 600 mg.[337,338] The guidelines recommend an initial dose of 400 mg daily. Patients with documented *KIT* exon 9 mutations may benefit from dose escalation up to 800 mg daily (given as 400 mg twice daily), as tolerated.

Baseline imaging is recommended prior to the start of preoperative imatinib. To assess response to TKI therapy, abdominal/pelvic CT or MRI is indicated every 8 to 12 weeks. PET may give an indication of imatinib activity after 2 to 4 weeks if rapid read-out is necessary. Since the optimal duration of preoperative therapy remains unknown, in patients with disease that is 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. Surgery is recommended if bleeding and/or symptoms are present. For patients with disease that is responding to treatment, response assessment imaging can be performed less frequently. Progression may be determined by abdominal/pelvic CT or MRI with clinical interpretation, relying on PET/CT as needed to clarify ambiguous results. Assess medication adherence before determining that therapy was ineffective. If there is no progression, continuation of the same dose of imatinib is recommended and resection should be considered, if possible. If there is progression, surgery is recommended after discontinuing imatinib. 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. Collaboration between the medical oncologist and the surgeon is necessary to determine the appropriateness of surgery following major response or stable disease.

However, the management of incidentally encountered small GISTs less than 2 cm remains controversial.[300] 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 has not been established. 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 (ie, irregular extra-luminal border, heterogeneous echo pattern, presence of cystic spaces, echogenic foci), periodic endoscopic or radiographic surveillance may be considered.[301,393]

Postoperative Treatment

Based on results of the ACOSOG Z9001 study and the randomized phase III study SSGXVIII/AIO (NCT00116935), the guidelines recommend postoperative imatinib following complete resection for primary GIST with no preoperative imatinib for patients at intermediate or high risk of recurrence (category 1).[345,348] The panel recommends that postoperative imatinib for at least 36 months should be considered for patients with high-risk GIST.[348,349]

Estimation of risk of recurrence is important in selecting patients who would benefit from postoperative therapy following complete resection. In the ACOSOG Z9001 study, risk stratification was based only on tumor size and postoperative imatinib improved RFS in patients with GISTs 3 cm or larger; however, it was statistically significant in patients with intermediate (6 cm or greater and less than 10 cm) and high risk (greater than 10 cm) of recurrence.[345,346] In the SSGXVIII/AIO study, risk stratification was based on tumor size, site, mitotic count, and rupture; survival benefit was seen in patients with high risk of recurrence (mitotic index of >5 mitoses/50 HPF, size >5 cm, non-gastric location, and tumor rupture).[348] Risk stratification after surgical resection should be based on tumor mitotic rate, size, and location.[394] Gold and colleagues have developed a nomogram, taking into account tumor size, site, and mitotic index, to predict RFS after resection of localized primary GIST.[395] This nomogram accurately predicts RFS after resection of localized primary GIST and might be useful for patient care, interpretation of study results, and selection of patients for postoperative imatinib therapy.

For patients with complete resection following preoperative imatinib, the panel agreed that continuation of imatinib (at the same dose that induced objective response) is warranted. The panel acknowledged that while data from single and multicenter studies support the continuation of postoperative imatinib for 2 years following surgery, the exact duration of postoperative imatinib in this group of patients has not been studied in randomized studies.[337-340] The long-term analysis of the RTOG 0132 study suggested that a high percentage of patients progressed after discontinuation of 2-year postoperative imatinib therapy.[396]

For patients with completely resected disease who did not receive preoperative imatinib, postoperative imatinib is recommended for patients with intermediate or high-risk disease (category 1). Observation can be considered for completely resected, low-risk disease.

In patients with persistent gross disease following resection (R2 resection) who received preoperative imatinib, 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 did not receive prior imatinib therapy.

Unresectable, Metastatic, or Recurrent Disease

Baseline imaging is recommended prior to initiation of treatment. Imatinib (category 1) is the primary treatment for patients with advanced, unresectable, or metastatic GIST. Imatinib has been shown to improve resectability and reduce surgical morbidity in patients with documented unresectable GIST or in patients for whom resection would carry the risk of severe postoperative functional deficit.[339,340] Several retrospective studies have demonstrated survival benefit of cytoreductive surgery following preoperative imatinib in patients with advanced or metastatic GIST responding to preoperative imatinib.[397-404] 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 studies are underway to assess whether or not resection changes outcome in patients with unresectable metastatic GIST responding to TKI therapy.

Providers should consider resection if complete resection can be obtained in primary metastatic disease. To assess response to TKI therapy, abdominal/pelvic CT or MRI is indicated every 8 to 12 weeks. PET may give an indication of imatinib activity after 2 to 4 weeks if rapid read-out is necessary. If there is no progression, resection can be considered following surgical consultation. Imatinib should be continued if resection is not feasible. At this time, continuous use of imatinib is recommended for metastatic GIST until progression. The patient should be maintained on the same dose, and the dose of imatinib should not be increased if patients remain stable without objective progression of the disease. Termination of imatinib 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.[405]

Recurrence following complete resection should be managed as described for unresectable or metastatic disease, because recurrent disease represents locoregional metastatic or infiltrative spread of the malignancy and carries essentially the same prognosis as distant metastases overall.

Progressive Disease

Progression is defined as the appearance of a new lesion or an increase in tumor size and may be determined by abdominal/pelvic CT or MRI with clinical interpretation, using PET/CT as needed to clarify ambiguous results. Medication adherence should be assessed prior to determining that therapy is ineffective.

Dose escalation of imatinib up to 800 mg daily (given as 400 mg twice daily) as tolerated or switching to sunitinib (category 1) are included as options for patients with progressive disease (limited disease or widespread systemic disease in patients with good performance status) on standard-dose imatinib.[332,353,354] All clinical and radiological data, including lesion density on CT and patient compliance to treatment with standard-dose imatinib, should be assessed prior to dose escalation of imatinib or switching to sunitinib.

For patients with limited progressive disease on standard-dose imatinib, second-line therapy with sunitinib should be initiated only if the majority of disease is no longer controlled by imatinib; consideration of other therapeutic interventions for progressing lesion(s) is warranted. Surgical resection should be considered in carefully selected patients with limited progressive disease that is potentially easily resectable.[397,402,406] However, incomplete resections are frequent with high complication rates. The guidelines have included, only for patients with limited progressive disease, continuation of imatinib at the same initial dose and treatment of progressing lesions with resection, RFA, chemoembolization (category 2B), or palliative RT (category 2B) for rare patients with bone metastases.[300]

Regorafenib (category 1) is recommended for patients with disease progression on imatinib and sunitinib.[376] Based on limited data,[378-390,392] the guidelines have also included sorafenib, dasatinib, nilotinib, pazopanib, and everolimus plus TKI as additional options for patients who are no longer receiving clinical benefit from imatinib, sunitinib, or regorafenib, although much of the data regarding the potential benefit of these agents were collected in the pre-regorafenib era.

In patients with progressive disease no longer receiving benefit from current TKI therapy, re-introduction of previously tolerated and effective TKI therapy for palliation of symptoms can be considered.[407,408] The results of a recent randomized study demonstrated that imatinib rechallenge significantly improved PFS and DCR in patients with advanced GIST after failure of at least imatinib and sunitinib.[408] However, the duration of survival benefit was brief due to continued progression of TKI-resistant clones.

Any patient who has disease progression despite prior therapy or who has a recurrence, regardless of presentation, should be considered for enrollment in a clinical trial, if an appropriate trial is available.

Continuation of TKI Therapy

The optimal duration of TKI therapy in patients with responding or stable disease is not known. The results of a prospective, multicenter, randomized phase III study (BFR14) show that there was a significant increase in the rate of progressive disease when imatinib therapy was interrupted in patients with advanced disease that was stable or responding to imatinib therapy.[409,410] A recent report from this study confirmed that patients with rapid disease progression after interruption of imatinib had a poorer prognosis.[411] More importantly, the quality of response upon reintroduction of imatinib did not reach the tumor status observed at randomization.

The panel strongly recommends that TKI therapy at the prescribed daily dose should be continued as long as patients are receiving clinical benefit (response or stable disease). The panel also feels that life-long continuation of TKI therapy for palliation of symptoms should be an essential component of best supportive care. However, short interruptions for one to two weeks, when medically necessary, have not been shown to negatively impact disease control or other outcomes.

Surveillance

Patients with completely resected, incompletely resected, or metastatic GIST should have a thorough H&P every 3 to 6 months; abdominal/pelvic CT scan should be performed every 3 to 6 months for 3 to 5 years, then annually. Less frequent surveillance may be acceptable for low-risk or very small tumors (<2 cm). Progression may be determined by CT or MRI with clinical interpretation; PET/CT can be considered to clarify ambiguous CT results.

Desmoid Tumors (Aggressive Fibromatoses)

Desmoid tumors, also known as aggressive fibromatoses, are unique mesenchymal neoplasms that are often considered to be locally malignant but nonmetastasizing neoplasms. Specifically, these tumors are an aggressive fibroblastic proliferation of well-circumscribed, locally invasive, and differentiated fibrous tissue. Desmoid tumors can cause functional morbidity and are often locally invasive, but they rarely metastasize. 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.

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. Although they do not exhibit the histopathologic features to classify them as sarcomas, desmoid tumors are often categorized as low-grade sarcomas because of their high tendency to recur locally after excision.

Desmoid tumors have been reported to occur in 7.5% to 16% of patients with FAP, and the relative risk of developing desmoid tumors is much higher in patients with FAP than in the general population.[22-25] Abdominal desmoids may be a component of FAP and may also arise through elective surgical intervention (eg, colectomy) in susceptible patients.[22,412,413] In patients who have been treated with prophylactic colectomy, desmoids now represent a more significant cause of morbidity than carcinoma of the colon.[414]

Mutations in the *CTNNB1* gene encoding the β-catenin pathway have been identified in sporadic desmoid tumors, although the correlation of *CTNNB1* mutation status with the clinical outcome remains uncertain.[415-419] Lazar and colleagues identified mutations in the *CTNNB1* gene in 85% of patients with desmoid tumors.[415] Three distinct mutations, 41A, 45F, and 45P, were identified in 59%, 33%, and 8% of cases, respectively. Mutation 45F was associated with a high risk of recurrence; 5-year RFS rate was 23% for patients harboring 45F mutation compared to 57% for those with 41A and 68% for those with no mutations.[415] In a retrospective study of patients with extra-abdominal desmoid tumors, Domont and colleagues reported *CTNNB1* mutations in 87% of patients, and the 5-year RFS rate was significantly worse in patients with β-catenin mutations, regardless of the genotype, compared with wild-type tumors (49% vs. 75%, respectively).[416] Columbo and colleagues also reported that mutation 45F was associated with higher rates of LR among patients with primary, completely resected, sporadic desmoid tumors and mutation 45F was more prevalent in extra-abdominal desmoid tumors compared to other sites.[418] In contrast to these findings, Mullen and colleagues reported that *CTNNB1* mutation status or the specific *CTNNB1* mutation was not associated with any statistically significant difference in recurrence risk in a subset of 115 patients with desmoid tumors who underwent macroscopically complete surgical resection.[419] At a median follow-up of 31 months, the 5-year RFS rates were 58% and 74%, respectively, for patients with *CTNNB1* mutations and for those with wild-type tumors. Additional prospective studies are needed to confirm whether genotyping of *CTNNB1* may provide important information regarding the risk of recurrence and the selection of patients for adjuvant treatment options.

Evaluation and Workup

The workup for desmoid tumors includes H&P (with evaluation for Gardner's syndrome/FAP) and appropriate imaging of the primary site with CT or MRI as clinically indicated. All patients should be managed by a multidisciplinary team. Biopsy should be performed for suspicious masses to confirm the diagnosis, and may not be necessary if complete resection is planned. The differential diagnosis for desmoids depends on location; it includes other sarcomas, other malignant carcinomas, and benign lesions. Desmoid tumors of the breast are difficult to differentiate from carcinomas, because they resemble carcinomas clinically and radiologically.[420-423]

Treatment Guidelines

Resectable Tumors

Surgery is the primary treatment for patients with resectable desmoid tumors.[424-428] Tumor location and size, patients' age, and margin status have been identified as factors associated with recurrence following resection. Extra-abdominal tumors have a higher risk of recurrence than abdominal tumors. In an analysis of 203 patients with desmoid tumors treated with surgery, Gronchi and colleagues reported significantly higher DFS rates for patients with abdominal wall tumors than those with extremity tumors. The 10-year DFS rates were 88% and 62%, respectively ($P < .01$).[429] In a more recent report involving 211 patients with desmoid tumors treated with surgery, Peng and colleagues also reported similar findings.[430] The median RFS was not reached following resection for patients with either abdominal wall or intra-abdominal tumors, whereas the median RFS was 29.4 months for patients with extra-abdominal tumors ($P < .001$).

The impact of positive resection margins on local control and risk of recurrence remains controversial.[431] Some studies have reported margin status as an independent prognostic factor of recurrence.[430,432-435] Other studies have failed to demonstrate any clear association between resection margins and risk of recurrence.[429,436] Recent data suggest no difference in outcomes between patients with R0 or R1 resection margins who undergo careful observation.[437-439] Therefore, R1 margins are acceptable if achieving R0 margins would produce excessive morbidity. However, a recent meta-analysis of 16 studies, including data from 1295 patients, found that R1 resections were associated with an almost 2-fold higher risk of recurrence (risk ratio, 1.78; 95% CI, 1.40–2.26).[435]

Several retrospective series have reported that postoperative RT significantly improves local control and PFS compared to surgery alone, suggesting that postoperative RT could be considered for patients who are at high risk of LR.[435,436,440-445] However, in another series of patients with desmoid tumors of the chest wall, postoperative RT did not reduce the risk of recurrence.[428]

The results of recent retrospective analyses suggest that observation may be appropriate for selected patients with resectable tumors (small size, asymptomatic, and tumors located at sites where increase in size will not alter the outcome of surgery or lead to functional limitation).[446,447] In a retrospective analysis of 142 patients with desmoid fibromatoses (74 with primary tumor and 68 with recurrence) reported by Fiore and colleagues, the 5-year PFS rates for patients with primary tumors were 47% for those who were treated with a "wait and see" approach (no surgery or RT) and 54% for those who received medical therapy (chemotherapy or hormonal therapy; $P = .70$).[447] The corresponding survival rates were 54% and 61% ($P = .48$) for patients with recurrence. Large tumors (greater than 10 cm in size) and tumors located on the trunk were associated with a high risk of recurrence.

Based on these results, the panel concluded that patients with desmoid fibromatoses can be managed appropriately with a careful "wait and see" approach if their tumors are asymptomatic and are not located in an area that could lead to functional limitations if the tumor increases in size. The guidelines have included observation as an option for selected patients with resectable tumors. Stable tumors can be followed with continued observation using H&P exam with appropriate imaging. If there is progression, patients can be treated with surgery and/or RT and/or systemic therapy.

For symptomatic patients with large tumors causing morbidity, pain, or functional limitation, treatment choices should be based on the location of the tumor and potential morbidity of the treatment. Options include surgery and/or RT and/or systemic therapy. Patients with resectable tumors should be treated with complete surgical resection when feasible. Microscopically positive margins may be acceptable if achieving negative margins would produce excessive morbidity. If surgical margins are negative after resection (R0 resection) or if there is complete radiographic response, patients may only be observed. For microscopically positive margins or minimal residual disease (R1 resection), observation or re-resection can be considered. Postoperative RT reduces the risk of recurrence in patients with positive margins and should be considered only if a subsequent relapse might lead to increased morbidity. Patients with macroscopic surgical margins (R2 resection) are treated as described below for unresectable disease.

For treating progressive or recurrent desmoid tumors, options include: systemic therapy; resection; resection plus RT (50 Gy, if not previously irradiated); or RT alone (50–56 Gy, if not previously irradiated).

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.[429,448] RT is a reasonable treatment option for patients with unresectable tumors, depending on the possible morbidity of treatment.[436,449-452]

In a retrospective analysis of 23 patients with extra-mesenteric desmoid tumors treated with RT for gross residual unresectable disease, 7 patients sustained LR, yielding a 5-year actuarial local control rate of 69%. In another retrospective analysis that included 13 patients with unresectable tumors treated with RT alone as a definitive local therapy, the actuarial 3-year freedom-from-recurrence rate was 92.3%.[436] In a multicenter, prospective phase II study of 44 patients with inoperable desmoid tumors of trunk and extremities treated with RT (56 Gy in 28 fractions), Keus and colleagues reported a 3-year local control rate of 81.5%, at a median follow-up of 4.8 years.[452] During the first 3 years, CR, PR, and stable disease were observed in 13.6%, 36.4%, and 40.9% of patients, respectively. Response to RT was slow, with continuing regression seen even after 3 years.[452]

Definitive RT (50–56 Gy in the absence of any prior RT only for desmoid tumors of the extremity head and neck or superficial trunk), systemic therapy, and observation are some of the options for patients with unresectable tumors. Radical surgery should be considered only if other treatment modalities fail. RT is not generally recommended for retroperitoneal/intra-abdominal desmoid tumors.

Systemic therapy using non-steroidal anti-inflammatory drugs (NSAIDs), hormonal or biological agents, or cytotoxic drugs have shown promising results in patients with desmoid tumors.[453,454] In a prospective study, tamoxifen in combination with sulindac resulted in disease stabilization in patients with progressive or recurrent tumors following surgery.[455] The results of a retrospective, non-randomized study showed that interferon alfa with or without tretinoin may be effective in prolonging the disease-free interval after intralesional or marginal surgery in patients with extra-abdominal desmoid tumors.[456] In case reports, toremifene has been effective in disease stabilization following surgery.[457-460] Doxorubicin-based chemotherapy has been effective in patients with recurrent or unresectable tumors.[461-464] The combination of methotrexate and vinorelbine or vinblastine has also been associated with prolonged stable disease in patients with unresectable or recurrent tumors.[463,465-467]

Imatinib and sorafenib have also been evaluated in patients with unresectable, progressive, or recurrent aggressive fibromatosis.[155,468-470] In a phase II multicenter study, imatinib resulted in an objective response rate of 6% and the 1-year PFS rate was 66% in patients with unresectable tumors.[469] Long-term follow-up results of the phase II study by the French Sarcoma Group also showed that imatinib resulted in objective responses and stable disease in a large proportion of patients with recurrent or progressive aggressive fibromatosis.[470] At a median follow-up of 34 months, the 2-year PFS and OS rates were 55% and 95%, respectively. The non-progression rates at 3, 6, and 12 months were 91%, 80%, and 67%, respectively. In a study of 26 patients (11 patients received sorafenib as first-line therapy and the remaining 15 patients had received a median of 2 prior systemic therapies), sorafenib induced PR in 25% of patients and 70% of patients had stable disease, with a median follow-up of 6 months.[155]

The guidelines have included NSAIDs (sulindac or celecoxib), hormonal or biological agents (tamoxifen, toremifene, or low-dose interferon), chemotherapy (methotrexate and vinblastine, doxorubicin-based regimens), and TKIs (imatinib and sorafenib) as options for systemic therapy for patients with advanced or unresectable desmoid tumors. The risk of cardiovascular events may be increased in patients receiving celecoxib, and patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. Physicians prescribing celecoxib should consider this information when weighing the benefits against risks for individual patients.

Surveillance

Every patient should have an H&P with CT or MRI every 3 to 6 months for 2 to 3 years and then every 6 to 12 months thereafter. Disease progression or recurrence should be managed as described under primary treatment for resectable or unresectable disease.

Rhabdomyosarcoma

RMS is more common among children and adolescents but is less common in adults accounting for 2% to 5% of all STSs.[471] RMS has three histologic subtypes: embryonal (including botryoid and spindle cell variants), alveolar (including a solid variant), and pleomorphic histologies.[472,473] Embryonal and alveolar variants occur mainly in children and adolescents. Although pleomorphic RMS occurs predominantly in adults, embryonal and alveolar variants are also well represented.[471,473-478]

The incidence of pleomorphic RMS increases with age and the overall prognosis of RMS in adults is poor.[479] In a study of 39 adult patients treated at a single institution, the incidence of pleomorphic RMS increased with age (0%, 27%, and 60%, respectively, for ages 16–19, 20–49, and 50 or older) and the median survival was 2.25 years after diagnosis.[479] Extremities, trunk wall, and genitourinary organs are the most common primary sites for pleomorphic RMS in adults.[480-482] In a recent SEER database analysis of 1071 adults (older than 19 years) with RMS, the most common primary sites included extremities (26%) and trunk (23%) followed by genitourinary tract (17%) and head and neck (9%).[477] Pleomorphic histologies (19% vs. 1% in children; *P* < .0001) and unfavorable sites (65% vs. 55% in children; *P* < .0001) were more common in adults; the estimated 5-year OS rates were 27% for adults compared to 63% for pediatric patients.[477]

Given the rarity of the clinical situation, there are very limited data (mostly from single-institution retrospective studies) available on the management of adults with RMS. Multimodality treatment (surgery, RT, and chemotherapy) has been used in all of these studies. In the largest retrospective single-institution study that evaluated 180 patients diagnosed with RMS (18 years or older; 143 patients with embryonal, alveolar, or RMS not otherwise specified; and 37 patients with pleomorphic histology), Ferrari and colleagues reported 5-year EFS and OS rates of 28% and 40%, respectively.[471] The overall response rate was 85% in patients with embryonal and alveolar RMS treated with chemotherapy according to the pediatric protocol. Surgery was the main treatment in patients with pleomorphic RMS (74% compared to 34% with non-pleomorphic histologies), and the EFS rate was 37% for patients who underwent complete resection compared to 0% in patients with unresectable tumors.[471]

Other retrospective studies from MD Anderson Cancer Center (82 adults) and Dana Farber Cancer Institute (39 patients) have also reported high overall response rates to chemotherapy (75% and 82%, respectively).[475,483] Survival was significantly better for patients with disease responding to chemotherapy than those with disease that did not. In the MD Anderson Cancer Center study, the 10-year metastasis-free survival was 72% for patients with disease that responded to chemotherapy compared to 19% for those with disease that failed to respond.[475]

In the series from Dana Farber Cancer Institute, metastatic disease at presentation and poor response to chemotherapy were independent predictors of poor prognosis; the 5-year survival rate was 57% for patients with a CR to chemotherapy compared to only 7% for those with poor response.[483] In this study, 5-year survival rates were also higher for patients who underwent complete resection than for those who did not (63% vs. 29% and 46% for those who underwent compromised or incomplete resections, respectively).[483] Hawkins and colleagues also reported that margin status after resection was predictive of disease-specific survival in adult patients (105 months for patients who underwent complete resection compared to 9 months for those with positive margins).[474]

Chemotherapy regimens used in adults with RMS are usually derived from the pediatric clinical trials on RMS conducted by international cooperative groups.[484] Vincristine, dactinomycin, and cyclophosphamide (VAC) has been the standard chemotherapy for pediatric nonmetastatic RMS (intermediate or high risk).[485] In a randomized study (D9803) from the Children's Oncology Group (COG), there was no significant survival benefit of adding topotecan to standard VAC regimen in children with intermediate-risk RMS. In this study, at a median follow-up of 4.3 years, the 4-year failure-free-survival (FFS) rate was 73% and 68%, respectively, for patients treated with VAC and VAC alternating with vincristine, topotecan, and cyclophosphamide (P = .30).[485] RT resulted in good local control for patients with alveolar RMS who underwent primary tumor resection before initiation of chemotherapy.[486]

The results of the Intergroup RMS Study (D9602) showed that newly diagnosed patients with low-risk RMS treated with vincristine and dactinomycin had similar 5-year FFS rates compared to those patients treated with vincristine, dactinomycin, and cyclophosphamide (89% and 85%, respectively), suggesting that vincristine and dactinomycin could be an appropriate option for patients with newly diagnosed, low-risk RMS.[487] Vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide (VAC-IE) was found to be effective for patients with intermediate-risk RMS.[488] A recent study from COG in primarily pediatric patients with metastatic RMS investigated intensive multiagent therapy with radiation that included blocks of vincristine/irinotecan, interval compression with VAC-IE, and vincristine/dactinomycin/cyclophosphamide. For patients with zero to one Oberlin risk factor, the 3-year EFS of 69% (95% CI, 52%–82%) was improved compared with historical controls, whereas high-risk disease had a 3-year EFS of 20% (95% CI, 11%–30%).[489]

Newer agents such as carboplatin,[490] irinotecan,[491-494] topotecan,[495-497] and vinorelbine[498,499] have also shown activity in the treatment of pediatric patients with metastatic, relapsed, or refractory RMS. A phase II study recently provided preliminary evidence for efficacy and tolerability of RT with concurrent irinotecan/carboplatin regimens for patients with intermediate or high-risk RMS.[500]

Retrospective studies on adults with RMS have used a variety of multidrug chemotherapy regimens, including cyclophosphamide or ifosfamide, doxorubicin, and/or dactinomycin with or without vincristine or other drugs such as cisplatin, carboplatin, and etoposide.[471,475,479,483,501] In the MD Anderson Cancer Center study, the 10-year overall, disease-free, and metastasis-free survival rates were 47%, 45%, and 59%, respectively, for adult patients treated with chemotherapy regimens containing vincristine and cyclophosphamide with dactinomycin or doxorubicin.[475] Esnaola and colleagues reported an overall response rate of 82%, with a CR rate of 45% in adults with RMS treated with vincristine, doxorubicin, and cyclophosphamide or other doxorubicin-based chemotherapy regimens.[483] Ogilvie and colleagues also reported that chemotherapy with vincristine, doxorubicin, and ifosfamide resulted in an overall response rate of 86% in 11 adult patients with pleomorphic RMS; the 2-year OS and DFS rates were 55% and 64%, respectively.[501] Additionally, a recent review suggested that vincristine, irinotecan, and temozolomide in combination with local therapy may provide some degree of disease control for relapsed RMS.[502]

These guidelines strongly recommend that all patients should be referred to institutions with expertise in treating patients with RMS. Evaluation by a multidisciplinary team involving pediatric, medical, surgical, and radiation oncologists is strongly encouraged. Multimodality treatment (surgery, RT, and chemotherapy) planning and risk stratification is required for all patients.[484] PET imaging may be useful for initial staging because of the possibility of nodal metastases and the appearance of unusual sites of initial metastatic disease in adult patients.[503]

Systemic chemotherapy options for RMS may be different than those used with other STS histologies. Pleomorphic RMS is usually excluded from RMS randomized clinical trials. Consideration to treat according to STS guidelines may be warranted for this group of patients. In the absence of data from prospective clinical trials, there are no definitive, optimal regimens for the management of adult RMS. See *Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma* in the algorithm for a list of chemotherapy regimens that are recommended for the management of adults with RMS.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7-30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29313949.

2. Ma GL, Murphy JD, Martinez ME, Sicklick JK. Epidemiology of gastrointestinal stromal tumors in the era of histology codes: results of a population-based study. Cancer Epidemiol Biomarkers Prev 2015;24:298-302. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25277795.

3. Brady MS, Gaynor JJ, Brennan MF. Radiation-associated sarcoma of bone and soft tissue. Arch Surg 1992;127:1379-1385. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1365680.

4. Zahm S, Fraumeni JJ. The epidemiology of soft tissue sarcoma. Semin Oncol 1997;24:504-514. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9344316.

5. Penel N, Grosjean J, Robin YM, et al. Frequency of certain established risk factors in soft tissue sarcomas in adults: a prospective descriptive study of 658 cases. Sarcoma 2008;2008:459386. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18497869.

6. Cancer Facts & Figures 2018. Atlanta: American Cancer Society; 2018. Available at: https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2018.html

7. Pisters PWT, Weiss M, Maki R. Soft-Tissue Sarcomas In: Haller DG, Wagman LD, Camphausen C, Hoskins WJ, eds. Cancer Management:A Multidisciplinary Approach Medical, Surgical, & Radiation Oncology (ed 14): UBM Medica LLC; 2011.

8. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9448617.

9. Voss RK, Chiang YJ, Torres KE, et al. Adherence to National Comprehensive Cancer Network Guidelines is Associated with Improved Survival for Patients with Stage 2A and Stages 2B and 3 Extremity and Superficial Trunk Soft Tissue Sarcoma. Ann Surg Oncol 2017;24:3271-3278. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28741122.

10. Li FP, Fraumeni JF, Jr., Mulvihill JJ, et al. A cancer family syndrome in twenty-four kindreds. Cancer Res 1988;48:5358-5362. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3409256.

11. Galiatsatos P, Foulkes WD. Familial adenomatous polyposis. Am J Gastroenterol 2006;101:385-398. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16454848.

12. Kleinerman RA, Tucker MA, Abramson DH, et al. Risk of soft tissue sarcomas by individual subtype in survivors of hereditary retinoblastoma. J Natl Cancer Inst 2007;99:24-31. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17202110.

13. Half E, Bercovich D, Rozen P. Familial adenomatous polyposis. Orphanet J Rare Dis 2009;4:22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19822006.

14. Postow MA, Robson ME. Inherited gastrointestinal stromal tumor syndromes: mutations, clinical features, and therapeutic implications. Clin Sarcoma Res 2012;2:16. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23036227.

15. Malkin D, Li FP, Strong LC, et al. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 1990;250:1233-1238. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1978757.

16. Nichols KE, Malkin D, Garber JE, et al. Germ-line p53 mutations predispose to a wide spectrum of early-onset cancers. Cancer Epidemiol Biomarkers Prev 2001;10:83-87. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11219776.

17. Ognjanovic S, Olivier M, Bergemann TL, Hainaut P. Sarcomas in TP53 germline mutation carriers. Cancer 2012;118:1387-1396. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21837677.

18. Kleihues P, Schauble B, zur Hausen A, et al. Tumors associated with p53 germline mutations: a synopsis of 91 families. Am J Pathol 1997;150:1-13. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9006316.

19. Olivier M, Goldgar DE, Sodha N, et al. Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype. Cancer Res 2003;63:6643-6650. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14583457.

20. Mitchell G, Ballinger ML, Wong S, et al. High frequency of germline TP53 mutations in a prospective adult-onset sarcoma cohort. PLoS One 2013;8:e69026. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23894400.

21. Bisgaard ML, Bulow S. Familial adenomatous polyposis (FAP): genotype correlation to FAP phenotype with osteomas and sebaceous cysts. Am J Med Genet A 2006;140:200-204. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16411234.

22. Gurbuz AK, Giardiello FM, Petersen GM, et al. Desmoid tumours in familial adenomatous polyposis. Gut 1994;35:377-381. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8150351.

23. Fallen T, Wilson M, Morlan B, Lindor NM. Desmoid tumors -- a characterization of patients seen at Mayo Clinic 1976-1999. Fam Cancer 2006;5:191-194. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16736290.

24. Nieuwenhuis MH, Casparie M, Mathus-Vliegen LM, et al. A nation-wide study comparing sporadic and familial adenomatous polyposis-related desmoid-type fibromatoses. Int J Cancer 2011;129:256-261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20830713.

25. Nieuwenhuis MH, Lefevre JH, Bulow S, et al. Family history, surgery, and APC mutation are risk factors for desmoid tumors in familial adenomatous polyposis: an international cohort study. Dis Colon Rectum 2011;54:1229-1234. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21904137.

26. Carney JA, Stratakis CA. Familial paraganglioma and gastric stromal sarcoma: a new syndrome distinct from the Carney triad. Am J Med Genet 2002;108:132-139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11857563.

27. Pasini B, McWhinney SR, Bei T, et al. Clinical and molecular genetics of patients with the Carney-Stratakis syndrome and germline mutations of the genes coding for the succinate dehydrogenase subunits SDHB, SDHC, and SDHD. Eur J Hum Genet 2008;16:79-88. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17667967.

28. Gill AJ, Chou A, Vilain R, et al. Immunohistochemistry for SDHB divides gastrointestinal stromal tumors (GISTs) into 2 distinct types. Am J Surg Pathol 2010;34:636-644. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20305538.

29. Gaal J, Stratakis CA, Carney JA, et al. SDHB immunohistochemistry: a useful tool in the diagnosis of Carney-Stratakis and Carney triad gastrointestinal stromal tumors. Mod Pathol 2011;24:147-151. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20890271.

30. Kleinerman RA, Schonfeld SJ, Tucker MA. Sarcomas in hereditary retinoblastoma. Clin Sarcoma Res 2012;2:15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23036192.

31. Korf BR. Neurofibromatosis. Handb Clin Neurol 2013;111:333-340. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23622184.

32. Brems H, Beert E, de Ravel T, Legius E. Mechanisms in the pathogenesis of malignant tumours in neurofibromatosis type 1. Lancet Oncol 2009;10:508-515. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19410195.

33. Domanski HA. Fine-needle aspiration cytology of soft tissue lesions: diagnostic challenges. Diagn Cytopathol 2007;35:768-773. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18008345.

34. Antonescu CR. The role of genetic testing in soft tissue sarcoma. Histopathology 2006;48:13-21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16359533.

35. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11122430.

36. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12170083.

37. Italiano A, Di Mauro I, Rapp J, et al. Clinical effect of molecular methods in sarcoma diagnosis (GENSARC): a prospective, multicentre, observational study. Lancet Oncol 2016;17:532-538. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26970672.

38. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12039929.

39. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15364967.

40. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11782370.

41. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11751490.

42. Amin MB, Edge SB, Greene FL, et al. AJCC Cancer Staging Manual, 8th edition. New York: Springer; 2017.

43. Zagars GK, Ballo MT, Pisters PWT, et al. Surgical margins and reresection in the management of patients with soft tissue sarcoma using conservative surgery and radiation therapy. Cancer 2003;97:2544-2553. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12733154.

44. O'Donnell PW, Griffin AM, Eward WC, et al. The effect of the setting of a positive surgical margin in soft tissue sarcoma. Cancer 2014;120:2866-2875. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24894656.

45. Gundle KR, Kafchinski L, Gupta S, et al. Analysis of Margin Classification Systems for Assessing the Risk of Local Recurrence After Soft Tissue Sarcoma Resection. J Clin Oncol 2018;36:704-709. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29346043.

46. Kainhofer V, Smolle MA, Szkandera J, et al. The width of resection margins influences local recurrence in soft tissue sarcoma patients. Eur J Surg Oncol 2016;42:899-906. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27107792.

47. Ecker BL, Peters MG, McMillan MT, et al. Implications of Lymph Node Evaluation in the Management of Resectable Soft Tissue Sarcoma. Ann Surg Oncol 2017;24:425-433. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27785659.

48. Naghavi AO, Fernandez DC, Mesko N, et al. American Brachytherapy Society consensus statement for soft tissue sarcoma brachytherapy. Brachytherapy 2017;16:466-489. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28342738.

49. Pohar S, Haq R, Liu L, et al. Adjuvant high-dose-rate and low-dose-rate brachytherapy with external beam radiation in soft tissue sarcoma: a comparison of outcomes. Brachytherapy 2007;6:53-57. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17284387.

50. Leibel SA, Fuks Z, Zelefsky MJ, et al. Intensity-modulated radiotherapy. Cancer J 2002;8:164-176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12004802.

51. Li XA, Chen X, Zhang Q, et al. Margin reduction from image guided radiation therapy for soft tissue sarcoma: Secondary analysis of Radiation Therapy Oncology Group 0630 results. Pract Radiat Oncol 2016;6:e135-140. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26852173.

52. Wang D, Zhang Q, Eisenberg BL, et al. Significant reduction of late toxicities in patients with extremity sarcoma treated with image-guided radiation therapy to a reduced target volume: Results of Radiation Therapy Oncology Group RTOG-0630 Trial. J Clin Oncol 2015;33:2231-2238. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25667281.

53. Tran PT, Hara W, Su Z, et al. Intraoperative radiation therapy for locally advanced and recurrent soft-tissue sarcomas in adults. Int J Radiat Oncol Biol Phys 2008;72:1146-1153. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18394818.

54. Albertsmeier M, Rauch A, Roeder F, et al. External Beam Radiation Therapy for Resectable Soft Tissue Sarcoma: A Systematic Review and Meta-Analysis. Ann Surg Oncol 2018;25:754-767. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28895107.

55. Davis AM, O'Sullivan B, Turcotte R, et al. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. Radiother Oncol 2005;75:48-53. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15948265.

56. Nielsen OS, Cummings B, O'Sullivan B, et al. Preoperative and postoperative irradiation of soft tissue sarcomas: effect of radiation field size. Int J Radiat Oncol Biol Phys 1991;21:1595-1599. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1938569.

57. Kuklo TR, Temple HT, Owens BD, et al. Preoperative versus postoperative radiation therapy for soft-tissue sarcomas. Am J Orthop (Belle Mead NJ) 2005;34:75-80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15789525.

58. Al-Absi E, Farrokhyar F, Sharma R, et al. A systematic review and meta-analysis of oncologic outcomes of pre- versus postoperative radiation in localized resectable soft-tissue sarcoma. Ann Surg Oncol 2010;17:1367-1374. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20217260.

59. Sampath S, Schultheiss TE, Hitchcock YJ, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma: multi-institutional analysis of 821 patients. International journal of radiation oncology, biology, physics 2011;81:498-505. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20888702.

60. Cheng EY, Dusenbery KE, Winters MR, Thompson RC. Soft tissue sarcomas: preoperative versus postoperative radiotherapy. J Surg Oncol 1996;61:90-99. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8606553.

61. Davis AM, O'Sullivan B, Bell RS, 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12431971.

62. Griffin AM, Dickie CI, Catton CN, et al. The influence of time interval between preoperative radiation and surgical resection on the development of wound healing complications in extremity soft tissue sarcoma. Ann Surg Oncol 2015;22:2824-2830. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26018726.

63. Zagars GK, Ballo MT, Pisters PWT, et al. Preoperative vs. postoperative radiation therapy for soft tissue sarcoma: a retrospective comparative evaluation of disease outcome. Int J Radiat Oncol Biol Phys 2003;56:482-488. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12738324.

64. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7917531.

65. Delaney TF, Kepka L, Goldberg SI, et al. Radiation therapy for control of soft-tissue sarcomas resected with positive margins. Int J Radiat Oncol Biol Phys 2007;67:1460-1469. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17394945.

66. Al Yami A, Griffin AM, Ferguson PC, et al. Positive surgical margins in soft tissue sarcoma treated with preoperative radiation: is a postoperative boost necessary? Int J Radiat Oncol Biol Phys 2010;77:1191-1197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20056340.

67. Alamanda VK, Song Y, Shinohara E, et al. Postoperative radiation boost does not improve local recurrence rates in extremity soft tissue sarcomas. J Med Imaging Radiat Oncol 2014;58:633-640. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24821569.

68. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9396401.

69. Gortzak E, Azzarelli A, Buesa J, et al. A randomised phase II study on neo-adjuvant chemotherapy for 'high-risk' adult soft-tissue sarcoma. Eur J Cancer 2001;37:1096-1103. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11378339.

70. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15542808.

71. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15520069.

72. Gronchi A, Ferrari S, Quagliuolo V, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. Lancet Oncol 2017;18:812-822. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28499583.

73. Edmonson JH, Petersen IA, Shives TC, et al. Chemotherapy, irradiation, and surgery for function-preserving therapy of primary extremity soft tissue sarcomas: initial treatment with ifosfamide, mitomycin, doxorubicin, and cisplatin plus granulocyte macrophage-colony-stimulating factor. Cancer 2002;94:786-792. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11857314.

74. Pisters PWT, Ballo MT, Patel SR. Preoperative chemoradiation treatment strategies for localized sarcoma. Ann Surg Oncol 2002;9:535-542. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12095968.

75. DeLaney TF, Spiro IJ, Suit HD, et al. Neoadjuvant chemotherapy and radiotherapy for large extremity soft-tissue sarcomas. Int J Radiat Oncol Biol Phys 2003;56:1117-1127. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12829150.

76. Mack LA, Crowe PJ, Yang JL, et al. Preoperative chemoradiotherapy (modified Eilber protocol) provides maximum local control and minimal morbidity in patients with soft tissue sarcoma. Ann Surg Oncol 2005;12:646-653. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15965732.

77. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16446334.

78. Kraybill WG, Harris J, Spiro IJ, et al. Long-term results of a phase 2 study of neoadjuvant chemotherapy and radiotherapy in the management of high-risk, high-grade, soft tissue sarcomas of the extremities and body wall: Radiation Therapy Oncology Group Trial 9514. Cancer 2010;116:4613-4621. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20572040.

79. Mullen JT, Kobayashi W, Wang JJ, et al. Long-term follow-up of patients treated with neoadjuvant chemotherapy and radiotherapy for large, extremity soft tissue sarcomas. Cancer 2012;118:3758-3765. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22180344.

80. Look Hong NJ, Hornicek FJ, Harmon DC, et al. Neoadjuvant chemoradiotherapy for patients with high-risk extremity and truncal sarcomas: a 10-year single institution retrospective study. Eur J Cancer 2013;49:875-883. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23092789.

81. Tseng WW, Zhou S, To CA, et al. Phase 1 adaptive dose-finding study of neoadjuvant gemcitabine combined with radiation therapy for patients with high-risk extremity and trunk soft tissue sarcoma. Cancer 2015;121:3659-3667. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26177983.

82. Davis EJ, Chugh R, Zhao L, et al. A randomised, open-label, phase II study of neo/adjuvant doxorubicin and ifosfamide versus gemcitabine and docetaxel in patients with localised, high-risk, soft tissue sarcoma. Eur J Cancer 2015;51:1794-1802. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26066736.

83. Tierney JF, Mosseri V, Stewart LA, et al. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7640234.

84. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Sarcoma Meta-analysis Collaboration. Lancet 1997;350:1647-1654. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9400508

85. Maki RG. Role of chemotherapy in patients with soft tissue sarcomas. Expert Rev Anticancer Ther 2004;4:229-236. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15056053.

86. Pervaiz N, Colterjohn N, Farrokhyar F, et al. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer 2008;113:573-581. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18521899.

87. Italiano A, Delva F, Mathoulin-Pelissier S, et al. Effect of adjuvant chemotherapy on survival in FNCLCC grade 3 soft tissue sarcomas: a multivariate analysis of the French Sarcoma Group Database. Ann Oncol 2010;21:2436-2441. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20439343.

88. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8201375.

89. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11230464.

90. Petrioli R, Coratti A, Correale P, et al. Adjuvant epirubicin with or without Ifosfamide for adult soft-tissue sarcoma. Am J Clin Oncol 2002;25:468-473. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12393986.

91. 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 [abstract]. J Clin Oncol 2007;25(18_Suppl):Abstract 10008. Available at: http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/10008.

92. Fakhrai N, Ebm C, Kostler WJ, et al. Intensified adjuvant IFADIC chemotherapy in combination with radiotherapy versus radiotherapy alone for soft tissue sarcoma: long-term follow-up of a prospective randomized feasibility trial. Wien Klin Wochenschr 2010;122:614-619. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20963638.

93. Le Cesne A, Ouali M, Leahy MG, et al. Doxorubicin-based adjuvant chemotherapy in soft tissue sarcoma: pooled analysis of two STBSG-EORTC phase III clinical trials. Ann Oncol 2014;25:2425-2432. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25294887.

94. Frustaci S, De Paoli A, Bidoli E, et al. Ifosfamide in the adjuvant therapy of soft tissue sarcomas. Oncology 2003;65 Suppl 2:80-84. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14586155.

95. Mouridsen HT, Bastholt L, Somers R, et al. Adriamycin versus epirubicin in advanced soft tissue sarcomas. A randomized phase II/phase III study of the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer Clin Oncol 1987;23:1477-1483. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3479329.

96. 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;7:1208-1216. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2504890.

97. Antman KH, Elias A. Dana-Farber Cancer Institute studies in advanced sarcoma. Semin Oncol. 1990;1:7-15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2106162

98. Buesa JM, Mouridsen HT, van Oosterom AT, et al. High-dose DTIC in advanced soft-tissue sarcomas in the adult. A phase II study of the E.O.R.T.C. Soft Tissue and Bone Sarcoma Group. Ann Oncol 1991;2:307-309. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1868027.

99. 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;11:1276-1285. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8315425.

100. Bramwell VHC, 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12917960.

101. Edmonson JH, Ryan LM, Blum RH, 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8315424.

102. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2067035.

103. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7602342.

104. Reichardt P, Tilgner J, Hohenberger P, Dorken B. Dose-intensive chemotherapy with ifosfamide, epirubicin, and filgrastim for adult patients with metastatic or locally advanced soft tissue sarcoma: a phase II study. J Clin Oncol 1998;16:1438-1443. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9552049.

105. Palumbo R, Neumaier C, Cosso M, et al. Dose-intensive first-line chemotherapy with epirubicin and continuous infusion ifosfamide in adult patients with advanced soft tissue sarcomas: a phase II study. Eur J Cancer 1999;35:66-72. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10211090.

106. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17634494.

107. Young RJ, Natukunda A, Litiere S, et al. First-line anthracycline-based chemotherapy for angiosarcoma and other soft tissue sarcoma subtypes: pooled analysis of eleven European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group trials. Eur J Cancer 2014;50:3178-3186. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25459395.

108. Savina M, Le Cesne A, Blay JY, et al. Patterns of care and outcomes of patients with METAstatic soft tissue SARComa in a real-life setting: the METASARC observational study. BMC Med 2017;15:78. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28391775.

109. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16496406.

110. 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 [corrected]. J Clin Oncol 2007;25:2755-2763. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17602081.

111. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17385194.

112. Garcia-Del-Muro X, Lopez-Pousa A, Maurel J, et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. J Clin Oncol 2011;29:2528-2533. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21606430.

113. Seddon B, Strauss SJ, Whelan J, et al. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. Lancet Oncol 2017;18:1397-1410. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28882536.

114. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14584078.

115. Trent JC, Beach J, Burgess MA, et al. A two-arm phase II study of temozolomide in patients with advanced gastrointestinal stromal tumors and other soft tissue sarcomas. Cancer 2003;98:2693-2699. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14669291.

116. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16134177.

117. Judson I, Radford JA, Harris M, et al. Randomised phase II trial of pegylated liposomal doxorubicin (DOXIL/CAELYX) 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;37:870-877. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11313175.

118. Anderson SE, Keohan ML, D'Adamo DR, Maki RG. A retrospective analysis of vinorelbine chemotherapy for patients with previously treated soft-tissue sarcomas. Sarcoma 2006;2006:15947. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17496991.

119. Kuttesch JF, Jr., Krailo MD, Madden T, et al. Phase II evaluation of intravenous vinorelbine (Navelbine) in recurrent or refractory pediatric malignancies: a Children's Oncology Group study. Pediatr Blood Cancer 2009;53:590-593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19533657.

120. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12910529.

121. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14990645.

122. 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 Research and Treatment of Cancer (EORTC) soft tissue and bone sarcoma group trial. J Clin Oncol 2005;23:576-584. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15659504.

123. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16110008.

124. Demetri GD, Chawla SP, von Mehren M, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. J Clin Oncol 2009;27:4188-4196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19652065.

125. Cesne AL, Judson I, Maki R, et al. Trabectedin is a feasible treatment for soft tissue sarcoma patients regardless of patient age: a retrospective pooled analysis of five phase II trials. Br J Cancer 2013;109:1717-1724. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24022187.

126. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial. J Clin Oncol 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26371143.

127. Le Cesne A, Blay JY, Domont J, et al. Interruption versus continuation of trabectedin in patients with soft-tissue sarcoma (T-DIS): a randomised phase 2 trial. Lancet Oncol 2015;16:312-319. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25680558.

128. Kawai A, Araki N, Sugiura H, et al. Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: a randomised, open-label, phase 2 study. Lancet Oncol 2015;16:406-416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25795406.

129. Blay JY, Leahy MG, Nguyen BB, et al. Randomised phase III trial of trabectedin versus doxorubicin-based chemotherapy as first-line therapy in translocation-related sarcomas. Eur J Cancer 2014;50:1137-1147. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24512981.

130. Le Cesne A, JY B, Cupissol D, et al. Results of a prospective randomized phase III T-SAR trial comparing trabectedin vs best supportive care (BSC) in patients with pretreated advanced soft tissue sarcoma (ASTS) [abstract] [abstract]. Presented at the ESMO Congress; Copenhagen.

131. Martin-Broto J, Pousa AL, de Las Penas R, et al. Randomized Phase II Study of Trabectedin and Doxorubicin Compared With Doxorubicin Alone as First-Line Treatment in Patients With Advanced Soft Tissue Sarcomas: A Spanish Group for Research on Sarcoma Study. J Clin Oncol 2016;34:2294-2302. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27185843.

132. Schoffski P, Ray-Coquard IL, Cioffi A, et al. Activity of eribulin mesylate in patients with soft-tissue sarcoma: a phase 2 study in four independent histological subtypes. Lancet Oncol 2011;12:1045-1052. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21937277.

133. Schoffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. Lancet 2016;387:1629-1637. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26874885.

134. Tap WD, Jones RL, Van Tine BA, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Lancet 2016;388:488-497. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27291997.

135. Kollar A, Jones RL, Stacchiotti S, et al. Pazopanib in advanced vascular sarcomas: an EORTC Soft Tissue and Bone Sarcoma Group (STBSG) retrospective analysis. Acta Oncol 2017;56:88-92. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27838944.

136. Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). J Clin Oncol 2009;27:3126-3132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19451427.

137. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012;379:1879-1886. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22595799.

138. Kawai A, Araki N, Hiraga H, et al. A randomized, double-blind, placebo-controlled, Phase III study of pazopanib in patients with soft tissue sarcoma: results from the Japanese subgroup. Jpn J Clin Oncol 2016;46:248-253. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26864131.

139. Coens C, van der Graaf WT, Blay JY, et al. Health-related quality-of-life results from PALETTE: A randomized, double-blind, phase 3 trial of pazopanib versus placebo in patients with soft tissue sarcoma whose disease has progressed during or after prior chemotherapy-a European Organization for research and treatment of cancer soft tissue and bone sarcoma group global network study (EORTC 62072). Cancer 2015;121:2933-2941. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26033286.

140. Kasper B, Sleijfer S, Litiere S, et al. Long-term responders and survivors on pazopanib for advanced soft tissue sarcomas: subanalysis of two European Organisation for Research and Treatment of Cancer (EORTC) clinical trials 62043 and 62072. Ann Oncol 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24504442.

141. Cassier PA, Gelderblom H, Stacchiotti S, et al. Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. Cancer 2012;118:1649-1655. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21823110.

142. Stacchiotti S, Negri T, Libertini M, et al. Sunitinib malate in solitary fibrous tumor (SFT). Ann Oncol 2012;23:3171-3179. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22711763.

143. Stacchiotti S, Negri T, Zaffaroni N, et al. Sunitinib in advanced alveolar soft part sarcoma: evidence of a direct antitumor effect. Ann Oncol 2011;22:1682-1690. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21242589.

144. Valentin T, Fournier C, Penel N, et al. Sorafenib in patients with progressive malignant solitary fibrous tumors: a subgroup analysis from a phase II study of the French Sarcoma Group (GSF/GETO). Invest New Drugs 2013;31:1626-1627. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24005614.

145. Butrynski JE, D'Adamo DR, Hornick JL, et al. Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. N Engl J Med 2010;363:1727-1733. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20979472.

146. Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med 2014;370:1189-1197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24670165.

147. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18184959.

148. 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;28:835-840. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20048174.

149. Davies DM, de Vries PJ, Johnson SR, et al. Sirolimus therapy for angiomyolipoma in tuberous sclerosis and sporadic lymphangioleiomyomatosis: a phase 2 trial. Clin Cancer Res 2011;17:4071-4081. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21525172.

150. McCormack FX, Inoue Y, Moss J, et al. Efficacy and safety of sirolimus in lymphangioleiomyomatosis. N Engl J Med 2011;364:1595-1606. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21410393.

151. Gennatas C, Michalaki V, Kairi PV, et al. Successful treatment with the mTOR inhibitor everolimus in a patient with perivascular epithelioid cell tumor. World J Surg Oncol 2012;10:181. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22943457.

152. Benson C, Vitfell-Rasmussen J, Maruzzo M, et al. A retrospective study of patients with malignant PEComa receiving treatment with sirolimus or temsirolimus: the Royal Marsden Hospital experience. Anticancer Res 2014;34:3663-3668. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24982384.

153. Italiano A, Delcambre C, Hostein I, et al. Treatment with the mTOR inhibitor temsirolimus in patients with malignant PEComa. Ann Oncol 2010;21:1135-1137. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20215136.

154. Santoro A, Comandone A, Basso U, et al. Phase II prospective study with sorafenib in advanced soft tissue sarcomas after anthracycline-based therapy. Ann Oncol 2013;24:1093-1098. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23230134.

155. Gounder MM, Lefkowitz RA, Keohan ML, et al. Activity of Sorafenib against desmoid tumor/deep fibromatosis. Clin Cancer Res 2011;17:4082-4090. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21447727.

156. Park MS, Patel SR, Ludwig JA, et al. Activity of temozolomide and bevacizumab in the treatment of locally advanced, recurrent, and metastatic hemangiopericytoma and malignant solitary fibrous tumor. Cancer 2011;117:4939-4947. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21480200.

157. Agulnik M, Yarber JL, Okuno SH, et al. An open-label, multicenter, phase II study of bevacizumab for the treatment of angiosarcoma and epithelioid hemangioendotheliomas. Ann Oncol 2013;24:257-263. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22910841.

158. Dickson MA, Tap WD, Keohan ML, et al. Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified well-differentiated or dedifferentiated liposarcoma. J Clin Oncol 2013;31:2024-2028. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23569312.

159. Dickson MA, Tap WD, Keohan ML, et al. Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified liposarcoma [abstract]. ASCO Meeting Abstracts 2013;31:10512. Available at: http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/10512.

160. Berry V, Basson L, Bogart E, et al. REGOSARC: Regorafenib versus placebo in doxorubicin-refractory soft-tissue sarcoma-A quality-adjusted time without symptoms of progression or toxicity analysis. Cancer 2017;123:2294-2302. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28295221.

161. Mir O, Brodowicz T, Italiano A, et al. Safety and efficacy of regorafenib in patients with advanced soft tissue sarcoma (REGOSARC): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol 2016;17:1732-1742. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27751846.

162. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17252290.

163. Schwab JH, Boland PJ, Antonescu C, et al. Spinal metastases from myxoid liposarcoma warrant screening with magnetic resonance imaging. Cancer 2007;110:1815-1822. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17724681.

164. Tateishi U, Hasegawa T, Beppu Y, et al. Prognostic significance of MRI findings in patients with myxoid-round cell liposarcoma. AJR Am J Roentgenol 2004;182:725-731. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14975976.

165. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11169942.

166. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12192559.

167. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15578712.

168. Schuetze SM. Utility of positron emission tomography in sarcomas. Curr Opin Oncol 2006;18:369-373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16721133.

169. Evilevitch V, Weber WA, Tap WD, et al. Reduction of glucose metabolic activity is more accurate than change in size at predicting histopathologic response to neoadjuvant therapy in high-grade soft-tissue sarcomas. Clin Cancer Res 2008;14:715-720. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18245531.

170. Benz MR, Czernin J, Allen-Auerbach MS, et al. FDG-PET/CT imaging predicts histopathologic treatment responses after the initial cycle of neoadjuvant chemotherapy in high-grade soft-tissue sarcomas. Clin Cancer Res 2009;15:2856-2863. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19351756.

171. Quak E, van de Luijtgaarden AC, de Geus-Oei LF, et al. Clinical applications of positron emission tomography in sarcoma management. Expert Rev Anticancer Ther 2011;11:195-204. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21342039.

172. Folpe AL, Lyles RH, Sprouse JT, et al. (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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10778952.

173. Schwarzbach MH, Dimitrakopoulou-Strauss A, Willeke F, et al. Clinical value of [18-F]] fluorodeoxyglucose positron emission tomography imaging in soft tissue sarcomas. Ann Surg 2000;231:380-386. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10714631.

174. Pisters PW, Leung DH, Woodruff J, et al. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol 1996;14:1679-1689. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8622088.

175. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10561352.

176. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11764430.

177. McKee MD, Liu DF, Brooks JJ, et al. The prognostic significance of margin width for extremity and trunk sarcoma. J Surg Oncol 2004;85:68-76. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14755506.

178. Biau DJ, Ferguson PC, Chung P, et al. Local recurrence of localized soft tissue sarcoma: a new look at old predictors. Cancer 2012;118:5867-5877. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22648518.

179. Alamanda VK, Crosby SN, Archer KR, et al. Predictors and clinical significance of local recurrence in extremity soft tissue sarcoma. Acta Oncol 2013;52:793-802. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22877243.

180. Clark MA, Thomas JM. Amputation for soft-tissue sarcoma. Lancet Oncol 2003;4:335-342. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12788405.

181. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7114936.

182. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10506627.

183. Lin PP, Guzel VB, Pisters PW, et al. Surgical management of soft tissue sarcomas of the hand and foot. Cancer 2002;95:852-861. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12209730.

184. Williard WC, Hajdu SI, Casper ES, Brennan MF. Comparison of amputation with limb-sparing operations for adult soft tissue sarcoma of the extremity. Ann Surg 1992;215:269-275. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1543400.

185. Stojadinovic A, Jaques DP, Leung DH, et al. Amputation for recurrent soft tissue sarcoma of the extremity: indications and outcome. Ann Surg Oncol 2001;8:509-518. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11456050.

186. 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. Ann Surg Oncol 2005;12:10-17. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15827772.

187. Alamanda VK, Crosby SN, Archer KR, et al. Amputation for extremity soft tissue sarcoma does not increase overall survival: a retrospective cohort study. Eur J Surg Oncol 2012;38:1178-1183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22985713.

188. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9440743.

189. O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet 2002;359:2235-2241. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12103287.

190. Alektiar KM, Velasco J, Zelefsky MJ, et al. Adjuvant radiotherapy for margin-positive high-grade soft tissue sarcoma of the extremity. Int J Radiat Oncol Biol Phys 2000;48:1051-1058. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11072162.

191. Jebsen NL, Trovik CS, Bauer HC, et al. Radiotherapy to improve local control regardless of surgical margin and malignancy grade in extremity and trunk wall soft tissue sarcoma: a Scandinavian sarcoma group study. Int J Radiat Oncol Biol Phys 2008;71:1196-1203. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18207661.

192. 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 2010;77:843-850. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20005638.

193. Gingrich AA, Bateni SB, Monjazeb AM, et al. Neoadjuvant Radiotherapy is Associated with R0 Resection and Improved Survival for Patients with Extremity Soft Tissue Sarcoma Undergoing Surgery: A National Cancer Database Analysis. Ann Surg Oncol 2017;24:3252-3263. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28741123.

194. Pisters PW, Harrison LB, Leung DH, et al. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. J Clin Oncol 1996;14:859-868. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8622034.

195. Alektiar KM, Leung D, Zelefsky MJ, et al. Adjuvant brachytherapy for primary high-grade soft tissue sarcoma of the extremity. Ann Surg Oncol 2002;9:48-56. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11829430.

196. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18612160.

197. Alektiar KM, Brennan MF, Singer S. Local control comparison of adjuvant brachytherapy to intensity-modulated radiotherapy in primary high-grade sarcoma of the extremity. Cancer 2011;117:3229-3234. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21264834.

198. 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 [abstract]. J Clin Oncol 2004;22(14_Suppl):Abstract 9007. Available at: http://meeting.jco.org/cgi/content/abstract/22/14_suppl/9007.

199. Beane JD, Yang JC, White D, et al. Efficacy of adjuvant radiation therapy in the treatment of soft tissue sarcoma of the extremity: 20-year follow-up of a randomized prospective trial. Ann Surg Oncol 2014;21:2484-2489. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24756814.

200. Cassier PA, Kantor G, Bonvalot S, et al. Adjuvant radiotherapy for extremity and trunk wall atypical lipomatous tumor/well-differentiated LPS (ALT/WD-LPS): a French Sarcoma Group (GSF-GETO) study. Ann Oncol 2014;25:1854-1860. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24914041.

201. Cahlon O, Spierer M, Brennan MF, et al. Long-term outcomes in extremity soft tissue sarcoma after a pathologically negative re-resection and without radiotherapy. Cancer 2008;112:2774-2779. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18429001.

202. O'Sullivan B, Griffin AM, Dickie CI, et al. Phase 2 study of preoperative image-guided intensity-modulated radiation therapy to reduce wound and combined modality morbidities in lower extremity soft tissue sarcoma. Cancer 2013;119:1878-1884. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23423841.

203. Tran QNH, Kim AC, Gottschalk AR, et al. Clinical outcomes of intraoperative radiation therapy for extremity sarcomas. Sarcoma 2006;2006:91671-91671. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17040093.

204. Call JA, Stafford SL, Petersen IA, Haddock MG. Use of intraoperative radiotherapy for upper-extremity soft-tissue sarcomas: analysis of disease outcomes and toxicity. Am J Clin Oncol 2014;37:81-85. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23111357.

205. Calvo FA, Sole CV, Polo A, et al. Limb-sparing management with surgical resection, external-beam and intraoperative electron-beam radiation therapy boost for patients with primary soft tissue sarcoma of the extremity: a multicentric pooled analysis of long-term outcomes. Strahlenther Onkol 2014;190:891-898. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24715241.

206. Sole CV, Calvo FA, Cambeiro M, et al. Intraoperative radiotherapy-containing multidisciplinary management of trunk-wall soft-tissue

sarcomas. Clin Transl Oncol 2014;16:834-842. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24481721.

207. Pan E, Goldberg SI, Chen YL, et al. Role of post-operative radiation boost for soft tissue sarcomas with positive margins following pre-operative radiation and surgery. J Surg Oncol 2014;110:817-822. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25111884.

208. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1444788.

209. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1995362.

210. Billing V, Mertens F, Domanski HA, Rydholm A. Deep-seated ordinary and atypical lipomas: histopathology, cytogenetics, clinical features, and outcome in 215 tumours of the extremity and trunk wall. J Bone Joint Surg Br 2008;90:929-933. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18591605.

211. Sommerville SMM, Patton JT, Luscombe JC, et al. Clinical outcomes of deep atypical lipomas (well-differentiated lipoma-like liposarcomas) of the extremities. ANZ J Surg 2005;75:803-806. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16173997.

212. Kooby DA, Antonescu CR, Brennan MF, Singer S. Atypical lipomatous tumor/well-differentiated liposarcoma of the extremity and trunk wall: importance of histological subtype with treatment recommendations. Ann Surg Oncol 2004;11:78-84. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14699038.

213. Kang J, Botros M, Goldberg S, et al. The use of radiation therapy in the management of selected patients with atypical lipomas. Sarcoma 2013;2013:485483-485483. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23401663.

214. Issels RD, Lindner LH, Verweij J, et al. Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study. Lancet Oncol 2010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20434400.

215. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17893504.

216. Al-Refaie WB, Habermann EB, Jensen EH, et al. Surgery alone is adequate treatment for early stage soft tissue sarcoma of the extremity. Br J Surg 2010;97:707-713. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20235085.

217. Kachare SD, Brinkley J, Vohra NA, et al. Radiotherapy associated with improved survival for high-grade sarcoma of the extremity. J Surg Oncol 2015;112:338-343. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26250782.

218. Fong Y, Coit DG, Woodruff JM, Brennan MF. Lymph node metastasis from soft tissue sarcoma in adults. Analysis of data from a prospective database of 1772 sarcoma patients. Ann Surg 1993;217:72-77. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8424704.

219. Judson I, Verweij J, Gelderblom H, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol 2014;15:415-423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24618336.

220. Young RJ, Litiere S, Lia M, et al. Predictive and prognostic factors associated with soft tissue sarcoma response to chemotherapy: a subgroup analysis of the European Organisation for Research and Treatment of Cancer 62012 study. Acta Oncol 2017;56:1013-1020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28431480.

221. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16199316.

222. Grunhagen DJ, de Wilt JHW, Graveland WJ, et al. Outcome and prognostic factor analysis of 217 consecutive isolated limb perfusions with tumor necrosis factor-alpha and melphalan for limb-threatening soft tissue sarcoma. Cancer 2006;106:1776-1784. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16541435.

223. Wray CJ, Benjamin RS, Hunt KK, et al. Isolated limb perfusion for unresectable extremity sarcoma: Results of 2 single-institution phase 2 trials. Cancer 2011;117:3235-3241. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21246524.

224. Deroose JP, Eggermont AMM, van Geel AN, et al. Long-term results of tumor necrosis factor alpha- and melphalan-based isolated limb perfusion in locally advanced extremity soft tissue sarcomas. J Clin Oncol 2011;29:4036-4044. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21931039.

225. Bhangu A, Broom L, Nepogodiev D, et al. Outcomes of isolated limb perfusion in the treatment of extremity soft tissue sarcoma: a systematic review. Eur J Surg Oncol 2013;39:311-319. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23351681.

226. Hegazy MAF, Kotb SZ, Sakr H, et al. Preoperative isolated limb infusion of doxorubicin and external irradiation for limb-threatening soft tissue sarcomas. Ann Surg Oncol 2007;14:568-576. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17094027.

227. Moncrieff MD, Kroon HM, Kam PC, et al. Isolated limb infusion for advanced soft tissue sarcoma of the extremity. Ann Surg Oncol 2008;15:2749-2756. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18648882.

228. Brady MS, Brown K, Patel A, et al. Isolated limb infusion with melphalan and dactinomycin for regional melanoma and soft-tissue sarcoma of the extremity: final report of a phase II clinical trial. Melanoma Res 2009;19:106-111. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19282789.

229. Turaga KK, Beasley GM, Kane JM, et al. Limb preservation with isolated limb infusion for locally advanced nonmelanoma cutaneous and soft-tissue malignant neoplasms. Arch Surg 2011;146:870-875. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21768436.

230. Mullinax JE, Kroon HM, Thompson JF, et al. Isolated Limb Infusion as a Limb Salvage Strategy for Locally Advanced Extremity Sarcoma. J Am Coll Surg 2017;224:635-642. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28214556.

231. Neuwirth MG, Song Y, Sinnamon AJ, et al. Isolated Limb Perfusion and Infusion for Extremity Soft Tissue Sarcoma: A Contemporary Systematic Review and Meta-Analysis. Ann Surg Oncol 2017;24:3803-3810. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29022281.

232. Kane JM, Finley JW, Driscoll D, et al. The treatment and outcome of patients with soft tissue sarcomas and synchronous metastases. Sarcoma 2002;6:69-73. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18521331.

233. Ferguson PC, Deheshi BM, Chung P, et al. Soft tissue sarcoma presenting with metastatic disease: outcome with primary surgical resection. Cancer 2011;117:372-379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20830769.

234. Okiror L, Peleki A, Moffat D, et al. Survival following Pulmonary Metastasectomy for Sarcoma. Thorac Cardiovasc Surg 2016;64:146-149. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25742552.

235. Chudgar NP, Brennan MF, Tan KS, et al. Is Repeat Pulmonary Metastasectomy Indicated for Soft Tissue Sarcoma? Ann Thorac Surg 2017;104:1837-1845. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29074153.

236. Baumann BC, Nagda SN, Kolker JD, et al. Efficacy and safety of stereotactic body radiation therapy for the treatment of pulmonary metastases from sarcoma: A potential alternative to resection. J Surg Oncol 2016;114:65-69. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27111504.

237. Dhakal S, Corbin KS, Milano MT, et al. Stereotactic body radiotherapy for pulmonary metastases from soft-tissue sarcomas: excellent local lesion control and improved patient survival. Int J Radiat Oncol Biol Phys 2012;82:940-945. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21277105.

238. Navarria P, Ascolese AM, Cozzi L, et al. Stereotactic body radiation therapy for lung metastases from soft tissue sarcoma. Eur J Cancer 2015;51:668-674. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25686482.

239. Whooley BP, Mooney MM, Gibbs JF, Kraybill WG. Effective follow-up strategies in soft tissue sarcoma. Semin Surg Oncol 1999;17:83-87. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10402642.

240. Whooley BP, Gibbs JF, Mooney MM, et al. Primary extremity sarcoma: what is the appropriate follow-up? Ann Surg Oncol 2000;7:9-14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10674442.

241. Kane JM, 3rd. Surveillance strategies for patients following surgical resection of soft tissue sarcomas. Curr Opin Oncol 2004;16:328-332. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15187887.

242. Patel SA, Royce TJ, Barysauskas CM, et al. Surveillance Imaging Patterns and Outcomes Following Radiation Therapy and Radical Resection for Localized Extremity and Trunk Soft Tissue Sarcoma. Ann Surg Oncol 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28058559.

243. Lewis JJ, Leung D, Casper ES, et al. Multifactorial analysis of long-term follow-up (more than 5 years) of primary extremity sarcoma. Arch Surg 1999;134:190-194. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10025462.

244. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11550159.

245. Choi H, Varma DG, Fornage BD, et al. Soft-tissue sarcoma: MR imaging vs sonography for detection of local recurrence after surgery. AJR Am J Roentgenol 1991;157:353-358. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1853821.

246. Arya S, Nagarkatti DG, Dudhat SB, et al. Soft tissue sarcomas: ultrasonographic evaluation of local recurrences. Clin Radiol 2000;55:193-197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10708612.

247. Briccoli A, Galletti S, Salone M, et al. Ultrasonography is superior to computed tomography and magnetic resonance imaging in determining superficial resection margins of malignant chest wall tumors. J Ultrasound Med 2007;26:157-162. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17255176.

248. Cheney MD, Giraud C, Goldberg SI, et al. MRI surveillance following treatment of extremity soft tissue sarcoma. J Surg Oncol 2014;109:593-596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24374823.

249. Billingsley KG, Burt ME, Jara E, et al. Pulmonary metastases from soft tissue sarcoma: analysis of patterns of diseases and postmetastasis survival. Ann Surg 1999;229:602-610. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10235518.

250. Zagars GK, Ballo MT, Pisters PWT, et al. Prognostic factors for disease-specific survival after first relapse of soft-tissue sarcoma: analysis of 402 patients with disease relapse after initial conservative surgery and radiotherapy. Int J Radiat Oncol Biol Phys 2003;57:739-747. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14529779.

251. Kim S, Ott HC, Wright CD, et al. Pulmonary resection of metastatic sarcoma: prognostic factors associated with improved outcomes. Ann Thorac Surg 2011;92:1780-1786. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22051274.

252. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1575625.

253. Catton C, Davis A, Bell R, et al. Soft tissue sarcoma of the extremity. Limb salvage after failure of combined conservative therapy. Radiother Oncol 1996;41:209-214. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9027935.

254. Torres MA, Ballo MT, Butler CE, et al. Management of locally recurrent soft-tissue sarcoma after prior surgery and radiation therapy. Int J Radiat Oncol Biol Phys 2007;67:1124-1129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17208389.

255. Canter RJ, Qin LX, Downey RJ, et al. Perioperative chemotherapy in patients undergoing pulmonary resection for metastatic soft-tissue sarcoma of the extremity : a retrospective analysis. Cancer 2007;110:2050-2060. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17828771.

256. Anaya DA, Lev DC, Pollock RE. The role of surgical margin status in retroperitoneal sarcoma. J Surg Oncol 2008;98:607-610. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19072853.

257. Bevilacqua RG, Rogatko A, Hajdu SI, Brennan MF. Prognostic factors in primary retroperitoneal soft-tissue sarcomas. Arch Surg 1991;126:328-334. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1998475.

258. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9256126.

259. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9742918.

260. Bremjit PJ, Jones RL, Chai X, et al. A contemporary large single-institution evaluation of resected retroperitoneal sarcoma. Ann Surg Oncol 2014;21:2150-2158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24615180.

261. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19047280.

262. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19047283.

263. Nussbaum DP, Rushing CN, Lane WO, et al. Preoperative or postoperative radiotherapy versus surgery alone for retroperitoneal sarcoma: a case-control, propensity score-matched analysis of a nationwide clinical oncology database. Lancet Oncol 2016;17:966-975. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27210906.

264. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15450519.

265. Yoon SS, Chen YL, Kirsch DG, et al. Proton-beam, intensity-modulated, and/or intraoperative electron radiation therapy combined with aggressive anterior surgical resection for retroperitoneal sarcomas. Ann Surg Oncol 2010;17:1515-1529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20151216.

266. Swanson EL, Indelicato DJ, Louis D, et al. Comparison of three-dimensional (3D) conformal proton radiotherapy (RT), 3D conformal photon RT, and intensity-modulated RT for retroperitoneal and intra-abdominal sarcomas. Int J Radiat Oncol Biol Phys 2012;83:1549-1557. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22270176.

267. Trans-Atlantic RPSWG. Management of primary retroperitoneal sarcoma (RPS) in the adult: a consensus approach from the Trans-Atlantic RPS Working Group. Ann Surg Oncol 2015;22:256-263. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25316486.

268. Zlotecki RA, Katz TS, Morris CG, et al. Adjuvant radiation therapy for resectable retroperitoneal soft tissue sarcoma: the University of Florida experience. Am J Clin Oncol 2005;28:310-316. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15923806.

269. Baldini EH, Wang D, Haas RL, et al. Treatment Guidelines for Preoperative Radiation Therapy for Retroperitoneal Sarcoma: Preliminary Consensus of an International Expert Panel. Int J Radiat Oncol Biol Phys 2015;92:602-612. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26068493.

270. Pawlik TM, Pisters PWT, 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16491338.

271. Tzeng CW, Fiveash JB, Popple RA, et al. Preoperative radiation therapy with selective dose escalation to the margin at risk for retroperitoneal sarcoma. Cancer 2006;107:371-379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16752414.

272. Baldini EH, Bosch W, Kane JM, 3rd, et al. Retroperitoneal sarcoma (RPS) high risk gross tumor volume boost (HR GTV boost) contour delineation agreement among NRG sarcoma radiation and surgical oncologists. Ann Surg Oncol 2015;22:2846-2852. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26018727.

273. Catton CN, O'Sullivan B, Kotwall C, et al. Outcome and prognosis in retroperitoneal soft tissue sarcoma. Int J Radiat Oncol Biol Phys 1994;29:1005-1010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8083069.

274. Le Péchoux C, Musat E, Baey C, et al. Should adjuvant radiotherapy be administered in addition to front-line aggressive surgery (FAS) in patients with primary retroperitoneal sarcoma? Annals of Oncology 2013;24:832-837. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23123508.

275. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11986186.

276. Sindelar WF, Kinsella TJ, Chen PW, et al. Intraoperative radiotherapy in retroperitoneal sarcomas. Final results of a prospective, randomized, clinical trial. Arch Surg 1993;128:402-410. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8457152.

277. Alektiar KM, Hu K, Anderson L, et al. High-dose-rate intraoperative radiation therapy (HDR-IORT) for retroperitoneal sarcomas. Int J Radiat Oncol Biol Phys 2000;47:157-163. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10758318.

278. Gieschen HL, Spiro IJ, Suit HD, et al. Long-term results of intraoperative electron beam radiotherapy for primary and recurrent retroperitoneal soft tissue sarcoma. Int J Radiat Oncol Biol Phys 2001;50:127-131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11316555.

279. Petersen IA, Haddock MG, Donohue JH, et al. Use of intraoperative electron beam radiotherapy in the management of retroperitoneal soft tissue sarcomas. Int J Radiat Oncol Biol Phys 2002;52:469-475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11872294.

280. Bobin JY, Al-Lawati T, Granero LE, et al. Surgical management of retroperitoneal sarcomas associated with external and intraoperative electron beam radiotherapy. Eur J Surg Oncol 2003;29:676-681. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14511617.

281. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12915599.

282. Krempien R, Roeder F, Oertel S, et al. Intraoperative electron-beam therapy for primary and recurrent retroperitoneal soft-tissue sarcoma. Int J Radiat Oncol Biol Phys 2006;65:773-779. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16682152.

283. Stucky CC, Wasif N, Ashman JB, et al. Excellent local control with preoperative radiation therapy, surgical resection, and intra-operative electron radiation therapy for retroperitoneal sarcoma. J Surg Oncol 2014;109:798-803. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24862926.

284. Roeder F, Ulrich A, Habl G, et al. Clinical phase I/II trial to investigate preoperative dose-escalated intensity-modulated radiation therapy (IMRT) and intraoperative radiation therapy (IORT) in patients with retroperitoneal soft tissue sarcoma: interim analysis. BMC Cancer 2014;14:617. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25163595.

285. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17084545.

286. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15160351.

287. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11466691.

288. Raut CP, Pisters PWT. Retroperitoneal sarcomas: combined-modality treatment approaches. J Surg Oncol 2006;94:81-87. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16788949.

289. Miura JT, Charlson J, Gamblin TC, et al. Impact of chemotherapy on survival in surgically resected retroperitoneal sarcoma. Eur J Surg Oncol 2015;41:1386-1392. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26251340.

290. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19671034.

291. Mendenhall WM, Zlotecki RA, Hochwald SN, et al. Retroperitoneal soft tissue sarcoma. Cancer 2005;104:669-675. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16003776.

292. Windham TC, Pisters PWT. Retroperitoneal sarcomas. Cancer Control 2005;12:36-43. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15668651.

293. Singer S, Corson JM, Demetri GD, et al. Prognostic factors predictive of survival for truncal and retroperitoneal soft-tissue sarcoma. Ann Surg 1995;221:185-195. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7857146.

294. Mullinax JE, Zager JS, Gonzalez RJ. Current diagnosis and management of retroperitoneal sarcoma. Cancer Control 2011;18:177-187. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21666580.

295. Angele MK, Albertsmeier M, Prix NJ, et al. Effectiveness of regional hyperthermia with chemotherapy for high-risk retroperitoneal and abdominal soft-tissue sarcoma after complete surgical resection: a subgroup analysis of a randomized phase-III multicenter study. Ann Surg 2014;260:749-754; discussion 754-746. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25379845.

296. Yoon SS, Chen Y-L, Kambadakone A, et al. Surgical placement of biologic mesh spacers prior to external beam radiation for retroperitoneal and pelvic tumors. Practical Radiation Oncology 2013;3:199-208. Available at: http://linkinghub.elsevier.com/retrieve/pii/S187985001200118X?showall=true.

297. MacNeill AJ, Miceli R, Strauss DC, et al. Post-relapse outcomes after primary extended resection of retroperitoneal sarcoma: A report from the Trans-Atlantic RPS Working Group. Cancer 2017;123:1971-1978. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28152173.

298. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9438854.

299. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006;23:70-83. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17193820.

300. Demetri GD, von Mehren M, Antonescu CR, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw 2010;8 Suppl 2:S1-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20457867.

301. Sepe PS, Moparty B, Pitman MB, et al. EUS-guided FNA for the diagnosis of GI stromal cell tumors: sensitivity and cytologic yield. Gastrointest Endosc 2009;70:254-261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19482280.

302. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol 2002;33:459-465. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12094370.

303. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. Science 2003;299:708-710. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12522257.

304. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12949711.

305. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med 2006;130:1466-1478. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17090188.

306. Lasota J, Miettinen M. Clinical significance of oncogenic KIT and PDGFRA mutations in gastrointestinal stromal tumours. Histopathology 2008;53:245-266. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18312355.

307. Lasota J, Corless CL, Heinrich MC, et al. Clinicopathologic profile of gastrointestinal stromal tumors (GISTs) with primary KIT exon 13 or exon 17 mutations: a multicenter study on 54 cases. Mod Pathol 2008;21:476-484. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18246046.

308. Corless CL, Schroeder A, Griffith D, et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. J Clin Oncol 2005;23:5357-5364. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15928335.

309. Janeway KA, Kim SY, Lodish M, et al. Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking KIT and PDGFRA mutations. Proc Natl Acad Sci U S A 2011;108:314-318. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21173220.

310. Italiano A, Chen CL, Sung YS, et al. SDHA loss of function mutations in a subset of young adult wild-type gastrointestinal stromal tumors. BMC Cancer 2012;12:408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22974104.

311. Oudijk L, Gaal J, Korpershoek E, et al. SDHA mutations in adult and pediatric wild-type gastrointestinal stromal tumors. Mod Pathol 2013;26:456-463. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23174939.

312. Pantaleo MA, Astolfi A, Urbini M, et al. Analysis of all subunits, SDHA, SDHB, SDHC, SDHD, of the succinate dehydrogenase complex in KIT/PDGFRA wild-type GIST. Eur J Hum Genet 2014;22:32-39. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23612575.

313. Doyle LA, Nelson D, Heinrich MC, et al. Loss of succinate dehydrogenase subunit B (SDHB) expression is limited to a distinctive subset of gastric wild-type gastrointestinal stromal tumours: a comprehensive genotype-phenotype correlation study. Histopathology 2012;61:801-809. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22804613.

314. Agaram NP, Wong GC, Guo T, et al. Novel V600E BRAF mutations in imatinib-naive and imatinib-resistant gastrointestinal stromal tumors. Genes Chromosomes Cancer 2008;47:853-859. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18615679.

315. Agaimy A, Terracciano LM, Dirnhofer S, et al. V600E BRAF mutations are alternative early molecular events in a subset of KIT/PDGFRA wild-type gastrointestinal stromal tumours. J Clin Pathol 2009;62:613-616. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19561230.

316. Miettinen M, Wang ZF, Lasota J. DOG1 antibody in the differential diagnosis of gastrointestinal stromal tumors: a study of 1840 cases. Am J Surg Pathol 2009;33:1401-1408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19606013.

317. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol 2005;29:52-68. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15613856.

318. Miettinen M, Makhlouf H, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. Am J Surg Pathol 2006;30:477-489. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16625094.

319. Wozniak A, Rutkowski P, Schoffski P, et al. Tumor genotype is an independent prognostic factor in primary gastrointestinal stromal tumors of gastric origin: a european multicenter analysis based on ConticaGIST. Clin Cancer Res 2014;20:6105-6116. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25294914.

320. Patrikidou A, Domont J, Chabaud S, et al. Long-term outcome of molecular subgroups of GIST patients treated with standard-dose imatinib in the BFR14 trial of the French Sarcoma Group. Eur J Cancer 2016;52:173-180. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26687836.

321. Prior JO, Montemurro M, Orcurto MV, et al. Early prediction of response to sunitinib after imatinib failure by 18F-fluorodeoxyglucose positron emission tomography in patients with gastrointestinal stromal tumor. J Clin Oncol 2009;27:439-445. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19064982.

322. Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. J Clin Oncol 2007;25:1753-1759. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17470865.

323. Dudeck O, Zeile M, Reichardt P, Pink D. Comparison of RECIST and Choi criteria for computed tomographic response evaluation in patients with advanced gastrointestinal stromal tumor treated with sunitinib. Ann Oncol 2011;22:1828-1833. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21289369.

324. Schramm N, Englhart E, Schlemmer M, et al. Tumor response and clinical outcome in metastatic gastrointestinal stromal tumors under sunitinib therapy: comparison of RECIST, Choi and volumetric criteria. Eur J Radiol 2013;82:951-958. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23518148.

325. Shinagare AB, Barysauskas CM, Braschi-Amirfarzan M, et al. Comparison of performance of various tumor response criteria in

assessment of sunitinib activity in advanced gastrointestinal stromal tumors. Clin Imaging 2016;40:880-884. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27179958.

326. Shinagare AB, Jagannathan JP, Kurra V, et al. Comparison of performance of various tumour response criteria in assessment of regorafenib activity in advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib. Eur J Cancer 2014;50:981-986. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24388774.

327. Benjamin RS, Choi H, Macapinlac HA, et al. We should desist using RECIST, at least in GIST. J Clin Oncol 2007;25:1760-1764. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17470866.

328. Young H, Baum R, Cremerius U, et al. Measurement of clinical and subclinical tumour response using [18F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group Eur J Cancer 1999;35:1773-1782. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10673991.

329. Chen K, Zhou YC, Mou YP, et al. Systematic review and meta-analysis of safety and efficacy of laparoscopic resection for gastrointestinal stromal tumors of the stomach. Surg Endosc 2015;29:355-367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25005014.

330. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12181401.

331. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15451219.

332. 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. Eur J Cancer 2005;41:1751-1757. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16098458.

333. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18235121.

334. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18235122.

335. von Mehren M, Heinrich MC, Joensuu H, et al. Follow-up results after 9 years (yrs) of the ongoing, phase II B2222 trial of imatinib mesylate (IM) in patients (pts) with metastatic or unresectable KIT+ gastrointestinal stromal tumors (GIST) [abstract]. J Clin Oncol 2011;29(15_Suppl):Abstract 10016. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/10016.

336. Casali PG, Zalcberg J, Le Cesne A, et al. Ten-Year Progression-Free and Overall Survival in Patients With Unresectable or Metastatic GI Stromal Tumors: Long-Term Analysis of the European Organisation for Research and Treatment of Cancer, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group Intergroup Phase III Randomized Trial on Imatinib at Two Dose Levels. J Clin Oncol 2017;35:1713-1720. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28362562.

337. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18942073.

338. McAuliffe JC, Hunt KK, Lazar AJF, 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18953611.

339. Fiore M, Palassini E, Fumagalli E, et al. Preoperative imatinib mesylate for unresectable or locally advanced primary gastrointestinal stromal tumors (GIST). Eur J Surg Oncol 2009;35:739-745. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19110398.

340. Blesius A, Cassier PA, Bertucci F, et al. Neoadjuvant imatinib in patients with locally advanced non metastatic GIST in the prospective BFR14 trial. BMC Cancer 2011;11:72. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21324142.

341. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15123459.

342. Gold JS, Dematteo RP. Combined surgical and molecular therapy: the gastrointestinal stromal tumor model. Ann Surg 2006;244:176-184. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16858179.

343. DeMatteo RP, Lewis JJ, Leung D, et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000;231:51-58. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10636102.

344. Guerin A, Sasane M, Keir CH, et al. Physician Underestimation of the Risk of Gastrointestinal Stromal Tumor Recurrence After Resection. JAMA Oncol 2015;1:797-805. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26204106.

345. Corless CL, Ballman KV, Antonescu CR, et al. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. J Clin Oncol 2014;32:1563-1570. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24638003.

346. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19303137.

347. Casali PG, Le Cesne A, Poveda Velasco A, et al. Time to Definitive Failure to the First Tyrosine Kinase Inhibitor in Localized GI Stromal Tumors Treated With Imatinib As an Adjuvant: A European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Intergroup Randomized Trial in Collaboration With the Australasian Gastro-Intestinal Trials Group, UNICANCER, French Sarcoma Group, Italian Sarcoma Group, and Spanish Group for Research on Sarcomas. J Clin Oncol 2015;33:4276-4283. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26573069.

348. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA 2012;307:1265-1272. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22453568.

349. Joensuu H, Eriksson M, Sundby Hall K, et al. Adjuvant Imatinib for High-Risk GI Stromal Tumor: Analysis of a Randomized Trial. J Clin Oncol 2016;34:244-250. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26527782.

350. Joensuu H, Eriksson M, Hall KS, et al. Risk factors for gastrointestinal stromal tumor recurrence in patients treated with adjuvant imatinib. Cancer 2014;120:2325-2333. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24737415.

351. Guilhot F. Indications for imatinib mesylate therapy and clinical management. Oncologist 2004;9:271-281. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15169982.

352. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19885836.

353. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17046465.

354. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19282169.

355. Reichardt P, Kang YK, Rutkowski P, et al. Clinical outcomes of patients with advanced gastrointestinal stromal tumors: safety and efficacy in a worldwide treatment-use trial of sunitinib. Cancer 2015;121:1405-1413. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25641662.

356. Reichardt P, Demetri GD, Gelderblom H, et al. Correlation of KIT and PDGFRA mutational status with clinical benefit in patients with gastrointestinal stromal tumor treated with sunitinib in a worldwide treatment-use trial. BMC Cancer 2016;16:22. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26772734.

357. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19213662.

358. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18752081.

359. Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet 2007;370:2011-2019. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18083403.

360. Torino F, Corsello SM, Longo R, et al. Hypothyroidism related to tyrosine kinase inhibitors: an emerging toxic effect of targeted therapy. Nat Rev Clin Oncol 2009;6:219-228. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19333228.

361. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14645423.

362. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15010069.

363. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16624552.

364. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18955451.

365. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20124181.

366. Cassier PA, Fumagalli E, Rutkowski P, et al. Outcome of patients with platelet-derived growth factor receptor alpha-mutated gastrointestinal stromal tumors in the tyrosine kinase inhibitor era. Clin Cancer Res 2012;18:4458-4464. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22718859.

367. Joensuu H, Wardelmann E, Sihto H, et al. Effect of KIT and PDGFRA Mutations on Survival in Patients With Gastrointestinal Stromal Tumors Treated With Adjuvant Imatinib: An Exploratory Analysis of a Randomized Clinical Trial. JAMA Oncol 2017;3:602-609. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28334365.

368. Heinrich MC, Maki RG, Corless CL, et al. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. J Clin Oncol 2008;26:5352-5359. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18955458.

369. Antonescu CR, Besmer P, Guo T, et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. Clin Cancer Res 2005;11:4182-4190. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15930355.

370. Heinrich MC, Corless CL, Blanke CD, et al. Molecular correlates of imatinib resistance in gastrointestinal stromal tumors. J Clin Oncol 2006;24:4764-4774. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16954519.

371. Wardelmann E, Merkelbach-Bruse S, Pauls K, et al. Polyclonal evolution of multiple secondary KIT mutations in gastrointestinal stromal tumors under treatment with imatinib mesylate. Clin Cancer Res 2006;12:1743-1749. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16551858.

372. Desai J, Shankar S, Heinrich MC, et al. Clonal evolution of resistance to imatinib in patients with metastatic gastrointestinal stromal tumors. Clin Cancer Res 2007;13:5398-5405. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17875769.

373. Gajiwala KS, Wu JC, Christensen J, et al. KIT kinase mutants show unique mechanisms of drug resistance to imatinib and sunitinib in gastrointestinal stromal tumor patients. Proc Natl Acad Sci U S A 2009;106:1542-1547. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19164557.

374. Guo T, Hajdu M, Agaram NP, et al. Mechanisms of sunitinib resistance in gastrointestinal stromal tumors harboring KITAY502-3ins mutation: an in vitro mutagenesis screen for drug resistance. Clin Cancer Res 2009;15:6862-6870. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19861442.

375. Nishida T, Takahashi T, Nishitani A, et al. Sunitinib-resistant gastrointestinal stromal tumors harbor cis-mutations in the activation loop of the KIT gene. Int J Clin Oncol 2009;14:143-149. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19390946.

376. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:295-302. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23177515.

377. Ben-Ami E, Barysauskas CM, von Mehren M, et al. Long-term follow-up results of the multicenter phase II trial of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of standard tyrosine kinase inhibitor therapy. Ann Oncol 2016;27:1794-1799. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27371698.

378. Kindler HL, Campbell NP, Wroblewski K, et al. Sorafenib (SOR) in patients (pts) with imatinib (IM) and sunitinib (SU)-resistant (RES) gastrointestinal stromal tumors (GIST): Final results of a University of Chicago Phase II Consortium trial [abstract]. J Clin Oncol 2011;29(15_Suppl):Abstract 10009. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/10009.

379. Park SH, Ryu MH, Ryoo BY, et al. Sorafenib in patients with metastatic gastrointestinal stromal tumors who failed two or more prior tyrosine kinase inhibitors: a phase II study of Korean gastrointestinal stromal tumors study group. Invest New Drugs 2012;30:2377-2383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22270258.

380. Montemurro M, Gelderblom H, Bitz U, et al. Sorafenib as third- or fourth-line treatment of advanced gastrointestinal stromal tumour and pretreatment including both imatinib and sunitinib, and nilotinib: A

retrospective analysis. Eur J Cancer 2013;49:1027-1031. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23140824.

381. Kefeli U, Benekli M, Sevinc A, et al. Efficacy of sorafenib in patients with gastrointestinal stromal tumors in the third- or fourth-line treatment: A retrospective multicenter experience. Oncol Lett 2013;6:605-611. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24137379.

382. Demetri GD, Casali PG, Blay JY, et al. A phase I study of single-agent nilotinib or in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors. Clin Cancer Res 2009;15:5910-5916. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19723647.

383. Montemurro M, Schoffski P, Reichardt P, et al. Nilotinib in the treatment of advanced gastrointestinal stromal tumours resistant to both imatinib and sunitinib. Eur J Cancer 2009;45:2293-2297. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19467857.

384. Sawaki A, Nishida T, Doi T, et al. Phase 2 study of nilotinib as third-line therapy for patients with gastrointestinal stromal tumor. Cancer 2011;117:4633-4641. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21456006.

385. Reichardt P, Blay JY, Gelderblom H, et al. Phase III study of nilotinib versus best supportive care with or without a TKI in patients with gastrointestinal stromal tumors resistant to or intolerant of imatinib and sunitinib. Ann Oncol 2012;23:1680-1687. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22357255.

386. Cauchi C, Somaiah N, Engstrom PF, et al. Evaluation of nilotinib in advanced GIST previously treated with imatinib and sunitinib. Cancer Chemother Pharmacol 2012;69:977-982. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22119758.

387. Dewaele B, Wasag B, Cools J, et al. Activity of dasatinib, a dual SRC/ABL kinase inhibitor, and IPI-504, a heat shock protein 90 inhibitor, against gastrointestinal stromal tumor-associated PDGFRAD842V mutation. Clin Cancer Res 2008;14:5749-5758. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18794084.

388. Trent JC, Wathen K, von Mehren M, et al. A phase II study of dasatinib for patients with imatinib-resistant gastrointestinal stromal tumor (GIST) [abstract]. J Clin Oncol 2011;29(15_Suppl):Abstract 10006. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/10006.

389. Ganjoo KN, Villalobos VM, Kamaya A, et al. A multicenter phase II study of pazopanib in patients with advanced gastrointestinal stromal tumors (GIST) following failure of at least imatinib and sunitinib. Ann Oncol 2014;25:236-240. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24356634.

390. Mir O, Cropet C, Toulmonde M, et al. Pazopanib plus best supportive care versus best supportive care alone in advanced gastrointestinal stromal tumours resistant to imatinib and sunitinib (PAZOGIST): a randomised, multicentre, open-label phase 2 trial. Lancet Oncol 2016;17:632-641. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27068858.

391. Blay JY, Shen L, Kang YK, et al. Nilotinib versus imatinib as first-line therapy for patients with unresectable or metastatic gastrointestinal stromal tumours (ENESTg1): a randomised phase 3 trial. Lancet Oncol 2015;16:550-560. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25882987.

392. Schoffski P, Reichardt P, Blay JY, et al. A phase I-II study of everolimus (RAD001) in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors. Ann Oncol 2010;21:1990-1998. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20507881.

393. Committee ASoP, Evans JA, Chandrasekhara V, et al. The role of endoscopy in the management of premalignant and malignant conditions of the stomach. Gastrointest Endosc 2015;82:1-8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25935705.

394. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18076015.

395. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19793678.

396. Wang D, Zhang Q, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumors: long-term follow-up results of Radiation Therapy Oncology Group 0132. Ann Surg Oncol 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22203182.

397. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16710031.

398. Rutkowski P, Nowecki Z, Nyckowski P, et al. Surgical treatment of patients with initially inoperable and/or metastatic gastrointestinal stromal tumors (GIST) during therapy with imatinib mesylate. J Surg Oncol 2006;93:304-311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16496358.

399. Andtbacka RH, Ng CS, Scaife CL, et al. Surgical resection of gastrointestinal stromal tumors after treatment with imatinib. Ann Surg Oncol 2007;14:14-24. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17072676.

400. DeMatteo RP, Maki RG, Singer S, et al. Results of tyrosine kinase inhibitor therapy followed by surgical resection for metastatic gastrointestinal stromal tumor. Ann Surg 2007;245:347-352. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17435539.

401. Gronchi A, Fiore M, Miselli F, et al. Surgery of residual disease following molecular-targeted therapy with imatinib mesylate in advanced/metastatic GIST. Ann Surg 2007;245:341-346. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17435538.

402. Sym SJ, Ryu M-H, Lee J-L, et al. Surgical intervention following imatinib treatment in patients with advanced gastrointestinal stromal tumors (GISTs). J Surg Oncol 2008;98:27-33. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18452195.

403. Mussi C, Ronellenfitsch U, Jakob J, et al. Post-imatinib surgery in advanced/metastatic GIST: is it worthwhile in all patients? Ann Oncol 2010;21:403-408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19628568.

404. Yeh C-N, Chen T-W, Tseng J-H, et al. Surgical management in metastatic gastrointestinal stromal tumor (GIST) patients after imatinib mesylate treatment. J Surg Oncol 2010;102:599-603. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20976730.

405. 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 [abstract]. J Clin Oncol 2004;22(14_Suppl):Abstract 3012. Available at: http://meeting.jco.org/cgi/content/abstract/22/14_suppl/3012.

406. Raut CP, Wang Q, Manola J, et al. Cytoreductive surgery in patients with metastatic gastrointestinal stromal tumor treated with sunitinib malate. Ann Surg Oncol 2010;17:407-415. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19898902.

407. Fumagalli E, Coco P, Morosi C, et al. Rechallenge with Imatinib in GIST patients resistant to second or third line therapy [abstract]. Connective Tissue Oncology Society (CTOS) 15th Annual Meeting; 2009:Abstract 39404. Available at: http://www.ctos.org/meeting/2009/program.asp.

408. Kang YK, Ryu MH, Yoo C, et al. Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2013;14:1175-1182. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24140183.

409. Blay JY, 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 versus continuation of treatment beyond 1 year: the French Sarcoma Group. J Clin Oncol 2007;25:1107-1113. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17369574.

410. Le Cesne A, Ray-Coquard I, Bui BN, et al. Discontinuation of imatinib in patients with advanced gastrointestinal stromal tumours after 3 years of treatment: an open-label multicentre randomised phase 3 trial. Lancet Oncol 2010;11:942-949. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20864406.

411. Patrikidou A, Chabaud S, Ray-Coquard I, et al. Influence of imatinib interruption and rechallenge on the residual disease in patients with advanced GIST: results of the BFR14 prospective French Sarcoma Group randomised, phase III trial. Annals of Oncology 2013;24:1087-1093. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23175622.

412. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11247896.

413. Durno C, Monga N, Bapat B, et al. Does early colectomy increase desmoid risk in familial adenomatous polyposis? Clin Gastroenterol Hepatol 2007;5:1190-1194. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17916546.

414. Nugent KP, Spigelman AD, Phillips RK. Life expectancy after colectomy and ileorectal anastomosis for familial adenomatous polyposis. Dis Colon Rectum 1993;36:1059-1062. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8223060.

415. Lazar AJ, Tuvin D, Hajibashi S, et al. Specific mutations in the beta-catenin gene (CTNNB1) correlate with local recurrence in sporadic desmoid tumors. Am J Pathol 2008;173:1518-1527. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18832571.

416. Domont J, Salas S, Lacroix L, et al. High frequency of beta-catenin heterozygous mutations in extra-abdominal fibromatosis: a potential molecular tool for disease management. Br J Cancer 2010;102:1032-1036. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20197769.

417. Le Guellec S, Soubeyran I, Rochaix P, et al. CTNNB1 mutation analysis is a useful tool for the diagnosis of desmoid tumors: a study of 260 desmoid tumors and 191 potential morphologic mimics. Mod Pathol 2012;25:1551-1558. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22766794.

418. Colombo C, Miceli R, Lazar AJ, et al. CTNNB1 45F mutation is a molecular prognosticator of increased postoperative primary desmoid tumor recurrence: An independent, multicenter validation study. Cancer 2013;119:3696-3702. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23913621.

419. Mullen JT, DeLaney TF, Rosenberg AE, et al. beta-Catenin mutation status and outcomes in sporadic desmoid tumors. Oncologist 2013;18:1043-1049. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23960186.

420. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11254428.

421. Yamaguchi H, Sakakibara T, Hino M, et al. A case of fibromatosis of the breast. Breast Cancer 2002;9:175-178. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12016399.

422. Kouriefs C, Leris ACA, Mokbel K, et al. Infiltrating fibromatosis of the breast: a potential pitfall. Int J Clin Pract 2002;56:401-402. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12137452.

423. Neuman HB, Brogi E, Ebrahim A, et al. Desmoid tumors (fibromatoses) of the breast: a 25-year experience. Ann Surg Oncol 2008;15:274-280. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17896146.

424. Lev D, Kotilingam D, Wei C, et al. Optimizing treatment of desmoid tumors. J Clin Oncol 2007;25:1785-1791. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17470870.

425. Pritchard DJ, Nascimento AG, Petersen IA. Local control of extra-abdominal desmoid tumors. J Bone Joint Surg Am 1996;78:848-854. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8666602.

426. Ballo MT, Zagars GK, Pollack A, et al. Desmoid tumor: prognostic factors and outcome after surgery, radiation therapy, or combined surgery and radiation therapy. J Clin Oncol 1999;17:158-167. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10458229.

427. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11146782.

428. Ma D, Li S, Fu R, et al. Long-term outcomes of 47 patients with aggressive fibromatosis of the chest treated with surgery. Eur J Surg Oncol 2016;42:1693-1698. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27425579.

429. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12663732.

430. Peng PD, Hyder O, Mavros MN, et al. Management and recurrence patterns of desmoids tumors: a multi-institutional analysis of 211 patients. Ann Surg Oncol 2012;19:4036-4042. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22972507.

431. Melis M, Zager JS, Sondak VK. Multimodality management of desmoid tumors: how important is a negative surgical margin? J Surg Oncol 2008;98:594-602. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19072851.

432. Huang K, Fu H, Shi YQ, et al. Prognostic factors for extra-abdominal and abdominal wall desmoids: a 20-year experience at a single institution. J Surg Oncol 2009;100:563-569. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19722232.

433. Stoeckle E, Coindre JM, Longy M, et al. A critical analysis of treatment strategies in desmoid tumours: a review of a series of 106 cases. Eur J Surg Oncol 2009;35:129-134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18760561.

434. Mullen JT, Delaney TF, Kobayashi WK, et al. Desmoid tumor: analysis of prognostic factors and outcomes in a surgical series. Ann Surg Oncol 2012;19:4028-4035. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22965569.

435. Janssen ML, van Broekhoven DL, Cates JM, et al. Meta-analysis of the influence of surgical margin and adjuvant radiotherapy on local recurrence after resection of sporadic desmoid-type fibromatosis. Br J Surg 2017;104:347-357. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28199014.

436. Gluck I, Griffith KA, Biermann JS, et al. Role of radiotherapy in the management of desmoid tumors. Int J Radiat Oncol Biol Phys 2011;80:787-792. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20615622.

437. Crago AM, Denton B, Salas S, et al. A prognostic nomogram for prediction of recurrence in desmoid fibromatosis. Ann Surg 2013;258:347-353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23532110.

438. Salas S, Dufresne A, Bui B, et al. Prognostic factors influencing progression-free survival determined from a series of sporadic desmoid tumors: a wait-and-see policy according to tumor presentation. J Clin Oncol 2011;29:3553-3558. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21844500.

439. Cates JM, Stricker TP. Surgical resection margins in desmoid-type fibromatosis: a critical reassessment. Am J Surg Pathol 2014;38:1707-1714. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25392923.

440. Goy BW, Lee SP, Eilber F, et al. The role of adjuvant radiotherapy in the treatment of resectable desmoid tumors. Int J Radiat Oncol Biol Phys 1997;39:659-665. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9336146.

441. Jelinek JA, Stelzer KJ, Conrad E, et al. The efficacy of radiotherapy as postoperative treatment for desmoid tumors. Int J Radiat Oncol Biol Phys 2001;50:121-125. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11316554.

442. Fontanesi J, Mott MP, Kraut MJ, et al. The role of postoperative irradiation in the treatment of locally recurrent incompletely resected extra-abdominal desmoid tumors. Sarcoma 2004;8:83-86. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18521399.

443. Baumert BG, Spahr MO, Von Hochstetter A, et al. The impact of radiotherapy in the treatment of desmoid tumours. An international survey of 110 patients. A study of the Rare Cancer Network. Radiat Oncol 2007;2:12-12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17343751.

444. Guadagnolo BA, Zagars GK, Ballo MT. Long-term outcomes for desmoid tumors treated with radiation therapy. Int J Radiat Oncol Biol Phys 2008;71:441-447. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18068311.

445. Santti K, Beule A, Tuomikoski L, et al. Radiotherapy in desmoid tumors : Treatment response, local control, and analysis of local failures. Strahlenther Onkol 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28044201.

446. Bonvalot S, Eldweny H, Haddad V, et al. Extra-abdominal primary fibromatosis: Aggressive management could be avoided in a subgroup of patients. Eur J Surg Oncol 2008;34:462-468. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17709227.

447. Fiore M, Rimareix F, Mariani L, et al. Desmoid-type fibromatosis: a front-line conservative approach to select patients for surgical treatment. Ann Surg Oncol 2009;16:2587-2593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19568815.

448. Lewis JJ, Boland PJ, Leung DH, et al. The enigma of desmoid tumors. Ann Surg 1999;229:866-872. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10363901.

449. Kiel KD, Suit HD. Radiation therapy in the treatment of aggressive fibromatoses (desmoid tumors). Cancer 1984;54:2051-2055. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6488135.

450. Ballo MT, Zagars GK, Pollack A. Radiation therapy in the management of desmoid tumors. Int J Radiat Oncol Biol Phys 1998;42:1007-1014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9869223.

451. Schulz-Ertner D, Zierhut D, Mende U, et al. The role of radiation therapy in the management of desmoid tumors. Strahlenther Onkol 2002;178:78-83. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11942041.

452. Keus RB, Nout RA, Blay JY, et al. Results of a phase II pilot study of moderate dose radiotherapy for inoperable desmoid-type fibromatosis--an EORTC STBSG and ROG study (EORTC 62991-22998). Ann Oncol 2013;24:2672-2676. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23868907.

453. Janinis J, Patriki M, Vini L, et al. The pharmacological treatment of aggressive fibromatosis: a systematic review. Ann Oncol 2003;14:181-190. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12562642.

454. de Camargo VP, Keohan ML, D'Adamo DR, et al. Clinical outcomes of systemic therapy for patients with deep fibromatosis (desmoid tumor). Cancer 2010;116:2258-2265. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20187095.

455. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14745880.

456. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10649274.

457. Benson JR, Mokbel K, Baum M. Management of desmoid tumours including a case report of toremifene. Ann Oncol 1994;5:173-177. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8186162.

458. Bus PJ, Verspaget HW, van Krieken JH, et al. Treatment of mesenteric desmoid tumours with the anti-oestrogenic agent toremifene: case histories and an overview of the literature. Eur J Gastroenterol Hepatol 1999;11:1179-1183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10524651.

459. Heidemann J, Ogawa H, Otterson MF, et al. Antiangiogenic treatment of mesenteric desmoid tumors with toremifene and interferon alfa-2b: report of two cases. Dis Colon Rectum 2004;47:118-122. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14719159.

460. Maseelall P, Robins JC, Williams DB, Thomas MA. Stabilization and regression of a recurrent desmoid tumor with the antiestrogen toremifene. Fertil Steril 2005;84:509. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16086575.

461. Patel SR, Evans HL, Benjamin RS. Combination chemotherapy in adult desmoid tumors. Cancer 1993;72:3244-3247. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8242548.

462. Poritz LS, Blackstein M, Berk T, et al. Extended follow-up of patients treated with cytotoxic chemotherapy for intra-abdominal desmoid tumors. Dis Colon Rectum 2001;44:1268-1273. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11584198.

463. Garbay D, Le Cesne A, Penel N, et al. Chemotherapy in patients with desmoid tumors: a study from the French Sarcoma Group (FSG). Ann Oncol 2012;23:182-186. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21444357.

464. Constantinidou A, Jones RL, Scurr M, et al. Pegylated liposomal doxorubicin, an effective, well-tolerated treatment for refractory aggressive fibromatosis. Eur J Cancer 2009;45:2930-2934. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19767198.

465. Weiss AJ, Horowitz S, Lackman RD. Therapy of desmoid tumors and fibromatosis using vinorelbine. Am J Clin Oncol 1999;22:193-195. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10199460.

466. Azzarelli A, Gronchi A, Bertulli R, et al. Low-dose chemotherapy with methotrexate and vinblastine for patients with advanced aggressive fibromatosis. Cancer 2001;92:1259-1264. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11571741.

467. Park KH, Choi YJ, Kim KW, et al. Combination chemotherapy with methotrexate and vinblastine for surgically unresectable, aggressive fibromatosis. Jpn J Clin Oncol 2016;46:845-849. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27365524.

468. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16505440.

469. Chugh R, Wathen JK, Patel SR, et al. Efficacy of imatinib in aggressive fibromatosis: Results of a phase II multicenter Sarcoma Alliance for Research through Collaboration (SARC) trial. Clin Cancer Res 2010;16:4884-4891. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20724445.

470. Penel N, Le Cesne A, Bui BN, et al. Imatinib for progressive and recurrent aggressive fibromatosis (desmoid tumors): an FNCLCC/French Sarcoma Group phase II trial with a long-term follow-up. Ann Oncol 2011;22:452-457. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20622000.

471. Ferrari A, Dileo P, Casanova M, et al. Rhabdomyosarcoma in adults. A retrospective analysis of 171 patients treated at a single institution.

Cancer 2003;98:571-580. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12879475.

472. Newton WA, Jr., Gehan EA, Webber BL, et al. Classification of rhabdomyosarcomas and related sarcomas. Pathologic aspects and proposal for a new classification--an Intergroup Rhabdomyosarcoma Study. Cancer 1995;76:1073-1085. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8625211.

473. Parham DM, Ellison DA. Rhabdomyosarcomas in adults and children: an update. Arch Pathol Lab Med 2006;130:1454-1465. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17090187.

474. Hawkins WG, Hoos A, Antonescu CR, et al. Clinicopathologic analysis of patients with adult rhabdomyosarcoma. Cancer 2001;91:794-803. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11241248.

475. Little DJ, Ballo MT, Zagars GK, et al. Adult rhabdomyosarcoma: outcome following multimodality treatment. Cancer 2002;95:377-388. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12124838.

476. Nascimento AF, Fletcher CDM. Spindle cell rhabdomyosarcoma in adults. Am J Surg Pathol 2005;29:1106-1113. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16006807.

477. Sultan I, Qaddoumi I, Yaser S, et al. Comparing adult and pediatric rhabdomyosarcoma in the surveillance, epidemiology and end results program, 1973 to 2005: an analysis of 2,600 patients. J Clin Oncol 2009;27:3391-3397. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19398574.

478. Yasuda T, Perry KD, Nelson M, et al. Alveolar rhabdomyosarcoma of the head and neck region in older adults: genetic characterization and a review of the literature. Hum Pathol 2009;40:341-348. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18973919.

479. Simon JH, Paulino AC, Ritchie JM, et al. Presentation, prognostic factors and patterns of failure in adult rhabdomyosarcoma. Sarcoma 2003;7:1-7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18521362.

480. Gaffney EF, Dervan PA, Fletcher CD. Pleomorphic rhabdomyosarcoma in adulthood. Analysis of 11 cases with definition of diagnostic criteria. Am J Surg Pathol 1993;17:601-609. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8333559.

481. Furlong MA, Mentzel T, Fanburg-Smith JC. Pleomorphic rhabdomyosarcoma in adults: a clinicopathologic study of 38 cases with emphasis on morphologic variants and recent skeletal muscle-specific markers. Mod Pathol 2001;14:595-603. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11406662.

482. Stock N, Chibon F, Binh MBN, et al. Adult-type rhabdomyosarcoma: analysis of 57 cases with clinicopathologic description, identification of 3 morphologic patterns and prognosis. Am J Surg Pathol 2009;33:1850-1859. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19898221.

483. Esnaola NF, Rubin BP, Baldini EH, et al. Response to chemotherapy and predictors of survival in adult rhabdomyosarcoma. Ann Surg 2001;234:215-223. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11505068.

484. Sultan I, Ferrari A. Selecting multimodal therapy for rhabdomyosarcoma. Expert Rev Anticancer Ther 2010;10:1285-1301. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20735314.

485. Arndt CAS, Stoner JA, Hawkins DS, et al. Vincristine, actinomycin, and cyclophosphamide compared with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan, and cyclophosphamide for intermediate-risk rhabdomyosarcoma: children's oncology group study D9803. J Clin Oncol 2009;27:5182-5188. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19770373.

486. Wolden SL, Lyden ER, Arndt CA, et al. Local Control for Intermediate-Risk Rhabdomyosarcoma: Results From D9803 According to Histology, Group, Site, and Size: A Report From the Children's Oncology Group. Int J Radiat Oncol Biol Phys 2015;93:1071-1076. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26581144.

487. Raney RB, Walterhouse DO, Meza JL, et al. Results of the Intergroup Rhabdomyosarcoma Study Group D9602 protocol, using vincristine and dactinomycin with or without cyclophosphamide and radiation therapy, for newly diagnosed patients with low-risk embryonal rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. J Clin Oncol 2011;29:1312-1318. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21357783.

488. Arndt CAS, Hawkins DS, Meyer WH, et al. Comparison of results of a pilot study of alternating vincristine/doxorubicin/cyclophosphamide and etoposide/ifosfamide with IRS-IV in intermediate risk rhabdomyosarcoma: a report from the Children's Oncology Group. Pediatr Blood Cancer 2008;50:33-36. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17091486.

489. Weigel BJ, Lyden E, Anderson JR, et al. Intensive Multiagent Therapy, Including Dose-Compressed Cycles of Ifosfamide/Etoposide and Vincristine/Doxorubicin/Cyclophosphamide, Irinotecan, and Radiation, in Patients With High-Risk Rhabdomyosarcoma: A Report From the Children's Oncology Group. J Clin Oncol 2016;34:117-122. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26503200.

490. Klingebiel T, Pertl U, Hess CF, et al. Treatment of children with relapsed soft tissue sarcoma: report of the German CESS/CWS REZ 91 trial. Med Pediatr Oncol 1998;30:269-275. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9544222.

491. Pappo AS, Lyden E, Breitfeld P, et al. Two consecutive phase II window trials of irinotecan alone or in combination with vincristine for the treatment of metastatic rhabdomyosarcoma: the Children's Oncology Group. J Clin Oncol 2007;25:362-369. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17264331.

492. Vassal G, Couanet D, Stockdale E, et al. Phase II trial of irinotecan in children with relapsed or refractory rhabdomyosarcoma: a joint study of the French Society of Pediatric Oncology and the United Kingdom Children's Cancer Study Group. J Clin Oncol 2007;25:356-361. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17264330.

493. Mascarenhas L, Lyden ER, Breitfeld PP, et al. Randomized phase II window trial of two schedules of irinotecan with vincristine in patients with first relapse or progression of rhabdomyosarcoma: a report from the Children's Oncology Group. J Clin Oncol 2010;28:4658-4663. Erratum in J Clin Oncol. 2011;4629(4610):1394. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20837952.

494. McNall-Knapp RY, Williams CN, Reeves EN, et al. Extended phase I evaluation of vincristine, irinotecan, temozolomide, and antibiotic in children with refractory solid tumors. Pediatr Blood Cancer 2010;54:909-915. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20405511.

495. Pappo AS, Lyden E, Breneman J, et al. Up-front window trial of topotecan in previously untreated children and adolescents with metastatic rhabdomyosarcoma: an intergroup rhabdomyosarcoma study. J Clin Oncol 2001;19:213-219. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11134215.

496. Saylors RL, Stine KC, Sullivan J, et al. Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumors: a Pediatric Oncology Group phase II study. J Clin Oncol 2001;19:3463-3469. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11481351.

497. Walterhouse DO, Lyden ER, Breitfeld PP, et al. Efficacy of topotecan and cyclophosphamide given in a phase II window trial in children with newly diagnosed metastatic rhabdomyosarcoma: a Children's Oncology Group study. J Clin Oncol 2004;22:1398-1403. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15007087.

498. Casanova M, Ferrari A, Bisogno G, et al. Vinorelbine and low-dose cyclophosphamide in the treatment of pediatric sarcomas: pilot study for the upcoming European Rhabdomyosarcoma Protocol. Cancer 2004;101:1664-1671. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15378498.

499. Casanova M, Ferrari A, Spreafico F, et al. Vinorelbine in previously treated advanced childhood sarcomas: evidence of activity in rhabdomyosarcoma. Cancer 2002;94:3263-3268. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12115359.

500. Dharmarajan KV, Wexler LH, Wolden SL. Concurrent radiation with irinotecan and carboplatin in intermediate- and high-risk rhabdomyosarcoma: a report on toxicity and efficacy from a prospective pilot phase II study. Pediatr Blood Cancer 2013;60:242-247. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22619050.

501. Ogilvie CM, Crawford EA, Slotcavage RL, et al. Treatment of adult rhabdomyosarcoma. Am J Clin Oncol 2010;33:128-131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19770626.

502. Setty BA, Stanek JR, Mascarenhas L, et al. VIncristine, irinotecan, and temozolomide in children and adolescents with relapsed rhabdomyosarcoma. Pediatr Blood Cancer 2018;65. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28748602.

503. Tateishi U, Hosono A, Makimoto A, et al. Comparative study of FDG PET/CT and conventional imaging in the staging of rhabdomyosarcoma. Ann Nucl Med 2009;23:155-161. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19225939.