

## NCCN Guidelines® Insights

## Soft Tissue Sarcoma, Version 2.2014

## Featured Updates to the NCCN Guidelines

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**Abstract**

These NCCN Guidelines Insights highlight the important updates to the NCCN Guidelines for Soft Tissue Sarcoma (STS) specific to the role of radiation therapy in the management of patients with retroperitoneal/intra-abdominal STS. The guidelines have also included recommendations for genetic testing and counseling for patients with a clinical and/or family history of genetic cancer syndromes associated with a predisposition for the development of STS. (*J Natl Compr Canc Netw* 2014;12:473–483)

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### Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to NCCN Guidelines for Soft Tissue Sarcoma
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Soft Tissue Sarcoma

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**Scott Schuetze, MD, PhD**, panel member, has disclosed the following relationships with commercial interests: grant/research support from AB Science; Janssen Pharmaceuticals, Inc.; Amgen Inc.; and ZIOPHARM Oncology, Inc. He is a consultant for Amgen Inc.

**Brian A. Van Tine, MD, PhD**, panel member, has disclosed that following relationships with commercial interests: advisor/speaker for Caris Life Sciences, Ltd.; GlaxoSmithKline; and DFINE, Inc. Advisor for EMD Serono, Inc. Grant funding from Polaris Pharmaceuticals, Inc.

**Mary Anne Bergman**, Guidelines Coordinator, has disclosed that she has no relevant financial relationships.

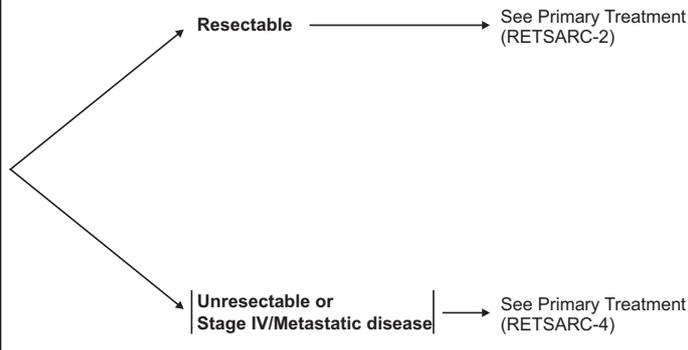
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## Soft Tissue Sarcoma, Version 2.2014

## 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
- Chest/abdominal/pelvic CT with contrast ± MRI
- Pre-resection biopsy not necessarily required; consider biopsy if there is suspicion of malignancies other than sarcoma
- Biopsy is necessary for patients receiving preoperative RT or chemotherapy
- Image-guided (CT or ultrasound) core needle biopsy is preferred over open surgical biopsy<sup>a</sup>
- 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 and Ovarian



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

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RETSARC-1

### 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.**

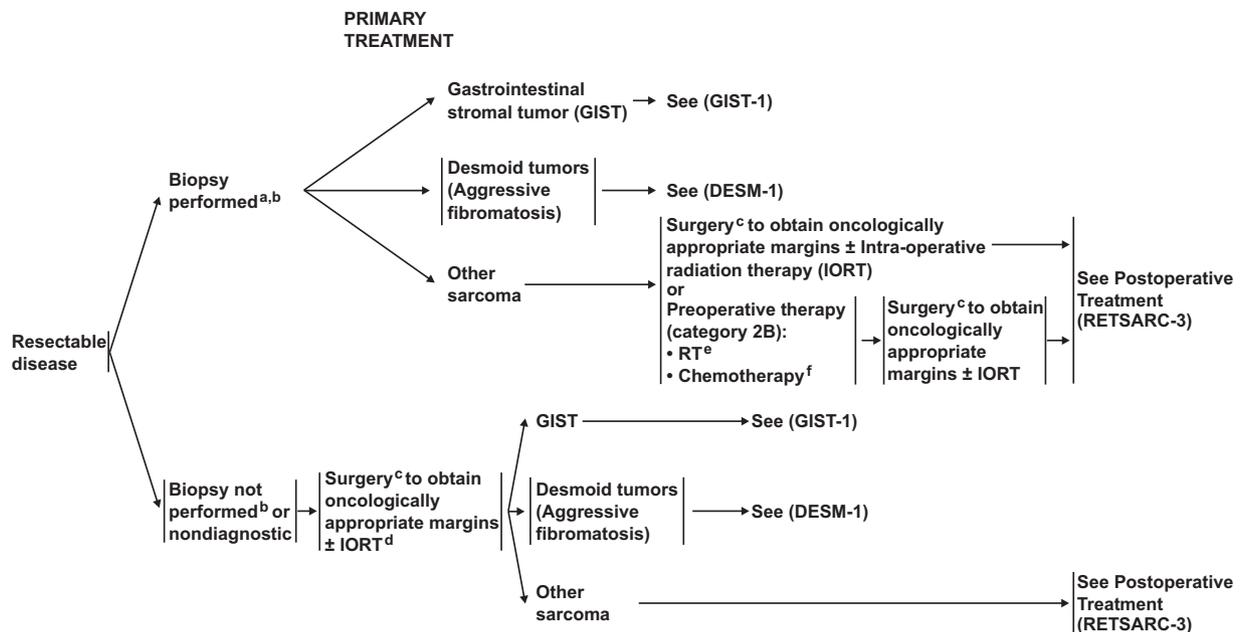
**Clinical trials:** NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

## Overview

Soft tissue sarcomas (STS) are a heterogeneous group of rare solid tumors with distinct clinical and pathologic features. In 2014, an estimated 12,020 people will be diagnosed with STS in the United States, and approximately 4740 will die of the disease.<sup>1</sup> Genetic cancer syndromes caused by germline mutations in several different genes have been associated with inherited predisposition for the development of STS.<sup>2-7</sup>

Radiation therapy (RT) and/or chemotherapy are often used as an adjunct to surgery for patients with retroperitoneal/intra-abdominal STS, because the risk of failure in the surgical bed can be high. Newer RT techniques, such as intraoperative RT (IORT) and intensity-modulated RT (IMRT), seem to have led to the improvement of treatment outcomes in patients with retroperitoneal/intra-abdominal STS.

These NCCN Guidelines Insights discuss the role of genetic testing and counseling in patients



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

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

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

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

<sup>e</sup>See Radiation Therapy Guidelines (SARC-D).

<sup>f</sup>See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-E).

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**RETSARC-2**

with genetic cancer syndromes with a predisposition for the development STS and the role of RT in the management of patients with retroperitoneal/intra-abdominal STS.

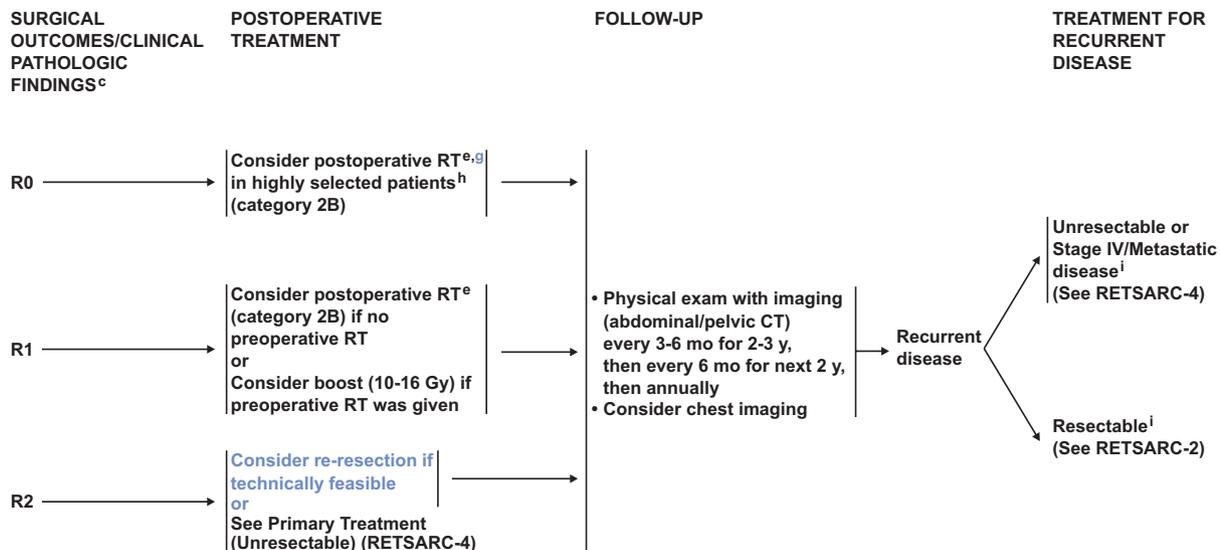
## Genetic Cancer Syndromes With a Predisposition to STS

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.<sup>2,8-10</sup> The incidence of STS ranges from 12% to 21% in individuals with *TP53* germline mutations.<sup>11-13</sup> In general, STS associated with Li-Fraumeni syndrome are diagnosed at significantly younger ages than the sporadic STS. The mean age at diagnosis, however, varies with histologic

subtype. In an analysis of 475 tumors in 91 families with *TP53* germline mutations, Kleihues et al<sup>11</sup> reported rhabdomyosarcomas, fibrosarcomas, and undifferentiated pleomorphic sarcoma as the most frequent histologic subtypes identified in 55%, 13%, and 10% of patients, respectively. The mean age at diagnosis for rhabdomyosarcomas was younger than 6 years and the mean age at diagnosis was older than 50 years for undifferentiated pleomorphic sarcomas.

Familial adenomatous polyposis (FAP) is an inherited autosomal-dominant colorectal cancer syndrome resulting from germline mutations in the adenomatous polyposis coli (*APC*) gene on chromosome 5q21.<sup>4,6</sup> FAP is characterized by adenomatous colorectal polyps that progress to colorectal cancer at 35 to 40 years of age. Gardner syndrome is considered as a variant of FAP with extracolonic manifestations such as osteomas, skin cysts, congenital hypertrophy of the retinal pigmented epithelium, and desmoid tumors (aggressive fibroma-

## Soft Tissue Sarcoma, Version 2.2014



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

<sup>e</sup>See Radiation Therapy Guidelines (SARC-D).

<sup>g</sup>Postoperative RT should not be administered routinely.

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

<sup>i</sup>If not previously administered, consider preoperative RT and/or chemotherapy.

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RETSARC-3

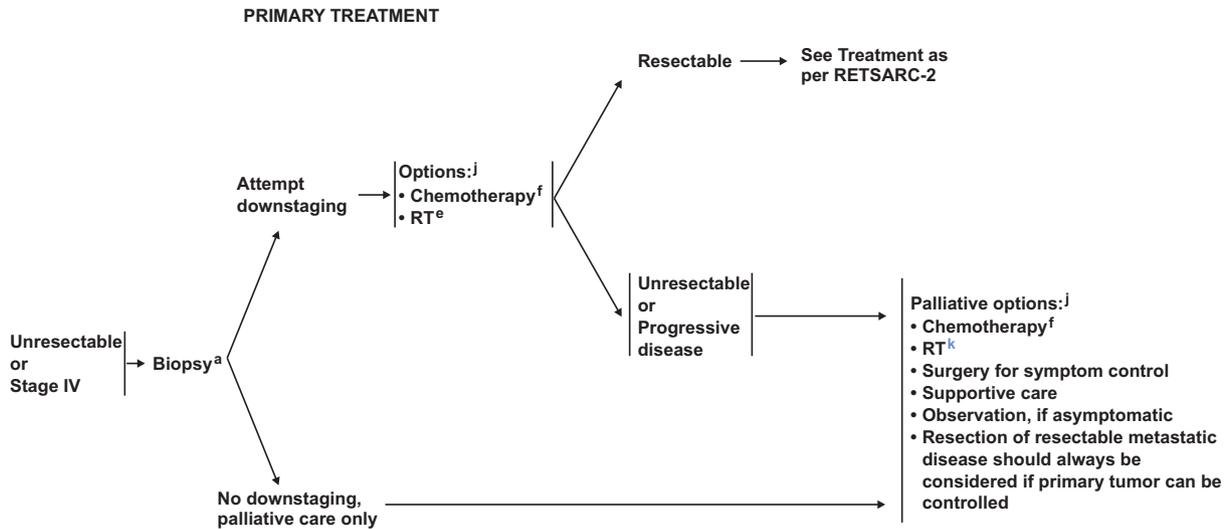
tosis).<sup>14</sup> Desmoid tumors have been reported to occur in 7.5% to 16% of patients with FAP, and the relative risk of developing desmoid tumors is much higher in patients with FAP than in the general population.<sup>15-18</sup> In an International Dutch Cohort study involving 2260 patients with 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.<sup>18</sup> The median age at diagnosis was 31 years, with most desmoid tumors arising in the intra-abdominal and abdominal wall areas (53% and 24%, respectively).

Carney-Stratakis syndrome is an autosomal-dominant familial syndrome characterized by predisposition to gastrointestinal stromal tumors (GIST) and paragangliomas.<sup>19</sup> Germline loss-of-function mutations within the *SDH* gene subunits (*SDHB*, *SDHC*, and *SDHD*) have been identified in individuals with GIST associated with Carney-Stratakis syndrome.<sup>20</sup> In an analysis

of 11 patients from 9 families presenting with GIST and paragangliomas associated with Carney-Stratakis syndrome, Pasini et al<sup>20</sup> identified germline mutations in *SDHB*, *SDHC*, or *SDHD* genes in 8 patients (from 7 untreated families) with GIST. The tumors also lacked activating *KIT* or *PDGFR $\alpha$*  mutations associated with sporadic GIST. GIST associated with Carney-Stratakis syndrome is also reported to be negative for *SDHB* expression by immunohistochemistry (IHC), in contrast to GIST with *KIT* or *PDGFR $\alpha$*  mutations or sporadic GIST.<sup>21,22</sup> *SDHB* IHC can be useful for diagnosing Carney-Stratakis syndrome and *SDH*-deficient GIST.

#### Genetic Testing and Counseling for Patients With Germline Mutations: NCCN Recommendations

- Patients (and their families) with personal and/or family history suggestive of Li-Fraumeni syndrome should be considered for further genetic assessment as outlined in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian Cancers.



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

<sup>e</sup>See Radiation Therapy Guidelines (SARC-D).

<sup>f</sup>See Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma (SARC-E).

<sup>j</sup>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.

<sup>k</sup>Palliative RT requires balancing expedient treatment with sufficient dose expected to halt the growth of, or cause tumor regression. Numerous clinical issues regarding rapidity of growth, the status of systemic disease, and the use of chemotherapy must be considered. Recommended only for patients with unresectable or progressive disease.

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**RETSARC-4**

- *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 *PDGFR $\alpha$*  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 syndrome is recommended for patients diagnosed with desmoid tumors (aggressive fibromatoses).

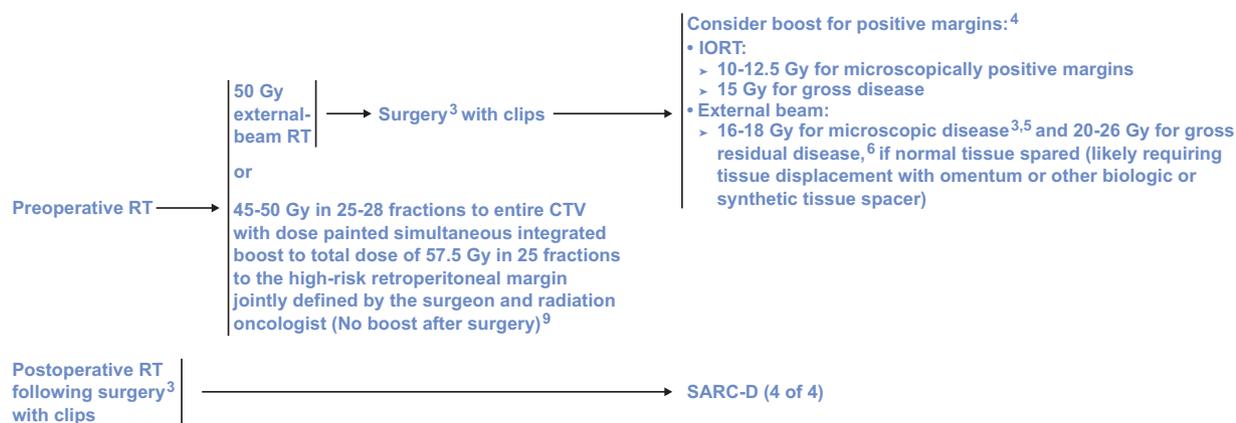
### Retroperitoneal/Intra-abdominal Soft Tissue Sarcomas: Role of RT

Surgery is the standard treatment for patients with retroperitoneal/intra-abdominal STS. However, complete or macroscopic surgical resection is achieved in fewer than 70% of patients with primary

tumors, because of their proximity to vital structures. Multimodality treatment (surgery with RT and/or chemotherapy) is therefore favored because of the inability to obtain negative surgical margins and high local recurrence rates.<sup>23</sup>

RT can be administered either as preoperative or postoperative treatment for patients with resectable disease, and as a primary treatment for those with unresectable disease. Newer RT techniques such as IMRT and 3-dimensional (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.<sup>24–27</sup> When external-beam RT 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.

## Soft Tissue Sarcoma, Version 2.2014

RADIATION THERAPY GUIDELINES FOR RETROPERITONEAL/INTRA-ABDOMINAL SARCOMA<sup>1</sup>

<sup>1</sup>If an R1 or R2 resection is anticipated, clips to high-risk areas for recurrence is encouraged. When external beam RT is used, sophisticated treatment planning with IMRT, tomotherapy, and/or protons can be used to improve the therapeutic ratio:

- Musat E, et al. Comparison of intensity-modulated postoperative radiotherapy with conventional postoperative radiotherapy for retroperitoneal sarcoma. *Cancer Radiother* 2004;8: 255-261;
- Alektiar KM, et al. Impact of intensity-modulated radiation therapy on local control in primary soft-tissue sarcoma of the extremity. *J Clin Oncol* 2008;26:3440-3444;
- Chung CS, et al. A comparison of 3D conformal proton therapy, intensity modulated proton therapy, and intensity modulated photon therapy for retroperitoneal sarcomas. *Int J Radiat Oncol Biol Phys* 2006;66(3S):116;
- 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.

<sup>3</sup>See Principles of Surgery (SARC-C).

<sup>4</sup>Total doses should always be determined by normal tissue tolerance. 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. (Al Yami, et al. *Int J Radiat Oncol Biol Phys* 2010;77:1191-1197.)

<sup>5</sup>RT does not substitute for definitive surgery with negative margins; re-resection may be necessary.

<sup>6</sup>See Resection Margins (SARC-C).

<sup>9</sup>Tzeng CW, Fiveash JB, Popple, 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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**SARC-D**  
**3 of 4**

### Preoperative RT

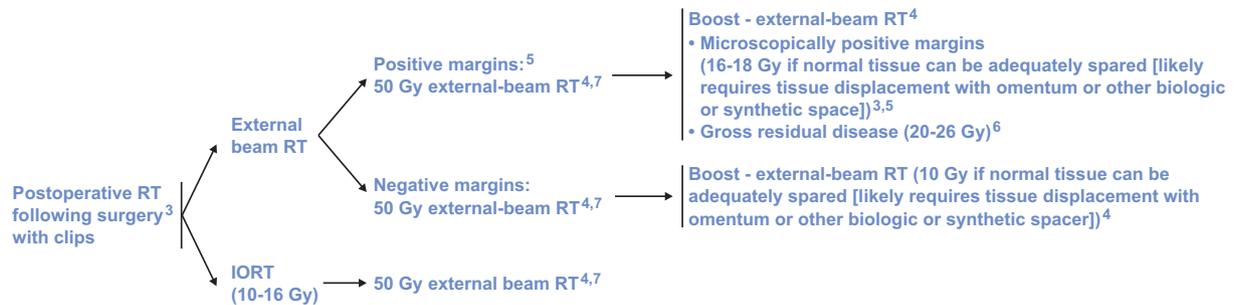
Preoperative RT is often preferred because it reduces the risk of tumor seeding at the time of surgery and may render tumors more amenable to resection.<sup>28</sup> Long-term results of 2 prospective studies showed favorable 5-year local relapse-free survival (RFS), disease-free survival (DFS), and overall survival (OS) rates (60%, 46%, and 61%, respectively) following R0 or R1 resection after preoperative RT in patients with intermediate- or high-grade retroperitoneal STS.<sup>29</sup>

The usual dose of preoperative RT is 50 Gy. In a single-institution study, Tzeng et al<sup>30</sup> 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

(CTV) judged to be at greatest risk for local tumor recurrence. 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, only 2 local recurrences were seen, with the actuarial 2-year local control rate of 80%. Because this approach is used in many NCCN Member Institutions, the guidelines have included this dosing schedule (45.0–50.0 Gy to the entire CTV with a dose-painted simultaneous integrated boost to a total dose of 57.5 Gy) as another option for preoperative RT (see SARC-D, 3 of 4, above). The panel recommends that higher-risk retroperitoneal tumor margins should be jointly defined by the surgeon and radiation oncologist.

### Postoperative RT

Postoperative RT has been associated with improved RFS in retrospective nonrandomized studies, with no improvement in OS.<sup>31,32</sup> In one study, the combined

RADIATION THERAPY GUIDELINES FOR RETROPERITONEAL/INTRA-ABDOMINAL SARCOMA<sup>10</sup>

<sup>3</sup>See Principles of Surgery (SARC-C).

<sup>4</sup>Total doses should always be determined by normal tissue tolerance. 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. (Al Yami, et al, *Int J Radiat Oncol Biol Phys* 2010;77:1191-1197.)

<sup>5</sup>RT does not substitute for definitive surgery with negative margins; re-resection may be necessary.

<sup>6</sup>See Resection Margins (SARC-C).

<sup>7</sup>For intra-abdominal or retroperitoneal tumors, external beam RT may be decreased to 45 Gy. A boost may not be possible if potential radiation morbidity is high.

<sup>10</sup>If an R1 or R2 resection is anticipated, clips to high-risk areas for recurrence are encouraged. When external beam RT is used, sophisticated treatment planning with IMRT, tomotherapy, and/or protons can be used to improve the therapeutic ratio:

- Musat E, et al. Comparison of intensity-modulated postoperative radiotherapy with conventional postoperative radiotherapy for retroperitoneal sarcoma. *Cancer Radiother* 2004;8: 255-261;
- Alektiar KM, et al. Impact of intensity-modulated radiation therapy on local control in primary soft-tissue sarcoma of the extremity. *J Clin Oncol* 2008;26:3440-3444;
- Chung CS, et al. A comparison of 3D conformal proton therapy, intensity modulated proton therapy, and intensity modulated photon therapy for retroperitoneal sarcomas. *Int J Radiat Oncol Biol Phys* 2006;66(3S):116;
- 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).
- Yoon SS, Chen YL, Kirsch DG, Maduekwue UN, Rosenberg AE, Nielsen GP, Sahani DV, Choy E, Harmon DC, and DeLaney TF. 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.

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**SARC-D**  
4 of 4

use of preoperative RT and postoperative brachytherapy resulted in significantly better DFS and OS in patients with low-grade tumors.<sup>33</sup> In a recent retrospective study, the use of conformal postoperative RT along with aggressive surgical resection was associated with a trend toward decreased local recurrence rate and improved RFS compared with surgery alone.<sup>34</sup> 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 groups. If postoperative RT is to be considered, a coordinated effort by the surgeon and radiation oncologist to displace the bowel from the tumor bed with omentum, or other tissue displacers, is recommended to reduce the risk of RT-related bowel toxicity.

### Intraoperative RT

The use of IORT has provided encouraging results in patients with retroperitoneal STS.<sup>35-41</sup> In patients with retroperitoneal STS prospectively treated at a

single institution with a protocol involving maximal tumor resection, high-dose-rate IORT, and postoperative external-beam RT, 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%;  $P=.4$ ).<sup>36</sup> The overall 5-year distant metastasis-free survival rate was 82% (100% for patients 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 external-beam RT has been effective in terms of local control and survival in patients with primary and recurrent retroperitoneal STS.<sup>37-39,41</sup> In a study that assessed the long-term outcome of patients with retroperitoneal STS treated with preoperative RT, resection, and IORT with electron-beam RT (IO-ERT), patients undergoing gross total resection and IOERT had better OS (74% and 30%, respectively)

## Soft Tissue Sarcoma, Version 2.2014

NCCN guidelines local control (83% and 61%, respectively) rates compared with patients who underwent only gross total resection.<sup>37</sup>

### NCCN Recommendations

The panel emphasizes that RT is not a substitute for definitive surgical resection with oncologically appropriate margins, and that re-resection may be necessary. If re-resection is not feasible, postoperative RT may be considered in highly selected patients in attempt to control microscopic residual disease in those who have not received preoperative RT, although this approach has not been validated in randomized trials.

**Resectable Disease:** Surgery (to obtain oncologically appropriate margins) with or without IORT is the primary treatment for most patients with resectable disease (see RETSARC-2, page 476).

Preoperative RT or chemotherapy could be considered before surgery in patients whose diagnosis has been confirmed through biopsy (see RETSARC-2, page 476). For patients treated with preoperative external-beam RT (50 Gy) followed by surgery, the guidelines recommend consideration of a postoperative RT boost for patients with positive margins, if this can be performed within the constraints of adjacent normal tissue. The guidelines recommend an external-beam RT boost of 16 to 18 Gy for microscopic residual disease, and 20 to 26 Gy for grossly positive margins (see SARC-D, 3 of 4, page 479). Alternatively, IORT (10.0–12.5 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 (see SARC-D, 3 of 4, page 479).

Postoperative treatment options are dependent on surgical outcomes and clinical or pathologic findings after surgery. Postoperative RT should not be administered routinely, but could be considered for patients with microscopic positive margins (R1 resection) who have not received preoperative RT, and after negative margin resection (R0 resection) in highly selected patients (eg, those with pathologic findings of high-grade disease, extremely large tumors, close surgical margins, or high risk of recurrence) (see RETSARC-3, page 477). Re-resection, if feasible, should be considered for patients with macroscopic positive margins (R2 resection). Alternatively, these patients could also be managed as de-

scribed later for unresectable disease. The options for postoperative RT include external-beam RT (50 Gy irrespective of surgical margins) or IORT (10 Gy followed by external-beam RT) (SARC-D, 4 of 4, page 480). For patients treated with postoperative external-beam RT, the NCCN guidelines recommend postoperative RT boost to the original tumor bed based on the margin status (10 Gy for negative surgical margin if normal tissue can be adequately spared by tissue displacement with omentum or other biologic or synthetic spacer; 16 to 18 Gy for microscopic residual disease and 20 to 26 Gy for gross residual disease). The dose recommendations mentioned earlier 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 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 or RT in an attempt to downstage tumors (see RETSARC-4, page 478). For patients undergoing definitive high-dose RT, favorable experience has been reported with tissue displacement spacers to keep bowel out of the high-dose RT volume.<sup>42</sup> Patients whose tumors become resectable after primary treatment should be managed as described earlier for resectable disease. If the tumor remains unresectable or if disease progression occurs after 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 a dose sufficient 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.

**Recurrent Disease:** For patients with resectable, unresectable, or disseminated recurrences, the NCCN

Guidelines recommend the same management after biopsy as outlined for primary disease. Enrollment in a clinical trial is preferred and should be considered if an appropriate trial is available.

## Summary

STS are a heterogeneous group of rare solid tumors with distinct clinical and pathologic features. Multimodality treatment (surgery with RT and/or chemotherapy) is often used for the management of patients with retroperitoneal/intra-abdominal STS. Most importantly, before initiation of treatment, all patients with STS should be evaluated and managed by a multidisciplinary team with extensive expertise and experience in the treatment of STS. Genetic testing and counseling should be recommended for patients with a clinical and/or family history of genetic cancer syndromes associated with a predisposition for the development of STS.

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## Soft Tissue Sarcoma, Version 2.2014

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### Posttest Questions

1. Germline mutations in which of the following genes are associated with a genetic predisposition for the development of soft tissue sarcomas (STS)?
  - a. TP53 tumor suppressor gene
  - b. Adenomatous polyposis coli (APC) gene
  - c. Succinate dehydrogenase (SDH) gene subunits
  - d. All of the above
2. Which of the following options are appropriate for the management of patients with resectable retroperitoneal/intra-abdominal STS?
  - a. Preoperative radiation therapy (RT)
  - b. Postoperative RT depending on surgical margins
  - c. Surgery with or without intraoperative radiation therapy (IORT)
  - d. All of the above
3. RT to downstage tumors is an appropriate treatment option for patients with unresectable or stage IV retroperitoneal/intra-abdominal STS.
  - a. True
  - b. False

