NCCN Guidelines® Insights

Soft Tissue Sarcoma, Version 2.2012

Featured Updates to the NCCN Guidelines

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Abstract

The major changes to the 2012 and 2011 NCCN Guidelines for Soft Tissue Sarcoma pertain to the management of patients with gastrointestinal stromal tumors (GISTs) and desmoid tumors (aggressive fibromatosis). Postoperative imatinib following complete resection for primary GIST with no preoperative imatinib is now included as a category 1 recommendation for patients with intermediate or high risk of recurrence. The panel also reaffirmed the recommendation for preoperative use of imatinib in patients with GISTs that are resectable with negative margins but associated with significant surgical morbidity. Observation was included as an option for patients with resectable desmoid tumors that are small and asymptomatic, not causing morbidity, pain, or functional limitation. Sorafenib is included as an option for systemic therapy for patients with desmoid tumors. (*JNCCN* 2012;10:951–960)

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Disclosures for the NCCN Soft Tissue Sarcoma Panel

Individual disclosures of potential conflicts of interest for the NCCN Soft Tissue Sarcoma Panel can be found online at NCCN.org.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines® Insights highlight important changes in the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further understanding of these changes by summarizing salient portions of the Panel's discussion, including the literature reviewed.**

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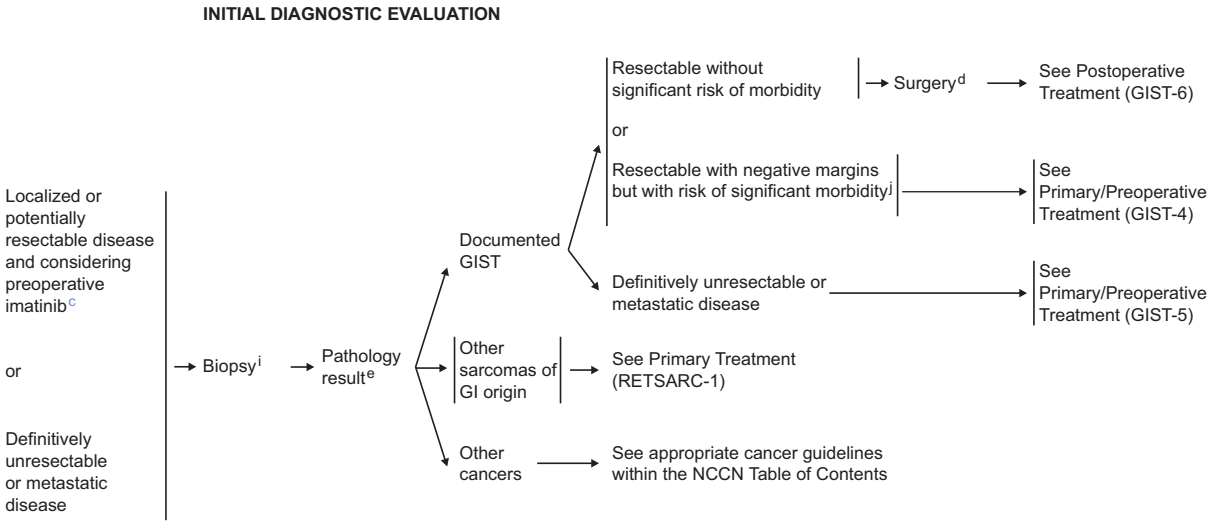

[c] Consider preoperative imatinib if surgical morbidity would be improved by reducing the size of the tumor preoperatively. Preoperative imatinib may prohibit accurate assessement of recurrence risk.
[d] See Principles of Surgery For GIST (GIST-C).
[e] Pathology report should include anatomic location, size, and an accurate assessment of the mitotic rate measured in the most proliferative area of the tumor. Mutational analysis may predict response to therapy with tyrosine kinase inhibitors. (See Principles of Pathologic Assessment for GIST [GIST-B])
[i] See Principles of Biopsy for GIST (GIST-A).
[j] Some patients may rapidly become unresectable; close monitoring is essential.

GIST-3

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

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract, resulting from activating mutations in one of the receptor protein tyrosine kinases, KIT (CD117) or platelet-derived growth factor receptor alpha (PDGFRA).[1–3] Most GISTs (80%) are KIT-positive, and 5% to 10% have mutations in the *PDGFRA* gene and express little or no KIT. Approximately 10% to 15% of GISTs have no detectable *KIT* or *PDGFRA* mutations (wild-type GIST). Recent studies have identified several germline mutations in the succinate dehydrogenase subunit in patients with wild-type GIST.[4] Therefore, the absence of *KIT* or *PDGFRA* mutations does not exclude the diagnosis of GIST. In addition to morphologic diagnosis, ancillary techniques, including immunohistochemistry and molecular genetic testing, would be beneficial to confirm the diagnosis of GIST. The introduction of imatinib, an inhibitor of multiple receptor tyrosine kinases including KIT,

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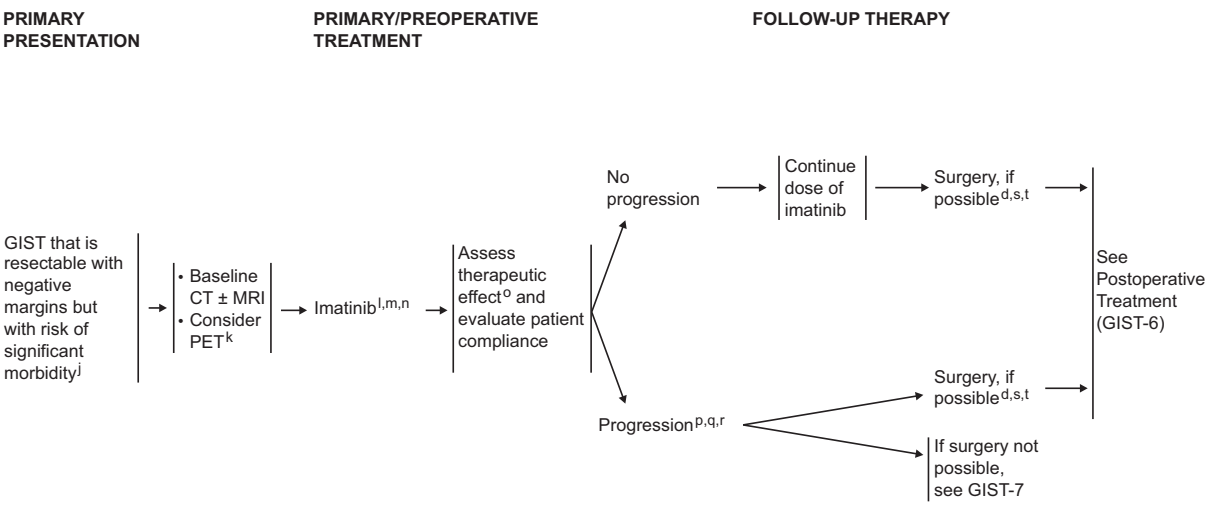


[d] See Principles of Surgery For GIST (GIST-C).
[j] Some patients may rapidly become unresectable; close monitoring is essential.
[k] PET is not a substitute for a CT.
[l] If life threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider sunitinib.
[m] Medical therapy is the usual course of treatment. However, patient may proceed to surgery if bleeding or symptomatic.
[n] See Dosage and Administration of Imatinib (GIST-D).
[o] PET may give indication of imatinib activity after 2-4 wks of therapy when rapid readout of activity is necessary; PET is not a substitute for diagnostic CT.
[p] Rarely, increase in tumor size may not indicate lack of drug efficacy; all clinical and radiographic data should be taken into account, including lesion density on CT.
[q] Progression may be determined by CT or MRI with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.
[r] Suggest referral to a sarcoma specialty center.
[s] Collaboration between medical oncologist and surgeon necessary to determine appropriateness of surgery, following major response or sustained stable disease.
[t] Imatinib can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications.

GIST-4

has significantly improved the outcome in patients with unresectable and/or metastatic disease.[5–7] Several prospective studies have also evaluated the efficacy of imatinib in the preoperative and postoperative setting to further improve outcomes after complete resection.

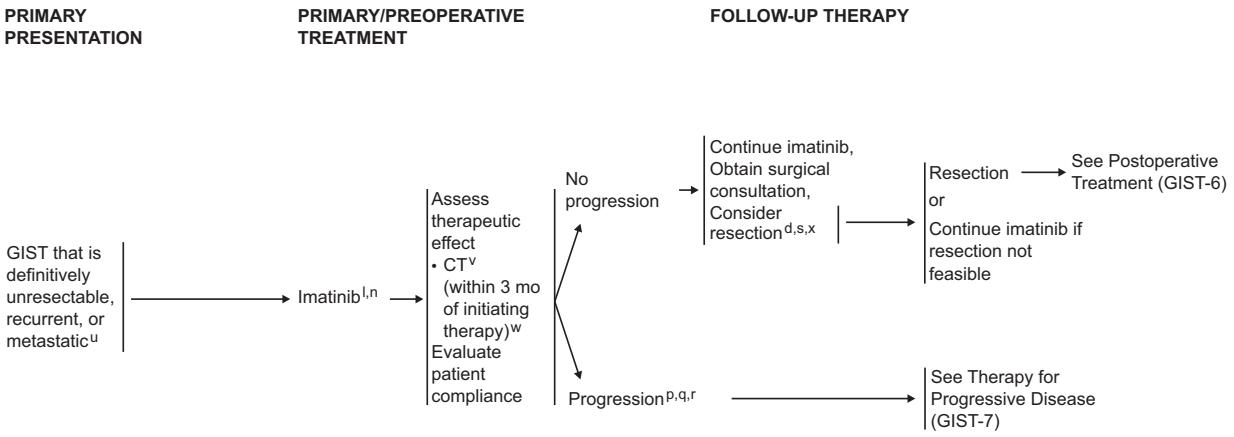
Desmoid tumors, also known as *aggressive fibromatoses*, are unique mesenchymal neoplasms, and are often considered "benign malignancies." Specifically, these tumors are an aggressive fibroblastic proliferation of well-circumscribed, locally invasive, differentiated fibrous tissue and are often categorized as low-grade sarcomas because of their high tendency to recur locally after excision.[8] Desmoid tumors can cause functional morbidity and also have a high recurrence rate. Although desmoid tumors are often locally invasive, they rarely metastasize and have a good prognosis.[9]

These NCCN Guidelines Insights include the major discussion points corresponding to the updates in the 2012 and 2011 guidelines.

Management of GISTs

Preoperative Imatinib

RTOG 0132/ACRIN 6665 is the first prospective study that evaluated the efficacy of preoperative imatinib (600 mg/d) in patients with potentially resectable locally advanced primary GISTs (intermediate- to high-risk; n = 30) or metastatic/recurrent disease (n = 22).[10] Patients experiencing partial response or stable disease after preoperative imatinib underwent resection and continued imatinib postoperatively for 2 years. Among patients with primary GISTs, partial response and stable disease after preoperative imatinib were observed in 7% and 83%, respectively. In patients with recurrent or metastatic GIST, partial response and stable disease were observed in 4.5% and 91% of patients, respectively. The estimated 2-year overall survival (OS) rates were 93% and 91% for those patients with primary GIST and for those with recurrent or metastatic GIST, respectively. The estimated 2-year progression-free survival



[d] See Principles of Surgery For GIST (GIST-C).
[l] If life threatening side effects occur with imatinib not managed by maximum supportive treatment, then consider sunitinib.
[n] See Dosage and Administration of Imatinib (GIST-D).
[p] Rarely, increase in tumor size may not indicate lack of drug efficacy; all clinical and radiographic data should be taken into account, including lesion density on CT.
[q] Progression may be determined by CT or MRI with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.
[r] Suggest referral to a sarcoma specialty center.
[s] Collaboration between medical oncologist and surgeon is necessary to determine the appropriateness of surgery, following major response or sustained stable disease.
[u] Consider baseline PET, if using PET during follow-up. PET is not a substitute for CT.
[v] Consider PET only if CT results are ambiguous.
[w] In some patients, it may be appropriate to image prior to 3 months.
[x] No definitive data exist to prove whether surgical resection improves clinical outcomes in addition to TKI therapy alone in metastatic GIST. Prospective randomized trials are underway to assess whether or not resection changes outcomes in patients with metastatic GIST responding to TKI therapy.

GIST-5

(PFS) rates were 83% and 77%, respectively. In this study, among patients with primary resectable GIST, R0 resection (complete removal of all gross and microscopic disease) was performed in 77% of patients, and partial organ-preserving and function-preserving surgery was reported in most of these cases. However, survival benefit could not be determined because all patients received postoperative imatinib for 2 years.

In another prospective study, Fiore et al.[11] reported that preoperative imatinib improved resectability and reduced surgical morbidity in patients with primary GISTs that were resectable through a major surgical procedure associated with significant surgical morbidity or those with unresectable GISTs. The median size reduction was 34% and the estimated 3-year PFS rate was 77%. Imatinib was continued postoperatively for 2 years in all patients.

In the subgroup analysis of patients with nonmetastatic locally advanced primary GIST treated with imatinib in the prospective BFR14 phase III trial, preoperative imatinib was associated with a partial response rate of 60% (15 of 25 patients); 36% (9 of 25 patients) of these patients underwent surgical resection of the primary tumor after a median of 7.3 months of preoperative imatinib; the 3-year PFS and OS rates for patients who underwent resection were 67% and 89%, respectively.[12] All patients who underwent resection were treated with postoperative imatinib.

The optimal duration of preoperative imatinib remains unknown. In the RTOG 0132 study, preoperative imatinib was administered for 8 to 12 weeks followed by resection in patients with responding or stable disease.[10] In other studies, preoperative imatinib was administered for 7 to 9 months.[11,12] A small prospective trial (19 patients) reported a response rate of 70% after 3 to 7 days of preoperative imatinib (600 mg/d) in patients undergoing surgical resection for primary or recurrent GISTs.[13] However, results showed no histologic evidence of cytoreduction within 3 to 7 days of preoperative imatinib.

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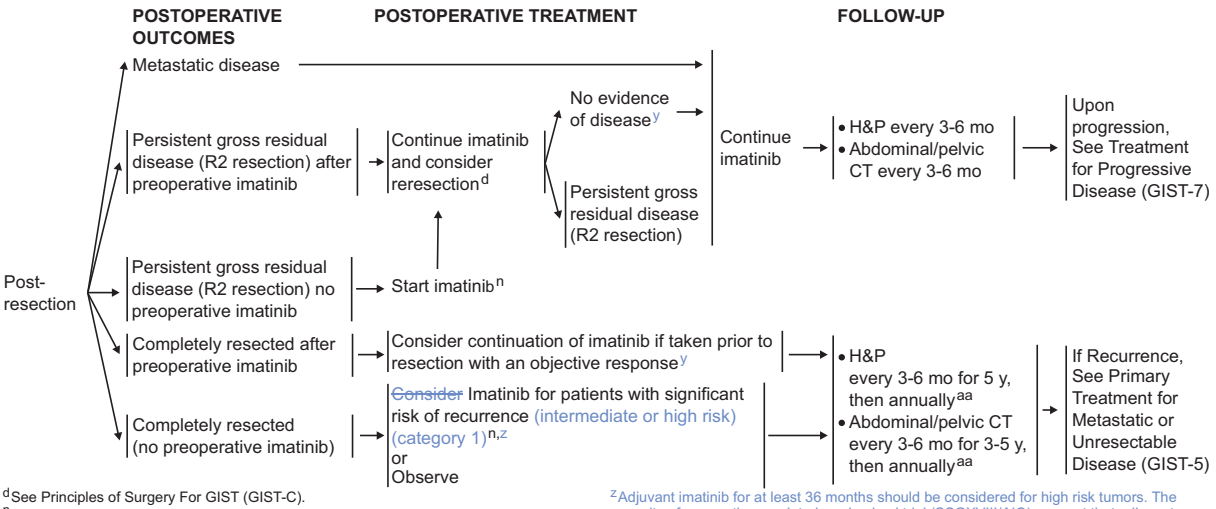

[d] See Principles of Surgery For GIST (GIST-C).

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

[y] For patients with complete resections following preoperative therapy, continued imatinib is warranted.The length of postoperative imatinib has not been studied in randomized trials; there are single and multi-institutional trials supporting the benefit for continuation of imatinib for two years post-surgery. (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; 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; 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; and 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).

[z] Adjuvant imatinib for at least 36 months should be considered for high risk tumors. The results of a recently completed randomized trial (SSGXVIII/AIO) suggest that adjuvant imatinib administered for 36 months improves relapse free survival (RFS) and overall survival (OS) compared to 12 months of adjuvant imatinib for patients with a high estimated risk of recurrence (tumor greater than 5 cm in size with high mitotic rate (> 5 mitoses/50 HPF) or a risk of recurrence of greater than 50%) after surgery (Joensuu H, Eriksson M, 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.) The results of ACOSOG trial Z9001 showed that adjuvant imatinib improved relapse free survival in patients with GIST ≥ 3 cm in size with the greatest benefit noted in tumors at higher risk of recurrence (intermediate and high-risk). (DeMatteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet. 2009;373(9669):1097-1104).

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

GIST-6

NCCN Recommendations: Surgery is the primary treatment for patients with primary localized GISTs (≥ 2 cm) that are potentially resectable without significant risk of morbidity (see GIST-3, on page 952).[14] The goal of surgical treatment is to achieve complete gross resection with negative microscopic margins and minimal surgical morbidity. Preoperative imatinib should be considered if surgical morbidity could be improved by reducing the tumor size before resection.[10,11] In prospective studies, preoperative imatinib has been tested at a daily dose of either 400 or 600 mg.[10–12] The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Soft Tissue Sarcoma recommend an initial dose of 400 mg/d (to view the full guidelines, visit NCCN.org). Patients with documented KIT exon 9 mutations may benefit from dose escalation up to 800 mg/d (given as 400 mg twice daily), as tolerated (see GIST-D, on page 956).[15–17] Collaboration between the medical oncologist and surgeon is necessary to determine the appropriateness of surgery in patients experiencing a major response or stable disease after receiving preoperative imatinib.

Preoperative imatinib is recommended as primary treatment for patients with GIST that is resectable with negative margins but with a risk of significant morbidity (see GIST-4, on page 953). However, the patient may proceed to surgery if bleeding or symptomatic. The NCCN Guidelines recommend continuation of preoperative imatinib until maximal response (defined as no further improvement between 2 successive CT scans, which can take as long as 6–12 months). Imatinib can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications.

Imatinib is recommended as primary treatment for patients with definitively unresectable, recurrent, or metastatic disease (see GIST-5, on page 954).[11] Data from retrospective studies have shown that surgery following imatinib may be beneficial in selected patients with recurrent or metastatic GIST respond-

DOSING AND ADMINISTRATION OF IMATINIB

Preoperative imatinib for GIST that is resectable with negative margins but with risk of significant morbidity:
- Initiate dosing at 400 mg daily. Patients with documented mutations in KIT exon 9 may benefit from dose escalation up to 800 mg daily (given as 400 mg twice daily), depending upon tolerance.[1,2,3]

Unresectable and/or metastatic GIST:
- Initiate dosing at 400 mg daily.[4] Patients with documented mutations in KIT exon 9 may benefit from dose escalation up to 800 mg daily (given as 400 mg twice daily), depending upon tolerance.[1,2,3]
- IF PROGRESSION OF DISEASE IS DOCUMENTED: Imatinib dose increase up to 800 mg daily (given as 400 mg twice daily) may be considered, as clinically tolerated, in patients showing objective signs of disease progression at a lower dose and in the absence of severe adverse drug reactions.[4]

Post operative imatinib:
- 400 mg daily following complete gross resection of GIST.[4]

Imatinib should be taken with a low fat meal and a large glass of water.

[1]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://jco.ascopubs.org/cgi/content/abstract/26/33/5360.
[2]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.
[3]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.
[4]Information from the FDA label. For more detailed information review the full content at: www.fda.gov.

GIST-D

ing to imatinib.[14] Prospective phase III trials are underway to assess whether surgical resection improves clinical outcome in patients with resectable metastatic GIST responding to tyrosine kinase inhibitor therapy. The guidelines recommend that response be assessed within 3 months of initiating imatinib to determine whether the GIST has become resectable. In selected patients, imaging can be performed before 3 months. At this time, continuation of imatinib is recommended until progression, if resection is not feasible, for all patients with unresectable, recurrent, or metastatic GIST.

Postoperative Imatinib

In the single-arm multicenter Intergroup phase II ACOSOG Z9000 trial, postoperative imatinib for 1 year after complete resection prolonged relapse-free survival (RFS) and improved OS in patients with primary GISTs at high risk of recurrence compared with historical controls.18 These findings were confirmed in a subsequent double-blind randomized phase III trial (ACOSOG Z9001), which randomized patients with primary localized GISTs (≥ 3 cm) to postoperative imatinib at 400 mg (359 patients) or placebo (354 patients) for 1 year after complete resection.19 At a median follow-up of 19.7 months, the estimated RFS rate at 1 year was significantly higher in the imatinib arm compared with the placebo arm (98% and 83%, respectively; $P < .001$). No difference in OS was seen between the arms (99.2% vs. 99.7%, respectively; $P = .47$). In the subset analysis, RFS statistically favored the imatinib arm in patients with intermediate-risk (≥ 6 cm and < 10 cm; 98% vs. 76% for placebo; $P = .05$) and high-risk tumors (≥ 10 cm; 77% vs. 41% for placebo; $P < .0001$).19

The results of the recently completed Scandinavian Sarcoma Group XVIII trial (SSGXVIII/AIO) suggest that postoperative imatinib administered for 36 months improves RFS and OS compared with 12 months in patients with a high-risk of recurrence after surgery.[20] This trial randomized patients with a

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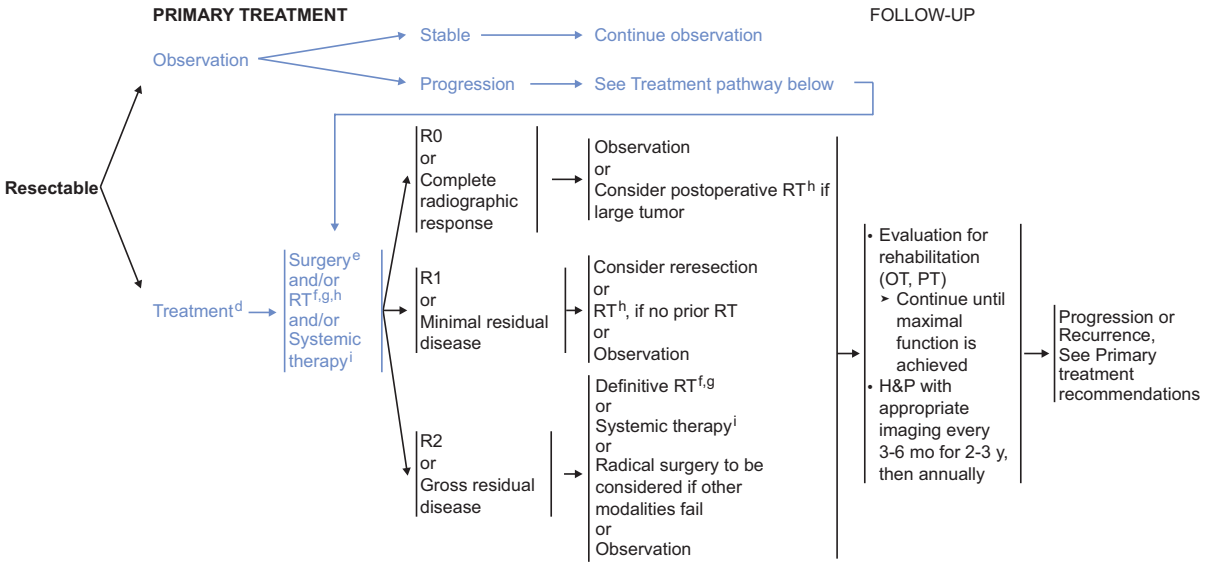

[d]For tumors that are symptomatic, or impairing or threatening function, patients should be offered therapy with the decision based on the location of the tumor and potential morbidity of the therapeutic option.
[e]For desmoids, microscopic positive margins are acceptable if achieving negative margins would produce excessive morbidity.
[i]See Principles of Systemic Therapy (SARC-E).
[f]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.
[g]Dose of definitive RT without surgery: 54-58 Gy in the absence of any prior radiation therapy.
[h]Dose of adjuvant/post-operative RT is 50 Gy. (Ballo MT, Zagars GK, Pollack A. Radiation therapy in the management of desmoid tumors. Int J Radiat Oncol Biol Phys 1998 42:1007-1014.)

DESM-2

high-risk of recurrence after surgery (tumor size > 10 cm or tumor with a mitotic rate of > 10 mitoses/50 high-power field [HPF] or tumor size > 5 cm and a mitotic rate of > 5 mitoses/50 HPF or tumor rupture) to either 12 months (n = 200) or 36 months (n = 200) of postoperative imatinib. At a median follow-up of 54 months, the RFS and OS rates were higher in the 36-month group compared with the 12-month group (5-year RFS: 66% vs. 48%, respectively; $P < .0001$; 5-year OS: 92% vs. 82%, respectively; $P = .019$).

NCCN Recommendations: Although complete resection is possible in approximately 85% of patients with primary tumors, many patients will develop recurrence after complete resection, and the 5-year survival rate is approximately 50% for patients with recurrent disease.[21–23] In randomized studies, postoperative imatinib has been associated with improved RFS after complete resection without prior imatinib.[19,20]

Estimation of risk of recurrence is important in selecting patients who would benefit from postoperative imatinib after complete resection. In the ACOSOG Z9001 trial, risk stratification was based only on tumor size, and postoperative imatinib improved RFS in patients with GISTs 3 cm or larger, but it was statistically significant in patients with intermediate (≥ 6 cm and < 10 cm) and high risk (> 10 cm) of recurrence.[19] In the SSGXVIII/AIO trial, risk stratification was based on tumor size, site, mitotic count, and rupture; survival benefit was seen in patients with high-risk of recurrence (mitotic count > 5 mitoses/50 HPF; size > 5 cm; nongastric location; and tumour rupture).[20]

Risk stratification after surgical resection should be based on tumor mitotic rate, size, and location.[24,25] Based on results of the ACOSOG Z9001 trial and the recently completed randomized SSGXVIII/AIO trial, the NCCN Guidelines recommend postoperative imatinib (400 mg; category 1) after complete resection of primary GIST with no preoperative imatinib in patients with intermediate or high risk of recur-

SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN DESMOID TUMORS (AGGRESSIVE FIBROMATOSIS)

- Sulindac [1] or other non-steroidal anti-inflammatory drugs (NSAIDS) including celecoxib [ϕ]
- Tamoxifen [2]
- Toremifene [3]
- Methotrexate and vinblastine [4]
- Low-dose interferon [5]
- Doxorubicin-based regimens [6,7,8]
- Imatinib [9,10]
- Sorafenib [11]

ϕThe risk of cardiovascular events may be increased in patients receiving celecoxib. Physicians prescribing celecoxib should consider this emerging information when weighing the benefits against risks for individual patients. (FDA Talk Paper T04-61, Dec 23, 2004)

[1]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.
[2]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.
[3]Benson JR MK, Baum M. Management of desmoid tumours including a case report of toremifene. Ann Oncol. 1994;5:173-177.
[4]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.
[5]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.
[6]Seiter K, Kemeny N. Successful treatment of a desmoid tumor with doxorubicin. Cancer 1993;71:2242-2244.
[7]Patel SR, Evans HL, Benjamin RS. Combination chemotherapy in adult desmoid tumors. Cancer 1993;72:3244-3247.
[8]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.
[9]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.
[10]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.
[11]Gounder MM, Lefkowitz RA, Keohan ML, et al. Activity of Sorafenib against desmoid tumor/deep fibromatosis. Clin Cancer Res 2011;17:4082-4090.

SARC-E

rence (see GIST-6, on page 955).[19,20] The panel recommends that postoperative imatinib for at least 36 months should be considered for patients with high-risk GIST (tumor > 5 cm in size and a mitotic rate > 5 mitoses/50 HPF).

For patients who have undergone complete resection after preoperative imatinib, the panel agreed that continuation of imatinib (at the same dose that induced objective response) following resection is warranted (see GIST-6, on page 955). The panel acknowledged that although data from single- and multi-institutional trials support the benefit for continuation of postoperative imatinib for 2 years after surgery,[10–13] the exact duration of postoperative imatinib in this group of patients has not been studied in randomized trials. The panel emphasizes that preoperative imatinib may prohibit accurate assessment of recurrent risk.

In patients with persistent gross residual disease (R2 resection), the guidelines recommend that postoperative imatinib be considered for all patients, including those who have received preoperative imatinib (see GIST-6, on page 955). Additional resection may be considered to remove residual disease. Imatinib treatment should be continued following re-resection, regardless of surgical margins, until progression.

Desmoid Tumors (Aggressive Fibromatoses)

"Wait and See" Approach for Selected Patients With Resectable Tumors

Surgery is the primary treatment for patients with resectable desmoid tumors.[26] The results of recent retrospective analyses suggest that observation may be appropriate for select patients with resectable tumors (small size, asymptomatic, and tumors located at sites where increase in size will not alter the outcome of surgery).[27–29] In a retrospective analysis of patients with desmoid fibromatoses (74 with primary tumor and 68 with recurrence), Fiore et al.[28] reported that

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 radiation therapy) and 54% for those who received chemotherapy or hormonal therapy (P = .70).[28] The corresponding survival rates were 54% and 61% (P = .48), respectively, for patients with recurrence. Large tumors (> 10 cm) and tumors located on the trunk were associated with high risk of recurrence.

NCCN Recommendations: In the 2011 NCCN Guidelines for Soft Tissue Sarcoma, based on these results, the panel discussed including observation as an option for patients with resectable tumors (see DESM-2, on page 957). However, some panel members were not in favor of including observation (until progression) as the initial treatment option preceding surgery for all patients with resectable disease. They felt that delaying surgery until after documented progression will make the tumor not amenable to resection. In addition, the panel also felt that patients with symptomatic or function-impairing tumors should be offered appropriate intervention (surgery, systemic therapy, or radiation therapy) as an initial treatment depending on the tumor location and potential morbidity. The panel concluded that patients with desmoid tumors can be managed appropriately with a careful "wait and see" approach if their tumors are asymptomatic and 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 this group of patients with resectable tumors. If progression occurs, they can be treated with surgery and/or radiation therapy and/or systemic therapy (see DESM-2, on page 957).

For symptomatic patients with large tumors causing morbidity, pain, or functional limitation, treatment choices (surgery and/or radiation therapy and/or systemic therapy) should be based on the location of the tumor and potential morbidity of the treatment. Postoperative treatment is dependent on the surgical margins (see DESM-2, on page 957). Treatment options include observation, radiation therapy, re-resection, or systemic therapy. In a recent report, sorafenib was active in patients (n = 26) with progressive disease on chemotherapy; it induced partial response in 25% of patients, and 70% experienced stable disease, with a median follow-up of 6 months.[30] Based on these results, the panel has included sorafenib as an option for systemic therapy (see SARC-E, on page 958). Other systemic therapy agents recommended in the guidelines include nonsteroidal anti-inflammatory drugs (sulindac or celecoxib), hormonal or biologic agents (tamoxifen, toremifene, low-dose interferon, or imatinib), and chemotherapy (methotrexate and vinblastine, or doxorubicin-based regimens).

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