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NCCN Clinical Practice Guidelines in Oncology™

Dermatofibrosarcoma Protuberans

V.1.2010

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NCCN Guidelines Panel Disclosures

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

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

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

See NCCN Categories of of Evidence and Consensus

Summary of the Guidelines updates

Summary of changes in the 1.2010 version of the Dermatofibrosarcoma Protuberans guidelines from the 1.2009 version include:

(DFSP-2)

- **Footnote "d"; First sentence: "(180-200 cGy fractions per day)" changed to "(200 cGy fractions per day)".**

Note: All recommendations are category 2A unless otherwise indicated.
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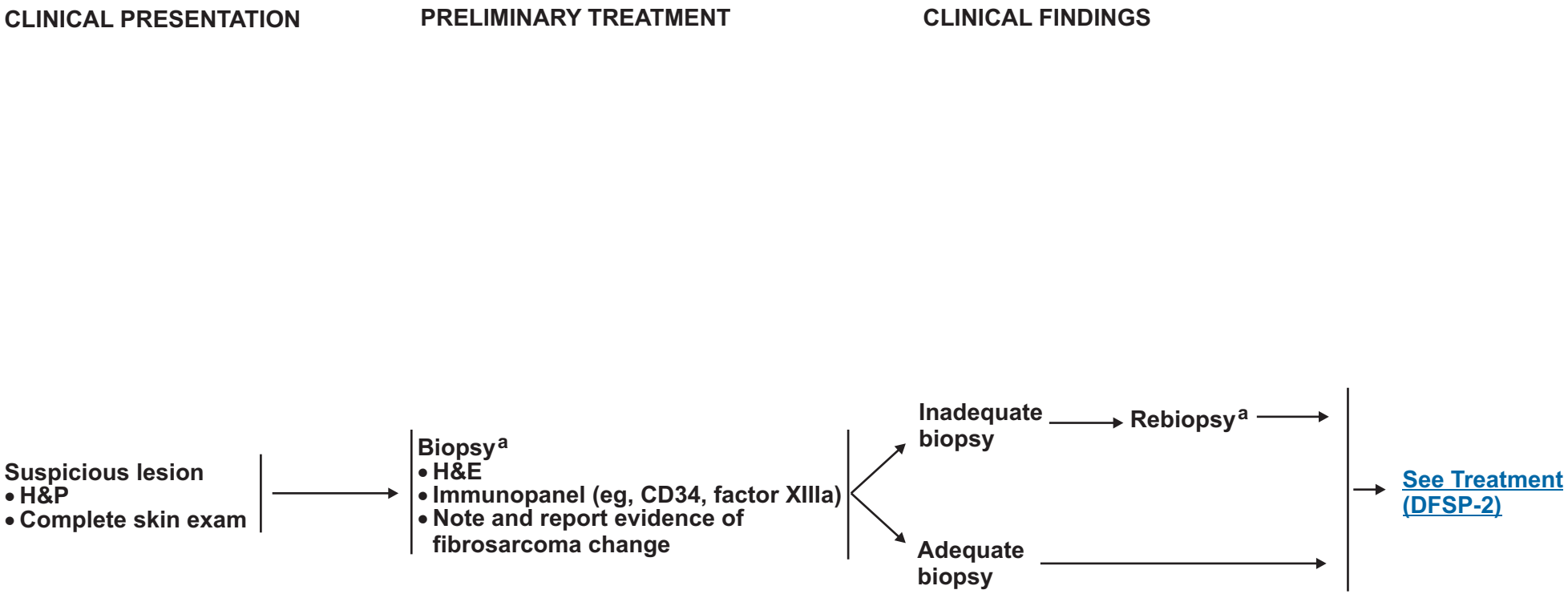

[a]This tumor is frequently misdiagnosed, even with multiple preliminary biopsies.

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

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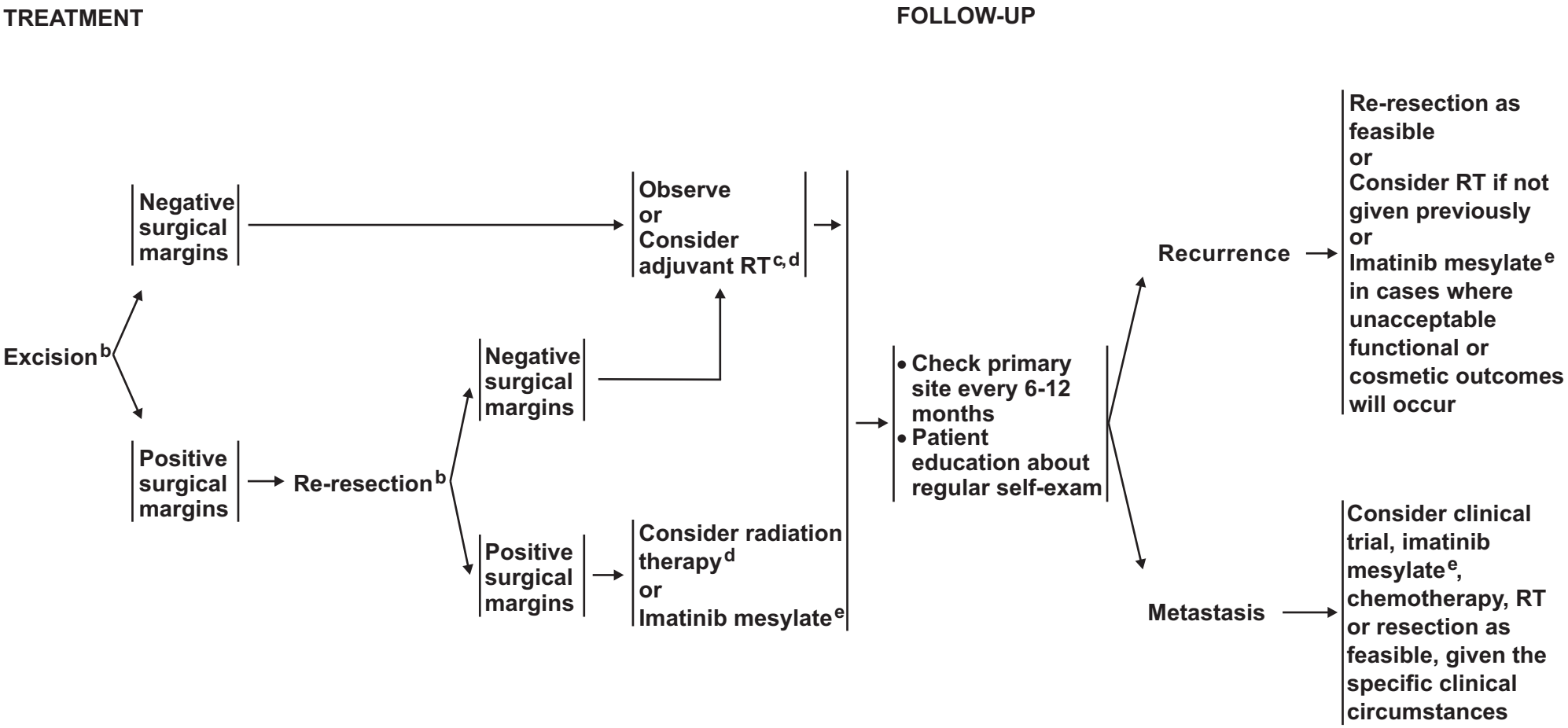

[b] The surgical approach to DFSP must be meticulously planned. Size and location of the tumor and cosmetic issues will dictate the most appropriate surgical procedure. See Excision (DFSP-A).

[c] Consider postoperative radiation therapy for large lesions or if there is concern about adequacy of surgical margins.

[d] 5,000-6,000 cGy for close-to-positive or positive margins (200 cGy fractions per day). Fields to extend widely beyond surgical margin (eg, 3-5 cm), when clinically feasible.

[e] Tumors lacking the t(17;22) translocation may not respond to imatinib. Molecular analysis of a tumor using cytogenetics may be useful prior to the institution of imatinib therapy.

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

PRINCIPLES OF EXCISION

Goal:
- **Every effort should be made to achieve clear surgical margins. Tumor characteristics include long, irregular, subclinical extensions.**
  See the NCCN Soft Tissue Sarcoma Guideline for Principles of Sarcoma Surgery (SARC-C)

Varied Approaches:
- **Mohs technique[1]**
- **Modified Mohs = Mohs technique with additional final margin for permanent section assessment.**
- **CCPDMA= Complete circumferential and peripheral deep-margin assessment.**
- **2-4 cm margins to investing fascia of muscle or pericranium with clear pathologic margins, when clinically feasible.**

Reconstruction:
- **Immediate reconstruction in most cases**
- **It is preferable to delay reconstruction involving extensive undermining or flaps until negative surgical margins are assessed and certified pathologically clear.**
- **If there is concern that the surgical margins are not completely clear, avoid undermining and consider split thickness skin grafting (STSG) to monitor for recurrence.**

[1]Mohs technique is used primarily in DFSP to insure complete removal and clear margins, and secondarily for its tissue sparing capabilities.

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

Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

NCCN Non-Melanoma Skin Cancer Panel has developed these guidelines outlining the treatment of dermatofibrosarcoma protuberans (DFSP) to supplement their other guidelines (NCCN Basal Cell and Squamous Cell Skin Cancers Guidelines and NCCN Merkel Cell Carcinoma Guidelines). The NCCN Soft Tissue Sarcoma Panel provided expert input in the development of DFSP guidelines. DFSP is an uncommon, low-grade sarcoma of fibroblast origin with an incidence rate of 4.2 to 4.5 cases per million persons per year in the United States.[1,2] It rarely metastasizes. However, initial misdiagnosis, prolonged time to accurate diagnosis, and large tumor size at the time of diagnosis is common. Three-dimensional reconstruction of DFSP[3] has revealed tumors with highly irregular shapes and frequent finger-like extensions.[4] As a result, incomplete removal and subsequent recurrence are common. The local recurrence rate for DFSP in studies ranges from 0-60%, whereas the rate of development of regional or distant metastatic disease is only 1% and 4-5%, respectively.[5]

Diagnosis

As with all solid tumors, clinical suspicion is confirmed by biopsy. In most cases, examination of hematoxylin and eosin-stained specimens by light microscopy results in an unequivocal diagnosis. However, differentiation of DFSP from dermatofibroma can be difficult, at times. In such instances, immunostaining with CD34, factor XIIIa, metallothioneins, tenascin, and/or stromelysin-3 may be useful.[5-9] Therefore, the panel recommends that appropriate and confirmatory immunostaining be performed in all cases of suspected DFSP. Finally, it is unclear whether the histologic features of a high mitotic rate or evidence of fibrosarcomatous change (typically in more than 5% of the surgical specimen) have prognostic significance in DFSP. Studies in the biomedical literature both support[10,11] and refute[12] this notion. Thus, the panel requested that these two features be noted in all pathology reports assessing this tumor.

When the clinician's suspicion for DFSP is high, but the initial biopsy does not support the diagnosis, re-biopsy is recommended and may reveal tumor presence. Multiple non-supportive or equivocal biopsies over time, before definitive diagnosis, are common in the clinical history for this tumor; thus, DFSP is frequently misdiagnosed. Because metastatic disease is rare, an extensive workup is not routinely indicated unless suggestive aspects in the history and physical examination (H&E) or adverse prognostic histologic features are present. Stage I is local disease, stage II is regional disease, and stage III is distant disease.

Treatment

Initial treatment of DFSP is surgical. Because of its proclivity for irregular and frequently deep subclinical extensions, every effort should

be made to completely remove this tumor at the time of initial therapy. The surgical approach to DFSP must be meticulously planned. Size and location of the tumor as well as cosmetic issues will dictate the most appropriate surgical procedure. As noted in the algorithm (DFSP-A), some form of complete histologic assessment of all surgical margins before reconstruction is preferred. See NCCN Soft Tissue Sarcoma Guidelines for principles of sarcoma surgery (SARC-C). Mohs or modified Mohs surgery,[3,4,13-20] and traditional wide excision,[21] typically with 2-4 cm margins to investing fascia that are subsequently verified to be clear by traditional pathologic examination, are all methods to achieve complete histologic assessment.[14,22] In a recent retrospective review of 48 patients, positive margins were more frequent with wide excision than with Mohs, but the local recurrence rates were statistically similar (3.6% vs 0%, respectively, P = 1.0).[23] Immediate reconstruction can be performed in most cases. If there is concern that the surgical margins are not completely clear, tissue rearrangement should be avoided, and split thickness skin grafting (STSG) should be considered to monitor for recurrence.

DFSP is characterized by a translocation between chromosomes 17 and 22 [t(17:22)] resulting in the over expression of platelet-derived growth factor receptor β (PDGFRB).[24-26] These findings suggest that targeting PDGF receptors may lead to the development of new therapeutic options for DFSP. In recently published results, imatinib mesylate, a protein tyrosine kinase inhibitor, has shown clinical activity against localized and metastatic DFSP tumors containing t(17:22).[27-30] Imatinib mesylate has recently been approved by the FDA for the treatment of unresectable, recurrent and/or metastatic DFSP in adult patients.[31] Because tumors lacking the t(17;22) translocation may not respond to imatinib molecular analysis of a tumor using cytogenetics may be useful prior to the institution of imatinib therapy.

Radiation has occasionally been used as a primary therapeutic modality for DFSP,[32] but it is more commonly used as adjuvant therapy after surgery.[33-35] Postoperative radiation therapy can also be considered for negative margins for large lesions or if there is concern about the adequacy of the surgical margins. Postoperative radiation therapy or imatinib mesylate should be considered for positive surgical margins following re-resection (DFSP-2), if further resection is not feasible (unresectable disease).

Radiation therapy, if not given previously, or imatinib mesylate should be considered for patients with recurrent disease, if additional resection would lead to unacceptable functional or cosmetic outcomes (DFSP-2). Clinical trials, imatinib mesylate, chemotherapy, radiation therapy or re-resection as feasible under specific clinical circumstances should all be considered in the rare event of metastatic disease.

Several clinical trials are underway for the treatment of DFSP with imatinib. To access current clinical trials, go to www.clinicaltrials.gov.

Follow-up

Finally, given the historically high local recurrence rates for DFSP, ongoing clinical follow-up of the primary site every 6-12 months is indicated, with re-biopsy of any suspicious regions. Although metastatic disease is rare, a guided H&E should be performed as well, with additional imaging studies as indicated.

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