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Dermatofibrosarcoma Protuberans

Clinical Practice Guidelines in Oncology

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Overview

The NCCN Non-Melanoma Skin Cancer Panel has developed these guidelines outlining the treatment of dermatofibrosarcoma protuberans (DFSP) to supplement their other guidelines (NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Basal Cell and Squamous Cell Skin Cancers and Merkel Cell Carcinoma; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). The NCCN Soft Tissue Sarcoma Panel provided expert input in the development of these 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

NCCN Clinical Practice Guidelines in Oncology for Dermatofibrosarcoma Protuberans

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, non-melanoma, skin cancer, dermatofibrosarcoma protuberans, sarcoma, Mohs surgery, adjuvant therapy, radiation therapy, imatinib *(JNCCN* 2012;10:312–318)

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.

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. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Dermatofibrosarcoma Protuberans Panel

At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Dermatofibrosarcoma Protuberans Panel members can be found on page 318. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit www.NCCN.org.

tumor size at the time of diagnosis are common. Three-dimensional reconstruction of DFSP[3] has shown 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% to 60%, whereas the rate of development of regional or distant metastatic disease is only 1% and 4% to 5%, respectively.[5]

Diagnosis

As with all solid tumors, clinical suspicion is confirmed with biopsy. In most cases, examination of hematoxylin and eosin-stained specimens using light microscopy results in an unequivocal diagnosis. However, differentiation of DFSP from dermatofibroma can sometimes be difficult. In these 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, whether the histologic features of a high mitotic rate or evidence of fibrosarcomatous change (typically in > 5% of the surgical specimen) have prognostic significance in DFSP is unclear. Studies in the biomedical literature both support[10,11] and refute[12] this notion. Thus, the panel requested that these 2 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, rebiopsy is recommended and may show tumor pres-

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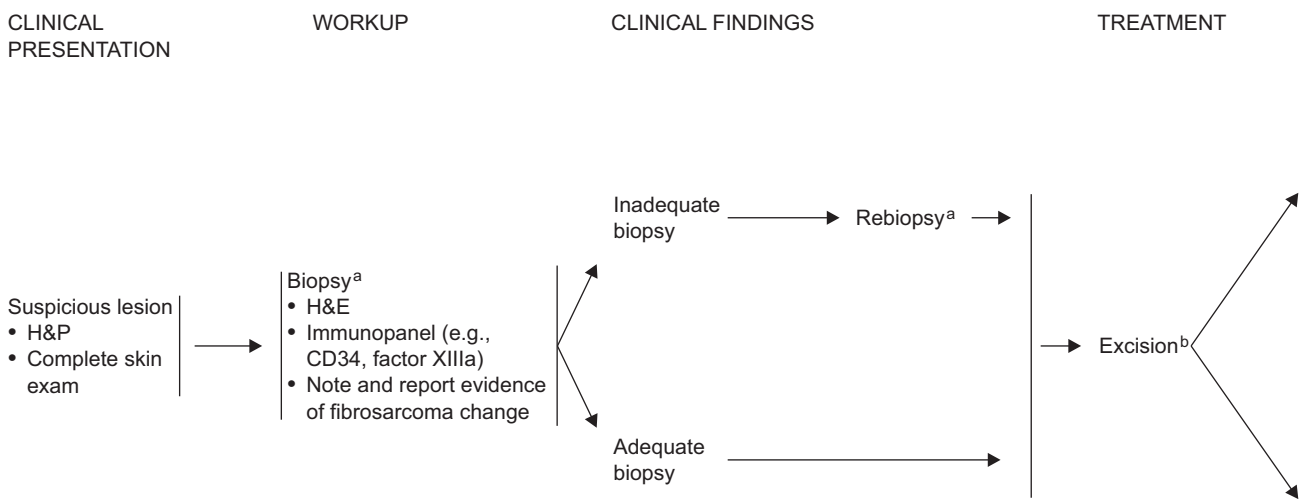

EXCISION

Goal:
- Every effort should be made to achieve clear surgical margins. Some form of complete histologic surgical margin examination is recommended, whenever possible. Tumor characteristics include long, irregular, subclinical extensions.
  See Principles of Sarcoma Surgery in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Soft Tissue Sarcoma (SARC-C). (To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.)

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

Reconstruction:
- It is recommended that any reconstruction involving extensive undermining or tissue movement be delayed until negative histologic margins are verified.
- If there is concern that the surgical margins are not completely clear, consider split-thickness skin grafting (STSG) to monitor for recurrence.

[a] This tumor is frequently misdiagnosed, even with multiple preliminary biopsies.
[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 (above).
[c] Mohs technique is used primarily in DFSP to insure complete removal and clear margins, and secondarily for its tissue sparing capabilities.
[d] Usually performed as a meticulous, comprehensive en face permanent section examination of all surgical margins.

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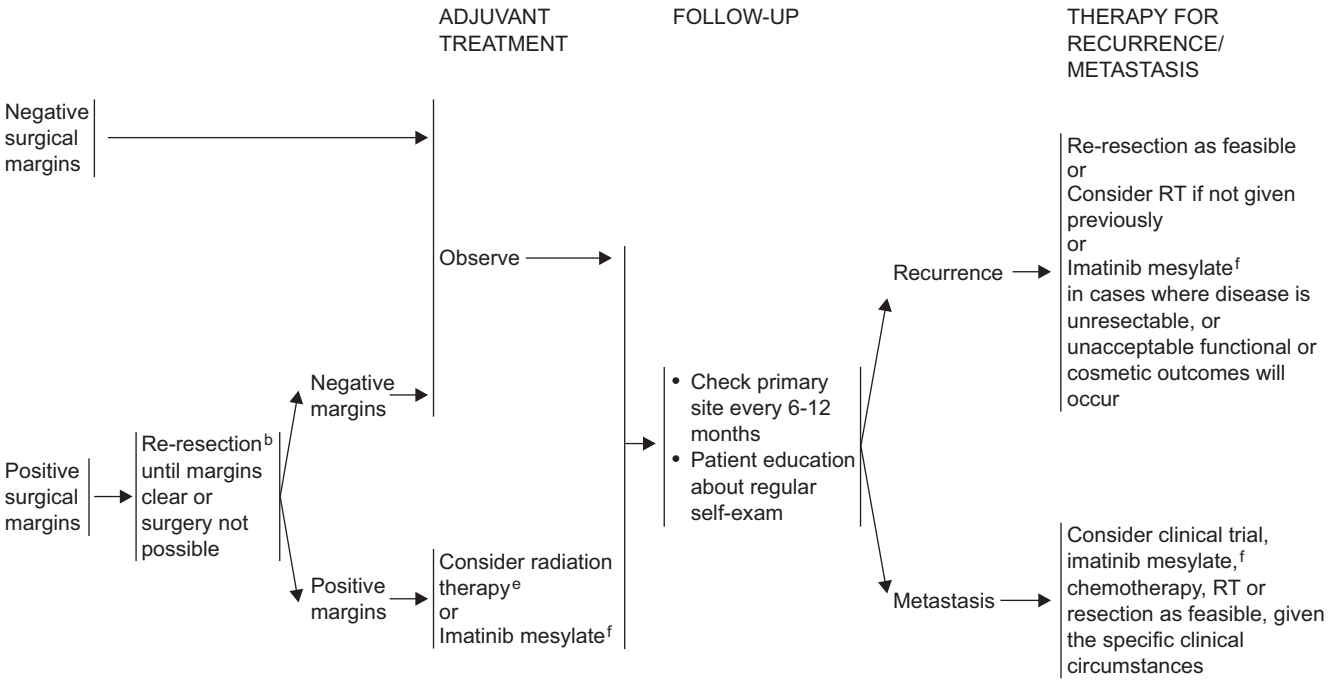

[b] The surgical approach to DFSP must be meticulously planned. Size and location of the tumor and cosmetic issues will dictate the most appropriate surgical procedure. See Excision (previous page).

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

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

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ence. Multiple nonsupportive 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&P) 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 initial therapy. If initial surgery yields positive margins, re-resection is recommended whenever possible, with the goal of achieving clear margins. 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. As noted in the algorithm, some form of complete histologic assessment of all surgical margins before reconstruction is preferred. See the NCCN Guidelines for Soft Tissue Sarcoma for principles of sarcoma surgery (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org [SARC-C]). Mohs or modified Mohs surgery[3,4,13–20] and traditional wide excision,[21] typically with 2- to 4-cm margins to investing fascia that are subsequently verified to be clear through traditional pathologic examination, are all methods to achieve complete histologic assessment.[14,22,23] In a recent series of 244 patients with DFSP, tumor depth was the only factor associated with disease-free survival in the primary setting, underscoring the importance to excise the deep fascia to remove any infiltrating tumor cells.[24] In another 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; $P = 1.0$).[25] Confirmation of negative margins should precede any reconstruction that requires extensive undermining or tissue movement. If concern exists that the surgical margins are not completely clear, tissue rearrangement should be avoided and split-thickness skin grafting considered to monitor for recurrence.

DFSP is characterized by a translocation between chromosomes 17 and 22 (t(17:22)) resulting in the overexpression of platelet-derived growth factor receptor (PDGFR) β.[26–28] These findings suggest that targeting PDGFRs 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).[29–33] Imatinib mesylate has recently been approved by the FDA for the treatment of unresectable, recurrent, and/or metastatic DFSP in adult patients.[34] Because tumors lacking the t(17;22) translocation may not respond to imatinib molecular, analysis with cytogenetics may be useful before initiating imatinib therapy.

Radiation has occasionally been used as a primary therapeutic modality for DFSP,[35] but it is more commonly used as adjuvant therapy after surgery.[36–38] Postoperative radiation therapy or imatinib mesylate should be considered for positive surgical margins if further resection is not feasible (unresectable disease). If a negative margin is achieved, no adjuvant treatment is necessary.

Recurrent tumors, whenever possible, should be resected. Radiation therapy, if not given previously, or imatinib mesylate should be considered if this is not possible, or if additional resection would lead to unacceptable functional or cosmetic outcomes. 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 (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 to 12 months is indicated, with re-biopsy of any suspicious regions. Although metastatic disease is rare, a guided H&P should also be performed, with additional imaging studies as indicated.

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Individual Disclosures for the NCCN Guidelines Panel for Dermatofibrosarcoma Protuberans					
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