National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Dermatofibrosarcoma Protuberans

NCCN Evidence Blocks™

Version 1.2020 — October 2, 2019

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Dermatofibrosarcoma Protuberans
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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.

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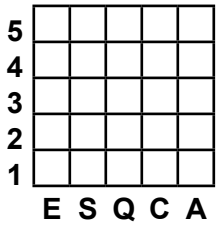
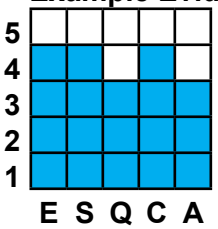
NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



Efficacy of Regimen/Agent

5	**Highly effective:** Cure likely and often provides long-term survival advantage
4	**Very effective:** Cure unlikely but sometimes provides long-term survival advantage
3	**Moderately effective:** Modest impact on survival, but often provides control of disease
2	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs
2	**Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent
1	**Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** One or more well-designed randomized trials
3	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s)
2	**Low quality:** Case reports or extensive clinical experience
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

CLINICAL PRESENTATION

Lesion suspicious for skin cancer[a]

WORKUP

- **H&P**
- **Complete skin exam**
- **Biopsy[b,c]**
  - **Hematoxylin and eosin (H&E)**
  - **Immunopanel (eg, CD34, factor XIIIa)**
  - **Note and report evidence of fibrosarcomatous change or other high-risk features[d]**
- **Consider MRI with contrast for treatment planning if extensive extracutaneous extension is suspected**

See Treatment (DFSP-2)

[a] For more information, see American Academy of Dermatology Association: https://www.aad.org/public/diseases/skin-cancer/dermatofibrosarcoma-protuberans.
[b] This tumor is frequently misdiagnosed due to inadequate tissue sampling/superficial biopsy. Punch, incisional, or core biopsy, preferably of deeper subcutaneous layer, is strongly recommended for sufficient tissue sampling and accurate pathologic assessment. If biopsy is indeterminate or clinical suspicion remains, rebiopsy is recommended. Wide undermining is discouraged due to the difficulty of interpreting subsequent re-excisions pathologically and of preventing possible tumor seeding.
[c] Principles of Pathology (DFSP-A).
[d] If fibrosarcomatous changes/malignant transformations are noted, see the NCCN Guidelines for Soft Tissue Sarcoma. Multidisciplinary consultation is recommended for other high-risk features.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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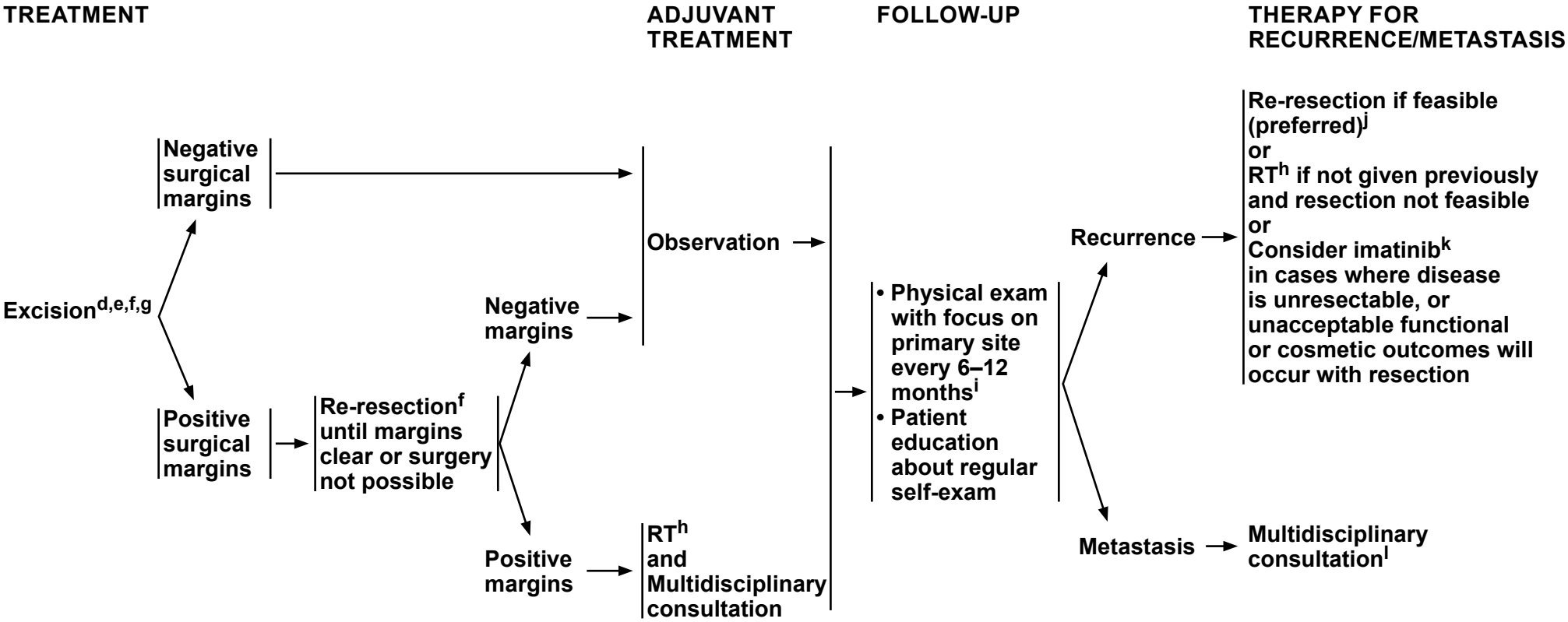

[d] If fibrosarcomatous changes/malignant transformations are noted, see the NCCN Guidelines for Soft Tissue Sarcoma. Multidisciplinary consultation is recommended for other high-risk features.

[e] 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 Principles of Excision (DFSP-B).

[f] Wide undermining is discouraged due to the difficulty of interpreting subsequent re-excisions pathologically and of preventing possible tumor seeding if margins are not histologically clear.

[g] Consider neoadjuvant imatinib in cases where disease is unresectable. See Evidence Blocks on DFSP-2A.

[h] See Principles of Radiation Therapy (DFSP-C).

[i] MRI with contrast may be helpful to detect early recurrence in patients with high-risk lesions or who have had more extensive reconstruction.

[j] For negative margins, RT is not recommended. RT can be considered for treatment of positive margins if not given previously and further resection is not feasible.

[k] 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.

[l] See NCCN Guidelines for STAGE IV Soft Tissue Sarcoma (EXTSARC-5).

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EVIDENCE BLOCKS FOR SYSTEMIC THERAPY

	Therapy for Recurrence* (DFSP-2)	Neoadjuvant Therapy** (DFSP-2)
Imatinib		

*Therapy for recurrence when disease is unresectable or unacceptable functional outcomes will occur with resection.
**For cases where disease is unresectable.

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PRINCIPLES OF PATHOLOGY[1]

- **The spindled cells arranged in a storiform or fascicular pattern are typically bland with minimal cytologic atypia.**
- **Immunohistochemistry for CD34 is mostly positive, and factor XIIIa negative.**
- **Fibrosarcomatous transformation (FS-DFSP) is reflected by a higher degree of cellularity, cytologic atypia, mitotic activity (>5/10 high-power fields [HPF]), and negative CD34 immunostaining.[2]**
- **For equivocal lesions, consider fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR), or conventional cytogenetics for translocation of collagen type I alpha 1 (COL1A1; on 17q22) with platelet-derived growth factor Beta (PDGFβ; on 22q13) to form the oncogenic chimeric fusion gene t(17;22)(q22;q13).**
- **Margin control during excision may require H&E sections supplemented by CD34 immunohistochemistry.**

[1] Currently, no AJCC or CAP synoptic reporting is defined.
[2] FS-DPSF should be noted when present as it is associated with a poor prognosis.

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PRINCIPLES OF 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. Specimens from debulking/Mohs excisions should be examined to identify fibrosarcomatous transformation (FS-DFSP) if present.**
  See the NCCN Guidelines for Soft Tissue Sarcoma for Principles of Sarcoma Surgery (SARC-D)

Varied Approaches:

- **CCPDMA = Complete circumferential and peripheral deep margin assessment.[1]**
- **Mohs micrographic surgery[2]**
- **Wide excision with at least 2-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 avoided or delayed until negative histologic margins are verified to prevent possible tumor seeding if margins are not histologically clear.**
- **If there is concern that the surgical margins are not completely clear, consider split-thickness skin grafting (STSG) to monitor for recurrence.**

[1] Should be performed as a meticulous, comprehensive, en face permanent section examination of all surgical margins.
[2] Mohs micrographic surgery is used in DFSP primarily to ensure complete removal and clear margins, and secondarily for its tissue-sparing capabilities. When Mohs micrographic surgery with margin assessment is being performed and the preoperative biopsy is considered insufficient for providing all the staging information required to properly treat the tumor, consider submission of the central specimen for permanent vertical sections.

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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.

PRINCIPLES OF RADIATION THERAPY

General Treatment Information

- **Adjuvant RT:**
  - **Positive Margins/Gross Disease**
    - ◊ **50–60 Gy for indeterminate or positive margins, and up to 66 Gy for positive margin or gross tumor (2-Gy fractions per day).**
    - ◊ **Fields to extend widely beyond surgical margin (eg, 3–5 cm) when clinically feasible.**
  - **Negative margins**
    - ◊ **RT is not recommended.**
- **Recurrence/Metastasis:**
  - **RT if not given previously and further resection is not feasible; 50–60 Gy for indeterminate or positive margins, and up to 66 Gy for positive margin or gross tumor (2-Gy fractions per day).**
  - **Fields to extend widely beyond surgical margin (eg, 3–5 cm) when clinically feasible.**

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.

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.

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 12/16/14

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Overview

Dermatofibrosarcoma protuberans (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 are 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 10% to 60%, whereas the rate of development of regional or distant metastatic disease is only 1% and 4% to 5%, respectively.[5]

The NCCN Non-Melanoma Skin Cancer Panel has developed these guidelines outlining the treatment of DFSP to supplement their other guidelines (NCCN Guidelines for Basal Cell and Squamous Cell Skin Cancers and NCCN Guidelines for Merkel Cell Carcinoma). This guideline also received expert input from the NCCN Soft Tissue Sarcoma Panel during its initial development.

Diagnosis

As with all solid tumors, clinical suspicion is confirmed by biopsy. A Principles of Pathology section has been added to the algorithm. Histologically, DFSP typically presents as a storiform or fascicular proliferation of bland spindled cells that extends from the dermis into the subcutis.[6,7] Virtually all cases are CD34-positive and factor XIIIa-negative with rare exceptions.[8,9] Currently, no synoptic reporting is recommended.

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, nestin, apolipoprotein D, and cathepsin K may be useful.[10-12] 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[13,14] and refute[15] this notion. Thus, the panel requested that fibrosarcomatous change and other high-risk features (such as deep lesions and high grade) be noted in all pathology reports assessing this tumor. Clinicians should consult the NCCN Guidelines for Soft Tissue Sarcoma when fibrosarcomatous transformations are present.

As the superficial aspect of a DFSP may appear similar to other benign lesions, panelists strongly recommend a deep subcutaneous punch biopsy or incisional biopsy. This will enhance pathologic assessment to avoid misdiagnosis. 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. Wide undermining of the skin is discouraged because it may potentially result in tumor-seeding. It can also interfere with pathologic examination of re-excisions.

Because metastatic disease is rare, an extensive workup is not routinely indicated unless suggestive aspects in the history and physical (H&P) examination or adverse prognostic histologic features are present. Patients with high-risk features may benefit from multidisciplinary consultation as it may optimize clinical and reconstructive outcomes.[16]

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. 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 as well as 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 NCCN Guidelines for Soft Tissue Sarcoma for principles of sarcoma surgery. Mohs or modified Mohs surgery,[3,4,17-24] and traditional wide excision,[25] typically with 2- to 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.[18,26,27] A large retrospective series of 204 patients with DFSP showed a very low local recurrence rate (1%) using wide excision with a standardized surgical approach, underscoring the importance of meticulous pathologic margin evaluation with any surgical technique.[27] Two systematic reviews found a lower rate of recurrence with Mohs surgery compared to wide local excision.[28,29] In a retrospective review of 48 patients, positive margins were more frequent with wide excision than with Mohs, but the local recurrence rates were statistically similar.[30] It is recommended that any reconstruction involving extensive undermining be avoided. Tissue movement, if necessary, should be delayed until negative histologic margins are verified to prevent possible tumor seeding if margins are not histologically clear. If there is concern that the surgical margins are not completely clear, split-thickness skin grafting should be considered to monitor for recurrence. A retrospective study of 19 patients suggests that coordinated efforts of a team of Mohs surgeon, surgical oncologist, dermatopathologist, and plastic surgeon can enhance oncologic and reconstructive outcomes.[16]

DFSP is characterized by a translocation between chromosomes 17 and 22 [t(17;22)(q22;q13)] resulting in the overexpression of platelet-derived growth factor receptor β (PDGFRB).[31-33] These findings suggest that targeting PDGF receptors may lead to the development of new therapeutic options for DFSP. In published results, imatinib mesylate, a protein tyrosine kinase inhibitor, has shown clinical activity against localized and metastatic DFSP tumors containing t(17;22)(q22;q13).[34-38] Imatinib mesylate has been approved by the FDA for the treatment of unresectable, recurrent, and/or metastatic DFSP in adult patients.[39] It may be considered in cases where the disease is unresectable following multiple resections, or if unacceptable functional or cosmetic outcomes would occur with further resection. 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,[40] but it is more commonly used as adjuvant therapy after surgery.[41-45] In a single-institution retrospective review of 53 patients, surgery and radiation achieved an excellent local control rate and disease-free survival of 93% at 10 years.[46] About half of the patients in the study presented initially with recurrent disease. Another small patient series reported that 86% of patients treated with radiation (mostly after surgery) remained disease-free at a median follow-up of 10.5 years.[47] Postoperative radiation therapy is a preferred option for positive surgical margins if further resection is not feasible. If a negative margin is achieved, no adjuvant treatment is necessary.

Recurrent tumors should be resected whenever possible. Adjuvant radiation may be considered after surgery. For patients who are not

surgical candidates, radiation therapy alone is an option if not given previously. Imatinib mesylate should be considered if this is not possible, or if additional resection would lead to unacceptable functional or cosmetic outcomes.

In the rare event of metastatic disease, multidisciplinary consultation is recommended to coordinate treatment. Clinical trials, imatinib mesylate, chemotherapy, radiation therapy, or re-resection as feasible under specific clinical circumstances should be considered. Combined or single-agent chemotherapy commonly used for sarcoma may be considered for DFSP. These include AIM (doxorubicin/ifosfamide/mesna), doxorubicin, ifosfamide, epirubicin, gemcitabine, dacarbazine, liposomal doxorubicin, temozolomide, vinorelbine, or pazopanib (see NCCN Guidelines for Soft Tissue Sarcoma).

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 with focus on 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 be performed as well. For patients with high-risk features or who have undergone extensive surgery, additional imaging studies may be useful in detecting recurrence.

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