# Diagnosis and treatment of dermatofibrosarcoma protuberans. European interdisciplinary guideline – update 2024

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European Journal of Cancer 218 (2025) 115265

Contents lists available at ScienceDirect

European Journal of Cancer

journal homepage: www.ejcancer.com

# Diagnosis and treatment of dermatofibrosarcoma protuberans. European interdisciplinary guideline – update 2024☆

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A R T I C L E I N F O

*Keywords:*
Dermatofibrosarcoma
Guideline

A B S T R A C T

Dermatofibrosarcoma protuberans (DFSP) is a cutaneous fibroblastic tumour that is locally aggressive, with a tendency for local recurrence, but rarely metastasizes. A collaboration of multi-disciplinary experts from the European Association of Dermato-Oncology (EADO), the European Dermatology Forum (EDF), the European Union of Medical Specialists (UEMS) and the European Academy of Dermatology and Venereology (EADV) was formed to update recommendations on DFSP diagnosis and treatment, based on current literature reviews and the experts' consensus. Diagnosis is suspected clinically and confirmed by pathology report, which should specify whether a transformation in higher-grade fibrosarcoma occurred. Detection of specific chromosomal

☆ On behalf of the European Association of Dermato-Oncology (EADO), the European Dermatology Forum (EDF), the European Union of Medical Specialists (UEMS) and the European Academy of Dermatology and Venereology (EADV)

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https://doi.org/10.1016/j.ejca.2025.115265
Received 26 January 2025; Accepted 27 January 2025
Available online 30 January 2025

translocations and/or fusion gene transcripts is useful to confirm diagnosis. Treatment is mainly surgical, intending to achieve complete resection of the tumour. To reduce the recurrence rate, the treatment of choice in DFSP is micrographically controlled surgery. Standard excision with a lateral safety margin of 2–3 cm is an acceptable alternative where only standard histopathological procedures are available. Imatinib is approved in Europe for treating inoperable primary tumours, locally inoperable recurrent disease, and metastatic DFSP. Use of imatinib has also been reported in extensive, difficult-to-operate tumours for preoperative reduction of tumour size, but clinical trials or large register data are required to confirm the usefulness of this approach. Therapeutic decisions for patients with fibrosarcomatous DFSP should be primarily made by an interdisciplinary oncology team ('tumour board').

## 1. Introduction

These guidelines have been created under the auspices of the European Association of Dermato-Oncology (EADO), the European Dermatology Forum (EDF), the European Union of Medical Specialists (UEMS) and the European Academy of Dermatology and Venereology (EADV). Their purpose is to aid clinicians across Europe in managing dermatofibrosarcoma protuberans (DFSP) patients, especially in nations without existing national guidelines. They encompass the full spectrum of DFSP management from diagnosis to treatment, including fibrosarcomatous transformation (FS-DFSP). While prevention issues are not covered, the guidelines aim to enhance integrated care across medical and paramedical specialities for patient benefit.

## 2. Methods

### 2.1. Societies in charge

The European Association of Dermato-Oncology (EADO) coordinated the authors' contributions as part of its Guideline Program in Oncology (GPO). Philippe Saiag served as the responsible editor and coordinator. These interdisciplinary guidelines were created with delegates of various national and international medical societies.

### 2.2. Financing of these guidelines

The guidelines were funded by grants from the EADO for guideline meetings. Authors contributed voluntarily without receiving honoraria or reimbursements. All members of the guideline development group declared their conflicts of interest in the relevant section.

### 2.3. Disclaimer



### 2.4. Scope

These guidelines are intended to assist clinicians in treating patients with dermatofibrosarcoma protuberans (DFSP). The update from the 2015 guidelines [1] was initiated due to advances in pathophysiology, treatment modalities, and imaging techniques, aiming to enhance patient care in clinical practice.

### 2.5. Target population

The present guidelines are published in one part that forms the integral guidelines.

### 2.6. Objectives and formulation of questions

The guidelines are designed to aid clinicians in managing DFSP patients. They focus on definitions, diagnosis, risk classification, updated staging systems, and treatment modalities. Clear sections are provided to support clinical practice.

### 2.7. Audience and period of validity

These guidelines are meant for healthcare providers managing DFSP patients according to current standards of care and evidence-based medicine. They are not intended to replace accepted national guidelines. The guidelines reflect the best available data at the time of publication. Users should interpret the data cautiously as future studies may alter conclusions or recommendations. Deviation from these guidelines for individual patients or special circumstances may be necessary. Adhering to or deviating from these guidelines should not be used as a defence against negligence claims. Updates are expected approximately every three years (expiration date: December 2027), but significant advances may necessitate earlier updates.

## 3. Methods

These guidelines update the 2015 European consensus-based (EDF/EADO/EORTC) interdisciplinary guidelines for the management of invasive DFSP [1]. They are based on other guidelines published since then, including the 2018 German guidelines [2] and the 2018 Spanish guidelines [3].

The authors also conducted a *de novo* literature search using Medline for English language publications up to September 1st, 2024. Search terms included: "dermatofibroscarcoma protuberans" combined with 'diagnosis, prognosis, staging, imaging, prevention, chemoprevention, guidelines, treatment, surgical excision, radiotherapy, adjuvant, systemic, imatinib, clinical trials, follow-up, and patient education". References in selected papers were also reviewed for relevant publications. The updated guidelines follow the standards of the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument [4].

Recommendations are based on the best quality evidence and good clinical practice (GCP). The levels of evidence are graded according to the Oxford classification (Table 1) [5], with recommendations classified as follows:

A: Strong recommendation. Syntax: 'shall'.
B: Recommendation. Syntax: 'should'.
C: Weak recommendation. Syntax: 'may/can'.
X: Should not be recommended.
0: Recommendation pending due to insufficient evidence.

Expert consensus was provided where adequate evidence was

unavailable.

### 3.1. Consensus building process

The consensus-building process was conducted in three main rounds:

1. **First Round**: Medical experts from the EADO, EDF and EADV were involved in producing an initial draft.
2. **Second Round**: A consensus meeting was held on November 8th, 2024, in Rome during an en-face EADO meeting resulting in:
   1. Approval of the text.
   2. Voting on the recommendations involved selecting 'Agree', 'Disagree', or 'Abstention', with the option to provide comments for disagree/abstention votes. A consensus rate of agreement of at least 80 % for recommendations is provided in structured boxes and figures.
3. **Validation** of these guidelines included a review by the corresponding authors of previous German (S Ugurel) and Spanish (B Llombart) DFSP guidelines and a Soft Tissue Sarcoma specialist (A Italiano). **Finalisation of the guidelines** occurred through email contacts.

## 4. Definition; pathophysiology

Dermatofibrosarcoma protuberans (DFSP) is a rare skin fibroblastic tumour known for its local aggressiveness and tendency to recur locally, although it rarely metastasises. The condition predominantly occurs sporadically and often presents a diagnostic challenge, leading to patients presenting with large tumours due to delayed diagnosis. DFSP is characterized by its locally infiltrative nature, with asymmetrical, subclinical horizontal finger-like extensions within the dermis, hypodermis, and potential invasion into deeper tissues.

Significant advances in cytogenetic and molecular studies have expanded our understanding of DFSP. A hallmark cytogenetic feature of DFSP is a reciprocal translocation t(17;22)(q22;Q13) predominantly with the presence of supernumerary ring chromosomes or less frequently balanced or unbalanced d(17;22) translocations [6]. This results in the fusion of the *COL1A1* and *PDGFβ* genes. This fusion gene causes the overexpression of normal PDGFB ligands after the removal of the COL1A1 protein leader sequence. These ligands bind to constitutively expressed PDGF receptors, activating downstream pathways in an autocrine fashion to stimulate DFSP cell growth. Alternative rearrangements are possible. These molecular insights have led to the development of new diagnostic tools and treatment strategies. Recognition of these genetic alterations has also helped classify giant cell fibroblastoma as a variant of DFSP.

Approximately 10 %-15 % of DFSP cases undergo fibrosarcomatous transformation (FS-DFSP), which is associated with a higher recurrence rate and, in some cases, distant metastasis [7]. This transformation generally retains the characteristic chromosomal translocation. FS-DFSP may show genomic gains in *COL1A1::PDGFB* copies, *TP53* mutations, microsatellite instability, disruption of the CDKN2A-CDK4-RB1 pathway and alterations in the mTOR signalling pathway [8–10].

### 4.1. Epidemiology

The few published population-based studies and national registries have shown that DFSP is a relatively rare tumour with age-adjusted rates of less than 1 per 100,000 inhabitants and year [11,12]. A national Danish study reported a crude incidence rate of 0.53 per 100,000 inhabitants and year (100k IaY) between 2000 and 2012 [13]. In the USA, two national epidemiological studies reported an age-standardized

**Table 1**
Oxford center for evidence-based medicine 2011 levels of evidence.

| Question | Step 1 (Level 1[a]) | Step 2 (Level 2[a]) | Step 3 (Level 3[a]) | Step 4 (Level 4[a]) | Step 5 (Level 5) |
|---|---|---|---|---|---|
| **How common is the problem?** | Local and current random sample surveys (or censuses) | Systematic review of surveys that allow matching to local circumstances[b] | Local non-random sample[b] | Case-series[b] | n/a |
| **Is this diagnostic or monitoring test accurate?** (Diagnosis) | Systematic review of cross-sectional studies with consistently applied reference standard and blinding | Individual cross-sectional studies with consistently applied reference standard and blinding | Non-consecutive studies, or studies without consistently applied reference standards[b] | Case-control studies, or "poor or non-independent reference standard[b] | Mechanism-based reasoning |
| **What will happen if we do not add a therapy?** (Prognosis) | Systematic reviewof inception cohort studies | Inception cohort studies | Cohort study or control arm of randomized trial[a] | Case-series or case-control studies, or poor-quality prognostic cohort study[b] | n/a |
| **Does this intervention help?** (Treatment Benefits) | Systematic reviewof randomized trials or *n*-of−1 trials | Randomized trialor observational study with dramatic effect | Non-randomized controlled cohort/ follow-up study[b] | Case-series, case-control studies, or historically controlled studies[b] | Mechanism-based reasoning |
| **What are the COMMON harms?** (Treatment Harms) | Systematic review of randomized trials, systematic review of nested case-control studies, *n*- of−1 trial with the patient you are raising the question about, or observational study with dramatic effect | Individual randomized trial or (exceptionally) observational study with dramatic effect | Non-randomized controlled cohort/ follow-up study (post-marketing surveillance) provided there are enough to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)[b] | Case-series, case-control, or historically controlled studies[b] | Mechanism-based reasoning |
| **What are the RARE harms?** (Treatment Harms) | Systematic review of randomized trials or *n*-of−1 trial | Randomized trialor (exceptionally) observational study with dramatic effect | | | |
| **Is this (early detection) test worthwhile?** (Screening) | Systematic review of randomized trials | Randomized trial | Non -randomized controlled cohort/ follow-up study[b] | Case-series, case-control, or historically controlled studies[b] | Mechanism-based reasoning |

[a] Level may be graded down based on study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.
[b] As always, a systematic review is generally better than an individual study.

incidence rate of 0.42 per 100k IaY between 1973 and 2002 [14] and 0.42 per 100k IaY between 2000 and 2010 [15]. In 2024, an analysis of the Surveillance, Epidemiology, and End Results (SEER) registry reported an age-standardized incidence rate of 0.62 (95 % CI, 0.59–0.66) per 100k IaY [16]. In England, crude incidence rates increased non-significantly from 0.27 [95 % confidence interval (CI) 0.23–0.32] in 2013–0.30 (95 % CI 0.26–0.35) per 100k IaY in 2019 [17].

The recent increase in incidence in some studies may be explained by a wider recognition of DFSP among pathologists [11]. In France, DFSP has become the most common form of skin sarcoma following the decline in the incidence of HIV-associated Kaposi sarcoma [18].

The literature reveals an equal distribution in men and women. The age at diagnosis ranges from 20 to 59 years for most patients, although cases can occur from birth to 90 years or older. Five-year relative survival rates found in recent population-based studies are high [12]. A 2024 analysis of the SEER registry gathered 7748 patients and reported a 1- and 5-year DFSP-specific survival rate of 99.9 % and 99.2 % [16].

### 4.2. Clinical diagnosis

In published retrospective series, the most frequent anatomic location of DFSP is the trunk (42–52.7 %), followed by lower limbs (12.3–25.4 %), head and neck (10.6–17.5 %) and upper limbs (6.8–12.7 %) [7, 19, 20]. Rare cases involving the distal extremities and acral sites have been reported [21].

DFSP is usually asymptomatic with slow progression, which can enter a rapid growth phase, potentially indicating fibrosarcomatous transformation (FS-DFSP) [22]. DFSP typically manifests as an indurated, skin-coloured, erythematous or brownish-yellow, elevated plaque with irregular borders that ranges in size from 2 to 5 cm. However, these lesions may be larger and exhibit solitary or multiple nodules on the plaque or satellite nodules. An atrophic variant has also been described, presenting as a gradually enlarging indurated depressed plaque [23,24].

The tumour is usually fixed to overlying skin, but not to deeper structures such as fascia, striated muscle, periosteum, and bone. However, recurrent or long-standing tumours may invade these structures and in 1 % of cases they can metastasize [25]. Rarely, DFSP can be pigmented, also known as a Bednar tumour. DFSP can rarely be only subcutaneous, with then possible association with *PDGFD* rearrangement or cervicofacial locations [26,27]. *PDGFD* rearranged DFSP have also been described in tumours in the breast [28].

An important clinical differential diagnosis of DFSP is hypertrophic scars or keloids. The clinical diagnosis of DFSP should be always suspected in the case of a solitary lesion mimicking a hypertrophic scar or keloids in the absence of an according history of previous surgical intervention, trauma or associated other multiple scars (acne scars). In doubtful cases, a small punch biopsy should be performed before extensive surgery to avoid mistreatment and further large keloid formation in the case of hypertrophic scars.

### 4.3. Dermatoscopy

The dermatoscopic features of DFSP have been described in limited case series [29] revealing no specific pattern [30,31]. The global dermatoscopic pattern of DFSP is often multi-component. The most frequent local features are pinkish background, structureless depigmented areas, structureless light brown areas, shiny white streaks, a delicate pigment network, and vessels [30–33].

Due to its limited imaging depth, confocal microscopy is of minimal assistance in DFSP diagnosis.

Clinical suspicion must be confirmed by pathology before a treatment decision.

### 4.4. Recommendation 1

| Histopathology in DFSP | Evidence based recommendation |
|---|---|
| Level of recommendation A<br>Level of evidence: 3 | Clinical suspicion shall be confirmed by histopathology before extensive surgery is performed<br><br>Consensus rate: 100 % (24/24) |

### 4.5. Pathology

The definitive diagnosis of DFSP is made by pathology on samples originating from deep incisional, or less frequently, excisional biopsy procedures. The evaluation by a qualified pathology specialist, with specific expertise in sarcoma/soft tissue pathology or dermatopathology is preferred (if available). Tumour samples should be fixed in formalin for no more than 72 h to allow molecular analysis. On a large tumour, a small fragment can be frozen. Hematoxylin and eosin stain typically shows a proliferation of uniform, medium-sized spindle cells with a storiform growth pattern in the dermis without associated epidermal hyperplasia [34]. This proliferation infiltrates the subcutaneous tissue in a lace-like or honeycomb pattern. The periphery is ill-defined, with frequent subtle tentacle-like extension along tissue planes and around lobules of subcutaneous adipose tissue. Less commonly, it can be localised in the adipose tissue, with limited dermal involvement. Mitotic figures are infrequent, and atypia is minimal. Diffuse strong staining of spindle cells for CD34, a useful immunostaining for DFSP, is characteristic.

Various subtypes of DFSP have been described: giant cell fibroblastoma (common in childhood, with numerous multinucleated giant cells); myxoid DFSP, with abundant pale myxoid stroma which can obscure the storiform pattern; pigmented DFSP or Bednar variant, with numerous dendritic cells containing melanin pigment and with frequent positive staining for S100 protein; myxoid DFSP, with pale nodules of spindle-shaped cells with eosinophilic cytoplasm, positive for SMA and negative for CD34 and desmin; plaque-like DFSP; sclerosing, and atrophic tumour.

FS-DFSP typically appears as an abrupt or gradual transition into cell-rich spindle-cell fascicles with cytological atypia and an increased mitotic rate. This transformation may form a discrete nodule in the background of DFSP, with often diminished or lost CD34 expression. This transformation can occur de novo or in recurrent tumours. Due to its prognostic significance [22], the presence or absence of areas with high mitotic rates or evidence of fibrosarcomatous changes should be noted in all pathology reports on DFSP.

On surgically resected tumours, the pathologist must evaluate all margins, with CD34 staining helpful for difficult slides. Reports should specify whether fibrosarcomatous transformation is present, and if so the mitotic rate and presence of necrosis should be provided.

Pathologically, the principal and important differential diagnoses of DFSP are benign atypical variants of dermatofibroma, which have less-uniform cytology, variable morphology of the spindle cell, and presence of other cell types (macrophages, lymphocytes, multinucleated giant cells). It is usually CD34 negative and lacks rearrangement of *PDGFB*, but morphology and immunohistochemistry are most often sufficient. Therefore, appropriate and confirmatory immunostainings (mainly CD34) are recommended in all cases of suspected DFSP. When the clinical suspicion of DFSP is high but the initial biopsy does not support the diagnosis, a repeat biopsy is recommended.

### 4.6. Recommendation 2

| Pathology Reports | Evidence based recommendation |
|---|---|

(*continued on next page*)

(*continued*)

| Pathology Reports | Evidence based recommendation |
|---|---|
| Level of recommendation A<br>Level of evidence: 3 | Pathology reports shall report the presence or absence of high mitotic rates and fibrosarcomatous changes.<br><br>Consensus rate: 100 % (24/24) |

### 4.7. Molecular analysis

Analysis of formalin-fixed, paraffin-embedded tumour samples by fluorescence in situ hybridization (FISH) or other techniques to detect chromosomal translocations and fusion gene transcripts is helpful in difficult cases, where diagnosis of DFSP cannot be confirmed based on hematoxin and eosin histopathology and immunohistochemistry. Indeed, more than 90 % of DSFP harbour a *COL1A1::PDGFB* chromosomal rearrangement responsible for the expression of a chimeric oncogenic protein. Besides aiding in diagnosis and differential diagnosis, it can also be useful to guide treatment with tyrosine kinase inhibitors [35]. Molecular techniques include the detection of *COL1A1::PDGFB* fusion on formalin-fixed paraffin-embedded tissue, by either fluorescent in situ hybridization (FISH) or by analysing RNA using massive parallel sequencing of cDNA (RNA-Seq). In about 8 % of DFSPs, the *COL1A1::PDGFB* fusion cannot be detected by FISH [6], because of either cryptic *COL1A1::PDGFB* fusion or rearrangements involving *PDGFD* (instead of *PDGFB*) with partners such as *COL6A3* [28], *EMILIN2* [36] or *tenascin C* [37]. The *COL6A3::PDGFD* fusion occurs more frequently in breast localization of DFSP [28]. The cutaneous spindle cell tumour with *TNC::PDGFD* fusion could be a rare entity distinct from DFSP [38]. Single cases of DFSP have been reported with fusions involving other genes [39–41], underlining the interest of RNA-Seq analysis in samples where *COL1A1::PDGFB* is not detected by FISH. Finally, the transformation of DFSP to FS-DFSP has been reported to be associated with several additional genetic alterations, including amplification of the *COL1A1::PDGFB* fusion, *TP53* mutations or microsatellite instability. Exceptional DFSP-like tumours without *PDGFB/D* rearrangements but with *ALK* rearrangements have recently been reported [42].

### 4.8. Recommendation 3

| Molecular analysis in DFSP | Evidence based recommendation |
|---|---|
| Level of recommendation B<br>Level of evidence: 3 | Molecular analysis, including FISH, should be performed when possible. When this technology is not available, an expert pathology opinion is advised.<br><br>Consensus rate: 100 % (24 voters) |

### 4.9. Initial evaluation

After the pathological confirmation of the DFSP diagnosis, the initial work-up aims to assess the tumoral local extension, the presence of distant metastases, and the status of the patient for future treatment planning.

As distant metastases are extremely rare, an extensive imaging workup is not routinely indicated except for patients with clinical suspicion of metastasis, recurrent disease, and FS-DFSP. Magnetic resonance imaging (MRI) techniques and, to a lesser extent, ultrasonography provide generally suboptimal information on real tissue infiltration but may be helpful for preoperative orientation in difficult situations. MRI may help to confirm preoperative clinical suspicion of FS-DFSP [43].

Initial assessment of a non-transformed DFSP essentially focuses on the evaluation of extension to deep tissues (fascia and beyond), for which soft tissue contrast-enhanced MRI is considered the most informative procedure [44]. Using high-resolution dynamic contrast-enhanced (DCE) MRI, DFSP usually appears as T2-hyperintense with marked enhancement [45], although variable enhancement patterns have been observed. Although soft tissue MRI is not considered mandatory in all cases [46], the size of the tumour (over 3 cm), its topography (head and neck, proximity to bony or articular structures) and the degree of clinical infiltration may make it desirable.

On CT-scan imaging, DFSP typically presents as an exophytic, non-calcified, circumscribed dermal mass that may infiltrate surrounding skin, subcutaneous tissue and fascia. CT-scan imaging is a useful procedure when bone invasion must be excluded (i.e. scalp). Ultrasound has been evaluated in small retrospective series [47]. The most common pattern consists of oval hypoechoic mass with pseudopod or digitiform projections and posterior hyperechoic regions. However, posterior hypoechoic regions can be absent, and mixed patterns can also be observed.

When transformation to fibrosarcoma or other sarcoma subtypes is identified, multidisciplinary consultation for the establishment of further treatment and surveillance is recommended, and the procedure should follow Soft Tissue Sarcomas guidelines. As FS-DFSP is associated with a metastasis risk of 15 %–20 %, it requires additional assessment based on CT scans of the pulmonary, abdominal and pelvis fields, as in most sarcomas [44].

### 4.10. Recommendation 4

| Initial imaging in DFSP | Evidence based recommendation |
|---|---|
| Level of recommendation C | Preoperative contrast-enhanced magnetic resonance imaging can enable estimation of the primary tumour extension and may be helpful in planning the treatment, especially in recurrent tumours and clinically suspected extensive subcutaneous extension. |
| Level of recommendation B | Disease staging imaging should not be routinely performed except in case of clinical suspicion of metastasis, recurrent disease or for FS-DFSP. In these cases, imaging techniques should be used, including CT scans |
| GCP | Consensus rate: 100 % (24 voters) |

### 4.11. Prognosis and staging

DFSP is a locally aggressive tumour, and, depending on treatment modalities, local recurrences can be relatively common. The reported rate of local recurrences varies widely in the literature (0–40 %), with decreased rates in recent studies. In one study, with a median follow-up of 59 months, the five-year recurrence-free survival was 86 %, while the ten-year recurrence-free survival was 76 % [48,49]. Another recent study included 200 patients with DFSP and 34 patients with FS-DFSP: in the DFSP group no patients developed distant metastases, while in the FS-DFSP 23.6 % of patients developed distant metastases, most commonly in lungs, soft tissues and bones [50].

There is no standard staging system for DFSP available. In the 2015 version of this guideline [1], the primary tumour was considered as stage I, lymph node metastasis as stage II and distant metastasis as stage III [1]. The UK staging system for DFSP is as for soft tissue sarcoma (STS), using the American Joint Committee on Cancer TNM classification for STS [23]. However, this staging classification is, as for other sarcomas, of uncertain interest [44]. In 2020 in the USA, a modified staging system was proposed for DFSP [49] based on the 2015 version of this guideline [1]. This 2020 staging system includes Stage I (non-protuberant lesions including atrophic or sclerotic plaques, macular lesions or small nodules), Stage II (protuberant primary tumour) divided into IIA (superficial tumour: without invasion of the underlying fascia) and IIB (deep tumour: either superficial to the fascia with infiltrating the fascia or occurred beneath the superficial fascia), Stage III (Lymph node

metastasis) and Stage IV (distant metastasis to other organs). We adopt this version of the staging classification for DFSP because it aligns well with other TNM classifications (Table 2). However, no external validation of this classification has been published.

## 5. Therapy

### 5.1. Surgical treatment

Surgery is considered first-line therapy for primary DFSP. However, complete resection (R0 surgery) may be challenging due to the tumour's local behaviour and subclinical extensions, which accounts for the classical high risk of local recurrence. Additionally, DFSP commonly presents as large tumours whose surgical resection induces wide defects with potential functional and cosmetic impairment. Both features make micrographically controlled surgery (MCS) an appropriate approach for DFSP management.

A recent metanalysis of surgery for DFSP found, in comparative studies, a non-significant although numerically superior advantage for Mohs micrographic surgery (MMS) in local recurrence (LR) compared to wide local excision (WLE) (LR rate 1.7 % after MMS and 3.7 % after WLE, odds ratio 1.549, 95 % CI, 0.710–3.381; p = 0.27). Non-comparative studies reported 1.5 % and 9.4 % LR rates for MMS and WLE, respectively [51]. For disease-specific mortality, another recent systematic literature failed to find significant differences between MMS and WLE (0.7 % vs 0.9 %) which is not surprising given the rarity of metastatic DFSP. However, for recurrent DFSP, the MMS group had a statistically significantly lower disease-specific mortality rate (1.0 %, CI 0.0–2.0, p = 0.046) compared with the WLE treatment group (3.5 %, CI 2.0–5.1, p < .001) [52]. Moreover, MCS can achieve tumour clearance with smaller margins and greater preservation of healthy tissue than wide local excision (WLE): the mean percentages of skin spared using MCS rather than wide local excision (WLE) were 49.4 % for a 2 cm lateral margin and 67.9 % for a 3 cm margin [53].

Regarding procedural issues, MCS has been carried out for DFSP either with intraoperative microscopic analysis of frozen sections, as in the classical MMS technique, or with formalin-fixed and paraffin-embedded tissue with deferred closure, usually named Slow Mohs technique. Whatever variations of surgical techniques are used, the excision should reach the deep fascia to remove any infiltrating tumour cells. In case of deep invasion, removing fascia and underlying superficial muscles is necessary. Regarding lateral safety excision margins, at least 1–1.3 cm seems sufficient with micrographic techniques allowing pathological tridimensional control of all margins. Neither procedural variant of MCS seems to influence the risk of local recurrence. A single institution comparative retrospective study compared patients treated with frozen section analysis and those treated using paraffin-embedded tissue [54]. After a mean follow-up duration of 25.4 months, although the local recurrence rate of the frozen MMS group (3.3 %) was lower than that of the paraffin MMS group (7.3 %), the difference was not statistically significant. Additionally, recurrence-free survival was not significantly different between the two groups (p = 0.168) [54]. A nationwide prospective, non-comparative cohort of patients treated with MMS reported a recurrence rate of 0.97 cases/100 person-years (95 % IC = 0.36–2.57). This study failed to demonstrate significant differences in local recurrence rates between tumours resected using frozen sections and those processed through paraffin-embedded and permanent sections (p = 0.6641)[55]. Thus, any procedures allowing the entire peripheral and deep margin assessment (PDEMA, 3D surgery, Tübingen torte, etc…) may be recommended as MCS procedures. Whatever the histopathological technique used, immunohistochemical staining with CD34 is useful to evaluate the tumour margins of the excised material. Direct closure, skin grafting, or second-intention healing should be prioritised for reconstructing defects resulting from DFSP surgery to favour the early detection of local recurrences.

These results support any variant of MCS as the preferred surgical treatment for DFSP. When intraoperative frozen section analysis is not available and three-dimensional permanent tissue analysis is not feasible, lateral clinical margins between 2 and 3 cm with deep excision including underlying muscle fascia are advisable [3,56]. When WLE yields positive margins, re-excision is mandatory, when possible, until achieving clear margins. In this clinical setting, MMS with margins of at least 1 cm beyond the scar in one single step is enough to achieve the complete removal of the incompletely excised tumour [57].

However, since data supporting MCS for the surgical management of DFSP are mostly based on retrospective or non-comparative series, recommendations are based on moderate- to low-quality evidence.

**Table 2**
Staging system of dermatofibrosarcoma protuberans.

| Stage | Criteria |
|---|---|
| Stage I | Non-protuberant lesions including atrophic or sclerotic plaque, macula or small nodules |
| Stage II | Protuberant primary tumour |
| Stage IIA | Superficial tumour: without invasion of the underlying fascia |
| Stage IIB | Deep tumour: either superficial to the fascia with infiltrating the fascia or occurred beneath the superficial fascia |
| Stage III | Lymph node metastasis |
| Stage IV | Distant metastasis to other organs |

### 5.2. Recommendation 5

| First-line treatment of DFSP | Evidence based recommendation |
|---|---|
| Level of recommendation A | The first-line treatment of resectable DFSP shall be surgery, with the aim to achieve microscopically complete resection of the tumour. |
| Level of evidence: 3 | Consensus rate: 100 % (24 voters) |

### 5.3. Recommendation 6

| Surgery of DFSP | Evidence based recommendation |
|---|---|
| Level of recommendation B | Surgery of DFSP should be meticulously planned, with size, type of margin control, location of the tumour and cosmetic issues influencing the most appropriate surgical procedure. |
| Level of evidence: 3 | Consensus rate: 100 % (24 voters) |

### 5.4. Recommendation 7

| Micrographically controlled surgery | Evidence based recommendation |
|---|---|
| Level of recommendation B | Any micrographically controlled surgery based on horizontal sections (Mohs surgery) or sectioning allowing the entire peripheral and deep margin assessment (Peripheral and Deep En Face Margin Assessment, 3D-surgery, histological section margin control, etc.), using in general paraffin-embedded specimen should be used as front-line surgical procedure. |
| Level of evidence: 3 | Consensus rate: 100 % (24 voters) |

### 5.5. Recommendation 8

| Wide local excision | Evidence based recommendation |
|---|---|

(continued on next page)

(*continued*)

| Wide local excision | Evidence based recommendation |
|---|---|
| Level of recommendation B | If no variant of micrographically controlled surgery is available, wide local excision with 2–3 cm safety lateral margin and resection of the underlying fascia can be performed. When margins are pathologically invaded, additional excision(s) should be performed until achieving R0, if feasible. |
| Level of evidence: 3 | Consensus rate: 100 % (24 voters) |

### 5.6. Recommendation 9

| Reconstruction of defects | Evidence based recommendation |
|---|---|
| Level of recommendation B | Reconstruction of defects resulting from DFSP surgery should avoid flaps and favour direct closure, skin grafting or secondary intention healing to facilitate early detection of local recurrences. |
| GCP | Consensus rate: 100 % (24 voters) |

### 5.7. Recommendation 10

| Recurrent DFSP tumours | Evidence based recommendation |
|---|---|
| Level of recommendation B | Recurrent DFSP tumours should be resected whenever possible using micrographically controlled surgery |
| Level of evidence: 3 | Consensus rate: 100 % (24 voters) |

### 5.8. Systemic treatment for DFSP

Systemic therapies offer an alternative for difficult-to-resect or unresectable DFSP. Targeted molecular therapies, particularly tyrosine kinase inhibitors (TKIs), aim to inhibit PDGF signalling, thus controlling tumour growth. The "Imatinib Target Exploration Consortium Study Group" investigated imatinib in different haematological malignancies and solid tumours, including a subset of locally advanced DFSP patients. In this cohort, all 8 patients responded to imatinib, with four achieving a complete response, which led to approval in Europe [58] for inoperable primary tumours, locally advanced and recurrent cases, and metastatic DFSP. A systematic review of 152 cases of imatinib-treated DFSP [59] found complete response in 5.2 % of patients, partial response in 55.2 %, stable disease in 27.6 %, and progression in 9.2 %. Dosages ranged from 400 to 800 mg/d, with no significant difference in response rate using 400 mg or 800 mg daily doses (67.5 % and 67.1 % complete or partial response, respectively; $p > .99$). Imatinib is a useful therapy in patients with DFSP who are not surgical candidates due to disease extension or significant cosmetic or functional concerns. Treatment typically starts at 400 mg/d, with the option to increase to 600–800 mg/d based on tumour response.

In a comparative review of TKI or radiotherapy (RT) in unresecable DFSP tumours, Henry et al. found a clinical benefit rate of 70 %-96 % for TKI [60], with RT providing tumour control or resolution in 90 % of DFSP cases. TKI can be applied across all histological types of DFSP when *COL1A1-PDGFB* is translocated, while RT is generally reserved for low-grade or classic DFSP [60]. TKI therapy, however, was noted to be more toxic than RT alone, but the long-term toxicity of RT was not studied [60].

Another approach for managing locally advanced difficult-to-treat DFSP involves neoadjuvant TKI therapy, often with imatinib or pazopanib, followed by surgery. A phase II study in France reported a 22 % response rate with 800 mg daily of pazopanib [61]. Additionally, DFSP patients (N = 27) treated from 2007 to 2017 with neoadjuvant pazopanib or imatinib showed a 38.5 % response rate and a 46.2 % stability rate [62]. Of these, nine patients had FS-DFSP. The median treatment duration was seven months, and micrographic surgery was performed in 89 % of cases, with 85 % of patients remaining disease-free after a median follow-up of 64.8 months [62]. This approach of neoadjuvant TKI therapy followed by complete surgery with micrographic analysis may be effective for long-term disease-free survival in patients with locally advanced tumours. However, tumours may dedifferentiate after systemic therapy, which could impact the reliability of micrographic surgery, as this approach depends on continuous tumour growth.

No effective chemotherapy regimens are currently established for DFSP. Furthermore, there is limited data on the efficacy of other therapeutic approaches, including immune checkpoint inhibition. Studies on the frequency of microsatellite instability (MSI) [63] and the tumour mutational burden (TMB) might indicate that DFSP patients are not good candidates for this treatment, but the expression of certain tumour antigens, such as PRAME, might offer avenues for immunotherapy [64]. For patients with injectable lesions, investigational intratumoral therapies may also be considered at specialized centres.

Overall, the systemic treatment of advanced DFSP or FS-DFSP should preferentially be discussed in a multidisciplinary tumour board at an expert centre, and clinical trials should be considered whenever available.

### 5.9. Recommendation 11

| imatinib in DFSP tumours | Evidence based recommendation |
|---|---|
| Level of recommendation B | The use of imatinib in DFSP should be proposed in a multidisciplinary tumour board.Imatinib should be proposed as neoadjuvant treatment for primary or recurrent tumour when surgical resection is not feasible or associated with unacceptable morbidity. Tumours which become operable should be operated. |
| Level of evidence: 3 | Consensus rate: 100 % (24 voters) |

### 5.10. Radiotherapy

Radiation therapy is never a substitute for adequate surgical excision, and is not indicated as a postoperative treatment for patients with tumor-free margins. Most evidence regarding the role of RT in DFSP management comes from retrospective case series [65] [66]. In the postoperative setting, RT may be considered an adjuvant treatment in the presence of risk factors, i.e. close margins, recurrent tumours, aggressive histological subtypes or as a salvage treatment in the presence of positive margins. A retrospective analysis including 184 patients reported that age, size of surgical margin, and histological subtype independently affect disease-free survival (DFS). In particular, a very narrow tumour-free margin and the presence of multiple lesions were predictors of recurrence after surgery; in these cases, adjuvant RT may be advisable [67]. Another series identified initial tumour size > 5 cm, multiple recurrences, or high-grade sarcomatous changes as potential indications for adjuvant RT [68]. In the salvage setting, including microscopic residual (R1) or macroscopic residual (R2), RT should be considered when further surgical treatment is not feasible. Moreover, RT can be considered an option for primary inoperable tumours, but the final decision-making should be made within the framework of a multidisciplinary tumour board. Concerning doses and fractionations, most studies report the use of conventional fractionation (2 Gy/day, 5 days per week) with a dose range from 50 up to 70 Gy, usually a total dose of 60 Gy (microscopic residual tumour) to 70 Gy (macroscopic residual tumour) may be given in treatment with curative intent. The

size of the irradiated volume should consider the location, the tumour bed, and the size of the surgical scar plus an additional safety margin of 3–5 cm.

### 5.11. Recommendation 12

| No indications for radiotherapy | Evidence based recommendation |
|---|---|
| Level of recommendation B<br>Level of evidence: 3 | Radiotherapy should not be offered for completely excised (R0) non-transformed tumours.<br><br>Consensus rate: 100 % (24/24) |

### 5.12. Fibrosarcomatous transformation

Approximately 10 %-15 % of DFSP cases are FS-DFSP [7]. FS-DFSP exhibits a more aggressive behaviour than DFSP, with lower recurrence-free survival and greater metastatic potential [69]. FS-DFSP may be suspected preoperatively by MRI findings [70], with signs such as multi-lobular morphology, T2W hypointensity compared with fat, internal flow voids and peri-tumoral oedema. In the case of FS-DFSP, the advice of a multidisciplinary specialised soft-tissue sarcoma tumour board is recommended. Work-up should include a CT scan of the thorax, abdomen and pelvis and lymph node ultrasonography.

The main objective of treatment remains complete surgical excision of the primary tumour. Excision with wide margins (≥2 cm), which in a systematic review prevented both local recurrence and metastasis [71], represents the standard treatment of FS-DFSP. Whether MMS can yield comparable results in FS-DFSP is currently unclear. Since MMS achieves less local recurrence than WLE, it can be considered in FS-DFSP, but this strategy has not been formally evaluated. Adjuvant radiotherapy has not been formally evaluated in FS-DFSP. Its indication should follow the rules of other soft tissue sarcomas depending on the quality of the resection ("en bloc" excision or not), histological margins (R0 versus R1), and size and grade of the tumour [44]. Non-resectable or metastatic FS-DFSP harbouring the *COL1A1::PDGFB* fusion gene can be treated with imatinib in the palliative setting or as an adjunctive treatment before surgery, although responses may be short-lasting [72]. Fluorescence in situ hybridisation (FISH) or multiplex reverse transcriptase-polymerase chain reaction (RT-PCR) to detect chromosomal translocations and fusion gene transcripts should be performed on the FS component before imatinib treatment. As the transformation of DFSP to FS-DFSP has been reported to be associated with several additional genetic alterations, analysing RNA using massively parallel sequencing of cDNA (RNA-Seq) may be useful to find another treatable target(s).

### 5.13. Recommendation 13

| FS-DFSP: special recommendation | Evidence based recommendation |
|---|---|
| Level of recommendation B<br>GCP | FS-DFSP should be discussed in a multidisciplinary tumour board including soft-tissue sarcoma expert(s).<br><br>Consensus rate: 100 % (24/24) |

### 5.14. Recommendation 14

| FS-DFSP treatment | Evidence based recommendation |
|---|---|
| Level of recommendation B | The main objective of FS-DFSP treatment should be complete surgical excision with micrographically controlled surgery. If no variant of micrographically controlled surgery is available, wide local excision with 2–3 cm safety margin can be performed |
| Level of evidence: 4 | Consensus rate: 100 % (24/24) |

### 5.15. Follow-up of non-transformed DFSP

The primary aim of follow-up in patients with DFSP is the early detection of local recurrences or rare lymph node metastases. DFSP recurrences are reported with higher frequency after wide standard surgical excision than after margins-controlled surgery techniques such as MMS and occur late, with a median of 55 months [50,73]. In a systematic review of MMS in DFSP [74], the mean time to recurrence was 68 months. The risk of recurrences has been associated with positive margins of excision and FS-DFSP change [7, 50, 73]. Metastases, though extremely rare, are mainly associated with FS-DFSP and large tumours [7, 50, 73]

There is no consensus and no sufficient evidence basis for optimal follow-up schedules. Clinical examination focusing on the primary site, every 6–12 months, for at least 5 years can be recommended to detect early recurrence [75]. For completely resected tumours, with typical pathology, clinical examinations are sufficient. Clinical examinations should include a careful inspection and even more, palpation of the scar and surrounding tissue to check for subcutaneous induration and nodules. In addition, palpation of the loco-regional lymph nodes should be performed. Follow-up with imaging techniques such as lymph node sonography or cross-sectional imaging is only useful in cases of known metastasis, suspicion of new metastases, FS-DFSP, or for primary tumours requiring extensive surgery [69,76]. For these patients, the follow-up examinations should be based on the recommendations for the follow-up of high-grade soft tissue sarcomas. These cases should be managed with linkage to sarcoma centres. Contrast-enhanced MRI can help to assess early local recurrence or tumour extent in cases where the clinical examination is inconclusive [75].

Any suspected recurrence should be confirmed by a deep biopsy and pathological examination. Closer intervals and longer duration of follow-up to detect rare late events (up to 10 years after surgery) are advised for patients with high-risk features including positive margins, extensive surgery, and FS-DFSP. Patients should also be educated about regular self-examination and self-detection.

### 5.16. Recommendation 15

| Follow-up in DFSP | Evidence based recommendation |
|---|---|
| Level of recommendation C | <u>For primary tumours, completely resected, without high-risk pathology:</u>Clinical examination focusing on the primary site aiming to detect early recurrences may be offered every 6-months for the first 3 years after excision and every 12 months for years 4–5. |
| GCP | Consensus rate: 96 % (23/24) |
| Level of recommendation C | <u>For tumours with high-risk features (recurrent tumours, narrow surgical margins):</u>Clinical examination and local assessment with MRI can be recommended at 6 months intervals for 2 years, every 6–12 months for years 3–5, at least one clinical examination yearly for years 6–10. |
| GCP | Consensus rate: 96 % (23/24) |
| Level of recommendation C | Patients with fibrosarcomatous transformation or metastatic disease should be managed and monitored within a multidisciplinary team preferably including a soft-tissue sarcoma expert. |
| GCP | Consensus rate: 96 % (23/24) |

## Funding

The guidelines were funded by grants from the EADO for guideline meetings.

## CRediT authorship contribution statement

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## Declaration of Competing Interest

Dr. Brochez has nothing to disclose.

Dr. Emile has nothing to disclose

Dr. Forsea has nothing to disclose.

Dr. Garbe reports personal fees from CeCaVa, MSD, NeraCare, and Philogen, outside the submitted work.

Dr. Harwood has nothing to disclose

Dr. Hauschild reports grants and personal fees from Amgen, BMS, MerckPfizer, MSD/Merck, Neracare, Philogen, Pierre Fabre, Regeneron, Sanofi-Genzyme, Replimune, and Novartis Pharma, personal fees from Curevac, Eisai, Kyowa Kirin, Highlight Therapeutics, Immunocore, Iovance, Curevac, Seagen, IO Biotech, Dermagnostix, Xenthera, Agenus, Almirall, Sunpharma, and Incyte, grants from Huya Biosciences, outside the submitted work.

Dr. Italiano reports Consulting or Advisory Role for Bayer, Boehringer, Daiichy-Sankyo, Merck, MSD, Novartis, and Roche, reports research Funding (Institution) from Bayer, Beigene, BMS, Boehringer, Daiichy-Sankyo, Invox Pharma, Merck, MSD, Novartis, Pharmamar, and Roche

Dr. Kandolf reports personal fees for advisory boards from Bristol Myers-Squibb, MSD, Novartis Roche, Janssen, and Abbvie, outside the submitted work.

Dr. Kelleners-Smeets reports personal fees from Sanofi, Novartis, MSD, and Sun Pharma, outside the submitted work.

Dr. Lallas reports personal fees from Avene, MSD, Regeneron, and BMS, outside the submitted work.

Dr. Lebbe reports personal fees from MSD, Pierre Fabre, BMS, Sanofi, and Immunocore, outside the submitted work.

Dr. Leiter reports personal fees from Regeneron, Sanofi, MSD, Novartis, Almirall Hermal, and Sun Pharma, outside the submitted work.

Dr Llombart reports Consulting or Advisory Role from Sun Pharma, Roche pharma and Merck, outside the submitted work.

Dr. Longo has nothing to disclose.

Dr. Malvehy reports grants and personal fees from Almirall, ISDIN, and La Roche-Posay, personal fees from MSD, and Pierre Fabre, grants from Philogen, Castle biosciences, BMS, non-financial support and others from Vivascope, Damae medical, Canfield, and Fotofinder, outside the submitted work.

Dr. Mijuskovic reports personal fees for advisory boards from Beiersdorf, Eli Lilly, Janssen, La Roche Posay, and Novartis, outside the submitted work

Dr. Moreno-Ramírez has nothing to disclose.

Dr. Mosterd has nothing to disclose

Dr. Tagliaferri has nothing to disclose

Dr. Saiag reports personal fees from Novartis, MSD, NeraCare, BMS, Pierre Fabre, Merck, personal fees and grants from Damae Medical, outside the submitted work.

Dr. Vieira has nothing to disclose.

Dr Ugurel reports research support from Bristol Myers Squibb and Merck Serono; speakers and advisory board honoraria from Bristol Myers Squibb, Merck Sharp & Dohme, Merck Serono, and Novartis; and meeting and travel support from Almirall, Bristol-Myers Squibb, IGEA Clinical Biophysics, Merck Sharp & Dohme, Novartis, Pierre Fabre, and Sun Pharma; outside the submitted work.

Dr. Zalaudek reports personal fees from Philogen, MSD, Novartis, Sanofi, La Roche Posay, Sunpharma, Biogena, Cieffe Derma, outside the submitted work

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