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S1 guidelines for dermatofibrosarcoma protuberans (DFSP) – update 2018

Guidelines commissioned by the Dermatological Oncology Group (ADO), the German Cancer Society (DKG) and the German Society of Dermatology (DDG)

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Summary

While dermatofibrosarcoma protuberans (DFSP) is a rare cancer entity overall, it is nevertheless the most common type of cutaneous sarcoma. The tumor is of fibroblastic origin and characterized by slow, undermining and locally destructive growth. Metastatic spread is very rare. Given its nonspecific clinical appearance, diagnosis is frequently delayed. Biopsy and subsequent histopathology are key diagnostic tools. Standard treatment for primary tumors consists of complete excision with surgical margins of 1 to 2 cm. Smaller margins are associated with high local recurrence rates. Inoperable and metastatic DFSP may be treated with radiation therapy. Approximately 80–90 % of DFSP lesions harbor a fusion gene that results in continuous activation of the PDGF-β signaling pathway. Consequently, molecular targeted therapy inhibiting PDGF-β is an effective option for advanced (inoperable) and metastatic DFSP. The first agent to be approved for systemic treatment of DFSP is the multikinase inhibitor imatinib, showing objective response rates of about 50 % in clinical trials.

1 Epidemiology and clinical presentation

Dermatofibrosarcoma protuberans (DFSP) is a fibroblastic tumor that exclusively originates from the skin. According to the WHO classification of mesenchymal tumors, DFSP is considered a locally aggressive, rarely metastasizing tumor of intermediate malignancy. The tumor exhibits a locally infiltrative and undermining growth pattern characterized by asymmetric, subclinical horizontal spread and infiltration of deeper structures. The tumor involves the dermis and/or the subcutis [1].

While DFSP is a relatively rare tumor (incidence less than 1 in 100,000 per year), it is nevertheless the most common type of cutaneous sarcoma. The average age at diagnosis is around 40 years. Both pediatric and congenital cases of DFSP do occur but are exceedingly rare. There is no gender

predilection. Given the extremely low metastatic rate, mortality is low.

Clinically, DFSP usually presents as an indurated, skin-colored or erythematous, sometimes brownish-yellow, mildly elevated plaque with irregular borders; growth is slow and spans years or decades. As the disease progresses, solitary or multiple tumor nodules arise. Sites of predilection include the trunk and the proximal extremities. If the tumor develops in atypical sites, such as the distal extremities, this is not associated with a poorer prognosis [2].

While DFSP commonly recurs locally, distant metastatic spread is uncommon (less than 1 % of all cases). DFSP with fibrosarcomatous transformation (DFSP-FS) is a variant associated with a higher rate of metastasis [3, 4]. Despite morphological differences, giant cell fibroblastoma is characterized by similar genetic changes as DFSP and must therefore be considered a DFSP variant. In addition, there are lesions that exhibit features consistent with both DFSP and giant cell fibroblastoma. Pigmented DFSP lesions are referred to as Bednar tumors.

2 Diagnosis

As it is not possible to definitively diagnose DFSP merely on clinical grounds, the diagnosis should be based on biopsy and subsequent histopathology.

Histologically, DFSP shows diffuse infiltration of the dermis and subcutaneous adipose tissue with tightly packed, cytologically rather uniform spindle-shaped CD34-positive neoplastic cells, arranged in a characteristic storiform (reminiscent of a straw mat or cartwheel) pattern. Purely subcutaneous DFSP variants are rare and usually found on the head [5]. One feature typical of DFSP is that the tumor cells spread along the septa of the subcutaneous adipose tissue with subsequent fat entrapment. Fibrosarcomatous DFSP (DFSP-FS) is characterized by abrupt or gradual transition to areas marked by spindle-cell fascicles with increased cellular and nuclear atypia as well as a high mitotic index. Histologically, DFSP must be distinguished from benign dermatofibroma variants such as plaque-like CD34-positive dermal fibroma or dermatomyofibroma on the one hand, and pleomorphic dermal sarcoma (formerly referred to as malignant fibrous histiocytoma or MFH), which has a more unfavorable prognosis, as well as leiomyosarcoma, malignant peripheral nerve sheath tumor (MPNST) and spindle cell melanoma on the other hand [1].

Molecular studies using fluorescence in-situ hybridization (FISH) and gene sequencing have shown that DFSP cells frequently harbor chromosomal translocations, the most common of involves chromosomes 17 and 22 (17q22; 22q13; more than 90 % of all cases). This translocation results in a fusion of the *COL1A1* and *PDGF*-β genes and is often associated with the formation of a ring chromosome [6]. The gene product, a COL1A1-PDGF-β fusion protein, binds to the constitutively expressed PDGF receptor (PDGF-R) and thus acts as an autocrine factor that continually stimulates growth of DFSP cells. A special DFSP variant is associated with a COL6A3-PDGFD fusion gene and typically occurs on the breast of females [7]. There have also been some reports of DFSP patients with an EMILIN2-PDGFD fusion gene [8]. Knowledge about these molecular changes allows for targeted therapy of DFSP.

Ultrasound (7.5–10 MHz) and MRI imaging may be useful in assessing the extent of the tumor prior to surgery. In case of local recurrence and/or suspected metastasis, useful diagnostic tests include lymph node ultrasound and cross-sectional imaging using CT or MRI.

3 Prognosis and staging

DFSP originates from the dermis or subcutis and spreads both horizontally and vertically, resulting in the destruction of surrounding structures. Given its infiltrative, undermining growth pattern, local recurrences are comparatively common. Published data on the frequency of local recurrence shows marked variation (10–80 %). The risk of local recurrence depends, among other factors, on the procedure and the surgical margins used during removal of the primary tumor [9]. Lymph node and distant metastases are uncommon; based on current data, less than 1 % of all DFSP cases will metastasize. Retrospective analysis of the US *National Cancer Institute's Surveillance, Epidemiology, and End Results* (SEER) database, which included 3,686 DFSP patients, showed age, male gender and tumor size to be significantly associated with an unfavorable prognosis [10]. Another retrospective analysis of the US *National Cancer Database* (5,249 DFSP cases) revealed the following factors to be relevant in terms of prognosis: insurance status, anaplastic histology and positive postoperative margins [11].

Even though there is no definitive staging system for DFSP, the following usually applies: stage I – primary tumor (localized disease); stage II – lymph node metastasis; stage III – distant metastasis.

4 Treatment

4.1 Surgical treatment

The recommended treatment for primary tumors is complete surgical excision. In this context, published recommendations regarding surgical margins to be employed range from 1 cm to 5 cm. If a procedure is chosen that involves three-dimensional micrographic margin control (according to Mohs or Breuninger), a surgical margin of 1 cm may possibly be

considered sufficient [9, 12]. In case of regular histopathological processing (conventional histological margin control), wider surgical margins of at least 2 cm are recommended. In a retrospective analysis of 61 DFSP patients, surgical margins of less than 2 cm were associated with a significantly increased risk of recurrence [13]. A systematic review of 23 nonrandomized trials comparing recurrence rates in patients treated with micrographic surgery versus wide local excision (combined with conventional histological examination of margins) revealed the former to be superior (recurrence rate 1.11 % versus 6.32 %) [9]. Consequently, three-dimensional micrographic surgical procedures are preferable to those using conventional histological examination of resection margins in terms of recurrence rates of DFSP. However, given that three-dimensional micrographic surgery is a much more complex procedure, it is not utilized at every center in Germany.

In case of local recurrence, it may be difficult to distinguish scar tissue from vital tumor tissue. The immunohistochemical marker CD34 is useful in determining the tumor boundaries within the excised tissue. Fibrosarcomatous DFSP (DFSP-FS) lesions should be treated according to the guidelines for surgical treatment of high-grade soft tissue sarcomas (see S1 guidelines for soft tissue sarcomas; AWMF 025/007). For best patient care, it is recommended that patients be referred to a center experienced in the treatment of sarcomas.

4.2 Radiation therapy

DFSP is considered to be comparatively sensitive to radiation. Thus, radiation therapy may be an important treatment option for cases in which the tumor is inoperable or postoperative margins are microscopically or macroscopically positive, or when the patient has already experienced multiple recurrences. Radiation therapy may also be considered a primary treatment option for patients in whom wide excision would result in significant cosmetic or functional impairment. The target volume includes the tumor itself, any postoperative scars as well as a safety margin of 3–5 cm. With curative intent, a single dose of 2 Gy is usually administered five times a week, up to a total dose of 60–66 Gy (microscopic evidence of tumor cells) or 66–70 Gy (macroscopic evidence of residual tumor) [14, 15]. In a palliative setting, and depending on tumor site and vital surrounding structures, a total dose of 50 Gy may be considered sufficient.

Adjuvant radiation of the tumor bed following complete excision of DFSP is not recommended. A recent systematic review of twelve retrospective clinical trials showed a tendency towards lower local recurrence rates after adjuvant postoperative radiation therapy compared to surgery alone; the difference, however, was not significant [16].

4.3 Pharmacological therapy

The goal of molecular targeted therapy in the treatment of DFSP is to disrupt the autocrine, PDGF-R-mediated stimulation of growth. In clinical trials, patients with inoperable or metastatic DFSP lesions showed response rates of approximately 50 % when treated with the multikinase inhibitor imatinib, a drug that – among others – also inhibits PDGF-R [17, 18].

Imatinib (Glivec©) at a daily dose of 800 mg has been approved for the treatment of adult patients with inoperable primary, recurrent or metastatic DFSP since 2011. Other clinical trials using a lower dose of 400 mg/day have likewise demonstrated response rates of roughly 50 %. Given that imatinib doses between 400 mg/day and 600 mg/day are associated with comparable effectiveness yet significantly fewer adverse events, they are possibly preferable to higher doses in everyday clinical practice. To date, there has been no clinical study directly comparing various imatinib doses in the treatment of DFSP. A real-world study of 31 patients treated with imatinib for advanced DFSP showed a progression-free 5-year survival rate of 58 % and an overall 5-year survival rate of 64 % (median follow-up of 5.3 years) [19]. Shorter survival times on imatinib were associated with the histological subtype of fibrosarcomatous DFSP (DFSP-FS) as well as with the presence of metastases [19].

Imatinib may be used to decrease tumor size prior to surgery of extensive lesions that are otherwise difficult to manage surgically. In two clinical trials, this neoadjuvant approach (using imatinib 600 mg/day) showed response rates of 36 % and 57 % with a median treatment duration of 2.0 months and 3.1 months respectively [20, 21]. Hence, if there is a clinically apparent decrease in tumor size on imatinib therapy, treatment should be continued for at least three months to achieve an objective tumor response. Histologically, the tumor remnants subsequently excised showed a decrease in tumor cellularity as well as prominent hyaline fibrosis. These morphological changes may make it even more challenging to histologically distinguish vital tumor cells from scar tissue. Imatinib is currently not approved for neoadjuvant treatment of DFSP (off-label use).

Both primary and secondary resistance to imatinib has been reported [17, 18, 21]. In a clinical trial of 30 patients with advanced or metastatic DFSP who experienced disease progression after an initial response to first-line treatment with imatinib, treatment with the multikinase inhibitor sunitinib led to a response rate of 40 % [22]. There have also been some cases in which a treatment response to other kinase inhibitors, e.g. pazopanib, was achieved after imatinib had become ineffective [23]. In cases of secondary resistance to imatinib, second-line treatment with another PDGF-R inhibitor may therefore be useful and has a good chance of

Table 1 Summary of the most important conclusions and recommendations of the S1 guidelines for DFSP (as of 2018).

Topic	Guideline statement/recommendation
Biological behavior and growth pattern	Tumor of intermediate malignancy; very slow but locally aggressive and infiltrative growth; local recurrences are common; metastases are rare (< 1 % of cases)
Epidemiology	Rare tumor entity (incidence < 1/100,000/year); no gender predilection
Clinical features	Skin-colored, erythematous or brownish, mildly elevated plaque, often studded with solitary or multiple nodules; usually located on the trunk or proximal extremities
Special variants	Fibrosarcomatous DFSP; pigmented DFSP (Bednar tumor); giant cell fibroblastoma
Diagnosis	Biopsy and histopathology; histomorphology: spindle-shaped, monomorphic tumor cells found in the dermis and/or subcutis; immunohistochemical marker: CD34; chromosomal translocation with fusion of the *COL1A1* and *PDGF*-β genes (90 % of cases)
Factors associated with an unfavorable prognosis	Advanced age; male gender; large tumor size; fibrosarcomatous transformation; positive postoperative margins
Surgical treatment	Excision of the primary tumor with the goal of achieving tumor-free margins; surgical margins to be used: at least 1 cm (in case of three-dimensional, micrographic surgery, e.g. Mohs surgery), and at least 2 cm (in case of conventional histological margin control). In patients with fibrosarcomatous DFSP: surgical treatment according to the guidelines for high-grade soft tissue sarcomas; referral to a sarcoma center
Radiation therapy	Good sensitivity to radiation; indications: inoperable primary tumor, microscopic or macroscopic evidence of residual tumor, history of multiple recurrences; Total dose: 60–66 Gy (microscopic evidence of tumor cells) or 66–70 Gy (macroscopic evidence of residual tumor). Adjuvant irradiation of the tumor bed following complete excision is not recommended.
Pharmacological therapy	PDGF-R inhibitors show good efficacy; the PDGF-R inhibitor imatinib (400–800 mg/day) has been approved by the EMA for the treatment of inoperable, locally advanced or metastatic DFSP, with response rates around 50 %; in case of resistance to imatinib, other PDGF-R inhibitors may be effective (e.g. sunitinib; off-label use) Chemotherapy: poor efficacy; not recommended Immunotherapy/checkpoint inhibitors: no studies available
Follow-up	Primary tumor stage: clinical examination every six months for at least five years (early detection of local recurrence) Lymph node metastases: clinical examination and imaging studies (lymph node ultrasound, cross-sectional imaging) every three months for two years, thereafter every six months for at least three years Fibrosarcomatous DFSP: follow-up at sarcoma center

success. Unlike imatinib, neither sunitinib nor any other PDGF-R inhibitors are approved for use in the treatment of DFSP (off-label use).

Moreover, it has been observed that imatinib treatment causes immunological changes both in tumor cells and the surrounding tissue [24]. These changes suggest that a combined or sequential treatment regimen consisting of imatinib and immunotherapy may be a possible option [25]. To date, there is no clinical trial data on the use of immune checkpoint inhibitors in the treatment of DFSP.

There is no known effective chemotherapy for DFSP. In patients with sarcomatous DFSP and rapidly progressive, metastatic disease, chemotherapeutic regimens otherwise used for soft tissue sarcomas may be attempted. It is recommended that these patients be referred to a clinical center experienced in the treatment of sarcomas.

5 Follow-up

No data has been published with respect to standardized follow-up of patients with DFSP. Follow-up is primarily aimed at early detection of local recurrence or lymph node metastases. For this purpose, it is recommended that patients be clinically evaluated every six months for at least five years.

Imaging studies, such as lymph node ultrasound or cross-sectional imaging, are only useful if there is a history of metastasis as well as for patients with fibrosarcomatous lesions (DFSP-FS) or very extensive primary tumors [3, 4]. In this patient group, follow-up should be performed based on the recommendations for follow-up of high-grade soft tissue sarcomas.

6 Consensus procedures

The guideline update was prepared on behalf of ADO/DGK (Dermatological Oncology Group of the German Cancer Society) and the German Society of Dermatology (DDG) by Selma Ugurel, Essen; Rolf-Dieter Kortmann, Leipzig; Peter Mohr, Buxtehude; Thomas Mentzel, Friedrichshafen; Claus Garbe, Tübingen; Helmut Breuninger, Tübingen; Sebastian Bauer, Essen; and Stephan Grabbe, Mainz, and was based on the "Interdisciplinary guidelines for diagnosis and treatment of malignant diseases (short version), chapter G5: Dermatofibrosarcoma protuberans" (published by DKG; W. Zuckschwerdt publishing house, Munich; 2008; pages 156–158).

This is an updated version of the previously valid guidelines from 2013 [26]. Passages that required no content-related changes were, in part, adopted verbatim. The most important recommendations of the present guidelines are summarized in Table 1.

Conflicts of interest

Experts with a possible conflict of interest were not involved in the development of recommendations for the corresponding topics. The guideline coordinator was the person responsible for assessing any possible conflicts of interest the various experts may have had. Any possible conflicts of interest the guideline coordinator may have had herself were assessed by the guideline representative of ADO/DGK.

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