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Original Research

Diagnosis and treatment of dermatofibrosarcoma protuberans. European consensus-based interdisciplinary guideline [☆]

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Abstract Dermatofibrosarcoma protuberans (DFSP) is a skin fibroblastic tumour that is locally aggressive, with a tendency for local recurrence, but rarely metastasizes. A unique collaboration of multi-disciplinary experts from the European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization of Research and Treatment of Cancer (EORTC) was formed to make recommendations on DFSP diagnosis and treatment, based on systematic literature reviews and the experts' experience. Diagnosis is suspected clinically and confirmed by pathology. Analysis by fluorescence in situ hybridisation (FISH) or multiplex reverse transcriptase-polymerase chain reaction (RT-PCR) to detect specific chromosomal translocations and fusion gene transcripts is useful

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to confirm a difficult DFSP diagnosis. Treatment is mainly surgical, with the aim to achieve complete resection of the tumour. In order to reduce the recurrence rate, the treatment of choice of DFSP seems to be Mohs' micrographic surgery (MMS) and related variants. In hospitals where only standard histopathological procedures are available, standard excision with lateral safety margin of 3 cm is advisable. Imatinib (Glivec®) is approved in Europe for the treatment of inoperable primary tumours, locally inoperable recurrent disease, and metastatic DFSP. Imatinib has also been given to patients with extensive, difficult-to-operate tumours for preoperative reduction of tumour size, but the usefulness of this attitude should be confirmed by clinical trials. Therapeutic decisions for patients with fibrosarcomatous DFSP should be primarily made by an interdisciplinary oncology team ('tumour board').

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1. Introduction

These guidelines have been written under the auspices of the European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization for Research and Treatment of Cancer (EORTC) in order to help clinicians treating dermatofibrosarcoma protuberans (DFSP) patients in Europe, especially in countries where national guidelines are lacking.

It is hoped that these guidelines will assist health care providers in defining local policies and standards of care, and to make progress towards a European consensus on the management of DFSP. It is not intended to replace recent national guidelines accepted in their original country. The guidelines deal with aspects of the management of DFSP from diagnosis to treatment, including fibrosarcomatous transformation. Prevention issues are not addressed. The guidelines are also intended to promote the integration of care between medical and paramedical specialties for the benefit of patients.

These guidelines reflect the best published data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary or even desirable to deviate from these guidelines in the interest of specific patients or under special circumstances. Just as adherence to the guidelines may not constitute defence against a claim of negligence, deviation from them should not necessarily be deemed negligent.

2. Methods

To construct this EDF–EADO–EORTC guideline, a PubMed search with terms “dermatofibrosarcoma protuberans” without any language restriction was conducted and the results were submitted to the writing panel. We excluded case reports and studies on specific localisations. We also searched for the latest versions of existing guidelines and for systematic reviews

using pubmed (<http://www.ncbi.nlm.nih.gov/pubmed>), Google (<https://www.google.com>), and Embase (<https://www.embase.com>).

To write the text, the panel looked for differences between retrieved guidelines. The guidelines were written during a workshop session held on April 2–3 2013 where consensus was searched. The text was circulated between readers from EADO, EDF and EORTC, allowing writing a final version.

3. Results

No randomised clinical trials were found. Only two guidelines were found and their latest revisions have been published in 2012 [1] or 2013 [2]. We found only one relevant systematic review on the efficacy of MMS in the treatment of DFSP [3] and one on the management of dermatofibrosarcoma protuberans with fibrosarcomatous transformation [4]. No important differences were found between German and US guidelines.

3.1. Definition; pathophysiology; epidemiology

DFSP is a skin fibroblastic tumour that is locally aggressive, with a tendency for local recurrence, but rarely metastasizes. Diagnosis is often delayed, and patients may present with large tumours. DFSP is locally infiltrative, with asymmetrical, subclinical horizontal finger-like extensions in the skin, which may be very long, as well as infiltration of deeper structures.

Molecular studies have transformed our knowledge on DFSP pathophysiology. A chromosomal translocation is found in more than 90% of cases, and involves 17q22; 22q13, with fusion of the genes COL1A1 and PDGFB, usually with ring chromosome formation. The gene product, a COL1A1-PDGFB fusion protein, binds to the constitutively expressed PDGF receptor and acts as an autocrine factor to stimulate the growth of DFSP cells. These discoveries have allowed the development of new diagnostic tools and new treatment strategies. They also helped to consider giant cell fibroblastoma as

a variant of DFSP. The Bednar or pigmented variant (with melanin-containing cells in an otherwise typical DFSP) is another infrequent form of DFSP. Fibrosarcomatous transformation within DFSP represents a rare event, where transformed cells may conserve or not the characteristic chromosomal translocation. It is characterised by higher rate of recurrence and some cases of distant metastases. Systemic dissemination is strongly associated with previous tumour recurrence.

The few published population-based studies have shown that DFSP is a relatively rare tumour with age-adjusted rates of less than 1 per 100,000 inhabitants per year) [5,6]. Recent increase in incidence may be explained by a wider knowledge of the tumour among pathologists [6]. Because of the decline in developed countries of the incidence of HIV-associated Kaposi's sarcoma, DFSP is nowadays in some countries the most common form of skin sarcoma. Age at diagnosis is between 20 to 59 years for most patients. DFSP may occur infrequently during childhood, or as a congenital neoplasia. The rate ratio of men to women is roughly 1. Five-year relative survival rates found in recent population-based studies are high (98–100%) [5].

4. Diagnosis

DFSP is localised mainly on the trunk and is usually a very slowly growing flesh-coloured or slightly yellow–brown skin tumour without epidermal invasion but with intracutaneous and subcutaneous spread. Sometimes the tumour presents as a reddish, flat elevated, firm lesion with irregular borders or multinodular appearance. Recent and rapid modification of the lesion is suggestive of fibrosarcomatous transformation. Clinical suspicion must be confirmed by pathology before definitive surgery is performed.

The definitive diagnosis of DFSP is made by incisional or less frequently excisional, biopsy procedure. Haematoxylin and eosin-stains typically show diffuse infiltration of the dermis and the subcutaneous fat by densely packed, cytological relatively uniform, spindle-shaped, CD34-positive tumour cells, arranged in a characteristic storiform shape. Tumour cells spread along the septae of the subcutaneous fatty tissue.

Fibrosarcomatous DFSP typically appears as an abrupt or gradual transition into cell-rich spindle-cell fascicles with cytological atypia and increased mitotic figure rate. Presence or absence of areas with high mitotic rate or evidence of fibrosarcomatous changes should be noted in all pathology reports on DFSP.

Pathologically, the principal and important differential diagnoses of DFSP are benign atypical variants of dermatofibroma, such as plaque-like CD34 positive dermal fibroma and dermatomyofibroma, and more severe diseases, such as pleomorphic sarcoma of the skin without further differentiation (previously known as “MFH”), leiomyosarcoma, *Malignant Peripheral Nerve*

Sheath Tumours (MPNST), and rare variants of spindle-cell malignant melanoma. Therefore, appropriate and confirmatory immunostainings (CD34, factor XIIIa, stromelysin-3) are recommended in all cases of suspected DFSP. Analysis of formalin-fixed, paraffin-embedded tumour samples by fluorescence in situ hybridisation (FISH) or multiplex reverse transcriptase-polymerase chain reaction (RT-PCR) to detect chromosomal translocations and fusion gene transcripts is a useful tool to confirm a difficult DFSP diagnosis [7]. When the clinician's suspicion for DFSP is high but the initial biopsy does not support the diagnosis, rebiopsy is recommended.

5. Initial workup

As distant metastases are extremely rare, an extensive workup is not routinely indicated except for patients with suspicion of metastasis on clinical examination, for patients with recurrent disease, and for DFSP with fibrosarcomatous transformation features. Diagnosis of metastatic disease requires lymph node ultrasound, chest radiograph, and abdominal ultrasound or CT scans. Ultrasound and magnetic resonance imaging techniques provide generally only limited information on real tissue infiltration, but may be helpful preoperatively in certain situations.

5.1. 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 most recently published studies. Lymph node and distant metastases are very rare in recent series. There is no standard staging system for DFSP. In general, the primary tumour is considered stage I, lymph node metastasis is stage II and distant metastasis stage III.

6. Therapy

6.1. Surgical treatment

Treatment of DFSP is mainly surgical. Because of frequent deep and lateral subclinical extensions, the aim is to completely remove DFSP at initial therapy. If initial surgery yields invaded margins, re-resection(s) is recommended whenever possible, until achieving clear margins. Complete assessment of all surgical margins before definitive reconstruction is recommended. Surgery of DFSP must be meticulously planned, with size, type of margin control, location of the tumour and cosmetic issues influencing the most appropriate surgical procedure.

Whatever variations of surgical techniques used, the excision of the deep fascia to remove any infiltrating

tumour cells seems important. Regarding lateral safety excision margins, 1–1.3 cm seems sufficient with micrographic techniques allowing pathological tridimensional control of all margins, preferably using delayed histological (3D histology with a paraffin section method, slow Mohs, Breuninger technique). In a recent systematic analysis, moderate-quality evidence (level B) was found for lower recurrence of DFSP after such techniques (1.11%; 95% CI, 0.02–6.03%) versus after wide local excision (6.32%, 95% CI and 3.19–11.02%) in four comparative non-randomised trials. A mean raw recurrence rate of 1.03% (95% CI, 0.37%–2.22%) was found after these techniques among 19 nonrandomised no comparative trials (low-quality evidence [level C]). Thus, a 2A weak recommendation was given in favour of MMS or similar surgical techniques with meticulous histologic evaluation of all peripheral and deep margins as the first-line therapy for DFSP, particularly in recurrence-prone regions. Therefore, the treatment of choice of DFSP seems to be the Mohs' micrographic surgery (MMS) and related variants.

This procedure is however not widely diffused, and standard histopathological procedures are used in many places. As these surgical techniques with standard histopathological procedures carry an increased rate of recurrence, a larger lateral safety margin of 3 cm is advisable. Whatever the histopathological technique used, immunohistochemical staining with CD34 is useful to evaluate the tumour margins of the excised material.

6.2. Other treatment techniques

Targeted molecular therapy of DFSP aims at interrupting the autocrine PDGF-regulated growth stimulus. The PDGF receptor-selective oral tyrosine kinase-inhibitor imatinib (Glivec[®]) is approved in Europe for the treatment of inoperable primary tumours, locally inoperable recurrent disease, and metastatic DFSP, with response in about 50% of treated patients. Imatinib has also been given to patients with extensive, difficult-to-operate tumours for preoperative reduction of tumour size [8,9], of whom fewer than half responded to treatment. This neo-adjuvant use of imatinib in DFSP should be confirmed by clinical trials before being widely accepted. Tolerance, costs and duration of treatment are important issues. Even with a long-term response to therapy, surgical removal of the remaining tumour components after imatinib treatment is recommended for histological confirmation of treatment success and to avoid recurrences. However, cytological changes induced by imatinib may alter the quality of histological margin control. Both primary and secondary resistances to imatinib have been reported. Moderate dosages of 400–600 mg/daily appear to be as equally effective as higher dosages (800 mg/daily) and are better tolerated.

There are no indications for radiotherapy for completely excised (R0) non-transformed tumours. Radiation treatment is an option for primary inoperable tumours, R1 or R2 resections, and prior multiple recurrences. The target volume includes the primary tumour volume, postoperative scarring, with a safety margin of 3–5 cm. An individual dose of 2 Gy, 5× per week, and a total dose of 60 Gy (microscopic tumour) to 70 Gy (macroscopic tumour) may be given in treatment with a curative intent.

There are no known effective chemotherapy regimens.

6.3. Fibrosarcomatous transformation

In case of fibrosarcomatous transformation, advice of a multidisciplinary specialised soft-tissue sarcoma tumour board is recommended. The main treatment objective remains complete surgical excision with 3D techniques or wide excision with margins of 3 cm, which prevented in a systematic review both local recurrence and metastasis [4]. When R0-resection is not feasible, adjuvant radiation should be considered. Non-resectable or metastatic transformed DFSP harbouring the COL1A1-PDGFB fusion gene should be treated with imatinib in the palliative setting or as an adjunctive treatment before surgery, although responses may be short-lasting. FISH or multiplex RT-PCR to detect chromosomal translocations and fusion gene transcripts should be performed before imatinib treatment.

6.4. Follow-up

There is no information on follow-up examinations in the literature at present. Follow-up examinations primarily target the early detection of local recurrences. Clinical examinations every six months for five years are advised, thereafter in yearly intervals because of infrequent late events until the end of the tenth year after surgery. In the recent systematic review of MMS in DFSP [3], the mean time to recurrence was 68 months. Imaging examinations are generally not required during follow-up, except for recurrent DFSP and DFSP with fibrosarcomatous transformation.

7. Summary

The present EDF–EADO–EORTC guidelines represent a European consensus-based interdisciplinary set of recommendations (S2 level) addressing all aspects of management of DFSP, from the diagnosis of primary tumour to the systemic treatment of fibrosarcomatous transformation of DFSP. The recommendations are based on current standards of care, existing guidelines and expert panel opinion. A summary of these guidelines is provided in Table 1.

Table 1

Summary of management recommendations DFSP by EDF–EADO–EORTC Expert panel.

Diagnostic and staging recommendations:

- The diagnosis of DFSP is frequently delayed and suspected on clinical features (very slowly growing flesh-coloured or slightly yellow–brown skin lesion without epidermal invasion but with intracutaneous and subcutaneous spread).
- Recent and rapid modification of the lesion is suggestive of fibrosarcomatous transformation.
- A biopsy or excision and histologic confirmation should be performed in all clinically suspicious lesions.
- Confirmatory immunostainings are recommended in all cases because of various differential diagnoses. Analysis of formalin-fixed, paraffin-embedded tumour samples by fluorescence in situ hybridisation (FISH) or multiplex reverse transcriptase-polymerase chain reaction (RT-PCR) to detect chromosomal translocations and fusion gene transcripts is a useful tool to confirm a difficult DFSP diagnosis.
- A chromosomal translocation is found in more than 90% of cases, and involves 17q22; 22q13, with fusion of the genes COL1A1 and PDGFB, usually with ring chromosomes formation. The gene product, a COL1A1–PDGFB fusion protein, binds to the constitutively expressed PDGF receptor and acts as an autocrine factor to stimulate growth of DFSP cells.
- The diagnosis of DFSP should prompt a complete examination of the entire skin and palpation of the regional lymph nodes for nodal involvement.
- As distant metastases are extremely rare, an extensive workup is not routinely indicated except for patients with suspicion of metastasis on clinical examination, for patients with recurrent disease, and for DFSP with fibrosarcomatous transformation features. Diagnosis of metastatic disease requires lymph node ultrasound, chest radiograph, and abdominal ultrasound or CT scans. Ultrasound and magnetic resonance imaging techniques provide generally only limited information on real tissue infiltration, but may be helpful preoperatively in certain situations.
- There is no standard staging system for DFSP.

Treatment recommendations:

- Treatment is mainly surgical, with the aim to achieve complete resection of the tumour. Complete assessment of all surgical margins before definitive reconstruction is necessary. Surgery of DFSP must be meticulously planned, with size, type of margin control, location of the tumour and cosmetic issues influencing the most appropriate surgical procedure.
- Whatever variations of surgical techniques used, the excision of the deep fascia to remove any infiltrating tumour cells seems important.
- In order to reduce the recurrence rate, the treatment of choice of DFSP seems to be Mohs' micrographic surgery (MMS) and related variants, with 1 to 1.3 cm lateral safety margins.
- In hospitals where only standard histopathological procedures are available, standard excision with lateral safety margin of 3 cm is advisable.
- Imatinib (Glivec®) is approved in Europe for the treatment of inoperable primary tumours, locally inoperable recurrent disease, and metastatic DFSP. Imatinib has also been given to patients with extensive, difficult-to-operate tumours for preoperative reduction of tumour size, but the usefulness of this attitude should be confirmed by clinical trials.
- Therapeutic decisions for patients with fibrosarcomatous DFSP should be primarily made by an interdisciplinary oncology team ('tumour board').

8. Validity period

These guidelines are planned to be updated at least every three years.

Finalised: June 2015, Next update planned: June 2018.

Conflict of interest statement

None declared.

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