European Dermatology Forum

Guideline on the diagnosis and treatment of dermatofibrosarcoma protuberans

Developed by the Guideline Subcommittee of the
European Dermatology Forum

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2	Consulting fee or honorarium	no	no	no	no
3	Support for travel to meetings for the study or other purposes	no	no	no	no
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no	no	no	no
5	Payment for writing or reviewing the manuscript	no	no	no	no
6	Provision of writing assistance, medicines, equipment, or administrative support	no	no	no	no
7	Other	no	no	no	no

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Relevant financial activities outside the submitted work					
1	Board membership	no	no	no	no
2	Consultancy	Yes	Yes	Yes	Yes
3	Employment	no	no	no	no
4	Expert testimony	no	no	no	no
5	Grants/grants pending	no	no	no	no
6	Payment for lectures including service on speakers bureaus	no	no	no	no
7	Payment for manuscript preparation	no	no	no	no
8	Patents (planned, pending or issued)	no	no	no	no
9	Royalties	no	no	no	no
10	Payment for development of educational presentations	no	no	no	no
11	Stock/stock options	no	no	no	no
12	Travel/accommodations/meeting expenses unrelated to activities listed**	Yes	Yes	Yes	Yes
13	Other (err on the side of full disclosure)	no	no	no	no

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Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	no	no	no	no

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2	Consulting fee or honorarium	no			
3	Support for travel to meetings for the study or other purposes	no			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no			
5	Payment for writing or reviewing the manuscript	no			
6	Provision of writing assistance, medicines, equipment, or administrative support	no			
7	Other	no			

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Relevant financial activities outside the submitted work					
1	Board membership	Amgen	BMS, GSK	MSD; Novartis	Roche
2	Consultancy	Amgen	BMS, GSK	MSD, Novartis	Roche
3	Employment	no			
4	Expert testimony	no			
5	Grants/grants pending	BMS	GSK	Roche	
6	Payment for lectures including service on speakers bureaus	Amgen	BMS, GSK	MSD, Novartis	Roche
7	Payment for manuscript preparation	no			
8	Patents (planned, pending or issued)	no			
9	Royalties	no			
10	Payment for development of educational presentations	no			
11	Stock/stock options	no			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	BMS	Roche		
13	Other (err on the side of full disclosure)	no			

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Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	no			

Conflicts of interests Jean Jacques Grob

The Work Under Consideration for Publication					
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2	Consulting fee or honorarium	0			
3	Support for travel to meetings for the study or other purposes	0			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	0			
5	Payment for writing or reviewing the manuscript	0			
6	Provision of writing assistance, medicines, equipment, or administrative support	0			
7	Other				

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Relevant financial activities outside the submitted work					
1	Board membership	Meda, Leo, galderma, almirall	*Unrelated to SCC* GSK, Roche, BMS, Merck, celgene,		
2	Consultancy	0			
3	Employment	0			
4	Expert testimony	0			
5	Grants/grants pending	0			
6	Payment for lectures including service on speakers bureaus	0			
7	Payment for manuscript preparation	0			
8	Patents (planned, pending or issued)	0			
9	Royalties	0			
10	Payment for development of educational presentations	Linked to SCC/KA Almirall	*Unrelated to SCC* GSK, Roche, BMS		
11	Stock/stock options	0			
12	Travel/accommodations/meeting expenses unrelated	0	*Unrelated to SCC* GSK, Roche,		

	to activities listed**				
13	Other (err on the side of full disclosure)	Institutional funding from approx.. 20 pharma companies (fee for service for commercial clinical trials)			

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Other relationships					
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Conflicts of interests Celeste Lebbe

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3	Support for travel to meetings for the study or other purposes				
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5	Payment for writing or reviewing the manuscript				
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Relevant financial activities outside the submitted work					
1	Board membership	BMS	MSD	ROCHE	Novartis, GSK Amgen
2	Consultancy			Roche	GSK
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6	Payment for lectures including service on speakers bureaus				
7	Payment for manuscript preparation				
8	Patents (planned, pending or issued)				
9	Royalties				
10	Payment for development of educational presentations				
11	Stock/stock options				
12	Travel/accommodations/meeting expenses unrelated to activities listed**			Support to go to the ASCO and ESMO meeting in 2014	
13	Other (err on the side of full				

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Conflicts of interests –JOSEP MALVEHY

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2	Consulting fee or honorarium	no			
3	Support for travel to meetings for the study or other purposes	no			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no			
5	Payment for writing or reviewing the manuscript	no			
6	Provision of writing assistance, medicines, equipment, or administrative support	no			
7	Other	no			

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Relevant financial activities outside the submitted work					
1	Board membership	LEO	ALMIRALL	MEDA	
2	Consultancy	LEO	ALMIRALL	MEDA	
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4	Expert testimony	no			
5	Grants/grants pending	no			
6	Payment for lectures including service on speakers bureaus	ALMIRALL	MEDA	ISDIN	
7	Payment for manuscript preparation	no			
8	Patents (planned, pending or issued)	no			
9	Royalties	no			
10	Payment for development of educational presentations	LEO	ALMIRALL	ISDIN	
11	Stock/stock options	no			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	LEO	ALMIRALL	MEDA	
13	Other (err on the side of full disclosure)	no			

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Other relationships					
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Conflicts of interests -- Véronique DEL MARMOL

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2	Consulting fee or honorarium	NO			
3	Support for travel to meetings for the study or other purposes	NO			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	NO			
5	Payment for writing or reviewing the manuscript	NO			
6	Provision of writing assistance, medicines, equipment, or administrative support	NO			
7	Other	NO			

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Relevant financial activities outside the submitted work					
1	Board membership	LEO	MEDA	ROCHE	ABBVIE
2	Consultancy				
3	Employment	NO			
4	Expert testimony	NO			
5	Grants/grants pending	NO			
6	Payment for lectures including service on speakers bureaus	NO	NO	NO	ABBVIE
7	Payment for manuscript preparation	NO			
8	Patents (planned, pending or issued)	NO			
9	Royalties	NO			
10	Payment for development of educational presentations	NO			
11	Stock/stock options	NO			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	NO			
13	Other (err on the side of full disclosure)	NO			

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Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	NO			

Conflicts of interests

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2	Consulting fee or honorarium	No			
3	Support for travel to meetings for the study or other purposes	No			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	No			
5	Payment for writing or reviewing the manuscript	No			
6	Provision of writing assistance, medicines, equipment, or administrative support	No			
7	Other	No			

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Relevant financial activities outside the submitted work					
1	Board membership				
2	Consultancy	Millenium, Amgen, Roche, Merck, GSK, AZ, BMS			
3	Employment	No			
4	Expert testimony	No			
5	Grants/grants pending	No			
6	Payment for lectures including service on speakers bureaus	No			
7	Payment for manuscript preparation	No			
8	Patents (planned, pending or issued)	No			
9	Royalties	No			
10	Payment for development of educational presentations	BMS			
11	Stock/stock options	No			
12	Travel/accommodations/meeting expenses unrelated	BMS, Merck			

	to activities listed**				
13	Other (err on the side of full disclosure)	Institutional funding from approx.. 20 pharma companies (fee for service for commercial clinical trials)			

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Other relationships					
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Conflicts of interests Hubert Pehamberger

The Work Under Consideration for Publication					
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3	Support for travel to meetings for the study or other purposes	No			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	No			
5	Payment for writing or reviewing the manuscript	No			
6	Provision of writing assistance, medicines, equipment, or administrative support	No			
7	Other	No			

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Relevant financial activities outside the submitted work					
1	Board membership	LEO	Almirall	Roche	BMS
2	Consultancy	LEO	Almirall	Roche	BMS
3	Employment	No			
4	Expert testimony	No			
5	Grants/grants pending	No			
6	Payment for lectures including service on speakers bureaus	No			
7	Payment for manuscript preparation	No			
8	Patents (planned, pending or issued)	No			
9	Royalties	No			
10	Payment for development of educational presentations	No			
11	Stock/stock options	No			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	BMS	LEO	Roche	
13	Other (err on the side of full disclosure)	No			

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Other relationships					
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Conflicts of interests – Ketty Peris

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1	Grant	no			
2	Consulting fee or honorarium	no			
3	Support for travel to meetings for the study or other purposes	no			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no			
5	Payment for writing or reviewing the manuscript	no			
6	Provision of writing assistance, medicines, equipment, or administrative support	no			
7	Other	no			

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Relevant financial activities outside the submitted work					
1	Board membership	LEO	Meda	Roche	Novartis
2	Consultancy	LEO	Meda	Roche	
3	Employment	no			
4	Expert testimony	no			
5	Grants/grants pending	no			
6	Payment for lectures including service on speakers bureaus	LEO	Meda	Roche	
7	Payment for manuscript preparation	no			
8	Patents (planned, pending or issued)	no			
9	Royalties	no			
10	Payment for development of educational presentations	no			
11	Stock/stock options	no			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	LEO	Meda	Roche	Abbvie
13	Other (err on the side of full disclosure)	no			

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Conflicts of interests Philippe Saiag

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1	Grant	0			
2	Consulting fee or honorarium	0			
3	Support for travel to meetings for the study or other purposes	MSD			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	0			
5	Payment for writing or reviewing the manuscript	0			
6	Provision of writing assistance, medicines, equipment, or administrative support	0			
7	Other	0			

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Relevant financial activities outside the submitted work					
1	Board membership	Roche-Genentec	GSK	Novartis	BMS, Merck
2	Consultancy	GSK			
3	Employment	0			
4	Expert testimony	0			
5	Grants/grants pending	Roche			
6	Payment for lectures including service on speakers bureaus	GSK	Roche		
7	Payment for manuscript preparation	GSK			
8	Patents (planned, pending or issued)	0			
9	Royalties	0			
10	Payment for development of educational presentations	0			
11	Stock/stock options	0			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	Roche-Genentec	GSK	Novartis	BMS, Merck
13	Other (err on the side of full	0			

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Conflicts of interests – Alexander J. Stratigos

The Work Under Consideration for Publication					
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1	Grant	no			
2	Consulting fee or honorarium	no			
3	Support for travel to meetings for the study or other purposes	no			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no			
5	Payment for writing or reviewing the manuscript	no			
6	Provision of writing assistance, medicines, equipment, or administrative support	no			
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Relevant financial activities outside the submitted work					
1	Board membership	LEO			
2	Consultancy	novartis	roche	LEO	MEDA
3	Employment	no			
4	Expert testimony	no			
5	Grants/grants pending	Jannsen-Cilag			
6	Payment for lectures including service on speakers bureaus	MSD	Pfizer	LEO	Roche
7	Payment for manuscript preparation	no			
8	Patents (planned, pending or issued)	no			
9	Royalties	MacGraw Hill (Pediatric dermatology atlas)			
10	Payment for development of educational presentations	no			
11	Stock/stock options	no			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	LEO	Jannsen-Cilag	Abbvie	

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Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	no			

Conflicts of interests Alessandro Testori

The Work Under Consideration for Publication					
		Name	**Name**	**Name**	**Name**
1	Grant	NO			
2	Consulting fee or honorarium	NO			
3	Support for travel to meetings for the study or other purposes	NO			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	NO			
5	Payment for writing or reviewing the manuscript	NO			
6	Provision of writing assistance, medicines, equipment, or administrative support	NO			
7	Other				

* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	GSK	BMS	AMGEN	ROCHE
2	Consultancy	NO			
3	Employment	NO			
4	Expert testimony	NO			
5	Grants/grants pending	NO			
6	Payment for lectures including service on speakers bureaus	NO			
7	Payment for manuscript preparation	NO			
8	Patents (planned, pending or issued)	NO			
9	Royalties	NO			
10	Payment for development of educational presentations	NO			
11	Stock/stock options	NO			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	NO			
13	Other (err on the side of full disclosure)	NO			

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Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	NO			

Diagnosis and Treatment of Dermatofibrosarcoma Protuberans. European Consensus-based Interdisciplinary Guideline

On behalf of the European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization for Research and Treatment of Cancer (EORTC)

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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 hybridization (FISH) or multiplex reverse transcriptase-polymerase chain reaction (RT-PCR) to detect specific chromosomal translocations and fusion gene transcripts is useful 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').

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 this guidelines will assist health care providers in defining local policies and standards of care, and to make progress towards an 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.

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 localizations. We also searched for the latest versions of existing guidelines and for systematic re-

views 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 guideline was written during a workshop session held on April 2-3 2013 where consensus was searched. The text was circulated between readers from EADO, EDF, EORTC, allowing writing a final version.

RESULTS

No randomized 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.

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 PDGFß, usually with ring chromosomes formation. The gene product, a COL1A1-PDGFß fusion protein, binds to the constitutively expressed PDGF receptor and acts as an autocrine factor to stimulate 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 characterized 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 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).

DIAGNOSIS

DFSP is localized 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. Hematoxylin 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 hybridization (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.

INITIAL WORKOUT

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.

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.

THERAPY

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 to 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, Breuniger 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 4 comparative non-randomized trials. A mean raw recurrence rate of 1.03% (95% CI, 0.37%-2.22%) was found after these techniques among 19 nonrandomized 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 histolopathological technique used, immunohistochemical staining with CD34 are useful to evaluate the tumour margins of the excised material.

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 to 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 x 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.

Fibrosarcomatous transformation

In case of fibrosarcomatous transformation, advice of a multidisciplinary specialized 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. Fluorescence in situ hybridization (FISH) or multiplex reverse transcriptase-polymerase chain reaction (RT-PCR) to detect chromosomal translocations and fusion gene transcripts should be performed before imatinib treatment.

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 a recent systematic review of MMS in DFSP, 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.

Disclosure of Potential Conflicts of Interests

Dr. Bastholt reports personal fees from Astra-Zeneca, personal fees from Bristol Myers Squibb, personal fees from Roche, personal fees from Merck, outside the submitted work; Dr. Garbe reports personal fees from Amgen, grants and personal fees from Bristol Myers Squibb, grants and personal fees from Glaxo Smith Kline, personal fees from Merck, personal fees from Novartis, grants and personal fees from Roche, outside the submitted work; Dr. Grob reports personal fees from Meda, personal fees from LEO, personal fees from Galderma, personal fees from Almirall, personal fees from Roche,outside the submitted work; .Dr. Lebbé reports personal fees from Bristol Myers Squibb, personal fees from Merck, personal fees from Roche, personal fees from Novartis, personal fees from Glaxo Smith Kline, personal fees from Amgen, outside the submitted work; .Dr. Malvehy reports personal fees from LEO, personal fees from Almirall, personal fees from MEDA, personal fees from ISDIN, outside the submitted work; Dr. del Marmol reports personal fees from LEO, personal fees from Roche, personal fees from MEDA, personal fees from AbbVie, outside the submitted work; Dr. Middleton reports personal fees from Millenium, personal fees from Amgen, personal fees from Roche, personal fees from Merck, personal fees from Glaxo Smith Kline, personal fees from Bristol Myers Squibb, outside the submitted work; Dr. Pehamberger reports personal fees from LEO, personal fees from Almirall, personal fees from Roche, personal fees from Bristol Myers Squibb, outside the submitted work; Dr. Peris reports personal fees from LEO, personal fees from MEDA, personal fees from Roche, personal fees from Novartis, personal fees from AbbVie, outside the submitted work; .Dr. Saiag reports personal fees from Merck, during the conduct of the study; personal fees from Bristol Myers Squibb, personal fees from Glaxo Smith Kline, personal fees from Merck, personal fees from Novartis, grants and personal fees from Roche, outside the submitted work; Dr. Stratigos reports personal fees from LEO, personal fees from Novartis, personal fees from Roche, personal fees from MEDA, grants from Jannsen-Cilag, personal fees from Pfizer, personal fees from AbbVie, outside the submitted work; Dr.Tesstori declared that he has no conflict of interests.

REFERENCES

1. Miller SJ, Alam M, Andersen JS, Berg D, Bichakjian CK, Bowen GM, Cheney RT, Glass LF, Grekin RC, Ho AL, Kessinger A, Liegeois N, Lydiatt DD, Michalski J, Morrison WH, Nehal KS, Nelson KC, Nghiem P, Olencki T, Perlis CS, Shaha AR, Tuli M, Urist MM, Wang LC, Zic JA. Dermatofibrosarcoma protuberans. J Natl Compr Canc Netw. 2012 Mar;10(3):312-8.

2. Ugurel S, Kortmann RD, Mohr P, Mentzel T, Garbe C, Breuninger H. Short German guidelines: dermatofibrosarcoma protuberans. J Dtsch Dermatol Ges. 2013;in press.

3. Foroozan M, Sei JF, Amini M, Beauchet A, Saiag P. Efficacy of Mohs micrographic surgery for the treatment of dermatofibrosarcoma protuberans: systematic review. Arch Dermatol. 2012 Sep 1;148(9):1055-63.

4. Voth H, Landsberg J, Hinz T, Wenzel J, Bieber T, Reinhard G, Holler T, Wendtner CM, Schmid-Wendtner MH. Management of dermatofibrosarcoma protuberans with fibrosarcomatous transformation: an evidence-based review of the literature. J Eur Acad Dermatol Venereol.. 2011 Dec;25(12):1385-91.

5. Rouhani P, Fletcher CD, Devesa SS, Toro JR. Cutaneous soft tissue sarcoma incidence patterns in the U.S. : an analysis of 12,114 cases. Cancer. 2008 Aug 1;113(3):616-27.

6. Kuzel P, Metelitsa AI, Dover DC, Salopek TG. Epidemiology of dermatofibrosarcoma protuberans in Alberta, Canada, from 1988 to 2007. Dermatol Surg. 2012 Sep;38(9):1461-8.

7. Walluks K, Chen Y, Woelfel C, Yang L, Cui T, Seliger C, Geier C, Knosel T, Hauke S, Petersen I. Molecular and clinicopathological analysis of dermatofibrosarcoma protuberans. Pathol Res Pract.. 2013 Jan 15;209(1):30-5.

8. Kerob D, Porcher R, Verola O, Dalle S, Maubec E, Aubin F, D'Incan M, Bodokh I, Boulinguez S, Madelaine-Chambrin I, Mathieu-Boue A, Servant JM, de Kerviler E, Janin A, Calvo F, Pedeutour F, Lebbe C. Imatinib mesylate as a preoperative therapy in dermatofibrosarcoma: results of a multicenter phase II study on 25 patients. Clin Cancer Res. 2010 Jun 15;16(12):3288-95.

9. Rutkowski P, Debiec-Rychter M, Nowecki Z, Michej W, Symonides M, Ptaszynski K, Ruka W. Treatment of advanced dermatofibrosarcoma protuberans with imatinib mesylate with or without surgical resection. J Eur Acad Dermatol Venereol. 2011 Mar;25(3):264-70.