Curr. Treat. Options in Oncol. (2017) 18: 56
DOI 10.1007/s11864-017-0498-5

Skin Cancer (SZ Aasi, Section Editor)

Dermatofibrosarcoma Protuberans

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Published online: 10 August 2017

This article is part of the Topical Collection on *Skin Cancer*

Keywords Dermatofibrosarcoma protuberans · Mohs micrographic surgery · Imatinib mesylate · Radiotherapy · Pathology · Surgery

Opinion statement

Dermatofibrosarcoma protuberans (DFSP) is a slow growing tumor with a very low metastatic potential but with significant subclinical extension and great capacity for local destruction. Thus, the first surgeon approached with such challenging tumor must attempt to cure the patient with a method that spares healthy tissue and ensures an optimal oncological, functional, and esthetic result. The treatment of DFSP often requires a multidisciplinary approach. Depending on location, dermatologic surgeons, surgical oncologists, head and neck surgeons, neurosurgeons, plastic surgeons, and occasionally medical oncologists may be involved with the management. Mohs micrographic surgery (MMS) is the preferred method when available. In our institution, most of the DFSP cases are often advanced cases; thus, dermatologic surgeons obtain clear margins peripherally and other surgical specialties assist with resection of the fascia and any critical deeper structures. When MMS is not available, wide local excision (at least 2- to 3-cm margins of resection) with exhaustive pathologic assessment of margin status is recommended, and it is best to confirm tumor extirpation prior to any reconstruction. Subclinical extension of the tumor could be related to the size; how long it has been growing or histological markers that are unknown right now. No clinical trials comparing MMS vs WLE are available, and further research should be focused on these subjects as well as the use of imatinib and other targeted therapies for recurrent and metastatic tumors and for neoadjuvant treatment.

Introduction

Dermatofibrosarcoma protuberans (DFSP) is a rare tumor with a high potential for local invasion and recurrence. It is almost invariably associated with a chromosomal translocation that ultimately drives oncogenesis by mitogen activation. Molecular methods for a precise diagnosis in equivocal cases are discussed as well as ongoing research on physiopathology. Recent articles describe the use of dermoscopy and confocal microscopy. Once patients have a confirmed histological diagnosis, contrast MRI is the imaging modality of choice to better characterize its extension; imaging should be considered in recurrent and large tumors or cases with a fibrosarcomatous change. There is no standard staging system for DFSP but multiple ones being used will be reviewed. Surgery is the treatment of choice. Due to its potential to recur, its eccentric tentacle-like projections, meticulous histopathological assessment of the margins is critical. MMS is the preferred option but conventional surgery with en face pathological margin assessment, when MMS is not available, may be an alternative. No randomized clinical trials have been performed to compare surgical treatment options; there are only few comparative nonrandomized case series and selected reviews in the literature. Radiation is used mainly in cases of unresectable DFSP or cases where negative margins cannot be obtained. Imatinib has also been used in unresectable cases.

History, epidemiology, genetics, and physiopathology

DFSP is a rare neoplasm of intermediate malignancy. Taylor first described it in 1890 but Darier was credited with establishing DFSP as a distinct clinicopathological entity in 1924, and finally, Hoffman established the term in 1925 [1–4].

Overall annual incidence has been estimated to be 4.2 per million, and the tumor accounts for approximately 0.1% of all malignancies. The incidence is almost double among blacks compared to whites and women have a higher incidence rate than men [5••]; the highest age-specific annual incidence rates are observed between the ages of 30 and 50 years. Most occur on the trunk (42%), followed by the upper extremities (23%), lower extremities (18%), and head and neck (16%) [6•]. Infrequently, it may affect the genitalia [7, 8]. DFSP in children has been reported to represent around 8% of cases with a male to female ratio of 0.86, 15% of them being congenital. The distribution is similar to that in adults [9].

Approximately 10% of DFSP report prior trauma, surgical or burn scars, and even immunizations at the site of disease but a causative relationship is unclear [4].

DFSP is characterized by translocation of t(17;22)(q22;q13) either in the form of supernumerary ring chromosomes or unbalanced linear translocation der [10]. Both ring chromosomes or linear der [10] contain a fusion of collagen type I alpha 1 (COL1A1) and platelet-derived growth factor subunit B (PDGFB) [11]. It is believed that the translocation is an early event and transfection with the chimeric sequence can transform normal cells into neoplastic ones [12]. The gene fusion places PDGFB under the control of the COL1A1 promoter [11]. PDGFB is a potent mitogen for mesenchymal cells; when constantly expressed, it activates PDGFB receptor leading to its autocrine activation and tumor development [13•].

Other oncogenic mechanisms have been described, but little is currently understood about COL1A1-PDGFB negative DFSP which represents around 8% of cases [13•]. A novel COL1A2-PDGFB fusion gene has also been described [14]. Recently, hormone receptor expression in DFSP was determined, looking for a potential role for antihormone therapies in the treatment of patients with DFSP. Loss of receptor expression was observed in all recurrent tumors warranting further

study [15]. Cyclin-dependent kinase inhibitor 2A (CDKN2A)/p16 loss has been implicated in imatinib-resistant DFSP and inhibition of cyclin dependent kinase 4 (CDK4) could be a potential therapeutic target for this type of tumor [16].

Understanding the molecular events of DFSP tumorigenesis led PDGFB receptor to become the therapeutic target. [17] Imatinib mesylate is a tyrosine kinase inhibitor which inhibits PDGFRA/B and is currently used for unresectable, recurrent, or metastatic DFSP [13•, 18].

Clinical assessment and histology

DFSP presents as an asymptomatic slowly growing violaceous nodule or plaque. On dermoscopy, multiple structures have been described including delicate pigmented network (87%), vessels (80%), structureless light brown areas (73%), white streaks (67%), pink background (67%), and structureless hypo- or depigmented areas (60%) [19, 20].

On confocal microscopy, loss of normal "edge papillae" with elongated bright cells corresponding to tumor cells has been described [21]. However, the role of dermoscopy and confocal microscopy for diagnosis of DFSP has not been established.

Clinical differential diagnosis includes neurofibroma, leiomyoma, malignant melanoma, morpheaform basal cell carcinoma, keloid, desmoid tumors, Kaposi sarcoma, fibrosarcoma, dermatofibroma, nodular fasciitis, and sarcoidosis [22•].

Incisional or excisional biopsy should be performed upon a suspicious lesion [4]. DFSP is a cellular neoplasm composed of storiform spindle cells with elongated nuclei, minimal cytological atypia, and a low mitotic count within a collagenous stroma. Tumor cells often spread along the septae of the subcutaneous fatty tissue (known as fat-trapping) [10]. Histologically, the differential diagnosis are other fibrous tumors like dermatofibroma, fibrosarcoma, pleomorphic sarcoma of the skin, leiomyosarcoma, malignant peripheral nerve sheath tumors, rare variants of spindle cell malignant melanoma, atypical fibroxanthoma, and nodular fasciitis [22•, 23••]. On immunohistochemistry, DFSP shows strong and diffuse expression of CD34; it is also positive for vimentin, nestin, and apolipoprotein D and is negative for cytokeratins, smooth muscle actin (SMA), S100, CD56 Factor XIIIa, Stromelysin 3, and Cathepsin K [4]. Histological subtypes include myxoid, pigmented or Bednar tumor, atrophic, sclerosing, granular cell, giant cell fibroblastoma, and tumors that have undergone fibrosarcomatous transformation (DFSP-FS) [4, 10].

Histologic characteristics associated with fascia invasion are the presence of a sheet-like pattern, a high degree of cellular pleomorphism, and more than one mitotic figure [24]. DFSP-FS is the most aggressive and is associated with the highest risk of local recurrence, distant metastasis, and even death [25••].

In difficult cases, to confirm DFSP fluorescence, in situ hybridization or multiplex reverse transcriptase polymerase chain reaction to detect translocation and gene fusion may be useful [23••, 26, 27, 28•].

Work up, imaging, staging, and prognosis

Although small lesions may be treated without obtaining imaging studies, imaging may provide a better understanding of the extension of disease and

more precise surgical planning in larger lesions [4]. An extensive workup is not routinely recommended since metastases are extremely rare [29]. It is recommended for patients with a clinical examination that is suspicious for metastases, recurrent disease, or DFSP-FS. Chest Xray and abdominal and lymph node ultrasound are recommended [23••]. Since DFSP-FS has a 14.5% risk of metastasis, usually to the lungs, routine CT or MRI may be warranted [25••, 30•].

On CT/MRI scans, DFSP presents as a noncalcified, superficial, nodular mass arising from the skin, which is isodense to muscles on CT and on MRI shows a T2 high and T1 low signal [31, 32]. It shows intermediate to marked enhancement on contrast CT/MRI [32]. A "claw" sign has been described at the lesion/skin interface that is evidenced in various imaging modalities [33]. MRI is the study of choice for the preoperative setting as well as postoperative surveillance [4]. 18F-FDG PET/CT has been used to predict aggressive behavior and response to imatinib in metastatic DFSP [34].

Although there is no standard staging system for DFSP, the European consensus interdisciplinary guidelines, a unique collaboration of multidisciplinary 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) consider the primary tumor stage I, lymph node metastasis stage II, and distant metastasis stage III [23••]. Some authors recommend staging according to the American Joint Commission on Cancer for sarcomas which classifies the tumor as T1 if the largest dimension is of 5 cm or less and T2 if the largest dimension is more than 5 cm; N0 if there is no nodal metastases and N1 with nodal metastases; histologic grade as G1 if it is low grade or well differentiated, G2 intermediate grade (moderately well differentiated), and G3 high grade (undifferentiated); and M0 if there is no distant metastasis, M1 if there is presence of distant metastasis. Most DFSP are stage I (Any T, N0M0G1). Stage II is defined as T1N0M0, G2 or G3, or T2N0M0G2; stage III T2N0M0G3 or any T, N1M0; and stage IV any T, any N, M1 [35, 36]. Other reports limit DFSP staging data to LRD staging system: localized, regional, or distant [5••].

The relative 5, 10, and 15-year survivals have been reported to be 99.2, 99.1, and 97.2% [5••, 6•]. Higher all-cause mortality was associated with increased age, male sex, tumor size, black race, and anatomic location of the limbs and head compared to the trunk [5••, 37••].

Fibrosarcomatous (FS) change has been reported in 3–20% of cases. When analyzing outcome by the presence or absence of FS change, the risk of local recurrence, metastasis, and death is higher in this group. The risk of local recurrence was 29.8% for the DFSP-FS group vs. 13.7% for DFSP; the risk for metastasis was 14.4 vs. 1.1% and death from disease was 14.7 vs. 0.8% [25••]. The outcomes were not statistically different depending on the proportion of FS change within the tumors [25••]. One year and 5-year recurrence-free survival for DFSP was 94 and 86% while for DFSP-FS it was 86 and 42%, respectively [38••].

Risk factors for recurrence include FS change, less than 1 mm to positive margins, increased cellularity, increased mitotic rate, and age older than 50 years [39]. Another risk factor for distant metastasis is tumor size; metastatic cases are significantly larger (most metastatic cases being larger than 10 cm) compared to nonmetastatic cases; this could be related to FS changes within the tumor. Local recurrence was not found to be related to metastases [40]..

Metastasis is detected on a mean time of 14.8 months and within a range from the initial visit to less than 5 years after the treatment [40]. Brain, pleura [41], pancreas [42], cervical lymph nodes [43], and orbit metastasis have been reported [44]..

Treatment

Complete surgical resection with microscopically negative margins is the cornerstone of treatment for localized DFSP [10, 45•]. Adjuvant radiotherapy has a role for unresectable DFSP and in those cases with positive margins when re-excision is not feasible. Radiation can also be considered as adjuvant treatment in recurrent cases. Imatinib is the first effective systemic therapy for advanced DFSP and could potentially be used for reducing tumor size in those considered initially unresectable so surgery may be feasible [45•].

Surgery

Conventional surgery

Initially, recurrence with conventional surgery was reported to be up to 50–60% due to conservative margins [46, 47]. In the earlier studies, there were no unified standards for margin of resection and patients rarely underwent adequate margin-controlled tumor extirpation [4]. When undefined or conservative margins were used, local recurrence rates ranged from 26 to 60% with a total recurrence rate of 39.7% [30•]. However, recurrence rates dropped with wider margins of 2–5 cm, to around 6% [48, 49].

The reason for recurrence is that microscopic projections are not removed adequately or assessed satisfactorily; the wider the margin, the higher the probability the tumor will be removed completely [10] and margin status has been shown to be an important predictor of recurrence [50]. Using 1-cm margins around the primary tumor leaves residual microscopic tumor in more than 70% of patients, 2-cm margins in 20–40% of patients, 3-cm in 9–15.5% of patients, and 5-cm in 5% of patients [51–53]. Peripheral margins of 5 cm have a close to 0% recurrence rate [54]. However, tumors are not circumferential and are asymmetric; DFSP mapping with Mohs micrographic surgery (MMS) has shown long tentacle-like projections that extend beyond 3 cm. Wider margins unnecessarily remove healthy tissue, increase the risk for complications, and may lead to suboptimal functional and cosmetic results [10, 55]. Wide resections may also not be practical in patients with tumors located in critical areas like the head and neck [30•], and intraoperative frozen section assessments have not been reliable for determining margin status [55]. When smaller peripheral margins are used, meticulous margin assessment is critical to avoid recurrences. Deep margins should always include excision of the deep fascia [23••]. In our personal experience when using 2-cm lateral margins, the deep margin is most commonly involved by tumor, and not infrequently, the complete resection of the tumor requires excision of the external outer table in the cranium; muscle in trunk and extremities; peritoneum in thin patients with DFSP located on the abdomen; sternum, clavicles; and vertebral apophysis when located on the thorax.

Due to subclinical extension and its tentacle-like projections, routine step-section pathological assessment of surgical margins is a potential pitfall [30•, 56•]. Bread loafing allows the assessment of 10% of the margin which may lead to false-negative results [4]; en face evaluation of surgical specimens allows for a more thorough assessment of surgical margins [57•]. Compared to the 6% recurrence rates described with wide local excision, en face pathologic evaluation with the use of 2-cm margins reported a local recurrence less than 1% [57•]. This approach cannot be cataloged as wide local excision (WLE) since it allows for the analysis of all the margins just as MMS. MMS assesses 100% of the margins, resulting in less healthy tissue removal and adequate margin assessment making it a better choice [52••] (see Fig. 1).

Mohs micrographic surgery

MMS has become the alternative to wide local excision. It analyzes 100% of the margins. Consequently, it detects the microscopic extensions and enables the surgeon to remove them more accurately. It uses, instead of representative vertical sectioning (used in conventional surgery), sequential horizontal sectioning with immediate microscopic examination of resected frozen tissue [51, 58]. Modified Mohs uses paraffin embedded sections [59] and has been used for DFSP with good outcomes and few recurrences [60•].

Table 1 lists selected review papers evaluating recurrence rates for WLE and MMS. The relative risk of recurrence for WLE vs. MMS patients was 15.9 (95% CI 7.2–35.5) [62•].

The disadvantages of MMS are that tumor cells can be confused with normal spindle cells of the dermis in frozen sections and CD34 staining of frozen sections, which can help, has high variability, and thus, some authors do not consider the technique entirely reliable [67, 68]. To circumvent this issue, some authors recommend excising an additional layer and sending it for permanent paraffin-embedded evaluation after achieving negative frozen margins [52••]. MMS is also time consuming, complex and a highly specialized method that requires considerable training and can be costly. Most reviews, however, suggest a lower recurrence with MMS than with WLE [30•, 51, 52••, 62•, 63•, 66•, 69••, 70, 71]. Randomized controlled trials are lacking; nonetheless and as

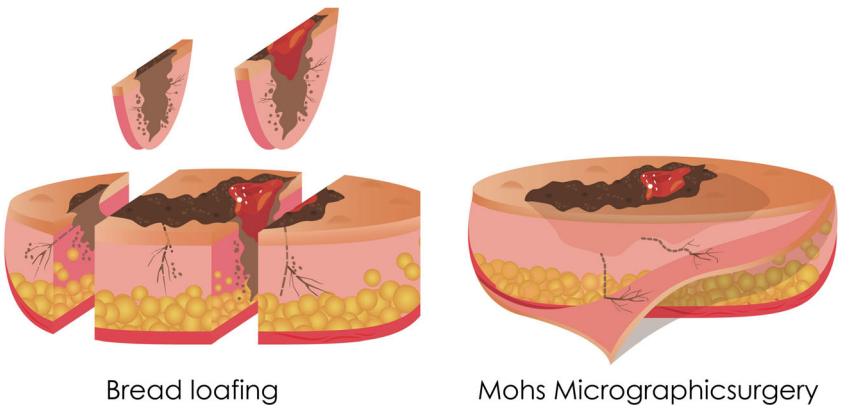

Fig. 1. Pathologic assessment of specimens through bread loafing may miss DFSP thin tentacles within the deep margin while MMS horizontal sectioning analyzes 100% of margins and thus would evaluate extending projections and tentacles of the tumor.

Table 1. Selected references reporting recurrence rates for different surgical approaches

Recurrence rate for conservative or undefined margins						
Author	Number of patients	Recurrence rate	Margin	Follow-up	Design	Level of evidence
Lemm [30•]	116 patients	Range 26 to 60% Total 39.7%	Undefined	1–23 years	Review of the literature	Level 2
Recurrence rate for WLE						
Author	Number of patients	Recurrence rate	Margin	Follow-up	Design	Level of evidence
Gloster [61]	39	10%	Not specified	Average 36 months	Comparative nonrandomized	Level 3
Paradisi [62•]	38	13.2%, 95% CI 4.4–28.1%	2 to 5 cm	4.8 years	Comparative nonrandomized	Level 3
Meguerditchan [63•]	28	3.6% (p = 1.0)	Median 2 cm	Median 49.9 months	Comparative nonrandomized	Level 3
Lowe [64••]	91	30.8% (p = .09)	Not specified	Mean 5.7 years	Comparative nonrandomized	Level 3
Paradisi [62•]	1394	20.7%, 95% CI 18.6–22.9%	Variable	0.1 to 30 years	Review of the literature meta-analysis of level 3 studies	Level 2
Lemm [30•]	661	Range 0 to 41% Total 8.8%.	Not specified	1.8–13.2 years	Review of the literature	Level 2
Mullen [65]	1404	Range 3–32% Range 0–50%	1-cm margin more than or equal to 3-cm margins	Not specified	Review of the literature	Level 2
Bogucki [22•]	1443	7.3%	0.5 to 5 cm	3 to 13 years	Review of the literature	Level 2
Recurrence rate for WLE with pathological en face or meticulous pathologic assessment of margins						
Author	Number of patients	Recurrence rate	Margin	Follow-up	Design	Level of evidence
Farma [57•]	204	1%	2 cm		Case series	Level 3
DuBay [49]	42	0%	1–2 cm	Median 4.4 years	Comparative nonrandomized	Level 3
Recurrence rate for MMS						
Author	Number of patients	Recurrence rate	Margin	Follow-up	Design	Level of evidence
Gloster [61]	15	6.6%	Minimum 0.5-cm margin	40 months	Comparative nonrandomized	Level 3
Paradisi [62•]	41	0%,95% CI 0–8.6%	Not specified	5.4 years	Comparative nonrandomized	Level 3
Meguerditchan [63•]	20	0% (p = 1.0)	0.5 to 1.0 cm	40.4 months	Comparative nonrandomized	Level 3
Lowe [64••]	67	3% (p = .09)	Not specified	4.8 years	Comparative nonrandomized	Level 3
DuBay [49]	11	0%	2 to 5 mm	4.4 years	Comparative nonrandomized	Level 4
Paradisi [62•]	463	1.3%, 95% CI 0.5–2.8%	Not specified	0.25 to 8.7 years	Review of the literature meta-analysis of level 3 studies	Level 2
Lemm [30•]	327	Range 0 to 8.3% Total 1.5%	Not specified	1.8 to more than 5 years	Review of the literature	Level 2
Bogucki [22•]	444	1.1%	Not specified	1.8 to more than 5 years	Review of the literature	Level 2
Foroozon [66•]	583	1.03% (95% CI, 0.37%–2.22%)	Not specified	26 to 127 months	Review of the literature of noncomparative nonrandomized studies	Level 2

previously stated, WLE is an acceptable treatment [10] if MMS is unavailable. Combined recurrence rate for WLE during the past 20 years is 7.3% compared with 1.1% for MMS [52••] (see Table 1).

MMS should be the preferred approach in anatomically challenging areas [51, 66•, 72, 73] and in the treatment of children since children have a smaller body surface area [9].

When using techniques that allow pathological tridimensional control of all margins starting with a lateral safety margin of 1–1.3 cm may be sufficient [23••, 74]. NCCN guidelines recommend 2-cm margins [75••]. If standard histopathological procedures are available, a lateral safety margin of 3 cm is advisable [23••].

Some authors recommend determining the peripheral margin based on the tumor's size and recurrence status (1 extra cm for tumors larger than 5 cm in diameter or recurrent tumors) [76]; others demonstrate tumors <2 cm will be cleared with 1.5-cm margins while >2-cm tumors will require 2.5-cm margins [53].

Referral to a multidisciplinary team that has broad knowledge and experience with DFSP, including the biology of the tumor and especially technical expertise on management, is mandatory [4]. The choice of surgical approach should be individualized, and the goals are to completely excise the tumor with negative margins, preserve function, optimize cosmesis, and minimize morbidity as well as minimize costs for the healthcare systems [65]. If MMS is unavailable, WLE with surgical margins of 3 cm is usually sufficient [23••]. Pathological tridimensional study of all margins is preferred and reconstruction should be delayed until margins are confirmed clear [23••].

Surgery is the first option for recurrent tumors [39, 75••].

Reconstruction

In cases of complex closures, a reconstructive surgeon must be consulted in order to preserve pedicles that may be required for flaps [49]. Undermining should be avoided since it can result in seeding of the tumor [49], or in cases of modified MMS when a second layer is necessary, scar tissue can make the interpretation difficult. Negative pressure dressings can be used before reconstruction while waiting for margin status [77].

Table 2. Selected references reporting recurrence rates or response for other treatment options for DFSP

Adjuvant radiotherapy recurrence rates				
Author	Number of patients	Recurrence rate	Design	Level of evidence
Y.-T Chen [79••]	167	11.74%	Meta-analysis	Level 2
Imatinib				
Author	Number of patients	Response rate	Design	Level of evidence
Imatinib Target Exploration Consortium Study 400 mg BID McArthur [81]	8 localized DFSP	50% complete response 50% partial response	Case series	Level 3
	2 metastatic DFSP	50% partial response		
Combined analysis of two phase II clinical trials EORTC 400 mg BID SWOG 400 mg once a day Rutkowski 2010 [82•]	24 total	46% partial response	Case series	Level 3

MMS allows greater preservation of tissue [69••]. The final defect size has been reported to be smaller when using MMS vs. WLE [49] reflected in that primary closure is reported to be used more frequently when MMS is performed whereas with WLE flaps, grafts, or other closures are more commonly used [64••]. A demonstrable reconstructive benefit can be seen in 80% of patients treated with MMS when compared to WLE [78]. WLE compared to MMS had incomplete margins in 24% of cases, less optimal reconstruction (more invasive/poorer esthetics) in 47%, and more destructive/disruption or loss of esthetic subunits in 9% [78].

Radiotherapy

Radiotherapy is indicated in primary inoperable tumors, patients with positive margins when further surgery is not possible, or as adjuvant therapy after re-resection in recurrent DFSP [23••, 75••].

Recurrence rate for patients with positive margins was found to be 14 and 0% in patients with negative margins [79••]; thus, radiation is indicated in positive-margin patients where further surgery cannot be performed [75••, 80]. Most studies recommend a dose of 55–65 Gy [79••]. The target volume should include the tumor and 3–5-cm margins [23••] (see Table 2).

Radiotherapy is not indicated in tumors completely resected with negative margins. The side effects of radiation include fibrosis, skin graft failures, necrosis, edema, and joint stiffness, and neoadjuvant radiotherapy increases the risk of wound complications [80, 83].

Systemic therapy

Chemotherapy

There is minimal role for conventional chemotherapy and response rates have been poor [4, 30•, 56•].

Imatinib

Imatinib is an FDA-approved treatment for DFSP [84]. Imatinib has been shown to inhibit DFSP cell growth [12]. It has been shown to have clinical activity against DFSP with t(17;22) but lacks activity against t(17;22)-negative DFSP [81]; thus, the detection of the COL1A1-PDGFB fusion is highly recommended using FISH or RT-PCR prior to the start of imatinib therapy [17]. The overall responses (partial response and stable disease) have been reported to be 46, 73, and 90% [81, 82•, 85]. The dosage is 400 mg BID and 400 mg once a day; results suggest 400 mg once a day may be sufficient [82•] (seeTable 2).

In surgically challenging tumors, size reduction with imatinib may allow more conservative surgery [18]. Two months of preoperative imatinib at a 600-mg dose daily showed 20% reduction of median tumor volume in 36% of cases [86•]. Three months showed an overall response of 57% with median tumor shrinkage of 31.5% [87].

Treatment with imatinib results in sclerotic, hypocellular areas that can harbor pockets of viable discontinuous and widespread tumor [88•]. Imatinib resistance has already been described and novel mutations in genes implicated in various signaling pathways have been found [89].

Cutaneous adverse effects of imatinib include maculopapular, lichenoid, psoriasiform eruptions, acute generalized exanthematic pustulosis, and Stevens-Johnson syndrome [90]. Other systemic adverse effects are congestive heart failure, hematologic, and liver toxicities [84].

Sunitinib has been evaluated for patients with imatinib-resistant DFSP with 40% of patients showing partial or complete response [91].

Follow-up

Three- to six-month interval follow-up is recommended for the first 3–5 years and an annual follow-up after that [9, 23••]. Recurrences after 5 years may occur [70, 92]. Clinical follow-up can be complemented with MRI imaging in selected cases.

Compliance with Ethical Standards

Conflict of Interest
Alvaro E. Acosta and Catalina Santa Vélez declare they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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