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A New Algorithm for the Management of Dermatofibrosarcoma Protuberans

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A NEW ALGORITHM FOR THE MANAGEMENT OF DERMATOFIBROSARCOMA PROTUBERANS.

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The purpose of this project was to design an algorithm for the management of Dermatofibrosarcom Protuberans (DFSP.) The National Cancer Center Network guidelines suggest immediate reconstruction in most cases after DFSP resection. We believe this algorithm is inadequate. Due to the infiltrating nature of DFSP, tumor margins are often positive after resection. Immediate reconstruction in the context of residual tumor is problematic because of the risk for spreading microscopic disease and the potential to compromise reconstructive options. At our institution we examined the prevalence of positive margins on permanent pathology after immediate closure following surgical resection of DFSP. Forty-one patients were identified; 25 had received treatment with surgical excision and 16 with Mohs surgery. Of the 25 patients that were treated with surgical excision, 20 underwent immediate closure and 5 underwent delayed closure after tumor resection. Eight out of 19 (40%) of patients who underwent immediate closure were found to have positive margins on permanent pathology. Given these findings, we propose a treatment algorithm focused on more conservative surgical management of DFSP in which negative margins are established before closure. Mohs surgery, which allows for immediate identification of pathology, plays a central role.

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Table of Contents

INTRODUCTION

Dermatofibrosarcoma protuberans (DFSP) is a rare, locally invasive soft tissue sarcoma with a propensity for extensive subclinical involvement. Originating in the dermal layer of skin, microscopic tendrils of tumor may extend far beyond the margin of clinically evident tumor. While painless and often indolent appearing, the tumor can grow quite large before receiving clinical attention. Local invasion can include subcutaneous tissue, muscle, fascia and bone. The local recurrence rate is high, in some studies upwards of 60%, likely reflecting a failure to remove occult extensions of tumor.[1] Fortunately, distant metastasis is rare (between 1 and 4%) and complete removal is considered curative.[2]

The cell of origin for DFSP is controversial. Several authors theorize that DFSP arises from fibroblasts, as tumor cell features that are consistent with modified fibroblasts have been observed on electron microscopy.[3] In addition, like fibroblasts, DFSP cells stain with vimentin and contain active endoplasmic reticulum that readily synthesize collagen.[4] However, several studies in tissue culture indicate that tumor cells may be histiocytes that have acquired fibroblastic elements. The growth pattern of DFSP resembles that of fibroblasts in the body, which serve to support tissue through formation of a lattice network around cells. DFSP cells mimic the fibroblast infiltrative growth pattern with pseudopod like extensions from a central mass that penetrate fat and adjacent tissue over time.[3] It may be that this similarity to the fibroblast growth pattern explains the low rate of blood borne metastasis, as fibroblasts tend to remain enmeshed in the area they stabilize.[5] Histologically, DFSP is characterized by a fibroblastic proliferation of tumor cells arranged about a central hub in a storiform pattern.[2] (Figure 1)

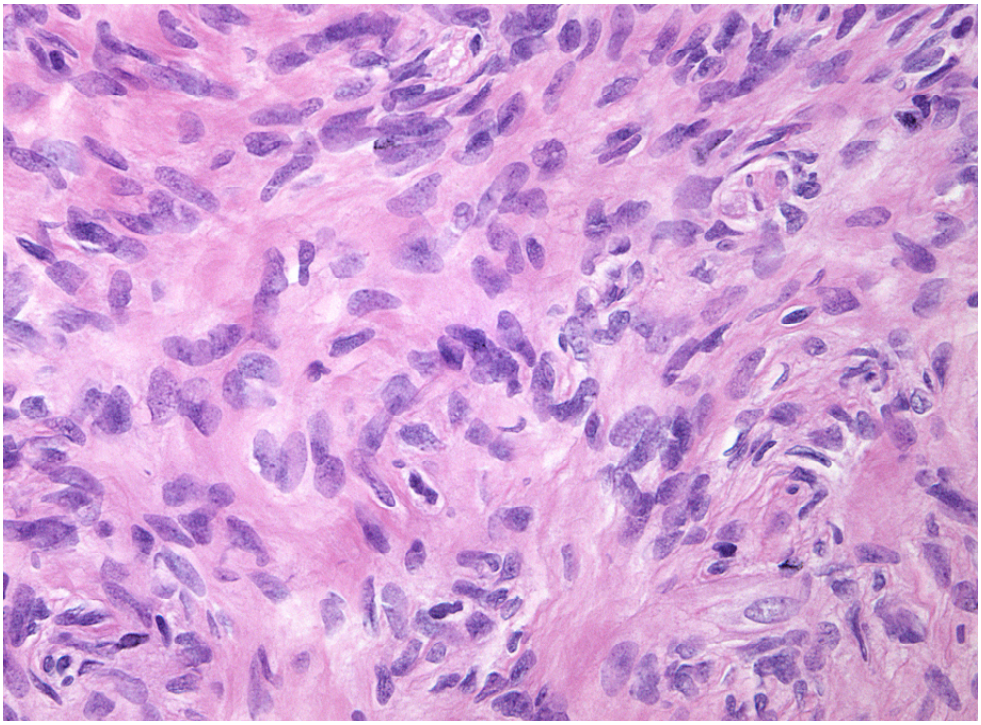


Figure 1. Microscopic appearance of DFSP

Ninety percent of DFSP tumor cells exhibit a chromosomal translocation of genes COL1A9 and PDGFβ (t17;22,) which encode the alpha chain of type I collagen and the beta chain of platelet-derived growth factors, respectively.[6] The fusion protein produced by this translocation causes continuous stimulation of the PDGF protein tyrosine kinase, resulting in increased production of PDGF and abnormal cellular proliferation.[7] Fibrosarcomatous-DFSP is a more aggressive variant of DFSP and likely represents dedifferation. The increased cellularity and mitotic activity observed on histology for these tumors are indistinguishable from the cytologic and architectural pattern of a high grade fibrosarcoma, and this variant is associated with a higher rate of recurrence and metastasis.[6,8,9]

The development of DFSP may be linked to traumatic wounds, scarring, and viruses. In a retrospective analysis by Yu et al., 24% of patients recalled an antecedent trauma at the site of tumor development.[10] Green et al. describe a 69-year old who presented with a DFSP located at a smallpox vaccination site.[11] At least six other accounts of DFSP exist in which the tumor developed in a site of prior immunization inoculation.[11] Persistent inflammation is thought to account in part for the association of scars with an increased risk of malignancy.[10]

Historically, surgical excision has been the treatment of choice for the resection of DFSP. However, the ideal width of margins remains undefined. Parker et al. mapped the subclinical tumor extension in 20 patients with Mohs surgery and measured the margins required to completely clear the tumor. A 2.5 cm margin through the deep fascia was shown to clear all tumor cells completely, and the tumors measuring less than 2 cm were completely cleared with a 1.5cm margin.[12] However, other studies have documented tumor projections that extend anywhere from 3 to 10 cm beyond the tumor center leading to recommendations for margins of up to 5cm.[4,13] A review of the literature by Gloster et al. found a trend of improving recurrence rates with increasingly wider resection margins. The recurrence rate decreased from an average of 43% to 18% in series with wider margins (defined as greater than or equal to 2 cm) compared to undefined or more conservative margins.[2] Even among studies where resection margins were 5 cm, the recurrence rate reached 23%.[14] Most authors currently suggest a margin of 2 to 3 cm with a three dimensional resection including skin, subcutaneous tissue, and the underlying investing fascia.[8]

Several authors have suggested that traditional surgical excision, which removes tissue in a concentric ring based on the macroscopic extent of the tumor, is not well suited for removal of DFSP. This surgical approach is predisposed to remove too much healthy tissue without eradicating the extensive, asymmetric projections of tumor cells.[13] In the last several decades, Mohs surgery has emerged as a promising treatment option that may achieve superior results to surgical excision.[15] Mohs surgery provides a method of eradicating tumor that rests on intraoperative evaluation of tumor margins. The tumor is resected in a stepwise fashion with tissue removal that is based on the presence of tumor cells. In addition to conserving tissue, the pathologic techniques used in Mohs surgery have been shown to provide an excellent rate of cure with very few documented recurrences.

After resection of DFSP, the National Comprehensive Cancer Network (NCCN) guidelines recommend immediate reconstruction in most cases, but state that "it is preferable to delay deep undermining or flap reconstruction until negative surgical margins are assessed."[16] These recommendations for treatment of DFSP are potentially problematic because of the emphasis on clinical judgment for determining whether to perform immediate or delayed reconstruction. It is often difficult to predict the extension of the tumor, because of the eccentric pattern of invasion characteristic of DFSP that mimics normal tissue.[17] Immediate reconstruction can compromise options for subsequent surgery if positive margins found on permanent pathology necessitate further excision. In addition, immediate reconstruction in the context of residual tumor may pose a risk for the spread of microscopic disease. For these reasons, we believe the current guidelines for the management of DFSP are inadequate.

STATEMENT OF PURPOSE

The purpose of our study is to design an algorithm for the management of DFSP focused on establishment of negative margins before closure.

METHODS

Patients were identified through the surgical pathology and dermatopathology laboratory database and stratified by surgical treatment type: surgical excision or Mohs surgery. Data was collected retrospectively and entered into de-identified research records.

Twenty-one patients were identified in the Yale surgical pathology database as having received surgical treatment for DFSP from 1990 to 2009. We included cases in which pathology of a biopsy of the lesion was consistent with DFSP. All patients who underwent surgery for DFSP were included. Patients were defined as having primary disease if they had never received previous treatment for DFSP, and recurrent disease if tumors arose at the site of previous resection. Patients with primary DFSP presented at our institution either for initial treatment or after previous inadequate surgery to undergo re-excision. Hospital and clinic outpatient charts were obtained and the following information was collected: age at onset, sex, disease state (primary presentation versus recurrence), tumor site, type of closure, size of margin, need for local tissue flaps and skin grafts in closure, status of margins on permanent pathology, and duration of follow up. We recorded the margin noted in the initial operative report as well as margins taken during subsequent resections. Margin size was missing for two patients. In addition, we recorded whether patients experienced disease recurrence (recurrent tumor after negive

pathology following resection) or extension of disease (recurrent tumor after incomplete resection.)

Twenty patients were identified by the Yale dermatopathology laboratory database as having been treated at this institution for DFSP from 1990, when the database was created, to 2009. These patients were stratified by the type of surgical treatment they received. Four patients were treated with surgical excision and 16 patients were treated with Mohs surgery. The patients who received surgical excision were grouped with the patients from the Yale surgery pathology database and evaluated for the same factors listed above. Information from the medical charts of the patients who received Mohs surgery was collected on tumor site, type of closure performed, number of stages and histologic sections during surgery, size of lesion, size of the postoperative defect (defined as the wound dimensions recorded in the operative report immediately prior to closure) and duration of follow up. Tumor size or size of postoperative defect was missing for two patients.

In addition to the above parameters, we wanted to compare the margin size for Mohs surgery with the margin size used during surgical excision to determine whether Mohs surgery conserved more normal tissue than surgical excision. Because data on excisional margins was not available for Mohs surgery patients, we calculated the margins in the following manner: the larger measurement of the preoperative defect size was subtracted from the larger measurement of the postoperative tumor size to obtain a total margin. This margin was divided in half based on the assumption that the margin was applied circumferentially around the lesion to yield the actual margin. The smaller measurement of the preoperative tumor size was also subtracted from the smaller

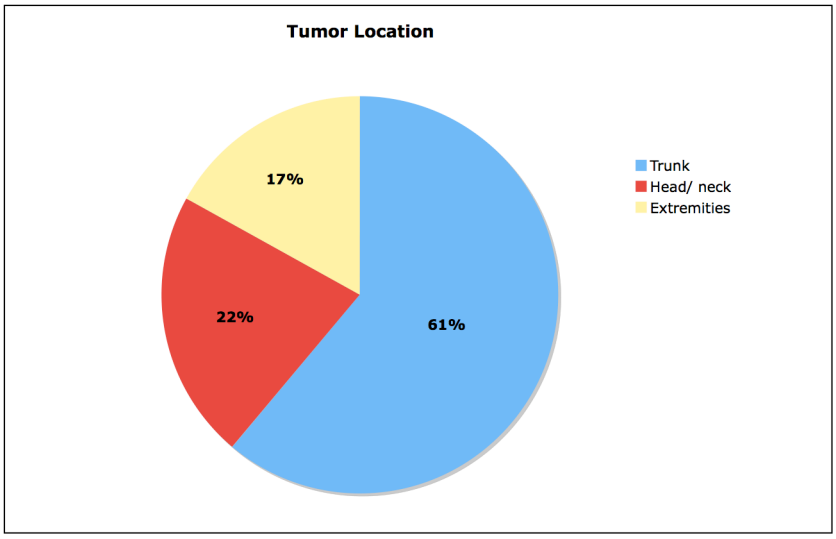
measurement of the postoperative defect size and divided in half. The two values were averaged to arrive at the excisional margin for each patient.

This study was approved by the Yale University Human Investigation Committee (HIC#0803003577).

RESULTS

Forty-one patients were treated for DFSP by surgical excision, Mohs surgery, or a combined approach at our institution from 1990-2009. The distribution of lesions is summarized in Figure 1. Overall, the trunk was the most common site for DFSP, followed by the head and neck. No patients had distant metastasis at the time of diagnosis. One patient presented with extension of disease after incomplete resection in the surgical excision group. No patients experienced recurrence (presentation of disease after negative surgical margins) in either the surgical excision or the Mohs surgery group. The average duration of follow up was 107.9 months for all patients.

Figure 2. Distribution of Lesions



Surgical Excision Group (Table 1)

Twenty-five patients underwent surgical treatment for removal of DFSP between 1990 and 2009 by 20 surgeons in the Division of Plastic Surgery, Department of Surgery, and Section of Dermatologic Surgery and Cutaneous Oncology in the Department of Dermatology. Excluding two patients for whom the state of disease was not reported 78.3% of patients presented with primary disease and 34.8% presented with recurrent disease. The age range was 12 to 84 years with a mean age of 46.1 years. Sixty-eight percent of patients were female and 32% were male.

Sixty-four percent of the lesions were found on the trunk, 28% were found on the head and neck, and the remaining lesions were found on the extremities. More specifically, there were five lesions on the back, four on the shoulder, three on the chest, three on the abdomen, and one on the breast. Two patients had lesions on their lower extremities. In the head and neck region, there were two patients with scalp lesions, two patients with lesions on or around the temple, one patient with a lesion over the parotid gland, and one patient with a lesion on the posterior neck. One DFSP lesion was found on the eyelid.

The average margin size for patients after initial surgical excision was 2.33 cm. The narrowest margin taken was .75 cm (for the patient with DFSP of the eyelid) and the widest margin was 4.5 cm. However, the average surgical margin including all subsequent surgical resections after permanent pathology was 2.79 cm, with a maximum width of 6 cm. The median margin size was 2.5 cm after initial surgical resection and 3 cm after including cumulative surgical resections. Five patients underwent delayed closure and 20 patients underwent immediate closure after resection. Twelve patients

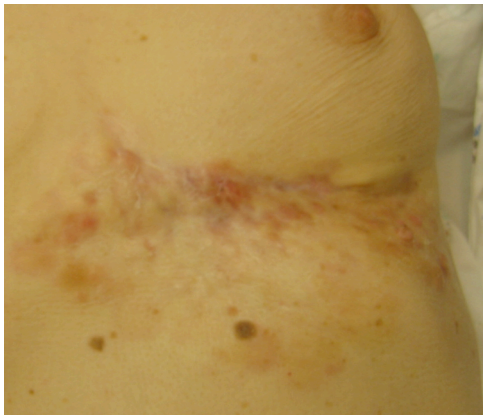
(48%) were found to have positive margins after initial resection. The duration of follow up ranged from 27 to 105.5 months, with an average of 105.5 months (8.75 years.)

Delayed Closure (Figure 1)

Five patients (20.8%) underwent delayed closure of the wound with planned re-operation and closure pending the results of permanent pathology. Two of these patients presented to our institution with recurrence, and one patient presented from an outside hospital for further resection after positive margins were found on initial resection. Allograft was placed on the wound as a temporary dressing for all five of these patients. The average time between the first and second surgery was 8.2 days, with a minimum of three days and a maximum of 13 days. Four of the five patients were found to have positive permanent pathology necessitating further resection. All but one patient was cleared histologically after a second resection.

Figure 3. Images of a patient treated with delayed reconstruction after resection of DFSP of the left chest wall. A. Gross appearance of lesion. B. Specimen. C. A 30 by 20 cm^2 defect was present after tumor resection. D. Allograft was used to temporarily close the defect. E. The results of permanent pathology showed tumor extension at the 7-8 o'clock margin, with skeletal muscle negative for malignancy. The patient underwent further resection 19 day later, with intraoperative frozen sections of the new margin found to be negative. Closure was performed with Gore-Tex mesh and bilateral external oblique myocutaneous flaps. No malignancy was found on permanent pathology after re-excision. E. Photograph from follow up appointment at clinic.

A.



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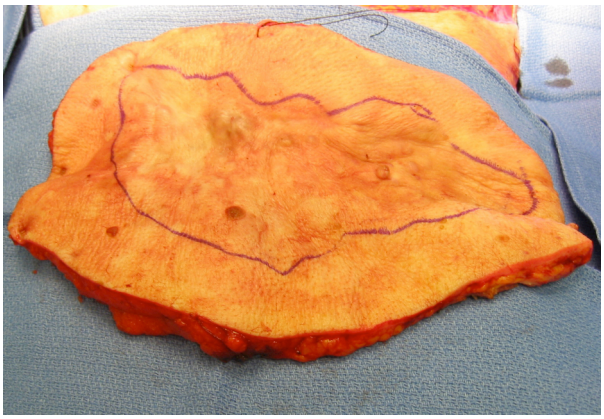

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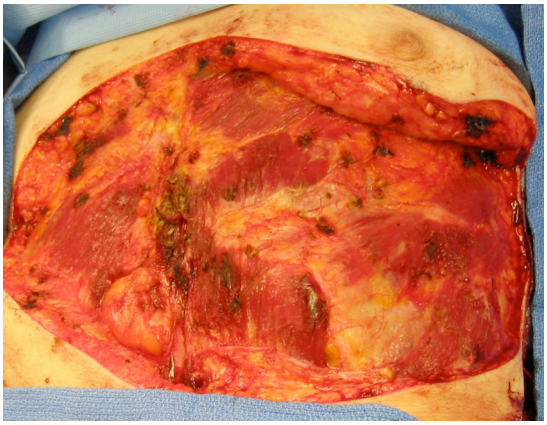

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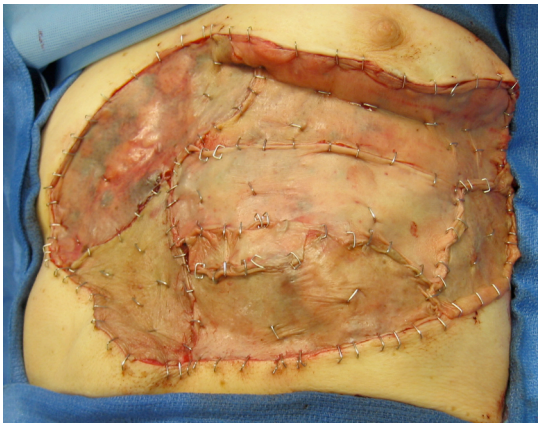

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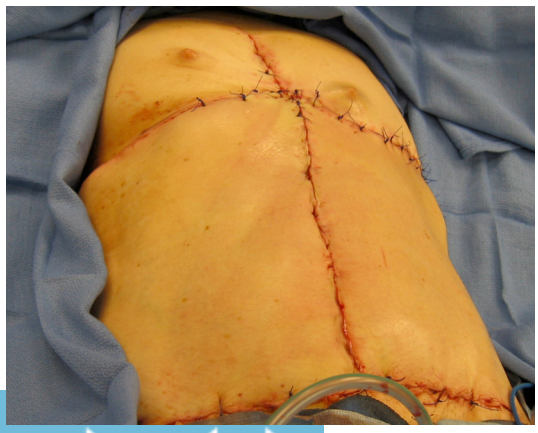

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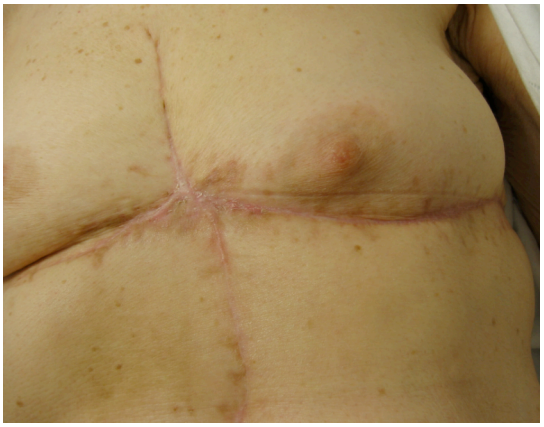


Immediate Closure

Twenty patients (80%) underwent immediate closure after surgical resection. Six of the patients who were treated with immediate closure had presented to our institution with recurrent disease. Eleven patients who received immediate closure required local flaps for reconstruction. One patient underwent immediate reconstruction with a radial forearm free flap.

Eight of the 20 patients (40%) who received immediate closure were found to have positive margins on permanent pathology. Three of these patients had undergone reconstruction with local flaps.

One patient received combined treatment with surgical resection followed by Mohs surgery. This was a 33 year-old woman who had previously been treated for DFSP of the forehead and upper eyelid at an outside hospital. She presented to the plastic and reconstructive surgery clinic at our institution with recurrent disease. She was treated with resection of tumor to the periosteum of bone. Intraoperatively, frozen sections showed negative margins. After surgery she received immediate reconstruction with a split-thickness skin graft. Permanent margins extending into the upper eyelid were found to be positive. She was referred for Mohs surgery where the resection was completed.

One patient in the surgical excision group presented with extension of disease after incomplete surgical excision. This was a 48 year-old female who received immediate reconstruction after resection of a large DFSP of the scalp and was found to have positive margins on permanent pathology. The patient was referred for radiation therapy, but elected to pursue observation of the lesion only. Two years later, the patient presented with nodules at the edge of the split thickness skin graft found to be DFSP. She

underwent further resection, this time with reconstruction of the defect with a fasciocutaneous flap from the posterior cervical muscles. On permanent pathology, the tumor approached within 1 mm at the deep margins. The patient elected to pursue radiation therapy, and has had no recurrences in the four years following treatment.

Table 1. *Permanent pathology results after surgical excision*

	Number of Patients (Percent)	Positive Margins (Percent)	Negative Margins (Percent)
Immediate Closure	19 (79.2%)	7 (36.8%)	12 (63.2%)
Delayed Closure	5 (20.8%)	4 (80%)	2 (20%)

Mohs Surgery Group (Table 2)

Mohs surgery was performed on 16 patients by three dermatologists in the Section of Dermatologic Surgery and Cutaneous Oncology in the Department of Dermatology. Like the surgical excision group, most lesions (56.3%) were found on the trunk. A greater percentage of lesions were found on the extremities than for surgical excision (31.3 vs. 8.0%), and fewer lesions were found on the head and neck (12.5 vs. 28.0%). More specifically, there were three lesions on the back, three on the shoulder, two on the abdomen, one on the chest, and one on the hip. Two patients had lesions on the clavicle and scalp at the hairline. Of the five patients with lesions on the extremities, 2 patients had lesions on the hand, two on the calf or lower leg, and one on the dorsum of the foot.

Thirteen lesions (81.3%) approached initially with Mohs surgery were cleared histologically after five stages of Mohs surgery. Three patients were referred for surgical excision because of failure to achieve clear margins with local anesthesia at the time of

Mohs surgery. These patients continued to have one histologic section positive after four stages of surgery and out of 9, 12, and 14 total histologic sections.

Most patients required several staged Mohs excisions to achieve complete tumor clearance. Thirty-one percent of lesions were excised in a single procedure, 12.5% were excised after two stages, 18.8% after three stages, 12.5% after four stages, and 6.3% after five stages. At each stage of resection, multiple histologic sections were required to analyze the entire peripheral margin. Excluding the three patients referred for further surgical excision, the average number of histologic sections taken was 8.6. The minimum number of sections was two and the maximum was 19.

Of the patients with lesions cleared by Mohs surgery, two patients (15.4%) were left to heal by secondary intention, 10 (76.9%) of the patients underwent complex linear closure, and one patient was referred to a plastic surgeon for wound closure. The average margin taken was 1.36 cm, with a median margin width of 1.17 cm. The maximum margin taken was 2.55 and the minimum margin was 0.74 cm.

No patient in the Mohs excision group experienced recurrence over a follow-up period ranging from 10.5 to 200.5 months, with an average duration of follow-up of 112 months.

Table 2. *Patient Characteristics and Results of Mohs Surgery*

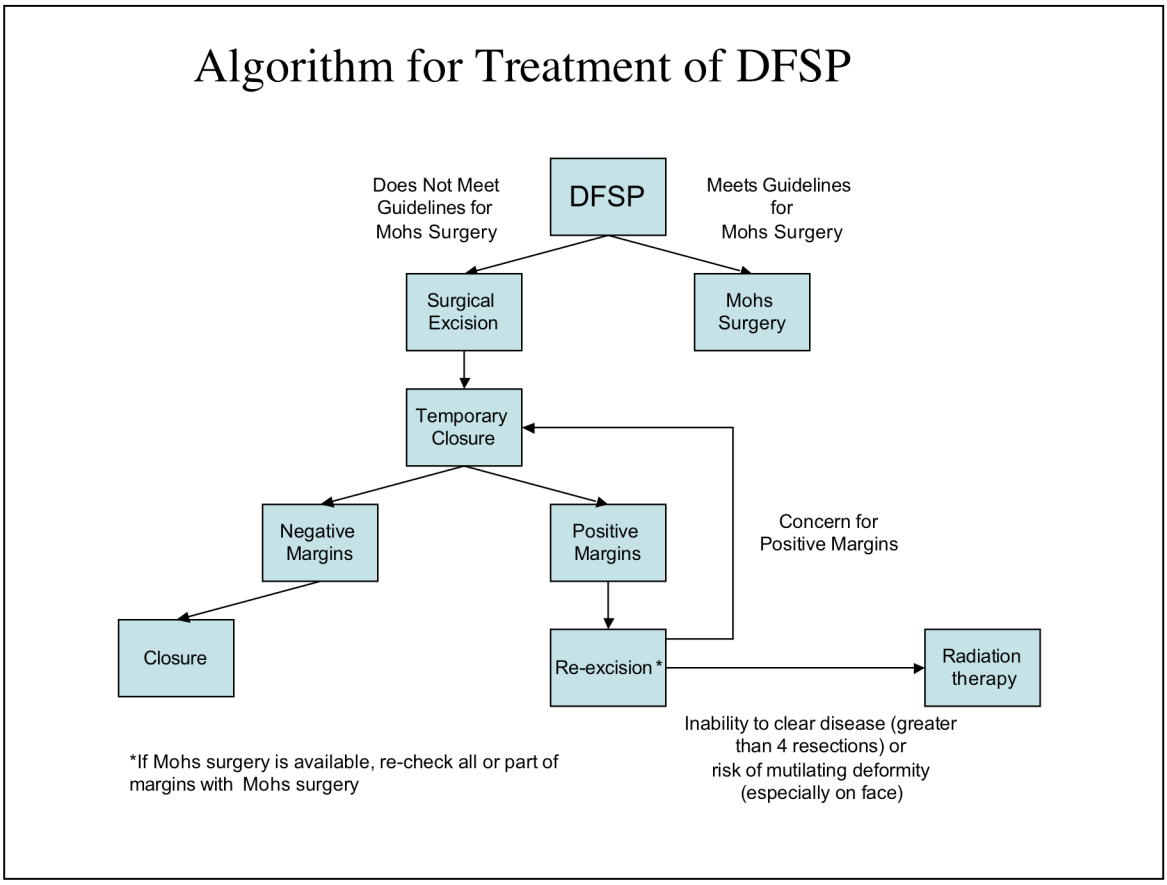
Patient	Location	Stages Required for Clearance	Total Sections	Closure Type	Size of Lesion (cm)
1	L lateral calf	1	4	Secondary intention	1.9 x 2
2	L dorsal hand	3	5	CLC	0.7 x 0.4
3	L shoulder	3	23	Delayed*	Not reported
4	L abdomen	2	14	CLC	7 x 1 scar
5	L deltoid	1	2	CLC	1 x 1.5
6	L hip	1	4	CLC	0.3 x 2.5
7	L dorsal hand	5	19	CLC, small area left to granulate	4.8 x 1.7
8	R lower leg	4	13	Secondary intention	2 x 1
9	R inf back	2	6	CLC	3 x 2.4
10	L flank	1	4	CLC	7.6 x 0.3
11	R ant sup Shoulder	4	12	CLC	0.9 x 0.7
12	R upper back	3	4	CLC	1.2 x 1.3
13	R abdomen	1	2	CLC	1.3 x 1.2
14	R clavicular area	4**	9	CLC*	3 x 1.5
15	Ant. R scalp at hairline	4**	14	Delayed*	2 x 5
16	Foot	4**	12	Delayed*	1 x 3

CLC: Complex linear closure
**negative margins not achieved with Mohs surgery.
*patients referred to plastic surgeon for further surgical resection and/ or closure

DISCUSSION

As mentioned above, the National Comprehensive Cancer Network (NCCN) guidelines for management of DFSP recommend immediate closure in most cases, although "it is preferable to delay reconstruction involving extensive undermining or flaps until negative surgical margins are assessed and certified pathologically clear."[16] Given the important prognostic relevance of establishing negative margins, we believe that reconstruction after tumor resection should be dependent on definitive clearance of the tumor. In light of the difficulty in judging the extent of DFSP, and the potential complications of reconstruction after positive margins are found, we feel that the treatment guidelines should be more conservative. Although multiple algorithms for the treatment of DFSP exist,[10,18] few incorporate closure guidelines into the recommendations. Here we present a new algorithm for surgical management of patients diagnosed with DFSP focused on the establishment of negative margins before closure (Figure 4.) Mohs surgery, which allows for immediate identification of pathology, plays a central role. Following a description of the algorithm, we will further discuss conservative treatment modalities such as Mohs surgery and surgical excision with delayed closure. Finally, we review reconstructive options after resection, and further therapy for metastatic DFSP and unresectable DFSP.

Figure 4.



The extent of DFSP is difficult to determine intraoperatively with traditional surgical excision, leading to a high rate of positive microscopic margins. In our analysis, nearly half of all patients (48%) had positive margins after initial tumor resection, despite wide surgical margins (median initial resection margin was 2.5 cm) that fell well within the accepted wide excision widths in the literature.[8] Rearrangement of tissue during closure may disseminate residual tumor cells, making re-resection of the positive margin inadequate to remove all disease. Resection with delayed closure ensures that further margins will be removed if permanent pathology is positive without tissue rearrangement

that may distort the tumor cell orientation. Therefore each step of the algorithm centers on establishing negative margins before closure.

Given the many advantages of Mohs surgery and the high safety profile that has been found, we believe that Mohs surgery should be the first line treatment when feasible. After clinical assessment of the tumor, all patients who are candidates for Mohs surgery should undergo this method of treatment where margins can be visualized in real time. Ultimately the decision of whether or not a patient will undergo Mohs surgery will be made on a case by case basis depending on the patient, location of the tumor with respect to the cutaneous tissue, and the experience of available clinicians. If Mohs surgery fails to achieve complete resection because the lesion extends into deep structures or the patient cannot tolerate further surgery under local anesthesia, the patient may be referred for surgical excision.

Patients for whom Mohs surgery is not feasible should undergo surgical resection of the tumor followed by temporary wound closure until the results of permanent pathology are known. As mentioned above, this will prevent rearrangement before full eradication of tumor cells. If pathology is found to be negative, reconstruction can proceed safely and without the risk of compromising any reconstructive options.

If positive margins are found on permanent pathology after resection, the lesion should be re-evaluated for Mohs surgery. In many cases, Mohs surgery can be applied to regions known to exhibit positive margins in order to minimize tissue loss. If Mohs surgery is not feasible, additional surgical excision should be performed. If there is a concern for positive margins, the patient should once again be left with a temporary

dressing with closure deferred until definitive negative pathology returns. This process should be repeated until permanent pathology demonstrates an absence of tumor cells.

Recurrent DFSP, lesions that continue to exhibit positive margins after multiple resections, and patients for whom complete tumor resection would cause a mutilating deformity require special considerations. These patients may benefit from radiation therapy in the postoperative or preoperative period. In addition, patients with the fibrosarcomatous high-grade variant of DFSP may require a more intensive treatment approach.[20]

After permanent pathology demonstrates an absence of tumor cells, reconstruction can be safely performed. When margins are known to be negative flap coverage is a safe and cosmetically superior method of closure. We believe that this algorithm will lead to systematic and successful extirpation of DFSP with a drastic reduction in recurrence rates as well as decreased tissue defects leading to improved cosmetic results.

Eighty percent of patients at our institution were treated with immediate closure following surgical excision of DFSP, and fifty percent of all patients underwent immediate closure with flaps. A significant number of patients (40%) who underwent immediate closure were found to have positive margins on permanent pathology. This necessitated re-opening of the previous closure for further excision of tumor cells and subsequent reconstruction of the defect. Three patients found to have positive margins had undergone more extensive immediate reconstruction with flaps. These findings are consistent with the unpredictable extent of DFSP; even patients with wide excisions have been found to have a high rate of positive margins.[9,17] This is likely due to the infiltrating

nature of DFSP and projecting tumor tendrils that mimic normal tissue and are therefore difficult to detect macroscopically.[9]

As mentioned above, immediate reconstruction after excision of a DFSP can be problematic if margins are found to be positive on permanent pathology. The first closure may limit subsequent reconstructive options, particularly in areas with large defects or around the head and neck, where reconstructive options are already limited. Immediate reconstruction in the context of residual tumor also poses risks for the spread of tumor cells. Undermining tissue for flap reconstruction, or simply tissue re-approximation, has the potential to open new tissue planes for tumor implantation. Dubay et al. reported their experience with a patient who had undergone immediate closure at an outside institution with bilateral rotation flaps and was found to have positive margins on permanent pathology. The initial tumor was described as less than 1 cm, and when flaps were re-resected, the tumor was found to extend through the entire undermined tissue plane beneath flaps, with no tumor noted in the overlying superficial adipose or dermal tissue.[19] This observation highlights the risk of infiltration of residual tumor cells into the plane of dissected tissue. It is also possible that the rearrangement of tissue during closure may disseminate tumor cells, making re-resection of the positive margin inadequate to remove all disease.

Achieving clear margins after the first resection of the tumor has been found to be critical to the prognosis of DFSP. In a review of the current management of DFSP, McArthur et al. highlighted the importance of achieving local control by adequate initial resection because locally recurrent and neglected lesions have a propensity for deep fascial, muscular, and bone invasion, as well as an increased likelihood of recurrence

leading to metastasis.[20] Arnaud et al. reviewed the outcomes of 114 patients who had undergone surgical treatment for DFSP with a mean follow-up time of 61 months.[21] Interestingly, the authors found that the rate of recurrence was not related to the size of the tumor. Two out of 41 patients treated with wide resection for a recurrent tumor developed further local disease and died of metastatic fibrosarcoma, compared with none of the 60 patients treated with wide initial resection. The authors concluded that accurate initial resection of the tumor is the most important prognostic factor for decreased recurrence and metastasis. Resection with delayed closure ensures that further margins will be removed if permanent pathology is positive without tissue rearrangement that may distort the tumor cell orientation.

Bowne et al. confirmed the importance of initial accurate resection in a large retrospective analysis of patients treated for DFSP at the Memorial Sloan-Kettering Cancer Center.[9] The authors analyzed clinicopathologic factors for disease-free survival in 159 patients at their institution. Patients were separated based on whether they exhibited the classic form of DFSP or the fibrosarcomatous "high grade" variant. As mentioned earlier, the fibrosarcomatous variant (FS-DFSP) is a much more aggressive tumor and carries a worse prognosis. Like Arnaud et al., the authors found that tumor size, site, and depth did not correlate with increased recurrence. However, positive or very close (less than 1 mm) to positive microscopic margins was a poor prognostic factor. Classic DFSP resected with negative microscopic margins was found to have a recurrence rate of 7%, while classic DFSP resected with positive microscopic margins was found to have a recurrence rate of 27% at five years. The more aggressive fibrosarcoma variant of DFSP was found to have a recurrence rate of 28% and 100% at

five years with negative and positive margins, respectively.[9] The authors concluded that incomplete resection of tumors cells was correlated with a high disease relapse rate.

A 2003 study by Khatri et al. further underscored the importance of adequate initial excision of DFSP. In this study, recurrent lesions were found to have a propensity for deep fascial, muscular, and bone invasion when compared to primary lesions.[8] In addition, there is a risk of de-differentiation of DFSP to the FS-DFSP variant, which as noted earlier is associated with a further increased recurrence rate and rate of metastasis.[8] Other studies have shown that metastases are usually preceded by multiple local recurrences after inadequate initial resection.[2]

No patients in our study experienced recurrence after treatment with surgical excision or Mohs surgery over an average follow-up period of 8.9 years. This recurrence rate is significantly lower than the 18%-43% averages found in a literature review.[2] One patient in our study presented with extension of disease after incomplete surgical excision. As mentioned above, this was a 48 year-old female with a 10 by 11 cm DFSP of the scalp. The tumor was initially excised with three centimeter margins and immediate closure was performed after resection with a split-thickness skin graft. After permanent pathology showed positive deep margins, the patient was referred for radiation therapy. She elected to pursue observation of the lesion only. Two years later, the patient presented with nodules at the edge of the split thickness skin graft found to be recurrent DFSP. She underwent further resection, this time with reconstruction of the defect with a fasciocutaneous flap from the posterior cervical muscles. On permanent pathology, the tumor approached within 1 mm at the deep margins. The patient elected

to pursue radiation therapy, and has experienced no further extension of disease in the 4 years following treatment.

Mohs Surgery

Mohs surgery provides a method of eradicating tumor that rests on intraoperative evaluation of tumor margins, without the need for deferral of closure. During Mohs surgery, frozen sections are taken in real time while the patient is awake. This offers several advantages over surgical excision, not the least of which is that the patient is not exposed to the inherent risks of prolonged general anesthesia. The tumor is resected in a stepwise fashion with the understanding that further sections will be removed but that tissue removal will be based on the presence of tumor cells. The processing for Mohs surgery involves drawing a map of the specimen and dividing this into smaller segments which can be frozen and color-coded with dyes in order to create a a comprehensive anatomic map that can be visualized histologically. Sections are cut along the periphery on a continuous plane from the surface at the edge to the deepest portion of the edge, allowing complete visualization of the margins.[22] For this reason, smaller surgical margins are possible with maximal preservation of unaffected healthy tissue. In our study, the median margin taken during Mohs surgery was over 1cm less than the median margin used in surgical excision (1.17 compared to 2.5 cm). When surgical margin was calculated including all subsequent resections, the difference between median margin size increased (1.17 compared to 3.00 cm). This finding is not surprising given the technique used in Mohs surgery. For areas of the body where generous excisional margins are not

practical, such as the face or extremities, this conservation of normal tissue represents a significant reconstructive advantage. In addition, Mohs surgery provides real-time definitive information about margins without requiring subsequent procedures and delayed closure.

Mohs surgery frozen sections must be differentiated from intraoperative frozen sections that may be processed during surgical excision. The role of intraoperative frozen sections for determining the status of margins in real time remains undefined. Intraoperative frozen sections are not routinely processed and analyzed with the same meticulous mapping technique as in Mohs surgery and therefore do not carry the same reliability. In comparison to Mohs frozen sections, intraoperative frozen sections are processed using a standard vertical step sectioning which permits examination of a random number of individual sections from the excised specimen.[1] Therefore the specimen is not comprehensively viewed by the pathologist, and a margin may be called falsely negative if the sections viewed by the pathologist do not contain tumor cells. Stojadinovic et al. compared intraoperative frozen sections to permanent pathology for 20 patients who were treated for DFSP of the head and neck at Memorial Sloan-Kettering Cancer Center between 1964 and 1999. The authors found that intraoperative frozen sections carried a sensitivity of 43% and a false negative rate of 57%, and concluded that intraoperative frozen sections do not assess resection margins accurately.[23] In our case series, two patients were found to have positive margins on permanent pathology despite negative intraoperative frozen sections. While intraoperative frozen sections may be used to guide resection, they are not reliable in assessing DFSP margins and should be used with caution when determining whether reconstruction can safely proceed.

While Mohs surgery provides a more accurate analysis of margin status than routine intraoperative frozen sections, the Mohs technique has several shortcomings when compared to permanent pathology processing. Several authors have described the difficulty delineating tumor borders during Mohs surgery at the periphery of frozen specimens where malignant cells become sparse and resemble normal fibroblasts.[24] These confounding cells are not found on paraffin sections. In cases where the extent of the tumor is difficult to judge, some authors advocate taking a biopsy of an analogous area to serve as a control in order to differentiate the normal distribution of fibroblasts from tumor cells. In addition, frozen sections in Mohs surgery do not routinely undergo the same immunohistologic staining that would be performed for permanent pathology analysis. Immunostaining was originally demonstrated on paraffin-embedded sections, and the application to frozen sections is anecdotal and unproven.[2] One such immunohistologic marker is CD 34, which is useful in differentiating DFSP from other fibrohistiocytic tumors.[25] This stain has been incorporated into the final stages of Mohs surgery at some institutions in order to confirm free margins.[10] Alternatively, authors have suggested preparing paraffin sections as a final layer for analysis after negative margins are found on MMS, which would allow for immunohistologic processing.[26]

Despite these concerns, the pathologic techniques used in Mohs surgery have been shown to provide an excellent cure rate. Although data is limited compared to surgical excision, very few recurrences have been reported. In one of the largest trails to date, Ratner et al. reviewed the records of 50 patients with DFSP treated with Mohs surgery. With an average follow up time of 4.8 years, the authors observed only one patient who developed a local recurrence.[13] Wacker et. al performed a literature review pooling 303

patients treated with Mohs surgery for DFSP. In this group, only six patients developed recurrent disease, resulting in a 2% recurrence rate.[26] Lower rates have been observed using modified Mohs surgery techniques, such as that proposed by Breuninger and Schaumburg-Lever, where paraffin-embedded sections are employed as well as immunohistochemistry for CD34.[27,28]

Exclusion criteria for treatment of DFSP with Mohs surgery varies by the institution and resources available (Table 3.) Tumors that are large, recurrent, previously irradiated, or aggressive are more likely to be found to be unresectable by Mohs surgery, however these same risk factors may also be indications for Mohs surgery.[29] Recurrent lesions provide additional challenges to Mohs surgeons because of tissue distortion and scarring. In very large lesions, there is an increased risk of extension of the tumor beyond the subcutis into vital structures such as bone, where paraffin sections may be necessary for accurate pathology. As Mohs surgery is usually performed under local anesthesia, larger lesions may limit the use of Mohs surgery when lidocaine toxicity is a concern. For lesions with these characteristics, surgical excision may be the treatment of choice.

Table 3. *Exclusion Criteria for Mohs Surgery*

Patient preference
Needle phobia
Large lesions (criteria dependent on the institution)
Lesion exceeds limits of local anesthesia

Mohs surgery may play a role in subsequent stages of tumor resection for lesions that were initially not amenable to Mohs surgery. As mentioned in our results, one patient with recurrent DFSP of the forehead was initially treated with surgical resection. She was referred for Mohs surgery when permanent pathology showed a foci of tumor cells extending into the upper eyelid. Mohs surgery permitted mapping of the remaining tumor and removal with minimal tissue loss.

Occasionally Mohs surgery is terminated intraoperatively when the margins are still known to be positive if the lesion extends into deep structures that may not be further removed under local anesthesia.[28] In our study three patients continued to exhibit positive margins after four stages of Mohs surgery. All of the patients presented with DFSP in a functionally or cosmetically important region - the anterior scalp along the hairline border, the clavicle, and the anterior foot with tumor extension into the anterior tendons. Due to the size of the defects (7.2 by 5.7 cm, 6.5 by 5.5cm, and 5 by 5 cm, respectively) a second stage procedure under general anesthesia was planned for reconstruction, and further surgical resection was performed at that time. Although full resection was not possible with Mohs surgery, initial resection with Mohs surgery served to the isolate the extension of tumor cells, and allowed for more focused surgical resection in areas where tissue conservation was critical.

Surgical Excision with Delayed Closure

Mohs-trained surgeons and specialized Mohs teams are less available than traditional surgical teams, and thus expense and resources may limit when Mohs surgery

can be performed. When Mohs surgery is not feasible because of logistical concerns or tumor characteristics, surgical re-excision of tumor positive areas until tumor-free margins are obtained has been found to ensure a high cure rate.[7] Delayed closure has been advocated by several authors as a method of ensuring complete tumor extirpation before reconstruction.[29,30] Sondak et al. describe a staged approach to surgery where the wound is covered with allograft with planned re-operation seven days later if primary closure without undermining is not possible. Using this approach, the authors found no recurrences among 45 patients.[29]

Full tumor resection with delayed closure has a high rate of cure even among these patients who are most at risk for recurrence. Thiele et al. analyzed the long term outcomes of seven patients who presented to their institution with recurrent DFSP of the head and neck.[31] Patients in the analysis were included only if at least one attempt to surgically cure the patient had been performed previously at a different institution, and patients had on average undergone surgery three times previously. One patient included in the study had undergone 12 operations for recurrent DFSP of the infraorbital region. As discussed earlier, recurrent lesions have been found to be significantly larger with a higher propensity for bone involvement, future recurrence, and metastasis.[8] In addition, DFSP of the head and neck have a notoriously high rate of recurrence, ranging between 50 and 80%.[2,31] These patients, therefore, represent a group that is extremely at risk for recurrence and disease progression. All patients in the study by Thiele et al. were treated with surgical excision of the tumor with a minimum 1 cm free surgical margin, followed by coverage with artificial skin until definite histopathologic examination confirmed free surgical margins. Six out of seven patients required at least two operations in order to

achieve complete free margins. After this treatment method, at five years the patient survival rate was 100%, and only one patient had experienced recurrence. This study shows that staged surgical resection with delayed closure can minimize recurrence rates even in the most challenging of cases.

In the interim between staged excisions, allograft is usually used as a temporary dressing. However, it is likely that other methods of temporary dressing may be equally if not more successful. Pearson and Amsberry reported their experience using a negative pressure wound dressing (Wound-Vac®) as a temporary dressing while waiting for final permanent pathology results after wide excision of a DFSP.[4] The authors found that the negative pressure wound dressing decreased wound care and dressing changes as compared to traditional dressings, and provided an optimal wound bed for definitive wound management.

Reconstruction

Due to the infiltrating nature of DFSP, tumor resection often results in large defects that require extensive undermining or reconstruction. In a retrospective study of 218 patients treated for DFSP, Fiore et al. found that one-third of patients required reconstructive surgery, and the need for reconstruction was more frequent in patients with tumors of the head and neck.[6] The NCCN guidelines promote the use of a STSG to monitor for recurrence when positive margins may be in question or when the clinician deems this appropriate. Historically, STSG have been used in closure for DFSP under the auspices that they would allow for better monitoring of local recurrence. For years

surgeons employed STSG to obtain closure after melanoma resection. This was done out of a concern that flap repair would camouflage early local recurrences in the bed of excision, and possibly increase the risk for local recurrence as a result of additional dissection.[31] However, it has not been shown that skin grafts increase the sensitivity of monitoring for recurrence. In addition, STSG provide poor aesthetic outcomes, with problems such as color mismatch, contour deformity, wound contracture, and disfigurement.[32] Cassileth et. al. surveyed 176 patients who had undergone Melanoma resection followed by grafted closure. The authors found that the deep scar depression from skin grafting led to increased psychological distress among patients following surgery.[33] Just as for melanoma, there is little evidence that STSG allows for improved surveillance of DFSP recurrence. Flap coverage has been shown to be safe, and provides significant advantages such as a superior cosmetic results, earlier post-operative ambulation and and faster mobilization when compared to skin grafts, resulting in a decreased length of hospital stay.[31,33] Given that complete removal of tumor cells is considered curative for DFSP[2] we believe that flap closure should be employed when possible after negative margins are demonstrated by permanent pathology.

Adjuvant Chemotherapy

Although fewer than 5% of patients with DFSP develop metastatic sarcoma, the prognosis of such patients is poor, with survival ranging from one to 48 months.[2,20,34,35] Metastasis predominantly occur through a hematogenous route to the lungs, but have also been reported in the brain, bone, and peritracheal area.[2] Chemotherapy that has

traditionally be used to treat sarcomas has not been found to be effective in treating DFSP.[7] Imatinib mesylate, (Gleevec; Novartis Pharmaceuticals, Basel, Switzerland) is a tyrosine kinase inhibitor that has proven clinical activity against chronic myelogenous leukemia expressing bcr-abl and gastrointestinal stromal tumors expressing c-kit.[35,36] As mentioned earlier, the pathology of DFSP is thought to result from a translocation resulting in production of a fusion protein that causing continuous stimulation of platelet PDGF protein tyrosine kinase, resulting in increased production of PDGF and abnormal cellular proliferation.[7] (Figure 4) Imatinib, which selectively inhibits PDGF alpha and beta receptors, has demonstrated activity against DFSP cells in vitro and vivo.[20] Due to this inhibition, imatinib has the potential to serve as a targeted treatment modality for DFSP.

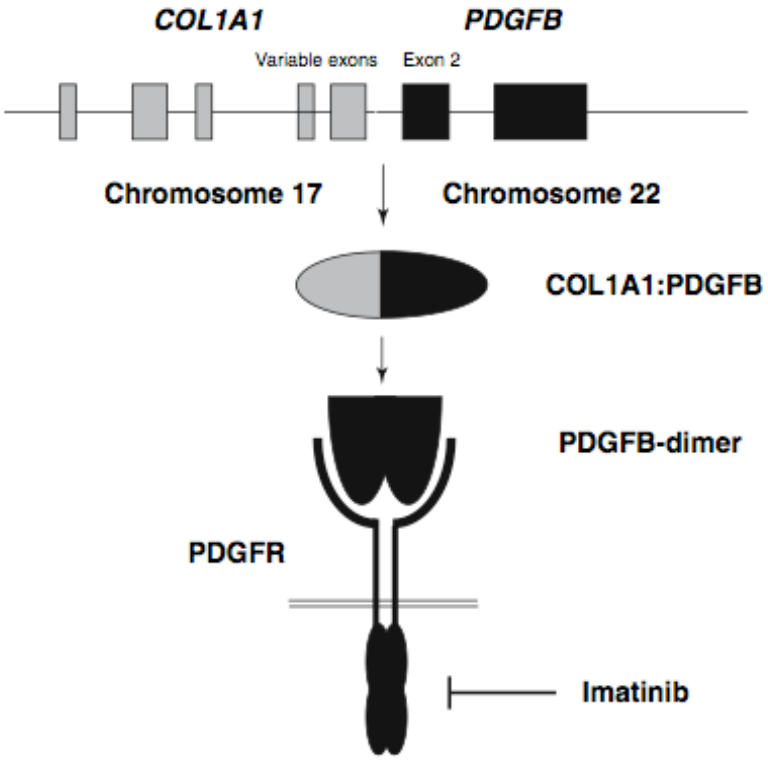


Figure 4. The pathology of Dermatofibrosarcoma protuberans results from the chromosomal translocation t(17;22) resulting in fusion of the COL1A1 and PDGFB genes. Protein product from this fusion causes continuous activation of the PDGFB receptor and oncogenic intracellular signaling. Imatinib inhibits PDFGR protein-tyrosine kinase. From McArthur G. Molecularly targeted treatment for dermatofibrosarcoma protuberans. Semin Oncol 2004 ; 31 (2 Suppl 6):30-6. Reprinted with permission from Elsevier. [20]

Labropoulos and Fletcher reported one of the first successes of imatinib therapy in the treatment of DFSP in 2005.[37] They described a 48 year-old woman with recurrent DFSP of the upper back. At the time of the third recurrence, she was found to have the fibrosarcomatous DFSP variant with metastasis to one lymph node in her axilla. A staging chest computed tomography scan showed three nodular lesions in the bilateral lungs, the largest measuring 8mm. The patient was initially treated with a combination chemotherapy regimen protocol that was traditionally used for high-grade soft tissue sarcoma, which consisted of three cycles of ifosphamide with MESNA and liposomal doxorubicin, but was unresponsive to the regiment. She was begun on imatinib mesylate therapy, and within one month there was a dramatic decrease in tumor size on the patient's back, and a CT of the chest showed resolution of the three lung nodules. The patient experienced minimal toxicity from imatinib and complete remission of the metastatic DFSP was observed at 20 months follow up. This is one of seven published case reports showing successful treatment of metastatic DFSP with imatinib.

The largest trial in the literature thus far - the Imatinib Target Exploration Consortium Study B2225 - shows promising results for 10 patients treated with imatinib.[38] Eight of the patients were treated for locally advanced disease and two were treated for metastatic disease. Half of the patients with locally advanced disease experienced complete disappearance of measurable and assessable disease. The other

half experienced a decrease of at least 50% in tumor diameter, which permitted full surgical resection of the tumor. Of the two patients with metastatic disease, one experienced a partial response that lasted seven months. The other patient experienced no change in tumor size and died on day 32 of the trial. This was the only patient in the study found to lack the t(17;22) abnormality. It seems that patients may have differential sensitivity to therapy, perhaps based on tumor expression of t(17;22.)[38,20]

Imatinib is currently approved for treatment of adult patients with unresectable, recurrent, and/or metastatic DFSP who are not eligible for surgery. It is possible that the role of imatinib may be expanded to include preoperative debulking of large tumors located in areas of cosmetic and functional importance. Mehrany et al. published a recent case report describing the use of imatinib as a neoadjuvant chemotherapeutic agent for tumor shrinkage in the case of unresectable DFSP. The authors followed a 46 year-old patient with a large DFSP of the left cheek who underwent therapy with imatinib before surgical resection of the lesion.[35] At the time of diagnosis, computed tomography and magnetic resonance imaging scans showed the tumor abutting and possibly invading muscles of facial expression. After initiation of therapy, the patient experienced a dramatic decrease in tumor size with concurrent softening of the tumor. By the 20th month of therapy, the tumor was small enough to be fully resected by Mohs surgery. Because of the decrease in tumor size, the patient maintained nearly full function of the muscles of facial expression. At eighteen months he has had no disease recurrence.

However, some pathologists have expressed concern that treatment with imatinib mesylate could complicate pathologic interpretation of lesions. In a letter to the editor, Ortiz et al. postulated that imatinib could create noncontinuous islands of tumor, giving

the false impression of clear margins after Mohs surgery.[39] Because of this risk, the authors proposed that imatinib be used as in the postoperative period rather than as a neoadjuvant therapy.[39] While larger, case controlled trials are needed to further understand the risks of imatinib, it is clear that this chemotherapeutic shows enormous potential for certain subgroups of patients with DFSP.

Radiation Therapy

Several authors have suggested a role for radiation therapy as an adjuvant to surgery in the treatment of DFSP for lesions with close or positive margins.[18,40] Ballo et al. reviewed 19 patients at the University of Texas M. D. Anderson Cancer Center who received radiation therapy with doses of 50-60 Gy for DFSP.[40] Ten of the patients presented with recurrent disease. Seventeen patients received postoperative radiation therapy, six with positive microscopic margins following surgery and 10 with negative microscopic margins and a surgical margin of less than 3 cm. The two patients that received preoperative radiation therapy achieved complete surgical resection. Only one patient developed recurrence during the median study follow-up of six years. This patient's course was complicated by prolonged wound healing which delayed radiation therapy, and regrowth of the disease before treatment was started.

A later study by Suit et al. at the Massachusetts General Hospital assessed the results of radiation therapy as a primary treatment for lesions not amenable to surgery.[41] Although the number of patients was small (n=3), local control was achieved and patients had no evidence of disease at 106, 85, and 108 months. These patients presented with

moderately sized tumors ranging from 3 by 5cm to 8.5 by 4.5 cm, on the upper anterior chest wall, the scalp behind the hairline, and the chin. In addition, all patients had excellent cosmetic results with the exception of atrophy and telangectasia in one patient.[41]

While promising, the data for radiation therapy is limited, and therapy may not be without risks. There are reports that radiation may induce new or high-grade tumors.[42] The National Comprehensive Cancer Network suggests consideration of radiation therapy for metastatic lesions or in cases of recurrent disease where unacceptable functional or cosmetic outcomes will occur.

In conclusion, we believe that the management of DFSP should be focused on establishment of negative pathology before reconstruction. Given our experience, we present a novel algorithm that minimizes the risk of residual microscopic disease. In addition to decreasing local and distant DFSP recurrence, we believe this algorithm will provide optimal aesthetic results for patients.

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