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Original Research

Treatment of dermatofibrosarcoma protuberans with fixed Mohs' micrographic surgery: A French cohort prospective study

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ABSTRACT

Background: Dermatofibrosarcoma protuberans (DFSP) presents a high recurrence rate after conventional excision. Mohs' micrographic surgery (MMS) ensures complete excision and minimal normal tissue loss. However, discriminating between residual tumor and normal skin can be difficult on frozen sections compared with fixed paraffin sections.

Objectives: To develop a MMS procedure in conjunction with fixed paraffin sections to treat DFSP with reduced lateral margins and to evaluate the long-term recurrence rate in a consecutive series of DFSP patients.

Methods: We prospectively collected 223 consecutive cases of DFSP (206 primary and 17 recurrent) treated with fixed-MMS between October 1998 and December 2014 in our skin cancer referral center. Follow-up was provided until October 2020. The fixed-MMS was favored to treat DFSP due to the frequent large size of MMS layer, which made analysis of frozen sections difficult. Determined on the basis of publications on MMS in DFSP, we decided to proceed with a first stage of fixed MMS including a 13 mm lateral margin and a deep margin extending to the underlying muscle fascia.

Results: Most patients (N = 196; 87.9 %) had a complete resection after the first stage. In cases with incomplete resection (N = 27; 12.1 %), only the deep margin was involved in most cases (N = 21/27; 77.8 %). Complete resection was always achieved with a second (N = 23) or third or more stages (N = 3). Only one local recurrence was observed (after 85.3 months) with a median follow-up of 63.9 months [4.4–243.9].

Conclusions: We report the largest cohort of DFSP treated with fixed-MMS. Only one tumor recurred (0.4 % recurrence rate).

1. Introduction

Dermatofibrosarcoma protuberans (DFSP) is a low- to intermediate-grade sarcoma with a very low metastatic potential but significant subclinical extension and great capacity for local destruction [1,2]. Its incidence is rare, about 0.8–5 cases per million a year (higher in Black patients). It most commonly occurs in the third through fifth decades of life and carries major scar sequelae. Distant metastasis is exceedingly rare, except in cases of fibrosarcomatous transformation, and most tumors are low grade [3].

The two most frequently used techniques are wide local excision (WLE) [4,5] and Mohs' micrographic surgery (MMS). Although past National Comprehensive Cancer Network (NCCN) guidelines have listed both MMS and WLE as first-line options, the last Version 2.2022 released on March 24, 2022, recommends Mohs' or similar techniques over WLE [6]. European Guidelines published in 2015 also slightly favor MMS over WLE, suggesting that, given the evidence, MMS "seems to be" the treatment of choice for DFSP [7]. MMS can significantly lower the 5-year recurrence rate compared to WLE (0–8.3 % versus 0–41 % respectively) with « made-to-measure » margins which are reduced to a mean of 2 cm [3,8].

We prospectively used a modified MMS technique in which the

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Mohs' samples were embedded in paraffin [9–12]. This procedure, known as fixed-MMS, combines the benefits of MMS with the quality of pathological examination after fixation and paraffin embedding. The latter allows immunostaining with an anti-CD34 antibody, discriminating between DFSP and other soft tissue tumors with high sensitivity [13,14], and fluorescence hybridization in situ (FISH) to reveal a specific fusion of collagen type Ia1 (COL1A1) and platelet-derived growth factor B-chain (PDGFB) genes (present in 92 % of DFSPs) [15]. The objectives of this study were to report our experience with a fixed-MMS procedure in a large prospective cohort of patients with DFSP and to evaluate the recurrence rate after prolonged follow-up.

2. Materials and methods

The fixed Mohs' technique was developed and favored in our department in 1998 to treat DFSP due to the frequent large size of the lesions (and lateral margins), which made analysis of frozen sections difficult. We decided to proceed with a first stage of fixed MMS including a 13 mm lateral margin (10 +3 mm) and a deep margin extending to the underlying muscle fascia. This lateral margin of 10 mm was determined on the basis of publications on standard MMS in DFSP, in which the average number of steps required to obtain clean margins was 2.5; adding all these margins together resulted in a lateral margin of around 10 mm. Thus, in most cases, our procedure aimed to achieve a complete excision with 10 mm lateral margins, to which an additional 3 mm Mohs' layer was added for histological confirmation of clear margins in their entirety. In depth, the deep margin had to include the fascia underlying the hypodermis to achieve complete excision in the first stage. All consecutive cases of confirmed DFSP treated with a fixed-MMS procedure in our referral center between October 1998 and December 2014 were prospectively included in this study. DFSP diagnosis was established beforehand on an initial partial or incisional formalin-fixed paraffin-embedded (FFPE) biopsy specimen, with haematoxylin and eosin stain + /- CD34 immunostaining. The fixed-MMS procedure was recommended during a multidisciplinary meeting, including dermatologists, dermato-oncologists, and dermatologic and plastic surgeons, both trained in this procedure. Depending on the size and/or site of the tumor, this procedure was performed either under local anesthesia by dermatologic surgeons or under general anesthesia by plastic surgeons.

A standardized report was filled out recording demographic information, the primary or secondary nature of the tumor, its site and its size (measured at 2 opposite diameters by marking the visible and palpable borders).

The tumor (or the residual scar if the tumor was no longer grossly visible due to previous excision) was first resected in one piece with a surrounding 10 mm margin of healthy skin and a deep margin comprising the hypodermis (debulking). This operative specimen was sent for conventional pathological analysis. A 3-mm thick layer was then removed from the entire surgical defect and deep into the underlying muscle fascia or the underlying muscle. This layer was sent to the dermatopathologists for rush processing, fixed in 10 % buffered formol, embedded in paraffin and included "en face" tangentially to the surgical margin to obtain tangential sections, which were stained with hematoxylin-eosin for the horizontal analysis. If necessary, at the pathologists' request, immunostaining with an anti-CD34 monoclonal antibody and/or FISH analyses with a dual color probe for COL1A1/PDGFB fusion detection could be added to confirm the diagnosis and/or the absence of residual tumor cells.

The surgical defect, which was systematically measured, was immediately closed by a direct oriented suture, if possible. If the pathological analysis of the 3-mm layer sample confirmed complete excision (absence of tumor cells), this suture was also the definitive closure. In cases where direct suture was not feasible, the surgical defect was healed by secondary intention while awaiting the pathology results, then by an additional closure technique if needed (skin graft or flap). In cases with lateral residual tumor, additional Mohs' layers had 3-mm lateral margins. When deep residual tumor remained, secondary excisions involved the underlying muscle with or without a fraction of peripheral skin for optimal sample orientation. In all these cases, definitive repair was only considered after the pathology results showed completely clear margins.

Annual follow-up with dermatologists from our department or private-practice dermatologists was recommended. All patients were reached between February 2016 and October 2020 to carry out a physical examination and confirm the absence of recurrence. Patients who did not wish to come to our center attested to the absence of any sign of recurrence over the phone (self-monitoring or private medical follow-up). For patients followed in our department, follow-up data was collected retrospectively from the medical files.

According to French Law, this study abided by standard medical practices and did not require a written informed consent nor a formal approval by one national ethical committee. However, consent was obtained orally from all patients. The study was conducted according to the principles of the declaration of Helsinki. Data Availability: the anonymized datasets analyzed during the current study are available from the corresponding author on reasonable request.

3. Results

A total of 224 consecutive patients with DFSP were treated in our center during the time period. Only one case of a tumor located on the hallux was excluded from the study because foot amputation was performed, and MMS procedure was not indicated. Thus, 223 patients, including 118 women (52.9 %), were included, and were treated according to this fixed-MMS protocol. The median age of the patients was 39 years [range 13–86], regardless of gender (data not shown). Among all cases, 206 (92.4 %) were primary tumors, including 45 (20.2 %) which had previously been treated with incomplete surgical excision, and 17 (7.6 %) were "true" recurrences (with a previous conventional surgical excision considered pathologically complete). Median tumor surface (defined by the product of opposite diameters) was 7.5 cm^2 [range: 0.1–144], the median largest diameter was 40 mm [10−170] and the median smallest diameter was 22 mm [1−120]. Tumor locations are shown in Table 1: the trunk was the most common site of involvement (N = 148; 66 %), followed by proximal extremities (N = 36; 16 %), head and neck (N = 19; 9 %) and genital area (N = 6; 3 %).

A large majority of cases (N = 196; 87.9 %) were successfully treated with only one stage of the fixed-MMS procedure, i.e. with a lateral surgical margin limited to 13 mm (10 +3). In only 23 cases (10.3 %), a secondary fixed-MMS excision was required because of incomplete initial resection and a third or more stages were required for only 3 (1.3 %) of these cases to obtain complete tumor resection. One case with an incomplete initial resection (residual tumor at deep margin) didn't have a secondary excision (reason not available), but he had no recurrence after 68.4 months. Residual tumor was more frequently present only at the deep margin (N = 21/27; 77.8 %) than only at the lateral margin (N = 4/27; 14.8 %) and two cases (N = 2; 7.4 %) had a residual tumor at both deep and lateral margins.

An analysis by fluorescence immunochemistry was performed in 18

Table 1
Location of DFSP.

	Total (n = 223)	%
Trunk	148	66
Proximal extremities	36	16
Head and neck	19	9
Cheek	8	4
Forehead	5	3
Neck	6	2
Genital area	6	3
Other	14	6

N: numbers, %: percentage.

cases and reported the presence of the COL1A1-PDGFB fusion gene in 16 cases.

As a result of the reduced margin, an immediate direct suture was possible in almost two-thirds of patients (N = 149; 66.8 %). The orientation of this suture allowed pin-pointed re-excision when pathology revealed a positive margin. The proportion of different methods of reconstruction used is summarized in Table 2. Most cases were treated by dermatologic surgeons under local anesthesia (N = 130; 58.3 %) while 93 cases (41.7 %) were treated by plastic surgeons under general anesthesia.

There were no postoperative complications except for one hemorrhage in a maxillary DFSP, which required hemostasis at the surgical site.

Only 17.0 % of patients (N = 38) were lost to follow-up. The median follow-up duration was 63.8 months [4.4–243.9]. Only one local recurrence was observed, after 85.3 months, in a patient whose primary tumor was localized on the neck. Surgical treatment of this recurrence was performed in another center (because the patient had moved in the meantime), without any subsequent recurrence in this patient (63.7 months of additional follow-up).

4. Discussion

We herein report to the best of our knowledge the largest prospective cohort of DFSP treated with fixed-MMS. The median age of patients in our series was 39 years [range 13–86], with a similar incidence in men and women and the tumors were mostly localized in the trunk, which is consistent with previous reports. A large majority of cases (88.8 %) were successfully treated with only one stage with a lateral surgical margin limited to 13 mm and a deep margin including the fascia. This reduced margin leads to an immediate direct suture in almost two-thirds of patients, fewer post-operative complications, and decreases the need for general anesthesia with its own morbidity. The recurrence rate was 0.4 % after a follow-up period exceeding 5 years. To note, one additional case, initially considered as a DFSP and treated with the fixed-MMS procedure, had a recurrence 26 months after the complete resection. Pathological analysis of the recurrence specimen and of the primary excision readjusted the diagnosis to undifferentiated pleomorphic sarcoma. Thus, this case was excluded from this study. This observation highlights that when a recurrence occurs, clinicians must reconsider the initial diagnosis.

Discrepancies between recurrence rates after DFPS surgery observed in the different published series can be explained by surgical and pathologic techniques. In conventional WLE-treated patients (≥3 cm margins), recurrence rates vary from 1 % to 50 %, while frozen MMS significantly reduces them to 0–1.5 %. The main studies using WLE and frozen MMS to treat DFSP are summarized in Table 3 [3–5,16–18]. Furthermore, other modified surgical techniques have been reported. Farma et al [19]. and Dubay et al [20]. found 0–1 % recurrence rates in patients treated with a modified WLE technique that uses horizontal processing of surgical specimens and narrow margins (1–2 cm), similar to the ones used by Mohs' surgeons. In 2017, Veronese compared his series of 73 DFSP cases treated with the Mohs' Tubingen technique (MTT) with standard surgical excision (SSE), WLE, or MMS [8]. MTT employs initial margins of 0.5 cm around the clinical borders of the DFSP. The resected specimen is oriented and sent for paraffin embedding. Then, a thin circular tissue strip from the margins and a slice from the bottom of the sample are cut and named the Tubingen Torte (cake). The rest of the procedure is almost identical to MMS, and the results are comparable [21]. The reported annual recurrence risk was 0.13 % and 0.5 % for MTT and MMS, respectively, whereas SSE and WLE had a higher annual recurrence risk (3.6 % and 1.5 %, respectively) [8]. In a systematic review including 23 trials totaling over 600 patients, Foroozan et al [16]. compared the efficacy of frozen MMS versus WLE: the recurrence rate was 1.11 % (95 % Confidence interval: 0.02–6.03) in MMS-treated patients and 6.32 % (95 % CI: 3.19–11.02) for WLE. The mean time to recurrence, specified in 5 reports, was 68 months: 50 % of these local recurrences occurred by 3 years, 75 % by 5 years post-surgery and 25 % after the recommended 5-year follow-up period. Considering these late recurrences, a follow-up period longer than 5 years should be considered for MMS-treated DFSPs. In "classic" WLE (conventional histology without careful evaluation of all peripheral and deep margins) 50 % of recurrences develop in the first 12 months and 80 % in the first 36 months [22].

To the best of our knowledge, few case series of DFSP managed with fixed-MMS have been reported (Table 4) [21,23–27]. Among MMS variants, fixed Mohs' applies less pressure on the pathology lab and allows for the preservation of tissue morphology, identifying residual tumor and performing immunohistochemistry studies [9–12]. Consequently, some authors suggest that fixed MMS should be considered the optimal treatment option for MMS in DFSP [23], provided that revision surgery be carried out rapidly before scar formation leads to a marked fibroblastic reaction (that can be difficult to distinguish from the DFSP itself). The largest retrospective series of DFSP treated with fixed MMS has been published recently by Serra-Guillen et al [24]. Only 2 out of the 222 tumors recurred (recurrence rate, 0.9 %) over a median follow-up of 63.5 months. They showed a mean minimum margin of 1.23 cm to achieve tumor clearance and 8.5 % of their cases invaded but did not cross the muscle fascia. In our cohort, while deep margins were involved in 85.2 % of our patients, the low frequency of only lateral margin involvement (14.8 %) confirmed the adequacy of a 13-mm lateral margin. Our results show a low recurrence rate (0.4 %) numerically lower than the previously reported ones

Our study has the advantage of using a standardized surgical procedure performed prospectively and of describing a large cohort with long-term follow-up of more than 60 months.

One limitation noted in this study was that 17.0 % of patients were lost to follow-up because of a change of residence and could not be reached.

Additionally, although this study has the advantage of using a standardized surgical procedure performed prospectively, further high-quality studies including a randomized trial comparing the fixed MMS procedure with frozen MMS and WLE, with extended follow-up periods are required. However, considering the very low recurrence rate for MMS-treated patients, planning such trials may raise technical and ethical difficulties [7].

5. Conclusion

Fixed MMS should be considered an optimal treatment option for MMS in DFSP. Similar to frozen MMS, fixed-MMS involves staged excisions with three-dimensional histological analysis and results in a smaller postoperative defect, a better cosmetic and functional outcome and a lower recurrence rate. Moreover, fixed-MMS provides other benefits such as better quality of pathological examination, the possibility of immunostaining and therefore fewer false-negative cases. The number of treated patients and the long follow-up period provide some evidence here as to the efficiency of this procedure, and DFSP patients should be addressed to centers routinely providing this procedure.

Table 2
Methods of reconstruction after fixed MMS procedure.

	Total (n = 223)	%
Direct suture	144	65
Skin flap	31	14
Skin graft	27	12
Secondary intention	21	9

N: numbers, %: percentage.

Table 3
Main series using WLE and frozen MMS.

	Snow et al.	Van Lee et al.	Durack et al.		Loghdey et al.	Saifuddin et al.	
Patients (number)	20	34	97	362	76	9	9
Surgical technique	MMS	MMS	MMS	WLE	MMS	WLE	MMS
Margin (cm) median [range]	NA	NA	4 [2–6]	3[2–5]	NA	NA	NA
Mohs' stages	NA	NA	1.9	NA	NA	NA	NA
- average	4.1 [2–12]						2 [1–3]
- median [range]							
Local recurrence rate (%)	0	0	0	1.7	1.5	11.1	0
Follow-up (months) median [range]	> 60 [60–240]	48 [36–72]	14.4 [4.6–36.1]	27.1 [7.9–48.9]	50 [2–132]	60 [42–135.6]	

NA: not available; MMS: Mohs micrographic surgery; WLE: wide local excision; %: percentage.

Table 4
Main series using fixed MMS.

	Serra-Guillén et al.	Tan et al.	Chaput et al.	Gonzalez et al.	Lee et al.	Nieto-Benito et al.
Patients (number)	222	35	35	27	41	163
Fixed-mohs stages -average (±SD)	1.47 (0.697)	NA	NA	1.6 (NA)	NA	NA
- median [range]	NA	2 [1–4]	1 [1–3]	NA	1 [1–4]	1 [1–3]
Local recurrence (%)	0.9	0	0	3.7	5.6	0.74
Follow-up (months) median [range]	63.5 [NA]	29.5 [6–146]	46 [35.2–60.2]	92.6 [16–225]	19.6 [0.7–85.8]	28.6 [17.3–44.9]

SD: standard deviation; NA: not available.

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CRediT authorship contribution statement

Jean F. Sei: Conceptualization, Data curation, Methodology, Validation, Writing – review & editing. **Chaussade Véronique:** Conceptualization, Methodology, Writing – review & editing. **Leire Gonzalez-Lara:** Conceptualization, Formal analysis, Validation, Writing – original draft, Writing – review & editing. **Aouidad Iman:** Data curation, Writing – review & editing. **Tchakerian Arnold:** Data curation, Writing – review & editing. **Serra Marc:** Data curation, Writing – review & editing. **Zimmermann Ute:** Data curation, Writing – review & editing. **Clerici Thierry:** Data curation. **Blom Astrid:** Data curation, Writing – review & editing. **Funck-Brentano Elisa:** Data curation, Writing – review & editing. **Philippe Saiag:** Conceptualization, Data curation, Formal analysis, Resources, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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