Mohs micrographic surgery for dermatofibrosarcoma protuberans (DFSP): A single-centre series of 76 patients treated by frozen-section Mohs micrographic surgery with a review of the literature

Mohamed Saleem Loghdeya,*, Sandeep Varma a, Sanjay M. Rajpara a, Haytham Al-Rawi a, Graeme Perks b, William Perkins a

a Department of Dermatology, Queens Medical Centre, Derby Road, Nottingham NG7 2UH, UK
b Department of Plastic Surgery, Queens Medical Centre, Derby Road, Nottingham NG7 2UH, UK

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Summary Dermatofibrosarcoma protuberans (DFSP) is a rare low-grade sarcoma that typically presents with local invasion but rarely metastasises. Surgical excision remains the first-line treatment for DFSP. There are no randomised controlled or prospective studies comparing wide local excision (WLE) with Mohs micrographic surgery (MMS), but available evidence from the retrospective studies and case series available has consistently shown higher recurrence rates for standard surgery and WLE than for MMS. Combined recurrence rates of data within the last 20 years for WLE have been reported at 7.3% compared with 1.1% for MMS. Our aim was to review the clinical details and recurrence rates of DFSP cases treated with frozen-section MMS in our centre between 1996 and February 2013. The relevant data were collected from the case notes. It involved 76 patients with nine of these patients lost to follow-up. In the remaining 67 (67/76) cases, the recurrence rate was 1.5% during the mean follow-up period of 50 months (2–132). This is comparable to recurrence rates for the MMS in the literature [20,21]. Our series is the largest series for frozen-section MMS reported to date.

KEYWORDS
Dermatofibrosarcoma Protuberans;
Mohs micrographic surgery;
Wide local excision;
Cutaneous sarcoma

* Corresponding author.
E-mail address: sloghdey@yahoo.com (M.S. Loghdey).

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Introduction

Dermatofibrosarcoma protuberans (DFSP) is a rare soft tissue tumour of mesenchymal origin that is locally aggressive. It extends deep into subcutaneous tissue and has a propensity to invade through fascial planes and into muscle with tentacle-like extensions contributing to a high risk of local recurrence after surgical excision. It is a rare tumour with a prevalence of 0.8–4.2 cases per million persons per year and accounts for between 2% and 6% of all soft tissue sarcomas and is the most common skin sarcoma.\(^6\) It involves the trunk in 50–60% of cases, the upper limbs in 25% of cases, followed by head and neck in 10–15% of cases, but can occur anywhere in the body.\(^3\) Although it may occur at any stage in life, the lesions are most common in the second to fifth decades, with a slight male predominance.\(^3,5\)

Clinically, DFSP is characterised by nodular or plaque-like lesions with a skin-coloured, brown-yellow, red-tinged, sclerodermiform, telangiectatic or atrophic surface (Photograph 1). Usually, it is fixed to the dermis, but freely moving over the deeper tissues except late in the course of the disease or in recurrent tumours. Long-standing lesions may ulcerate. DFSP may increase in size over a period of months to years, to produce large protuberant nodules, for which it is named.\(^1\) It has a propensity to invade through fascial planes and into muscle.\(^1\) Histologically, DFSP is characterised by a monomorphous proliferation of bland-looking spindle cells (frozen-section Photomicrograph 1) with a fascicular and storiform architecture, low mitotic activity and deep, honeycomb infiltration into subcutaneous adipose tissue (frozen-section Photomicrograph 2). Early lesions may have a grenz zone histologically. There are several variants described, which include pigmented (Bednar tumour), myxoid, myoid, granular cell, sclerotic, atrophic, giant cell fibroblastoma variants and DFSP with fibrosarcomatous areas. The tumour margin can be difficult to gauge clinically because the irregular, tentacle-like projections of neoplastic cells can diffusely infiltrate the surrounding dermis and subcutis and deeply invade fascia and muscle. Approximately 85–90% of all DFSPs are low-grade lesions. The remaining 10–15% contain a high-grade fibrosarcomatous (DFSP-FS) component showing a ‘herringbone’ pattern histologically (frozen-section Photomicrograph 3), and this accounts for 5% of the tumour volume. These lesions have a significantly higher rate of local recurrence and increased risk of distant metastases.\(^6\)

Low-grade DFSP carries a small risk of metastasis (0.5%), and this is usually preceded by multiple local recurrences. In cases of metastasis, the lung (4%) is the most common site, with metastasis to other areas including regional lymph nodes (1%), brain, bone and heart being reported.\(^7,8\)

Based on these findings and the current literature evidence, we advocate MMS as the treatment of choice for DFSP in all locations.

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histopathology report, use of CD34 stain for diagnosis and during MMS, prior treatment, details of MMS including the number of stages and sections required, type of surgical repair, length of follow-up and incidence of recurrence.

All patients underwent standard MMS using the fresh frozen tissue technique. The clinically palpable border of the primary lesion or scar margin was marked for debulking, with complete removal of the previous attempted excision in all but one case (our one case of recurrence after MMS). The debulk layer was taken at this marked margin followed by subsequent Mohs layers. Mohs layers were taken at 1-cm margin at each stage on the body and at 0.5-cm margin on the head and neck areas (Photograph 2). Tumescent local anaesthesia was used in all but three cases (general anaesthesia used in two paediatric cases aged 5 and 12 years and epidural/spinal anaesthesia used in the vulval case). The Mohs layer of tissue with underlying fat was removed en bloc and divided into smaller blocks for frozen sectioning. A Mohs map was prepared illustrating the location of the lesion and the blocks into which it was divided. Orientation tissue nicks were placed on the tissue removed and on the area from which it was removed. Each block was then further orientated by the placement of dyes on the tissue edges as outlined on the Mohs maps to demonstrate the position of each block within the larger tissue specimen. Each block of tissue was then placed on cryostat chucks and the tissue was then embedded in an optimum cutting temperature (OCT) compound. The tissue was frozen at −23 °C and sectioned into 7-μm-thick specimens at 200-μm intervals and stained with H&E. Representative specimens from each block were examined microscopically. In this manner, the entire epidermis, dermis and underlying fat were assessed allowing 100% analysis of surgical margins. If the tumour was present in any area of the specimen, a further layer of tissue was removed from the area known to be positive for tumour. The process was repeated until all margins were clear. In the initial few patients, a final Mohs layer was sent for permanent paraffin sections and examination by the dermatopathologist. For the first 5 years, additional tissue was sent for permanent sections to confirm results from frozen sectioning if equivocal areas were present in the section.

Patients underwent reconstruction by the Mohs surgeon on the same day or by a plastic surgeon the following day. No patient had adjuvant radiotherapy (RT). Patients were followed up at 7–14 days post-operatively for suture removal. Subsequently, they were seen at 6 and 12 months post-operatively and followed up annually for a minimum of 5 years.

Results

Seventy-six patients (76), 35 male and 41 female patients, were treated during this period. Sixty-seven (67/76) cases were primary and nine (9/76) were recurrent lesions with the duration of recurrence ranging from 6 months to 14 years. Five (5/9) of the recurrent lesions had previous incomplete excisions and four (4/9) had multiple incomplete excisions. One (1/9) of the recurrent lesions had Modified/‘Slow’ permanent section Mohs elsewhere. The average duration of the lesions was 83 months with a range of 2–480 months and the mean age of patients was 45 years with an age range of 5–82 years.

The location of the tumours is shown in Figure 1, with the trunk (50%) being the most common site of involvement followed by the limbs (39%) and head and neck (11%). The diagnosis of DFSP was made by excision biopsies in 55 patients, by incision biopsy in 19 patients and by punch biopsy in two patients.

The margins required for tumour extirpation with clear margins are shown in Figure 2. Complete tumour clearance was achieved with a margin of <2 cm in 80% of cases (61/76), and a margin of <3 cm was needed in 91% of cases (69/76). Nine percent (8/76) of cases required a margin of >3 cm for tumour clearance. In the nine cases of recurrent tumours, seven of these cases (7/9) were clear with a margin of ≤2 cm. The remaining two recurrent cases required 3- and 5.5-cm margins for tumour clearance.

Twenty-eight percent (21/76) of patients were referred to plastic surgeons and one to the gynaecologist, by prior arrangement, for reconstructive procedures the following day with the remainder of patients having their wounds reconstructed by the Mohs surgeon on the same day. The method of reconstruction post MMS is shown in Figure 3 with 73% of cases (55/76) sutured directly.

Follow-up data were not available in nine patients (12%). In the remaining 67 patients, the average duration of follow-up was 50 months (range 2–132 months). More than half of the (35/67) patients have completed ≥5 years of follow up. Just over two thirds of the patient population (46/67) has been followed up for at least 3 years. There has been one recurrence during this time giving the recurrence rate in our study of 1.5% (1/67). Patients will continue to be monitored annually until 5 years post-operatively by the Mohs surgeon, and lifetime monitoring will continue beyond this point by each patient and their family physician.

Discussion

Complete surgical resection remains the primary treatment and the mainstay of therapy for DFSP. The single most important factor in the complete removal of DFSP with resultant negative margins is the complete assessment of the surgical margin (NCCN guidelines). The tumour’s ability
to invade local fascia and muscle with tentacle-like projections poses a challenge to achieve clear margins by any technique that does not observe 100% assessment of the surgical margins. Increased levels of hyaluronic acid in the tumour helps with tumour invasion; this may be a possible factor contributing to the formation of difficult-to-resect microinfiltrates. Microscopic outgrowth of tumour cells may extend vertically and horizontally beyond the macroscopic tumour margins, and this is probably responsible for the higher recurrence rates observed with standard vertical histological sectioning. Because of this non-concentric extension of tumour cells, a circular excision regardless of the size of the lateral margin can never guarantee complete excision of the lesion and sacrifices abundant healthy tissue. Standard histological vertical sectioning with WLE assesses <2% of the total tumour margin, whereas in MMS the entire specimen width, sides and depth (100% of the surgical margins) are assessed, thus allowing the tentacle-like projections to be traced and removed whilst conserving normal tissue (Figure 4). Fields et al. have shown with multivariate analysis that the disease-free survival of primary DFSP is dependent on the depth of the tumour underscoring the importance of excising the deep fascia to remove any infiltrating tumour cells. In the case of recurrent DFSP, Fields et al. have shown with multivariate analysis that disease-free survival is dependent on clear histological margins. This emphasises the importance of using a technique that assesses 100% of the surgical margin. The characteristics of DFSP tumours that make MMS a suitable and effective technique are the extensive contiguous subclinical extensions in primary lesions, the high risk of local recurrence, the low risk of distant metastasis, the indolent growth pattern and the tumour being readily identified in frozen tissue sections. As large portions of the true margins are not evaluated with standard vertical histological tissue sections and because of the difficulty in identifying the characteristic occult, finger-like projections, the recurrence rates are higher with standard surgery and WLE where standard histological vertical tissue sectioning is used (Figure 4). Based on the tumour volume excised with MMS, Ratner et al. predicted that concentric margins of 2, 3 and 5 cm around the macroscopic tumour would have left the residual microscopic tumour in 39.7%, 15.5% and 5.2% of cases, respectively. Local recurrence rates ranged from 26% to 60% in
116 patients treated with undefined or conservative margins in five studies.\textsuperscript{2}

WLE is not well defined in the literature with little agreement among authors on the most appropriate surgical margin to take.\textsuperscript{20} Most authors consider margins between 2 and 4 cm wide, and these are recommended by NCCN guidelines for standard excision of DFSP.\textsuperscript{25} As is evident from our study, a margin of \(>4\) cm was needed in four \(4/476\) patients with 95\% of patients \(72/76\) needing \(<4\) cm to achieve tumour clearance. Using a 3-cm margin would have cleared 89\% of patients \(68/76\). Only one \(1/68\) patients needed a 3-cm margin all around; of the remaining 67 patients, six needed a 3-cm margin only in part with 80\% of patients \(61/76\) being clear with margins of \(<2\) cm. Treating all the above patients with a 2–4-cm WLE margin would have resulted in excessive tissue removal in 80\% of cases \(61/76\) and inadequate margins in 5\% of cases \(4/76\) making MMS a better choice.

Recent reviews of the literature show the raw pooled data for WLE-treated patients within the last 20 years having recurrence rates between 6.3\% and 7.3\%.\textsuperscript{19,20} Glorster et al. report that 50\% of DFSP recurrences after WLE surgery are observed within the first year and 80\% within the first 3 years.\textsuperscript{4}

Farma and colleagues report a recurrence rate of \(<1\%\) after WLE.\textsuperscript{29} In their series, relatively narrow surgical margins of 1–2 cm were needed to achieve clear margins. Twenty percent of their cases required multiple excisions to achieve clear margins, and no surgical defect was closed until negative histological margins were obtained. The technique used by Farma et al. is a modified WLE procedure (CCPDMC) similar to the Modified/Slow Mohs procedure and may be more representative of this technique than that of traditional WLE (Figure 4).\textsuperscript{28} Similar techniques termed the ‘vertical modified technique’ used by Hersant et al. and ‘three-dimensional histology’ used by Irazarzaval et al. were recently reported.\textsuperscript{30,34}

For MMS-treated patients, recent reviews of the literature show raw pooled data of these patients having a low recurrence rate approaching 1%.\textsuperscript{19,20} The recurrence rate in our study of 1.5\% is not significantly different to this.

To date, ours is the largest series of DFSP treated with MMS in the literature. There was only one case of recurrence post MMS identified in our series. In this case, the tumour was originally excised with WLE and reconstructed with a skin graft 5 years prior to us performing MMS. The patient was referred to us for MMS to remove this recurrence post WLE on the proximal end of the skin graft repair (Photograph 3). This patient presented with a recurrence post MMS on the dorsum of the left foot at the distal end of the original skin graft (Photograph 4). This recurrence was in an area on the original skin graft where the distal portion of the original graft over the web spaces was not removed during MMS in an attempt to prevent damage to the web space structures. This was not in keeping with our standard protocol where the entire skin graft would normally be excised and evaluated to ensure complete removal of non-contiguous tumour recurrence. He had the recurrence in the distal portion of the original skin graft 4 years post MMS.

In a recent review, the mean time to recurrence for the 7/673 recurrent cases in pooled data post MMS was 68 months. The authors suggest that in view of these late recurrences, consideration should be given to extending follow-up period beyond 5 years for patients having DFSP treated with MMS. More than half of patients \(35/67\) in our series were followed up for \(>5\) years. Just over two thirds of patients \(46/67\) were followed up for at least 3 years. As mentioned earlier, patient follow-up will continue for 5 years post-operatively by the Mohs surgeon and lifelong monitoring will continue beyond this point by each patient and their family physician. All treated patients were educated about the importance of long-term follow-up and self-monitoring. It is hoped that this education would result in detection of recurrences and referral back to our department in the nine patients lost to follow-up. Thus far, our attempts to contact these nine patients have been unsuccessful and we have not received communication from these patients or their family physicians about any recurrences. It is our intention to submit an updated report on the entire cohort of patients once all patients have completed 5-year follow-up.

There are certain limitations of frozen-section MMS. There is a time and cost consideration with the estimated cost for WLE with local anaesthesia to be £150 versus £900 for MMS (U.K. National Health Service Cost codes 2011). The amount of time and labour involved in processing larger lesions and tissue sections can be technically challenging requiring around 4 hours to complete a case. Complete excision with tumour-free margins may not always be attainable with MMS, e.g. cortical bone involvement. MMS needs a specialised team and several stages can be required to achieve complete removal. The Mohs surgeon should be familiar with and have experience in reading frozen sections for DFSP. Some authors suggest that identifying negative margins on MMS sections are difficult and unreliable, especially in cases where previous excision was attempted with resultant scar formation. To guard against this potential problem, many authors send a final stage for formalin-fixed paraffin-embedded sections after clearing the tumour with frozen-section MMS. Other authors have also described performing Modified/‘Slow’ Mohs when treating DFSP by sending their mapped tissue for permanent paraffin-embedded sectioning with good results.\textsuperscript{12,22,31} This technique has the disadvantage of taking many days to complete and possibly requiring multiple patient visits with a resultant delay in surgical repair.\textsuperscript{32,35} The evidence does not demonstrate superiority of either frozen-section MMS or Modified/‘Slow’ permanent-section Mohs.\textsuperscript{21} Permanent sections whether in the setting of final stage with frozen-section MMS or in Modified/‘Slow’ Mohs allow for immuno-histochemical staining (CD34) to help confirm clear margins. Other potential histological pitfalls with frozen-section MMS are the difficulty in detecting neoplastic cells at the periphery of the tumour due to the presence of normal scattered dermal spindle cells/fibroblasts (CD34 + ve) (frozen-section Photomicrograph 5) which are more commonly seen on frozen sections than on paraffin sections.\textsuperscript{24} Furthermore, it can be difficult to differentiate neoplastic cells from very small blood vessels (CD34 positive/Factor 13a positive) normally found within fat lobules (frozen-section Photomicrograph 4). The advantage of frozen-section MMS are a quicker margin status evaluation, thereby allowing completion of surgery and surgical repair on the same day. The safety limits for the cumulative dose
of local anaesthesia needs careful consideration and it may be inadequate for patient comfort when defect extends deep to the fascia.\(^1^8\) The use of tumescent anaesthesia generally avoids this problem. For the recurrent, large tumours, tumours involving the head/nose, cosmetically important structures and vital structures, a multidisciplinary approach involving respective surgical specialities is important for complete removal of the tumour and also for the reconstruction. In certain cases, a multidisciplinary approach involving Mohs surgeon and plastic, ear, neck and throat (ENT) or head and neck surgeon is required for the optimal treatment of this rare tumour.\(^3^3\)

RT has been used for local control of gross disease and post-operative RT reduces the risk of local recurrence in patients with narrow or positive margins.\(^1^3\) RT has occasionally been used as a primary therapeutic modality for DFSP, but it is more commonly used as adjuvant therapy after surgery. When used in conjunction with standard surgery, RT has shown to reduce the recurrence rates.\(^1^4\) Its role in the routine management of DFSP, however, has not been evaluated. The NCCN 2014 guidelines suggest that post-operative RT or imatinib mesylate should be considered for positive surgical margins if further surgery is not feasible (unresectable disease).

Imatinib mesylate, a tyrosine kinase inhibitor and inhibitor of platelet-derived growth factor receptor b (PDGFRB), has been shown to be useful in reducing tumour size preoperatively in large tumours and partial to good response in cases of metastatic, recurrent and locally advanced disease. The response varies in different studies and could be due to resistance mutation in the PDGFB receptor.\(^1^5\) Tumours lacking t(17; 22) and possibly not depending on signalling through PDGFRs do not seem to respond to imatinib or have a variable response to it.\(^1^6,1^7\) Imatinib leads to reduced cellularity and hyalinisation of the tumour.

The NCCN 2014 guidelines currently recommend that imatinib be considered in cases of DFSP recurrence where RT was used previously and that are deemed unresectable.\(^2^5\)

Most authors recommend that all cases of DFSP be evaluated for the COL1A1–PDGFB fusion gene before commencing treatment with imatinib. Imatinib is generally well tolerated. Standard chemotherapy regimens have not been shown to be useful for locally advanced and/or metastatic DFSP.\(^4\)

**Conclusion**

There are no current published guidelines based on any levels of evidence for the management of DFSP.\(^2^6\) There is also no consensus about the role of MMS in DFSP management. A recent critical appraisal by Matin et al.\(^2^1\) and a systematic review by Foroozan et al.\(^1^9\) weakly recommend MMS as the preferred treatment of DFSP based on lower recurrence rates. These lower recurrence rates are more evident in recurrence-prone and more difficult regions, such as the head and neck area. Their recommendation is qualified by the need for a definitive randomised controlled trial (RCT). Barlow et al.\(^2^2\) highlight that the rarity of DFSP, lower recurrence rates with MMS in nonrandomised trials and that a lack of clinical equipoise would make it difficult to undertake an RCT.

We report the largest case series of DFSP patients treated by frozen-section MMS. Our recurrence rate is similar to that quoted in the recent literature and suggests that MMS is the optimal treatment for DFSP in all body sites enabling tissue preservation and possibly allowing for less complicated closures with a low recurrence rate.

**Conflict of interest**

None.

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None.

**Ethical approval**

Not applicable.

**Appendix A. Supplementary data**

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.bjps.2014.05.021.

**References**

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