Protocol for a 10-year review of surgical management of Dermatofibrosarcoma Protuberans (DFSP) in the UK

Research question: What is the local recurrence rate (at 3 years) for dermatofibrosarcoma protuberans when comparing Mohs micrographic surgery and wide local excision?

Background:
Dermatofibrosarcoma protuberans (DFSP) is a rare, indolent but locally aggressive cutaneous sarcoma. It affects all races and most commonly arises in adulthood between the ages of 20 and 50 years but can arise at birth (1, 2). The reported annual incidence of DFSP in large epidemiological studies is around 4-5 per million cases per year (3,4,5). In England, the average number of new cases over a ten year period from 2002 to 2011 was 2.6 cases per million (6). Non-melanoma skin cancer is under reported in the UK which may explain the apparent lower incidence. However, the average incidence has demonstrated a sustained increase after 2007 with figures continuing to rise (7).

Although metastatic disease is very rare, DFSP can recur locally even after excision with apparently adequate surgical margins. Recurrence and consequent surgical management can incur significant morbidity, may be associated with an increased risk of fibrosarcomatous change (8), and increases use of precious NHS resources. In the UK, there are two main clinical pathways for management of DFSP; Sarcoma Specialist Teams and Skin Cancer Specialist Teams (including both Dermatological and Plastic surgeons). The latter usually treat DFSP limited to superficial fascia (9), although in practice, this is not a distinction which can be accurately made pre-operatively.

There is significant variation in the current surgical management of DFSP. Conventionally, it has been managed by wide local excision (WLE) with margins ranging between 1cm and 5cm (12-18). Recurrence rates are reported to be from 0 to 60% (10-18). Mohs micrographic surgery (MMS) limits excision to histologically involved tissue, and has been reported to achieve recurrence rates of 0% to 8.3% (2, 11, 19-27). However, these data are based on retrospective and/or non-comparative studies that are heterogeneous in study design and potentially subject to bias. There have been no randomised controlled trials comparing these surgical treatments and little robust long-term follow up data.

The literature regarding management of DFSP does not allow clinicians or patients to make informed evidence-based decisions. As a result there appears to be clinical equipoise across those who manage this condition. In 2011, the British Society for Dermatological Surgery (BSDS) issued a position statement (http://www.bsds.org.uk/BSDS_position_statement_for_DFSP_Dec_11_final.pdf), identifying MMS as ‘the initial treatment of choice for all DFSP’. However, some UK clinicians contest this, maintaining that WLE offers equally effective results albeit based on data from small retrospective case series (28). There have been two systematic reviews (29, 30), which both concluded that the published literature confers a weak recommendation in favour of MMS or similar surgical techniques with careful margin control, but suggested the need for high quality trials with sufficient follow up periods. The observational nature of the data, small numbers and lack of standardized technique for either procedure make it very difficult to draw conclusions regarding the comparative outcome of these
treatments. If an RCT could demonstrate lower recurrence rates with MMS, which is cost-effective, this would support BSDS opinion to increase Mohs-trained surgeons and guide management.

Given the absence of a strong evidence base for managing DFSP, and the wide variation in practice across the UK, we have undertaken a 10-year retrospective case-note review of current clinical practice. Findings from this review will inform the feasibility of undertaking a future randomized clinical trial, which would evaluate recurrence rates comparing MMS and WLE.

Aims:

a) To establish current surgical management of primary and recurrent DFSP in the UK over a 10 year period
b) To determine local recurrence rates for primary DFSP comparing surgical management using MMS versus WLE
c) To evaluate survival outcomes for DFSP treated with MMS compared with WLE
d) To establish a collaborative network of Dermatologists and Plastic Surgeons who manage patients with DFSP

Outcomes:

Primary:
Local recurrence rates at 3 years for primary DFSP following MMS and WLE.

Secondary:

a) Time to first recurrence
b) Histological clearance
c) Number of surgical procedures to achieve adequate histological clearance
d) Post-operative complication rate
e) Distant recurrence-free survival
f) Recurrence-free survival

Methodology:
The study design is a retrospective case-note series of patients with DFSP (Jan 2004 – Jan 2014).

Clinicians (Dermatologists and Plastic surgeons) were recruited via invitation to join the study through the UK Dermatology Clinical Trials Network (UK DCTN), the British Association of Dermatologists regional trainee representatives and the Reconstructive surgical trials network (RSTN). Contributors obtained local Research & Development department approval. Clinicopathological data were collected using a pre-designed Excel proforma and included: demographic data, clinical history of the lesion, tumour site, surgical/therapeutic details, histological information, post-operative events,
follow up. All data were anonymised and submitted to the review lead (AD) via secured email (NHS.net).

Analysis:
Demographic and clinicopathological data will be reported for the two surgical groups. Means (SDs) or medians (IQRs) will be used for continuous data and percentages for categorical data. T-tests, Mann-Whitney-U or Chi-squared tests will be used to compare the two groups at the univariate level.

For primary DFSP patients, the crude local recurrence rates at 3 years will be calculated by dividing the number of recurrences over 3 years from surgery by follow-up time, for each surgical group. Multivariate Cox Proportional Hazard Modelling will be used to determine adjusted hazard ratios comparing the rate of recurrence in the two groups, after adjusting for confounders. Confounders will be identified if the adjusted hazard ratio, for each potential confounder, changes by more than 10% compared to the unadjusted hazard ratio. The proportional hazards assumption will be checked.

For primary and recurrent DFSP patients separately, the following will be conducted:

i. Time to recurrence will be measured from the date of surgery to the date of histologically confirmed local recurrence. The Kaplan-Meier method will be used. The median time for the two groups will be calculated.

ii. The odds ratio of histological clearance following surgery, comparing the two groups, adjusted for confounders, by using multivariate logistic regression.

iii. The odds ratio of post-operative complication rates comparing the two groups, adjusted for confounders, by using multivariate logistic regression.

iv. Time to metastases will be measured from the date of surgery to the date of confirmed distant metastases. The Kaplan-Meier method will be used. The median time for the two groups will be calculated. Multivariate Cox Proportional Hazard Modelling will be used to determine adjusted hazard ratios comparing the rate of recurrence in the two groups, after adjusting for confounders.

v. Recurrence-free survival will be measured from the date of surgery to the date of recurrence or death. The Kaplan-Meier method will be used. The median time for the two groups will be calculated. Multivariate Cox Proportional Hazard Modelling will be used to determine adjusted hazard ratios comparing the rate of recurrence in the two groups, after adjusting for confounders.

Dissemination:
The target audience for this study will be those involved in managing DFSP including, but not limited to, Dermatological surgeons, Plastic surgeons and Sarcoma specialists. A report of the findings will be written and submitted to a peer-reviewed journal, and findings will be presented at relevant academic conferences.
References


