Rates of re-excisions and recurrences of dermatofibrosarcoma protuberans in the Netherlands between 1989-2016

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ABSTRACT

Dermatofibrosarcoma protuberans (DFSP) is a rare soft tissue tumour of which the quality of care is poorly studied. Therefore, rates of re-excisions and recurrences were determined using data from the Netherlands Cancer Registry between 1989-2016. Of the 1,890 DFSP included, 87% were treated with standard excision, 4% with Mohs micrographic surgery (MMS), and 9% otherwise or unknown. Linked pathology data was retrieved for 1,677 patients. Half of all excisions (847/1,644) were incomplete and 29% (192/622) of all re-excisions were incomplete. The cumulative incidence of a recurrence was 7% (95% CI 6-8) during a median follow-up of 11 years (IQR 6-17). After MMS (n = 34), there were no recurrences during a median follow-up of four years (IQR 3-6). Due to the found high rate of incomplete standard excisions and recurrences after excision, this study supports the European guideline, which recommends treating DFSP with MMS to decrease the rate of recurrence.

INTRODUCTION

Dermatofibrosarcoma protuberans (DFSP) is a rare soft tissue tumour which originates from a translocation of chromosome 17 and 22, resulting in tumour cell proliferation of fibrohystiocytic lineage. Unlike most skin cancers, DFSP is a non UV related skin cancer. The overall standardized incidence rates in the Netherlands and the United States are 4 per 1,000,000 person-years.[1-3] Men and women are equally affected and the peak incidence age is between 20 and 50 years.[4-6] Although DFSP mostly occurs in adults, DFSP rarely occurs in children (1.0 per 1 million). DFSP is commonly located on the trunk (50%), proximal extremities (20-30%) or head and neck (10-15%).[4-6] It presents as an asymptomatic, slowly growing, skin coloured indurated plaque. Although DFSP rarely metastasize, they do grow in a locally invasive manner into subcutaneous fat, muscles and sometimes to bone.[4,5,7] Clinically and with imaging tests (e.g. MRI or CT) DFSP are difficult to delineate because the tentacle-like invasion into subcutaneous tissue is often greater than suspected. As a result, multiple surgical procedures may be required to ensure complete clearance of DFSP.

Until 2015, DFSP guidelines were lacking and in The Netherlands the majority of DFSPs were treated with standard excision. The European consensus-based interdisciplinary guideline which is available since 2015, recommends to treat DFSP with Mohs micrographic surgery (MMS) in order to reduce the assumed high recurrence rate after standard excision.[8]

To date, outcome data for DFSP management are based on small patient cohorts with limited information on lost to follow-up.[5,9] Previous studies report a wide range of rates of DFSP re-excisions (3%-81%) and recurrences (0%-46%).[5-7,10,11] This nationwide cohort study with long term follow-up of DFSP aims to determine the rate of re-excisions and recurrences, which is needed to inform patients, clinicians, and health policy makers to plan optimal treatment strategies and surveillance schedules.

METHODS

Patients

This cohort study included all patients with a histologically confirmed DFSP in the Netherlands between January 1989 and December 2016 (Figure 1). Data were obtained from the Netherlands Cancer Registry (NCR), which collects data on all newly diagnosed cancer patients in the Netherlands since 1989. Registration is primarily based on notification by the nationwide network and registry of histopathology and cytopathol-

ogy (PALGA), which contains all pathology reports of all Dutch pathology laboratories. Completeness of NCR incidence data on cutaneous malignancies is 93%.[12] All used data for this study from the NCR (i.e. patients sex and age, DFSP location, type of treatment and physician) were collected from the medical records of hospitals by special trained NCR employees. Tumour localization and morphology were registered according to the International Classification of Disease (ICD-O-3). Location of the primary tumour was categorized into face/scalp/neck (C44.0-C44.4), trunk (C44.5), arm/shoulder (C44.6), leg/hip (C44.7), genital (C51.0, C51.9, C63.2) or other (C44.8, C44.9). Vital status and date of death or emigration of the included patients were obtained by annual linkage with the Dutch Municipality Registers.

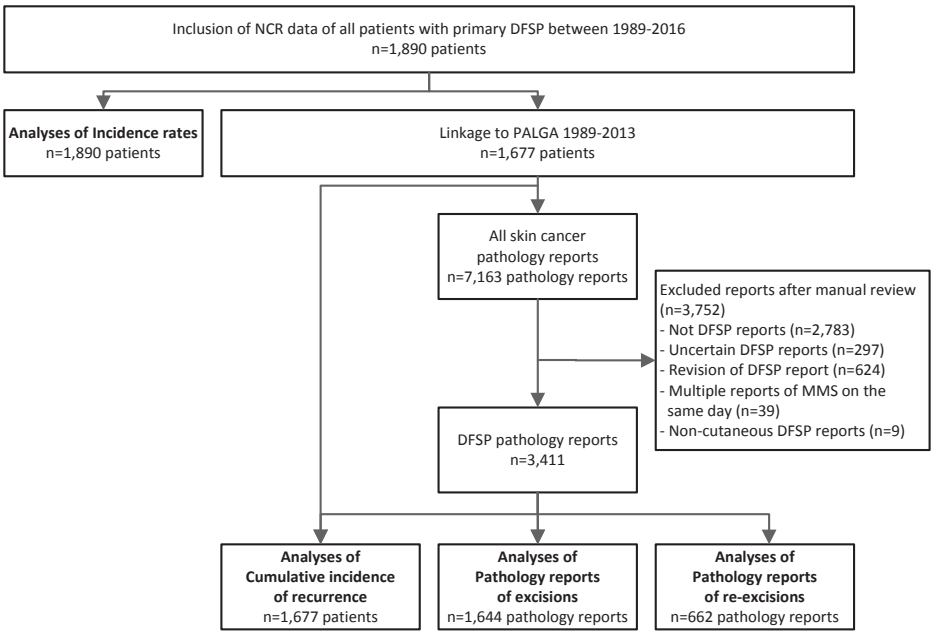

Figure 1. Flowchart of material and methods.
DFSP, dermatofibrosarcoma protuberans; MMS, Mohs micrographic surgery; n, number; NCR, Netherlands Cancer Registry; PALGA, Dutch nationwide pathology database.

Study outcome

The primary outcome was the rate of incomplete DFSP excisions and recurrences. The NCR registers DFSP only at time of the first primary diagnosis. Therefore, to detect all re-excisions and recurrences during follow-up, the included patients from the NCR registry were linked to PALGA. In order to have at least two years of follow-up, PALGA data were retrieved only for patients who were diagnosed with a DFSP before 1 January 2014. Follow-up time of the patients started on the day of the primary DFSP diagnosis

and ended on the day of death or emigration, or last date of NCR-PALGA linkage which was performed for this study at 1 February 2015.

Conclusions from the PALGA pathology reports were manually reviewed (WK,EIVC,LH,CBVL) and scored on the following variables: diagnosis (DFSP, possible DFSP, other), immunohistochemical staining with CD34 (positive, negative, not performed), anatomical location (according to ICD-O3), type of specimen (biopsy, diagnostic excision, wide local excision, re-excision, MMS, Breuninger surgery, other, unclear), histological clearance (yes, no, unknown, not applicable in the case of diagnostic biopsies), invasion into muscle (yes, no, possibly), fibrosarcomatous changes (yes, no, possibly) and clinical excision margins (in mm). Invasion into muscle, immunohistochemistry for CD34, fibrosarcomatous changes and clinical excision margins were missing for 50-99% cases and therefore not included in the final analysis.

All pathology reports with uncertain DFSP diagnosis (i.e. when the pathologist was in doubt of the diagnosis or if the pathology report was unclear) were excluded from the analyses (n = 297). Incompletely excised DFSP included DFSP which histologically invaded the inked surgical margin. Local DFSP recurrence included histologically proven DFSP that occurred at least four months after the previous pathology report, because it was assumed that re-excisions would occur within this period.

Statistical analysis

Annual incidence rates were calculated by sex, age groups and body sites per 1,000,000 person-years from 1989-2016, using the annual population size acquired from Statistics Netherlands (www.statline.cbs.nl). Standardized incidence rates were calculated using the European standard population (2013). Descriptive statistics were used to report the baseline characteristics of patients, DFSP, treatment and study outcome. In order to estimate the number of surgical procedures during follow-up (i.e., including the first surgical treatment of the primary DFSP and all re-excisions and/or recurrences), the mean cumulative count was calculated, which is equal to the sum of the cumulative incidences of all surgical procedures.[13] To estimate the probability of the first DFSP recurrence during follow-up, a cumulative incidence curve (CIC) was calculated, which takes the competing risk of death into account.[14] Statistical analyses were performed using STATA (version 15), SAS 9.4 statistical software (SAS Institute Inc., Cary, NS, USA), R statistical software version 3.4.1 (www.r-project.org). P-values < 0.05 (two-sided) were considered statistically significant.

RESULTS

Incidence and treatment of the first DFSP

A total of 1,890 patients were diagnosed with a DFSP in the Netherlands between 1989 and 2016 (Table 1). Both the crude and European standardized incidence rate of DFSP were 4.2 per 1,000,000 person-years. The incidence rate of DFSP was stable between 1989-2016. Incidence rates were comparable for men and women. Half of the 1,890 patients with a DFSP were women (51%) and overall median age at diagnosis was 41 years (IQR 31-41). DFSP were most commonly located on the trunk (45%) followed by arm/shoulder (24%), leg/hip (16%), head and neck (13%), and genital area (1%) (Table 1).

The majority of the 1,890 patients with a primary DFSPs were treated with excision (87%). Data from the NCR on the first primary DFSP showed that more than half of the 1,890 patients (56%) underwent a single standard excision, whereas 25% underwent two excisions and 6% underwent three or more excisions. Only 4% of patients underwent MMS as a primary treatment or as additional treatment after excision, and 1% were not treated at all. Nonsurgical treatments included postoperative radiotherapy (6%) and or other types of treatment, such as tyrosine kinase inhibitors (1%). The majority of the first treatment for DFSPs were performed by surgeons (38%), while dermatologists treated only 11% of DFSP. The other DFSPs were treated by plastic surgeons (6%), or general practitioners (2%), or by physicians who worked in a multidisciplinary team (13%), or it was unknown (30%).

Re-excisions

For 1,677 patients who were diagnosed between 1989-2013, linked pathology data were retrieved from PALGA (Table 2). Patient and tumour characteristics were similar to patients without linked pathology data [data not shown]. Of the 1,677 patients, 35% underwent a single surgical treatment for a primary DFPS during a median follow-up of 11 years (IQR 6-17). Half of all patients (51%: (588+180+78)/1,677) underwent multiple surgical treatments. The number of surgical treatments was unknown for 14% (n = 240) of all patients. Of all 1,644 pathology reports of DFSP excisions, 32% (n = 524) were completely excised, 52% (n = 847) were incompletely excised and histological clearance was unknown for 17% (n = 273) of all reports. Of all 662 pathology reports of DFSP re-excisions, 61% (n = 401) were completely excised, 29% (n = 192) were incompletely excised and histological clearance was unknown for 69 reports (10%). The mean cumulative count of surgical treatments per patient was 1.4 (95% CI 1.3-1.4) after a follow-up of six months and remained stable thereafter (Figure 2).

Table 1. Description of patients which were diagnosed with a primary dermatofibrosarcoma protuberans in the Netherlands between 1989 and 2016 according to data of the Netherlands Cancer Registry (NCR).

	DFSP patients 1989-2016 n = 1,890 (%)
Sex	
Men	926 (49)
Women	964 (51)
Age in years	
0-19	114 (6)
20-39	741 (39)
40-59	718 (38)
60-79	257 (14)
≥ 80	60 (3)
Anatomical location	
Trunk	848 (45)
Arms/shoulder	463 (24)
Leg/hips	305 (16)
Face/scalp/neck	239 (13)
Genitals	12 (1)
Other	20 (1)
Unknown	3 (0)
Surgical treatment for first primary DFSP	
1 Excision	1053 (56)
2 Excisions	469 (25)
≥ 3 Excisions	109 (6)
MMS	81 (4)
Non-surgical treatment	
Postoperative RT	119 (6)
Others[a]	18 (1)
Unknown	15 (1)
No treatment	14 (1)
Physician	
Surgeon	707 (38)
Dermatologist	209 (11)
Plastic surgeon	105 (6)
General practitioner	42 (2)
Multidisciplinary	240 (13)
Unknown	591 (30)

Percentages were rounded.

DFSP, dermatofibrosarcoma protuberans; MMS, Mohs micrographic surgery; n, number; RT, radiotherapy.

[a] Others included e.g. tyrosine kinase inhibitors.

Table 2. Re-excisions and recurrences of dermatofibrosarcoma protuberans which were primary diagnosed between 1989 and 2013 for whom followed-up until 31 December 2015 from the Dutch nationwide pathology database (PALGA) was retrieved.

	DFSP patients 1989-2013 n = 1,677 (%)
Follow-up in years, median (IQR)	10.5 (5.6-16.6)
Surgical treatments during follow-up[a]	
1	591 (35)
2	588 (35)
3	180 (11)
≥ 4	78 (5)
Unknown	240 (14)
Recurrences	
None	1,517 (90)
1	145 (9)
≥ 2	15 (1)

Percentages were rounded.

DFSP, dermatofibrosarcoma protuberans; IQR, inter quartile range; n, number.

[a] Surgical treatments during follow-up excluded biopsies, treatments of primary DFSPs, and treatments of cases of which the histological DFSP diagnosis was unclear. Surgical treatments included excision and Mohs micrographic surgery (n = 34).

Recurrences

During a median follow-up of 11 years (IQR 6-17), 9% (n = 145) of 1,677 patients experienced one local recurrence and 1% (n = 15) of patients had two or more local recurrences. The cumulative incidence curve showed that the majority of the recurrences occurred within five years (98 of 128, 77%), although some recurrences occurred even after ten years (Figure 3). After 20 years of follow-up, the cumulative incidence of local recurrence was 7% (95% CI 6-8). None of the 34 patients who underwent MMS between 1989 and 2013, experienced any recurrence during a median follow-up of four years (IQR 3-6).

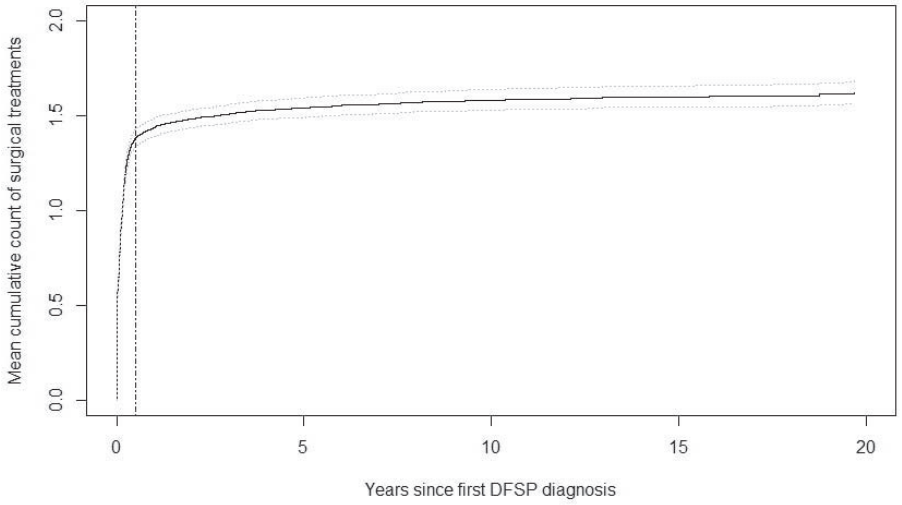

Figure 2. Mean cumulative count of surgical treatments of dermatofibrosarcoma protuberans which were diagnosed between 1989 and 2013 and followed-up until 2015 using data from the Dutch nationwide pathology database (PALGA). The majority of surgical treatments occurred within the first six months (indicated by the vertical line).
DFSP, dermatofibrosarcoma protuberans.

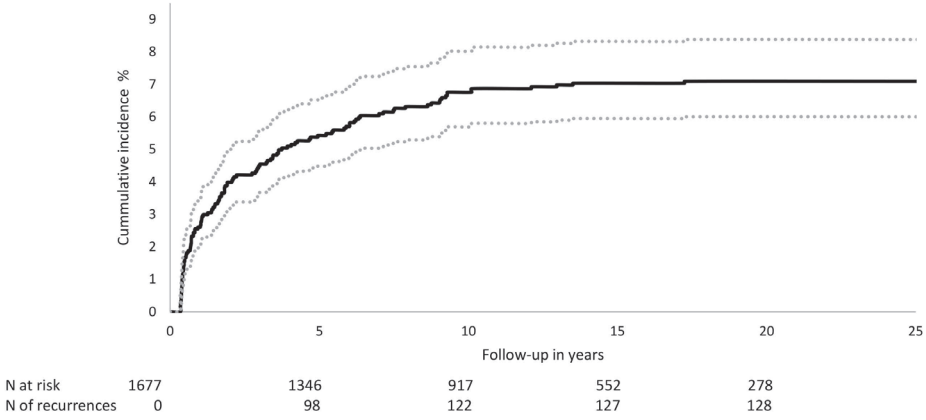

Figure 3. Cumulative incidence curve of the first recurrence with 95% confidence interval of dermatofibrosarcoma protuberans which were diagnosed between 1989 and 2013 and followed-up until 2015 using data from the Dutch nationwide pathology database (PALGA). The majority of recurrences occurred within 5 years of follow-up.
N, number.

DISCUSSION

This large nationwide cohort study of patients with a DFSP shows that the efficacy of standard excision is poor given the high rate of patients who underwent multiple surgical excisions (51%) to clear all tumour cells. This study also showed, that 10% of all patients experienced at least one recurrence during a median followed-up of 11 years (IQR 6-17).

In concordance with other studies, the ratio of incidence rate for men and women was 1:1.The majority of DFSPs occurred among young people (median age 41 years), and the most common location was the trunk (45%).[4,5]

The majority of DFSP excisions were performed by surgeons. This is due to the referral pattern of general practitioners in the Netherlands, who tend to refer patients with a sarcoma or a relatively large tumour to surgeons. Ideally, these patients are referred to dermatologists in specialized centres where multidisciplinary experts work together in order to plan optimal treatment strategies.

While the European guideline recommends to treat DFSP with MMS, this study shows that only 4% of all DFSP were treated with MMS.[8] The low percentage of patients that was treated with MMS is due to the introduction of the Dutch guideline in 2015 (while the cases were included between 1989-2016) and only in a single university medical centre DFSP are treated with MMS since 2008.

Only a few cases were treated with postoperative radiotherapy in our study, because it is still unclear, whether radiotherapy is effective in slowly growing tumours such as DFSP. Also, only a few cases were treated with tyrosine kinase inhibitors (imatinib), because systemic treatment for DFSP is only indicated for metastasized tumours or for tumours which could not be surgically treated, which is rarely the case for DFSPs.[15,16]

We observed that in our large population-based sample 51% of DFSPs were re-excised and 10% recurred. Rates of re-excision and recurrence range vary widely between studies, respectively between 3%-81% and 0%-46%.[5-7,10,11] This variation is most likely due to the small cohort size of the studies (range 14-451), and to the heterogeneity of included patients regarding anatomical locations (e.g. head and neck only versus all body sites), surgical treatments used (e.g. wide local excision versus MMS), clinical excision margin size (e.g. small versus wide), physician (e.g. surgeon, plastic surgeon, dermatologist), methodology of collecting follow-up data (e.g. from the patient files, patients consult

by phone or doctors visit), length of follow-up (few months up to several years) and numbers of patients lost during follow-up (often non specified).[5,9]

The observed DFSP re-excision rate of 51% is much higher than the known re-excision rates for basal cell carcinoma (BCC) (7-30%) and squamous cell carcinoma (SCC) (0-25%).[17-19] Multiple aspects contribute to the high re-excision rate for DFSP when compared to BCC and SCC. First, DFSP is a rare tumour and therefore physicians may be less familiar with the clinical recognition and delineation of the extent of a DFSP. Second, it is difficult to delineate the extent of a DFSP preoperatively because of the subcutaneous tentacle-like invasion, which might be invisible to the naked eye both clinically and on imaging tests (e.g. MRI or CT). Third, DFSP does not grow in a symmetrical manner around the clinical visible centre. Therefore, a clinical tumour free margin even up to several centimetres around the clinical visible tumour centre often results in histologically tumour positive margins at one side of the tumour while on the other side healthy tissue is unnecessarily excised.

Our observed recurrence rate of DFSP during a median follow-up period of 11 years (IQR 6-17) of 10% is within the range of known recurrence rates for BCC (12%), SCC (10%) and melanoma (12%).[18-21] Most likely, histopathological missed residual tumour continued to grow and presented in time as a recurrent DFSP. DFSP might be absent on the evaluated slides while still being present in the patient because with the standardized bread loaf technique only a few vertical slides through the excised specimen are examined representing only a small portion of the true excision margins.

Although this study only presented 34 patients that were treated with MMS, none of the patients developed a recurrence during a median follow-up of four years (IQR 3-6), which is in line with previous studies. A possible lack of aggressiveness of DFSPs treated with MMS compared to DFSPs treated with standard excision, cannot explain this finding, because only a single University centre performed MMS for all DFSPs treated in their centre since 2007. Other University centres performed standard excision for DFSPs. There were thus no referral patterns that could explain this finding. Therefore, our results suggests that MMS is an appropriate treatment for DFSP.[22-25]

The observation that the majority of DFSP recurrences occurred within the first five years of follow-up implies that follow-up of at least five years is reasonable, especially because of the difficulty to clinically distinguish a tumour's origin from a scar tissue or from a recurrence.[4,5]

Strengths of this study are the use of nationwide cancer registry data which resulted in a large number of DFSP cases, a robust dataset to detect re-excision and recurrence rates using the nationwide pathology database, and the long term follow-up period (up to 26 years). Limitations include a lack of information concerning high risk features for most pathology reports, such as invasion into muscle and fibrosarcomatous changes. Another limitation is that 17% of the pathology reports of primary excisions and 10% of the pathology reports of re-excisions did not contain conclusive information on the histological clearance. Therefore, the rate of DFSP incomplete excisions and recurrences was probably underestimated.

In conclusion, this study reports a high rate of incomplete DFSP standard excisions (51%) and a clinically relevant high recurrence rate (10%) during a median follow-up of 11 years. Multiple surgical procedures can lead to poor functional and cosmetic outcome for patients with higher costs to society. This study shows that there is a need to improve the quality of care for DFSP and the results support the current European guideline which recommend to treat DFSPs with MMS instead of excision (8).

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