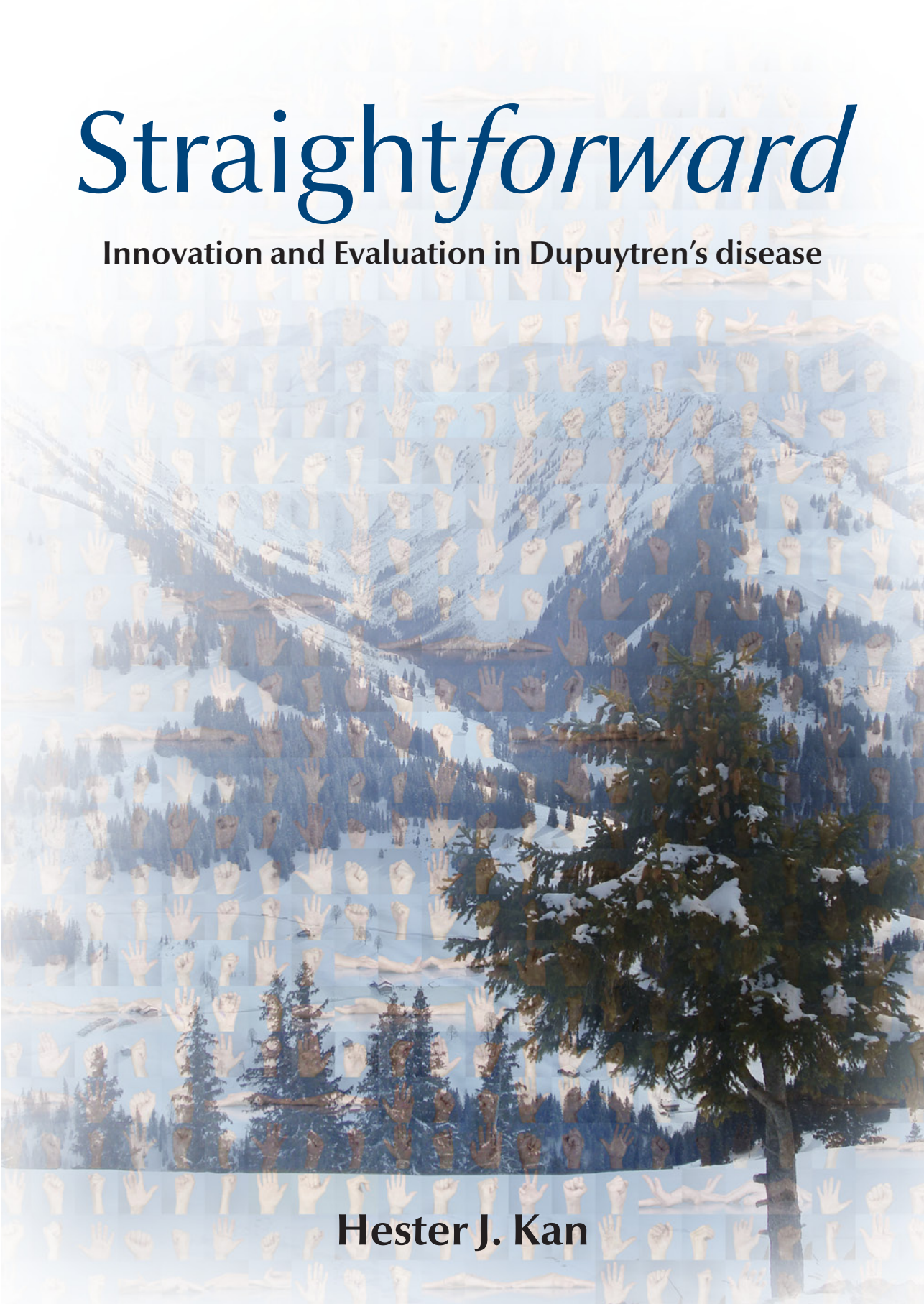
Straight*forward*

Innovation and Evaluation in Dupuytren's disease



Hester J. Kan

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Hester J. Kan, MD

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Straight*forward*:
Innovation and Evaluation in Dupuytren's Disease

Recht*vooruit*:
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Erasmus Universiteit Rotterdam
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	prof. dr. P.M.N. Werker

voor mijn vader, Raphaël Kan

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Part I

Introduction

Chapter 1

General introduction & Outline of the thesis

Partly derived from:

Regenerative Approach to Dupuytren's Contracture with Fat Grafting; Steven E. R. Hovius, MD, PhD; **Hester J. Kan, MD**; Jennifer S. N. Verhoekx, MD, PhD; Roger K. Khouri, MD, FACS; Clinics of Plastic Surgery 2015

Lipofilling as a new treatment strategy for Dupuytren's Disease – from basic science to clinical results: Steven E.R. Hovius, MD, PhD; Jennifer S.N. Verhoekx, MD, PhD; **Hester J. Kan, MD**; Roger K. Khouri, MD, FACS; Federation of European Societies for Surgery of the Hand (FESSH) handbook 2015

GENERAL OVERVIEW OF DUPUYTREN'S DISEASE

Dupuytren's disease (DD) is a chronic progressive fibroproliferative disease characterized by flexion contractures of the fingers, especially in the metacarpophalangeal (MP) and proximal interphalangeal (PIP) joints[1]. In DD the formation of palmar nodules has classically been described as the first sign of the disease, which is the result of myofibroblast proliferation and extracellular matrix synthesis[2]. Myofibroblasts are the cells responsible for the development of the disease[3]. In the later stages of DD, nodules mature to form collagen rich, acellular, fibrotic cords, which lead to digital contractures[4].

Hand function may be compromised due to these digital contractures. Especially fine motoric skills and reaching for objects where a straight hand is necessary (such as grabbing things under a closet, wearing gloves and shaking hands) are difficult for patients with DD [5]. Therefore, reported patient burden can be high[6].

Associated diseases and symptom signs of DD are Peyronie's disease, Ledderhose disease and Garrod's knuckle pads. Peyronie's disease affects the tunica albuginea of the penis and leads to a curvature in erection. When the plantar fibromatosis is affected it is named Ledderhose disease, characterized by nodules under the feet in the plantar fascia that cause walking and weight bearing problems. Garrod's knuckle pads are nodules at the dorsum of the PIP-joints[1].

HISTORY

The first reports mentioning fixed finger contractures dated from the 12th and 13th century in Orkney and Iceland. However, the first real description of the disease is from Felix Plater from Basel in 1614 (Figure 1A). Also Sir Henry Cline (1808) and Ashley Cooper (1818) were earlier in describing a surgical treatment for DD than baron Guillaume Dupuytren.

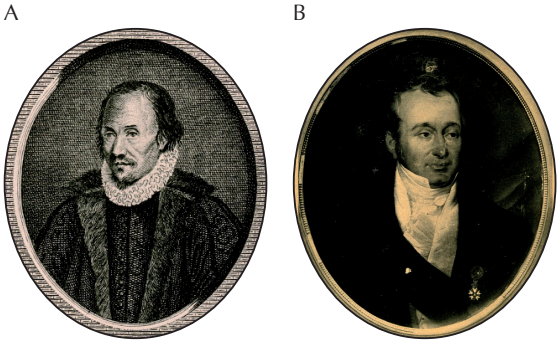

Figure 1: (A) Felix Plater, (B) baron Guillaume Dupuytren (Wellcome Library, London; Iconographic Collections)

The reason the disease was named after Guillaume Dupuytren (Figure 1B) and not Felix Plater, Henry Cline or Ashley Cooper were the lectures Dupuytren gave in Hotel Dieu in Paris and his publication 'permanent retraction of the fingers, produced by an affection of the palmar fascia' in the Lancet in 1834[7-10].

EPIDEMIOLOGY AND RISK FACTORS

The disease is more prevalent in the Northern part of Europe. Males are more affected than females and it is more common in older patients[11-13]. Prevalence rates have been reported ranging from 0.2% to 56% in varying age and population groups[14]. This large range can be explained by the fact that many studies mention 'incidence' rates but in fact calculate 'prevalence' rates, making it difficult to compare studies and blurring our view on the demographic distribution of DD[14].

Family predisposition and genetic pathways are described for DD[15, 16]. Other factors such as smoking, alcohol consumption, excessive vibrations, manual labor, hand trauma, diabetes and epilepsy have also been linked to DD[17-25]. These risk factors have been questioned because many studies are of low methodological quality and may not be based on representative samples of the general population[13, 26]. However, a larger en more representative prevalence study from the Netherlands did find a relation with hand injury in the past and excessive alcohol consumption[13].

CLINICAL VARIATION

The clinical presentation of hands with DD differs tremendously (Figure 2). Most commonly, the fourth and fifth digit of the hand are affected, but it can also be seen in the other digits and interdigital webspaces[27, 28].

One of the reasons of this clinical variation is the severity of the underlying biology of the disease, which is called Dupuytren's diathesis[16]. Bilateral hand involvement, ectopic disease, family members with DD and an early onset of the disease are factors that influence the Dupuytren diathesis[29]. A more severe diathesis will result in higher recurrence rates and may lead to multiple surgeries during lifetime. One study even reports a formula for Dupuytren diathesis to predict the risk for recurrent disease:

$$^2/_3Z + 3.83 = 0.97X_1 + 0.84X_2 + 0.96X_3 + 1.77X_4 + 2.24X_5 + 2.29X_6$$

This approximates to D = a + b + c + d + e + f, in which D is the diathesis score, a = bilateral hand involvement (with = 1, without = 0), b the little finger surgery (with = 1, without = 0), c the early onset of the disease (with = 1, without = 0), d the plantar fibrosis (with = 2, without = 0), and e the knuckle pads (with = 2, without = 0). This

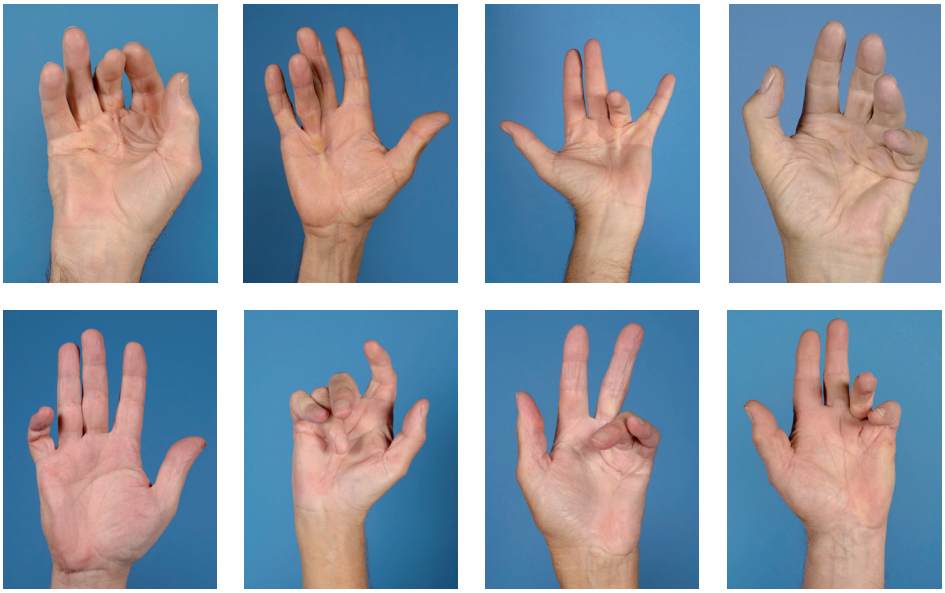

Figure 2: Clinical variations of Dupuytren's disease.

study showed a high risk of recurrence and extension when the diathesis score was greater than four and a low risk when the diathesis score was less than four[30].

The second reason for the clinical variation is the different kind of retention-ligaments (lateral digital sheath, superficial fibrofatty palmar and dorsal fascia and Grayson's ligaments) that can become pathologic components of the Dupuytren cord[31]. For example, the spiral cord can originate from five different kinds of fascial structures and can cause a spiral nerve. In addition, the central cord, with its origin from the pretendinous band and palmar superficial fibrofatty fascia with its insertion into the skin over the proximal phalanx, is the most common cause of combined MP-joint and

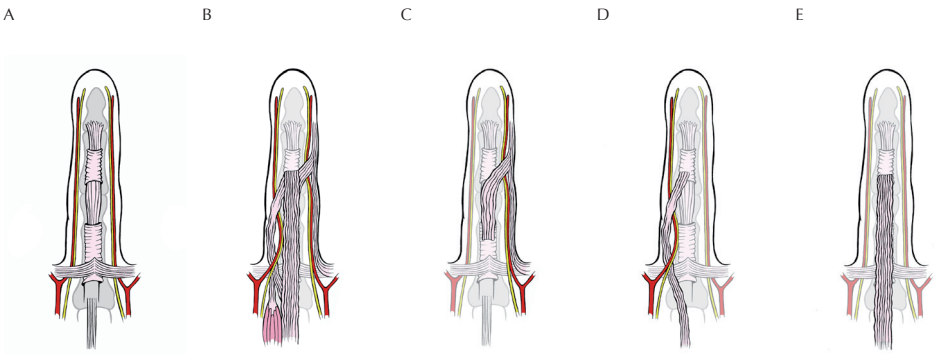

Figure 3: Anatomic differences of digital cords: (A) central cord; (B) lateral cord; (C) isolated digital cord; (D) retrovascular cord; (E) thumb pretendinous cord. (Drawings made by C.F. Wilbrink)

PIP-joint contractures[31]. Because of these variations, knowledge about the anatomy of the Dupuytren fibers is essential for successful treatment (Figure 3).

TREATMENT OPTIONS AND THEIR OUTCOMES

Many treatment options are available in clinical practice, such as radiotherapy, collagenase injection, needle aponeurotomy, limited fasciectomy and dermofasciectomy.

Radiotherapy is popular in Germany. Studies have shown that radiotherapy reduces progression of the early signs of the disease (nodules and palpable cords). Radiotherapy treatment normally includes two separate treatment sessions with an interval of six weeks of five daily fractions of 3.0 Gy each to a total dose of 30 Gy. Radiotherapy has been reported as effective for preventing disease progression; one study reported progression of the disease in 13 years in 10% of the patients[32]. However, it is unclear if radiotherapy can be used to treat DD contractures[33-35].

Collagenase injections are gaining more popularity, since it is minimally invasive and no operation room (OR) is needed[36]. Collagenase is injected at several points along the cord. The next day the cord can be broken[37]. The main disadvantages of this technique are that only one finger can be treated at one time. Furthermore the injections itself are very expensive, however studies have shown that the overall costs are lower compared to limited fasciectomy[38]. Relatively low major complication rates have been reported compared to surgical treatments; however, minor complications such as edema and hematomas are high[39, 40]. Since this technique has only been used for a few years, follow-up data on large study populations are lacking[41].

Needle aponeurotomy (NA) has been introduced by sir Henry Cline and was already used by baron Guillame Dupuytren in the 18th century[8]. In the beginning, the technique was performed as an open transection of the Dupuytren cord. Today, the cord is transected percutaneously[42, 43]. This minimal invasive technique has low overall complication rates, but reported recurrence rates range from 50% up to 84.9% after 5 years[44-47].

Limited fasciectomy (LF) may be the most commonly used technique in clinical practice. When using this technique, a longitudinal or Brunner incision is made into the palm overlying the affected area and extended towards the finger. The pathologic fascia is removed and neurovascular bundles and the flexor tendon sheaths are identified and protected[1]. The skin will be transposed by a Z-plasty or other technique to lengthen the scar, to prevent scar contractures[1, 31]. While complication rates are higher compared to NA, recurrence rates are lower[46, 47]. Time needed to return to daily activity is about 4 weeks[48].

Hueston has proposed *Dermofasciectomy*[49, 50]. In this technique the affected fascia and the skin are removed and a full thickness graft is used to close the wound. This technique is mainly used to treat patients with severe diathesis and recurrent cases. The

idea is that the skin grafts act as a local 'fire-break' to prevent recurrence. Recurrence under the skin graft has hardly been seen[51]. However, the recurrence rate of dermofasciectomy after mean follow-up of 13 years is reported to be up to 47% and other reported recurrence rates ranges from 0% to 60%[52-54]. Dermofasciectomy compared with fasciectomy even show the same recurrence rates of 12% after 36 months[53]. The question remains what kind of definitions were used to define recurrence, and if recurrence was seen under the graft or if it was an extension outside of the graft area.

RECURRENCE

Overall, the currently available treatment strategies only treat or alter the symptoms of the disease rather than treat the underlying pathology. Therefore recurrence will occur sooner or later. Reported recurrence rates vary between 0% and 100%[53-58]. Several studies have identified factors that influence these rates, such as follow-up time and diathesis[16, 30, 59]. Since the treatment type may also influence recurrence rates, these recurrence rates are also an important aspect for assessing the effectiveness of treatment. However, a review by Becker and Davis concluded that the outcome of surgery is inconsistent and that this inconsistency may be related to the different definitions of the term „recurrence"[60]. Subsequently, evaluating the effectiveness of treatment methods is therefore impossible.

NEW MINIMAL INVASIVE SURGICAL TECHNIQUE

In an attempt to overcome high recurrence rates after minimally invasive needle fasciotomy, Roger K. Khouri from the Miami Hand Clinic proposed a new treatment strategy, in which extensive percutaneous aponeurotomy is combined with lipofilling.

The concept of the percutaneous aponeurotomy and lipofilling (PALF) is the disintegration of the fibrous cord through an extensive percutaneous needle aponeurotomy technique, applying numerous superficial nicks along the cord. Following percutaneous release of the skin from the subcutaneous layer with a needle, the treated area is injected with autologous lipoaspirate to restore the subdermal fat deficiency and to act as a 'fire break' graft[61].

In this technique, lipofilling is added since DD is associated with subdermal fat deficiency and atrophy as the pathologic fibrosis displaces the fat[62]. In addition, the lipoaspirate used in this treatment strategy contains stem cells, and there is increasing evidence stem cells may be used as a treatment strategy to treat fibrotic diseases[63, 64]. Studies showed that adipose-derived stem cells inhibit proliferation of the contractile myofibroblasts and mediate these effects by soluble factors, influenced by cell contact[65]. Since myofibroblasts are the key cells leading to the development of fibrosis

and flexion contractures in DD, inhibiting myofibroblasts using lipoaspirate containing adipose-derived stem cells may avoid or reduce the development of recurrent contractures[3].

AIMS OF THIS THESIS

The main aim of this thesis is to evaluate the effectiveness of extensive percutaneous aponeurotomy and lipofilling (PALF). This was initially performed in a pilot study of a cohort of patients treated in Miami and Rotterdam, and subsequently in a multicenter randomized controlled trial.

One of the difficulties in describing outcome in the treatment of DD however, is which definition of recurrence of disease is best to be used. Especially since recurrent rates are inconsistently defined in literature. In order to define recurrence, we studied the effect of different definitions in literature on a single data set and developed a Delphi study to propose a uniform consensus definition.

Furthermore, an important assumption of the new PALF technique, but also an assumption in other minimal invasive techniques such as collagenase and needle aponeurotomy is the fact patients prefer minimal invasive techniques in order to have a faster recovery after treatment. This assumption, however, has never been studied in this population and it is unclear how patients evaluate convalescence following contracture correction, recurrence rate and complication rate. Therefore, we developed a discrete choice experiment (DCE) to determine preferences for different techniques for treatment of DD.

OUTLINE OF THIS THESIS

1. To evaluate the effect of different definitions for recurrence of DD and to develop a new uniform definition. (Chapter 2 and Chapter 3)
2. To study the relative importance of characteristics of DD treatment and the trade-offs patients are willing to make. (Chapter 4)
3. To study and describe the long-term results of the treatment of patients with severe diathesis following flap surgery for both hands and feet. (Chapter 5)
4. To analyze the outcome of the new PALF technique, retrospectively and prospectively and to compare the outcome with the most commonly used surgical technique. (Chapter 6 and Chapter 7)

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Part II

Evaluating the effect of different definitions for recurrence of DD and to develop a new uniform definition

Chapter 2

The consequences of different definitions for recurrence of Dupuytren's disease.

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ABSTRACT

Background: Recurrence rates are important in the evaluation of the effectiveness of treatment for Dupuytren's disease (DD). In literature, recurrence rates vary between 0% and 100%. The definition of recurrence of DD after treatment is inconsistently used. The aim of this study is to review all definitions of recurrence after treatment of DD and to evaluate the impact of using these definitions on a single cohort of patient's treatment for DD.

Methods: A literature search was performed in PubMed and Embase to identify studies. Titles and abstracts were analyzed to collect all articles that described recurrence rates or definitions of recurrence. Two independent reviewers selected relevant studies and extracted data. The different definitions of recurrence were applied on our dataset of 66 patients.

Results: Of the 113 articles reporting recurrent rates of DD, 56 (49%) presented a definition of recurrence. We could categorize the definitions into three groups. By applying the different definition on our dataset of a randomized controlled trial the recurrence rates ranged from 2% to 86%.

Conclusions: In literature, different definitions of recurrence of DD are used and many authors failed to define recurrence. This study shows that the wide range of reported recurrence rates may largely be contributed by inconsistency in recurrence definitions. As a result, it is difficult or even impossible to compare recurrence rates between different treatments reported in the literature. The study indicates that consensus on a recurrence definition is needed.

INTRODUCTION

Although the evidence for effectiveness of treatments for Dupuytren's disease (DD) is still scarce, different treatment options are available in clinical practice, such as fasciectomy, aponeurotomy, and, more recently, collagenase injections[1-3]. However, since current treatments only remove or alter the symptoms of the disease rather than treat the underlying pathology, recurrences occur. In literature, reported recurrence rates vary between 0% and 100%[4-10]. Several studies have identified factors that influence these rates, such as follow-up time and diathesis[11-12]. Since treatment type may also influence recurrence rates, it is an important aspect for assessing the effectiveness of treatment.

In a recent review, Becker and Davis concluded that the outcome of surgery is inconsistent and that this inconsistency may be related to the different definitions of recurrence used[13]. Therefore, the first aim of this study was to identify all definitions of recurrence after treatment of DD reported in literature. Subsequently, we performed an analysis by applying the different definitions to a cohort of patients treated for primary DD, evaluating the effect of different definitions on the recurrence rate of these patients.

METHODS

Literature Search

To identify relevant articles on the recurrence of DD, we searched for studies published from January 1985 up to April 2011 using PubMed and Embase. Keywords related to recurrent DD were included, such as 'Dupuytren', 'reappear', 'recurrence', 'return', 'predict', 'prognosis', 'residual', 'remain', and 'outcome'. The complete search strategy can be found in Table 1.

Inclusion criteria and study selection

The search strategy results from Embase and PubMed were combined and duplicates were discarded. Titles, abstracts and subsequently full text of the articles were analyzed individually by two independent reviewers to determine whether they met the following inclusion criteria: 1) the main subject of the article was DD; 2) the study used an original data-set of cases; 3) the study population consisted of at least five patients; 4) patients were 18 years or older. Only articles written in English, German, French or Dutch were included. If disagreement on inclusion of a publication arose a consensus between the two reviewers was met. If this disagreement persisted a third reviewer was consulted.

Data extraction

Two reviewers independently extracted the data. Reported recurrence rates, definitions of recurrence and definitions that could be extracted from the text were identified. For example, in some studies, authors defined recurrence as the presence of new nodules or cords, without giving an explicit definition. Furthermore, characteristics such as authors, publication year or type of surgery were extracted.

Comparing definitions using our dataset

To evaluate the effect of different definitions of recurrence found in literature, we applied the different definitions of recurrence on a single dataset of the Dupuytren Rotterdam Trial (Du Ro Trial) (NTR1692). This dataset consisted of preliminary data from patients who participated in the randomized controlled trial and were treated by limited fasciectomy or extensive percutaneous aponeurotomy and lipofilling (PALF) technique consists of extensive percutaneous aponeurotomy that completely disintegrates the cord and separates it from the dermis. Autologous fat from the abdomen is injected in the operated area. In a recent study, we described this technique in detail and published data from a initial cohort study [14]. For the present study, we analyzed data from patients that were included in the Du Ro trial between May 2009 and October 2010. Medical ethical approval was obtained for this study and all subjects signed informed consent (MEC-2008-264).

We used the passive range of motion (ROM) data of the most affected digit, measured at two weeks and six months postoperatively. Extension goniometry was measured with all joints (MP, PIP and DIP) maximally extended. Further, peroperatively, the surgeon visually estimated the passive range of motion. Since all joints of the treated digits were measured with goniometry, the total passive extension deficit (TPED) could be calculated, representing the sum of joint angels of the MP-joint, PIP-joint and DIP-joint.

RESULTS

Literature search

The initial search resulted in the identification of 606 studies from PubMed and Embase. After analyzing the titles, abstracts and full text, 113 articles were included (Figure 1). One article could not be found online or requested at the medical library of the Netherlands and medical library of England. Therefore this article was excluded from analysis[15].

Recurrence definitions

Of all 113 included articles describing a recurrence rate, only 56 articles described a definition of recurrence. Definitions found in the articles could be categorized into

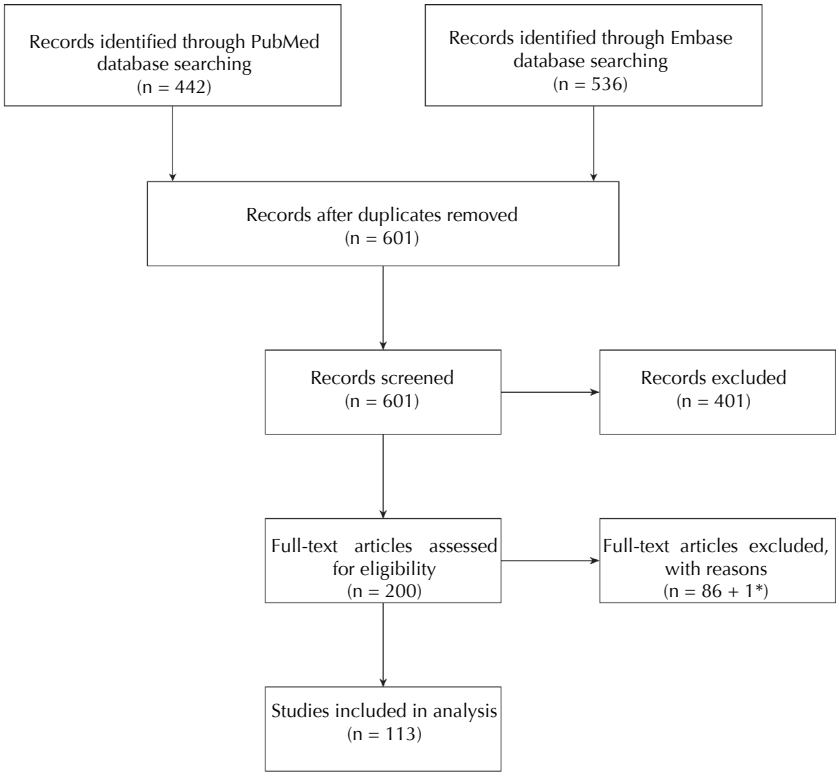

Figure 1: A flow chart of literature search is shown. PubMed and Embase were used to find articles about recurrence of Dupuytren's disease. From the total 606 articles 113 articles were included for this study.
* Stankovic P; Early Surgery of Dupuytren Contracture/Fruhoperation einer Dupuytrenschen Kontraktur; Internist (Berl) 1997 (38); 482-483

three groups. Table 2 describes these definition categories, the corresponding studies and the exact definition used in the individual studies. The first category (type I) defines recurrent DD based on the return of disease (nodules or cords) in the operated area or in the operated hand (63% of all studies used this definition). The second category (type II) defines recurrent DD based on the return of contractures, with the minimal degree of contracture required for defining recurrence varying from 1 degree ('any increase in contracture') to 50 degrees (27%). The third category (type III) is based on the patient's self report of a recurrence or based on whether a recurrent surgery was performed (10%).

Figure 2 summarizes the recurrence rates for the different treatment types and recurrence definition categories. The recurrence rates reported in the studies ranged from 0% to 100%. We found that all types of definition categories (I-III) were used for all types of treatments. However, articles on collagenase injections were the most consistent in the type of definition that was used (type II) (Figure 2 and Table 2).

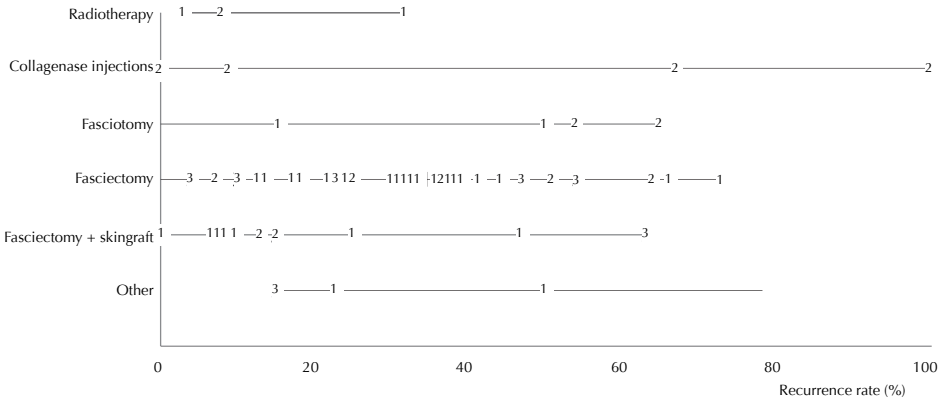

Figure 2: Graphical representation of all recurrence rates in literature, sorted by their corresponding treatment category. The numbers (1-3) represent the definition categories described in Table 2. The location of placement of the numbers indicates the percentage of the recurrence rate reported in the individual article. The grey lines indicate the range of recurrence rates reported for that specific treatment category. Since not all articles reporting a recurrence rate also report a definition of recurrence, the grey lines sometimes exceed the location of the numbers.

Applying the definitions on our dataset

We used data from 66 patients (56 males and 10 females) affected by primary DD from the Du Ro trial. Since the extensive percutaneous aponeurotomy and lipografting technique does not remove any tissue and since therefore a palpable nodule is always present in the operated hand, we could not apply the first definition category to our data.

Figure 3 shows the different recurrence rates when using different angular threshold for the category-2 definitions. The lower dark line represents the difference in joint angle between two weeks postoperative and six months postoperatively, analyzed in the most affected joint only. This recurrence rate strongly decreases from 49% when applying a change of five degrees in angle as the threshold for recurrence, to 2% when applying a 50 degrees threshold. The upper light-grey line, indicating the threshold in angle of the most affected joint when comparing peroperative data with the six months follow-up, shows the same pattern. Since more extension is measured peroperatively than at two weeks follow-up, higher recurrence rates are found. Because some authors used the total passive extension deficit (TPED), we added two extra lines for the TPED, showing a similar pattern compared to using the most affected joint only (Figure 3).

Since the Du Ro trial was not designed for this study purpose, patient-reported recurrence was not measured. Furthermore, this is an ongoing study and recurrent surgeries were not performed within six months of the initial operation. Therefore, the third definition category could not be evaluated using the Du Ro dataset.

Definition category		Year	Author	Explicitly defined	Definition
1. Recurrence based on nodules or cords	Irrespective of the operated area	2010	Betz et al.	No	Return of nodules or cords in the operated field, or both in and out the operative field.
		2007	Abe et al.	No	Nodules or cords under the skin graft or outside of the skin graft.
		2000	Armstrong et al.	No	Return of nodules or cords.
		1997	Hall et al.	No	Return of nodules or cords under the graft or on the edge of the graft.
		1997	Moermans	Yes	The presence of a nodule or of an identifiable cord without taking the loss of extension into account. The reappearance of a nodule anywhere in an operated ray was considered as a recurrence even if that precise location was not directly in the original surgical field.
		1996	Moermans	Yes	
		1996	De Maglio et al.	Yes	The simple occurrence of a nodule without contracture.
		1992	Searle et al.	No	Clinically recurrent disease, observed as nodules at the graft inset.
		1992	Kelly et al.	No	Recurrence of the disease within the same ray as the skin graft, under the graft or outside of the graft.
		1991	Andrew et al.	Yes	The presence of any detectable disease in the operated ray.
		1987	Langenberg	No	Return of nodules, in or out of the operated ray.
		1985	Herbst et al.	No	Recurrence only observed at the edge of the irradiated field.
	In operated area	2009	Balaguer et al.	Yes	The reappearance of DD in a zone previously operated on.
		2008	Jurisic et al.	Yes	The development of new Dupuytren's disease lesions including the smallest palpable nodule irrespective of a presenting contracture in the same area where fasciectomy had been performed.
		2006	Hindocha et a.	Yes	
		2007	Anwar et al.	Yes	Disease within previously operated sites.
		2005	Del Frari et al.	Yes	Reappearance of contracturecords in the operated area, including the reappearance of isolated nodules or cords.
		2005	Citron et al.	Yes	Any new nodule of disease in the operative field under the flaps (Leclerq, 2000).
		2004	Abe et al.	Yes	
		2004	Abe et al.	Yes	
		2004	Abe et al.	Yes	
		2003	Citron et al.	Yes	The reappearance of Dupuytren's tissue in the operative field. This included isolated nodules, without contracture, but did not include extension beyond the operative field.

Definition category		Year	Author	Explicitly defined	Definition
		2000	Ketchum et al.	No	A reactivation of disease in the nodules 1 to 3 years after the last injection, necessitating one or more injections.
		1995	Foucher et al.	Yes	Disease reappearing in a site which had been operated on, in contrast to an extension of the disease process when it appeared at a distance from the previous operative site.
		1992	Foucher et al.	Yes	
		1994	Cools et al.	Yes	New DD within the operated field.
		1992	Adam et al.	Yes	The appearance of Dupuytren's disease in an area already cleared by operation.
		1991	Moermans	Yes	The reappearance of Dupuytren' s tissue in an area already cleared by operation, recurrent nodules without any sign of contraction have been interpreted as true recurrences.
		1991	Ebelin et al.	No	Recurrences under the graft.
		1989	Rombouts et al.	Yes	The appearance of new lesions (bands or nodules) determined by appearance and palpation in an already operated area.
		1987	Merlo et al.	Yes	The appearance of new fascial nodules or bands, determined by appearance and palpation where fasciectomy had been previously performed.
		1987	Ketchum et al.	No	Recurrence of Dupuytren's disease to the grafted area of the palm.
		1986	Schneider et al.	No	Definite recurrence in the operative field.
		1986	Leclercq et al.	Yes	Return of clinical disease, including isolated nodules, in the operative field.
		1985	Logan et al.	No	Return of disease beneath the graft.
2. Recurrence based on degrees of contracture	Contracture only	2010	Watt et al.	Yes	Any increase in the degree of contracture of the injected joint compared with maximal extension achieved after injection.
		2010	Gilpin et al.	Yes	An increase in joint contracture to 20° or greater in the presence of a palpable cord at any time during the study in joints that attained a reduction in contracture to 0° to 5° of normal.
		2009	Hurst et al.	Yes	An increase in joint contracture to 20 degrees or more in the presence of a palpable cord at any time during the study, was evaluated in primary joints that reached the primary end point (a reduction in primary-joint contracture to 0 to 5 degrees of full extension).
		2009	Walton et al.	Yes	Residual contracture present at six months post-operation.
		2009	Mavrogenis et al.	No	Recurrent proximal interphalangeal joint contracture of >20°.

Definition category		Year	Author	Explicitly defined	Definition
		2007	Badalamente et al.	Yes	Return of contracture (20°) in successfully treated joints (reduction in deformity to within 0° (normal) to 5° (flexion) of normal (0°)).
		2006	van Rijssen et al.	Yes	A Total Passive Extension Deficit increase during follow-up of 30° or more compared to the immediate postoperative measurements.
		2000	Ebskov et al.	No	Changes in extension: Same = change of 10° or less during the stated period; increase of 10° to 40° in the contracture; increase of more than 40° in the contracture.
		1998	Foucher et al.	No	Increased contracture (29° mean in the presented recurrent cases).
		1985	Gonzales	No	Recurring contracture in fully released joints.
	Contracture or nodules	2009	Villani et al.	Yes	The presence of nodules, plaques, cords or extension deficit in the operative field.
		2001	Seegenschmiedt et al.	No	New nodules, new cords, or increased flexion deformity of palm or any finger in the range of 10–50°.
		1991	Zemel	Yes	Nodules and contractures reappearing in the area of the previous operation.
		1987	Ebelin et al.	Yes/No	Dupuytren's disease under the graft / Extension deficit above 30 degrees.
		1986	Mayer et al.	Yes	Return of skin contractions, nodules or flexion contracture.
3. Recurrence stated otherwise	Self-reported by patients	2009	Degreef et al.	Yes	Self-reported, Self-reporting of recurrence implies that he or she feels that the effect of the surgical correction was lost, which is basically the problem of recurrent disease.
		2003	Wilbrand et al.	Yes	The patient's response to "the fingers operated on are beginning to bend again'' in one of the questions, or reports of medical examinations in the patient records.
	Repeated operation	2006	Dias et al.	Yes	The reappearance of a contracture sufficient to require surgery, according to Hueston's table-top test (Hueston, 1982). This correlates with any deformity greater than a mild metacarpophalangeal joint contracture in the images of our questionnaire.
		1999	Wilbrand et al.	No	Patients had more than two operations, indicating a definite recurrence or extension of disease.
		1996	Shaw et al.	No	Recurrence requiring repeat surgery.
		1992	Foucher et al.	No	Recurrence severe enough to necessitate another operation.

Table 2: This table shows all articles that report a definition of recurrence. We categorized the definitions into 3 categories, based on 1. the presence of nodules or cords the operated hand, 2. joint contracture in degrees, 3. patient's self-report or recurrent surgeries. When the author explicitly defined recurrence, this was stated as 'yes' in the fourth column; if the definition was extracted from the context it was stated as 'no'.

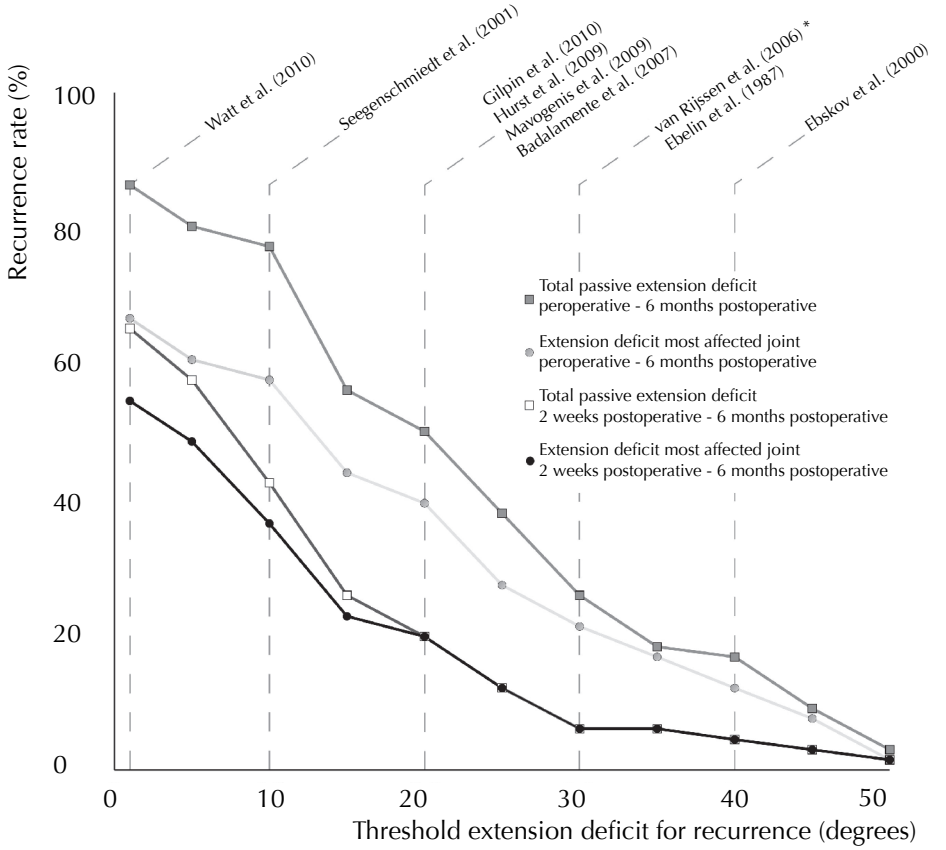

Figure 3: Relation between the acquired extension deficit and the recurrence rate in the single dataset. The extension deficit was based on the most affected joint per hand (n = 66). The lower dark line represents the difference in joint angle between two weeks postoperative and six months postoperatively. For example, when one degree extension deficit is applied as a threshold for recurrence, we found that 55% of our patients had a change in angle that exceeded this threshold and that would therefore have a recurrence. With a 30 degrees threshold, however, only six percent of our cohort has a recurrence. The upper light-grey line indicates the same threshold in angle, however using peroperative data as the initial baseline data instead of data two weeks postoperative. Furthermore the TPED was used instead of the most affected joint. The vertical lines are the specific angular thresholds used in different articles; they indicate how these different thresholds lead to incomparable recurrence rates when applied to the same data. * Used TPED for the definition

DISCUSSION

Reporting recurrence rates is an essential part of evaluating the effectiveness of treatment for DD[13]. In this literature study, we found a wide range of different definitions for recurrence after treatment of DD. This resulted in recurrence rates within one dataset ranging from 2% to 86% when using different types of definitions. This study shows that the wide range of reported recurrence rates may largely be contributed by incon-

Literature database	Search query
Pubmed	(Dupuytren*[tw]) AND (reappear*[tw] OR recurr*[tw] OR return*[tw] OR predict*[tw] OR prognos*[tw] OR residu*[tw] OR remain*[tw] OR outcome*[tw]) AND (english[lang] OR dutch[lang] OR german[lang] OR french[lang])
Embase	(Dupuytren*):de,ab,ti AND (reappear* OR recurr* OR return* OR predict* OR prognos* OR residu* OR remain* OR outcome*):de,ab,ti AND ([english]/lim OR [dutch]/lim OR [german]/lim OR [french]/lim)

Table 1: Complete search strategy which was used for this study.

sistency in recurrence definitions. As a result, it is presently difficult or even impossible to compare recurrence rates between different treatments reported in the literature.

In this study, we found that 51% of the publications reporting recurrence rates did not present a definition of recurrence, while the remaining articles could be grouped into three main categories. In general, these categories are based on 1) the return of nodules and cords, 2) the return of joint contractures, or 3) the patient's self-report of a recurrence or whether a recurrent surgery was performed. When visualizing all reported recurrence rates, we still found wide ranges even for the same treatment and definition categories (Figure 2). We found that recurrence rates at six months follow-up can range from 2 to 86% in the same dataset, based on applying different angular thresholds, different baseline measurement and different selected joints.

Most studies base definitions of recurrence on the reappearance of nodules or cords in the operated hand (category 1). While this may be suitable to define recurrences when performing a fasciectomy, it is less suitable when performing a needle aponeurotomy or injecting collagenase since these techniques leave nodules and cords in place[16]. This may explain why most of the recent trials on needle aponeurotomy and on collagenase injection use contracture-based definitions (category 2)[1-2]. In addition, it can be argued that the return of nodules alone should not be the main aspect of a recurrence definition, since the indication for operation generally is not based on nodules or cords alone, but on the severity of the joint contracture[17].

Within category 2, angular threshold for defining recurrence varied from 1 to 50 degrees[10, 18]. Our analysis shows that this threshold should be chosen carefully because of its great influence on the recurrence rate. Furthermore, while some authors describe recurrence as relapse of contracture of the treated finger in degrees relative to 'normal', they did not define 'normal'[19-20]. Since the maximum degree of extension is different in each person, this 'normal' should be carefully defined. Other authors compared the relapse of contracture at follow-up with the peroperative measurement or with the first measurement after surgery[1, 10]. Within our dataset this difference alters the recurrence rate up to 20% (Figure 3). In contrast, our data showed little difference between using data of the most affected joint and using the TPED. A reason for this may be that the change in TPED is largely based on the change in the most affected joint (Figure 3).

The third category of definitions was based on the patient's self-report of a recurrence or whether a recurrent surgery was performed. While the patients' perceptive is an important indicator for operation and important to measure after intervention, it may be influenced by many factors, such as the patient's overall satisfaction with the treatment process and the patient's profession. Therefore, we suggest that patient's perspective may be more suited as an addition to more objective definitions of recurrence. While the performance of recurrent surgery is also an important variable, the operation indication may be influenced by many patient-related factors as well as the surgeons' indication criteria.

Our study has a number of limitations. First, we excluded all articles to use for this review that were written in a language other than English, French, German or Dutch. We also excluded publications before 1985. However, overall, we believe that this will not have affected the main message of this study that definitions for recurrence are inconsistently used, leading to widely varying recurrence rates. Another limitation was that the data set used for the analysis was not constructed specifically for this study. Therefore, the definitions based on nodules and cords and those based on patients' perception or operation indication could not be applied to our data. Despite of this, we feel that we were able to demonstrate the importance of a clear definition of recurrence and the effect of applying different angular thresholds for recurrence.

From the present study, it is clear that an international consensus on the definition of recurrence is needed to allow comparison of recurrence rates of treatments. The present review highlights a number of important points to consider for such an international consensus. First of all, since a number of recent treatments do not remove cords or nodules, we suggest using a contracture-based definition in degrees. In such a definition, it is important to establish consensus which joints are evaluated. From this study, we suggest to evaluate the most contracted joint (MP or PIP) of the most contracted finger only. Including multiple joints or digits from a similar patient has well-described statistical problems[21]. When using a contracture-based definition, postoperative long-term measurements should be related to early postoperative measurements (for instance after two weeks) since not all joints are completely corrected. In addition, peroperative measurements lead to higher recurrence rates than postoperative measurement at two weeks. The angular threshold for recurrence is more or less arbitrary. However, it is important to have a threshold that is larger than the inherent measurement errors of goniometry of approximately five to ten degrees[22]. As the angular threshold, the duration for the follow-up measurement may be more or less arbitrary but should be standardized. From a clinical point of view, longer follow-up measurement may express more precisely the amount or recurrent surgeries that are needed. However, from a research perspective, a one-year follow-up measurement may already show differences between techniques. In addition, it should be noted that dichotomizing recurrence as

a "yes" or "no" per patient reduces the amount of information compared to reporting exact angular changes in degrees per patient. A more sensitive measure could therefore be to compare the change in joint contracture between groups over time, leading to a higher statistical power.

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Chapter 3

Recurrence of Dupuytren's Contracture: A consensus-based definition

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ABSTRACT

Background: One of the major determinants of Dupyutren disease (DD) treatment efficacy is recurrence of the contracture. Unfortunately, lack of agreement in the literature on what constitutes recurrence makes it nearly impossible to compare the multiple treatments alternatives available today. The aim of this study is to bring an unbiased pool of experts to agree upon what would be considered a recurrence of DD after treatment; and from that consensus establish a much-needed definition for DD recurrence.

Methods: To reach an expert consensus on the definition of recurrence we used the Delphi method and invited 43 Dupuytren's research and treatment experts from 10 countries to participate by answering a series of questionnaire rounds. After each round the answers were analyzed and the experts received a feedback report with another questionnaire round to further hone in of the definition. We defined consensus when at least 70% of the experts agreed on a topic.

Results: Twenty-one experts agreed to participate in this study. After four consensus rounds, we agreed that DD recurrence should be defined as "more than 20 degrees of contracture recurrence in any treated joint at one year post-treatment compared to six weeks post-treatment". In addition, recurrence should be reported individually for every treated joint and afterwards measurements should be repeated and reported yearly.

Conclusion: This study provides the most comprehensive to date definition of what should be considered recurrence of DD. These standardized criteria should allow us to better evaluate the many treatment alternatives.

INTRODUCTION

Recurrence of disease following any technique to correct the contractures is one of the major setbacks in the treatment of Dupuytren's disease (DD). Since present techniques only treat the symptoms of this chronic and progressive disease, recurrence over time is inevitable in the majority of patients. Therefore, assessment of recurrence rates is an essential element in describing and comparing the efficacy of different treatment options for DD.

Two separate systematic reviews have recently identified dire need for consensus on how to define recurrence of DD[1, 2]. This lack of a clear definition may partly explain why reported recurrence rates vary from 0% to 100%[3-8]. In addition, we have shown that applying the different definitions on a single dataset can change the resulting recurrence rates from 2% to 86% (Figure 1)[1].

To obtain an internationally accepted and wide supported definition of recurrence for DD, a consensus agreement based on the experience and knowledge of an international group of renowned experts is needed. Therefore, the goal of this international study was to develop consensus on a single definition of recurrence of DD that is applicable in clinical and research settings.

METHODS

In this study we used the Delphi method, which is designed to reach consensus between individuals using questionnaire-based surveys[9]. Experts in the field of Dupuytren's disease (DD) were invited to participate in our Delphi study. To identify these experts, we selected all clinical DD-related PubMed articles that were published between 2005 and 2012. In addition, we used the articles from our systematic review to identify experts in the field of DD[1]. Either the first or last author of each article, based on the number of publications in the field of DD, was invited to participate. When multiple experts were identified from the same institution, only the most experienced expert was invited to participate. We excluded experts that did no longer participate in the field, for example due to retirement, or authors who published only a single DD-related paper.

In November 2012, 42 experts from ten countries in four continents were invited to participate. All experts were provided with information on the Delphi study as well as with a draft of our systematic review. Following Delphi guidelines, 51% agreement is considered consensus. However, we aimed for a minimal of 70% agreement for consensus. The identities of the other participating experts were not disclosed to the experts during the process.

In the first round, experts were asked to score the relevance of four different dimensions of recurrence to be included in a single definition of DD recurrence (first two

columns of Table 1) using a zero to ten numerical scale and multiple choice questions. For example, we asked "On a scale from zero to ten, how important is it to include the return of Dupuytren's nodules based on palpation or visual inspection in the definition of recurrence?" After each question, the experts could add a comment or explanation.

The first two authors analyzed the results and discussed the outcomes with the other authors. If 70% of the experts scored five or higher, the item was considered important

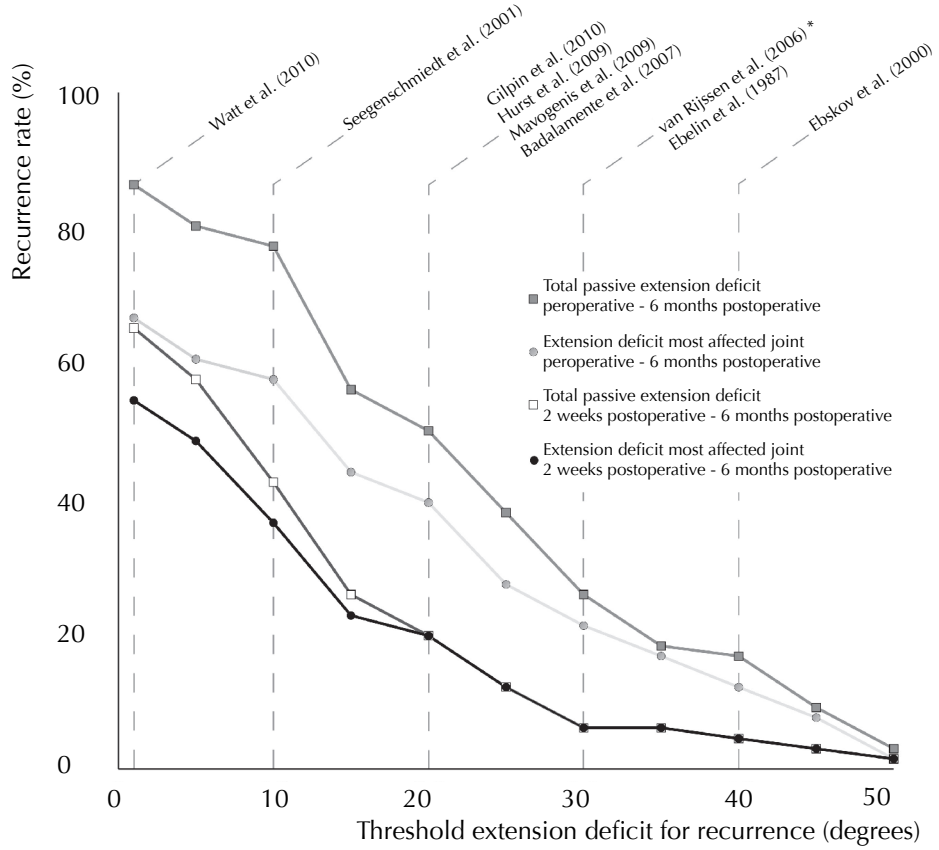

Figure 1: Relation between the acquired extension deficit and the recurrence rate in the single dataset. The extension deficit was based on the most affected joint per hand (n = 66). The lower dark line represents the difference in joint angle between two weeks postoperative and six months postoperatively. For example, when one-degree extension deficit is applied as a threshold for recurrence, we found that 55% of our patients had a change in angle that exceeded this threshold and that would therefore have a recurrence. With a 30 degrees threshold, however, only six percent of our cohort has a recurrence. The upper light-grey line indicates the same threshold in angle, however using peroperative data as the initial baseline data instead of data two weeks postoperative.
Furthermore the TPED was used instead of the most affected joint. The vertical lines are the specific angular thresholds used in different articles; they indicate how these different thresholds lead to incomparable recurrence rates when applied to the same data. * Used TPED for the definition

for further consideration. These included items were discussed more in-depth in the following rounds.

In each following round, we provided feedback to the experts by summarizing the answers on the previous round in combination with a synopsis of anonymous comments. After this feedback, we asked the experts to answer each question again on which consensus was not yet reached. Topics on which consensus was reached were also presented but only with the opportunity for the experts to give additional comments. If experts did not complete a previous round before the deadline, they were still invited to the next round.

	Dimensions	Consensus	% Experts
1	Location of recurrence	All treated joints	70% - 80%
2	Inclusion of nodules, cords and contractures	20° contracture	86%
		No modules or cords	56% - 60%
3	Baseline measurements and follow-up	6 weeks post treatment	79%
		1 year post treatment	86%
4	Patient characteristics & Patient-reported recurrence	Excluded	75%

Table 1: The dimensions (numbered 1- 4) were presented to the experts and the resulting consensus on each dimension is presented. The last column shows the percentage of experts that agreed on each consensus or a range of percentages, when the outcome differed in more than one round of the Delphi study.

RESULTS

Twenty-one experts (64%) from 10 countries participated in this study: seven from North-America, 13 from Europe, and one from Australia. A total of four rounds were needed to reach consensus. The response rate varied per round between the 76% and 90% (Figure 2).

A first dimension scored by the experts was location of recurrence. Consensus was that recurrence of Dupuytren's disease (DD) should be located in the operated area only in order to differentiate recurrence from disease extension to other joints. In addition, since DD can affect multiple joints, fingers and hands, consensus was that recurrence should be measured in all treated joints, fingers and hands regardless if full extension was reached during treatment. Experts also reached consensus that all treated joints should be scored individually to count as a recurrence rate (Table 1).

The second dimension was whether a recurrence should be assessed based on the presence of nodules, cords and/or joint contractures. Experts agreed DD nodules and cords should not be explicitly taken into account, furthermore a recurrent joint contracture of at least 20 degrees in one joint is needed for a recurrence.

A third dimension was the timing of baseline measurements and follow-up. Experts agreed recurrence should be measured at one year post-treatment and should be com-

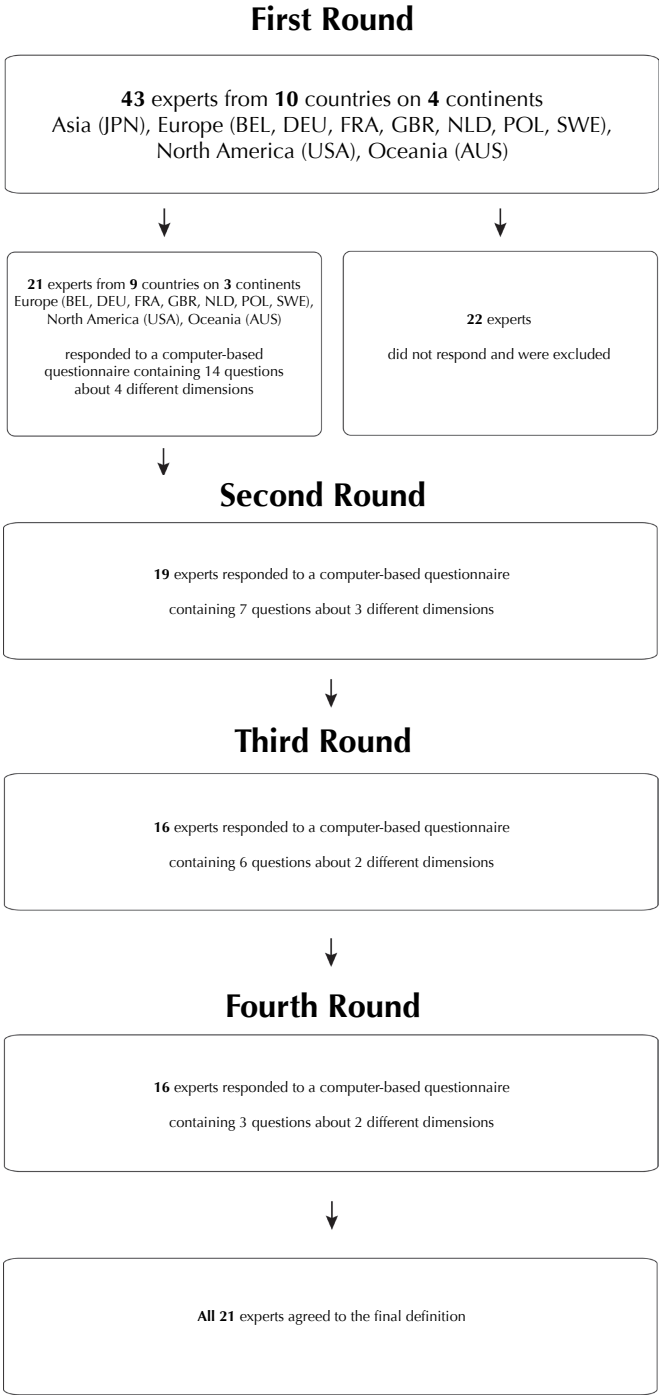

Figure 2: Figure shows the number of experts who were included in the study rounds and their country of origin.

pared to a baseline measurement. Consensus was that intra-operative measurements should not be used as a baseline value and, therefore, an assessment at six weeks after treatment was selected as a baseline. Since it is presently unclear from literature how recurrence develops over time, experts agreed to recommend yearly repeated measurements when feasible.

A fourth dimension consisted of scoring patients' characteristics, such as diathesis and patient perception of recurrence. Although it is clear that diathesis has a significant influence on recurrence, the experts agreed that information on diathesis should not be included into the definition, although it should be scored in every study. The experts also agreed that, while patient-rated information about recurrence can be relevant, it should not be included in a single definition of recurrence of DD.

After the last round, all 21 experts agreed to define recurrence of Dupuytren's disease after treatment as *"an increase in joint contracture in any treated joint of at least 20 degrees at one year post-treatment compared to six weeks post-treatment"*. Additionally, although not part of the definition, the experts advised the community to 1) conduct studies that repeat measurements yearly to study the development of recurrence, and 2) measure and report recurrence rates for all treated joints individually (Table 2).

Patient	Hand	Joint	Extension deficit prior treatment (degrees)	Extension deficit 6 weeks post treatment (degrees)	Extension deficit 1 year post treatment (degrees)	Recurrence (Yes / No)	Recurrence rate (%)
1	Left	MP 4	60	10	10	No	5/14 joints = 36%
		MP 5	75	0	20	Yes	
	Right	MP5	20	0	0	No	
		PIP 5	90	40	60	Yes	
2	Left	MP 5	30	10	15	No	
		PIP 5	80	20	35	No	
3	Right	MP 4	10	0	10	No	
		MP 5	15	0	15	No	
		PIP 5	40	0	20	Yes	
4	Left	PIP 5	90	10	25	No	
5	Left	MP 3	60	10	30	Yes	
		MP 4	40	0	15	No	
		MP 5	30	0	15	No	
		PIP 5	60	5	25	Yes	

Table 2: A fictitious cohort of patients with Dupuytren's disease is presented and the table shows when recurrence has occurred by using the consensus definition. It also shows the recurrence rate that should be described in the paper.

DISCUSSION

Since the present lack of a consensus for recurrence of Dupuytren's Disease makes it impossible to compare results between different studies, we conducted this international study to obtain consensus on a universal definition for recurrence of DD after treatment. Based on this, we propose to define recurrence of DD after treatment as *"an increase in joint contracture in any treated joint of at least 20 degrees at one-year post-treatment compared to six weeks post-treatment*".

The definition established in this study was obtained by evaluation four different dimensions of recurrence. The first dimension was location of recurrence. Consensus was that only the operated or treated area should be considered and that all treated hands, fingers and joints should be included to calculate recurrence rates, which allow to distinguish recurrence (in the same area) from disease extension (outside of the treated area). In addition, although additional measures such as a total passive extension deficit (TPED) can also be of value, consensus was that individual joint measurements should be used primarily. One expert stated: 'TPED is measured while all joints are being simultaneously passively extended. As such, it represents fixed joint contractures. This will yield a different measurement than the sum of measurements made of individual joint passive extension, while the proximal joint or distal joints in that same ray are allowed to flex.' Furthermore, a disadvantage of a TPED is that it includes non-affected joints and newly affected joints (disease extension), creating possible false-positive recurrence rates.

A second dimension considered including palpable nodules, palpable cords and contractures in the definition of recurrence. The experts unanimously agreed to include increase of contracture in the definition of recurrence. Furthermore, they agreed to exclude nodules and cords. The angular threshold for the contracture to be considered a recurrence was set at 20 degrees. There were two reasons for this threshold. Firstly, inherent measurement errors of goniometry are approximately 5-10 degrees and therefore a larger threshold is needed[10]. Secondly, 15-20 degrees is often considered an indication for a new intervention, for example in the Hueston Table-top test[11].

The exclusion of the presence of nodules and cords in the definition was more controversial in our group of experts. While the main reason to include palpable nodules and palpable cords in the definition was that reappearing nodules and cords are the earliest signs and often the cause of recurrence, the majority of the experts mentioned three main reasons to exclude palpable nodules and palpable cords in the definition. Firstly, nodules and cords by themselves very seldom cause any disability, or require surgical treatment. Secondly, minimal invasive techniques are meant to disconnect Dupuytren tissue that forms cords or nodules. However, these cords and nodules are left in place during these techniques[5, 12]. This makes it difficult to identify newly formed

nodules and cords because the old ones remain. Thirdly, it is challenging to reliably identify the presence of nodules and cords in the presence of post-surgical scarring.

A third dimension considered timing of baseline and follow-up measurements. Consensus was to perform baseline measurements at six weeks post treatment, mainly because experts concluded that wound healing takes time following surgery. Furthermore, hand function will return in approximately two to four weeks and it also has been demonstrated that the results at six weeks post treatment were better compared to one-week post treatment[13, 14]. Therefore, six weeks was considered a first time-point evaluation for treatment success. The follow-up time was more controversial. Experts mentioned from a clinical point of view, longer follow-up measurements might express more precisely the amount of recurrent treatments that are needed. However, from a research perspective, a one-year follow-up may already express the main differences between techniques. One expert stated: 'recurrence progresses with time. But this progression is non-linear. Either our scientific community develops standardized time-to-recurrence charts, or we all decide to evaluate all patients at a given point in time.' After four rounds, consensus was to measure recurrence after one year. In addition, the experts advised yearly repetition of measurements in studies that cover multiple follow-up years since more knowledge is needed on how recurrence progresses over time.

A last dimension included patient characteristics and patients' perception. Consensus was that patient factors (e.g. diathesis) can predict the risk of developing recurrence, but are not a characteristic of recurrence itself[15]. Therefore, it was excluded. In addition, while all experts concluded that patients' perception is very important, it was also excluded[16]. One experts stated 'while we can pat ourselves on the back for a great range of motion improvement, or feel we did not achieve our goal, the patient's own perception is the bottom line of what matters the most. Unfortunately, we do not have very objective measures (of subjective improvement) and any measure will be invariably affected by factors unrelated to the medical treatment delivered'. Since, there are no objective measures to measure patients' perception about recurrence, it is not included in this definition.

Our study has a number of weaknesses and strengths. Firstly, only the minimal amount of experts generally assumed to be needed for a Delphi study participated in our study[9]. Unfortunately the invited experts from the Asian continent did not respond and are therefore not represented in this Delphi study. However, all responded experts represent countries from all over the world and are clearly renowned in the field. Experts completed all rounds with an average response rate of 80% and, at the end of the process, all experts agreed on the final definition of recurrence. Secondly, this Delphi study was conducted with computer-based questionnaires. A disadvantage of this method is that it lacks the ability to stimulate discussion and can lead to misinterpretation of comments given by experts. On the other hand, computer-based questionnaires allow

anonymous responses from the experts, and thus avoiding possible peer-pressure. A third limitation was that the goniometric measurement protocol needed for this definition was not part of the Delphi consensus rounds. To our knowledge, an internationally recognized guideline for measuring joint angle is presently lacking. In our experience, most researchers and clinicians measure joint angle dorsally[17]. As some of the experts as well as a reviewer of this manuscript have correctly noted, it is important to control for the adjacent joints when measuring a specific joint, especially when a cord spans multiple joints. Fortunately, since the present definition is based on a change in joint angle of time, differences between goniometric measurement techniques may lead to different absolute angles, but difference may be much smaller when analyzing the change in joint angle over time. A final limitation is that while our goal was to obtain one clinically relevant and easily applicable definition for recurrence of DD after treatment, it may not be possible to reflect the complexity of recurrence of DD in this single definition. Table 2 shows an example of how a typical dataset from a clinical study should be interpreted to calculate a recurrence rate. From this table, it is also clear that this single recurrence rate does not capture the complexity of the data. Therefore, we do not advocate researchers to only use this single measure, but we do advocate this is the minimal measure to report. Additional secondary measures may be needed to also describe the presence of the disease or disease extension, for example the presence of palpable nodules and cords. Also, in addition to using a threshold for recurrence, it could also be valuable to describe the average change in joint angle between baseline and follow-up or to report recurrence rate per joint separately.

In conclusion, we present a uniform definition that for the first time allows comparison between future studies, thereby improve our understanding of the effectiveness of different treatment methods.

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Part III

Relative importance of characteristics of DD treatment

Chapter 4

Patients' preferences for treatment for Dupuytren's disease: a Discrete Choice Experiment

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ABSTRACT

Background: While in modern medicine, patients' preferences are important, these have never been defined for characteristics of Dupuytren treatment. This study determines these patients' preferences using a discrete choice experiment.

Methods: A multicentre discrete choice experiment study was conducted among patients with Dupuytren's disease who had been previously treated. Patients were asked on their preferences for attributes of Dupuytren treatments using scenarios based on: treatment method, major and minor complication rates, recurrence rates, convalescence, residual extension deficit after treatment and aesthetic results. The relative importance of these attributes and the trade-offs patients were willing to make between them were analysed using a panel latent class logit model.

Results: Five-hundred-and-six patients filled in the questionnaire. All above-mentioned attributes proved to influence patients' preferences for Dupuytren treatment ($p<0.05$). Preference heterogeneity was substantial. Males who stated to perform heavy labour made different trade-offs than females or males who did not perform heavy labour. In general, recurrence rate (36%) and extensive deficit (28%) were the most important attributes in making treatment choices, followed by minor complication rate (13%). Patients accepted an increase of 11% recurrent disease if they could receive needle aponeurotomy (NA) treatment instead of limited fasciectomy.

Conclusion: This study confirms the importance of low recurrence rates and complete contracture corrections, but also emphasizes the significance of low complication rates. Convalescence was not an attribute, which scored high. The preference heterogeneity shows that patient consultations need to be targeted differently, which may result in different treatment decisions depending on patient characteristics and preferences.

INTRODUCTION

While many surgeons may still consider limited fasciectomy (LF) as the golden standard for treating Dupuytren's disease, in recent years, minimal invasive techniques, especially needle aponeurotomy (NA) and collagenase, have become increasing popular[1-5]. The most optimal of these techniques cannot easily be decided, since each technique has specific strengths and weaknesses. For example, collagenase is a minimal-invasive strategy with shorter recovery time but may have higher recurrence rates than the more invasive LF[2, 3, 6]. In addition, NA also has a shorter recovery time than LF, but has a much higher minor complication and recurrence rate[2, 7].

Due to these different pros and cons of present techniques, the decision which treatment method is preferred to treat patients with DD depends on the relative importance of these factors. Amongst others, degree of contracture, expertise of the surgeon, expected commitment of the patient to the postoperative care and follow-up and patients' expectations may all play an important role in this choice[8, 9]. In addition, data on recurrence rates, surgical outcome and complication rates play an important role in advice to patients and in clinical decision making[10].

At present, it is unclear how a patient would weigh a better reduction in contracture correction compared to an increase in the major complication rate or to what extend patients were willing to accept an increase in recurrent disease for a reduction in duration of recovery. Insight in these preferences can contribute to patient-centred care and information for patients. Therefore, the aim of this study is to determine which treatment attributes are important for patients when choosing a DD treatment option and to what extent patients are prepared to make trade-offs between these attributes.

METHODS

Discrete Choice Experiment

To quantify patients' preferences for health care interventions, discrete choice experiments (DCEs) are increasingly used[11]. DCEs assume that health care interventions can be characterized by a combination of attributes (e.g. degree of contracture correction, complication rates) and attribute levels (e.g. major complication rates: 2%, 5%), and that this combination determines patients' preferences[12]. In a DCE, respondents are repetitively offered hypothetical choices between two or more alternative health care interventions, which are presented as different combinations of attribute levels[13, 14].

Attributes and attribute levels

To define possible attributes and their levels for this DCE study, we conducted a literature study to evaluate which outcomes parameters are evaluated in clinical studies[1-3, 6, 7, 15-17]. Furthermore, experiences from the Dupuytren Rotterdam (Du Ro) trial and

the expert opinion of two hand surgeons from the Erasmus University Medical Centre (Erasmus MC) were used for establishing attributes. In total, seven relevant attributes with their levels were determined: (1) treatment method, (2) major complication rate (3) minor complication rate, (4) convalescence, (5) recurrence rate, (6) degree of residual contracture after correction, and (7) aesthetic result (Table 1).

Attributes and Attribute levels	
Attributes	Levels
Treatment method	Limited fasciectomy Needle aponeurotomy (NA) Extensive percutaneous aponeurotomy and lipofilling (PALF) Collagenase injections
Major complication rate	2% 5% 10%
Minor complication rate	5% 20% 60%
Convalescence	5 days 30 days 60 days
Recurrence rate within 5 years	30% 60% 90%
Residual extension deficit after treatment	0 degrees 20 degrees 40 degrees 60 degrees
Aesthetic result	Moderate Good Excellent

Table 1: DCEs assume that health care interventions can be characterized by a combination of attributes and attribute levels. This table shows the different attributes and levels that are used in this study.

Study design and questionnaire

The combination of five attributes with three levels and two attributes with four levels resulted in 3.888 hypothetical treatment alternatives. As it is not feasible to present a single patient with all alternatives, an efficient DCE design by maximizing D-efficiency (using Ngene software, version 1.1.1, http://www.choice-metrics.com/) was created with 24 choice sets to estimate all main effects. Since response reliability decreases with more than 16 choice-sets per respondent, we used a blocked design dividing these 24 choices into two questionnaires[18, 19].

Each questionnaire consisted of 12 choice-sets (Figure 1). One choice-set was repeated in all subjects to check for consistency. Each choice-set consisted of two treatment options for DD and a 'no treatment' option to allow an 'opt out'. The questionnaire was specifically designed not to favour any type of treatment option using an unlabelled DCE design[20].

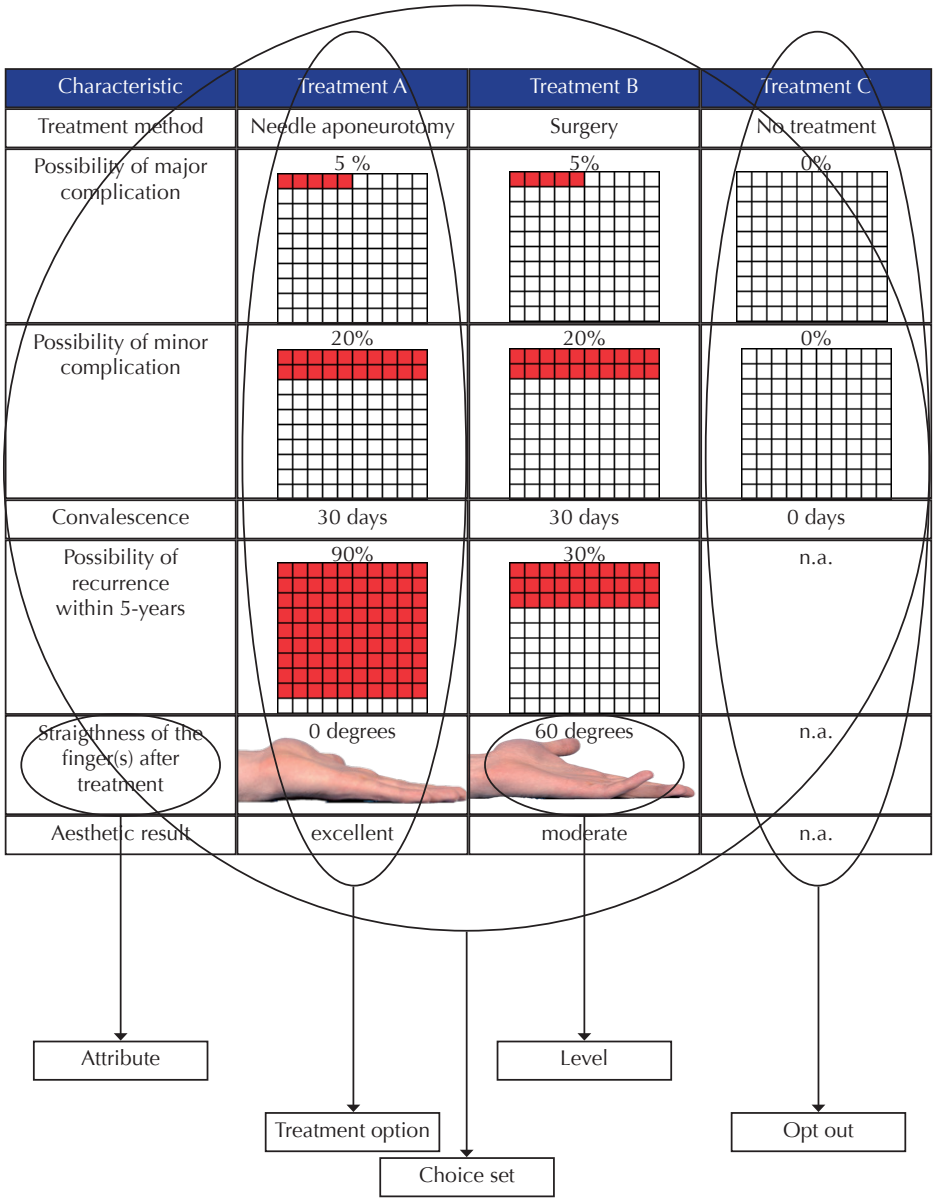

Figure 1: This figure shows an example of a choice set. Patients received 12 different choice sets in order to measure their preferences. It was explained that if 'opt out' was chosen it would indicate that the disease would progressively worsen.

To evaluate if patients were able to interpret the questions, three sample questions at the beginning of the questionnaire were asked. This was examined as a pilot in 26 patients.

Attached to the questionnaire was a detailed description of the attributes and their levels. Photographs were included to demonstrate 'moderate' aesthetic result, 'good' aesthetic result and 'excellent' aesthetic result. We defined minor complications as hematoma, oedema and mild pain complaints whereas major complications included tendon injury, nerve injury, arterial lesions, and complex regional pain syndrome (CRPS). General questions about history of DD, satisfaction with previous treatment, profession and level of education were asked in an additional questionnaire.

Study sample

This multicentre DCE study was conducted at Erasmus MC and Sint Franciscus Gasthuis (SFG) and at seven locations of the Xpert Clinic in the Netherlands. Patients who received any kind of treatment for DD between January 2009 and August 2012 were included. These patients received either LF with or without skin graft, extensive percutaneous aponeurotomy and lipofilling (PALF), NA, injection with collagenase or a combination of these treatments.

Invitations were sent to all patients. Patients could either fill in a web-based version of the questionnaire or a paper copy. A reminder was sent after 6 weeks to all non-responders.

This study received approval by the Medical Ethical Committee of Erasmus MC in Rotterdam (MEC-2012-330). All patients gave their informed consent.

Statistics

We used a panel latent class logit model for the analysis of patients' choices[21, 22]. This latent class logit model is a conditional logistic regression analysis that can identify whether different groups with similar preferences (class segments) exist in the population. The model is flexible in that the probability that sampled respondents belong to a particular class can be linked to covariates (e.g. gender, manual labour and treatment history); hence allowing for some understanding as to the makeup of the various class segments[22]. The latent class logit model accounts for the panel nature of the data in which each respondent completed 12 choice tasks. To determine the number of classes, we selected the model with the best fit based on the Akaike information criterion (AIC). We tested a number of different specifications for the utility function (i.e., categorical or numerical attribute levels) and found that the optimal utility function was:

$V_{nsj} = \beta_{0|c} + \beta_{1|c}$ treatment_palf$_{nsj|c} + \beta_{2|c}$ treatment_needle$_{nsj|c} + \beta_{3|c}$ treatment_collegenase$_{nsj|c}$ $\beta_{4|c}$risk of major complications$_{nsj|c} + \beta_{5|c}$risk of minor complications$_{nsj|c} + \beta_{6|c}$convalescence (days)$_{nsj|c} + \beta_{7|c}$risk of recurrence within 5-years$_{nsj|c} + \beta_{8|c}$residual extension deficit after treatment$_{nsj|c} + \beta_{9|c}$aesthetic result_good$_{nsj|c} + \beta_{10|c}$aesthetic result_very good$_{nsj|c}$

Where:

$V_{nsj|c}$ represent the observable utility that respondent n belonging to class segment c has for alternative j in choice set s;

$\beta_{0|c}$ represents an alternative-specific constant for a certain class;

$\beta_{1\text{-}10|c}$ are class-specific parameter weights (coefficients) associated with each attribute (level) of the DCE;

Hence, all attributes were acted as linear attributes, except for the attributes treatment method and aesthetic results (both categorical variables). The reference levels for 'treatment method' and 'aesthetic results' were 'surgery' and 'moderate', respectively.

Interpretation of the coefficients:

1) The statistical significance of a coefficient (p-value ≤ 0.05) indicated that, conditional on belonging to that class, respondents considered the attribute important when making stated choices.
2) In terms of the class assignment parameters (i.e., the covariates), statistically significant parameter estimates indicate that the covariate can be used to distinguish between the different classes. For example, if the covariate male gender is negatively and significantly associated with a particular class in the assignment model, then it is indicative that men are less likely to belong to that particular class than women.
3) The sign of the coefficient reflects whether the attribute had a positive or negative effect on preference for a treatment.
4) The value of each coefficient represents the importance respondents assign to an attribute (level). However, different attributes utilize different units of measurement. For example the coefficient 'major complication rate' represented the importance per 1% complication rate. When looking at a treatment that generates 5% protection rate, the coefficient must be multiplied 5 times (5 times coefficient of 'major complication rate of a treatment' of 1% = coefficient of 'major complication rate of a treatment' of 5%).

We used NLogit 4.0 software (www.limdep.com) to estimate the latent class models and SPSS 21.0 software (http://www-01.ibm.com/software/analytics/spss/) for all other analysis.

Importance scores and trade-offs

We translated the preference coefficients of all attributes to importance scores and the clinically relevant trade-offs. This will give us more information about which attribute was most important and the willingness to trade different attribute levels for 'recurrence rate' and 'contracture correction'. In more detail, we calculated class specific importance scores (IS) to visualize the relative importance of a given attribute in that class by dividing the difference in utility between highest and lowest level for a single attribute by the sum of the differences of all attributes for that class[13]. Hence, the IS are calculated rates, indicating how much one decision is based on a specific attribute (e.g. x% of the decision for a specific treatment option is based on recurrence rate, and y% of the decision is based on reduction of extension deficit; all rates together count up to 100% and counts as 1 decision for a specific treatment). Additionally, we determined the ranking IS of each attribute. That is, an attribute with a ranking IS of 1 represents the most important attribute, while an attribute with a ranking IS of 7 represents the least important attribute. Furthermore, we also calculated overall importance scores, by taking class probability into account.

Additionally, we calculated the willingness to trade different attribute levels for 'recurrence rate' and 'contracture correction' by taking the ratio of the coefficients of the different attributes with 'recurrence rate' or 'contracture correction' as the dominator. For example, a value that represents how much change of recurrence or reduction of contracture correction a patient is willing to sacrifice for one unit change in the attribute of interest (e.g. major complications). Confidence intervals of this trade-off were estimated using the Krinsky and Robb procedure[22, 23].

RESULTS

Participants

A total of 506 out of 973 patients (59%) filled in the questionnaire. One-hundred-thirty-three patients did not want to participate in the study. Furthermore, we were not able to contact eight patients due to wrong postal addresses. Sixty-seven patients either did not return or completed the questionnaire. Two-hundred-fifty-nine patients did not respond at all (26.6%). In total, 393 men and 113 women participated in this study. The mean age of the population was 64 years old. This study population is comparable to patients suffering of DD, who visit the outpatient clinic (Table 2).

Discrete choice experiment results

Three groups in the latent class model were identified (Table 3), indicating that three different choice patterns could be identified between the different patients. The prob-

ability to belong to one of the three groups within the sampled population was 0.40, 0.11 and 0.49 for latent classes 1, 2, and 3, respectively.

The probability to belong to a specific class was dependent on two socio-demographic variables: gender and conducting heavy manual labour. More specifically, males conducting manual labour more frequently belonged to class 2. Other socio-demographic variables were not significantly explaining class assignment probabilities.

Baseline characteristics		
	Respondents (N = 506)	
Characteristics		
Mean age + SD (years)	64(9)	
Sex		
male	393	78%
female	113	22%
Education level		
low	63	12%
intermediate	218	43%
high	225	45%
Civil class		
married / living with partner	433	86%
partner, living apart	12	2%
single / divorced	44	9%
widow(er)	17	3%
Heavy manual labor		
yes	142	28%
no	364	72%
Family with Dupuytren's disease (DD)		
first / second degree	248	49%
third / fourth degree	16	3%
no family member with DD	147	29%
not clear	95	19%
Ectopic disease		
M. Ledderhose	79	15,5%
M. Peyronie	16	3%
M. Ledderhose and M. Peyronie	8	1.5%
no ectopic disease	403	80%
Previous treatment		
surgery *	273	54%
minimally invasive technique **	123	24%
surgery and minimally invasive technique	110	22%

Table 2: In this table the patients' characteristics are mentioned.
* limited fasciectomy and dermofasiectomy
** needle apeneurotomy (NA), extensive percutaneous apeneurotomy with lipofilling (PALF), collagenase

Panel latent class model with three latent classes							
Attributes	Latent class 1		Latent class 2		Latent class 3		Overall
	Coefficient	IS %(rank)	Coefficient	IS %(rank)	Coefficient	IS %(rank)	IS %(rank)
Constant	−5.578		−1.808		−7.585		
Treatment characteristics							
Treatment method							
Surgery	−0.005**		0.951**		−0.106**		
PALF	−0.070	4.4% (5)	−0.948*	27.7% (2)	−0.280*	8.4% (4)	9% (4)
NA	0.171*		0.014		0.444*		
Collagenase injection	−0.097		−0.018		−0.058		
Major complication rate (%)	−0.029*	3.8% (6)	−0.048*	5.6% (5)	−0.077*	7.2% (5)	6% (5)
Minor complication rate (%)	−0.004*	5.9% (4)	−0.008*	9.4% (4)	−0.020*	18.9% (2)	12% (3)
Convalescence (days)	−0.003*	3.1% (7)	−0.004	3.4% (7)	−0.009*	6.1% (6)	5% (6)
Recurrence rate (%)	−0.017*	27.2% (2)	−0.020*	28.7% (1)	−0.038*	43.9% (1)	36% (1)
Extension deficit (degrees)	−0.051*	49.3% (1)	−0.025*	21.6% (3)	−0.019*	12.8% (3)	28% (2)
Aesthetic result							
Moderate	−0.206**		−0.143**		−0.124**		
Good	0.031	6% (3)	0.038	3.6% (6)	0.020	2.6% (7)	4% (7)
Excellent	0.175*		0.106		0.103*		
Class probabilities	0.396		0.111		0.493		
Constant	−0.316		−2.678*		-		
Sex	0.240		1.098*		-		
Heavy labor	−0.340		0.757*		-		

Table 3: Abbreviations: * significant; ** reference group; IS: importance score

This table shows the results of the panel latent class model. The coefficients indicating the increase (positive sign) or decrease (negative sign) in preference for a certain treatment when all other attribute levels remain the same. For example, the coefficient of −0.029 for major complication rate indicates that the preference for a specific surgery decreases by 0.029 with the complication rate increases with 1%.

Overall, almost all coefficients of the linear attributes were significant. Preference for a certain treatment decreased (indicated by a negative coefficient) with increasing major and minor complication rates, longer convalescence, higher recurrence rate and larger post-treatment extension deficit. The coefficients of the categorical attributes (i.e., treatment method and aesthetic results) showed that (I) in latent class 1 and 3 the effect of preferring NA was significantly higher than surgery (0.171 vs –0.005, and 0.444 vs. –0.106, for latent class 1 and 3 respectively); (II) in latent class 2 the effect of preferring surgery was significantly higher than PALF (0.951 vs. –0.948); (III) in all latent classes a very good aesthetic result was preferred over a moderate aesthetic result.

Importance scores

The relative importance of the different attributes, as described by the importance scores in Table 3 were different between the subjects belonging to the different latent classes. Subjects in class 1 predominantly made their choice based on extension deficit (50%) and recurrence rate (27%). In class 2, subjects chose primarily based on recurrence (29%), treatment method (28%), and residual contracture (22%). In class 3, subjects made their choice predominantly on recurrence (44%) and minor complication (19%). Overall, recurrence rate (36%) and residual contracture (28%) were the most important attributes determining treatment choice.

Trade-offs

In Table 4 trade-offs are presented that patients were willing to make for 'recurrence of disease' and 'contracture correction'. Amongst others, patients accepted an increase of 10.5% recurrent disease if they could receive NA treatment instead of LF. Furthermore, patients were willing to accept an increase of two percent for getting recurrent disease for a reduction of one percent of major complications; this means they accept an increase of 10% of recurrent disease for a reduction of five percent in major complications. In addition, for every 9 degrees increase of residual contracture after treatment, patients were willing to trade 10% less risk of recurrent disease.

DISCUSSION

The aim of this study was to determine which attributes are important for a patient when choosing a DD treatment option and to what extent a patient is willing to make trade-offs between characteristics of treatment options. We found that treatment method, major complication rate, minor complication rate, convalescence, recurrence rate, degree of residual contracture after treatment, and aesthetic result, all proved to influence patients' preferences for Dupuytren treatment. Preference heterogeneity was substantial. Males who stated to perform heavy labour made different trade-offs than

	Willingness to trade attributes		
Attribute	Willingness to trade recurrence (%;CI)	Willingness to trade extension deficit (degree; CI)	With
Treatment method	−9.8 (−12.5 to −7.4)*	−8.45 (−11.1 to −6.2)*	PALF instead of surgery
	10.5 (8.0 to 13.2)*	9.0 (6.7 to 11.8)*	NA instead of surgery
	−2.5 (−4.6 to 0.4)	2.2 (0.4 to 4.0)*	collagenase instead of surgery
Major complication rate	2.0 (1.7 to 2.3)*	1.7 (1.4 to 2.0)*	1% less risk of major complicatons
Minor complication rate	0.5 (0.4 to 0.5)*	0.4 (0.3 to 0.5)*	1% less risk of minor complications
Convalescence	0.2 (0.3 to 0.3)*	0.2 (0.1 to 0.2)*	1 day faster recovery
Recurrence rate	n.a.	0.9 (0.8 to 0.9)*	1% less risk of recurrence
Extension deficit	1.2 (1.1 to 1.3)*	n.a.	1% less residual extension deficit
Aesthetic results	1.0 (−0.7 to 2.6)	0.8 (−0.7 to 2.2)	good instead of moderate result
	4.8 (3.1 to 6.5)*	4.1 (2.7 to 5.7)*	excellent instead of a moderate result

Table 4: This table shows the results of the trade-offs patients were willing to make. For example, patients were willing to accept an increase of two percent for getting recurrent disease for a reduction of one percent of major complications.

females or males who did not perform heavy labour. Overall, recurrence rate (36%) and extensive deficit (28%) were the most important attributes in making treatment choices, followed by minor complication rate (13%). Patients accepted an increase of 11% recurrent disease if they could receive NA treatment instead of LF.

Our study has a number of specific strengths and limitations. The main strengths of this study are the large study population (506 analysed questionnaires) and the thorough and state-of-the-art design and analysis of the DCE. Furthermore, in this study we included patients already treated for DD because they are familiar with the disease and the impact of a surgical or minimal invasive surgery. However, this strength is also a limitation. Because patients were previously treated, they may have 'defended' their own treatment (i.e. cognitive discordance), or they may have previous positive or negative treatment experiences. This may have biased our results. On the other hand, they represent the general population that visits the outpatient clinic. However, when comparing patients that received different treatments previously, we found no specific choice-pattern based on the prior surgeries. This indicates that patients previously treated by an invasive surgery made no other choices than patients treated with a minimal invasive technique. In other words, we believe these study outcomes are valid and therefore relevant for future practice and further understanding of patients' preferences. Additionally, although we did not find evidence for cognitive discordance, we recommend repeating the study for patients not having been treated for DD to determine the robustness of our results. A second limitation is, inherent to DCE where

a larger number of attributes are important, that discrete choice questionnaires can be difficult to understand for patients. Due to the high number of attributes, patients may have difficulty overseeing all attributes and their levels when asked to select a specific treatment. Therefore, to evaluate the task understanding, we repeated one of the questions in the questionnaire at the end. This consistency test showed that 19% of the patients did not answer the question consistent. However, we found that these participants had patient characteristics (gender, age etc.), and similar preferences compared to the group that correctly answered the consistency question. Therefore, we did not exclude this group from the study population.

Unfortunately, few comparative studies are available to compare the attribute levels of different treatments within the same population and with the same measurement protocol. We showed that patients are willing to trade 11% increase in recurrence rate within five years to receive NA instead of LF. This may be in line with findings from a recent randomized controlled trial. This trial reported similar patients satisfaction early after surgery. However, at five years, almost 50% higher recurrence rate for NA (84%) compared to LF (32%) was reported, resulting in less patients satisfaction after five years in the NA group[2]. However, van Rijssen et al. reported that patients with a contracture recurrence after NA would prefer NA again because of the better convalescence, which is not in line with our finding that patients find convalescence less important than recurrence rate[2].

Furthermore, contractures are more likely to be completely released after open surgery whereas some minimally invasive techniques lack the ability to release the joint contracture and/or lateral or spiral cord completely after one intervention[1, 3]. We showed that this attribute was of high importance (28%). However, patients were willing to trade nine degrees of residual contracture for receiving NA instead of LF. In addition, they were willing to trade two degrees of residual contracture for receiving collagenase instead of LF, indicating that patients are willing to trade joint contracture for a less invasive technique.

In conclusion, lately, minimally invasive interventions for Dupuytren's contracture have received increased attention because of their rapid convalescence and lower complication risk[1-3]. However, this study shows patients find low recurrence rates and complete contracture correction the most important attributes when selecting a specific treatment. Convalescence, which is often mentioned as an important advantage of minimal invasive techniques, was found to be less important for treatment selection in our study[1, 7]. This study may give the surgeon awareness of the patients' preferences towards certain treatment attributes. They can use this information when consulting patients by focussing more on the most relevant attributes. In that way the surgeon and patient can decide together which treatment is best for that specific patient, by a shared-decision making.

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Part IV

New surgical methods

Chapter 5

Long-term follow-up of flaps for extensive Dupuytren's and Ledderhose disease in one family

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ABSTRACT

Dupuytren's and Ledderhose disease can be a cumbersome condition in patients with a severe diathesis with a very early onset. Two brothers are described with a reversed radial forearm flap on both hands and two upper lateral arm flaps on both feet with a long-term follow-up ranging from 14 to 25 years. They had multiple procedures of both hands before the flaps were considered.

No recurrence occurred under the flap. In very severe diathesis flaps should be considered in an earlier phase to prevent multiple procedures and early recurrence.

INTRODUCTION

Patients with a severe diathesis in Dupuytren's Disease (DD) are known to have a poor surgical outcome after long-term follow-up with a recurrence rate of the disease ranging form 12% to 47% after dermofasciectomy[1,2]. All depends of course on the definition of recurrence. Furthermore, most authors report no recurrent disease under the full thickness graft[3, 4]. In addition, recurrent surgeries lead to high complication rates and social burden. Also the financial implications for society are high[5].

In search for less recurrence different kind of free flaps have been described as alternative treatment for severe DD cases[6, 7]. However, no long-term follow-up has been reported following this extensive surgery surgery.

The aim of this report is to describe the long-term follow-up in two brothers with a severe diathesis following flap surgery for both hands and feet.

PATIENTS

Case 1

In 1978 a 30-year-old Caucasian male with a history of DD was referred to our hospital. In the following eight years twelve faciectomies combined with full thickness skin grafts (FTG) were performed on his right hand, left hand and left foot. He is a smoker and consumes four units of alcohol per day.

In 1986 the severity of his diathesis and the frequent recurrence of the disease prompted us to perform a reversed radial forearm flap (Rev. RFF), to cover the palm and the proximal phalanges of all fingers of the left hand excluding the thumb (Figure 1).

In 1991 his right hand was also operated with a Rev. RFF. In 1988 and 1996 both feet were operated with a free vascularised upper lateral arm flap (ULAF) following excision of painful large nodules impeding normal gait (Figure 3). Additional surgeries over the years were for an arthrodesis of the PIP joint of the fifth finger due to a painful degenerative arthritis, to resolve the residual syndactylies of both hands following flap surgery and to bury a pre-existent painful neuroma in the palm of the right hand.

In 2010, 24-years after surgery of the left hand and nearly 20 years after surgery of the right hand, no recurrent DD tissue has been noted under the flaps. The feet, respectively 15 and 22 years postoperatively, have been free of recurrence since the initial free flap.

Case 2

In 1986 a 37-year-old Caucasian male, brother of case one, was operated on both hands by using a Rev. RFF, after an extensive history of recurrent surgeries (over 30 for both hands and two for both feet) for DD since 1974 (Figure 2). He consumed 5-8 units of alcohol per day and had no history of smoking. The residual syndactylies of both hands following flap surgery were resolved in 1988 and in 1990.

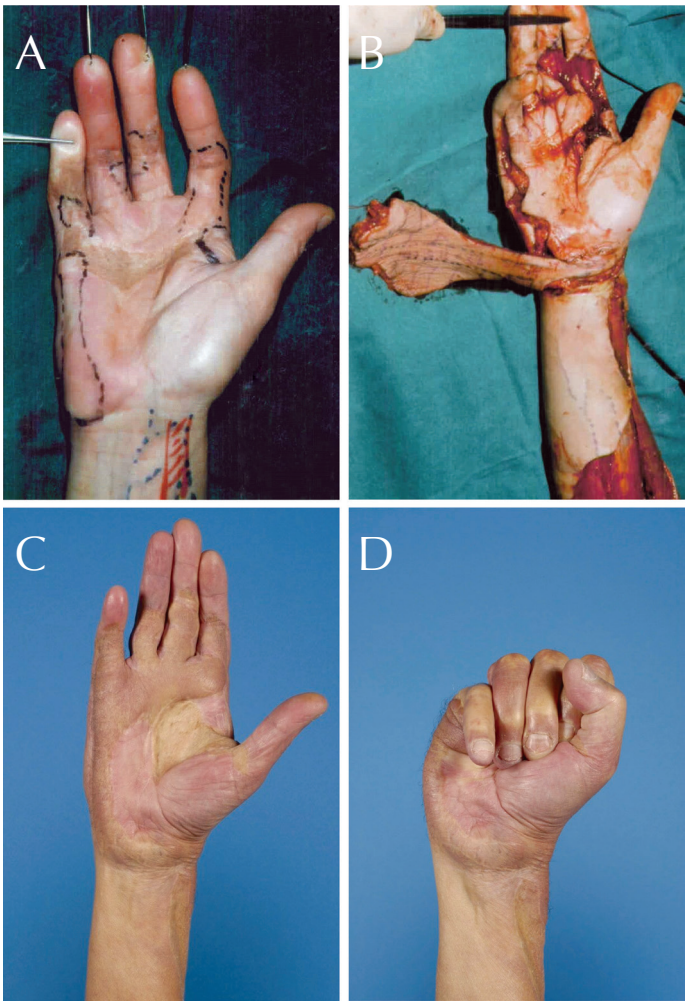

Figure 1: This figure shows the preoperative (A) and peroperative (B) photograph of the right hand of our first patient. At that time he was 43 years old. Twenty years after surgery the patient is able to extent the fingers (C) and to make a fist (D).

Between 1986 and 1990 two fasciectomies with FTG were performed on the first web space of his left hand and on his right foot outside the area of the flap. Arthrodesis of his DIP joint from his fifth finger of his left hand was performed in 1994, due to a painful hyperextension.

The right foot was operated with a free vascularised ULAF in 1997, with a complicated postoperative recovery due to systemic co-morbidity, i.e. heart failure and jaundice. The flap survived. The left foot was therefore not operated (Figure 3).

After 25 years, the patient had no recurrence of DD tissue under the Rev. RFF, but he did suffer from extensions at the sides of the flaps. Fourteen years postoperative the right foot has been free of recurrence since the initial free flap. He still suffers from painful noduli in his left foot.

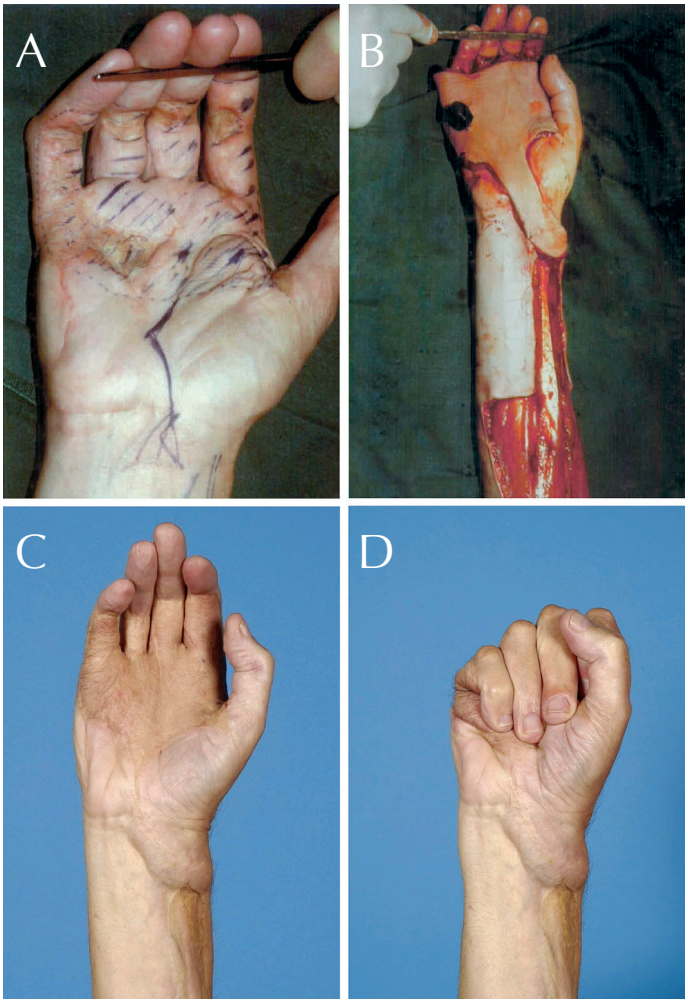

Figure 2: This figure shows the preoperative (A) and peroperative (B) photograph of the right hand of our second patient. At that time he was 37 years old. Twenty-five years after surgery the patient is able to extent the fingers (C) and to make a fist (D).

METHODS

In both patients extensive measurements were performed during regular follow-up. The passive range of motion (ROM), grip strength (Jamar), and sensibility (Semmes and Weinstein monofilaments) were measured. Furthermore the Disability for Arm Shoulder and Hand (DASH), Cold Intolerance Scale (CISS), VAS pain scale and a satisfaction questionnaire were completed by both patients.

RESULTS

Both patients cannot fully extend the fingers. Flexion is possible except in the small finger of the right hand of the first patient and in the small finger of the left hand of the

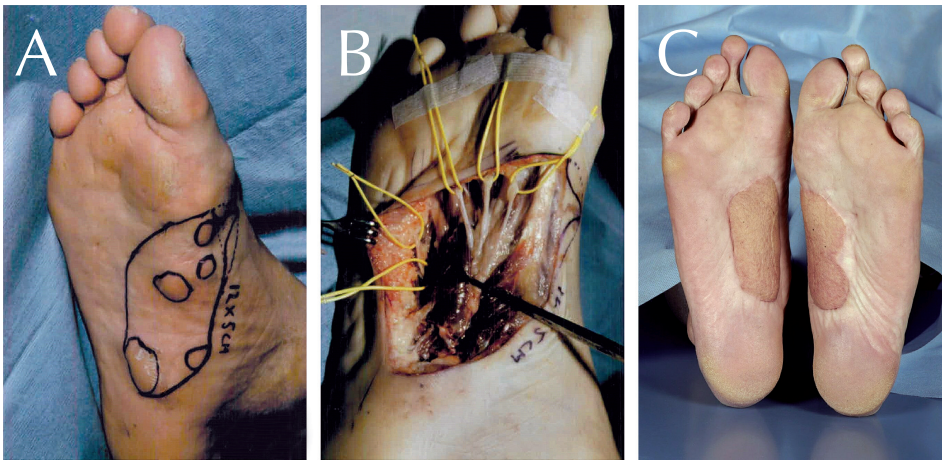

Figure 3: The surgical course of the feet of both patients is shown. Not all photographs were available. Therefore we can only show preoperative (A) and peroperative (B) photographs of the second patient and the 22-year follow-up photograph (C) of the first patient.

second patient (Table 1, Figure 1 and Figure 2). Grip strength was diminished with on average 10 kg. compared to their age group (C1: 26.02 kg. right hand; 26.65 kg. left hand and C2: 32.22 kg. right hand; 32.06 kg. left hand)[8].

The first patient reports pain only when using his hands (VAS score 5 to 7.9 out of 10). This pain is especially in his right hand. The second patient had no pain in his right hand, but does suffer from a constant pain of 2.2 out of 10 in his left hand. During daily activity this pain rises to 4.6 out of 10. The feet were not painful, except the left foot of the second patient which was not operated. Both brothers scored above 30 points on the CISS and the DASH score was 36 out of 100 for the first and 25 out of 100 for the second patient. They experience some difficulties in daily activity, but overall they are very satisfied with the outcome of the surgery (8.4 out of 10 and 8.7 out of 10 VAS scale) and would not hesitate to do it again. They advised to perform the surgery earlier in the course of the disease.

DISCUSSION

Two patients with a severe diathesis of Dupuytren's Disease (DD) are described, in which reversed radial forearm flaps (Rev. RFF) were used for both hands and free vascularised upper lateral arm flaps for the feet, as an ultimate treatment solution after multiple procedures. Their hand function is acceptable and the patients are very satisfied with the overall results following the flap surgery in both hands and feet. No recurrence developed under the flap since the use of the flaps and patient burden was reduced extensively. It should be noted that these patients have been operated multiple

times and therefore demonstrate pain, cold intolerance and disability regardless of the use of flaps. The pain already existed prior to flap surgery. In the first patient a neuroma was buried in the palm of the right hand.

Skin grafts have been reported to act as a local 'fire-break' to prevent recurrence. Extensive dermofasciectomy with FTG is therefore treatment of choice for patients with a severe diathesis[9-10]. However, the recurrence rate of dermofasciectomy, after mean follow-up of 13 years, is reported to be up to 47%[2]. Dermofasciectomy compared with fasciectomy even shows the same recurrence rates of 12% after 36 months[1].

In studies using free vascular flaps for soft tissue coverage after palm and digit defects DD patients are mentioned, although survival of the flap and not recurrence of DD was the outcome[6, 11]. However, the circumflex scapular artery perforator flap has been described with good clinical outcome in one patient with a one-year- follow-up[7].

Any large flap is an aggressive but alternative treatment for patients with severe DD; we used the Rev. RFF for this purpose. In very severe diathesis of DD's with an early onset (3rd to 4th decade) we offer this kind of extensive surgery to these patients. However, nearly all patients decline this type of surgery in a very early stage. Only after multiple corrections the need for a different treatment is recognised. We have performed four more flaps to the hand for severe diathesis but with far less long-term follow-up when compared to the patients described. All these patients have not demonstrated recurrence under the flap until now. To reduce the patient burden and to lower costs it can be a good option to consider large flaps covering the palm of the hand and proximal fingers earlier.

		Case 1					**Case 2**				
	Digit:	1	2	3	4	5	1	2	3	4	5
		Extension / Flexion					Extension / Flexion				
Right hand	MP	0° / 38°	−17° / 90°	0° / 53°	−18° / 74°	−5° / 70°	−3° / 37°	6° / 102°	−10° / 96°	−11° / 90°	−13° / 94°
	PIP	−18° / 54°	34° / 99°	10° / 97°	5° / 94°	45° / 45°	−12° / 71°	40° / 98°	13° / 100°	6° / 84°	20° / 86°
	DIP		−23° / 47°	−20° / 31°	−5° / 43°	−12° / 10°		−1° / 54°	0° / 0°	−15° / 4°	20° / 38°
Left hand	MP	−12° / 42°	−18° / 78°	−13° / 90°	−10° / 88°	−13 / 87°	−5° / 48°	2° / 86°	8° / 87°	45° / 97°	30° / 88°
	PIP	−12° / 47°	5° / 90°	4° / 90°	32° / 102°	17° / 90°	−25° / 56°	25° / 83°	23° / 86°	26° / 64°	28° / 36°
	DIP		−27° / 38°	−10° / 22°	−14 / 10°	−7° / 32°		3° / 32°	−17° / 24°	5° / 7°	45° / 45°

Table 1: This table shows the passive extension and passive flexion of the fingers of both hands of both patients. Both patients can extent and flex the fingers. Our second patient received an arthrodesis for his PIP5 of the left hand.

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Chapter 6

Extensive Percutaneous Aponeurotomy and Lipofilling (PALF): A New Treatment for Dupuytren's disease

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ABSTRACT

Background: Surgical resection of Dupuytren's contracture is fraught with morbidity and prolonged recovery. This paper introduces a novel minimally invasive alternative for Dupuytren's Disease and its outcome.

Methods: The procedure consists of an extensive percutaneous aponeurotomy that completely disintegrates the cord and separates it from the dermis. Subsequently the resultant loosened structure is grafted with autologous lipoaspirate. After one week of post-operative extension splinting patients are allowed normal hand use and are advised to use night splints for three to six months. We treated and report on our experience with 91 patients (99 hands) operated in Miami and Rotterdam; from 50 patients we report on goniometry (average follow-up of 44 weeks).

Results: The contracture from the PIP joint improved significantly from 61 degrees to 27 degrees and the MP joint from 37 degrees to –5 degrees. Ninety-four percent of patients returned to normal use of the hand within two to four weeks and 95% were very satisfied with the result. No new scars were added and a supple palmar fat pad was mostly restored. Complications were one digital nerve injury; one post operative wound infection and four patients with CRPS.

Conclusion: This new invasive technique shortens recovery time, adds to the deficient subcutaneous fat and leads to scarless supple skin. By its ability to treat multiple rays, it addresses the pathology in the entire hand. The procedure is safe and effective, especially for the primary cases. Currently comparative prospective randomized studies are in process to fully determine its role in treatment of Dupuytren's contracture.

INTRODUCTION

Dupuytren's disease (DD) is a benign, progressive, fibroproliferative, chronic disorder that results in abnormal scar-like tissue in the palmar fascia of the hand. Extension to the digits causes progressive digital flexion contractures. Treatment of DD is mainly surgical. Limited fasciectomy and limited dermofasciectomy are the techniques mostly used[1]. Although excisional surgery seems to be the standard treatment, the procedure is fraught with a significant rate of complications[1]. However, the greatest drawback of surgery is the associated morbidity and the time required until return to normal use of the hand. This need for less morbidity and shorter recovery time opened the door for less invasive treatment alternatives[2, 3].

Collagenase injections are a less invasive treatment option that can significantly reduce flexion contractures. The drawback seems to be the inflammatory reaction caused by collagenase and its potential harm to tendons and surrounding tissues. The results are promising, but the treatment is not widely available yet, no long-term follow-up data are available and a comparison to other treatment alternatives is lacking[4, 5]. Radiotherapy is another less-invasive treatment alternative. However, radiotherapy has only been administered for early stage DD[6].

Percutaneous release of contracted cords by needle aponeurotomy only is also less invasive and is recognized to promote fast postoperative recovery[7, 8]. However, a 65% recurrence rate after 32 months has been reported using the standard procedure which consists of a few full thickness cord cuts with a needle[8].

Despite its great appeal to patients, our experience with percutaneous aponeurotomy was also disappointing due to the rapid recurrence of the contracture. Having found that fat grafting is beneficial in softening scars in other clinical conditions, one of the co-authors (RKK) decided to combine fat grafting with a novel minimally invasive percutaneous release technique that is permissive to fat grafting. In this study, we describe this new surgical method of extensive percutaneous aponeurotomy with lipofilling (PALF) and report our first results from a cohort of 50 patients.

METHODS

A Surgical technique

Fat harvesting

Prior to operating on the hand, the abdomen and ipsilateral flank are prepped and draped. Through two to three puncture sites with a 14G hypodermic needle we diffusely inject in the subcutaneous fat 500 – 600ml of a tumescent solution containing 50ml of 2% Lidocaine and 1ml of 1:1000 Epinephrine per litre of physiologic solution. We then harvest the fat by manual liposuction using a 12G (2.7mm) 12 (1x2mm) holes 25cm long cannula connected to a syringe pulling a steady 300 mmHg vacuum suction. To

separate the graft from the serum and tumescent solution, the collected lipoaspirate is then allowed to sediment on the side table while the extensive percutaneous aponeurotomy is performed.

Extensive Percutaneous Aponeurotomy

Under regional or general anesthesia, the extremity is tightly exsanguinated. This collapses the vessels into cord-like structures and minimizes the damage from the needle. The digits are placed under maximal extension tension using a firm lead-hand retractor (Figure 1). Then, progressing in an orderly fashion from proximal to distal, multiple palmar puncture wounds are made with a needle-like sharp-tipped bevelled piercing instrument. Working along a wide area around the contracture, the palpable cords under tension are progressively and extensively severed through slight transverse oscillations at each puncture point. Tension is maintained by constantly extending the digits as the contracture progressively gives way. Residual restricting bands are localized by palpation and addressed in the same fashion. In order to maintain tension on the

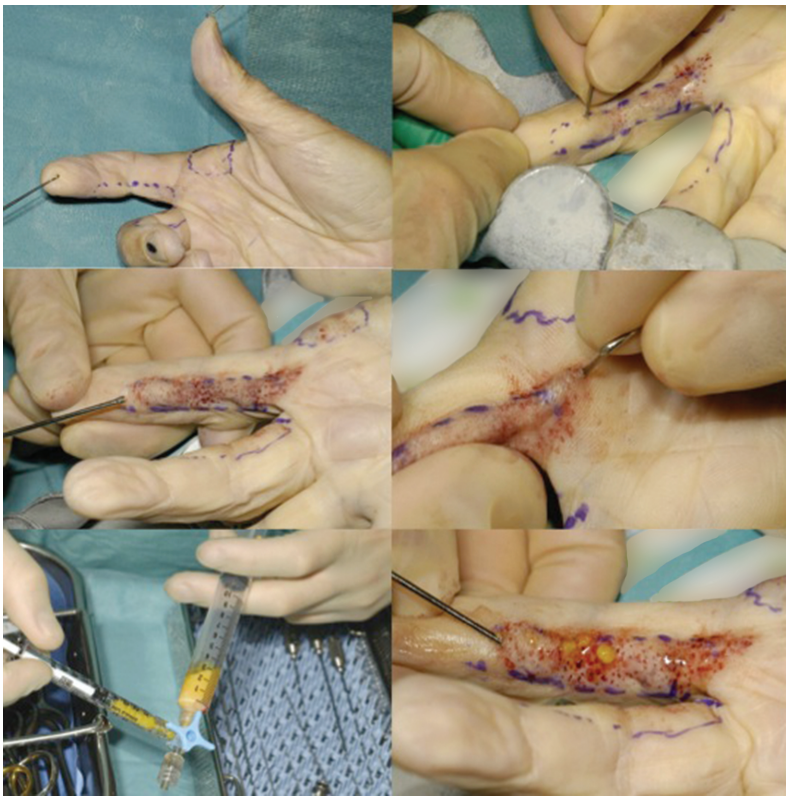

Figure 1: Peroperative photographs showing the peroperative release of the cord and lipografting of the same patient. Note the multiple puncture sites.

released area, we carefully avoid skipping to a distal site until the proximal site is fully released and soft (Figure 1).

The differential cutting effect provided by the tension on the cords is crucial. Tight constricting bands are most susceptible to be cut and torn by the small nicks, while the relatively looser neurovascular structures are spared. Since the internal collagen fibrous structure of the cord is a spiral-like weave, we only need to sever the fibres during their superficial course to inflict attrition damage to the entire weave and break it apart (Figure 2).

The other important safety aspect is the depth of penetration that never exceeds 3mm proximal to the transverse palmar crease and 2mm in the distal palm and digits since the digital nerve can be located dangerously superficial by a spiral cord. Depending upon the severity of the contracture and the size and firmness of the nodules this process often requires up to 50 puncture wounds per digital ray. Skin wrinkles and pits are released by severing the dermal attachments of the cord with a windshield wiper motion of the "L" shaped cutting device (Dupuytome™; Marina Medical, Sunrise, Florida, 33326 USA).

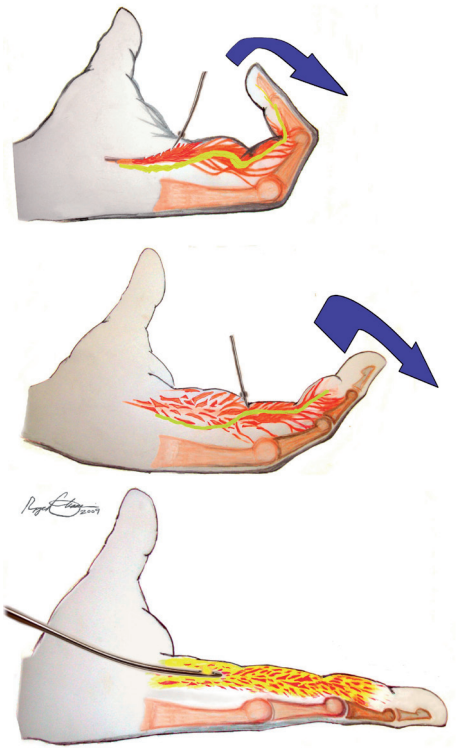

Figure 2: Schematic representation of the intervention. Under maximal tension the cord (red) is released from proximal to distal with multiple needle nicks. The digital nerve is yellow. After total release of the cord a 3D space is created in which fat can be injected.

The hand is ready for lipografting once the contracture is fully released, the skin fully supple and separated from the cord, and the nodules are completely chopped and soft.

Lipografting

We inject the released and loosened fibrous structure with the supernatant of the lipoaspirate harvested from the abdomen or flanks. Through two to three needle entry sites in the palm and the digit, using a spatulated single side hole blunt tip 14G cannula, the lipoaspirate graft is injected in multiple planes, while retracting the cannula along fanning tunnels. We usually inject a total of 10ml per digital ray and expect some of it to escape through the needle release sites. The very dilute injectate provides a margin of safety against over grafting. The tumescent effect of loose fat injection slightly balloons up the palmar skin to reveal any residual tethering dermal band that are then further released by the windshield wiper effect of the sharp tipped Dupuytome™.

postoperative care

A conforming dressing over the palmar skin that incorporates a plaster extension splint is kept for five to seven days. After removal of the intra-operative dressing, the patient is allowed to return to his normal activities and advised to use a night extension splint for up to 20 weeks.

B Patient population

Over a 32-month period, extensive percutaneous aponeurotomy combined with lipofilling was performed on a total of 91 patients and 99 hands eight patients were treated on both hands 69 males and 22 females) in Miami or Rotterdam. Patients were eligible for this procedure when the table-top-test was positive, regardless of whether the contraction was in the MP or PIP joint. Thirteen patients suffered from recurrent DD and had previously been operated using a fasciectomy. A medical ethical approval was obtained for analysis of the clinical data used for this study (MEC-2010-283; Erasmus MC, Rotterdam, The Netherlands).

As a part of the clinical routine, goniometry data were collected (Rotterdam) and clinical pictures of the hands were taken (Rotterdam and Miami). From a total of 52 patients, both preoperative and postoperative goniometry data of the MP-joint and PIP-joint were recorded or could be measured from the clinical pictures[9-11]. Reasons for incomplete goniometry data were the inability or unwillingness of patients to come for follow-up (many patients, especially in Florida, live abroad). Also a number of patients were deceased. Two of the 52 patients had a first web contracture and were left out the analysis. From the 50 patients, 15 had a MP-joint contracture, 11 had a MP-joint contracture, and 24 had both a PIP-joint and MP-joint contracture. The amount of con-

tracture was transformed to the Tubiana grading system to establish the total amount of improvement per ray.

Complications, satisfaction with the operation, gain in hand function and amount of time to full recovery was scored and we asked patients if they would recommend the same procedure again.

Statistical analysis

For each patient, we evaluated the most severely affected finger joint in the treated hand. We performed a paired t-test on the range of motion to compare preoperative versus postoperative contracture of the PIP joint and the MP joint. A Wilcoxon sum rank test was performed on the Tubiana grading group distribution.

RESULTS

Experiences during the operation

We were able to perform the procedure with a similar operating room time as for a fasciectomy. Operative time, including harvesting the grafts, was approximately 1 to 1.5 hours, depending on the amount of rays treated and was therefore comparable to conventional open fasciectomy times in our institutions.

We typically treated the entire palm of the hand and all the affected digital rays. Intraoperatively we achieved full MP-joint extension in all patients. Full PIP-joint extension was not always achieved as severe contractures were mostly combined with capsular contractures. The cord could always be fully released. There were no skin deficiencies in the primary cases, even in the most severe contractures. Only in two recurrent cases, the old scar ripped open during the release, requiring a small flap and a graft.

Follow-up data

In the 50 patients from who complete data were available at a mean follow-up of 44 weeks, we found a significant flexion contracture correction of the PIP joint from 61 degrees to 27 degrees and the MP-joint from 37 degrees to –5 degrees (Table 1). When we selected the PIP-joint and MP-joints with a flexion contracture of 45 degrees or more, the PIP-joint improved significantly from 70 degrees to 29 degrees and the MP-joint improved significantly from 54 degrees to –4 degrees. Following surgery 88% patients obtained Tubiana stage 1 (Table 2).

From experience during follow-up at the out patients clinic, the most impressive finding was the restoration of a supple subcutaneous fat pad. The treated skin previously overlying the cords could be pinched off the deep fascia just like normal healthy palmar skin, which is rarely seen in the scarred hand following conventional limited fasciectomy (Figure 3).

	Preoperative (SD)	Postoperative (SD)	Improvement (%)	P-value	Follow-up (weeks)
PIP-joint contracture (n = 39)	61.3° (24.5°)	26.7° (21.7°)	34.6° (56.4%)	<0.001	43.8
MP-joint contracture (n = 35)	36.5° (18.9°)	−5.1° (8.2°)	41.6° (114.0%)	< 0.001	42.2
PIP-joint contracture ≥ 45° (n = 32)	69.8° (17.2°)	29.4° (21.3°)	40.3° (57.7%)	<0.001	43.8
MP-joint contracture ≥ 45° (n = 15)	54.3° (8.9°)	−3.6° (6.5°)	57.9° (106.6%)	<0.001	44.3

Table 1: Results of the 50 patients of whom goniometric data were available. Extension deficit is shown in degrees. The third column shows the improvement of extension in percentages. Follow-up is in weeks after surgery. Results are presented separately for patients with a relatively mild joint contracture (<45 degrees) en more severe joint contractures (≥45 degrees)

Tubiana grading: Extension deficit of three joints combined		Preoperative: Number of patients per group	Postoperative: Number of patients per group
1	0° - 45°	9	44
2	45° - 90°	26	6
3	90° - 135°	14	0
4	≥135°	1	0

Table 2: Distribution of the patients over the different Tubiana gradings. The Tubiana grading is defined based on the total extension deficit of the three finger joints combined. Postoperatively, almost all patients had a total extension deficit in the worst finger of less than 45˚ according to the Tubiana grading.

Clinical experience: convalescence and complications

Our clinical experience was that except for four patients, in the total group of 91 patients, recovery and regained use of their hand for activities of daily living was acquired approximately one week after surgery. Return to either work or vocational activities was within two to four weeks. The four patients with a longer recovery time were all women with severe diathesis who had symptoms of CRPS such as swelling, diminished function and pain. Two of these patients had a history of CRPS in the other hand after open surgery for Dupuytren's contracture and described their symptoms after the present procedure as less severe. There were no tendon injuries. There was one digital nerve injury (1.1%) and one post-operative wound infection (1.1%). Both complications occurred in previously operated hands. Except for one patient with wound infection, no delayed wound healing occurred.

Patient Satisfaction

Of the 91 patients 87 (95.6%) were very satisfied and would recommend the surgery to family and friends. All 13 patients who had previous open surgery preferred this new procedure over their previous experience. The procedure left no visible scar, and led to subjective improvement in the feel and softness of the entire hand.

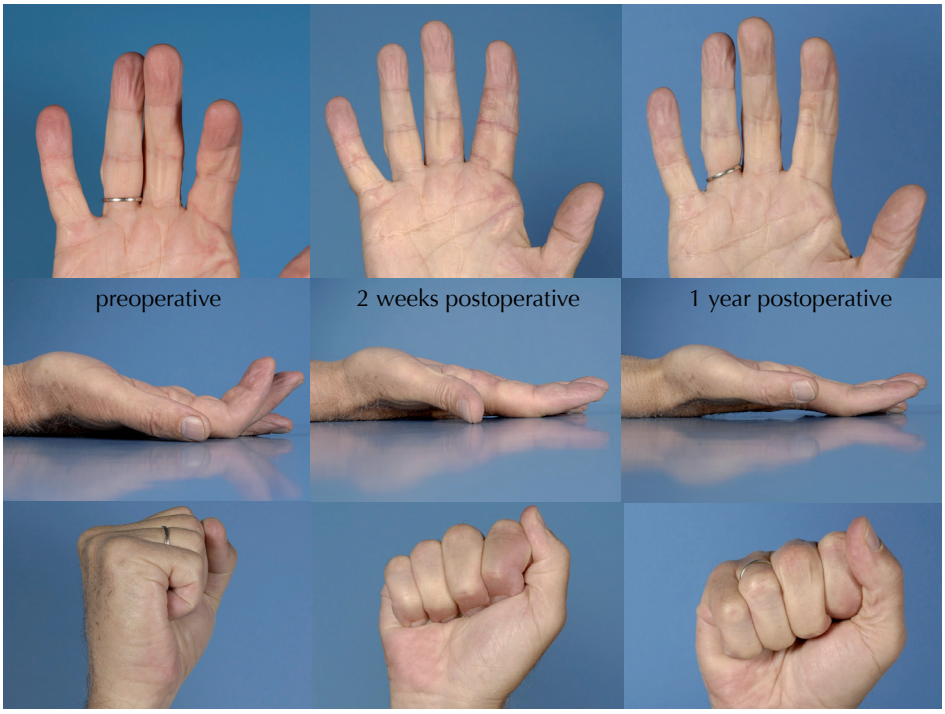

Figure 3: Illustrations of a 63-year-old male patient with Dupuytrens contracture in the second ray. The palmar, lateral view and fist position are shown preoperative, two weeks postoperative and one year postoperative from left to right.

Three of the four patients with post-operative CRPS stated they would not choose this type of surgery again. Interestingly, the fourth will still recommend this same procedure to family and friends. Another patient was not satisfied, despite a positive outcome, because the operated other hand was straighter.

DISCUSSION

The most striking result during extensive percutaneous aponeurotomy was the release of the skin and cord even in fully flexed fingers. Operating time of PALF was comparable to limited fasciectomy or dermofasciectomy. In our experience, the main gain of the minimally invasive technique is the short recovery time compared to the open surgical technique, especially if more rays are involved. However, a randomized controlled trial is needed to directly compare both techniques.

Open fasciectomy is the recognized standard treatment for Dupuytren's contracture. The complication rate of 18 to 29%, the recurrence rate of 27 to 70% after five years and the inherently long recovery time of fasciectomy however, have fueled the emergence of less invasive techniques, such as the injection of collagenase[1, 10-12]. A

recent randomized clinical trial (RCT) compared collagenase injections with a placebo. Patients received up to three direct injections thirty days apart, requiring an average of 56 days. At thirty days follow-up, MP-joint and PIP-joint contractures significantly improved. Two tendon ruptures and one case of CRPS were reported[13]. While the procedure seems to have merit, the treatment is costly and long-term follow-up data is lacking. Collagenase has not been compared directly to a non-placebo alternative and is presently limited to one affected joint at a time.

Needle aponeurotomy (NA) is another minimally invasive technique[8, 14, 15]. In a RCT comparing needle aponeurotomy versus limited fasciectomy, a 75% reduction in MP-joint extension deficit and a 33% reduction in extension deficit for the PIP-joint at six weeks follow-up was reported in the needle aponeurotomy group[7]. The minor complication rate was 50% in the NA patients versus 30% after open surgery; major complication rates were 0% and 5%. This is in line with reported complications of skin rupture, infection, digital nerve transaction, tendon ruptures and even the development of a false aneurysm[16, 17]. At the 2010 European Association of Plastic Surgeons meeting in Manchester, van Rijssen et al. reported an 85% recurrence rate at 5-year follow-up in the needle aponeurotomy group[18].

The needle technique in our new procedure was refined compared with conventional NA by using multiple superficial nicks in the pathological region. The essence of the needle technique is not to use the needle too deep, especially more distally. To ensure this, the bevel of the needle is never completely out of sight. There is no attempt to transect the cord with one needle cut; this would take the needle to deep, which could be damaging other tissues than the diseased fascia. There is no limit for the amount of rays that are treated; even nodules in other rays can be treated in the same session.

Fat grafting is a critical component of this new procedure. One reason for this is to provide supple skin by supplying fat. Dupuytren's contracture is associated with subdermal fat deficiency as the pathological fibrosis displaces the fat to adhere to the dermis. This new procedure releases the fibrous scar from the dermis and restores a subcutaneous fat layer over the affected area. A second reason is that interposed grafts are reported to prevent the recurrence of Dupuytren's contracture[19]. In our procedure, interposed fat grafts in the space created by the released fibers might have a similar beneficial effect. Furthermore, since these fat grafts come from the abdomen, a region of the body not prone to contracture, it is likely that they will not have the same tendency to convert into fibrous bands. A third reason is that fat grafting is known to be a rich source of stem cells with regenerative potential[20]. Fat grafting has been shown to improve the quality of the skin and to be beneficial in the treatment of radiation damage, chronic ulceration and scar tissue around breast capsular contractures[20, 21]. Since the pathophysiology of Dupuytren's contracture is akin to that of a scar, it would seem logical that fat grafts would also be beneficial in this disease setting.

PALF notably differs from NA, an office procedure done under local dermal anesthesia. NA specifically avoids lidocaine infiltration of the neurovascular bundles such that an attentive patient with sensate nerves is the safeguard against nerve injury during deep full thickness needle transections of the cord. In contrast, PALF is performed on a prepped and draped hand in the operating theatre under regional block with a tourniquet ischemia and sedation. Safety from nerve injury is inherent in the PALF design as a result of the difference in stiffness of the stretched cords and the nerves (see Methods).

Drawbacks of our new technique could be accidental damage of surrounding nerves, digital arteries and tendons. In our combined series treated in Rotterdam and Miami no tendon lesions were encountered and only one infection. One nerve was injured in a recurrent diseased finger and in four cases a CRPS evolved. Two of these patients already had a CRPS in the contralateral hand following earlier open surgery. Another drawback of PALF is that the arthrogenic part of the flexion contracture cannot be corrected. With PALF only the dermatofibrous contractures can be released, which may leave a residual capsulogenic contracture. Many experienced surgeons, however, are often also not inclined to release a capsulogenic contracture during open surgery because of the potential stiffness of the PIP-joint or reactive recurrence of the PIP-contracture.

Our clinical study has of course limitations. We have treated 91 patients and can report on goniometry data from only 50 patients. As we do not have long-term follow-up results recurrence rates do not seem appropriate yet. In addition, our patients may not reflect the normal Dupuytren population since the Erasmus University Medical Center is a referral center with 39% of its patients having a severe diathesis. Another limitation was that an independent researcher measured the range of motion and therefore there was no blinding.

Comparing the PALF-results with the NA-results in the literature is difficult as we selected the worst finger per patient instead of adding all rays regardless of number of patients. Furthermore, the number of patients differs, follow-up time differs and the percentage of patients with severe diathesis is high in our series. It seems, however, that our data concerning the MP-joint are favorable, as improvement is 100% compared to 79% and 75% in NA treated patients[7, 16]. For the PIP joint our contractures were significantly more severe (preoperative mean 61.3° compared to 37°)[16]. Improvement of the PIP-joint was 56% in our study compared to 65% in Foucher's and 33% in van Rijssen's article[7, 15].

Based on these preliminary results, extensive percutaneous needle aponeurotomy with subdermal fat grafting has a great potential. Patients with DD mostly need multiple surgeries during their life, so a less invasive surgical method should be a treatment of first choice. To achieve a higher level of scientific evidence, we started a single blind multicenter RCT in Rotterdam to compare the new minimal invasive surgery with the surgical limited or (dermo)fasciectomy.

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Chapter 7

Percutaneous Aponeurotomy and Lipofilling (PALF) versus Limited Fasciectomy in Patients with Primary Dupuytren's Contracture; a Prospective Randomized Controlled Trial

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ABSTRACT

Background: As an alternative to the needle aponeurotomy (NA) release and the limited fasciotomy (LF) treatment of Dupuytren contracture, we introduced the extensive percutaneous aponeurotomy and lipofilling (PALF) procedure. In our previous retrospective study, we reported that contractures significantly improved and most patients returned to normal use of the hand within two to four weeks. To establish the safety and efficacy of PALF, we compared it to the standard LF in a single-blinded multicenter, prospective, controlled, randomized trial.

Methods: Patients with a primary Dupuytren's contracture were randomly assigned to the LF-group or the PALF-group. Patients were measured at baseline and at two weeks, three weeks, six months and one year post-operatively. Primary outcome of the trial was contracture correction and convalescence time. Groups were compared using a mixed models approach.

Results: Eighty patients were included in this study and randomized to PALF or LF. In both groups, almost full MP-joint contracture correction was obtained while for the PIP-joint some residual contracture remained. In addition, the patients in the PALF-group returned significantly earlier to their normal daily activity. At one-year post surgery, no significant differences in recurrence rate and hand function were present. However, LF seems to have a higher incidence of permanent complications than PALF.

Conclusion: PALF demonstrates a significantly shorter convalescence; similar operative contracture correction; lower incidence of long-term complications and no significant difference regarding one-year postoperative results when compared to LF. PALF is therefore a valuable minimally invasive alternative to the treatment of Dupuytren's disease.

INTRODUCTION

Dupuytren's disease (DD) is a benign fibroproliferative disorder that causes progressive digital flexion contractures[1]. The most common treatment of DD is limited fasciectomy (LF), an invasive procedure that excises the diseased fascia and requires flaps or grafts to reconstruct the released contracture. While LF has well-accepted low long-term recurrence, it has a relatively high complication rate due to the extensive dissection required and the postoperative return to normal hand function for daily activities (convalescence) is typically quite prolonged[1-3].

Percutaneous release of the fibrotic cord, also referred to as needle aponeurotomy (NA), is a less invasive alternative technique that promotes faster recovery[3-5]. A trial comparing NA with LF reported lower complication rates, faster recovery, but lesser contracture correction after six weeks[3]. Furthermore, five years postoperatively, NA had a significantly higher recurrence (85%) than LF (32%)[6].

To improve on NA, we developed another minimally invasive procedure consisting of an extensive percutaneous aponeurotomy and lipofilling (PALF)[7]. This technique completely disintegrates the cord, separates it from the dermis, and turns it into a loosened recipient scaffold for grafting with autologous lipoaspirate. Lipofilling has many benefits: First, it reduces the density and cell-to-cell contact of contractile myofibroblasts[8]. Second, adipose-derived stem cells (ADSC) in the lipoaspirate were found to reduce the recruitment of additional myofibroblasts by inhibiting their proliferation[8]. Third, fat grafts may also function as interposed tissue grafts while interposed tissues, such as cellulose, are reported to prevent the recurrence of Dupuytren's contracture[9]. Fourth, Dupuytren's contracture is associated with subdermal fat deficiency as the pathological fibrosis displaces the fat to adhere to the dermis; therefore, fat grafting may provide supple padding to this diseased region[10, 11].

In our recent retrospective review of 50 patients treated with PALF, we found a significant contracture improvement preserved at one year, while 94% of patients returned to normal use of the hand within 2 to 4 weeks, and 95% were very satisfied with the result[7]. In order to compare this novel technique with established alternative treatment options, we performed a single-blinded, multicenter prospective, controlled randomized trial comparing it with LF. The primary outcome measures were convalescence and contracture correction.

METHODS

Study population

Between the 24th of February 2009 and the 1st of October 2011, we enrolled at Erasmus MC and Sint Franciscus Gasthuis (SFG) 80 patients with primary Dupuytren's contracture and a flexion contracture of at least 20° at the MP-joint or at least 30° at

the PIP-joint, or both. Patients were excluded if the affected finger had a prior intervention, or if anticoagulants could not be stopped. To standardize patient instructions, a short movie explained the trial before patients consulted with the researcher and their surgeon. All included patients gave informed consent. The Medical Ethical Committee of the Erasmus MC in Rotterdam (MEC-2008-264) approved this study and it was registered at the Dutch Trial Register in March 2009 (NTR1692).

Randomization

Patients were randomly assigned to the LF-group or the PALF-group through sealed envelopes. A computer random number generator selected random-permuted blocks of ten patients. The patients received a trial number and the correspondingly numbered envelope was given to them, with either a 'PALF' or 'LF' note inside. Bilaterally affected patients who requested surgery for their contralateral hand served as their own control with the contralateral hand given the opposite treatment.

Surgical techniques

Four surgeons (S.H., C.N, E.W. and X.S.) performed both alternative procedures at both centers. Patients were operated following complete exsanguination, tourniquet ischemia, and under general or regional anesthesia with or without sedation. In both groups, patients received hand therapy and instructions to wear an extension splint at night for six months.

Extensive Percutaneous Aponeurotomy and Lipofilling (PALF): The technique is previously described in Clinics of Plastic Surgery[12]. Briefly, the digital contractures are placed under maximal tension in extension using a firm hand retractor. Then, progressing in an orderly fashion from proximal to distal along the palpable contracture, multiple palmar puncture wounds are made with a 19-gauge needle. Tension is maintained by constantly extending the digits as the contracture progressively gives way. Skin wrinkles and pits are released by severing the dermal attachments of the cord with a windshield wiper motion of an "L" shaped needle. The hand is ready for lipografting once the contracture is fully released, the skin fully ironed out and separated from the cord, and the nodules are completely 'chopped' and soft. We then inject 8-10ml of non-centrifuged, simply sedimented lipoaspirate per digital ray and expect some of it to escape through the needle release sites. A conforming dressing over the palmar skin that incorporates a plaster extension splint is kept for five to seven days (Figure 1).

Limited fasciectomy (LF): A longitudinal or Brunner incision was made into the palm overlying the affected area and extended into the finger. A Z-plasty was performed to lengthen the incision when a longitudinal incision was used. In case of a Brunner inci-

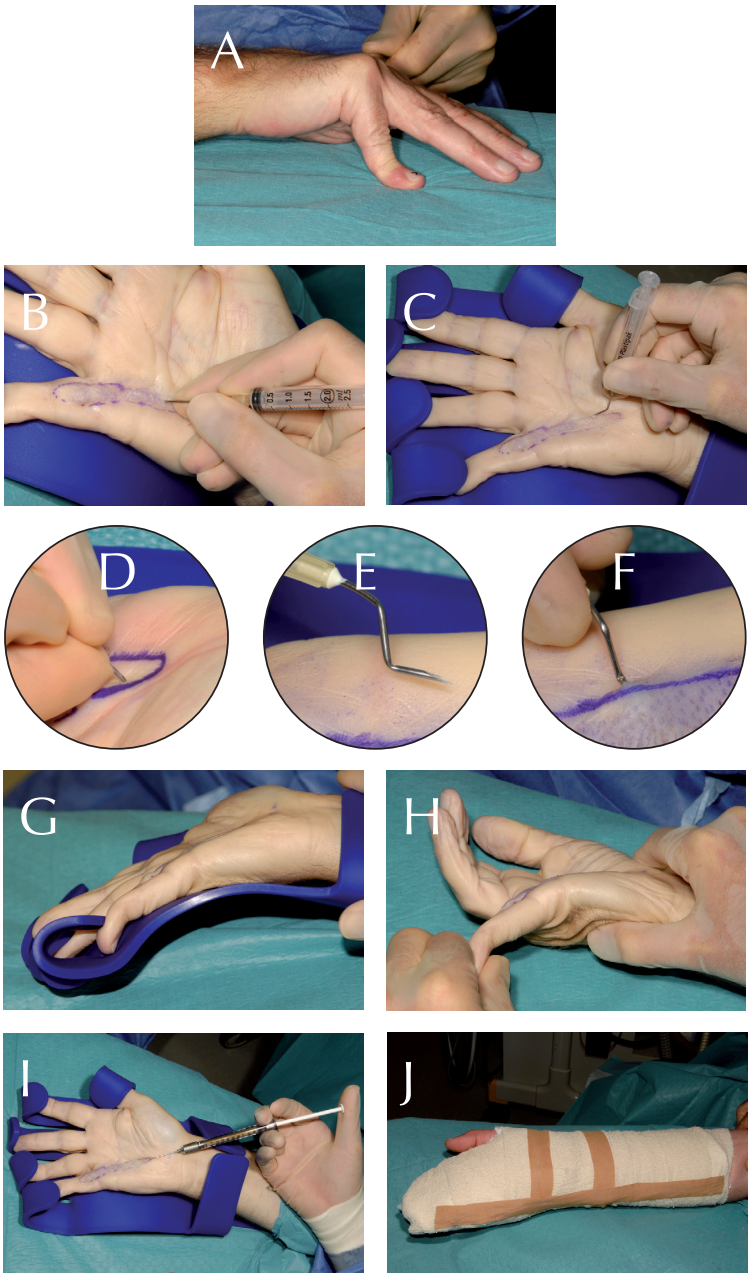

Figure 1: PALF technique illustration: preoperative photo of a patient with a Dupuytren contracture of the fifth digit on the right hand (A). Making of multiple nicks from proximal to distal with a 19-gauge needle (B and D). Releasing dermal attachments of the cord with a windshield wiper motion of an "L" shaped needle (C, E and F). Placement of the digital contractures under maximal tension in extension, using a firm hand retractor during the whole operation (G). The hand is ready for lipografting once the contracture is fully released (H). Injection of 8-10 ml. of non-centrifuged, simply sedimented lipoaspirate per digital ray (I). Plaster extension splinting, kept on for five to seven days (J).

sion the skin was closed in a V to Y fashion. First the diseased fascia was dissected off the skin. Then, the diseased fascia was removed off the deeper structures as adequately as possible. Neurovascular bundles and the flexor tendon sheaths were identified and protected. The skin was closed primarily using interrupted sutures. If the skin was affected too much it was removed and a full thickness graft was used to close the wound. The hands were splinted for five to seven days and the sutures were removed after 14 days.

Measurements

Patients were measured at baseline and at two weeks, three weeks, six months and one year post-operatively. Trained examiners from the clinical movement analysis lab of the department of Rehabilitation Medicine collected all baseline and outcome measures. To blind the examiners to the treatment allocation, patients wore blue non-latex gloves during the measurements and were instructed not to discuss their treatment with the examiners. Patients, surgeons, hand therapists, and the trial coordinator (HJK) were not blinded for group allocation.

Primary outcome measures were contracture correction and convalescence period. To determine contracture correction and recurrence rate, we measured the passive extension deficit of the MP, PIP and DIP joints at all time points. Convalescence was estimated as the ability to flex the MP, PIP and DIP joints based on goniometric measures and based on a diary questionnaire asking about the number of days till return to all normal daily activities.

Secondary outcome measures were patient-reported hand function, pain, recurrence rates, patient satisfaction, and complication rates. To assess hand function, we asked the patients to fill in the Dutch translation of the Disabilities of the Arm, Shoulder and Hand (DASH)[13]. Pain during activity was measured by using a visual analogue scale (VAS)[14]. Recurrence rate was based on a recently published consensus definition, describing a recurrence as an increase in joint contracture in any treated joint of at least 20 degrees at one year post-treatment compared to six weeks post-treatment[15]. However, since at the time of study design, this definition was not yet available, we used our three weeks measurements instead of 6 weeks.

Patient-satisfaction was measured by a questionnaire consisting of seven questions (see Table 2). To determine the complication rate, after surgery, a plastic surgeon inspected the wounds for infections and healing complications and for the presence of a complex regional pain syndrome type 1 (CRPS-1; scored using the Bruell classification) or other complications. In addition, any complication during surgery, such as nerve or arterial damage, was scored.

Baseline characteristics			
	PALF	LF	p-value
Characteristics			
Mean age + SD (years)	63 (9)	63 (8)	0.951
Sex			
Male	37	25	0.508
Female	7	7	
Most severe affected finger			
dig 1	0	0	0.517
dig 2	1	0	
dig 3	2	0	
dig 4	10	8	
dig 5	31	24	
Number of treated fingers			
1	15	14	0.185
2	9	6	
3	5	0	
4	0	0	
5	1	0	
Family history with DD			
Yes	25	16	0.556
No	19	16	
Both hands affected			
Yes	41	28	0.398
No	3	4	
Ectopic disease			
Yes (Ledderhose/Peyronie)	13	4	0.078
No	31	28	
Alcohol a day (units)	2.2 (1.7)	2.3 (2.2)	0.827
Smoking			
Yes	8	12	0.145
No	10	7	
Former	26	13	
Diabetes Mellitus			
Yes	4	5	0.384
No	40	27	
Heavy manual labor			
Yes	12	11	0.605
No	32	21	
Median DASH score (preoperative)	10	10	0.816
Median VAS score for pain (preoperative)	0.3	0.6	0.669
Mean exsanguination time + SD (minutes)	48 (17)	46 (19)	0.615

Table 1: Baseline characteristics of both groups. Shown are means (SD) and numbers of patients and the p-value of the difference between groups.

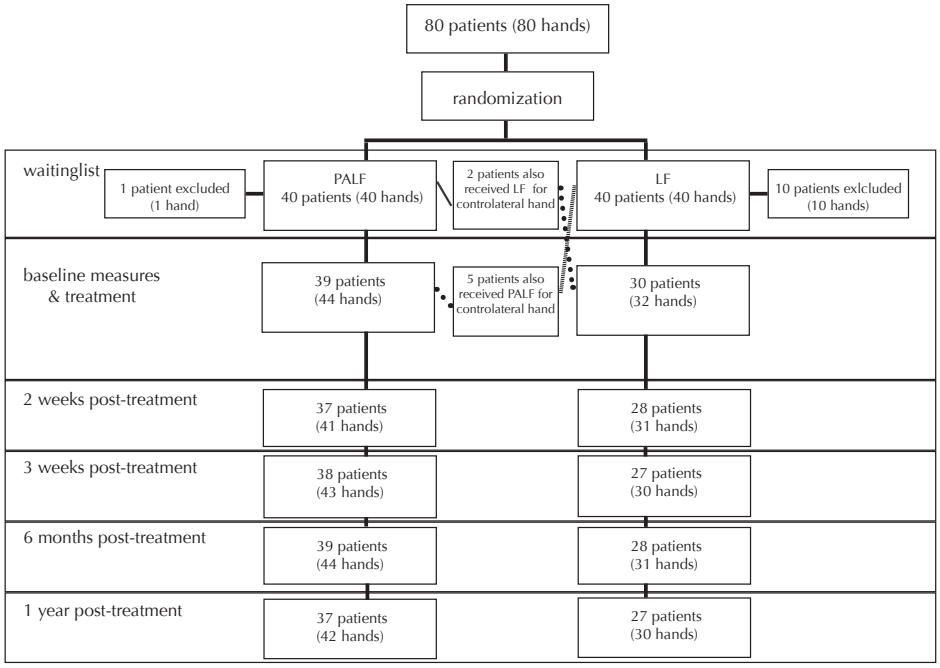

Figure 2: Flow diagram

Sample size estimation

For the power analysis, we assumed that a 10 degrees difference in contracture is a clinically relevant difference that should be detected with this method. Based on an alpha of 0.05, an SD of 15 degrees, a beta of 0.80 and based on a two-sided independent sample t-test, we needed 37 patients per arm[7].

Statistical analysis

Patient demographics and outcome variables at baseline were compared between treatment groups to ensure comparability of the groups and described using mean and standard deviation for continuous variables and percentages for categorical variables. Continuous variables were compared with use of the Student's *t*-test, whereas differences in categorical variables were compared using the Pearson chi-squared test.

To avoid dependency in outcome measures when multiple fingers and joints are analyzed within the same patients, we selected only the most affected finger at the preoperative measurement for further analysis based on the sum of the extension deficits in degrees from the MP-joint and PIP-joint.

All measurements repeated over time (goniometry, DASH and VAS) were assessed using a mixed models approach. The Mann-Whitney-U test was used for comparing the days needing to return to normal daily activities and the satisfaction questionnaire.

A Chi-square test was used for comparing the difference in recurrence rates and complication rates and the last two questions of the satisfaction questionnaire. All analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL).

RESULTS

Patients

Eighty patients with 88 treated hands were included in this study and randomized to PALF or LF treatment. One patient from the PALF-group and 10 patients from the LF-group were excluded before surgery while still on the waiting list (Figure 2), largely due to its length in both centers (mean 22±17 weeks). The reason for exclusion before surgery for the PALF patient was reported fear of surgery in general. He did not receive any other treatment in our center. The reasons for exclusion before surgery in the LF-group were waiting list length (three), other medical problems (two cancer, one intermittent claudication), unhappy with randomization into LF (two), decision not to be treated anymore (one), and family circumstances (two). There were no significant differences in the characteristics between those patients who were excluded from both treatment groups.

In total, five patients initially treated with LF received PALF on the contralateral hand and three initially treated with PALF had LF on their contralateral hand, resulting in a total of 44 PALF treated and 32 LF treated hands. Loss to follow-up was minimal and was mainly due to practical reasons for missing a specific measurement point. At six months, follow-up in the PALF-group was 100% while in the LF-group one patient did not return for assessment for personal reasons. At 12 months, two patients in both groups did not return for measurements (Figure 2).

Overall, patients were predominantly males, the fourth and fifth digit were most affected, and many had ectopic disease (Table 1). Baseline characteristics were not significantly different between groups.

Contracture correction

Figure 3 and Figure 4 show the goniometric measurements at a different time of follow-up. Significant contracture correction was obtained in both groups. Comparing groups, the overall interaction effect between time and group was not statistically significant (p=0.35), indicating a similar change in both groups over time. Evaluating affected PIP-joints and MP-joints separately, we found that treated MP-contractures obtained almost full contracture correction and remained at this level at all follow-up times in both groups; for the PIP-contractures some residual contracture remained in both groups and contracture increased again later after surgery. Again, no significant interaction effects between treatment and time were found, indicating that the curves were not significantly different between groups.

Questions	6 months					1 year				
	PALF		LF		p-value	PALF		LF		p-value
Are you satisfied with the overall treatment outcome of the operation?	8.8		8.8		0.940	7.8		9.4		0.006*
Do the results of the operation meet your expectations?	8.9		8.6		0.742	7.8		9.4		0.007*
Are you satisfied with the contracture correction?	7.9		8.6		0.220	7.4		9.1		0.011*
Are you satisfied with the function of your hand?	8.9		8.6		0.460	8.7		9.3		0.125
Are you satisfied with the cosmetic appearance of the operated hand?	9.0		9.0		0.825	9.0		8.8		0.142
	yes	no	yes	no		yes	no	yes	no	
Would you choose the same operation?	88%	12%	81%	19%	0.335	81%	19%	80%	20%	0.920
Would you recommend the same operation to your family and friends?	90%	10%	87%	13%	0.598	80%	20%	80%	20%	0.920

Table 1: Patient satisfaction at six months and one year after surgery. For the satisfaction questions, medians are shown. For the questions on whether patients would choose the same operation of recommend the operation, percentages of patients are shown.

Convalescence

Total flexion movement was generally lowest at two weeks after surgery, indicating a loss in the ability to make a full fist (Figure 5). The initial values, representing normal ability to make a fist, were regained again after surgery in both groups. However, we found a significantly improved ability to make a fist early after surgery with PALF (p=0.008).

In line with the better total flexion movement early after surgery with the PALF, we found that they returned significantly earlier to their normal daily activity: median nine days for PALF compared to a median of 19 days for LF-group (p=0.001).

Recurrence

At one year postoperative, 15 of the 85 (18%) PALF treated joints had some recurrence compared to five of the 58 (9%) LF treated joints. This was not a statistically significant difference (p=0.107). This finding is in line with the earlier reported non-significant difference in the goniometry curves of both groups of the TPED and the PIP-joint and MP-joint.

Patient-reported outcomes

Pain scores before and after surgery where generally low in both groups and we found no interaction effect of time and group for pain (p=0.593). Hand function, as measured with the Quick DASH, significantly improved over time in both groups (p=0.007). However, mean DASH scores were not significantly different (p=0.315) at baseline between treat-

ment groups (Figure 6). At six months postoperative, there was no significant difference in any of the satisfaction questions (see Table 2). At one year after surgery, LF-treated patients were significantly more satisfied on the overall treatment outcome, contracture correction, and whether treatment expectations were met. However, no significance difference was found in percentages of patients who wanted to receive the same operation again

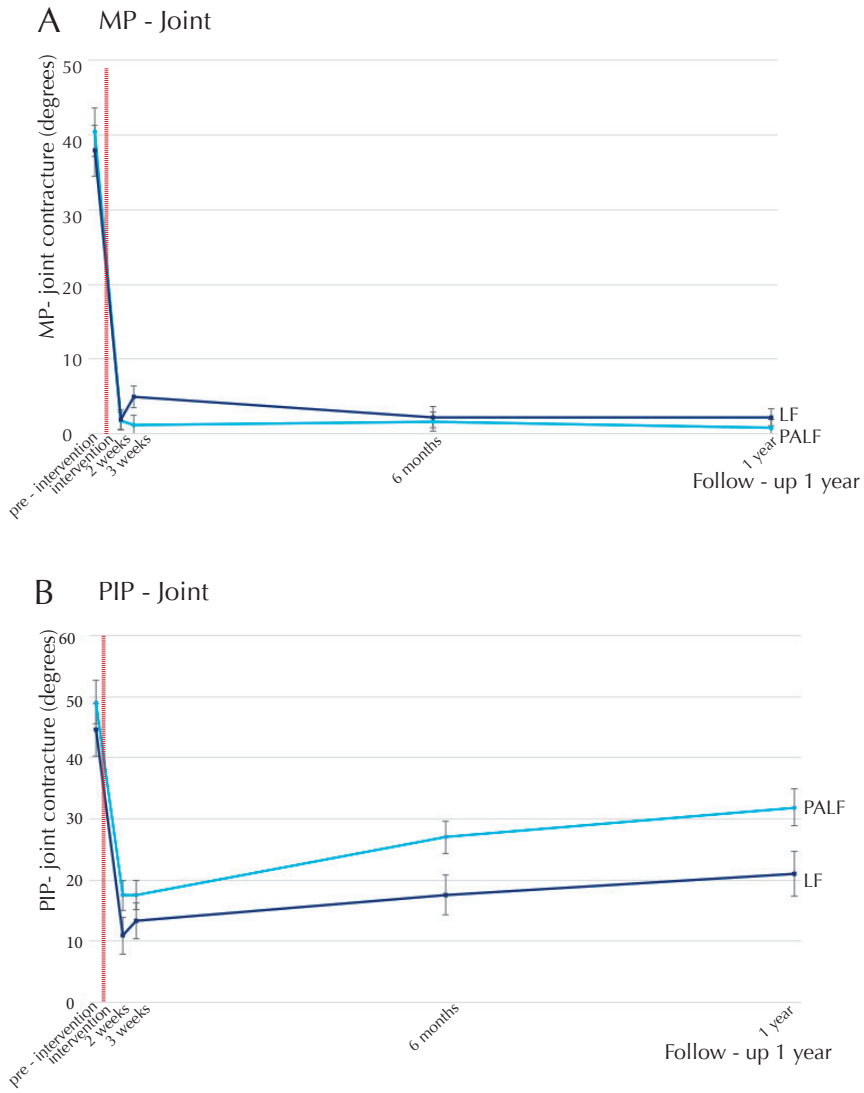

Figure 3: Contracture correction (MP-joint and PIP-joint): goniometric outcomes measured preoperatively and at 2 weeks, 3 weeks, 6 months and one-year after surgery. These figures indicate the amount of PIP joint contracture (A) and MP joint contracture (B) at the different time points.

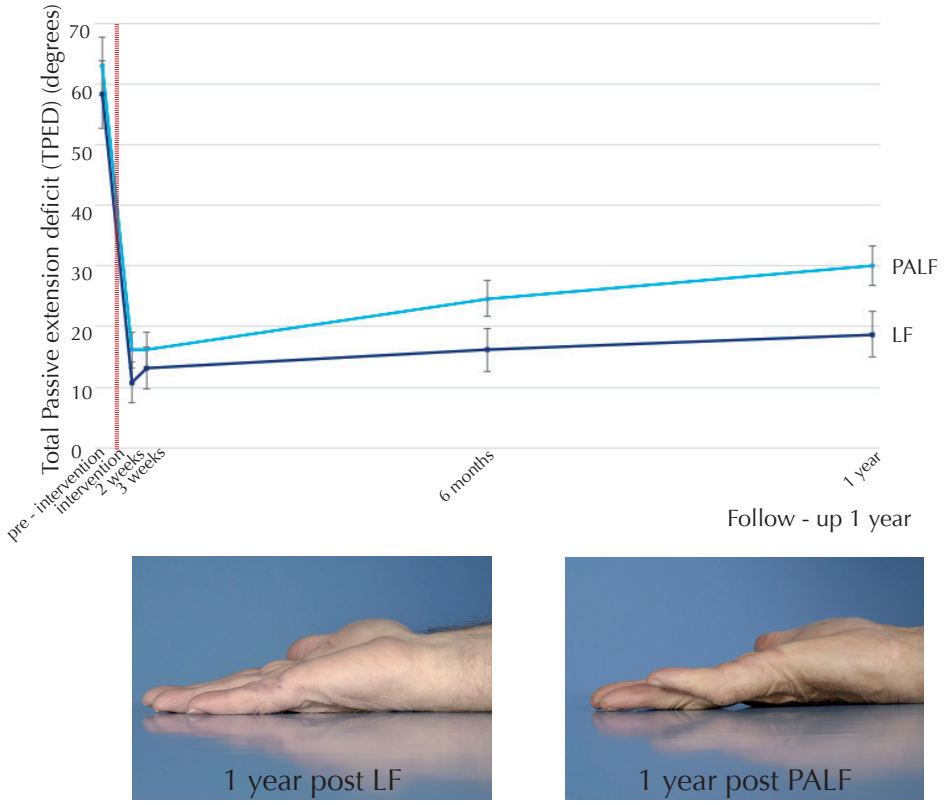

Figure 4: Contracture correction in total passive extension deficit (TPED): goniometric outcomes measured preoperatively and at two weeks, three weeks, six months and one-year after surgery. This graphs shows the total passive extension deficit (TPED) between PALF and LF. Photographs below the graph show the difference in amount of contracture for each technique measured at one year.

and who wanted to recommend their type surgery to family and friends. Also all other satisfaction-related questions were similar between groups (Table 2).

Complications

The overall complication rate was not significantly different among the groups (p=0.402). Two patients (5%) within the PALF-group developed severe complications: both involved CRPS reactions, leading to longer rehabilitation and hand therapy. Both patients fully recovered at one-year. There were no wound healing complications and none of the 44 hands treated with PALF suffered a neurovascular or tendon injury. Three patients (9%) in the LF-group developed severe complications: one patient developed a persistent CRPS, which led to a serious loss of function of this hand at one year after surgery. Two of the 32 LF treated hands suffered a neurovascular injury (6%), one had an intraoperative arterial lesion, which was immediately reconstructed. The other suffered an intraoperative nerve

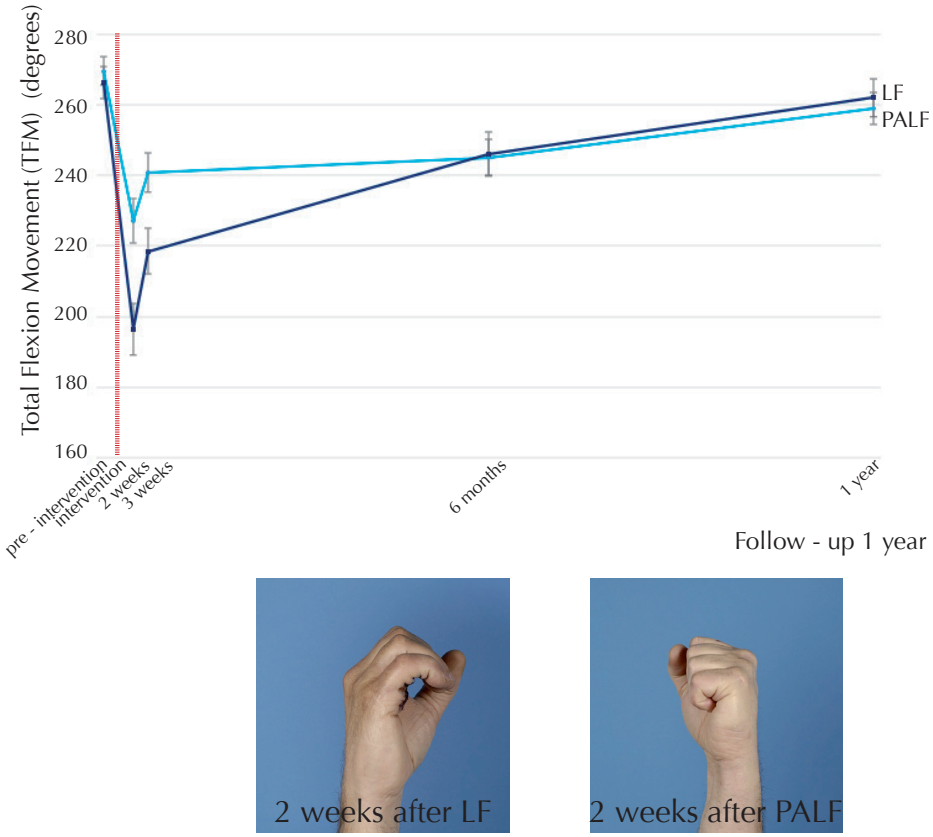

Figure 5: Total flexion movement (TFM): goniometric outcomes measured preoperatively and at two weeks, three weeks, six months and one-year after surgery. This graph shows the difference of the ability to make fist as a measure of convalescence based on the total flexion movement of all joints (TFM). Photographs below the graph show the difference in the ability of making a fist measured at two weeks post surgery.

lesion, which was immediately reconstructed but led to loss of sensation one year after surgery. After one year, two patients of the LF-group still had persistent problems resulting from their surgery versus none of the patients of the PALF-group.

DISCUSSION

The aim of this prospective single-blinded randomized study was to compare percutaneous aponeurotomy and lipofilling (PALF), a novel minimally invasive procedure, with the gold standard LF in the treatment of patients with primary Dupuytren's contracture. We found no significant difference in contracture correction as both groups obtained almost full MP-joint contracture release that persisted for the entire one year follow up, while some residual extension contracture remained and persisted for the PIP-joint in

both groups. However, PALF-treated hands healed significantly faster, returned earlier to their normal daily activity, and were able to make a full fist significantly earlier than LF-treated hands. At one-year postoperatively, there were no significant differences between groups in terms of recurrence rate and hand function. Patient satisfaction was

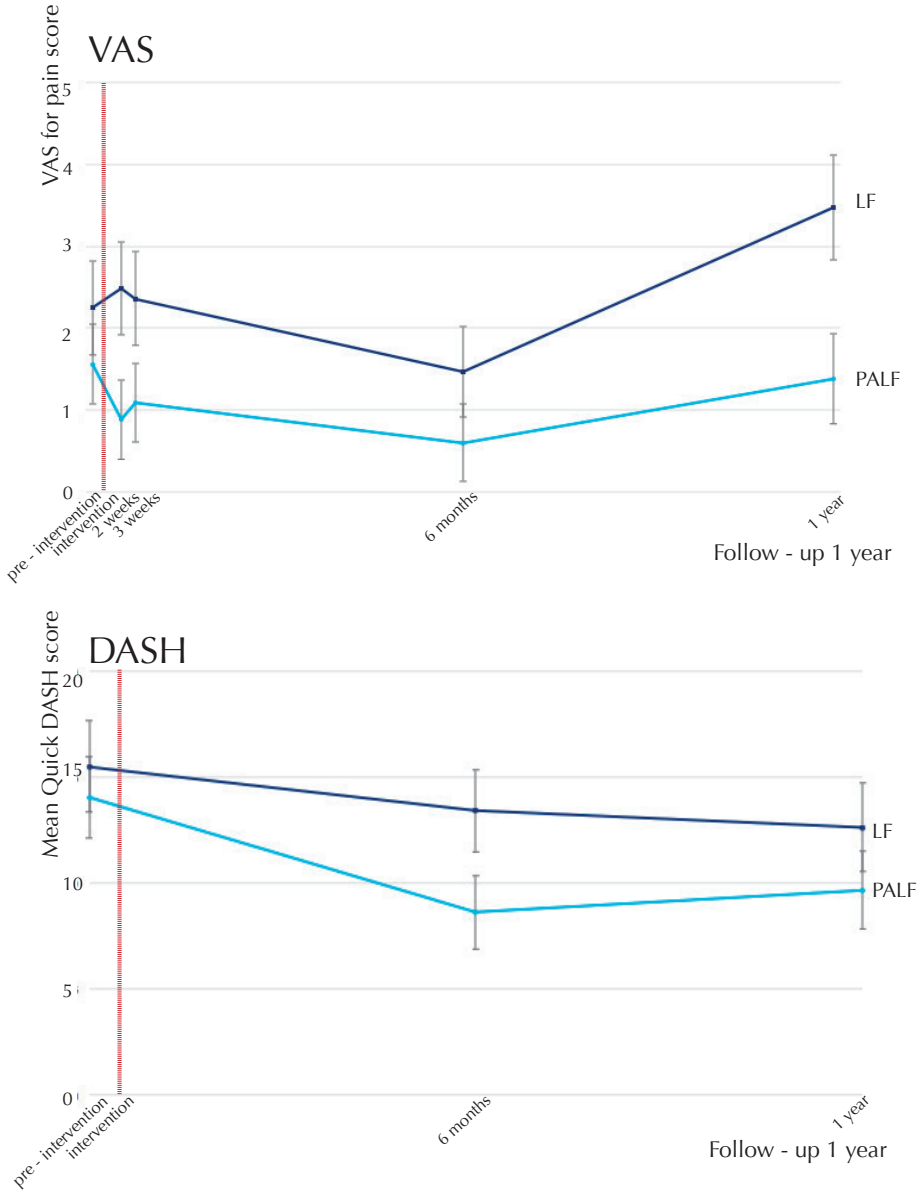

Figure 6: Patients' reported outcomes are shown. The quick DASH scores (A) and pain score (B) measured with a visual analogue score (VAS) from 0-10 for the PALF and LF-group.

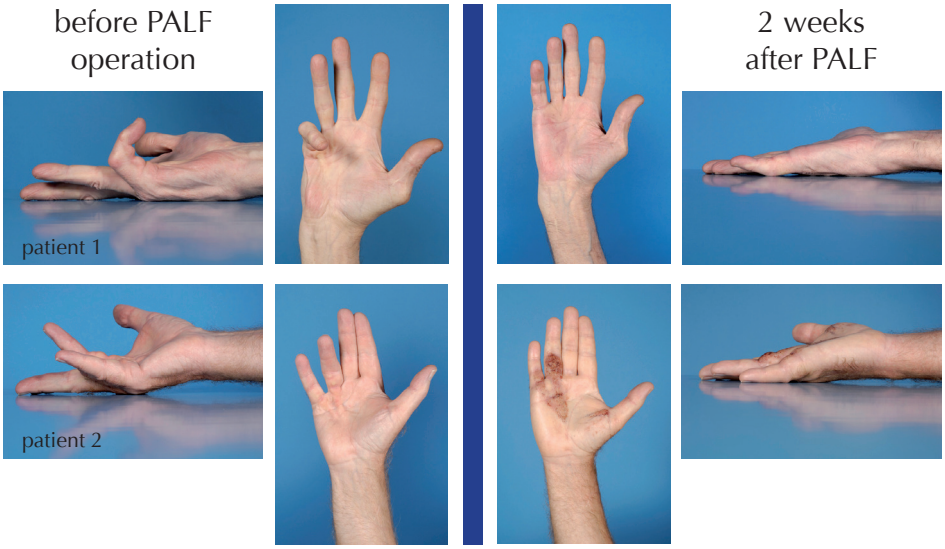

Figure 7: This figures shows to different examples of patients treated with PALF. Patient A is suffering of DD of the fifth digit. Patient B is suffering of DD of the first, fourth and fifth digit.

similar in both groups at six months and was better at one year in the LF-group. The LF-group had a six percent permanent complication rate compared to zero percent in the PALF-group; this was however not significant with the present sample size.

The PALF technique used in the present study differs from conventional needle aponeurotomy (NA) in many aspects. First, PALF is performed in the OR under regional block anesthesia and tourniquet ischemia while NA is commonly performed in the office under limited dermal anesthesia. Second, in PALF, the fibrous cord is disintegrated using an extensive percutaneous needle aponeurotomy technique, applying numerous (up to 40) superficial nicks along the entire extent of the cord while it is maintained under a strong extension force, whereas NA releases the cord by transecting it only at a couple of locations without specifically applying an extension force. Herein lies a major technical difference; by continuously providing maximal tension as the contracture is released, the small nicks are more likely to cut the tight cords that restrict extension than the looser neurovascular bundles. Tension also allows the surgeon to localize the residual restricting bands by palpation. Therefore, while the safety of NA is provided by dermal anesthesia that preserves protective sensation to the underlying nerve, it is the differential cutting ability of a needle for structures under strong tension that provides the PALF safety.

The other major distinction with NA is lipofilling. The multiple nicks of PALF transform the solid cord into a recipient scaffold that provides space and interface for fat graft survival. Fat grafting restores the subdermal fat deficiency of DD and acts as inter-

posed tissue to prevent the transected fibers from re-scarring together[9]. Furthermore lipoaspirate is known to contain stem cells that can treat fibrotic diseases and inhibit proliferation of contractile myofibroblasts responsible for DD through soluble factors[8].

The study by van Rijssen comparing conventional NA with LF found that the degree of initial contracture correction was similar among groups but that recurrence rates were much higher in the NA-group[3, 6]. The present study also shows that PALF yields similar outcome correction as LF, but with no difference in recurrence at one year after surgery. However, PIP-joint corrections show a trend that might indicate more recurrences for PALF over a longer follow-up. A long-time outcome (e.g. five years) may be valuable to further evaluate this trend. Furthermore, similar to us, van Rijssen found 5% severe complications after LF-group and 0% after NA, compared to 9% after LF and 5% after PALF in our study[3]. Clearly, LF is more complication prone than both NA and PALF.

Concerning satisfaction, no significant difference was measured between LF and PALF at six months. Since no general satisfaction questionnaires are available to our knowledge, we asked a number of specific questions concerning satisfaction. However, these questions were not validated before. Furthermore, since the main difference in hand function was found at three weeks post intervention it is possible that satisfaction was different at that specific time point as well. Most patients will forget their fast recovery at six months and one year, however they may have different problems concerning less straight fingers or recurrence.

We have extensive clinical experience, beside this clinical trial, with this procedure. Our experience confirms the safety of PALF; we have only transected one nerve and one tendon in more than 400 Dupuytren digital contractures released with PALF over the past eight years[7, 12]. Furthermore, PALF avoids the morbidity of flaps and grafts; only two very severe cases required a small transposition flap in the past eight years. This is because the staggered nicks of PALF expand the contracture to address the tissue deficiency in a fashion akin to mesh-expansion of a skin graft. Fat grafting the tiny slit interstices then regenerates the missing tissue. Khouri et al. have shown that PALF can also be used to treat other contractures and is a minimally invasive regenerative alternative to the classic flap transfers[16].

The strength of this study is that it is one of the few randomized controlled trials for DD. However, it also has some limitations. Powered to detect a difference in contracture correction, it may not be sufficiently powered to detect potential differences for other outcome variables, such as DASH score, pain score and recurrence rate. In our recent unpublished studies the Michigan Hand Questionnaire has taken over the DASH questionnaire, as the DASH does not distinguish hand conditions very well. Furthermore, more patients dropped out from LF and we cannot exclude this was because they were unhappy with this allocation. However, despite of this, both groups were similar at baseline.

In our statistical analysis, we only analyzed the pre-operatively most affected digit in order to avoid outcome measures dependency with multiple fingers and joints analyzed within the same patient[17]. Since only the most severe contractures were included, our data may underestimate contracture correction in both groups. While this should be taken into account when comparing our results with others, it should not influence the direct comparison between groups in our study.

Because the trial has only two arms with LF as the control standard reference, we cannot determine whether the outcome is due to a more elaborate and extensive aponeurotomy than NA, to the addition of lipofilling, or most likely, to their combination[18]. However, early in our experience, when we performed the extensive aponeurotomy without lipofilling our patients had rapid recurrences just as in NA. It is only after we brought in the biologic, anti-fibrotic effect of fat grafting that the recurrence rate dropped.

Because it is minimally invasive, PALF has the great advantage of being able to simultaneously address multiple digital rays, and can be performed repetitively something LF cannot safely offer. PALF is a radical departure from the invasive excisional surgery, instead of removing the pathology; it treats the fibrosis by morselizing it and adding tissue with regenerative potential. In a sense, PALF is a regenerative alternative to traditional excisional surgery and flaps in the treatment of DD. While it is not a panacea and it might not affect the course of severe Dupuytren diathesis, this prospective randomized study shows that PALF offers a similar degree of contracture correction for the first year as the gold standard LF with a faster recovery and lesser long-term complications. We conclude PALF is a safe and effective treatment for DD. While it should be offered in the whole spectrum of treatment modalities of DD, it is currently our preferred treatment alternative for primary Dupuytren contractures.

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Part V

General discussion and Summary

Chapter 8

General discussion

This thesis presents research on the effectiveness of an innovative treatment for Dupuytren's disease (DD) as well as a number of methodological studies related to evaluating effectiveness of DD treatment and patient preferences for specific treatment characteristics. In the following sections we elaborate on the main findings in this thesis and discuss the implications these might have on research and treatment on DD. In addition, possible directions for future research will be discussed.

THE EFFECT OF DIFFERENT DEFINITIONS FOR RECURRENCE AND A NEW DEFINITION

Reporting recurrence rates is an essential part of evaluating the effectiveness of treatment for DD[1]. In **Chapter 2**, we reviewed the different definitions for recurrence after treatment of DD in literature and we evaluated the effect of these different definitions on the resulting recurrence rate. We found that 51% of the publications reporting recurrence rates did not present a definition of recurrence[2]. The reported definitions could be grouped into three main categories, based on 1) the return of nodules and cords, 2) the return of joint contractures, or 3) the patient's self-report of a recurrence or whether a recurrent surgery was performed[2]. Furthermore, we found that recurrence rates at six months follow-up can range from 2 to 86% in the same dataset of DD patients, based on applying different thresholds for degrees of contracture, different baseline measurements, and different selected joints (Figure 1)[3-11].

Due to the lack of a uniform definition and the results from **Chapter 2** showing the very large effects of applying different definitions on the same dataset, we decided to develop a new definition for recurrence of DD using a Delphi method with an international group of experts (**Chapter 3**)[12]. After five consensus rounds, the experts agreed to define recurrence as *"an increase in joint contracture in any treated joint of at least 20 degrees at one-year post-treatment compared to six weeks post-treatment."* This new definition will give us the opportunity to compare the effectiveness of treatments for DD in near future when applied by different authors in the same way.

While we believe that this new definition is an important step forward, lack of clearly defined outcome measures may still apply to several other aspects of DD treatment. For example, an internationally recognized guideline for measuring joint angle is presently lacking. Since there is no agreement on how joint angles should be measured this may lead to differences between studies. For instance, should a joint be measured passively or actively? Furthermore, should the outcome of different joint measurements be combined, which is done when presenting a total passive extension deficit (TPED) or a total flexion movement (TFM), or presented separately? In addition, hand function is often studied by using a questionnaire[11]. The questionnaire most often used to measure hand function of patients with DD is the Disability of the Arm Shoulder and

Hand (DASH) questionnaire. As the name implies, this questionnaire is not primarily designed for patients with only hand problems, such as patients suffering of DD[13, 14]. As a result, patients suffering of DD express that the disabilities they experience are not even mentioned in the questionnaire, such as grabbing things under a closet, trying on gloves, etcetera. This will result in DASH scores that might imply less disability than patients' actual experience.

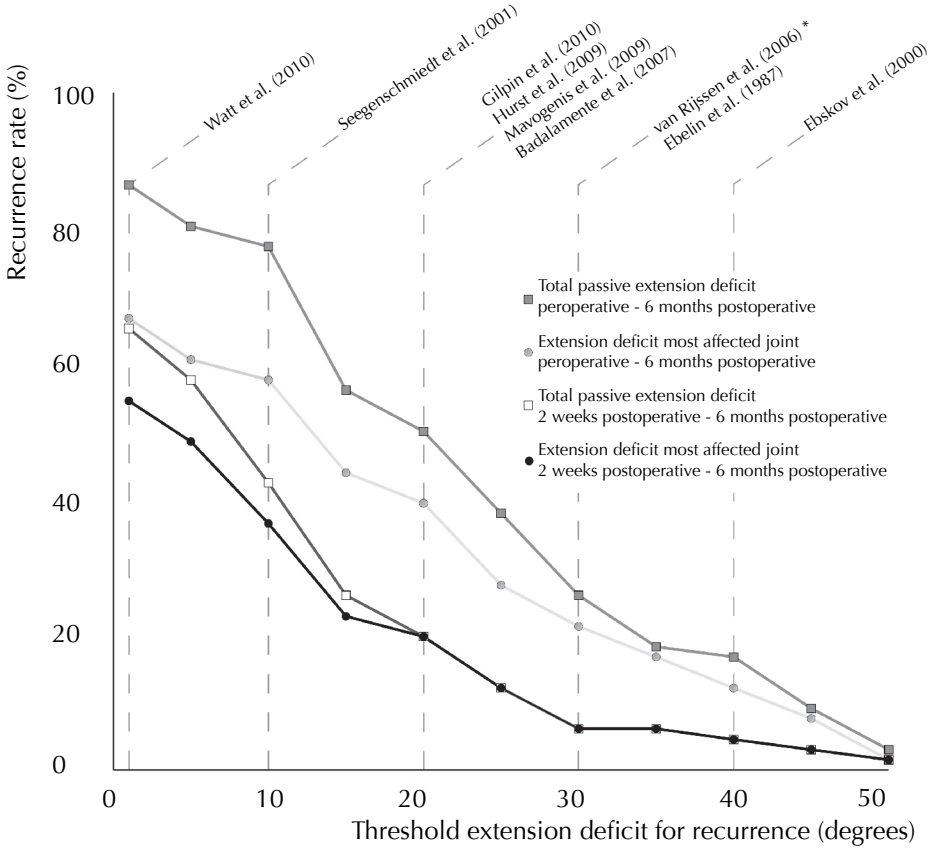

Figure 1: Relation between the acquired extension deficit and the recurrence rate in the single dataset. The extension deficit was based on the most affected joint per hand (n = 66). The lower dark line represents the difference in joint angle between two weeks postoperative and six months postoperatively. For example, when one degree extension deficit is applied as a threshold for recurrence, we found that 55% of our patients had a change in angle that exceeded this threshold and that would therefore have a recurrence. With a 30 degrees threshold, however, only six percent of our cohort has a recurrence. The upper light-grey line indicates the same threshold in angle, however using peroperative data as the initial baseline data instead of data two weeks postoperative.
Furthermore the TPED was used instead of the most affected joint. The vertical lines are the specific angular thresholds used in different articles; they indicate how these different thresholds lead to incomparable recurrence rates when applied to the same data. *Used TPED for the definition

Another outcome measure that may need international consensus is the aspect of 'patient satisfaction'. First of all, satisfaction questionnaires asking about the outcomes of Dupuytren interventions are presently lacking to our knowledge. As a result, researchers make their own questionnaires that often include 'yes' or 'no' questions or a visual analog scale (VAS)[15, 16]. Beside the fact it is also never been invested if 'satisfaction' is best measured with 'yes' or 'no' or 'VAS' questions, these questionnaires are also never validated. For example the question *'are you satisfied with the outcome of the surgical treatment?'* can be interpreted in many ways, such as: are you satisfied that your finger is straight again, or are you satisfied your hand function has been improved, or maybe are you satisfied with how the scar looks'?

The last outcome measures we want to address and that may need more international consensus are complications and complication rates. When describing new treatment interventions it is imminent to describe the complications of that intervention. In many studies these complications are subcategorized in minor and major complications[6, 11]. However, in some studies, definitions of these minor or major complications are lacking. Besides the fact that it is hard to define a complication, it may be even harder to evaluate all complications during a study follow up. For example, not all patients seek for help by their surgeon with a hematoma or numbness of the finger or edema of the hand. They might go to the general practitioner (GP) instead. On the other hand, is edema of the hand a complication when you have operated the entire hand for DD? We have described that it is difficult to define, assess and categorize complications. Therefore, it may seem obvious when only the overall complication rates are presented in a study it may not give the reader transparent information.

It should be noted that we do not believe that it is possible to reflect the complexity of recurrence and other outcome measures for DD in a single definition or single outcome measure. However, it is necessary to find consensus in how to measure and present outcome measures when describing DD interventions, so it will be possible to compare studies and effectiveness of DD interventions in the best manor in near future.

Patient-rated importance of different characteristics of DD treatment

In **Chapter 4** we present a study on which characteristics of DD treatment are rated by patients as most important, such as contracture correction, recurrence and complications. Insight in patients' preferences can contribute to patient-centered care and information for patients. In addition, understanding which aspects of treatment are most valuable for patients can help us to determine which outcome parameters of treatment should be evaluated when comparing treatments. Therefore, we performed a discrete choice experiment (DCE) including a large study population (506 analyzed questionnaires). We found that recurrence rate (36%) and extensive deficit (28%) were the most important attributes in making treatment choices, followed by minor complication rate

(13%) (Table 1). Multiple trade-offs could be calculated, for example patients accepted an increase of 11% recurrent disease if they could receive NA treatment instead of LF.

A number of the findings of the DCE were, in our experience, surprising. For example, we found that minor complications were more important for patients compared to major complications. An explanation may be that patients are more focused on the minor complications since it is more obvious to encounter minor complications (such as edema, hematoma) after an intervention than major complications (such as nerve lesions and infections).

A second surprising finding may be that patients in our study prefer low recurrence rates and less extension deficit above the short convalescence. This may be surprising since minimally invasive treatment interventions are increasingly popular and considered beneficial for many patients[6, 16-18]. The focus towards the minimal invasive techniques may be related to a number of factors, such as decreased direct medical costs, decreased indirect costs due to less absence of work, and complaints from patients about long convalescence after intervention[19-21]. However, patients' preferences for different characteristics of DD treatment have never been directly studied. Our findings may indicate that patients focus mainly on solving the problem, which is a contracture correction, with a minimal chance of having a recurrent contracture. Convalescence is than considered less important. Our findings may indicate that patients suffering of DD may make different choices than their treating hand surgeons. In future, it may be interesting to compare hand surgeons' preferences and patients' preferences.

Long-term results of flap surgery for severe diathesis

In **Chapter 5** we were interested in the treatment of the relatively small group of patients with very severe diathesis[22]. These specific patients are known to have a poor surgical

	Important scores (IS)			
	Latent class 1	Latent class 2	Latent class 3	Overall
Recurrence rate within 5 years	27.2%	28.7%	43.9%	36%
Residual extension deficit after treatment	49.3%	21.6%	12.8%	28%
Minor complication rate	5.9%	9.4%	18. 9%	12%
Treatment method	4.4%	27.7%	8.4%	9%
Major complication rate	3.8%	5.6%	7.2%	6%
Convalescence	3.1%	3.4%	6.1%	5%
Aesthetic result	6%	3.6%	2.6%	4%

Table 1: The importance scores are calculated rates, indicating how much one decision is based on a specific attribute (e.g., x% of the decision for a specific treatment option is based on recurrence rate, and y% of the decision is based on reduction of extension deficit; all rates together count up to 100% and counts as 1 decision for a specific treatment). The relative importance of the different attributes was different between the subjects belonging to the different latent classes.

outcome with a recurrence or extension rate up to 47% even after dermofasciectomy[23, 24]. In Rotterdam, we have performed a radical fasciectomy and extensive flap surgery for both hands and feet in these specific patients. In this chapter, we describe the long-term outcome (25 years after treatment) of a case-series of two brothers with a severe diathesis of DD. We found that hand function was acceptable and both patients were very satisfied with the overall results following the flap surgery. Most importantly, no recurrence developed under the flaps. In this study, we demonstrated that patients with severe diathesis sometimes need special and radical surgical interventions by using either pedicled axial flaps or free vascularized flaps. In the past, studies using free vascular flaps for soft tissue coverage after palm and digit defects for DD patients have been reported[25-27]. However, these studies only focused on survival of the flap and not on recurrence of DD and hand function. Although we only describe two patients, our results suggest that large flap surgery should be considered as an aggressive but alternative treatment for patients with severe DD.

Results of the PALF surgery

The last part of this thesis compared the outcome of an innovative extensive percutaneous aponeurotomy and lipofilling (PALF) technique with the most commonly used surgical technique, limited fasciectomy (LF). First, in **Chapter 6** we evaluated first retrospectively the outcome of patients treated with PALF in Miami and Rotterdam (Figure 2). Despite this study was originally designed to describe the surgical method we were able to report goniometry data of 50 of the 91 patients. We found that MP-joint and PIP-joint contractures could be successfully treated with this new technique, including the more severe contractures. Patients reported a short recovery time and were satisfied with the results[15]. However, a randomized controlled trial was needed to compare this new treatment with a golden standard.

Therefore, in **Chapter 7**, we presented data of a single blind multicenter randomized controlled trial (RCT). We found that in both PALF and LF, almost full MP-joint contracture was obtained while for the PIP-joint some residual contracture remained. However, we found no significant differences in contracture correction between groups. In addition, we found that patients in the PALF-group returned significantly earlier to their normal daily activity while at one-year post surgery, we found no significant differences in recurrence rate and hand function (Figure 3 and Figure 4). At one year after surgery, LF-treated patients were significantly more satisfied on the overall treatment outcome, contracture correction, and whether treatment expectations were met. However, no significance difference was found in percentages of patients who wanted to receive the same operation again and who wanted to recommend their type surgery to family and friends. Also all other satisfaction-related questions were similar between groups.

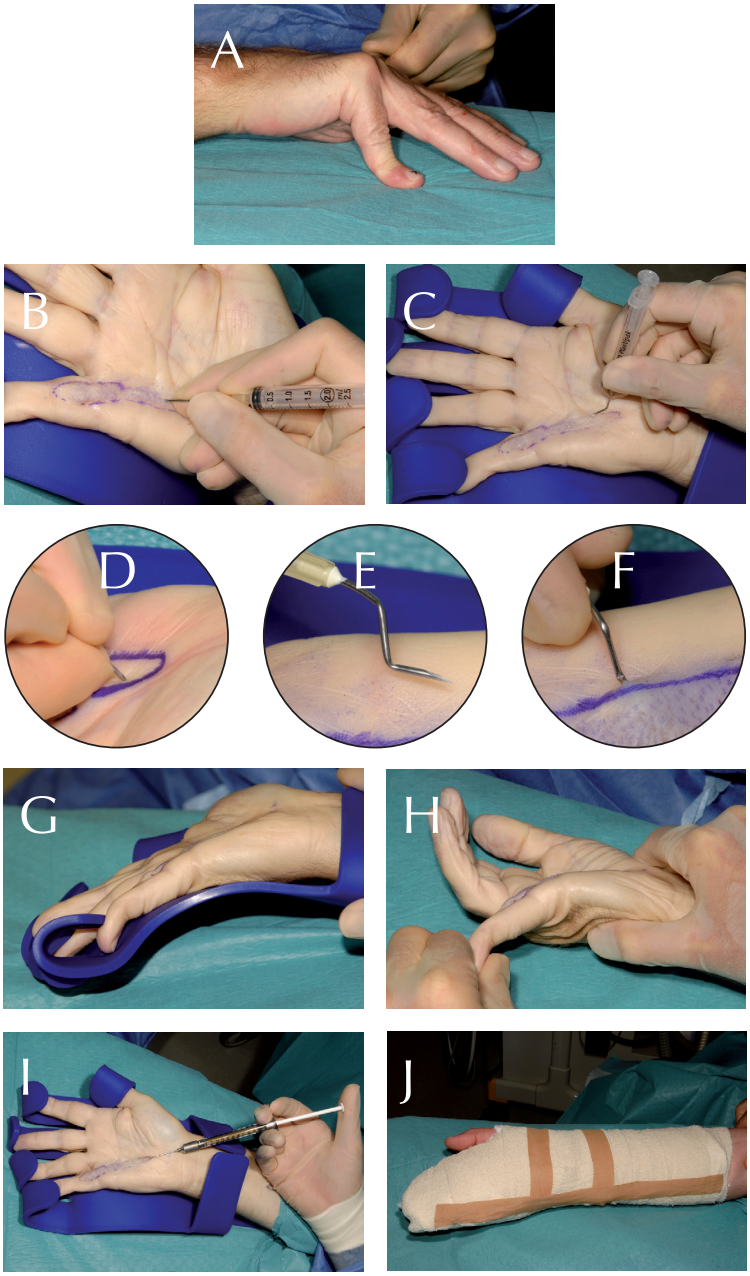

Figure 2: PALF technique illustration: preoperative photo of a patient with a Dupuytren contracture of the fifth digit on the right hand (A). Making of multiple nicks from proximal to distal with a 19-gauge needle (B and D). Releasing dermal attachments of the cord with a windshield wiper motion of an "L" shaped needle (C, E and F). Placement of the digital contractures under maximal tension in extension, using a firm hand retractor during the whole operation (G). The hand is ready for lipografting once the contracture is fully released (H). Injection of 8-10 ml. of non-centrifuged, simply sedimented lipoaspirate per digital ray (I). Plaster extension splinting, kept on for five to seven days (J).

The results from the cohort study (**Chapter 6**) and the RCT (**Chapter 7**) together show that extensive percutaneous needle aponeurotomy with lipofilling (PALF) is a good technique to treat patients with DD. Especially patients suffering of MP-joints contractures are good candidates for this technique. Furthermore, patients suffering of DD in multiple rays can be treated in one surgical session in contrast with LF were more surgeries might be needed.

An important challenge in analyzing the results of the trial is the fact that individual patients can be operated on one of both hands, one or more fingers, and, within a finger, one or more joints[28]. To solve this problem, for analysis of all the RCT data (**Chapter 7**), we selected the most severely affected finger. In this way we were able to simplify the problem that some patients are suffering of DD in more than one finger on

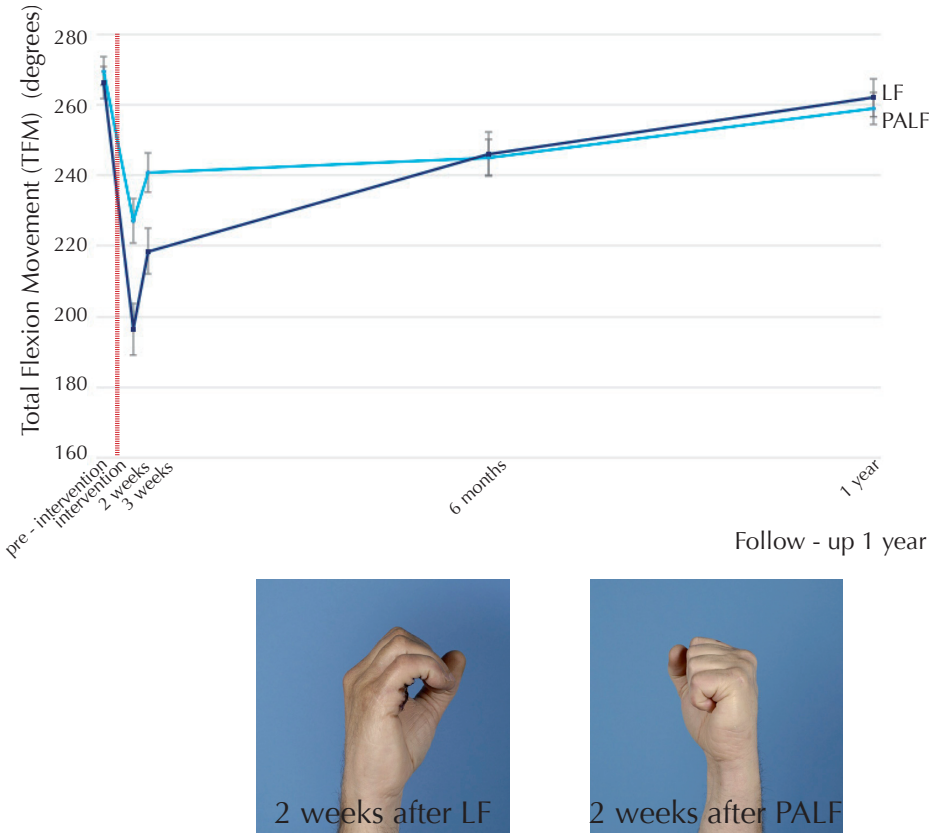

Figure 3: Total flexion movement (TFM): goniometric outcomes measured preoperatively and at two weeks, three weeks, six months and one-year after surgery. This graph shows the difference of the ability to make fist as a measure of convalescence based on the total flexion movement of all joints (TFM). Photographs below the graph show the difference in the ability of making a fist measured at two weeks post surgery.

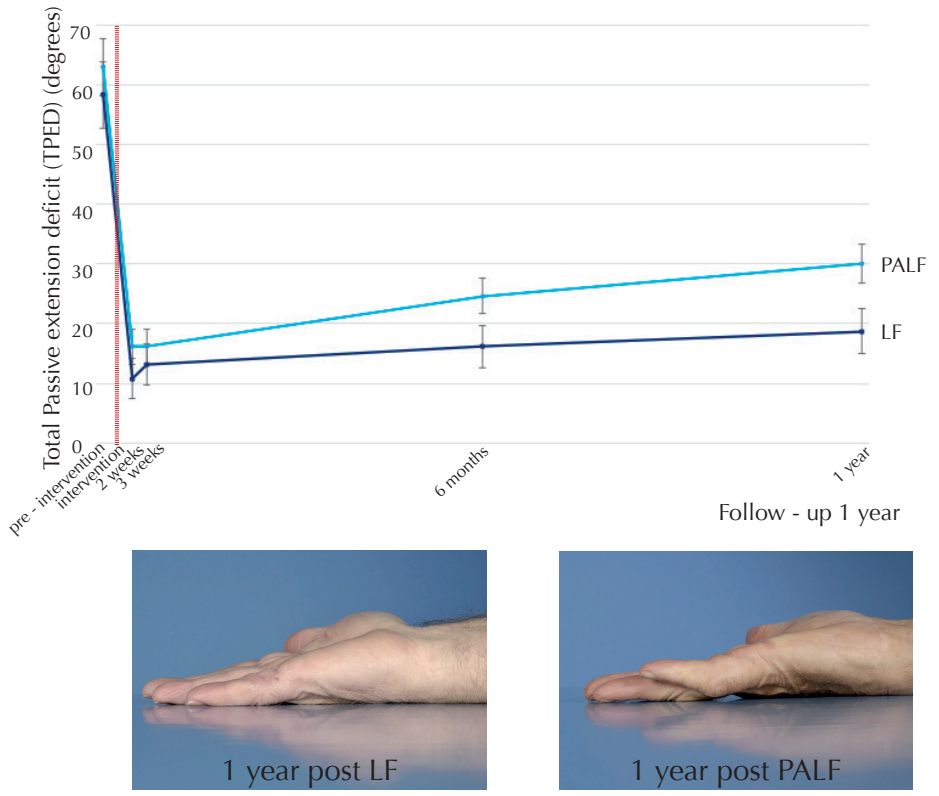

Figure 4: Contracture correction in total passive extension deficit (TPED): goniometric outcomes measured preoperatively and at two weeks, three weeks, six months and one-year after surgery. This graphs shows the total passive extension deficit (TPED) between PALF and LF. Photographs below the graph show the difference in amount of contracture for each technique measured at one year.

the same hand. This was earlier suggested in a review, which described the statistical issues when dealing with both hands and/or multiple affected fingers[28]. Since we found no significant difference in the amount of affected fingers between the PALF-group and LF-group, we feel there is no bias between these groups. However we may overestimate the residual deficit and the amount of relapse of both groups since it is known that more affected fingers are less likely to treat to full release and are more prone to relapse sooner.

We decided, when designing the randomized trial, to use LF as a control group because we considered LF the most commonly used treatment for this patient group. As a result, we cannot establish whether differences in outcome are related to this particular extensive needle aponeurotomy technique compared to standard needle aponeurotomy or related to the lipofilling, or both. We know that in-vitro studies showed fat stem cells to be beneficial in inhibition of the contractility of the myofibroblast[29]. However,

in-vivo studies such as a comparison with PALF and needle aponeurotomy would be needed to determine if the extensiveness of the needle aponeurotomy and the addition of fat are in conjunction better than needle aponeurotomy alone. This will be studied in the near future by matching our RCT data with prospective collected conventional aponeurotomy data of the Xpert Clinic.

For both the prospective cohort as well as the RCT, no long-term follow-up data beyond one year is yet available. Therefore long-term recurrence rates cannot be presented. In future, we will measure the patients treated with PALF and LF again at five-year follow-up. Since we found that patients prefer contracture correction and low recurrence rates above short convalescence, these future data on recurrence are of great value to guide patients straightforward in making the decision of being treated with PALF or LF.

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Chapter 9

English summary

This thesis presents research on the effectiveness of an innovative treatment for Dupuytren's disease (DD) as well as a number of methodological studies related to evaluating effectiveness of DD treatment and patient preferences for specific treatment characteristics. In the following sections we briefly summarize the outcome of all studies.

THE EFFECT OF DIFFERENT DEFINITIONS FOR RECURRENCE AND A NEW DEFINITION

Recurrence rates are important in evaluating effectiveness of treatment for Dupuytren's disease (DD). In literature, recurrence rates vary between 0% and 100% and the definition of recurrence of DD after treatment is inconsistently used. In **Chapter 2**, we reviewed the different definitions for recurrence after treatment of DD in literature and evaluated the effect of these different definitions on the resulting recurrence rate. We found that 51% of the publications reporting recurrence rates did not present a definition of recurrence. The reported definitions could be grouped into three main categories, based on 1) the return of nodules and cords, 2) the return of joint contractures, or 3) the patient's self-report of a recurrence or whether a recurrent surgery was performed. Furthermore, recurrence rates at six months follow-up ranged from 2 to 86% in the same dataset of DD patients, based on applying different angular thresholds, different baseline measurement, and different selected joints. Based on this, we conclude that it is presently difficult or even impossible to compare recurrence rates between different treatments reported in the literature and that consensus on a recurrence definition is needed.

Based on the results from **Chapter 2**, we decided to develop an expert consensus definition for recurrence of DD (**Chapter 3**). To do so, we used the Delphi method and invited 43 Dupuytren's research and treatment experts from 10 countries to participate by answering a series of questionnaire rounds. After each round the answers were analyzed and the experts received a feedback report with another questionnaire round. Twenty-one experts agreed to participate in this study. After four consensus rounds, they agreed that DD recurrence should be defined as "*more than 20 degrees of contracture recurrence in any treated joint at one year post-treatment compared to six weeks post-treatment*". In addition, it was recommended that recurrence should be reported individually for every treated joint and that ideally measurements should be repeated and reported yearly.

PATIENT-RATED IMPORTANCE OF DIFFERENT CHARACTERISTICS OF DD TREATMENT

While in modern medicine, patients' preferences are important; these have never been defined for characteristics of Dupuytren treatment. Insight in these patients' preferences

can contribute to patient-centered care and information for patients. Furthermore, understanding which aspects of treatment are most valuable for patients can help us to determine which outcome parameters of treatment should be evaluated when comparing treatments. In **Chapter 4** we present a multicentre discrete choice experiment on which characteristics of DD treatment are rated by patients as most important. Patients were asked on their preferences for attributes of Dupuytren treatments using scenarios based on treatment method, major and minor complication rates, recurrence rates, convalescence, residual extension deficit after treatment and aesthetic results. The relative importance of these attributes and the trade-offs patients were willing to make between them were analysed using a panel latent class logit model.

Five-hundred-and-six patients filled in the questionnaire. All above-mentioned attributes proved to significantly influence patients' preferences for Dupuytren treatment and preference heterogeneity was substantial; males who perform heavy labour made different trade-offs than females or males who did not. In general, recurrence rate (36%) and extensive deficit (28%) were the most important attributes in making treatment choices, followed by minor complication rate (13%). Patients accepted an increase of 11% recurrent disease if they could receive needle aponeurotomy (NA) treatment instead of limited fasciectomy. We concluded that this study confirms the importance of low recurrence rates and complete contracture corrections, but also emphasizes the significance of low complication rates. The preference heterogeneity shows that patient consultations need to be targeted differently, which may result in different treatment decisions depending on patient characteristics and preferences.

LONG-TERM RESULTS OF FLAP SURGERY FOR SEVERE DIATHESIS

In **Chapter 5** we were interested in the treatment of this relatively small group of patients with very severe diathesis, which are known to have a poor surgical outcome with a recurrence rate up to 47% after dermofasciectomy. In Rotterdam, we have performed extensive flap surgery for both hands and feet and in this chapter, we describe the long-term outcome (14 to 25 years after treatment) of a case-series of two brothers with a severe diathesis of DD. We found that hand function was acceptable and that both patients were very satisfied with the overall results following the flap surgery. Importantly, no recurrence developed under the flaps. We concluded that in very severe diathesis, flaps should be considered in an earlier phase to prevent multiple procedures and early recurrence.

RESULTS OF THE PALF SURGERY

Surgical resection of Dupuytren's contracture is fraught with morbidity and prolonged recovery. In **Chapter 6** we introduce an innovative extensive percutaneous aponeu-

rotomy and lipofilling (PALF) technique and describe the early results. This procedure consists of an extensive percutaneous aponeurotomy that completely disintegrates the cord and separates it from the dermis. Subsequently the resultant loosened structure is grafted with autologous lipoaspirate. After one week of post-operative extension splinting, patients are allowed normal hand use and are advised to use night splints for 3-6 months. In this chapter, we report on our experience with 91 patients (99 hands) operated in Miami and Rotterdam; from 50 patients we report on goniometry (average follow-up of 44 weeks). We found that the contracture from the PIP-joint improved significantly from 61 degrees to 27 degrees and the MP-joint from 37 degrees to –5 degrees. Ninety-four percent of patients returned to normal use of the hand within 2–4 weeks and 95% were very satisfied with the result. No new scars were added and a supple palmar fat pad was mostly restored. Complications were one digital nerve injury, one post-operative wound infection and four patients with CRPS. We concluded that this new invasive technique shortens recovery time, adds to the deficient subcutaneous fat and leads to scarless supple skin. By its ability to treat multiple rays, it addresses the pathology in the entire hand.

However, since **Chapter 6** did not include a comparison group, a randomized controlled trial was needed to directly compare this new treatment with a golden standard. Therefore, in **Chapter 7**, we designed a single-blind multicenter randomized trial comparing the effectiveness of PALF with limited fasciectomy (LF). Patients with a primary Dupuytren's contracture of at least 20° (MP-joint) or 30° (PIP-joint) were randomly assigned to the LF-group or the PALF-group. Patients were measured at baseline and at two weeks, three weeks, six months and one year post-operatively. Primary outcome of the trial was contracture correction and convalescence.

Eighty patients with 88 treated hands were included in this study and randomized to PALF or LF treatment. In both groups, almost full MP-joint contracture was obtained while for the PIP-joint some residual contracture remained. However, no significant differences in contracture correction between groups were detected. In addition, the patients in the PALF-group returned significantly earlier to their normal daily activity. At one-year post surgery, no significant differences in recurrence rate and hand function were present. We concluded that PALF is a valuable addition to the treatment methods of DD, showing similar operative contracture correction to LF treatment and no significant difference regarding one-year postoperative results and a significantly shorter convalescence.

In **Chapter 8** we discuss our main findings of all studies, furthermore we make some suggestions for future research purposes.

Chapter 10

Nederlandse Samenvatting

In dit proefschrift wordt onderzoek naar de effectiviteit van een nieuwe behandeling van Morbus Dupuytren (M. Dupuytren) beschreven. Ook komen er verschillende methodologische studies aan bod naar de effectiviteit van de behandelingen van M. Dupuytren en een studie naar patiënten voorkeuren. In de volgende alinea's zullen we de uitkomsten van deze verschillende onderzoeken kort beschrijven.

HET EFFECT VAN VERSCHILLENDE DEFINITIES VOOR DE TERUGKEER VAN DE ZIEKTE VAN DUPUYTREN

Het percentage patiënten met een terugkeer van M. Dupuytren na operatie is een belangrijke parameter om de effectiviteit van de verschillende behandeling te evalueren. In de literatuur worden percentages beschreven variërend tussen de 0% en 100%, waarbij de terugkeer van M. Dupuytren zeer inconsequent gedefinieerd wordt. In **Hoofdstuk 2** hebben we de verschillende definities beschreven en hebben we geevalueerd wat het effect van deze verschillende definities was op de gerapporteerde terugkeer van M. Dupuytren binnen een cohort van patiënten. We vonden dat 51% van de publicaties geen definitie beschrijft. Verder konden we de gepubliceerde definities onderverdelen in drie categorieën. Deze categorieën waren gebaseerd op 1) de terugkeer van nodules en strengen, 2) de terugkeer van gewrichtscontracturen, en 3) de door patiënten zelf-gerapporteerde terugkeer van ziekte of het ondergaan van een nieuwe operatie. Bovendien konden we aantonen dat de percentage terugkeer van ziekte kunnen variëren tussen 2% en 86% in dezelfde dataset van patiënten, afhankelijk van de gekozen definitie. Daarom concluderen we dat het tot op heden niet mogelijk is om verschillende percentages van verschillende studies met elkaar te vergelijken. Daarom is een consensus over een nieuwe definities noodzakelijk.

De resultaten van **Hoofdstuk 2** hebben geleid tot **Hoofdstuk 3**, waarin we samen met experts een definitie voor de terugkeer van M. Dupuytren hebben ontwikkeld. In totaal zijn er 43 experts uit 10 verschillende landen op gebied van M. Dupuytren gevraagd mee te doen aan een Delphi studie. In verschillende ronden werd gevraagd om verschillende vragen te beantwoorden. Na elke ronde werden de antwoorden geanalyseerd en een feedbackrapport terug gestuurd naar de experts. Op basis daarvan werden eventueel nieuwe vragen gesteld. Uiteindelijk deden er 21 experts mee aan deze studie. Na vier ronden werd er consensus bereikt waarbij de terugkeer van M. Dupuytren werd gedefinieerd als: 'een terugkeer van ten minste 20 graden flexie contractuur in een geopereerd gewricht gemeten op een jaar na behandeling vergeleken met zes weken na de behandeling'. Tevens werd er door de experts geadviseerd om de gewrichten afzonderlijk van elkaar te vermelden en om metingen waar mogelijk elk jaar te herhalen.

PATIËNTVOORKEUREN VOOR VERSCHILLENDE KARAKTERISTIEKEN VAN DE BEHANDELING VAN M. DUPUYTREN.

Patiëntvoorkeuren worden in de gezondheidszorg steeds belangrijker, maar zijn nog nooit bestudeerd voor de behandeling naar M. Dupuytren. Inzichten in deze patiëntvoorkeuren kunnen een bijdrage leveren aan doelgerichte zorg waar de patiënt centraal staat. Daarbij kan het begrijpen van patiëntvoorkeuren helpen de juiste uitkomstparameters te kiezen in een onderzoek.

In **Hoofdstuk 4** presenteren we een multicenter discrete choice experiment (DCE) naar karakteristieken van de behandeling van M. Dupuytren die door patiënten als 'meest belangrijk' worden gescoord. Patiënten werd naar hun voorkeur gevraagd via een vragenlijst waarin hypothetische behandelscenario's werden voorgelegd. Deze scenario's verschilden op basis van behandelmethode, incidentie van complicaties, terugkeer van ziekte, snelheid van herstel, rechtheid van de vinger na de behandeling en esthetisch resultaat. De relatieve belangrijkheid van deze attributen en de trade-offs die patiënten bereid zijn te maken tussen deze attributen werden geanalyseerd.

Vijfhonderden-zes patiënten hebben de vragenlijst ingevuld. Alle hierboven beschreven attributen beïnvloedden significant de patiëntvoorkeuren bij een Dupuytren behandeling. Over het algemeen waren terugkeer van ziekte (36%) en rechtheid van de vinger na behandeling (28%) voor patiënten de meest belangrijke attributen, gevolgd door milde complicaties (13%). Patiënten accepteerden verder een 11% hoger risico op terugkeer van ziekte als zij behandeld konden worden met naaldaponeurotomie in plaats van selectieve fasciectomie. We concluderen uit deze studie dat lage kans op terugkeer van ziekte en volledige rechtheid van vingers na een behandeling de belangrijkste attributen zijn voor patiënten, gevolgd door een kleine kans op complicaties.

LANGE TERMIJN RESULTATEN VAN LAP OPERATIE VOOR PATIËNTEN MET EEN ERGE DUPUYTREN DIATHESE

In **Hoofdstuk 5** waren we geïnteresseerd in een behandeling van een relatief kleine groep patiënten met een ernstige Dupuytren diathese. Het is algemeen bekend dat deze patiëntengroep een grote kans heeft op terugkeer van de ziekte. Er zijn percentages terugkeer van M. Dupuytren beschreven van meer dan 47% na een dermofasciectomie. In Rotterdam hebben we uitgebreide (vrije danwel gesteelde) lap operaties verricht aan de handen en voeten van verschillende patiënten. In dit hoofdstuk beschrijven we de lange termijn resultaten (14 tot 25 jaar na behandeling) van twee broers met een ernstige Dupuytren diathese. We vonden dat handfunctie redelijk was en dat beide patiënten erg tevreden waren met het gehele resultaat na de lap operatie. Belangrijk is dat er geen terugkeer van M. Dupuytren was onder de lappen. We kunnen hieruit concluderen dat bij een ernstige Dupuytren diathese (vrije en gesteelde) lappen eerder

moeten worden overwogen om te voorkomen dat deze patiënten veelvuldig worden geopereerd.

RESULTATEN VAN PALF CHIRURGIE

Chirurgische resectie van een Dupuytren contractuur heeft een relatief hoge morbiditeit en lange herstelperiode. In Hoofdstuk 6 hebben we een nieuwe innovatieve chirurgische methode geïntroduceerd, de uitgebreide percutane aponeurotomie en lipofilling (PALF). Deze methode bestaat uit een uitgebreide percutane naaldaponeurotomie waardoor de Dupuytren streng volledig uit elkaar valt en los maakt van de huid. Vervolgens wordt er tussen de huid en de kapotte streng autoloog vet geïnjecteerd. Gedurende een week na de operatie heeft de patiënt een extensie spalk, daarna wordt er geadviseerd om wederom te starten met normale handfunctie en een nachtspalk voor drie tot zes maanden. In dit hoofdstuk beschrijven we onze ervaringen van 91 patiënten (99 handen) die zijn geopereerd in Miami en Rotterdam. Van 50 patiënten konden we ook goniometrische data presenteren met een gemiddelde follow-up van 44 weken. We vonden dat het PIP-gewricht significant was verbeterd van 61 graden naar 27 graden en dat het MCP-gewricht van 37 graden naar -5 graden verbeterde. Vierennegentig procent van de patiënten hadden binnen twee tot vier weken weer een volledige handfunctie en 95% was tevreden met het resultaat. Er werden geen nieuwe littekens gemaakt en het palmaire vet werd in de meeste gevallen hersteld. Wel werden er verschillende complicaties gezien, waaronder een digitaal zenuwletsel, een postoperatieve wondinfectie en vier patiënten ontwikkelde een CRPS. We kunnen concluderen dat deze nieuwe minimaal-invasieve methode een kortere herstelperiode heeft vergeleken met de conventionele technieken. Verder hebben we gezien dat het toevoegen van vet leidt tot een soepele huid in de palm van de hand met weinig littekens. Omdat het bij deze techniek mogelijk is om meerdere aangedane stralen te behandelen kan bovendien pathologie van een gehele hand worden behandeld.

Omdat er in **Hoofdstuk 6** naast de patiëntengroep die behandeld werden met PALF geen controlegroep aanwezig was, was een gerandomiseerde studie nodig om de nieuwe techniek te vergelijken met een gouden standaard. Daarom hebben we een enkel-geblindeerde multicenter gerandomiseerde studie opgezet waarbij we het effect van PALF vergelijken met de selectieve fasciectomie (SF), beschreven in **Hoofdstuk 7**. Patiënten met een primaire Dupuytren contractuur van ten minste 20° (MCP-gewricht) of een 30° (PIP-gewricht) werden gerandomiseerd over de SF-groep en PALF-groep. Patiënten werden preoperatief, op twee weken, drie weken, zes maanden en een jaar post-operatief gemeten. De primaire uitkomstmaten waren contractuurcorrectie en herstelperiode.

Tachtig patiënten met 88 geopereerde handen werden geïncludeerd in deze studie en gerandomiseerd tussen PALF en SF. In beiden groepen werd een bijna volledige MCP-contractuurcorrectie behaald, hoewel er voor het PIP-gewricht een postoperatieve extensiebeperking bleef bestaan. Er was geen significant verschil in contractuurcorrectie tussen de twee groepen. Wel konden patiënten in de PALF-groep significant eerder hun dagelijkse activiteiten uitvoeren. Een jaar na de behandeling werd er geen verschil gevonden in ratio van terugkeer van ziekte en handfunctie. We concluderen dan ook dat PALF een waardevolle toevoeging is in het palet van behandelingen van M. Dupuytren.

In **Hoofdstuk 8** bediscussiëren we onze hoofdbevindingen van alle studies, verder benoemen we een aantal suggesties voor toekomstig onderzoek.

Part VI

Appendices

Acknowlegements (dankwoord)

Funding (Sponsoren)

List of publications

PhD Portfolio

About the author

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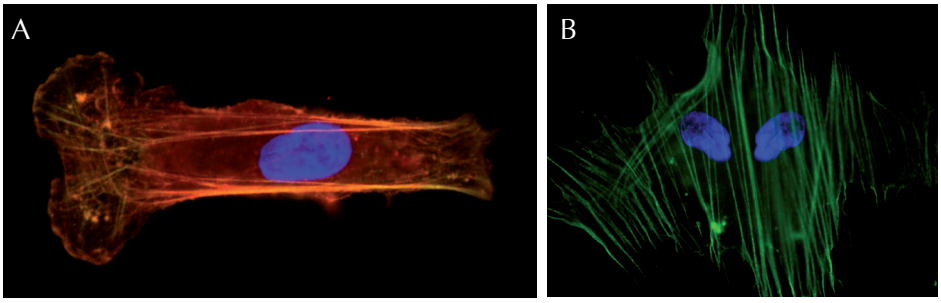

figure 1: Figure shows photographs of myofibroblasts, the Peyroniecel (A) and the little gosth (B).

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2. S.E.R. Hovius MD, PhD; **H.J.Kan, MSc**; R.W. Selles, PhD; X. Smit, MD, PhD; E. Cardoso, MD; R. Khouri, MD; Extensive percutaneous aponeurotomy and lipografting: a new treatment for Dupuytren's Disease.
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PHD PORTFOLIO

PHD TRAINING 2009 - 2015

General courses		**ECTS**
2011	BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	1,4
2011	Biomedical English Writing and Communication	0.4
2011	Research Integrity, Pfizer	0.3
Specific courses		
2007 - 2010	NIHES Master programme, Clinical Research	130
Seminars and Workshops		
2011- 2014	Microsurgery in Skills Lab (weekly)	7,5
2013	Kortjakje: Breast reconstruction	0.3
2014	Kortjakje: Lipofilling	0.3
Presentations		
2010	Oral presentation at IFSSH, Seoul, South Korea	0.7
2010	Oral presentation at NVvH, Lelystad	0.7
2010	Oral presentation at Handtherapy conference, Rotterdam	0.7
2011	Oral presentation at NVPC, Den Bosch	0.7
2012	Oral presentation at AAHS/ASPN/ASRM, Las Vegas, USA	0.7
2013	Oral and Poster presentation, IFSSH, Delhi, India	0.7
2014	Oral presentation at NVPC, Amsterdam	0.7
2015	Oral presentation at Dupuytren symposium, Groningen	0.7
(Inter)national conferences		
2009	ECSAPS	0.3
2010	Esser Course: To straighten out DD, what to do?	0.3
2010	IFSSH congres in Seoul, South Korea	1.4
2011	NVvH, Aviodrome Lelystad	0.3
2011	Esser Course: Dupuytren's disease: live surgery event	0.3
2012	NVPC wetenschappelijke dag, Den Bosch	0.3
2013	ASPN in Las Vegas, USA	1.2
2014	IFSSH congress in New Delhi, India	1.4
2014	Esser Course Breast reconstruction	0.3
2015	NVPC wetenschappelijke dag, Amsterdam	0.3
2015	Dupuytren symposium, Groningen	0.6

Congress organization

2010	15th Esser course: To straighten out DD, what to do?	9
2011	17th Esser course: Dupuytren's Contracture: live surgery event	9
2014	22th Esser course: Breast reconstruction: live surgery event	5

Lecturing

2010	Lecture about DD for medical students	0.7
2011	Lecture about chronic hand disorders for medical students	0.7
2011	Lecture about DD for medical students	0.7

Supervising practicals and tutoring

2010	Second and third year medical students with research project	0.9
2010, 2011	Practical 'swollen joints'; fourth year medical students	0.3
2010 - 2011	Master student from the TU Twente on the echo project	10
2011 - 2013	Medical student with research project: DCE and cord analysis	30
2011	Second year medical student with research project	0.9
2012 - 2013	Medical student with research project, review and Delphi	20
2011	Practical macro suturing; third year medical students	0.15
2011, 2014	National micro suturing course	1,2
2011	International micro suturing course	0.6
2011	Medical student with research project, DCE	10

Grants	**Amount**
Nuts– Ohra Foundation	€ 110.000
Stichting Coolsingel	€ 30.000
Trustfonds	€ 1.700
Gerrit Jan Mulder Stichting	€ 1.000
KNAW, van Walree Foundation	€ 1.400

ABOUT THE AUTHOR

Hester Janneke Kan was born on February 9th 1986 in Hoorn, the Netherlands. After graduating from the Murmellius Gymnasium, Alkmaar she went on to study Biomedical Science at the VU University of Amsterdam in 2004. In 2005, she started to study Medicine at the Erasmus University of Rotterdam. During her second year of Medical School Hester was selected to participate in a special program for medical students organized by the Netherlands' Institute of Health Sciences (NIHES) and was supervised by prof. dr. Steven E.R. Hovius during her Master thesis. This program enabled her to combine Medical school with the Master of Science in Clinical Research. During this program she participated in a Summer Program at John's Hopkins University and obtained her Masters degree in Clinical Research in 2009. She started her PhD-program in 2010 after obtaining two grants (Stichting Nuts Ohra and Stichting Coolsingel) at the Department of Plastic and Reconstructive Surgery and Hand Surgery. Hester completed her MD-training in January 2014 and started in May 2014 as resident at the department of Plastic and Reconstructive Surgery and Hand Surgery at Erasmus Medical Center in Rotterdam. Currently, she is working as resident at the department of Cardiothoracic Surgery at Onze Lieve Vrouwen Gasthuis (OLVG) in Amsterdam.