Dupuytrens Disease

by Chao Zhou

MEASURE   COMPARE   PREDICT?

Stellingen

Bij proefschrift

DUPUYTREN'S DISEASE: Measure. Compare. Predict?

1. In carefully selected patients, percutaneous needle aponeurotomy and Collagenase injection can be just as effective as limited fasciectomy at reducing contractures within the first 3 months of treatment. (this thesis)
2. Propensity score analyses enable investigators to make valid inferences about the comparative effectiveness of treatments for Dupuytren's disease using real-world data. (this thesis)
3. People with Dupuytren's contracture care about the appearance of their hand, and so should providers if they seek to improve satisfaction. (this thesis)
4. Open surgery is still the closest thing to a cure for Dupuytren's contracture. (this thesis)
5. Although the number of procedures a surgeon performs for Dupuytren's disease influences outcomes, patient factors matter more. (this thesis)
6. Studies comparing surgical techniques for Dupuytren's disease should account for the expertise of the surgeons in order to minimize the risk of bias. (this thesis)
7. Surgeons should not fear the eccentricity of lipofilling or Collagenase as a treatment for Dupuytren's contracture, for every treatment now accepted was once eccentric.
8. Despite the large number of studies describing outcomes of treatments for Dupuytren's disease, little high-quality evidence is available to guide decision-making between these treatments.
9. "In all affairs, including the treatment of Dupuytren's disease, it's a healthy thing now and then to hang a question mark on the things you have long taken for granted." Adaptation from B. Russell, mathematician and Nobel laureate. (1)
10. "Basic research efforts are needed to fully unravel the pathogenesis of Dupuytren's disease and offer the greatest promise to find a cure." Adaptation from G. Dolmans and P. Werker et al. (2)
11. "Most people use statistics like a drunk man uses a lamp post; more for support than illumination." A.E. Housman, classicist and poet. (3)

CHAO ZHOU

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Dupuytren's Disease:
Measure. Compare. Predict?

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Proefschrift

ter verkrijging van de graad van doctor aan
de Erasmus Universiteit Rotterdam

op gezag van de rector magnificus

Prof. dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
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door

Chao Zhou
geboren te China

Dedicated to my parents.

Contents

1 General Introduction

Introduction

Dupuytren's disease is a chronic, mostly progressive, debilitating disease of the palmar and digital fascial structures of the hand.[1] It is characterized by the nodular thickening and contracture of these structures. Patients experience varying degrees of functional impairment and diminished quality-of-life[2], depending on how the disease has manifested itself. The search for better treatments for the disease has both challenged and attracted clinicians and scientists over the past decades.[3]

Epidemiology

Dupuytren's disease occurs in people from various ethnicities.[4] Prevalence, however, is highest among those of northern European ancestry. Historically, the disease has therefore been referred to as a Nordic as well as a Viking's disease.[5] Overall prevalence estimates range from 2 to 22% in study populations in the Netherlands, which vary depending on the definition of disease and geographical location sampled.[6] Incidence increases with advancing age and men are six times more often affected than women.[7]

Genetic and environmental risk factors have both been identified for Dupuytren's disease.[8] Studies have suggested an autosomal dominant inheritance pattern with variable penetrance.[9] Risk factors that have been reported include repetitive trauma, epilepsy, smoking, diabetes and alcoholism.[10] These relations, however, were generally weak, suggesting that they exacerbate an underlying genetic predisposition rather than being an independent risk factor for developing the disease.[1]

History

Contrary to common belief, Guillaume Dupuytren was not the first to describe the disease. Instead it was probably Felix Plater who did so in 1614 in *Observationum in Hominis affectibus*. Herein, he described a role of the palmar fascia in the development of the observed contractures.[15] Guillaume Dupuytren did, however, provide one of the most thorough descriptions of the disease during a series of lectures at Hotel-Dieu, Paris, in December 5th, 1831. He reported a case with contractures affecting his ring and little fingers whom he treated with what now would be considered an open fasciotomy approach. It is believed that, in part, these lectures and subsequent reports

on the disease increased awareness for the disease, eventually resulting the disease to be named after him instead of Felix Plater.

Anatomy and disease manifestation

The superficial and deep fascias of the palm provide a firm but mobile framework for the soft tissues of the palm to adhere to. In Dupuytren's disease, the normal superficial palmar fascia (palmar aponeurosis) transforms to thickened pathologic cords. This is the result of the contractile forces generated by myofibroblasts and deposition of Collagen type I and III.[11] In contrast, the deep fascia is not involved.

The formation of nodules and lumps that develop into fibrotic cords, which can then lead to contractures over time, characterizes the natural course of disease: this progression is pathognomonic (Figure 1). A diagnosis is usually made when patients present somewhere along this disease spectrum. The earliest clinical signs, however, are dimpling and pits in the palmar skin, which precedes nodule formation. Although pits, nodules, and cords form anywhere from finger tip to as proximal as the wrist crease, they usually occur in the ulnar region of the palm.[12] While complaints associated with these pits and nodules include tightness and/or discomfort to pressure at the palm of the hand, they typically are pain free.

Figure 1. The characteristic disease progression in Dupuytren's disease from nodules into cords, which then lead to contractures. Source: Patientplus.info.

With disease progression, longitudinal and (spiral) cords develop mostly from the palm that extend into the fingers. The ring and little fingers are most commonly involved. Although the course of the digital cords can vary substantially, they mostly do not extend past the midphalanx. Usually, the MCP joint becomes affected first, followed by the PIP

joint. Alternatively, nodules can form just proximal to the PIP joint creating isolated PIP contractures. As a result, patients complain about limitations in daily activities such as difficulty in shaking hands, fitting a hand into a pocket, and grasping objects.[2,13,14]

Several lesions and conditions are associated with Dupuytren's disease, including "knuckle pad's", Garrod's nodules and Peyronie's (penile fibromatosis) and Ledderhose's disease (plantar fibromatosis). Penile fibromatosis is found in a small percentage of patients with Dupuytren's disease (1-3%) and presents as a painless plaque on the dorsum of the penis. Plantar fibromatosis is slightly more common (5-20%) and presents as nodular thickening of skin of the arch of the foot without contracture of the toes. These conditions, however, are beyond the scope of this thesis.

Indications

Current treatment of Dupuytren's disease aims to restore hand function and to improve disability by reducing the degree of contracture and deformity. Unfortunately, a curative therapy has yet to be found. Indications and timing for treatment depend primarily on the extent of functional impairment, the degree of contracture, and the joints involved. For example, accepted indications for surgery include contracture of 30 degrees at the MCP joint level and, for most providers, any degree of contracture at the PIP joint level that causes functional impairment. The joint collateral ligaments shorten easily at the PIP joint level. Specific additional contractures include small finger abduction contracture, and first-web adduction contractures.

Absolute contraindications for treatment do no exist. Treatment outcomes are poor for longstanding PIP joint contractures. Such cases may require other interventions such as arthrolysis, arthrodesis or sometimes even amputation in the most advanced cases. Severe tobacco use, previous surgery with or without neurovascular injury, and use of anticoagulants increases the risks of treatment, but are considered relative contraindications at our centers.

Treatment

A wide array of treatments for Dupuytren's contracture exist that may be categorized into non-operative, injection, and surgical interventions. Surgery has been the mainstay

of treatment because it provides the most long lasting corrections.[16] However, all existing treatments including surgery are fraught with complications, disease recurrence and extension.

Surgery is typically divided into aponeurotomy (i.e. fasciotomy) and aponeurectomy (i.e. fasciectomy) techniques. In aponeurotomy or fasciotomy (Figure 2), pathologic tissue and cords are weakened, perforated, and/or divided without actually removing any tissue. Fasciotomy or aponeurotomy is mostly performed percutaneously but can also be performed through an open approach.[17] In fasciectomy or aponeurectomy, extensive palmar and digital dissection is performed and the diseased fascia is removed. Various fasciectomy techniques differ depending on the extent to which the tissue is removed as well as how the skin is managed. Although many variations in the two techniques exist, two of the most popular techniques are percutaneous needle aponeurotomy or fasciotomy (PNA) and limited fasciectomy (LF, Figure 3).[18]
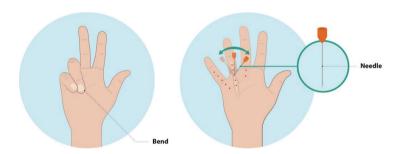

Figure 2. Percutaneous needle aponeurotomy/fasciotomy. Source: Patientplus.info.
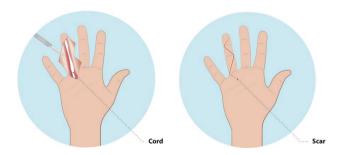

Figure 3. Limited fasciectomy. Source: Patientplus.info.

Compared with LF, PNA is far less invasive and involves the division of pathologic cords at two or more levels under local anesthesia. Traditionally, PNA is considered most suitable for mild to moderate contractures at the MCP joint level. Experienced providers, however, have dared to travel more distal and found that it can also effectively treat PIP contractures. PNA's largest drawback is that contractures tend to recur more rapidly after treatment.[16] The only randomized clinical trial comparing PNA with LF found a 85% recurrence rate at 5 years compared with 21% for LF.[16] In LF, macroscopically abnormal tissue is removed in the palm and fingers as mentioned previously. As normal appearing fascial structures are still left behind, the risk for disease recurrence remains but is much lower. Treatment is under regional of general anesthesia and with the use of an arm tourniquet. Fasciectomy can be used to treat the mildest to most severe forms of Dupuytren's contracture. For contractures at the PIP joint and severe cases, it continues to be the mainstay of treatment.[19]

Injection treatment for Dupuytren's disease goes back to 1952, when corticosteroids were proposed and used as a postoperative adjunct.[20] To date, steroid injections are considered to have a limited role in the treatment of a painful nodule but does not have any efficacy in terms of reducing contractures. The idea of injecting enzymes that target and degrade pathologic Dupuytren's tissue dates back to 1907. Hueston reported promising results using a mixture of hyaluronidase, trypsin, and xylocaine.[21] However, treatment using such non-specific enzymes became unpopular because of serious adverse effects including tendon ruptures and severe neurovascular injury. More recently, Collagenase Clostridium Histolyticum (CCH) has emerged as a "non-surgical" treatment for Dupuytren's contracture (Figure 4).[22] In CCH, which selectively disintegrates collagen, a small volume of collagenase solution is injected into the pathologic cord, thereby weakening the treated areas to allow subsequent rupture. Over the past years, multiple placebo-controlled randomized clinical trials have demonstrated the efficacy and safety of injectable CCH.[4,23-30]
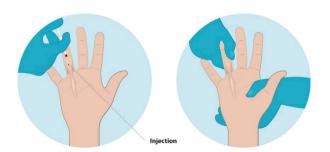
Figure 4. Injection with Collagenase Clostridium Histolyticum. Source: Patientplus.info.

Current issues

Although Dupuytren's disease has been treated for over many decades using various techniques, it continues to present a challenge for anyone who treats these patients. Since the first description of the disease, clinicians and researchers have sought to increase our understanding of its etiology, natural course, and explored various methods of treatment. Although much progress has been made, the wide array of existing treatments highlights the lack of a single ideal treatment that can fully meet the needs of each individual patient. In this thesis, we sought to address a number issues we regarded as the most controversial from a clinical perspective.

The first issue relates to the fact that, while many previous studies have reported the outcomes of each of the previously mentioned treatments individually, a wide range of assessment methods and different definitions for outcomes are used.[31] This severely impairs the ability to make meaningful comparisons between different treatments – some investigators even consider comparison of outcomes across invidivual studies to be impossible. A recent Cochrane review on surgery of Dupuytren's contracture even concluded that "Currently, insufficient evidence is available to show the relative superiority of different surgical procedures." Head-to-head comparisons of treatments not only helps to fully elucidate their unique pros and cons, but are essential for delineating the optimal position of each treatment in the management of Dupuytren's disease. As such, the need for well-designed comparative studies is clear.

A second issue relates to our incomplete understanding of the patient perspective in patients with Dupuytren's disease. Traditionally, interventional studies have used objective measures such as the degree of residual contracture, incidence of

complications and rates of disease recurrence to gauge their efficacy.[14] Although these provider-centric outcomes probably determine the extent to which patients are satisfied, they do not substitute a direct evaluation of patient reported satisfaction and outcomes. In the current patient-oriented health care system, patient satisfaction is increasingly used as a indicator for the quality of care delivered.[32-40] Although this outcome measure seems particularly well suited for the evaluation of treatments for Dupuytren's disease, the factors that determine why some patients are satisfied with their outcome while others are not remain poorly understood. Research in this area will increase our understanding of how patients view their treatments, and may offer unique perspectives on the definition of therapeutic success.

A third issue has to do with the fact that existing treatments are still being updated and improved upon. In an attempt to combine the best characteristics of the existing treatments, Hovius and Khouri pioneered a surgical procedure that combines an extensive form of percutaneous needle release with autologous fat grafting: extensive percutaneous aponeurotomy with lipofilling (or in short 'PALF').[41] Early results of a randomized, single-blinded, clinical trial comparing PALF with LF were promising, indicating comparable 1-year results in terms of residual contracture.[42] However, whether this hybrid technique offers results that are just as long-lasting as those from open surgery remains an exciting question that has yet to be answered.

The last issue addressed in this thesis is the considerable variation in treatment outcomes across individual patients and what factors influence this variation. Outcomes of surgical procedures in Dupuytren's disease depend on which specific procedure is employed, but may also depend on who and how often he or she has performed the procedure in the past. For certain major surgical procedures, studies have demonstrated clear associations between the number of these procedures a surgeon performs on an annual basis (surgeon annual procedure volume) and subsequent outcomes.[43-47] Whether this also the case for Dupuytren's surgery, and if so to what extent is currently unknown. Insight into what factors may be modified to improve the outcomes of Dupuytren's disease treatment, including surgeon volume, may help to identify strategies for improving outcomes. Importantly, the answer to this question also helps to inform the current debate regarding who should operate patients with Dupuytren's disease and who not.

1

Efficacy or effectiveness?

The gap between research and practice is well known. *Efficacy* is the extent to which a (surgical) intervention does more good than harm under *ideal circumstances*[48,49]. In contrast*, effectiveness* is the extent to which a (surgical) intervention does more good than harm when provided under *usual circumstances of health care practice.* Variability and imperfections in health care delivery explain that the results achieved in *effectiveness* studies (broadly generalizable across populations and settings) sometimes do not mirror those seen in *efficacy* studies (controlled, complex, and more standardized). Generally, there is much more known about the efficacy of treatments than their effectiveness in the real world. As such, recent reports have highlighted the gap between efficacy and effectiveness research as well as the pivotal role of observational studies to help bridge this gap.

General aims and outline

The first aim of this thesis is to examine the comparative *effectiveness* of LF, PNA and CCH – three treatments that have already been demonstrated to be *efficacious* (Part I). The second aim is to examine LF from the patient perspective by using patient satisfaction as the primary outcome (Part II). A third aim is to examine the long-term efficacy of PALF and compare it with that of LF (Part III). The fourth and last aim is to clarify the extent to which the number of procedures a surgeon performs annually for Dupuytren's disease is associated with his or her surgical outcomes (Part IV). This thesis is therefore structured accordingly as seen on the next page.

Part I. Comparative Effectiveness

PNA vs. LF. It has been more than a decade since the only randomized trial to date was published that compared the efficacy of PNA and LF.[18] In the next chapter (Chapter 2), the aim was to compare the real-world effectiveness of both treatments because the results of such a comparison can support patients in their decision-making.

CCH vs. LF. CCH is now considered an efficacious and safe treatment for Dupuytren's contracture.[50] The aim in Chapter 3 was to compare CCH with LF in terms of both objective and subjective outcomes. A secondary aim was to validate propensity score matching as a tool that enables valid comparisons between two treatments for Dupuytren's disease using observational data.[51]

CCH vs. PNA. In Chapter 4, our aim was to compare CCH with PNA because of proposed similarities and characteristics between the two treatments. Our secondary aim was to focus on possible differences between the two minimally invasive treatments in terms of impact on specific domains in hand-function as well as objective outcomes such as degree of contracture and complications.

Part II. Patient Satisfaction

In Chapter 5, we sought to examine patient satisfaction with hand function after surgical fasciectomy for Dupuytren's contracture and determined which preoperative patient- and disease-specific factors predicted this satisfaction.

Part III. Long-Term Comparative Efficacy of PALF

In Chapter 6, the aim was to report the long-term results of a randomized, controlled, single-blinded clinical trial comparing the efficacy of PALF with LF.[42]

Part IV. Volume and Outcomes

In Chapter 7, we aimed to clarify the possible relations between annual surgeon procedure volume and three important objective outcomes of Dupuytren's surgery among a group of fully practicing hand-surgeons.

1

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Part **I**

COMPARATIVE EFFECTIVENESS

2

Comparative Effectiveness Of Percutaneous Needle Aponeurotomy And Limited Fasciectomy For Dupuytren's Contracture: A Multicenter Observational Study

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Abstract

Background: Percutaneous needle aponeurotomy is a less invasive surgical alternative to limited fasciectomy for Dupuytren's contracture, but appeared less efficacious in a previous randomized clinical trial. This study compared the effectiveness of both techniques in contemporary clinical practice.

Methods: The authors evaluated prospectively gathered data from all patients who were treated with percutaneous needle aponeurotomy or limited fasciectomy between 2011 and 2014 at six hand surgery practice sites in The Netherlands. The degree of total active extension deficit, Michigan Hand Outcomes Questionnaire subscores, and complications evaluated at 6 to 12 weeks after treatment were compared after propensity score-based inverse-probability weighting to account for the differences in baseline characteristics between the treatment groups.

Results: After inverse-probability weighting, 78 percutaneous needle aponeurotomy patients and 103 limited fasciectomy patients remained with similar characteristics (88 percent Tubiana grade I or II). The degree of total residual extension deficit at follow-up was similar between the weighted groups (percutaneous needle aponeurotomy, 21 degrees; limited fasciectomy, 18 degrees; p = 0.330). Furthermore, percutaneous needle aponeurotomy was associated with a lower mild complication rate (percutaneous needle aponeurotomy, 5.2 percent; limited fasciectomy, 24.3 percent; p < 0.001) and larger increases in the subdomain scores of satisfaction (p < 0.001), work performance (p < 0.001), activities of daily living (p = 0.009), and overall hand function (p = 0.001).

Conclusions: This multicenter observational study found that, among patients with mildly to moderately affected digits, percutaneous needle aponeurotomy reduced contractures as effectively as limited fasciectomy does in clinical practice. Furthermore, percutaneous needle aponeurotomy provided a more rapid functional recovery and had a lower rate of mild complications.

2

Introduction

Although novel techniques for treating Dupuytren's contracture, such as collagenase injection[1], have emerged, surgery remains the mainstay of treatment. Two of the most commonly used surgical techniques are Limited Fasciectomy (LF) and Percutaneous Needle Aponeurotomy (PNA). LF continues to be the most established technique for proximal interphalangeal joint (PIP) contractures and advanced cases. PNA is an accepted surgical alternative to LF that seeks to minimize complications and morbidity.

Questions, however, persist regarding the comparative effectiveness of PNA and LF. Numerous studies have described the results for each technique separately but recent reviews of these studies have underscored the complexity of making meaningful comparisons because of differences in study populations and definitions for outcomes.[2-4] To date, there has been one randomized clinical trial comparing PNA and LF.[5] In this study, PNA resulted in 18% less reduction in total passive extension deficit evaluated at 6 weeks postoperatively, primarily due to PNA's inferior efficacy for advanced cases. As a consequence, the authors concluded that PNA seemed particularly useful for treating patients with mild to moderate disease.

As of this writing, nearly a decade has past since the publication of the abovementioned trial, which should have allowed sufficient time to pass for its findings to disseminate into contemporary practice. This study compared the effectiveness of PNA and LF using prospectively gathered data from 6 different hand surgery practice sites in the Netherlands.

Methods

This is a retrospective study of data from a consortium of 6 hand surgery practice sites. Data were gathered in a registry that was developed for research and quality improvement purposes, and included a wide range of patient and treatment characteristics. Patient characteristics included age, gender, comorbidities, bilateral and recurrent disease, and family history. Treatment characteristics included the technique used, digits treated and the joint levels affected. Our institutional review board approved the study protocol and waived the requirement for informed consent due to the retrospective nature of the study.

For this study, all patients who underwent PNA or LF between October 2011 and March 2014 at one of the practice sites were identified. We restricted our analyses to patients with available pre-operative data on the degree of contracture. There were no significant differences in the characteristics of patients with and without data available. In addition, we excluded patients with thumb contractures, isolated MP contractures with less than 20 degrees of contracture who were treated for other purposes than functional disability, and those with a concomitant hand condition or simultaneously undergoing another procedure (e.g. carpal tunnel release) on the treated side to prevent confounding of outcome assessments. Patients treated for recurrent disease were included if they met all other criteria.

Treatments

Treatments were performed by one of the 17 hand surgeons of the practice sites through shared decision-making.

LF was performed in an operating theatre with tourniquet exsanguination and loupe magnification under axillary block or general anesthesia. Cords were excised after Bruner type or longitudinal incisions with Z-plasties. Care was taken to prevent injury to the digital neurovascular bundles. Compressive dressings were applied for 2 weeks. All patients were offered a supervised program of hand therapy with instructed use of removable night splints for 3 months.

PNA was performed under local anesthesia. Cords were released using 25 gauge needles at as many levels as possible in the palm and fingers. Patients were instructed to report paresthesias to avoid nerve injury. After release, the treated digit was extended

with a progressive force to maximize contracture reduction. Patients were encouraged to flex and extend their fingers immediately following treatment and to restart normal use of their hands after 24 hours. Patients were offered identical rehabilitation and splinting programs as patients undergoing LF.

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Outcomes

The primary outcome was the degree of total residual extension deficit. Certified hand-therapists examined patients before and at visits occurring between 6 and 12 weeks after surgery. The degree of extension deficit was assessed using a finger goniometer by summing up the degree of active extension deficit at the MP, PIP and DIP joint levels for each affected digit. Hyperextension at the individual joints was defined as 0 degrees to prevent underestimation of extension deficit. To increase comparability between patients with single versus multiple digit involvement, we used data from the digit that was most severely affected at baseline (e.g. highest total extension deficit).

The impact of PNA and LF on patient-reported hand function was assessed using the Michigan Hand Questionnaire (MHQ). The MHQ is a self-reported 37-item hand-specific assessment tool evaluating 6 aspects of hand function for each hand separately: overall hand function, ability to perform activities in daily life (ADL), work performance, aesthetics, pain and satisfaction. It is thoroughly developed and well-validated for Dupuytren's disease.[6-8] Scores range from 0(poorest function) to 100(best function). Because functional restoration was considered the primary treatment objective, we excluded all pain outcomes from our analysis. Only the outcomes pertaining to the treated side were considered.

Treatment-related complications were prospectively documented and classified into a mild (neuropraxia, skin fissure, scar and wound healing sequelae) and a serious category (nerve laceration, uncorrectable contracture, wound infection requiring antibiotic treatment, arterial laceration, tendon rupture, cold intolerance, palmar or digital hematoma).

Statistical analyses

Sample size

Sample-size calculations showed that a total number of 144 patients (72 each group) would provide 85% power (β=0.15, α=0.05) to detect a 5° difference in total extension deficit between the treatment groups with the use of two-sided tests.

Adjustment for between-group differences in baseline characteristics

We anticipated differences in the baseline characteristics between the PNA and LF groups because we expected LF to be the preferred treatment for advanced cases. Such differences in the factors that influence the treatment decision between both treatments threaten the validity of a comparison due to treatment selection bias. Propensity score analyses provide a statistical approach for investigators to minimize this form of bias by accounting for the differences in such factors, given that there are patients who are suitable candidates for both techniques.[9-11] The assumption that there are PNA patients who could have been treated with LF and vice versa is likely met, as decisions often depend on patient preference.[12] In the present study, the propensity score is defined as the probability of undergoing PNA based on factors influencing the decision between LF and PNA, including age, primary or recurrent disease, the number of digits affected, the joint levels affected and the degree of extension deficit at these joints. To calculate this probability (propensity score), we used multivariate logistic regression modeling with the pretreatment factors as independent variables and treatment technique as the dependent variable. To minimize the risk of further bias[13,14], we also included possible confounders of the relation between treatment and outcomes, including gender[15], diabetes, smoking status, bilateral and familial history of the disease.

As PNA and LF were the two treatments available, the probability of receiving LF is 1 minus the probability of undergoing PNA (inverse probability) and vice versa. Patients with a high-probability of undergoing LF would therefore have a low-probability of undergoing PNA and vice versa. By weighting patients based on the inverse of their propensity score, patients with a similar probability of undergoing PNA and LF receive more weight while those with a high-probability of undergoing either treatment receive less weight. Consequently, patients with similar baseline characteristics are weighted more than those with dissimilar characteristics, thus resulting in more balanced treatment groups.

Propensity-score based inverse probability weighting was used as the primary method to account for the between-group differences. To verify whether the groups were indeed more balanced afterwards, we compared the groups before and after this approach. As compared with propensity-score based matching approaches, inverse probability weighting minimizes the exclusion of patients, thereby increasing the ability to generalize from the results.[13,14]

Comparison of outcomes

Baseline characteristics were compared using Pearson chi-square tests for categorical variables and Student's t-tests for continuous variables. To compare the degree of total residual contracture and MHQ scores at follow-up among the treatment groups, we used repeated measures analyses of variance with the treatment group as a between-subjects factor. To compare complication rates of mild and serious complications, we used using Pearson chi-square or Fisher's exact tests.

To test the robustness of our findings, we performed additional sensitivity analyses using data from patients in the PNA and LF groups who did not have severe PIP contractures (defined as >40 degrees extension deficit).[16] This approach assumes that having a severe PIP contracture is the only factor influencing the decision between NA and LF that should be accounted for. Descriptive statistics are presented as percentages for categorical variables and as means ±SD for continuous variables. Significance thresholds were set at p≤0.05.

Results

There were a total of 368 patients who underwent PNA (25%) or LF (75%) for Dupuytren's contracture between 2011 and 2014. After applying the eligibility criteria, 293 patients remained to form the study sample. Of these, 78 patients (27%) underwent PNA and 215 patients (73%) underwent LF (Figure 1).
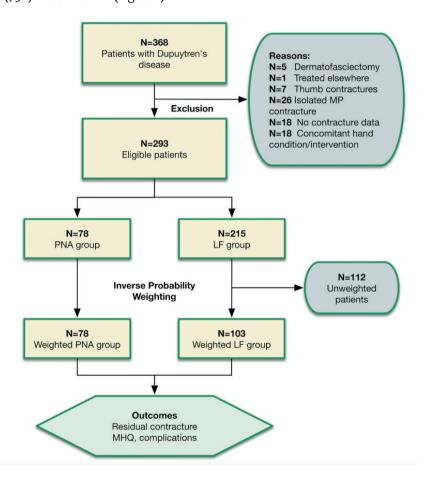
Figure 1. Patient selection flowchart. PNA; Percutaneous needle aponeurotomy, LF; Limited fasciectomy

Table 1 shows the baseline characteristics of the study sample before and after inverse probability weighting. Before weighting, PNA patients had, on average, fewer affected digits, 14° less total extension deficit, less advanced PIP joint contractures, and were more likely to have primary disease, demonstrating that LF was the preferred technique for advanced cases. The PNA group also had relatively more women.

Table 1. Baseline characteristics before and after inverse probability weighting, by treatment group.*

	Not Weighted			Weighted		
	PNA	**LF**	**p**	**PNA**	**LF**	**p**
	(N=78)	(N=215)		(N=78)	(N=103)	
Demographics						
Age –yrs.	65±8	63±9	0.103	65±8	65±8	0.837
Male gender –%	68	81	0.014	68	72	0.571
Diabetes –%	18	8	0.014	18	10	0.106
Current smoker –%	14	14	0.974	14	10	0.361
Disease Characteristics						
Bilateral disease –%	47	57	0.157	47	52	0.592
Recurrent disease –%	19	36	0.006	19	28	0.166
Positive family history –%	49	47	0.792	49	53	0.533
No. digits affected			0.009			0.600
1 –%	64	45		64	60	
2 –%	23	29		23	28	
>2 –%	13	26		13	12	
Outcomes						
Extension deficit† – degrees						
Total	60±28	74±37	0.003	60±28	62±26	0.702
MP joint level	38±29	25±25	<0.001	38±29	40±24	0.740
PIP joint level	19±19	41±28	<0.001	19±19	19±22	0.957
DIP joint level	3±8	7±12	0.001	3±8	3±9	0.736

* Plus-minus values are means ±SD.
† Values are reported for all joints.
PNA, Percutaneous Needle Aponeurotomy; LF, Limited Fasciectomy; MP, metacarpophalangeal; PIP, proximal interphalangeal; DIP, distal interphalangeal; SD, standard deviation.

After inverse probability weighting, all baseline characteristics were well-balanced among the treatment groups (Table 1). This was in part due to 112 LF patients (52%) with such a high probability of receiving LF that they received a weight of zero in further analyses (Figure 1). These patients, as compared with the other weighted patients, had, on average, 21 degrees more total extension deficit preoperatively, more advanced PIP and DIP contractures, and 8 degrees worse residual contracture postoperatively, further demonstrating that LF was used for patients with advanced disease and the need to account for such differences.

Among the weighted treatment groups, the mean age was 65 years. The majority of digits involved (88%) were Tubiana grade I (<45°) or grade II (45°-90°), 10% grade III (90°-135°) and 2% grade IV (>135°). The majority of digits had isolated MP contractures (42%) or contractures of both the MP and the PIP joint (37%). Eleven percent of digits had
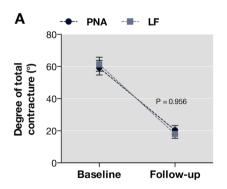
an isolated PIP contracture. The remaining digits had a DIP contracture combined with an affected PIP joint (6%), MP joint (2%) or a contracture spanning all three joints (3%).

All patients in the weighted groups had follow-up data available on the degree of total residual extension deficit and complications. The average follow-up duration was 10 weeks (range, 6–12 weeks) and similar between groups (P=0.891). Sixty-seven percent of the PNA patients as compared to 83% of the LF patients completed the MHQ at follow-up with no differences in the baseline characteristics between those who did and did not complete the MHQ.

Residual contracture

Among the weighted treatment groups, the degree of total residual extension deficit at follow-up was not significantly different (PNA, 20° vs. LF, 18°; Figure 2A), which corresponded with an improvement from baseline of 66% (39°) for PNA and 71% (43°) for LF (Figure 2B).
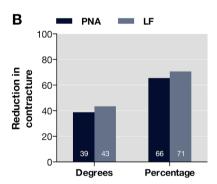
Figure 2. Degree of total contracture (total active extension deficit) in the weighted PNA and LF groups at baseline and follow-up (A). Means and standard errors are plotted. Corresponding improvement in contracture expressed in absolute degrees and percentual improvement from baseline (B). PNA; Percutaneous needle aponeurotomy, LF; Limited fasciectomy.

When separately evaluating MP from PIP contractures, the degree of residual extension deficit was not significantly different among the weighted groups for neither the affected MP joints (PNA, 10° vs. LF, 8°; Figure 3A) nor affected PIP joints (PNA, 18° vs. LF, 13°; Figure 3B).
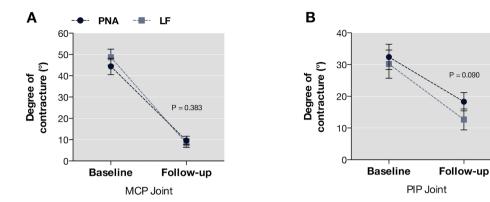
Figure 3. Degree of contracture (active extension deficit) for affected MCP (A) and affected PIP (B) joints in weighted PNA and LF groups at baseline and follow-up. Means and standard errors are plotted. MCP; metacarpophalangeal, PIP; proximal interphalangeal, PNA; percutaneous needle aponeurotomy, LF; Limited fasciectomy.

Patient-reported outcomes

Significantly larger improvements in the MHQ subscore of satisfaction, work performance, ADL, and overall hand function were found in the weighted PNA group as compared with the weighted LF group (Figure 4). However, the hand appearance subscore showed a similar improvement.
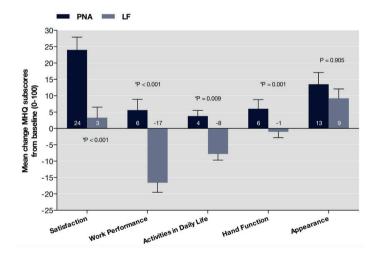
Figure 4. Change in MHQ scores in the weighted PNA and LF groups at follow-up from baseline. Asterisks (*) denote significant differences among the adjusted treatment groups. PNA; percutaneous needle aponeurotomy, LF; Limited fasciectomy.

Complications

Table 2 compares complication rates among the weighted groups. Although the rate for serious complications did not significantly differ among the groups (PNA, 2.6% vs. LF, 1.7%), mild complications occurred significantly less frequently after PNA than after LF (PNA, 5.2% vs. LF, 24.3%).

Table 2. Complications rates in the inverse probability weighted PNA and LF groups.*

| Complication	PNA (N=78)	LF (N=103)	P value
Serious			0.579
Nerve Laceration	1.3	0.0	
Uncorrectable contracture	1.3	0.0	
Wound infection	0.0	1.3	
Arterial Laceration	0.0	0.0	
Tendon Rupture	0.0	0.0	
Cold Intolerance	0.0	0.0	
Hematoma	0.0	0.0	
Extensive edema	0.0	0.4	
Mild			
Neuropraxia	2.6	17.4	
Scar sequelae	0.0	4.9	
Skin Fissure	2.6	0.0	
Wound healing	0.0	1.9	<0.001

* Values are percentages.
PNA, Percutaneous Needle Aponeurotomy; LF, Limited Fasciectomy.

Recurrence subgroup

Comparing only patients who were treated for recurrent disease among the weighted groups, there was no significant difference in the baseline degree of total extension deficit. The degree of total residual extension deficit at follow-up was also not significantly different between the recurrence subgroups (PNA, 24° vs. LF, 18°; P=0.101).

Sensitivity analyses

Sensitivity analyses performed using data from 65 PNA and 95 LF patients without severe PIP contractures yielded similar results for the outcome comparisons. However, the two groups differed in several baseline characteristics, indicating that inverse probability weighting achieved more balance and thus more precise inferences about the treatment effects.

Discussion

Interest in comparative effectiveness research has exploded in recent years, because the results from such studies may better reflect real-world practice than those obtained by strictly controlled clinical trials.[17,18] The purpose of this multicenter study was to compare the effectiveness of PNA and LF for treating Dupuytren's contracture in contemporary clinical practice. We found that both techniques provided a similar degree of contracture reduction among patients who have mild to moderately affected digits. These findings were similar when separately evaluating affected MP joints from affected PIP joints. However, PNA was associated with larger improvements in most MHQ subscores and a significantly lower rate of mild complications.

Despite that PNA has become an accepted treatment for Dupuytren's contracture, questions persist regarding its effectiveness as compared with LF. To date, there has been one randomized clinical trial comparing the efficacy of the two treatments.[5] In this trial, PNA achieved 18 percent less reduction in total passive extension deficit than LF assessed at 6 weeks postoperatively. However, subgroup analyses indicated that this difference was primarily due to PNA's inferior results for more advanced cases, while similar results were found for those graded as Tubiana I and II. Hence, the authors concluded that PNA seemed particular useful as a treatment for patients with mild to moderately severe contractures. The similar degree of contracture reduction achieved among the two treatment groups in this study consisting of primarily (88%) of Tubiana grade I and II patients demonstrates that PNA was indeed used to treat patients with less advanced disease at the practice sites involved, and appeared as effective as LF at reducing contractures in contemporary practice.

The evaluation of changes in MHQ subscores following treatment allowed comparison of the early impact of PNA and LF on different aspects of hand function. Larger improvements in the subscores of overall hand function, satisfaction, work performance and ADL were found in the PNA group, which primarily shows that the technique restores hand function more rapidly than LF does and highlights its less invasive nature. The similar improvement in the subscore of hand appearance among the treatment groups suggests that both treatments help to address concerns patients may have about the appearance of their hand.[19]

The significantly lower rate of mild complications after PNA than after LF is consistent the findings of previous reports[20] and related to the high rate of neuropraxia found in the LF group. With the exception of neuropraxia, all other complications were unique to each treatment group. Although the low incidence of complications in this study merits careful interpretation, this finding is in line the clinical observation that complications arise as a consequence of the nature of the technique. For example, the reported skin fissures are likely to have occurred because of the percutaneous and blind nature of PNA, whereas the scar and wound healing sequelae found in the LF group can be expected from any open surgical technique. Until sufficiently powered studies are performed directly comparing the risk profile of both techniques among comparable patients, we feel that both the differences in mild complication rates and the type of complications occurring after PNA and LF may be informative for patient counseling.

Strengths of this study include the of inverse probability weighting to account for the differences in baseline characteristics to minimize bias. This approach allowed comparison of the effectiveness of PNA and LF in actual clinical practice using data from 6 practice sites that were prospectively gathered by therapists who had no knowledge of this study. Although both treatment groups were well-balanced after inverse probability weighting, however, the possibility remains for unobserved confounding factors to have influenced our findings, such as patients' genetic constitution.[21] Another limitation was that a substantial proportion of patients who underwent LF for advanced PIP and DIP joint contractures were not weighted in the analyses, thus our findings do not apply to such patients.

The largest drawback of this study is its short follow-up duration. Although this allowed for a comparison of short-term outcomes, recurrence rates may be just as important to patients when selecting between treatments.[12] Considering that PNA has become the preferred technique for less severe cases in contemporary practice, there is a need for long-term studies assessing whether the previously reported 64% higher recurrence rate at 5 years as compared with LF is still accurate.[22]

The present study provides information that may be used to help Dupuytren's disease patients and clinicians decide between PNA and LF. It shows that PNA, in the short-term, reduces mild to moderately affected digits as effective as LF does in routine practice, confirming recent recommendations that PNA has most value as a first-line

treatment.[23,24] Furthermore, PNA provided a faster functional recovery and had a lower rate of mild complications. Besides an evaluation of treatments, this study highlights inverse probability weighting as a useful and feasible tool in assessing the comparative effectiveness of different treatment techniques for Dupuytren's disease.[25]

This approach could be of increasing importance considering the expanding number of treatment strategies for Dupuytren's disease, many of which may never be compared to each other in randomized clinical trials.

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Collagenase Clostridium Histolyticum versus Limited Fasciectomy for Dupuytren's Contracture: Outcomes from a Multicenter Propensity Score Matched Study

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Abstract

Background: Controversy exists about the relative effectiveness of injectable collagenase (collagenase clostridium histolyticum) and limited fasciectomy in the treatment of Dupuytren's contracture. The authors compared the effectiveness of both techniques in actual clinical practice.

Methods: This study evaluated all subjects treated with collagenase clostridium histolyticum or limited fasciectomy for metacarpophalangeal and/or proximal interphalangeal joint contractures between 2011 and 2014 at seven practice sites. The authors compared the degree of residual contracture (active extension deficit), Michigan Hand Outcomes Questionnaire scores, and adverse events at follow-up visits occurring between 6 and 12 weeks after surgery or the last injection with the use of propensity score matching.

Results: In 132 matched subjects who were treated with collagenase (n = 66) or fasciectomy (n = 66), the degree of residual contracture at follow-up for affected metacarpophalangeal joints was not significantly different (13 degrees versus 6 degrees; p = 0.095) and affected proximal interphalangeal joints had significantly worse residual contracture in the collagenase group compared with those in the fasciectomy group (25 degrees versus 15 degrees; p = 0.010). Collagenase subjects experienced fewer serious adverse events than did fasciectomy subjects and reported larger improvements in the Michigan Hand Outcomes Questionnaire subscores evaluating satisfaction with hand function, activities of daily living, and work performance.

Conclusion: This propensity score-matched study showed that collagenase clostridium histolyticum was not significantly different from limited fasciectomy in reducing metacarpophalangeal joint contractures, whereas proximal interphalangeal joint contractures showed slightly better reduction following limited fasciectomy. Collagenase provided a more rapid recovery of hand function than did fasciectomy and was associated with fewer serious adverse events.

Introduction

Dupuytren's disease is an incurable fibro-proliferative disease involving the palmar fascia of the hand. Abnormal deposition of collagen initially leads to the formation of palpable palmar nodules. As the disease progresses, cords typically develop that cause flexion contractures at the affected finger joints. Ultimately, these contractures can severely impair hand function and diminish quality of life.[1]

Collagenase Clostridium Histolyticum (CCH), which selectively disintegrates collagen, is a recently popularized enzymatic treatment option for Dupuytren's contracture.[2] The technique involves the injection of a small volume of collagenase solution into the pathologic cord(s), thus weakening the treated areas to allow for subsequent rupture by manipulation of the contracted finger. While several large clinical trials have demonstrated the efficacy[2] (N=308) and safety[3] (N=587) of the injections, these studies were placebo-controlled[4], and therefore do not provide evidence on the relative effectiveness of CCH and the available surgical techniques.

Limited fasciectomy (LF) remains the most widely accepted surgical standard of care for Dupuytren's disease. As of this writing, few studies have directly compared LF with CCH: the only two comparative studies we are aware of reported that the two techniques were similar in reducing joint contractures.[5,6] However, these studies had relatively small sample sizes (N=46 in the largest study), which may have precluded the authors from finding significant differences due to limited statistical power. Another weakness inherent to such observational studies relates to the risk of confounding by indication. Since the choice of performing CCH and LF is partly influenced by patient and clinical characteristics, such as diathesis factors, the severity of the disease, and the joint levels involved, these should be accounted for to ensure valid comparisons between treatment groups.

The purpose of this study was to directly compare the early clinical results of CCH and LF while minimizing the risk of confounding by indication bias with the use of propensity score matching. Propensity score matching is a statistical approach that allows investigators to account for a large number of observed confounding variables, and is particularly useful in circumstances where randomized treatment allocation is unfeasible or unethical.[7] Since randomized clinical trials evaluating CCH versus LF are

currently lacking, this approach allowed for a timely comparison of the effectiveness of both techniques in reducing contractures and restoring hand function in actual clinical practice.[8]

Methods

After approval of the study by the Medical Ethics Committee of the Erasmus MC, all subjects with Dupuytren's disease undergoing CCH and LF between August 2011 and March 2014 at 7 practice sites in the Netherlands were identified using a prospectively maintained database.

Patient characteristics derived from this database were age, gender, hand dominance, and comorbidities. Disease specific characteristics included bilateral presence of the disease, primary versus recurrent disease, family history of Dupuytren's disease. In case data were missing from the database, electronic health records were abstracted.

Subjects with the diagnosis of Dupuytren's disease, who were 18 years or older, and with the ability to complete the study questionnaires in Dutch were included in the study. Exclusion criteria included multiple finger involvement, concomitant hand conditions or interventions (e.g., carpal tunnel release) on the affected side, and the lack of baseline data on the degree of contracture. Subjects undergoing revision treatment for recurrent disease were included if other eligibility criteria were met. This study was conducted in accordance with the declaration of Helsinki.

Treatments

Treatments were performed as part of routine care by the hand surgeons of the 7 sites through shared decision-making.

CCH was administered according to manufacturer instructions, without local anesthesia. Injections were limited to 0.25mL and 0.20 mL for MP and PIP joint contractures, respectively. Compressive dressings were applied afterwards. Treated fingers were manipulated after 24 to 72 hours to attempt rupturing of the weakened cords under local anesthesia. Up to 3 injections were offered at 4 week-intervals if subjects were dissatisfied with the achieved level of contracture correction but were not mandatory.

LF, which is the preferred technique for treating Dupuytren's disease in the Netherlands[9], was performed with tourniquet exsanguination and loupe magnification under axillary block or general anesthesia in an operating theatre. Cords were approached and excised after Bruner type or longitudinal incisions with Z-plasties. Care was taken to prevent injury to the digital neurovascular bundles. Compressive dressings were applied for 2 weeks. All patients were offered a similar supervised program of hand therapy with instructed use of removable night splints for 3 months.

Outcome Assessments

The primary outcome of this study was the degree of residual contracture assessed at follow-up visits occurring between six and twelve weeks after surgery or the last injection. Certified hand therapists performed goniometry to determine the degree of active extension deficit at baseline and follow-up according to a standardized assessment protocol. Hyperextension was classified as 0° to prevent underestimation of extension deficit.

Secondary outcomes assessed included whether affected joints achieved clinical improvement (defined as a greater than 50% reduction from baseline contracture) adverse events, and self-reported hand function assessed using the Michigan Hand Outcomes Questionnaire (MHQ). The MHQ is a self-reported functioning scale consisting of 37 items evaluating 6 functional subdomains for each hand separately: overall hand function, ability to perform activities in daily life (ADL), work performance, aesthetics, pain and satisfaction with hand function. The MHQ has been rigorously designed and used for a variety of hand conditions[10] including Dupuytren's disease.[11,12] Scores range from 0 (poorest function) to 100 (best function). Because functional restoration was considered the primary treatment objective, we excluded all pain outcomes from our analysis. Only the outcomes pertaining to the treated side were used.

Adverse events were graded based on their severity into two categories: serious (non-transient or requiring an intervention) and mild (transient or not requiring an intervention).

Given the increasing clinical and policy implications of patient satisfaction data[13], we performed a post-hoc analysis of the specific items that constitute the satisfaction

subdomain of the MHQ. These items examine satisfaction with overall hand function, finger motion, wrist motion, hand strength, and sensation, and are assessed using a 5-point Likert scale, with possible answers ranging from "very satisfied" (1 point) to "very dissatisfied" (5 points). Subjects who rated their satisfaction as "very satisfied" (1 point) or "somewhat satisfied" (2 points) were classified as "satisfied" and all others as "dissatisfied".

Statistical Analysis

Continuous variables were reported as means ±SD and categorical variables were summarized with the use of frequencies. Sample-size calculations revealed that a total number of 32 MP contractures (16 each group) and 70 PIP contractures (35 each group) would provide 80% power ($\beta = 0.20$, $\alpha = 0.05$) to detect a 10° difference in residual contracture between the two treatment groups with the use of two-sided tests.

Propensity score matching was used to minimize the risk of confounding by indication bias.[14] The propensity score was defined as the probability of receiving CCH conditional on 8 baseline factors. We used logistic regression modeling to estimate a score for each subject with the treatment type as the independent variable and the following baseline variables as dependent variables: age, gender, family history of Dupuytren's disease, bilateral involvement, recurrent disease, and the degree of contracture at the three joint levels. The scores were then used to match CCH subjects to LF subjects on a 1-to-1 basis using a nearest-neighbor algorithm while allowing for a matching tolerance width of 0.2SD of the logit of the propensity score. We excluded unmatchable subjects from further analysis. To examine whether the matching approach improved balance among the matched treatment groups, significance testing was performed.

For joint contracture and MHQ outcomes, we used a mixed-models repeated measures approach to compare the change from baseline with least-square means and corresponding standard errors plotted graphically. An advantage is that this approach estimates missing values and accounts for the within-subject dependency of the repeated measures.[15,16] Joint contracture was evaluated separately for affected MP and PIP joints.

Our primary outcome analysis included all affected joints. However, in some CCH subjects with two affected joints in the same finger one of the contractures was specifically treated with CCH (mostly MP) because the degree of contracture of the other affected joint was improved to such an extent that further injections were deemed unnecessary.[2] To assess whether the inclusion of all affected joints in our analysis influenced our results, we performed a subgroup analysis of only the primary targeted joint contractures.

The incidence of serious adverse events was compared between the groups using a Fisher's exact test. Mild adverse events were not compared because many of these were considered to be CCH specific or a natural consequence of surgery.

Significance thresholds were set at $P<0.05$. Statistical analyses were performed using R (version 2.14) and SPSS (version 20.0).

Results

There were a total of 397 subjects with Dupuytren's disease who were treated with CCH or LF by one of the 15 surgeons of the practice sites. To improve comparability among the two treatment groups, 36% of the subjects who underwent LF for contractures involving multiple fingers were excluded. After exclusion of another 9% of subjects due to the other criteria, there remained a total of 218 eligible subjects of whom 48% were treated with CCH and 52% with LF (Figure 1).
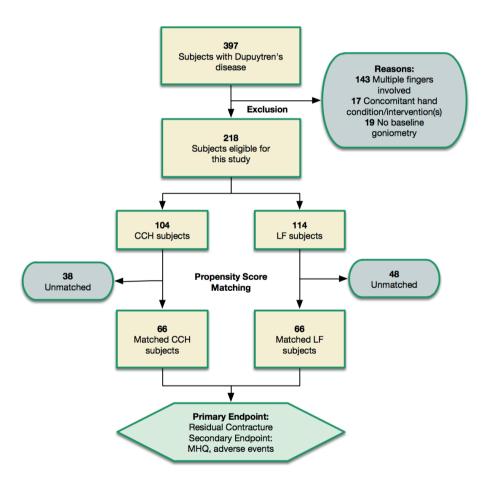

Figure 1. Subject selection flowchart. Clostridium Collagenase Histolyticum; LF, Limited Fasciectomy; MHQ, Michigan Hand Outcomes Questionnaire.

Table 1 shows the baseline characteristics of the study sample before and after propensity score matching. Before matching, the CCH group had relatively milder PIP and DIP joint contractures but worse MP joint contractures. Additionally, the proportion of subjects treated for recurrent disease was smaller in the CCH group and the distribution of the involved fingers was different.

Table 1. Baseline characteristics before and after propensity score matching, by treatment group.*

	All Subjects			Matched Subjects		
	CCH (N=104)	LF (N=114)	p	CCH (N=66)	LF (N=66)	p
Demographics						
Age –yrs.	61±10	63±9	0.410	61±10	63±8	0.334
Male gender –%	80	81	0.868	82	76	0.394
Diabetes –%	3	9	0.087	6	5	0.698
Current tobacco use –%	9	16	0.090	8	15	0.170
Disease Characteristics						
Recurrent disease –%	26	38	0.063	33	30	0.709
Bilateral disease –%	85	83	0.797	89	89	1.000
Treated side is dominant –%	58	53	0.453	53	61	0.380
Positive family history Dd –%	54	60	0.388	59	49	0.222
Treated finger			0.003			0.789
Little –%	48	72		55	61	
Ring –%	37	24		33	32	
Other –%	15	4		12	8	
Outcomes						
Contracture† –degrees						
MP joint	29±24	19±27	0.002	26±25	23±25	0.632
PIP joint	22±25	44±27	<0.001	27±26	33±25	0.221
DIP joint	1±4	8±14	<0.001	1±14	2±14	0.547
Total MHQ score (0-100)	75±14	74±15	0.844	77±13	75±14	0.545

Plus-minus values are means ±SD.
† Values are reported for all joints.
CCH, Collagenase Clostridium Histolyticum; LF, Limited Fasciectomy; Dd, Dupuytren's disease.

Using propensity scores, we were able to match 66 CCH subjects with mean baseline contractures of 39° degrees for 43 affected MP joints and 41° for 43 affected PIP joints to 66 LF subjects with mean baseline contractures of 39° degrees for 39 affected MP joints and 41° for 52 affected PIP joints with similar characteristics.

Ninety-six percent of affected joints in the matched LF group had follow-up data available as compared to 80% in the matched CCH group. Follow-up duration for the

treatment groups was on average 11 weeks (range, 6–12 weeks) and was not significantly different between groups.

Joint Contracture

For affected MP joints, the degree of residual contracture (CCH, 13° vs. LF, 6°; Figure 2A) at follow-up and the proportion of joints achieving clinical improvement (Figure 3) were not significantly different among the matched treatment groups.
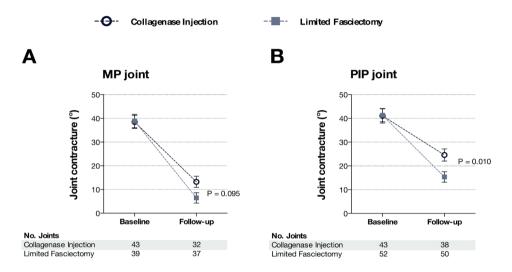
Figure 2. Degree of contracture for affected metacarpophalangeal (A) and proximal interphalangeal (B) joints in the matched collagenase injection and limited fasciectomy groups at baseline and follow-up. Least-square means and standard errors from a repeated measures model are plotted.
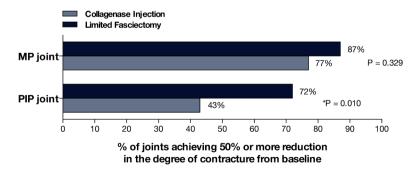

Figure 3. Percentage of affected joints meeting clinical improvement defined as more than 50% improvement from baseline in the degree of contracture.

For affected PIP joints, however, the degree of residual contracture was significantly worse in the CCH group than in the LF group (CCH, 25° vs. LF, 15°; Figure 2B). In line with this, relatively fewer affected PIP joints achieved clinical improvement in the CCH group than in the LF group (Figure 3).

Self-Reported Outcome

MHQ (sub)scores at baseline were similar among the matched treatment groups. CCH subjects reported significantly larger improvements than did LF subjects in the MHQ subdomain scores assessing satisfaction, ADL and work performance (Figure 4).

Change in MHQ score						
Collagenase Injection	19.8	2.3	2.4	7.7	3.6	4.4
Limited Fasciectomy	4.2	-3.5	-6.3	9.0	1.2	1.6
P Value	*0.003	*0.033	*0.029	0.821	0.506	0.363
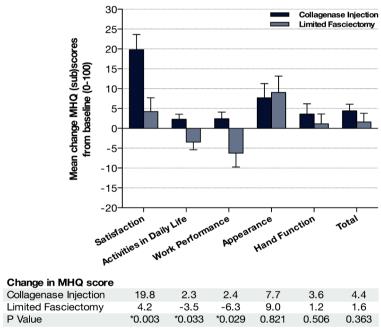
Figure 4. Change in MHQ scores in the matched collagenase injection and limited fasciectomy groups at follow-up as compared with baseline. Asterisks (*) denote significant differences between the matched treatment groups.

The proportion of subjects who were satisfied with each of the items that make up the satisfaction subdomain of the MHQ was similar between the matched treatment groups at baseline. The proportion of subjects who were satisfied with their finger mobility and hand function had similarly increased at follow-up among the two treatment

groups. However, as compared with LF subjects, more CCH subjects were satisfied with their hand strength and sensation (Figure 5).

Figure 5. The proportion of subjects who were satisfied with five specific items constituting the satisfaction subdomain of the Michigan Hand Questionnaire in the matched collagenase injection and limited fasciectomy groups at baseline and follow-up.
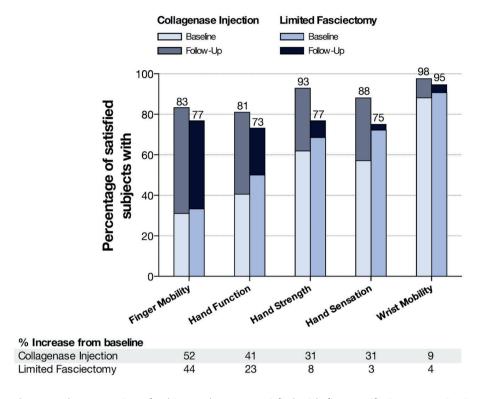
Adverse Events

Table 2 lists the adverse events noted in the matched groups, graded by severity.

Table 2. Adverse events, by matched treatment groups.*		
Adverse event	**CCH** (N=66)	**LF** (N=66)
Serious		
Tenosynovitis	0 (0)	3 (5)
Nerve Injury	0 (0)	1 (2)
Arterial Injury	0 (0)	0 (0)
Tendon Rupture	0 (0)	0 (0)
Cold Intolerance	0 (0)	0 (0)
CRPS	0 (0)	0 (0)
Mild		
Peripheral Edema	49 (74)	n.a.
Contusion	42 (64)	n.a.
Extensive	3 (5)	n.a.
Mild	39 (59)	n.a.
Pain in Extremity	17 (26)	n.a.
Blood Blister	9 (14)	n.a.
Skin Fissure	5 (8)	0 (0)
Paresthesia	3 (5)	3 (5)
Axillary Tenderness	6 (9)	n.a.
Erythema	3 (5)	n.a.
Wound Dehiscence	0 (0)	2 (3)
Pruritus	3 (5)	n.a.
Lymphadenopathy	2 (3)	n.a.
Neuropraxia	0 (0)	1 (2)
Flare Reaction	1 (2)	0 (0)
* Values are numbers (percentages).		
CRPS; Complex Regional Pain Syndrome; n.a. not assessed.		

All serious adverse events occurred after LF; three events of tenosynovitis requiring an intervention and one nerve injury were noted as compared with zero events after CCH (P=0.042). Arterial injuries, cold intolerance complaints and tendon ruptures were not seen in either of the matched groups.

Three of the most frequently noted mild adverse events after CCH were peripheral edema (74%), contusion (64%), and extremity pain (26%).

Subgroup Analysis of the Joints Affected by Recurrent Disease

Evaluating only the joints affected by recurrent disease, we found no significant differences in the baseline degree of contracture among the matched treatment, although affected MP joints were on average 8° worse in the CCH subgroup than in the LF subgroup.

Comparison of these two groups showed that while the degree of residual contracture at follow-up was not significantly different for affected MP joints (CCH, 19° vs. LF, 10°; Figure 6A), affected PIP joints in the CCH subgroup were significantly worse as compared with those in the LF subgroup (CCH, 33° vs. LF, 22°; Figure 6B).
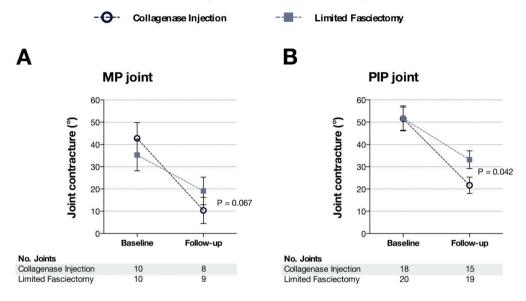
Figure 6. *Degree of contracture for metacarpophalangeal (A) and proximal interphalangeal (B) joints affected by recurrent disease in the matched collagenase injection and limited fasciectomy groups at baseline and follow-up. Least-square means and standard errors from a repeated measures model are plotted.*

Subgroup Analysis of Primary Targeted Joints

Evaluation of only the joints that were specifically targeted with CCH also showed a similar degree of residual contracture as compared to all affected MP joints in the LF group (data not shown). However, the PIP joint contractures that were specifically targeted with CCH showed significantly worse residual contracture as compared with the LF group.

Discussion

The aim of this study was to compare the effectiveness of CCH and LF while accounting for the baseline variables that contribute to treatment selection bias using propensity score matching.[17] Our primary finding was that the degree of residual contracture in the two treatment groups was not significantly different for contractures at the MP joint level, while affected PIP joints showed a relatively small but significantly worse residual contracture in the CCH group as compared with the LF group. Nevertheless, subjects in the CCH group reported larger functional improvements than did LF subjects at early follow-up, and experienced fewer serious adverse events.

Previous comparative studies on CCH have reported 10° of residual contracture for affected MP joints[6,18] of and 23°-26° for affected PIP joints[6,18] at early follow-up, which is similar to the 13° and 24° found in the present study. The 6° and 15° for affected MP and PIP joints found in our LF group is consistent with the 5° and 14° degrees reported at 6 weeks follow-up by van Rijssen and colleagues.[19] However, our finding that LF was superior to CCH for affected PIP joints contrasts the few available studies comparing the two techniques.[5,6] Although one retrospective study found that LF achieved an average of 9° more contracture reduction after examining a total number of 24 affected PIP joints, this difference was not significant.[18] The only other head-to-head study we are aware of, reported similar results after evaluating only 18 affected PIP joints.[6] In contrast, the present study included more subjects with PIP joint involvement and was therefore more powered to detect significant differences. Another reason may lie in the fact that the two procedures differ fundamentally: CCH is a closed technique which relies on enzymatic fasciotomy, whereas an open technique such as LF allows for extensive excision of the cord and the performance of ancillary surgical efforts, such as the division of the collateral ligaments, check-rein ligaments and occasionally the release of the volar plate, to maximize joint correction. However, it should also be noted that the results of in the CCH group reflect the injection technique as recommended by the manufacturer, that is, injecting only in one part of the cord. Injection into multiple areas, as recently suggested by Murphy and colleagues, may translate into better results at the PIP joint level and should be explored in future investigations.[8]

As compared with those who underwent LF, CCH subjects reported larger functional improvements in the MHQ subdomains assessing ADL, work performance and satisfaction with hand function at follow-up. As a recent study reported a gradual improvement in MHQ scores in the first year following LF[12], we believe that this finding primarily shows that hand function recovers more rapidly after CCH than after LF, which is consistent with what was previously reported by an observational study that used the DASH questionnaire[5].

This study has several limitations. While most previous reports evaluated only primary cases, our study included subjects with joints affected by primary as well as recurrent disease. Although our subgroup analysis of only the subjects with recurrent disease showed that the comparative effectiveness of the two techniques was similar to that of the overall groups, future studies with a larger number of recurrent cases are required to confirm these findings. Moreover, the relatively higher incidence of serious adverse events noted in the LF group warrants careful interpretation due to the small number of events, but is in line with a previous systematic review showing that CCH has a more favorable risk profile than LF.[20]

Another concern is that our study only evaluated early clinical results, leaving uncertainty about the durability of these outcomes. However, we decided on this approach because, as of this writing, few studies have directly compared CCH to LF in terms of their associated risks and their effectiveness in reducing contractures and restoring hand function. Although studies have shown acceptable long-term outcomes for each technique separately, meaningful comparisons have proven to be challenging due to the heterogeneity of their study samples and the wide variety of endpoints used.[21-24] Although there is some evidence suggesting that better original contracture corrections correspond to a lower risk of developing recurrence[25-27], a comparison of the two techniques in terms of recurrence and revision rates is urgently needed to provide patients and providers with more nuanced information required to improve clinical decision-making.

Finally, we acknowledge the inherent drawbacks of propensity score analyses. For example, our matching procedure only accounted for imbalance in observed variables whereas randomization, when properly conducted, would also account for the differences in possible hidden confounding factors such as patients' genetic constitution.

It also resulted in the exclusion of a sizeable proportion of subjects with more comparatively more advanced PIP joint contractures in the LF group to whom the results of this study do not apply.

Taken together, the findings of the present study suggest that CCH offers an alternative to LF for subjects with MP contractures and those with affected PIP joints who are willing to trade slightly better contracture correction for faster recovery of hand function and a lower risk of serious adverse events. Besides an evaluation of treatments, this study highlights the use of propensity-score matching methods for making inferences on the effectiveness of treatments for Dupuytren's disease in actual clinical practice. Future head-to-head studies are required to delineate the long-term effectiveness of CCH and the established surgical techniques, particularly for those subjects with multiple finger involvement and advanced PIP contractures.

3

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4

Comparative Effectiveness of Needle Aponeurotomy and Collagenase Injection for Dupuytren's Contracture: A Multicenter Study

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Abstract

Background: Although the efficacy of collagenase clostridium histolyticum (CCH) injections has been demonstrated by randomized clinical trials, the relative effectiveness of CCH remains uncertain. Our aim was to compare the outcomes of CCH with those of percutaneous needle aponeurotomy (PNA) in daily clinical practice.

Methods: We analyzed data from patients undergoing PNA or CCH between 2011 and 2014 at 7 practice sites in the Netherlands. We examined the degree of improvement in contracture and adverse effects at 6-12 weeks after surgery or the last injection. Additionally, we invited patients to complete the Michigan Hand Questionnaire before and at 6-12 months follow-up. To minimize the risk of bias, we used propensity score matching.

Results: Among 130 matched patients (93% Tubiana I or II) undergoing PNA (n = 46) and CCH (n = 84), improvement in contracture was similar: 26 degrees (65% improvement from baseline) for PNA versus 31 degrees (71%) for CCH for affected metacarpophalangeal joints (P = 0.163). This was 16 degrees (50% improvement) versus 17 degrees (42%) for affected proximal interphalangeal joints (P = 0.395), respectively. No serious adverse effects occurred in either of the 2 treatment groups. Of the mild adverse effects, only skin fissures and sensory disturbances were seen in both groups. Through 1-year follow-up, patients reported similar improvements in the overall Michigan Hand Questionnaire score (PNA 5.3 points versus CCH 4.9 points; P = 0.912).

Conclusion: In patients with mild contractures (Tubiana I or II), CCH was as effective as PNA in reducing contractures. Both treatments were safe and improved hand function to a similar extent in daily practice.

Introduction

Dupuytren's disease is an incurable proliferative disorder of the palmar fascia, characterized by the development of palmar nodules and cords.[1] Over time, the cords can contract and limit finger extension. Patients report a variable extent of functional impairment and diminished quality of life.[2,3]

Percutaneous needle aponeurotomy (PNA) and Collagenase *Clostridium Histolyticum* (CCH) have gained popularity as less-invasive treatment alternatives to limited fasciectomy – the current standard of care.[4-7] With PNA, originally popularized by French rheumatologists, surgeons use a hypodermic needle to release cords at multiple levels after which the affected finger is extended to improve contracture. With CCH, which selectively dissolves collagen, a small volume of collagenase solution is injected into the cords. This weakens the treated areas, allowing for subsequent release through forceful manipulation. To date, two randomized clinical trials have compared the two techniques, both reporting that their efficacy is comparable.[8,9] Nevertheless, the extent to which these results can be translated into clinical practice remains incompletely understood because the controlled conditions in such trials may not reflect clinical practice. Patients' choices, selection and compliance with treatment regimens in trials can differ substantially from that in actual practice, resulting in a discrepancy in the results achieved in trials versus those in practice.[10-12]

The aim of this study was to compare the outcomes of PNA and CCH in daily practice using data gathered at multiple practice sites in the Netherlands. We studied the impact of both treatments on the degree of contracture, different domains of hand function, and associated adverse effects.

Methods

Study design

This is a study of data compiled from two previous comparative studies[4,13] performed between 2011 and 2014 at 7 hand surgery practice sites in the Netherlands, including one academic institution and a consortium of 6 dedicated hand surgery sites.

Briefly, patients were eligible if they were adults with a diagnosis of primary or recurrent Dupuytren's disease, underwent PNA or CCH, and had contractures affecting the MCP and/or PIP joints. Patients were excluded if they underwent treatment for a concomitant hand condition that could confound outcomes assessments (e.g. carpal tunnel release). For this study, we also excluded patients who underwent simultaneous treatment for multiple digits to increase comparability between the groups. Our local institutional review board exempted this study from formal review due to the retrospective nature of this study.

Procedures

Treatments were performed as part of standard clinical practice by the surgeons of the participating practice sites. Hence, treatment selection occurred through shared-decision making.

PNA was performed under local anesthesia. Cords were released using 25 gauge needles at as many levels as possible in the palm and fingers. Patients were instructed to report paresthesias to avoid nerve injury. After release, the treated digit was extended with a progressive force to maximize correction. Patients were encouraged to flex and extend their digits immediately following treatment and to restart normal use of their hands after 24 hours.

CCH was administered according to manufacturer instructions, without local anesthesia. Injections were limited to 0.25mL and 0.20 mL for MCP and PIP joint contractures, respectively. Afterwards, compressive dressings were applied. Treated digits were manipulated after 24 to 72 hours to attempt release of the weakened cords under local anesthesia. Up to 3 injections were offered at 4 week-intervals if patients were dissatisfied with the achieved level of correction but were not mandatory. All

patients were offered a similar rehabilitation and splinting program as patients undergoing PNA.

Outcome measures

The primary outcome was early improvement in degree of contracture. The degree of contracture (active extension deficit) was assessed by certified hand-therapists using a finger goniometer before treatment and at visits occurring between six to twelve weeks after surgery or the last injection. Any hyperextension was defined as 0° to prevent underestimation of total extension deficit. At the same visits, adverse effects were noted, which were divided based on their severity into two categories: serious (non-transient or requiring an intervention) and mild (transient or not requiring an intervention).

Lastly, we examined the impact of both treatments on different aspects of hand function using the Michigan Hand outcomes Questionnaire (MHQ).[14] Because we assumed that some patients would require at least 6 months for full functional recovery after treatment, we asked patients to complete the MHQ before and between 6 months and 1 year after treatment. The MHQ consists of 37 items evaluating 6 subdomains for each hand separately: overall hand function, ability to perform activities in daily life (ADL), work performance, hand appearance, pain and satisfaction with hand function. The fact that the MHQ includes a subdomain assessing hand appearance increases its scope[15] and makes it particularly well-suited for some patients with Dupuytren's contracture.[16,17] Scores range from 0 to 100 (with 100 indicating best hand performance). As this study was directed at assessing improvement in contracture rather than pain reduction, we excluded all pain-related outcomes. We only used the outcomes pertaining to the treated side.

Propensity-score matching

In practice, the choice between PNA versus CCH is not random but related to clinical factors, such as the degree of contracture and patient characteristics, as a consequence of differences in patient selection and preference. Therefore, we expected that the PNA and CCH groups would differ with respect to their baseline characteristics. To account for such differences that can otherwise threaten the validity of a comparison due to

treatment selection bias, we applied propensity score matching.[18,19] This approach has been used previously to examine the comparative effectiveness of treatments for Dupuytren's contracture, including PNA and CCH.[4,13]

Propensity scores for the probability of undergoing CCH and PNA were developed using a logistic regression model with the following baseline characteristics as explanatory variables: age[20], gender[21], family history of the disease[22], primary or recurrent disease[23], the baseline degree of contracture[24] at the MCP, PIP and DIP joint levels and which joints were affected[25]. These variables were included because they were considered related to 1) either the choice between CCH or PNA or 2) clinical outcomes. After calculating the individual scores, we attempted to match each patient from the PNA group with two patients from the CCH group with the closest propensity scores (i.e. who had the most similar characteristics) using a nearest-neighbor algorithm with replacement. We repeated this process until matches had been attempted for all patients from the PNA group. To examine whether propensity score matching improved similarity among the treatment groups, significance testing was performed before and after matching.

Statistical analysis

Sample size calculations estimated that a total 32 affected MCP joints (16 each group) and 70 proximal interphalangeal contractures (35 each group) would provide 80 percent power to detect a 10-degree difference in contracture between the two treatment groups with the use of two-sided tests.[4]

For improvement in contracture (both in percentage and in absolute degrees) and MHQ scores, we used Student t-tests to compare the change at follow-up from baseline between treatment groups with corresponding means and two standard errors plotted graphically. The proportion of joints with clinical improvement, defined as improvement of ≥ 50 percent in the degree of contracture, was compared with Chi-square tests. Outcomes were analyzed separately for affected MCP and PIP joints because results at the PIP joint are typically worse. Rates of adverse effects were compared using the Chi-square or Fisher's exact test if effects occurred in both treatment groups.
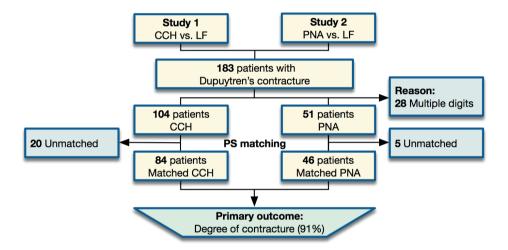
Continuous variables were reported as means ± SD and categorical variables with the use of frequencies. P-values of <0.05 were considered to indicate statistical significance.

4

Results

Study sample

There were a total of 183 patients of whom 79 underwent PNA and 104 CCH. After excluding 28 patients who were treated with PNA for multiple digits, a total of 155 eligible patients remained: 51 underwent PNA and 104 underwent CCH (Figure 1.).

Figure 1. *Patient selection flowchart. CCH, Collagenase Clostridium Histolyticum; PNA, percutaneous needle aponeurotomy; LF, limited fasciectomy; PS, propensity score.*

Differences between the PNA and CCH groups before propensity score matching included that patients undergoing CCH were more often men, were, on average, younger, had less total extension deficit, and proportionally fewer affected MCP joints (Table 1. *left*).

Table 1. Characteristics of Clostridium Collagenase Histolyticum and percutaneous needle aponeurotomy treatment groups, before and after propensity-score based matching.

	Unmatched			Matched		
	PNA (N=51)	**CCH** (N=104)	**p**	**PNA** (N=46)	**CCH** (N=84)	**p**
Demographics						
Age –yrs.	65±8	61±10	0.021	63±8	64±8	0.466
Men–%	65	80	0.050	72	75	0.686
Alcohol use –%	73	59	0.092	72	60	0.232
Current smoker –%	18	16	0.839	15	18	0.701
Epilepsy –%	0	2	1.000	0	2	0.539
Disease characteristics						
Tubiana –%			0.315			0.562
Grade I	33	47		51	42	
Grade II	53	45		45	50	
Grade III or IV	14	8		4	6	
Recurrent disease –%	22	26	0.550	22	21	0.840
Positive family history –%	43	54	0.210	41	48	0.489
Outcomes						
Extension deficit –degrees						
Total	62±30	52±29	0.053	49±23	54±30	0.317
MCP joint level						
All joints	39±23	29±24	0.010	31±21	33±24	0.518
Affected joints –%	90	75	0.026	89	81	0.226
PIP joint level						
All joints	20±21	22±25	0.498	17±19	19±22	0.546
Affected joints –%	63	61	0.795	63	57	0.513
DIP joint level						
All joints	3±9	1±4	0.063	1±5	1±5	0.966
Affected joints –%	14	6	0.093	9	7	0.751

* Plus-minus values are means ±SD.
PNA, Percutaneous Needle Aponeurotomy; CCH, Collagenase Clostridium Histolyticum; MCP, metacarpophalangeal; PIP, proximal interphalangeal; DIP, distal interphalangeal; SD, standard deviation.

This further highlights the need to account for these differences before comparing the two groups since all these factors have been previously found to influence outcomes.[21-24] At the same time, all remaining characteristics were not significantly different, showing that the indications for CCH and PNA were not substantially different at the participating sites.

With the use of propensity scores, we were able to match 46 PNA patients to 84 CCH patients who were similar in terms of their baseline degree of contracture and proportions of affected MCP joints (PNA, 34 degrees for 41 joints vs. CCH, 41 degrees for 68 joints) and affected PIP joints (PNA, 30 degrees for 26 joints vs. CCH, 35 degrees for 46 joints). All other characteristics were also similar between groups (Table 1. *right*).

Among the matched treatment groups, the average degree of total extension deficit was 52 degrees. This corresponded to 93% of patients being graded as Tubiana I

(<45 degrees) or II (45-90 degrees), which indicated that the majority had mildly affected digits. Follow-up data was available for 91% of the primary outcome (degree of contracture), which was assessed at an average follow-up duration of 8 weeks (range 6-12 weeks). There were no significant differences in baseline characteristics between those who did and did not have primary outcome data available (Supplementary Table 1).

Supplemental Table. 1. Characteristics of the matched patients, divided by those with (respondent) and without data (non-respondents) available on the primary outcome (degree of contracture).

	Respondent (N=118)	Non-respondent (N=12)	*p*
Demographics			
Age –yrs.	63±8	64±5	0.978
Male gender –%	75	67	0.562
Alcohol use –%	64	67	0.999
Current smoker –%	17	17	0.999
Epilepsy –%	2	0	0.532
Disease characteristics			
Tubiana –%			0.179
Grade I	45	50	
Grade II	50	33	
Grade III or IV	5	17	
Recurrent disease –%	21	17	0.999
Positive family history –%	43	67	0.120
Outcomes			
Extension deficit –degrees†			
Total	62±30	52±29	0.053
MCP joint level	39±23	29±24	0.010
PIP joint level	20±21	22±25	0.498
DIP joint level	3±9	1±4	0.063

* Plus-minus values are means ±SD.
† Values are reported for all joints.
MCP, metacarpophalangeal; PIP, proximal interphalangeal; DIP, distal interphalangeal; SD, standard deviation.

Sixty percent of PNA patients and 72% of CCH patients completed the MHQ to such an extent that the baseline overall score could be calculated. Of these, 64% in the PNA group and 76% in the CCH group had follow-up data available. We found no significant differences in the baseline characteristics between those with and without MHQ follow-up data.

Change in angular correction

For affected MCP joints, the improvement in contracture at follow-up was not significantly different among the matched treatment groups, in percentage correction and in absolute degrees (Figure 2. *left and middle*). The proportion of MCP joints reaching clinical improvement, defined as an improvement of ≥ 50 percent in the degree of contracture, was also similar between the treatment groups (Figure 2. *right*).

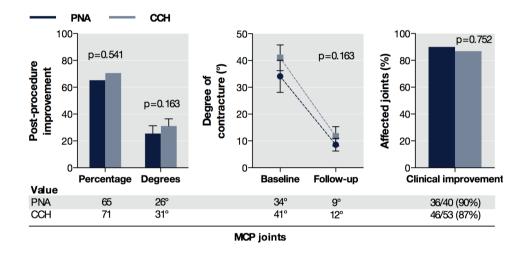| Value					
	Percentage	Degrees	Baseline	Follow-up	Clinical improvement
PNA	65	26°	34°	9°	36/40 (90%)
CCH	71	31°	41°	12°	46/53 (87%)

MCP joints

Figure 2. Improvement in contracture for affected MCP joints (left and middle) and proportion of joints with clinical improvement (right) among the matched Collagenase Clostridium Histolyticum and percutaneous needle aponeurotomy groups at early follow-up.

For affected PIP joints, improvement in contracture was also not significantly different among the matched treatment groups (Figure 3. *left*). Consistently,

improvement in contracture in degrees was similar (Figure 3. *left and middle*).

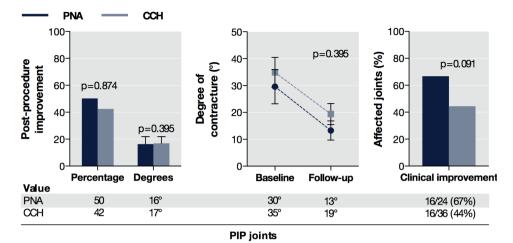| Value					
PNA	50	16°	30°	13°	16/24 (67%)
CCH	42	17°	35°	19°	16/36 (44%)

Figure 3. Improvement in contracture for affected PIP joints (left and middle) and proportion of joints with clinical improvement (right) among the matched Collagenase Clostridium Histolyticum and percutaneous needle aponeurotomy groups at early follow-up.

The proportion of clinically improved PIP joints in the CCH group was not significantly different between groups (Figure 3. *right*).

Adverse effects

No serious adverse effects occurred in either of the matched treatment groups (Table 2).

Table 2. Adverse effects in the matched treatment groups, by severity grade.*		
Adverse effect	PNA (N=46)	CCH (N=84)
Mild		
Peripheral edema	n.a.	70
Contusion	n.a.	62
Mild	n.a.	54
Severe	n.a.	8
Pain	n.a.	31
Blood blister	n.a.	11
Axillary tenderness	n.a.	8
Skin fissure	4	8
Sensory disturbance	2	1
Pruritus	n.a.	4
Erythema	n.a.	4
Lymphadenopathy	n.a.	1
Scar sequelae	0	0
Wound healing problems	0	0
Serious		
Nerve laceration	0	0
Uncorrectable contracture	0	0
Wound infection	0	0
Arterial laceration	0	0
Tendon rupture	0	0
Cold intolerance	0	0
CRPS	0	0

* Values are percentages.
PNA, Percutaneous needle aponeurotomy; CCH, Clostridium collagenase histolyticum; CRPS, complex regional pain syndrome.

Three of the most common mild adverse effects in the CCH group were peripheral edema, contusion, and transient pain. The only events occurring in both treatment groups were skin fissures and sensory disturbances, which did not significantly differ in their relative incidence between groups (p=0.491 and p=1.000, respectively).

Changes in hand function

The overall MHQ score was similar at baseline in the matched PNA and CCH groups. At an average of 11 months follow-up, patients also reported a similar improvement in the overall score (PNA, 5.3 points vs. CCH, 4.9 points; p=0.912).

There were, however, differences between the two groups in the extent to which several subdomain scores improved. PNA patients as compared with CCH patients reported, on average, larger improvements in the MHQ subscores of satisfaction (18 points) and hand appearance (8 points), although only the difference in the satisfaction
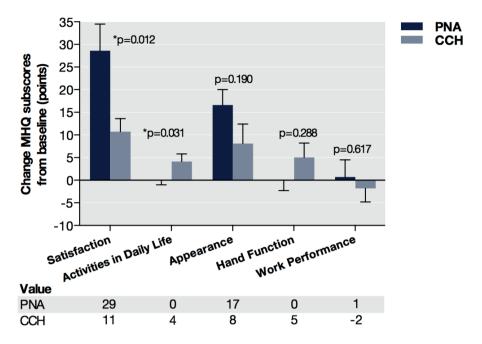
subscore reached significance (Figure 4).

Figure 4. Change in MHQ scores in the matched Clostridium Collagenase Histolyticum and percutaneous needle aponeurotomy treatment groups.

CCH patients, in turn, reported significantly larger improvements in the ADL subscore (4 points). Further exploring these differences, all subdomain scores in absolute terms were similar between-groups at baseline and follow-up with the exception that the satisfaction and appearance subscores were an average of 7 and 9 points, respectively, lower in the PNA group than in the CCH group at baseline (p=0.204 and p=0.057, respectively).

Discussion

Despite the large number of studies describing the outcomes of various treatments for Dupuytren's contracture, scarce evidence is available to guide decision-making in the disease.[26,27] The aim of this study involving multiple practice sites in the Netherlands was to assess the outcomes of PNA versus CCH in clinical practice. We found that, among patients with mildly contractures (93% Tubiana I or II), improvement in contracture with PNA as compared with CCH was similar for affected MCP and PIP joints. No major adverse effects occurred in any of the two treatment groups. Over time, the overall MHQ score also improved to a similar extent in both groups.

As evidenced by both the relative improvement and in absolute degrees, the level of contracture correction achieved in our study at the MCP joint level after CCH was similar to that after PNA. Two previous clinical trials reported similar findings.[8,9] In the present study, affected MCP joints improved by 31 and 26 degrees after CCH and PNA, respectively. This agrees well with the similar degree of improvement reported by Scherman and colleagues (46 and 47 degrees for CCH and PNA at 3 months, respectively)[8] and by Strömberg and colleagues (48 and 46 degrees, respectively).[9] The smaller improvement in contracture in absolute terms in our study can be explained by differences in baseline severity of contracture among the study samples as well as differences in assessment methods (passive versus active goniometry). Affected PIP joints in our study improved by 17 and 16 degrees after CCH and PNA, respectively. In comparison, Scherman and colleagues reported in their study that PIP joints also improved to a similar extent (8 and 11 degrees after CCH and PNA, respectively). Again, the difference in absolute improvement can be explained by slight differences in patient inclusion. Collectively, these findings show that the effectiveness of CCH at reducing contractures is similar to that of PNA in actual clinical practice, despite that decision-making processes and compliance in this study probably differed from that in previous clinical trials. We therefore believe that they are an addition to the evidence-base available on CCH and PNA.

We found no serious adverse effects following either treatments, which is consistent with what has previously been reported.[9] Skin fissures and sensory disturbances were the only mild adverse effects that occurred after both CCH and PNA

but were rare. All other minor effects were unique to the CCH group among which peripheral edema, contusion and pain in the extremity were the three most common. We believe that these findings primarily highlight the different modes of action of the two treatments.

During the first year after treatment, we found that the overall MHQ score improved to a similar extent after PNA and CCH. This underscores the effectiveness of both treatments at improving hand function for patients, even for those with mild contractures. Interestingly, the subdomain scores of satisfaction and appearance showed larger improvements after PNA than after CCH at follow-up, while the scores in absolute terms were similar. We feel that this is due to the comparatively lower scores in these subdomains in the PNA group at baseline. Considering that both treatment groups were similar with respect to their baseline characteristics, including demographics and disease severity, this suggest less satisfaction and more concern with the appearance of their hands among those opting for PNA. Further research is warranted in this area, which we believe can address a knowledge gap regarding the concerns and needs that influence treatment decision-making among patients with Dupuytren's disease.[28-30]

The resources required for CCH and PNA may also be important to consider when deciding between the two treatments, particularly considering that associated costs can differ substantially. Although these will vary depending on geographic region, the direct costs of CCH will be higher in most settings due to the low material costs of PNA. In addition, two visits are required with CCH whereas PNA requires only a single visit. CCH may therefore be regarded as the least cost-effective option of the two, which then ought to be justified by objective advantages (i.e. superior outcomes). To date, we are unaware of any study showing these advantages. Previous economic evaluations have, however, underlined the complexity in comparing the cost-effectiveness of different treatments in Dupuytren's disease due to the lack and quality of existing literature.[27,31] The data presented in the current study allow for refining such economic models that help to identify treatment algorithms for Dupuytren's contracture that are both cost-effective and broadly applicable.

Our study has several strengths. First, it used prospective data from 7 practice sites that were gathered as part of daily clinical practice, making it a comparative effectiveness study.[32] The results from such studies, compared with strictly controlled

trials, may be more broadly generalizable because they better reflect the actual decision-making processes, patient compliance, and, ultimately, the outcomes achieved in daily practice.[10,32,33] Second, we examined the relative change in MHQ scores rather than a cross-sectional assessment, which enabled a comparison of the impact of CCH and PNA on different aspects of hand function.[34] Other strengths include the relatively large sample analyzed, completeness of outcome data (91% primary outcome) and the use of propensity scores to minimize the risk of bias due to observed differences. Despite this study design, a potential limitation of this study is that propensity analyses cannot account for selection bias related to unmeasured characteristics (i.e. genetic constitution). A second limitation is that we could not reliably assess rates of recurrence, which may be as relevant to patients in treatment decision-making as early outcomes, because of the limited time-horizon of our study.[30] Thirdly, only a subset of patients completed the MHQ. Although this might have influenced our results, the possibility for attrition bias seems small because there were no differences in the characteristics between those who did and did not complete the MHQ at follow-up. Finally, the rare incidence of adverse effects in both treatment groups precludes strong inferences to be made about the comparative risk profile of both treatments.

In conclusion, we found that, among patients with mildly affected digits, CCH and PNA were similarly effective at improving contractures. Even among these patients, we found a significant and similar improvement in overall hand function, which reinforces the usefulness of both treatments as first-line treatments. Our findings also underscore the safety of both techniques in daily practice. Until longer-term studies are conducted that are urgently needed to better understand the durability of the outcomes of both treatments, we believe that these findings may help patients with Dupuytren's disease, payers and providers decide between these two minimally invasive treatment options.

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4

Part **II**

PATIENT SATISFACTION

5

Predictors of Patient Satisfaction with Hand Function after Fasciectomy for Dupuytren's Contracture

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Abstract

Background: This study examined patient satisfaction with hand function after fasciectomy for Dupuytren's contracture and determined which preoperative patient- and disease-specific factors predicted this satisfaction.

Methods: Demographics and disease-specific factors were assessed from a prospective cohort of 194 patients who completed the Michigan Hand Outcomes Questionnaire preoperatively and underwent limited fasciectomy between 2011 and 2014 at six hand surgery practice sites. To evaluate satisfaction with hand function, patients were asked to complete the Michigan Hand Outcomes Questionnaire during the first year after fasciectomy. After patients were classified into a satisfied and an unsatisfied category using the question that specifically pertains to satisfaction with hand function, the authors applied multivariate logistic regression modeling to identify independent predictors of patient satisfaction.

Results: At an average of 10 months (range, 6 to 12 months) after fasciectomy, 84 percent (n = 163) of the patients were satisfied with their hand function. In multivariate analyses adjusting for the degree of postoperative residual contracture ($p < 0.001$) and complications ($p < 0.001$), a higher preoperative Michigan Hand Outcomes Questionnaire hand appearance subscore and male gender predicted a higher likelihood of becoming satisfied after fasciectomy. Other patient- and disease-specific factors did not show evidence for an association with patient satisfaction.

Conclusion: The findings of this study suggest that providers should consider assessing concerns about the appearance of the hand in patients with Dupuytren's contracture. They also highlight the importance of complication prevention and full contracture correction from the patient's perspective.

Introduction

Dupuytren's disease is characterized by the development of cords that may contract and cause disfiguring flexion deformities.[1] Surgical fasciectomy remains the standard against which the results of all other techniques ought to be compared.[2] The technique effectively reduces contractures with acceptable complication rates and provides a relatively low risk of recurrence.[3] However, outcomes that are good from a provider's perspective do not necessarily satisfy patients. It is important to identify the factors that matter most to patients, in order to understand the patient perspective and maximize satisfaction rates.

Patient satisfaction is a broad yet increasingly important construct, and may be subdivided into different domains, such as satisfaction with the provider, convenience of care, and functional outcomes. In general, satisfied patients better adhere to treatment regimens, and are more compliant and more loyal towards providers.[4] Moreover, satisfaction data are increasingly used to judge the quality of surgical care.[5,6] Although our knowledge of the factors influencing patient satisfaction remains incomplete, what is evident is that it not only depends on the treatment delivered but also on patient factors, such as demographics, functional status, and pretreatment expectations.[7,8] Previous studies have reported variable satisfaction rates following fasciectomy[9] but the factors contributing to this variation remain poorly understood.[10,11]

The aim of the present study was to identify preoperative factors that influenced satisfaction with hand function after fasciectomy for Dupuytren's contracture. Satisfaction with hand function is important, as the premise of the treatment is to restore hand function for patients. Preoperative factors were assessed because identification, prior to treatment, of those at risk of becoming unsatisfied may help providers to better address individual concerns or needs preoperatively, and prompt them to manage patients differently.

5

Methods

Study sample

After our local institutional review board approved our study protocol, we identified all patients who underwent fasciectomy for Dupuytren's contracture between 2011 and 2013 at 6 hand surgery practice sites using a prospectively maintained database that was designed for clinical and research purposes. Demographic and disease specific characteristics derived from this database were age, gender, occupational status, comorbidities, current tobacco and alcohol use, family history of Dupuytren's disease, hand dominance, number of treated rays, bilateral disease, whether fasciectomy was performed for primary or recurrent disease, and the degree of contracture.

We included all adult patients with a diagnosis of Dupuytren's contracture who underwent fasciectomy and who had the ability to complete the study questionnaire. Patients were excluded if they had a diagnosis of a hand condition or underwent a concomitant intervention (e.g., carpal tunnel release) on the affected side that could confound patient satisfaction. Patients undergoing treatment for recurrent disease were included if they met the other eligibility criteria.

Primary outcome: patient satisfaction with hand function

The Michigan Hand Outcomes Questionnaire (MHQ) was mailed to all study participants before, and between 6 months and 1 year after surgery. The minimum 6 months follow-period was decided upon based on previous research showing that the majority of patients are functionally recovered after fasciectomy at this time point.[12] The MHQ is a thoroughly-developed and sensitive hand-specific instrument that assesses 6 domains of hand function: overall hand function, activities of daily living, pain, work performance, hand appearance, and patient satisfaction, with scores ranging from 0 (poorest function) to 100 (best function). The fact that the MHQ includes a scale that assesses hand appearance increases the scope of this instrument.[13]

Satisfaction with hand function was assessed using one of the questions from the satisfaction domain of the MHQ that specifically asks patients about their satisfaction with overall hand function. Patients responded using a five-point Likert scale with the following possible answers: "Very satisfied", "Somewhat satisfied", "Neither Satisfied

Nor Dissatisfied", "Somewhat Dissatisfied", or "Very Dissatisfied". We considered patients who selected "Very satisfied", "Somewhat satisfied" as being satisfied with their hand function and all others as unsatisfied. Although dichotomization of ordinal data may result in some information loss, we decided upon this approach for two important reasons. First, our purpose was to specifically focus on the difference between patients who had at least some degree of satisfaction and those who reported no satisfaction at all. Second, previous other investigators have successfully used this approach to identify determinants of satisfaction in other hand conditions.[14] Only the outcomes pertaining to the treated side were used.

Clinical outcomes

We anticipated that postoperative outcomes would influence patient satisfaction. To account for their possible influences, we assessed the occurrence of complications, whether a secondary procedure had been performed for recurrent contracture, and the degree of postoperative total residual contracture. The occurrence of complications and whether a revision procedure had been performed for recurrent disease within the follow-up period of the study was assessed through retrospective analyses of patients' health records and office charts. Because it was assumed that any type of complication could impact patient satisfaction, we included all complications noted including neuropraxia, scar sequelae, wound healing problems, wound infection, hematoma, tenosynovitis, edema, cold intolerance, sympathetic dystrophy, persistent pain and nerve division, arterial injury. The degree of total residual contracture was assessed by certified hand therapists during visits occurring between 6 and 12 weeks after treatment by summing up the degree of active extension deficit at the MCP, PIP and DIP joint levels. Any hyperextension was converted to 0 degrees to prevent underestimation of the total degree of extension deficit. To improve the comparability between patients with a single affected versus those with multiple affected digits, we used the measurements pertaining to the most severely contracted digit.

Statistical analysis

Descriptive statistics included means and standard deviations for continuous variables and numbers for categorical variables. A power analysis determined that a sample of 160 patients would provide 80% power (alpha 0.05, beta 0.20) to detect a significant difference of 10 points in the MHQ overall hand function score between satisfied and unsatisfied patients and assuming a standard deviation of 18 points and a satisfied to unsatisfied ratio of 4:1.[15]

Preliminary analyses examined possible bivariate relationships between patient satisfaction with hand function and a diverse set of demographic variables, clinical factors and the preoperative MHQ subdomain scores of overall hand function, ability to perform activities in daily life, work performance, satisfaction and hand appearance using Student *t* test's for continuous variables and chi-square tests for categorical variables. Then, all factors showing a relationship (p<0.10) were included in multivariate logistic regression models (primary analyses) that accounted for the possible influences of postoperative outcomes on patient satisfaction to identify independent predictors of patient satisfaction. To explore possible mechanisms underlying the factors associated with satisfaction, interaction effects were assessed afterwards. Significance thresholds were set at P<0.05.

Results

There were a total of 236 patients who underwent fasciectomy by one of the 16 hand surgeons from the participating sites. After excluding 42 patients based on our eligibility criteria, 194 patients remained to form our study sample. Of these, all patients completed the question pertaining to satisfaction with overall hand function. The mean age in our study sample was 63±9 years and 73% were men. At an average of 10 months (procedure to survey completion, range 6-12) after fasciectomy, 84% (N=163) of our study population were satisfied with their hand function while 16% (N=31) were unsatisfied. Satisfaction rates were not significantly different between the surgeons (P=0.777) and practice sites (P=0.291). The time from procedure to survey completion was similar between satisfied and unsatisfied patients (P=0.648).

Table 1 shows the bivariate associations between preoperative characteristics and patient satisfaction with hand function.

Table 1. Bivariate associations between demographics, clinical characteristics and self-reported outcomes at baseline with patient satisfaction with hand function during the first year after fasciectomy.*

Variable	Satisfied (N=163)	Unsatisfied (N=31)	P
Age –yrs	65 ± 9	62 ± 9	0.172
Male gender –%	76	58	0.038
Occupational status –%	42	36	0.517
Diabetes –%	7	10	0.712
Smoking –%	4	10	0.158
Alcohol –%	4	7	0.616
Positive family history –%	50	42	0.442
Bilateral disease –%	37	42	0.635
Primary disease –%	70	55	0.100
Dominant side treated –%	52	58	0.731
No. of treated fingers	1.7	1.8	0.289
Joint level affected			
MP joint –%	44	32	0.218
PIP joint –%	79	87	0.306
Total Extension deficit –degrees	70 ± 24	64 ± 36	0.248
MHQ subdomain score (0-100)			
Satisfaction	60 ± 24	52 ± 20	0.081
Activities in Daily Life	90 ± 14	87 ± 13	0.368
Overall Function	67 ± 16	63 ± 13	0.228
Appearance	71 ± 19	58 ± 16	0.001
Work Performance	83 ± 24	79 ± 21	0.293

* Plus-minus values are means ±SD.

MP, metacarpophalangeal; PIP, proximal interphalangeal; SD, standard deviation; MHQ, Michigan Hand Outcomes Questionnaire.

More men were satisfied. Satisfied patients had, on average, higher preoperative MHQ hand appearance subscores as compared with those who were unsatisfied. All other subscores, preoperative patient factors, and disease specific characteristics, including occupational status, bilateral disease, recurrent disease, and the degree of preoperative contracture, showed no relationship with satisfaction.

As expected, postoperative outcomes influenced patient satisfaction. Satisfied patients had less residual total extension deficit (29 degrees vs. 18 degrees; P<0.001) and a lower rate of complications (20% vs. 52%; P<0.001; Table 2).

Table 2. Complications, by patient satisfaction with hand function.*

	Satisfied (N=163)	Unsatisfied (N=31)	P
No complication †	80 (131)	48 (15)	<0.001
Neuropraxia	9 (14)	16 (5)	
Scar sequelae	5 (8)	10 (3)	
Wound infection	2 (3)	0 (0)	
Wound healing problems	2 (3)	10 (3)	
Edema	1 (1)	3 (1)	
Cold Intolerance	0 (0)	3 (1)	
Sympathetic dystrophia	0 (0)	3 (1)	
Persistent pain	0 (0)	3 (1)	
Stiffness	0 (0)	3 (1)	
Tenosynovitis	1 (1)	0 (0)	
Arterial injury	1 (1)	0 (0)	
Hematoma	1 (1)	0 (0)	

* Values are percentages (numbers).
† There were no significant differences in the preoperative degree of contracture and joint levels involved between the two groups.

Notably, the incremental change in the degree of contracture was not related to satisfaction (P=0.683). Within the follow-up period of this study, none of the patients underwent a secondary procedure for recurrent contracture, which precluded inclusion of this outcome as a possible predictor in further analyses.

The most parsimonious multivariate model that accounted for the influence of the degree of residual contracture (P=0.017) and complications (P=0.002) on patient satisfaction accounted for 32% of the variation in satisfaction response. In this model, the MHQ hand appearance subscore remained as the only significant preoperative predictor

of satisfaction with hand function, whereas gender approached significance (Table 3). More specifically, patients who had a higher preoperative hand appearance score of 10 points were about 1.4 times as likely to be satisfied with their hand function. Men, as compared with women, were about 2.5 times as likely to be satisfied.

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Table 3. Preoperative predictors of satisfaction with hand function during the first year after fasciectomy from the final multivariable logistic regression model, with adjustment for the postoperative degree of total residual contracture and complications.

Predictor	OR (95% CI)	P
MHQ hand appearance subscore* (per 10 point incremental change)	1.37 (1.12-1.62)	0.003
Male gender	2.54 (0.98-6.64)	0.056

OR, Odds Ratio; CI, Confidence Interval; MHQ, Michigan Hand Questionnaire.

Further exploring the possible mechanisms underlying the effects of hand appearance on satisfaction, we found that the interaction effects between the preoperative hand appearance subscore and postoperative residual contracture (P=0.482) and complications (P=0.604) were not significant. The interaction effects between gender and residual extension deficit (P=0.645) and complications (P=0.202) on satisfaction were also not significant.

Discussion

The present study examined satisfaction with hand function and its determinants in patients undergoing fasciectomy for Dupuytren's contracture. Eighty-four percent of patients were satisfied during the first year after treatment. In light of the similar rates previously reported on fasciectomy[9,11,12], this finding shows the effectiveness of fasciectomy from the patient perspective[16] yet implies that the procedure may not be fully meeting patients' needs.[17] We found that a higher preoperative MHQ hand appearance score and male gender predicted a higher likelihood of becoming satisfied after adjusting for the influence of postoperative outcomes. We found no relations between satisfaction and other patient- and disease-specific factors.

In this study, valuing appearance of the hand more positively before surgery was associated with higher satisfaction with hand function afterwards. This highlights the concern about the appearance of the hand patients with Dupuytren's contracture may have as well as the detrimental impact of such concerns on satisfaction. After all, the hand is prominently visible and fulfills a crucial role in interaction with our environment, physical expression and social functioning.[18,19] Dupuytren's disease is characterized by the formation of contractures that may cause a variable degree of disfigurement and deformity[11,20], which is further substantiated by the inverse correlation between the preoperative degree of contracture and the MHQ hand appearance subscore in the present study. Previous studies found that, among patients with other hand deformities, hand appearance significantly impacted their lifestyle due to feelings of anxiety, lowered self-esteem and negative self-perceptions.[19,21-23] It may be that similar mechanisms contribute to the dissatisfaction in those who are concerned about the appearance of the hand in Dupuytren's disease.[20] In light of recent studies showing that hand appearance improves after fasciectomy[24,25], it seems logical that, among those who have such concerns, satisfaction increases after their contractures and deformity have improved following the fasciectomy. We believe that these findings should raise awareness among hand surgeons for the concerns patients with Dupuytren's disease may have about the appearance of the hand and possibly their need for restoration of a more normal hand appearance in addition to the unquestionable importance of functional restoration.

We found that men were about 2.5 times as likely to be satisfied as compared with women, which shows a gender disparity in satisfaction for which the underlying mechanisms are probably complex. Dupuytren's disease occurs less frequently in women[26], and it could be that they have different attitudes towards the disease and its consequences. The few studies examining gender differences in Dupuytren's disease found primarily that clinical outcomes were better in men than women.[27,28] Although this might explain why men were more satisfied, no such differences were found in the present study. Moreover, the negative interaction effect between gender and postoperative outcomes indicated that men and women were equally dissatisfied if a complication occurred or the degree of correction did not meet their expectation. As such, the forum is open for discussion as to why men were more satisfied after fasciectomy. Perhaps women experienced the impact of open fasciectomy more severely or they had higher expectations prior to the procedure. Future studies that are qualitative in nature may clarify these questions. Until then, however, the gender difference in satisfaction found in this study underscore the need for providers to consider adjusting for such differences before presenting satisfaction data in Dupuytren's disease.

Less residual contracture was associated with higher rates of patient satisfaction, whereas the degree of contracture before and incremental change after surgery did not. This suggests that satisfaction depends more on the absolute postoperative result than the (potential) change in contracture. It also emphasizes the relevance of achieving full corrections from the patient perspective. Furthermore, our study reinforces the importance of the prevention of complications, as they also had a detrimental effect on patients' satisfaction. The finding that other patient factors, such as recurrence, did not influence satisfaction suggests that patient satisfaction depends on how Dupuytren's disease is experienced by each patient.

Strengths of this study include its prospective design and large sample size by virtue of the participation of 6 practice sites. This allowed for multivariate analyses to identify predictors of satisfaction, after taking into account the significant influences of postoperative outcomes. However, it also resulted in a high number of surgeons performing the procedures.

Although the satisfaction rates between the surgeons and practice sites involved did not differ significantly in the present study, the possibility exists for performance bias (i.e. bias due to performance variability between surgeons) to have influenced our findings.[29]. A second limitation is that patient satisfaction was assessed during the first year after fasciectomy whereas most contractures tend to recur after this time-horizon. As such, the extent to which levels of satisfaction change and its determinants remain similar over time remains unknown. Third, we only included patients undergoing fasciectomy, thus our findings may not apply to patients undergoing less invasive techniques. Fourth, we did not assess psychological factors, although these have been previously linked to patient-reported satisfaction[30], which merits further research in this area.[31] Finally, to increase the likelihood of finding predictors of patient satisfaction, we used the sensitive and well-validated hand-specific Michigan Hand Outcomes Questionnaire.[4] However, the Unité Rhumatologique des Affections de la Main (URAM) is a more recently developed questionnaire specific to Dupuytren's disease, which particularly focuses on the functional problems experienced by patients.[32] Investigators should consider incorporating the URAM in future satisfaction studies as this would increase our understanding of what factors affect satisfaction in Dupuytren's disease.

This study addresses a gap in knowledge regarding the determinants of patient satisfaction with hand function in Dupuytren's disease, which is essential for understanding the patient perspective and improving satisfaction. Patient satisfaction was higher in patients who had higher self-rated hand appearance preoperatively, in men, and those who had better postoperative outcomes. These findings show that providers should consider assessing concerns about the appearance of the hand in patients with Dupuytren's contracture. They also highlight the relevance of full contracture corrections and the prevention of complications for patients.

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Part **III**

LONG-TERM COMPARATIVE EFFECTIVENESS OF PALF

6

Percutaneous Aponeurotomy and Lipofilling (PALF) versus Limited Fasciectomy for Dupuytren's contracture: 5-year Results from a Randomized Controlled Trial

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Abstract

Background: In the DuRo trial, a randomized clinical trial, percutaneous aponeurotomy with lipofilling (PALF) was as effective as limited fasciectomy (LF) in correcting primary Dupuytren's contracture after 1-year follow-up. The purpose of the present study is to report the 5-year results of this trial, especially focusing on recurrence of contractures.

Methods: We invited all patients who had undergone PALF or LF to participate in a post-trial follow-up assessment. Thirty-one PALF patients and 21 LF patients were assessed by an independent examiner for the degree of contracture and whether patients had undergone a secondary procedure. The primary composite endpoint was recurrence rate, defined as either 20° or greater worsening in contracture (relative to week 3) or as having undergone a secondary procedure for a new or worsening contracture.

Results: At 5 years, more joints in the PALF group than in the LF group had a recurrence (74% vs. 39%, p = 0.002). When re-defining recurrence as a worsening in total extension deficit of at least 30° for treated digits, this was 77% vs 32% (p = 0.001). Total extension deficit was also worse for PALF-treated digits (53 degrees vs. 31 degrees, p < 0.010).

Conclusions: While we previously reported that PALF offers a shorter convalescence, fewer long-term complications but a similar degree of contracture correction, at 5 years, the corrections were less durable for PALF than for LF.

Introduction

The standard of care for Dupuytren's disease remains surgery, with open limited fasciectomy (LF) and percutaneous needle fasciotomy (PNF) being the two most established techniques.[1] In comparison, PNF offers benefits because it is less invasive[2], may be performed at the outpatient clinic, and is associated with a lower mild complication rate[3] and a more rapid return to normal use of the hand.[3,4] The largest drawback of PNF, however, is that its results may be less durable over time than for LF, with reported recurrence rates ranging from 50-85%[4,5] while rates for LF range from 12-39%.[4,5]

In an attempt to improve the durability of the results of PNF, we developed an alternative treatment approach that relies on a more extensive percutaneous release than classical PNF, followed by subdermal autologous lipografting (Percutaneous Aponeurotomy with LipoFilling; PALF).[6,7] Preclinical studies have demonstrated that the grafted lipoaspirate contains adipose-derived stem cells that may inhibit contractile myofibroblasts[8], which are the cells primarily responsible for fibrosis and the pathogenesis of the contractures in Dupuytren's disease. Although these studies imply a potential, long-term benefit of lipofilling in concurrence with aponeurotomy for Dupuytren's disease, data from clinical studies are sparse.[1,7]

The Dupuytren Rotterdam (DuRo) trial was originally designed to compare the efficacy and safety of PALF and LF in patients with primary disease.[9] We found that during the first postoperative year, PALF corrected contractures as effective as LF while no significant difference in recurrence was found between both groups. In the current study, we report results after an extended follow-up period of 5 years in patients who previously participated in DuRo.

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Methods

Study design

The design of the DuRo trial and the one-year follow-up data have been described previously (Dutch Trial Register NTR1692).[9] In short, the study was a prospective, randomized, single-blind, clinical trial designed to compare PALF with LF at 1 year after treatment. Patients with primary Dupuytren's disease and a flexion contracture of at least 20° at the MP joint and/or 30° at the PIP joint were eligible, while excluding patients with contractures affecting the thumb or patients using anticoagulant therapy.

While we previously reported the data collected preoperatively and at 2 and 3 weeks, 6 months and 1 year after treatment, this study compared the 5-year results between both groups. All surviving patients originally assessed at baseline in DuRo were considered eligible and contacted by phone.

Treatments

PALF and LF were performed under exsanguination by tourniquet and under regional or general anesthesia. Detailed descriptions of the techniques have been previously reported and a video demonstrating the PALF technique can be found in the Digital Content Supplementary.[6,7] All patients were offered a comparable rehabilitation program under supervision of hand therapists and were instructed to use an extension splint at night for 6 months.

Follow-up examinations

The 5-year follow-up examination was performed by a single examiner (RW) who was not involved in the previous trial and, prior to assessment, was unaware of the treatment allocation. The degree of contracture was assessed using a goniometer after reaching a firm endpoint during passive extension of the digits at the MP, PIP and DIP joint levels. Total extension deficit was defined as the sum of the degree of extension deficit of MP, PIP and DIP joints and hyperextension at joint level was defined as 0 degrees to prevent underestimation of the total extension deficit. To increase comparability between patients who underwent treatment for a single digit and those treated for multiple

digits, we analyzed the digit most severely affected in patients with more than 1 affected digit.

Primary and secondary outcome measures

The primary endpoint was a composite measure of recurrence assessed at the level of affected joints. Recurrence was defined as either having undergone a secondary procedure for a new or worsening contracture, or as an increase in extension deficit of more than 20 degrees relative to week after treatment. The latter was based on a recent Delphi-based definition for recurrence of contracture that used a similar definition, although using one year as follow-up.[10] To facilitate comparison with the randomized trial by van Rijssen et al comparing LF with NA without lipofilling, we also defined recurrence as an increase in total passive extension deficit of at least 30 degrees at the level of treated digits (relative to week 3).[11]

To assess the patient perspective[12], we asked patients who had not undergone a secondary procedure at the time of follow-up to complete the Disability of Arm Shoulder and Hand questionnaire (DASH) and a number of ad-hoc visual analogue scale (VAS) questions pertaining to the satisfaction with the overall treatment result, restoration of hand function, position of the fingers, appearance of the area treated of the hand, and whether patients' expectations were met concerning the overall treatment result.

Statistical Analysis

The primary outcome analysis, assessing recurrence of contracture, was performed at the level of individual joints. The proportion of affected joints meeting this primary endpoint was compared between groups using the chi-square tests.

To compare the degree of extension deficit between treatment groups, we used two-sided Student's t-tests. Since 5-year extension deficit was unavailable for patients who had undergone a secondary procedure at the time of follow-up, and since excluding these patients may underestimate degree of total extension deficit, we imputed the degree of extension deficit at 5 years using the pre-treatment degree of extension deficit in these patients.

Uni- and multivariable logistic regression modeling were used to identify factors predicting recurrence at the level of treated digits. All baseline clinical factors showing

evidence for an association (p<0.100) in univariable analyses were included in multivariable models using a stepwise backward elimination approach.

Results

Study sample

Between October 2015 and February 2016, 52 patients agreed to participate in the present 5-year study of whom 4 were bilaterally treated and assessed, resulting in a total of 56 treated hands (see Figure 1).
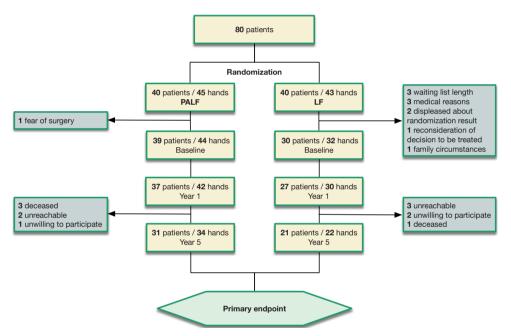

Figure 1. Flow diagram of the complete study, for which we now report the 5-year results.
PALF; extensive percutaneous needle aponeurotomy with lipofilling; LF; Limited Fasciectomy.

Baseline characteristics were not significantly different between the treatment groups (Table 1). Respondents and non-respondents also did not differ in baseline characteristics, including diathesis factors (see Supplemental Table 1), with the exception that respondents more often had a family member with Dupuytren's disease. The average follow-up duration for both treatment groups was similar (PALF 5.4 vs. LF 5.5 years, p=0.685).

Table 1. Baseline characteristics of the study sample, divided by treatment group.*

	PALF (31 patients / 34 hands)	**LF** (21 patients / 22 hands)	*p*
Patient characteristics			
Age –yrs.	62±9	62±7	0.103
Male gender –%	82	82	0.959
Diabetes –%	9	9	0.973
Alcohol –units per week	2	2	0.741
Disease-specific variables			
Positive family history –%	59	67	0.561
Ectopic disease –%	29	19	0.391
Ledderhose's disease –%	21	14	0.556
Peyronie's disease –%	12	10	0.796
No. rays treated			0.253
1 –%	52	69	
>1 –%	48	31	
Outcomes			
Extension deficit –degrees			
Total flexion deformity	61±34	58±35	0.772
MP joints	21±26	26±25	0.488
No. affected MP joints	18	15	0.258
PIP joints	39±28	31±29	0.311
No. affected PIP joints	28	16	0.391

* Plus-minus values are means ±SD.
PALF, Extensive Percutaneous Needle Aponeurotomy with Lipofilling; LF, Limited Fasciectomy; MP, metacarpophalangeal; PIP, proximal interphalangeal; DASH, Disability of Arm Shoulder and Hand; SD, standard deviation.

The mean age was 62 years in the overall group and 82% were men. The majority of the digits analyzed were Tubiana grade I (36%) or II (46%) before surgery. Our primary outcome analyses were based on 77 affected joints; 46 in the PALF group and 31 in the LF group.

Supplemental Table 1. Baseline characteristics, divided by patients who were able and willing to participate (respondent) with the present study and those who were unable or unwilling to participate (non-respondent).

	Respondent (52 patients / 56 hands)	Non-respondent (17 patients/ 20 hands)	p
Patient characteristics			
Age –yrs.	62±8	64±9	0.599
Male gender –%	82	80	0.832
Diabetes –%	9	20	0.188
Alcohol –units per week	2±2	2±2	0.896
Disease-specific variables			
Positive family history –%	62	30	0.015
Ectopic disease –%	26	15	0.339
Ledderhose's disease –%	18	10	0.393
Peyronie's disease –%	11	5	0.437
No. rays treated	1.6±0.9	1.4±0.5	0.430
Outcomes			
Extension deficit –degrees†			
Total	60±34	64±35	0.612
MP joint	23±25	16±24	0.287
PIP joint	36±28	46±21	0.092
DASH score –points	14±14	17±20	0.631

* Plus-minus values are means ±SD.

† Values are reported for all joints.

MP, metacarpophalangeal; PIP, proximal interphalangeal; DASH, Disability of Arm Shoulder and Hand; SD, standard deviation.

Recurrence rate and residual contracture

While at one year after surgery the recurrence rate was not significantly different between groups, more affected joints in the PALF group (74%) than in the LF group (39%) had a recurrence at 5 years, based on our composite outcome endpoint analysis of either having undergone a secondary procedure or having an increase in extension deficit of more than 20 degrees relative to week after treatment (see Figure 2).
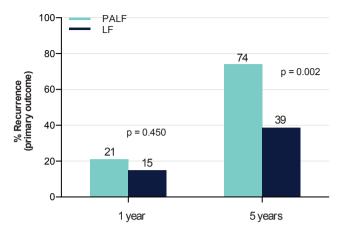
Figure 2. Recurrence rates in the percutaneous aponeurotomy with lipografting (PALF) and the limited fasciectomy (LF) groups based on the composite endpoints at 1 and 5 years after surgery.

When defining recurrence as an increase in total passive extension deficit of at least 30 degrees (relative to week 3) for treated digits, following van Rijssen et al., we also find that more digits in the PALF group (77%) met the definition for recurrence at 5 years than in the LF group (32%; p=0.001). At 5 years postoperatively, the estimated degree of total passive extension deficit was also significantly worse for PALF than LF treated digits (53 degrees vs 31 degrees; see Figure 3).
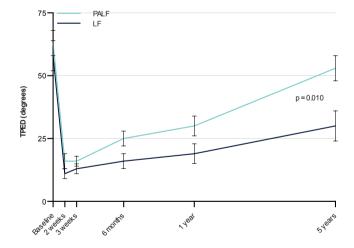
Figure 3. Estimated total passive extension deficit (TPED) in both groups preoperatively and at all recorded follow-up visits. The p-value corresponds to the difference between both groups at 5 years after surgery.

When analyzing MP and PIP joints separately, for MP, the proportion of joints with a recurrence based on the composite endpoint analysis at 5 years in the PALF group was higher than in the LF group but was not significant (61% vs. 33%, p=0.166). The estimated degree of extension deficit was also higher for affected MP joints after PALF than after LF (24 degrees vs. 11 degrees, Figure 4).
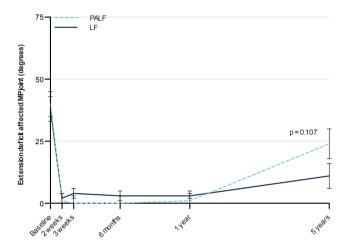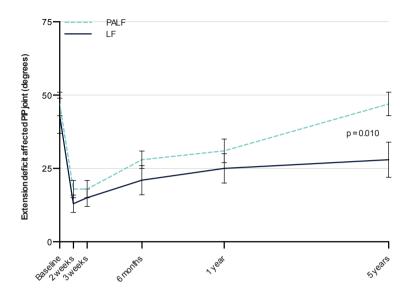

*Figure 4.* Estimated extension deficit for affected MP joint in both treatment groups preoperatively and at all recorded follow-up visits. The p-values correspond to the differences between both groups at 5 years after surgery.

For PIP, however, more affected joints in the PALF group met the primary endpoint than in the LF group (82% vs. 44%, p=0.017). The estimated degree of extension deficit was also higher for affected PIP joints after PALF than after LF (47 degrees vs. 28 degrees, Figure 5).

Figure 5. *Estimated extension deficit for affected PIP joints in both treatment groups preoperatively and at all recorded follow-up visits. The p-values correspond to the differences between both groups at 5 years after surgery.*

Patient-reported outcomes

A total of 18 PALF treated patients and 17 LF-treated patients, i.e., the patients who had not yet undergone a revision procedure, completed the study questionnaires at 5 years after surgery. Among this subset of patients, 5-year DASH scores were not significantly different between groups (PALF, 10.5 points; LF, 9.3 points; see Figure 6).
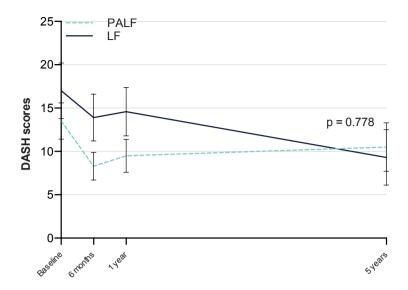
Figure 6. DASH scores in both groups preoperatively and at all recorded follow-up visits. The p-value corresponds to the difference between both groups at 5 years after surgery.

Satisfaction was also not significantly different between groups (Table 2).

Table 2. Satisfaction scores using a Visual Analogue Scale from 0-10 in the PALF and LF subgroups at 5 years after surgery.

Question	PALF (n=18)	LF (n=17)	p
Are you satisfied about the overall result of the surgical procedure?	7.1±3.1	8.5±2.1	0.138
Does the overall result of the surgical procedure meet your expectations?	7.3±3.1	8.0±2.8	0.495
How satisfied are you about the position of your fingers?	6.5±3.3	7.6±2.8	0.316
How satisfied are you about the extent to which your hand function was restored?	7.0±3.1	8.4±2.2	0.130
How satisfied are you about the way your hand/operated area looks?	7.8±2.8	8.2±2.5	0.643
Would you choose the same surgical procedure again? (%)	83	77	0.691
Would you recommend the same surgical procedure to friends, family, and acquaintances? (%)	89	88	0.952

PALF, Extensive Percutaneous Needle Aponeurotomy with Lipofilling; LF, Limited Fasciectomy; MP, metacarpophalangeal; PIP, proximal interphalangeal; DASH, Disability of Arm Shoulder and Hand; SD, standard deviation.

Risk factors for recurrence

Significantly more patients with an affected PIP joint had a recurrence at 5 years. All other baseline characteristics, including ectopic disease, family history of the disease, diabetes, epilepsy were unrelated.

In multivariable analysis (Table 3), we found that the presence of an affected PIP joint remained to show a trend for an independent association with a higher likelihood of developing a recurrence.

Table 3. Baseline independent risk factors for 5-year recurrence at the level of treated digits from the final multivariable logistic regression model.

Risk factor	OR	95% CI	p
Treatment type*	0.16	0.04-0.54	0.002
Affected PIP joint	4.08	0.92-18.2	0.065

*Values are reported for LF with PALF as the reference group.
OR, odds ratio; CI, Confidence Interval.

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Discussion

Long-term results of treatments are highly relevant to patients with Dupuytren's disease, as recurrence rate was recently found to be among the most important attributes for patients in making treatment choices.[13] Attempting to reduce the relatively high recurrence rate of traditional needle aponeurotomy for Dupuytren's contracture, we developed an alternative approach using an extensive and fundamentally different percutaneous release technique and subsequent autologous lipografting (PALF). The purpose of the present study was to assess the 5-year results of a randomized controlled trial comparing this treatment with standard limited fasciectomy (LF) for primary Dupuytren's contracture. We found that at 5 years follow-up significantly more joints in the PALF group than in the LF group had a recurrence (74% versus 39%, p < 0.001), based on either having undergone a secondary procedure or having an increase in extension deficit of more than 20 degrees. In line with this finding, the degree of total extension deficit was significantly worse after PALF than after LF. Extension deficit was worse for PIP joints compared with MP joints, and for PIP joints the difference in extension deficit between both treatment groups was also larger than for MP joints. No differences were found in patient-reported outcomes.

In this study, PALF-treated digits had a recurrence rate that was 35% higher than that of LF-treated digits at 5 years after treatment (74% versus 39%). This finding is in line with the previously reported higher rate for conventional needle aponeurotomy. A question that remains is whether the recurrence of PALF is better than for conventional needle fasciotomy. Comparison with previous literature requires caution because differences in definitions can importantly influence recurrence rate.[14,15] In addition, factors such as patient selection can influence outcome in different studies. Having said this, when we compare our results with the only other randomized study comparing fasciectomy and needle fasciotomy for Dupuytren's disease to date, using a comparable TPED-based definition for recurrence, the 45% difference found in the present study (32% vs 77%) is smaller than the previously reported 64% higher recurrence rate of traditional needle aponeurotomy (PNF) as compared with LF at 5 years (21% versus 85%).[11] Without a direct head to head comparison of traditional needle aponeurotomy and PALF,

accounting for baseline differences and using similar outcome measurements, however, it can not be concluded whether this difference is statistically significant.

The inferior recurrence rate of PALF is particularly evident at the PIP joint level, as indicated by the larger between-treatment group differences in 5-year recurrence rates and extension deficit for affected PIP joints (38% and 19 degrees) than for MP joints (28% and 14 degrees). This finding confirms the general observation that PIP contractures are more difficult to treat and, as a result, have comparatively poorer results. It also suggests that PALF may be more valuable for patients with affected MP joints than for PIP joints, since MP joints generally have a smaller change of a recurrent contracture.

This study has a number of limitations. A first limitation is the loss-to-follow-up. Reasons for this were diverse and are inherent to this Dupuytren population, such as a number of patients who deceased or who were not in sufficient health to participate in the long-term follow-up. Despite this, baseline characteristics were similar between the treatment groups included in the 5-year follow-up. A second limitation is that our study included a relatively high proportion of patients with diathesis factors, which limits the generalizability of the results. This may also have contributed to the relatively high recurrence rates of LF (i.e., 21% in Van Rijssen et al. compared to 32% when applying a similar definition in our study). A third limitation is that we estimated the degree of extension deficit for those patients who had underwent a secondary procedure at the 5-year follow-up examination using their preoperative contracture. This assumed that patients' threshold for undergoing treatment remains unchanged over time, which may not always be correct. Despite of this, this allowed us to estimate extension deficits for patients while without this analysis; only patients with limited recurrence would have been included. Fourth, we used a composite endpoint of recurrence that does not take into account when in time patients who had underwent a revision procedure reached this endpoint. Future studies may take this individual variation into consideration in order to allow for time-to-event type analyses to predict longer-term outcomes, such as risk of recurrence, at the individual patient level. Finally, we had limited power to assess the long-term outcomes separately for affected MP and PIP joints due to the small sample size, which may have precluded us from finding significant differences at the MP joint level.

In conclusion, we found that among patients with primary Dupuytren's disease, percutaneous needle aponeurotomy and lipofilling provided less durable corrections as compared with LF at 5 years follow-up, although the 35% higher rate may be lower than previously has been reported for traditional PNF. After LF, convalescence is typically long, impeding an early return to work or daily manual activities.[16,17] In contrast, patients treated with PALF returned to normal use of the hand after an average of 9 days as compared with an average 17 days for LF patients in our previous study.[9] This highlights the less-invasive nature of the technique. In addition, both contracture correction and recurrence after PALF is better for MP joints than for PIP joints. Taken together, when comparing both techniques in primary disease, PALF provides good short term outcome with quick convalescence and less complications when compared with LF, while LF offers straighter fingers at 5-year follow-up.

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Part **IV**

VOLUME AND OUTCOMES

7

Surgeon Volume and The Outcomes Of Dupuytren's Surgery: Results From A Dutch Multicenter Study

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Abstract

Objective: For a number of major complex surgical procedures, the outcomes are better when performed by surgeons with higher procedure volumes. The purpose of this study was to examine the relations between surgeon procedure volume and the outcomes of Dupuytren's surgery.

Design: Observational study from 2011-14

Setting: Consortium of 6 dedicated hand surgery practice sites in The Netherlands

Participants: 588 patients who underwent surgery for Dupuytren's contracture by one of the 16 surgeons from the participating sites.

Main exposure variable: Annual surgeon volume

Main outcome measures: The degree of residual contracture, full release rate and any postoperative adverse event examined within 3 months of surgery.

Results: Mean annual surgeon volume was 51 among the 16 surgeons, and ranged from 4 to 86 procedures. The majority of patients had primary Dupuytren's contracture (79%) and underwent open fasciectomy (74%). Multivariable regression analyses showed that surgeon volume was linearly related to all three outcomes, and identified no optimal volume threshold. Performing 10 additional procedures per year was independently associated with nearly 0.8 degree less residual contracture (p=0.002), 9% higher odds of attaining a full release (p=0.037), and 11% lower odds of experiencing an adverse event (p<0.001). Nonetheless, patient-related factors had larger impacts on all three clinical outcomes than surgeon volume.

Conclusion and relevance: In this study of practicing hand surgeons, surgeon volume varied widely, and a higher volume was associated with less postoperative residual contracture, higher full release rates, and fewer adverse events. These findings imply that increasing surgeon procedure volume provides an opportunity for improving the outcomes of Dupuytren's surgery.

Introduction

For certain major high-risk surgical procedures, associated outcomes are better for surgeons performing a large number of such procedures.[1-3] For example, lower mortality rates have been consistently linked to a higher procedure volume for various complex oncologic and cardiovascular procedures.[4-9] Such findings are important because they provide the premise on which surgical training and specialization is based. They have also prompted recent recommendations for the centralization of complex surgical care.[10] Whether such volume-outcome relations exist for common relatively minor surgical procedures remains less well understood.[11,12]

Dupuytren's disease is a very common, progressive fibromatosis of the hand.[13] It begins with the formation of nodules and scar-like tissue underneath the palmar skin. Over time, cords typically develop that extend, thicken and contract, causing flexion contractures of the affected finger joints. Contractures typically involve the metacarpophalangeal (MCP) and/or the proximal-interphalangeal (PIP) joint. The ring and little fingers are most times affected. As a result, hand function may be impaired and quality of life diminished.[14-16] Although it occurs among people from all ethnicities, global prevalence rates range from 3 to 6% in Caucasians.[17-19] The exact cause remains incompletely understood, but there is a strong genetic component.[20]

Surgery is the mainstay of treatment for Dupuytren's contracture, which aims to improve contractures to restore function. Two of the most common techniques are open fasciectomy, in which the pathologic tissue is surgically removed, and needle fasciotomy, in which cords are only transected through the skin.[19,21-23] However, the outcomes of both treatments vary widely across individual patients, depending on patient-, and disease-specific characteristics.[24] For example, contractures at the level of the MCP joint typically have more favorable prognosis than those of the PIP joint.[25-28] On the other hand, outcomes may depend as much on the surgeons' experience and how often he/she performs both procedures, with higher volume surgeons being more likely to attain successful outcomes and attaining fewer adverse events.

Using data from a consortium of 6 practice sites in the Netherlands, we sought to clarify the relation between surgeon procedure volume and the outcomes of Dupuytren's surgery. Our specific aim was to quantify the magnitude of effect of surgeon

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volume on three objective clinical outcomes – the degree of residual contracture, the probability of a full contracture release, and the risk of any type of adverse event – relative to other clinical predictors.

Methods

Study design and patients

This study was based on an analysis of data from a consortium of 6 dedicated hand surgery practice sites in the Netherlands of all patients undergoing a surgical procedure for Dupuytren's contracture between November 2011 and February 2014.

All participating sites submitted the data into a registry including a wide range of information on patient demographics, disease characteristics and treatment characteristics. Patient factors derived from the database were patients' age, gender and coexisting conditions. Disease characteristics included the severity of contracture, the number of digits treated, bilateral disease, which fingers and joint levels were affected, and family history of Dupuytren's disease. Treatment characteristics included the type of surgical procedure and whether patients had recurrent disease. Trained hand-therapists prospectively gathered the data as part of standard clinical practice and used it to direct therapy, ensuring the completeness and accuracy of the data.

We included all adult patients with a diagnosis of Dupuytren's disease who underwent open fasciectomy or needle fasciotomy. We excluded patients with an isolated MCP contracture of less than 20 degrees and those undergoing concomitant surgery (e.g. carpal tunnel release) on the treated side that could confound outcome assessments. Patients with recurrent disease were accepted if they met the other eligibility criteria.

Our local institutional review board approved this study, which was performed in accordance with STROBE guidelines.[29]

Primary and secondary outcomes

The primary outcome for this study was the degree of total residual contracture. Certified hand-therapists examined the degree of active extension deficit at baseline and at visits occurring between 6 weeks and 3 months of surgery using a finger goniometer for each affected finger. Specifically, extension deficit was examined at the MCP, PIP and DIP joint levels for each finger, and summed to obtain the total degree of residual contracture. To allow for comparison between patients with single versus multiple-digit

involvement, we used the data from the digit most severely affected at baseline (e.g., highest total extension deficit).

Secondary outcomes were the probability of a full release, defined as less than 10 degrees of total extension deficit, and the occurrence of an adverse event assessed up until the same time point. Adverse events included sensory disturbances, scar sequelae, wound-related problems, infection, edema, cold intolerance, neurovascular problems, loss of hand strength, hematoma, tenosynovitis, skin fissures, flare reaction, thenar atrophy, and skin flap necrosis. The outcomes chosen in this paper were influenced by the findings from a previous study from our group examining the preferences patients with Dupuytren's disease have regarding their treatment.[33] Moreover, we decided on early outcomes because we assumed that they would better reflect the proficiency of a surgeon than longer-term outcomes, such as recurrence, which may depend more on patient factors[30-32].

Main exposure variable: surgeon volume

Our main exposure variable, surgeon procedure volume, was examined at the surgeon-level. For each procedure, the identity of the treating surgeon was obtained from the database or, in case data were missing, from electronic health records. Providers who had no knowledge of this study entered the identity of the surgeon at the first preoperative consultation but had the opportunity to change the identity at subsequent time-points in case someone other than the original surgeon performed the procedure. Surgeon volume was defined as the average number of surgical procedures per year each participating surgeon performed for Dupuytren's contracture during the study period. For statistical modeling and inferences, all outcomes were examined at the patient-level.

Analysis

First, we categorized surgeons into volume strata according to tertiles and summarized the unadjusted outcomes among these strata using descriptive statistics. Continuous variables were reported as means±SD and categorical variable using frequencies.

We used multivariable linear and logistic regression models to examine possible relations between surgeon procedure volume and the degree of total residual

contracture, the probability of a full release, and the risk of any type of adverse event. Since the factors affecting each outcome may differ, we adjusted for a separate set of covariates for each of the outcomes that were determined using a backward stepwise selection approach, a systematic search of literature using the QUIPS tool[34] (unpublished data), and based on clinical validity. The final linear regression model for the degree of residual contracture ultimately included patients' age, gender, the joint levels affected, number of digits treated, bilateral disease, primary or recurrent disease, pre-treatment degree of extension deficit, surgical technique and surgeon experience (the number of years in practice of the operating surgeon) as covariates. The logistic regression model for the incidence of full release included patients' age, gender, diabetes, whether a PIP joint was affected, the number of digits treated, primary or recurrent disease, pre-treatment degree of extension deficit, surgical technique, and surgeon experience. The logistic regression model for the incidence of an adverse event included patients' age, gender, diabetes, whether a PIP joint was affected, the number of digits treated, primary or recurrent disease, pre-treatment degree of extension deficit, surgical technique, and surgeon experience. To assess the general form of the relationships between volume and outcomes, we tested for non-linearity by assessing whether non-linear models fitted the data significantly better than the linear models. In addition, we used receiver-operating curves relating various thresholds for surgeon volume to the clinical outcomes to identify optimal volume-thresholds associated with improved outcomes.[35] Based on the abovementioned regression models, we plotted the adjusted outcomes against surgeon volume to illustrate the effect of surgeon volume on the three outcomes. To assess the relative magnitude of effect of surgeon volume as compared with clinical predictors, we created forest plots with the beta-coefficients and log-odds of volume and clinical factors that were significantly associated with each of the outcomes of interest.

The sample of our study population of nearly 600 cases was based on the data available and insights regarding the number of factors associated with outcomes.[21,36] As a general rule, each independent covariate requires about 10-20 cases when using linear regression,[37] indicating an adequate sample size.

The probability of Type1 error was set at 0.05 for all analyses. All analyses were performed with SPSS(version 22.0) and RStatistical software(version 3.3.0).

Results

Patient and surgeon characteristics

We identified a total of 666 patients undergoing a surgical procedure for Dupuytren's disease between 2011 and 2014. After applying our eligibility criteria, 588 patients
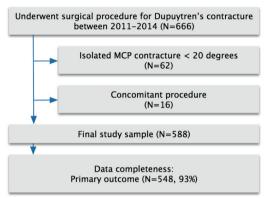

Figure. 1. Selection of patients for inclusion in the study.

remained to form our study sample (Figure 1). The majority were men and had primary Dupuytren's disease. Seventy-four percent underwent open fasciectomy and 26% underwent needle fasciotomy. Table 1 details demographic and clinical characteristics of our sample.

Table 1. Demographic and disease-specific characteristics of the study sample (n=590).

Variable	
Age, years.	63 ± 10
Male gender, %	77
Diabetes, %	11
Recurrent disease, %	29
Bilateral disease, %	60
Family history of disease, %	48
N treated digits	1.7 ± 0.8
Tubiana grade	
I, %	30
II, %	45
III, %	20
IV, %	5
Baseline extension deficit, degrees	
Total†	70 ± 36
MCP joint level	27 ± 25
PIP joint level	37 ± 27
DIP joint level	6 ± 12

Plus-minus values are means ± SD.

†Both affected and unaffected joints are included in these values.

A total of 16 surgeons performed all procedures at 6 different practice sites. They were trained at 7 different institutions, and their mean experience (number of years in practice) was 9.7 years (range, 6 months to 29 years). Twenty-five percent of the surgeons were female. Mean annual surgeon volume was 51 and ranged from 4 to 86 procedures. Surgeons differed in terms of the proportions of primary cases (p=0.027), bilateral cases (p<0.001), patients with affected MP joints (p=0.009), and the mean number of digits (p<0.001) they treated, indicating a need to adjust for these factors.

Follow-up data was available for the primary outcome (residual contracture) for 93% (n=547) of patients. All patients had follow-up data available for adverse events. Patients who lacked data on the primary outcome were not significantly different from those with data available in terms of baseline characteristics with the exception that those with follow-up data were treated for more digits (Suppl.Table 1).

Suppl. Table 1. Demographic and disease-specific characteristics compared between patients with and without data available on the primary outcome (total residual contracture).

Variable	Data available (n=547)	Data unavailable (n=41)	*p*
Age, years.	63 ± 9	62 ± 12	0.512
Male gender, %	77	76	0.843
Diabetes, %	11	12	0.812
Recurrent disease, %	30	20	0.143
Bilateral disease, %	60	61	0.917
Family history of disease, %	47	59	0.160
No. treated digits	1.7 ± 0.8	1.3 ± 0.8	0.002
Total extension deficit, degrees†	70 ± 37	62 ± 29	0.128

Plus-minus values are means ± SD.
†Both affected and unaffected joints are included in these values.

Clinical outcomes

Overall, the average degree of total contracture improved from 70 degrees from baseline to 24 degrees residual total contracture at follow-up. About one-fourth of digits were fully released. (Figure 2). Forty-seven percent (n=278) of patients experienced at least one adverse event.
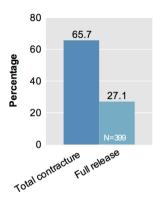

Figure 2. Percentage change in the degree of total contracture (active extension deficit) at follow-up from baseline and the rate of full release in the study sample (n=547).

The three most common adverse events were sensory disturbances, scar sequelae and wound-healing problems (Table 2).

Table 2. Adverse events in the study sample (n=590).	
Sensory disturbances	12 (72)
Scar sequelae	12 (71)
Wound healing	8 (47)
Edema	4 (25)
Wound infection	3 (18)
Cold intolerance	2 (10)
Circulatory problems	2 (9)
Nerve injury	1 (7)
Subjective loss of hand strength	1 (7)
Hematoma	1 (6)
TVS	1 (4)
Skin fissure	1 (3)
Flare reaction	1 (3)
Necrosis skin flap	1 (3)
Thenar atrophy	0 (1)
Values are percentages (numbers).	

Surgeon volume and outcomes

Figure 3 shows that the unadjusted clinical outcomes among the three volume strata improved with increasing volume.
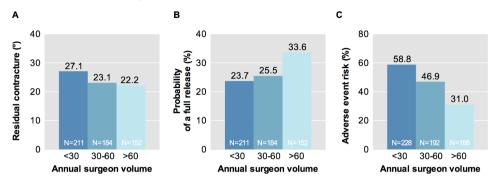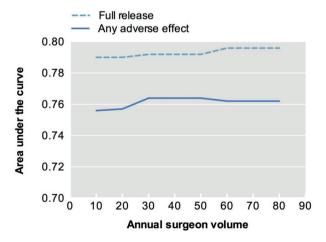

Figure 3. The unadjusted degree of residual contracture (A), probability of a full release (B), and the risk of at least one postoperative adverse effect (C) among three surgeon volume strata.

For none of the outcomes (degree of residual contracture, full release and adverse events), non-linear models were a significantly better fit compared to the linear models (p=0.053, p=0.517, and p=0.517, respectively). This indicated that the relation was linear for all three outcomes, which was further substantiated by the receiver-operating curves showing no obvious optimal volume thresholds (Suppl.Figure 1). Therefore, we analyzed surgeon volume as a linear term.

Suppl. Figure. 1. The influence of various surgeon volume-thresholds (at 10, 20, 30, 40, 50, 60, 70, 80 surgical procedures per year) on the ability of the multivariable models to distinguish (area under the curve statistic) between patients with and without a full release (dotted line) and patients who had at least 1 postoperative adverse event and those who did not (continued line).

In multivariable regression analyses, surgeon volume was significantly and inversely related to the degree of residual contracture at follow-up (beta coefficient=0.8, p=0.002). Hence, with every 10 additional procedures per year the degree of residual contracture improved by 0.8 degrees (Figure 4).
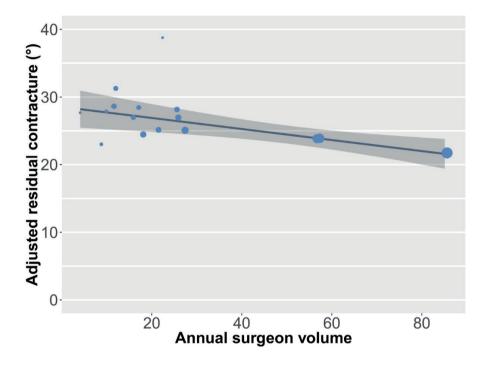

Figure 4. *The relation between surgeon volume (mean number of surgical procedures performed for Dupuytren's disease per year) and the degree of postoperative residual contracture, adjusted for patient factors, treatment characteristics, and number of years in practice. Each dot represents 1 of the 16 participating surgeons. The size of each dot corresponds to the relative contribution of each surgeon to the multivariable model. The thin lines represent 95% confidence intervals.*

As compared with other clinical predictors, such as an affected proximal-interphalangeal joint, and type of procedure, however, this magnitude of effect of surgeon volume was relatively small (Figure 5).
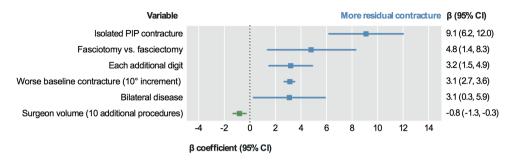

Variable	More residual contracture	β (95% CI)
Isolated PIP contracture		9.1 (6.2, 12.0)
Fasciotomy vs. fasciectomy		4.8 (1.4, 8.3)
Each additional digit		3.2 (1.5, 4.9)
Worse baseline contracture (10° increment)		3.1 (2.7, 3.6)
Bilateral disease		3.1 (0.3, 5.9)
Surgeon volume (10 additional procedures)		-0.8 (-1.3, -0.3)

β coefficient (95% CI)

Figure 5. Plot showing clinical factors that were significantly associated with the degree of residual contracture from the final multivariable regression model that also adjusted for age, gender, primary or recurrent disease, and the number of years in practice. The corresponding horizontal lines represent the 95% confidence intervals.

Surgeon volume was also directly related to the probability of attaining a full release (odds ratio=1.09, p=0.037): with every 10 additional procedures per year, the odds of a full release increased with 9% (Figure 6). Again, this magnitude of effect was small in comparison with other clinical predictors (Figure 7).
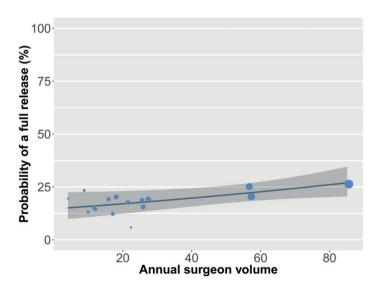

Figure 6. The relation between surgeon volume (mean number of surgical procedures performed for Dupuytren's disease per year) and the probability of a full release, adjusted for patient factors, treatment characteristics, and number of years in practice. The thin lines represent 95% confidence intervals.

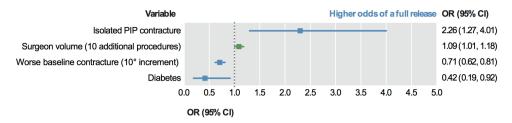| Variable	Higher odds of a full release	OR (95% CI)
Isolated PIP contracture		2.26 (1.27, 4.01)
Surgeon volume (10 additional procedures)		1.09 (1.01, 1.18)
Worse baseline contracture (10° increment)		0.71 (0.62, 0.81)
Diabetes		0.42 (0.19, 0.92)

OR (95% CI)

Figure 7. Plot showing clinical factors that were significantly associated with the probability of a full release from the final multivariable regression model that also adjusted for age, gender, primary or recurrent disease, diabetes, and the number of years in practice. The corresponding horizontal lines represent the 95% confidence intervals.

Lastly, the odds of any type of adverse event decreased with increasing surgeon volume (odds ratio=0.89 p<0.001; Figure 8); with every 10 additional procedures the odds decreased by 11%. Again this effect was smaller than that of the two other significant predictors (the number of treated digits and type of procedure) in the model (Figure 9).
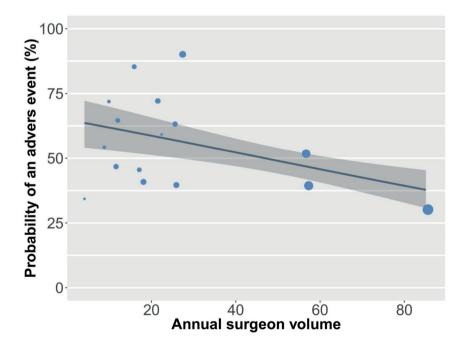
Figure 8. The relation between surgeon volume (mean number of surgical procedures performed for Dupuytren's disease per year) and the probability of any adverse effect, adjusted for patient factors, treatment characteristics, and number of years in practice. The thin lines represent 95% confidence intervals.
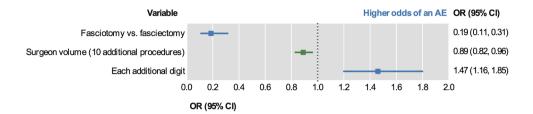
Figure 9. Plot showing clinical factors that were significantly associated with the risk of any adverse effect from the final multivariable regression model that also adjusted for age, gender, preoperative contracture, diabetes, affected PIP joint, type of procedure, and the number of years in practice. The corresponding horizontal lines represent the 95% confidence intervals.

7

Discussion

In this study involving 16 practicing surgeons from 6 hand surgical practice sites in the Netherlands, we examined whether the number of surgical procedures they performed annually for Dupuytren's contracture was related to the subsequent outcomes. We found that surgeon volume varied widely, and that a higher volume was an independent predictor of three objective clinical outcomes: less residual contracture, a higher odds of a full release, and a lower odds of an adverse event.

In this study, performing 10 additional procedures per year was associated with nearly 1 degree less residual contracture. From a functional perspective, this finding may be of limited value. However, each 10 additional procedures per year was also independently associated with 9% higher odds of attaining a full release and 11% lower odds of experiencing an adverse event, both of which are of greater importance considering the tendency of contractures to recur after treatment and the burden of a required reintervention over time and adverse events. Notably, the general form of the relations remained linear up to over 80 procedures per year. This is similar to what has been reported for several major complex surgical procedures[2,38,39], such as abdominal aortic aneurysm repair and lung cancer resection, but differs from the behavior of the volume-outcome association found in, for example, groin hernia repair, another relatively minor, although quite different, surgical procedure.[40] We believe that these findings underscore the technical difficulty of achieving a full release for patients with Dupuytren's contracture while simultaneously minimizing the risk of any type of adverse event.

For all three outcomes, the impact of surgeon volume on outcomes was relatively small compared to a variety of clinical characteristics. Although only few high quality prognostic studies have specifically assessed the predictors of outcomes of Dupuytren's treatment and, to our knowledge, none previously considered surgeon volume as a factor, this finding may not be surprising. Many clinicians will surely recognize the poor prognosis associated with certain clinical factors such as PIP joint involvement.[25,41,42] We feel that the strong and independent associations between patient factors and all three outcomes emphasizes the importance of deciding when to intervene in Dupuytren's contracture. Furthermore, the range of independent predictors of outcomes identified in

this study may be used to better design future prognostic studies as well as to more accurately counsel patients about their expected surgical outcomes. For example, we found that 10 degrees of worse contracture preoperatively corresponds to 29% lower odds of a full release whereas each additional digit treated increases the risk of an adverse event by 47%.

Finally, our findings may have direct implications for those responsible for assessing the quality of surgical care delivered to Dupuytren's disease patients. The limitations of the current methods for ensuring a surgeon's competence and proficiency, such as continuing medical education initiatives, are well acknowledged as they are not directly linked with actual outcomes or performance standards..[43,44] As clinical registries similar to the one used in the present study become more widely available, we expect that outcomes-based assessment of surgeons will become more feasible.[45] The link between higher procedure volume and improved outcomes in this study shows that tracking the number of procedures a surgeon performs for Dupuytren's disease may provide a much more direct way of assessing his or her proficiency in treating this condition.

Current understanding of volume-outcome relations is limited to a large extent to major complex surgery.[40] By virtue of quality data from the participating sites, we were able to examine whether such relations hold true for Dupuytren's surgery using three objective outcomes. These data were complete (93% primary outcome) and prospectively gathered by independent hand-therapists. Moreover, it allowed for a rigorous adjustment for a wide range of clinical characteristics. Some, however, may question the decision to only include fasciectomy and needle aponeurotomy in determining surgeon volume. By doing so, we did not take into account the potential volume-effects of other, perhaps similar, procedures in the hand and assumed that the magnitude of effect was equal for needle and open Dupuytren's surgery. However, when assessing whether there is a link between volume and outcomes for a previously unexplored surgical procedure, one has to manage with the data available. After identifying these associations, a next step could be to examine the extent to which they are mediated by type of procedure and/or other surgeon characteristics. Another limitation is that we only had access to data from trained, practicing surgeons who operated at dedicated hand surgical practice sites. Our findings may therefore not apply

to those working in a different context. Finally, although we observed clear associations between surgeon volume and outcomes, we cannot prove causality. Higher volume surgeons may have had better outcomes because they were more proficient as a result of performing more procedures (practice-makes perfect hypothesis) or they may have already more proficient and therefore attracted more patients (selective-referral hypothesis).[1] In the Netherlands, patients with Dupuytren's disease, however, are mostly referred by family practitioners, and we believe referrals to depend more on proximity of services rather than the recognition of surgeon's outcomes, making the first explanation more likely.

Surgical outcomes and how often a surgeon performs a procedure will always vary.[10] In this study among fully trained practicing surgeons performing Dupuytren's surgery, surgeon volume varied widely, and a higher volume was associated with less residual contracture, a higher probability of a full release, and a lower risk of adverse events. These findings imply that increasing a surgeon's procedure volume provides an opportunity for improving their outcomes in Dupuytren's surgery. The insights about the relative extent to which procedure volume affects outcomes is also critical to informing the discussions concerning optimization of provider-related factors and the proposed pros and cons of regionalization of Dupuytren's disease care.

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8 **Summary and Discussion**

Overview

This thesis addressed a number of controversial questions and gaps in our knowledge on the treatment and outcomes in Dupuytren's disease. We did so according to 4 specific aims. The first aim was to examine the comparative effectiveness of CCH (Clostridium Collagenase Histolyticum) injections, PNA (percutaneous needle aponeurotomy) and LF (limited fasciectomy) in daily clinical practice. The second aim was to examine the extent to which patients were functionally satisfied after LF and determine what predicts this satisfaction. The third aim was to evaluate the long-term efficacy of PALF (extensive percutaneous needle aponeurotomy with lipofilling) versus LF. The fourth and last aim was to clarify the extent to which the operating surgeon, in particular how many procedures performed per year, was related to outcomes.

Hence, we structured this thesis into 4 *Parts*: 1. comparative effectiveness, 2. patient satisfaction, 3. Long-term comparative efficacy of PALF, and 4. volume and outcomes. In this chapter, we summarize and discuss each part, followed by a general discussion and future perspectives.

Part I. Comparative effectiveness

The myriad of existing treatment options for Dupuytren's contracture highlight the lack of a single, optimal, treatment technique that fully meets the needs of every patient.[1] Each technique has proposed unique pros and cons. What defines optimal varies from patient to patient, depending on clinical disease manifestation, functional limitations, and their needs and expectations.[2] Given the uncertainty about the effectiveness of all existing treatments relative to eachother, an evaluation of the results of the most popular techniques (LF, PNA and CCH) was urgently needed to clarify this issue.[3]

PNA versus LF

In Chapter 2, we compared the results between PNA and LF.[4] Outcomes assessed included the degree of total residual contracture, MHQ scores, and complications. To account for differences in baseline characteristics between treatment groups we applied inverse-probability weighing. This novel statistical approach eliminates selection bias due

to such differences by weighing each patient based on their probability of receiving PNA or LF given known cofactors.[5] This probability is expressed as a propensity score.

After propensity score-based inverse probability weighing, 78 PNA and 103 LF patients who were very similar at baseline remained for the outcome comparison. The degree of total residual contracture at follow-up (6-12 weeks) was not significantly different (PNA, 21 degrees; LF, 18 degrees). However, the PNA group showed a lower mild complication rate (PNA, 5.2 percent; LF, 24.3 percent) and reported significantly larger increases in the MHQ scores of satisfaction, work performance, ADL, and overall hand function.

The authors of the only randomized clinical trial comparing the efficacy of LF and PNA suggested the appropriateness of PNA for mild contractures.[6] The findings of our study, which are based on data gathered as part of standard practice, reinforce that, for such cases, PNA can be as effective as LF at reducing contractures in the short-term – at a lower risk of complications.

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CCH versus LF

Large, placebo-controlled studies have demonstrated the efficacy and safety of injectable CCH for Dupuytren's contracture.[7-12] In some countries, CCH is now increasingly accepted as an alternative to surgery in select patients.[13] To assess the comparative effectiveness of CCH in actual practice, we designed a study (Chapter 3) assessing the treatment versus LF – the current surgical standard.[14] Outcomes assessed included the degree of residual contracture, MHQ scores, and complications assessed at 6-12 weeks after surgery or the last injection. In this study, we analyzed affected MCP joints separately from PIP joints because the latter tend to have poorer outcomes. Prior to these outcome comparisons, we applied propensity score analysis to account for differences between the two treatment groups.

In the 132 matched patients who underwent treatment (n = 66 CCH or n=66 LF), we found that the degree of residual contracture for affected MCP joints was not significantly different (13 degrees versus 6 degrees; p = 0.095). Affected PIP joints showed worse residual contracture in the CCH group as compared with LF group (25 degrees versus 15 degrees; p = 0.010). However, CCH was associated with fewer serious

complications and larger improvements in the MHQ scores of satisfaction, ADL, and work performance.

In this study comparing CCH to LF for Dupuytren's contracture, the short-term contracture correction achieved was similar among the treatment groups. Hand function recovers faster after CCH. CCH therefore requires consideration for patients as a treatment alternative to LF, particularly for those who seek a minimally invasive treatment option and a more rapid return to use of their hand.

CCH versus PNA

In Chapter 4, we report the results of CCH compared with PNA, which remains the most popular minimally invasive treatment for Dupuytren's contracture.[15] Because relative changes in outcomes may be more meaningful to patients than absolute outcomes, we assessed the extent both treatments *improved* outcomes.[16] In addition to early objective outcomes, we also assessed the change in MHQ scores through 1 year-follow-up.[17,18]

Among the 130 patients (93% Tubiana I or II) who were matched based on their propensity scores (n=46 PNA and n=84 CCH), post-intervention improvement in contracture was similar: 26 degrees (65% improvement from baseline) for PNA vs. 31 degrees (71%) for CCH for affected MCP joints (p = 0.163). For affected PIP joints, this improvement was 16 degrees (50% improvement) vs. 17 degrees (42%; p = 0.395), respectively. No serious complications were noted in either of the two treatment groups. Of the mild adverse effects, only skin fissures and sensory disturbances were seen in both groups. Through 1-year follow-up, patients reported similar improvements in the overall MHQ score (PNA, 5.3 points vs. CCH, 4.9 points; p = 0.912).

In Tubiana grade I or II patients (mild cases), CCH and PNA appeared equally effective at reducing contractures. Both treatments improve overall hand function, which was maintained through 1-year follow-up.

Part 2. Patient satisfaction

Most surgeons continue to regard open LF as the surgical standard of care, particularly in cases of PIP joint involvement and advanced cases. The previous chapters confirm that LF effectively reduces contractures at an reasonable complication rate. Yet outcomes

that seem good from a clinician's perspective may not necessarily satisfy patients. In Chapter 5, we examined patient satisfaction with hand function after LF, and identified preoperative factors that predicted this satisfaction.[19]

Demographics and disease-specific factors were assessed from a prospective cohort of 194 patients treated with LF. After patients were classified into a satisfied vs. unsatisfied category using the question of the MHQ pertaining to satisfaction with hand function, multivariate regression modeling identified predictors of patient satisfaction. At a mean 10 months (range, 6 to 12) after fasciectomy, 84 percent were satisfied with their hand function. In multivariate analyses adjusting for the significant effects of the degree of postoperative residual contracture (and complications, a higher preoperative hand appearance subscore and male gender was associated with a higher likelihood of becoming satisfied after fasciectomy. Other demographic- and clinical factors were not independently predictive of patient satisfaction.

The independent relations between objective outcomes and patient satisfaction identified in this study emphasize the importance of complication prevention and full releases from the patient perspective. The finding that the extent patients value the appearance of their hand predicts satisfaction shows that restoration of a normal hand appearance may be important to Dupuytren's disease patients.

Part 3. Long-term comparative efficacy of PALF

Attempting to improve on existing treatment options for Dupuytren's contracture, Hovius and Khouri introduced *extensive* percutaneous needle aponeurotomy with lipofilling (PALF) in 2011.[20] In this hybrid technique, a more elaborate PNA technique is applied where multiple to hundreds of 1-2 mm deep perforations through the skin are made with a needle. These then disrupt the structural integrity of the underlying fascial structures, allowing them to lengthen under tension. In contrast to the few discrete transverse fasciotomies in classical aponeurotomy, the large number of perforations and cuts creates a mesh that is permissive to fat grafting in addition to releasing the cords. Autologous lipoaspirate is then grafted into the subcutaneous dissection plane.[21]

The initial results of a single-blinded, multicenter, randomized clinical in which this PALF is compared with standard limited fasciectomy have been published previously.[22]

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Eighty patients were randomly assigned to each treatment group. Through 1-year follow-up of this, almost full release of affected MCP joints was obtained in both groups, whereas some residual contracture remained at the level of the PIP joint. Patients undergoing PALF resumed normal use of the hand more rapidly. In Chapter 6, we report the 5-year results of this study, focusing on long-term recurrence rates. Thirty-one PALF and 21 LF patients participated in this extended post-trial follow-up assessment. At 5 years, more affected joints in the PALF group than in the LF group met our primary composite endpoint for recurrence (74% vs. 39%, p = 0.002).

Hence, we conclude that PALF is safe, provides a quick full recovery with mild complications, effectively reduces contractures, and has a good 1-year recurrence rate. However, the technique unfortunately does not provide as durable corrections over time as does LF.

Part 4. Volume and outcomes

Practice makes perfect; Luft and colleagues first highlighted this common concept by demonstrating that the number of procedures a surgeon performs (surgeon procedure volume) affected his or her outcomes.[23] For a variety of major complex surgical procedures, such relations between volume and outcomes are now established[24-29], which have had substantial policy and clinical implications.[30] In Chapter 7, we examined whether similar volume-outcome relations existed for Dupuytren's surgery in practicing hand surgeons.

Using data from 6 hand surgical practice sites in the Netherlands, we clarified the relations between surgeon volume and three clinical outcomes in 588 patients who underwent a surgical intervention (PNA or LF) for Dupuytren's contracture. Annual procedure volume ranged from 4-86 procedures per year, and was related to all three outcomes in a linear fashion. After rigorous adjustment for a wide range of patient- and treatment factors, performing 10 additional procedures per year was associated with nearly 0.8 degrees of less residual contracture (p=0.002), 9% higher odds of attaining a full release (p=0.037), and 11% lower odds of experiencing an adverse event (p<0.001). Compared with patient-related factors, the effect of surgeon volume on clinical outcomes was relatively small, however.

In conclusion, the number of procedures performed for Dupuytren's surgery per year varied among practicing surgeons. Higher procedure volume was independently associated with improved clinical outcomes, that is, with less residual contracture, a higher probability of a full release, and a lower risk of adverse events. However, the effect of procedure volume on outcomes was smaller than that of a variety of patient factors.

General discussion, limitations, and future perspectives

Considering the studies in Part 1 (Comparative Effectiveness of CCH, PNA and LF) together, the primary finding was that while certain outcomes differed across the three techniques others did not.[4,14,15] For both functional recovery and complications, CCH and PNA were superior to LF in the short-term. As compared with LF, CCH resulted in fewer serious complications and larger improvements in the MHQ scores of satisfaction, ADL, and work performance examined within 3 months of treatment. PNA also resulted in larger improvements in the same MHQ scores and had a lower mild complication rate than LF. In contrast, the degree of short-term contracture correction achieved in daily practice was comparable for all three treatments with the exception that affected PIP joints had a relatively small but significantly worse residual contracture after CCH than after LF. These results underline the usefulness of CCH and PNA for less advanced cases, in particular for those seeking the benefits of a minimally invasive treatment.

In Part 2, we focused on patient satisfaction after LF and the influence of initial correction, complications, and preoperative factors on this satisfaction.[19] The majority of patients (84%) were satisfied with their hand function after surgery. We found, after accounting for the positive effect of better correction and avoidance of complications on patient satisfaction, that a higher preoperative MHQ hand appearance score and male gender predicted a higher level of satisfaction. The link between patient satisfaction with the degree of correction and complications highlights the importance of these two objective outcomes from the patient perspective as well as provides some reassurance regarding the validity of patient satisfaction as an outcome in Dupuytren's disease. The independent link between hand appearance and satisfaction suggests that restoration of a normal hand appearance may be relevant to patients. After all, the hand is considered

to be the most visible part of the body only second to the face, and fulfils a crucial role in social interaction, functioning, physical expression.[31,32] These findings highlight that providers should not only assess the detrimental impact flexion deformities can have on the physical well-being of Dupuytren's disease patients, but also their possible impact on patients' psychological well-being.

In part 3, we compared the long-term efficacy of PALF versus LF and found that at 5-years significantly more affected joints after PALF had a recurrent contracture than after LF (PALF, 74% vs. LF, 39%). Given the earlier results of this RCT, we concluded that PALF is safe and effective at reducing contractures and has a reasonable long-term recurrence rate. The recurrence rate for PALF seems lower than what has previously been reported for classical PNA (85%) by van Rijssen and Werker et al. but was not as good as anticipated. Given these findings, we feel that this technique holds a unique position among the other available treatment options in being most suited for patients who seek a fast recovery, low risk of complications and a long-term recurrence rate that lies between that of LF and classical PNA, while it can be used to treat multiple rays at once.

In all previously mentioned studies, it became evident that objective clinical outcomes varied widely across individual patients independent from the treatment technique used. In Part 4, we sought to clarify whether the number of procedures a surgeon performs per year (surgeon volume) could explain this variation in individual patient outcomes. Surgeon volume varied considerably, and a higher volume was associated with three objective clinical outcomes. Performing 10 additional procedures per year was associated with nearly 1 degree less residual contracture, 9% higher odds of attaining a full release, and 11% lower odds of experiencing a complication. Given the higher risk of early recurrence in patients with a poor initial correction *ref*, these findings may have significant long-term clinical implications for patients. The independent link between volume and complications suggests an opportunity for surgeons to minimize their complications by increasing their surgical volume. However, the impact of surgical volume on these three outcomes was smaller than that of various patient characteristics. This emphasizes the importance of proper patient selection and adequate timing of treatment in achieving optimal outcomes in Dupuytren's disease.

The studies in this thesis have limitations that are worth considering. First, treatment assignment in the comparative effectiveness studies in Part 1 was not random. This leaves the possibility of confounding by indiciation bias, which could have influenced our results. However, to minimize the risk of bias due to non-random treatment assignment, we applied propensity score analyses.[33] This approach also allowed us to use data that were gathered as part of standard practice to make valid comparisons of treatments using one of the largest cohorts of Dupuytren's disease patients studied. Our findings may therefore be more externally valid (i.e. more broadly generalizable) than those obtained from strictly controlled clinical trials. In Part 2, we focused specifically on satisfaction with hand function, whereas patient satisfaction may be subdivided in other subdomains such as satisfaction with proximity of services, the actual treatment given, or the clinicians involved. We decided upon satisfaction with hand function because the primary goal of treatment in Dupuuytren's disease is to restore hand function. Nevertheless, all other domains of satisfaction may be important in judging the quality of Dupuytren's disease care, and the extent to which they are related to objective clinical outcomes is an important future research topic. Third, the follow-up duration in nearly all our studies (with the exception of Part 3) did not allow for reliable assessment of long-term results of the treatments examined while long-term outcomes may be just as important to patients as short-term outcomes when considering treatments.[34] Our studies therefore do not provide evidence on the long-term comparative effectiveness of CCH, PNA and LF. Fortunately, several clinical trials are currently underway that aim to address this knowledge gap.[35,36] Finally, our volume-outcome study in Part 4 only investigated the relations between surgeon procedure volume and three provider-oriented outcomes. Clarification of the possible relations between procedure volume more subjective outcomes may provide us with unique perspectives and opportunities on how we can optimize Dupuytren's disease care from the patient perspective.

Future perspectives

The need for more comparative studies is clear, in particular RCT's that help to further establish the comparative effectiveness of current treatments for Dupuytren's disease. However, the person who plans to undertake such a trial is bound to face practical,

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financial, and even ethical challenges. One of the biggest challenges in recruitment, in our experience, is that patients are usually reluctant to participate in a trial if they risk randomisation to an entirely different technique (e.g. injection with Collagenase versus surgical fasciectomy). The studies in Part I underscored propensity score analyses as a useful tool in assessing the comparative effectiveness of different treatment techniques for Dupuytren's disease. Considering the ever-expanding number of treatment strategies and questions about their effectiveness, we believe that future studies that make appropriate use of such statistical techniques and observational, real-world data will be of increasing importance.

Disease manifestation in Dupuytren's disease is very heterogeneous. One of the problems encountered in practice as a result of this is the difficulty of applying averaged study results to individual patients. For example, using the findings in Chapter 4 to counsel patients who are considering CCH and PNA by stating that, on average, MCP contractures improve by 71% after CCH as compared with 65% for PNA is probably the best we can do from an evidence based medicine perspective. However, this may be quite inaccurate in many cases. A critical question that remains is whether the performance of more comparative studies provides the most effective approach of solving this issue of applying global evidence ("average treatment effects" measured as population means) to individual cases (individual patients who may differ from the population mean).

Clinicians are obviously aware that the same procedure can have different effects on different patients, and take multiple patient factors into account when counselling patients about possible outcomes. However, they do so in a largely, subjective and, mostly implicit, manner. Prognostic research has the potential to change the way this is done by proving tools that allow for a more objective, accurate estimation of the probability of certain outcomes. In contrast to comparative studies that focus on the effect of a single factor (difference between two treatments) on outcomes, prognostic studies aim to accurately predict outcomes from multiple factors. The previously mentioned tools have been given various names such as prediction model, prediction rule and prognostic models.[37-39] Many of such tools are now ingrained in the daily practice of providers across various medical and surgical specialties because of the prognostic value they provide. The Adjuvant! Online prediction model for breast cancer

recurrence is perhaps one of the best examples of how such a tool can fundamentally change and improve the way pretreatment consultations and decision making processes take place.[40-42] If efforts are undertaken to formalize outcome-prediction in Dupuytren's disease, we are confident that the same can be achieved for this population. Future investigators who plan to travel this road are recommended to use the secondary findings from Chapter 8 in their study design.

It seems that Collagenase, needle aponeurotomy, fat grafting, and fasciectomy will all have a role in the future treatment of Dupuytren's disease. Fortunately, investigators will be able to rely on both traditional and newer study designs to help unravel the best indications of each technique. Our findings support the value of Collagenase injection and needle aponeurotomy as first-line treatments in less advanced cases. Starting with these two minimally invasive techniques in such cases is an appropriate approach because of similar early outcomes in comparison with open surgery. Fasciectomy seems best reserved for advanced cases (i.e. severe diathesis, long-standing PIP contractures, multiray and/or recurrent disease) and/or those who seek the most durable corrections. Ultimately, each patient is unique and has his or her own concerns, needs, and expectations from treatment. Which treatment is most appropriate probably depends as much on these subjective factors as on similarities or differences in clinical outcomes. Until we find a cure for this chronic disease, the quest for more effective and safer treatment strategies continues – as it has for many decades.

8

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9 Dutch Summary
Nederlandse Samenvatting

Chapter 9

Dit proefschrift addresseert een aantal controversiele vraagstukken over de behandeling van de ziekte van Dupuytren. We hebben dit gedaan aan de hand van een viertal doelstellingen. Het eerste doel was om de relatieve effectiviteit van Collagenase injecties (CCH), percutane naaldfasciotomie (PNA) en selectieve fasciëctomie (LF) te beoordelen in de dagelijkse praktijk (Deel 1). Als tweede hebben wij de mate waarin patiënten na LF tevreden zijn bepaald én welke factoren hierop van invloed waren onderzocht (Deel 2). Onze derde doelstelling was om de lange termijn resultaten van extensieve percutane naaldaponeurotomie met lipofilling (PALF) te onderzoeken (Deel 3). Ons vierde en laatste doel was om te verhelderen in welke mate de chirurg, in het bijzonder hoeveel ingrepen hij of zij per jaar uitvoert voor Dupuytren, van invloed is op klinische behandeluitkomsten (deel 4).

De huidige behandelingen voor de ziekte van Dupuytren bieden bepaalde voor en nadelen. In hoofdstuk 2 vergeleken we PNA en LF op basis van de mate van restkromstand, verbetering in handfunctie (beoordeeld met de MHQ) en complicaties na behandeling. We maakten gebruik van propensity score-gebaseerde inverse probility weighing (IPW) om te corrigeren voor eventuele selectiebias. Na IPW bleven er 78 PNA en 103 LF vergelijkbare patiënten over. Deze twee groepen hadden geen significante verschillen in restkromstand na 6-12 weken follow-up (PNA, 21 graden LF, 18 graden). PNA had minder complicaties en resulteerde in significant grotere toenames in de MHQ scores van tevredenheid, werkprestaties en algemene hand functie. Deze resultaten laten zien dat PNA, op korte termijn, net zo effectief kan zijn als LF in het corrigeren van contracturen bij geselecteerde patiënten terwijl het risico op complicaties kleiner is.

In hoofdstuk 3 vergeleken we CCH met LF. In sommige landen wordt CCH in toenemende mate als alternatief op chirurgie gezien. We vergeleken beide behandelingen op basis van dezelfde uitkomsten als in het vorige hoofdstuk. Ook hier maakten we gebruik van propensity score analyses om te corrigeren voor baseline verschillen in beide groepen voor de behandeling. Bij de 132 propensity-score gematchede patienten (N=66 CCH en N=66 LF) vonden we dat de mate van restkromstand voor aangedane MCP gewrichten tussen beide behandelingen niet significant verschillend was (13 graden vs 6 graden, p=0.095). Aangedane PIP gewrichten in de CCH groep hadden echter meer restkromstand dan die in de LF groep (25 graden vs 15 graden, p=0.010). CCH resulteerde in minder ernstige complicaties en meer toename in

de tevredenheid, ADL en werkprestatie subdomein scores van de MHQ. Deze resultaten laten zien dat CCH een effectief alternatief kan zijn voor LF, met name voor patienten met een aangedaan MCP gewricht én de voordelen van een minder invasieve ingreep zoeken.

In hoofdstuk 4 vergeleken we CCH met PNA – waarschijnlijk de meest gebruikte minimaal invasieve behandeling op dit moment voor de ziekte van Dupuytren. Onder de 130 (93% Tubiana I of II) patiënten die vergelijkbaar waren (N=46 PNA vs N=84 CCH) was na behandeling de mate van verbetering in kromstand vergelijkbaar in beide groepen (65% verbetering voor PNA versus 71% voor CCH) voor MCP contracturen. Dit was ook het geval voor PIP contracturen (50% voor CCH versus 42% voor PNA). We vonden geen ernstige complicaties, en patiënten rapporteerden een vergelijkbare verbetering in de MHQ totaal score gedurende 1 jaar follow-up. Deze resultaten laten zien dat CCH en PNA vergelijkbaar zijn wat betreft hun effectiviteit in het corrigeren van de kromstand, verbeteren van hand functie en complicaties.

In hoofdstuk 5 bepaalden we patiënttevredenheid met hand functie na LF, en onderzochten wij welke preoperatieve factoren hierop van invloed waren. Nadat patiënten gecategoriseerd waren als tevreden of ontevreden met behulp van het specifieke item van de MHQ vragenlijst die over tevredenheid met handfunctie gaat, hebben we multivariabele regressie gebruikt om de voorspellende factoren te identificeren. Van alle patiënt was 84% tevreden met hun hand functie. Rekening houdend met de significante invloed van de mate van restkromstand én het optreden van een complicatie op tevredenheid, vonden we dat een hogere preoperatieve waardering voor het uiterlijk van de hand en het mannelijk geslacht gerelateerd waren aan een hogere kans om tevreden te zijn. Deze resultaten suggeren dat het herstel van het uiterlijk van de hand bij de ziekte van Dupuytren belangrijk is voor patienten. Ook helpt het inschatten in welke mate het legitiem is om patiënttevredenheid als uitkomstmaat voor kwaliteit te gebruiken bij de ziekte van Dupuytren.

In hoofdstuk 6 onderzochten wij lange termijn resultaten van PALF in een RCT. In totaal werden 80 patienten gerandomiseerd naar PALF of LF. Op 5-jaar vonden wij dat significant meer aangedane gewrichten in de PALF groep dan in de LF groep voldeden aan onze samengestelde primaire uitkomstmaat voor recidief (PALF 74% versus 39%). Wij beschouwen PALF als een innovatieve en veilige techniek die leidt tot een snel herstel

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tegen een laag complicatierisico. De lange termijn-resultaten van PALF zijn echter wat teleurstellender dan gehoopt.

In hoofdstuk 7 onderzochten we of er een relatie bestaat tussen hoeveel ingrepen een chirurg op jaarbasis uitvoert voor de ziekte van Dupuytren en de behandeluitkomsten. Voor veel verschillende algemeen chirurgische ingrepen is ondertussen een sterk verband aangetoond. Voor Dupuytren chirurgie is dit echter niet eerder onderzocht en onbekend. We hebben dit bij 588 patiënten onderzocht. Na rekening te houden met een diversiteit aan patient-factoren, vonden we dat het uitvoeren van 10 extra ingrepen op jaarbasis leidt tot bijna 1 graad minder restkromstand, 9% meer kans op een volledige release, én 11% minder kans op complicaties. De invloed van operatief volume is echter klein ten opzichte van de effecten van patiënt-factoren op deze uitkomsten.

De bevindingen van de studies in Deel 1 laten zien dat CCH, PNA en LF - bij patienten die geschikt zijn voor alle drie de behandelingen - even goede verbetering van de kromstand kan worden bereikt *op korte termijn*. Hand functie herstelt sneller na CCH en PNA in vergelijking tot LF, en ernstige complicaties komen minder vaak voor bij beide minimaal invasieve behandelingen. De resultaten in Deel 2 laten zien dat objectieve uitkomstmaten zoals restkromstand of complicaties van invloed zijn op de tevredenheid met de hand functie, maar dat deze patiënttevredenheid ook afhangt van hoe iemand zijn of haar aangedane hand eruit vindt zien. De hand is tenslotte, na het gezicht, het meest zichtbare lichaamsdeel en vervult een cruciale rol in het dagelijks functioneren en sociale interactie. Dit suggereert dat flexiecontracturen niet alleen functioneel beperkend zijn maar ook een negatieve invloed kunnen hebben op de psychische gesteldheid van patiënten met de ziekte van Dupuytren. De resultaten in Deel 3 laten zien dat PALF veilig en effectief is en geassocieerd is met een acceptabele lange-termijn recidiefkans. De recidiefkans van 74% lijkt lager dan dat van traditionele naaldfasciotomie technieken. Derhalve zijn we van mening dat PALF een unieke plek in de behandeling van de ziekte van Dupuytren inneemt. De resultaten van Deel 4 laten zien dat individuele patiëntuitkomsten erg uiteenlopen, en daarnaast dat hoe vaak een chirurg Dupuytren opereert van invloed is op zowel de mate van contractuurcorrectie als complicaties. Deze bevinding laat zien dat het verhogen van het operatief volume een strategie kan zijn om uitkomsten te verbeteren, zelfs bij ervaren gecertificeerde handchirurgen. Patiënt

factoren hebben echter een nog grotere impact op deze uitkomsten wat het belang van zorgvuldige patiëntselectie en timing van een operatie benadrukt.

De studies in dit proefschrift hebben tekortkomingen. Onze vergelijkende studies waren niet gerandomiseerd waardoor er risico is op zogenaamde "verborgen bias" (bias door factoren die je niet hebt gemeten die wel van invloed zijn op uitkomsten). We hebben niet onderzocht in welke mate operatief volume van invloed is op patient-gerapporteerde uitkomsten wat ons zou helpen het patientperspectief beter te begrijpen. Daarnaast was de follow-up duur in de meeste studies kort, waardoor we geen uitspraak kunnen doen over de lange-termijn effectiviteit van behandelingen.

Het is duidelijk dat we meer vergelijkende studies nodig zullen hebben, in het bijzonder RCT's met een lange follow-up duur. Tegelijkertijd zal de onderzoeker die dit wil doen geconfronteerd worden met praktische, financiële en ethische kwesties. Wij verwachten derhalve een grotere rol voor observationale studies die slim gebruik maken van nieuwe statistische methodes en de steeds groter wordende datasets die verzameld zijn in de dagelijkse praktijk. De vraag is echter in welke mate inzichten van RCTs en dergelijke vergelijkende studies betere zorg voor de individuele patiënt te leveren. Hoe de ziekte van Dupuytren zich uit verschilt enorm van patiënt tot patiënt. Het is de vraag in welke mate de gemiddelde resultaten van dergelijke studies in de praktijk van toepassing zijn op individuele patiënten.

In tegenstelling tot vergelijkende studies die zich richten op het effect van 1 factor op uitkomsten (verschil tussen behandelingen) beogen prognostische studies uitkomsten te voorspellen op basis van meerdere factoren. Dergelijke studies kunnen tools leveren om artsen helpen accurater en objectiever een inschatting te maken van de uitkomsten bij een bepaalde patient. Zulke tools heten ook wel een predictiemodel, predictieregel of een prognostisch model. Er zijn legio voorbeelden te geven uit andere medische velden waar dergelijke studies de manier waarop patienten worden geinformeerd en keuzes worden gemaakt hebben getransformeerd. Wij zijn ervan overtuigd dat hetzelfde kan worden bereikt bij de ziekte van Dupuytren. Toekomstige onderzoekers die van plan zijn dergelijke initiatieven te ondernemen worden sterk geadviseerd de nevenbevindingen van hoofdstuk 8 te gebruiken in hun studieontwerp.

Het lijkt erop dat Collagenase, fasciotomie, lipofilling én open chirurgie allemaal een rol zullen blijven spelen in de behandeling van de ziekte van Dupuytren. Diverse

onderzoeksontwerpen zullen nodig zijn om de indicaties van iedere techniek verder te verscherpen. De resultaten van dit proefschrift suggereren een aanpak waarin eerst CCH of PNA worden geprobeerd, met name bij patiënten met minder ernstige contracturen. Hoewel fasciëctomie de minste kans op recidieven geeft is deze behandeling ook het meest invasief en risicovol. Open chirurgie kan dus waarschijnlijk het beste worden bewaard voor patienten die minder geschikt zijn voor minimaal invasieve behandelingen. Uiteindelijk is iedere persoon met de ziekte van Dupuytren uniek met zijn of haar eigen zorgen en verwachtingen ten aanzien van een behandeling. Wij hopen dat de beschreven resultaten in dit proefschrift patiënten en clinici zal helpen bij het maken van keuzes in de behandeling.

Part **V**

APPENDICES

List of Publications
PhD Portfolio
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List of Publications

Advances in Minimally Invasive Treatment of Dupuytren Disease.
Hovius SE, **Zhou C**.
Hand Clinics. 2018 Issue devoted to Dupuytren's disease. Invited Article

Surgeon volume and the outcomes of Dupuytren's surgery: Results from a Dutch multicenter study.
Zhou C, Ceyisakar I, Hovius SER, Feitz R, Slijper HP, Lingsma HF, Selles RW.
Plast Reconstr Surg. 2018 Jul.

Comparative Effectiveness of Needle Aponeurotomy and Collagenase Injection for Dupuytren's Contracture: A Multicenter Study.
Zhou C, Hovius SER, Pieters AJ, Slijper HP, Feitz R, Selles RW.
Plast Reconstr Surg. Glob Open. 2017 Sep 25;5(9):e1425.

Comparative Effectiveness of Percutaneous Needle Aponeurotomy and Limited Fasciectomy for Dupuytren's Contracture: A Multicenter Observational Study.
Zhou C, Selles RW, Slijper HP, Feitz R, van Kooij Y, Moojen TM, Hovius SE.
Plast Reconstr Surg. 2016 Oct;138(4):837-46.

Predictors of Patient Satisfaction with Hand Function after Fasciectomy for Dupuytren's Contracture.
Zhou C, Hovius SE, Slijper HP, Zuidam MJ, Smit X, Feitz R, Selles RW.
Plast Reconstr Surg. 2016 Sep;138(3):649-55.

Percutaneous Aponeurotomy and Lipofilling (PALF) versus Limited Fasciectomy in Patients with Primary Dupuytren's Contracture: A Prospective, Randomized, Controlled Trial.
Kan HJ, Selles RW, van Nieuwenhoven CA, **Zhou C**, Khouri RK, Hovius SE.
Plast Reconstr Surg. 2016 Jun;137(6):1800-12.

Patients' preferences for treatment for Dupuytren's disease: A discrete choice experiment.
Kan HJ, de Bekker-Grob EW, van Marion ES, van Oijen GW, van Nieuwenhoven CA, **Zhou C**, Hovius SE, Selles RW.
Plast Reconstr Surg. 2016 Jan;137:165–173.

Collagenase Clostridium Histolyticum versus Limited Fasciectomy for Dupuytren's Contracture: Outcomes from a Multicenter Propensity Score Matched Study.
Zhou C, Hovius SE, Slijper HP, Feitz R, Van Nieuwenhoven CA, Pieters AJ, Selles RW.
Plast Reconstr Surg. Jul 2015;136(1):87-97.

Percutaneous aponeurotomy and lipofilling (PALF) versus limited fasciectomy for Dupuytren's contracture: 5-year results from a randomized clinical trial
Zhou C*, Selles RW*, Kan JH, Wouters RM, Van Nieuwenhoven CA, Hovius SE
Plast Reconstr Surg. (*equal contribution) Under Review.

Name PhD candidate: Chao Zhou
PhD period: 2013-2018
Erasmus MC, Department of Plastic and reconstructive surgery, and hand surgery
Promotor: Prof.em.dr S.E.R. Hovius
Copromotor: Dr. R.W. Selles

1. PhD Training

Epidemiology, study design, and statistics courses	Year	Workload
M.Sc. Clinical epidemiology NIHES	2013-2015	1960 hrs

Research integrity courses	Year	Workload
BROK and Good Clinical Practice	2013	30 hrs
Erasmus Research integrity	2014	3 hrs

Oral, poster presentations	Year	Workload
Oral – Comparative effectiveness of percutaneous needle aponeurotomy and Collagenase injection for Dupuytren's contracture: A multicentre observational study – Dutch Society for Surgery of the Hand (NvVH)	2017	20 hrs
Oral – Surgeon procedure volume and the outcomes of Dupuytren's surgery – Federation of European Societies for Surgery of the Hand	2016	20 hrs
Oral – Patient satisfaction and its determinants after fasciectomy for Dupuytren's contracture – International Dupuytren Symposium	2015	20 hrs
Oral – Comparative effectiveness of Clostridium Collagenase Histolyticum and limited fasciectomy – International Dupuytren Symposium	2015	20 hrs
Oral – Predictors of patient satisfaction with hand function after fasciectomy for Dupuytren's contracture – American Association of Hand Surgery	2015	20 hrs
Poster – Comparative effectiveness of Clostridium Collagenase Histolyticum and limited fasciectomy – American Association of Hand Surgery	2015	20 hrs
Oral – Surgeon volume and the outcomes of Dupuytren's surgery – Dutch Society for Plastic Surgery (NVPC)	2015	20 hrs
Oral – Patiënttevredenheid met handfunctie na fasciectomie en voorspellende factoren – Dutch Society for Plastic Surgery (NVPC)	2014	20 hrs
Oral – M. Dupuytren: klinisch onderzoek door een symbiose tussen de academie en periferie – Dutch Society for Plastic Surgery (NVPC)	2015	20 hrs
Oral – Collagenase injecties versus selectieve fasciëctomie voor de ziekte van Dupuytren: een propensity-score analyse studie – Dutch Society for Plastic Surgery (NVPC)	2014	20 hrs
Oral – Pulse at Xpert Clinic en Erasmus MC– Dutch Society for Movement Sciences	2014	20 hrs

Conferences and seminars (attendance)	Year	Workload
FESSH annual meetings	2016	2 dys
NVvH biannual meetings	2014-2017	12 hrs
NVPC biannual meetings	2014-2017	42 hrs
Kortjakje	2015-2017	12 hrs
ASSH / AAHS annual meetings	2014-2105	60 hrs

Awards and Funding (applications)	Year	Workload

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Michael Porter Value Based Health care prize	2014	60 hrs
Best initiative on patient outcomes		
Achmea Quality Award	2013	30 hrs

2. Teaching

Supervised M.Sc. thesis	*Year*	*Workload*
Katja Bogomolova (Erasmus MC)	2016	60 hrs
Yara Blok (VU Medical Center)	2015	60 hrs
Hanneke Pieters (Erasmus MC)	2015	100 hrs

Lecturing	*Year*	*Workload*
Musculoskeletal elective: common acute and chronic hand conditions	2013-2015	30 hrs

Skills	*Year*	*Workload*
Dutch course in microsurgery (coaching)	2013-2015	40 hrs
International course in microsurgery (coaching)	2014-2015	60 hrs

3. Organizing activities

Conferences and symposia	*Year*	*Workload*
22nd Esser Course "What's new in breast reconstruction?"	2014	50 hrs

Thanks Carin Oostdijk for the hundreds of e-mails, taking care of the administrative side of things and so much more.
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Dear Mieke Claushuis, thank you for all your love, advice, and caring in the past 12 years.
Thank you to all my friends in Amsterdam, Utrecht, and my new buddies in Maastricht for all the fun and laughter we've had.
Dear mom and dad, I addressed this thesis to you. Your empathy for people and drive to do good inspired me to go into medicine in the first place. Thank you for your unconditional love and support throughout my life. I feel blessed to be able to call you my parents.
Dear Dorith, lieve Do, jij zet mijn wereld op zijn kop. Jij maakt het leven anders, spannend en de moeite waard. Jij hangt al meer dan 12 jaar de slingers voor ons op. Dank je dat je onderdeel bent van mijn leven.

Chao Zhou was born in China but grew up the larger part of his life in the Netherlands. After graduating from *het Utrechts Stedelijk Gymnasium*, he started his medical studies after being decentrally selected by the VUmc school of Medical Sciences in Amsterdam. He developed his scientific interests during an internship at Harvard at the department of Neurosurgery of Childrens Hospital Boston (Joseph Madsen). However, his interest in reconstructive and hand surgery was sparked by professors Marco Ritt and Steven Hovius towards the end of his medical training in 2013. After his graduation, he decided to further develop his scientific skills, and went on to work on this thesis, receiving support and guidance from Steven, Reinier Feitz, Harm Slijper, and Ruud Selles. In 2014, they were awarded the Michael Porter Value Based Health Care prize on patient outcomes for Pulse, a web-based outcomes assessment tool, and how Erasmus MC and Xpert Clinic had been using it for clinical and research purposes. During this period, he obtained a Masters degree in Clinical epidemiology at NIHES. In 2016, he strengthened his clinical skills as a resident at the departments of plastic and reconstructive surgery at Erasmus MC (Léon van Adrichem) and Viecuri MC (John Sawor). In 2017, he was accepted into the competitive plastic surgery training program at Maastricht UMC+, directed by professor René van der Hulst. He is currently completing his 2-year general surgery pretraining as part of this program (professor Laurents Stassen). This year, he will co-found a company in his spare time with Andre Fialho and David Hawig that aims to transform health care delivery through natural language processing, artificial intelligence, and mobile technologies.

He now lives with Dorith Claushuis in the beautiful city of Maastricht.

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DUPUYTREN'S DISEASE:
MEASURE. COMPARE. PREDICT?

"Dupuytren's disease affects millions of people worldwide.

The authors of this thesis set out to fill a number of knowledge gaps concerning current treatments for the disease. In a series of clinical studies, they assessed the effectivenenes, patient satisfaction, and long-term results of these treatments.

In one of the largest studies to date, other factors besides treatment technique, such as a surgeon's annual procedure volume, are also explored to what extent they impact clinical outcomes.

It seems that needle aponeurotomy, Collagenase injection, fat grafting, and open fasciectomy may all continue to play a part in the management of this debilitating disease in the years to come.

Fortunately, future investigators can rely on both traditional and newer study designs, such as propensity score analysis, to further clarify which technique works best for whom- and under what circumstances.

Until we find a cure, the quest for safer and more effective treatment for this chronic disease continues - as it has for many decades."