# On minimally invasive treatment of Dupuytren's contracture

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Cover illustration: Apollo and Asclepius by Stig Blomberg, with a needle added by the author. This mural statue is 12 meters high and was placed on the wall of the main building at Sahlgrenska University Hospital in 1959. Apollo is holding the bow (without needle) in front of the rising sun of tomorrow, and Asclepius is still a child. The three triangles on the fundament symbolize the mission of a university hospital: to teach, to treat and to do research. The subject of this thesis covers all three: the author has trained numerous residents in PNF and has overseen the introduction of this method in the region, he has treated hundreds of patients and have finally written this thesis which provides a provisional answer to a specific, highly clinical question- how should moderate Dupuytren contractures be treated?
The answer has been added to Apollo's bow.

*To my surprise*

"(An operation) is an evil alternative which nothing other than an absolute necessity should force the surgeon to choose…"

Guillaume Dupuytren (1777-1835)

# Abstract

Dupuytren's disease is a common, benign disease in which myofibroblasts in the aponeurosis of the hand start to proliferate, contract and produce pathological collagen. This results in a Dupuytren cord, which eventually tethers the involved finger and reduces the extension of the involved joints- a Dupuytren contracture. The Dupuytren cord can be divided either mechanically through percutaneous needle fasciotomy (PNF) or by chemical digestion using injectable collagenase *Clostridium Histolyticum* (CCH). The latter treatment is considerably more expensive.

## Aim

The overall aim of this thesis was to compare the clinical and morphological results after percutaneous needle fasciotomy and collagenase treatment for Dupuytren's contracture.

## Methods

A randomized, single-blinded controlled study was designed and enrolled 156 patients with a Dupuytren contracture of at least 20° in the metacarpophalangeal (MCP) joint in a single finger. Between 2012 and 2014, 78 patients were randomized to needle fasciotomy, and 78 to treatment with collagenase. A single surgeon administered all the treatments, and all the patients were seen after one week and blinded to further follow-up.
Between November 2013 and October 2014, 39 patients were also examined by ultrasound before and after treatment in order to compare the morphological appearance of the cord rupture. The patients were assessed after six months, one year and two years by a single physiotherapist who was blinded to the treatment each patient had received. Outcome measures included measurements (joint motion, recurrence, prevalence of a Dupuytren cord) and patient reported outcome measures (URAM, Quick-DASH and VAS scales).

Study I reported the immediate results after treatment and at the one-year follow-up in 140 of the patients (71 treated by needle fasciotomy and 69 by collagenase), while Study III reported the final results at the two-year follow up for all 156 patients. The ultrasonographic evalutation before and after

treatment in 39 patients was reported in Study II and these results were correlated to the clinical results in 38 of these patients after two years in Study IV.

## Results

The ultrasonographic evaluation of the cord showed no significant difference in the rupture length of the cord between the CCH and PNF groups (Study II). The patients treated by CCH had significantly more pain and larger skin ruptures than the patients treated by PNF, but there were no other significant differences between the two methods after one year (Study I). Ninety-seven percent of the patients were examined after two years and 58 patients (76%) treated by CCH and 60 (79%) treated by PNF still had a straight MCP joint in the treated finger. In over 50 percent of the patients, no cords were detectable after two years. There were no significant differences in the reduction of PIP contracture, range of motion and patient reported outcomes between the two treatments (Study III) Correlations between the ultrasonographic properties of the cord before treatment showed that the vast majority of patients with recurrence or residual disease had iso-or hyperechogenic cords with nodular components at treatment two years earlier (Study IV).

## Conclusions

To summarize, there were no significant differences between PNF and CCH in terms of treatment effect at any time during this study, except for significantly larger skin ruptures and higher levels of pain reported by patients in the CCH group immediately after treatment. Both treatments disrupt the Dupuytren cord in a similar way and most patients were satisfied and retained a straight finger after two years. CCH was not found to have any superior results that could justify the difference in cost in a government-funded health-care system.

## Keywords

Dupuytren's disease, Dupuytren's contracture, Dupuytren cord, percutaneous needle fasciotomy, collagenase *Clostridium Histolyticum,* ultrasound

# Sammanfattning på svenska

Dupuytrens kontraktur är ett tillstånd som kännetecknas av att en sträng bildas på fingrets insida som successivt hindrar detta från att sträckas ut helt, vilket leder till krokiga fingrar. Denna sträng består av nybildad bindväv, och uppskattningsvis 5-10% av befolkningen har detta tillstånd som även kallas "vikingasjukan" eftersom det är vanligast i de nordiska länderna. Vanligen drabbas lill- och ringfingrar, men alla fingrar och tummen kan drabbas.

Tidigare har det enda behandlingsalternativet varit kirurgi. Den vanliga metoden har varit att man opererar med öppen teknik och avlägsnar hela strängen på en vanlig operationsavdelning, men de senaste åren har dock två nya metoder för att behandla detta tillstånd börjat användas.

På Handkirurgiska kliniken, Sahlgrenska universitetssjukhuset, infördes 2010 en ny metod för att räta ut fingrarna med ett minimalt ingrepp- nålfasciotomi. Vid denna metod skärs strängen som kröker fingret av via nålstick genom huden, och ingreppet kan ske i lokalbedövning på mottagningen. Detta är en väl etablerad metod i andra delar av Europa men har av olika anledningar inte använts i Sverige i större utsträckning. I stora delar av övriga landet infördes 2011 ett läkemedel (Xiapex®) som är ett enzym som försvagar strängen så att den kan delas. Läkemedlet injiceras i strängen på mottagningen, och dagen efter får patienten komma tillbaka och i lokalbedövning kan man då oftast räta ut fingret.

Båda metoderna upplevs som betydligt enklare för patienterna än öppen kirurgi, och införandet av dessa har också fått som konsekvens att man flyttat behandlingarna från operationsavdelningar till mottagningar. Emellertid är behandlingen med läkemedlet betydligt dyrare: en dos kostar idag cirka 6 500: -, medan nålfasciotomi betingar en materialkostnad på cirka 150: -. Läkemedelsbehandlingen kräver också två besök till läkare istället för ett, och är alltså mer resurskrävande.

Målet med studierna i denna avhandling har varit att undersöka om det finns någon skillnad i resultat mellan de två metoderna som kan motivera den högre kostnaden för läkemedelsbehandling

Mellan 2012 och 2014 lottades 156 patienter med Dupuytrens kontraktur på minst 20° i knogleden till behandling med antingen nålfasciotomi eller läkemedel.

Behandlingarna utfördes av en och samma handkirurg (förf.), och efter dessa kontrollerades resultaten av en och samma fysioterapeut efter 6 månader och ett och två år. Förutom objektiva mätningar av rörelseomfång fick patienterna även fylla i enkäter och självskattningsskalor. På 39 patienter gjordes även en undersökning av Dupuytrensträngen före och efter behandling med ultraljud av en röntgenläkare. Efter två år jämfördes ultraljudsfynden med resultaten för att undersöka om det fanns något samband mellan det ultraljudsmässiga utseendet hos strängen och risken att fingret skulle bli krokigt igen.

Studie I redovisar de kliniska resultaten hos 138 patienter efter ett år. Patienter som behandlades med läkemedlet angav högre grad av smärta i samband med behandlingen, och hade också större hudbristningar än de som behandlats med nålfasciotomi. I övrigt kunde inga skillnader noteras, och den absoluta majoriteten av de behandlade fingrarna var fortfarande raka och dess ägare nöjda.

Studie II visar att det ultraljudsmässiga utseendet efter det att strängen delats inte skiljer sig hos de flesta patienter som behandlats med nålfasciotomi eller läkemedel: strängen går av på ett ställe, och det avstånd mellan ändarna som uppstår är lika stort oavsett behandlingsmetod.

Studie III redovisar de kliniska resultaten hos 152 (97 %) patienter efter två år. De flesta behandlade fingrar (76 % respektive 79 %) var fortfarande raka, och det förelåg ingen signifikant skillnad i något avseende mellan metoderna. Intressanta fynd var att resterna av de delade strängarna reducerats eller till och med försvunnit hos över hälften av patienterna, och att de flesta patienter som hade en krokighet i leden framför knogleden fortfarande var raka i denna led trots att behandlingen inte utförts på denna nivå.

Studie IV visar att de patienter i studie II som hade tecken på återkomst av Dupuytrensträngar efter två år uppvisade nodulära förändringar och en viss signalstruktur på ultraljud före behandling. Någon jämförelse mellan de två behandlingarna kunde inte göras i detta avseende, och studien ger endast en anvisning om att ultraljudsundersökning före behandling kan korreleras till långtidsresultat.

Sammanfattningsvis kunde inga kliniska eller ultraljudsmässiga skillnader mellan de båda metoderna påvisas efter två år som skulle kunna rättfärdiga den högre kostnaden för läkemedelsbehandling med Xiapex®) när nålfasciotomi förefaller att ge samma resultat.

# List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I.     Strömberg J, Ibsen-Sörensen A, Fridén J.

**Comparison of treatment outcome after collagenase and needle fasciotomy for Dupuytren contracture: a randomized, single-blinded, clinical trial with a 1-year follow-up.**

Journal of Hand Surgery (Am) 2016: Vol 41: 873-80

II.    Strömberg J, Vanek P, Fridén J, Aurell Y.

**Ultrasonographic examination of the ruptured cord after collagenase or needle fasciotomy for Dupuytren's contracture.**

Journal of Hand Surgery (Eur) 2017: Vol 42:683-688

III.   Strömberg J, Ibsen-Sörensen A, Fridén J.

**Percutaneous needle fasciotomy versus collagenase treatment for Dupuytren´s contracture- a randomized, controlled trial with a two-year follow-up.**

Accepted for publication in The Journal of Bone and Joint Surgery

IV.    Vanek P, Strömberg J, Fridén J, Aurell Y.

**Morphological patterns of the pretendineous cord in Dupuytren's disease - a predictor of clinical outcome?**

Submitted.

# Contents

# Abbreviations

| | |
|---|---|
| **CCH** | Collagenase *clostridium histiolyticum* |
| **DASH** | Disabilities of Arm, Shoulder and Hand |
| **DC** | Dupuytren contracture |
| **DD** | Dupuytren's disease |
| **IQR** | Interquartile range |
| **MCP** | Metacarpophalangeal joint |
| **MRI** | Magnetic resonance imaging |
| **PIP** | Proximal interphalangeal joint |
| **PNF** | Percutaneous needle fasciotomy |
| **PREM** | Patient reported experience measure |
| **PROM** | Patient reported outcome measure |
| **p-value** | Level of significance |
| **RCT** | Randomized Clinical Trial |
| **URAM** | Unité Rhumatologique des Affections de Main |
| **US** | Ultrasound |
| **VAS** | Visual analog scale |

# Introduction

## Dupuytren's contracture – a brief history

Descriptions of permanent contractures of the fingers can be found in the Icelandic sagas from the 11th century, but the diagnostic entity known today as Dupuytren's disease was first described in Basel in 1614 by Felix Platter[1]. Had he not erroneously concluded that the flexor tendons caused the contracture, the eponym could have been his forever thereafter. Instead, it would take another 200 years until Baron Guillaume Dupuytren presented his findings to the Hotel-Dieu Hospital in Paris, thus claiming what is probably the most commonly used eponym in medicine today. In the same year as Dupuytren was born, Henry Cline Sr dissected two hands at St Thomas Hospital in London and found that the palmar aponeurosis was the origin of the cord and proposed its division by a cut through the skin, i.e. open fasciotomy[2]. This method was popularized by Dupuytren who performed his first operation on 12 June 1831 and lectured himself into the history of medicine on the subject. Interestingly enough, Dupuytren made a note that secondary wound healing after an open cut of the cord together with splinting in a straight position yielded superior results compared with a more minimal division with a small knife. Open fasciotomy for Dupuytren's contracture prevailed as the only treatment option until the dawn of modern surgery in the 19th century, when anesthesia was introduced and more thorough excisions of the pathological cords could be performed[3]. Until the 21th century, open fasciectomy was unchallenged as the most widespread treatment for Dupuytren contractures- the clinical end-result of Dupuytren's disease in the hand.

## Clinical aspects

The etiology of Dupuytren's disease remains unknown, and what have been believed to be risk factors over the years (e.g. horse wagon driving, hard manual labor, smoking, exposure to vibration and alcohol) have not been easily proved to be so[4]. Genetic factors, however, appear to be of importance as indicated by the significantly larger number of patients treated in the Nordic countries[5], where the prevalence has been estimated as 10% in men and 2% in women[6]. With age, the prevalence increases from approximately 12% at the age of 55 to 29% at 75 in an international population[7].
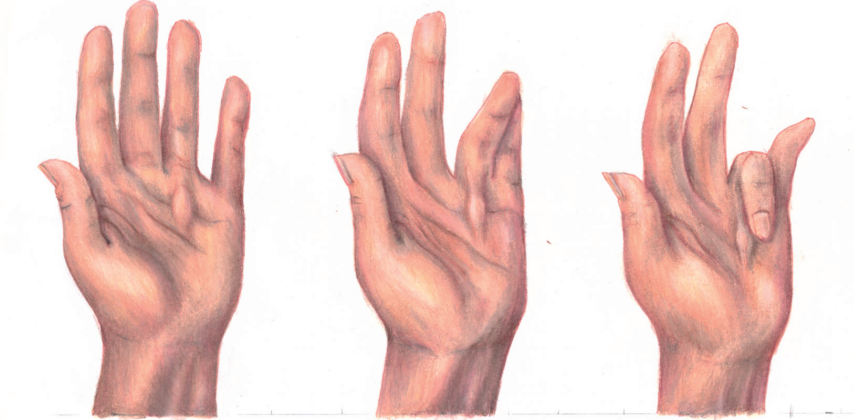


**Figure 1**. The development of a Dupuytren contracture. From one or more nodules, a cord is formed that eventually tethers the finger. (Illustration by Stella Funnemark)

Even though the etiology is unknown, the pathoanatomic changes are well described. Proliferation of the palmar aponeurosis leads to the formation of a rigid cord[8,9] that eventually compromises extension in the affected finger, a Dupuytren contracture (Figure 1). The rate at which this may occur in an individual patient is not easy to predict: in some patients, the only manifestation of DD is a single nodule over the years[10], while other patients have a rapid formation of DC over multiple joints and fingers resulting in a deterioration in hand function.

The reason why most patients seek medical care is usually an inability to fully extend one or more fingers, which leads to restrictions in hand function in activities of daily living and quality of life[11]. Adaptive strategies during the progression of the contracture are common, and a large number of patients report that the contracted finger is more of an inconvenience than a genuine problem in the early stages of the contracture. All treatments for Dupuytren's contracture aim to re-establish normal extension or at least significantly improve the extension of the contracted finger and to this day no treatment option provides a guaranteed cure for this condition. Recurrence, defined as the development of a contracture in a previously treated and straight finger, is notorious in Dupuytren's contracture, regardless of the method that is used[12] and constitutes an important outcome measure in all clinical studies. The definitions of the correction of contracture and recurrence are not, however, universal in studies regarding Dupuytren's disease.[13]

Indications for treatment are also difficult to compile: measurement of the degree of extension deficit as measured by a finger goniometer is probably the most common clinical procedure. The exact degree at which a patient should be recommended treatment is, however, largely dependent on the method. For instance, Hueston's statement that a contracture of approximately 30° in the MCP joint would indicate open fasciectomy[14] has been challenged with the introduction of CCH, with an indication for treatment at 20° in the same joint[15].

## Pathomorphological aspects

The development of a Dupuytren cord (Figure 2) has been described as a progression through three distinct histological phases - proliferative, involutional and residual[9]. In the early stages, the nodules formed in the palmar aponeurosis contain myofibroblasts with contractile properties, which eventually contract and deposit pathological collagen type III[16,17]. This collagen is usually absent in the normal adult fascia.[18] Morphological

studies of Dupuytren cords performed on specimens excised during open fasciectomy have shown that myofibroblast-rich nodules are abundant in the early stages of contracture, but that fibrillar cords without nodules are hypo-cellular[19] and correlate with greater contracture[20].
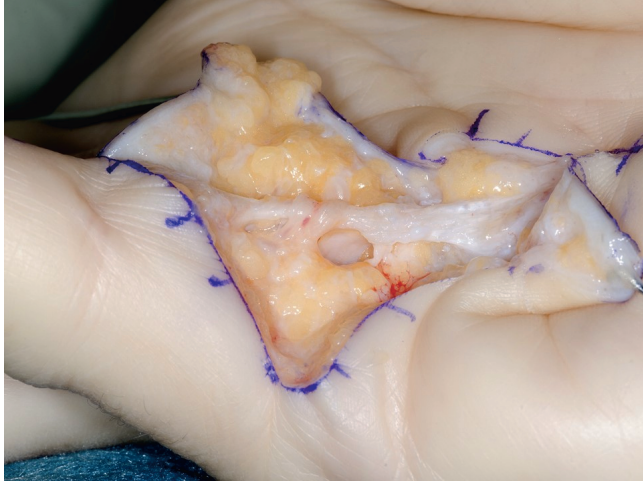


**Figure 2**. The Dupuytren cord exposed. In open fasciectomy, the skin is opened to allow the complete or limited excision of the cord and adjacent pathologic tissue

Rombouts *et al* proposed a histological staging of the cord structure according to cellularity and correlated these stages to the results after open fasciectomy after five years, where high cellularity indicated a higher incidence of recurrence after treatment[21]. Balaguer *et al.* confirmed these results 20 years later and concluded that histological staging is a reliable method for predicting recurrence of DD and that the pathologist can easily distinguish the three histological groups[22]. Bisson suggested that cells derived from DD are triggered to respond by contraction to loading[23]. There are few other studies that correlate any morphology of the Dupuytren cord to clinical outcome after treatment for Dupuytren's contracture.

# Treatment

The following section outlines the three most common treatment options for Dupuytren's contracture, ranging in invasiveness from open surgery through an extensive skin incision to minimally invasive treatments, i.e. the percutaneous methods of PNF and CCH. There are other "non-surgical" procedures such as radiation therapy[24] and extracorporal shockwave therapy but these are perhaps (if at all) indicated in patients with significantly less advanced Dupuytren's disease than in the patients in this thesis. There are also surgical procedures for patients with more advanced stages of Dupuytren's disease, e.g. recurrences after fasciectomy or with secondary joint contractures, which are beyond the scope of this thesis but are nevertheless required to cover the entire spectrum of Dupuytren treatment. The original operation, open fasciotomy, has become obsolete in the era of percutaneous procedures. Given the severity of the Dupuytren contracture of the participating patients in the following studies in this thesis, all three of these methods would be regarded as optional for this cohort.

## *Fasciectomy*

Limited fasciectomy is the most common treatment for Dupuytren's contracture in Europe today, but the rate of more serious complications is higher than for any other procedure[4,25]. The purpose of fasciectomy is to remove as much diseased palmar aponeurosis as possible and to attain full extension of the involved fingers (Figure 2). The procedure is generally performed in a regular operating theater under regional or general anesthesia. There are various skin incisions through which the Dupuytren cord and tissue can be accessed and the surgeon needs to be prepared for a situation with inadequate skin coverage after correction of a severe contracture. After closure of the skin, the hand is usually placed in a splint for at least a few days.

As already mentioned, a 30° contracture of the MCP joint would be regarded as an indication for treatment by most surgeons but there is no consensus in the literature regarding this.

The PIP joint is generally more difficult to treat due to secondary joint contractures that might be difficult to address even during open surgery and some studies have reported a poorer outcome if the preoperative contracture exceeds 60°[26]. However, the hyperextension of an unaffected MCP joint might well compensate for a moderate PIP contracture, since the patient will still be able to put the affected palm of the hand on a table. Complications are reported at a high rate after fasciectomy: as many as 26-34% of the patients in some studies[12,27] have reported nerve or volar plate injuries, hematoma, pain, loss of sensibility, delayed healing, stiffness or scar hypertrophy[28]. Recurrence rates vary from 11% to 27% in different studies[29,30] and recurrences after fasciectomy are generally regarded as more difficult to treat, regardless of the method that is used.

## *Percutaneous needle fasciotomy*

The percutaneous treatment of Dupuytren´s contracture by injection a corticosteroid into the cord with subsequent extension of the finger was first described by Madame de Seze in 1957[31]. A group of French rheumatologists refined the technique to divide the cord mechanically[32], and PNF became a popular method in some European countries in the 1990s[33].
PNF is usually performed in an outpatient setting under local anesthesia and the Dupuytren cord is divided by inserting a thin needle percutaneously at one or more locations in the cord. Various techniques for performing PNF have been described[34,35], e.g. a sweeping motion of the needle in the transverse plane of the cord or repeated perforations in different directions in the same plane (Figure 3).
The procedure can be repeated at multiple levels and in multiple fingers at the same time[36] and the patient is generally allowed to use the treated hand

immediately after treatment. The use of corticosteroids in addition to the mechanical division was proposed by Lermusiaux[33], but this has been the subject of debate. McMillan found a significantly higher range of motion in the treated joint after triamcinolone injections in conjunction with PNF at 24 months in a RCT[37], but the results of this study have been questioned on account of possible selection bias[38].
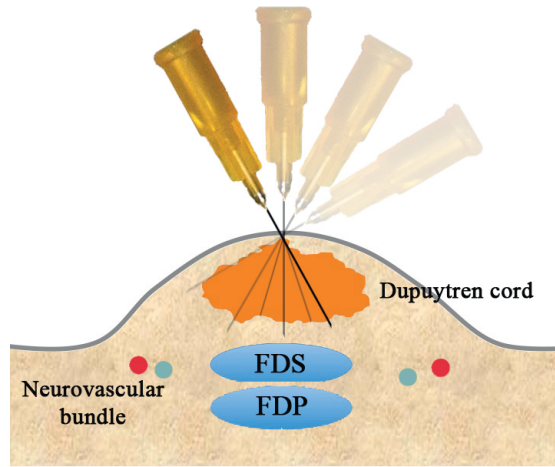


**Figure 3**. Schematic illustration of PNF: a needle is passed through the skin at one puncture site, and is used to divide the Dupuytren cord in one plane.

Complications after PNF are rare, where the most common is rupture of the skin during the extension maneuver, which has been reported to occur in 5-16%[33,39]. Periprocedural damage to the digital nerves or tendons is extremely rare[40,41]. Recurrences after PNF are reported at a high rate; van Rijssen et al. reported a discouraging recurrence rate of 85 % in 115 fingers after five years in a RCT in 2012[42]. However, 53% of the patients with a recurrence preferred another PNF. Pess at al. found a total recurrence rate of 48%, but with a large discrepancy between the MCP (20%) and PIP (65%) joints[39]. Higher age appears to be a success factor for PNF: both Van Rijssen and Pess have found an inverted correlation between age and risk of recurrence[39,42].

## Collagenase clostridium histolyticum

The concept of "pharmacodynamic exeresis", or enzymatic fasciotomy of Dupuytren cords was introduced in 1965, when Bissot injected a mixture of enzymes into the Dupuytren cords and reduced the contracture in two patients[43]. Although the results were promising, it would take another 44 years before a commercial product became an alternative for patients with Dupuytren's contractures. In 2009, Hurst *et al.* published a milestone study that introduced a new enzymatic treatment by collagenase derived from clostridium histolyticum bacteria[15]. This RCT compared the new collagenase (CCH) with placebo injections in 308 patients with a contracture of at least 20° and found a reduction in the treated joint to 0-5° 30 days after injection in 64% in the CCH group compared with 7% in the placebo group. A new era in which patients could be treated with a single injection had begun and CCH was soon approved by the U.S. Food and Drug Administration (Xiaflex®) and by the European Medicines Agency (Xiapex®) in 2011.

CCH injections are usually given in an outpatient setting. The drug is supplied in solid form and is reconstituted prior to injection with a specific volume of sterile diluent dependening on the joint that is going to be treated. For MCP joints, 0.39 mL is used and the mixture is injected into the pretendineous cord at three different levels through the same injection site (Figure 4). The patients are sent home with a light bandage and instructed not to use their hands until the follow-up visit, which used to be the next day. At the follow-up, a local anesthetic is injected and the affected finger is extended until the Dupuytren cord breaks.

Local adverse events in the injection area are common: in a multicenter study of patients treated with two doses of CCH, more than 75% of the patients had a contusion, injection site pain and edema after the injection. Skin ruptures were described in 11% of the patients and hematomas in 37% in the original study[44], while a later study by Peimer of 1082 patients reported skin ruptures in 16% of the patients and hematomas in 78%[45].
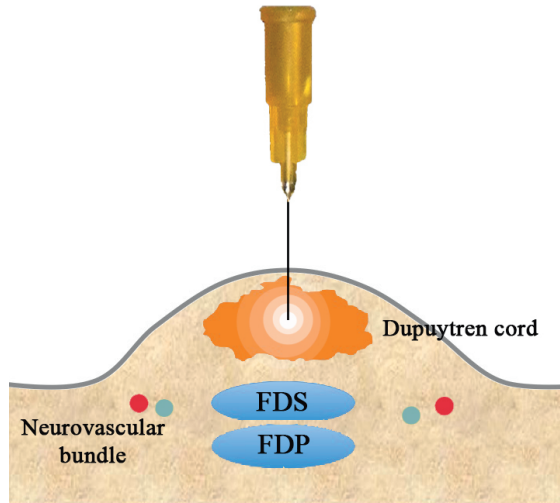


**Figure 4**. Schematic illustration of a CCH injection at one of multiple levels in the Dupuytren cord. The collagenase is injected centrally into the cord and an enzymatic breakdown of collagen starts. The next day, the patient returns and the cord is ruptured.

Peimer at al enrolled 643 out of 950 (68%) patients from five previous CCH studies in 2013 and reported a total recurrence rate of 35% (27% MCP, 56% PIP)[46] after three years. In the five-year data, the number of recurrences (defined as an increase of 20° in extension deficit) had increased to a total of 47% (39% MCP, 66% PIP)[47].

## *The role of hand therapy and splinting*

During the postoperative period after fasciectomy, collaboration between the patient, the surgeon and a hand therapist is strongly recommended[48] to ensure that good hand function is recovered.

There is no evidence for splinting after fasciectomy for Dupuytrens contracture[49], but the practise supposedly has a very long tradition in most hand surgery units. The evidence regarding the role of routine splinting after minimally invasive treatment is still largely lacking, with an exception of the study by Skirven *et al* concerning PIP splinting after CCH[50]. Joint changes secondary to the Dupuytren contracture, e.g. ligament shortening and capsular contraction, are initially unaffected by the division of the Dupuytren cord but can be overcome over time (Figure 5).
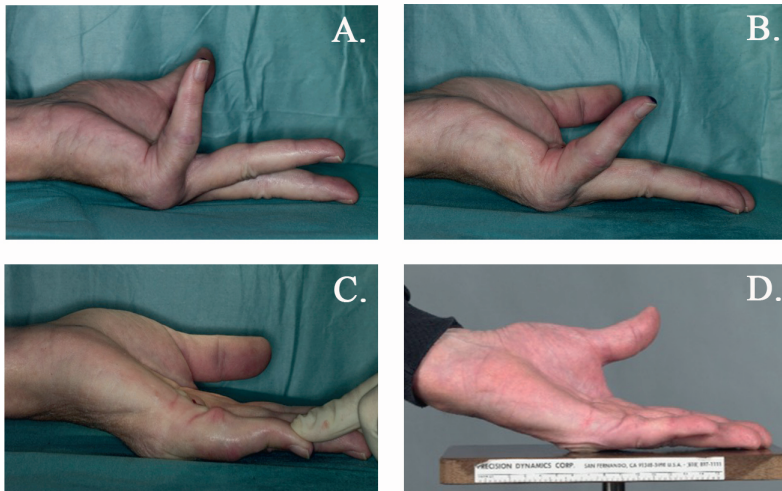


**Figure 5**. An illustration of a joint contraction secondary to a Dupuytren contracture, and the correction of this over time. A. Maximum active extension in the patient with a severe MCP contracture before PNF. B. The maximum active extension immediately after PNF.
C. The maximimum passive extension at the same time. To overcome these secondary changes to the joint, the patient was provided with a night splint for three months.
D. The active extension one year after PNF.

Even though the advantages of night splinting are not proven, disadvantages beside from possible patient discomfort are not likely. In our study we chose to give a night splint to patients who had a discrepancy between active and passiv extension of more than 10°.

## Outcome measures

There is little consistency in the reporting of outcomes of interventions in patients with Dupuytren's disease, which makes it difficult to compare the efficacy of different treatment protocols. A systematic review of the outcomes after treatment for Dupuytren's contracture found that the measurement of joint motion by using finger goniometry was included in all 91 articles, but patient reported outcome measures were only mentioned in 22 (24%), of which the DASH was the most common (12%)[51]. Disease-specfic questionnaires, such as URAM or SDSS, were rare. The following paragraphs briefly introduce the scientific foundation for the outcome measures used in this thesis.

### *Finger goniometry*

The extension deficit in one or more fingers is the hallmark symptom of Dupuytren's contracture and a dorsally placed finger goniometer is considered to be the gold standard for measurements of finger joints[52]. The results from a study by Engstrand et al[53] show that the interrater reliability of goniometric measurements of the finger joints in patients with DD is high or very high, with a measurement error of 3°.

## Patient reported outcome measures

### The URAM scale

Until 2011, no standard measurement was available to assess specific hand function in Dupuytren's disease and there was an obvious need for a patient-reported outcome to assess the severity of the disease and the efficacy of treatments. A questionnaire was developed and validated by a group of French rheumatologists to assess disability specific to Dupuytren's disease - the URAM (Unité Rhumatologique des Affections de la Main) scale[54,55] (Figure 6). The scale compromises nine simple tasks with five grades of difficulty and yields a result ranging from 0 (no difficulty) to 5 (impossible) for each item. The scale is easy to use, for both the patient and the examiner, and provides a specific patient-reported functional measure for Dupuytren's disease. The estimated clinically important change when evaluating the responsiveness of the scale has been reported to be 2.9 points[54]. A comparison with other instruments found that the response time for assessing disability was shorter with the URAM scale than with the CHFS or DASH questionnaire[55]. The relevance of the URAM-scale has been questioned[56,57] and an English questionnaire, the Southhampton Dupuytren´s Scoring Scheme (SDSS) has been developed. It challenges the URAM-scale[58].

| Table 5. English version of the Unité Rhumatologique des Affections de la Main (URAM) scale | | | | | | |
|---|---|---|---|---|---|
| Can you. . . | Without difficulty (0) | With very little difficulty (1) | With some difficulty (2) | With much difficulty (3) | Almost impossible (4) | Impossible (5) |
| 1. Wash yourself with a flannel, keeping your hand flat? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. Wash your face? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. Hold a bottle in one hand? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. Shake someone's hand? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 5. Stroke something or caress someone? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 6. Clap your hands? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 7. Spread out your fingers? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 8. Lean on your hand? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 9. Pick up small objects with your thumb and index finger? | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

**Figure 6.** The Unité Rhumatologique des Affections de Main questionnaire

**The Quick-DASH scale**

The most commonly used patient reported outcome measure (PROM) for any condition involving the hand is the Disability of Arm, Shoulder and Hand (DASH) questionnaire, or the short form: the Quick-DASH[59]. Its usefulness in Dupuytren's disease is limited since most patients have low scores before treatment (flooring effect), thus making it difficult to detect significant improvements after treatment. A survey of the clinician's use of the DASH and Quick-DASH did not mention Dupuytren's disease as a specific condition to be monitored by this instrument[60]. However, a change in the score may be of interest when comparing the results of different treatment modalities[61]. Budd *et al.* found a significant reduction from 15 to 8 points in 69 patients treated with fasciectomy, and concluded that the Quick-DASH is an acceptable PROM for tretment for Dupuytren's contracture [62].

**Visual Analog Scales**

The visual analog scale is a linear scale for the evalutation of pain and treatment satisfaction, in which the patients are asked to respond to a specific question[63,64]. The main advantage of this measure is that it measures changes over time in the same individual and VAS scales has been reported to have good interrater reliability[61]. In this study, we used VAS scales to assess PROMs (procedural pain one week after treatment, patient self-evaluation of treatment effect and satisfaction with treatment) and PREM.

*Patient reported experience measures*

In addition to the patient reported effect of the treatment described above, the individual patients' views of their experience whilst receiving care are becoming increasingly important to investigate. These patient experienced outcome measures are an indicator of the quality of patient care, although they do not measure it directly[65]. The difference between a PROM and a

PREM could be illustrated thus: the patient reports a successful reduction of a Dupuytren contracture by URAM and VAS scales compared to baseline (PROM), but his or her dissatisfaction with the time waiting for the surgeon to show up is expressed by a low score on a VAS-scale (PREM).

## Economic aspects of treatment

Percutaneous needle fasciotomy and CCH are similar in many respects: they require less resources since patients can be treated in an outpatient environment and the need for follow-up visits and hand therapy after treatment is significantly reduced compared with patients treated by fasciectomy. However, the cost of one dose of CCH and the subsequent second visit that is required make economic comparisons necessary, at least in a publicly funded health-care system.

Two American studies, one from the US in 2011 and one from Canada in 2013, have compared the cost-effectiveness of open fasciectomy, PNF and CCH. These analyses have taken account of all the costs associated with health-care providers and the need for hand therapy related to each treatment. Both studies concluded that limited fasciectomy was not costeffective, but the authors also stressed that a decision to refrain from this procedure would be a misinterpretation of the results - some patients with Dupuytren contracture will always need open surgery. Chen et al[66] also concluded that PNF is cost effective if the success rate is high, and that CCH treatment is cost effective when priced under USD $945. The Canadian study, which was performed before the introduction of CCH, went further and concluded that non-surgical management was the most cost-effective treatment and that PNF should be the preferred technique, if CCH was not introduced at a discounted price compared with the US market[67].

To date, no similar cost-effectiveness studies have been conducted in Europe and there are large variations in the use of CCH in the European countries[68]. Given the long tradition of PNF in France, it is no surprise that CCH is not reimbursed by the national health service, but other countries such as the UK (and some parts of Sweden) provide CCH in a hospital-financed context. In other countries, CCH is only available in the private market. The situation in Germany highlights the importance of the need for studies such as this: CCH was approved in 2011, but a new law (EMB-early benefit assessment) was passed the same year that demanded evidence of additional benefit for any drug compared with cheaper treatment options. Facing a probable unfavorable outcome from the assessment by Germany's Institute for Quality and Efficiency in Health Care (IQWiG), the manufacturer chose to withdraw CCH from the German market in 2012[69].

## Imaging Dupuytren cords

Even though they are easy to describe clinically, there are few published studies of the imaging of Dupuytren cords *in vivo* and even fewer with regard to morphological changes after treatment. Creteur *et al* investigated the echogenic properties of various stages of Dupuytren contracture by ultrasound and found that, in the early stages, the cord was predominantly hypoechogenic compared with the flexor tendon. In advanced contractures they found that the cord was iso- or hyperechogenic [70].

Uehara *et al.* reported that displaced neurovascular bundles could be detected by high-resolution ultrasound and that the severity of the contracture of the joint did not influence the distance between the neurovascular bundle and the cord[71]. Ultrasonography of Dupuytren cords has also been used to examine the cord prior to PNF[72] and CCH treatment[73] in order to minimize periprocedural damage to the neurovascular bundles, but neither of these studies examined the patient after treatment.

One exception to the absence of descriptive studies after treatment is the magnetic resonance imaging (MRI) study by Crivello *et al*. In this study, the volume of the pathological Dupuytren tissue in five patients with Dupuytren's contracture was measured before and after CCH treatment[74]. They found a significant reduction in the volume of the cord one month after injection compared with the baseline investigation of the palmar fascia and cord. Yacoe *et al* conducted another MRI study in which they investigated patients before limited fasciectomy and correlated the images to gross and histological examination of the excised cords. The study concluded that MRI was able to detect the nodular changes described in earlier morphological studies[75].

However, there are no reports on the ultrasonographically detectable changes in the cord after any type of local treatment and there are no studies that correlate ultrasonography of the cord to clinical outcome after treatment.

## Pilot studies

The following two studies, which present yet unpublished material, are included to provide an understanding of the rationale for the published studies in this thesis. In the first study[76], we followed the first 44 patients treated with PNF one year after treatment to ensure that this procedure could be a safe and efficient option for Dupuytren patients at our clinic. The second study focuses on the economic aspects of the introduction of PNF in an outpatient ward in a context where open fasciectomy in a regular operating theater used to be the only treatment option.

## Pilot study I: The introduction of PNF

**Introduction**: Until 2010, the only treatment offered at our department was open partial fasciectomy and an approximate indication was considered to be a contracture of at least 40° in the MCP joint. When percutaneous needle fasciotomy was introduced, we decided to initiate a study to follow the outcome of this novel treatment in order to ensure that complications were kept at a small number. The Regional Ethical Committee approved the study protocol (2011:805-11).

**Methods**: This study was a prospective study of all patients with Dupuytrens contracture treated with needle fasciotomy at the Department of Hand Surgery between November 2010 and March 2012. The main indications were the presence of a Dupuytren cord suitable for PNF and a flexion contracture, which limited the hand function of the patient. Both MCP and PIP joint contractures with well-defined Dupuytren cords were included. No specific flexion contracture was defined and recurrent Dupuytren cords were treated, as well as multiple fingers in the same hand. The patients were evaluated preoperatively, per-operatively, at two, 12 and 26 weeks and after one year. The treated hand was photographed throughout the study. The degree of the contracture, grip strength, pain, complications, presence of a Dupuytren cord, recurrence, need for reoperation and sick leave were recorded.

A total of 58 fingers in 44 patients were included. The majority of fingers were little fingers (n=24) and ring fingers (n=19). Four of the operated fingers were recurrences after fasciectomy. The median age of the patients was 68 years and the vast majority were men (n=42). The patients were allowed to use their hands normally immediately after the procedure.

**Results**: Most MCP and PIP contractures were corrected by PNF and retained the result after one year (Table 1). Recurrence (defined as a >20° extension deficit compared with the postoperative result) was observed in five fingers: three PIP and two MCP joints.

| | Preoperative | Postoperative | One year |
|---|---|---|---|
| Fingers (n) | 58 | 58 | 53 |
| MCP passive extension | 45° | 0° | 1° |
| PIP   passive extension | 34° | 10° | 20° |
| Pretendineous cords (n) | 53 | – | 29 |

**Table 1**. The main median results of the pilot study after one year.

There were few complications: the most severe was a reported transient hemi-digital paresthesia that resolved after three months in a patient treated for a PIP contracture. No cases of lesions of flexor tendons, hematomas or infections were registered. Superficial skin ruptures were seen in 16 fingers with a median length of 4 mm (3-6 mm). All these superficial wounds healed within two weeks. One interesting aspect of the results was that almost half of the pretendineous cords that were treated had disappeared after one year (Figure 7).
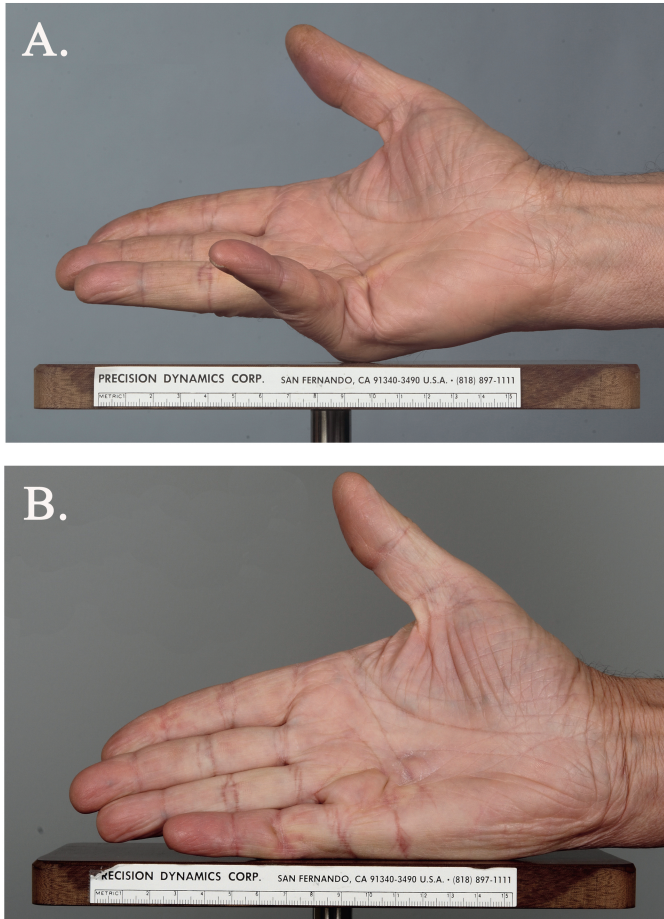
**Figure 7**. The same hand before treatment with PNF (A) and at the one-year follow-up (B). Note that the well-defined pretendineous cord before treatment had disappeared completely after one year.

**Conclusion**: Needle fasciotomy was regarded as an alternative to limited fasciectomy in selected cases with well-defined Dupuytren cords and the method was introduced as standard procedure at the department.

## Pilot study 2: Economic aspects of the introduction of PNF

**Introduction**: At the time of this stuyd, most regional hospitals in Sweden offered open fasciectomy as the only treatment option for Dupuytren's contracture. This study was designed to measure the economic impact of changing from open fasciectomy to PNF in suitable cases at a regional hospital. The study was conducted by Dr Per Holmdahl at Alingsås Regional Hospital between October 2012 and April 2013 under the supervision of the author.

**Method:** This was a prospective study of patients with Dupuytren's contracture with well-defined cords who met the criteria for open fasciectomy, defined as an extension deficit of 35°in the MCP-joint, but who could be treated with needle fasciotomy. During a period of six months, all 28 patients referred to a regional hospital in western Sweden with Dupuytren's disease were assessed for the study: six had minor symptoms or other conditions which excluded them from any intervention, eight patients had DD where arthrolysis of the PIP joint was expected and they were scheduled for open fasciectomy, and 14 patients were scheduled for percutaneous needle fasciotomy (Figure 9). Ten of these 14 patients met the inclusion criteria for this study and would thus have undergone open fasciectomy. The patients who were treated with PNF were assessed by telephone interview three months after the procedure. The hospital's economic department calculated all the costs associated with the two different procedures; an uncomplicated open fasciectomy was € 2,921 and PNF was € 361.

**Results**: After three months, eight of the 10 patients in the study group reported that they were satisfied with the result and did not need further evaluation. The other two patients were dissatisfied with the results and were assessed and offered open fasciectomy. One patient underwent surgery, the other declined because of the anticipated postoperative rehabilitation period. The difference in procedural costs was calculated at €20,500.
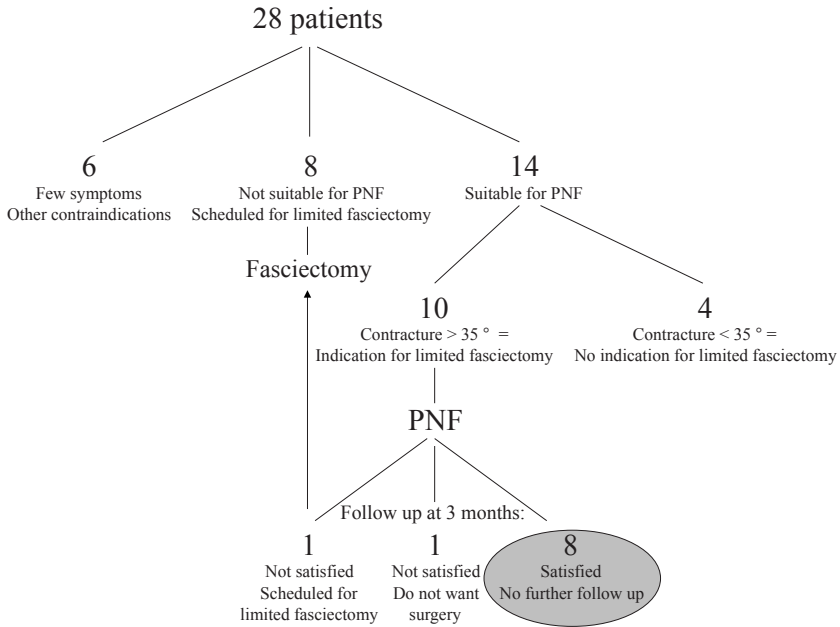
**Figure 9.** Flowchart of the patients in the economic pilotstudy. Out of 28 patients, 10 were treated by PNF and eight of these were satisfied after three months.

**Conclusion**: Percutaneous needle fasciotomy is a less expensive method to treat Dupuytren's disease and this study concluded that eight patients who met the criteria for open surgery were successfully treated with PNF, which reduced the procedural costs for these patients by €20,500.

## The rationale for this thesis

The introduction of percutaneous needle fasciotomy in the Region Västra Götaland outlined in the pilot studies above meant that a group of patients with Dupuytren contracture could be offered considerably easier treatment than open surgery. Secondary gains were also obvious, since PNF could be performed in the outpatient ward even at the first assessment and required significantly less rehabilitation.

In 2011, collagenase *clostridium histolyticum* (CCH, Xiapex®) was introduced in Sweden. The long-term effects of this new treatment were not known at that time and the difference in costs compared with PNF was obvious. In September 2012, the Orthopedic Board of the Region Västra Götaland (population 1.7 million) decided to await the introduction of CCH in the orthopedic units in the region until a comparative study of PNF and CCH had been conducted[77], hence this study.

The clinical and patient reported outcome parameters by which the two methods would be compared were fairly easy to define, since CCH had been compared with placebo in a randomized, double-blind study in 2009[15]. A description of any morphological aspects of either treatment was, however, largely lacking, but the general hypothesis was that CCH would not only rupture the pathological Dupuytren cord but also remove pathological collagen. From observations during open surgery, we had found that a Dupuytren cord treated by "open" needle fasciotomy, i.e. cords exposed in patients who underwent limited fasciectomy, ruptured and left a gap between the two remaining parts of the cord (Figure 8)
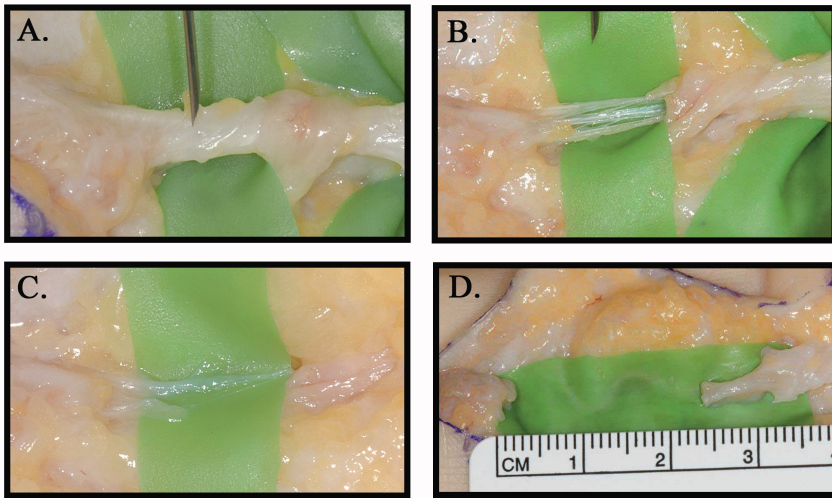
**Figure 8**. "Open" needle fasciotomy in a patient with a Dupuytren contracture of 60° in the MCP joint that was not considered suitable for PNF. The cord was exposed and needle fasciotomy was initiated while the finger was gently extended (A). After ten perforations, the cord started to rupture and the needle was removed (B). Greater force was applied to the finger, with subsequent total rupture (C), and the MCP joint was eventually straightened completely, while a gap of 25 mm could be measured.

Our hypothesis was that this gap could be visualized by ultrasonography, and that changes to the remaining cord after CCH could also be described. Furthermore, an evaluation of the structural elements of Dupuytren cords before treatment could yield interesting information when correlated to outcomes after treatment. To achieve this, an ultrasonographic part of the study was added.

The observations regarding the Dupuytren cord in the first pilotstudy (Figure 7) prompted us to pay extra attention to the presence of any residual cords at follow-up.

# Aims

The overall aim of this thesis was to compare the clinical and morphological results after percutaneous needle fasciotomy (PNF) and injectable collagenase *clostridium histolyticum* (CCH) for Dupuytren's contracture in the metacarpophalangeal (MCP) joint.

Specific aims:

To compare the clinical outcomes between patients treated by either PNF or CCH during a two-year period, including objective measurements and patient reported outcome measures (Study I and III)

To investigate the morphological changes to the Dupuytren cord after PNF and CCH treatment by ultrasound (Study II)

To investigate a possible correlation between the clinical outcomes after PNF and CCH after two years and the morphological properties of the Dupuytren cord prior to treatment (Study IV)

To investigate whether the remaining pathological collagen in ruptured Dupuytren cords is resorbed after treatment by CCH and PNF (Study III)

# Patients and Methods

## Study design

This is a prospective, single-blinded, single-surgeon, parallel group, randomized controlled trial with 156 patients treated between November 2012 and October 2014 at the Department of Hand Surgery, Sahlgrenska University Hospital. The timeframes and number of patients assessed in each study are outlined below (Figure 10).
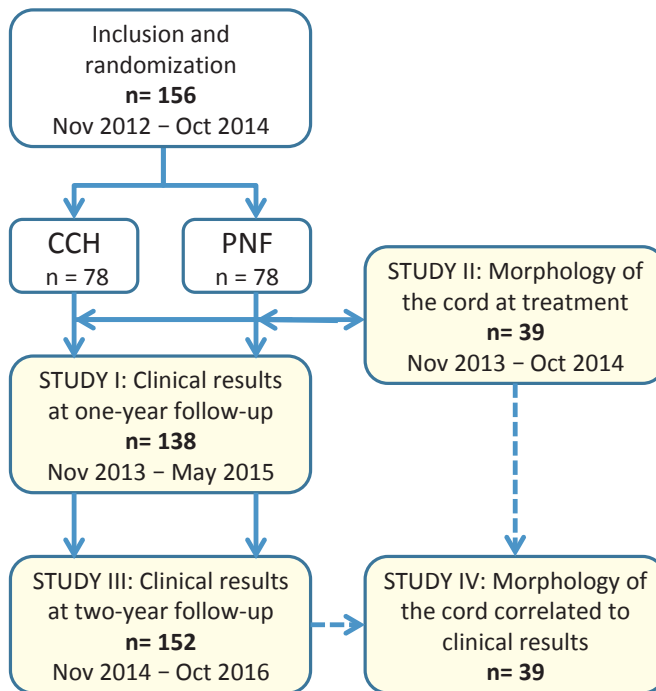


**Figure 10**. The relationship of the individual studies to the main study.

## Ethical approval, registration of the study and concordance with the CONSORT statement

The study protocol was approved by the Regional Ethical Committee of Gothenburg (EPN 2012:513-12). All patients signed an informed consent prior to inclusion. The study was registered in a database for prospective trials (www.researchweb.org, project number 213221). The results were reported according to the CONSORT statement for randomized controlled trials[78].

## Studies I and III- The RCT

*Inclusion and exclusion criteria*

The inclusion criteria were

- The presence of a palpable Dupuytren cord over the MCP joint
- An extension deficit of at least 20° in the same MCP joint
- A contracture of a single finger on one hand
- An adult patient
- The patient agreed to participate and signed the written informed consent form

A concomitant contracture of the PIP joint in the same finger was not regarded as a contraindication if the patient agreed that the MCP joint was the primary target for treatment (Figure 11).
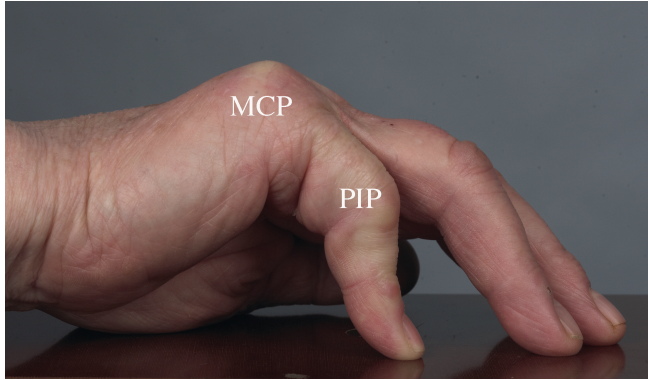
**Figure 11.** A patient with a primary MCP engagement of 80° but with a concomitant PIP contracture of 40°. In order to participate, the patient agreed that no specific treatment for the PIP joint would be administered (the other fingers were unaffected)

The exclusion criteria were:

- Any other earlier treatment or surgery on the finger to be treated (regardless of cause of intervention)
- Any other pathological condition or limited range of motion in the finger to be treated (e.g. earlier fracture or ligament injury)
- Any contraindications to CCH treatment (for example, anticoagulant treatment or intake of acetylsalicylic acid exceeding 150 mg/d)
- Any clinical signs of medical records indicating alcohol or drug abuse
- Any chronic neuromuscular disease compromising hand function

*Sample size*

An *a priori* sample size estimate indicated that 67 patients were required in each group, given a significance level ($\alpha$) of 0.05 and a power ($\beta$) of 0.85 for a minimal clinically important difference of 5° in passive joint extension between the two groups. Anticipating a loss to follow-up, 11 patients were added in each group.

*Recruitment, baseline data, randomization and allocation*

All the regional orthopedic clinics in the Region Västra Götaland were informed about the study and asked to refer patients who met the inclusion criteria above for consideration for the study. New patients were included consecutively and a new treatment cycle was initiated when ten patients had been accumulated on the waiting list.

All baseline data, including case history, measurement of joint motion, grip strength and prevalence of Dupuytren cords were recorded by the same hand surgeon prior to final inclusion in the study. The patients were informed that randomization to CCH would require a follow-up visit the next day.

Ten patients were treated in one cycle: five patients were randomized to CCH and five to needle fasciotomy according to a computer-generated block randomization process before treatment. The randomization was made using a statistical software program (MEDSTAT, Version 2.1, ©Astra Group A/S, 1988, Denmark). The outcomes were either A or B and ten numbered envelopes were prepared for each set of ten patients beforehand by a secretary according to the list. Before treatments began for each group, the surgeon decided which of the two letters would correspond to either treatment using a simple lottery. The envelopes were then opened consecutively and treatment was chosen accordingly.

*Treatment*

Both CCH injections and PNF treatment were performed in a small operating room in the outpatient ward at the Department of Hand Surgery. The patient's forearm was prepared and draped with an arm cover, according to the standard procedure for minor surgery (Figure 12).



**Figure 12.** The sterile setup for CCH injection or PNF treatment.

**Percutaneous needle fasciotomy**

A 2.5-mL syringe with 1 mL of methylprednisolone (Depomedrol, Pfizer, 40 mg/mL) and 1.5 mL of mepivacaine (Carbocain, AstraZeneca, 20 mg/mL) was used with a 25-gauge needle (Figure 13). A small volume was injected volarly and dorsally of the pretendineous cord at MCP level and, with the finger gently extended passively, the needle was passed through the cord repeatedly in various directions from the skin puncture site until the cord ruptured (for a detailed description of the technique, see Appendix 1).

**Collagenase treatment**

Collagenase *Clostridium Histolyticum* 0.58 mg (Xiapex, Pfizer, New York, NY) was reconstituted in 0.39 mL of sterile diluent and injected into the pretendineous cord at MCP level in three portions according to the instructions from the manufacturer (Figure 13). A bulky dressing was then applied and the patient was given instructions not to use the hand. The next day, 2.5 mL of mepivacain (Carbocain, 20 mg/mL; AstraZeneca, Cambridge, UK) was injected with a 25-gauge needle around the first injection site to provide local anesthesia. A forced extension maneuver was performed to disrupt the cord and, if this was not accomplished after three trials, the patient was scheduled for a second treatment after a month.
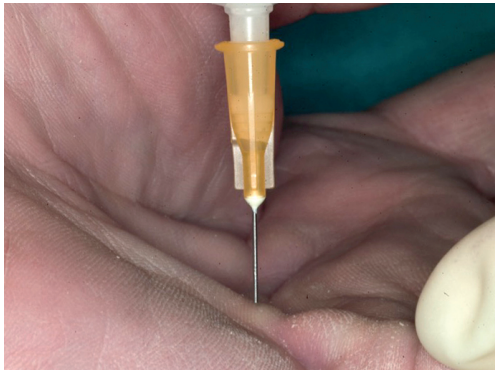


**Figure 13**. A 25-gauge needle inserted in the center of the Dupuytren cord.
The same type of needle is used for PNF and CCH injections.

The patients in both groups were assessed by the hand surgeon at a follow-up visit one week after treatment, at which all the postoperative results were recorded, including joint movement, grip strength, flexor tendon and nerve function and any other side-effects of the given treatment. Patients who had a difference of 10° between active and passive extension of the MCP joint were referred to an occupational therapist for a volar night splint with full extension of the finger to be used for three months. No specific training

instructions were given other than instructions to stretch the finger passively. Patients with cords that did not rupture after three extension maneuvers were offered another treatment after one month, thus entering another treatment cycle. All the patients who had disrupted cords were randomized to blinded follow-up identities by choosing a sealed envelope with a number referring to the treatment group and an identification letter, e.g. "4B".

## *Blinded follow-up*

The patients were examined six, 12 and 24 months after treatment by a single physiotherapist who was unaware of the treatment each patient had received. A special administrative protocol was established in which an assistant nurse, who had access to the identities of the patients, made appointments. Given only the blinded identities, the physiotherapist was unable to check any medical records relating to the patients, who were reminded not to provide any information on the treatment they had received. In order to detect recurrence, which was defined as a loss of extension of 20° compared with the postoperative results, the physiotherapist had access to these measurements for MCP and PIP joint movement. Clinical examination included the measurement of joint movement with the same goniometer used at inclusion and visual and palpatory examination for remaining Dupuytren cords. The patients also completed the URAM and Quick-DASH questionnaires, as well as VAS scales for patient satisfaction and experience at every follow-up.

## *Clinical outcomes*

### Primary outcome

The primary endpoint was a straight finger, defined as a passive extension of the MCP joint to < 5° (Figure 14). The sample size for the entire study was calculated for this endpoint. All measurements throughout the trial were made with one specific finger goniometer (Zimmer, Lauf/Baden, Germany).
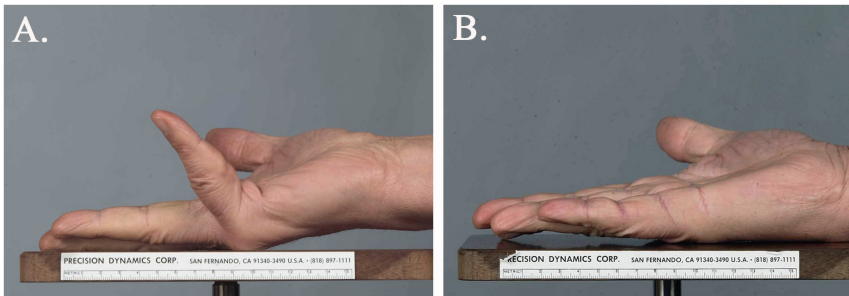


**Figure 14.** Demonstration of the primary outcome of this study. This patient had a severe MCP contracture before he was randomized and treated with PNF (A), but he still had a straight finger after one year (B).

### Secondary outcomes

CLINICAL ASSESSMENT

*1. Recurrence.* A patient who had reached the primary endpoint of <5° in the MCP or PIP joint after treatment but had a new passive extension deficit of 20° or more in the same joint was considered to have a recurrent contracture[79,80].

*2. Joint movement.* In addition to the passive extension of the MCP joint, active extension, active flexion and range-of-motion of the MCP joint were also recorded. Regarding the PIP joint, active and passive extension, active flexion and range of motion were recorded. Any improvement in joint motion compared with baseline was also calculated for the MCP and PIP

joints.

3. *Presence of a Dupuytren cord.* The treated finger was assessed for Dupuytren cords at either the MCP or PIP joint level, defined as "a continuous bulk of longitudinal subcutaneous tissue volar to the joint which tightens when the finger is passively extended".

PATIENT REPORTED OUTCOME MEASURES (PROMs)

1. *URAM score.* The Unité Rhumatologique des Affections de Main questionnaire has been described previously.

2. *Quick-DASH score.* The short version of the DASH questionnaire is the most common generic instrument for self-evaluating hand function after treatment for Dupuytren's contracture.

3. *Visual analog scales.* The use of VAS scales for evalutation has been discussed previously. In this study, the patient was asked to mark a response to a specific question on a line from 0 to 10 or 0 to 100 as the endpoints.

a. Treatment effect. The patient's response to the question: "How much straighter do you consider your finger to be after the treatment?", where 0 was defined as "unchanged" and 10 "totally straight". The procedural risk exceeds the risk of recurrent stroke day 0 to 2 in the studies in this thesis. To allow for patients to report a poorer outcome than before treatment, a second VAS-scale was added with the question "How much more crooked do you consider your finger to be after treatment?", where 0 was defined as "unchanged" and 10 as "totally crooked".

b. Treatment satisfaction. The patient's response to the question: "How satisfied are you with the result of the treatment?", where 0 was defined as "totally unsatisfied" and 100 "totally satisfied".

PATIENT EXPERIENCED OUTCOME MEASURES

c. Consultation satisfaction. The VAS scale was used to investigate how the patients felt about their consultation and the circumstances associated with treatment and follow-up visits. The patient's response to the question: "How satisfied are you with your reception at the clinic during your treatment?", where 0 was defined as "totally unsatisifed" and 100 "totally satisifed".

## *Statistical methods*

Cross-tabulations were used to compare the treatment groups. Non-parametric data were analyzed with the Mann-Whitney *U* test to compare the distribution of the two unmatched groups. Categorical data were analyzed with Pearson's chi-square test. Fishers test did not apply to any data. Repeated individual measurements were analyzed with Wilcoxon's signed-rank test. A significance level of 5% ($\alpha=0.05$) was used for all statistical tests of the outcome, so that a p-value of $<0.05$ was considered significant. SPSS software version 22-24 and Excel: Mac 2011 were used for the statistical analysis.

## Studies II and IV – The ultrasonographic studies

### *The ultrasonographic pilot study*

In order to investigate whether Dupuytren cords could be visualized by ultrasound and to construct a method for evaluation, we conducted a pilot study. Between September and November 2013, seven patients treated with PNF and five patients treated with CCH were examined by ultrasound before and directly after treatment. After one week, five patients treated by PNF and four patients treated by CCH were re-examined by ultrasound. All 12 patients who were examined before and directly after treatment displayed a distinctive gap in the ruptured Dupuytren's cord, regardless of the method that was used (Figure 15). The thickness of the cord as well as the structure and echogenicity, were easily assessed.
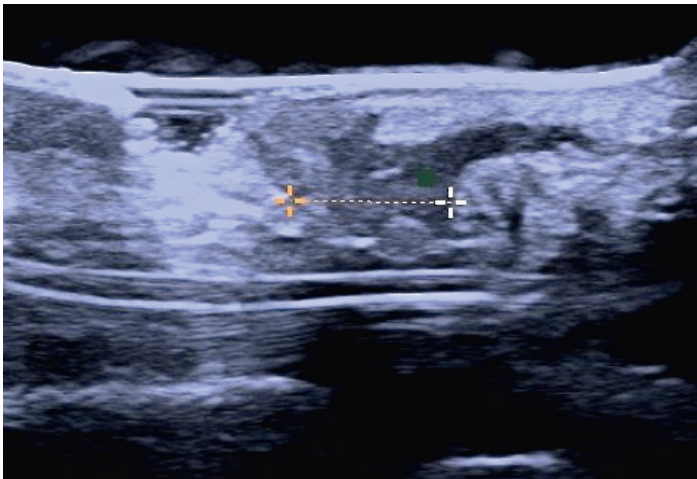


**Figure 15.** An example of an ultrasonographic image of a ruptured cord after CCH treatment. A distinctive gap can be visualized and measured (compare with Figure 8 of the "open" needle fasciotomy).

The ultrasound system used throughout the study was a BK Medical flex Focus 500 "point of care-system" (BK ultrasound: Analogic Corp., Peabody, MA, USA) equipped with an 18-6 MHz linear-array transducer, Type 8870 and a small "hockey stick" 15-6 MHz linear-array transducer Type 8809 with an adjustable angle between the handle and the "footprint" of the transducer.

The 13 patients who were examined after one week had no distinctive ultrasonographic features, i.e. no gaps could be visualized in the area of the ruptured cords. We therefore concluded that ultrasound assessment after one week would yield no further information on the treated Dupuytren cord.

## *The study protocol and setup*

From the result of this pilot study, we constructed a study protocol for the ultrasonographic evaluation of the cord morphology prior to treatment, together with a standardized method to measure the rupture length after treatment.

- *Cord echogenicity*: hyper-, iso- or hypoechogenic. The flexor tendons were isoechogenic and used as a reference.
- *Structure:* predominantly nodular or fibrillar
- *Cord thickness* measured volarly to the MCP joint.
- *Distance and orientation in relation to adjacent tendons*
- *Distance and orientation in relation to the neurovascular bundle*
- *The length of the rupture after treatment* was measured twice on frozen images stored locally in the ultrasound machine by the two investigators in consensus.
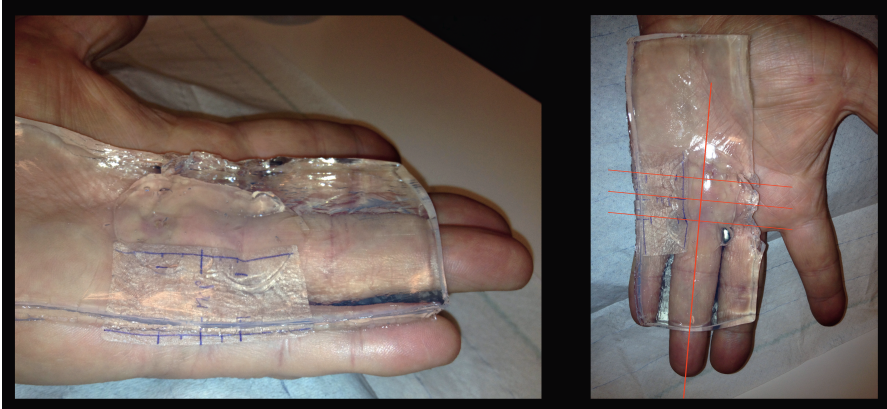
**Figure 16**. The position of the hand during the examination. The lines indicate the standard projections for longitudinal and transverse examination of the cord.

The longitudinal projection was used to measure the thickness of the cord over the MCP joint. The same projection was also used to evaluate the cord structure and to detect nodules within the cord. Images in the transverse plane were obtained over the MCP joint and 1 cm proximal and distal to the MCP joint. For this purpose a tape measure was applied to the patient's finger prior to the examination. The transverse projection was used to localize the neurovascular bundle as well as the relationship of the cord to the adjacent tendons (Figure 16).

After examining of the cord, the patients were treated by either PNF or CCH and a second ultrasonographic examination was performed after the cord had been ruptured. When the gap between the proximal and distal end of a ruptured cord was visualized, the maximum size of the rupture gap was measured in the sagittal plane.

After two years, the specific results of the clinical study indicating recurrent disease, i.e. the recurrence (defined as a loss of extension of 20°) and the presence of a pretendineous cord, were correlated to the ultrasonographic parameters described above.

# Results

## Summarized results

A total of 884 patients with Dupuytren contracture were referred to the Department of Hand Surgery between October 2012 and October 2014 and 169 patients were initially enrolled. A secondary assessment by the hand surgeon (the author) prior to allocation concluded that 14 of these failed to fulfill the inclusion criteria and were thus excluded. Of the 156 patients who were included, 78 were allocated to each group (Figure 17). The groups were considered homogeneous in terms of baseline characteristics (Table 2).

A total of 27 patients in the CCH group and 25 in the PNF group had a concomitant PIP contracture of more than 5°. The Dupuytren cord was ruptured in all patients in the PNF group and in all but two patients in the CCH group. One of these patients had a CCH injection with subsequent rupture after one month, but the other refused another injection at the time.

The percentage of patients assessed at each follow-up was > 96% (Figure 17). Study I reported the outcome after treatment and after one year in 138 patients out of the first 140 treated, Studies II and IV reported an ultrasonographic evaluation of the pretendineous cord before and after treatment in 39 patients and Study III reported the total outcome for the entire RCT in 152 of 156 treated patients after two years.
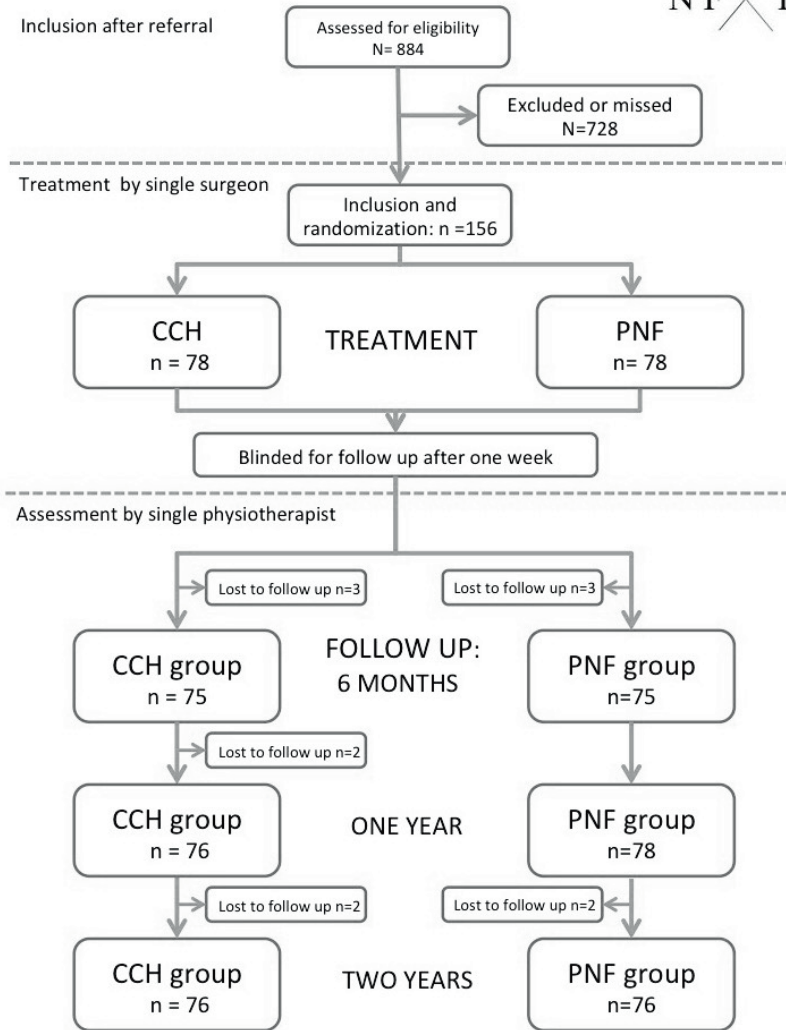
**Figure 17**. Flowchart of the clinical study.

| Patient characteristics at baseline | | CCH n=78 | PNF n=78 |
|---|---|---|---|
| Age, yrs | Median | 66 | 69 |
| | Range | 42-80 | 29-86 |
| Male, n (%) | | 65 (83%) | 68 (87%) |
| Female, n (%) | | 23 (17%) | 20 (13%) |
| Finger involved: | | | |
| | Little | 40 | 40 |
| | Ring | 32 | 33 |
| | Middle | 6 | 5 |
| Passive MCP extension | Median | 44° | 45° |
| | Range | 20°-90° | 20°-87° |
| Active range of motion- MCP joints | Median | 41° | 41° |
| | Range | 6°-73° | 3°-68° |
| Passive PIP-extension – all PIP joints | Median | 0° | 0° |
| | Range | -20°-74° | -20°-48° |
| Active range of motion- all PIP joints | Median | 85° | 84° |
| | Range | 30°-116° | 42°-116° |
| Grip strength in affected hand, | Kgs | 45 | 40 |
| | Range | 13-68 | 19-63 |
| Isolated MCP-contracture , no (%) | | 51 (65 %) | 52 (67 %) |
| MCP and PIP involvement*, no (%) | | 27 (35 %) | 25 (32 %) |
| Duration since first symptoms, yrs | Median | 5 | 5 |
| | Range | 1-20 | 1-30 |
| Family history – no | | 38 | 41 |
| Diabetes – no | | 5 | 7 |
| URAM score | Median | 11 | 10 |
| | Range | 0-29 | 0-33 |
| Quick DASH score | Median | 16 | 11 |
| | Range | 0-59 | 0-63 |

**Table 2.** Patient characteristics at baseline

## Study I

*Results within the first week of treatment*

The first 140 patients treated in the study were assessed on the periprocedural aspects of either treatment. After the extension maneuver regardless of treatment, any skin ruptures were recorded and measured. In the CCH group, special attention was paid to the presence of hematomas and swelling prior to local anesthesia and extension.

- All 140 patients were seen one week after treatment. The vast majority of the patients (88% CCH, 90% PNF) had reached the primary outcome of a <5° MCP contracture
- The increase in MCP extension from baseline was 48° for CCH and 46° for PNF.
- The median MCP extension reflected hyperextension of the MCP joint (-4° CCH, -2° PNF).
- There was a tendency towards a reduced grip strength in the CCH group compared with the pre-treatment results, but no significant difference compared with PNF.

No patients had signs of nerve injury, tendon injury or infection. The patients in the CCH group reported significantly more pain than the patients in the PNF group (Table 3), and had larger skin ruptures (Figure 18 A). Hematomas were common in the CCH group, but they were not seen in the PNF group (Figure 18 B).

| | CCH (n=69) | PNF (n=71) | *P*-value |
|---|---|---|---|
| PAIN | | | |
| Procedural pain, median (range)* | 4.9 (0-10) | 2.7 (0-10) | .032 |
| COMPLICATIONS | | | |
| Skin rupture at forced extension, n (%) | 34 (49) | 27 (38) | NA |
| Skin rupture size, mm | 7.5 | 2.8 | .0008 |
| Hematoma, n (%) | 39 (58) | 0 (0) | NA |
| Swelling, n (%) | 17 (25) | 0 (0) | NA |
| Night splint required, n (%) | 31 (46) | 35 (50) | NA |
| Other complications [#] | 6 | 0 | NA |

* Visual analog scale. The patient's response to "what was the maximum level of pain during the whole procedure?", 0 meaning "no pain" and 10 "maximal pain".
NA: non applicable
[#] Distal ischemia 20 minutes after extension (1), blood blister (2), axillar node swelling (1), Need for further wound care by district nurse. (1)

**Table 3.** Assessment of pain, adverse events and complications immediately after treatment or after one week.
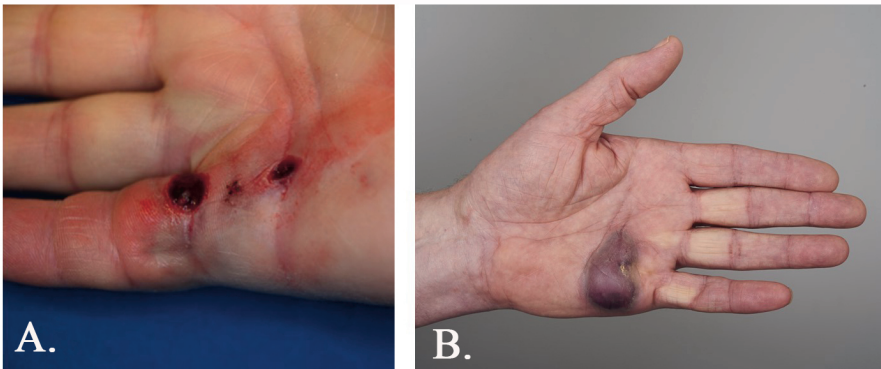


**Figure 18.** A. An example of a skin rupture immediately after PNF
B. An example of a hematoma one week after CCH treatment

*Results after one year*

Two patients in the CCH group were lost to follow-up after one year, and telephone contact revealed that one of the patients had moved and the other did not wish to attend any follow up. All the patients in the PNF group were assessed. Efficacy results after one year were based on 138 MCP-joints. Only three patients had an MCP-contracture of $>20°$ in the treated finger; a recurrent contracture was seen in one patient in each group who had reached the primary endpoint of an extension deficit of less than five degrees.

The only patient with an incomplete rupture of the cord after CCH treatment still had less contracture of the treated finger than before treatment. None of the patients in either group was interested in further treatment after one year. Patient related outcome measures showed that patients in both groups had a significant reduction in impairment as measured by the URAM scale, and that the estimated effect of the treatment was similar in both groups.

There were no significant differences between the two groups as far as patient related outcome was concerned. Progressive outcome results showed a vast improvement from baseline in both groups but no significant differences between CCH and PNF when it came to a reduction in MCP contracture or URAM-score.

The detailed results from the one-year follow-up are reported with the results of the two-year follow up in Study III (Figures 21, 22 A-D, 23 and 24)

## Study II

Between November 2013 and October 2014, 40 patients from the clinical RCT were initially included in this ultrasonographic study. One patient had a contracture of less than 20° when re-examined before treatment and was therefore excluded. All patients were examined by ultrasound before and after treatment. .

| Patient characteristics at baseline Ultrasonographic study | | CCH N=20 | PNF n=19 |
|---|---|---|---|
| Age, yrs | Median | 65 | 67 |
| | Range | 47-75 | 54-76 |
| Male, n (%) | | 17 (85%) | 17 (89%) |
| Female, n (%) | | 3 (15%) | 2 (11%) |
| Finger involved: | | | |
| | Little | 10 | 10 |
| | Ring | 8 | 8 |
| | Middle | 2 | 1 |
| Passive MCP extension | Median | 43° | 42° |
| | Range | 22°-90° | 22°-80° |
| Thickness of cord at MCP joint, mm | Median | 5 | 6 |
| | Range | 3-7 | 2-8 |
| Grip strength in affected hand, kgs | Median | 45 | 35 |
| | Range | 13-68 | 20-55 |
| Time from onset, yrs | Median | 5 | 6 |
| Family history – no | | 9 | 5 |

**Table 4.** Baseline characteristics of patients in Study II and IV

Twenty patients were randomized to CCH injection and 19 to PNF and both procedures were carried out directly after randomization by the surgeon, who was unaware of the results of the ultrasound examination. The baseline characteristics of the patients were similar in both groups

(Table 4). All pretendineous cords could be readily visualized by ultrasound and the thickness of the cord could be measured before treatment, as well as cord echogenicity and structure (used in Study IV).

The proximal and distal ends of the ruptured cord could be easily visualized in 35 patients (19 PNF, 16 CCH). The length of the rupture (Figure 19 A) was measured twice on frozen images stored locally in the ultrasound machine by the two investigators. The inter-class correlation between the two was calculated and was 0.72 for all measurements. The median length of the rupture between them was 18 mm in both the CCH and PNF group.
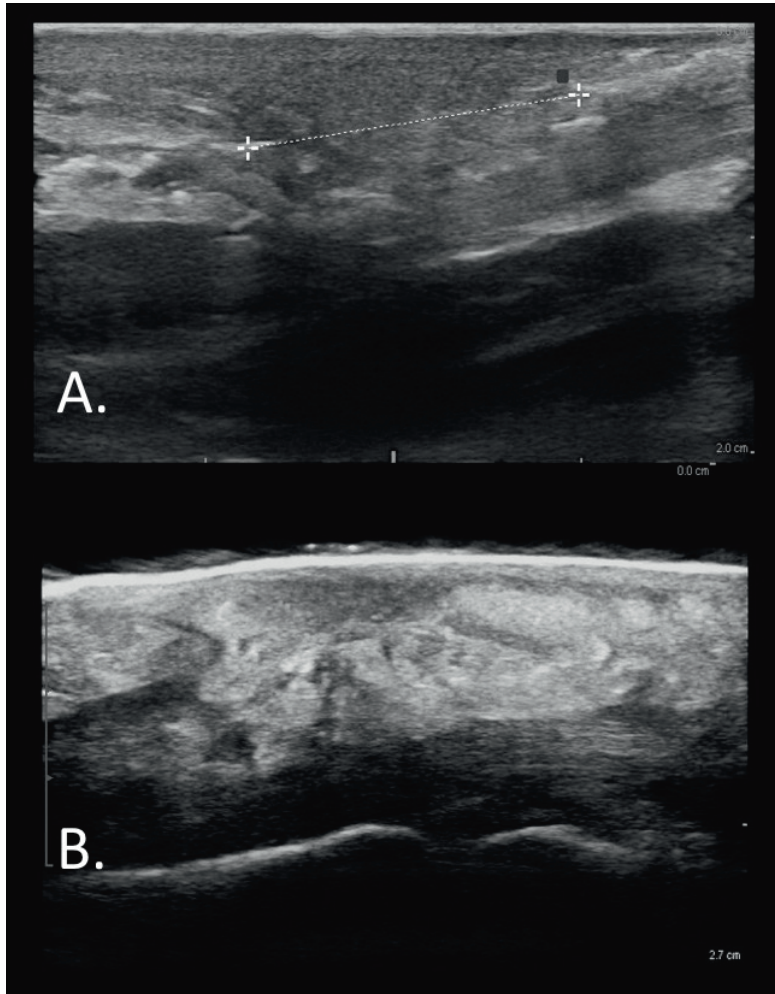
**Figure 19**. A. Example of an ultrasonographic image after treatment by PNF. The dotted line indicates the rupture gap. B. Hypoechogenic (darker) areas within a cord treated by CCH

Multiple hypoechogenic areas in the cord in the absence of one distinct rupture were found in four patients treated by CCH (Figure 19 B)

All the patients in both groups reached the primary endpoint of a reduction in contracture to less than 5°, with a median reduction in contracture of 46° in the PNF group and 53° for patients in the CCH group. No serious adverse events were recorded, but seven patients in both groups had skin ruptures. There were no significant differences between the CCH and PNF groups in the size of the rupture or gain in mobility (Figure 20).
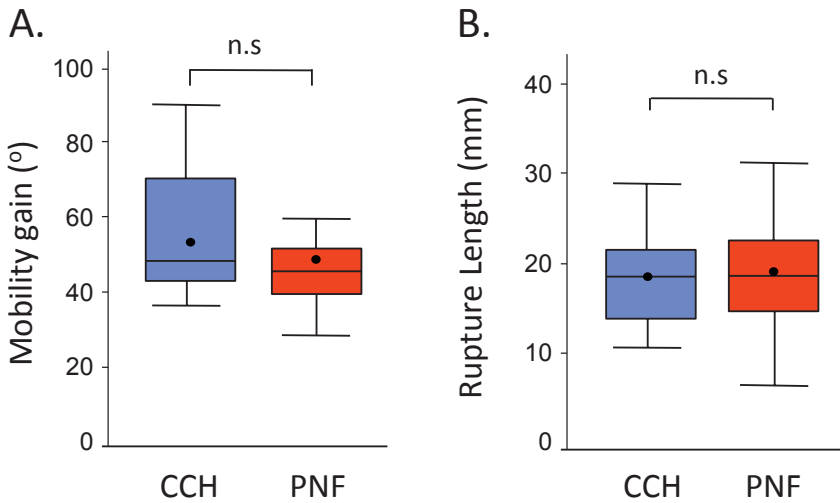


**Figure 20**. Results. A. The increase in movement of the MCP joint after treatment compared with baseline. B. The length of the rupture measured by ultrasound after treatment. The boxes represent the interquartile ranges, the bars in the boxes represent the medians, the whiskers represent minimum and maximum measurements and the black dots represent the means.

## Study III

A total of 152 patients (97%) were assessed after two years. Two patients in each group were lost to follow-up or were excluded after two years. In the needle fasciotomy group, one patient died one year after treatment and the other patient did not wish to attend any follow-up. In the collagenase group, one patient had moved and the other patient had received treatment in the same finger after a year due to a recurrence of the Dupuytren contracture, which led to exclusion from further follow-up.

There were no significant differences between the CCH and PNF group.

*Primary outcome and recurrent contractures*

The majority of patients retained a straight finger throughout the study, defined as a passive extension of the MCP joint of 5° or less (Figure 21). Recurrent contractures were found in an increasing number between the one- and two-year follow-up, with an increase from one to ten recurrences in the CCH group (1-13%) and from two to nine in the PNF group (3-12%). Seventy-five percent of the treated patients did not have any signs of recurrent disease whatsoever, i.e. no cords and no recurrence after two years.
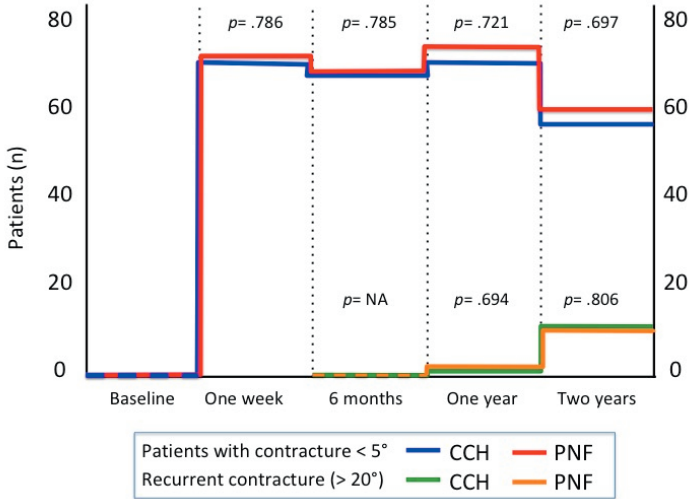
**Figure 21**. The total number of patients (out of 78 in each group) in which the primary outcome measure in the MCP joint at follow-up was achieved/maintained and the number of recurrent contractures throughout the study.

## *Secondary outcomes- the MCP joint and PROMs*

The CCH and PNF groups were equally similar regarding all secondary outcomes (Figure 22 A-D) and the prevalence of Dupuytren cords at the MCP joint level decreased significantly during the study (Figure 22 D).

**A.** MCP Passive extension (degrees)

p = .559
p = .498
p = .167
p = .231

CCH
PNF

Baseline   6 months   1 year   2 years

**B.** URAM SCORE

p = .552
p = .438
p = .539
p = .570

CCH
PNF

Baseline   6 months   1 year   2 years

**C.** Quick-DASH SCORE

p = .301
p = .698
p = .804
p = .119

CCH
PNF

Baseline   6 months   1 year   2 years
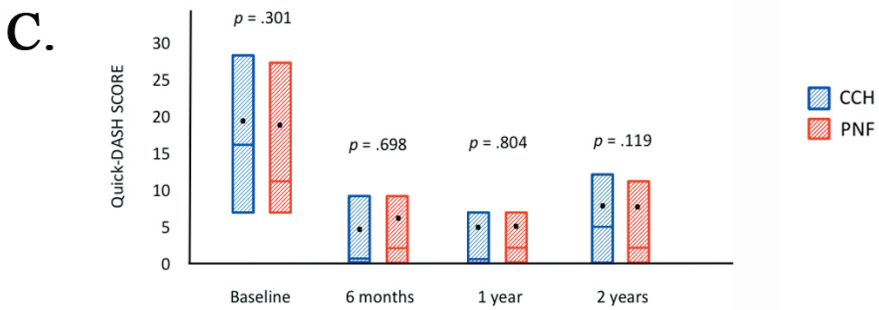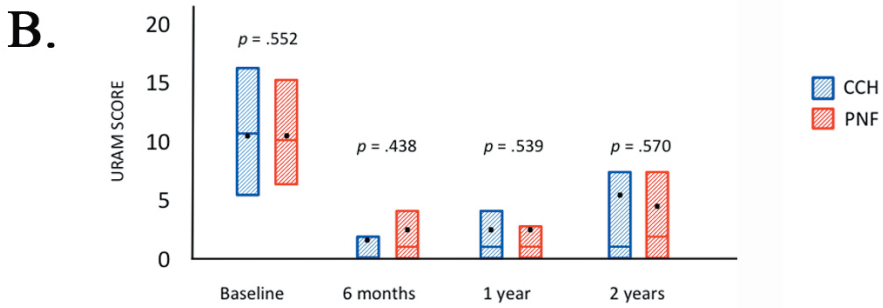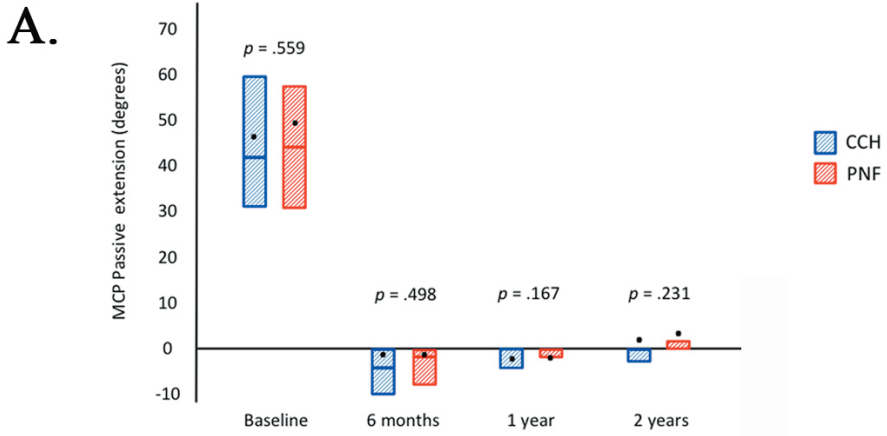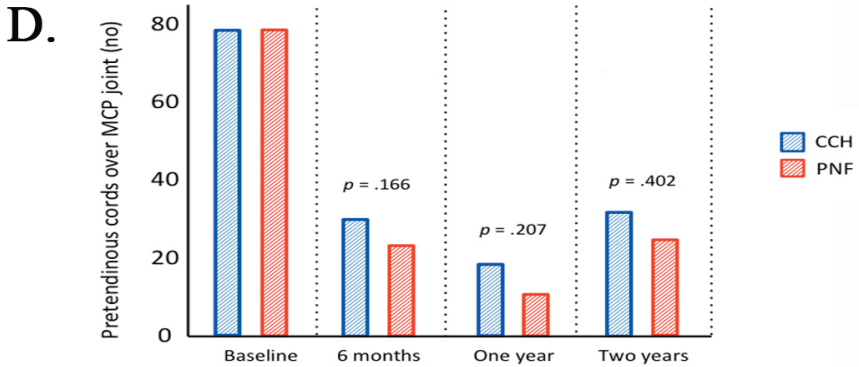
**Figure 22**. Four secondary outcome measures at baseline and at follow-up at six months and after one and two years. A. Passive extension of the metacarpophalangeal joint B. Patient score using the Unité Rhumatologique des Affections de la Main (URAM) C. Patient score using the Quick-DASH (Disabilities of Arm, Shoulder and Hand) questionnaire. Boxes represent the interquartile ranges, bars represent the medians and dots the means. D: Palpable pretendineous cords at the metacarpophalangeal joint level in all patients.

The patient-estimated effect of treatment and satisfaction with treatment as measured with the VAS was very high in both groups throughout the study, without any significant differences. After two years, the median for treatment effect was 8 out of 10 for patients in both groups. The corresponding estimated satisfaction with treatment was 9 out of 10 for patients in both the CCH and the PNF group.

## Secondary outcomes- the PIP joint

A total of 52 patients had concomitant contractures of at least 5° in the PIP joint in the same finger as the MCP contracture: 27 of these patients were randomized to CCH treatment and 25 to PNF. Even though the involved finger was treated exclusively at the MCP level, all these patients had a reduction in the contracture at the PIP level (Table 6). At the one-week follow-up, nine patients (33%) in the CCH group and 10 patients in the PNF group (38%) had a passive extension of <5° in the PIP joint. After two years, eleven patients in the CCH group (41%) and nine in the PNF group (35%) retained a straight PIP joint (Figure 23). Recurrent contractures after two years were found in six patients (22%) in the CCH group and in two patients (8%) in the PNF group but this did not turn out to be statistically significant ($p$=0.156). Furthermore, the prevalence of Dupuytren cords over the PIP joint decreased significantly during the study (Figure 24)

| The PIP joint in patients with concomitant contracture > 5° | CCH | PNF | *p*-value |
|---|---|---|---|
| Passive PIP extension (°), median (IQR), n | | | |
| Baseline | 30 (18-45), n=27 | 20 (13-38), n=25 | NA |
| One week | 10 (4-16), n=27 | 10 (0-18), n=25 | .671 |
| 6 months | 6 (0-18), n=26 | 10 (1-18), n=24 | .651 |
| 1 year | 8 (0-23), n=27 | 10 (0-20), n=25 | .707 |
| 2 years | 10 (0-35), n=27 | 14 (0-26), n=25 | .339 |
| | | | |
| Improvement in PIP extension from baseline (°), median (IQR), n | | | |
| One week | 17 (10-29), n=27 | 12 (8-19), n=25 | .164 |
| 6 months | 20 (10-28), n=27 | 12 (1-21), n=24 | .660 |
| 1 year | 15 (8-28), n=26 | 14 (4-18), n=25 | .336 |
| 2 years | 12 (3-23), n=27 | 10 (3-18), n=25 | .414 |

**Table 6.** Baseline passive extension deficit in the PIP joint and the results after treatment.
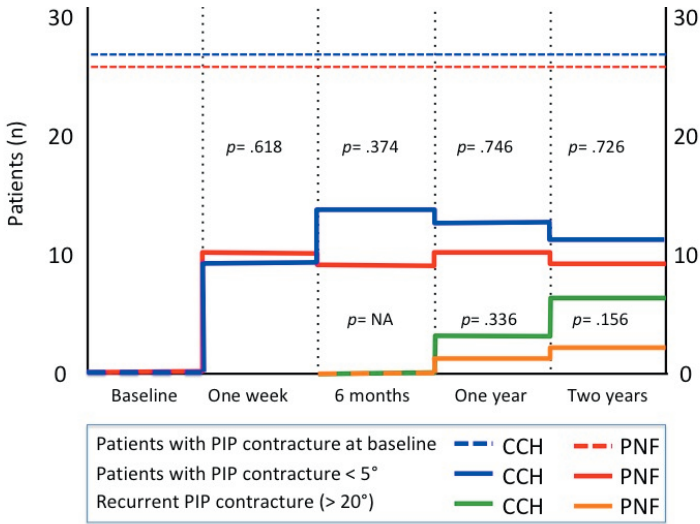
**Figure 23**. The total number of patients with a concomitant PIP contracture at baseline who had a with a straight (<5°) PIP joint at follow-up and the number of recurrent contractures throughout the study.
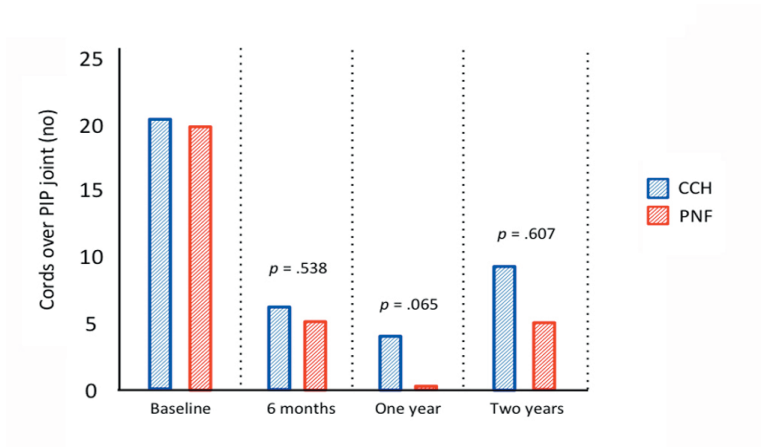


**Figure 24**. Cords over the proximal interphalangeal (PIP) joint in patients with concomitant PIP contracture.

## Secondary outcomes- VAS scales (PROM and PREM)

The patients' satisfaction with the treatments and their experience of the reception at the clinic was, with a few exceptions, altogether excellent and most patient reported a high degree of correction of the contracture (Table 7).

| Visual Analog Scales | CCH | PNF | P-value |
|---|---|---|---|
| Treatment effect† (PROM) median (IQR); range | | | |
| One week | 9 (8-10); 2-10 | 9 (8-9); 1-10 | .559 |
| 6 months | 9 (8-10); 0-10 | 9 (8-9); 4-10 | .588 |
| 1 year | 9 (7-10); -3-10 | 8 (7-10); -2-10 | .471 |
| 2 years | 8 (5-10); -4-10 | 8 (4-9); -7-10 | .337 |
| Treatment satisfaction ‡ (PROM) median (IQR); range | | | |
| 6 months | 97 (88-98); 2-100 | 95 (74-99);18-100 | .609 |
| 1 year | 97 (86-99); 2-100 | 95 (79-98); 0-100 | .513 |
| 2 years | 89 (35-98); 0-100 | 90 (70-98); 0-100 | .571 |
| Consultation satisfaction* (PREM) median (IQR); range | | | - |
| 6 months | 98 (96-99); 48-100 | 99 (97-100);74-100 | - |
| 1 year | 98 (97-100); 85-100 | 98 (97-99); 4-100 | - |
| 2 years | 98 (97-99); 6-100 | 98 (97-100); 55-100 | - |

**Table 7**. Two PROMs and the PREM. VAS for the patient's response to:
†   "How much straighter do you consider your finger to be after the treatment?" where 0 was defined as "unchanged" and 10 "totally straight"
‡   "How satisfied are you with the result of the treatment?", where 0 was defined as "totally unsatisifed" and 100 "totally satisifed".
*   "How satisfied are you with your reception at the clinic during your treatment?" where 0 was defined as "totally unsatisifed" and 100 "totally satisifed"

## Study IV

Between November 2013 and October 2014, the pretendineous cords in 39 patients were categorized according to the study protocol. Echogenicity and structure could not be characterized in one cord due to a flexion deformity of 90°. A total of 38 cords were analyzed and all the patients were seen at follow-up after two years.

Both strictly hyperechogenic (n=10, 25%) and isoechogenic (n=4, 9%) cords were found but the majority of cords contained both hyper- and isoechogenic portions (n=24, 64%).
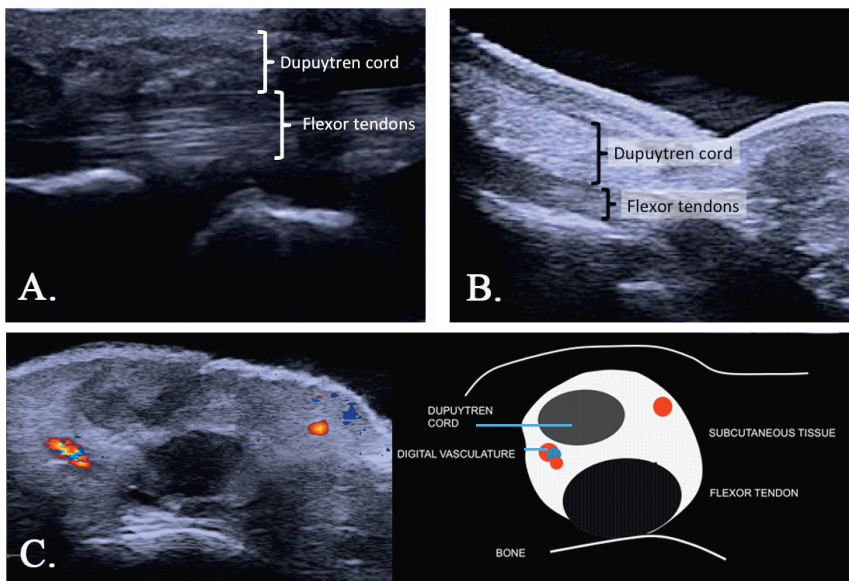


**Figure 25**. A. Longitudinal projection of a cord of nodular type with mixed echogenicity compared with the flexor tendons. B. Longitudinal projection of a predominantly fibrillar cord, which is hyperechogenic compared with the flexor tendons. C. Transverse projection of a pretendineous cord and its relationship to the flexor tendons and neurovascular bundles.

No hypoechogenic cords were found. The structure of the cord was less organized than in the tendon. A total of 32 cords (84%) showed a variying

number of echo-poor, rounded, relatively well-circumscribed nodules within the cord (Figure 25 A). Fibrillary portions of the cord could be detected between these nodules. Nodules were absent of very few in six cords (16%), which were predominantly of a fibrillary pattern (Figure 25 B).

The position of the cord in relation to the neurovascular bundle and the flexor tendon was variable. In twenty-eight cases (72%) the cord followed the flexor tendon trajectory on the palmar side (Figure 25 C). In eleven cases (28%) the cord was identified parallel to the flexor tendon (laterally or medially to it), switching from one side of the tendon to the other crossing the plane of the tendon. The median thickness of the cord was 4.9 mm (2.5-8.5).

No cord was found exclusively radially or ulnarly to the tendon. In the transverse projection the digital vasculature was visualized in sixteen fingers (41%). In six cases of these cases at least one of the digital vessels was surrounded by the cord, while in ten cases there was no observed contact. Digital nerves could only be localized in three fingers. Reliability was tested on the original saved ultrasonography images regarding cord thickness and nodularity: both the primary investigator (P.V.) and the senior radiologist (Y.A.) analyzed the images. The intraclass correlation (ICC) for inter-rater reliability was 0.63 (0.40-0.79) for a 95% confidence interval for cord thickness, using ICC Model 3, type 1 in which each subject is assessed by each rater and reliability is calculated from one single measurement (two-way mixed effects, consistency, single measurements according to SPSS). Cohen's kappa agreement for nodularity was 0.38.

After two years, 21 (54%) patients had retained a straight finger without the formation of a new cord and 18 patients were found to have signs of residual disease in the treated finger. Three patients (8%) had a recurrent contracture and a retrospective analysis showed that all of these patients had had cords with mixed echogenicity and nodules before treatment. Fifteen patients (38%) were found to have a palpable pretendineous cord with or without a flexion contracture of the finger, and the majority of these had had cords with mixed echogenicity and nodular structure before treatment

(Table 8). All but one of these palpable cords were classified as nodular in the pretreatment investigation.

| Structure:<br>Echogenicity: | Fibrillar | Nodular |
|---|---|---|
| Isoechogenic | 0 (0 %) | 1 (7 %) |
| Hyperechogenic | 1 (7 %) | 5 (33 %) |
| Mixed | 0 (0 %) | 8 (53 %) |

**Table 8.** Distribution of preoperative findings in relation to echogenicity and structure in 15 patients with a palpable pretendineous cord two years after treatment.
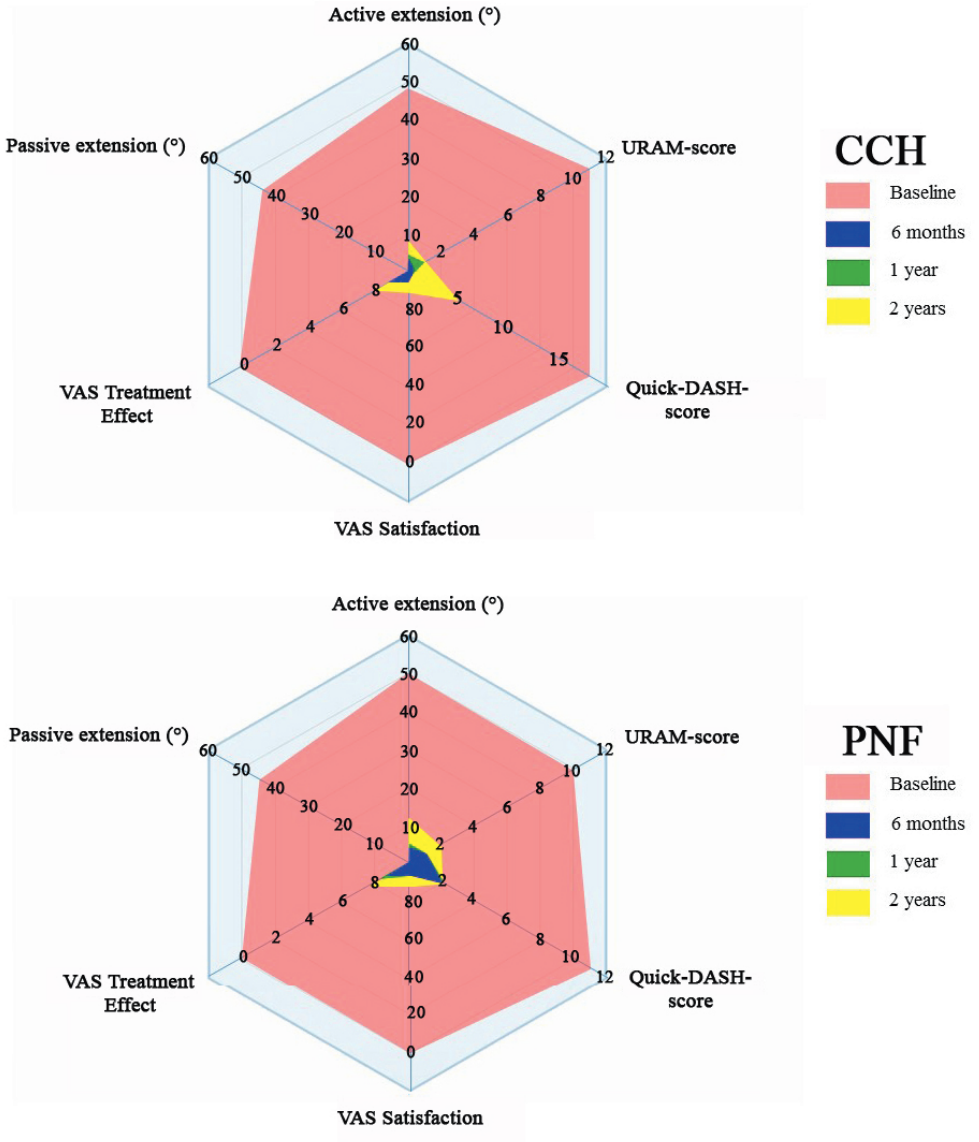
**Figure 26.** The median effect of CCH and PNF treatment over time as measured by six different outcome measures. The red area represents improvement from baseline.

# Discussion

## General discussion

The vast majority of the patients in the clinical part of this study had an excellent result with regard to all the outcome measures, regardless of which treatment they received for their Dupuytren contracture. Figure 26 shows the median changes in the course of the study for six different outcome measures relating to the MCP joint: objective measurements of active and passive extension, PROMs (URAM and Quick-DASH) and VAS scales for treatment effect and patient satisfaction at baseline and during follow-up. This illustrates the overall excellent effect of both methods, since the red area between the baseline and the follow-up represent the median improvement.
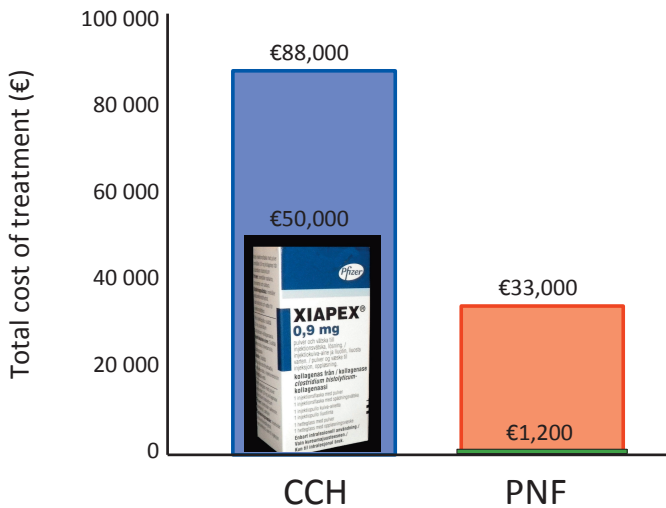


**Figure 27**. The overall cost of treatment for 78 patients in both groups. The total cost of the drug is indicated within the blue box, while the green box represents the total cost of the local anesthetic, corticosteroids and materials for patients treated with PNF.

In this study, the total cost of treating 78 patients with CCH was calculated at €88,000 compared with €33,000 for 78 patients treated with needle fasciotomy, i.e. almost three times more expensive (Figure 27). Even though this calculation is far from a correct health-economic assessment, these results pinpoint what might be the only true difference between the two methods in this study - the fact that CCH is more expensive than PNF.

Both minimally invasive treatments have revolutionized the treatment of Dupuytren's disease in providing a simpler, less expensive treatment option for both patients and health-care providers. Operating theater time that could be used for other patients has been saved, and the need for postoperative hand therapy and follow-up visists has been reduced for a large number of, but not all, patients. However, economic aspects must be taken into account if both methods continue to be equally effective with regard to all outcome measures.

## Other studies that compare CCH with PNF

In the course of this study, two other RCTs comparing CCH with PNF have been published. Scherman *et al*[81] reported a multi-center study of 96 fingers with a predominantly MCP engagement and found no significant differences in outcomes between the two methods after one year. A Danish study by Skov *et al* compared PNF at the PIP joint level with CCH and reported a significantly inferior outcome for CCH after two years, whereas the clinical improvement in the needle fasciotomy group was similar to our results[82].

The possibility that the long-term results may detect significant differences between CCH and PNF cannot be ruled out, but, given the intermediate results of these three RCTs, a scenario of this kind would be very unlikely. Moreover, the ultrasonographic part of this thesis has provided new insights into the morphology of the ruptured Dupuytren cord that make a possible long-term difference even more unlikely.

Future studies to compare CCH with fasciectomy, omitting the equally simple treatment of PNF, are not likely to present any important new insights beyond what is already known: minimally invasive methods should be regarded as a welcome option to open surgery for Dupuytren contractures.

## Consequences of changing the indication for treatment

The indication for treatment has widened with the introduction of minimally invasive procedures; a patient with an MCP contracture of 20° would not have been considered for fasciectomy at our department before 2010 and would most likely have been sent home to wait for the advancement of the contracture to approximately 40°. In an analysis of all patients treated by PNF at our department in 2011, the author found that this change from a 40° to a 20° indication led to a 30% increase in the number of treated patients. In the US, the introduction of CCH has increased the percentage of minimally invasive techniques for Dupuytren contracture from 14% in 2007 to 39% in 2013, while the number of needle fasciotomies remained steady and open surgeries declined throughout the study period[83]. The general awareness of the new treatment options in the population, as well as the targeted marketing of CCH could possibly account for this change.

## Treatment of multiple joints and off-label use of CCH

The injection technique of CCH has evolved since this study started and instead of treating a single joint, multiple joints can now be treated at the same time. Verheijeden reported the use of the whole dose of CCH in an average of 2.5 cords in 144 patients, with results for all joints similar to those produced by one injection[84]. The precautions have been due to the possible systemic effects of CCH, but Coleman *et al.* reported the results of two concurrent injections of CCH in the same hand in 60 patients and found no adverse events that would deter from this practice[85]. A longer

time span between the injection of CCH and the extension maneuver up to 72 hours has also been proposed. The current recommendation for CCH is treatment of a maximum of two joints at the same time. If additional contractures are to be treated, the patient has to wait for another four weeks[86].

Since PNF is mainly a mechanical procedure, the precautions associated with CCH treatment do not apply to this treatment option. Instead, the number of joints treated at the same time by PNF is dependent on the patient's tolerance of the treatment, the surgeon's preferences and logistical considerations. Beaudreuil *et al.* treated a minimum of four joint contractures at the same time in the same hand in 30 patients and reported no adverse events from this expansion of the indication for PNF[36].

Off-label techniques for injecting CCH are occasionally presented and the method of injecting CCH in this study might be considered outdated by some surgeons who advocate the use of CCH. However, until such alternative techniques have been properly studied and published, they should be regarded at best as expert opinions. The interests of the pharmaceutical companies that manufacture CCH are obvious and larger studies without funding from these companies are few and far between. In the author's opinion, there is a tendency towards omitting comparisons between CCH and PNF and focusing on comparisons between CCH and open fasciectomy, along with downplaying the recurrence rates for CCH that are now reported at approximately the same rate as those for PNF[39,47].

## The complications of minimally invasive treatments

Krefter *et al.* have recently published a systematic review of complications in relation to Dupuytren treatment in which 113 studies were assessed. The treatment with the highest pooled incidence of reported complications was CCH (78%), while all other treatments had a lower incidence of complications: PNF (19%), fasciectomy (17%) and dermofasciectomy (12%)[87]. However, an analysis of the severity of the reported complications

revealed that the complications related to CCH treatment and PNF were transient in comparison to the more severe complications after open surgery, e.g. nerve injuries. No serious complications were seen in this study.

## Hematomas and patient-reported procedural pain

Hematomas at the injection site were the most common adverse events in the CCH group (in 58% of the patients), but the consequence of this is probably negligible. Other local signs after the injection of CCH also resolved within a week. The significant difference in reported pain levels between the treatments is interesting and has not previously been reported. One explanation could be that the second injection before the extension maneuver was performed in skin already affected by the CCH injection.

## Skin ruptures

The patients in this study were found to have skin ruptures at a much higher frequency than reported by other authors[33,39,45]: 49% of the patients in the CCH group and 38% in the PNF group. However, no infections were recorded for these patients and all skin ruptures healed without complications. From the author's experience, skin ruptures should not be feared and are unavoidable in some patients with skin adhering over the Dupuytren cords if the contracture is to be fully reduced. In order to investigate the possible correlation between skin ruptures and recurrence, a large sample would possibly be needed: two of nine of the patients with recurrence in the PFN group after two years had skin ruptures during the extension maneuver, and five of ten in the CCH group. The skin ruptures were significantly larger in the CCH group, which might be due to enzymatic action in the dermal-epidermal interval that weakens the skin[88].

## *Nerve and flexor tendon injuries*

There were no nerve or flexor tendon injuries in any patients treated in this study. Accidental injury to the neurovascular bundle and flexor tendons are in fact very rare complications of PNF and CCH treatment and have been reported at a frequency of 0-0.3 %[40,41,45]. They can, however, occur as direct mechanical injuries when the needle is passed through the subcutaneous tissue (PNF and CCH) or as secondary consequences of the enzymatic breakdown of collagen (CCH). Tendon ruptures are extremely rare: a study found 26 tendon ruptures in 49,000 injected fingers (0.005%)[89]. Even so, most patients treated with CCH are advised not to use their treated hand in power grips for at least one week. In PNF, perforations by the needle are not enough to divide the flexor tendons (Figure 28)
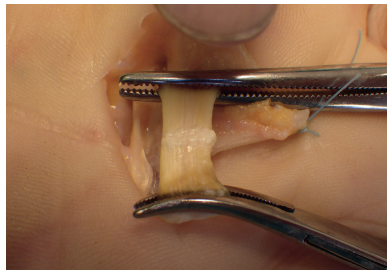


**Figure 28**. An FDS tendon at the MCP level in a cadaver hand has been perforated by a needle passed tbrough the tendon 200 times, but the author is still not able to pull the tendon apart.

## The PROMs in this study

An analysis of the responsiveness of the questionnaires used in this study is interesting; the vast majority of all patients reported a far better outcome than the minimal clinical change of 2.9 as measured by the URAM scale after two years compared with baseline (median 11 to 1 for CCH, and median 10 to 2 for PNF). For QuickDASH, no minimal clinical change has been determined, but the patients had results that were easily comparable to

those described after fasciectomy by Budd *et al*[62] (median 16 to 5 for CCH and median 11 to 2 for PNF). A disease-specific PROM, such as the URAM scale or similar should be used in all future studies relating to Dupuytren's disease, but the use of the more general Quick-DASH could be debated.

## The fate of the collagen in the ruptured cords

In the author's opinion, the hypothesis that CCH acts as a chemical fasciectomy[74] that enzymatically reduces pathological collagen instead of just dissolving it enough to permit a simple rupture is yet to be proved. Even though four cases of "microruptures" were seen in the ultrasonographic study, most Dupuytren cords ruptured at one level. Furthermore, more than half the cords vanished in the course of this study, regardless of treatment, indicating that the process is far more complicated that just enzymatic breakdown: patients treated by a percutaneous section of the cord had the same results!

In the absence of mechanical stress, the pathological cord collagen appears to be resorbed to some extent in some patients. It has been proposed that tension in the palmar fascia promotes early recurrence after surgery[90] and tension acting as an enforcer of cord formation and contracture progression could be a plausible hypothesis that concurs with our results. A new Dupuytren cord is probably formed *de novo* in some patients, but a significant amount of pathological tissue is resorbed in others.

In the light of this, the industry-sponsored MRI study by Crivello of five patients that concluded that CCH reduces collagen should be challenged by another study that should include a second group of patients treated with PNF. If our results are correct, there would be no difference between the groups since the mechanisms of this reduction are beyond enzymatic digestion or mechanical division. The cellularity of the Dupuytren cord may also be a factor: a mature cord with a hyperechogenic fibrillar structure would probably be more prone to be resorbed after rupture than a nodular

one, given that these ultrasonographic properties mirror the cell content of the cords.

## Minimally invasive treatments and their relationship with other treatment modalities- the author's perspective

A surgeon who treats patients with Dupuytren's contracture needs to be familiar with a palette of treatment options in order to manage each individual case. One universal treatment option is yet to be invented and, as the patients' awareness of different treatment options increases, the surgeon has a corresponding increasing responsibility when recommending them treatment. A recent survey investigating surgeons experience showed that, even though more invasive procedures result in a longer time to recurrence, the patient burden is higher in terms of the recovery of hand function and the frequency of complications.[25]

Figure 29 depicts the author's view of the relationship between the different currently available and future treatment modalities for Dupuytren's disease and the severity of the Dupuytren contracture, from the first symptom to the left (a nodule) to a severe contracture (with an advanced cord) to the right. The circles represent each treatment going from non-invasive to the left through minimally invasive to highly invasive from left to right, and the crossing circles represent a possible overlap in indications for the same patient. PNF and CCH are considered equally suitable as minimally invasive treatments. For instance a patient with a moderate contracture could be treated by either minimally invasive methods (PNF or CCH) or by fasciectomy (represented by the area of the crossing circles).

ABSENT ⟶ MILD ⟶ MODERATE ⟶ SEVERE CONTRACTURE

RADIOTHERAPY
?

PNF OR
CCH

DERMO-
FASCIECTOMY

FUTURE GENE
THERAPY ?

FUTURE DRUG
THERAPY ?

FASCIECTOMY

AMPUTATION

Nodules        Cords ⟶

Other factors:

Recurrence ⟶

MCP-involvement      PIP-involvement ⟶

Diathesis ⟶

Secondary joint changes ⟶
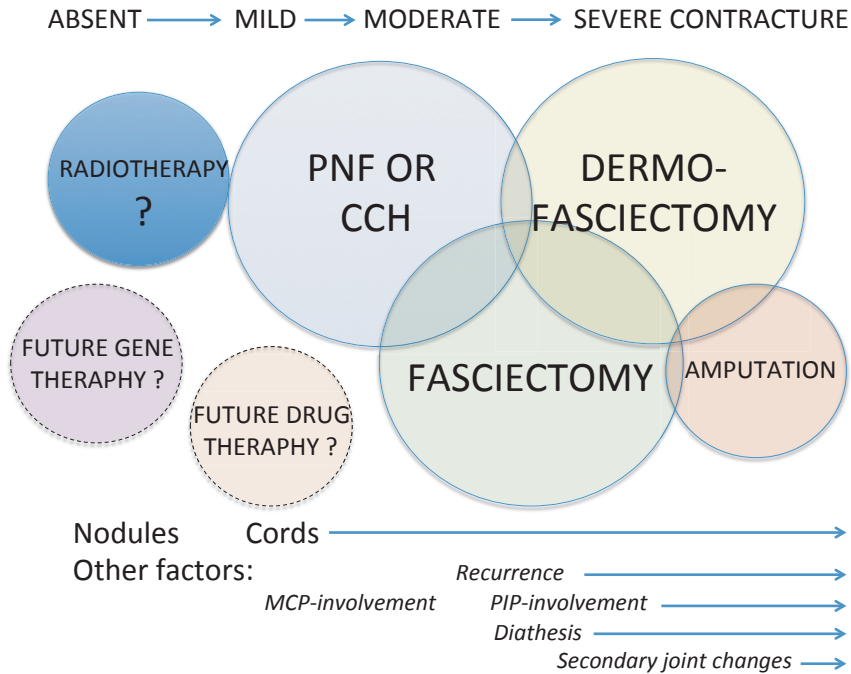
**Figure 29**. The treatment palette for Dupuytren's contracture

Another patient might be suitable for dermofasciectomy due to an advanced contracture but might prefer a minimally invasive procedure with shorter rehabilitation and accept the risk of recurrence and perhaps the incomplete correction of the contracture. A patient with a contracture suitable for PNF would not be considered for amputation (the circles do not cross).

Other factors that influence the treatment decision are outlined below the circles: a recurrent contracture or joint involvement would suggest more invasive treatment, secondary joint changes cannot be corrected by minimally invasive treatments and so on. The circles with dotted lines represent the patients in whom future treatments yet to be discovered would be considered: gene therapy would be a prophylactic measure even before the first symptom of Dupuytren's disease and any drug therapy

would possibly have to be initiated before Dupuytren cords are formed.

Given the significantly simpler option of minimally invasive treatment, the author would suggest either PNF or CCH as the first line of treatment for most patients with one or more readily palpable cords with contracture(s). If economic factors and immediate adverse events are to be taken into account and multiple joints are to be treated, PNF would be the treatment of choice. Even in more complicated cases, an informed and compliant patient could agree to testing whether PNF is able to provide sufficient symptom relief even with a residual contracture. Telephone contact a few weeks later would determine whether the patient is satisfied for the time being, or whether he or she should be scheduled for fasciectomy or dermofasciectomy.

## Methodological considerations and limitations

*Power analysis.* A power analysis was only performed for the outcome measure passive extension in clinical Studies I and III. However, the number of patients included in this study compared with other RCTs of CCH and PNF is high (Scherman *et al.* included 96 fingers[81] and Skov *et al.* 50 [82]), which should eliminate any risk of a Type 2 error.

*Study design.* A noninferiority trial to test whether CCH is as efficacious as PNF could have improved the quality of this work, but this would have required a different study design, which could not be constructed afterwards[91].

*The time frame of Studies I and III.* A two-year follow-up should only be regarded as an intermediary result, since other studies of Dupuytren contracture have shown a great increase in recurrence up to five years[42,47].

*Overall selection bias.* Only a small proportion of the referred patients (18 %) were enrolled in the study, but this can be explained by the specific definitions of the study group. The patient would have to accept treatment on only one finger (and, in some cases, only the MCP joint since no second PNF for the PIP joint was performed). Furthermore, the patient should not have received any previous treatment on the affected finger. Our unit is also the last referral unit for more complex cases and most recurrences from all the orthopedic clinics in the region are likely to be referred to our department.

*The blinding process* relied heavy on patient cooperation: the patients were instructed not to tell the physiotherapist which treatment they had received or their personal ID number and the physiotherapist had no access to the patient's files, but it was possible to circumvent this since the patient was very aware of his/her treatment. A blinded design would have added quality, but this was ruled out due to the obvious side-effects of CCH.

*The external validity of a single-surgeon study* could be questioned. We have already reported a considerably higher rate of skin ruptures than other authors, and the treatment results are dependent on the skills of the one surgeon and not necessarily universally applicable. It could be argued that the author's technique for injection is now outdated and have been replaced by more efficient injections of CCH, but at the time this study was intiated our protocol followed the recommendations of the manufacturer. The author had performed over a hundred PNFs when CCH was introduced, and could inject CCH into the cord with adequate precision as to where the needle was located.

*The external validity of the ultrasonograhic evaluation.* The same reasoning as above applies to the radiologist in Studies II and IV, even though interrater correlations were assessed. Due to the exploratory design of the study and since ultrasonography for this diagnosis is not a standard procedure, the radiologist had a steep learning curve within Studies II and IV. The difference between examining the patient and reviewing frozen ultrasonographic images could be considerable since the analysis is highly dependent on the projection in which the measurements are made. We did not repeat the ultrasound examination but the measurements of the gap on the stored images were made twice in order to estimate their reliability. Further studies of intra-observer and inter-observer reliability are required before ultrasonography can be regarded as a reliable and reproducible test for the post-treatment effects on Dupuytren's contracture.

*The correlation analysis in Study IV.* The assumptions made from the differences in echogenicity and structure between the cords lack any certain correlation in the absence of a histological examination *in vitro.* Furthermore, the cohort was relatively small, especially in order to subcategorize the different echogenic and structural findings.

*Quality of the ultrasound machine.* Another shortcoming was that the used ultrasound system was not a truly high-end system, which implied a limitation in both imaging resolution and sensitivity.

*Bias.* The author has been deeply involved in the introduction of PNF, at both local and regional level, and could therefore be accused of a more positive attitude towards this treatment than towards CCH. However, the blinded design of the study and the measurements by an independent physiotherapist would have prevented any such tendencies. As for the ultrasonographic parts of the study, these were performed by an independent examiner.

*Presence of cords.* We chose to define a cord as "a continuous bulk of longitudinal subcutaneous tissue volar to the joint which tightens when the finger is passively extended", and whether or not this is a proper assessment of residual collagen could be the subject of debate. The author did not examine the hands of the patients himself at follow up, but the physiotherapist who determined whether or not a cord was present aquired sufficient experience by consulting the author during the first follow-up groups.

# Conclusion

This thesis concluded that:

- There were no significant differences between treatment outcomes for CCH and PNF treatment for Dupuytren's contracture at any time during the study period of two years, with the exception that
-  Patients treated with CCH reported a higher level of periprocedural pain compared with patients treated with PNF and were found to have larger skin ruptures
- Most patients treated by either method had good to excellent overall results, but the incidence of recurrence increased between one and two years
- The ultrasonographic appearance of the ruptured cord is similar after both treatments, suggesting that the mode of action of CCH is a simple disruption instead of "enzymatic fasciectomy"
- The residual Dupuytren cord tissue appeared to be resorbed to some extent in more than half the patients at the site of intervention (MCP joint level) and in patients with concomitant PIP contractures
- Concomitant PIP joint contractures were reduced significantly even though the Dupuytren cord was divided at the MCP level
- Ultrasound can be used to investigate the morphology of Dupuytren cords, and nodules similar to those described by histopathology and MRI studies could be found by ultrasound.

This study was not able to find any additional patient value from CCH treatment that could justify the higher cost compared with PNF.

# Future perspectives

The rationale for this thesis was to investigate if CCH would provide additional benefit to the patients compared with PNF. If so, CCH should be introduced in the government-funded health services. This thesis was unable to find such evidence, and the regional Orthopedic Board of Region Västra Götaland has decided accordingly and does not recommend introduction of CCH for the time being.

This thesis raises further questions that need to be answered about the intriguing condition that is Dupuytren's disease. The first and most obvious, is the need for further follow-up of the patients in this study. A two-year follow-up should be regarded as an intermediate result at best. Some patients with a recurrence have already had a second treatment, most of them by PNF, and the results from follow-up after five years will enable correlations to the long-term results relating to fasciectomy and CCH.

In the booming era of evidence-based medicine, there are now three RCTs that compare CCH to PNF and the future will probably see multiple systematic reviews in which theses studies will represent at least level II evidence. Three-legged randomized studies between fasciectomy and minimally invasive treatments have been proposed and would provide solid evidence, but are difficult to orchestrate.

Meanwhile, a study to describe how the treatment for Dupuytren's disease have changed from open surgery to minimally invasive methods on a national level, and the economic consequences of this change, would be interesting.

The morphology of the Dupuytren cord before and after treatment needs to be further investigated and a study combining ultrasound and MRI on patients treated by PNF would investigate the reliability of ultrasonographic measurements of the rupture of the cord. Furthermore, an MRI study designed like the study by Crivello et al[74] but with a longer follow-up would

provide answers about the fate of the collagen after the Dupuytren cord has ruptured, and could possibly explain why some cords are resorbed over time. Histopathology on excised cords that have been investigated by ultrasound would determine whether the same correlation exists as in Yahoes *et al.* MRI-study.

Recent years have seen a shift from a total focus on objective measurements in studies towards the importance of assessing the individual patient's subjective perspective on any treatment. Mulley *et al* have postulated that "doctors cannot recommend the right treatment without understanding how the patient values the trade-off"[92] and this is especially true in Dupuytren's disease since no certain cure can be offered. Qualitative studies of patients with Dupuytren's disease are very rare, but this methodology could be useful for investigating the patient's perspective on recurrence and repeated treatments. An answer as to why some patients prefer repeated minimally invasive procedures in a finger with a recurrence instead of open fasciectomy would be very interesting.

Finally, someone should try to study the medico-cultural aspects of DD treatment and find an answer to this question: why didn't PNF revolutionize the treatment of DD in the 1990ties in the same way as CCH did 20 years later? The author's own hypothesis is that the authors who refined and described the method were rheumatologists, not surgeons, that they wrote in French and that there was no business potential in using a simple needle…

# Acknowledgements

# The Quiz

Amazingly enough, some people claim that other people usually read the acknowledgements first. To prove them incorrect, please answer the following questions in order to proceed to the rest of this section:

1. This study compared the outcomes after percutaneous needle fasciotomy (PNF) and collagenase (CCH, Xiapex) for Dupuytrens contracture after two years. The primary outcome was a straight finger, secondary outcomes included effect on concomitant PIP contractures and patient-reported outcome measures. What do you consider to be the main conclusion?

   A. There were no significant differences in outcome between the two methods at any time during the study.
   B. PFN is a cheaper treatment option, but more recurrences were seen after two years compared with CCH.
   C. CCH is more cost-effective than PFN, there is no difference between the two methods and the author seems heavily biased.
   D. Patients treated with PFN reported significantly higher satisfaction than patients treated with CCH.

2. The number of patients who are treated for Dupuytrens disease has increased over the last years. One explanation for this could be that there are alternatives to open surgery, such as CCH and PNF. How much more expensive is CCH compared to PNF?

   A. At least twice as expensive
   B. At least five times as expensive
   C. At least ten times as expensive
   D. There is no difference in cost

ANSWERS: If you need to check the answers you haven't read this thesis! Go back and make yourself worthy of turning to the next page………. ;-)

I also want to extend my sincere gratitude to:

**Jan Fridén**, my main supervisor. Somewhat of a legend in your time, I'm honored that you agreed to see this thesis through. Thank you for your great enthusiasm, for teaching me tetrahand surgery and your tendency to use superlatives in emails. You know I had my doubts at the entrance of this gauntlet, but it has been fun most of the time. Really.

**Ylva Aurell**, my co-supervisor, for your skills in ultrasonography and the effort you put into making Petr a top-notch Dupuytren ultrasonographer. Also thank you for the translation of the French articles.

**Petr Vanek**, co-author, for taking on the difficult task of ultrasonography of Dupuytren cords. Few radiologists have ventured into this field, so you are likely to be the only one in Sweden. Without your efforts, there would be no morphology in this thesis.

**Allan Ibsen Sörensen** Black belt needle fasciotomist (and pretty good with Xiapex too), for introducing me to needle fasciotomy thus making this thesis possible, and for sharing your cool Danish perspective on most things over the years.

**Lena Nyblom-Andersson,** for all the extra time you put into this study. Without your coordination skills and perseverance, there would have been no study whatsoever.

**Marie Medbo**, master NFXIA physiotherapist, for the follow-up of all patients over the years.

**Niclas Löfgren** och **Åsa Bell,** photographers, for the hundreds of pictures you took with short or no notice and without any formal referral note.

**Stella Funnemark** for the first illustration in this thesis.

**Cina Holmér**, for your patience in explaining the logisitics of PhD studies and your support with all practical matters.

**Helena Brisby**, head of the Department of Orthopedics at the Institute for Clinical Sciences, for rhapsodic encouragement and the promise that time would be no issue - you were right.

**Carina Reinholdt, Ann Nachemson, Anders Nilsson and Anna Elander**, my past and present Heads of (various) Departments for your support and for facilitating the completion of this thesis. Special thanks to Anders for arranging the financial support to launch this study in 2012, and to Carina for the time you allotted me to write this thesis. Nobody will ever pay me to write a book again.

**The regional orthopedic board of Region Västra Götaland**, for your decision not to introduce Xiapex in any orthopedic clinic until this (or a similar) study had been completed.

**All orthopedic surgeons** in the region who referred their patients to me.

**Lotta Mellander,** for introducing me to global medicine and for (eventually) convincing me that it is the responsibility of clinicians to do clinical research.

**Annki Grönvall and Agneta Carling**, operation nurses, for keeping the spirits high in the small, window-less, submarine-like environment of the operating theater during long days.

**Ingemar Olsson** and **Klas Hellgren,** my mentors during my first shaky years in surgical training at Alingsås lasarett. Worlds apart in personality, you created a kind and trustful environment in which I thrived.

**Kristian Samuelsson** and **Ola Rolfson**, for your relentless scrutiny of my work at half-time, and Kristian for trying to introduce proper health economic assessments and non-inferiority methodology in Study III.

And now to the most important part which some of you might have skipped large parts (if not the whole) thesis to find: the author thanking his closest family.

I will probably never write another book, therefore I would like to cram in all the love and gratitude I can to the people who really matter to me. Since I misused the dedication to some extent, this might be my last chance to make amends to the ones who have suffered some during this PhD process. However, my PhD studies have taught me to be stringent and that is why I paid a professional editor to delete all emotional outbursts and mushy claims in the following text directed to my family.

This is what he left you:

[redacted] beloved wife Sofia, hustrusyster. [redacted] quarter of a century [redacted] in Medical school [redacted] DIY [redacted] joy and fun [redacted] surgical and semiacademic careers [redacted] !!! And to our great children: Elin, Olle, Erik and Ellen [redacted] Elin, 16 [redacted] greatest [redacted] Olle, at the age of 14 [redacted] magnificent [redacted] Erik, 10 [redacted] cool [redacted] Ellen, 2 years of [redacted] Simmis [redacted] meaning of [redacted] you forever!

**(DELETED PICTURE)**
**Figure 30.** The author with his family poolside in Lysekil.

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# Appendix I

## Percutaneous needle fasciotomy- author's preferred method

# Percutaneous needle fasciotomy - author's preferred method

*These instructions convey the author's experience and technique as they have been taught at the Department of Hand Surgery, Sahlgrenska University Hospital, to numerous residents from regional hospitals in the Region Västra Götaland in 2011-2015. These instructions are commonly referred to as "Needle fasciotomy for dummies" and has been handed to the newborn needle fasciotomist at the completion of the supervised training.*

## INTRODUCTION

Percutaneous needle fasciotomy (PNF) is a safe simple method for treating mild to moderate Dupuytren contractures with a palpable cord and an extension deficit in the joint to be treated. Dupuytren cords at the metacarpophalangeal (MCP) joint are generally easier to treat, with less risk of damage to adjacent nerves and tendons, than those in the proximal Interphalangeal (PIP) joint. The needle fasciotomist to-be is advised to gain experience of the method at the MCP joint level prior to starting with the PIP joint, and to ensure that the modified technique described below is used.

## INDICATIONS FOR TREATMENT

- A readily palpable Dupuytren cord with a concomitant extension deficit. When the finger is extended passively, the tension of the cord should increase accordingly.
- The passive extension deficit should be ≥ 20 ° in the MCP joint and > 40° in the PIP joint.
- In PIP contractures, arthrolysis should not be anticipated.

Anticoagulant therapy or recurrent contracture is not a contraindication for PNF, and multiple fingers and different levels of the cord can be treated at the same time if the patient so wishes.

## THE METHOD AT THE MCP JOINT

PNF can be performed after local disinfection of the skin over the cord, without sterile gloves and in a regular outpatient office in simple cases. The patient should be lying down and the surgeon should be positioned so that the his/her non-dominant hand keeps the finger extended throughout the procedure (Figure 1). The extension deficit should be measured with a finger goniometer before treatment.

## MATERIAL

3 ml syringe with

1 ml of Depomedrol and

2 mls 2% carbocain without adrenaline

25 gauge needle, preferably short



Figure 1

There is some evidence that the use of corticosteroids reduces the risk of recurrence, but this has been the subject of debate. A more concentrated local anesthetic compensates for the dilution by the corticosteroid and the use of a shorter 25 gauge needle will provide better directional and depth control while penetrating the cord.

1. The puncture site should be chosen at the thinnest part of the cord and should also avoid skin creases to minimize the risk of skin ruptures (Figure 2)

2. Inject a small volume subcutaneously volarly to the cord, retract the needle and wait for a short while.


Figure 2

3. Pass the needle through the cord at the same puncture site while tensioning the cord by passive extension - note the loss of resistance when the needle passes through the cord dorsally. Inject a larger volume, retract the needle and wait for a short while.
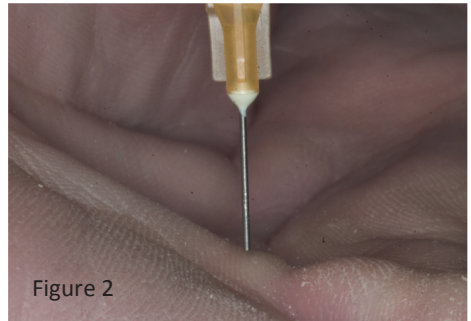
4. Tension the cord by passive extension of the finger throughout the whole procedure. Pass the needle through the cord in a fan-shaped pattern (Figure 3) in a transverse plane without retracting the needle through the skin. An obvious loss of resistance should be felt when the needle is passed through the cord. Pull the needle back and choose another direction. If this loss of resistance is difficult to detect, increase the tension of the cord by applying more force to extend the finger passively.


Figure 3
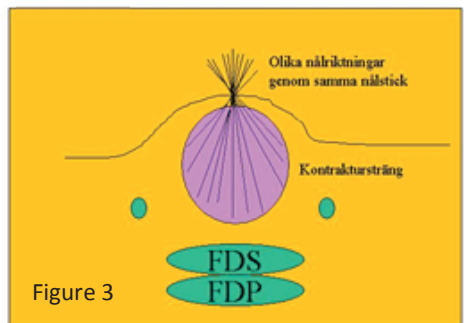
5. Keep perforating the cord in different directions in one plane until a rupture of the cord is either felt or heard and the finger starts to straighten. Remove the needle, put a sterile dressing over the puncture site and extend the finger firmly to a hyperextension of at least 10°. Show the resulting full passive extension to the patient and put a bandage on the puncture site.

6. If a skin rupture occurs show it to the patient and reassure him/her that this is a well-known complication that will heal by secondary intention within a couple of weeks. Do not attempt any other closure of the skin, regardless of the size of the rupture. Put on a tourniquet and instruct the patient to remove it the next day and to wash the skin rupture with soap and water before applying a simple bandage. If there are doubts about compliance with these recommendations refer the patient to a district nurse.

7. Measure the passive extension using a finger goniometer before and after treatment and record these measurements in the patient's notes. If there is a discrepancy of >10° between the active and passive extension of the joint, consider a volarly based night splint with straight fingers for three months. This is usually not needed for MCP contractures.

8. Instruct the patient to stretch any residual extension deficit using the other hand. Encourage the patient to use the hand immediately and to integrate daily stretching during his/her spare time, e.g. while watching TV or traveling by a bus for as long as needed. Regular hand therapy is very rarely indicated. Inform the patient about the risk of recurrence and ensure that the patient knows how to renew contact if this should occur.

## THE METHOD AT THE PIP JOINT

The risk of injury to the neurovascular bundle and the flexor tendons increases at the PIP level. The PIP joints are considerably more difficult to treat and other procedures such as limited fasciectomy should be considered. PNF could, however, be a reasonable option especially in the presence of a thin, superficial cord.

Contrary to the central pretendineous cord at the MCP level, the cords engaging the PIP joints are usually located ulnarly or radially to the joint, i.e. in close proximity to the neurovascular bundle. The following modification to the method described above is therefore recommended:

1. Instruct the patient carefully to report any paresthesia in the finger during the procedure.

2. Use only a minimal volume of local anesthetic subcutaneously between the intended puncture site and the cord; anesthesia of the digital nerve should be avoided!

3. Perform needle fasciotomy as described above. Tension the cord maximally and change direction when the needle has passed through the cord. If possible, choose a dorsolateral angle away from the neurovascular bundle and flexor tendons. If repeated needling is required test sensibility distally in the finger occasionally to ensure intact nerve function.

4. When the cord starts to rupture inject a larger volume of local anesthetic and retract the needle. Wait for a while and perform the extension maneuver. Do not continue to needle!

Joakim Strömberg

Department of Hand Surgery, Sahlgrenska University Hospital

# Appendix II

# Study protocol NFXIA

N F X I A

# STUDY PROTOCOL NFXIA
## Randomized prospective study between collagenase and needle fasciotomy for Dupytren's contracture

| VISIT | | DATE | EXAMINER |
|---|---|---|---|
| 1: | First consultation | ……………… | ……………… |
| 2: | Randomization and treatment | ……………… | ……………… |
| 3: | Postoperative control (1 week) | ……………… | ……………… |

**Blinding procedure after postop control
(protocol is kept at Dr Joakim Strömbergs office in elevhemmet)**

| | | | |
|---|---|---|---|
| 4: | 6 months –follow up | ……………… | ……………… |
| 5: | One year follow up | ……………… | ……………… |
| 6: | Two year follow up | ……………… | ……………… |
| 7: | | ……………… | ……………… |
| 8: | | ……………… | ……………… |

Joakim Strömberg 2012

# VISIT 1 – First consultation   1/3

**CHECKLIST**
   **CASE HISTORY**
   **STATUS**
   **INFORMATION IN WRITING AN ORALLY**
    **INFORMED CONSENT, COPY TO PATIENT**
   **PROMs**

**CASE HISTORY**

| | | |
|---|---|---|
| Gender | Male | Female |
| Dominant hand | Right | Left |
| Hand to be treated | Right | Left |
| Duration since onset of symptoms | …………………years | |

Family history            No          Yes, …………………………...

Occupation            Retired

                Sick leave due to…………………………

                profession ……………………………..

Other diseases        …………………………………………………

ASA-class        I        II        III        IV

Finger to be treated:    V
            IV
            III
            II

Joakim Strömberg 2012

# VISIT 1 – First consultation   2/3

**Hand grip strength    :**        RIGHT                …………………kgs

                                             LEFT                 …………………kgs

## FINGER TO BE TREATED:        V
                                                        IV
                                                        III
                                                        II

                    MCP joint            Active MCP flexion        …………………..°

                                             Active MCP extension      …………………..°

                                             Passive MCP extension     …………………..°

                    PIP joint             Active PIP flexion         …………………..°

                                             Active PIP extension       …………………..°

                                             Passive PIP extension      …………………..°

Joakim Strömberg 2012

# NF︱IA

# VISIT 1 – First consultation   3/3

**FINGER TO BE TREATED:**          V
                                   IV
                                   III
                                   II **DIG V**

**CORD**          MCP          Pretendineous          Y-cord to    ………..

                  PIP          Central          Ulnar          Radial



Joakim Strömberg
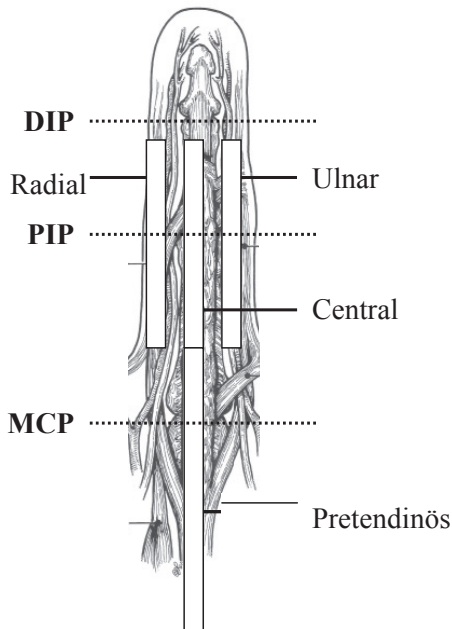
# VISIT 2 – Operation (1/3)

**Randomization group**          **no ……………….**

**Needle fasciotomy**:

Residual passive extension defect in MCP joint before bandage:

| | | |
|---|---|---|
| **MCP** | **DIG V** | …………………° |
| **MCP** | **DIG IV** | …………………° |
| **MCP** | **DIG III** | …………………° |
| **MCP** | **DIG II** | …………………° |

Residual passive extension defect in PIP joint before bandage:

| | | |
|---|---|---|
| **PIP** | **DIG V** | …………………° |
| **PIP** | **DIG IV** | …………………° |
| **PIP** | **DIG III** | …………………° |
| **PIP** | **DIG II** | …………………° |

| Complications | FDS/FDP- injury | Yes | No |
|---|---|---|---|
| | Skin rupture | Yes, ……….mm | No |
| | Hematoma | Yes | No |
| | Nerve injury | Yes, ………. | No |

Comments:  ……………………………………………………………………….

Night splint for three months?          Yes          No

Procedural pain (the patient marks a response):

**How painful was the extension maneuver of the finger?**

No
pain
(0)

Maximum
pain
(10)

# NF✕IA

# VISIT 2 – Operation (2/3)

## Xiapex – Day 1

Injektion performed accordint to protocol          Yes …………………………..ml
                                                   No

Comments   :          …………………………………………………………………………

                      ……………………………………………………………………………

---

## Xiapex – Day 2

Pain at the injection site (the patient marks a response):

### How much pain have you had since yesterday?

No _____ Maximum
pain                                                  pain
(0)                                                   (10)

Spontaneous rupture of cord?                    Yes              No

Rupture of the cord at extension maneuver strängen?    Ja              Nej

Local anestesia                          ………………..ml Carbocain

### How painful was the extension maneuver of the finger?

No _____ Maximum
pain                                                  pain
(0)                                                   (100)

# VISIT 2 – Operation (3/3)

## cont. Xiapex – Day 2

Residual passive extension defect in MCP joint before bandage:

| | | |
|---|---|---|
| **MCP** | **DIG V** | …………………° |
| **MCP** | **DIG IV** | …………………° |
| **MCP** | **DIG III** | …………………° |
| **MCP** | **DIG II** | …………………° |

Residual passive extension defect in PIP joint before bandage:

| | | |
|---|---|---|
| **PIP** | **DIG V** | …………………° |
| **PIP** | **DIG IV** | …………………° |
| **PIP** | **DIG III** | …………………° |
| **PIP** | **DIG II** | …………………° |

| Complications | FDS/FDP- injury | Yes | No |
|---|---|---|---|
| | Skin rupture | Yes, ……….mm | No |
| | Hematoma | Yes | No |
| | Nerve injury | Yes, ………. | No |

Comments:  …………………………………………………………………………

Night splint for three months?          Yes                    No

N F X I A

# VISIT 3 – Postoperative control at one week (1/2)

| **SKIN STATUS** | Signs of infection? | Yes | No |
|---|---|---|---|
| | Hematoma | Yes | No |
| | Swelling | Yes | No |
| | If skinrupture- healed? | Yes | No |
| | Normal 2 P-D | Yes | No |

Comments : …………………………………………………………………………

…………………………………………………………………………

Passive extension defect in MCP   joint until prevented by pain :

**MCP**     **DIG V**     …………………°
**MCP**     **DIG IV**     …………………°
**MCP**     **DIG III**     …………………°
**MCP**     **DIG II**     …………………°

Residual passive extension defect in PIP joint until prevented by pain

**MCP**     **DIG V**     …………………°
**MCP**     **DIG IV**     …………………°
**MCP**     **DIG III**     …………………°
**MCP**     **DIG II**     …………………°

**Hand grip strength**   **:**     RIGHT     …………………kgs

LEFT     …………………kgs

# VISIT 3 – Postoperative control at one week (2/2)

**PAIN**

**What was the maximum level of pain during the whole procedure?**

No                                                                                              Maximum
Pain _____ Pain
(0)                                                                                                (10)

**EXTENSION OF THE FINGER**

If you consider your finger to be *straighter* after the treatment, mark your response to question 1 and disregard question 2. If you consider your finger *more crooked* after the treatment, disregard question 1 and mark your respons to question 2.

**1. How much straighter do you consider your finger to be atfer the treatment?**

Unchanged _____ Totally
(like before)                                                                                straight
(0)                                                                                                (10)

**2. How much more crooked do you consider your finger to be atfer the treatment?**

Unchanged _____ Totally
(like before)                                                                                crooked
(0)                                                                                                (10)

# FOLLOW-UP VISITS

# BLINDED PATIENT

| VISIT | | DATE |
|-------|--|------|
| **2:** | **Randomization and treatment** | **………………** |
| **4:** | **6-months follow-up** | **………………** |
| **5:** | **One year follow-up** | **………………** |
| **6:** | **Two years follow-up** | **………………** |
| **7:** | | **………………** |
| 8: | | ……………… |

N F X I A

**VISIT**        ☐ 4.   6 months follow-up     (1/2)
                   5.   One year follow-up
                   6.   Two years follow-up
                   7.   ……………………………
                   8.   …………………………

**TREATED FINGER:**                V
                                   IV
                                   III
                                   II

**MCP joint**        Active MCP flexion      …………………..°

                     Active MCP extension    …………………..°

                     Passive MCP extension   …………………..°

**PIP joint**        Active PIP flexion      …………………..°

                     Active PIP extension    …………………..°

                     Passive PIP extension   …………………..°

Recurrence (MCP>20.°)?            Yes (contact Joakim)     No

Pain, stiffness, other comlication?     Yes (contact Joakim)     Nej

Comments: ………………………………………………………………………

## N F X I A

**VISIT**  □ 4.  6 months follow-up  (2/2)
5.  One year follow-up
6.  Two years follow-up
7  ……………………………
8.  …………………………

**EXTENSION OF THE FINGER**

If you consider your finger to be *straighter* after the treatment, mark your response to question 1 and disregard question 2. If you consider your finger *more crooked* after the treatment, disregard question 1 and mark your respons to question 2.

**1. How much straighter do you consider your finger to be atfer the treatment?**

| Unchanged | | Totally |
| (like before) | | straight |
| (0) | | (10) |

**2. How much more crooked do you consider your finger to be atfer the treatment?**

| Unchanged | | Totally |
| (like before) | | crooked |
| (0) | | (10) |

**VISIT**      ☐ 4.   6 months follow-up      (2/2)
                 5.   One year follow-up
                 6.   Two years follow-up
                 7   …………………………….
                 8.   ……………………………

**CORD**        MCP          Pretendineous        Y-cord to    ………..

                PIP          Central              Ulnar        Radial



DIP

Radial ——    —— Ulnar

PIP

            —— Central

MCP

            Pretendinös
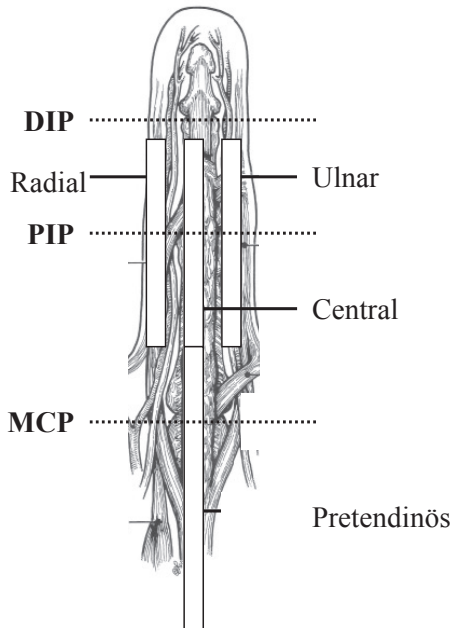
# Appendix III

## The Quick-DASH questionnaire

# *Quick*DASH

Please rate your ability to do the following activities in the last week by circling the number below the appropriate response.

| | NO DIFFICULTY | MILD DIFFICULTY | MODERATE DIFFICULTY | SEVERE DIFFICULTY | UNABLE |
|---|---|---|---|---|---|
| 1. Open a tight or new jar. | 1 | 2 | 3 | 4 | 5 |
| 2. Do heavy household chores (e.g., wash walls, floors). | 1 | 2 | 3 | 4 | 5 |
| 3. Carry a shopping bag or briefcase. | 1 | 2 | 3 | 4 | 5 |
| 4. Wash your back. | 1 | 2 | 3 | 4 | 5 |
| 5. Use a knife to cut food. | 1 | 2 | 3 | 4 | 5 |
| 6. Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.). | 1 | 2 | 3 | 4 | 5 |

| | NOT AT ALL | SLIGHTLY | MODERATELY | QUITE A BIT | EXTREMELY |
|---|---|---|---|---|---|
| 7. During the past week, *to what extent* has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups? | 1 | 2 | 3 | 4 | 5 |

| | NOT LIMITED AT ALL | SLIGHTLY LIMITED | MODERATELY LIMITED | VERY LIMITED | UNABLE |
|---|---|---|---|---|---|
| 8. During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem? | 1 | 2 | 3 | 4 | 5 |

| Please rate the severity of the following symptoms in the last week. *(circle number)* | NONE | MILD | MODERATE | SEVERE | EXTREME |
|---|---|---|---|---|---|
| 9. Arm, shoulder or hand pain. | 1 | 2 | 3 | 4 | 5 |
| 10. Tingling (pins and needles) in your arm, shoulder or hand. | 1 | 2 | 3 | 4 | 5 |

| | NO DIFFICULTY | MILD DIFFICULTY | MODERATE DIFFICULTY | SEVERE DIFFICULTY | SO MUCH DIFFICULTY THAT I CAN'T SLEEP |
|---|---|---|---|---|---|
| 11. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? *(circle number)* | 1 | 2 | 3 | 4 | 5 |

*Quick*DASH DISABILITY/SYMPTOM SCORE = $\left(\left(\dfrac{\text{sum of n responses}}{n}\right) - 1\right) \times 25$, where n is equal to the number of completed responses.

A *Quick*DASH score may **not** be calculated if there is greater than 1 missing item.

# Appendix IV

# VAS scales for patient's satisfaction and PREM

**Personnummer** (ååååmmdd-nnnn): ☐☐☐☐☐☐☐☐ — ☐☐☐☐

## PATIENTENKÄT (arm/hand)

Namn (texta):                                    Postnummer (t ex 123 45):

Gatuadress:                                      Ort:

Datum för ifyllande av enkät (åååå-mm-dd) ☐☐☐☐ - ☐☐ - ☐☐

Jag är (ange den hand du skriver med): ☐ Vänsterhänt ☐ Högerhänt ☐ Tvåhänt

Arm/hand som har opererats:      ☐ Vänster      ☐ Höger

Enkäten gäller de besvär du har haft **den senaste veckan,** i den **arm/hand** som har opererats. Kryssa för det svarsalternativ som stämmer bäst överens med dina ev. besvär.

**1. Smärta vid belastning**

Inga problem  0 10 20 30 40 50 60 70 80 90 100  Värsta tänkbara problem
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

**2. Smärta vid rörelser utan belastning**

Inga problem  0 10 20 30 40 50 60 70 80 90 100  Värsta tänkbara problem
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

**3. Vilovärk**

Inga problem  0 10 20 30 40 50 60 70 80 90 100  Värsta tänkbara problem
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

**4. Stelhet**

Inga problem  0 10 20 30 40 50 60 70 80 90 100  Värsta tänkbara problem
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

**5. Svaghet**

Inga problem  0 10 20 30 40 50 60 70 80 90 100  Värsta tänkbara problem
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

**6. Domningar/stickningar i fingrarna ("sockerdrickskänsla")**

Inga problem  0 10 20 30 40 50 60 70 80 90 100  Värsta tänkbara problem
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

**7. Köldkänslighet (obehag/besvär när du utsätts för kyla)**

Inga problem  0 10 20 30 40 50 60 70 80 90 100  Värsta tänkbara problem
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

**8. Förmåga att utföra dagliga aktiviteter**

Inga problem  0 10 20 30 40 50 60 70 80 90 100  Värsta tänkbara problem
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

**9. Hur upplever Du resultatet av operationen?**

☺ Helt nöjd  0 10 20 30 40 50 60 70 80 90 100  Helt missnöjd ☹
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

**10. Hur upplever Du bemötandet på kliniken under behandlingstiden?**

☺ Helt nöjd  0 10 20 30 40 50 60 70 80 90 100  Helt missnöjd ☹
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Question 9:     How satisified are you with the result of the operation?
Question 10:    How satisfied are you with your reception at the clinic during your treatment?