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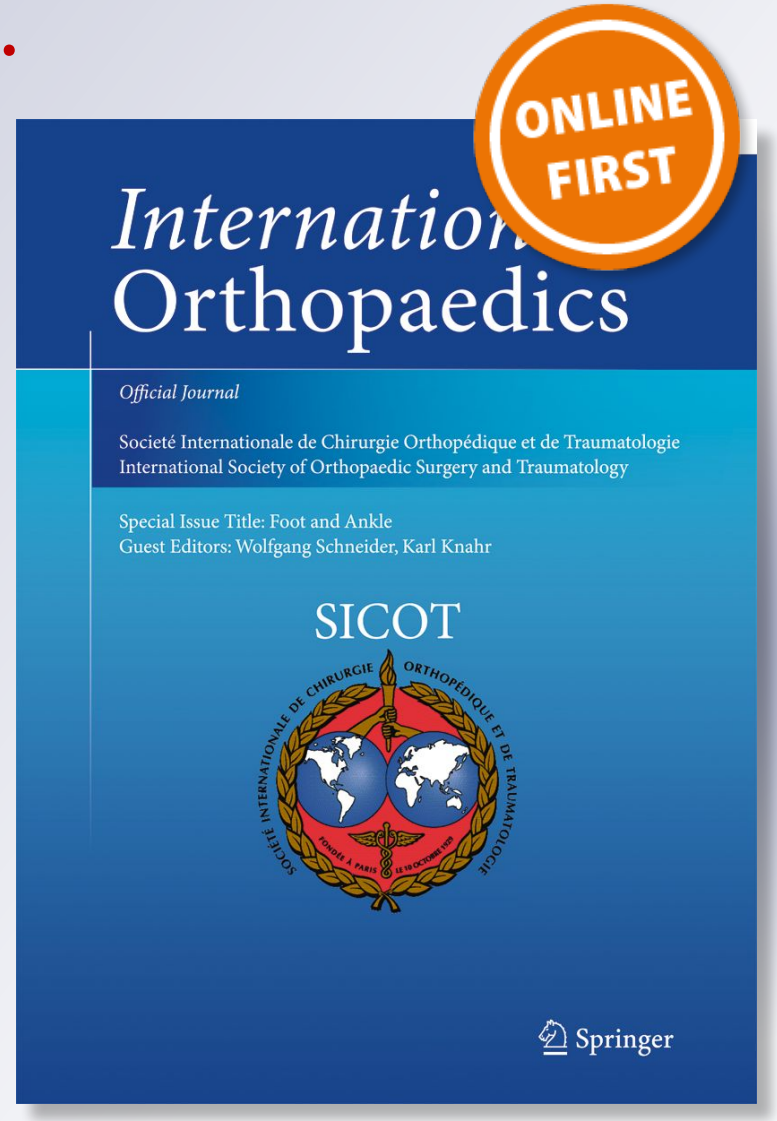

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ORIGINAL PAPER

Factors influencing recurrence and progression of Dupuytren's disease treated by Collagenase Clostridium histolitycum

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Abstract

Aim of the study The purpose of this study was to determine the recurrence rate, possible adverse reactions and factors influencing recurrence and progression of Dupuytren's disease (DD) treated with Collagenase from Clostridium histolyticum (CCH).

Method This was a prospective study of 71 patients with DD treated with CCH from 2011 to February 2013, with a minimum follow-up period of four years. Clinical, functional, patient satisfaction, drug safety and factors influencing recurrence and disease progression were evaluated.

Results In all patients, the rupture of the cord was achieved after the injection, reducing joint contracture. In five patients (7%) we verified the existence of disease recurrence during the follow-up. In 11 patients (15.5%) there was a disease progression. Three patients have been surgically operated on, without added surgery difficulty; the rate of recurrence and progression was higher in grades III and IV of Tubiana, in proximal interphalangeal (PIP) punctures, and was earlier in patients younger than 60 years.

Discussion No serious local complications or general complications were observed with this method. The recurrence of DD, following criteria of Felici, is mainly observed in young patients with greater severity of the disease and at the PIP level. Progression is influenced by the same factors. Patients operated on after recurrence have no added difficulty in the surgical technique, as it has also been published in other studies.

Conclusions Patients with the lowest rates of recurrence and progression were those with a single cord in the metacarpophalangeal (MCP), a grade II of Tubiana, and were older than 60 years.

Keywords Collagenase Clostridium histolitycum · Dupuytren's disease · Recurrence and progression

Introduction

Dupuytren's disease (DD) is a progressive fibroproliferative disorder characterised by the development of collagen nodules and cords at the superficial palmar aponeurosis level that causes progressive fingers closure [1].

There is no cure for DD, recurrence and progression of this disease are considered unavoidable throughout the patients' life [1].

DD recurrence is frequent after its surgical treatment [2], especially in young patients [1]. The recurrence rate after surgery is highly variable and according to the publications varies from 0% to 85% depending on the patient characteristics, the disease and the type of surgery performed [1].

This variability in the DD recurrence rate is due to the lack of consensus and subjectivity in the definition of recurrence—reappearance of the DD typical tissue in a previously operated area—which makes necessary a more precise and objective definition that will allow us to compare the rate of recurrence of DD among the different treatments published in the literature [1, 3].

In 2014, Felici et al. defined as a recurrence the existence of a passive extension deficit of more than 20° in at least one of the treated joints, in the presence of a palpable cord, comparing with the results obtained 6–12 weeks before [4].

The surgical treatment of DD has a significant morbidity, with an index of complications around 17%, including skin problems, haematoma, nerve damage, and CRPS [5]. In some

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published studies the complication index increased to 39% in both the surgical and post-operative stages [6].

Collagenase from Clostridium histolyticum (CCH) is another approved pharmacological treatment for DD treatment. It is a molecular entity formed by the fixed percentage mixture of two purified collagenolytic enzymes (AUX-I and AUX-II) isolated from a culture of Clostridium histolyticum [7]. This treatment has been established as an effective and safe modality for DD treatment by reducing the contracture degree of the affected fingers [8].

The objective of this study was to evaluate the recurrence rate of DD patients treated with CCH and to determine the factors that influence the recurrence onset and disease progression.

Materials and methods

This was a prospective, protocolled study of 71 patients with DD who were treated with CCH in the period from February 2011 to February 2013 with a minimum follow-up period of four years.

Inclusion criteria were adult patients with DD, age greater than 60 years except in cases where the patient, by express request, opted for this treatment alternative, with a palpable cord in at least one finger, excluding the thumb, with a contracture of at least 20–90° at the metacarpophalangeal (MCP) level and/or 80 degrees at the proximal interphalangeal (PIP).

Exclusion criteria were patients with haemorrhagic disorders or recent stroke, with other neuromuscular disorders on the hand, patients who have received treatment including DD surgery in the last 90 days, allergy to CCH or excipients, use of doxycycline in the last 14 days or of anticoagulant drugs in the last seven days, according to the recommendations of this drug.

Tubiana classification was used to determine the DD severity (Table 1).

Operative technique

All patients were treated on outpatient surgery and administered a CCH injection, taking into account the specific doses of both solvent and collagenase required depending on the joints to be treated according to the recommendations of the product (Xiapex®).

CCH was administered by local injection directly into the palpable cord. Half an hour earlier, a topical anaesthetic ointment (EMLA—lidocaine and prilocaine) was placed in the puncture area. After the puncture, a compressive bandage was placed on the patient.

Finger extension and cord rupture was performed after 24–36 hours in an outpatient operating room with loco-regional anaesthesia or sedation and subsequent compression bandaging of the hand for a week. In severe contractures, rigid immobilisation, a plasticized splint type, was used discontinuously for three to six weeks. In patients who had had skin dehiscence, periodic cures of the wound were made until its healing (2–3 weeks).

Table 1 Tubiana's classification of study patients

Grades	Angles	Patients	Percentage
I	1–45	12	16.9%
II	46–90	25	35.2%
III	91–135	21	29.6%
IV	>135	13	18.3%

Assessment

Follow-ups were performed weekly, every two weeks, every month, every three months, every six months, and then every year. In the first reviews, the presence of local complications (haematoma, skin dehiscence), decreased joint contracture and increased range of motion were evaluated. In the long-term post-injection follow-up, the DD recurrence and progression was verified (Fig. 1).

Measurements were performed with a standard goniometer assessing joint contracture and range of motion according to the criteria of the International Federation of Societies for Surgery of the Hand (IFSSH).

CCH injection **result** was define as the range of mobility that is obtained a month after the puncture. **Recurrence** of DD is the loss of passive extension of more than 20° in at least one of the treated joints associated with a palpable cord compared to the result of the injection. **Progression** of DD is the loss of passive extension of the entire finger (summed all joints) plus 20° compared to the result of the injection.

Patient satisfaction with procedure and outcome and drug safety (complications evaluation) was assessed.

Statistical analysis

The quantitative variables are presented with the mean and the standard deviation and the qualitative variables according to their distribution of frequencies.

The association of qualitative variables was analysed using the Pearson Chi-square test. If the number of cells with expected values lower than 5 was greater than 20%, the Fisher's exact test was used or the likelihood ratio test for variables with more than two categories. The time to recurrence was analysed using Kaplan Meier's analysis and mortality tables.

The data has been analysed with the statistical software IBM SPSS Statistics version 20.0 for Windows. Values of $p < 0.05$ will be considered statistically significant.

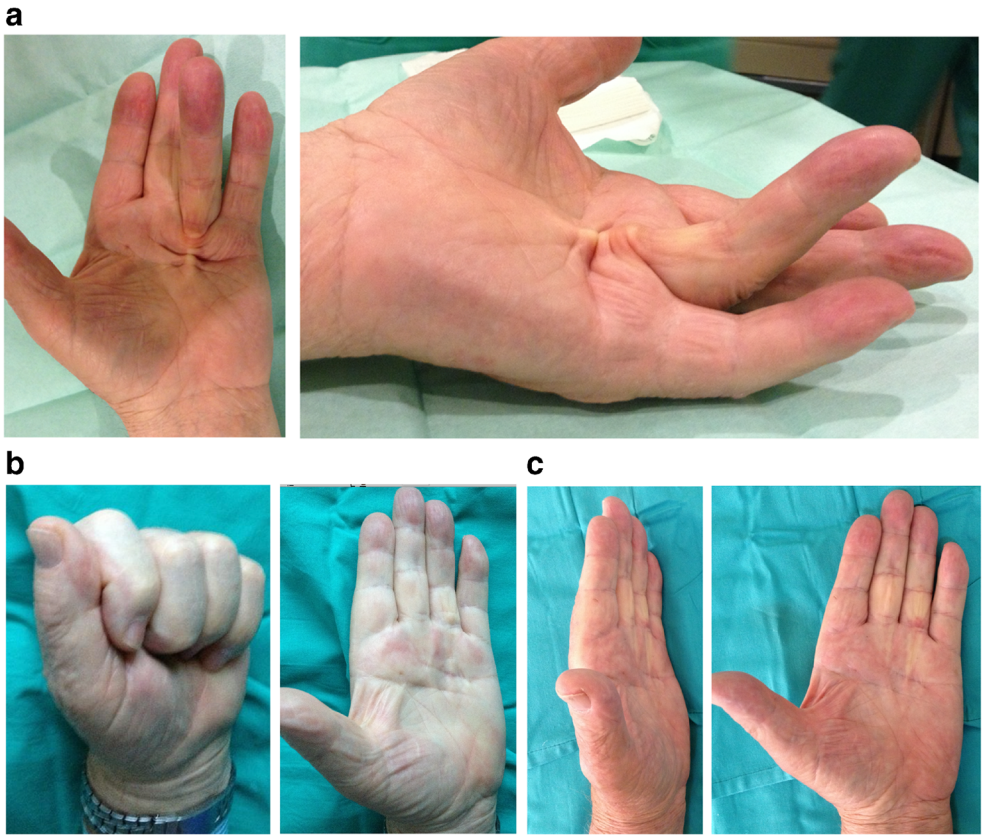


Fig. 1 An 80-year-old patient with DD **a** Preoperative. **b** One month postinjection (result). **c** State at five years, without recurrence or progression

All patients signed a treatment specific consent prior to the injection of CCH. The study was approved by the Hospital's Clinical Research Ethics Committee (PI 17-548- CINV 16-56).

Results

Clinical characteristics and immediate post-operative follow-up

Of the 71 DD patients, 66 were men (93%) and five women (7%), aged between 45 and 89 years, with a mean of 68.8 years.

The severity of the disease was determined by Tubiana's classification as shown in Table 1.

A single injection of CCH was given to all patients; 67 patients (94.4%) were injected in a palpable cord at the MCP level, of which 55 patients (77.5%) were injected in a single cord, 12 patients (16.9%) in Y-cords affecting two fingers, and four patients (5.6%) in a cord at the PIP level (Graph 1).

In all the patients, the cord rupture was achieved in the surgical act gaining range of movement, obtaining better results in the single cord level punctures in the MCP (Graph 2) and in the grades I and II of the Tubiana's classification (Graph 3).

In 34 patients (47.9%) dehiscence of the skin occurred during the finger stretching that was resolved without complication with local cures; 52 patients (73.2%) had haematoma and/or phlyctenas in the puncture area; there were no local, vascular, tendon, nerve or infection complications. In two patients (2.8%), axillary adenopathy was detected hours after the puncture, which disappeared in the first 48 hours, and two patients (2.8%) had axillary pain without adenopathy palpation.

The functional recovery of the patients was fast (less than 1 month) and painless, and only 11 patients (15.4%) required physiotherapeutic treatment.

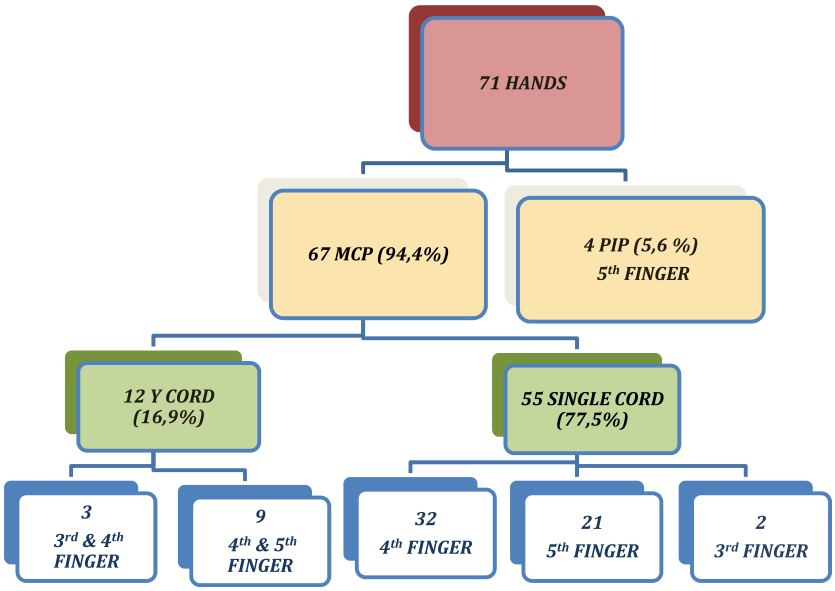
Long-term postoperative follow-up

Recurrence

In five patients (7%) the existence of disease recurrence was verified, with a minimum follow-up period of four years.

The DD recurrence onset was from the second year of the puncture result and progressively increased in the third and fourth years (Fig. 2).

According to the disease severity at the injection time, it was observed that the recurrence rate was higher in grades I,



Graph 1 Distribution of patients according to the CCH administration level

III and IV in the Tubiana's classification and the likelihood ratio test had a *p*-value of 0.165 (Fig. 3).

Comparing the DD recurrence rate with age, it appears more frequently and earlier in patients younger than 60 years old with a p-value of 0.224 (Fig. 4).

The DD recurrence was greater in patients in whom CCH had been injected at the PIP level and the likelihood ratio test had a p-value of 0.472 (Fig. 5).

Progression

In 11 patients (15.5%), we verified the existence of DD progression with a minimum follow-up period of four years. In these patients, the finger retraction degree was significantly lower than that prior to CCH injection; for example, in a patient having MCP and PIP affected, if full extension of MCP is achieved with injection, even with disease progression and increased retraction of the PIP, there is less complete retraction and hindering of the whole finger than before the CCH injection. Only one patient who had an MCP extension deficit of 25° prior to puncture and a cord of difficult identification had an MCP joint extension deficit of 45° in the fourth year.

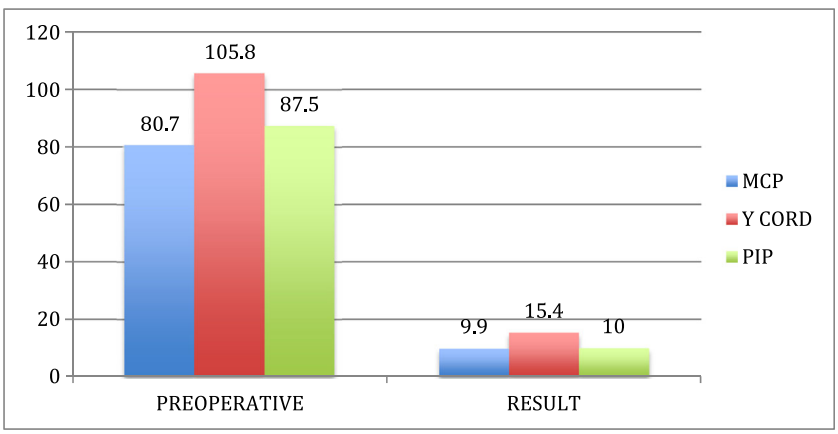
It was observed that the DD progression occurrence was from the first year of puncture and increased progressively in the second, third and fourth years (Fig. 2).

According to the disease severity at the injection time, the progression rate was higher in grades III and IV in Tubiana's classification and the likelihood ratio test presented a *p*-value of 0.06 (Fig. 3).

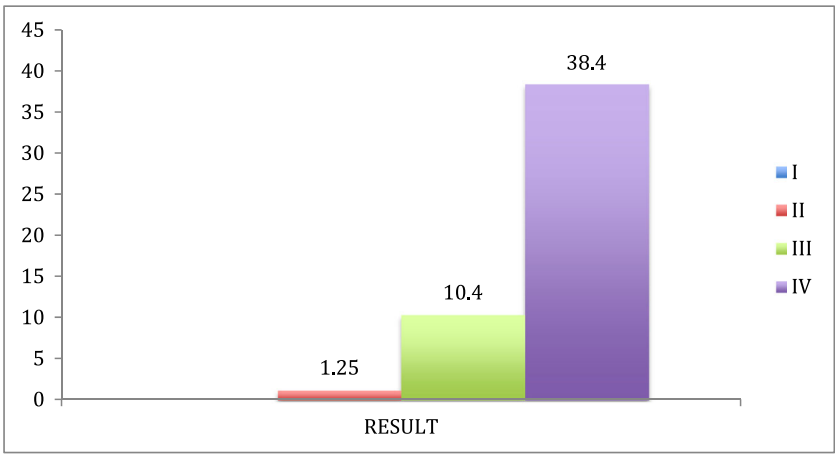
Comparing the DD progression rate with age it is observed that it appears more frequently and earlier in patients younger than 60 years old with a p-value of 0.341 (Fig. 4).

The DD progression was greater in patients in whom CCH had been injected at the PIP level and the likelihood ratio test had a p-value of 0.497 (Fig. 5).

Three of the patients in the study had been surgically operated by performing selective fasciectomy and zetaplasty: two



Graph 2 Results of CCH injection according to the puncture level (degrees of contracture)



Graph 3 Results of CCH injection according to Tubiana's classification (degrees of contracture)

patients in whom the articular contracture of the PIP increased after the treatment and the patient who had a greater retraction than before the puncture, not having a clear cord that made the CCH injection difficult, observing a fibrosis zone at the puncture site level without creating difficulties for surgery.

In the immediate post-operative period, two of these operated patients had skin dehiscence in the old puncture area treated by local cures without issues for secondary scarring.

Discussion

The therapeutic options for DD treatment are multiple depending on the patient's characteristics and the disease itself. Option include surgical treatment such as fasciectomies, dermofasciectomies, and fasciotomies, or pharmacological treatment such as local injection of CCH [9].

CCH is a new therapeutic alternative and another approved pharmacological option for the treatment of adult patients with DD, avoiding complications associated with surgery [10]. Several published studies confirm the efficacy of CCH in DD with clinical and functional improvement in all patients in whom it has been administered, with a rapid recovery [1, 5, 7, 8].

The best results in our study have been obtained after the CCH injection in patients in whom the puncture has been performed at the level of a single tangible cord in the MCP joint and in those patients in whom the degrees of contracture of the DD are lower as we have observed in other studies [1, 5–8].

We observed safety in the CCH administration, as there were few local complications which were minor and had easy resolution; we did not observe any serious local complications (tendon, vascular or nervous injury) or general complications [11]. However, there are publications documenting serious complications such as ruptured tendons by intratendinous puncture and important cutaneous necrosis [12, 13]. Compared with overall complication rates after surgery, according to different studies, between 4 and 39% [6], it is a treatment with fewer complications. It is also less invasive and therefore an alternative to DD treatment, especially in elderly patients with multiple associated pathologies, who are limited in daily activities, in which surgery supposes an increase in the local and general complication rates [14].

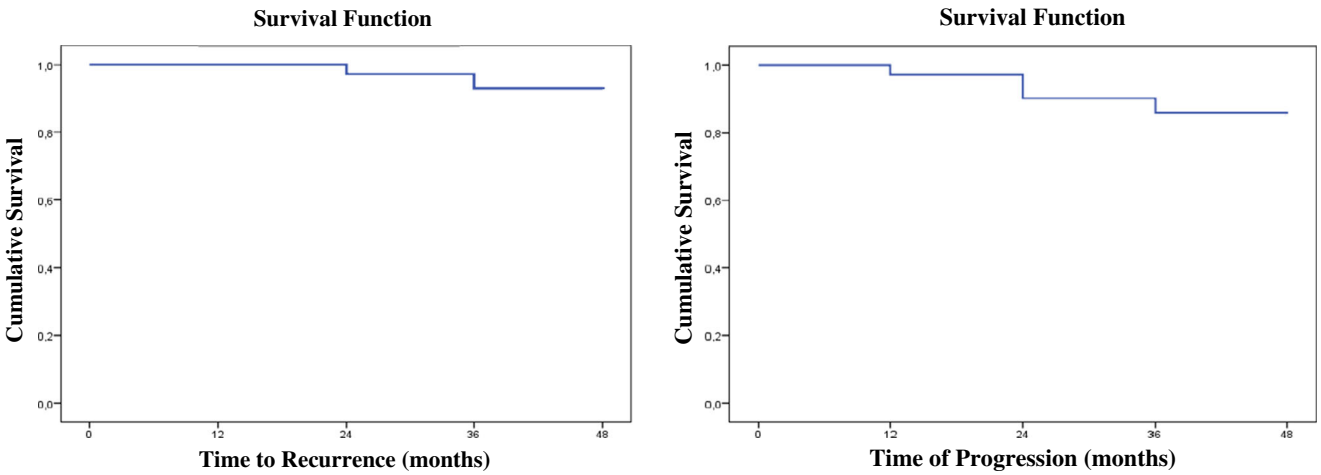


Fig. 2 Kaplan-Meier index. Time until DD recurrence or progression

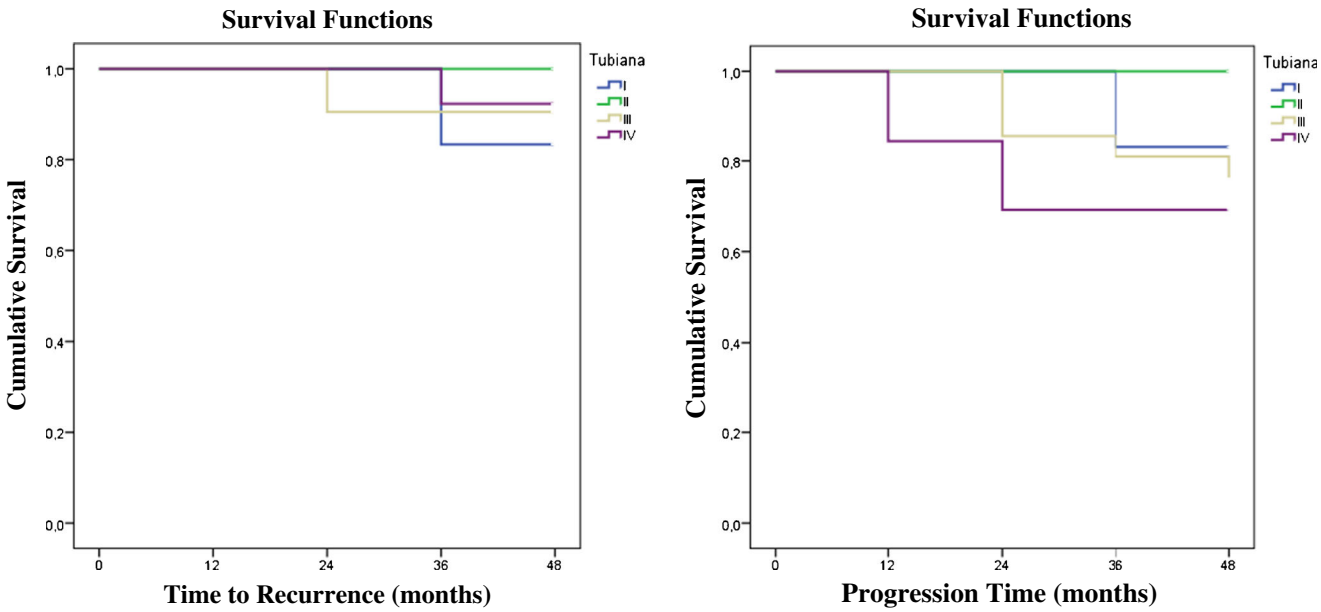


Fig. 3 Time of DD recurrence or progression in relation to the DD severity (Tubiana's classification)

It is important to differentiate between recurrence and progression in DD, especially in patients treated with CCH in a single joint, to determine the actual efficacy of drug therapy, since DD is a progressive disease that can affect other joints with time regardless of treatment.

In five patients (7%) we verified the existence of disease recurrence during the follow-up, based on the International Consensus on the definition of recurrence published by Felici et al. [4]. Patients with a lower risk of recurrence are those with a single cord in MCP, with a grade II of Tubiana's classification and over 60 years old.

The recurrence and progression rate was higher in grades III and IV in the Tubiana's classification in punctures at the PIP level, as in other published studies [1, 5], and in patients under the age of 60 years.

We believe the paradoxical existence of a higher percentage of recurrence in patients with grade I of Tubiana in our study was due to the difficulty of the puncture, because there was no clear cord for the CCH injection, which makes the CCH inoculation less effective.

The recurrence and progression rate is higher at the PIP level. This may be because the flexion of the PIP joint is caused by the retraction of the longitudinal fibres of the

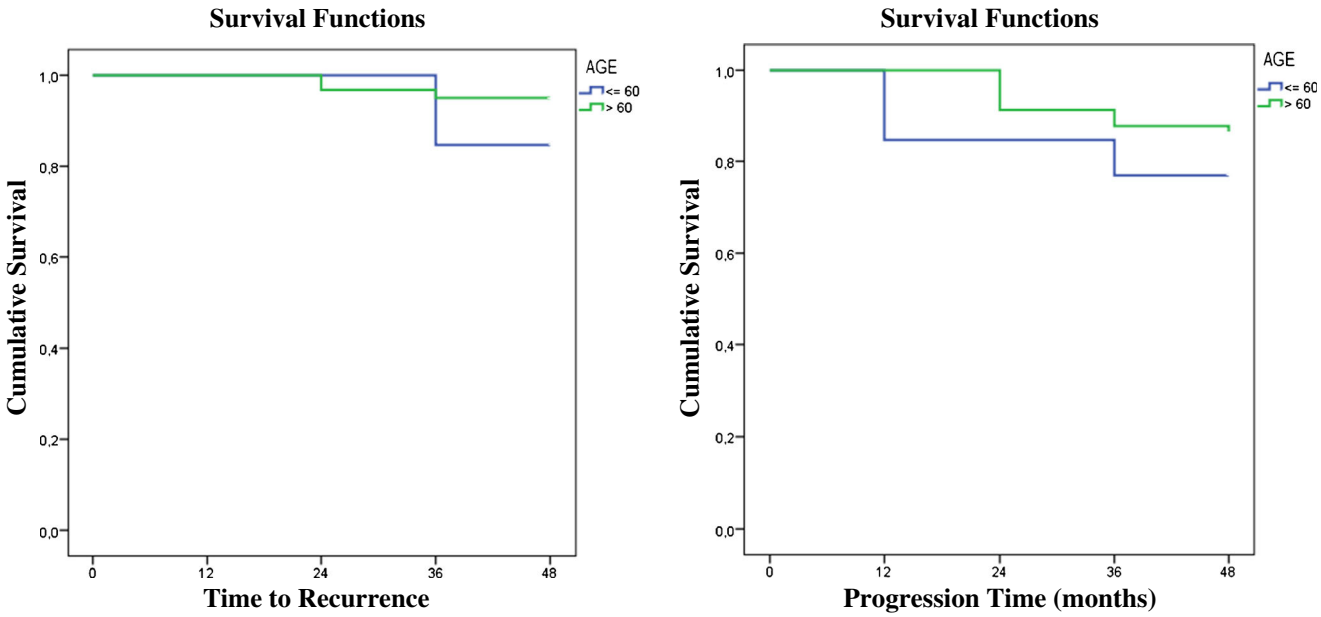


Fig. 4 Time of DD recurrence or progression in relation to age

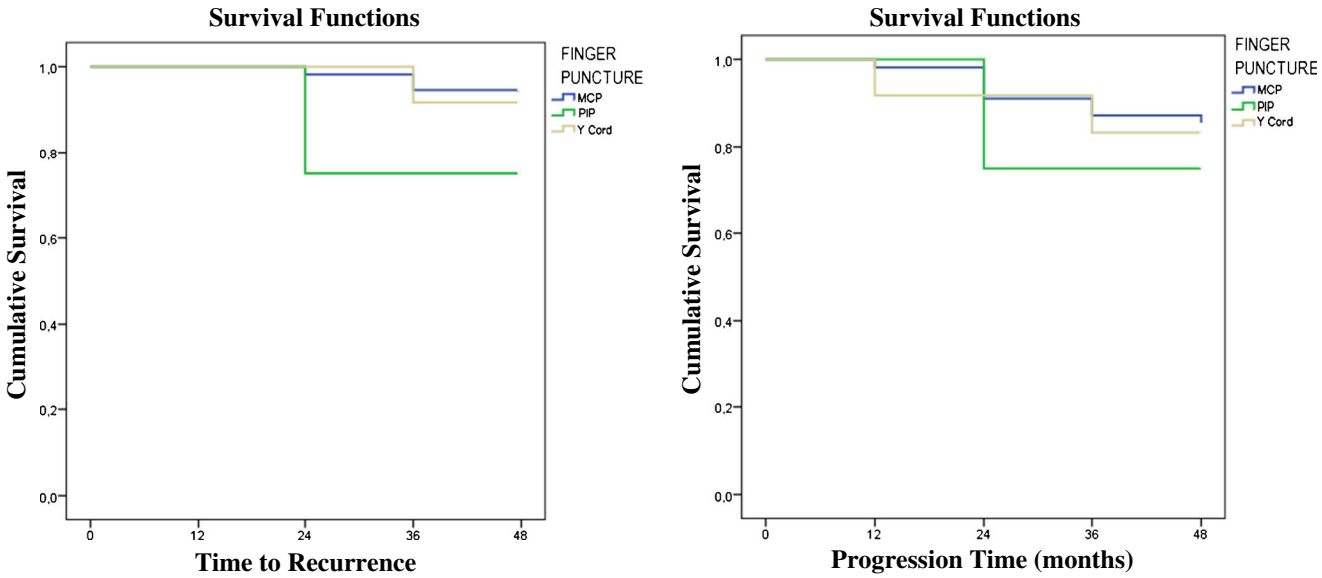


Fig. 5 Time of DD recurrence or progression according to the CCH administration area

palmar aponeurosis and also by other isolated digital cords, lateral or spiroid, without insertions in the palmar aponeurosis, and which are difficult to locate for CCH injection. When the MCP and PIP joints are involved, the hyperflexion manoeuvre of the MCP allows us to determine the existence of these lateral cords, spiroid or isolated digital, if it did not improve the PIP contraction after performing it [15].

Although there is a clear trend in the dependence relations between factors that influence recurrence and progression, there is no statistical significance, but in some variables it is very close to a p-value <0.05. We thought that this trend would clearly manifest itself with a larger sample size.

Patients who had a DD recurrence or progression during follow-up have a high degree of satisfaction, since the degree of retraction of the affected finger is significantly lower than that prior to injection in all patients except one. This explains why only three patients underwent a new procedure.

None of the three patients wanted a second CCH injection and therefore underwent surgery by performing selective fasciectomy and zetaplasty. In these patients who have required surgery after CCH injection, we found a fibrosis zone in the product puncture area, without difficulty in the surgical technique, as it has also been published in other studies [16, 17].

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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