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Alternative and Adjunctive Treatments for Dupuytren Disease

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KEYWORDS

• Dupuytren • Radiotherapy • Pharmacotherapy • Firebreak skin graft • Dermofasciectomy

KEY POINTS

- There is a subset of patients that exhibit an aggressive form of Dupuytren disease with unpredictable results and early recurrence after standard treatment.
- Researchers have suggested disease control treatment strategies to slow down the disease process (radiotherapy, tamoxifen, 5-fluorouracil).
- Firebreak skin grafting and dermofasciectomy are used in an effort to reduce the chance of recurrence.
- Lack of the use of clear definitions of recurrence and poor study design (low levels of evidence) hamper the development of unequivocal treatment guidelines.

INTRODUCTION

Dupuytren disease is a common, chronic disease of the elderly in the Western world. Systematic analysis of the available prevalence studies has shown that this varies between 0.6% and 31.0%.¹ Its phenotype is also quite variable and the role of the genotype,^{2–4} environmental factors (including lifestyle, leisure habits, and work^{5–7}), and associated diseases (diabetes mellitus, epilepsy, and liver disease)⁸ is becoming clearer. In a study in which the overall prevalence was more than 20% in people older than 50 years, most people (80%) had only nodules or pits in the palms of their hands without flexion contracture.⁹ Only 4% of that population exhibited the picture we as clinicians are so familiar with, showing flexion contractures of 1 or more joints in variable patterns.¹⁰ Only rarely a patient was seen with a Dupuytren diathesis, a term coined by Hueston¹¹ in the 1960s

and that in recent decades has been further elaborated on. In these patients, the disease starts early, is bilateral, has a clear familial trade, often exhibits ectopic disease (Ledderhose disease, Peyronie disease, and/or Garrod pads), develops early recurrence after standard treatment, and more frequently involves the radial side of the hand.^{11–13}

Patients with Dupuytren diathesis form the biggest challenge for surgeons, and the standard Dupuytren “tool box” (limited fasciectomy, needle fasciotomy, and collagenase treatment) does not seem to be adequate to provide optimal care with durable results.^{14–17} They often need repetitive treatment, and sometimes end up with great functional deficits, disturbed sensibility, or even finger amputations, despite our best efforts.

The purpose of this article was to review what has been attempted or is advocated to try to

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control the disease, which is most needed for the aforementioned subgroup of patients. Some of these adjunctive treatments are well known and accepted (although evidence is not strong), whereas others have only been reported once, or have not been investigated thoroughly, and therefore have not become accepted as good alternative approaches. All are presented, using the available evidence to discuss the effectiveness, durability, advantages, and disadvantages of each option. At the end of the article, the authors give a glimpse into the future of the treatment of complex cases.

OVERVIEW OF ATTEMPTS AT EARLY DISEASE CONTROL

Radiotherapy

Ionizing radiation can control cell growth of rapidly proliferating cells by damaging DNA, leading to apoptosis. As such, radiotherapy has been proposed as a therapeutic option for Dupuytren disease. Low-dose radiotherapy (30 Gy) may inhibit fibroblast proliferation and induce an anti-inflammatory effect.^{18,19} The radiation is administered in portions of 3 Gy per day on 5 consecutive days, and after a period of approximately 6 weeks the scheme is repeated.

Available evidence on efficacy of radiotherapy in Dupuytren disease is of low quality. The published reports are retrospective studies on patients with mild disease (Tubiana stage N or 1), in which radiotherapy was prescribed with the intent to stabilize or inhibit the progression of Dupuytren disease.^{20,21} Zirbs and colleagues²² reported less progression in a retrospective cohort analysis: 20% instead of an “expected” 50%. Likewise, the earlier report of Betz and colleagues²¹ is compared with the same average 50% number, introduced by Millesi²³ in his book in 1981 in a 6-year follow-up group. Only 1 randomized controlled trial (RCT) has examined this issue, reported by Seegenschmiedt and colleagues in 2001.¹⁸ However, they only compared different settings of radiotherapy without an untreated control group. Moreover, only preliminary results after 1-year follow-up were available, and no further data were reported later. All available conclusions on radiotherapy outcomes thus report possible improvement but lack an untreated control group. Therefore, true evidence for the efficiency of radiotherapy in the prevention of Dupuytren contractures is unavailable today, and a long-term possible post-radiotherapy increase in disease progression cannot be excluded.²² Reported side effects are acute erythema in up to 40% and late skin atrophy in fewer than 10%. Although

no post-radiation malignancies have been reported yet, an absolute 0.02% risk increase is estimated.²⁴ Salvage surgery is reported to remain safe, although no statistical comparative data or evidence are available. Although the aim of radiotherapy is cell death of myofibroblasts in Dupuytren disease, late radiation fibrosis is a well-known side effect of radiotherapy in general. These long-term effects necessitate a longer follow-up in patients with Dupuytren disease, with respect to effects of radiation on recurrence, progression, and surgical complexity if surgical intervention is ultimately required.

In conclusion, irradiation as a preventive measure for disease progression is inconclusive today. In mild forms, side effects and late malignancy risk must be weighed against the use of radiotherapy. In extreme disease progression, the patient may consider radiotherapy in a multidisciplinary setting with the patient's hand surgeon and radiation oncologist, certainly if surgery may be challenging or is not feasible due to recurrent or extensile Dupuytren contractures. However, because outcome is unsure, even unexpected disease progression after radiotherapy cannot be ruled out as a possible complication as an irradiation side effect.

On balance, radiotherapy should be considered an unproven treatment for early Dupuytren disease due to a scarce evidence base and unknown long-term adverse effects. Well-designed randomized controlled studies are required to confirm the benefits of radiotherapy treatment.

Pharmacotherapy

Pharmaceutical control of myofibroblast activity is an interesting area of translational research that seeks to reduce progression or recurrence of contractures after Dupuytren disease treatment. Conceptually, pharmacotherapy can be applied topically, injected or implanted locally, or administered systemically. Clearly, benefits of possible disease control must outweigh possible risks of treatment, given that Dupuytren disease is a benign entity.²⁵ Numerous drugs have been suggested, but few level I evidence research studies on pharmacotherapy in Dupuytren disease exist. Treatment options can be categorized as anti-inflammatory drugs (treating Dupuytren disease as an inflammatory process), anti-mitotic drugs (treating Dupuytren disease as a neoplasm), and other pharmacologic targets (eg, hormonal therapy).

Anti-inflammatory drugs

Anti-inflammatory drugs, such as cortisone, interferon, and colchicine, have been suggested for

Dupuytren disease control, but limited evidence is available. Baxter and colleagues²⁶ first reported on a possible benefit of cortisone in 5 patients in 1946. However, disappointing effects of postoperative *systemic* cortisone was reported 5 years later in 7 of 19 operated patients.²⁷ Bernstein²⁸ mentioned a “remission” state in 14 cases after postoperative systemic cortisone treatment without symptoms of recontracture.

Almost 50 years later, Meek and colleagues²⁹ focused on transforming growth factor (TGF)-beta in fibrosis and advocated further research for clinical immunomodulation in Dupuytren disease. They studied the role of programmed cell death in steroid treatment and found that steroids reduced specific Dupuytren fibroblast proliferation with increasing rates of apoptosis of both fibroblasts and inflammatory cells.²⁹

A 97% success rate was reported after *intralesional* steroid injections in 63 patients with mild nodular forms of Dupuytren disease.³⁰ The nodules softened or flattened temporarily and this was considered disease regression, although recurrence was seen in 50%. Recently, an RCT in needle fasciotomy with steroid injection compared with placebo in 47 patients, demonstrated increased clinical result with improved finger extension and lower retreatment rates in a 6-month follow-up.³¹

Reports on topical cortisone treatment are only expert opinion and case series level of evidence.

On anti-inflammatory drugs other than cortisone, even less evidence is available. In 1992, the administration of colchicine, known to induce collagenase activity and decrease collagen synthesis, was reported in 3 patients with fibrosis. One of them had Dupuytren disease. His tumor size reduced and contracture improved.³² Oral administration of colchicine improved penile contractures in 24 patients with Peyronie disease. However, the concomitant Dupuytren contractures in these patients, did not improve.³³

Gamma-interferon is a cytokine produced by T-helper lymphocytes; it is known to decrease fibroblast replication, activation, and collagen production. In a clinical pilot study, gamma-interferon was injected into the nodules of 14 Dupuytren patients and appeared to reduce nodule size and symptoms.³⁴ However, no further reports on these preliminary observations are available. Interferon-alpha2b appeared to decrease myofibroblast contractility of 3 paired strains of Dupuytren fibroblasts versus control in collagen lattice models.³⁵

Anti-mitotic drugs

Anti-mitotic drugs, like 5-FU (5-fluorouracil) and anti-TNF (tumor necrosis factor), have also been

suggested for Dupuytren disease control, but again, limited evidence is available. The cytostatic drug 5-FU inhibits thymidylate synthase needed for DNA synthesis. Its inhibitory effect on proliferation and differentiation has been demonstrated in vitro on Dupuytren myofibroblasts.³⁶ However, an RCT in 15 patients with intraoperative 5-minute topical application of 5-FU failed to show any beneficial effect.³⁷

The cytokine TNF, implicated in tumor regression, was shown in vitro as a key regulator of myofibroblast differentiation/activity in early Dupuytren disease, TNF blockade led to downregulation of the myofibroblast. These findings suggest that local injection of anti-TNF may prevent progression of nodules to contractures.³⁸ However, no clinical trial reports are available.

The literature contains sporadic reports to suggest further research for the use of other antiproliferative drugs to modify the course of Dupuytren disease. A possible short-term beneficial effect of N-sulfonylpyridimide derivative was mentioned, and Amidino-substituted bezimidazo quinolone may exert a nonspecific antiproliferative activity.³⁹

Other pharmacologic agents

As androgen receptors are expressed by the myofibroblasts in Dupuytren nodules, the effect of 5 alpha-dihydrotestosterone was investigated on cultured Dupuytren cells in 2003.⁴⁰ Fibroblast activation and proliferation increased, with secondary downregulation of the androgen receptors.

Similar in vitro work on Dupuytren myofibroblast contractility on collagen lattices suggested that tamoxifen, a synthetic nonsteroidal antiestrogen known to modulate TGF (beta) production, might be of value in the treatment of Dupuytren disease.⁴¹ This nonsteroidal antiestrogen decreased Dupuytren fibroblast contractility and TGF-beta2 production. In a level I translational clinical trial in high fibrosis diathesis patients with Dupuytren disease, tamoxifen significantly improved short-term outcome of segmental fasciectomy in Dupuytren disease, identified with the Abe score.⁴² However, the beneficial effect was lost within 2 years, and the side effects of high-dosage estrogen were not well tolerated in the predominantly male Dupuytren population.

Other pharmaceutical suggestions without clinical trials are numerous.²⁵ Likewise, numerous topicals are used in Dupuytren treatment, but hardly any trials are reported.

Interposition Materials

To increase the effect of segmental fasciectomy and to isolate the affected skin from the underlying myofibroblasts of Dupuytren tissue, the use of

interposing implant materials has been suggested. In 2013, a thin absorbable cellulose implant, shaped to the required firebreak size, was studied in a case control series of 30 patients with a high probability for recurrent disease. The intention was to improve the effect of segmental cord interruption by creating an increased “firebreak” effect with this inert resorbing implant.⁴³ Finger extension, pain, and patient satisfaction were all significantly better in the cellulose implant group compared with matched controls who did not get the implant. Unfortunately, although it had been successfully used for more than 5 years, cellulose is no longer commercially available as of the publication of this article. Similarly, based on reported lower recurrence rates under a full-thickness skin graft,⁴⁴ acellular dermal matrix, which has a common inhibitory effect on underlying myofibroblasts, was studied in 2014.⁴⁵ In a retrospective cohort study, 20 patients with open fasciectomy were compared with an experimental group with acellular dermal matrix of 23 in a median follow-up of 1.8 years. Recurrence of contracture was observed in 1 of 23 patients in the group receiving acellular dermal matrix, compared with 5 of 20 in the control group ($P = .045$).

Alternative Surgical Approaches

Variations in incisions

An enormous variety of incisions has been described for limited fasciectomy.⁴⁶ However, most surgeons will use either zig-zag (Bruner) incisions and use Y-V plasties to close defects, or longitudinal incisions incorporating Z-plasties at the flexion creases at the time of wound closure. In 1964, McCash⁴⁷ described an approach that became quite popular in the United Kingdom. He advocated transverse incisions in the distal palm and along the finger joint creases to access and remove the pathology (Fig. 1). The transverse incision in the palm had actually already been used by Dupuytren while performing open fasciotomy in 1833⁴⁸ and by Skoog⁴⁹ in the 1950s (Fig. 2). The incisions give good access to the pathology. An important aspect of the technique is that, after fasciectomy and contracture release, often a skin shortage results, making it impossible to close all wounds. This is not a problem, as McCash⁴⁷ has shown: the wounds in the fingers can usually be closed, and the remaining defect in the palm will heal secondarily within 6 to 8 weeks. The technique even carries the advantage that a hematoma will drain easily. Jacobsen and Holst-Nielsen⁵⁰ have advocated a combination of the McCash⁴⁷ technique and a midlateral ulnar incision for the fasciectomy of the little finger in case of severe

Fig. 1. The planned incision for the open palm technique. Note proximal convexity of incisions at proximal interphalangeal joints. (From McCash CR. The open palm technique in Dupuytren's contracture. *Br J Plast Surg* 1964;17:273; with permission.)

contractures. They describe excellent access to the pathology without any vascular compromise of the flap and wound healing within 3 to 6 weeks (Fig. 3). Thirty years later, Tripoli and Merle⁵¹ confirmed the usefulness of the technique, especially in Tubiana stage III and IV cases. They used it in 98 cases and found its application relatively simple, allowing good exposure for correction of severe contractures. They further advocated it as an alternative for dermofasciectomy and even as an option to avoid amputation of badly contracted digits.⁵¹ In contrast to the inventors, these investigators did report vascular compromise of the flap in 1 case, neurovascular injury in 3 cases, and vascular compromise necessitating amputation in 2 cases. Complex regional pain syndrome (CRPS) occurred in 10% of cases and was resolved with conservative measures. No hematomas or infections were encountered.

Skin grafting defects and skin replacements (dermofasciectomy)

As an alternative to leaving the wounds open as in the McCash⁴⁷ technique, Ketchum and Hixson⁵² has proposed the use of skin grafts to close

Fig. 2. A 63-year-old man with primary Dupuytren disease of the right index, ring, and little fingers. (A, B) Pre-operative photographs. (C) At the end of the procedure, there was limited fasciectomy using Skoog's approach (transverse incision in the palm and longitudinal with Z-plasty in the little finger and short scar longitudinal for ring finger). The cord in the index finger ray was released by needle fasciotomy. Note the defect in the palm that is left to heal secondarily. (D) Photograph of hand 4 weeks postoperatively.

remaining defects. In their view, this not only resulted in faster wound healing, but they also claimed to have seen no recurrences under the grafts following application of this technique in 68 patients between 1970 and 1985. In 8% of cases,

they noted extension of the disease outside the full-thickness grafts. In line with Hueston,^{44,52} they like to look on the grafts as “firebreaks” to prevent recurrence. Ullah and colleagues⁵³ tested this concept in a randomized clinical trial in 90 fingers,

Fig. 3. Jacobsen and Holst-Nielsen modification of the McCash technique. (From Tripoli M, Merle M. The “Jacobsen Flap” for the treatment of stages III–IV Dupuytren’s disease: a review of 98 cases. *J Hand Surg Eur Vol* 2008;33(6):780; with permission.)

in which they used a longitudinal incision for fasciectomy. In all fingers, closure with tension-free Z-plasties was possible. However, in approximately half of the cases, they randomly replaced the Z-plasty with a skin graft. The overall recurrence was 12% over 3 years, with no differences between the 2 groups, thereby challenging the findings of Hueston and Ketchum and Hixson.⁵³

In the late 1960s, Hueston^{11,54–57} drew attention to his view about the effectiveness of skin grafts in the prevention of recurrence and wrote extensively about this and the role of the skin in Dupuytren disease. The “dogma” that resulted from this work was that Dupuytren disease does not recur under a skin graft. This, however, needed to be nuanced after reports started to appear in the 1980s about recurrence under the grafts. In some of these reports, in retrospect, the investigator felt that not all Dupuytren “source” tissue might have been removed.⁵⁸ In another case, at reoperation, pathology was found behind the neurovascular bundle.⁵⁷ In 1997, Hall and colleagues⁵⁹ described the 24 to 100 months of follow-up results of 90 rays in 67 patients who had been treated by dermofasciectomy and skin

grafting. In this and 2 subsequent studies, an 8% recurrence rate was found and in two-thirds of these cases the recurrence was located under the graft.^{59,60} These investigators felt that this recurrence rate was nevertheless very much lower than following limited fasciectomy and recommended their technique “for all cases of recurrent Dupuytren’s disease requiring reoperation and as a primary procedure when there is significant skin involvement.”⁵⁹ The dermofasciectomy is performed as follows⁵⁸: all tissues overlying the flexor tendon sheath and the neurovascular bundles are excised including the overlying skin, extending from the distal palmar crease to the distal interphalangeal crease and to the midaxial line on either side of the finger. We usually stop our excision where the pathology ends, which is usually halfway along the middle phalanx, in an effort to preserve some of the native skin if there is no sign of disease (Fig. 4). In some cases, this proved too optimistic, and a second dermofasciectomy to the level of the distal interphalangeal joint had to be performed later. The flexor tendon sheath is bared, as are the neurovascular bundles, which are left in their bed unless there is clearly affected tissue deep to them. Leaving the neurovascular bundles in their bed is done to try to preserve as much vascularization to the digit as possible. The authors’ personal experience has found that this is only seldom possible. Especially in recurrences, the bundles are usually encased by affected fascia, because Cleland ligaments are often involved.^{61,62} Full-thickness skin grafts are preferably taken from the ipsilateral forearm or arm, and donor sites are closed primarily. Grafts from the groin are not used because they typically develop brown pigmentation and hair growth, which is detested by the recipients, and they tend to become bulky. Rents in the flexor sheath, which often occur because the pathology often ends on the A4 pulley, are of no concern: they can be covered by the skin graft, which will bridge them. Logan and colleagues⁵⁸ immobilized the skin graft with a tie over bolster and rested the hand in a full hand bandage. We use damp gauzes (wet with normal saline [0.9%]) on top of a paraffin gauze and flush out the space underneath the graft before bandaging the hand. In addition, a plaster splint is applied with the fingers in extension for the first week. This is replaced by a removable thermoplastic splint, which can be removed intermittently for limited flexion and extension exercises.

The convalescence time after dermofasciectomy is longer than after limited fasciectomy, especially in manual workers,⁶³ as it takes longer for them to return to full flexion and to their work. Delay of return to full flexion is a consequence of the postoperative regimen, because the operated fingers are protected

Fig. 4. This 61-year-old man with marked Dupuytren diathesis previously underwent more than 10 procedures (both fasciectomy and collagenase injections). He has significant recurrence in both hands; treatment with dermofasciectomy is planned for the left ring and small fingers as well as the right middle and little fingers. (A) Pre-operative photograph. (B) Immediately following dermofasciectomy and full-thickness skin grafting of the left hand. (C) Eight months after surgery of the left hand and 2 months after surgery of the right hand.

in a splint longer than after limited fasciectomy (LF). Once healed, grafts typically become robust and develop sensibility similar to the skin that has been elevated during LF.⁵⁸ The most common problem observed following dermofasciectomy and skin grafting was tightness of the radial and ulnar skin graft margin scars, most likely caused by the fact that the graft to normal skin margin runs from proximal-palmar to more dorsal distally. However, none of the patients experienced such discomfort or dissatisfaction that they needed scar revision.⁵⁹

Distant flaps and free flaps in the treatment of Dupuytren disease

In an ultimate attempt to prevent recurrence, Kan and Hovius⁶⁴ have applied free flaps after dermofasciectomy in very advanced cases. In 2013, they presented a report on 2 brothers in whom 2 reverse radial forearm flaps were used to cover defects in their hands, and 2 lateral arm flaps were used to reconstruct defects after dermofasciectomy of the soles of their feet. After a follow-up of up to 25 years, no recurrence was noted.⁶⁴

SUMMARY

For the clinical practice of surgeons treating patients with Dupuytren disease, the most relevant findings of this article are as follows:

- There is at present no evidence that radiotherapy is able to prevent progression, while the long-term effects of the treatment are uncertain.
- Pharmacologically, many treatments have been attempted, but no treatment has proved uniformly successful in the short or longer run, and many have had serious side effects. Consequently, no such treatment is at present available for routine use to prevent progression or recurrence.
- Dermofasciectomy and skin grafting may be the best surgical treatment for recurrent cases, especially in patients with a strong diathesis, because a recurrence under a skin graft is only rarely seen. Notwithstanding this, supporting evidence is mostly limited to case series, and the only available RCT did not show a difference between Z-plasties and skin replacement.

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