Xstrahl MEDICAL

CLINICAL ARTICLE

Radiotherapy for Dupuytren's Disease of the Hand

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1. Radiotherapy for Benign Diseases

Radiotherapy is the medical use of X-Rays and other forms of ionising radiation to treat disease. It is mostly used to treat cancer, but due to its anti-inflammatory and anti-proliferative effects it is also used to treat benign disease. For example, the anti-proliferative effect of radiotherapy can be used to reduce the risk of heterotopic ossification following hip replacement, and the anti-inflammatory effect can be used for the treatment of thyroid eye disease. The doses of radiotherapy used for the treatment of benign conditions are generally below the range used to treat cancer, and so for most patients acute toxicity is not a problem. The use of radiotherapy for benign disease widely varies between different countries, but its use is particularly prevalent in Germany, as seen in a study from 134 German institutions surveyed in 1994 – 96, which showed that approximately 20,000 patients were treated for benign conditions annually, with 146 of these being for Dupuytren's disease [Seegenschmiedt, (2000)].

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2. Dupuytren's Disease – An Overview

Dupuytren's disease of the hand is a benign proliferative disorder of the palmar fascia. It forms part of a group of fibromatoses that also includes plantar fibromatosis (Ledderhose disease) and penile fibromatosis (Peyronie's disease). The causes of these diseases are unknown, but they appear to have a genetic component. Additional risk factors for Dupuytren's disease include trauma to the hand, epilepsy and anti-epileptic use, diabetes mellitus, smoking, and alcoholism.

Dupuytren's disease is a common condition, particularly prevalent in Northern European Caucasians, occurring in males more than females, with onset typically at the ages of 50 - 60 years. The early stage of Dupuytren's disease consists of subcutaneous palmar nodules, skin retraction and cord formation. Eventually the cords thicken and contract and cause fixed flexion of the metacarpophalangeal or proximal interphalangeal joints of the fingers, known as Dupuytren's contracture.

The speed and eventual extent of the disease is very variable, but is more severe in males, those with a positive family history, early age of onset, bilateral disease, and where there are ectopic lesions (e.g. Ledderhose disease). The staging of Dupuytren's disease is illustrated in Table 1, where stage N is disease with no contracture, stage N/I is disease with up to 5 - 10 degrees of contracture, and subsequent stages indicate disease with more severe contracture.

Stage	Clinical symptoms	Extent of extension deficit
N	Nodules, cords, skin retraction etc.	None
N/I*	As stage N + deformity of fingers	1 - 10°
I	As stage N + deformity of fingers	11 - 45°
II	As stage N + deformity of fingers	46 - 90°
III	As stage N + deformity of fingers	91 - 135°
IV	As stage N + deformity of fingers	> 135°

Table 1: Staging Classification of Dupuytren's disease [Tubiana (1966), Keilholz (1996)]

3. Treatment of Dupuytren's Disease

a. Treatment options overview

Radiotherapy is effective in the early stages of the disease to prevent the formation of contractures i.e. to "keep straight fingers straight". Despite increasing evidence of the effectiveness of radiotherapy in this context, the disease is often only treated in the advanced stages, where there is significant (e.g. > 30 degrees) contracture, and particularly where hand function is impaired. Management in the advanced stage of the disease, where there are established contractures of the fingers, is directed towards releasing the contracture and improving function. There are three main methods for release of contractures:

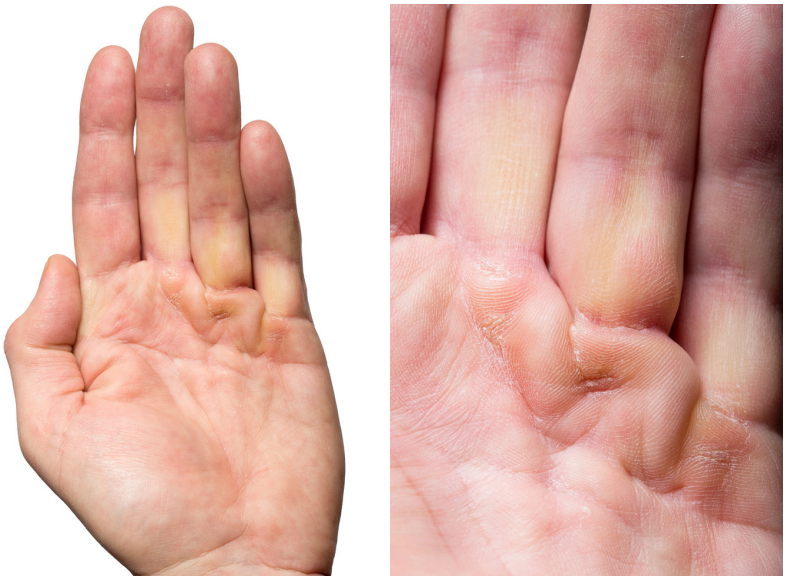

Figure 1: Images of Dupuytren's disease

i. Fasciectomy is the most common approach. There are several variations of this approach. In a "limited" fasciectomy, the contracture is corrected and some diseased tissue is removed; In a "radical" (total fasciectomy), the contracture is corrected with attempted removal of all fascia and disease, which can also be combined with removal of overlying diseased skin with the insertion of skin grafts (dermofasciectomy). These procedures are associated with a long recovery time and a considerable complication rate. The reported range of recurrence rates is wide at 18 - 73% [Citron (2005), Jurisic (2008)] and depends on follow-up time and definitions of recurrence [Werker (2012), Becker (2010)].

ii. Needle aponeurotomy: A needle is used to puncture the fibrous cord in order to weaken it until it can be broken by mechanical force. This is minimally invasive, but is associated with a recurrence rate of 65% at three years [Van Rijssen, (2006)].

iii. Collagenase (Xiapex) is the injection of an enzyme that dissolves the collagen in the Dupuytren's cord, which can then be mechanically broken. In those fingers that are successfully straightened, there is a 35% three-year contracture recurrence rate [Peimer, (2013)].

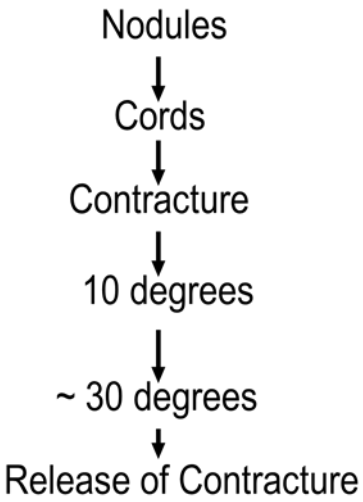

Figure 2: Traditional flowchart for treatment of Dupuytren's disease (above)

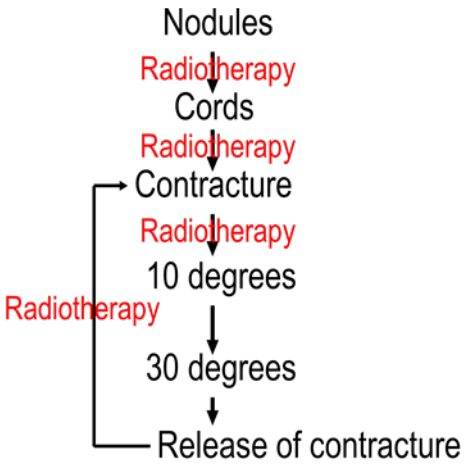

Figure 3: New flowchart for treatment of Dupuytren's disease (above)

b. Radiotherapy for Dupuytren's Disease

i. *Indications*

Radiotherapy is effective in the early stages of Dupuytren's disease, where there is no contracture (stage N) or a contracture of up to 10 degrees (N/I). Due to the variable progression of this disease, only patients whose disease has progressed within the last 6 - 12 months should be treated. Patients with more advanced disease should be not be treated with radiotherapy, and may be offered surgical release.

Stage	N	N/I	I	II	III	IV
RT	Y	Y				
Collagenase			Y	Y		
NA		Y	Y	Y	Y	Y
Surgery			Y	Y	Y	Y

Table 2: Treatment of Dupuytren's Disease According to Disease Stage

ii. *Radiotherapy details*

The aim is to treat nodules and cords to the periostium of the hand bones, for a depth of 5 - 15 mm. Therefore, the use of superficial/orthovoltage X-Rays at e.g. 80 – 150 kV, or electrons (up to 6 MeV with appropriate bolus) would be reasonable. There is no evidence of a difference in effectiveness between these two treatments. Proximal and distal margins of 1 - 2 cm on palpable nodules and cords, with 0.5 - 1cm lateral margins, should be used. The effective dose is 30 Gy in 10 fractions, consisting of two phases of 15 Gy in 5 fractions with a gap of 6 - 12 weeks between the two phases. An alternative fractionation is 21 Gy in 7 fractions on alternate weekdays over two weeks.

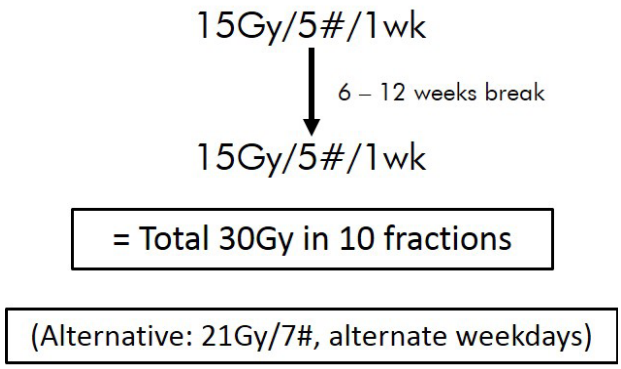

Figure 4: Typical Treatment

iii. *Radiotherapy Side-effects*

The most common side-effects during treatment are mild skin changes including redness, soreness and dryness. There is a small chance of mild chronic skin changes and subcutaneous fibrosis.

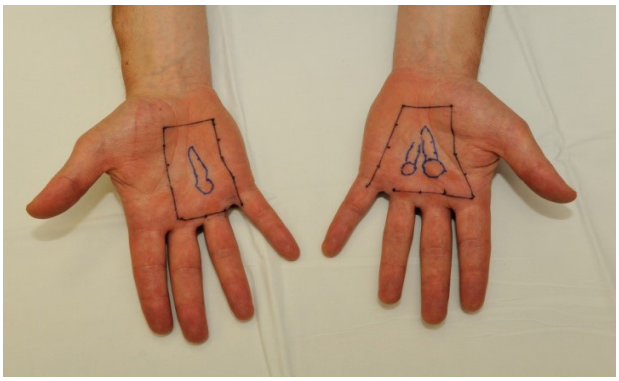

Figure 5: Treatment Mark Up

There is a small theoretical risk of malignancy as a result of radiotherapy for Dupuytren's disease. There have been no documented cases of malignancy as a result of radiotherapy for Dupuytren's disease. The dose of radiation is lower than that generally used to treat cancer and is given to a peripheral part of the body. The risk is certainly very low, perhaps a 0.01 - 0.1% lifetime risk [The International Dupuytren Society. (2013)]. The risk of developing a malignancy is higher in younger patients and reduces markedly above the age of 60 years.

iv. *Radiotherapy Effectiveness*

There are many retrospective studies in the literature going back many decades that have indicated the efficacy of radiotherapy for Dupuytren's disease. However, their usefulness is generally limited by baseline differences in patients and disease characteristics, radiotherapy doses and fractionations, definitions of endpoints, and short follow-up periods. A prospective trial randomising patients between two dose levels (with no control group) looked at 129 patients (198 hands) [Seegenschmiedt, (2001)]. All of them had disease that had progressed within the last six months. Patients were treated with 120 kV at 40 cm FSD, with the aim to treat to a depth of 5 – 15 mm (down to the periostium of hand bones). The treated area was palpable disease with margins of 1 – 2 cm proximally and distally, and a lateral margin of 0.5 – 1 cm. Untreated areas were shielded with lead. Patients were randomised to two phases of 15 Gy in 5 fractions each (as above, with an eight week gap between the phases, total dose 30 Gy), or 21 Gy in 7 fractions, given on alternate days over a period of 15 days. The treatment was generally well tolerated, with acute grade 1 toxicity of 38% and grade 2 toxicity of 6%. There was a chronic toxicity rate of 5% at 12 months. At 12 months follow-up, the overall treatment failure rate was 8%, with 2% needing corrective surgery. Progression by stage was: 0% in stage N, 3% in N/1, 15% in St 1, 40% in St II. There was no significant difference in efficacyor toxicity between the two dose groups. A long-term follow-up of this study, published as a textbook chapter [Seegenschmiedt], looked at the outcomes of patients followed up for at least 5 years (median follow-up of 102 months). 406 patients (812 hands) were treated with radiotherapy, (total dose 21 Gy or 30 Gy (as above, although the gap between the two phases was quoted as 10-12 weeks), and a non-randomised control group of 83 patients (166 hands) consisting of patients who chose to be observed rather than treated. All had progressive disease in the last 6 - 12 months. Side-effects in the irradiated group were: Acute toxicity in 28% (2% grade 2); chronic toxicity in 14% (all grade 1). Acute and chronic toxicity rates were increased in the 21 Gy group compared with the 30 Gy group. Overall disease progression by stage was: stage N = 10%, N/I = 41%, I = 58%, II-IV = 89%. Regarding efficacy, significant reduction in disease progression and the need for surgery was demonstrated in both treatment groups compared with the control group, although there was no significant difference between the two treatment groups (Table 3,below).

Dose	Regression/ stable (%)	Progression (%)	Surgery (%)
Control (n=122)	38	62	30
21 Gy (n=243)	76	24	12
30 Gy (n=245)	80	20	8

Table 3: Outcome of Radiotherapy for Dupuytren's Disease at a median 8.5 years follow-up in the Seegenschmiedt study [Seegenschmiedt, (2012)].

4. Conclusion

Radiotherapy is an effective and well-tolerated treatment when used in early Dupuytren's disease. It reduces the formation of contractures and the need for corrective surgery.

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