Radiotherapy in Dupuytren's Disease: A systematic review of the evidence

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Abstract: Radiotherapy has been advocated as an alternative treatment in early Dupuytren's Disease. We have systematically reviewed the evidence on the use of radiotherapy in Dupuytren's disease. Only six articles met a minimum set standard, five of which were retrospective cohort studies and one a randomised controlled study. A total of 770 Dupuytren's hands, nearly all with Tubiana stage 0-1 disease, were irradiated with an average 30 Gy. Disease regression ranged from 0-56%, stability from 14-98% and progression from 2-86%. Salvage surgery was successful in all cases of disease progression post-radiotherapy. There were no reports of adverse wound healing problems associated with such surgery or radiotherapy-associated malignancy. On balance, radiotherapy should be considered an unproven treatment for early Dupuytren's disease due to a scarce evidence base and unknown long-term adverse effects. Well-designed randomised controlled studies are required to confirm the benefits of radiotherapy treatment.

Level of evidence: II

Introduction

Radiotherapy is sometimes used as an adjunct in the treatment of benign conditions, such as keloid scars, which are characterized by increased proliferative cellular activity. In Dupuytren's disease, it has been proposed that low dose irradiation may inhibit fibroblast proliferation and induce an anti-inflammatory effect mediated by inhibition of the innate immune response and activation of nitric oxide synthetase (NOS) pathways (Arenas et al., 2012; Seegenschmiedt et al., 2001). A dosage of 30-32 Gy is widely used in the treatment of benign diseases and similar doses have been used to treat Dupuytren's disease (Royal College of Radiologists., 2015). The only prospective study of radiotherapy in Dupuytren's disease advocates its use in early stage disease only, as "the radiobiological potential of ionizing radiation is limited to early stages, as long as proliferating fibroblasts exist as the predominant radiosensitive target" (Seegenschmiedt et al., 2001).

Radiation fibrosis is a well-characterized late effect of radiotherapy (Barker et al., 2015) and the use of a fibrosis-inducing modality of therapy to treat a fibrosing condition may, perhaps, seem counter-intuitive. Hence, the use of radiotherapy in Dupuytren's disease remains both limited and controversial amongst hand surgeons. Specifically, the efficacy of radiotherapy in managing Dupuytren's disease remains uncertain, the longer-term risks unclear and whether irradiation may complicate subsequent surgery remains a concern. In the UK, current National Institute for Health and Care Excellence (NICE) guidance permits the use of radiotherapy in early Dupuytren's disease and there are a small number of NHS and private clinics that offer this service.

The aim of this study was to review the available evidence for the treatment of Dupuytren's disease with radiotherapy.

Methods

An advanced search was performed on PubMed, Google Scholar and the Cochrane Library. Specific vocabulary terms, key words and synonyms were entered as part of a systematic search strategy. The terms and keywords were also joined together in differing combinations. The search terms used included: *Dupuytren's disease, Dupuytren's contracture, Dupuytren Disease, Dupuytren Contracture, morbus Dupuytren, radiotherapy, radiation, therapy and non-surgical*. The majority of articles published on the use of radiotherapy were in German. As a result, German articles were translated and included. No specific date range was used and articles were found dating back to 1985. The reference lists for all included papers were screened for any outstanding articles. Papers using repeated data sets were removed to avoid duplication. This was achieved by comparing author names and number of patients. All included articles were evaluated in terms of level of evidence, taking into account the study design and quality. Finally, an advanced search of guidance on the use of radiotherapy was performed, namely focusing on NICE Guidelines (NICE., 2010). In each included article, we actively searched for specific outcome measures. These included the disease response

outcome (regression rate, disease stability or progression rate), short and long-term complications of radiotherapy and the conversion rate to surgery. The search and review process was initially performed by two independent authors based on analysis of the study title and abstract (Table 1). Before analysis of the full text, another independent author was used as a referee for the initial screening process. This process was then repeated for the full text analysis. The PRISMA statement guidelines were adhered to throughout this systematic review.

Table 1: Screening questions

Question	Minimum Criteria
Does it address the study question?	Radiotherapy treatment
Does it address the topic?	Dupuytren's disease
Is it a clinical study?	Yes
What is the level of evidence?	Case series
How many patients were included?	N > 10
Does it address outcome measures?	Any of: Progression rates, stability rates, regression rates, conversion to surgery and complication rates.

Results

A search in the Cochrane database revealed no published review articles on radiotherapy in Dupuytren's disease. A total of 39 articles were found on PubMed and 227 using Google Scholar (Supplementary Figure 1). Only six articles met our strict inclusion criteria (Table 1). These six articles had a cumulative cohort of 698 patients with Dupuytren's disease with a total of 770 irradiated hands. The mean age was 58.5 years. Staging of disease was performed via the modified Tubiana classification in all articles, which is based on the total flexion deformity or extension deficit of the involved MP and PIP finger joints (Stage N: no flexion deformity, stage N/I: 1-5^{o}, stage I: 6-45^{o}, stage II: 46-90^{o}, stage III: 91-135^{o}, stage IV: >135^{o}) (Keilholz et al., 1996; Seegenschmiedt et al., 2001). According to the Tubiana classification, 47.2% were stage N, 16% were stage N/I, 30.2% were stage I,

5.1% were stage II, 0.9% were stage III and 0.5% were stage IV. Interestingly, there was a higher proportion of females in the included studies (male to female ratio of 1.6:1) compared to what is typically observed in practice (male to female ratio of 3:1). This may be due to a preference towards radiotherapy treatment rather than surgical management in females.

Five of the six articles utilised a retrospective cohort study design, whilst one was a prospective randomised controlled study (Table 2). All six studies were performed in Germany. The total radiation dose ranged from 21 to 42 Gy, with 30 Gy being most commonly used (Table 2), and doses were fractionated to deliver 3 Gy per fraction or 8 Gy per fraction. The median follow-up was five years (range: 1-13 years). Three main outcome measures were assessed, namely disease regression (reduction in the number and consistency of cords or nodules and a reduction in extension deficit), stability (neither regression or progression of disease according to objective clinical measures) and progression. Three studies reported overall results across all stages, between 0-56% for regression, 37-98% for stability, and 2-20% for progression (Herbst and Regler., 1986; Seegenschmiedt et al., 2001; Zirbs et al., 2015). The other three studies reported results separately for each Tubiana stage: 6-16% (stage N), 12-30% (stage N/I), 6-20% (stage I) and 0-38% (stage II) for regression; 21-81% (stage N), 12-54% (stage N/I), 20-32% (stage I) and 14-62% (stage II) for stability; 13-16% (stage N), 30-33% (stage N/I), 62-65% (stage I) and 83-86% (stage II) for progression (Keilholz et al., 1997; Adamietz et al., 2001; Betz et al., 2010) (Supplementary Table 1).

Table 2: The type, total dosage and follow-up length for each included study.

Study (year)	Type of study	MRC level of evidence	Total dose of Radiotherapy	Number of fractions	Dose per fraction (Gy)	Mean follow-up length (years)
Herbst and Regler (1985)	Retrospective cohort	3	<42 Gy	3-14	3	1.5
Keilholz et al. (1997)	Retrospective cohort	3	30 Gy	10	3	6
Adamietz et al. (2001)	Retrospective cohort	3	30 Gy	10	3	10
Seegenschmiedt et al. (2001)	Randomised controlled study	2	30 Gy	10	3	1
			21 Gy	7	3	
Betz et al. (2010)	Retrospective cohort	3	<30 Gy	2	3	13
Zirbs et al. (2015)	Retrospective cohort	3	32 Gy	4	8	4

The randomised controlled trial by Seegenschmiedt et al. (2001) is the best quality paper available to us. This study did not include an untreated control however and we have downgraded it from level 1 evidence to level 2. The authors randomised Dupuytren's patients to receive either 10 fractions of 3 Gy (total dose 30 Gy, Group A) or 7 fractions of 3 Gy (total dose 21 Gy, Group B). Group A consisted of 63 patients (95 hands), whilst group B had 66 patients (103 hands). There were no statistically significant demographic differences between groups A and B and disease stages were similar. Both subjective (patient assessed) and objective measures (physician assessed via inspection for skin fixation, skin retraction and measurements of nodules, cords and the degree of extension deficit) of disease regression, stability and progression rates were compared to results measured prior to radiotherapy, highlighting a statistically significant improvement ($p < 0.01$) (Seegenschmiedt et al., 2001). No statistically significant difference in objective measurements existed between the two radiation doses, although this may reflect the relatively short one-year follow-up used in the study.

The proportion of patients undergoing surgery because of disease progression following radiotherapy ranged from 3.1-10% (Adamietz et al., 2001; Betz et al., 2010; Keilholz et al., 1996;

Seegenschmiedt et al., 2001). Salvage surgery was successful in all cases (Adamietz et al., 2001; Betz et al., 2010; Keilholz et al., 1996; Seegenschmiedt et al., 2001). Radiotherapy did not appear to increase complication rates of surgical treatment in the short and long-term (Adamietz et al., 2001; Betz et al., 2010; Keilholz et al., 1996; Seegenschmiedt et al., 2001), but none of the papers addressed this in depth.

Long-term outcomes were reassessed in four studies by a self-reported questionnaire. Relief of symptoms such as sensations of tightness and pruritus were reported in 66 to 87% of patients following irradiation. Four studies measured short-term complications, which occurred in 20 to 43% of patients and included erythema, drying of the skin and desquamation (Supplemental Table 1). Long-term complications were assessed by four studies and included skin dryness (5-64%) and atrophy (5-13%). No cases of skin ulceration or radiation-induced malignancy have been reported.

Discussion

Radiotherapy is currently used in Dupuytren's disease with the intention to stabilise disease progression, thereby delaying or preventing surgical intervention. In this systematic review, we analysed six studies that delivered similar radiation schedules. The majority of patients included in these studies (93%) were Tubiana stage N, N/I or I. The studies all suggest an improvement in overall outcome, with significant degrees of remission and stabilisation, although none of these studies had an untreated control group. Early use of radiotherapy may lead to a more favourable outcome as demonstrated by improved disease regression and decreased progression in stages N and N/1 compared to stage 2 (Adamietz et al., 2001; Betz et al., 2010). Only one of the six studies reviewed (Keilholz et al., 1996) reported better outcomes in more advanced disease compared to early-stage Dupuytren's. Updated NICE guidelines for the treatment of Dupuytren's disease with radiotherapy (NICE., Dec 2016) comment on the limited availability of evidence and recommends that radiotherapy should only be used with "special arrangements for clinical governance, consent, audit

and research". NICE highlight that the use of radiotherapy in Dupuytren's disease aims to prevent progression and prevent surgery. However, not all cases of Dupuytren's disease progress. For example, a recent study describing the short-term disease course of Dupuytren's disease in 247 participants showed that up to 75% of patients have differing patterns of progression, stability and regression (Lanting et al., 2016). In an 18 year follow-up of Dupuytren's disease progression, 35% of patients with early Dupuytren's disease (stage N) progressed to develop contractures (Gudmundsson et al., 2001). This is a higher rate of progression than those treated with radiotherapy, but no direct comparison can be made as the follow up times for patients treated with radiotherapy were shorter. One other study with a shorter follow-up of 8.7 years found that only 8.5% of patient's disease progressed sufficiently to warrant surgical treatment (Reilly et al., 2005). Therefore, the use of radiotherapy may impose unnecessary treatment on patients, along with side effects and long-term risks.

As expected, both acute (erythema) and late (skin atrophy) side effects were observed in irradiated patients. Approximately 20-40% of patients experienced acute complications with less than 10% experiencing late changes. No radiation-induced malignancies were reported but the median follow-up across all studies of five years is insufficient (Hall and Giaccia., 2006; Trott and Kamprad., 2006). The increase in absolute risk of radiation-induced malignancies has previously been estimated to be 0.02% (Dupuytren's International Society., 2013).

From the available evidence, salvage surgery for disease progression after radiotherapy may be feasible but the available data is poor. The authors report that progression of symptoms was the main indication for surgery, but fail to address the threshold for operative management in detail. Specific types or numbers of complications after conversion to surgery were not reported. Furthermore, complication rates of salvage surgery post-radiotherapy were not compared to those after surgery in radiation-naive hands.

Although the studies seem to show a benefit in early Dupuytren's disease, various limitations exist. Five of six articles were retrospective cohort studies with a modest number of patients included. Patient-reported outcomes were more subjective and may have been susceptible to response bias. The one randomised study compared two treatment groups, therefore lacking a control group to compare radiotherapy with other modalities of treatment or no treatment. The safety outcomes measured in the RCT were reported collectively, rather than being group-specific, leading to difficulty in analysing the safety of radiotherapy in different stages of disease. Although irradiation protocols were largely similar, some differences existed in fractionation schedules. Biological equivalent dose calculations would be useful in order to meaningfully compare doses from different schedules. Furthermore, half of the studies reviewed did not differentiate between the stage of Dupuytren's treated, which must be considered a flaw since the literature suggests radiotherapy is most efficacious in early stages. Limitations may also exist in the review mainly as a result of incomplete retrieval of published papers. The authors did attempt to minimise this risk by performing three cycles of advanced searches on each database.

On balance, the evidence for the use of radiotherapy in early Dupuytren's disease is weak and does not clearly support its use in practice. Well-designed, randomised control studies are required to elucidate its efficacy further and its place in the evidence-based management of Dupuytren's disease. This requires high-level co-operation between clinical oncologists and hand surgeons with careful study design and recruitment.

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