



RADIATION ONCOLOGY—ORIGINAL ARTICLE

Radiotherapy in fascial fibromatosis: A case series, literature review and considerations for treatment of early-stage disease

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Conflict of interest: None.

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Submitted 4 November 2013; accepted 4 March 2014.

doi:10.1111/1754-9485.12178

Abstract

Introduction: Palmar and plantar fascial fibromatoses are benign hyperproliferative disorders of the deep fascia of the palm and sole. This study seeks to examine the role of radiotherapy in the management of fascial fibromatosis.

Method: Six consecutive cases of early-stage fascial fibromatosis treated with radiotherapy at the Adelaide Radiotherapy Centre between July 2008 and May 2011 were analysed. The results of the case series were compared with a systematic review of the literature.

Results: All six cases regressed or showed a reduction of symptoms following radiotherapy. Treatment was well tolerated with minor toxicities. Median follow-up for the case series was 38.5 months. The systematic review identified seven studies describing the use of radiotherapy as primary treatment for fascial fibromatosis between 1946 and 2013. The literature indicates that radiotherapy can prevent disease progression and improve symptoms for early-stage disease, with low likelihood of significant toxicities.

Conclusion: Early results from our case series are consistent with the literature, showing that radiotherapy can provide an effective management option for patients with early-stage fascial fibromatosis, and justify consideration of radiotherapy as a primary treatment for early-stage disease.

Key words: Dupuytren's contractures; Ledderhose; palmar fibromatosis; plantar fibromatosis; radiotherapy.

Introduction

Palmar and plantar fascial fibromatoses (FF), or Dupuytren's contractures, are benign hyperproliferative disorders of the deep fascia of the palm and sole, respectively. The disease often starts in the fourth decade or later.¹⁻⁴ The incidence varies in different parts of the world, the disease being most common among people of Northern European ancestry. Approximately 1–2% of the general white/Caucasian population are affected, while in northern European countries the prevalence reaches 40% or more for selected populations and age groups.^{1,3,4} More men than women are affected, with studies reporting gender ratios of 3:1 to 6:1.^{5,6} Men are also usually affected earlier in life.³

The aetiology and pathogenesis of the disease are not well understood. Family history is an important risk factor, indicating this is a genetic disease, but the exact genetic mechanism is unclear.^{2,7} Other predisposing

factors hypothesised include alcohol and nicotine abuse, liver cirrhosis, epilepsy, diabetes mellitus, and vascular and autoimmune disorders.^{1,3-5,8} Trauma and a history of manual labour have been suggested, but these associations are now considered less likely.^{4,9} Palmar disease is more common than plantar disease. Concomitant palmar and plantar disease is possible, especially in the presence of a strong family history.¹

The first sign of the disease is often a palpable nodule, which may be fixed to overlying skin. Tough cords can then develop along the tendons. Progressive disease of the palms leads to shortening of the fascia, with disabling and painful flexion contractures. Advanced plantar disease patients often have walking difficulties due to pain of the soles of the feet.

Disease onset occurs long before clinical symptoms are reported, with fibrous deposits occurring within the deep connective tissues. Chronologically, disease progression can be divided into three stages: (1) a

proliferative stage with the presentation of fibroblasts and beginning nodule and cord formation; (2) an involutinal stage, with myofibroblasts and flexion contractures; and (3) a residual stage with increased collagen fibres. In the residual stage, the normal type I collagen is replaced by type III collagen.^{1,10,11} Myofibroblasts are thought to be transformed fibroblasts, with contractile properties similar to those of smooth muscle cells.^{10,12}

The most commonly used classification system for palmar FF was initially developed by Tubiana *et al.* based on the measurable extension deficit of the palm and involved finger joints. Stages range from stage 0 (no nodule or cord lesion, no extension deficits) and stage N (nodule or cords without extension deficit) through stages I to IV (progressively increasing extension deficits).⁴ No similar classification system exists for plantar FF, which seldom manifests as measurable contractures.

Treatment options for FFs include observation, symptomatic treatment with medication and physiotherapy, surgery or local radiotherapy. Observation may be a reasonable option for early stages where the lesions remain stable with no or minimal progression. In general, approximately 50% of lesions will progress within a 5-year period.⁴ Rarely, there may be spontaneous disease regression. Corticosteroids may assist in pain control and, for some patients, may assist in slowing disease progression by increasing the rate of apoptosis in affected tissue.¹³ Injectable *Clostridium histolyticum* collagenase has also been investigated as a treatment option.¹⁴ Surgery has traditionally been the main treatment modality and is usually undertaken for advanced stages of the disease affecting activities of daily living. Surgical options range from local excision of nodules and cords to total fasciectomy.^{4,15}

Radiotherapy may be used during the early stages of disease, with the aim being to halt disease progression and preserve function, and can be a useful treatment modality for patients who wish to avoid surgery. This case series examines the role of radiotherapy in the management of palmar and plantar FFs.

Method

Patient details

A search of Adelaide Radiotherapy Centre's treatment record databases identified six patients treated for fascial fibromatosis between July 2008 and May 2011. Due to bilateral involvement in three cases, a total of nine sites were analysed. Mean age was 54 years.

Patient symptoms and signs ranged from an asymptomatic nodule to pain and restriction of movement (Figs 1,2). According to Tubiana *et al.*'s classification system, all three cases of palmar FF could be described as early-stage (stage N or I). Details of individual cases are summarised in Table 1.



Fig. 1. Palmar fascial fibromatosis in a patient from our case series showing a tangential view of the left palm with nodules and cords affecting tendons of the fourth and fifth digits.

Management

Radiotherapy was delivered in two phases. In the first phase, patients received 15 Gy in five fractions at 3 Gy per fraction prescribed to 100% using a single direct 6-MeV or 9-MeV electron field, with each field treated daily, Monday to Friday, for 1 week, followed by a 6-week break. The second phase was a repeat of the first phase. All patients were CT-planned at simulation to determine lesion thickness and corresponding electron energy.

The target volume consisted of the palpable lesions with a 1-cm margin. Care was taken to allow for radiation fields narrower than 4 cm. A tissue-equivalent bolus of 0.5 cm in thickness was used across the whole field. Individualised cut-outs were used to provide shielding to surrounding tissues.



Fig. 2. Direct view of the left palm of the same patient as in Figure 1.

Table 1. Summary of patient cases

Case	1	2	3	4	5	6
Age	55	58	65	44	50	52
Sex	F	M	F	M	M	M
Palmar/plantar	Palmar	Palmar	Palmar	Plantar	Plantar	Plantar
Family history	Not stated	Both parents	Distant cousin	Strong family history	Father, paternal uncle	Nil
Site	Right hand: nodule between right fourth and fifth digits on the palm	Bilateral hands: bilateral contractures of ring finger flexor tendons; nodules on flexor tendons of fifth, third and second left fingers	Left hand: two nodules (3 mm, 5 mm) in the palm of the left hand between the fourth and fifth digits, with cording extending a few mm distal to the 5-mm lesion	Bilateral feet: 6 x 4-cm mass in medial aspect of central left plantar region; 5 x 3-cm lesion of right foot	Left foot: three thin prominent cords (4, 3 and 4 cm in length), tender to deep palpation	Bilateral feet: 2 x 2-cm firm, tender lesion of the left sole on the side of the first digit; 10 x 12-mm smooth, tender lesion of the right sole
Stage (Tubiana classification)	N	I	N	n/a	n/a	n/a
Symptoms	Asymptomatic nodule	Some limitation of movement	Uncomfortable lesion in left hand, no restriction of movement	Pain in bilateral feet; reduction of movement of the left fifth digit	Pain	Tender nodules in bilateral feet
Symptom duration	2 months	Left hand: 5 years; right hand: 1 year	6 weeks	Left foot: 15 years; right foot: 7 years	>9 years	Left foot: 10 years; right foot: 6 months
Previous treatments	Nil	Nil	Nil	Left foot surgery; recurrence within 1 year of surgery	Surgery to bilateral palms and left foot in 2000, with subsequent recurrence and progression; planned for further surgery to palms	No previous treatment to soles; surgery to right hand on four separate occasions
Other sites affected (not irradiated)	Nil	Nil	Nil	Left hand: 6 x 3-cm lesion involving the fifth and fourth digits	Bilateral palms: thickening of tendons, in particular the middle digit, with some deformity in the left palm	Right hand: 8 x 2-cm and 4 x 2-cm cords with a flexion contracture; left hand: 3 x 3-cm cord
Result	Decrease in size of nodule	Decrease in size of lesion	Nodules flatter, less hard; no pain or discomfort; no restriction of movement	Left foot lesion no longer painful; right foot pain significantly better; lesions approximately 1 cm smaller circumferentially	Regression of lesions (reduction in size by 2 mm at end of second course)	Bilateral tenderness resolved; lesions unchanged in size
Follow-up	34 months	42 months	35 months	61 months	42 months	29 months

For treatment of the palms, two different treatment positions were used. In one position, patients were either seated on a chair next to the treatment couch or standing next to the couch, with the open palm resting on the treatment couch. The alternative position was for the patient to lie prone on the treatment couch, with arms above the head resting supported on the couch with palms facing up. For treatment of the soles, patients lay prone on the treatment couch with ankles extended.

Results

Response to radiotherapy was confirmed either objectively as reduction in size of the target lesion(s) or subjectively as improvement in pain or discomfort. Two patients already had symptomatic improvement when reviewed prior to commencement of the second phase of treatment. All four palmar FF sites regressed in size. For the plantar FF sites, all five sites responded symptomatically, with three sites reduced in size.

All patients proceeded through the course of treatment as initially planned. Radiotherapy was well tolerated, with acute side effects limited to minimal fatigue, mild local oedema and erythema. There was no restriction to activities of daily living during treatment and no convalescence period following treatment. No disease progression was observed during a median follow-up of 38.5 months.

Literature review

A literature search was performed of the MEDLINE databases for the period from 1946 to January 2014 to investigate the role of primary radiotherapy in the management of fascial fibromatosis. The search was limited to articles relating to human subjects and used the search terms 'Dupuytren', 'Ledderhose', 'palmar fibromatosis' and 'plantar fibromatosis' combined with 'radiotherapy'. In cases of multiple papers published by the same institution, only the most recent or relevant articles discussing outcomes were considered. Although radiotherapy has also been used in the adjuvant setting with the aim of decreasing disease recurrence following surgery, this review is limited to studies where radiotherapy has been used as a primary modality of treatment.

In total, seven studies describing the use of radiotherapy for fascial fibromatosis were found. These are summarised in Table 2 in chronological order of publication.

Only one prospective randomised trial has been performed in this field. Seegenschmiedt *et al.* report on early results of a study comparing two different dose fractionation regimens for palmar FF.²⁰ Both fractionation schedules achieved similar results at 1-year follow-up. Treatment was well tolerated, with only mild acute and late toxicities, although slightly increased acute side

Table 2. Studies of radiotherapy as primary management of fascial fibromatosis

Author(s), year	Patients/sites	Palmar/plantar	Dose fractionation	Clinical outcome	Follow-up period
Finney, 1953 ¹⁶	25	Palmar	Radium mould, 3000 rad	76% improved (32% full functional recovery), 24% unchanged	Not known
Lukacs <i>et al.</i> , 1978 ¹⁷	106/158	Palmar	2 × 8 Gy, repeated at 8-week intervals; total dose 32 Gy	81% improved, 19% stable	Not known
Köhler, 1984 ¹⁸	31/38	Palmar	10 × 2 Gy, 5 days/week	21% regression, 61% stable, 18% progression	1–3 years
Herbst and Regler, 1986 ¹⁹	33/46	Palmar	3–14 × 3 Gy, 5 days/week; total dose 9–42 Gy	98% stable, 2% progression	18 months
Seegenschmiedt <i>et al.</i> , 2001 ²⁰	129/198	Palmar	Prospective study of two groups: group A, two courses of 5 × 3 Gy, 5 days/week, with 8-week break between each course (total dose 30 Gy); group B: 7 × 3 Gy within 2 weeks (total dose 21 Gy)	Group A: 56% regression, 37% stable, 7% progression; group B: 53% regression, 38% stable, 9% progression	1 year
Betz <i>et al.</i> , 2010 ²¹	135/208	Palmar	Two courses of 5 × 3 Gy, 5 days/week; 6–8-week break between courses; total dose 30 Gy	Overall (all stages): 59% stable, 10% improved, 31% regressed; early stages: 87%/70% stable or regressed	13 years
Heyd <i>et al.</i> , 2010 ²²	24/33	Plantar	28 sites received two courses (5 × 3 Gy 5 days/week, 6–8-week break between courses, total dose 30 Gy); five sites received a single course (2 × 4 Gy repeated at 4-week intervals, total dose 24–32 Gy)	33.3% complete remission, 54.5% improved, 12.1% unchanged	22.5 months (median)

effects were seen for the patient group treated over a single phase. Disease progression was more likely for stage I or II disease, with none of the stage N cases progressing further. Longer-term analysis is awaited.

In the largest retrospective study, Betz *et al.* analysed a total of 208 hands treated with orthovoltage X-rays.²¹ Early-stage disease was more likely to respond to treatment in terms of both symptom control and prevention of progression. In cases where disease progression prompted later surgery, the previous radiotherapy did not increase complication rate. Only minor late toxicities were observed.

Various dose fractionation regimens were used in the earlier retrospective studies. The clinical outcome achieved by Köhler using a lower total dose was inferior to those of the more recent studies that followed a similar fractionation schedule to the Seegenschmied trial.¹⁸

Data reported by the earlier studies are incomplete in many aspects, including follow-up period and details on treatment received. Since these studies were done, there have been many developments in radiotherapy technique, and it may be difficult to draw conclusions regarding outcomes. Nevertheless, the studies by Finney, Lukacs *et al.*, Köhler, and Herbst and Regler, as described, support the use of radiation for early stages of the disease.^{16–19}

Only one study involving plantar FF was identified. Heyd *et al.* report retrospectively on radiotherapy for symptomatic early-stage disease, using a fractionation schedule similar to that in our case series.²² Disease progression was halted in all cases, with complete remission of cords or nodules in a third of the sites. Pain relief and improvement of gait were achieved in 68% and 73% of patients, respectively.

Discussion

The radiobiological mechanism of action of radiotherapy is believed to be a complex interaction of different cell types. The early stages of palmar and plantar FF are characterised by hyperproliferation of fibroblasts and myofibroblasts. It has been suggested that radiotherapy may inhibit this proliferation process, with a mechanism of action similar to that in the treatment of other hyperproliferative fibrous diseases such as keloids.⁴ Several growth factors, including fibroblast growth factor, transforming growth factor beta and platelet-derived growth factor, as well as cellular receptors for these, are found in increased levels in affected palmar and plantar tissues, and these may also provide possible radiosensitive targets for ionising radiation, especially at the early stages of the disease.^{4,10}

Surgery has traditionally been the standard treatment of the disease. It is generally reserved for the later stages where functional impairment has affected daily activities, or where there is significant associated pain.

Surgery may not be an option for some patients due to medical comorbidities or personal factors such as the need for time off work for postoperative convalescence. Postoperative rehabilitation and hand therapy are recommended following surgery, and during this period of several months, there may be significant restrictions on activities of daily living and the ability to work.^{2,15,23} Complications are common, reportedly occurring in 15% of cases, depending on the magnitude and complexity of surgery.^{15,23,24} These include infections, painful scar formation, joint stiffness, delayed wound healing and haematoma.^{1,2,15,23} Surgery alone is associated with a high recurrence rate, with studies indicating recurrence rates between 20% to 60%.^{25–27} In our limited case series, two of the patients had previously undergone surgery to the site treated with radiotherapy, with subsequent disease recurrence and progression.

The literature indicates that radiotherapy can provide an effective management option by preventing symptom progression of early-stage FF.^{4,16–22} Surgical intervention may thus be avoided altogether. Early results from our case series are consistent with the literature, with radiotherapy providing a well-tolerated treatment option for patients who wish for active management rather than an observational approach and do not wish to undergo surgery. It should again be noted that the main role of radiotherapy is in the early stages of disease, where prevention of disease progression can provide ongoing functional integrity. For more advanced cases, surgical intervention remains the mainstay of treatment for fit candidates. Previous radiotherapy for early-stage disease should not be a barrier to future corrective surgery in the case of disabling disease progression.²¹

Potential acute side effects of radiotherapy include lethargy, a local skin reaction, local oedema and pain. Mild subcutaneous fibrosis and skin changes are potential late toxicities. Only mild acute and late toxicities were reported in the studies considered above.^{16–22} In contrast to surgery, there are no significant functional restrictions of the hand or foot during or immediately following radiotherapy.⁴

The main long-term concern for this relatively young patient population is the risk of development of a secondary malignancy. Jansen *et al.* have estimated the carcinogenic risk involved in radiotherapy for benign disease.²⁸ Although FFs are not specifically considered, the results for other benign diseases, such as heel spurs, may be applicable. For an irradiated area of 80 cm², the increase in risk for a 25-year-old man is calculated to be 0.1%, while for a 50-year-old man it is 0.05%. It should be noted that in the case of palmar and plantar FF, the irradiated area is usually much smaller.

The literature estimates a theoretical risk of 0.5–1% for induction of soft tissue sarcoma or skin cancer after latency periods of 8–30 years.^{4,28,29} It should be noted that much of this work was based on older techniques and relatively higher doses of radiotherapy. The risk of a

secondary malignancy from irradiation with modern techniques and lower doses should be significantly lower. There have been no published cases in the literature where patients have acquired a malignancy directly attributed to their radiation treatment for palmar or plantar FF. In our series, median follow-up was only 38.5 months.

Based on the literature and our limited case series, we encourage consideration of radiotherapy as a primary treatment for early-stage FF, with minimal associated interruption of activities of daily living during and following treatment. The option of surgery can be retained for any patients who progress to advanced disease.

Conclusion

Early results from our case series are consistent with the literature, showing that radiotherapy can provide an effective management option for patients with early-stage fascial fibromatosis, and justify consideration of radiotherapy as a primary treatment modality for early-stage disease. Studies providing longer-term data utilising modern radiotherapeutic techniques are required.

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