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Research Article

Feet Don't Fail Me Anymore! Single-Centre Results Using Low-Dose Radiation Therapy for Feet Inflammatory Disorders and Review of Current Evidence

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Received Date: 02-10-2022; Accepted Date: 18-10-2022; Published Date: 25-10-2022

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Abstract

Background: Plantar fasciitis- and tendinopathy-related foot pain are common cause of functional disability. Low-Dose Radiation Therapy (LDRT) has proven to be effective in the symptomatic relief of these disorders.

Material and methods: Between February 2016 and December 2021, 31 patients were included in this prospective register. Seventeen patients suffered from calcaneodynia, 11 from tendonitis and 3 from osteoarthritis. 6 Gy (1 Gy/fraction) or 3 Gy (0,5 Gy/fraction) were delivered and repeated after 12 weeks if no adequate relief. Response was evaluated at the end of the planned courses, after 3 months and subsequently every 6 months using Visual Analogic Score (VAS), the Von Pannewitz Score (VPS) and daily analgesic drug needs.

Results: Overall, 87% of the patients experienced pain relief. Patients with a VAS score above 5 dropped from 35.5% at the end of LDRT to 32%, 13% and 6% after 3, 6 and 12 months, respectively. According to the VPS, 74% showed improvement and 26% remained stable. Lastly, 39% of patients stopped or reduced analgesic intake. Nine patients have been followed up for more than 12 months. The median pre-treatment VAS score in this group was 9 (range

Montero A | Volume 3; Issue 3 (2022) | JOSR-3(3)-042 | Research Article

Citation: Montero A, et al. Feet Don't Fail Me Anymore! Single-Centre Results Using Low-Dose Radiation Therapy for Feet Inflammatory Disorders and Review of Current Evidence. J Ortho Sci Res. 2022;3(3):1-12.

DOI: <https://doi.org/10.46889/JOSR.2022.3304>

7-10), whereas median VAS scores after 3, 6 and 12 months stood at 5 (range 1-7), 3 (range 0-6) and 1 (range 0-6), respectively (Fig. 2). An improvement in functionality was reported by 7 out of 9 individuals (77.7%). No acute or late complications were observed.

Conclusion: LDRT appears to be useful for symptomatic treatment of inflammatory and degenerative disorders of the foot.

Keywords

Plantar Fasciitis; Foot Tendinopathy; Low-Dose Radiation Treatment

Key Points

- Foot-pain syndromes, including plantar fasciitis and tendinopathy of various locations, are frequent causes of functional disability especially at older ages
- Conservative treatments, pharmacologic interventional measures and instrumental electrophysical procedures have variable success rates and low patient satisfaction
- Low-Dose Radiation Treatment (LDRT) and its well-known anti-inflammatory properties have been associated with acceptable rates of pain relief in different musculoskeletal inflammatory and degenerative disorders and could be an attractive alternative for symptomatic relief

Introduction

The mechanical overload of the different structures of the foot due to obesity, prolonged standing or walking, repetitive (micro) trauma, poor foot biomechanics or intense physical exercise are the origin of many inflammatory and degenerative disorders, such as osteoarthritis, plantar fasciitis or tendinopathies, that cause persistent and sustained foot pain. This is relatively frequent, especially at older ages. Its prevalence in adults over 18 years of age is 17-24%, which increases to 42% in those over 65 years of age and nearly to 75% in those over 75 years of age, having a significant impact on their quality of life [1,2].

Both conservative treatments, such as relative rest, the use of orthopedic devices or physical rehabilitation exercises and interventional measures, including non-steroidal anti-inflammatory drugs, local injections of corticosteroid and local anesthetic, hyaluronic acid or botulinum toxin injections, autologous whole blood or platelet-rich plasma, extracorporeal shock waves, microwaves, ultrasounds, dry needling, lasers or magnetic treatment have variable success rates

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and none of them have proven to be more effective in the definitive eradication of foot pain [3-10].

The anti-inflammatory properties of Low-Dose Radiotherapy (LDRT) are well known and so this treatment has been widely used for the relief of non-malignant disorders, showing that it is not only effective but also a safe option [11-13]. In this paper, we present the results of our experience using LDRT for the symptomatic treatment of foot pain associated with heel inflammatory and degenerative disorders and foot tendinopathies. We also review existing evidence for its use.

Material and Methods

Adult patients with painful foot syndromes refractory to other treatments were offered LDRT. The local Ethics and Clinical Research Committee approved this study and the use and analysis of patient data (Ref: 15.03.760-GHM). All the patients enrolled signed an informed consent document prior to their inclusion.

Evaluation and response to LDRT

We evaluated clinical response to treatment based on three aspects:

1. The Visual Analogic Scale (VAS) for pain level
2. The Von Pannwitz Score (VPS) for joint functionality [14] (1: Complete response, pain free; 2: Partial response, substantial pain improvement; 3: Minor response, moderate pain improvement; 4: No change, pain unchanged; 5: Progressive disease, worse pain)
3. The daily need for analgesic drugs at the last radiotherapy session, 3 months post-radiotherapy and subsequently every 6 months

Any patients not achieving subjective adequate pain relief after 12 weeks of treatment were offered a second identical course of LDRT.

The appearance of any acute or late adverse effect attributable to the treatment was recorded according to the CTCAE 5.0 grading scale.

The differences between the parameters studied before and after radiation therapy were calculated for each patient and compared using the Wilcoxon test for non-parametric paired samples. Pearson's chi square test for categorical variables was used to compare characteristics among different subgroups regarding pain relief and statistical significance was considered where $p < 0.05$. SPSS (IBM SPSS Statistics for Windows, Version 19.0 (Armonk, NY; IBM Corp) software was used for calculations.

LDRT Procedure

All the patients treated underwent LDRT with a 6-MV LINAC up to a total dose of 3-6 Gy delivered in six single fractions of 0.5-1 Gy every other day. All patients were simulated in the supine position with affected foot/feet extended forward and palms resting on the CT couch, using an individualized AccuForm™ cushion (Coralville, Iowa, USA) and a thermoplastic mask to ensure reproducibility of positioning for radiotherapy (Fig. 1). Target volumes were defined according to the published atlas and guidelines and comprised the painful area for the Clinical Target Volume (CTV) with an isotropic 5 mm expansion to create PTV (Planning Target Volume) (Fig. 1) [15]. Clinical dosimetry was achieved by using the RayStation® (RaySearch Laboratories AB, Stockholm, Sweden) planning system (Fig. 1). Dose at nearby organs at risk was guided by the ALARA principle (keep the dose as low as reasonably achievable).

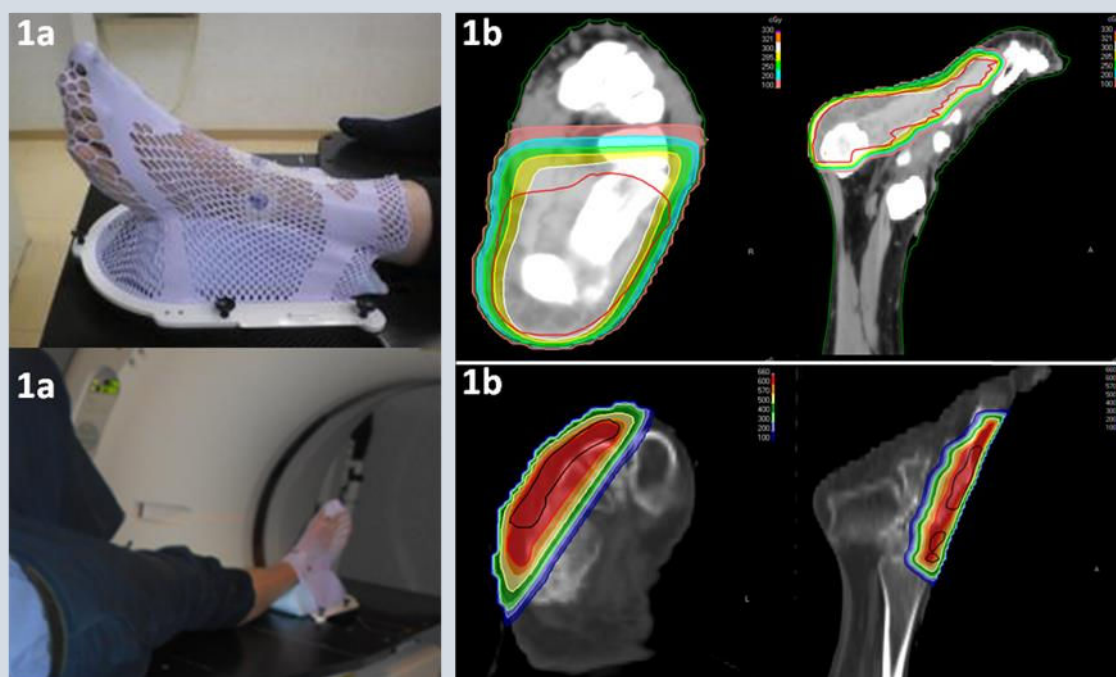


Figure 1: Patient immobilization with tailored thermoplastic mask (1a) and dose distributions for plantar fasciitis (upper) and tibialis tendonitis (lower) treatments (1b).

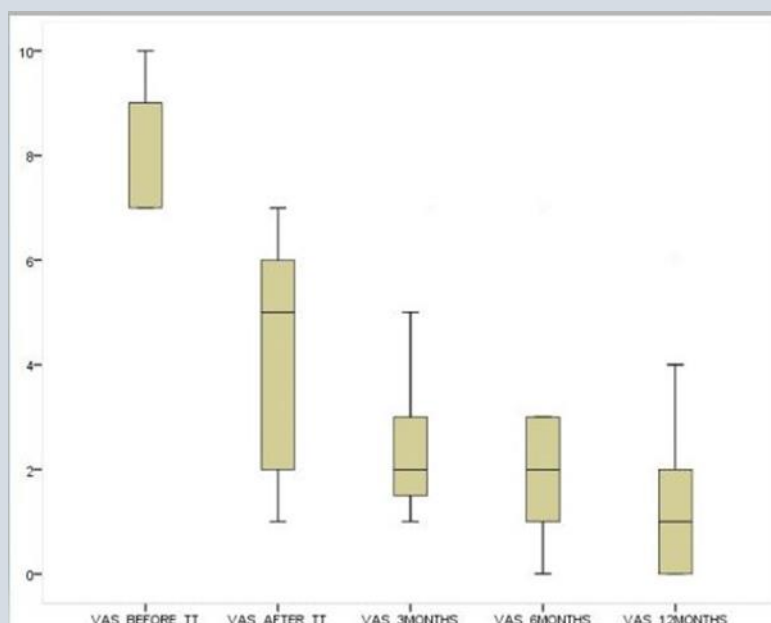


Figure 2: Box plot figures of pain level according to the VAS before and at completion of LDRT and subsequently at 3, 6 and 12 months.

Results

Between February 2016 and December 2021, 31 patients with a median age of 64 years (range 48-72) and a previous diagnosis of foot musculoskeletal conditions were treated in our department. Seventeen patients (55%) were suffering from calcaneodynia, 11 patients (35%) from foot tendonitis and 3 patients (10%) from foot osteoarthritis. The left foot was treated more frequently (52%) than the right foot (48%). The complete characteristics of the patients treated are detailed in Table 1.

The median pain level determined according to the VAS score before LDRT was 8 (range 6-10), with 10% of patients reporting VAS10; 32% of patients VAS9; 19% of patients VAS8; 36% of patients VAS7 and 3% of patients VAS6. Twenty-two patients (71%) were irradiated with a fractionated dose of 1 Gy up to a total dose of 6 Gy and 9 patients (29%) with a fractionated dose of 0.5 Gy up to a total dose of 3 Gy.

All patients were evaluated at the end of the planned courses of LDRT, at 3 months and subsequently every 6 months. After the first course of treatment, 35.5% recorded a pain VAS score above 5. After the first 3 months, 10 patients still had a VAS score above 5; after 6 months, 4 patients reported a VAS score above 5 and only 2 patients reported a VAS score above 5 after 12 months, representing an 87% overall response. Twenty-six patients (84%) underwent a second course of treatment with the same schedule at a median time interval of 16 weeks (range 9-52) after the first course, because of insufficient response in 24 patients or no

response in 2 patients. After the second course, 4 of them (13%) maintained a VAS score above 5; 14 patients (45%) reported a VAS score between 3 and 6 and 13 (42%) reported a pain VAS below 3.

Patients' subjective evaluation of joint functionality, according to the VPS, showed painless functionality in 23%, a notable improvement in 45% and a slight improvement in 6%. The remaining 26% reported a stable condition with no patient reporting worsening functionality. In the 9 patients with longer follow-up, an improvement in functionality (VPS) was reported by 7 (78%). Lastly, when patients were asked about daily analgesia intake, 16% reported the same oral treatment, but 39% of the patients stopped taking oral pills or reduced them. The rest of the patients had no scheduled analgesia before LDRT.

Nine patients have been followed for more than 12 months. The median pre-treatment VAS score in this group was 9 (range 7-10), whereas median VAS scores after 3, 6 and 12 months were 5 (range 1-7), 3 (range 0-6) and 1 (range 0-6), respectively (Fig. 2). Differences in median values before LDRT and over this time were statistically significant as shown in Table 2.

We did not find significant differences in the final VAS score for any of the factors analyzed, including gender, location, side, total radiation dose, pre-treatment VAS score or the number of radiation courses (Table 3).

		N (%)
Sex	Male	11 (35)
	Female	20 (65)
Age	Me = 64 years old [48-72]	
Location	Calcaneodynia	17 (55)
	Tendonitis	11 (35)
		Extensor digitorum: 4 (13)
		Tibialis anterior: 4 (13)
		Tibialis posterior: 3 (12)
	Osteoarthritis	3 (10)
Side	Right	15 (48)
	Left	16 (52)

Table 1: Population characteristics (N = 31).

	VAS before RT	VAS 3 months	VAS 6 months	VAS 12 months
Median	9 (7-10)	5 (1-7)	3 (0-6)	1 (0-6)
Comparison test (Wilcoxon)		p<0.001	p<0.001	p<0.001

Table 2: Comparative analysis of variations in median pain intensity (VAS) before and after LDRT.

6 Gy vs 3 Gy total LDRT dose	71% vs 29% p = 0.98
Female vs male	35% vs 65% p = 0.28
Left vs right	52% vs 48% p = 0.43
Pre-treatment VAS score >6 vs <6	82% vs 18% p = 0.23
One course vs two courses LDRT	19% vs 81% p = 0.48

Table 3: Univariate analysis of pain relief after LDRT.

Discussion

Foot pain syndromes related to alterations in the plantar fascia of the heel, in the Achilles tendon or surrounding structures or with ailments in the tendons and associated bursae of the different muscles that regulate the mobility of the feet and toes, mainly affecting the older population, represent a tough challenge for treatment [3-5].

The efficacy and safety of LDRT for the symptomatic treatment of OA refractory to other treatments is supported by numerous pre-clinical and clinical studies demonstrating its anti-inflammatory capacity. The anti-inflammatory efficacy of low-dose radiotherapy (0.5-1.5 Gy) is due to known radiobiological mechanisms, including inhibition of the interactions between leukocytes and endothelial cells, a decrease in the production of endothelial adhesion molecules, a decrease in inflammatory mediators and reduced expression of pro-inflammatory cytokines. Low-dose irradiation also results in a decrease in levels of NO synthetase (iNOS), L- and E- selectins, Reactive Oxygen Species (ROS), Tumor Necrosis Factor alpha (TNF- α) and the secretion of IL-beta 1 in conjunction with an increase in the production and expression of anti-inflammatory cytokines, such as the Transforming Growth Factor of anti-inflammatory cytokine β 1 (TGF- β 1) and of mediators of apoptosis, such as nuclear factor kappa-beta (NF- κ B), leading to a local anti-inflammatory environment [16-17]. LDRT using both orthovoltage and megavoltage techniques achieves good rates of symptomatic response with pain relief, a reduction in the daily need for analgesic intake and an improvement in functionality, constituting an attractive option. Numerous publications support this therapeutic alternative, especially in elderly patients with degenerative osteoarticular disorders, although it can also be useful in younger people who subject their lower limbs and feet to extreme stress, as in the case of the athlete Usain Bolt, who underwent LDRT for a tendon injury in his right foot, as can be

seen in his biographical documentary *I am Bolt* and with the particularity that the analgesic effects of low-dose radiotherapy are late-onset with significantly greater efficacy compared to immediate response [13,18-20].

Several prospective and retrospective trials have evidenced the efficacy and safety of LDRT for symptomatic relief of musculoskeletal inflammatory/degenerative disorders. Recently, two randomized studies did not show any benefit from LDRT, although some limitations, such as the short follow-up of only 3 months, the absence of re-treatments, the limited irradiation volumes or the poor selection of patients, could have contributed to the lack of apparent benefit reported by the authors [21-23]. Table 3 summarizes results published since the year 2000 using LDRT for foot and ankle pain syndromes [19,20,24-45]. Overall, 9,735 patients with a median age of 69 years and diagnoses of painful foot musculoskeletal disorders received LDRT for anti-inflammatory and analgesic purposes. Most of the 24 studies were a retrospective [14] or prospective analysis but 6 studies were randomized, 5 of them comparing two different radiation treatment schedules and 1 comparing LDRT with local injection [4]. Most studies focused on patients diagnosed with calcaneodynia or plantar fasciitis, while 6 studies analyzed the results in patients with achillodynia, tendinopathies or tarsal and metatarsal osteoarthritis [17]. With a median follow-up, in those studies where it was thus specified, of 21 months (3-54 months), 4 out of 5 patients treated reported significant pain relief. The total doses administered ranged from 0.6 Gy to 8 Gy (median 6 Gy) and dose per fraction varied from 0.25 Gy to 4 Gy (median 1 Gy). The median number of patients who required more than one course of irradiation was 49.5%. The results of 5 of the randomized studies showed that there were no significant differences in the efficacy of administering total doses of 3 Gy in fractions of 0.5 Gy vs 6 Gy in fractions of 1 Gy, but that a final dose of 0.6 Gy in fractions of 0.1 Gy was significantly inferior for pain relief compared to higher doses. The study by Canylmalz et al. comparing LDRT (6 x 1 Gy) versus local corticosteroid and anesthetics injections in patients with plantar fasciitis demonstrated significantly greater pain relief in the arm randomized to LDRT [36]. None of these 24 published studies observed acute or late complications attributable to LDRT. Our experience compares well with the data reported in the literature, achieving an improvement in functionality according to the VPS in 74% and pain relief in 87% of patients, with a reduction in the VAS value that was even more marked in patients with longer follow-up, although 84% of patients required more than one course of treatment. We did not observe any differences in the final results regarding total dose (6 Gy vs 3 Gy) or in pain intensity at attendance (VAS >6 vs <6). As in the experiences published, we did not observe any adverse effects of LDRT either acutely during treatment or in subsequent follow-up.

We are aware of some strengths and weaknesses in our study. The low number of patients and the short follow-up, in many cases related to the characteristics and circumstances of the patients treated, could be masking the real magnitude of the benefit observed. Likewise, the absence of a control arm with exclusively conventional treatment does not allow a direct

comparison of efficacy, although the clinical results support the utility of LDRT. On the other hand, all patients were treated following the same quality standards applied to cancer radiotherapy and evaluated by the same two physicians (BA and AM) to minimize possible bias.

Conclusion

Foot pain is one of the leading causes of functional disability and poor quality of life. Greater life expectancy, obesity and an increase in sports activities are all factors raising its prevalence. Despite being a benign pathology, its treatment represents a tough challenge, with no definitive measures to alleviate it. LDRT and its well-known anti-inflammatory properties have been associated with acceptable rates of pain relief in different musculoskeletal inflammatory and degenerative disorders. Our experience treating these foot-related conditions confirms the feasibility and high tolerance of LDRT. However, well-designed randomized trials with longer follow-up are desirable to definitively confirm the results observed.

Acknowledgement

To Alyson Kim Turner, for reviewing, revising and editing this manuscript for English Language grammar and syntax.

Ethical Approval and Informed Consent

All procedures performed were in accordance with the ethical standards of the institutional research committee and with the Helsinki declaration and informed consent was obtained from all individuals participants included in this study.

Authors' Contributions

BA, AM: study design, data analysis, manuscript writing. All the authors contributed to manuscript writing, editing and reviewing, reviewed previous drafts and provided comments and contributed to the final draft.

Conflict of Interest

All the authors declare no conflict of interest regarding any aspect of the manuscript.

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DOI: <https://doi.org/10.46889/JOSR.2022.3304>

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