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Original Article

Radiotherapy for Ledderhose disease: Results of the LedRad-study, a prospective multicentre randomised double-blind phase 3 trial ☆

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ABSTRACT

Background and purpose: Radiotherapy is considered a treatment option for Ledderhose disease. However, its benefits have never been confirmed in a randomised controlled trial. Therefore, the LedRad-study was conducted.

Materials and methods: The LedRad-study is a prospective multicentre randomised double-blind phase three trial. Patients were randomised to sham-radiotherapy (placebo) or radiotherapy. The primary endpoint was pain reduction at 12 months after treatment, measured with the Numeric Rating Scale (NRS). Secondary endpoints were pain reduction at 6 and 18 months after treatment, quality of life (QoL), walking abilities and toxicity.

Results: A total of 84 patients were enrolled. At 12 and 18 months, patients in the radiotherapy group had a lower mean pain score compared to patients in the sham-radiotherapy group (2.5 versus 3.6 ($p = 0.03$) and 2.1 versus 3.4 ($p = 0.008$), respectively). Pain relief at 12 months was 74% in the radiotherapy group and 56% in the sham-radiotherapy group ($p = 0.002$). Multilevel testing for QoL scores showed higher QoL scores in the radiotherapy group compared to the sham-radiotherapy group ($p < 0.001$). Moreover, patients in the radiotherapy group had a higher mean walking speed and step rate with barefoot speed walking ($p = 0.02$). Erythema, skin dryness, burning sensations and increased pain were the most frequently reported side effects. These side effects were generally graded as mild (95%) and the majority (87%) were resolved at 18 months follow-up.

Conclusion: Radiotherapy for symptomatic Ledderhose disease is an effective treatment resulting in a significant pain reduction, improvement of QoL scores and bare feet walking abilities, in comparison to sham-radiotherapy.

Ledderhose disease, also known as plantar fibromatosis, is a benign hyperproliferative disease of the plantar fascia of the feet. [1] Clinically, patients develop nodules and/or cords in the soles of their feet, usually located on the medial and central bands of the plantar fascia. [2] Ledderhose disease can be painful and may negatively affect daily activities and quality of life. [3] Ledderhose disease is associated with Dupuytren' s disease in the hand and Peyronie's disease in the penis. [3–6] The aetiology and prevalence of Ledderhose disease is not precisely known. [5–6].

At present, there is no evidence based treatment guideline for symptomatic Ledderhose disease. Several conservative options are offered to manage symptoms and to support and/or improve functional outcome. The scientific evidence for these options varies widely and some are based solely on expert opinion. [5–6] In the early phase of this disease, orthotics are often used to relieve pressure in the affected area and to support the feet during daily activities. [6] If symptoms increase, possible treatment options include intralesional cortisone injections, extracorporeal shock wave ther-

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apy, surgery (limited fasciectomy) and radiotherapy. [5–7] Currently, surgery is not offered routinely, since the risk of recurrence is high and may result in complications such as painful scars and nerve problems. [5–6,8].

In recent decades, radiotherapy has emerged as a treatment option for Ledderhose disease. Between 2003 and 2022 the effect of radiotherapy as primary treatment for patients with Ledderhose disease has been investigated in four retrospective studies (Table S1). [9–12] These studies showed reduction of pain with minimal toxicities. However, the added value of radiotherapy has never been investigated in a randomised controlled trial. Therefore, the LedRad-study was designed to test the hypothesis that radiotherapy is an effective treatment for patients with symptomatic Ledderhose disease.

Materials and methods

Study design

The LedRad-study is a prospective multicentre randomised double-blind phase III trial investigating the efficacy of radiotherapy in patients with symptomatic Ledderhose disease. Patients were randomly assigned to receive either sham-radiotherapy (arm 1) or radiotherapy (arm 2) (Fig. 1).

Approval for the study was obtained from the central institutional ethical review-board at the University Medical Center of Groningen (UMCG; METc 2017/397). The study was conducted in four different centres in the Netherlands under the auspices of the institutional review board of each participating centre. Ethical Principles of Good Clinical Practices were followed. Data collection was performed by the local radiation oncologists and data management, and data analysis by the coordinating investigators at the UMCG.

Study population

Inclusion criteria were:

- Age $\geq$ 18 years
- WHO performance score 0–2
- Pain score related to Ledderhose disease $\geq$ 2
- Good understanding of the Dutch language
- Ability and willingness to attend follow-up visits and complete several questionnaires in Dutch

Exclusion criteria were:

- Previous treatment with radiotherapy and/or surgery for Ledderhose disease in the affected foot
- Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol or follow-up schedule
- Being unable to lie in a prone position for at least fifteen minutes
- Pregnancy at entry or planning to become pregnant within six months

Written informed consent was received from each patient prior to enrolment.

Randomisation and masking

ALEA Clinical (FormsVision Company, the Netherlands) was used for the randomisation. Stratification factors were age (<40 years, between 40 and 60 years and $\geq$ 60 years) and gender (male versus female). Pocock's minimization strategy was used to ensure adequate balancing of factors in both arms. Deblinding was performed at 18 months follow-up (FU).

Treatment

The radiation field was delineated by marking all Ledderhose nodules and/or cords on the sole of each affected foot with a margin of 2.5 cm in proximal–distal direction and a margin of 1.5 cm in medial–lateral direction. A custom lead mould of at least 10 mm thick was made for each patient. The purpose of this lead mould was to only irradiate the Ledderhose nodule(s) with the direct surrounding skin by shielding the remaining part of the foot.

Radiotherapy was administered in two separate courses of five daily fractions of 3 Gy each to a total dose of 30 Gy. Both courses started on a Monday and the interval between the two courses was 10 weeks. Depending on the nodule thickness, either 8 MeV electrons ($\leq$1 cm) or 10 MeV electrons (>1 cm) were used.

Patients assigned to arm 1 were subjected to the same preparation- and treatment procedures as patients assigned to arm 2. However, during sham-treatment, patients did not receive actual radiation, but heard a sound-recording of the linear accelerator (radiation machine/device) mimicking the radiation treatment.

Endpoints and assessments

Evaluation and study assessments were performed prior to treatment (baseline), at the start of the second treatment course, and at 6, 12 and 18 months FU.

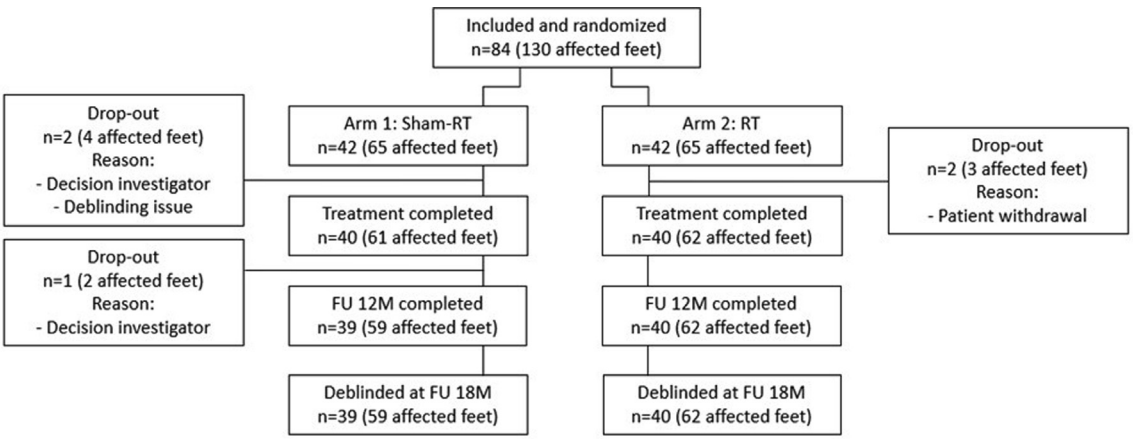

Fig. 1. Flowchart of patients in the LedRad-study. Abbreviations: FU: follow-up; M: months; RT: radiotherapy.

The primary endpoint of the study was pain reduction, relative to baseline, at 12 months FU, measured with the Numeric Rating Scale (NRS). Secondary endpoints were pain reduction at 6 and 18 months FU; quality of life, measured with the EURO-QoL-5D-5L questionnaire and visual analogue scale; walking speed and step rate, measured with the 10-meter straight line walk test; and toxicity of radiotherapy, measured as adverse events (AEs).

The NRS is an 11-point scale ranging from 0 (no pain) to 10 (excruciating pain). [13] Pain scores from Ledderhose disease in the affected feet were obtained at all time points. Mean pain scores of the treated feet in the two treatment arms were compared. Additionally, pain response categories were evaluated based on the difference in pain score between baseline and during FU. A complete pain response was defined as a pain score of 0 points. A partial pain response was defined as a decrease in pain score of at least two points combined with a remaining pain score $\geq$ 1 point. Stable pain was defined as a one or zero pain score point change in either direction. Progressive pain was defined as an increase in pain score of at least two points.

The EuroQoL-5D-5L instrument comprises a short descriptive system questionnaire and a visual analogue scale (EQ VAS). [14] The questionnaire provides a simple descriptive profile of a respondent's health state, based on the societal perspective (i.e., what the general population thinks about the value of the health state). The descriptive questions of the EQ–5D cover five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The results of the questionnaire can be used to describe health states as index values, which reflect how good or bad a health state is according to the preferences of the general population, expressed on a scale from 0 to 1. The EQ VAS visual analogue scale provides information about the patient's perspective on their current overall health on a scale ranging from 0 to 100. [15] Higher scores indicate a better quality of life. The scores were compared with the EQ-5D-5L reference values from the Dutch general population. [16].

During the 10-meter straight line walk test patients had to walk wearing their own shoes and barefoot at two speed levels: at patient's own comfortable speed and speed walking. This test measured the impact of Ledderhose disease on walking speed and step rate. [17] Barefoot walking was added to the study protocol after 15 patients were included.

The number of AEs was reported from baseline up to and including the 18 months FU. The following items were recorded for each AE: grading (mild, moderate, severe, life-threatening, death related to AE), relation to treatment (unrelated, unlikely, possible, probable, definite), seriousness (yes, no) and if the AE was ongoing. Scoring for AEs was done before the deblinding at 18 months. All AEs were divided into categories and the categories with the most AEs were analysed in more depth.

Sample size calculation and statistical analysis

Enrolment of 80 patients was required to detect an absolute difference in pain response (complete and partial) of 35% at 12 months FU (accounting for a 25% placebo effect and 60% response in the radiotherapy arm), with a 90% power and a type I error of 5%.

Analyses were performed according to the intention-to-treat principle and included all randomised patients. Data were analysed using the statistical package SPSS for Windows 23.0 (SPSS Inc, Chicago, IL, USA). Continuous endpoints at each time point were tested on statistical significance using the Mann-Whitney U test. Categorical endpoints were tested on statistical significance using the Chi-Square Tests. Multilevel testing was performed to test changes over time considering the following items: patient, feet, and time-points. All reported p-values were two-sided with 0.05 as threshold for statistical significance.

Results

From January 2018 to October 2019, 84 patients (27 men and 57 women) were enrolled. Mean age at baseline was 55.8 years (SD: 9.4 years). Baseline characteristics are shown in Table 1. A total of 130 feet (25 left sided, 13 right sided and 46 patients with both feet) were treated. 65 Feet (in 42 patients) were allocated to arm 1 and 65 feet (in 42 patients) to arm 2. Five patients dropped-out prior to completing the 12 months FU (Fig. 1).

The results regarding pain score and pain response are shown in Table 2 and Fig. 2, respectively. At 12 months FU, the mean pain score in arm 2 was significantly lower compared to that in arm 1 (2.5 vs. 3.6; p = 0.03). The pain response rate (cumulative complete- and partial pain response) at this time point was 74% in arm 2 and 56% in arm 1. The overall pain response, including all four pain response categories, differed significantly between the two arms (p = 0.002). At 6 months FU, the mean pain scores and pain response rates in both arms were comparable. At 18 months FU, the mean pain score in arm 2 was still lower than the mean pain score in arm 1 (2.1 vs. 3.4; p = 0.008) and the pain response rate was comparable to the rate at 12 months FU; 77% in arm 2 versus 54% in arm 1. The overall pain response differed significantly between the two arms (p = 0.002). Multilevel testing showed a significantly higher overall pain reduction for patients in arm 2 compared to patients in arm 1 (p = 0.03).

For the EQ-5D index value scores at baseline and at 6 months FU, the mean score of patients in arm 1 improved from 0.71 to 0.77 and from 0.63 to 0.82 for patients in arm 2. At 12 months FU, the mean score of patients in arm 1 remained stable (0.77), relative to the score at 6 months FU, and further improved to 0.85 for

Table 1
Baseline characteristics of the patients included in the LedRad-study.

Patient characteristics	Arm 1: sham-radiotherapy (n = 42)	Arm 2: radiotherapy (n = 42)
Age at inclusion ± SD (yrs.)	55.8 ± 8.6	55.9 ± 10.2
Gender	14	13
Male	(33%)28	(31%)29
Female	(67%)	(69%)
Age category	3	2
< 40 years	(7%)25	(5%)26
40–60 years	(60%)14	(62%)14
≥ 60 years	(33%)	(33%)
WHO-performance	34	34
status	(81%)8	(81%)8
0	(19%)	(19%)
1		
Affected foot	12	13
Left	(28%)7	(30%)6
Right	(17%)23	(15%)23
Both	(55%)	(55%)
Number of nodes left	7	8
foot*	(20%)14	(22%)15
0	(40%)6	(42%)8
1	(17%)7	(22%)4
2	(20%)1	(11%)1
3	(3%)	(3%)
4		
Number of nodes		
right foot*	6	6
0	(20%)13	(21%)16
1	(44%)7	(55%)6
2	(23%)2	(21%)1
3	(7%)1	(3%)0
4	(3%)1	(0%)0
8	(3%)	(0%)

*Based on physical examination.
Abbreviations: SD: standard deviation, yrs.: years.

Table 2
Mean pain scores of the treated feet of patients, measured with the Numeric Rating Scale, and mean walking speed (m/sec) and step rate (steps/sec) during barefoot speed walking for both treatment arms (Arm 1: sham-radiotherapy; Arm 2: radiotherapy).

	Arm 1 (SD; number of feet)	Arm 2 (SD; number of feet)	p-value	Arm 1 Arm 2 (SD; n) (SD; n)	p-value	Arm 1 Arm 2 (SD; n) (SD; n)	p-value
	Mean pain score	**Mean pain score**		**Walking speed Walking speed**		**Step rate Step rate**	
Baseline	5.6 (±2.1; 65)	5.8 (±2.1; 65)	0.49	1.56 (±0.31; 35) 1.53 (±0.27; 34)	0.71	2.24 (±0.58; 35) 2.18 (±0.26; 34)	0.72
At 6 months	3.4 (±2.5; 61)	3.2 (±2.6; 62)	0.55	1.59 (±0.26; 31) 1.61 (±0.27; 28)	0.99	2.15 (±0.23; 31) 2.25 (±0.27; 28)	0.13
At 12 months	3.6 (±3.0; 59)	2.5 (±2.5; 62)	0.03	1.61 (±0.26; 31) 1.65 (±0.23; 28)	0.51	2.18 (±0.21; 31) 2.28 (±0.28; 28)	0.12
At 18 months	3.4 (±2.8; 59)	2.1 (±2.3; 62)	0.008	1.58 (±0.30; 32) 1.65 (±0.26; 32)	0.36	2.12 (±0.22; 32) 2.25 (±0.26; 32)	0.10

Abbreviations: n: number of patients; SD: standard deviation.

patients in arm 2. At 18 months FU, the mean score remained stable for both arms, relative to scores at 12 months FU: 0.76 for arm 1 and 0.84 for arm 2. The reference value of the age-matched Dutch population for the EQ-5D index value was 0.86 (Fig. 3). The mean scores at baseline and at 6 months FU for the EQ VAS score improved from 71.9 to 74.8 for patients in arm 1 and from 67.8 to 74.8 for patients in arm 2. At 12 months FU, the mean score remained stable (74.0), relative to score at 6 months FU, for patients in arm 1 and further improved to 78.8 for patients in arm 2. At 18 months FU, the scores remained stable for both arms, relative to scores at 12 months FU: 73.8 for arm 1 and 76.8 for arm 2. The reference value of the Dutch population for the EQ VAS score was 80.6. Overall improvement for both scores was more pronounced among patients in arm 2 compared to those in arm 1 ($p < 0.001$ and $p = 0.04$, respectively).

No differences between the two treatment arms were found for walking either on shoes or barefoot at a comfortable speed, at any of the FU time points. Results for barefoot speed walking are shown in Table 2. Multilevel testing showed a higher mean walking speed and higher mean step rate for barefoot speed walking for patients in arm 2 compared to patients in arm 1 ($p = 0.02$ for both variables).

Erythema, skin dryness, burning sensations and increased pain were the four most frequently reported AEs (n = 98; Table S2). Five of those (5%) were graded as moderate (grade II) and all others as mild (95%; grade I). Relation to treatment was probable for 13 AEs (13%), possible for 84 AEs (86%) and unlikely for one AE (1%). At the 18 months FU six patients had ongoing erythema and seven patients ongoing skin dryness. In all patients, burning sensations and increased pain were resolved.

Regarding AEs, the only difference between the two treatment arms was the scoring of relation to treatment for erythema ($p = 0.003$). In arm 1 one erythema was scored as unlikely related to treatment and nine as possible related. In arm 2 five erythema were scored as possible related to treatment and ten as probable related.

Four patients experienced a serious adverse event (SAE; n = 3 in arm 1 and n = 1 in arm 2); anaphylactic reaction to MRI contrast agent, hospitalisation after fall from stairs (unrelated to Ledderhose disease), ileus due to diverticulitis (hospitalisation and surgery needed) and collapse (observational hospitalisation). These SAEs were all considered unrelated to the study treatment.

Discussion

This is the first RCT assessing the effect of radiotherapy for symptomatic Ledderhose disease. Our results showed that radiotherapy is an effective treatment modality with only mild toxicities.

At 12 months FU, radiotherapy resulted in a significantly lower mean pain score compared to sham-radiotherapy. This significant difference sustained at 18 months, with further decrease in the mean pain score for patients in the radiotherapy arm. In a retrospective study, with a median follow-up > 4 years, the mean pain score decreased after radiotherapy from 5.7 to 1.7 ($p < 0.001$). [12] This mean pain score is lower compared to the pain score found in our study at 18 months FU. This might indicate that the pain score can still further improve over time. In other retrospective studies, the reported range of pain response rates after radiotherapy (60–81%) are in line with the pain response rates in the radiotherapy arm found in our study (74% at 12 and 77% at 18 months FU). [9–11].

At 6 months FU no differences in mean pain scores between the two arms were found and a high and unexpected pain response was found in the sham-radiotherapy arm. There are several factors

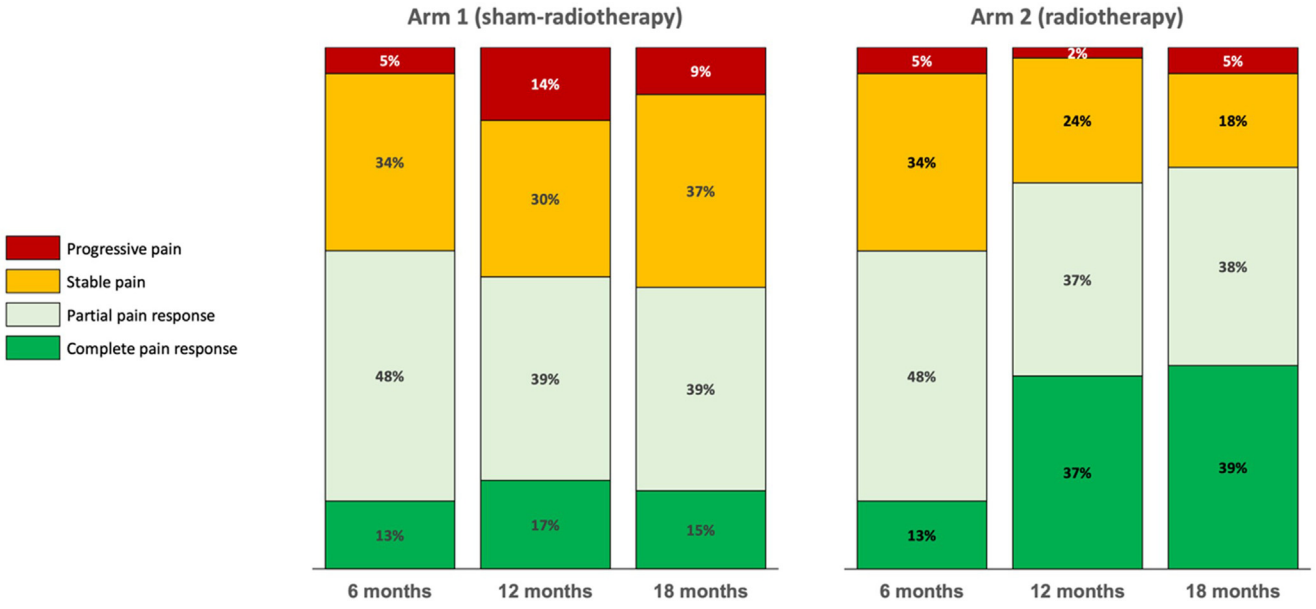

Fig. 2. Pain responses (%) of the treated feet at follow-up, per group and timepoint. Pain responses are based on the differences in pain score between baseline and the follow-up visit.

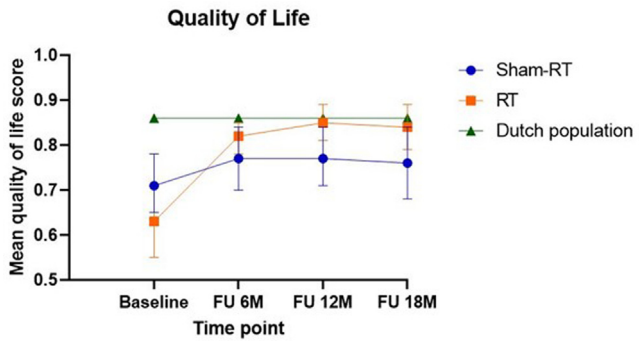

Fig. 3. Mean QoL-scores (EQ-5D index value scores), including 95% CI for the Mean, for both treatment arms at baseline, 6, 12 and 18 months after end of (sham)-radiotherapy. The horizontal green line represents the reference value from the age-matched Dutch population. Abbreviations: CI: confidence interval; FU: follow-up; M: months; RT: radiotherapy.

which might contribute to high responses after placebo/sham-treatment. Patient treatment expectancy is considered a major determinant of the treatment response. [18] Other factors can be fluctuations in symptoms, response to concurrent treatments, the natural course of the disease, or response bias from reporting of subjective symptoms. [19–20].

Quality of life scores in our study increased significantly after radiotherapy compared to sham-radiotherapy. The mean scores at 12 and 18 months FU were comparable to the mean scores of the age-matched general Dutch population. This indicates that the intensity of health-related problems after radiotherapy is low and at the level of the general population. Comparable results were found in the retrospective study with a median follow-up > 4 years. [12] This might indicate that the high quality of life scores sustain after a longer follow-up.

A significant improvement of barefoot speed walking, the most demanding walking situation for patients with Ledderhose disease, was found after radiotherapy. Although improvements in walking abilities were not studied in the same way, improvement in walking was also reported in one of the retrospective studies. [10] In this study, when looking at gait (no limitations, limitations after > 1 km, limitations after $\leq$ 1 km and complete limitation), 73% of patients reported improvement after radiotherapy and 60% of patients had no limitations any longer. Prior to radiotherapy all patients had limitations.

Two mild toxicities from radiotherapy were previously reported: erythema and skin dryness. In general, erythema was reported as acute toxicity and skin dryness was reported both as acute- and late toxicity. [9–12] In our study, increased pain and burning sensations were also frequently reported as toxicities. In general, these toxicities were graded as mild and resolved spontaneously. At 18 months FU, some patients (n = 13) still had mild erythema and/or mild skin dryness, however, without any impact on quality of life.

After radiotherapy, there is a risk of radiation-induced malignancy. As there is no report in the literature of a radiation-induced malignancy after radiotherapy for Ledderhose disease, this is considered a theoretical drawback. Based on experience of other disease sites, the lifetime risk of a radiation-induced malignancy is estimated to be 0.02%. [21–22] Another possible toxicity over time from radiotherapy is fibrosis. [23] Radiation dose and intrinsic radiosensitivity are the main risk factors for this toxicity. [24] Fibrosis was not found within the 18 months follow-up period in our study and was not reported in the retrospective studies. [9–12] The follow-up periods in all studies were short and compared to cancer patients treated with radiotherapy, the radiation dose given for Ledderhose disease is relatively low. For both radiation-induced malignancy and fibrosis a life-long follow-up and patient education is suggested.

Information on the radiobiological mechanism behind radiotherapy for Ledderhose disease is limited, and mainly based on the treatment for other benign conditions, like Dupuytren's disease. It has been suggested that the effect of radiotherapy in this disease is predominantly based on inhibition of fibroblast and myofibroblast proliferation, eventually resulting in symptoms and progression of nodules. [25] It should be noted that the optimal dose and fractionation for Ledderhose disease remains to be determined. In retrospective studies, the total dose ranged from 21 – 32 Gy, using different fractionation schedules. [9–12] In the current study, the total dose of 30 Gy, delivered in two portions of 5x3 Gy, was chosen as this was the most commonly schedule

in Ledderhose disease. Further research on the radiobiological mechanisms as well as the most optimal dose and fractionation is warranted.

Our study has several strengths: the multicentre randomised double-blind placebo-controlled design with stratification for age and gender, the use of validated outcome measurements, the use of one treatment modality (electrons) and the well-defined homogeneous patient population.

A limitation of our study is that no direct knowledge about the natural course of the disease and fluctuation of symptoms was gained. A third arm including a watch-and-wait policy might have provided this information. There are also two limitations with regard to clinical applicability. First, from this study no conclusions can be drawn with regard to the effectivity of radiotherapy when orthovolt is used as treatment modality. However, retrospective studies showed that treatment outcomes achieved with orthovolt were similar to the results from treatment with electrons. For this reason, we believe that in clinical practice both treatment modalities can be used, based on preferences and site availability. Second, in our study previous surgery for Ledderhose disease was an exclusion criteria and therefore it is uncertain whether radiotherapy will have the same effect on previously operated patients who experience a recurrence.

In conclusion, compared to sham-radiotherapy, radiotherapy for symptomatic Ledderhose disease is an effective treatment, resulting in a significant pain reduction, improvement of QoL scores and bare feet walking abilities, without increased toxicity.

Data sharing statement

The LedRad-study can be found in the Groningen Data Catalogue: https://doi.org/10.34760/61f945bf5d8b7.

The principal investigator can be contacted for data requests (restricted access).

Trial registration numbers

NCT03507010, NL62429.042.17.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: P.M.N. Werker was a SERB member and is currently a DMC member of Fidia Ltd, Milan, Italy.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.109718.

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