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Published in:
Radiotherapy and Oncology

DOI:
[10.1016/j.radonc.2022.01.031](https://doi.org/10.1016/j.radonc.2022.01.031)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2022

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

de Haan, A., van Nes, J. G. H., Werker, P. M. N., Langendijk, J. A., & Steenbakkens, R. J. H. M. (2022). Radiotherapy for patients with ledderhose disease: long-term effects, side effects and patient-rated outcome. *Radiotherapy and Oncology*, 168, 83-88. <https://doi.org/10.1016/j.radonc.2022.01.031>

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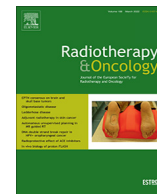
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Original Article

Radiotherapy for patients with Ledderhose disease: Long-term effects, side effects and patient-rated outcome



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ARTICLE INFO

Article history:

Received 19 November 2021
Received in revised form 18 January 2022
Accepted 20 January 2022
Available online 29 January 2022

Keywords:

Radiotherapy
Ledderhose disease
Plantar fibromatosis
Benign disease

ABSTRACT

Background: The purpose of this study was to investigate the long-term effects of radiotherapy for patients with Ledderhose disease.

Methods: Questionnaires were sent to all patients with Ledderhose disease who had been treated with radiotherapy at our centre between 2008 and 2017 and who consented to participate. Radiotherapy was performed with orthovolt or electrons in two separate courses of five daily fractions of 3 Gy. The questionnaires addressed items such as pain from Ledderhose disease (Brief Pain Inventory), quality of life (EURO-QOL-5D-5L), long-term side effects, and patients' levels of satisfaction with the effect of treatment. Descriptive statistics and non-parametric tests were used to analyse the results.

Results: A total of 102 feet were irradiated in 67 patients (28 men, 39 women). Radiotherapy resulted in significant pain reduction: the mean pain score prior to radiotherapy, collected retrospectively, was 5.7 and 1.7 at time of assessment (p -value < 0.001). The following pain response scores were reported: progressive pain (0%), no change (22%; 22 feet), partial pain response (37%; 38 feet) and complete pain response (absence of pain) (41%; 42 feet). Seventy-eight percent of patients were satisfied with the treatment effect and 57% did not consider radiotherapy burdensome. The scores for societal perspective (0.856) and patients' perspective on quality of life (82.3) were each comparable to the reference values from the Dutch population in the same age category (0.857 and 80.6, respectively). The most commonly reported residual long-term side effect was dryness of the skin ($n = 10$; 15%).

Conclusion: Radiotherapy for Ledderhose disease results in long-term pain reduction in the majority of patients and has limited side effects. The treatment is well tolerated, patients feel satisfied, and quality of life is comparable to the reference population.

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Ledderhose disease, also called plantar fibromatosis, is a benign hyperproliferative disease of the plantar fascia and was first described by Georg Ledderhose in 1897 [1]. The disease is characterized by the formation of nodules and/or cords under the sole of the foot, often located on the medial and central bands of the plantar fascia [2–4]. These nodules can be asymptomatic, though patients may experience some discomfort [4]. The discomfort can vary in intensity from slight tenderness to severe pain and can appear during activity as well as while at rest. With disease progression, the symptoms can lead to functional disability and may have a negative impact on quality of life. Ledderhose disease is

associated with Dupuytren's- and Peyronie's disease, but the exact etiology and prevalence are not yet understood [5–8].

Several treatment options for Ledderhose disease are offered, such as surgery, radiotherapy, extracorporeal shock wave therapy, cortisone injections, orthotics and shoe modifications. However, the level of scientific evidence for efficacy of these options varies [2–4,8]. Surgery might be an effective option, especially for severe cases, but it cannot prevent the recurrence and often leaves painful scars and other complications [8]. Only three clinical retrospective studies have investigated the efficacy of radiotherapy for Ledderhose disease (Table 1), all with relatively short term follow up [9–11]. In the first two studies, 33 and 36 feet were irradiated in 24 and 25 patients respectively. After a median follow-up of 23 and 38 months, no disease progression was seen and pain reduction or disappearance in $\geq 60\%$ of patients was observed. Minimal side effects were reported, such as erythema and skin dryness. The third study evaluated the effect of electron radiotherapy for

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Table 1

The four retrospective studies performed investigating the effect of radiotherapy in patients with Ledderhose disease.

	Number	RT	Radiation Schedule	Median FU mths	Response	Toxicity
Seegenschmiedt 2003 [4]	25 patients 36 feet	Orthovolt	5x3 Gy, 8–12 wks split, 5x3 Gy	38	0% PD or surgery 44% decrease in number or size of nodules 54% decrease in number or length of cords 50% improved gait 60% reduced or no pain 50% patient satisfaction on VAS	5 nodules: slight erythema (CTC 1) during or within 3 months from RT 11% skin dryness > 1 year after RT
Heyd 2010 [5]	24 patients 33 feet	21 Orthovolt (28 feet) 3 Electrons 5–9 MeV (5 feet)	5x3Gy, 6 wks split, 5x3Gy (n = 20, 28 feet) or 2x4Gy, 4 wks split, 2x4Gy 4 wks split, until 24–32 Gy (n = 4, 5 feet)	23	Change in nodules: • 33% CR • 55% PR • 12% stable • 0% progressive 68% pain remission 73% improved gait 92% patient satisfaction	25% slight erythema (RTOG grade 1) 13% soft tissue fibrosis and skin dryness (RTOG grade 2) No RTOG grade > 2
Schuster 2015 [6]	33 patients 45 hands 15 feet	Electrons 6–12 MeV	7x3Gy or 5x3Gy, 6–8 wks split, 5x3Gy	31	81% improved pain with strain 70% improved pain in rest 81% relieved itch/burn sensations 95% stabilized or improved site pressure sensation 94% patient satisfaction	<u>Acute toxicity</u> 20% erythema 13% dryness <u>Late toxicity</u> 25% dryness No grade 2 or more
de Haan 2021	67 patients 102 feet	9 Orthovolt (12 feet) 58 Electrons 8–10 MeV (90 feet)	5x3Gy, around 10 wks split, 5x3Gy	49	Pain response: • 41% CPR • 37% PPR • 22% SP • 0% PP 78% patient satisfaction	15% skin dryness 3% erythema

Abbreviations: RT: radiotherapy; FU: follow-up; mths: months; wks: weeks; PD: progressive disease; CR: complete remission; PR: partial remission; CPR: complete pain response; PPR: partial pain response; SP: stable pain; PP: progressive pain.

Ledderhose as well as Dupuytren’s disease. A total of 33 patients were included (60 hand/feet). After a median follow-up of 31 months, 80% of patients experienced a decrease in complaints and 94% reported an overall success with radiotherapy, defined as a report from the patient whether they felt the treatment had been successful or not. No grade 2 side-effects were reported in this study.

However, less is known about the long-term outcome of radiotherapy for Ledderhose disease, especially from patients’ perspective. Therefore, we conducted a cross-sectional study to investigate the long-term effects of radiotherapy in a cohort of patients treated for Ledderhose disease.

Methods

Patients

The patient population was composed of a consecutive series of all patients with Ledderhose disease who were treated with radiotherapy at the University Medical Centre Groningen between 2008 and 2017. Only patients who were at minimum 2 years following completion of radiotherapy were approached by mail in 2019 to participate in this cross-sectional study (NCT04229147). Approval for the study was obtained from the UMCG institutional ethical review-board (METc 2019/203) and all patients provided written informed consent.

Radiotherapy

Radiotherapy was performed using orthovolt (150 kV) or electrons. Radiation with electrons was done with 8 or 10 MeV,

depending on nodule thickness. Two separate courses of five daily fractions of 3 Gy each were administered to a total dose of 30 Gy. The interval between the two courses was around 10 weeks.

Patients were positioned prone with their feet in knee support with the plantar surface facing up. The Ledderhose nodules and radiation field were marked on the soles of the feet by the radiation-oncologist. The following margins were used: 2.5 cm in distal-proximal direction and 1.5 cm in lateral-medial direction (Fig. 1). For electrons, an individually custom lead mould of at least 10 mm thick was made to irradiate only the target area and to protect the rest of the body for receiving radiation.

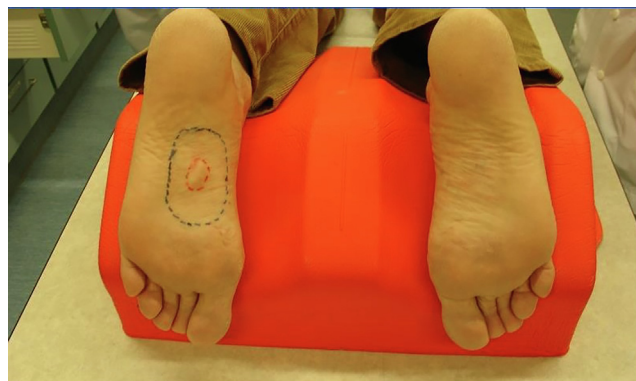


Fig. 1. Marked Ledderhose nodule (red line) and radiation field (blue line) on the affected sole of the left foot. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Data collection

Data collection started after receipt of a completed informed consent letter which was mailed to the patients together with a patient information leaflet. Patient and treatment characteristics were collected through MOSAIQ®, the patient management information system of Elekta, used at our department. Information on pain from Ledderhose disease, quality of life, patients' levels of satisfaction and side effects of radiotherapy was collected using questionnaires that were mailed to the patients and then filled out and returned by the patients.

Questionnaires

The following questionnaires were used: Brief Pain Inventory (BPI), EURO-QOL-5D-5L and a self-developed questionnaire, named the LedRad Long Term Effects (LedRad-LTE) questionnaire.

The validated BPI was used to assess how much pain from Ledderhose disease interfered with seven daily activities - including general activity, mood, walking, work, relations with others, sleep and enjoyment of life - during the 24-hours prior to completing the questionnaires. For each activity the level of interference was scored using a numeric rating scale from 0 to 10 (no interference to complete interference). Overall pain interference was scored as the mean of the seven interference items.

The validated EURO-QOL-5D-5L consists of a descriptive system with five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with five answer levels on each domain. Domain scores were converted into a single summary index score, representing the societal perspective on quality of life. As well as the descriptive system with five domains, the EURO-QOL-5D-5L also contains a visual analogue scale ranging from 0 to 100 (worst to best imaginable health state), representing patients' perspective on quality of life. For both perspectives, higher scores indicate a better quality of life. Scores were compared with EURO-QOL-5D-5L reference values from the Dutch general population in the same age range [12].

The LedRad-LTE questionnaire is a non-validated custom-made questionnaire that contains questions about patients' levels of satisfaction with the effect of the radiotherapy (very satisfied to very unsatisfied), evaluation of the treatment burden (not burdensome to very burdensome), side-effects of radiotherapy (such as erythema, dryness of the skin and oedema of the foot), current status of the disease according to the patient, pain from Ledderhose disease before start of radiotherapy and current pain (both collected at time of completing questionnaires). Pain scores were obtained using a numeric rating scale from 0 to 10, where 0 is no pain and 10 is excruciating pain.

Statistical analysis

A complete pain response was a current pain score of 0 points together with a decrease of the initial pain score by at least two points. A partial pain response was defined as a current pain score of at least 1 point together with a decrease of the initial pain score by at least two points. No change in pain was defined as one or zero pain score point change in either direction from the initial pain score. Progressive pain was defined as an increase in the initial pain score of at least two points [13].

Follow-up time was defined as time between last day of radiation and completion of questionnaires and expressed in months.

Sub-analyses were performed to investigate the effect of several factors on outcome variables, such as gender (males versus females), time after completion of radiotherapy (<4.10 years versus ≥4.10 years; based on median of 4.10 years), age at end of radiotherapy (<56.42 years versus ≥56.42 years; based on median of

56.42 years) and surgery prior to radiotherapy (no surgery versus surgery).

All data were analysed using the statistical package SPSS for Windows 23.0 (SPSS Inc, Chicago, IL, USA). Descriptive data are given as mean (±standard deviation, SD) or median (range). All tests were two-tailed with 0.05 as level of significance.

Results

In total, 82 patients were identified as potential participants for this study and invited to participate. Ultimately, 85% (71 patients) consented to participate. Of these, two patients could not be reached to complete the questionnaires, one patient was wrongly included (treated for verruca vulgaris of the right foot instead of for Ledderhose disease), and one patient withdrew consent prior to completing the questionnaires. Therefore, questionnaires of 67 patients (28 men and 39 women) were available for this analysis. Median follow-up time was 49 months (range: 24–132 months). Mean age at end of radiotherapy was 55 years (SD: 9.6 years). Forty patients (60%) also suffered from Dupuytren's disease and four male patients (14%) from Peyronie's disease. Fifty percent of patients reported a positive family history of Ledderhose-, Dupuytren's- and/or Peyronie's disease.

The 67 included patients together comprised 102 treated feet; 20 patients were treated solely on the left foot, 12 on the right foot and 35 patients on both feet. Nine feet were treated with orthovolt and 93 feet with electrons. One patient was re-irradiated on both feet due to new nodules located outside the previous given radiation field. Thirteen patients (14 feet) underwent surgery for Ledderhose disease prior to the radiotherapy. None of the included patients received surgery after radiotherapy.

The mean of the retrospectively collected pain score for all feet before radiotherapy was 5.7 (SD: 2.5) and the mean of the follow-up pain score for all feet was 1.7 (SD: 2.1) ($p < 0.001$) (Fig. 2A). A complete pain response was reported in 42 feet (41.2%), a partial pain response in 38 feet (37.3%) and no change in 22 feet (21.5%). There was no instance of progressive pain (Fig. 3A). The mean of the pain interference score was 1.3 (SD: 1.8). Statistically significant higher pain scores and lower pain responses for females were found compared to males (Figs. 2B and 3B). For the other factors (time after completion of radiotherapy, age at end of radiotherapy and surgery prior to radiotherapy), no effect on pain scores and pain responses was found.

A total of 64 patients completed the EURO-QOL-5D-5L questionnaire (Table 2). The mean age of these patients was 59.8 years (SD: 9.7 years). The mean of the score for societal perspective on QoL was 0.856 (SD: 0.130) and the mean of the score for patients' perspective on QoL 82.3 (SD: 14.5). Reference values of the Dutch general population in the same age category (50–60 years) were 0.857 (SD: 0.183) and 80.6, respectively. No significant effect of any of the factors from the sub-analyses was found.

Two residual long-term side effects were reported: dryness of the skin ($n = 10$, 15%) and erythema ($n = 2$, 3%). Nine patients (26%), reporting on presence of dryness, were in the cohort of 34 patients who were more than 4.10 years after end of treatment ($p = 0.05$). Six of the 14 feet (43%) which received surgery prior to radiotherapy suffered from dryness of the skin at time of assessment compared to 9 of 88 feet (10%) which did not receive surgery prior to radiotherapy.

A total of 69% of patients reported a permanent positive effect of the radiotherapy on pain and 78% of patients were satisfied with the effect of the treatment. Fifty-seven percent of the patients considered the treatment not burdensome. A statistically significant difference was found between sexes concerning the intensity of

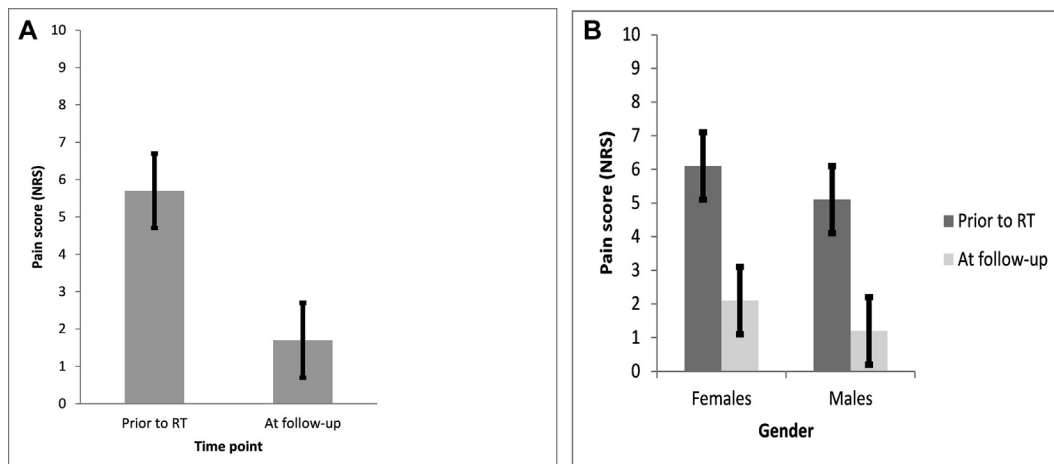


Fig. 2. (A) Mean pain scores for the whole cohort prior to RT and at follow-up* and (B) Mean pain scores for females compared to males prior to RT and at follow-up*.

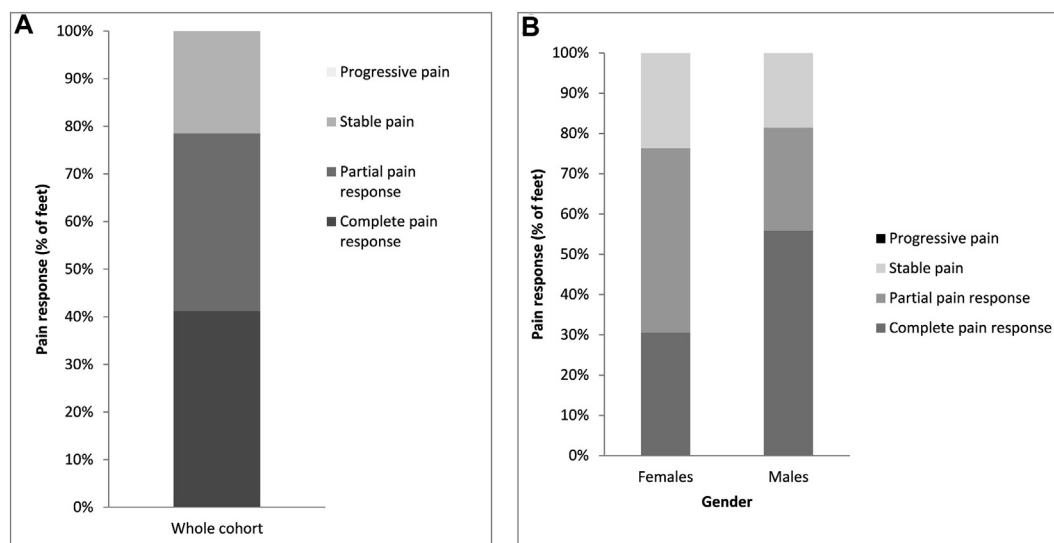


Fig. 3. (A) Pain response scores for the whole cohort and (B) Pain response scores for females compared to males*

Table 2
Mean scores from the EURO-QOL-5D-5L questionnaire.

	Patients (N)	Feet (N)	Mean age in years (SD)	Societal perspective on QoL		Patient's perspective on QoL	
				This study (SD)	Dutch reference (SD)	This study (SD)	Dutch reference
Whole cohort	64		59.8 (9.7)	0.856 (0.130)	0.857 (0.183)	82.3 (14.5)	80.6
Gender	Males	27	56.1 (11.9)	0.866 (0.133)	0.857 (0.183)	82.0 (14.7)	80.6
	Females	37	62.5 (6.6)	0.848 (0.128)	0.839 (0.179)	82.5 (14.5)	80.6
Years after end of RT	<4.1 yrs	32	58.7 (10.4)	0.866 (0.122)	0.857 (0.183)	83.1 (14.3)	80.6
	≥4.1 yrs	32	60.9 (8.9)	0.846 (0.138)	0.839 (0.179)	81.5 (14.8)	80.6
Age	<56.42 yrs	32	52.7 (7.7)	0.838 (0.145)	0.857 (0.183)	79.6 (16.5)	80.6
	≥56.42 yrs	32	66.9 (5.1)	0.874 (0.112)	0.839 (0.179)	84.9 (11.7)	80.6
Surgery prior to RT	No	84	60.7 (9.6)	0.857 (0.122)	0.839 (0.179)	82.9 (14.6)	80.6
	Yes	13	58.3 (7.2)	0.819 (0.164)	0.857 (0.183)	78.5 (15.9)	80.6

None of the differences between the scores within a factor were statistically significant.
Abbreviations: RT: radiotherapy; yrs: years.

treatment: almost 57% of females found the treatment somewhat burdensome or burdensome compared to 25% of males ($p < 0.05$).

No differences on the outcomes were found between the feet treated with orthovolt and the feet treated with electrons.

Discussion

To the best of our knowledge, this is the largest study with the longest follow-up to investigate the long-term effects of radiotherapy in patients with Ledderhose disease. Our results show that the previously reported shorter-term pain relief after radiotherapy for Ledderhose disease sustains. Quality of life is comparable to the reference population. Patient satisfaction with the outcome of radiotherapy is high and side effects are minimal.

The patient's perspective is arguably the most important item when evaluating the effect of a treatment. The high level of satisfaction with the effect of radiotherapy in our patient cohort is comparable to the short-term levels of satisfaction reported in previous studies (Table 1) [9–11]. In addition, evaluating the level of satisfaction with treatment effect, we also evaluated patient's perspective on treatment burden. This was not reported in previous studies. It should, however, be born in mind that we collected this data retrospectively and recall bias might be an issue. Therefore, we suggest it is valuable to evaluate patient's perspective on treatment burden immediately during treatment, in order to be able to ascertain whether the efforts to undergo the treatment ultimately outweigh its results. In this study, because intensity of treatment was mainly considered not burdensome and levels of satisfaction with treatment effect were high, we conclude, despite the retrospective character of the data collection, that the achieved results outweighed the efforts.

Dryness of the skin was the most reported residual side-effect of this study. It was reported in 15% of patients, which is comparable to the percentages found in the three previous studies (Table 1) [9–11]. Dryness of the skin is a common side effect of radiotherapy, especially in breast cancer [14]. In the long term, it might have a negative effect on physical and mental wellbeing [14]. Skin dryness from radiotherapy for Ledderhose disease seems to persist over time, as the residual dryness was reported more often in the patients who were more than 4 years after end of treatment. Therefore, we suggest including the evaluation of skin dryness in the follow-up and, when present, discuss with patients whether there is an impact on wellbeing and if any treatment is needed.

We found several differences between men and women: compared to male patients, females reported significantly higher initial and follow-up pain scores, significantly higher pain interference score and significantly lower pain response scores (complete pain response 30% in females vs. 56% in males). Finally, a significant difference was found concerning the perception of the treatment burden: females found radiotherapy more burdensome than males. In previous studies, no differences in pain scores and pain responses between men and women were described [9–11]. In previous literature it was found that gender is an important factor in response to pain [15]. In this regard, it should be emphasized that evaluating the effect of treatment on pain is complex and may be affected by several mechanisms, factors (social, biological and cultural) and their interactions [15].

The risk of developing radiation-induced cancer after radiotherapy for Ledderhose disease within the area of the sole of the foot, where high and low dose radiation was received, is very small, being estimated at 0.02% [16,17]. This risk is predominantly of skin cancer or soft tissue sarcoma. Radiation-induced skin cancer has only been described once for a patient treated at young age with radiotherapy for palmar hyperhidrosis [18]. To the best of our knowledge, it has not been reported in patients treated with radio-

therapy for Ledderhose disease. Despite the very low incidence, we suggest discussing this risk with patients during first consultation.

This study has three limitations. The first is its retrospective design; the pain score prior to treatment was collected at time of completing the questionnaires, where recall bias might be an issue. It is recommended that pain scores are obtained during all patient visits, with the first consultation as a starting point. Pain scores can easily be obtained with the numeric rating scale (NRS), which is a valid and reliable scale [19]. Because we collected the pain score prior to treatment retrospectively, this might either over- or underestimate the real effect of radiotherapy on pain. The second limitation is that the natural course of Ledderhose disease could not be evaluated in a control group. Preferably, the effect of radiotherapy should be evaluated in a randomized controlled study, which is currently underway. The third limitation is the duration of the follow-up. Although it is the longest follow-up, so far, for patients with Ledderhose disease treated with radiotherapy, it might still be too short considering the life expectancy of this patient population. Therefore, in a prospective randomized controlled study it should be considered to include a follow-up lasting for decennia or preferably life lasting.

Conclusions

The results of this cross-sectional study suggest that radiotherapy for Ledderhose disease results in long-term pain reduction in most patients. Radiotherapy is well tolerated, leaves patients satisfied, and the resulting quality of life of patients is comparable to the reference population. However, more prospective research, with a long-term follow-up, is needed to evaluate the definitive effect of radiotherapy for Ledderhose disease.

Funding statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability statement

Research data are stored in an institutional repository and will be shared upon request to the corresponding authors.

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 is member of SERB of Fidia Ltd, Milan. The other authors declare that they do not have any known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We thank all patients who took the time to respond to our questionnaires.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2022.01.031>.

References

- [1] Ledderhose G. Zur pathology des Aponeuroses des Fusses und Hand. Arch Klin Chir 1897;55:694–712.

- [2] Espert M, Anderson MR, Baumhauer JF. Current concepts review: plantar fibromatosis. *Foot Ankle Int* 2018;39:751–7. <https://doi.org/10.1177/1071100718768051>.
- [3] Carroll P, Henshaw RM, Garwood C, Raspovic K, Kumar D. Plantar fibromatosis: pathophysiology, surgical and nonsurgical therapies: an evidence-based review. *Foot Ankle Spec* 2018;11:168–76. <https://doi.org/10.1177/1938640017751184>.
- [4] Fuiano M, Mosca M, Caravelli S, Massimi S, Benedetti MG, Di Caprio F, et al. Current concepts about treatment options of plantar fibromatosis: a systematic review of the literature. *Foot Ankle Surg* 2019;25:559–64. <https://doi.org/10.1016/j.fas.2018.06.001>.
- [5] Cavolo DJ, Sherwood GF. Dupuytren's disease of the plantar fascia. *J Foot Surg* 1982;21:12–5.
- [6] Meyerding HW, Shellito JG. Dupuytren's contracture of the foot. *J Int Coll Surg* 1948;11:595–603.
- [7] Pickren JW, Smith AG, Stevenson TW, Stout AP. Fibromatosis of the plantar fascia. *Cancer* 1951;4:846–56. [https://doi.org/10.1002/1097-0142\(195107\)4:4<846::AID-CNCR2820040422>3.0.CO;2-N](https://doi.org/10.1002/1097-0142(195107)4:4<846::AID-CNCR2820040422>3.0.CO;2-N).
- [8] Young JR, Sternbach S, Willinger M, Hutchinson ID, Rosenbaum AJ. The etiology, evaluation, and management of plantar fibromatosis. *Orthop Res Rev* 2019;11:1–7. <https://doi.org/10.2147/ORR.S154289>.
- [9] Seegenschmiedt MH, Attassi M. Radiation therapy for morbus ledderhose - indication and clinical results. *Strahlentherapie und Onkol* 2003. <https://doi.org/10.1007/s00066-003-0994-3>.
- [10] Heyd R, Dorn AP, Herkströter M, Rödel C, Müller-Schimpfle M, Fraunholz I. Radiation therapy for early stages of morbus ledderhose. *Strahlentherapie und Onkol* 2010;186:24–9. <https://doi.org/10.1007/s00066-009-2049-x>.
- [11] Schuster J, Saraiya S, Tennyson N, Nedelka M, Mukhopadhyay N, Weiss E. Patient-reported outcomes after electron radiation treatment for early-stage palmar and plantar fibromatosis. *Pract Radiat Oncol* 2015.
- [12] Versteegh MM, Vermeulen KM, Evers SMAA, de Wit GA, Prenger R, Stolk EA. Dutch tariff for the five-level version of EQ-5D. *Value Heal J Int Soc Pharmacoeconomics Outcomes Res* 2016;19:343–52. <https://doi.org/10.1016/j.jval.2016.01.003>.
- [13] Chow E, Wu JSY, Hoskin P, Coia LR, Bentzen SM, Blitzer PH. International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. *Radiother Oncol J Eur Soc Ther Radiol Oncol* 2002;64:275–80. [https://doi.org/10.1016/s0167-8140\(02\)00170-6](https://doi.org/10.1016/s0167-8140(02)00170-6).
- [14] Chu C-N, Hu K-C, Wu R-C, Bau D-T. Radiation-irritated skin and hyperpigmentation may impact the quality of life of breast cancer patients after whole breast radiotherapy. *BMC Cancer* 2021;21:330. <https://doi.org/10.1186/s12885-021-08047-5>.
- [15] Pieretti S, Di Giannuario A, Di Giovannandrea R, et al. Gender differences in pain and its relief. *Ann Ist Super Sanita* 2016;52:184–9. <https://doi.org/10.4415/ANN.16.02.09>.
- [16] Jansen JTM, Broerse JJ, Zoetelief J, Klein C, Seegenschmiedt HM. Estimation of the carcinogenic risk of radiotherapy of benign diseases from shoulder to heel. *Radiother Oncol J Eur Soc Ther Radiol Oncol* 2005;76:270–7. <https://doi.org/10.1016/j.radonc.2005.06.034>.
- [17] McKeown SR, Hatfield P, Prestwich RJD, Shaffer RE, Taylor RE. Radiotherapy for benign disease; assessing the risk of radiation-induced cancer following exposure to intermediate dose radiation. *Br J Radiol* 2015;88:20150405. <https://doi.org/10.1259/bjr.20150405>.
- [18] Campanelli A, Lubbe J. Palmar squamous-cell carcinoma. *N Engl J Med*. 2019;381(11):1058. doi:10.1056/NEJMicm1814119.
- [19] Karcioğlu O, Topacoglu H, Dikme O, Dikme O. A systematic review of the pain scales in adults: Which to use? *Am J Emerg Med* 2018;36:707–14. <https://doi.org/10.1016/j.ajem.2018.01.008>.