A randomised multicentre, prospective, double blind phase III trial investigating the effect of radiotherapy on patients with Ledderhose disease.

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The aim of this study is to determine the efficacy and durability of radiotherapy as treatment for patients with Ledderhose disease and to compare this to the natural course of Ledderhose disease.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Connective tissue disorders (excl congenital)
Study type	Interventional

Summary

ID

NL-OMON50442

Source
ToetsingOnline

Brief title
LedRad study

Condition

- Connective tissue disorders (excl congenital)

Synonym
fibromatosis plantaris fascialis, Ledderhose

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Ledderhose, pain, radiation, toxicity

Outcome measures

Primary outcome

Numeric Rating Scale (NRS) score at 12 months:

The most important complaint of a patient with Ledderhose disease is pain, generally irrespective of the size of the nodules. Therefore, the primary endpoint will be pain relief at 12 months after treatment, measured by the Numeric Rating Scale. This 11-point-scale is used to assess the worst pain experienced by the patient in the previous week with scale endpoints from 0 (no pain) to 10 (worst imaginable pain) points.

The pain response (complete or partial) is defined as a decrease of the initial NRS-score by at least two points. Complete response is a NRS-score of 0 points. A partial response is defined as a remaining NRS-score of at least 1 point. Stable disease is defined as one or zero NRS-score point change in either direction from the initial NRS-score. Progressive disease is defined as an increase in the initial NRS-score of at least two points. Time to response and time to progression are calculated from the date of randomisation until the date of response and date of progression, respectively.

* A complete response (CR): NRS-score = 0.

* A partial response (PR): NRS-score = 1 and/or at least 2 points decrease from initial NRS-score

* A stable disease (SD): 1-point NRS-score change from initial NRS-score in either direction.

* A progressive disease (PD): Increase in at least 2 NRS-score points from the initial NRS-score.

Secondary outcome

NRS-score at 6 and 18 months:

The NRS-score at 6 and 18 months will be scored the same way as NRS-score at 12 months.

Size of Ledderhose nodules at 12 months:

The size of the Ledderhose nodules will be measured using MRI and ultrasound at 12 months and compared with MRI and ultrasound at baseline.

10 meter straight line walk test

Patients will be asked at different time points to walk in a straight line for 10 meters at their usual (self-selected) speed and their maximum walking speed. The VAS-score will be assessed before and after walking. Time points are baseline, 6, 12 and 18 months.

PEDAR (UMCG only)

Pedobarography is a technique which can measure dynamic plantar foot pressure during walking. Time points are baseline and 12 months.

Pain medication

The amount of pain medication will be scored at different time points. Time points are baseline, 6, 12 and 18 months. The amount of pain medication consumed in the week before each time point will be scored.

Questionnaires:

The RAND-36 and the brief pain inventory are questionnaires that will be filled in at different time points. Time points are baseline, 6, 12 and 18 months, and from 2 years annually until the end of follow-up.

* The RAND-36 item Health Survey (RAND-36): This is a short version of the RAND Health Insurance Study Questionnaire and is almost identical to the Medical Outcome Study (MOS) Short-Form-36 (SF-36). These questionnaires are used to measure patient health.

* The brief pain inventory: This tool measures both the intensity of pain and the interference of pain in the patient*s life.

* The EURO-QoL-5D: This is a standardised instrument to measure generic health status.

Study description

Background summary

Ledderhose disease is a benign thickening of the plantar aponeurosis of the foot. The disease appears as one or more subcutaneous painless nodules which grow slowly. The nodules can become painful during walking, and are sometimes disabling when they increase in size. Pain at rest does occur as cramps in the affected foot and/or leg. The effect of conservative treatment with physiotherapy, footpads and drugs is limited and can have the opposite effect. When the symptoms become worse, a fasciectomy can be performed. However, this surgical procedure is controversial because of the high risk of side effects

and limited durability. Radiotherapy has been proposed as an alternative treatment. In studies investigating the effect of radiation on patients with Ledderhose disease as primary treatment (see section existing evidence of effectiveness), radiotherapy was effective in 60-88% and only minimal side effects were seen. In a report of the Healthcare Insurance Board (CVZ), it was concluded that the efficacy of radiotherapy for Ledderhose disease is unproven as it has not been investigated in a randomised controlled trial (RCT). Moreover, CVZ noticed that in one study that investigated postoperative radiotherapy for Ledderhose disease, there were severe side effects and long-term follow-up data missing. Therefore, it was advised that radiation therapy for this indication should not be reimbursed. In contrast, based on the same data as the CVZ report, the National Society of Radiotherapy and Oncology (NVRO) stated that radiotherapy is a viable treatment option for patients with Ledderhose disease. Furthermore, due to the high morbidity and recurrence rates after surgery, patients only seldom receive surgery for Ledderhose disease in The Netherlands anymore. Therefore, there is no effective treatment available in The Netherlands that is covered by insurance companies. We plan to perform an RCT to compare the effect of radiotherapy to the natural course of patients with Ledderhose disease. The study will comprise adults with painful Ledderhose disease who opt for radiotherapy after comprehensive consultation with a plastic surgeon and a radiation oncologist.

Study objective

The aim of this study is to determine the efficacy and durability of radiotherapy as treatment for patients with Ledderhose disease and to compare this to the natural course of Ledderhose disease.

Study design

This study will be a multicentre, double blind RCT. To correct for placebo effect or knowledge bias, we decided on a double-blind design.
* Arm 1: Sham-radiotherapy
* Arm 2: Radiotherapy
After randomisation, patients receive either sham-radiotherapy (arm 1) or radiotherapy (arm 2). Patients assigned to the sham-radiotherapy arm will be subjected to the same preparation procedures as patients assigned to the radiotherapy arm. However, during sham treatment, patients will not receive radiation, but only sounds of the treatment machine will be heard by the patient. Neither the patient nor the treating radiation oncologist is aware of the allocated treatment arm. The study will be unblinded for each patient at 18 months after treatment. Patients in the sham-radiotherapy (arm 1) will have the opportunity to be treated with radiotherapy if complaints did not improve or became worse.

Intervention

Radiotherapy:
After consultation of a plastic surgeon (who will confirm that the patient has Ledderhose disease), patients will be referred to the radiotherapy department. The patient will be first seen by a radiation oncologist who will explain the study, the radiotherapy procedure and possible side effects. The possible side effects are mild erythema of the skin, temporary increase of pain (about two weeks) and very small chance (< 0.02% lifetime risk) of radiation induced tumour. If the patients is willing to enter the study and has signed the informed consent form, the patient will be randomised and the radiotherapy procedure will be started. This procedure is identical in both treatment arms, except that patients in treatment arm 1 (sham radiation) will not actually be treated with radiation.

Patients will be positioned prone with their feet in a knee support. The Ledderhose nodules will be marked and for the radiation field, margins will be taken into account. Bolus material of 1 cm thickness will be placed over the entire irradiated area. No specific OARs are defined. In general, all recommended radiation protection measures will be applied especially to minimize the risk of cancer from radiotherapy.

A custom lead (equivalent) mould of at least 10 mm thickness will be made for each patient. Therefore, only the Ledderhose nodule and the skin directly surrounding the nodule will be irradiated. The rest of the feet will be shielded by this lead mould, in order to avoid unintended irradiation to the rest of the body.

Radiotherapy will be performed using a linear accelerator with the capability to radiate electrons. Radiotherapy will be administered in two separate courses, each with five daily fractions of 3.0 Gy prescribed at each fraction. The total dose will be 30 Gy. The interval between the two courses will be 10 weeks. Patients will be irradiated with 8-10 MeV electrons.

Study burden and risks

Burden:
* MRI, to measure the size of the Ledderhose nodules
* Ultrasound, to measure the size of the Ledderhose nodules
* 10 meter straight line walk test and PEDAR
* Patient-rated outcome measures (PROMs):
* MRS-score
* Pain medication
* Rand-36 item Health Survey
* The brief pain inventory
* EURO-QoL-5D

Risks:
Patients randomized to placebo arm will first not receive any treatment.

Very low chance on developing radiation induced malignancy (estimated risk: 0.02% long life)

Justification:
With this study the effectiveness of Radiotherapy as a treatment option for Ledderhose Disease can be proven.
Every patient randomized for placebo arm will get the opportunity to be treated with Radiotherapy after 18 months.
The chance on developing radiation induced malignany is neglectable.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Patients with painful Ledderhose disease. The pain score measured with the

VAS score and is at least 2 on the 11-point scale (0 = no pain to 10 = worst imaginable pain).
• Age >= 18 years
• WHO performance status 0, 1 or 2
• Before patient randomisation, written informed consent must be given according to ICH/GCP, and local regulations
• Able and willing to complete quality of life questionnaires in English or Dutch
• Must be accessible for treatment follow-up

Exclusion criteria

• Surgical intervention before for Ledderhose disease
• Previous radiation treatment for Ledderhose disease
• Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
• Not able to lay prone for at least fifteen minutes
• Females who are pregnant at entry or who want to become pregnant within six months.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-01-2018
Enrollment:	80

Type:	Actual

Ethics review

Approved WMO Date:	18-10-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-01-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-03-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-05-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-06-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-12-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-04-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-11-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	15-01-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-10-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-06-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-10-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL62429.042.17
Other	volgt