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Original Article

An economic evaluation of radiotherapy for patients with symptomatic Ledderhose disease ☆

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ABSTRACT

Background: Evidence for effectiveness of radiotherapy for Ledderhose disease was demonstrated in the LedRad-study. However, the health economic impact of Ledderhose disease is unclear. Therefore, an economic evaluation alongside the LedRad-study was planned.
Methods: The economic evaluation was performed as a cost-effectiveness and cost-utility analysis from the societal perspective. Primary outcome parameters were pain burden and Quality Adjusted Life Years (QALY), until 12 months after the end of treatment. Secondary analyses were performed with outcomes until 18 months. Incremental cost-effectiveness (ICER) and cost-utility ratios (ICUR) were calculated to express costs per unit improvement in pain burden and costs per QALY gained, for radiotherapy compared to sham-radiotherapy. Bootstrap replication was used to assess uncertainty surrounding the ratios and to construct cost-effectiveness acceptability curves for QALY gain.
Results: Previous analysis showed a statistically significant improvement in pain- and QoL scores in favour of radiotherapy at 12 and 18 months. At these timepoints and excluding treatment costs, cumulative total costs were considerably lower in the radiotherapy group. The ICER until 12 months after treatment was 4987 euro per unit of pain burden reduction. The ICUR was 14249 euro per QALY gained. Most of the bootstrap replications were in the upper right quadrant, indicating that health gain can be achieved at higher costs. At increasing levels of willingness to pay for a gain in QALY, the probability of cost-utility gradually increased to approximately 85%.
Conclusions: In patients with symptomatic Ledderhose disease, radiotherapy, at a moderate threshold for willingness to pay, is cost-effective in terms of QoL gain.

Ledderhose disease or plantar fibromatosis, is a benign hyperproliferative disease of the plantar fascia of the feet.[1] Clinically, patients present with nodules and/or cords in the soles of their feet, which can become painful, especially with disease progression.[2,3] Symptomatic Ledderhose disease can negatively affect daily activities and quality of life (QoL).[3] Several treatment options are reported in the literature.[2,3] The treatments, e.g. orthotics such as insoles, intralesional cortisone injections, extracorporeal shock wave therapy, radiotherapy, and surgery are not curative, but are aimed at managing symptoms and improving functionality. However, the effectiveness of these treatments is not well-established and a treatment guideline is missing. This may cause a burden on healthcare budgets without proven clinical benefits for patients with Ledderhose disease.

In the past, radiotherapy seemed to be an effective treatment option, but estimates of effectiveness could only be derived from retrospective studies.[4,5,6,7] This lack of scientific evidence for effectiveness, impaired reimbursement for radiotherapy as a treatment modality, also in the Netherlands.[8] Therefore, the LedRad-study was conducted as a prospective multicentre randomized double-blind phase III clinical trial, comparing radiotherapy with sham-radiotherapy (placebo) in patients with symptomatic Ledderhose disease. This study is recently published and showed that radiotherapy resulted into a significantly more pain reduction and improvement of QoL compared to sham-radiotherapy, with only minor toxicities.[9].

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Besides clinical effectiveness, insight in the costs from different perspectives in relation to expected health benefits needs to be considered. The balance between costs and health benefits can be assessed in an economic evaluation.[10] As an economic evaluation was prospectively planned alongside the LedRad-study, this study provides insights in both effectiveness of treatment with radiotherapy (health benefit) as well as the related costs (economic consequences). This paper presents the results of the economic evaluation.

Materials and methods

Trial design and outcome LedRad study

The trial design and patient eligibility criteria for the LedRad-study (NCT03507010) have been described previously.[9] In short, the LedRad-study is a prospective multicentre randomized double-blind phase III trial investigating the efficacy of radiotherapy in patients with symptomatic Ledderhose disease. Patients were randomised between sham-radiotherapy (placebo, arm 1) or radiotherapy (arm 2). Radiotherapy consisted of a total dose of 30 Gy, administered in two separate courses of five daily fractions of 3 Gy, with an interval of 10 weeks between the two courses. Patients assigned to receive sham-radiotherapy underwent the same preparation- and treatment procedures, but the treatment was simulated. The primary outcome of the study was pain reduction at 12 months after end of treatment. Main secondary outcomes were pain reduction at 6 and 18 months, QoL and toxicity of radiotherapy. Pain was measured with the Numeric Rating Scale (NRS), an 11-point scale ranging from 0 (no pain) to 10 (excruciating pain).[11] The validated EURO-QoL-5D-5L questionnaire was used to collect data on societal- and patients‘ perspective on QoL. [12].

Economic evaluation

The economic evaluation was performed as a cost-effectiveness and cost-utility analysis from the societal perspective.[10] The primary outcome parameters were cumulative pain burden and quality-adjusted life-years (QALY) until 12 months after the end of treatment. Secondary analyses were performed with outcomes until 18 months.

Cumulative pain burden was calculated based on pain scores at the patient level, taking the average of both feet for patients with bilateral involvement. Mean pain score was calculated for each interval during follow-up using the trapezoid rule and multiplied by time. QALY's were calculated in a similar way by adjusting life-years in each interval for utility. The utilities were obtained using the Dutch Tariff for the Five-Level Version of EQ-5D that was administered at each follow-up visit.[13] For cost calculations, questionnaires were used to collect data regarding health care consumption inside and outside the hospital, travel and time costs, household support and informal care, out–of–pocket costs, and productivity loss. These questionnaires were completed at baseline, reflecting the six-month period prior to study entry, and at 6-month intervals after the end of study treatment, simultaneously with pain and QoL measurements. Using the outcomes and cost data, the incremental cost-effectiveness ratio (ICER) and the cost-utility ratio (ICUR) were calculated, as specified below, to express costs per unit improvement in pain burden and costs per QALY gained for radiotherapy compared to sham-radiotherapy.

Cost items and unit costs

Cost items and unit prices included in the economic evaluation are specified in Table 1. Unit prices were determined according to Dutch guidelines (2014)[14], standard prices were used if available and applicable. Since hospital admission for Ledderhose disease

Table 1
Unit costs used in the calculations.

Unit	Price	Source/remark
Outpatient visits		**Dutch guidelines**
Plastic surgery	€ 78.96	Surgery, mixed university/non-university
Radiotherapy	€ 98.42	General outpatient visit, mixed university/non-university
Rehabilitation	€ 78.96	No reference value, see surgery
Other	€ 98.42	General, mixed university/non-university
Time cost work absence	€ 37.59	Average friction costs for male and female, per hour
Visits other healthcare professionals		**Dutch guidelines**
General practitioner	€ 35.69	
Podotherapist	€ 34.61	Mixed price for paramedic visit
Other	€ 34.61	Mixed price paramedic visits
Household support and informal care		**Dutch guidelines**
Light household care	€ 21.63	Household care, per hour
Informal care	€ 15.14	Costs of informal care, per hour
Out of pocket costs	Real costs	**Dutch guidelines**
Paid work		**Dutch guidelines**
Frictionperiod (days)		85
Frictionperiod (weeks)		12.1
Productivitycost/hour	€ 37.59	Average for male and female, per hour
Travel costs		**Dutch guidelines**
Car	€ 0.21	Euro/km, parking costs € 3.24 per visit
Public transport	€ 0.21	Euro/km
Taxi	€ 2.88	Euro/km, start costs € 3.19 per ride
Unknown	€ 0.21	Euro/km
Average travel distances		
General Practitioner	1.1 km	
Physiotherapist/podotherapist	2.2 km	
Costs of radiotherapy treatment	€ 2325.4	**Dutch guidelines, see** Table S1

Prices were indexed to 2020 price levels. Dutch guideline prices from 2014 were indexed by 1.082.

does not occur, this was not included in the questionnaire, only outpatient visits and visits to paramedics were recorded. For the outpatient visits, standard prices were used, and travel costs were calculated based on distances from hospital postcode to patient postcode, and with the information regarding mode of travel (car, public transport, or taxi) provided by the patients. Time costs were also included in the questionnaire, but since these were not consistently reported these were omitted from the evaluation. For visits to paramedics, mean distances for the Netherlands were used in accordance with Dutch guidelines. Productivity loss was calculated using the friction cost method. Time of absence from work was calculated and maximized at 85 days or 12.1 weeks. Average hourly friction costs for the Dutch population were used and multiplied by the number of hours of absence. Out-of-pocket costs concerned costs of pain medication and mainly adapted shoes and orthotics. The costs of the radiotherapy treatment were calculated based on a top-down approach for the situation at the University Medical Center Groningen (UMCG). All unit prices were indexed to the price level of 2020 and were expressed in euros (Table S1).

Cost-effectiveness and cost-utility ratios

For the cost-effectiveness- and cost-utility ratios, cumulative pain burden and QALY were used as described above. For the comparison of treatments, the difference in pain burden was inverted to reflect improvement of pain, so a smaller pain burden, as a higher score for ease of interpretation. Incremental cost-effectiveness and cost-utility ratios were calculated after bootstrap replication to reflect uncertainty surrounding the ratios based on study data.[15] Based on 5000 replications, 95% confidence intervals for the incremental cost-effectiveness ratios were calculated. Bootstrapped data were also presented graphically in a cost-effectiveness plane and were the basis for the cost-effectiveness acceptability curve (CEAC) to show the probability of cost-effectiveness for various threshold values for willingness to pay for a gain of one QALY. Since the sham-radiotherapy treatment did not constitute a real-life treatment alternative, the CEAC was only constructed for the radiotherapy treatment.

Results

From January 2018 to October 2019, 84 patients (27 men and 57 women) participated in the LedRad-study. Mean age at admission was 56 years (SD 9 years). In total 130 feet were treated; 65 feet (42 patients) in the sham-radiotherapy group and 65 feet (42 patients) in the radiotherapy group. Five patients dropped-out prior to completing the 18 months follow-up visit. Due to missing data in the questionnaires, 71 patients (35 in the sham-radiotherapy group and 36 in the radiotherapy group) with a follow-up of 12 months could be included in the economic evaluation and 69 patients (34 and 35 in the respective groups) with a follow-up of 18 months.

Patients in the radiotherapy group did not have a significantly different pain burden at 12 and 18 months after treatment compared to patients in the sham-radiotherapy group (95% confidence intervals of mean differences −2.51 to 2.94 and −3.04 to 4.37 for 12 and 18 months, respectively, Table 2). Quality adjusted life-years were also not significantly different, but both QoL and pain burden indicated prolonged effects until 18 months after treatment.

Mean overall cumulative costs at 12 months and 18 months after the end of treatment and costs per category at baseline, 12 and 18 months are shown in Tables 2 and 3, respectively. Baseline data show that patients with Ledderhose disease have high healthcare consumption regarding outpatient visits to various disciplines, as well as costs of household care. At 12 months after end of treatment, cumulative total costs were considerably lower in the radiotherapy group compared to patients in the sham-radiotherapy group, not including treatment costs. When treatment costs were included the difference in costs was statistically significantly different in favour of the sham-radiotherapy group. At 18 months after treatment, cost differences became more pronounced and were statistically significant for costs of visits to healthcare professionals outside the hospital and out-of-pocket costs in favour of the radiotherapy group. Overall total costs including treatment were still significantly higher in the radiotherapy group. More details of costs by visit are provided in Table S2. This shows that many patients did not incur any costs at all.

Table 2 shows the data that were used for the bootstrap replications and the resulting estimates for incremental cost-effectiveness ratios at 12 and 18 months. Mainly due to the treatment costs, total costs in the radiotherapy group were higher compared to those in the sham-radiotherapy group.

The ICER at 12 months after treatment based on pain burden was 4987 euro per unit of pain burden reduction. With QALY as the outcome the incremental cost-utility ratio (ICUR) was 14,249 euro per QALY gained. At 18 months after treatment, mean difference in pain burden was slightly larger and mean cost difference was slightly lower than at 12 months, indicating more favourable

Table 2
Mean outcomes (before bootstrap) and incremental cost-effectiveness and cost-utility ratios (bootstrap results).

Outcome	12 months after end of treatment (n = 36 vs 35)	18 months after end of treatment (n = 34 vs 35)
Mean pain burden*		
Radiotherapy	7.15	9.00
Sham radiotherapy	7.36	9.67
Mean difference (95% CI)	−0.21 (-2.51 – 2.94)	−0.67 (-3.04 – 4.37)
Mean QALY		
Radiotherapy	1.099	1.524
Sham radiotherapy	1.016	1.408
Mean difference (95% CI)	0.083 (-0.197 – 0.032)	0.116 (-0.265 – 0.034)
Mean costs		
Radiotherapy	3052.4	3338.3
Sham radiotherapy	1849.6	2213.0
Mean difference (min, max)**	1196.9 (-1532.3 – 3391.0)	1129.6 (-2808.2 – 3551.5)
Incremental cost-effectiveness ratio***	4987.1	1661.2
Incremental cost-utility ratio ***	14248.8	9737.9

*: calculated as area under pain score curve from baseline to 12 or 18 months, higher values are worse. Mean difference was inverted for ICER calculations and CE plane.
**: due to the distribution of values after bootstrap mean difference can be different from difference between means.
***: calculated based on mean differences for costs and effects; 95% confidence intervals after bootstrap not informative due to outliers for effect differences close to zero.

Table 3
Mean costs by category and treatment group at baseline and mean cumulative costs by category and treatment group at 12 and 18 months.

	Baseline		12 months[a]		18 months[b]	
	Radiotherapy (n = 40)	Sham treatment (n = 39)	Radiotherapy (n = 35)	Sham treatment (n = 36)	Radiotherapy (n = 35)	Sham treatment (n = 34)
Outpatient visits						
Direct costs	130.4 (98.4, 0–590.5)	105.5 (79.0, 0–650.0)	10.4 (0, 0–98.4)	7.9 (0, 0–196.8)	19.1 (0, 0–196.8)	8.1 (0, 0–196.8)
Travel costs	44.9 (23.6, 0–200.4)	23.8 (0, 0–267.5)	1.6 (0, 0–25.1)	1.4 (0, 0–47.6)	4.4 (0, 0–70.6)	1.4 (0, 0–47.6)
Time costs	178.6	96.9	7.3	1.1	7.5	1.1
Patient	(0, 0–1503.6)	(0, 0–2706.5)	(0, 0–150.4)	(0, 0–37.6)	(0, 0–150.4)	(0, 0–37.6)
Accompanied	139.8	170.7	1.6	1.1	1.6	1.0
	(0, 0–1240.5)	(0, 0–3947.0)	(0, 0–56.4)	(0, 0–37.6)	(0, 0–56.4)	(0, 0–37.6)
Total costs	497.9	393.4	20.9	11.4	32.6	11.7
	(119.4, 0–2345.1)	(41.5, 0–7150.8)	(0, 0–273.9)	(0, 0–244.5)	(0, 0–273.9)	(0, 0–244.5)
Other HCP visits						
Direct costs	49.7	50.2	27.1	95.1	32.9	120.3*
	(0, 0–519.2)	(34.6, 0–380.7)	(0, 0–244.2)	(0, 0–1142.1)	(0, 0–244.2)	(34.6, 0–1211.4)
Travel costs	0.70	0.54	0.4	1.2	0.46	1.6*
	(0, 0–6.9)	(0.23, 0–5.1)	(0, 0–2.9)	(0, 0–15.3)	(0, 0–2.9)	(0.3, 0–16.2)
Total costs	50.4	50.7	27.5	96.3	33.3	121.8*
	(0, 0–526.1)	(35.1, 0–385.8)	(0, 0–247.0)	(0, 0–1157.4)	(0, 0–247.0)	(35.1, 0–1277.5)
Other costs						
Out of pocket costs	64.7	146.0	122.5	237.6	159.5	316.1*
	(0, 0–325.0)	(40.0, 0–870.7)	(0, 0–940.0)	(209.0, 0–1204.0)	(30.0, 0–1154.0)	(240, 0–1204.0)
Household care	184.2	92.33	439.3	683.8	667.2	918.7
	(0, 0–2361.8)	(0, 0–1239.4)	(0, 0–4856.0)	(0, 0–10416)	(0, 0–5890.3)	(0, 0–14352.7)
Friction costs	NA	NA	116.9	820.5	120.3	844.7
			(0, 0–4210.1)	(0, 0–18193.6)	(0, 0–4210.1)	(0, 0–18193.6)
Total costs						
Total costs, excluding	803.1	661.6	727.0	1849.6	1012.9	2213.0
treatment	(401.9, 0–2884.4)	(356.2, 0–7380.7)	(96.1, 0–5945.4)	(340.0, 0–20357.3)	(240.0, 0–6970.6)	(543.1, 0–20762.4)
Treatment costs	NA	NA	2325.4	0	2325.4	0
Total costs, including	803.1	661.6	3052.4	1849.6*	3338.3	2213.0*
treatment	(401.9, 0–2884.4)	(356.2, 0–7380.7)	(2421.5, 2325.4–8270.8)	(340.0, 0–20357.3)	(2565.4, 2325.4–9296.0)	(543.1, 0–20762.4)

Data presented as mean (median, min–max); [a]: cumulative costs (end of treatment (14 weeks), 6 months and 12 months after end of treatment); [b]: cumulative costs (12–18 months after end of treatment added to cumulative costs until 12 months); *: $p < 0.05$, Mann-Whitney U-test; NA: not applicable.

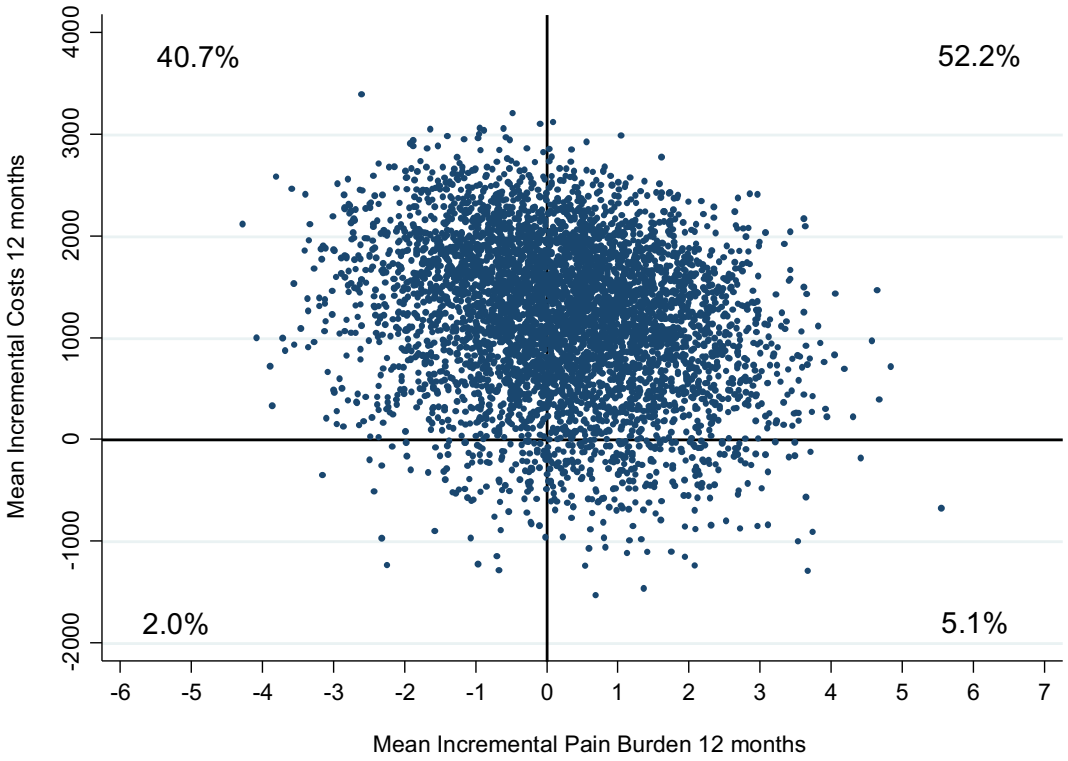

Fig. 1a. Bootstrap results of incremental pain burden and incremental costs at 12 months after end of treatment. Positive difference in pain burden indicates better pain reduction after radiotherapy. Percentages indicate proportion of bootstrap replications in respective quadrants.

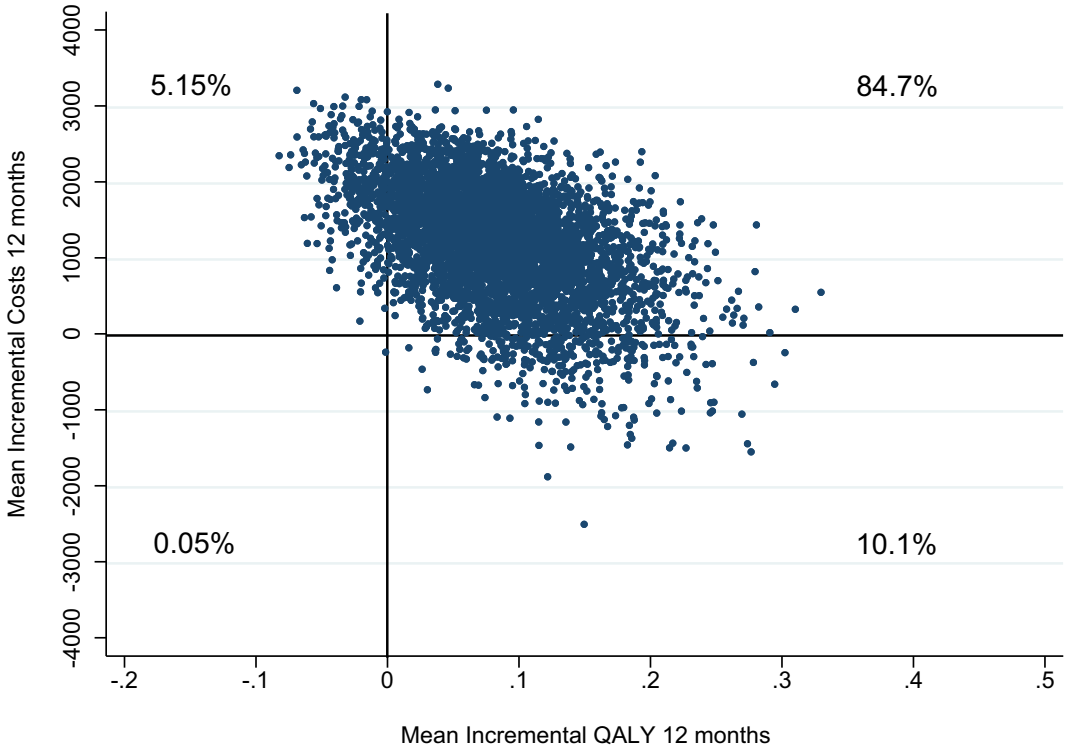

Fig. 1b. Bootstrap results of incremental QALY and incremental costs at 12 months after end of treatment.

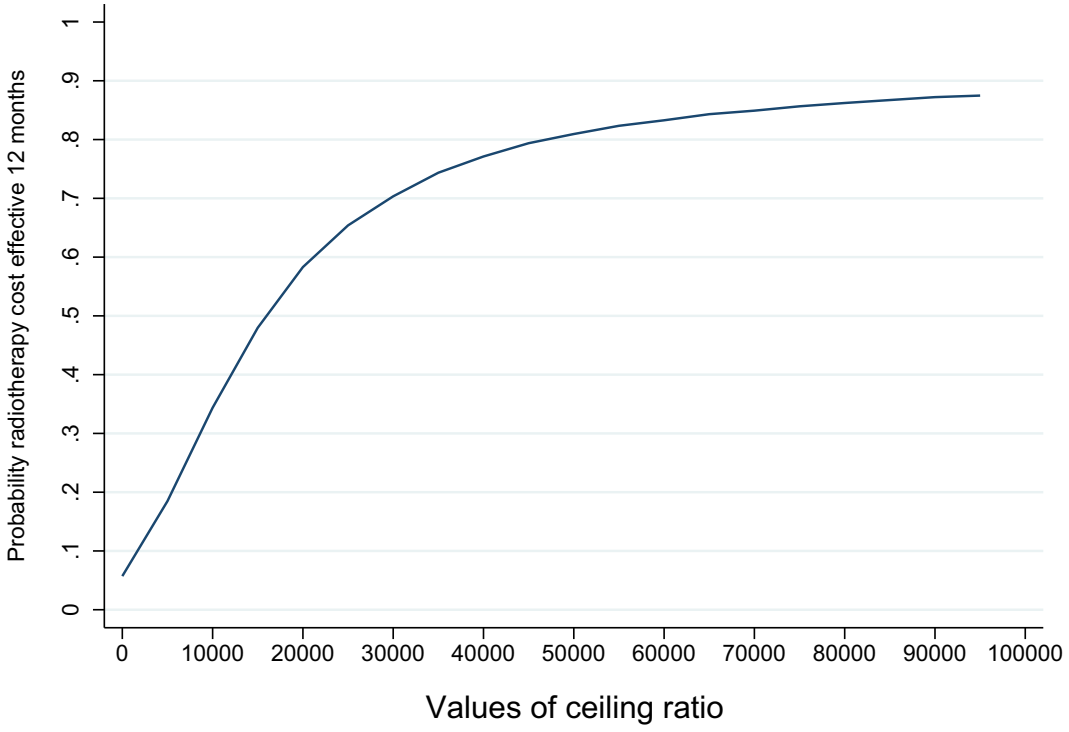

Fig. 2. Cost-effectiveness acceptability curve displaying probability of cost-effectiveness in relation to ceiling values for willingness to pay per QALY gained up to 12 months after end of treatment. Probability of cost-effectiveness at 20,000 Euro per QALY: 58.3%; at 100.000 US $ (€ 95.000) per QALY: 87.5%.

cost-effectiveness. The difference in QALY at 18 months was also more pronounced in favour of the radiotherapy group. This was also reflected in the ICER and ICUR based on these secondary outcomes.

The results of the bootstrap replications for pain burden and QALY up to 12 months are presented in Figs. 1a and 1b. For both outcomes, most of the replications were in the upper right quadrant, indicating that health gain can be achieved at higher costs,

although a substantial proportion of replications suggested increased pain burden. The probability of cost-effectiveness of the radiotherapy treatment at various threshold values for willingness to pay for one QALY gained is shown in Fig. 2. The probability of cost-effectiveness gradually increased to approximately 85%, with a corresponding threshold value of 70,000 euro. At 20,000 euro per QALY, the threshold value in the Netherlands for diseases with a low disease burden (0.1 – 0.4), the probability of cost-effectiveness was 58%. At 80,000 euro per QALY, the threshold value in the Netherlands for diseases with a high disease burden (0.71 – 1.0), the probability was approximately 86%. At 95,000 euro per QALY, which equals the commonly used threshold value in the United States of $100,000, the probability was 88%.

Discussion

In this study, the economic consequences of radiotherapy for symptomatic Ledderhose disease were assessed alongside the LedRad-study. To our knowledge, this is the first economic evaluation prospectively assessing radiotherapy for Ledderhose disease in a randomized comparison with sham-radiotherapy.

The results of this economic evaluation suggest that radiotherapy is a cost-effective healthcare intervention for Ledderhose disease. The favorable cost-effectiveness ratios were achieved through lower costs and positive effects on pain and QoL, as demonstrated in the main study. At 12 months after treatment, the mean total costs (without costs for radiotherapy) for patients treated with radiotherapy were 1122 euro lower than those for patients treated with sham-radiotherapy. At 18 months, this difference in mean total costs remained (1200 euro). The lower costs for patients from the radiotherapy group are probably related to the favorable effects of radiotherapy on pain and QoL, resulting in less need for other healthcare. Patients from the sham-radiotherapy group had higher costs, especially for visits to various paramedics and out of pocket costs, probably as they were still confronted with the complaints and negative impact of their Ledderhose disease and therefore sought other help.

A randomized controlled trial is the best design to make sure that the observed effects are a result of the intervention. Usually in clinical trials, less attention is paid to economic data, leading to insufficient data for cost-effectiveness analysis. The strength of our study is that the economic evaluation was planned prospectively and therefore the required data was collected in detail, appropriate for the cost-effectiveness analysis, including comparable controls in terms of demographic and clinical characteristics. Limitation of this economic evaluation is the relatively small sample size. The sample size was based on the clinical outcomes of the study and not on the outcomes for the economic evaluation. Outliers might affect the results, but this risk is covered by applying bootstrap analysis.

The primary analysis of the main study data showed that radiotherapy is an effective treatment which significantly reduced pain and improved quality of life compared to sham-radiotherapy for symptomatic Ledderhose disease.[9] For the economic evaluation, the outcomes of pain and QoL were calculated according to applicable guidelines for economic evaluations, and therefore the results of these outcomes differ from the overall results in the main study. These different results should not be used for interpretations with regard to effectivity of treatment, but are only applicable to the economic evaluation.

In conclusion, in addition to previously shown clinical effectiveness of radiotherapy for patients with symptomatic Ledderhose disease, our economic evaluation shows that this treatment is also cost-effective compared to most commonly accepted thresholds for willingness to pay per QALY gained.

Trial registration numbers

NCT03507010, NL62429.042.17

CRediT authorship contribution statement

Anneke de Haan: Conceptualization, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration, Funding acquisition. **Henk Groen:** Conceptualization, Methodology, Software, Validation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization, Funding acquisition. **Johanna G. H. van Nes:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition. **M. Willemijn Kolff:** Conceptualization, Investigation, Resources, Writing – review & editing, Project administration, Funding acquisition. **Peter-Paul van der Toorn:** Investigation, Resources, Writing – review & editing, Project administration. **A. Helen Westenberg:** Investigation, Resources, Writing – review & editing, Project administration. **Paul M.N. Werker:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition. **Johannes A. Langendijk:** Conceptualization, Resources, Writing – review & editing, Supervision, Funding acquisition. **Roel J.H.M. Steenbakkers:** Conceptualization, Investigation, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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.2023.109890.

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