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Chapter 8

Low-Dose Radiotherapy of Painful Heel Spur/Plantar Fasciitis as an Example of Treatment Effects in Benign Diseases

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Abstract

Degenerative changes in the plantar fascia may cause the so-called "painful heel" with typical projections of tenderness. This condition is often associated with a plantar heel spur. Radiotherapy with low doses (LD-EBRT) has been well known for its anti-inflammatory potential. In the recent years, several microbiological mechanisms were elucidated to explain immunomodulation by LD-EBRT. Furthermore, a randomized study proved the clinical efficacy of this therapy in plantar fasciitis. Two other trials defined a fractionation schedule of 6 × 0.5 Gy twice weekly as the new standard therapy. Taken together, LD-EBRT is an effective and safe therapeutic option for patients over 30 years of age and after exclusion of pregnancy. In case of an insufficient response, a second course can be offered to the patient. There are still open questions concerning target volume definition and fractionation of LD-EBRT. Furthermore, studies randomizing LD-EBRT with other conservative therapeutic approaches are missing.

Keywords: low dose radiotherapy, heel spur, plantar fasciitis, *reizbestrahlung*, target volume definition

1. Incidence and etiology of plantar fasciitis

About 7% of the population >65 years suffer from a painful heel, even though younger people are often affected, too [1]. The most common cause of this symptom is the so-called "plantar fasciitis" [2]. This term is widely used, although "plantar fasciopathy" or "plantar fasciosis" would be a better description to point out the degenerative nature of the disease. However, as

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more than 1100 citations in Pubmed quote "plantar fasciitis" (in comparison with only 50), we will use the traditional term in the following.

Plantar fasciitis has been associated with obesity, with acute or chronic work overload, or with work on hard surfaces [2, 3]. It seems that physiological degeneration of the fascia at the calcaneal insertion exacerbates due to repetitive microtraumas caused by vertical compression [4]. This causes inflammatory tissue reactions. As a result, the fascia is thickened with an associated fluid collection to 4.0 mm and more in ultrasonography [5]. Furthermore, this inflammation may trigger bone formation, the so-called "plantar heel spur." This process has been studied intensively by Kumai and Benjamin [6]. They proposed three stages of spur growth: "(a) an initial formation of cartilage cell clusters and fissures at the plantar fascia enthesis; (b) thickening of the subchondral bone plate at the enthesis as small spurs form; and (c) development of vertically oriented trabeculae buttressing the proximal end of larger spurs" [6]. The first description of this spur formation and correlation with the clinical symptoms was carried out by Plettner in 1900 [7]. However, not every heel spur is associated with heel pain, as these spurs are found in 11–16% of the normal asymptomatic population [4]. On the other hand, some patients with painful plantar fasciitis do not have a radiographic confirmation of a spur formation.

A similar mechanism (although caused by longitudinal traction and not by vertical compression) of bone formation has been described at the insertion of the Achilles tendon [8].

According to the American clinical practice guidelines from 2010, diagnosis is established by the typical anamnesis and the characteristic localizations of tenderness. Still, weight-bearing radiographs are also recommended [9].

2. Treatment with LD-EBRT

2.1. Biological effects of LD-EBRT on lymphocytes and inflammatory processes

Single doses of external beam radiotherapy (EBRT) in the range of 0.3–1 Gy are called "low dose EBRT" (LD-EBRT). These single fractions are applied two or three times a week until a total dose of about 3–6 Gy is reached. Such radiotherapeutic concepts are used for diverse nonmalignant conditions, e.g., osteoarthrosis, tendinopathy, epicondylitis, or bursitis. A comprehensive review of the historical developments in LD-EBRT for benign diseases is given by Trott [10].

In contrast, EBRT in oncology is characterized by much higher single and total doses. "Normofractionation" describes single doses of 1.8–2 Gy, applied about five times a week. To treat breast cancer, the total doses of about 62 Gy are necessary, in prostate cancer even more than 72 Gy. From a radiobiological point of view, these high cumulative doses are used to induce DNA double strand breaks. Due to errors in a repair mechanism (nonhomologous end joining), dicentric chromosomes can occur. These can result in unfinished mitoses, the so-called "mitotic catastrophe," the main mechanism to reduce clonogenic survival in tumor cells [11]. High doses of EBRT induce local inflammation and tissue reactions.

The much lower doses of LD-EBRT act via different mechanisms. In the last two decades, several anti-inflammatory effects have been discovered, contrary to the effects of the above-mentioned high EBRT doses.

(a) *In vitro* LD-EBRT has been shown to induce apoptosis in peripheral blood mononuclear cells (PBMC) [12]. Interestingly, there was not a linear correlation between dose and the amount of apoptotic cells. Instead, the maximal induction of apoptosis was observed after a single dose between 0.3 and 0.7 Gy, higher doses (up to 3 Gy) not being more effective [12].

(b) Furthermore, doses between 0.1 and 0.5 Gy reduced the adhesion of PBMC significantly to endothelial cells (ECs) *in vitro*, probably by suppressing the expression of L-selectin on the surface of PBMC [13]. This is a very important finding, as the adhesion of leukocytes to the cells of the vessel wall is the first event of tissue invasion in inflammatory processes [13]. Another reason for the reduced adhesion between PBMC and EC was identified by Rödel et al. [14]: In irradiated EC mRNA expression and protein secretion of transforming growth factor β1 (TGF-β1) were highest after 0.5 Gy, higher doses resulted in a decline to basal levels [14]. Neutralization TGF-β1 with specific antibodies restored the adhesion between PBMC and EC. These *in vitro* results were confirmed *in vivo* in a mouse model for 0.3 Gy [15]. TGF-β expression is dependent on activation of the nuclear factor-kappa B (NF-κB) [16]. Also, NF-kB DNA-binding activity showed a biphasic response to LD-EBRT with a first maximum at 0.5 Gy, a relative minimum between 0.6 and 0.8 Gy, and a second increase at 1 and 3 Gy [16]. The above-mentioned findings show a biphasic time course with reduced adhesion of PBMC 4 and 24 h after LD-EBRT, with a relative maximum of adhesion after 12h [17].

(c) A third mechanism was the suppression of nitric oxide (NO) production in activated macrophages by LD-EBRT between 0.3 and 1.25 Gy [18]. As the expression of inducible nitric oxide synthases (iNOS) proteins was not altered, the LD-EBRT seemed to act at the translational or posttranslational level. Furthermore, a dose of 0.5 Gy significantly reduced oxidative burst and superoxide production of stimulated macrophages [19]. A diminished release of reactive oxygen species (ROS) can also contribute to the anti-inflammatory effects of LD-EBRT.

Taken together, all of these pathways and mechanisms showed a similar dose dependence with a maximum effect between 0.3 and 0.7 Gy regarding a discontinuous dose-effect relation [20].

There are several *in vivo* studies in different animal models about the effects of LD-EBRT, especially on osteoarthritis. A comprehensive overview is given in Ref. [20], however, as they are not directly related to calcaneodynia, we will not further comment on them.

2.2. Results of randomized trials on radiotherapy for painful heel spur

Since 1937 [21] for decades, large retrospective studies on the efficacy of LD-EBRT in calcaneodynia have been published (overview in 22). In 1970, one negative randomized trial was reported and heavily criticized but had not been repeated [23]. Starting in the 1980s, patients were systematically clinically examined and interrogated in a structured manner to try to control for diverse risk factors and to compare the efficacy of different fractionation schemes and total doses [24].

It took until the past decade to perform and report prospectively randomized trials to proof the efficacy of LD-EBRT and to identify the optimal dose fractionation schedule. In the following, we report the design and the results of these trials. **Table 1** gives a short overview of the studied dose concepts and the results. Due to methodological reasons, we will describe the studies not following their publications dates, but according to a systematic order.

Author	Year	N	Standard arm	Experimental arm	Results	Conclusions
Niewald et al. [26]	2012	66	6 × 1 Gy twice a week	6 × 0.1 Gy	3 months: VAS/CS/SF12 sig. better with standard	1. Dose-response relationship
					1 year: less second treatment series with standard	2. Proof of therapeutic effect of LD-EBRT
Heyd et al. [30]	2007	130	6 × 1 Gy twice a week	6 × 0.5 Gy	6 months: CS no sig. differences	6 × 0.5 Gy as standard fractionation
Ott et al. [32]	2014	457	6 × 1 Gy twice a week	6 × 0.5 Gy	6 weeks, 2.5 years: VAS/CS no sig. differences	6 × 0.5 Gy as standard confirmed
Niewald et al. [25]	2015	127	6 × 1 Gy twice a week	12 × 0.5 Gy thrice a week	3 months: VAS/CS/SF12 no sig. differences	Efficacy not increased with 12 × 0.5 Gy standard still 6 × 0.5 Gy

Table 1. Summary of contemporary randomized trials on LD-EBRT of painful heel spurs: tested schedules, results, and conclusions.

2.2.1. Clinical proof of the efficacy of LD-EBRT

Since the publication of the first randomized trial on LD-EBRT in 1970, the efficacy of LD-EBRT was questioned [23]. Goldie et al. randomized 399 patients, however, only nine patients suffered from calcaneodynia. This is why these results cannot be extrapolated to LD-EBRT of a painful heel spur. Furthermore, endpoints were not clearly defined, and therapy was started in an acute stage of the disease [25].

The landmark study to prove the efficacy of LD-EBRT was performed by the German cooperative group on the radiotherapy for benign diseases (GCGBD) under the responsibility of Niewald et al. [26]. A very low dose EBRT (6 × 0.1 Gy applied twice a week up to a total dose of 0.6 Gy) was randomized to a standard dose LD-EBRT (6 × 1 Gy twice a week up to a total dose of 6 Gy). In the case of an unfavorable response after 3 months, the patient was offered a second treatment series ("reirradiation") applying a standard dose. The dosage of the experimental arm was chosen to examine if very low doses are effective at all. Second, it acted as a placebo irradiation, as a sham irradiation was regarded unethical. LD-EBRT was applied using a linear accelerator (4- to 6-MV photons) using lateral parallel opposing fields.

Inclusion criteria were tenderness of the calcaneus with a limitation of the painless walking distance and duration of the symptoms for more than 6 months. Furthermore, a radiological proof of a heel spur was required, and the patients had to be least 40 years of age. Patients with previous traumata to the foot, rheumatic or vascular diseases, lymphatic edema, pregnancy, or breastfeeding were excluded. Concomitant therapy with oral analgesics was not limited. However, local injections with steroids during the study period were not permitted.

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Initially, 200 patients were planned [27] to detect a difference of 10% in the quality of life (QOL) sum score (SF-12) [28] and calcaneodynia sum score (CS) [29] (**Table 2**) with a power of 80% and an error probability of 5%. Furthermore, the visual analogue scale (VAS) to evaluate pain intensity was used. However, after randomization of 66 patients and interim analysis of 62 patients (4 had to be excluded due to a withdrawal of informed consent or violation of the inclusion criteria), the differences in efficacy between the two treatment arms were so pronounced, that the trial was closed early.

Criteria	Extent of symptoms/alteration	Points
1. Pain symptoms	S = Pain at **strain**	6 / 4 / 2 / 0
(total: 30%)	N = Pain during **night time**	6 / 4 / 2 / 0
	D = Pain during **day time** (continuously)	6 / 4 / 2 / 0
	R = Pain at **rest** (following any kind of strain)	6 / 4 / 2 / 0
	I = Pain at **initiation of movement**/morning stiffness	6 / 4 / 2 / 0
per single criterion	none = 6 ; slight = 4 ; moderate = 2 ; severe = 0 points ⇨	
2. Use of appliances	None	15
(total: 15%)	Orthopedic shoe, insoles, heel cushion	10
	One cane or crutch	5
	Two canes or crutches	0
	⇨	
3. Professional activities	No limitation, maximum professional strain possible	20
	Slight limitation, normal professional work possible	10
(total: 20%)	Moderate limitation, reduced professional activity	5
	Severe limitation, daily professional work impossible	0
	⇨	
4. Daily/leisure activities	No limitation of daily and leisure activities and sports	15
(total: 15%)	Slightly limitation/reduced leisure activities and sports	10
	Moderate limitation/no leisure activities and sports	5
	Complete limitation of any daily and leisure activities	0
	⇨	
5. Gait/limp	No limp, normal walking is possible without a limitation	20
(total: 20%)	Slightly altered, limp after walking **> 1 km (2 blocks)**	10
	Moderately altered, limp after walking **< 1 km (2 blocks)**	5
	Severely altered, normal walking is impossible	0
	⇨	
Total score	**Sum of the single scores 1 + 2 + 3 + 4 + 5** ⇨	

Table 2. Calcaneodynia score of the GCG-BD [29], based on [31].

The mean age of patients was 54 years in the standard dose group and 58 years in the 6 × 0.1 Gy group. Sixty-one patients had a plantar, one patient a dorsal heel spur. In mean, patients in the standard dose group suffered for 15.3 months before the start of LD-EBRT, in the 6 × 0.1 Gy group for 18.8 months. Twenty-one patients had symptoms on both sides. In 28 patients the pain irradiated into the calf, only in 18 patients it was localized to the sole of the foot. Two patients had received surgery for LD-EBRT.

Three months after therapy VAS values, CS- and QOL-scores were significantly better after the standard dose in comparison with the very low dose treatment arm. The higher pain relief resulted in a better QOL. Twelve months after therapy about 64% of the patients after 6 × 0.1 Gy had to receive a second treatment series due to insufficient treatment results, in comparison with only 17% of the patients in the standard dose treatment group. As the second series was applied with a standard dose (6 × 1 Gy), patients in the 6 × 0.1 Gy group who were reirradiated showed equally favorable results compared with those in the standard-dose group who did not receive a second course [26]. This is why the second treatment series in this clinical setting acted as a "salvage therapy." Another interesting finding was that patients with a good response already at 3 months remained stable or even improved at 12 months. Furthermore, this underlines the long-lasting efficacy of LD-EBRT.

Acute side effects or long-term toxicity did not occur.

In conclusion, this randomized trial established a dose-response-relationship of the analgesic effect of LD-EBRT, thus providing a clinical and methodological proof of the efficacy of 6 × 1 Gy LD-EBRT on the clinical course of painful heel spurs. The early termination of the study was justified due the interim analysis showing significant differences in the clinical outcome between both treatment arms. Still, the trial was not blinded, so both the patients and the staff were aware of the received dose. With modern linear accelerators, a complete blinding of the staff is nearly impossible. The only option would be a shame irradiation with closed collimator jaws, reducing the dose to the unavoidable "leakage" radiation. A much easier and straight forward way was used in the above-mentioned study by application of a minimal physical dose with 0.1 Gy. Another critical point might be that only half of the patients were examined 12 months after therapy ($n = 36$). This reduces the reliability of the study results at this time point. However, this does not affect the results concerning treatment efficacy 3 months after LD-EBRT.

Another potential confounder not only in this study but also in all other published prospective and retrospective case series might be that a lot of the patients had received diverse and other conservative therapies before being referred to LD-EBRT. An interaction between one of these other treatments and LD-EBRT cannot be ruled out due to methodological reasons. This reflects clinical reality. Still, an interaction between one of these therapies and LD-EBRT is rather unlikely and counter-intuitive, as patients were referred to LD-EBRT after the clinical failure of all the other conservative treatments.

2.2.2. Looking for the minimum effective dose: optimization of fractionation and total dose of LD-EBRT

2.2.2.1. Single dose 0.5 vs. 1 Gy

Two randomized studies investigated the efficacy of 0.5 Gy single dose in comparison to 1 Gy.

The first trial was conducted by Heyd et al. [30]. They randomized 130 patients between 6 × 0.5 Gy twice weekly (low dose) and 6 × 1 Gy (standard dose). A linear accelerator was used, applying a single field technique.

Inclusion criteria were clinical signs of a painful heel spur, radiological evidence of spur formation, patient age ≥30 years and a relapse after previous conservative treatments, in

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patients >45 years LD-EBRT could be used as the primary treatment. Endpoints of the study were changes in the "original" calcaneodynia score [31], that was documented before LD-EBRT, at the end of the course, and 6 weeks and 6 months afterward.

One hundred and thirty patients were randomized. Mean age was 58.4 years. A 102 patients suffered from a plantar, one patient from a dorsal, and 27 patients from combined spurs. In mean, patients had been suffering from symptoms for 9.8 months. The symptoms had been present in 58 patients for less than 6 months, in 72 patients for a longer time. In 7 heels LD-EBRT was the first therapeutic approach.

At the end of LD-EBRT, 66% in the low dose group vs. 59% in the standard dose experienced an improvement in symptoms, 6 weeks later 80 vs. 85%. At this time point, 1.5% in each group reported an increase in symptoms, 19 vs. 14% no change. No statistically significant differences were noted. In case of insufficient treatment results patients were offered a second EBRT series. Thus 26 vs. 37% were treated a second time. Six weeks after that, 71 vs. 79% of these patients reported a further improvement. Six months after LD-EBRT 88% of the patients in both groups had an amelioration of their symptoms, the remaining patients reported no change. During the EBRT series a slight increase in pain was reported by 26 vs. 29% of the patients. No other acute or late toxicity occurred.

In conclusion, 6 × 0.5 Gy twice weekly was as effective as 6 × 1 Gy.

These results were confirmed by a second randomized trial [32, 33]. Ott et al. randomized 457 patients between 6 × 0.5 Gy (low dose) and 6 × 1 Gy (standard dose). In contrast to the above-cited "Heyd-study" [30] an X-ray unit (orthovoltage) and not linear accelerators was used. Patients received a single field (6 × 8 cm on the plantar calcaneus) with 150 kV, 15 mA, 1 mm Cu-filter, with source-to-skin distance (SSD) of 40 cm. Six weeks after the LD-EBRT a second series was offered to patients with an insufficient response. The endpoint was pain reduction. CS score and VAS values were measured before and at the end of LD-EBRT (early response), 6 weeks (delayed), and 2.5 years (long-term) afterward.

With a median follow-up of 32 months the mean VAS values before treatment, for early, delayed, and long-term response for the 0.5 and 1.0 Gy groups were 65.5 ± 22.1 and 64.0 ± 20.5 (p = 0.19), 34.8 ± 24.7 and 39.0 ± 26.3 (p =0.12), 25.1 ± 26.8 and 28.9 ± 26.8 (p =0.16), and 16.3 ± 24.3 and 14.1 ± 19.7 (p =0.68) [31]. Similar results were obtained for the CS score without any significant differences between both dose groups.

Taken together, the above-mentioned studies proofed an equivalent clinical efficacy of 6 × 0.5 Gy in comparison to 6 × 1 Gy, thus defining a new clinical treatment standard with six times 0.5 Gy twice weekly as the minimum effective dose.

Before proofing 0.5 Gy as the new standard single dose, another randomized study tried to increase efficacy in reaching the "old" cumulative dose of 6 Gy with a single dose of 0.5 Gy. Niewald et al. randomized between 6 × 1 Gy twice a week (old "standard dose") and 12 × 0.5 Gy three times a week ("experimental dose") [25]. The aim was not just to get comparable results, but to further improve the analgesic effects. Linear accelerators (6 MV photons) applying a lateral opposing field technique were used.

Inclusion and exclusion criteria were quite similar to the ones used in the landmark study [26]: Clinical evidence of a painful heel spur, and duration of the symptoms for more than 6 months; radiological proof of a spur formation; age at least 40 years; Karnofsky-Index at least 70%. Patients with previous radiotherapy or previous trauma to the foot, rheumatic or vascular diseases, lymphatic edema, pregnancy, breastfeeding, or severe psychiatric disorders were excluded. Concomitant therapy with analgesics was allowed. However, patients receiving surgery or shock wave therapy after randomization were excluded.

Endpoints were the SF-12 sum score, the CS sum score (**Table 2**), and VAS. Follow-up was scheduled every 6 weeks for 1 year.

Two-hundred and forty patients were calculated to detect a difference of 15% in the VAS and CS score, with a power of 80%, and an error probability of 5%. After randomization of 127 patients and an interim analysis of 107 patients, the study was closed early, as the intended increase in analgesic efficacy by the experimental treatment was very unlikely to be achieved.

The mean age of the patients in the standard group was 56.1 Gy in comparison with 58.1 Gy in the experimental group. The mean duration of symptoms before initiation of LD-EBRT was 17 vs. 16 months. In 98% of the standard group and 93% of the experimental group a plantar spur was treated, in 2 and 7% a combined (plantar and dorsal) spur.

Results after 3 months have been issued so far [25], longer follow-up has yet to be published. After 3 months, there were no significant differences neither in the VAS (standard 42.3 vs. experimental 44.4) nor the CS sum score (28 vs. 28.4) nor in the QOL (SF-12) scores. Although longer follow-up has to be awaited, a further increase in the analgesic effect by applying 12 × 0.5 Gy three times a week is unlikely. This is why this fractionation schedule is currently not recommended, as it does not follow the "as low as reasonable achievable" principle of radiation protection.

2.2.2.2. Single dose 0.3 vs. 1 Gy

Further reduced single doses in LD-EBRT (with the exception of 0.1 Gy [26]) have never been tested in a prospectively randomized clinical trial. In radiotherapy of degenerative joint disorders, single doses of about 0.3–0.4 Gy were established by von Pannewitz in the late 1920s and published in 1933 and 1970 [34, 35]. However, two studies on calcaneodynia have raised serious concerns on single doses as low as 0.3 Gy.

Seegenschmiedt et al. analyzed treatment efficacy in 141 patients (170 irradiated heels), who were treated from 1984–1994 with X-ray units (250 kV/200 kV, 20 mA, 40 cm SSD), applying a single field of 6 × 8 cm [24]. Seventy-two heels received 12 Gy with 6 × 1 Gy (three times a week) –6 weeks break – 6 × 1 Gy (group A), 50 heels were treated with 10 × 0.3 Gy every day (group B1), and 38 heels 10 × 0.5 Gy every day (group B2). The endpoint was the value of a semiquantitative pain score 3 months and in mean 4 years after LD-EBRT.

The median age of patients was 55 years in group A and 59 years in group B1/B2. The mean duration of symptoms before LD-EBRT was 8 months, in one-third, the symptoms persisted for more than 6 months.

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Complete pain remission was achieved in 68–71% of the patients without significant differences between the treatment groups. However, there were differences in the clinical course of patients with partial remission of the symptoms: The best results in these patients were achieved during longer follow-up in group B1 (10 × 0.5 Gy), followed by group A (6 × 1–6 × 1 Gy), followed by group B2 (10 × 0.3 Gy). The latter group showed a significantly worse amelioration of symptoms than the other groups.

A reduced efficacy was also reported in another retrospective case series, comprising 673 heels treated with a single dose of 0.3 Gy three times weekly up to 1.5 Gy (X-ray) [36]. In case of insufficient treatment results the patients were offered a second course. After the first treatment, only 13% reported CR, nearly all patients had undergone a second LD-EBRT.

Taken together, to the best of our current knowledge a single dose of 0.5 Gy is standard of care and should only be modified in controlled clinical trials.

2.3. Risk factors potentially associated with treatment failure

In **Table 3** selected contemporary randomized trials and patient series are shown broken down into several factors that might be correlated with treatment efficacy. For a better overview, we did not differentiate between univariate and multivariate analyses. We did not try to collect all ever published data.

2.3.1. History of symptoms

Duration of symptoms before start of LD-EBRT has been shown to be correlated with treatment efficacy in numerous studies.

Muecke et al. analyzed in a retrospective multicenter study 502 patients [22]. Duration of symptoms ≤6 months was associated with 76% treatment success vs. 44% after a history >6 months. Also Seegenschmiedt et al. found in their large collectives a correlation between the duration of heel pain and treatment outcome [24]. A significant influence of duration of symptoms before LD-EBRT was also reported in 73 heels by Schneider et al. [37]. With a history of 3–6 months, the VAS value was reduced by 85%, 28 months after LD-EBRT in comparison with a reduction of 58% with a history > 6 months. Similar results were obtained by Hermann et al. in 285 heels comparing <12 month history of pain vs. >12 months [38].

In contrary, another study could not confirm these results [30].

2.3.2. Gender

To the best of our knowledge, in no study, an influence of gender on treatment outcome has been confirmed [22, 24, 30, 38, 39]. In contrast to radiotherapy for oncological indications with high doses, efficacy and tolerability of LD-EBRT seems to be the same concerning gender.

Study (citation)	[30]	[26]	[24]	[37]	[39]	[22]	[38]	[40]	[83]
Type	Rand	Rand	Prospect	Prospect	Retrospect	Retrospect	Retrospect	Retrospect	Retrospect
Number of heels	130	66	170	73	623	502	285	161	7947
Energy	MV	MV	KV	MV	KV	MV, KV	MV	KV	MV, KV
Target volume	calcaneus	calcaneus	calcaneus	entire dorsal and middle foot	insertion of plantar fascia	calcaneus	calcaneus vs. insertion of calcaneus	calcaneus	entire dorsal foot vs. calcaneus vs. insertion of plantar fascia
Dose	6 × 1 vs. 6 × 0.5 Gy	6 × 1 Gy vs. 6 × 0.1 Gy	12, 3, 5 Gy	5 Gy (increasing single dose)	1.5 (1–3) up to 9–12 Gy (1–45)	5–10 × 0.5–1 Gy	6 × 1 Gy6 × 0.5 Gy	6 × 1 Gy	0.3–1.5 Gy; 2–3x weekly 2.5–18.76 Gy
Potential factors									
History of symptoms	0	n.i.	+	+	0	+	+	+	+
Gender	0	n.i.	0	n.i.	0	0	0	n.i.	n.i.
Patient's age	0	n.i.	0	+	0	+	+	+	n.i.
Initial worsening of pain during LD-EBRT	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.	n.i.
MV vs. KV	n.i.	n.i.	n.i.	n.i.	n.i.	+	n.i.	n.i.	0
Number of therapy series	n.i.	n.i.	n.i.	+	n.i.	+	n.i.	n.i.	+
Heel stress during LD-EBRT	n.i.	0	n.i.	+	n.i.	n.i.	n.i.	n.i.	n.i.

Note: 0: no correlation with treatment outcome; +: correlation with treatment outcome; n.i.: not investigated; prospect: prospective case series; rand: randomized clinical trial; retrospect: retrospective case series; KV: kilovoltage; MV: megavoltage.

Table 3. Factors associated with treatment efficacy in contemporary studies.

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2.3.3. Patients' age

Several studies described a correlation between older age and better treatment results, at least 6 weeks after LD-EBRT [37]. Age somewhat over 50 years seems to be important: >50 years [40], > 53 [38], or > 58 [22]. For a possible explanation see Section 2.3.7.

However, other studies found no influence of this patient characteristic on treatment outcome [24, 30, 39].

2.3.4. Initial increase in pain during LD-EBRT

A very precise registration of changes in pain intensity (VAS) was done by Schneider at al. [37]. Sixty-two patients (73 treated heels) were prospectively scored every week during LD-EBRT, at the end of therapy, 6 weeks, 28 months, and 40 months later. Additionally, subjective mechanical heel stress during LD-EBRT was estimated. A linear accelerator (10 MV) was used, applying one single field with a size of 12 × 17 cm. Patients were treated twice a week to a total dose of 5 Gy, with increasing single fraction doses (0.25 – 0.25 – 0.5 – 1 – 1 – 1 – 1 Gy). Mean patient age was 54 years, and all had a radiologically proven plantar spurn, mean symptom duration before LD-EBRT was 6.5 months. Nearly all patients had received other conservative therapies before LD-EBRT with insufficient results.

Interestingly, VAS scores decreased continuously during LD-EBRT: before treatment the mean value was 6.3 ± 1.5, after the first week of LD-EBRT 6.2 ± 1.8, after the second week 5.5 ± 2 ($p < 0.05$), after the third 4.7 ± 2.4, and 3.8 ± 2.1 at the end of therapy ($p < 0.001$). Six weeks later the value further decreased to 3 ± 2.5 ($p < 0.004$), 28 months after LD-EBRT to 1.6 ± 2.2 ($p < 0.01$). One year later no further decrease was noticed (1.8 ± 2.3). Only two patients reported intensification of pain during the LD-EBRT series. However, these data are not to be extrapolated, as increasing single doses (see above) were used to avoid this phenomenon.

In standard schedules with fixed single doses a slight increase in pain during the treatment series was reported by 26% (during 6 × 0.5 Gy) vs. 29% (6 × 1 Gy) of the patients [30]. Unfortunately, a possible correlation of this phenomenon with definite treatment results was not investigated.

Without further quantification, another study (6 × 1 vs. 6 × 0.1 Gy) stated, that this initial increase in symptoms "had no influence on the final pain relief 3 and 12 months after treatment" [26]. Older studies postulated a temporary reduction of the pH value in the irradiated tissues at the beginning of the treatment series, without consequences for the long-term efficacy of LD-EBRT [41].

This is contrasted by observations of LD-EBRT in peritendinitis humeroscapularis [42]. In 73 patients (86 shoulders) initial increase of pain during the treatment course was significantly associated with a good response.

2.3.5. Use of megavoltage techniques/linear accelerators

Muecke et al. analyzed in a retrospective multicenter study the influence of different treatment techniques in 502 patients [22]. Treatment failure was defined as pain persistence after

LD-EBRT and recurrence of pain during follow-up. Treatment with MV (6–10 MV) was a significant prognostic factor for pain relief in multivariate analysis, as MV was associated with an eight-year event-free probability of 68 vs. 61% after X-ray beams (175 kV). There are two possible explanations for this finding: besides the possibility of a random result, the authors postulate a more homogenous dose distribution with MV treatment in comparison with KV [22].

2.3.6. Number of therapy courses required

Schneider et al. reported an efficacy of just one-third after a second LD-EBRT course (so-called "re-irradiation") in comparison with the effects of the first course [37]. Out of 73 heels treated with 5 Gy LD-EBRT 18 heels received reirradiation due to insufficient treatment response. However, pain reduction measured by means of changes in VAS shortly after the second course and during long-term follow-up was significantly diminished in comparison with the efficacy of the first course (about 30% reduction in pain at the last evaluation vs. 86%).

Similar results were obtained in the large retrospective series (502 patients) by Muecke et al. [22]. Treatment failure was significantly associated with the number of treatment series: eight-year event-free probability was about 70% after the first course in comparison with just about 30% after reirradiation.

A systematic study on the efficacy of a reirradiation has been published by Hautmann et al. [43]. Eighty-three patients (101 heels) with insufficient response to the first course or recurrent pain afterward due to plantar fasciitis (83 heels), or achillodynia (28 heels) received a second LD-EBRT course in median 10 weeks (range 4 weeks to 63 months) after the first LD-EBRT. About 75% of the patients were treated with 6 × 1 Gy, the others 6 × 0.5 Gy. The pain was assessed using the numeric rating scale (NRS) before and at the end of LD-EBRT, 6, and 12 weeks, and 6, 12, and 24 months thereafter.

Before reirradiation NRS values were 6 (interquartile range 5–8), at the end of LD-EBRT 5 (2–6), 6 weeks later 2 (1–4), at 12 weeks 1 (0–3), at 6 months 0 (0–2), at 12 and 24 months 0 (0–1). Interestingly, not only the patients with recurrent pain after the first course but also patients with insufficient responses to the first course experienced a profound and long-lasting amelioration of their symptoms after the second course.

This is why a second treatment course should be recommended in case of insufficient efficacy of the first course.

2.3.7. Heel stress during LD-EBRT

A significant correlation between avoidance of heel stress during LD-EBRT and efficacy of LD-EBRT 6 weeks after therapy was reported by Schneider et al. in 73 heels [37]. With a Pearson's correlation coefficient of -0.467 ($p < 0.01$) there was an impressing influence of this variable on pain reduction measured by VAS values. However, this correlation was not seen 28 and 40 months after LD-EBRT.

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An intuitive explanation is given by the authors [37]: As patient age was associated with positive treatment results, too, they proposed that older patients are often retired, thus being able to take more care of their heels.

2.3.8. Spur size

Interestingly, all randomized trials required the radiological proof of a heel spur before including patients into the studies. Furthermore, most of the prospective and retrospective series warranted such an objective sign. However, as a substantial part of the patients suffers from plantar heel pain without having developed a heel spur, LD-EBRT should be effective in these patients, too.

Hermann et al. analyzed treatment efficacy in 250 patients (285 heels), who received LD-EBRT predominantly with 6 × 1 Gy [38]. In this series, 33% of the treated heels were without radiological evidence of a spur. In 185 patients a spur was confirmed with a mean length of 6.5 mm (range 0.6–25 mm). Patients without evidence of a plantar heel spur had a significantly higher chance of CR after LD-EBRT (43 vs. 35%). Furthermore, the length of the spurs correlated directly with treatment outcome. Spurs >6.5 mm had just a 30% chance of experiencing CR in comparison with shorter ones. No statistical differences were found between treatment results of heels without spurs and those with spurs ≤6.5 mm.

Miszczyk et al. reported on 327 patients (623 LD-EBRT series) mostly treated with X-ray (180 kV, usually 1mm Cu filters) with single doses of 1.5 Gy (range 1–3 Gy) up to a total dose between 9 and 12 Gy (range 1–45 Gy) [39]. Mean spur size was 9 mm (range 1–30 mm). With a mean follow-up of 74 months, no correlation between spur size and duration of pain relief was found. Analysis concerning spur length and treatment outcome in itself were unfortunately not reported.

2.3.9. The combination of different factors

Multivariate logistic regression enables the identification of factors independently predicting treatment outcome. By combining these factors, models can be calculated, that predict treatment outcome with a high probability. An example from the study of Hermann et al. is given in **Table 4**: in 285 heels treated with 6 × 1 Gy/6 × 0.5 Gy the influences of the patient characteristics age, spur length, and duration of symptoms before LD-EBRT alone and in combination were calculated [38]. The best results were obtained for patients > 53 years, spur length <6 mm, and a duration of symptoms <12 months with a probability for CR of 55% (CI 36–73%) and PR of 38% (CI 22–58%). Without these characteristics, the chance for CR was just 18% (CI 9–33%), for PR 31% (17–48%).

2.4. Technique

In modern radiotherapeutic departments, X-ray sources are less and less available. This is why nowadays most patients are treated with linear accelerators, which were initially developed for the treatment of oncological diseases. However, these machines can be used in the treatment of benign diseases without any modifications or problems. Due to the high efforts in physical, technical, and organizational quality assurances for the operation of an accelerator or an X-ray source, the concentration on accelerators and their use for all indications is recommended.

Patient's age >53	No spur or spur ≤6.5 mm	Duration of symptoms <12 months	Probability of		
			No change	Partial remission	Complete remission
1	1	1	0.07 (0.03–0.14)	0.38 (0.22–0.58)	0.55 (0.36–0.73)
1	1	0	0.13 (0.07–0.28)	0.37 (0.21–0.57)	0.50 (0.30–0.70)
1	0	1	0.15 (0.06–0.24)	0.53 (0.33–0.72)	0.32 (0.17–0.53)
1	0	0	0.25 (0.13–0.45)	0.48 (0.27–0.69)	0.27 (0.13–0.48)
0	1	1	0.17 (0.10–0.31)	0.33 (0.19–0.50)	0.50 (0.33–0.66)
0	1	0	0.34 (0.20–0.53)	0.40 (0.24–0.59)	0.26 (0.13–0.45)
0	0	1	0.30 (0.20–0.46)	0.29 (0.18–0.43)	0.41 (0.27–0.56)
0	0	0	0.51 (0.35–0.69)	0.31 (0.17–0.48)	0.18 (0.09–0.33)

Table 4. Probabilities (95%-CI) for NC, PR and CR calculated by polytomous logistic regression in dependence of the risk factors age, spur length, and duration of symptoms before LD-EBRT according to Hermann et al. in a collective of 285 heels treated with 6 × 1/6 × 0.5 Gy (taken from [38]).

For irradiation of the heel, the patient has to be placed on the treatment couch with the feet toward the gantry of the accelerator (so-called "feet first"). Two different patient positions are widely used. He can be placed in supine position, with the irradiated leg is stretched out, while the other leg is angled. Another option is to place the patient in a lateral decubitus position on the side of the involved heel. Again, the symptomatic leg is stretched, while the contralateral leg is bent, with a cushion placed beneath the knee. Using X-rays, the ipsilateral knee is bent by 90% and the foot is positioned on the treatment table. One anterior-posterior (AP) beam is usually applied in this technique.

For the treatment itself, there are also two different options. Irradiation may be given as a single stationary field (SSD 100cm by convention). Alternatively, parallel opposing fields from 0° and 180° gantry position (in decubitus position) or lateral opposing fields (90° and 270° in supine position) are also applicable but take a little bit longer in daily clinical practice. The hypothetical advantage of using two opposing fields is a uniform dose distribution in the entire beam path in the calcaneus (**Figure 1**). However, there has never been a clinical proof, whether this theoretical assumption translates into any clinical advantage for the patient. When applying opposing fields, the dose is specified according to the ICRU 50 report, normally in the center of the calcaneus.

A third option is the so-called "plantar field" with the patient lying in prone position. A single field is positioned directly over the plantar insertion/calcaneus, potentially with rotations of the patient table and the gantry to compensate for inclinations of the patients surface in the irradiated field. However, this technique is regarded problematic when using linear accelerators due to the dose build-up effect in the critical tissue depth. This problem is illustrated in **Figure 2**: photons with 6 MV reach just the half of the prescribed dose at the skin level, 100% is reached at 1.5 cm tissue depth. This would result in an insufficient dose in the critical structures (plantar fascia and heel spur). To overcome this problem, a silicone flap of about 1 cm diameter must be positioned on the skin before radiation.

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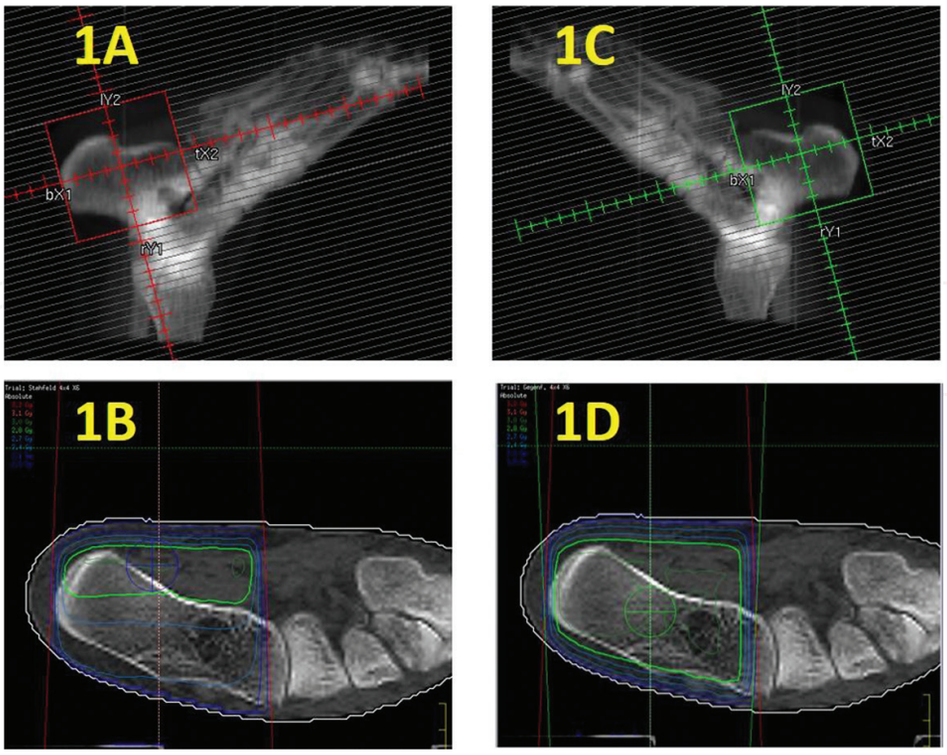


Figure 1. Dose distribution of two different treatment techniques generated in a treatment planning system (XIO®). In A and B just one single 6 MV photon field (8 × 8 cm) is applied, while C and D shows the dose distribution with two opposing fields from 0 and 180°. In the upper row, the so-called "beams eye views" are given, while in the lower row the respective dose distributions on an axial CT scan directly at the calcaneal insertion are shown. Note the more uniform dose distribution with opposing fields. The 95% isodose is given as a green line (2.85 Gy). This dose encompasses larger parts of the calcaneal bone in D (opposing fields) than in B (single field). More information is given in Section 2.4.

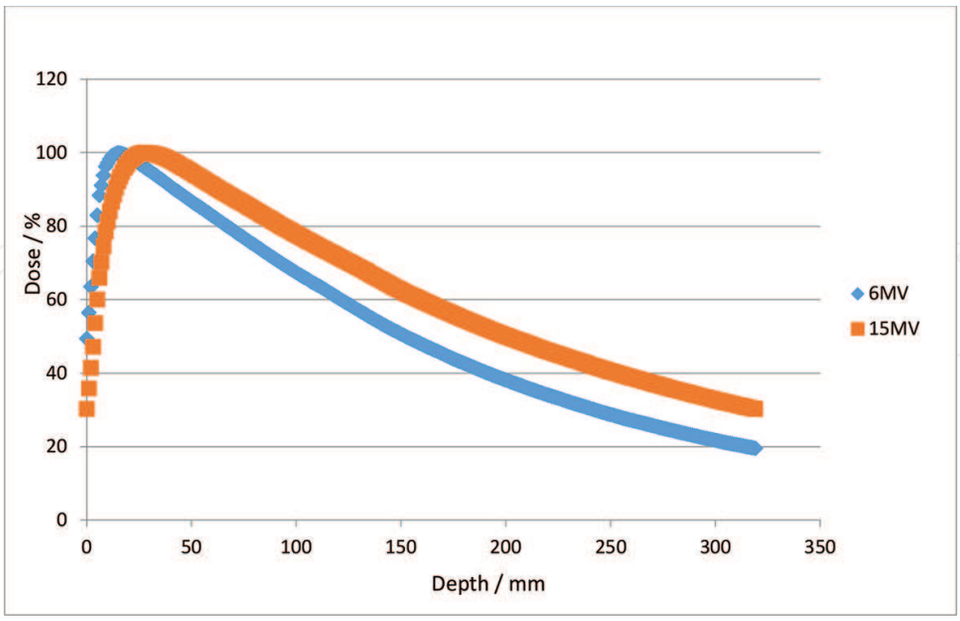


Figure 2. Depth curves of different megavoltage energies. Blue 6 MV photons, red 15 MV photons. At the surface of the body/skin (depth 0 mm), only half (or even less with 15 MV) of the prescribed dose is applied. By physical interactions between photons and the tissue/water, there is a steep increase in dose. A 100% is reached at 1.5 cm depth with 6 MV and at about 3 cm depth with 15 MV. KV-radiation reaches the maximum dose directly under the surface/skin (not shown). More information is given in Section 2.4.

3. Toxicity and potential risks of LD-EBRT

Patients are often sent to the radiotherapist after a long unsuccessful history of diverse conservative treatments. The reason for this is a widespread fear among general practitioners that LD-EBRT might be associated with severe side effects and risks. These fears are not substantiated, as reactions of the nerves or vessels require much higher doses than used for LD-EBRT. For example, a dose of 45 Gy in normofractionated oncological therapy is considered to be safe for the spinal cord and therefore daily clinical practice [44]. Peripheral nerves are even more radioresistant. Acute or chronic side-effects have never been reported in all contemporary studies on LD-EBRT.

3.1. Acute reactions of the skin

Acute side effects are negligible, as very low doses of ionizing radiation (in comparison with oncological treatments) are applied to a distal extremity. The total dose of LD-EBRT with 3 or 6 Gy is far too low to cause any acute or late reactions on the skin overlaying the calcaneus. During normofractionated EBRT (single doses of 1.8–2 Gy, treatment on 5 days a week) erythema and mild edema develop at about 30 Gy [45]. Hyperpigmentation occurs at about 45 Gy, moist epitheliolyses at about 50 Gy. A 50–60 Gy might cause telangiectasias years after the therapy. This is why there is no report on acute treatment side effects in LD-EBRT until now to the best of our knowledge.

3.2. Initial increase in pain during LD-EBRT

About one-third of the patients might experience a slight increase in pain during LD-EBRT. In the randomized trial by Heydt et al. this phenomenon was seen in 26% (during 6 × 0.5 Gy) vs. 29% (6 × 1 Gy) [30]. It does not seem to be correlated with treatment outcome; further detailed information is given in Section 2.3.4.

3.3. Impairment of gonad function

The dose scattered to the male gonads is somewhat higher than to the ovaries. Jansen et al. calculated for 6 × 0.5 Gy about 1.5 mSv received by the testes and 0.75 mSv to the ovaries [46]. Comparable results have repeatedly been measured in the past [47, 48].

Taken together, the dose received by the gonads is insignificant. As the distal extremity is irradiated, scattered dose to the gonads is comparable to normal diagnostic radiological imaging [49]. The hereditary effects of these doses are very small and very likely negligible [46].

Although spermatogonial cells are very radiosensitive, a single dose of at least 100 mSv is needed to induce a temporary failure of spermatogenesis [50]. A single dose of 1000 mSv (equivalent to 1 Gy photon irradiation) results in an azoospermia for 9–18 months [51]. Interestingly, fractionated doses harm these cells even more. A temporary oligospermia is reported after receiving several fractions up to a cumulative dose of 160 mSv [52]. An azoospermia lasting for 14–22 months has been reported for fractionated doses of 620–860 mSv [53]. The actually during LD-EBRT received testicular dose is about 100 times smaller than the lowest dose causing temporary changes in testicular tissues.

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The dose to the testicles can be further reduced by utilizing a special testicular shielding. However, clinically meaningful dose reductions have been only measured in MV treatment of subdiaphragmatic/pelvine lymphatic regions or tumors [54, 55].

The mean lethal dose for human oocytes has been estimated at 2 Gy (2000 mSv) [56]. Permanent ovarian failure after radiotherapy is age dependent: in perimenopausal women, a dose of 6 Gy is sufficient [57], while in younger women up to 20 Gy are tolerated. The dose scattered to the ovaries during LD-EBRT for calcaneodynia cannot cause such sequelae (0.75 mSv).

Naturally, pregnancy has to be excluded in all premenopausal women before beginning with LD-EBRT, to avoid any risk to the fetus.

3.4. Induction of malignancies

So far, no studies with long-term observation periods have been published, describing a case of malignancy induced by LD-EBRT for calcaneodynia. However, induction of malignancies is a stochastic effect of ionizing radiation. This means that there is no threshold dose—in contrast for example to the above-mentioned reactions of the skin. A photon can accidentally trigger a mutation, which in turn leads to tumor formation many years later. The higher the radiation dose, the higher the probability of such an event occurring.

The best available data on tumor induction of full dose EBRT in oncology has been collected in patients treated with breast cancer. Almost 11,000 patients have been followed for over 20 years. The risk of a radiation-induced tumor was approx. 1% per decade after radiotherapy [58].

To estimate the risk associated with much lower doses of LD-EBRT, mathematical models on the basis of epidemiological long-term observations of atomic bomb victims have been developed by the ICRP [59].

Jansen et al. applied the ICRP model on LD-EBRT of a painful heel spur [46]. Assumed was a single field entering at the foot sole with a size of 8 × 10 cm, 200 kV photons, SSD 40 cm. For an LD-EBRT series with 6 × 1 Gy the average attributable lifetime risk for induction of a fatal tumor was calculated to be about 0.5 in a thousand patients. An important risk factor for radiogenic-induced cancer is the patient's age by the time the radiation exposure occurs. The risk is already reduced in the 3rd decade of the patient's life, it starts to decrease steadily from the age of 40 [60]. Applying these calculations, the estimated lifetime risk per one thousand patients for a fatal tumor accounts for the age of 25 0.6 (male)/0.8 (female), for the age of 50 0.2/0.3, for the age of 75 0.07/0.1 [46].

However, it must be critically noted that this mathematical model was developed for radiation protection and relates to the exposure of complete organ systems with approx. 1 Gy. Therefore, other groups argue that a significantly lower risk of radiogenic cancer induction—approx. ten times less—should be adopted [49, 61]. Furthermore, taken the new standard scheme with 6 × 0.5 Gy into account, these risks are additionally halved.

This risk (max. 1/1000, very likely much lower) must be seen in relation to the tumor risk of the not additionally radiotherapeutical-treated population. In 2008, the lifetime risk of a man

in Germany to suffer from cancer was 50.7% (25.9% to die from malignancy), in women 42.8% and 20.2% respectively [62].

By limiting the application of LD-EBRT treatment to patients > 30 years of age, an exposure of the juvenile "relatively higher risk" patient population is avoided.

4. Future perspectives: Definition of questions in further randomized trials and future research

4.1. Target volume definition in LD-EBRT

Traditionally target volume definition has been quite large. Field sizes of 12 × 17cm were treated, including the entire dorsal and middle foot, and not just the calcaneus [37, 82] (**Figure 3A**).

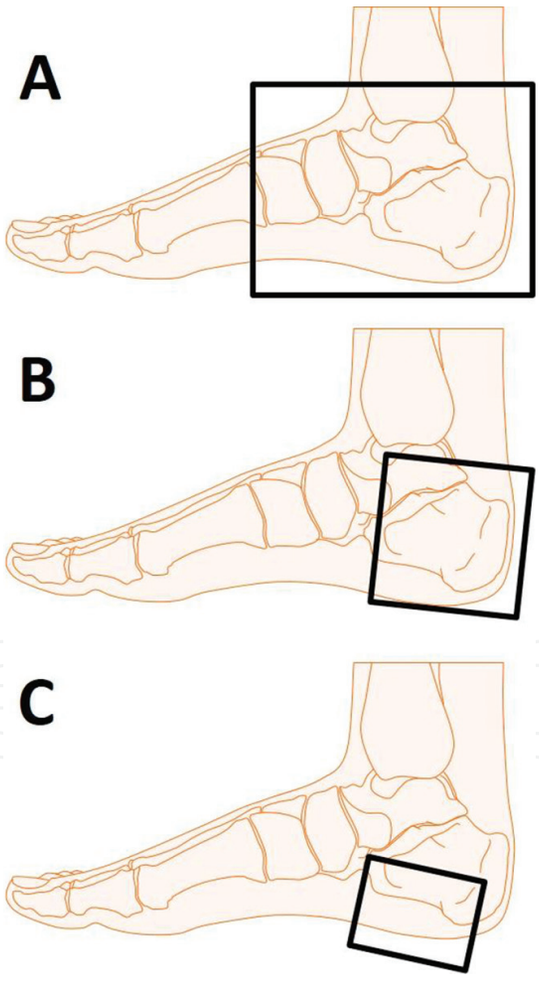


Figure 3. Field definitions in LD-EBRT of a painful plantar heel spur/fasciitis. (A) traditional field definition including the entire dorsal and middle foot. (B) In randomized trials and large prospective series commonly used field definition encompassing the entire calcaneus, including insertion of the plantar fascia and the Achilles tendon. (C) Proposed small field definition for localized painful plantar fasciitis/plantar spur, encompassing only the painful area with 2 cm margins extending into the neighboring areas (calcaneus, fascia, fat pad).

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In the recent randomized trials and prospective observational studies target volume definition was more restricted and confined to the calcaneus (**Figure 3B**). "The target volume consisted of the calcaneus and the region of the plantar aponeurosis" [26]. "The ventral margin is corresponding to the ventral surface of the calcaneus, the plantar and dorsal margins are surrounding the soft-tissue border, and the cranial margin is below the ankle" [30]. "Target volume is the calcaneus, normally with a field size of 6 cm × 8 cm" [32]. "The calcaneus and the plantar aponeurosis were included in the target volume" [25].

In a German national survey 2001 on LD-EBRT of painful heel spurs the target volume definition "large" (dorsal and middle foot) vs. "small" (entire calcaneus) was not correlated with treatment outcome [83]. Consequently, very large field definitions should be regarded as obsolete.

However, as the pathophysiological cause of calcaneodynia is thought to be a localized inflammatory process (see Section 1), it is questionable, whether the entire calcaneus has to be irradiated (as long as there are not a plantar as well as a painful dorsal spurs). There are some clinical data that support a further restriction of target volume definition.

Field sizes have been given in the study by Miszczyk et al. on 327 patients treated with X-ray beams [39]. Target volume was "… the insertion of the plantar fascia with a calcaneal spur and a reasonable margin. The field size varied from 27 to 150 cm^2 (mean 47 cm^2)." However, although not explicitly stated, no correlation was found between field size and duration of pain relief after LD-EBRT. Treatment efficacy in itself was apparently not investigated.

In the above-mentioned series of 285 heels Hermann et al. analyzed treatment efficacy in dependence of field sizes, too [38]. The mean field size was 74 cm^2. No correlation between field size (smaller vs. larger than 74 cm^2) with treatment efficacy was found. Further analyses of small fields (< 6 × 6 cm), medium-sized fields (36–64 cm^2) and larger fields revealed no significant differences.

This is why it seems to suffice to encompass the painful region with 2 cm margins extending into the neighboring areas (calcaneus, fascia, fat pad; **Figure 3C**). However, this recommendation is deducted from pathophysiological considerations and the above-mentioned case series. A randomized trial is necessary to proof clinical equivalence of a field definition "entire calcaneus" (**Figure 3B**) vs. "insertion of the plantar fascia" (**Figure 3C**).

4.2. Fractionation of LD-EBRT

The optimal fractionation schedule has not been elucidated yet. All randomized trial used twice weekly treatments. Only one experimental arm was scheduled three times a week [25]. In a National Survey in Germany with 146 answering institutions, about 45% applied two fractions and 37.5% three fractions weekly [83].

Interestingly, in the landmark study by von Pannewitz a fractionation schedule of only once per week was established [34]. Until now, there is no proof of a higher efficacy applying LD-EBRT twice or three times per week.

In radiotherapy of another benign disease (endocrine orbitopathy) a 1 Gy per week over 20 weeks schedule was more effective than the standard schedules (10 × 2 Gy or 10 × 1 Gy every working day) [84]. Although other immunological mechanisms cause endocrine orbitopathy in comparison with plantar fasciitis, there is sufficient clinical evidence to test in a randomized trial different fractionation schedules (twice a week vs. once a week, possibly thrice a week).

4.3. Comparison of LD-EBRT with other therapies

Other therapies than LD-EBRT have been applied in painful heel spur. In the following, just a rough overview can be given.

Different kinds of insoles and foot orthoses have been developed. The goal was to reduce plantar contact pressure and to distribute the pressure uniformly over the whole rearfoot [63]. Magnetic insoles do not seem to provide additional benefit [64]. As a short-term treatment, low-Dye taping techniques are often used. However, in a randomized trial only a modest improvement in 'first-step' pain was seen in comparison with sham-intervention [65].

Manual stretching is often recommended. A systematic review of six studies found only statistically significant differences in comparison with the control in one study combining calf muscle and plantar fascia stretches [66].

Several trials have investigated acupuncture. A systematic review from 2010 showed (limited) evidence for the effectiveness [67]. A randomized trial published in 2014 recruited 84 patients [68]. The authors concluded, that "dry needling provided statistically significant reductions in plantar heel pain, but the magnitude of this effect should be considered against the frequency of minor transitory adverse events."

Ultrasound therapy has led to questionable results [69], but a randomized trial on cryo-ultrasound with about 100 patients published in 2014 showed good effectiveness [70].

Low-level laser light (635 nm), given twice a week for a total of six applications, reduced in a randomized trial VAS scores significantly after 8 weeks in comparison with placebo [71]. However, the study comprised of just 69 patients; other similar studies have not been reported so far.

Extracorporeal shock waves are widely applied. Three metaanalyses comprising at least five randomized trials found significant short-term pain relief and improved functional outcomes for this therapeutic option [72–74]. Another study compared the analgesic efficacy of ultrasound and shock wave therapy in 47 patients [75]. The results suggested that the shock wave therapy had greater analgesic efficacy.

Another basic approach is the oral administration of nonsteroidal anti-inflammatory drugs (NSAID) to achieve a symptomatic relief. Injections into the painful area are also recommended. A recent review summarized ten randomized trials on corticosteroid injections into the plantar fascia [76]. A significant effect of the steroids on the pain has been shown. However, it was usually short-term, lasting 4–12 weeks in duration. No advantage of ultrasound-guided injection techniques in comparison with palpation guidance was found, and no superiority of one type of corticosteroid over another was seen. A longer lasting pain relief has been suggested

by a small randomized trial of botulinum toxin injections [77]. Another option is the injection of autologous platelet-rich plasma. A recent review identified three randomized trials, all showing promising results [78]. However, a very small trial challenged this method of plasma preparation, as the same clinical effectivity was observed after the injection of whole blood [79].

Different surgical approaches have been developed. Releases of the plantar fascia are done, in some studies combined with a spur resection [80]. Due to a probably faster recovery after surgery with comparable functional results endoscopic procedures are recommended nowadays [81]. Surgery is usually indicated after failure of conservative therapies as the ultimate "salvage-therapy."

There is only a limited amount of studies randomizing patients between LD-EBRT and the above-mentioned alternative therapies.

Canyilmaz et al. randomized 123 patients between LD-EBRT (6 × 1 Gy, three times a week) and 1 ml injection of 40 mg methylprednisolone and 0.5 ml 60 mg 1% lidocaine under the guidance of palpation [85]. After 3 and 6 months, VAS values and CS-scores were compared between both groups. After 3 months, the results in the radiotherapy arm were significantly superior compared with those after injections.

To corroborate these findings, similar studies should be conducted. Furthermore, more studies randomizing LD-EBRT against other therapies (e.g. extracorporeal shock waves) are needed. A minimum size of 50 patients per treatment arm should be assured to gain more statistically relevant results. Recruiting patients without prior excessive other therapies for these studies would be optimal.

The goal must be an evidence-based algorithm defining the therapeutic sequence of the different conservative treatment modalities for plantar fasciitis.

5. Conclusions

LD-EBRT for painful plantar fasciitis/heel spur is an effective and safe treatment option for patients over 30 years of age and after exclusion of pregnancy. A fractionation of 6 × 0.5 Gy twice weekly up to a total dose of 3 Gy is currently recommended. In the case of an insufficient response a second course can be offered to the patient.

Randomized trials on target volume definition and further optimization of LD-EBRT fractionation are currently in the process of planning. Further trials to compare the different conservative therapies for plantar fasciitis with each other are necessary to allow the development of an evidence-based treatment algorithm.

Acknowledgements

This chapter is dedicated to Professor Gisela Hermann-Brennecke on the occasion of her 70th birthday.

Abbreviations

AP	anterior-posterior
CI	confidence interval
CR	complete remission
CS	Calcaneodynia score
Cu	chemical element symbol for copper
EC	endothelial cells
GCG-BD	German Cooperative Group on Radiotherapy for Benign Diseases
Gy	Gray
ICRP	International Commission on Radiological Protection
IL	interleukin
iNOS	inducible nitric oxide synthases
KV	kilovoltage
LD-EBRT	low dose external beam radiotherapy
mA	milliampere
mRNA	messenger ribonuclein acid
mSv	milliSievert
MV	megavoltage
NC	no change
NF-κB	nuclear factor kappa B
NO	nitric oxide
NSAID	non-steroidal anti-inflammatory drug
PBMC	peripheral blood mononuclear cells
PR	partial remission
QOL	quality of life
ROS	reactive oxygen species
SSD	skin-to-source distance
TGF-β_1	transforming growth factor β_1
VAS	visual analogue scale

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