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ORIGINAL ARTICLE

Radiotherapy of painful heel spur with two fractionation regimens

Results of a randomized multicenter trial after 48 weeks' follow-up

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Abstract
Background In this randomized multicenter trial, we compared the effect of a lower single dose of 0.5 Gy vs. a standard single dose of 1 Gy concerning pain relief and quality of life, while maintaining a uniform total dose of 6 Gy. On the basis of laboratory observations, the lower single dose would be expected to be more effective.
Patients and methods A total of 127 patients suffering from painful heel spur were randomized: Patients in the standard group were treated with single fractions of 6 × 1 Gy twice a week, while the experimental group was treated with single fractions of 12 × 0.5 Gy three times a week. Patients who did not show satisfactory pain relief after 12 weeks were offered re-irradiation with the standard dose. The study's primary endpoints were pain relief and quality of life. Therapy results were evaluated and compared based on follow-up examinations after 12 and 48 weeks.
Results The data of 117 patients could be evaluated. There was no significant difference between the groups concerning the results of a visual analogue scale (VAS), Calcaneodynia Score (CS), and the somatic scale of the 12-Item Short-Form Health Survey(SF-12). Patients undergoing re-irradiation showed a significant benefit concerning pain relief. Their total outcome was comparable to patients showing a good response from the beginning. No relevant acute or chronic side effects were recorded.
Conclusion Both patient groups showed good results concerning pain relief. A fractionation schedule of 12 × 0.5 Gy was not superior to the current standard dose of 6 × 1 Gy. Further trials are necessary to explore the best fractionation schedule.

Keywords Radiotherapy · Calcaneal spur · Pain · Quality of life · Analgesia

Author contributions B. Prokein wrote the manuscript, performed follow-up examinations, and was responsible for the data acquisition. M. Niewald is the principal investigator of this trial, enrolled the patients, performed follow-up examinations, supervised the data acquisition and evaluation, and corrected the manuscript. H. Holtmann performed follow-up examinations, was responsible for the data acquisition, and corrected the manuscript. M.G. Hautmann and H.-P. Rösler enrolled and treated patients in their departments, performed the follow-up examinations, and corrected the manuscript. S. Graeber was responsible for the data evaluation and statistics. Y. Dzierma was responsible for the physical plans for the patients, created the figures, and revised the manuscript. J. Fleckenstein supervised the daily radiotherapy of the patients and revised the manuscript. C. Ruebe supervised the radiotherapy and revised the manuscript. All authors read and approved the final manuscript.

Strahlentherapie des Fersensporns mit 2 Fraktionierungsschemata

Ergebnisse einer randomisierten Multizenterstudie nach 48 Wochen Follow-up

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Zusammenfassung

Hintergrund In dieser randomisierten Multizenterstudie wurde der Effekt einer niedrigen Einzeldosis von 0,5 Gy hinsichtlich Schmerzen und Lebensqualität mit demjenigen einer Standarddosis von 1,0 Gy verglichen, dies bei konstanter Gesamtdosis von 6 Gy. Nach Laborergebnissen war eine Überlegenheit der niedrigen Einzeldosis zu erwarten.

Patienten und Methodik Es wurden 127 Patienten randomisiert – einerseits in die Standardgruppe mit 6 Fraktionen à 1,0 Gy 2-mal pro Woche, andererseits in die experimentelle Gruppe mit 12 Fraktionen von 0,5 Gy 3-mal pro Woche. Patienten mit ungenügendem Ansprechen nach 12 Wochen wurde eine zweite Strahlentherapieserie mit der Standarddosis angeboten. Die Endpunkte waren die Schmerzlinderung sowie die Besserung der Lebensqualität. Diese Parameter wurden 12 und 48 Wochen nach Strahlentherapie ausgewertet.

Ergebnisse Die Daten von 117 Patienten waren auswertbar. Es fand sich kein signifikanter Unterschied zwischen den Gruppen hinsichtlich der Ergebnisse auf einer visuellen Analogskala (VAS), des Calcaneodynie-Scores und des somatischen Teils des SF-12-Fragebogens. Patienten mit ungenügendem Ansprechen profitierten deutlich von einer zweiten Therapieserie. Deren Ansprechen war ebenso gut wie bei Patienten, die bei der ersten Serie gut auf die Therapie angesprochen hatten. Akute und chronische Nebenwirkungen wurden nicht beobachtet.

Schlussfolgerung Beide Patientengruppen zeigten ein gutes Ansprechen hinsichtlich Schmerzlinderung und Lebensqualität. Die Ergebnisse nach der geringeren Einzeldosis mit 12-mal 0,5 Gy waren hingegen nicht besser als diejenigen nach der Standarddosis von 6-mal 1 Gy. Weitere Studien zur Festlegung der optimalen Einzeldosis sind notwendig.

Schlüsselwörter Strahlentherapie · Fersensporn · Schmerz · Lebensqualität · Analgesie

Background

In 1900, on the basis of radiological findings, Plettner described the presence of a bony heel spur on the medial surface of the calcaneus at the insertion spot of the plantar aponeurosis [1]. The incidence of heel spurs in an unselected population ranges from 8 to 88% [2, 3] and increases with age [4, 5]. Further risk factors are obesity, women aged >40 years [4], as well as rheumatoid and chronic arthritis [6]. Data on the symptoms, pathomechanisms, and other therapy treatment options are reported elsewhere [5, 7].

Recent laboratory studies have shown that single doses in the range of 0.3–0.7 Gy might be more effective than higher single doses of 1 Gy concerning anti-inflammatory effects. Hildebrandt et al., for example, observed reduced adhesion of mononuclear cells to EA.hy926 endothelial cells by up to 40% in vitro 24 h after irradiation with doses of 0.3–0.6 Gy [8]. In the same range of 0.3–0.7 Gy, Roedel et al. showed a minimum adhesion of peripheral blood mononuclear cells (PBMCs) to endothelial cells and reduced expression of E-selectin. Apoptosis of macrophages was highest in the range of 0.3–0.5 Gy. Endothelial cells showed the highest induction of transforming growth factor beta1 (TGF-β1) and interleukin 6 (IL-6) at 0.5 Gy [9–11]. Nuclear factor (nf)-κB DNA-binding activity in EA.hy.926 endothelial cells was increased at 0.5 Gy [9]. Gaipl et al. described a peak in activity-induced cell death in polymorphous nuclear cells at 0.3 Gy [12]. In 2002, Roedel et al. showed that low-dose radiotherapy in the range of 0.6–1.25 Gy reduced nitric oxide (NO) production and inducible nitric oxide synthetase (iNOS)-protein expression in stimulated macrophages. The iNOS-mRNA expression was not affected [10]. Additionally, Hildebrandt et al. observed a reduction of iNOS in macrophages in vitro after single doses of 0.6 Gy [13]. Furthermore, single doses of 0.5–1 Gy were associated with a reduction of TGF-β1 induced CCL-20-chemokine expression and reduced adhesion of granulocytes to endothelial cells [14]. Activator protein-1 (AP-1) shows a biphasic induction and transcriptional activity with a first relative maximum at 0.3 Gy, followed by a decrease at doses between 0.5 and 1 Gy and a subsequent increase again at 3 Gy [15]. Expression of X-linked apoptosis inhibitor (XIAP) in activated EA.hy926 endothelial cells exhibited a relative maximum at doses of 0.5 Gy and 3 Gy and a minimum of apoptotic cell death at 0.5 Gy [16]. Single doses of 0.5–0.7 Gy led to a reduced E-selectin and L-selectin expression and a reduced expression of IL-1 and CCL-20 from macrophages and polymorphous nuclear cells [17]. After low-dose radiation, Large et al. showed discontinuous expression and enzymatic activity of glutathione peroxidase (GPx) in EA.hy926 and human dermal microvascular endothelial cells (HMVEC). Simultaneously, the DNA-binding activity of Nrf2 (transcription factor) was reduced. These effects exhibited a maximum at single doses of 0.5 Gy [18]. Another publication by Schaue et al. reported increased levels of hemioxigenase-1 (HO-1) with a maximum at single doses of 0.5 Gy and 1 Gy in mice [19].

Based on these findings, we conducted a clinical prospective randomized multicenter trial in order to explore and compare the analgesic effects of the (at that time) standard single dose of 1 Gy with a reduced dose of 0.5 Gy using a uniform total dose of 6 Gy. In addition, we investigated the effects on quality of life.

Patients and methods

In order to participate in this study, the following inclusion criteria were required:

- Clinical evidence of a painful plantar heel spur with a persistence of symptoms for over 6 months
- Radiological proof of the spur on a plain lateral radiograph of the heel
- Favorable general health status
- Age ≥ 40 years

Excluded from this trial were patients showing:

- Previous radiation therapy to the concerned foot
- Trauma to the foot area
- Rheumatic disease
- Arterial or venous diseases
- Lymphatic edema of the concerned foot/leg
- Pregnancy, breastfeeding
- Severe psychotic disorders

The use of analgesics before and during this trial was not limited, nor was former refractory treatment. Patients undergoing surgery or shockwave therapy after enrolment were excluded. For enrolment in this trial, all patients gave their written informed consent to radiation therapy and participation. After that, they were randomized by the statistician to one of the following therapy groups:

1. Standard dose group: single doses of 1 Gy applied twice weekly up to a total dose of 6 Gy (irradiation on Monday and Thursday or Tuesday and Friday)
2. Experimental dose group: single doses of 0.5 Gy applied three times a week up to a total dose of 6 Gy (irradiation on Monday, Wednesday, and Friday)

Patients who did not show satisfactory pain relief after the first radiotherapy series were offered a re-irradiation treatment after 12 weeks with the current standard dose of 6 × 1 Gy.

Follow-up examinations were performed every 6 weeks up to 48 weeks after radiation, based on our retrospective experience that the vast majority of beneficial effects become apparent after less than 1 year. Patients were either questioned in the clinic or by mail.

Primary endpoints were:

- Pain relief:
  - Visual analogue scale (VAS; 0 = no pain, 100 = maximum imaginable pain intensity)
  - Calcaneodynia Score (CS; 100 = complete freedom of symptoms, 0 = maximum of pain and disability) [20]
- Quality of life:
  - 12-Item Short-Form Health Survey (SF-12) sum score (high values = good quality of life) [21].

Radiotherapy was applied using linear accelerators by lateral opposing 6-MV photon beams. The target volume included the calcaneus and the plantar aponeurosis.

The results of a previous trial published by Niewald et al. [7, 22] were the basis for the calculation of the number of patients necessary: 120 patients were required in each therapy arm for a duration of 48 weeks in order to detect a difference of 15% in the VAS and CS with a power of 80% and an error probability of 5% including a calculated drop-out rate of 10% in each therapy arm.

Categorical variables were compared using the chi-square test and Fisher's exact test. Owing to the fact that the quantitative variables were not distributed normally, the Mann–Whitney U test was applied for comparison of the groups. Statistical significance was set at $p \leq 0.05$.

Statistical analysis was performed using MEDLOG (Parox, Münster, Germany) and SPSS statistics (version 22; IBM, Armonk, N.Y.) by the statistician after 12 and 48 weeks of follow-up. A detailed trial protocol to this study as well as the first results after 12 weeks' follow-up have been published elsewhere [5, 23].

Results

A total of 127 patients were randomized: 111 patients were treated at the Saarland University Medical Center, 11 patients were treated at the University Hospital of Regensburg, and five patients were treated at the University Hospital of Mainz. After randomization, nine patients had to be excluded owing to refusal to participate or radiotherapy with an incorrect dosage. One further patient could not be evaluated because of a critical lack of data, so that 117 patients were treated per protocol. In the standard dose group, 59 patients were treated. The remaining 58 patients were treated in the experimental dose group. In all, 52 patients of the standard dose group and 49 patients of the experimental dose group could be followed-up for 48 weeks. The comparison of patient groups as well as the results after 12 weeks' follow-up have been published by Niewald et al. [23]. Therefore, in this paper we only present the unpublished data from the 48 weeks' follow-up.

Results after 48 weeks' follow-up

In the VAS, the mean difference after 48 weeks compared with the values before radiotherapy was 59.4 in the standard dose group and 61.6 in the experimental dose group (p = 1.0). CS increased by 40.1 in the standard dose group and 40.4 in the experimental dose group (p = 0.679). Concerning pain relief, no statistically significant difference was found between the groups. Comparing the SF-12 scores for evaluating quality of life, it can be concluded that the results

Table 1 Results after 48 weeks' follow-up

Item	Value	Standard dose group	Experimental dose group	*p*
VAS (48)–(0)	*n*	52	49	–
	Mean	–59.4	–61.6	–
	SD	24.2	19.1	–
	Minimum	–90	–90	–
	Maximum	10	0.0	–
	p	–	–	>0.999
CS (48)–(0)	*n*	51	49	–
	Mean	40.1	40.4	–
	SD	22.0	14.9	–
	Minimum	–16	–10	–
	Maximum	81	65	–
	p	–	–	0.679
SF-12, somatic, patient (48)–(0)	*n*	51	49	–
	Mean	11.0	11.8	–
	SD	13.9	8.9	–
	Minimum	–24	–11	–
	Maximum	41	28	–
	p	–	–	0.740
SF-12, somatic, doctor (48)–(0)	*n*	51	49	–
	Mean	12.8	13.5	–
	SD	13.4	9.0	–
	Minimum	–24	–11	–
	Maximum	41	32	–
	p	–	–	0.915
SF-12, psychic, patient (48)–(0)	*n*	51	49	–
	Mean	3.9	3.5	–
	SD	8.4	8.3	–
	Minimum	–16	–11	–
	Maximum	31	35	–
	p	–	–	0.704
SF-12, psychic, doctor (48)–(0)	*n*	51	49	–
	Mean	2.9	0.3	–
	SD	9.1	7.7	–
	Minimum	–29	–12	–
	Maximum	29	24	–
	p	–	–	0.038

VAS (0), CS (0), SF-12 (0): values before radiotherapy. VAS (48), CS (48), SF-12 (48): values after 48 weeks of follow-up
VAS*:* linear scale; 0 = no pain; 100 = maximum imaginable pain; improvement = negative difference; worsening = positive difference
CS*:* linear scale based on criteria such as pain, use of aids, problems at work, in daily life, or sports, gait; 0 = maximum pain and disability; 100 = complete freedom of symptoms; improvement = positive difference; worsening = negative difference
SF-12*:* complex scales using 12 items on quality of life; improvement = positive difference; worsening = negative difference
Doctor: evaluation was performed either by doctor, student, or patient's close acquaintance
CS Calcaneodynia Score*, SF-12* 12-Item Short-Form Health Survey*, VAS* visual analogue scale

corresponded well to those concerning pain relief. Nevertheless, a statistically significant difference in the psychic scale of the SF-12 and the doctor's judgment could be found ($p = 0.038$). Other parameters did not show any statistically significant differences between the groups. No relevant side effects were reported. Details are summarized in Table 1.

Results after 12 vs. 48 weeks' follow-up

A further benefit was detected when comparing the published results after a follow-up period of 12 weeks [23] with the results after 48 weeks. The VAS score decreased in the standard dose group by 14.8 and in the experimental dose group by 16.6 ($p = 0.744$). In addition, CS showed a further improvement, increasing by 11.0 in the standard dose group and by 11.1 in the experimental dose group ($p = 0.931$). For pain relief, no statistically significant difference between the groups was found. The parameters for quality of life compared well with the results of pain evaluation. Here, too, no statistically significant differences were found (see Table 2 for details).

Results following re-irradiation after 48 weeks' follow-up

A total of 28 patients underwent re-irradiation. Of these patients, 15 were previously randomized to the standard dose group and 13 patients to the experimental dose group. Complete data of 24 patients could be evaluated. Of these, patients who had undergone re-irradiation experienced an insignificant difference concerning pain relief compared with patients who showed a good response to radiation therapy from the beginning. In the re-irradiation group, the VAS score decreased to 56.5 compared with 61.5 in the group without re-irradiation ($p = 0.597$). Concerning CS, the re-irradiation therapy group showed an increase of 33.7 compared with the group without re-irradiation with an increase of 42.2 ($p = 0.175$). Regarding quality of life, the results agreed well with those concerning pain relief. However, a statistically significant difference was observed in the somatic scale of the SF-12 and the doctor's judgment ($p = 0.049$). Further details can be found in Figs. 1, 2 and 3.

Results after re-irradiation therapy: 12 vs. 48 weeks' follow-up

Patients who underwent re-irradiation owing to poor response to the primary radiation treatment showed a reduction in the VAS score by 28.5 compared with 11.6 in the group without re-irradiation therapy ($p < 0.001$). Regarding CS, the re-irradiation therapy group showed an increase of 24.3 compared with 7.0 in the non-re-irradiated group ($p < 0.001$). The results concerning quality of life showed sta-

Table 2 Comparison of pain/quality of life data at 48 weeks vs. 12 weeks after radiation therapy

Item	Value	Standard dose group	Experimental dose group	*p*
VAS (48)–(12)	*n*	50	48	–
	Mean	–14.8	–16.6	–
	SD	25.5	24.5	–
	Minimum	–90	–70	–
	Maximum	50	70	—
	p	–	–	0.744
CS (48)–(12)	*n*	49	48	–
	Mean	11.0	11.1	–
	SD	21.2	20.2	–
	Minimum	–40	–55	–
	Maximum	58	67	–
	p	–	–	0.931
SF-12, somatic, patient (48)–(12)	*n*	50	48	–
	Mean	2.7	3.5	–
	SD	10.2	5.6	–
	Minimum	–31	–7	–
	Maximum	25	18	–
	p	–	–	0.915
SF-12, somatic, doctor (48)–(12)	*n*	49	48	–
	Mean	3.2	3.5	–
	SD	9.3	6.9	–
	Minimum	–20	–7	–
	Maximum	25	35	–
	p	–	–	0.879
SF-12, psychic, patient (48)–(12)	*n*	50	48	–
	Mean	1.7	2.0	–
	SD	9.1	6.2	–
	Minimum	–19	–11	–
	Maximum	32	25	–
	p	–	–	0.707
SF-12, psychic, doctor (48)–(12)	*n*	49	48	–
	Mean	1.6	0.3	–
	SD	9.8	5.8	–
	Minimum	–26	–14	–
	Maximum	33	13	–
	p	–	–	0.559

VAS (12), CS (12), SF-12 (12): values after 12 weeks of follow-up
CS Calcaneodynia Score, *SF-12* 12-Item Short-Form Health Survey, *VAS* visual analogue scale

tistically significant benefits for patients with re-irradiation treatment concerning the somatic scale but not the psychic scale (see Figs. 1, 2, and 3 for more details). Patients with re-irradiation benefited significantly more than those without.

Discussion

Based on the laboratory findings described in the previous section, the aim of this study was to compare the analgesic effects of a lower single dose of 0.5 Gy with a standard single dose when using the same total dose. At the time this study was planned and the protocol was prepared, the standard dose in the therapy of plantar heel spur was 6 Gy applied in two fractions of 1 Gy per week given over 3 weeks. In this study we could not find any statistically significant differences after 48 weeks' follow-up concerning pain relief between the groups. Concerning quality of life, the results in general correspond well to those concerning pain relief; however, one parameter (psychic scale, doctor's judgment) showed statistically significant differences that cannot be reasonably explained by the authors.

In the meantime, during the enrolment and follow-up period, a new standard for the radiotherapeutical treatment of painful heel spur was established with a total dose of 3 Gy applied in two fractions per week with single doses of 0.5 Gy for a duration of 3 weeks [24], according to the results of Heyd et al. [25] and Ott et al. [26, 27].

Owing to the fact that we did not find any benefits in escalating single doses of 0.5 Gy to a total dose of 6 Gy, we support the current standard dose. Laboratory in vitro results, indicating a clinical benefit of lower single doses, can obviously not be directly translated into improved clinical pain relief.

The authors are well aware of the limitations of this clinical trial. Importantly, the aim of enrolling 120 patients for each therapy group could not be reached. When Ott et al. reported that there was no benefit in pain relief using a total dose of 6 Gy (6 × 1 Gy) in comparison with a total dose of 3 Gy (6 × 0.5 Gy) at a high level of evidence [26, 27], the standard total dose in Germany was lowered to 3 Gy according to the ALARA principle (keep the dose *as low as reasonably achievable*). This led to an ethical conflict regarding the enrolment of more patients. Furthermore, the use of analgesics was not limited before or during the follow-up, which may have confounded the results. The trial was not blinded to the patient or the physician. Using a linear accelerator for therapy, it seemed impractical and unethical to perform blinded radiotherapy. Even though patients were not explicitly informed about their therapy group (standard dose group or experimental dose group), the assignment was evident from the radiation schedule (six fractions in the standard dose group vs. 12 in the experimental group). During the follow-up examinations, one got the impression that in some cases the evaluation of the patients was influenced by emotional events and therefore did not exclusively reflect the evaluated parameter itself.

Numerous trials have shown the benefit of low-dose radiotherapy in the treatment of painful heel spur. Never-

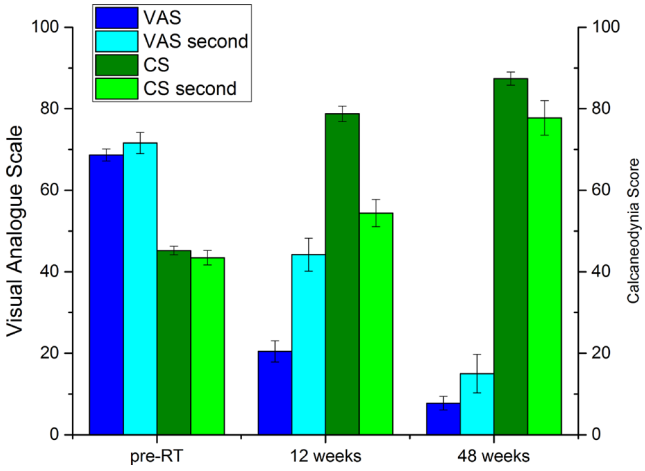

Fig. 1 CS and VAS scores during follow-up. *Second* patients had undergone second irradiation series, *error bars* standard error, *VAS* visual analogue scale, *CS* Calcaneodynia Score

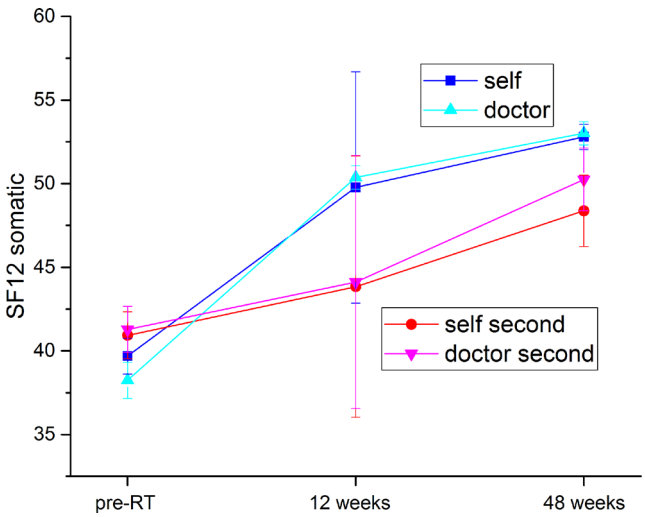

Fig. 2 SF-12 scores (somatic scale). *Second* patients had undergone second irradiation series, *error bars* standard error, *SF-12* 12-Item Short-Form Health Survey

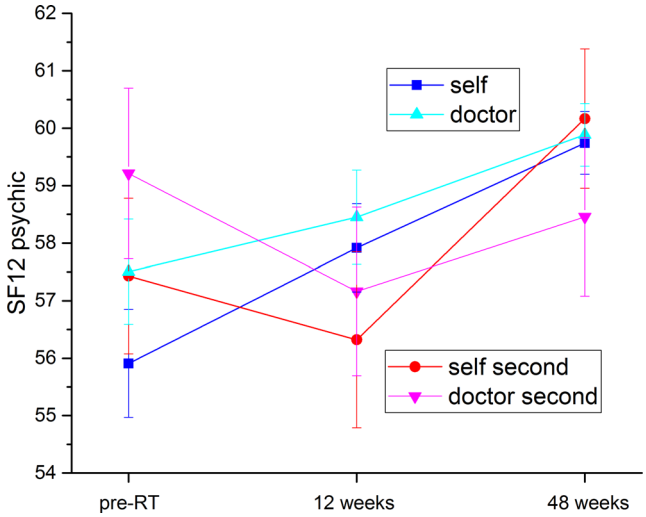

Fig. 3 SF-12 scores (psychic scale). *Second* patients had undergone second irradiation series, *error bars* standard error, *SF-12* 12-Item Short-Form Health Survey

theless, a placebo effect is still under discussion. Goldie et al. published a double-blinded study in 1970, showing a benefit in pain relief in 60% of patients in both groups, whether they were irradiated or not [28]. The study has been criticized for lacking clearly defined endpoints and because of the irradiation in the acute stage of the disease without considering that there might be spontaneous pain remission. However, many trials have reported the analgesic effect of radiotherapy. Niewald et al. compared a therapeutical dose of 6 × 1 Gy with a very low dose of 6 × 0.1 Gy, which converged to a placebo dose. The group irradiated with 6 × 1 Gy showed a statistically significant superiority in pain relief compared with the group irradiated with 6 × 0.1 Gy [7]. In 2007, Heyd et al. performed a prospective randomized trial with 130 patients, showing that no statistically significant benefit could be found comparing doses of 6 × 0.5 Gy vs. 6 × 1 Gy [25]. The same results could be found with a bigger patient collective by Ott et al., as mentioned earlier [26, 27]. A trial comparing three different therapy schedules was performed by Seegenschmiedt et al. The group irradiated with 10 × 0.5 Gy (total dose of 5 Gy) showed the best results in pain relief compared with the groups receiving 10 × 0.3 Gy (total dose of 3 Gy) and 12 × 1 Gy (total dose of 12 Gy) [3]. However, these trials did not compare a uniform total dose.

In this trial, we showed that patients who did not benefit from the primary radiation therapy may benefit at a statistically significant level when irradiated again after 12 weeks. This underlines the results of a publication by Hautmann et al., who showed that patients benefit from re-irradiation [29]. In our trial, the results after 48 weeks' follow-up concerning pain relief are comparable to those of patients showing a good response after the first irradiation. Therefore, re-irradiation can be recommended. Comparing the results after 12 weeks' follow-up [23] with those after 48 weeks' follow-up, it can be concluded that the main effects on pain relief occur in the first 12 weeks but continue to improve for a period of up to 48 weeks.

Conclusion

Once again, low-dose radiation therapy for painful heel spur (plantar fasciitis) showed its efficiency concerning pain relief. Recent encouraging findings from laboratory studies showing a benefit of doses in the range of 0.3–0.7 Gy compared with higher doses could not be translated into clinical practice. The reason is still unknown. A fractionation

schedule with single doses of 0.5 Gy vs. single doses of 1 Gy keeping a uniform total dose of 6 Gy did not show a statistically significant benefit in our setting with a limited patient number.

Further randomized prospective trials using the new standard of a 3-Gy total dose will be necessary to explore the best fractionation schedule.

Compliance with ethical guidelines

Conflict of interest B. Prokein, H. Holtmann, M.G. Hautmann, H.-P. Rösler, S. Graeber, Y. Dzierma, C. Ruebe, J. Fleckenstein, and M. Niewald declare that they have no competing interests.

Ethical standards Informed consent was obtained from all patients included in this study.The ethics committee of the Saarland Physicians' chamber approved the study protocol (number 14/07 on 09/05/2012). Furthermore, the study was approved by the DEGRO expert comittee and is in compliance with the Declaration of Helsinki in its current version.

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