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ORIGINAL ARTICLE

Radiotherapy for benign achillodynia

Long-term results of the Erlangen Dose Optimization Trial

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Abstract
Background The aim of this study was to evaluate the long-term efficacy of two dose-fractionation schedules for radiotherapy of achillodynia.
Patients and methods Between February 2006 and February 2010, 112 evaluable patients were recruited for this prospective trial. All patients received orthovoltage radiotherapy. One course consisted of 6 fractions/3 weeks. In the case of insufficient remission of pain after 6 weeks, a second series was performed. Patients were randomly assigned to receive either single doses of 0.5 or 1.0 Gy. The endpoint was pain reduction. Pain was measured before, right after (early response), 6 weeks after (delayed response), and approximately 2 years after radiotherapy (long-term response) with a questionnaire-based visual analogue scale (VAS) and a comprehensive pain score (CPS).
Results The median follow-up was 24 months (range, 11–56). The overall early, delayed, and long-term response rates for all patients were 84%, 88%, and 95%, respectively. The mean VAS values before treatment for early, delayed, and long-term responses for the 0.5-Gy and 1.0-Gy groups were 55.7±21.0 and 58.2±23.5 ($p=0.53$), 38.0±23.2 and 30.4±22.6 ($p=0.08$), 35.5±25.9 and 30.9±25.4 ($p=0.52$), and 11.2±16.4 and 15.3±18.9 ($p=0.16$), respectively. The mean CPS values before treatment for early, delayed, and long-term responses were 8.2±3.0 and 8.9±3.3 ($p=0.24$), 5.6±3.1 and 5.4±3.3 ($p=0.76$), 4.4±2.6 and 5.3±3.8 ($p=0.58$), and 2.2±2.9 and 2.8±3.3 ($p=0.51$), respectively. No significant differences in long-term response quality between the two arms was found ($p=0.73$).
Conclusion Radiotherapy is a very effective treatment for the management of benign achillodynia. For radiation protection, the dose for a radiotherapy series should not exceed 3.0 Gy.

Keywords Achillodynia · Pain · Radiotherapy · Benign degenerative disease · Randomized trial

Strahlentherapie bei Achillodynie
Langzeitergebnisse der Erlanger Dosisoptimierungsstudie

Zusammenfassung
Hintergrund Ziel war die Untersuchung der Langzeiteffektivität zweier Dosisfraktionierungskonzepte bei der Strahlentherapie von Patienten mit Achillodynie.
Material und Methode Zwischen 2006 und 2010 wurden 112 auswertbare Patienten in diese prospektive und randomisierte Phase-IV-Studie eingeschlossen. Alle Patienten erhielten die Bestrahlung in Orthovolt-Technik. Eine Bestrahlungsserie bestand aus 6 Fraktionen/3 Wochen. Bei ungenügendem Ansprechen der Schmerzsymptomatik nach 6 Wochen wurde eine zweite Bestrahlungsserie durchgeführt. Die Patienten wurden auf die beiden Studienarme randomisiert verteilt und erhielten je nach Ergebnis Einzeldosen von 0,5 bzw. 1,0 Gy. Der Endpunkt der vorliegenden Analyse war die Schmerzreduktion. Die Schmerzintensität wurde vor, nach („early response“), 6 Wochen nach („delayed response“) sowie etwa 3 Jahre nach der Strahlentherapie („long-term response“) mittels Visueller Analogskala (VAS) und einem umfassenden Schmerzscore (CPS) gemessen.

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Ergebnisse Die mediane Nachbeobachtungszeit für die Langzeitevaluation betrug 24 (11–56) Monate. Die Raten für das frühe, verzögerte und Langzeitansprechen aller Patienten betrugen 84, 88 und 95 %. Die mittleren VAS-Werte vor Behandlung, für das frühe, verzögerte und Langzeitansprechen lagen für die Gruppe mit 0,5 und 1,0 Gy bei 55,7 ± 21,0 und 58,2 ± 23,5 ($p = 0{,}53$), 38,0 ± 23,2 und 30,4 ± 22,6 ($p = 0{,}08$), 35,5 ± 25,9 und 30,9 ± 25,4 ($p = 0{,}52$) sowie 11,2 ± 16,4 und 15,3 ± 18,9 ($p = 0{,}16$). Die entsprechenden mittleren Werte im Schmerzscore betrugen 8,2 ± 3,0 und 8,9 ± 3,3 ($p = 0{,}24$), 5,6 ± 3,1 und 5,4 ± 3,3 ($p = 0{,}76$), 4,4 ± 2,6 und 5,3 ± 3,8 ($p = 0{,}58$) sowie 2,2 ± 2,9 und 2,8 ± 3,3 ($p = 0{,}51$). Es wurden keinerlei statistisch signifikante Unterschiede in der Qualität des Langzeitansprechens zwischen den beiden Studienarmen festgestellt ($p = 0{,}73$).
Schlussfolgerung Die Strahlentherapie ist langfristig eine sehr effektive Maßnahme zur Behandlung der Achillodynie. Aus Strahlenschutzgründen sollte eine Gesamtdosis von 3 Gy pro Bestrahlungsserie nicht überschritten werden.

Schlüsselwörter Achillodynie · Schmerz · Strahlentherapie · Gutartige degenerative Erkrankung · Randomisierte Studie

Achillodynia is a general term for various diseases causing heel pain including, for example, paratenonitis, tendinitis, tendinitis with partial rupture, insertional tendinitis, subachilles and retroachilles bursitis, Haglund's deformity, and calcaneal spur. Typical histological findings usually 2–4 cm cranial to the calcaneus are collagen fiber disorientation without accompanying inflammatory cells, hypocellularity, rarefied blood vessels, necroses, calcification, low perfusion levels, tissue hypoxia, and insufficient cell nutrition [1].

Achillodynia is more common in male subjects and usually appears after the age of 30 years. Therapeutic options in the acute phase are reduction of strain, a decrease of body weight, local and systemic antiphlogistics, as well as cryo- and electrotherapy. In the postacute phase, physiotherapeutic approaches such as stretching, muscle detonization, massages, and ultrasound treatments are recommended [1].

For decades, radiotherapy has been successfully applied in the treatment of benign hyperproliferative and degenerative diseases [2–4] including achillodynia [5], but in contrast to painful shoulder or elbow syndrome, clinical outcome data after radiotherapy for achillodynia are very rare and it is still not clear what constitutes an optimal radiotherapy regimen. For the treatment of inflammatory degenerative diseases, single doses of 0.5–1.0 Gy and total doses of 3–6 Gy per series are generally accepted [6, 7].

Pain in achillodynia mainly results from inflammation of the Achilles' tendon or the bursa. Since low-dose radiation has been proven in preclinical models to exert anti-inflammatory effects predominantly in a single dose range of 0.3–0.7 Gy, a dose reduction in the clinics from 1.0 to 0.5 Gy is reasonable [8]. The present prospective and randomized Erlangen Dose Optimization Trial (EDO-Trial) was initiated to find out the optimal radiation dose strategy in terms of efficacy and radiation protection. While results on early response in this trial have been published previously [5], the present analysis focuses on long-term efficacy.

Patients and methods

Between February 2006 and February 2010, a total of 116 consecutive patients with calcaneodynia were treated at the Erlangen University Hospital. Of these, three refused study participation and one patient could not be included in the analysis because of incomplete data. At the time of radiotherapy, the median age of the 112 evaluable patients was 51 years (range, 34–83). All patients participated in our prospective EDO Trial with a total of more than 1,000 patients recruited. Written informed consent was obtained from all patients. Additional information on patient and treatment characteristics may be found in our previous report on early and delayed response rates [5].

Treatment

All patients received radiotherapy with an orthovoltage technique (Siemens Stabilipan, 180 kV, 20 mA, 0.2-mm Cu filter, focus–skin distance 40 cm) usually with a single field of 6 × 8 cm directly positioned on the Achilles' tendon insertion area including the distal part of the tendon. One radiotherapy series consisted of six single fractions delivered in 3 weeks with an interfractional radiation-free interval of at least 2 days. In the case of no pain remission (NC) or the patient subjectively not satisfying the assessment of partial remission of pain (PR) 6 weeks after the end of the first series, a second radiation series was performed. In the case of complete remission of pain (CR) after the first treatment, the second series was abandoned. Patients were randomly assigned (ratio 1:1) to receive either single doses of 0.5 or 1.0 Gy throughout the treatment.

Endpoint and statistical analysis

The endpoint of this clinical trial was pain reduction. Pain levels were measured with a standardized questionnaire immediately before (baseline), directly after (early response), 6 weeks after (delayed response), and approximately 2 years after completion of radiotherapy (long-term response). The pain level was determined using a graphical visual analogue scale (VAS) with levels from 0 (no pain) to

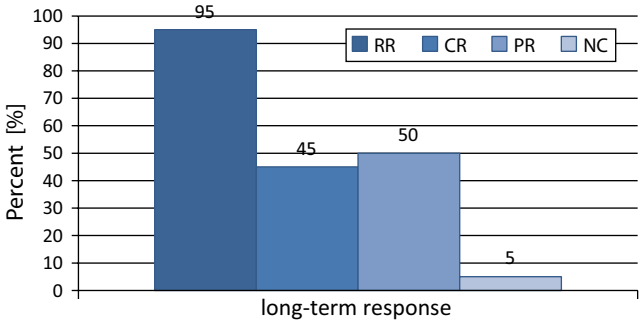

Fig. 1 Long-term overall response rates (comprehensive pain score). *RR* response rate, *CR* complete response, *PR* partial response, *NC* no change

100 (maximum conceivable pain) and a modified von Pannewitz pain score [9] adapted from Seegenschmiedt et al. und Keilholz L [6]. With this score, the treatment response was evaluated with regard to pain symptoms grouped into five categories (pain at strain, pain at night, persistent pain during daytime, pain at rest, and morning stiffness) and four grades (none =0 points, mild =1 point, moderate =2 points, and severe =3 points). The points of the five categories were added to a comprehensive pain score result with values ranging from 0 to 15. Treatment results were judged as "complete response" (CR) with a score of 0 points, as "partial response" (PR) with a score >0 and better than the baseline score, and as "no change" (NC) with score values equal to or higher than the baseline score. The use of additional functional orthopedic sores may be reasonable for achillodynia but were not part of our trial.

Data management and statistical analysis were carried out with IBM SPSS Statistics for MS Windows (SPSS Inc., Chicago, Ill.), release 21. For statistical comparisons between groups, the Mann–Whitney *U* test and Pearson's chi-square test were used as appropriate.

In addition to the previously published early and delayed treatment results [5], this present analysis concentrates on long-term efficacy. For this evaluation, another questionnaire was sent out to the study participants approximately 2 years after completion of radiotherapy.

Results

The questionnaire for long-term evaluation was sent out to 100 of 112 patients with available and complete contact information. Approximately three quarters of the patients (73/100, 73%) completed the questionnaire and returned it to the study office. The median follow-up for long-term evaluation was 24 months (range, 11–56). Because of incomplete data provision by the patients, 62 of 73 datasets were admissible for further CPS analysis, and 72 of 73 for further VAS analysis of long-term pain control.

Table 1 Long-term response rates (comprehensive pain score) and single fraction dose

	Cases[a] (*n*)	RR (%)	CR (%)	PR (%)	NC (%)	*p*
Long-term response						
0.5 Gy	35	94	48	46	6	0.73
1.0 Gy	27	96	41	55	4	

RR response rate, *CR* complete response, *PR*, partial response, *NC* no change.

[a]Number of cases accessible for evaluation.

The overall early, delayed, and long-term CPS-based response rates (CR + PR) for all patients were 84%, 88%, and 95%, respectively, while the CR rates were 1%, 12%, and 45% (see Fig. 1). The response rates for the 0.5-Gy subgroup were 79%, 77%, and 94%, respectively, while the CR rates were 2%, 15%, and 48%, respectively; for the 1.0-Gy subgroup they were 90%, 100%, and 96%, respectively, and 0%, 8%, and 41%, respectively. The mean CPS baseline values for early, delayed, and long-term response were 8.2±3.0 and 8.9±3.3 ($p=0.24$), 5.6±3.1 and 5.4±3.3 ($p=0.76$), 4.4±2.6 and 5.3±3.8 ($p=0.58$), and 2.2±2.9 and 2.8±3.3 ($p=0.51$) for the 0.5-Gy and 1.0-Gy arm, respectively. The CPS-based long-term response analysis revealed a significant increase in the CR rates in both study arms but no statistically significant differences between the 0.5-Gy and 1.0-Gy groups (see Table 1).

The mean VAS baseline values for early, delayed, and long-term response for the 0.5-Gy and 1.0-Gy groups were 55.7±21.0 and 58.2±23.5 ($p=0.53$), 38.0±23.2 and 30.4±22.6 ($p=0.08$), 35.5±25.9 and 30.9±25.4 ($p=0.52$), and 11.2±16.4 and 15.3±18.9 ($p=0.16$), respectively (see Fig. 2).

In summary, considering both the results of the VAS and the CPS analysis no statistically significant differences in long-term treatment efficacy were found between the trial arms (see Tab. 1 and Fig. 2).

In the long-term analysis questionnaire, patients were asked if they had additional radiation series or any other additional treatment because of persisting or recurrent achillodynia after completion of the study treatment. Additional radiation series had been applied in 2 of 40 patients (5%) in the 0.5-Gy arm, and in 0 of 35 cases in the 1.0-Gy group ($p=0.18$). Any further treatment (including radiotherapy) was registered in 14 of 40 (35%) and 13 of 35 (37%) patients ($p=0.85$), respectively (see Table 2).

Furthermore, the patients were asked if they would recommend radiotherapy for the treatment of achillodynia very much, rather yes, rather not, or not at all (see Table 3). In the 0.5-Gy arm, patients recommended radiotherapy (very much + rather yes) in 80% of cases (31/39), whereas in the 1.0-Gy arm it was 70% (24/34). No significant differences regarding patients' recommendation values were found ($p=0.45$).

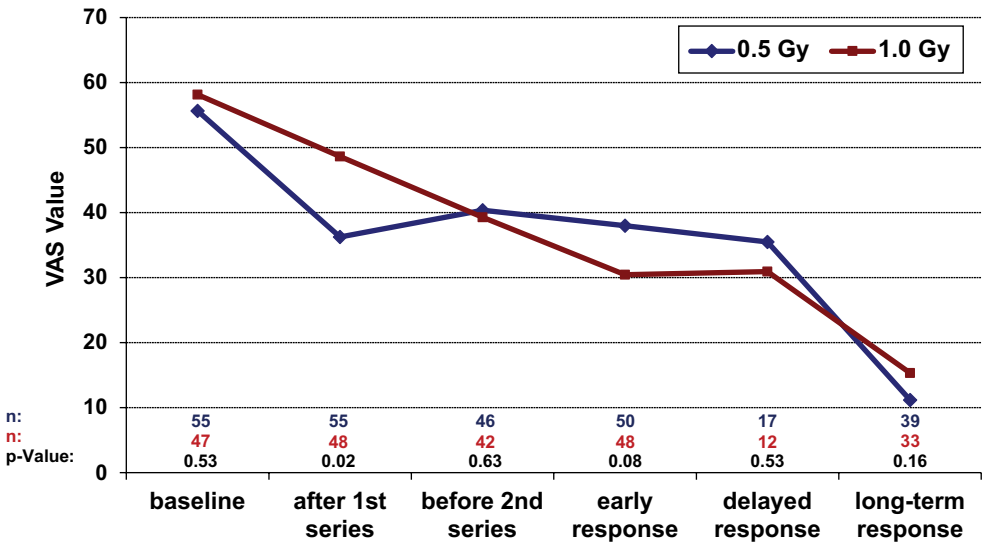

Fig. 2 Visual analogue scale (*VAS*) results and single fraction dose

Table 2 Follow-up, further treatments, and single fraction dose

	0.5 Gy	1.0 Gy	*p*
Median FU (months)	24 (11–56)	24 (11–55)	0.88
Additional RT series during FU, *n/N* (%)	2/40 (5)	0/35 (0)	0.18
Any further treatment during FU, *n/N* (%)	14/40 (35)	13/35 (37)	0.85

RT radiotherapy, *FU* follow-up.

Table 3 Patients' recommendation statement on radiotherapy for the treatment of achillodynia at long-term evaluation

Patients' recommendation	0.5 Gy	1.0 Gy	*p*
Very much	20/39 (52)	12/34 (35)	0.45
Rather yes	11/39 (28)	12/34 (35)	
Rather not	4/39 (10)	7/34 (21)	
Not at all	4/39 (10)	3/34 (9)	

Discussion

Published data on radiotherapy for achillodynia are quite rare. Our analysis is one of the first presentations in the field that exclusively focuses on achillodynia. In the very rare publications dealing with achillodynia, the condition is usually subsumed under heel pain syndromes including calcaneodynia [10].

The present comparison between the two EDO Trial arms for the treatment of achillodynia found no persistent significant differences considering the VAS and CPS analysis, which supports the preclinical hypothesis that single doses of 0.5 Gy are at least as equally effective as single doses of 1.0 Gy [8]. During follow-up, for patients with single doses of 0.5 Gy no increased rates of additional radiation series or any additional treatment for persisting or recurrent achillodynia were detected (see Table 2). According to the long-term patients' recommendation analysis, they did not experience lower levels of satisfaction with the radiotherapy success compared with patients in the 1.0-Gy arm (see Table 3). Therefore, we conclude that single doses of 0.5 Gy are equally effective, at least, and should be regarded as a standard option in order to decrease the potential risks of ionizing radiation.

Heyd et al. [11] reported on a comparable trial of 130 patients with painful heal spurs that were randomized to receive either single doses of 0.5 Gy to a total dose of 3.0 Gy/3 weeks (low-dose group; $n=65$) or single doses of 1.0 Gy to a total dose of 6.0 Gy/3 weeks (high-dose group; $n=65$). In 18 % (24/130) of cases in the high-dose group and 13 % (17/130) of cases in the low-dose group, a second radiotherapy series was given. At the 6-month follow-up, radiotherapy led to a highly significant reduction of pain symptoms in both groups. The comparison between the trial arms revealed no statistically significant difference of response to radiotherapy between both groups.

Muecke et al. [12] reported on a retrospective analysis of 502 cases with calcaneodynia after a median follow-up of 26 months. In 341 patients (68 %), radiotherapy was performed twice a week with a single 6–10-MV photon field, in 161 patients (32 %) three times a week with a single 175-kV X-ray field. With 6 MV, ten fractions of 0.5 Gy were applied to 100 patients, five to six fractions of 1.0 Gy were applied to 140 patients. With 10 MV, five fractions of 1.0 Gy were applied to 101 patients. In all patients treated with 175-kV X-rays, six fractions of 1.0 Gy were given. Patients treated with a second RT series received the same single and total dose as in the first RT series. Pain measurement was performed with the von Pannewitz score [9] and 61 % of the treated patients were still satisfied with the therapeutic effect of the radiation treatment. In an univariate subgroup analysis to determine prognostic factors for pain control, single doses of 0.5 Gy led to better event-free probability compared with 1.0 Gy (86.2 % vs. 55.1 %; $p=0.009$). But

the advantage for single doses of 0.5 Gy no longer remained significant in multivariate analysis.

Another analysis of Seegenschmiedt et al. [13] compared the clinical effect of three different dose concepts in the radiotherapeutic treatment of painful heel spurs: group A ($n=72$) received 12 Gy total radiation dose in 3 fractions per week and 2 series (6×1 Gy/series) separated by 6 weeks; group B ($n=98$) received 3 Gy total radiation dose in 10 fractions of 0.3 Gy ($n=50$) or 5 Gy (10×0.5 Gy; $n=48$) with conventional fractionation in 1 series. Radiotherapy was very effective: At the last follow-up, 67% (group A) and 71% (group B) remained completely free of pain. The CR rate was not different between the three radiation concepts. However, significant differences were observed with regard to PR rates. More favorable results were achieved in patients receiving a total dose of 5 Gy or 12 Gy, while patients with total doses of 3 Gy had significantly worse results. In analogy to our trial, this analysis also emphasizes that the time interval between radiotherapy and distinct pain control may take several months, perhaps years.

Comparing our two evaluation tools, the VAS analysis and the CPS score, we found no significant differences regarding study endpoints. Hence we assume that both scores are representative tools for the scientific description of pain reduction after radiotherapy for painful benign degenerative conditions. However, from a practical point pf view, for the patients the VAS was much easier to handle than the CPS score (one question vs. five questions). Incomplete CPS data provision led to a significant amount of invalid CPS datasets when patients did not answer all five questions. Therefore, for future work we recommend using simple VAS analysis combined with a simple global von Pannewitz score for pain reduction outcome measurements in radiotherapy of benign diseases.

Although a placebo-controlled trial is still lacking to formally prove the efficacy of the radiotherapy of selected benign degenerative painful diseases and will perhaps never be performed owing to ethical reasons, the huge body of evidence demonstrates low-dose radiotherapy as a very effective tool in the symptomatic treatment of painful degenerative inflammatory conditions, especially in patients who did not persistently benefit from other non-radiation conservative therapies. Recently, a randomized trial was published that compared single/total doses of 1/6 Gy vs. 0.1/0.6 Gy, 2 fractions per week, in a total of 62 evaluable patients [14]. Compared with the very low dose arm, the higher-dose arm led to a significant advantage in terms of pain control, which demonstrates radiotherapy is a dose-dependent effective option in the treatment of painful calcaneodynia. Comparable studies regarding achillodynia are lacking because it is a rare condition.

Although tumor induction by ionizing radiation is still under critical discussion [15], no significant numbers of patients with radiotherapy-associated tumors have been published. Nevertheless, additional civilizatoric ionizing irradiation should be avoided whenever possible. From the viewpoint of radiation protection, together with Heyd et al. [11] our trial supports the hypothesis that radiotherapy with lower single doses of 0.5 Gy might be, in the long run, equally effective to single doses of 1.0 by substantially decreasing the potential radiation risk.

Conclusion

Radiotherapy proved to be a highly effective option for sustained pain control in the treatment of achillodynia. In our prospective phase IV trial, single doses of 0.5 Gy were equally effective to single doses of 1.0 Gy. Therefore, for radiation protection purposes we recommend the standard use of single doses of 0.5 Gy and total doses of 3.0 Gy per radiation series in the treatment of benign achillodynia.

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Conflict of interest O.J. Ott, C. Jeremias, U.S. Gaipl, B. Frey, M. Schmidt, and R. Fietkau state that there are no conflicts of interest.

All studies on humans described in the present manuscript were carried out in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form). Informed consent was obtained from all patients included in studies.

References

1. Geyer M (2005) [Achillodynia]. Orthopade 34:677–681
2. Ott OJ, Hertel S, Gaipl US et al (2012) Benign painful shoulder syndrome: initial results of a single-center prospective randomized radiotherapy dose-optimization trial. Strahlenther Onkol 188:1108–1113
3. Ott OJ, Hertel S, Gaipl US et al (2012) Benign painful elbow syndrome. First results of a single center prospective randomized radiotherapy dose optimization trial. Strahlenther Onkol 188:873–877
4. Ott OJ, Jeremias C, Gaipl US et al (2013) Radiotherapy for calcaneodynia. Results of a single center prospective randomized dose optimization trial. Strahlenther Onkol 189:329–334
5. Ott OJ, Jeremias C, Gaipl US et al (2013) Radiotherapy for achillodynia: results of a single-center prospective randomized dose-optimization trial. Strahlenther Onkol 189:142–146
6. Seegenschmiedt MH, Keilholz L (1998) Epicondylopathia humeri (EPH) and peritendinitis humeroscapularis (PHS): evaluation of radiation therapy long-term results and literature review. Radiother Oncol 47:17–28
7. Niewald M, Fleckenstein J, Naumann S, Ruebe C (2007) Long-term results of radiotherapy for periarthritis of the shoulder: a retrospective evaluation. Radiat Oncol 2:34

8. Rodel F, Frey B, Gaipl U et al (2012) Modulation of inflammatory immune reactions by low-dose ionizing radiation: molecular mechanisms and clinical application. Curr Med Chem 19:1741–1750
9. von Pannewitz G (1970) Degenerative Erkrankungen. In: Diethelm I, Heuck F, Olsson O, Rauninger K, Strnad F, Vieten H, Zuppinger A (eds) Handbuch der medizinischen Radiologie, Vol. 17, Springer, Berlin, pp 73–107
10. Sautter-Bihl ML, Liebermeister E, Scheurig H, Heinze HG (1993) [Analgetic irradiation of degenerative-inflammatory skeletal diseases. Benefits and risks]. Dtsch Med Wochenschr 118:493–498
11. Heyd R, Tselis N, Ackermann H et al (2007) Radiation therapy for painful heel spurs: results of a prospective randomized study. Strahlenther Onkol 183:3–9
12. Muecke R, Micke O, Reichl B et al (2007) Demographic, clinical and treatment related predictors for event-free probability following low-dose radiotherapy for painful heel spurs—a retrospective multicenter study of 502 patients. Acta Oncol 46:239–246
13. Seegenschmiedt MH, Keilholz L, Stecken A et al (1996) [Radiotherapy of plantar heel spurs: indications, technique, clinical results at different dose concepts]. Strahlenther Onkol 172:376–383
14. Niewald M, Seegenschmiedt MH, Micke O et al (2012) Randomized, multicenter trial on the effect of radiation therapy on plantar fasciitis (painful heel spur) comparing a standard dose with a very low dose: mature results after 12 months' follow-up. Int J Radiat Oncol Biol Phys 84:e455–e462
15. Trott KR, Kamprad F (2006) Estimation of cancer risks from radiotherapy of benign diseases. Strahlenther Onkol 182:431–436