Radiotherapy for calcaneodynia, achillodynia, painful gonarthrosis, bursitis trochanterica, and painful shoulder syndrome - Early and late results of a prospective clinical quality assessment

Oliver Micke 1,* Eyup Ugrak 2, Stefan Bartmann 3, Irenaues A. Adamietz 4, Ulrich Schaefer 5, Rebecca Bueker 5, Klaus Kisters 2, M. Heinrich Seegenschmiedt 6, Khashayar Fakhrian 4 and Ralph Muecke 4, 7

Abstract

Background: The aim of this prospective clinical quality assessment was to evaluate the short-term and long-term efficacy of low dose radiotherapy (RT) for calcaneodynia, achillodynia, painful gonarthrosis, painful bursitis trochanterica, and painful shoulder syndrome.

Methods: Between October 2011 and October 2013, patients with calcaneodynia, achillodynia, painful gonarthrosis, painful bursitis trochanterica, and painful shoulder syndrome were recruited for this prospective clinical quality assessment. Single doses of 0.5-1.0 Gy and a total dose of 6.0 Gy per series were used. Pain was measured before and directly after RT (early response) with a visual analogue scale (VAS). Additionally, pain relief was measured with the four-scale pain score according to "von Pannewitz" (VPS) immediately at the end of RT and during follow-up. Within this context we defined a good response as complete pain relief and markedly improved. The assessment of the long-term efficacy was carried out by a telephone survey.

Results: 703 evaluable patients (461 female, 242 male) with a mean age of 63.2 years (28-96) were recruited for this prospective clinical quality assessment. In 254 patients RT was performed with the linear accelerator, 449 patients received orthovoltage radiotherapy. After a median follow-up of 33 months (3-60) 437 patients could be reached for evaluation of follow up results. The mean VAS value before treatment was 6.63 (1.9-10) and immediately on completion of RT 4.51 (0-10) (p < 0.001). Concerning the VPS immediately on completion of RT, a good response could be achieved in 264/703 patients (37.6%), and with the follow up in 255/437 patients (58.4%) (p < 0.001). Only in patients with gonarthrosis we could not observe a significantly improved long-term success in comparison to the results immediately after RT (30.2% versus 29.9%).

Conclusion: Low dose RT is a very effective treatment for the management of calcaneodynia, achillodynia, painful gonarthrosis, painful bursitis trochanterica, and painful shoulder syndrome. Due to the delayed onset of analgesic effects low dose RT results in a significantly improved long-term efficacy in comparison to the results immediately after RT particularly in patients with calcaneodynia, achillodynia, bursitis trochanterica, and shoulder syndrome.

Keywords: Benign diseases, Radiotherapy, Calcaneodynia, Gonarthrosis, Bursitis trochanterica, Shoulder syndrome
Background
There is a long tradition for low dose radiotherapy (RT) of painful benign skeletal diseases in Central Europe. RT of benign diseases accounts for about 8–10% of all RT procedures in Germany. This development of radiotherapy for benign disorders in the last years can be reasonably regarded as real renaissance.

As much as 70% of these indications represent painful disorders in the locomotor system [1–5].

Recent radiobiological experiments show that low doses of radiation have a modulatory activity on several inflammatory pathways and immune components like endothelial cells, mono- and polynuclear leukocytes and macrophages [6].

For this treatment, single doses of 0.5 to 1.0 Gy and total doses of 3.0 to 6.0 Gy per series are generally accepted.

The aim of this prospective clinical quality assessment was to analyse the therapeutic effect of low dose irradiation immediately after completion of RT and during follow-up and to identify possible prognostic factors in patients with calcaneodynia, achillodynia, painful gonarthrosis, painful shoulder syndrome and painful bursitis trochanterica. It is a well-known observation, that the pain relief after RT often occurs after a longer period of time, generally 6 to 12 weeks [1–3]. However, this phenomenon is not well described and possible implication are not known. Therefore, we examined with this prospective clinical quality assessment, whether a delayed onset of analgesic effects of RT leads to a significantly improved long-term success in comparison to the results immediately after RT.

Methods
Between October 2011 and October 2013, patients with calcaneodynia, achillodynia, painful gonarthrosis, painful bursitis trochanterica, and painful shoulder syndrome were recruited for this prospective quality assessment. All patients had given their informed consent to the radiotherapy and to the participation in this prospective clinical quality assessment before enrolment.

RT was performed with both linear accelerator and orthovoltage conditions. Single doses of 0.5-1.0 Gy and a total dose of 6.0 Gy per series were used.

Pain was measured before and right after RT (early response) with a 10 scale visual analogue scale (VAS) (0 - no pain, 10 - strongest pain) [7]. Additionally, pain relief was measured with the four-scale pain score according to “von Pannewitz” (VPS) (complete pain relief, markedly improved, slightly improved, unchanged) immediately on completion of RT and during follow-up [8]. Within this context, we defined a good response as complete pain relief and markedly improved. The assessment of the long-term efficacy was carried out by a systematic telephone survey. The results were recorded in an Excel spreadsheet and then transferred to SPSS for evaluation after completion of the survey. A part of all treated patients were irradiated with a second series (n = 51), if there was no or only slight improvement after the first RT series. These results have been included in the evaluation.

Statistics
All data were stored and analyzed using the SPSS statistical package 15.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics were computed for continuous and categorical variables. The statistics computed included mean and standard deviations of continuous variables, and frequencies and relative frequencies of categorical factors. Testing for differences in continuous and categorical variables within the groups was accomplished by the Wilcoxon Signed Rank Test. Testing for differences in continuous variables between the groups was accomplished by the Mann-Whitney U test, and in categorical variables between the groups with the Fisher's Exact Test, as appropriate. All P values were two-sided statistical tests, and values of P < .05 were considered statistically significant.

Results
Patients
703 evaluable patients (461 female, 242 male) with a mean age of 63.3 years (28-96) were recruited for this prospective trial. The following diagnoses were given: 286 x calcaneodynia, 46 x achillodynia, 139 x gonarthrosis, 70 x bursitis trochanterica, and 162 x shoulder syndrome. Patient characteristics are given in Table 1.

| Diagnosis               | Number | Mean Age (years) | Female/Male | Fractionation 12 x 0.5 Gy / 6 x 1.0 Gy | Technique Orthovolt / Linac | Median Follow up (months) |
|-------------------------|--------|-----------------|-------------|-------------------------------------|----------------------------|--------------------------|
| Calcaneodynia           | 286    | 56.8 (30-87)    | 219/67      | 265/21                              | 284/2                      | 34 (21-40)               |
| Achillodynia            | 46     | 54.7 (28-76)    | 11/35       | 33/13                               | 45/1                       | 33 (23-39)               |
| Gonarthrosis            | 139    | 70.9 (38-90)    | 78/61       | 112/27                              | 53/86                      | 19.5 (3-40)              |
| Bursitis trochanterica  | 70     | 64.6 (43-88)    | 56/14       | 66/4                                | 8/62                       | 29 (3-39)                |
| Shoulder Syndrome       | 162    | 69.5 (39-96)    | 97/65       | 120/42                              | 56/106                     | 42 (6-60)                |
| All patients            | 703    | 63.2 (28-96)    | 461/242     | 596/107                             | 446/257                    | 33 (3-60)                |
Table 2 Median VAS-values before and immediately on completion of RT

| Diagnosis            | Median VAS value before RT (interquartile range) | Median VAS value immediately on completion of RT (interquartile range) | P-Value |
|----------------------|-------------------------------------------------|-----------------------------------------------------------------------|---------|
| Calcaneodynia        | 7.0 (5.4-25-8)                                  | 4.0 (2.5-6)                                                           | < 0.001 |
| Achillodynia         | 6.0 (5-7.125)                                   | 4.0 (2-5)                                                             | < 0.001 |
| Gonarthrosis         | 6.0 (5-8)                                       | 4.5 (3-6)                                                             | < 0.001 |
| Bursitis trochanterica | 7.0 (6-8)                                    | 5.0 (3.725-7.125)                                                    | < 0.001 |
| Shoulder Syndrome    | 7.0 (5-8)                                       | 5.0 (3-6)                                                             | < 0.001 |
| All patients         | 7.0 (5-8)                                       | 4.5 (3-6)                                                             | < 0.001 |

Comparison of results for the different disorders

Treatment results regarding the comparison between the different disorders are given in Table 4. In general, there was better effect of RT for the enthesiopathies in comparison with gonarthrosis.

VPS immediately on completion of RT

A total of 29 patients (4.1%) were free of pain, 234 (33.3%) were much improved, 233 (33.1%) reported slight improvement, and 207 (29.5%) experienced no change.

VPS follow up

After a median follow-up of 33 months (3-60 months) 437 patients could be reached for evaluation of follow up results. 155 patients (35.5%) were free of pain, 100 (22.9%) had marked improvement, 65 (14.8%) had some improvement, and 117 (26.8%) experienced no change.

Comparison of VPS

A good response immediately on completion of RT could be achieved in 264/703 patients (37.6%), and with the follow up in 255/437 patients (58.4%) (p < 0.001). Only in patients with gonarthrosis we could not observe an increase of good response (30.2% immediately on completion of RT versus 29.9% at the follow up time).

Results for the different diagnoses are given in Table 3.

Table 3 Good Response (%) immediately on completion of RT and during follow up

| Diagnosis               | Good Response on completion of RT | Good Response - Follow up | P-Value |
|-------------------------|----------------------------------|----------------------------|---------|
| Calcaneodynia           | 46.0% (131/286 patients)         | 80.7% (113/140 patients)  | < 0.001 |
| Achillodynia            | 39.1% (18/46 patients)           | 88.9% (24/27 patients)    | =0.001  |
| Gonarthrosis            | 30.9% (43/139 patients)          | 29.2% (33/113 patients)   | =0.612  |
| Bursitis trochanterica  | 27.1% (19/70 patients)           | 46.3% (31/67 patients)    | =0.012  |
| Shoulder Syndrome       | 32.7% (53/162 patients)          | 60% (54/90 patients)      | < 0.001 |
| All patients            | 37.6% (264/703 patients)         | 58.4% (255/437 patients)  | < 0.001 |

Discussion

The above shown results of our prospective clinical quality assessment confirm the results of recently published retrospective and prospective randomized studies with a good analgesic effect of low dose radiotherapy for patients with calcaneodynia, achillodynia, painful gonarthrosis, painful bursitis trochanterica, and painful shoulder syndrome [9–23].

The precise pathophysiological mechanisms of pain relief after RT are still not well defined. Recent radiobiological experiments show that low doses of radiation have an anti-inflammatory efficacy based on the modulation of a multitude of inflammatory pathways and cellular components. This includes immune components like endothelial cells, mononuclear leukocytes, and macrophages, and an influence on the vascular endothelium with improved tissue perfusion, destruction of inflammatory cells (in particular lymphocytes) with release of cytokines and proteolytic enzymes, modulation of the vegetative nervous system, altering of the tissue pH and...
increased membrane permeability. Most likely, irradiation does not act through a single mechanism but through a complex interaction of different effects [6].

We observed a significantly improved long-term efficacy in comparison to the results immediately after RT in patients with calcaneodynia, achillodynia, bursitis trochanterica, and shoulder syndrome. This could be due to the delayed clinical onset of effects, which is most likely due to the also delayed onset of above mentioned radiobiological mechanisms. However, the group of patients with gonarthrosis was the only one without this observed delayed effect. Most likely, with low dose RT we can achieve more complete remissions in patients with calcaneodynia, achillodynia, bursitis trochanterica, and shoulder syndrome. In contrast, gonarthrosis is described to be an irreversible pathological process, with cartilaginous and bony destructions, which cannot reversed by radiotherapy. These irreversible destructions initiate a variety inflammatory processes leading to pain, swelling etc. under the clinical picture of activated osteoarthritis [8, 9]. Here, low doses RT may be helpful by alleviation of inflammation and pain in these acute episodes of this chronic joint disorders. However, the underlying pathophysiological problem remains more or less unchanged by RT, even so RT can arrest and slow down the progressive joint destruction in osteoarthritis by the anti-inflammatory effect of low dose RT. Therefore, the analgesic effect is only moderate compared to other indications, in particular the enthesiopathies [1, 4, 8].

Clearly, a possible placebo effect of low dose RT for pain treatment cannot completely be excluded. In previously published early double-blinded studies from the 1970s, a large variety of different degenerative skeletal

| Diagnosis             | Good Response on completion of RT | P-Value | Good Response - Follow up | P-Value |
|-----------------------|------------------------------------|---------|--------------------------|---------|
| Calcaneodynia         | 46.0%                              |         | 80.7%                    |         |
| Achillodynia          | 39.1%                              | =0.388  | 88.9%                    | =0.312  |
| Calcaneodynia         | 46.0%                              |         | 80.7%                    |         |
| Gonarthrosis          | 30.9%                              | =0.003  | 29.2%                    | < 0.001 |
| Calcaneodynia         | 46.0%                              |         | 80.7%                    |         |
| Bursitis trochanterica| 27.1%                              | =0.004  | 46.3%                    | < 0.001 |
| Calcaneodynia         | 46.0%                              |         | 80.7%                    |         |
| Shoulder Syndrome     | 32.7%                              | =0.006  | 60.7%                    | =0.001  |
| Achillodynia          | 39.1%                              |         | 88.9%                    |         |
| Gonarthrosis          | 30.9%                              | =0.307  | 29.2%                    | < 0.001 |
| Achillodynia          | 39.1%                              |         | 88.9%                    |         |
| Bursitis trochanterica| 27.1%                              | =0.177  | 46.3%                    | < 0.001 |
| Achillodynia          | 39.1%                              |         | 88.9%                    |         |
| Shoulder Syndrome     | 32.7%                              | =0.419  | 60.7%                    | =0.006  |
| Gonarthrosis          | 30.9%                              | =0.307  | 29.2%                    | < 0.001 |
| Bursitis trochanterica| 27.1%                              | =0.572  | 46.3%                    | =0.021  |
| Gonarthrosis          | 30.9%                              |         | 29.2%                    |         |
| Shoulder Syndrome     | 32.7%                              | =0.741  | 60.7%                    | < 0.001 |
| Bursitis trochanterica| 27.1%                              |         | 46.3%                    |         |
| Shoulder Syndrome     | 32.7%                              | =0.401  | 60.7%                    | =0.075  |

| Parameter             | Good Response on completion of RT | P-Value | Good Response - Follow up | P-Value |
|-----------------------|------------------------------------|---------|--------------------------|---------|
| One series (n = 652)  | 38.4%                              |         | 58.8%                    |         |
| Two series (n = 51)   | 27.5%                              | =0.102  | 55.3%                    | =0.673  |
| 12 × 0.5 Gy (n = 596) | 38.6%                              |         | 58.5%                    |         |
| 6 × 1.0 Gy (n = 107)  | 32.7%                              | =0.25   | 58.6%                    | =0.982  |
| Female (n = 461)      | 38.1%                              |         | 55.2%                    |         |
| Male (n = 242)        | 36.8%                              | =0.726  | 64.1%                    | =0.071  |
diseases were treated with low-dose RT. These studies could not prove a significantly higher response for the RT group in comparison to the placebo group \[24–26\].

Radiation side effects did not occur in any of our patients. This corresponds to the reported absence of chronic or acute adverse effects in the literature \[9–23\].

**Conclusion**

Low dose RT is a very effective treatment for the management of calcaneodynia, achillodynia, painful gonarthrosis, painful bursitis trochanterica, and painful shoulder syndrome. Due to the delayed onset of analgesic effects low dose RT results in a significantly improved long-term efficacy in comparison to the results immediately after RT particularly in patients with calcaneodynia, achillodynia, bursitis trochanterica, and shoulder syndrome.

### Abbreviations

Gy: Gray; RT: Radiotherapy; VAS: Visual analogue scale; VPS: von Pannewitz Score

### Acknowledgements

Commemorating the 30th anniversary of death of Günther von Pannewitz (1900–1987), the most important pioneer in field of radiotherapy of benign diseases.

His clinical and scientific merits are the everlasting base for the modern radiation treatment of non-malignant disorders.

### Availability of data and materials

Please contact author for data requests.

### Authors’ contributions

OM and RM were the principle investigators of the prospective clinical quality assessment. OM, EU, SB, IAA, US, RB, KK, MHS, KF and RM participated in the design of the prospective clinical quality assessment, its coordination, and performed a part of the statistical analysis. OM, EU, SB, US, RB and KK participated in the patient accrual and the follow-up examinations. OM, RM, IAA, US, KK and MHS drafted the manuscript. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

This prospective quality assessment study contains only established treatment concepts. Therefore, an ethical approval was not needed. Nevertheless, a written informed consent was obtained from every patient.

### Competing interests

The authors declare that they have no competing interests.

### Publisher’s Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

### Author details

1. Department of Radiotherapy and Radiation Oncology, Franziskus Hospital Bielefeld, Kiskerstrasse 26, D-33615 Bielefeld, Germany. 2. Department of Internal Medicine, St. Anna Hospital, Herne, Germany. 3. Department of Urology, Lippe Hospital, Detmold, Germany. 4. Department of Radiotherapy and Radiation Oncology, Marien Hospital Heme, Ruhr University Bochum, Bochum, Germany. 5. Department of Radiotherapy, Lippe Hospital, Lemgo, Germany. 6. Center for Radiotherapy, Hamburg, Germany. 7. Radiotherapy RheinMainNahe, Bad Kreuznach, Germany.

### Received

13 December 2017 | Accepted: 12 April 2018

### Published online

19 April 2018

### References

1. Seegenschmiedt MH, Micke O, Muecke R, German Cooperative Group on Radiotherapy for Non-malignant Diseases (GCG-BD). Radiotherapy for non-malignant disorders: state of the art and update of the evidence-based practice guidelines. Br J Radiol. 2015;88(1050):20150080.

2. Seegenschmiedt MH, Micke O. Radiotherapy of non-malignant disorders: Past, present and future. Strahlenther Onkol. 2012;188(Suppl. 3):272–90.

3. Seegenschmiedt MH. New future for radiation therapy of non-malignant diseases? Radiother Oncol. 2005;74:1–2.

4. Seegenschmiedt MH, Micke O, Willich N. Radiation therapy for non-malignant diseases in Germany. Current concepts and future perspectives. Strahlenther Onkol. 2004;180:718–30.

5. Micke O, Seegenschmiedt MH. German Working Group on Radiotherapy in Germany (GCG-BD). Consensus guidelines for radiotherapy of benign diseases: a multicentre approach in Germany. Int J Radiat Oncol Biol Phys. 2002;52:496–513.

6. Reichl B, Block A, Schaefer U, Bert C, Mueller R, Jung H, Roedel F. German Working Group on Radiotherapy in Germany(GCG-BD). DEGRO practical guidelines for radiotherapy of non-malignant disorders: part I: physical principles, radiobiological mechanisms, and radiogenic risk. Strahlenther Onkol. 2015;191:701–9.

7. Boett B, Doering N. Forschungsmethoden und Evaluation für Human- und Sozialwissenschaftler. Heidelberg: Springer; 2006, ISBN 3-540-33305-3, S. p. 177.

8. von Pannewitz G. Radiotherapy for degenerative arthritis, technique and clinical results. Radiologie. 1970;10:496–513.

9. Ott DJ, Niewald M, Weitmann HD, Jacob I, Adamietz IA, Schaefer U, Keilholz L, Heyd R, Muecke R. German Cooperative Group on Radiotherapy for Benign Diseases (GCG-BD). DEGRO guidelines for the radiotherapy of non-malignant disorders: part II: painful degenerative skeletal disorders. Strahlenther Onkol. 2015;191:1–6.
10. Ott OJ, Jeremias C, Gaipl US, Frey B, Schmidt M, Fietkau R. Radiotherapy for benign achillodynia: long-term results of the Erlangen dose optimization trial. Strahlenther Onkol. 2015;191:979–84.

11. Ott OJ, Jeremias C, Gaipl US, Frey B, Schmidt M, Fietkau R. Radiotherapy for benign calcaneodynia: long-term results of the Erlangen dose optimization (EDO) trial. Strahlenther Onkol. 2014;190:671–8.

12. Ott OJ, Jeremias C, Gaipl US, Frey B, Schmidt M, Fietkau R. Radiotherapy for calcaneodynia. Results of a single center prospective randomized dose optimization trial. Strahlenther Onkol. 2013;189:329–34.

13. Ott OJ, Jeremias C, Gaipl US, Frey B, Schmidt M, Fietkau R. Radiotherapy for achillodynia: results of a single-center prospective randomized dose-optimization trial. Strahlenther Onkol. 2013;189:142–6.

14. Nieveld M, Seegenschmiedt MH, Micke O, Graeber S, Muecke R, Schaefer V, Scheid C, Fleckenstein J, Licht N, Ruebe C, German Cooperative Group on Radiotherapy for Benign Diseases (GCCBD) of the German Society for Radiation Oncology (DEGRO). 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. 2012;84:e455–62.

15. Muecke R, Seegenschmiedt MH, Heyd R, Schaefer U, Prott FJ, Glatzel M, Micke O, German Cooperative Group on Radiotherapy for Benign Diseases (GCCBD). Radiotherapy in painful greater trochanteric pain syndrome-target volume definition and treatment outcome. Strahlenther Onkol. 2017;193:260–8.

16. Goldie I, Rosengren B, Moberg E, Hedelin E. Evaluation of the radiation treatment of painful conditions of the locomotor system. A double blind study. Acta Radiol Ther Phys Biol. 1970:9:311–22.

17. Valtonen EJ, Lilius HG, Malmio K. The value of roentgen irradiation in the treatment of painful degenerative and inflammatory musculoskeletal conditions. A double-blind study. Scand J Rheumatol. 1975;4:247–9.

18. Pienkonen A. Calcifying tendinitis of the shoulder: a critical study of the value of x-ray therapy. Radiology. 1952;59:384–9.