Editor's Corner

Dear Colleagues and Friends of Radiation Medicine,

Our newsletter BenigNews is further growing and now moving into its 3rd year. The internet appearance (http//:www.benign-news.de) is well accepted and has received several thousand hits. Moreover, our German Cooperative Group on Radiotherapy for Benign Diseases (GCG-BD) has conducted its 6th annual symposium at the Alfried Krupp Hospital in Essen from May 3 - 4, 2002. The international faculty of speakers and an excellent national and international attendance from Germany, Austria, Switzerland, Belgium and Netherlands demonstrate the growing interest in our scientific work and clinical study collaboration. As in former years, our symposium booklet (more than 250 pages) with a summary of all presentations is available for purchase for the interested reader.

Meanwhile, important publications from members of our group have been published in renown journals such as the International Journal of Radiation Oncology, Biology Physics, British Journal of Radiology and others (O. Micke, M.H. Seegenschmiedt: Consensus guidelines for radiation therapy of benign diseases: a multicenter approach in Germany. Int. J. Radiat. Oncol. Biol. Phys. 52, 496-513, 2002; O. Micke, M.H. Seegenschmiedt, F. Bruns, et al.: [Radiotherapy in allogenic renal transplantation: An indication for local graft irradiation?] Strahlenther. Onkol. 178, 280-285, 2002; M.H. Seegenschmeidt, H.-Br. Makoski, O. Micke: Radiation prophylaxis for heterotopic ossification about the hip – A multiceneter study. Int. J. Radiat. Oncol. Biol. Phys. 51, 756-765, 2001; U. Schäfer, S. Hesselmann, O. Micke, et al.: A long-term follow-up study after retro-orbital irradiation for Graves' ophthalmopathy. Int. J. Radiat. Oncol. Biol. Phys. 52, 192-197, 2002; S. Hesselmann, O. Micke, T. Marquardt, et al.: Kasabach-Meritt syndrome: a review of the therapeutic options and a case report of successful treatment with radiotherapy and interferon alpha. Br. J. Radiol 75, 180-184, 2002; St. Hesselmann, O. Micke, U. Schäfer, et al.: Systemic mast cell disease (SMCD) and bone pain. Strahlenther. Onkol. 178, 275-279, 2002). As in the previous three years, the last 43rd ASTRO meeting in San Francisco from November 4 – 8, 2001, had a special focus on Benign Diseases and the upcoming 44th ASTRO meeting in New Orleans from October 6 – 10, 2002 will have a special panel discussion on "Radiotherapy of Painful Joints".

In contrast, the upcoming ESTRO meeting in Praha (Chechoslovacia) unfortunately has not included any scientific panel, discussion forum or poster session on benign diseases despite growing clinical research. This may have several reasons: (1) in North America the Euopean leaders of countries in charge of ESTRO are not clinically experienced in the treatment of most patients with benign disorders, which is the case in most Scandinavian countries, e.g. Denmark, or Belgium, The Netherlands and Great Britain. (2) Legal restrictions and / or medical misconceptions currently prevent the renewed implementation of radiation treatment for benign disorders such as the professional concept of "Malpractice Suit" declaring a medical treatment as illegal when deviating from the defined standard professional approach with all consequences for the radiation specialist, which is the case in the US; however, this behaviour is self-supporting, as only research will change current practice, but clinical research on an "illegal basis" is nearly impossible. It is simple to say : without research no practice and without practice no (new) evidence ! (3) European health care systems still differ in terms of organisation of interdisciplinary medical care including radiotherapy for non-malignant disorders, e.g. major organisational and emotional problems exist to provide routine radiotherapy in a "Comprehensive Cancer Center" for non-malignant disorders, both for involved physicians and their patients. (4) The most important reason for the nonacceptance of radiotherapy for benign diseases is the continuing lack of new scientific evidence, which provides the strongest arguments for misjudgement or even opposition against its use. Long-term clinical experience and single-center trials do not count for the unconvinced modern radiation oncologist. Nowadays we should consequently ignore clinical studies lacking adequate control groups, appropriate endpoints, sufficient follow-up data or a insufficiently small sample size. All countries which are not routinely involved in radiotherapy of benign diseases require sufficient and convincing data from controlled clinical studies to start changing their daily clinical practice. In this regard they really need help from outside ! ***But from Whom ?***

This help has to come from our "**experienced centers**" in Germany or Central Europe which practice radiotherapy for benign diseases on a routine basis. If we only change our practice in some patients to support controlled clinical trials, we may survive with this routine practice in the near future, as the growing and united Europe will change our German health care system and require solid data derived from "Evidence Based Medicine (EBM)". Thus, old experience will be challenged under new regulations and only with convincing new clinical data we can help others and ourselves to convert our old-fashioned "empirical based medicine" into an "evidence based medicine".

The GCG-BD is now prepared to introduce several randomized trials for various painful joint or tendon insertion conditions, e.g. painful heel (calcaneodynia), elbow (epicondylopathia), shoulder (periarthritis humeroscapularis = subacromial syndrome) or some joints (osteoarthrosis of the knee, hip or thumb). These disease entities can be easily studied with an established orthopaedic perspective including the use of subjective and objective orthopaedic scores for prospective clinical evaluation. Nevertheless, randomised clinical studies will become more difficult to start in Germany, as the German authorities will adopt the new European perspective which requires an official approval by the Federal Bureau of Radiation Protection (= Bundesamt für Strahlenschutz). A written protocol has to be prepared and submitted. The formal approval process will take several weeks to months to get through; patients also have to be covered by an insurance.

However, besides clinical studies basic radiobiological research using in-vitro and in-vivo models is still required to detect the principles behind the efficacy of ionizing radiation at low doses for various benign disorders.

In this issue of BenigNews we present a prospective clinical study from the Department of Radiotherapy at the Ruhr University in Bochum by Schneider and colleagues and a retrospective study from the community hospital in Weiden by Mücke et al.; they applied objective and subjective scoring to evaluate the treatment response. Another interesting paper is presented by Glatzel et al. who report in radiotherapy of gonarthrosis. Micke summarizes his recently published paper on the German guidelines for treatment of benign disorders. As a rare clinical case we present: Systemic Mastocytosis.

In addition an evaluation score for the assessment of radiation treatment of epicondylopathia humeri is provided in a German and an English version for use in clinical practice.

Finally Schäfer et al. summarize the new clinical developments on intravascular brachytherapy and other treatment options for restenosis prophylaxis such as Tacrolimus / Sirolimus, which will help us to critically assess the future role of the radiation therapist in this treatment.

We like to thank our readers for their continued interest in this News Letter and encourage you to further submit articles, case reports and comments to us.

With best regards,

M. Heinrich Seegenschmiedt, Essen (Germany)
& Hans-Bruno Makoski, Duisburg (Germany)

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Contents

Original Contribution:

Effectiveness and Prognostic Factors of Radiotherapy of Painful Plantar Heel Spurs

O. Schneider, C.A. Stückle, C. Gott, K. Wagner, I.A. Adamietz
Department of Radiotherapy and Radio-Oncology, Universitätsklinik Marienhospital Herne,
Ruhr-Universität Bochum, Germany

SUMMARY

Aim: Evaluation of heel pain during and after radiotherapy and prognostic factors having impact on pain relief.

Patients and Methods: According to a prospective study design, from January 2000 to October 2000, 74 patients (102 heels) were treated for painful heel spurs. 70 patients (97 heels) with a mean age of 55 years (range 28-84 yrs.) were evaluated. All patients were referred to a defined scheme (one radiation series, direct portal, linear accelerator, 10MV photons, SSD 100 cm, field size 12 x 17 cm). Total dose was 5 Gy in 7 fractions, given twice a week at a single dose sequence of 0.25-0.25-0.5-1.0-1.0-1.0-1.0 Gy. 10 heels (10.3 %) received previously no other treatment. Mean duration of heel pain before RT was 4 months (range 1-120 months). Quantitative self-assessment of heel pain, using a visual analogue scale (VAS) was done before, thrice within RT and twice after RT, including evaluation of mechanical heel stress extent during RT. Effectiveness was estimated using patients´ judgment on subjective pain reduction.

Results: 6 weeks after RT pain relief was achieved in 82 cases (84.5 %). Sufficient pain relief (> 80 % to initial extent) was obtained in 29 heels (29.9 %), including 23 heels (23.7 %) with complete pain relief. Partial improvement (50-80 % pain reduction) was observed in 33 cases (34.0 %) and minor partial improvement (10-50 % pain reduction) in 20 cases (20.6 %). No change was seen in 13 cases (13.4 %) and in 2 heels (2 %) pain was increased. Older patients (>50 years) showed a significantly better pain relief (37.1 % vs. 11.1 %; $p<0.01$). Patients avoiding heel stress during period of RT showed a significantly better treatment success (Pearson´s correlation coefficient = -0.391; $p < 0.01$). However, no significant differences in the extent of heel pain reduction were observed depending on the period of heel pain before RT.

Conclusion: The results confirm high efficacy of radiotherapy in painful plantar spur. Pain relief can be expected during radiation treatment. Especially for older patients, radiotherapy should be considered as a primary treatment. Reduction of mechanical heel stress during radiotherapy may ameliorate the results.

INTRODUCTION

The effectiveness of treatment in diminishing plantar heel pain has not been finally elucidated (3). Radiotherapy (RT) is reported to be a suitable method, however optimal dosage, fractionating concepts, point of application time of ionizing radiation within an integrated treatment concept and prognostic factors are not clear (2, 4, 5, 7, 9, 11-12, 15, 17). To gain further evidence, results of a prospective study on efficacy of RT for pain reduction in heel spurs and prognostic factors were analysed.

PATIENTS AND METHODS

From January 2000 to October 2000, 74 patients (102 heels) were treated with refractory painful heel spurs in our Department of Radiotherapy, Marienhospital Herne. In 4 patients (5 heels) evaluated data are not complete. These patients were excluded from analysis.

In total 70 patients (20 male, 50 female, mean age 55 years, range from 28 to 84 years) were evaluated (97 heels, 52 left side, 47 right side). 14 patients received RT for right and left spur.

All patients were referred to the same RT therapy and technique, using high voltage photons (10 MV, Linear accelerator Saturne I; CGR, Buc, France), source-skin-distance 100 cm and one lateral field, sized 12 x 17 cm. Prescribed total dose was 5 Gy, in 7 fractions, twice a week, at a single dose sequence of 0.25-0.25-0.5-1.0-1.0-1.0-1.0 Gy.

10 heels (10.3 %) had previously received no other treatment, 87 heels (89.7 %) had received at least one other treatment option, e.g. insole support (n=72), local injections (n=67), systemic non-steroidal antiphlogistics (n=22), physiotherapy (n=9), and others (n=19).

Mean pain duration before RT was 4 months (range from 1 to 120 months). Patients were divided into groups relating to their period of pain. 41 patients reported a short pain anamnesis less than 3 months, 39 patients between 3 and 12 months and 17 patients reported a pain period of more than 12 months.

The analysis included only first courses of RT, however 19 patients (21 heels; 21.6%) received second courses of RT beyond the study.

Before, within (1, 2 and 3 weeks after starting RT), immediately after and 6 weeks after RT patients were asked to complete a questionnaire. Quantitative assessment included duration of heel pain before RT, prior treatment, intensity of pain, specified by a visual analogue scale (from 0 [no pain] to 10 [maximal pain]) and extent of mechanical heel stress during RT (range from 0 [indicating no stress] to 10 [indicating maximal heel stress] during period of RT). In addition, patients underwent physical examination before, after and 6 weeks after RT. Effectiveness was estimated on the basis of patients´ subjective pain reduction. Statistical analysis was performed using a commercial SPSS-package (version 10.0).

RESULTS

Pain relief was observed in most patients. In 82 heels (84.5 %) pain was reduced, no change was seen in 13 cases (13.4 %) and in 2 heels (2 %) pain was increased 6 weeks after RT. Complete pain relief was achieved in 23 heels (23.7 %), sufficient pain relief (relative pain reduction > 80 % of initial extent) in 29 heels in total (29.9 %), partial improvement (50-80 % pain reduction) in 33 cases (34.0 %) and minor partial improvement (10-50 % pain reduction) in 20 cases (20.6 %).

Heel pain was decreased during RT (Figure 1). Intensity of pain was 6.1 ± 1.5 VAS (mean ± SD) before RT, 6.0 ± 1.9 after 1 week of RT, 5.0 ± 2.1 after 2 weeks, 4.3 ± 2.2 after 3 weeks and 3.4 ± 2.1 at the end of RT. 6 weeks after RT 2.7 ± 2.3 on the VAS Was achieved.

Patients revealing a complete or sufficient pain reduction (80-100 % VAS) are significantly older with 63.6 ± 2.2 years (mean ± SEM, n=29, $p< 0.001$) than patients with an insufficient pain relief (< 80 % VAS) at the age of 53.4 ± 1.6 years (n=68).

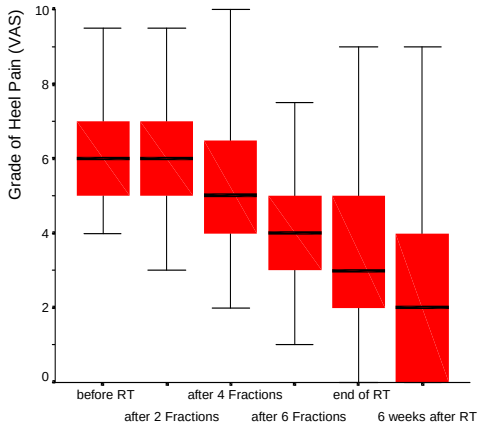

Fig. 1: Boxplots showing median, standard deviation and 25 and 75 % percentiles of extent of heel pain demonstrated by patients subjective evaluation with a visual analogue scale (VAS) before, within (1-3 weeks) and after RT (directly and after 6 weeks)

Patients aged 50 years and older showed sufficient pain relief (80-100 %) in 26 cases (37.1 %; n=70), whereas younger patients (< 50 years) show a significantly poor pain reduction (3 cases; 11.1 %; n=27; p<0.01) (Figure 2.).

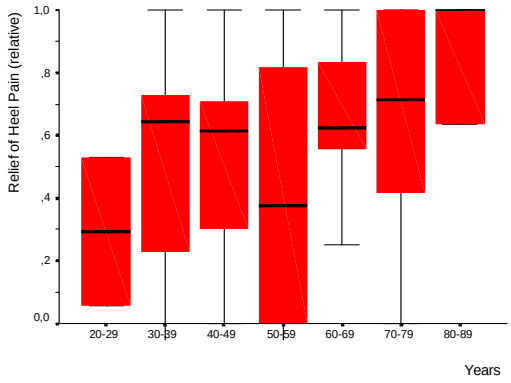

Fig. 2: Boxplots showing median, standard deviation and 25 and 75 % percentiles of relative pain relief, comparing the pain before RT and 6 weeks after RT, depending on the age of patients

Patients avoiding mechanical heel stress during the period of RT showed a significantly better treatment result (Pearson's correlation coefficient = -0.391; p < 0.01) (Figure 3).

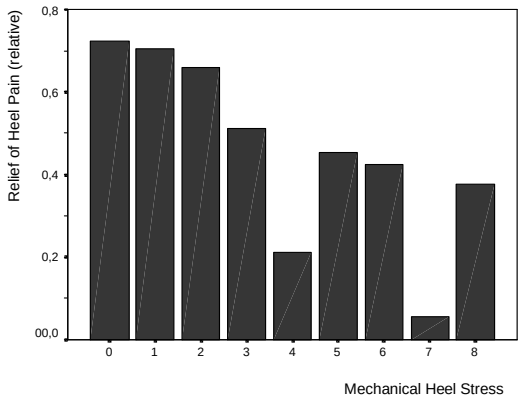

Fig. 3: Bar graph showing heel pain relief depending on patients' subjective heel stress, 0 indicating no stress and 10 indicating maximal stress, during period of RT

However, no significant differences in the extent of heel pain reduction were obtained in our study concerning duration of pain period before RT (Figure 4).

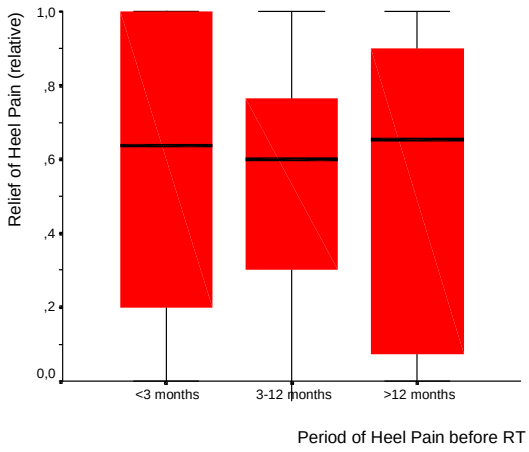

Fig. 4: Boxplots showing median, standard deviation and 25 and 75 % percentiles of extent of relative pain reduction, before RT and 6 weeks after RT, depending on the period of heel pain before RT

Patients with a pain duration less than 3 months demonstrated a relative pain reduction of 57.7 ± 6.2 % (mean ± SEM; n=36), patients with a period ranging between 3 and 12 months reported 52.1 ± 5.7 % pain relief (n=35) and patients with a period of more than 12 months showed 55.0 ± 9.9 % reduction of plantar pain (n=16) (p>0.5). The dynamical development of heel pain within these 3 groups of patients showed no significant differences (Figure 5).

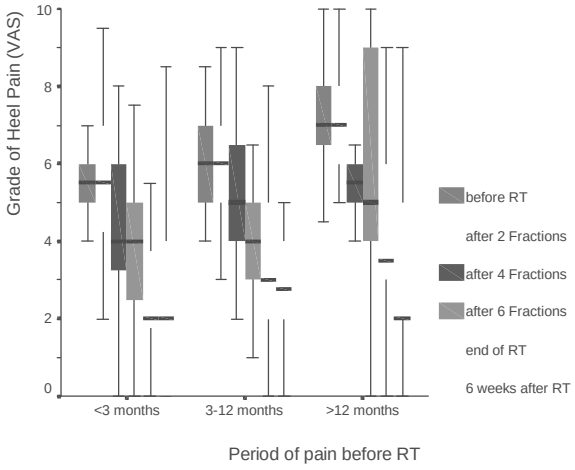

Fig. 5: Boxplots showing median, standard deviation and 25 and 75 % percentiles of the extent of heel pain before, within (1-3 weeks) and after RT (direct and after 6 weeks) depending on period of heel pain (scheduled in 3 intervalls)

DISCUSSION

In Germany, radiotherapy is a well-accepted and a very common indication to treat osteoarthritis and periarthritis, including radiation therapy for painful heel spurs (14) although, there are no results of randomised trials evaluating radiotherapy against a control population available (3). In the micro milieu, the empirically based anti-inflammatory radiotherapy of benign diseases appears to act through specific modulation of different pathways of inflammatory reactions such as the nitric oxide pathway in stimulated macrophages (6). The synovial membrane may be the critical

target of radiotherapy for osteoarthritis (16). However, results of previous clinical studies indicate a high efficacy of radiotherapy for painful heel syndrome. Our results confirm these results of low-dose radiotherapy. The problem of an optimal radiotherapy concept has not finally been solved. Dose concepts in the last years used a single dose ranging from of 0.3 (7) to 1.0 Gy (4-5, 11-12, 14). In the literature, prescribed total dose range from 3 to 12 Gy. We used a total dose of 5.0 Gy, as total dose of 5.0 Gy with 0.5 Gy fractions is shown to be superior to a total dose of 3.0 Gy with 0.3 Gy fractions and use of 12.0 Gy with 1.0 Gy fractions did not yield any better result. Total dose was proven to be a prognostic parameter. (15). In a previous study we confirmed the equivalent effectiveness of 10.0 Gy with 1.0 Gy fractions in comparison to 5.0 Gy with 0.5 Gy fractions in reducing heel pain (1).

Response rates from 65 to 100 % and rates of complete remission of heel pain from 12 to 81 % were observed (2, 4, 5, 7, 9, 11-12, 15, 17). Orthovoltage and high voltage radiotherapy were used. We used high voltage radiotherapy and found a response rate of 84.6 % and a rate of complete pain relief of 23.7 %. One aim of our analysis was the development of heel pain during and shortly after RT, so that we may underestimate the final total clinical response rates. Seegenschmiedt et al (15) found delayed complete pain relief in 45 % of treated heels.

To evaluate patients' subjective grade of heel pain, we used the sensitive visual analogue scale (VAS) to measure pain development already during RT. As some authors observed, and this confirms our clinical impression, pain intensifies shortly after initiation of RT, we started our RT sequence with 0.25 Gy – 0.25 Gy and 0.5 Gy (continuing with a single dose of 1.0 Gy). Increasing heel pain was just observed in 2 cases (2.1%) and significant decreasing grade of heel pain started after the second week of radiotherapy, at a dose of 2.0 Gy. After the following fractions, heel pain was observed to reduce constantly until the end of the RT period. Further relief of pain was achieved after 6 weeks of RT. Decreasing grade of pain could be expected, as delayed response is reported by other authours (8-10, 16). Schäfer et al. (11) reported a complete pain relief of 58 % of patients, with a median follow-up of 42 months and Seegenschmidt et al (15) observed recurrent pain 0-9 %, with a mean follow-up of 1.5 years.

To predict sufficient pain relief, we found patients` age to be a prognostic parameter. In our study 37.1 % of the subjects older than 50 years experienced sufficient pain relief, whereas only 11.1 % of the younger ones (age < 50 years) demonstrated sufficient pain relief. Glatzel et al. (4) reported age as a prognostic factor for pain relief, too.

In our study, we revealed another prognostic parameter, the mechanical heel stress during RT. Patients avoiding mechanical heel stress during the period of RT showed significantly better treatment results.

In contrast to some authors (4, 15) and to some of our own previous data (13), our current data show no significant differences in the grade of heel pain reduction observed in different groups, concerning period of pain before RT. The dynamical development of heel pain within these 3 groups of patients showed no significant differences.

CONCLUSION

Our results confirm high efficacy of radiotherapy in painful plantar spur. Pain relief can be expected during radiation treatment. Especially for older patients, radiotherapy should be considered as a primary treatment and should not be solely regarded as a last resort due to its low costs and high efficacy. Reduction of mechanical heel stress during radiotherapy may ameliorate the treatment results.

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Announcements

Archive of Benign Diseases: To achieve and maintain an overview about currently published data, the German Working Group "Radiotherapy for Benign Diseases" and BenigNews will establish an "Archive of Benign Diseases". We would like to ask clinicians any potential authors, who have recently published an article about radiotherapy of benign diseases, to send a reprint to the editorial office of BenigNews. Furthermore, any interested person is encouraged to send a copy of any interesting publication about radiotherapy of benign disease to the editorial office of BenigNews.

The best article per year is awarded with € 50,-!

Original Contribution:

Radiotherapy of Painful Heel Spurs – a Retrospective Study of 117 Patients Treated with 6-MeV-Photons

R. Mücke[1], K. Schönekaes, O. Micke[2], D. Berning[2], R. Heyder[1]
(1) Abteilung für Strahlentherapie, Radioonkologie und Nuklearmedizin, Klinikum Weiden, Germany
(2) Klinik und Poliklinik für Strahlentherapie – Radioonkologie, Universitätsklinikum Münster, Münster, Germany

Summary
Background: We present an analysis of treatment results concerning pain relief in 117 patients treated with radiotherapy (RT) for painful heel spurs, between 1996 and 2000.
Patients and methods: 71 women (60.7 %) and 46 men (39.3%) with a mean age of 58 years (30-84) and 136 heel spurs were irradiated in one (n=104) or two series (n=13).
There were 94 plantar, 5 dorsal and 18 bilateral heel spurs. 82 patients (70%) had prior therapy and in 35 patients (30%) radiotherapy (RT) was the primary treatment.
RT was performed twice a week with a 6-MV photon single beam. Single doses of 0,5 Gy were given up to a total dose of 5,0 Gy. Results were evaluated on completion and during follow up using the "von Pannewitz"-score (no symptoms, much improved, improved, no change).
Results: On completion of RT 27 patients (23,1%) were free of pain, 40 (34,2%) patients showed marked improvement, 31 (26,5%) reported a slight improvement and 19 (16,2%) patients experienced no change. After a mean follow up of 20 months (1-63 months) by the time of March 2001 75 out of 100 patients were free of pain. 12 had marked and 3 patients some improvement. 10 patients showed no change in their symptoms.
The mean duration of pain before RT was 6 months (1-60 months). RT 6 months after the onset of symptoms resulted in long lasting improvement in 94,2% (n=70). An interval of 6 months until the initiation of RT resulted in only 72,8% (n=30) of patients in an improvement (p=0,045).
Conclusion: Irradiation with 6-MV photons showed a long lasting benefit in 70% of the patients. RT should begin during the first 6 months of symptoms. Further prospective studies with validated scores should be conducted.

Introduction
Radiotherapy (RT) has been known to show good results in heel spurs and other musculoskeletal degenerative and inflammatory entities.
The goal of this retrospective study was to analyse the therapeutic effect of irradiation with 6-MV photons immediately after completion of RT and during long term follow-up, using a telephone survey. This could also lead to the identification of prognostic factors.

Patients and Methods
At the Department of Radiotherapy, Radiation Oncology and Nuclear Medicine of the Klinikum Weiden a total of 117 patients (71 female, 46 male) with painful heel spurs were treated between January 1996 and December 2000. The median age was 58 with a range from 30 to 84 years. 104 patients received a single irradiation, 13 patients were treated for a second time after three months. A total of 136 heel spurs had been treated (43 left and 55 right foot, 19 bilaterally). 112 spurs were plantar and 5 spurs were dorsal. All bony lesions were radiographically detectable. 82 patients (70%) received other treatments prior to RT: local analgesic injections (n=42; 35.9%), orthopaedic insoles (n=18; 15.4%), non-steroidal anti-inflammatory agents (n=13; 11.1%) and physiotherapy (n=8; 6.8%). One patient had prior surgery (0.9%). In 35 cases (29.9%) RT was the primary treatment.
Indications for RT were the clinical syndrome of tenderness in the typical location and a functional deficit with a decreased range of pain free motion.
Treatment planning was done in the therapy simulator. The complete calcaneus including the insertion of the Achilles tendon included in the field.
The dose maximum, i.e. in 1,6 cm tissue depth when using 6-MV photons, was given twice weekly with a single beam and a single dose of 0,5 Gy up to a total dose of 5 Gy. Patients treated with two courses received the same single and total dose.
Therapy results were evaluated using the "von Pannewitz" score (16).
The patients were interviewed at the end of the RT. Long term follow-up was conducted during a telephone survey in March 2001 with a median follow-up time of 20 months (range 1-63 months). The interviews with 100 patients were used.
Statistical analysis was done using the program SPSS.

Results
Table 1 gives a summary of the results at the end of RT. At this time 27 patients (23,1%) were free of pain, 40 patients (34,2%) showed considerable improvement, 31 (26,5%) had some improvement and 19 patients (16,2%) felt no change.
Owing to persistent pain 13 patients (11,1%) received a second course of RT after three months.
The telephone survey yielded follow-up data for 100 patients. After a median of 20 months (range 1-63 months) 75 patients were free of symptoms, 12 reported a considerable improvement and some improvement was observed by 3 patients. 10 patients showed no change (table 2). In relation to the number of RT courses 78 out of 87 patients (89.7%) who received a single course compared to 9 out of 13 patients (69.2%) with two courses had long term pain control.
The long-term pain control (free of pain, considerable and some improvement) for all 100 patients using the Kaplan-Meier method the rate was 86.2% (Table 1).

Result	Patients (n = 117)
1	27 (23,1%)
2	40 (34,2%)
3	31 (26,5%)
4	19 (16,2%)

Tab. 1: Results at the end of radiotherapy
(1 no symptoms, 2 much improved, 3 improved, 4 no change)

The mean duration of symptoms was 6 months (range 1-60 months) before RT. Initiation of RT within the first 6 months of symptoms (n=70) led to a long term pain control in 94.2% of patients. RT given after more than 6 months of clinical complaints (n=30) resulted in long term pain control in 72,8% of cases (p=0.04) (Table 2).

Result	Patients (n = 100)
1	75
2	12
3	3
4	10

Tab. 2: Results at the time of data analysis
(1 no symptoms, 2 much improved, 3 improved, 4 no change)

Patients with a single course of RT (n=88) had long term pain control in 92.6%. Patients who received a second course (n=12) had long term pain control in 72.9% (p=0.0842) (Figure 1).

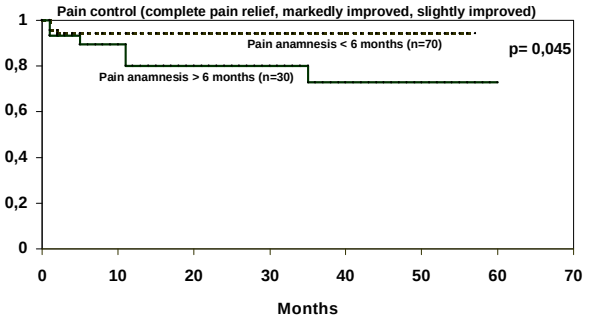

Fig. 1: Univariate analysis (Logrank) for pain control (60month) depending on duration of pain anamnesis

No part of the study (immediately after RT and during follow-up) revealed acute or chronic side effects.

Discussion

There is a long tradition for radiotherapy of benign, degenerative or inflammatory- lesions. The percentage of this application among all RT procedures is 8-10% in the german-speaking countries (19). Numerous studies have described the effectiveness of radiotherapy under orthovoltage- as well as megavoltage-conditions (1, 2, 5, 8, 11, 14, 15, 16, 18, 19, 20, 21, 24) (Table 3). The improvement rate in these studies was 65-100%.

Unfortunately the description of the patient details and possible influencing factors in some reports are not precise. Furthermore different evaluation scores were used. Our results with improvement rates (free of pain, considerably improved and improved) of 83.8% immediately after RT seem to confirm previous studies. After a rapid initial pain relief the effect lasts up to years. In our study 75% of patients reported no residual pain in a telephone survey after a median of 20 months (range 1-63 months). This success is confirmed in the Kaplan-Meier analysis (diagram 1). Although only a few studies report long term results our data confirm the long term studies by Schäfer et al.(19) .

The only prospective study so far investigated different dose regimens. In 72 cases a total dose of 12 Gy was applied in two courses of 6x1 Gy over two weeks. In 50 cases 10x0,3 Gy and in 48 cases 10x0.5 Gy were used. The best response was observed with a total dose of 5 Gy given in 0.5 Gy single doses. Fractionating with 3x1 Gy per week up to 12 Gy total dose did not improve the response rate. During long term follow-up the dose group with 5 Gy and 12 Gy proved to be better than the group with a total dose of 3 Gy and a single dose of 0.3 Gy (21).

The single dose should not be lower than 0.3 Gy. This is regarded as the threshold dose for a tissue alkalosis which some authors see as the underlying cause for the pain relief (17). Many authors recommend a single dose of 0.3-0.5 Gy up to a total dose of 3-6 Gy (1, 8, 14, 19, 21, 24). Better responses with higher doses in one single study have not yet been clinically correlated (21, 23).

The role of the placebo effect in RT for pain treatment is not clear. So far there are no studies that deal specifically with the treatment of heel spurs. A double blinded placebo-controlled study could answer this question.

The precise mechanism of pain relief after RT remains unclear. An arthritis model using rabbits showed an anti-inflammatory effect with decreasing synovitis after irradiation (22).

Other theories describe an influence on the vascular endothelium with improved tissue perfusion; destruction of inflammatory cells the exudates (especially lymphocytes)with release of cytokines and proteolytic enzymes; modulation of the vegetative nervous system; altering of the tissue pH; increased membrane permeability (10, 12, 22, 23). Recent studies showed, that there are also effects of low dose ionising radiation on the molecular and cellular level involving adhesion molecules, cytokine expression and inflammation cascade (6, 7, 13).

Probably irradiation acts not through a single mechanism but through a complex interaction of different effects.

Reference	Patients	Heels	Type of RT	Response Rate (%)	CR (%)	PR (%)	NC (%)
Pannewitz 1933 (16)	88	88	OV	92			
Mitrovv (1967) (14)	1520	1520	OV	88	50	38	12
Zschache (1972) (24)	49	49	OV	86	12	74	14
Mantell (1978) (11)	17	26	240-300 kV	65	53	12	35
Basche (1980) (1)	102	102	120 kV	90	32	58	10
Sautter-Bihl (1993) (18)	15	15	Cobalt	80	60	20	20
Schäfer (1995) (19)	18	21	HV	67	58	8	33
Seegenschmiedt (1996) (21)	141	72 Pat 12 Gy 98 Pat 3-5 Gy	200-250 kV	100 95	67 72	33 23	0 5
Oehler (2000) (15)	212	258	OV	88	81	7	12
Koeppen (2000) (8)	673	673	250 Kv	78	13	65	22
Scheiber (2000) (20)	70	87	6MV	86	67	29	14
Heyd (2001) (5)	105	127	6MV	88	46	42	12
Glatzel (2001) (2)	141	161	175 kV	89	63	26	11

Tab. 3: Review of literature
(OV Orthovolt radiotherapy, HV Highvolt radiotherapy)

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 (Table 3).
Some authors describe an initial increase in symptoms after the first dose fractions (4, 19). This is attributed to a transient local acidosis (10).
Many colleagues from non-radiotherapy specialties are reluctant to recommend RT because they are concerned with the potential of damage to the gonads or tumor induction. However one has to point out, that there is no increased tumor rate in the published literature for the chosen dose range (9, 18). The applied gonad dose during the treatment of heel spurs lies in the range of diagnostic imaging (3). When standard radiation protection measures are taken (minimal field size, gonad shields etc.) the risk of RT in this subpopulation of mostly elder patients can almost be neglected, but still should be mentioned. The risk of medical treatments should be taken into consideration.
A prognostic factor for therapy failure in the univariate analysis was the duration of pain before the initiation of RT. Long term pain control after a history of 6 months occurred in 94.2% compared to 72.8% long term pain control after a history of 6 months (p=0.04). These results correspond to the published data by Seegenschmiedt et al. (21)**.**
Another prognostic factor was the overall tendency toward better response after the first RT course. 13 out of those 19 patients who showed no change immediately after the completion of RT received a second course. To judge the therapy response one has to wait for about 3 months because improvements can occur up to this point (21).

Conclusion

Radiotherapy with 6-MV photons is successful in more than 80% of patients during long term follow-up. RT showed no side effects and should not be considered as a "last resort". It should rather begin during the first 6 months of symptoms.
The precise physiologic effect of RT and the role of the placebo effect are still not known.

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Original Contribution:

Results of Radiotherapy for Gonarthrosis

M. Glatzel, D. Fröhlich, A. Krauß, S. Bäsecke
Department of Radiotherapy, Zentralklinikum Suhl gGmbH, Albert-Schweitzer-Str. 2,
98527 Suhl, Germany

Summary
Purpose: The aim of this retrospective analysis was to evaluate the effect of x-ray depth therapy for gonarthrosis on our own patients.
Patients and methods: From 1996 to 2000, 214 knee joints in 163 patients were irradiated. By analyzing patient records and using an additional questionnaire, 151 knee joints (right: 39, left: 38, bilateral 37) could be analyzed. The mean age of the 114 patients (31 male, 83 female) amounted to 64 (42-89) years. In 85 knee joints (56.3%), the pain symptoms had been present for > 1 year. Radiotherapy was performed using an orthovoltage machine with 175 kV via 2 fields (lateral and medial) with a field size of 10x15 cm. With a fractionation of 3 fractions per week, single doses/total doses of 0.5/3.0 (n=11), 0.75/4.5 (n=52) and 1.0/6.0 (n=88) Gy / field were applied. 23 knee joints (15.2%) received a second course of radiotherapy after an interval of 12 weeks.
Results: At the end of treatment, in 85 knee joints (57.6%) a pain reduction could be detected. (free from pain: 1.3%; substantial improvement: 26.5 %; improvement: 29.8%). This proportion was increased to 103 knee joints (68.2%) after 3 months. Of these, 14 (9.3%) achieved complete freedom from symptoms. Besides, 53 knee joints (35.1%) showed an improved mobility after radiotherapy. After a mean follow-up of 29 months, in 57 of the 103 successfully treated knee joints, the pain recurred, in 36 of these patients during one year. A positive long term effect of this treatment (i.e. lasting longer than 12 months) could therefore be observed in 67/151 knee joints (44.4%).
Conclusion: A rate of pain reduction of 68.2 % and a positive long-term effect (> 1 year) in 44.4 % are an impressive argument for the value of analgesic radiotherapy in the treatment of gonarthosis.

Introduction
Radiotherapy of inflammatory and/or degenerative diseases is a conservative treatment measure that has long been known for its good analgetic effect, which has been described in a large number of publications with high numbers of patients.
Radiotherapy cannot change the morphologic aspect of a radiologically proven arthrosis. Rather the pain relief is induced by influencing the concomitant reactive synovialitis with its corresponding pain symptoms and impairment of joint mobility.

In the last few decades, the indication for radiotherapy of degenerative skeletal diseases was drastically reduced in favor of other treatment modalities like analgesics, antiphlogistics and surgical measures (e.g. synthetic joint replacement).

Since the installation of the x-ray depth therapy equipment, we could however demonstrate a – if discontinuous – increase of referrals for analgesic radiotherapy for gonarthrosis in for our own patients (Figure 1 shows a typical example).
This increase motivated us to evaluate the effect of radiotherapy for patients with painful gonarthrosis within the framework of quality control in the clinical routine.

Patients and Methods
During the evaluation period from 1996 to 2000, 214 knee joints in 163 patients were irradiated for painful gonarthrosis at the Department of Radiotherapy of the Zentralklinikum Suhl gGmbH. The evaluation of treatment results was done according to the patient records and, additionally, with the help of a retrospective survey for the assessment of long-term results.

Fig. 1: Radiograph of a knee joint showing typical radiological signs of gonarthrosis

151 knee joints in 114 patients were evaluable. Bilateral treatment had been carried out in 37 patients (32.4%). There was no preference of the left or right side: 76 right and 75 left knee joints were irradiated. With 83 women and 31 men referred for radiotherapy, a marked preference of the female sex was found. The mean age of these patients was 64 years with the youngest patient being 42, the oldest 89 years old. Most patients were referred to us by orthopedic specialists (48%), followed by general practitioners (24%) and surgeons (14%). In 85 knee joints (56.3 %), pain symptoms had been present for more than 1 year, in 57 knee joints in less than 1 year. In 9 treated joints, the length of pain history could not be investigated any more (Figure 2).

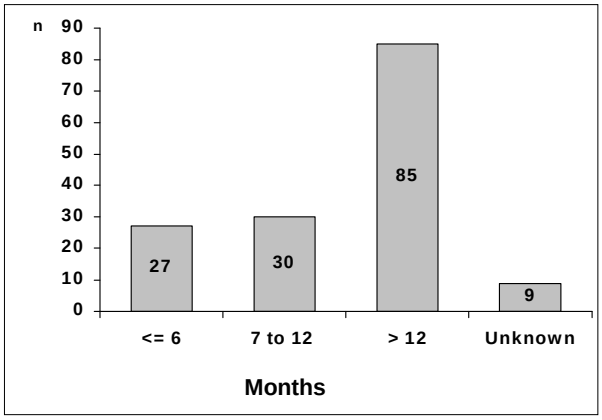

Fig. 2: Duration of pain symptoms before start of radiotherapy

The majority of patients had been unsuccessfully treated with other therapeutic measure before (Figure 3).

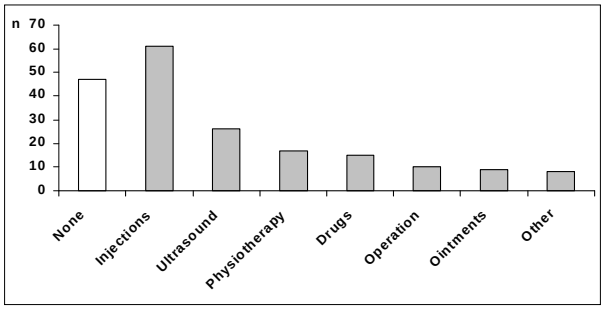

Fig. 3: Pretreatment

Radiotherapy was carried out with an orthovoltage appliance with 175 kV through opposing medial and lateral fields directed on the knee joint with a field size of 10 x 15 cm (width x height). 6 fractions were applied over 2 weeks with the following single and total doses: 0.5 / 3.0 (n=11), 0.75 / 4.5 (n=52) and 1.0 / 6.0 (n=88) Gy. Both fields were irradiated during each session. 23 knee joints (15.2 %) received a second course of radiotherapy after an interval of 12 weeks if the first treatment did lead to no or insufficient pain reduction. The treatment response with respect to pain relief was classified as follows (modified after von Pannewitz (1)):

1. free from symptoms:	**no pain at all**
2. substantial improvement:	**generally pain free, no restriction of everyday activity, sometimes pain with changing weather**
3. moderate improvement:	**marked reduction of symptoms, pain does continue, but is reduced to a tolerable amount**
4. unchanged:	**pain continues in the same way as before treatment**
5. worse :	**increased pain**

The categorization of treatment response into to these 5 categories was only done according to the subjective statements of the patients. Additionally, they were interviewed if they had detected any change in the mobility of their knee joints.
The use of scores and the systematic evaluation of x-ray files were impossible because of the retrospective character of this analysis. The mean follow-up of the patients amounted to 29 months.

Results

At the end of therapy, in 85 knee joints (57.6%) an effective pain relief could be observed. Freedom from pain was only found in 1.3%, a substantial improvement was reported by 26.5% of patients. A moderate analgesic effect could be found in 29.8% of patients.
After 3 months, the proportion of successfully treated patients increased to 68.2% (103 knee joints). Of these, 9.3% (14 knee joints) achieved complete freedom from pain, 26.5% showed a substantial improvement and 32.5% a moderate improvement of their symptoms (Figure 4).

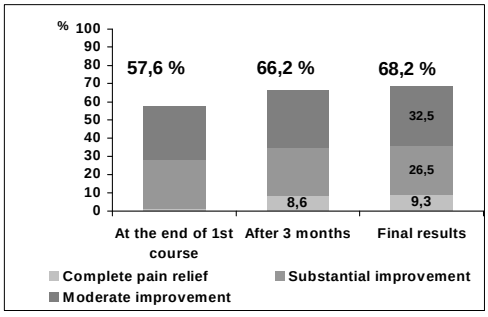

Fig 4: Treatment results

Additionally in 53 knee joints (35.1 %) an improved mobility was reported after the end of radiotherapy. In nearly all patients, the improvement had taken place during the first 3 months after the end of therapy (Figure 5).

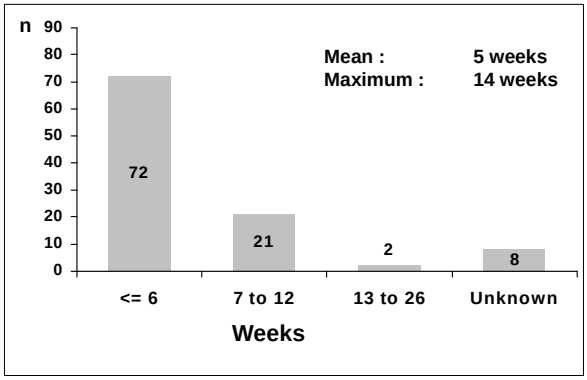

Fig. 5: Time period until the full effect of radiotherapy

After a mean follow-up of 29 months, 57 of the 103 successfully treated knee joints developed a recurrence of the pain symptoms. In 36 knee joints, this took place during the first year after the end of treatment. A positive long-term effect of the treatment (i.e. duration of improvement of over 1 year) was observed in 67 of the 151 treated joints (44.4 %). The probability of pain recurrence after successful radiotherapy – calculated using the Kaplan-Meier statistic – amounted to 43 % after 1 year, 63 % after 2 years and 74 % after 3 years.

Discussion

The present retrospective analysis mainly served the purpose of estimating the effect of analgesic radiotherapy for gonarthrosis in our own patients.
Our results are comparable with data from literature, especially from the 2nd half of the last century (2-8). Other authors report about substantially higher response rates and higher percentages (> 20 %) of pain-free patients (9-14). When low single and total doses were used, despite of high response rates, only few patients became free from symptoms (15) (Table 1a and 1b).

a)

AUTHOR	YEAR	n	RESPONSE	COMPLETE PAIN RELIEF
WIELAND (12)	1965	341	97 %	62 %
FRIED (9)	1934	126	93 %	23 %
MITROV und HARBOV (13)	1967	820	90 %	56 %
v.PANNEWITZ (1)	1970		89 %	25 %
HARTWEG et al. (14)	1973	124	87 %	29 %
SAUTTER-BIHL et al. (6)	1993	42	86 %	12 %
ZSCHACHE (4)	1972	461	84 %	6 %
BAKKE (10)	1939		83 %	38 %
PAPE und GÖLLES (15)	1954	190	82 %	3 %

b)

AUTHOR	YEAR	n	RESPONSE	COMPLETE PAIN RELIEF
COCCHI (11)	1943	188	70 %	25 %
GLATZEL et al. (8)	2001	151	68 %	9 %
KEILHOLZ et al. (7)	1998	49	64 %	13 %
KEIM (3)	1965	38	63 %	Not mentioned
HESS und BONMANN (2)	1955	366	60 %	12 %
LINDNER und FREISLEDERER (5)	1982	105	57 %	9 %
			57 – 97 %	3 – 62 %

Tab. 1: Results of radiotherapy for gonarthrosis

In our opinion, the higher response rates after radiotherapy of gonarthrosis in publications from the 1920s and 1930s can be mainly put down to the fact that, with diverse treatment

modalities available today, a negative selection of patients referred for radiotherapy takes place. On the other hand, even from our data it can be deducted that radiotherapy is effective in treatment-resistant patients even after multiple pre-treatments.

According to our analysis, we could also determine that a good assessment of the treatment effect is possible after 3 months. Patients only responding after a longer period of time were rare in our collective. For the present analysis, the assessment of treatment response was however only possible by the subjective judgment of the patients**.**

Further studies of the importance of prognostic factors are being prepared. The use of objective scores for the assessment of treatment success and the systematic evaluation of x-ray films shall be made possible by prospective analyses.

From this analysis, we can state that radiotherapy is an effective and low-risk treatment modality for the therapy of painful gonarthrosis that also only causes low treatment costs.

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Original Contribution:

Patterns of Care Study for Postoperative Keloid Prophylaxis

J. Kutzner[1], L. Schneider[2], M.H. Seegenschmiedt[3]
and German Cooperative Group on Radiotherapy for Benign Diseases (GCG-BD)
(1) Diagnostic Radiology & Radiation Oncology, Johannes Gutenberg University, 55131 Mainz, Germany
(2) Radiation Oncology, Community Hospital, 63069 Offenbach, Germany
(3) Radiation Oncology, Therapeutic Radiology and Nuclear Medicine, Alfried Krupp Hospital, 45133 Essen, Germany

Introduction

The term keloid is credited with two etymologies. It was derived from the Latin meaning "claw of a crustacean" due to its occasional tentacle-like appearance on the skin. The second meaning is derived from the Greek word "tumor". Keloids and hypertrophic scars are quite similar disorders, but in fact represent different stages of the same pathological process, namely an excessive mass of connective tissue arising within, along and around surgical scars. The connective tissue response to cutaneous injury somehow exceeds the physiological needs appropriate to the degree of injury and body site. In fact, the cutaneous trauma appears to be a decisive precondition. There appears to be an unexplained breakdown in the normal balance between fibrohyalinization and fibrohyalinolysis.

Keloids occur more often at young age (highest incidence in the first three decades), among Asians, Africans and Afro-Americans and females (female : male = 2 : 1). A 1 – 3% occurrence of familial cases of keloid formation is known, but a chromosomal abnormality is not known. This supports the theory of *Bohrod* (1937) that the tendency to develop keloids is transmitted genetically, and it is thought to be an autosomal gene of incomplete dominance and variable expressivity. Face, earlobes, shoulder and upper torso are mostly affected. Keloids are quite distressing for cosmetic reasons especially for young adults; they cause irritating symptoms and pain or interfere with functional aspects of involved body parts. Keloids are neither neoplastic nor progressive in the manner of desmoids, but constitute a localized over-production of scar tissue.

Surgical excision of primary / recurrent keloids is often followed by local relapse. Kryotherapy has improved surgical results (10, 31, 35). Steroid (13, 17) and retinoic acid injections (26) have not established long-term success. Postoperative silicon-occlusive taping has achieved a high local control rate, but long-term data are lacking (12, 16, 25).

Prophylactic RT after surgical re-excision is regarded as effective "salvage measure". Once keloids are fully developed primary RT is possible, but less successful than prophylactic RT after surgical resection. Depending upon the involved body site linac photons > 4MV with a 0.5 – 1.0cm bolus or electrons of various energies and orthovolt X-rays may be applied; LDR or HDR brachytherapy has been only rarely applied. Fractionated RT (total 12 – 20Gy) has been reported to be effective as well as a single 8 - 10Gy RT fraction. Many clinical studies suggest a high response rate and a low incidence of radiological sequelae (including carcinogenesis and late skin and organ damage).

Postoperative RT is a nationally (21) and internationally accepted RT indication (24), but so far no "gold standard" has been established regarding timing, dose concept (single and total RT dose) and objective / subjective analysis of clinical outcome. Following a general national patterns of care study, a multi-center cohort clinical study was conducted to analyse the RT concepts for treatment of keloids in Germany.

Material & Methods

Between 1997 and 2000, a structured questionnaire (**Appendix A**) was mailed to all German RT institutions to assess the different institutional policies regarding the clinical indication, the applied RT dose concept (timing, single / total RT dose, fractionation) and the type of retrospective or prospective analysis to assess the long-term clinical outcome. Moreover, the overall and annual patient accrual rate were questioned. A specific interest of this national PCS regarded the long-term outcome of patients.

Clinical indications for the use of prophylactic RT were related to the actual timing of RT within the treatment process (RT for primary or recurrent keloids). The applied RT concepts and schedules were evaluated regarding timing (postoperative start of RT) and dose prescription (median, range of single / total RT doses). Long-term outcome was assessed in institutions with ≥ 2 years follow-up after RT.

Results

A total of 134 RT institutions returned the mailed questionnaire: 33 (24%) noted to have no clinical experience with prophylactic RT of keloids either due to lack of referral from dermatology, plastic surgery or general medicine or due to lack of own experience; 5 (4%) institutions provided selected data to a few aspects; thus, 96 (72%) RT institutions remained with sufficient own clinical experience and an almost complete data set on institutional policies including indication and RT technique. These RT institutions represented 18 of 32 (56%) university hospitals and 78 of 130 (60%) community hospitals in Germany. A total of 77 (80%) institutions specified their clinical data on 1.672 treated patients between 1962 – 2000, while the 19 (20%) other institutions were unable to provide the exact numbers of patients and adequate follow-up data on their patients who received prophylactic RT. Table 1 and Table 2 summarize the patient accrual rate and the duration of prospective documentation in the different RT institution which contributed to this PCS.

Table 1: Number of Irradiated Patients per Institution

1 – 10 Patients	39 (41%)	Institutions
11 – 50 Patients	31 (32%)	Institutions
51 – 100 Patients	4 (4%)	Institutions
101 – 200 Patients	3 (3%)	Institutions
not specified	19 (20%)	Institutions

Median 35 (1 – 194) Pts.; total: 77 (80%) Institutions

Table 2: Duration of Prospective Documentation

1 - 2 Years	13 (13%)	Institutions
3 - 5 Years	16 (17%)	Institutions
6 - 10 Years	23 (24%)	Institutions
11 - 15 Years	17 (18%)	Institutions
over 15 Years	8 (8%)	Institutions
not specified	19 (20%)	Institutions

Median: 8 (1 – 35) Years; total: 77 (80%) Institutions

50 (53%) institutions used an orthovolt equipment with 50 - 200kV X-rays. 62 (65%) applied linear accelerator electrons, 8 (8%) applied beta-X-rays with Strontium-90 plates, and 4 (4%) used other RT techniques (1x cobalt photons, 2x caesium-137 photons, 1x iridium-192 implant) (Table 3).

Table 3: Applied Radiation Techniques for Keloid RT

Orthovoltage Equipment	50 (52%) Institutions
< 60kV = 25; 60 – 100kV = 16 >100kV = 9	
Linear Accelerator Electrons	62 (65%) Institutions
< 6 MeV = 54; > 6 MeV = 10 multiple MeV = 4; Bolus = 8	
Strontium-90 Dermal Plate	8 (8%) Institutions
Other RT Techniques	4 (4%) Institutions
i.e. 2x Cs-137-RT; 1x Ir-192-AL 1x Cobalt-Photons	

The median applied single RT dose was 3 (range: 0.5 – 5) Gy (Table 4) and the median applied total RT dose was 15 (1.5 – 30) Gy (Table 5); variations of the single and total doses occurred in 46 (48%) and 43 (45%) RT institutions, respectively. The median number of fractions was 5 (1 - 7) per week and any variation of the fraction number occurred in 22 (23%) institutions (Table 6).

Table 4: Radiation Concept - Single RT Doses

< 2 Gy SD	16 (17%) Institution
= 2 Gy SD	26 (27%) Institution
= 3 Gy SD	12 (13%) Institution
= 4 Gy SD	5 (5%) Institution
2 – 5 Gy SD	36 (38%) Institution
> 5 Gy SD	3 (3%) Institution
variable SD	46 (48%) Institution

Median 3 (0,5 – 7) Gy; total: 94 (98%) Institutions

Table 5: Radiation Concept – Total RT Doses

< 5 Gy TD	5 (5%) Institution
6 - 12 Gy TD	49 (51%) Institution
13 - 20 Gy TD	46 (48%) Institution
21 - 30 Gy TD	10 (10%) Institution
10 - 20 Gy TD	83 (86%) Institution
variable TD	43 (45%) Institution

Median 15 (1,5 – 30) Gy ; total: 83 (86%) Institutions

Table 6: Radiation Concept – Fractions per Week

1 – 2 x / week	3 (3%) Institutions
3 x / week	18 (19%) Institutions
3 – 4 x / week	10 (10%) Institutions
3 – 5 x / week	13 (14%) Institutions
5 x / week	39 (41%) Institutions
1 – 5 x / week	5 (5%) Institutions
7 x / week (HF !)	1 (1%) Institution

Median 5x (1 – 7x) / weak; total: 89 (93%) Institutions

In only 4 (4%) RT institutions prophylactic RT was delivered prior to the surgical procedure, while in all other institutions (88, 93%) RT was applied during or immediately after the surgical resection of the keloid. RT was rarely applied as the sole treatment for primary or recurrent MD lesions, namely in 3 (3%) institutions. The median duration from the surgical procedure to the first RT session was usually not longer than 1 day (range: 0 - 7 days) (Table 7)

Table 7: Interval from Surgery to 1st RT Session

OP day		18 (19%) Institutions
OP / 1st	post OP day	25 (26%) Institutions
1st	post OP day	15 (16%) Institutions
2nd	post OP day	10 (10%) Institutions
1st – 3rd	post OP day	6 (6%) Institutions
1st – 4th	post OP day	5 (5%) Institutions
1st – 7th	post OP day	5 (5%) Institutions

Median: 1st (0 – 7th) POD; total: 83 (86%) Institutions

A total of 880 patients from 49 (51%) RT institutions were followed for at least 2 years
after the completion of prophylactic RT: 31 (32%) institutions reported on a total of 1 – 10 patients, 9 (9%) institutions on 11 – 20 patients, 7 (7%) institutions on 21 – 100 patients and 2 (2%) institutions on 101 – 150 patients. Of the 880 patients 101 (11,5%) relapsed within a median period of 6 (2 – 24) months after RT, but the
majority within 6 months after RT; thus, the local control rate was 88,5%.

Side Effects: So far, no induction of a secondary malignancy has been reported within or around the irradiated volume. Long-term treatment sequelae included the development of teleangiectasia in 6 (0.7%) patients and skin depigmentation or other atrophic skin changes in 19 (2,2%) patients.

Discussion

This first national PCS on prophylactic RT for keloids reveals interesting details on the variations of this treatment concepts within a defined geographic region. It can be concluded from a technical point, that appropriate RT facilities are nowadays well distributed and equally developed in all regions of Germany. Our study confirms, that postoperative RT has been proven to be a very effective method to prevent local relapses after surgical resection of keloids.

In the literature review (Table 8), overall 80% will achieve a long-term local control and about 20% will develop a local recurrence despite RT. As most relapses occur within 6 months, the achieved local control rate of this multi-centre German PCS can be regarded as an excellent result. The type and technique of irradiation, either orthovolt-X-rays, linac photons or electrons or brachytherapy with Iridium-192, plays no role for the treatment outcome, as long as a sufficient total RT dose is applied within a suitable time frame to prevent the excessive fibroblast proliferation after an adequate skin trauma (including surgery). Nevertheless, no “golden standard” exists with regard to RT dose and fractionation concept. Following the ALARA principle future clinical RT studies should try to assess the lowest effective RT dose to prevent keloid relapses.

Success of prophylactic RT is independent from body site, and most series present various locations. For example, Ship et al. (33) treated sternal keloids after surgical resection and skin transplantation and applied 3 x 5Gy RT within two weeks after surgical excision; they observed only one relapse in long-term follow-up (1 - 24 years). Chaudhry et al. (5) summarized results of 36 patients with keloids of the earlobe who received 3 x 6Gy within 5 - 7 days after surgery. At a mean follow-up of 5.6 years only one relapse was observed. Busch et al. (4) successfully treated a vaginal keloid by HDR-Ir-192 brachytherapy. Table 8

presents a summary of clinical studies with different dose concepts.
Radiologically induced side effects are quite rare and may depend on the applied single RT dose. Redness, change of pigmentation and atrophic skin changes have reported (29). Depending on the quality and energy of radiation the gonads have to be protected for RT treatments at the lower abdomen and upper-limb. In these regions, 30 – 100 kV orthovolt or low energy electrons should be preferred. Takahashi (34) reported on a rare side effect in a child 23 years after prophylactic keloid RT at the sternum which lead to a cardial and tricuspidal insufficiency.

Concluding from this study, the German Cooperative Group on Benign Diseases has defined a consensus on the treatment of keloids, which can be summarized as follows: RT prophylaxis should be started as soon as possible, but no more than 24 hours after the surgical resection of the (recurring) keloid(s). Conventional fractionation is the preferred option with the single RT doses ranging from 2 - 5Gy and the total RT doses ranging from 10 - 20Gy (e.g. 3 x 4Gy). Before signing an informed consent, all patients should be informed about possible other treatment options (local corticosteroid and retinoic-acid injections, local cytotoxic drugs or silicon adhesive tapes). Possible radiologically induced side effects have to be fully explained, especially for younger patients at an Age below 20 years.

Authors	Year	Pats (N)	RT Dose Concept	FU (yrs)	Relapse	Response
Cosman et al. (6)	1961	226	4 x 800 rad	1		53%
Ollstein et al. (23)	1981	68	3 x 5 Gy	1		72%
Emhamre & Hammar (9)	1983	62	Various	0.5		89%
Borok et al. (3)	1988	393	Various	--		92%
Kovalic & Perez (19)	1989	113	Various	1		73%
Sallstrom et al. (32)	1989	117	3 x 6 Gy	2		92%
Handl-Zeller et al. (15)	1990	69	5 – 8 x 2 Gy	0.5 - 8	9%	
Lo et al. (20)	1990	168	Various	1 mos		87%
Doornbos et al. (7)	1990	208	Various	1		85%
Escarmant et al. (11)	1993	570	Brachytherapy Low-Dose Ir-192	5 - 10	21%	
Ship et al. (33)	1993	11	3 x 5 Gy	1 - 24		
Chaudhry et al. (5)	1994	36	3 x 6 Gy	5,5	3%	
Durosinmi et al. (8)	1994	454	2 x 6 Gy or 3 x 5 Gy	2		93%
Prott et al. (29)	1997	84	4 – 5 x 3 Gy	1	22%	
Kutzner / Roesler et al. (30)	1998 1993	50	Various	12		80%
Guix et al. (14)	2001	169	4 x 3 Gy p.o. 6 x 3 Gy RT alone High-Dose Ir-192	1 - 7	3,4% p.o. 13,6% RT alone	95%
PCS GCG-BD in Germany	**2002**	**880**	**Various**	**> 2**	**11,5%**	**88,5%**

Tab. 8: Clinical Outcome with Different Treatment Concepts of RT Prophylaxis

Conclusion
Postoperative RT prophylaxis is a well established and accepted treatment for keloids after surgical resection in Germany. Despite some variations of the RT-prophylaxis concept a very large number of patients with keloids were treated effectively (low relapse rate) and without major side effects.
Future prospective clinical studies should assess the most practical approach to apply the lowest effective dose to control recurrent keloids.

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Book Review:

The Radiation Therapy of Benign Diseases – Current Indications and Techniques, ed. by J.L. Meyer

The Radiation Therapy of Benign Diseases - Current Indications and Techniques
33rd San Francisco Cancer Symposium, San Francisco, Calif., April 1999
Editor: Meyer, J.L. (San Francisco, Calif.)
XII + 222 p., 44 fig., 31 tab., hard cover, 2001
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(Frontiers of Radiation Therapy and Oncology, Vol. 35)

The Radiation Therapy of Benign Diseases covers a broad spectrum of benign conditions, starting off from a survey of current treatment programs and a review of old and new indications for radiotherapy in benign diseases. The biological basics on cellular as well as tissue and cytokine effects are well described. The remaining chapters encompass the clinical use of radiation in the treatment of benign conditions, sorted by anatomy.

One major area of clinical research and work in progress is the conformal and/or stereotactically guided treatment of benign central nervous system tumors. The authors present the indications and outcome data for several entities like arterio-venous malformations (AVM), acoustic neurinomas, meningeomas, and pituitary adenomas. The focus is laid on clinical results, and most of the data were obtained by gamma knife surgery. Modern techniques like intensity-modulated radiotherapy (IMRT) or proton beam therapy are not covered.

The next chapters deal with ophthalmologic diseases. A well-collected overview of pros and contras of radiotherapy in age-related macular degeneration (AMD) is presented and discussed in detail. The chapter does not include the negative results from the randomized RAD study from Heidelberg, which caused most radiotherapists in the German speaking countries to discontinue the recommendation of radiotherapy for AMD. Instead, a new technique for conformal irradiation of the macula is discussed in detail.

Next, radiotherapy of desmoid tumors is discussed in a multidisciplinary context. All relevant information is included in detail. Further chapters provide up-to-date information on radiotherapy of skeletal diseases and keloids.

The chapter on skeletal conditions is rather short despite of the widespread use of radiotherapy in conditions like periarthritis humeroscapularis (PHS) or calcaneal spur.

A further area that has received quite a lot of interest in the last few years is intravascular radiotherapy for the prophylaxis of restenosis after percutaneous transluminal angioplasty (PTA). An extensive overview provides the reader with historical, pathophysiological, clinical and technical aspects of restenosis and its treatment. Clinical results from the STRESS, WRIST, SCRIPSS, START and BETA-CATH trials are discussed in detail. Future aspects like gene therapy and cytostatic therapy are also covered. Further chapters deal with the underlying biological mechanisms of restenosis and its prevention and with dosimetric considerations in vascular brachytherapy.

The Radiation Therapy of Benign Diseases is an extensive and interesting book that covers most major indications of radiotherapy for non-malignant diseases. Its major drawback is that – though published in 2001 – it is based on data from the 33rd Francisco Cancer Symposium, 1999. Later results were seemingly not included (like the RAD trial for AMD). If the reader is aware of this, he or she receives a handy compendium that provides a summary of nearly all available information about radiotherapy of benign diseases.

P. Schüller (Münster)

APPENDIX A / Prospective Documentation of Prophylactic Keloid Irradiation (©GCG-BD)

Refering Institution ……... Administrative Nr: ……..

……..…….... ……..
Patient Name Date of Birth First Contact

……..…….... ……..
Home Address Phone / Fax Family Physcian

DOCUMENTATION Keloid Existence since Weeks / Months / Years

Possible Causes Trauma / Burning / Other Causes: ……..……

Number(s) Localisation(s): ……...

Dimensions Length Width Depth

Special Features Extension Color

Clinical Symptoms Pain Itching Other Sy

Sensitivity of Skin Inflammation Infection

Prior Treatment(s) Surgery Radiotherapy Other Treatments

Time / Period ……....

Actual RT Concept **OP** yes / no **RT** yes / no **Other Tx :**

Informed Consent Physician Date ……

Treatment Course OP-Date OP-Start OP-End

RT-Timing Pre-OP (hr /d) post-OP (hr /d)

Orthovolt-RT kV SSD
Linac-RT MeV SSD

Sr-90 Source Reference Dose Reference-Point

RT Dose Concept Single RT Dose Total RT Dose Fx / Week

Toxicity (CTC) Skin Changes Other Side Effects

Actual Follow-Up Date Time after RT (months / years)

Relapse Yes / No Skin Changes (LENT-Grade)

Cosmesis Good / Moderate / Poor Other Side Effects (LENT-Grade)

Overall Outcome Objective Result (VAS) Subjective Result (VAS)

Special Remarks : ……...

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Bony Pain Caused by Systemic Mast Cell Disease (*SMCD*)
- A Case Treated with Radiotherapy and a Literature Overview -

S. Hesselmann, O. Micke, U. Schaefer, N. Willich
Department of Radiotherapy, Muenster University Hospital, Albert-Schweitzer-Str. 33,
D-48149 Muenster, Germany

Summary:
Systemic mast cell disease (*SMCD*) is a rare disease characterized by a multitopic proliferation of cytologically and/or functionally abnormal tissue mast cells. *SMCD* preferentially involves the skin, spleen, liver, lymph nodes and the bone marrow. The cause of *SMCD* is unknown. Bony pain, caused by mast cell infiltration of the marrow cavity, is present in up to 28% of cases and is frequently chronic and difficult to palliate with medical therapy. Patient and Method: We report one case of refractory bone pain in a 54-year-old female Caucasian patient with advanced *SMCD* and associated bony involvement, which was treated with radiotherapy for pain palliation. Between 1995 and 1998, the patient was irradiated at four different locations (I. right shoulder and proximal right humerus, II. both hands, III. both knees, IV. left humerus) with a total dose of 40 Gy in 2.0 or 2.5 Gy daily fractions.
Different results of pain palliation were achieved. In one location the pain was reduced for 55 months until her death due to disease progression, whereas in two other locations a pain control was maintained for 3 and 6 months after radiotherapy. In one location, no pain reduction was achieved. Severe side-effects were not observed. Conclusion: Palliative radiotherapy has a role in the control of severe intractable bone pain in patients with advanced *SMCD*, though in some cases the effect may be short or incomplete. The observed palliation of pain can even differ in the same patient.

Introduction:
Systemic mast cell disease (*SMCD*) is a rare disease characterized by increased numbers of mast cells in different organs. The cause of *SMCD* is unknown. Several observations support the concept that *SMCD* probably is a type of myeloproliferative disorder. The classification of *SCMD* is controversial, but there is increasing support for the differentiation of at least two major subtypes that differ in prognosis: (I) a benign or "indolent" variant in which skin involvement is usual, but associated malignant hematological disorders are rare; and (II) a malignant or "aggressive" variant where skin involvement is usually absent but concomitant malignant hematological disorders are very common (6). The vast majority of cases represent the most indolent form also known as *„urticaria pigmentosa"*. However, some patients have a progressive form leading to an overt leukaemic phase surviving only 2 to 3 years after the initial diagnosis (1). As little is known about the pathogenesis of mastocytosis and a curative therapy has not been found, the treatment has largely been focused on clinical control of symptoms with antihistaminics, sodium cromoglycate, anticholinergics, epinephrine, diphosphonate, PUVA, prostaglandin synthesis inhibitor, nonsteroidal anti-inflammatory drugs, splenectomy, interferon alpha, chemotherapy and radiotherapy (1, 3, 5, 12, 14, 18, 21). Bone pain is present in up to 28% of unselected cases of *SMCD* (20) and is often chronic and difficult to manage with medical therapy. We report one case with refractory bone pain due to *SMCD* which was irradiated at four different locations for pain palliation.

Case report:
A 54-year-old female patient with systemic mastocytosis, hematologic disorder and severe bone pain in the right proximal shoulder and humerus was referred to the Radiation Oncology Department, University - Hospital Muenster in 1995 for treatment. The *SMCD* was initial diagnosed in 1970. In 1992, an extensive bone marrow replacement by mast cells resulting in an anemia was diagnosed. Bone marrow expansion into both hands and feet was observed and extramedullar hematopoesis was found especially in the spleen and also in the liver. Despite therapy with dapsone, hydroxycarbamid, corticosteroids and interferon alpha, she had progressive disease. In 1995, her disease was characterized by the involvement of the skin, bone marrow, liver and spleen. She had clinical signs of diffuse cutaneous lesions, hepatosplenomegaly, ascites, and myelofibrosis with ineffective erythropoesis. Anaphylactic reactions have been provoked by nonsteroidal anti-inflammatory drugs (acetylsalicylic acid, indometacin, diclofenac, piroxicam) and metamizol. She has had Hashimoto's disease. Furthermore, atrial fibrillation and mitral incompetence (MI) were diagnosed**,** which may be coincidental or in some cases cardiovascular manifestations of *SMCD*. Because of bone lysis and severe bone pain in the area of the right shoulder and proximal right humerus, she received 40 Gy (2 Gy, 5 days weekly, 10 MV photons) by AP/PA portals for pain palliation and reossification. Following radiotherapy, there was a subsequent varying pain level for 6 months resulting in an excellent resolution of her pain in this area which maintained until her death. Because of her progressive disease with severe refractory bone pain unresponsive to medical therapy, the patient was irradiated at three different locations for pain palliation in 1998. She was irradiated at both knees (40 Gy, 2.0 Gy 5 days weekly, AP/PA portals, ^{60}Co), both hands (40 Gy, 2.5 Gy 5 days weekly, AP portal, ^{60}Co) and the left humerus (40 Gy, 2.0 Gy 5 days weekly, AP/PA portals, ^{60}Co). In two locations (both hands and both knees) a good palliative effect was achieved for 3 and 6 months after radiotherapy whereas one location (left humerus) shows no palliation after radiotherapy. The patient tolerated the radiation therapy well without clinical or hematologic sequelae. 29 years after the initial diagnosis, she died due to disease progression in 1999.

Discussion:
Ellis (4) reported the first pathologically documented case of *SMCD* in 1949. Radiographic evidence of bone involvement in patients with urticaria pigmentosa was first reported by Sagher et al. in 1952 (17), but it was not until 1956 that these bone lesions were proved histologically to be due to mast cell infiltration (19). The typical bone marrow lesions seen in adults with *SMCD* are foci of spindle-shaped mast cells in a fibrotic matrix and are found in up to 90% of adults with *SMCD* (15). Radiographically, the skeletal changes of *SMCD* consists of either a wide-spread mixture of bone lysis and osteosclerosis or generalized osteoporosis. Radiographic bone lesions have been reported in 70% of *SMCD* patients – diffuse in 52% of cases and circumscribed in 18% of cases. Arthralgias have been observed in 21% of unselected cases of *SMCD* and pathologic fractures were present in 16% at the initial diagnosis. Bone pain is present in up to 28% (20). In the treatment of bony pain caused by metastases and in multiple myeloma radiotherapy is of well-described benefit

(2, 9, 10, 13, 11, 22). Until now, only a few data are available on the use of radiotherapy for bony pain palliation in *SMCD*. Janjan (7) describes the case of a 68-year-old female patient who received 30 Gy palliative irradiation from T8 to the sacroiliac joints through a posterior portal totaling 30 Gy/11 fractions with 6 MV photons over 18 treatment days. Palliation of back pain was achieved within two weeks and maintained until the patient died 10 months after completion of irradiation (Table 1). Johnstone (8) reports three cases of refractory bone pain in two patients with advanced *SMCD* and bony involvement, which were treated with radiotherapy. In the first case the disease was characterized by pathologic fractures of both femoral necks, acetabuli, and multiple vertebral bodies. The patient developed lower back pain with radiations to the posterior thighs bilaterally. Ten fractions of 3 Gy were delivered over 17 days. One month later ten 3 Gy fractions were delivered over 15 days to his painful left shoulder. The second patient received 2 Gy five times weekly to 30 Gy to her bilateral lower extremities. For the first patient, radiotherapy reduced the pain from a severe to a moderate level by 1 month postreatment, with subsequent varying pain until death four month after his second radiotherapy. The second patient received an excellent pain relief while on treatment. This effect proved durable for 9 months until death due to disease progression (Tab. 1). Harrison (5) describes one case of *SMCD*, which did not appear to respond to interferon alpha but which clearly showed good, although incomplete, symptomatic improvement following radiotherapy. The patient received 20 Gy incident dose to T7-T11 and to L2-L5 inclusive, both in five fractions over 7 days. There was a resolution of his thoracic and high lumbar back pain with an increase in his general mobility. This improvement was maintained for four month, whereas the lower lumbar pain radiating into the right leg has continued. Further radiotherapy with 20 Gy incident dose in five fractions has been given to the sacroiliac joints without additional effect (Table 1).

Author	Radiotherapy	Treatment area	Results
Janjan 1992	30 Gy (6x 3.0 Gy + 5x 2.5 Gy)	T8 – bilateral sacroiliac joints	Back pain was palliated within 2 weeks of the end of radiotherapy
Johnstone 1994	1. 30 Gy (10x 3 Gy) 2. 30 Gy (10x 3 Gy) 3. 30 Gy (15x 2 Gy)	1. T11 – L3 2. Left shoulder 3. Bilateral lower extremities	1. significant pain relief 2. from 8/10 to 4/10 (pain score) 3. pain relief while receiving radiotherapy, from 10/10 to 5/10
Harrison 1994	1. 20 Gy (5x 4 Gy) 2. 20 Gy (5x 4 Gy) 3. 20 Gy (5x 4 Gy)	1. T7 – T11 2. L2 – L5 3. Sacroiliacal joints	Resolution of his thoracic and high lumbar back pain with an increase in his general mobility. Lower lumbar pain radiating into the right leg has continued. Further radiotherapy without additional benefit.
Hesselmann 2001	1. 40 Gy (20x 2 Gy) 2. 40 Gy (20x 2 Gy) 3. 40 Gy (16x 2.5 Gy) 4. 40 Gy (20x 2 Gy)	1. right shoulder and proximal right humerus 2. both knees 3. both hands 4. left humerus	1. excellent resolution of her pain 2. good palliation for 6 months 3. good palliation for 3 months 4. no effect at all

Tab. 1: Literature overview of reported cases of *SMCD* with bony involvement treated with radiotherapy.

Despite data suggesting that mast cells are relatively radioresistant (16) and encouraged by literature data (5, 7, 8), we elected to treat our patient with radiotherapy after failure of medical therapy. In three out of four locations, radiotherapy resulted in less pain (3-55 months) and no severe clinical or hematologic sequelae were noticed. As Harrison and Johnstone (5, 8) we observed that the effect of pain palliation can sometimes be short or incomplete and even differ in the same patient (Tab. 1). The reason for these different effects of pain palliation is unclear. Though it can be concluded that radiotherapy can effectively be applied in treatment of *SMCD* without significant morbidity, it is essential that hematologic parameters, plasma histamine levels, and clinical symptoms are carefully monitored while on treatment.

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German Cooperative Group (GCG) on RT for Benign Diseases

Ellenbogen - Score

anwendbar für : **Epicondylopathia humeri** radialis (lateralis) / ulnaris (medialis)

Zeitpunkt: Wochen / Monate / Jahre **vor** RT ; **während** RT ; **nach** RT

Einzelkriterien	Ausmaß der Veränderung	Punkte
A. Schmerzen	B = Belastungsschmerzen	0 / 2 / 4 / 6
	N = Nachtschmerzen	0 / 2 / 4 / 6
(gesamt: 30%)	D = Dauerschmerzen (tagsüber)	0 / 2 / 4 / 6
	R = Ruheschmerzen (nach Belastung)	0 / 2 / 4 / 6
pro Einzelkriterium	S = Steifigkeit (am Morgen) / Anlaufschmerzen	0 / 2 / 4 / 6
	(keine = 6; leichte = 4; mittlere = 2; schwere = 0 Punkte)	
	⇨	
B. Alltagsfunktion	Rückentaschengriff (z.B. Geldbörse)	0 / 1
	Normales Aufstehen vom Stuhl	0 / 1
(gesamt: 12%)	Tragen schwerer Gegenstände (5 – 10kg)	0 / 1
	Normales Anziehen der Kleidung	0 / 1
pro	Normale Genital- / Analpflege	0 / 1
Einzelkriterium 1Pkt	Waschen der Axilla der Gegenseite	0 / 1
	Gegenstände zu sich heranziehen	0 / 1
	Gegenstände wegwerfen / wegschieben	0 / 1
	Normales Essen mit Besteck	0 / 1
Ja = 1 / Nein = O	Haarpflege (z.B. Kämmen, Bürsten)	0 / 1
	Normale Arbeitsfähigkeit im Beruf	0 / 1
	Normale sportliche Aktivitäten:	0 / 1
	⇨	
C. Normale Kraft (*)	Flexion (< 2kg / 2,0 – 4,0kg / 4,1 – 6,0kg / > 6kg)	0 / 1 / 3 / 5
	Extension (< 2kg / 2,0 – 6,0kg / > 6kg)	0 / 2 / 4
(gesamt: 15%)	Pronation (< 2kg / 2,0 – 4,0kg / 4,1 – 6,0kg / > 6kg)	0 / 1 / 2 / 3
	Supination (< 2kg / 2,0 – 4,0kg / 4,1 – 6,0kg / > 6kg)	0 / 1 / 3 / 5
	Messung mit geeichtem Pondmeter (bis maximal 7,5kg)	
	⇨	
D. Beweglichkeit (*)	Flexion (< 30° / 31 – 50° / 51 - 70° / 71 - 90° / 91 - 100° / 101 - 110° / 111 - 120° / > 120°)	0 / 3 / 6 / 9 / 11 / 13 / 15 / 17
	Extension (< 10° / 11 – 30° / 31 - 50° / 51 - 70° / > 70°)	0 / 2 / 5 / 7 / 8
(gesamt: 37%)	Pronation (pro Grad 0,1 Punkt, maximal: 6 Punkte ab 60°)	0 – 6
	Supination (pro Grad 0,1 Punkt, maximal: 6 Punkte ab 60°)	0 – 6
	⇨	
E. Instabilität (*)	Anterior/Posterior: ≤ 15mm,15° / < 10mm,10° / < 5mm,5° / keine	0 / 1 / 2 / 3
(gesamt: 6%)	Medial / Lateral: ≤ 15mm,15° / < 10mm,10° / < 5mm,5° / keine	0 / 1 / 2 / 3
	⇨	
Summenscore	**Summe der Einzelscores A + B + C + D + E** ⇨	

(*) Originaltext von Morrey et al. (1985) enthält keine Angaben zur Durchführung der Messungen; nach Seegenschmiedt et al. (1998)

Subjektive Einschätzung des Gesamtbefindens durch den Patienten (X) :

☹☹ ☹ 😐 ☺ ☺☺

[---------i---------i---------i---------i---------I---------i---------i---------i---------i---------]

Datum **Arzt – Unterschrift**

German Cooperative Group (GCG) on RT for Benign Diseases

Elbow - Score

Applicable for : **Epicondylopathia humeri** radialis (lateralis) / ulnaris (medialis)

Evaluation: Weeks / Months / Years **before** RT ; **during** RT ; **after** RT

Criteria	Extent of Symptoms / Alteration	Points
A. Pain Symptoms	S = Pain at **Strain**	0 / 2 / 4 / 6
	N = Pain during **Night Time**	0 / 2 / 4 / 6
(total: 30%)	D = Pain during **Day Time** (continuously)	0 / 2 / 4 / 6
	R = Pain at **Rest** (following any kind of strain)	0 / 2 / 4 / 6
	I = Pain at **Initiation of Movement** / Morning Stiffness	0 / 2 / 4 / 6
per single criterion:	(none = 6 ; slight = 4 ; moderate = 2 ; severe = 0 points)	
	⇨	
B. Daily Activities	Use back pocket (e.g. purse)	0 / 1
	Normal rise from chair	0 / 1
(total: 12%)	Lifting heavy weights (5 – 10kg)	0 / 1
	Normal daily dressing	0 / 1
	Normal perineal care	0 / 1
per single criterion: 1pt	Wash opposite axilla	0 / 1
	Pulling objects	0 / 1
	Throwing objects	0 / 1
	Normal eating with utensil	0 / 1
Ja = 1 / Nein = O	Normal hair care (e.g. comb, brush)	0 / 1
	Do usual professional work	0 / 1
	Do usual sport activities:	0 / 1
	⇨	
C. Strength (*)	Flexion (< 2kg / 2,0 – 4,0kg / 4,1 – 6,0kg / > 6kg)	0 / 1 / 3 / 5
	Extension (< 2kg / 2,0 – 6,0kg / > 6kg)	0 / 2 / 4
(total: 15%)	Pronation (< 2kg / 2,0 – 4,0kg / 4,1 – 6,0kg / > 6kg)	0 / 1 / 2 / 3
	Supination (< 2kg / 2,0 – 4,0kg / 4,1 – 6,0kg / > 6kg)	0 / 1 / 3 / 5
	Measurement with calibrated pond meter (maximum: 7,5kg)	
	⇨	
D. Motion (*) Neutral-Zero-Method	Flexion (< 30° / 31 – 50° / 51 - 70° / 71 - 90° / 91 - 100° / 101 - 110° / 111 - 120° / > 120°)	0 / 3 / 6 / 9 / 11 / 13 / 15 / 17
	Extension (< 10° / 11 – 30° / 31 - 50° / 51 - 70° / > 70°)	0 / 2 / 5 / 7 / 8
(total: 37%)	Pronation (pro Grad 0,1 Punkt, maximal: 6 Punkte ab 60°)	0 – 6
	Supination (pro Grad 0,1 Punkt, maximal: 6 Punkte ab 60°)	0 – 6
	⇨	
E. Instability (*)	Anterior/Posterior: ≤ 15mm,15° / < 10mm,10° / < 5mm,5° / keine	0 / 1 / 2 / 3
(total: 6%)	Medial / Lateral: ≤ 15mm,15° / < 10mm,10° / < 5mm,5° / keine	0 / 1 / 2 / 3
	⇨	
Total Score	**Sum of single criteria A + B + C + D + E** ⇨	

(*) Original text from Morrey et al. (1985) provides no details for the performance of measurements; from Seegenschmiedt et al. (1998)

Subjective Estimation of the overall Quality of Life by the Individuum (X) :

☹☹ ☹ 😐 ☺ ☺☺

[---------i---------i---------i---------i---------|---------i---------i---------i---------i---------]

Datum **Arzt – Unterschrift**

Consensus Guidelines for Radiation Therapy of Benign Diseases
- a Multi-Center Approach in Germany -

O. Micke[1], M.H. Seegenschmiedt[2]
and German Cooperative Group on Radiotherapy for Benign Diseases (GCG-BD)
(1) Department of Radiotherapy, Muenster University Hospital, 48149 Muenster, Germany
(2) Radiation Oncology, Therapeutic Radiology and Nuclear Medicine, Alfried Krupp Hospital, 45133 Essen, Germany

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The term "radiotherapy for benign diseases" relates to treatment of non-malignant diseases with ionizing radiation, but does not necessarily exclude diseases with invasive and expansive growth patterns, harmful or life threatening behavior as well as loss of organ function and quality of life (1, 2). These features justify the use of radiation therapy (RT) not only for malignancies, but also for non-malignant disorders (1). Outside Europe the use of RT to treat benign diseases is not well established (3) and often regarded with skepticism (4).

So far the last written recommendations for treatment of non-malignant diseases in the United States date back to 1977 from the Bureau of Radiological Health. However, since then many new treatment indications (5) have been introduced and well accepted like the prophylactic irradiation to prevent heterotopic ossifications (6, 7, 8, 9, 10, 11) or vascular restenosis (12, 13).
The treatment of benign diseases with ionizing irradiation belongs to the tasks of the radiation therapist for several reasons (1). On the basis of theoretical and practical education, the profession is familiar with all technical and clinical aspects of ionizing radiation. This includes working with various treatment machines, history taking and clinical examination, setting up the indication, theoretical planning and practical realization of a RT concept in daily routine and all aspects of radiation protection, long term follow-up and documentation (14, 15).
Although RT of benign diseases is usually carried out with much lower RT doses than that of malignant tumors, the radiation therapist has the same duties to prepare, carry through, completely document, and follow-up the whole treatment process with the utmost care and attention as it is the case with all malignant diseases (14, 15, 16). On this background there is a need for special guidelines for RT for benign diseases similar to those of malignant disorders (17, 18) and from other medical societies for special treatment procedures (19, 20, 21, 22, 23, 24, 25). The aim of our work was to develop modern written guidelines for RT for benign diseases to warrant quality assurance and outcome research (17).

Methods
In 1995 the German Working Group on "Radiotherapy for Benign Diseases" was founded together with the German Radiation Oncology Society. In 1996 a national conference on RT for benign diseases was held and treatment guidelines were anticipated. In 1997 the consensus process started, and in 1999 it was finalized. The method for benign disorders was adopted from former consensus guideline developments (14, 17, 21, 22, 23, 26).
The process started with the formation of an expert panel, in which initially all chairmen of RT institutions at university and non-university hospitals participated and members of the German Working Group on "Radiotherapy for Benign Diseases". Pertinent information and data from the literature were reviewed and most important scientific articles identified (5, 17). The level of evidence for each disease entity was determined and graded according to international recommendations (22, 23). In addition, a patterns of care study (PCS) was conducted to obtain a nation-wide survey of the treatment standards of RT for benign diseases (27).
The expert panel prepared a first consensus statement which was open for propositions and comments from all participating institutions. After completion of the discussion, a final consensus statement was written, discussed and agreed on during a national radiotherapy conference. The written statement was forwarded to the Cooperative German Group of Scientific Medical Societies.

Results
The written guidelines consist of the following components which are addressed in the following paragraphs: (a) general indications for RT; (b) radiobiological basis for RT; (c) radiation protection issues; (d) quality assurance procedures; (e) indication set-up; (f) patient's informed consent; (g) standard documentation; (h) follow-up; (i) special treatment concepts.

General Indications for RT
The potential clinical indications for RT of benign diseases are various, but not always an interdisciplinary agreement has been coordinated. A unified definition of indications and a special coverage for RT of benign diseases are missing (28). In German-speaking countries and in Central and East Europe regions, the following indications are currently known (5):

(a) **Acute and chronic inflammatory disorders**, e.g. axillary sweat gland abscess, furuncula, carbuncula, panaritium, and other infections not responing to antibiotics etc.;
(b) **Acute / chronic painful degenerative diseases**, e.g. insertion tendinitis, and chronic or acute painful osteoarthritic diseases of various joints (hip, knee, etc.);
(c) **Hypertrophic (hyperproliferative) disorders of soft tissues**, e.g. prophylactic RT in early stages of Morbus Dupuytren and Ledderhose, and Morbus Peyronie (Induratio penis plastica); postoperative prophylaxis of recurrence for keloids and pterygium;
(d) **Functional diseases**, such as Graves' orbitopathy, arterio-venous malformations, age-related macular degeneration; persisting lymphatic fistula;
(e) **Other indications**: prophylaxis of heterotopic ossification at various joints; prophylaxis of neointimal hyperplasia, e.g. after arterial dilatation or stent implantation; obstruction of haemangiomas and other vascular disorders of various organs;
(f) **Dermatologic diseases**, e.g. pruritus due to itching dermatoses and eczemas; inaccessible psoriatic focuses (e.g. subungual focuses); basalioma.

Radiobiological Mechanisms
Biological mechanisms of ionizing irradiation in various benign disorders are incompletely investigated and understood (29, 30). Corresponding to the various RT indications there are several hypotheses as to its effect, e.g. increase in capillary permeability and tissue perfusion (perfusion theory), destruction of inflammatory cells and release of mediators, cytokines and proteolytic enzymes (fermentative theory), impact on the autonomous nervous system (neuro-regulatory theory) and on the composition of the tissue milieu (electrochemical theory) (29, 30, 31, 32, 33, 34, 35). Another target is the prevention of proliferation of mitotic cells (anti-proliferative effect) (36, 37). Probably

none of these mechanisms by itself may explain the efficacy rather than a complex collaboration of several of these effects. Different biological mechanisms and target cells can be responsible for the radiation effect. To achieve an optimal effect, RT should be applied at the appropriate time over a suitable period of time and with sufficient dose. The dose can vary from disease to disease and also among individuals. So far most RT concepts have not been strictly investigated from a radiobiological standpoint.

Radiation Protection

All means of radiation protection have to be applied including the following measures: selection of the smallest effective single and total dose concept; use of several portals or smallest effective field size for a given target volume; orientation of the entry direction of the radiation beam pointing away from the body stem or radiosensitive organs (e.g. thyroid, gonads, eye lens); application of shielding (individual and / or standardized lead absorbers) in radiation portals and use of lead capsule (for the male gonads), lead collar (in the neck area) or lead apron (in the pelvic area).

According to Broerse et al. (38, 39) the carcinogenic risk of RT for benign diseases may decrease after the 3rd to 4th decade to the general risk of the normal population. This underlines the importance of radioprotection especially in younger patients by individual lead shielding to reduce normal tissue dose outside the target volume. It has been demonstrated for orbital irradiation in Graves' orbitopathy (39), that individual shielding can markedly reduce the tissue dose outside the target volume and consecutively the carcinogenic risk.

Quality Assurance

Quality assurance is a main focus of these guidelines, which partially cover radioprotection or standardization of treatments as well. In analogy to regulations for the treatment of malignant tumors, the same quality criteria have to be applied for RT of benign diseases as in malignant tumors (1, 14, 15, 16, 17). Especially the following aspects have to be considered:

Prior to RT the radiation therapist sets up a treatment plan as a written document. It contains exact instructions on the positioning of the patient, the set-up parameters of the RT machine, the target volume definition and the dose specification. All RT portals and set-up conditions should be documented using photographs (e.g. Polaroid); minimum requirement is a written form and a graph which exactly and unambiguously allows to reproduce the treatment setup in the daily routine by any RT technician or physician.

Standardized RT set up is recommended including a treatment plan, target volume definition and dose specification in accordance to the ICRU-50 report; therefor it is necessary to define the target volume in its whole geometric extension and depth thereby replacing former dose concepts (e.g. the „surface dose") by the defined „dose in the reference point".

For all indications adequate RT technology should be applied, e.g. high energy linear accelerator photons in the prevention of heterotopic ossifications or low energy orthovoltage photons in the treatment of degenerative disorders of the small joints. Special immobilization devices, like individual head masks or vacuum pillows should be used, where needed. Always, both the radiation therapist and the medical physicist need to be involved in the treatment planning and the survey of the treatment performance.

Outcome research is mandatory for appropriate quality assurance. It requires the definition of reliable endpoints. Depending on the degree and duration of the disease different endpoints can be considered: e.g. reduction of pain and other pathological signs, preservation of organ functions, and avoidance of invasive treatment measures (e.g. surgery). Nowadays the subjective evaluation scales, which have been applied in former times, are inadequate for the evaluation of treatment success. Thus, objective scores for the evaluation of functional and radiological changes, visual analogue scales for evaluation of pain and questionnaires for daily body functions should be applied (16). Assessment of quality of life using standardized questionnaires (QLQ-C30, SF 36) has been validated and internationally recognized (27).

Indication Set-up

The treatment indication should be discussed and decided interdisciplinarily. The admission of a patient to RT provides a commission for treatment, but the radiation therapist has to affirm and document the correct indication for RT in a written form. Thus, medical history, physical examination and possibly diagnostic measures are necessary steps to an appropriate RT indication. Sometimes physicians of other disciplines have to be consulted. In case of rejection of a RT indication the reasons should be given to the referring physician.

Informed Consent

Prior to RT relevant medical information regarding disease and therapy have to be provided for the patient to achieve appropriate informed consent (40) including the following aspects:

(a) The natural cause and individual disease status have to be explained. It should be checked and explained whether RT is indicated correctly (differentiated RT indication) thereby taking all applied previous and other possible treatment options into account (therapeutic alternatives). The possible treatment goal has to be defined prior to RT. Generally, RT is a correctly indicated, if the other treatment options had no success, have more side-effects, cannot be carried out, or are explicitly refused by the patient.
(b) The general RT concept should be explained using sketches and written information on special informed consent forms. Patients should know the important features of RT technique (target volume, portal field size, direction of beam, use of individual shielding) and RT dose concept (single and total dose, fractionation and timing).
(c) The explanation of acute and chronic side effects after RT is required including information on possible carcinogenesis and other genetic risks depending on the age of the patient, the size and localisation of the target volume and the applied RT dose. It is of utmost importance to judge possible benefits and risks in the younger patients (up to about 30 - 40 years), because of their long life expectancy.
(d) After initial consultation patients require sufficient time for their decision. Generally, the first RT should not be carried earlier than one day after informed consent. In case of pre- or postoperative RT, the judgement of the patient must not be impaired. All relevant clinical data provided by the physician and the informed consent by the patient have to be documented in written form including date and signature.

Documentation

Subjective and objective evaluation criteria are part of a standardized documentation. Exact documentation of each individual case belongs to the duties of the radiation therapist (41). It has to be emphasized that for forensic reasons patient information and informed consent have to be documented in a written form (40). It is also recommended to document the medical history, physical exam at admission and discharge and follow-up exams (photographic documentation, consultations) in the patient's chart. Details of RT (treatment time, dose and localization) have to be documented in the treatment protocol. If possible, simulation and verification films should be taken regularly. German legislation requires to preserve all documents connected with RT for a minimum of 30 years.

After RT the referring physician should receive a RT summary report. The necessity of standardized long-term follow-up should be mentioned therein.

An example for standardized documentation has been recently published with regard to RT of Dupuytren's contraction (42).

Follow-up

As far as possible, 3 months and 1 year after RT clinical follow-up exams should be carried out. It is most important to assess disease specific symptoms which have led to the indication for RT. If higher RT doses have been used, sequelae to normal tissues have to be analysed using the same scores as for radiation oncology (16), e.g. RTOG or LENT-SOMA scores.

Treatment Concepts

Specific treatment recommendations regarding single and total doses and fractionation have been elaborated by the expert panel which are part of these guidelines (Appendix A).

The treatment indications and RT dose concepts mentioned herein correspond to literature data collected since the beginning of the 50s (4, 5, 43, 44, 45, 46, 47, 48) and to the evaluation of a questionnaire of the Working Group on "Radiotherapy for Benign Diseases" of the German Society of Radiation Oncology (DEGRO) from 1994 – 1996 (27). For single and total doses and the number of fractions the range of all statements from the various institutions is given. Therefor, however, it is not an acceptable practice to combine maximum values for single doses and numbers of fractions together. Thus, for better explanation the most frequently used treatment concepts have been stated as a recommendation for these guidelines. These recommended RT concepts are mostly based on studies of clinical evidence levels I and II (7, 8, 9, 10, 11, 49, 50, 51), as most scientific and clinical knowledge on RT indications of benign diseases result from retrospective clinical series with up to 7,000 patients reported in one study (44, 45) over a period of almost 100 years (43, 44, 45, 46, 47, 48, 52, 53, 54, 55, 56, 57) and from other personal and clinical experience in RT practice. This results in a relatively low evidence level III to V. Consecutively, so far the recommendations have to be graded B to D.

Discussion

"Practice guidelines are systematically developed statements to assist practitioner and patient decisions about health care for specific clinical circumstances" states the ASCO Health Service Research Committee for the definition of guidelines (58). The attributes of guidelines include validity, reliability, reproducibility, clinical applicability, multidisciplinary process, review of evidence and documentation (19, 20, 24). Utilization of guidelines may improve patient outcome and medical practice, minimize daily practice variations, provide decision tools for practitioners and a reference for medical decision making and continuous medical education. It may also provide criteria for self-evaluation and assistance with reimbursement issues and health insurance coverage decisions (24). These criteria and definitions are promoted by ASCO guidelines (19, 20, 21, 24, 25, 26) and usually applied in cancer therapy or supportive care. As RT for benign disorders should be conducted under similar conditions as for malignancies (14), guidelines for RT of benign diseases should cover the same aspects.

So far only few preclinical studies are available which explain the basic radiobiological mechanisms in benign diseases (27, 29, 30). The presented guidelines herein point out some explanation models for radiation effects based on recent experimental data (29, 30, 31, 32, 33, 34, 35, 36, 37) and intend to stimulate further experimental research. This should help to overcome skepticism against RT for benign diseases, e.g. in Anglo-American countries (3, 4).

There are also concerns about potential hazards of tumor and leukemia induction and somatic changes after RT exposure for benign disorders (59). Broerse et al. (38, 39) and Jung (60) found very small increase in the risk of tumor induction calculated in mathematical models, but the overall contribution to anyone's general life-time risk remains unclear. Broerse et al. (38, 39) stated that after the fourth decade the attributable life-time risk may be decreased below the average level of the general population. Thus, we recommend to treat preferentially patients above 30 - 40 years. In younger patients the carcinogenic risks should be carefully weighted against possible benefits, and the indication set up should be restricted. These findings also support the request for most accurate radiation protection measures in RT for benign diseases.

RT for benign diseases covers many disorders (1, 4, 5) (Appendix A). Some indications are not well accepted on an international level (3), because the RT practice is mostly based on long-term experience (57) rather than on well defined clinical evidence. As most European literature on these topics is not written in English (5), it is rarely considered in reviews (4). A few former controlled studies have not found an advantage for RT in painful degenerative disorders, but they had an inadequate study design and poor endpoint definition (61, 62, 63). In contrast, some recent studies serve as good examples for improved clinical research, e.g. in Graves' orbitopathy (50, 51 and heterotopic ossification prophylaxis (7, 8, 9, 10, 11). Modern prospective clinical studies also include objective scores and defined subjective criteria for better endpoint definition (49, 54, 55, 56). Nevertheless, in Germany still only 4% of RT institutions have been involved in prospective clinical studies (27). Thus, guidelines should support prospective clinical trials and broaden the evidence of using RT for benign diseases.

Evidence based medicine (EBM) cannot be the only standard for RT of benign diseases. As Jones & Sagar (64) stated, EBM answers only questions open to its technique and therefor randomized trials are its capstone. However, other forms of evidence like long-term observation or clinical experience, are ranked lower and are oftenly discounted. Nevertheless, for rare disorders and an increasing number of subgroups of patients, as in benign diseases, a higher level of evidence will never be achievable. EBM does not provide good guidance when trying to cope with situations for which better evidence is lacking. Furthermore, in patients who typically fail other treatments prior to the indication and implementation of RT, different treatment options have to be presented to the patient to elicit informed consent. Some patients may prefer to receive a treatment which has only achieved a low level of evidence so far. Thus, it may be difficult for practitioners to apply RT to patients according to EBM criteria.

New information strategies can be implemented on an international level including electronic media (e.g. internet) (65) and databases (e.g. Medline, Embase, Science Citation Report) (28) to improve practical and scientific data exchange for physicians working on benign diseases (1, 28). Material for clinical practice (information and leaflets for patients, family physicians and the public), questionnaires (for specific benign diseases) and special report forms for rare benign disease and their specific RT treatment should be developed.

In addition, standardized nomenclature has to be correctly applied. In the textbook of Order & Donaldson (4) 86% of radiotherapists would treat lethal midline granuloma, while only 17% would treat polymorphic reticulosis, which is in fact the same disease. This example reveals the discrepancy of some RT indications due to unclear nomenclature. Thus, the use of the International Classification of Diseases (ICD-10 codes) is recommended for the classification of benign diseases (66, 67).

In addition, decision making based on an appropriate standard of care is difficult for some rare benign disorders (4, 68). To overcome the lack of data for rare benign disorders the consensus guidelines recommend to implement a special

registry and forms for rare benign diseases to centrally collect and analyze treatment and outcome (1).

Besides the medical rationale to improve treatment decisions and prove better guidance to carry out appropriate RT indication set up and informed consent, irradiation and follow up according to standard of care, guidelines are also important for legal aspects (69). Increasingly jurisdiction refers to clinical guidelines and official standards of care (4, 69, 70), e.g. in malpractice suits of Anglo-American countries, where malpractice is defined as deviation from standard of care (4); nowadays a similar trend can be observed in European and German speaking countries (70). Thus, written clinical guidelines are explicitly needed (69) and well accepted by medical practitioners and specialists as well as scientific societies (17 ,26, 71).

An important instrument to determine the standard of care, which may vary largely between different countries, geographic regions and institutions, is to conduct patterns of care studies (PCS). The cornerstone of the German guidelines for benign disease was a national PCS (27). It provided a survey about the current standard of care for RT of benign diseases. The German Working Group on "Radiotherapy for Benign Diseases" is prepared for further PCS to exactly determine standard of care for specific RT indications such as heterotopic bone formation (72), keloids, aggressive fibromatosis and Graves' orbitopathy. While PCS provide a good guide to the patterns of medical practice, they do not necessarily guide therapy of individual patients. Similarly, guidelines cannot always account for variations among individual patients. They are not intended to supplant the physician's judgment with respect to individual patients or special clinical conditions and cannot be considered as including all proper methods of care or excluding other treatments reasonably directed at obtaining the same results. Adherence to clinical guidelines is voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances (18, 24).

Conclusion

It is for the first time, that written consensus guidelines for RT of benign diseases have been developed using a multi-center collaboration of all involved RT institutions in Germany. These guidelines may serve as a starting point for continuous quality assessment, design of prospective clinical trials and outcome research in this field. Similarly to the national process an international consensus initiative should be started to develop an updated international standard of care for utilization of RT for benign conditions.

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Appendix A: Treatment concepts for selected benign diseases

1. Degenerative diseases

(a) Treatment Refractory Insertion Tendinopathy (Tendonitis)

Indication: Painful periarthropathia humeroscapularis (= PHS), epicondylopathia humeri (= EPH) radialis or ulnaris, calcaneodynia = plantar or dorsal calcaneal spur, refractory to conventional and drug treatment.

Dose concept:

Single dose	Fractionation	Total dose
0.5 – 1.0 Gy	2 – 3x / week	3 – 12Gy
Recommended: every 2 days 0.5 – 1.0 Gy x 6 up to a maximum of 6.0 Gy total dose; in the case of slow response second series after 6 - 12 weeks		

(b) Painful Treatment Refractory Degenerative Joints (Osteoarthritis)

Indication: Acute exacerbated painful osteoarthrosis of the hip (coxarthrosis), of the knee (gonarthrosis), the shoulder (omarthrosis), the finger joints (polyarthrosis) and of the thumb joint (rhizarthrosis) as well as arthroses of other joints, refractory to conventional and drug treatment

Dose concept:

Single dose	Fractionation	Total dose
0.5 – 1.0 Gy	2 – 3x/ week	3 – 10 Gy
Recommended: every 2 days 0.5 – 1.0 Gy x 6 up to a maximum of 6.0 Gy total dose; in the case of slow response second series after 6 - 12 weeks		

2. Hypertrophic / hyperproliferative diseases

(a) Morbus Dupuytren, Morbus Ledderhose

Indication: In the early stage (with progressive node or strand formation without extension deficit and symptoms in the last 6 months; a maximum of extension deficit stage I: < 45°) for the prevention of surgery in more advanced stages.

Dose concept:

Single dose	Fractionation	Total dose
2.0 – 4.0 Gy	2 – 5x/ week	20 – 40 Gy
Recommended: 10 x 2 Gy in 2 – 3 weeks up to a maximum of 20 Gy, or: 5 x 3 Gy every 2 days repeated after 6 - 12 weeks up to a maximum of 30 Gy		

(b) Morbus Peyronie (Induratio Penis Plastica)

Indication: In the early stage (progressive node or strand formation, slight penis deviation) primarily for pain alleviation and decrease of cohabitation problems and secondarily for the prevention of surgery in the advanced stages.

Dose concept:

Single dose	Fractionation	Total dose
2.0 – 3.0 Gy	3 – 5x/ week	15 – 30 Gy
Recommended: 10 x 2 Gy in 2 – 3 weeks up to a maximum of 20 Gy, or: 5 x 3 Gy every 2 days repeated after 6 - 12 weeks up to a maximum of 30 Gy		

(c) Keloid (Skin) and Pterygium (Conjunctiva)

Indication: Postoperative prophylaxis of a new recurrence.

Dose concept:

Single dose	Fractionation	Total dose
2.0 – 3.0 Gy	3 – 5x/ week	12 – 20 Gy
Recommended: first irradiation directly after surgery (during few hours) after the surgical excision of the keloid tissue; e.g. 5 x 3 Gy up to a maximum of 15 Gy		

3. Functional diseases

(a) Gynecomastia

Indication: *Prophylactic irradiation* of the virile mammary gland (mamilla) for the prophylaxis of a painful breast enlargement under hormonal therapy; *therapeutic irradiation* has lower chances of success in the case of manifest gynecomastia.

Dose concept:

Single dose	Fractionation	Total dose
Prophylactic: 3.0 – 4.0 Gy	4 – 5 x / week	12 – 20 Gy
Recommended: 5 x 4.0 Gy in of a week up to a maximum of 20 Gy		

Single dose	Fractionation	Total dose
possibly therapeutic: 2.0 – 4.0 Gy	4 – 5 x / week	20 – 30 Gy
Recommended: 10 x 2.0 Gy in 2 - 3 weeks up to 20 Gy		

(b) Endocrine Orbitopathy (Graves' Orbitopathy)

Indication: Progressive ocular symptoms with or without autoimmune thyreopathy or other thyroid disease: irradiation of the retroorbital space either as definitive treatment or combined with other therapeutical measures, e.g. steroids.

Dose concept:

Single dose	Fractionation	Total dose
1,5 – 2.0 Gy	4 – 5x/ week	10 – 20 Gy
Recommended: 10 x 2.0 Gy in 2 - 3 weeks up to 20 Gy		

4. Other indications

(a) Age-related (Moist) Macular Degeneration

Indication: Prophylactic irradiation of the retina and the subretinal tissue for the preservation of the visual acuity in case of humid macular degeneration in the senium.

Dose concept:

Single dose	Fractionation	Total dose
1.5 – 2.0 Gy	4 – 5x/ week	12 – 20 Gy
Currently no fixed dose recommendation (controlled studies still to be conducted)		

(b) Prophylaxis of Heterotopic Ossifications

Indication: Prophylaxis of heterotopic ossifications (HO) after trauma or surgery of large joints (hip, knee, shoulder, elbow, other joints), after severe polytrauma with CNS involvement (large joints) and for prophylaxis of recurrence after surgical removement of scar bone (thoracic and abdominal wall)

Dose concept:

Single dose	Fractionation	Total dose
Fractionated RT: 2.0 – 4.0 Gy	3 - 5 times after surgery	8.0 – 12.0 Gy
Recommended:	3 x 4.0 Gy or 5 x 2.0 Gy (24 – 72 hours) after surgery;	

Single dose	Fractionation	Total dose
Single fraction: 6.0 – 8.0 Gy	1 x before/after surgery	6.0 – 8.0 Gy
Recommended:	1 x 7.0 Gy (1 - 4 hours) pre- or postoperatively	

(c) Prophylaxis of Restenosis of Coronary and Peripheral Arteries

Indication: prophylaxis of restenosis after invasive interventions of coronal and peripheral arterial vessels (balloon dilatation, stent implantation, AV shunt).

Because this treatment is still being clinically tested and the target tissues and dose concepts have not been sufficiently established yet, at the moment no RT concept can be recommended. The treatment should take place under clinically controlled study conditions.

Possible dose concept:

Single dose	Fractionation	Total dose
12 – 18Gy	1 x post interventionem	12 - 18Gy, currently yet unclear: minimal/maximal dose

(d) Further Indications:

e.g. AV malformations, other vascular processes; itching dermatoses and eczematous diseases; inaccessible focuses of psoriasis (e.g. subungual focuses).

Dose concept: Currently no special dose recommendations following the statements in textbooks and singular references.

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Review:

Coronary In-Stent Restenosis: Drug-coated Stents (Sirolimus)

U. Schäfer
Department of Radiotherapy and Radiooncology,
University-Hospital Muenster, Albert-Schweitzer-Str. 33, D-48149 Muenster, Germany

Introduction

Percutaneous transluminal coronary angioplasty (PTCA) is a highly effective procedure to reduce the severity of stenotic coronary atherosclerotic disease. But its long-term success is significantly limited by the high rate of restenosis (1).

Compared to PTCA alone, coronary stenting has a more favorable outcome (2). However, in-stent restenosis (ISR) occurs in over 30%-60% of patients (3). The reason of in-stent restenosis is mechanical arterial injury that incites acute and chronic inflammation in the vessel wall (4). The subsequent release of cytokines and growth factors induces multiple signaling pathways to activate smooth muscle cell migration and proliferation.

All systemic drug therapies to prevent in-stent restenosis have been disappointing (5).

The only successful treatment for ISR to date is brachytherapy. In the INHIBIT randomized controlled trial 24 (15%) patients in the radiated group had the primary safety endpoint of death, myocardial infarction, or repeat target lesion revascularisation over 290 days compared with 15 (31%) in the placebo group (p=0·0006) (6).

The development of drug-coated stents

The development of local drug delivery systems requires the development of three technologies together; stent design and manufacture, coating technology and drug pharmacology.

Metallic stents have a thrombogenic tendency and are associated with a marked inflammatory reaction, which can causes in restenosis. Polymer coatings have been suggested to decrease this side effects of metallic stents. In addition, polymers can be formulated with dispersion of drug. Drug release occurs by diffusion through and/or breakdown of the base polymer. Up to now, the current lead investigational drugs are Sirolimus (Rapamycin), Paclitaxel and its derivatives, and Dactinomycin .

Sirolimus, a microbial product isolated from the actinomycete Streptomyces hygroscopius, was initially discovered as an antifungal agent in the mid-1970s. Because of its immunosuppressive effects, it was not further developed for clinical use as an antibiotic. After clinical trials demonstrated that sirolimus suppresses rejection in organ allografts, it was approved by the FDA for use in 1999 (7,8).

A characteristic feature of sirolimus is its ability to inhibit growth factor signaling for both immune and nonimmune cells (9,10). This effect includes at least fibroblasts, endothelial cells, and smooth muscle cells (11). This antiproliferative effect of sirolimus renders it a promising compound for the prevention of postangioplasty and in-stent restenosis.

Studies

In vitro studies

The effect of sirolimus on proliferation was investigated in cell culture of human and rat vascular
smooth muscle cells. Sirolimus inhibited DNA synthesis and cell growth (12). In addition, it could be
demonstrated that sirolimus inhibited PDGF-induced migration in rat and human smooth muscle cell cultures (10).

Systemic animal studies

In vivo systemic sirolimus has been shown to inhibit restenosis in pig coronary arteries after balloon angioplasty. The animals received sirolimus intramuscular 3 days prior to angioplasty and continued for 14 days at a dose of 0.25 mg/kg. Sirolimus administration was associated with a significant inhibition in coronary stenosis (13).

Animal studies with stents

Stents coated with a nonerodable polymer (< 20 m thick) incorporating sirolimus were implanted in iliac arteries of
rabbits and compared with uncoated stents. The follow-up period was 28 days. Neointimal formation was reduced by 23% with a low-dose formulation and 45% with a high-dose formulation compared to control animals. The polymer coating did not provoke exaggerated intimal formation or local inflammation (14).

In addition, stent-based sirolimus was investigated in a 30-day porcine coronary artery model. Stainless steel stents were coated with a 5 m thick layer of a synthetic nondegradable polymer containing sirolimus. Bare and polymer-coated stents were compared. It was demonstrated that the coating significantly reduced neointimal hyperplasia by 30% compared to the uncoated stent group (15).

Clinical studies

A phase I clinical evaluation was performed with sirolimus as an open-label safety study (16). In this study, 45 patients with de novo coronary artery lesions were included. The results showed 0% restenosis.

The recently reported Rapamycin-Eluting Versus Plain Polymer Stents (RAVEL) trial randomized 238 patients to a sirolimus-coated stent or conventional stent for de novo
coronary lesions. After 210-day follow-up a zero restenosis rate in the sirolimus group was reported (vs. 26%, $p < 0.0001$) (17).

Remaining open questions are the toxicity and how multiple or overlapping drug-eluting stents can be used safely. There has also been the observation that stent-based drug delivery results in marked spatial variations in delivered drug dose (18) and reports of late stent thrombosis (19).

In long-term clinical studies, the results should be carefully evaluated in regard to benefits and possible complications. Finally, drug-coated stents have to demonstrate their efficacy against endoluminal brachytherapy in randomized trials.

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"Benign" Calendar of Events

For publication of any relevant events, please notify early enough the **Managing Editor**: Dr. med. Oliver Micke, Westfälische Wilhelms-Universität, Klinik und Poliklinik für Strahlentherapie – Radioonkologie, Albert-Schweitzer-Str. 33, 48129 Münster, Germany, Tel: +49 (0)251 8347839, Fax +49 (0)251 8347355, e-mail: omicke@uni-muenster.de

CZ-Prag
21st Annual ESTRO Meeting

17.09-21.09.2002
21rd Annual Meeting of the European Society for Therapeutic Radiology and Oncology (ESTRO 2002)
In *Prague,Czech Republic*
Contact: Internet: http://www.estro.be

06.10-10.10.2002
44rd Annual Meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO 2002)
In *New Orleans, LA, USA*
Contact: Internet: http://www.astro.org
Panel: Radiation Therapy of Non-Malignant Diseases – The Challenge of Degenerative Disorders
Moderator: M.H. Seegenschmiedt, MD, Alfried Krup Krankenhaus, Germany

01.12.-06.12.2002
87th Scientific Assembly and Annual Meeting of the Radiological Society of North America (RSNA 2002)
In *Chicago, IL, USA*
Contact: Internet: http://www.rsna.org