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CLINICAL INVESTIGATION **Benign Disease**

CONSENSUS GUIDELINES FOR RADIATION THERAPY OF BENIGN DISEASES: A MULTICENTER APPROACH IN GERMANY

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Purpose: To overcome the lack of written guidelines for radiation therapy (RT) of benign diseases, the German Working Group on Radiotherapy of Benign Diseases initiated a consensus process in 1999 to warrant continuous quality assurance and outcome research in this field.

Methods: An expert panel was convened to define key issues and develop written guidelines for RT of benign diseases. Pertinent information and data from published literature were reviewed, and data of most importance were identified. In addition, a patterns of care study was conducted to obtain a nationwide survey on the current status and treatment standards.

Results: From the data gathered, the expert panel prepared a first consensus statement that was open to propositions and comments from all participating institutions. After completion of the multicenter discussion, a final written consensus statement was compiled, discussed, and finally agreed on during a national conference of radiation therapists. For each individual nonmalignant disease, the accepted RT concepts were documented. Finally, specific evaluation tools and recommendations for follow-up examinations were defined.

Conclusions: For the first time, written consensus guidelines for RT of nonmalignant diseases have been developed by the interaction of all institutions involved. These guidelines may serve as a starting point for quality assessment, prospective clinical trials, and outcome research. **© 2002 Elsevier Science Inc.**

Radiotherapy, Nonmalignant disease, Benign disease, Consensus guidelines, Patterns of care study.

INTRODUCTION

The term "radiotherapy for benign diseases" relates to treatment of nonmalignant diseases with ionizing radiation; the term does not necessarily exclude diseases with invasive and expansive growth patterns or with harmful or life-threatening behavior, nor does it exclude diseases that threaten organ function or quality of life (1, 2). These features justify the use of radiation therapy (RT) not only for malignancies, but also for nonmalignant disorders (1). Outside Europe, the use of RT to treat benign disease is not well established (3) and often regarded with skepticism (4). The textbook of Order and Donaldson compiles almost 100 indications for RT of benign conditions, but only 10 of these would be treated by more than 90% of North American radiation oncologists, according to a 1990 survey; as many as 30 indications would be treated by only a minority of 30% of radiation oncologists surveyed (4).

The last written recommendations for the treatment of nonmalignant disease in the United States were made by the Bureau of Radiologic Health in 1977. Since then, however, many new treatment indications (5) have been introduced and well accepted, such as prophylactic irradiation to prevent ectopic ossifications (6–11) or vascular restenosis (12, 13).

The treatment of benign diseases with ionizing irradiation is the task of the radiation therapist, for several reasons (1). With its foundation of theoretical and practical knowledge, the profession is familiar with all technical and clinical aspects of ionizing radiation. This includes working with various treatment machines, taking histories, performing clinical examinations, setting up the indication, and theoretical planning; radiation therapists have practical knowledge of the daily routine and all aspects of radiation protection, long-term follow-up, and documentation (14, 15). Although RT of benign disease is usually carried out with much lower RT doses than those used for malignant tumors, the radiation therapist has the same duties: preparing, carrying through, documenting completely, and following up the whole treatment process with the utmost care and attention, as is the case with all malignant diseases (14–16).

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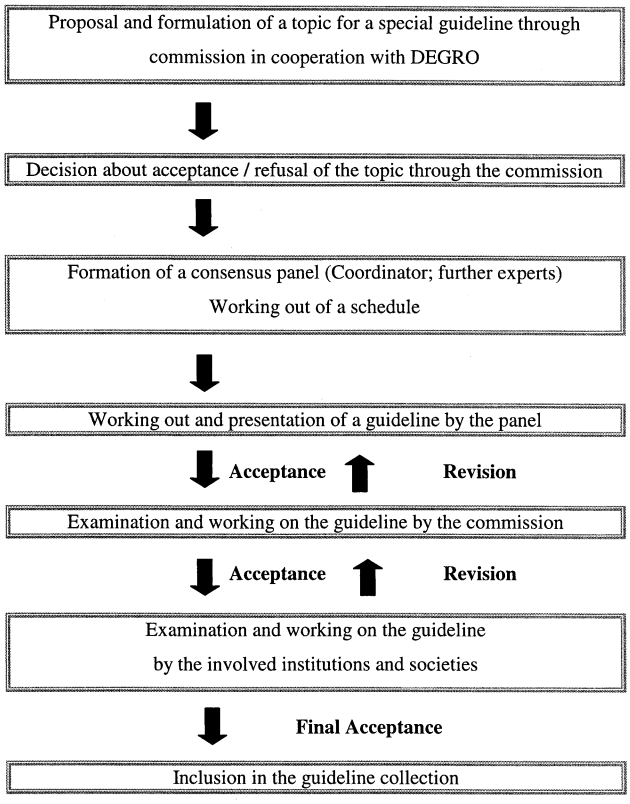


Fig. 1. The process used by the German Radiation Oncology Society (DEGRO) to develop guidelines for treating benign disease with radiotherapy (14).

Given this background, there is a need for special guidelines, similar to those for malignant disorders, for RT of benign diseases (17, 18); there is also a need for medical societies to create guidelines for special treatment procedures (19–25). The aim of our work was to develop modern written guidelines for RT of benign diseases to warrant quality assurance and outcome research (17).

METHODS AND MATERIALS

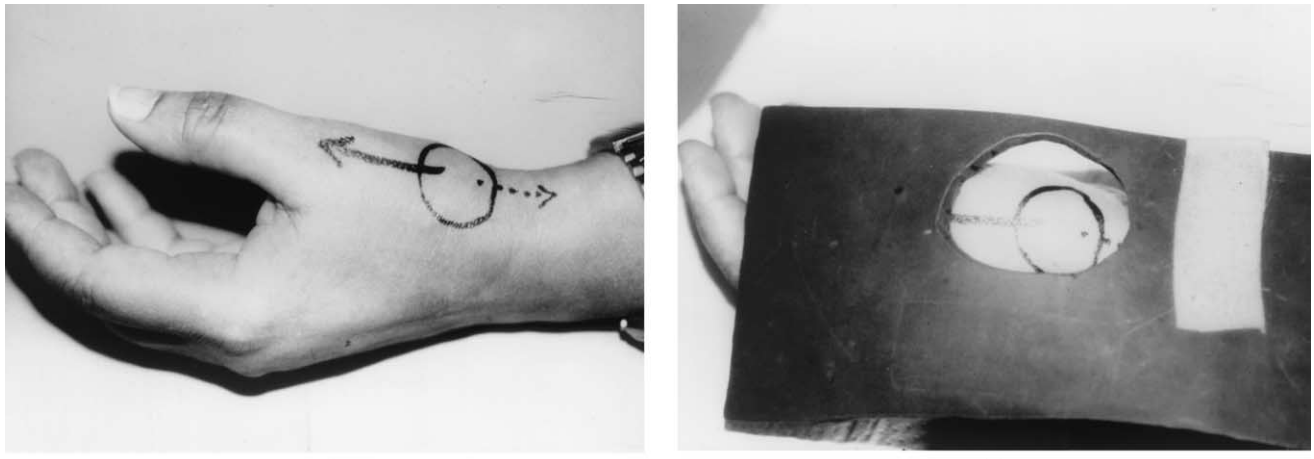
In 1995 the German Working Group on Radiotherapy of Benign Diseases was founded, together with the German Radiation Oncology Society. In 1996 a national conference on RT for benign diseases was held, and treatment guidelines were anticipated. In 1997 the consensus process started, and in 1999 it was finalized. The method for treating benign disorders was adopted from former consensus guidelines (14, 17, 21–23, 26). A schematic diagram of the consensus process is shown in Fig. 1 (14). The process started with the formation of an expert panel; initially, the chairmen from all university and nonuniversity hospitals with radiotherapy departments participated, as well as members of the German Working Group on Radiotherapy of Benign Diseases (Appendix A). Pertinent information and data from the literature were reviewed, and articles of most scientific importance were identified (5, 17). The level of evidence for each disease entity was determined and graded according to international recommendations (22, 23) (Table 1). In addition, a patterns of care study (PCS) was conducted to obtain a nationwide survey of treatment standards for RT of benign diseases (27). The PCS provided a survey of nearly 90% of all German RT facilities. RT equipment, specific treatment indications, number of patients per year, and individual RT concepts were assessed in 134 German institutions. From this survey, it was concluded that more than 20,000 patients were reported each year as having been treated for about 16 different indications.

The expert panel prepared a first consensus statement that was open to 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.

Table 1. Levels of evidence and grade of recommendation*

Level	Type of evidence
I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies. Randomized trials with low false-positive and low false-negative errors (high power)
II	Evidence obtained from at least one well-designed experimental study. Randomized trials with high false-positive and/or negative errors (low power)
III	Evidence obtained from well-designed, quasi-experimental studies such as nonrandomized, controlled single-group, pre-post, cohort, and time or matched case-control series
IV	Evidence from well-designed, nonexperimental studies such as comparative and correlational descriptive and case studies
V	Evidence from case reports
Grade	**Grade of recommendation**
A	There is evidence of Level I or consistent findings from multiple studies of types II, III, or IV
B	There is evidence of Level II, III, or IV, and findings are generally consistent
C	There is evidence of Level II, III, or IV, but findings are inconsistent
D	There is little or no systematic empirical evidence

* See refs. 21 and 22.



(a) (b)

Fig. 2. (a) Patient with rizarthrosis of the left thumb. The pain maximum is marked with ink. Arrows indicate the direction of pain and the geographic extension of pain radiation. (b) Individual shielding with lead foil that encompasses the target volume (base joint of thumb). The X-ray treatment is adapted, and dose fall at the field edges is considered.

RESULTS

The written guidelines consist of the following components, which are addressed in the following paragraphs: (*1*) general indications for RT, (*2*) radiobiologic basis for RT, (*3*) radiation protection issues, (*4*) quality assurance procedures, (*5*) indication setup, (*6*) patient's informed consent, (*7*) standard documentation, (*8*) follow-up, and (*9*) special treatment concepts.

General indications for RT

The potential clinical indications for RT of benign diseases are various, and an interdisciplinary agreement has not always been coordinated. A unified definition of RT indications, with the issue of RT of benign diseases addressed specifically, does not exist (28). In German-speaking countries and in central and Eastern European regions, the following indications are currently known (5):

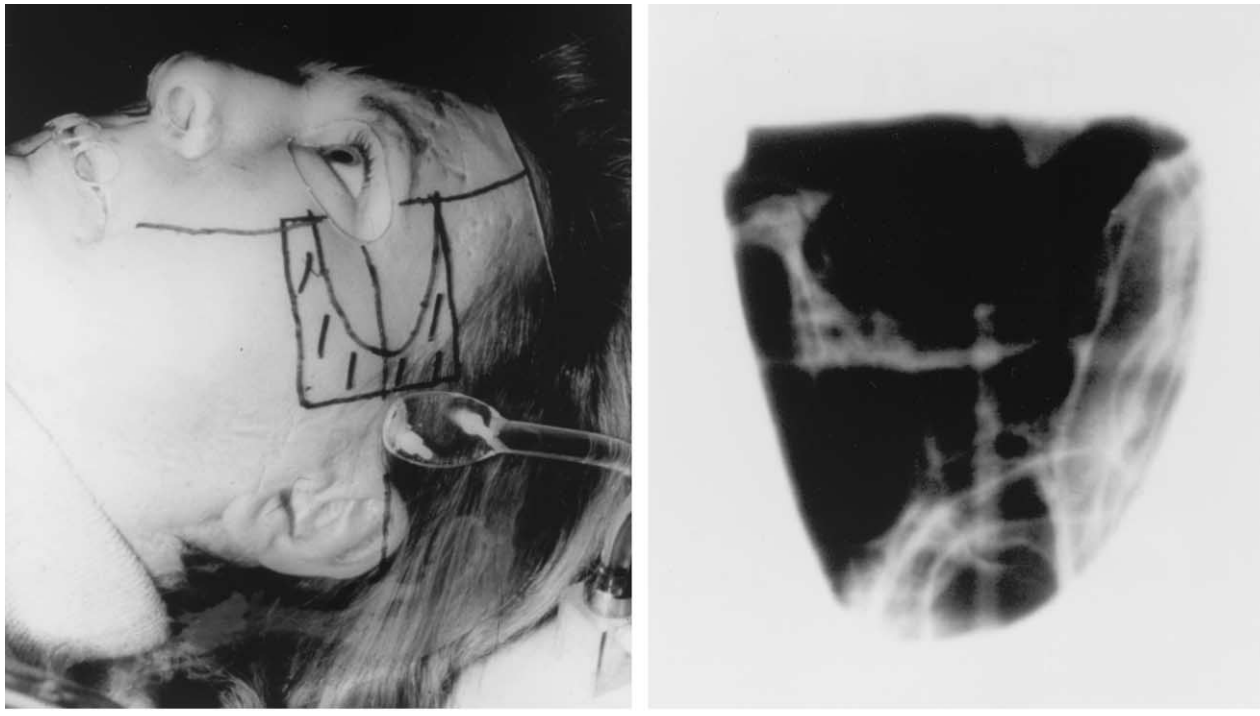
1. *Acute/chronic inflammatory disorders*, e.g., axillary sweat gland abscess, furuncula, carbuncula, panaritium, and other infections not responding to antibiotics, etc.;
2. *Acute/chronic painful degenerative diseases*, e.g., insertion tendinitis and chronic or acute painful osteoarthritic diseases of various joints (hip, knee, etc.);
3. *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;
4. *Functional diseases*, such as Graves' orbitopathy, arteriovenous malformations, age-related macular degeneration, persisting lymphatic fistula;
5. *Other indications*, such as prophylaxis of heterotopic ossification at various joints, prophylaxis of neointimal hyperplasia, e.g., after arterial dilatation or stent implantation, obstruction of hemangiomas and other vascular disorders of various organs;
6. *Dermatologic diseases*, e.g., pruritus due to itching dermatoses and eczemas, inaccessible psoriatic focuses (e.g., subungual focuses), basalioma.

Radiobiologic mechanisms

Biologic 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 (neuroregulatory theory), and impact on the composition of the tissue milieu (electrochemical theory) (29–35). Another goal is preventing mitotic cells from proliferating (antiproliferative effect) (36, 37). Probably no mechanism by itself can explain the efficacy; it is rather a complex collaboration of several of these effects. Different biologic 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 radiobiologic standpoint.

Radiation protection

All means of radiation protection must be applied, including the following: 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 radiation beam's direction of entry away from the body stem or radiosensitive organs (e.g., thyroid,



(a) (b)

Fig. 3. (a) Orbital irradiation of Graves' ophthalmopathy using head mask fixation, individual lead shielding, and parallel opposed linear accelerator fields. (b) Verification of the irradiation portal with an individualized field configuration to reduce dose to normal tissue.

gonads, eye lens); application of shielding (individualized 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). A good example of individualized shielding is shown in Figs. 2a and 2b, which demonstrate a 3-mm-thick lead rubber sheet used during orthovoltage therapy for treatment of rhizarthrosis of the thumb. Such lead shields can be cut to properly fit the target volume and to reduce dose to surrounding normal tissue.

According to Broerse *et al.* (38, 39), after a patient's third to fourth decade, the carcinogenic risk of RT for benign diseases may decrease to that of general risk for cancer in the normal population. This underscores the importance of radioprotection with individualized lead shielding especially for younger patients, to reduce normal-tissue dose outside the target volume. It has been demonstrated for orbital irradiation of Graves' orbitopathy (39) that individual shielding can markedly reduce the tissue dose outside the target volume and consequently the carcinogenic risk (Figs. 3a and 3b).

Quality assurance

Quality assurance is a main focus of these guidelines, which cover radioprotection and standardization of treatment, as well. Just as quality criteria must be applied to RT of malignant disease, the same standards apply to RT of benign disease (1, 14–17). The following aspects especially must be considered.

Before RT, the radiation therapist prepares a written treatment plan. It contains exact instructions on the positioning of the patient, the setup parameters of the RT machine, the target volume definition, and dose specification. All RT portals and setup conditions should be documented with photographs (e.g., Polaroid); the minimum requirement is a written form and graph that exactly and unambiguously allow any RT technician or physician to reproduce the routine daily treatment setup.

Standardized RT setup is recommended, including a treatment plan, target volume definition, and dose specification in accordance with the ICRU-50 report; therefore, 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, for example, high-energy linear accelerator photons for the prevention of heterotopic ossification or low-energy orthovoltage photons for the treatment of degenerative disorders of the small joints. Special immobilization devices such as individual head masks (Fig. 3a) or vacuum pillows should be used where needed. Both the radiation therapist and medical physicist should be involved in treatment planning and execution of treatment.

Outcome research is mandatory for appropriate quality assurance. It requires the definition of reliable end points. Depending on the degree and duration of the disease, different end points can be considered: e.g., reduction of pain and other pathologic signs, preservation of organ functions,

and avoidance of invasive treatment measures (e.g., surgery). Nowadays, the subjective evaluation scales applied in former times are inadequate for evaluating treatment success. Thus, objective scores for evaluating functional and radiologic changes, visual analog scales for evaluating pain, and questionnaires on daily bodily 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 setup

The treatment indication should be discussed and decided using an interdisciplinary approach. The admission of a patient to RT provides a *commission for treatment*, but the radiation therapist has to affirm and document in a written form the correct indication for RT. Thus, medical history, physical examination, and, possibly, diagnostic measures are essential for an appropriate RT indication. Sometimes physicians from other disciplines must be consulted. In the case where an indication for RT is rejected, the reasons should be given to the referring physician.

Informed consent

Before RT, relevant medical information regarding disease and therapy must be provided, so the patient can give appropriate informed consent (40), as follows:

1. Both natural cause and individual disease status must be explained. It should verified and explained that RT is correctly indicated (*differentiated RT indication*), thereby taking into account all previously applied and alternative treatment options (*therapeutic alternatives*). The possible treatment goal must be defined before RT. Generally, RT is 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.
2. 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).
3. 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 location of the target volume, and the applied RT dose. It is of utmost importance to judge possible benefits and risks in younger patients (up to about 30–40 years), because of long life expectancy.
4. After the initial consultation, patients require *sufficient time* for their decision. Generally, the first RT should not be carried out sooner than 1 day after informed consent. In the case of preoperative or postoperative RT, the judgment of the patient must not be impaired. All relevant clinical data provided by the physician, as well as informed consent by the patient, must 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 is the duty of the radiation therapist (41). It must be emphasized that for forensic reasons, patient information and informed consent must be in written form (40). It is also recommended that medical history, physical examination at admission and discharge, and follow-up exams (photographic documentation, consultations) are documented in the patient's chart. Details of RT (treatment time, dose, and localization) must be documented in the treatment protocol. If possible, simulation and verification films should be taken regularly. German legislation requires that all documents connected with RT be preserved for a minimum of 30 years. After RT, the referring physician should receive an RT summary report. The necessity of standardized long-term follow-up should be mentioned therein. An example of standardized documentation has recently been published with regard to RT of Dupuytren's contraction (42).

Follow-up

As often as possible, follow-up exams should be carried out 3 months and 1 year after clinical RT. It is most important to assess *disease-specific symptoms* that have led to the indication for RT. If higher RT doses have been used, *sequelae to normal tissues* must be analyzed using the same scoring systems used for radiation oncology (16), e.g., RTOG or LENT-SOMA. Sometimes *rehabilitational measures* must be thought of, also.

Treatment concepts

Specific treatment recommendations regarding single and total doses and fractionation have been elaborated by the expert panel that formulates these guidelines (Appendix C). The treatment indications and RT dose concepts mentioned herein correspond to literature data collected since the beginning of the 1950s (4, 5, 43–48) and to the evaluation of a questionnaire by the Working Group on Radiotherapy of Benign Diseases of the German Society of Radiation Oncology (DEGRO) from 1994 to 1996 (27). For single and total doses and number of fractions, the range of all statements from the various institutions is given. Therefore, it is not an acceptable practice to combine maximum values for single doses and numbers of fractions. Thus, to better explain the results, the most frequently used treatment concepts have been presented as recommended guidelines. These recommended RT concepts are based mostly on studies with clinical evidence Levels I and II (7–11, 49–51), because most scientific and clinical knowledge about indications for RT of benign disease result from retrospective clinical series with up to 7,000 patients reported in one study (44, 45) over a period of almost 100 years (43–48, 52–57) and from other personal and clinical experience in

RT practice. This results in relatively low evidence Level III to V. Consequently, the recommendations so far must 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 American Society of Clinical Oncology Health Service Research Committee for the definition of guidelines (58). The guideline attributes include validity, reliability, reproducibility, clinical applicability, multidisciplinary process, review of evidence, and documentation (19, 20, 24). Use of guidelines may improve patient outcome and medical practice, minimize daily practice variations, and provide decision tools for practitioners and a reference for medical decision making and continuous medical education. Use of guidelines 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 the American Society of Clinical Oncology (19–21, 24–26) and are usually applied in cancer therapy or supportive care. Because RT for benign disorders should be performed under conditions similar to those for malignancies (14), guidelines for RT of benign disease should cover the same aspects.

So far, only a few preclinical studies are available that explain the basic radiobiologic mechanisms in benign diseases (27, 29, 30). The guidelines presented herein describe some explanatory models for radiation effects based on recent experimental data (29–37) and are intended to stimulate further experimental research. This should help overcome skepticism about RT for benign diseases, for example in Anglo-American countries (3, 4).

There are also concerns about the 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 little increase in the risk of tumor induction calculated with mathematical models, but the overall contribution to a patient's general lifetime risk remains unclear. Broerse *et al.* (38, 39) stated that after the fourth decade of life, the attributable lifetime risk may be lower than that for the general population. Thus, we recommend that patients be older than 30–40 years. In younger patients, the carcinogenic risks should be carefully weighed against possible benefits, and the indication setup should be restricted to special indications. These findings reinforce the requirement that radiation protection measures during RT for benign diseases be as accurate as possible.

RT for benign diseases covers many disorders (1, 4, 5) (Appendix C). Some indications are not well accepted on an international level (3), because RT practice is based mostly 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 controlled studies performed earlier did not find an advantage in using RT for painful degenerative disorders, but their study design was inadequate, and end point definition was poor (61–63). In contrast, some recent studies serve as good examples for improved clinical research, e.g., in Graves' orbitopathy (50, 51) and in heterotopic ossification prophylaxis (7–11). Modern prospective clinical studies also include objective scores and defined subjective criteria for better end point definition (49, 54–56). Still, only 4% of RT institutions in Germany 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 and Sagar (64) have stated, EBM only answers questions open to its technique, and therefore randomized trials are its capstone. However, other forms of evidence, such as long-term observation or clinical experience, are ranked lower and often discounted. Nevertheless, for rare disorders and for an increasing number of patient subgroups, as well as for benign disease, 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, different treatment options must be presented to patients who typically fail, to elicit informed consent before the indication and implementation of RT. Some patients may prefer to receive a treatment that has achieved only 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, including electronic media (e.g., the internet) (65) and databases (e.g., Medline, Embase, Science Citation Report) (28), can be implemented on an international level 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 diseases (Appendix B) and their specific RT treatment should be developed.

In addition, standardized nomenclature must be correctly applied. The textbook of Order and Donaldson (4) notes that 86% of radiotherapists would treat lethal midline granuloma, whereas only 17% would treat polymorphic reticulosis, which is, in fact, the same disease. This example reveals the discrepancy of some RT indications because of unclear nomenclature. Thus, the International Classification of Diseases (ICD-10 codes) is recommended for classifying 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 on rare benign disorders, the consensus guidelines recommend implementing a special registry with forms for rare benign diseases (Appendix B), to centrally collect and analyze treatment and outcome (1).

For legal as well as medical reasons, it is important to

establish guidelines to improve standards of care (69). Increasingly, the legal system refers to clinical guidelines and official standards of care (4, 69, 70), for example in Anglo-American countries, where malpractice is defined as deviation from standards of care (4). Nowadays, a similar trend can be observed in European and German-speaking countries (70). Thus, explicitly written clinical guidelines are needed (69) and well accepted by medical practitioners and specialists, as well as by scientific societies (17, 26, 71).

An important instrument for determining standards of care, which can vary greatly between countries, geographic regions, and institutions, is the PCS. The cornerstone for German guidelines on benign disease was a national PCS (27). It provided a survey on the current standard of care for RT of benign diseases. The German Working Group on Radiotherapy of Benign Diseases is prepared to further define the PCS, to determine exact standards of care for specific RT indications, such as heterotopic bone formation (72), keloids, aggressive fibromatosis, and Graves' orbitopathy. Although PCS provide good guides for the practice of medicine, they do not necessarily guide the 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; guidelines cannot be considered to include all proper methods of care or to exclude 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 light of each patient's individual circumstances (18, 24).

CONCLUSION

For the first time, written consensus guidelines for RT of benign diseases have been developed by means of a multicenter collaboration of all institutions in Germany involved with RT. These guidelines may serve as a starting point for continuous quality assessment, design of prospective clinical trials, and outcome research in this field. Similar to the national process, an international consensus initiative should be undertaken to develop updated international standards of care for RT of benign conditions.

REFERENCES

1. Seegenschmiedt MH. Thoughts about benign and not so benign diseases. *BenigNews* 2000;1(1):2.
2. Posner MC, Shui MH, Newsome JL. The desmoid tumor—not a benign disease. *Arch Surg* 1989;124:191–196.
3. Leer JWH, van Houtte P, Daelaar J. Indications and treatment schedules for irradiation of benign diseases: A survey. *Radiother Oncol* 1998;48:249–257.
4. Order S, Donaldson SS. Radiation therapy of benign diseases. 2nd ed. New York: Springer; 1998. p. 1–258.
5. Makoski HB. Gutartige Erkrankungen. In: Scherer E, Sack H, eds. Strahlentherapie-Radiologische Onkologie. 4th ed. Berlin: Springer; 1996. p. 293–314.
6. Lo TCM. Radiation therapy for heterotopic ossification. *Semin Radiat Oncol* 1999;9:163–170.
7. Seegenschmiedt MH, Martus P, Goldmann AR, *et al.* Preversus postoperative radiotherapy for prevention of heterotopic ossification (HO): First results of a randomized trial in high-risk patients. *Int J Radiat Oncol Biol Phys* 1994;30:63–73.
8. Seegenschmiedt MH, Keilholz L, Martus P, *et al.* Prevention of heterotopic ossification about the hip: Final results of two randomized trials in 410 patients using either preoperative or postoperative radiation therapy. *Int J Radiat Oncol Biol Phys* 1997;39:161–171.
9. Kölbl O, Knelles D, Barthel T, *et al.* Preoperative irradiation versus the use of non-steroidal anti-inflammatory drugs for prevention of heterotopic ossification following total hip replacement: The results of a randomized trial. *Int J Radiat Oncol Biol Phys* 1998;42:397–401.
10. Knelles D, Barthel T, Karrer A, *et al.* Prevention of heterotopic ossification after total hip replacement. Prospective randomised study using acetylsalicylic acid, indomethacin and fractional or single-dose irradiation. *J Bone Joint Surg Br* 1997;79:596–602.
11. Gregoritch SJ, Chadha M, Pelligrini VD, *et al.* Randomized trial comparing pre- versus postoperative irradiation for prevention of heterotopic ossification following prosthetic total hip replacement: Preliminary results. *Int J Radiat Oncol Biol Phys* 1994;30:55–62.
12. Crocker I. Radiation therapy to prevent coronary artery stenosis. *Semin Radiat Oncol* 1999;9:134–143.
13. Tripuraneni P, Giap H, Jani S. Endovascular brachytherapy for peripheral vascular diseases. *Semin Radiat Oncol* 1999;9:190–202.
14. Müller RP, Seegenschmiedt MH, eds. Leitlinien in der Radioonkologie. DEGRO, Eigenverlag Tübingen; 1999.
15. Seegenschmiedt MH, Müller RP, Bamberg M. [Quality assurance in radio-oncology/radiotherapy: Basic considerations]. *Schweiz Rundsch Med Prax* 1999;88:526–532.
16. Seegenschmiedt MH. Interdisciplinary documentation of treatment side effects in oncology. Present status and perspectives. *Strahlenther Onkol* 1998;174(Suppl. 3):25–29.
17. Seegenschmiedt MH, Müller RP. [Development of guidelines in radiation oncology]. *Strahlenther Onkol* 1997;173:345–351.
18. Minsky BD, Coia L, Haller D, *et al.* Treatment systems guidelines for primary rectal cancer from the 1996 patterns of care study. *Int J Radiat Oncol Biol Phys* 1998;41:21–27.
19. American Society of Clinical Oncology. American Society of Clinical Oncology recommendations for the use of hematopoetic colony-stimulating factors: Evidence-based clinical practice guidelines. *J Clin Oncol* 1994;12:2471–2508.
20. Bennett CL, Weeks JA, Somerfield MR, Feinglass J, Smith TJ, for the Health Services Research Committee of the American Society of Clinical Oncology. Use of hematopoietic colony-stimulating factors: Comparison of 1994 and 1997 American Society of Clinical Oncology surveys regarding ASCO clinical practice guidelines. *J Clin Oncol* 1999;17:3676–3681.
21. Hillner BE, Ingle JN, Berenson JR, *et al.* American Society of Clinical Oncology guideline on the role of bisphosphonates in breast cancer. *J Clin Oncol* 2000;18:1378–1391.
22. Cook DL, Guyatt GH, Laupacis A, *et al.* Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest* 1989;102(Suppl. 2):305S–311S.
23. Sackett DL. Rules of evidence and clinical recommendations

on the use of anti-thrombotic agents. *Chest* 1989;102(Suppl. 2):2S–4S.
24. Desch CE, Benson AB, Smith TJ, *et al.* Recommended colorectal cancer surveillance guidelines by the American Society of Clinical Oncology. *J Clin Oncol* 1999;17:1312–1321.
25. Hensley ML, Schuchter LM, Lindley C, *et al.* American Society of Clinical Oncology clinical practice guidelines for the use of chemotherapy and radiotherapy protectants. *J Clin Oncol* 1999;17:3333–3355.
26. Bowman GP, Levine MN, Mohide EA, *et al.* The practice guidelines development cycle: A conceptual tool for practice guidelines and implementation. *J Clin Oncol* 1995;13:502–512.
27. Seegenschmiedt MH, Katalinic A, Makoski HB, *et al.* Radiation therapy for benign diseases: Patterns of care study in Germany. *Int J Radiat Oncol Biol Phys* 2000;47:195–202.
28. Micke O. Increasing number of publications in international scientific literature—quantity meets quality? *BenigNews* 2000;1(1);3.
29. Trott KR. Therapeutic effects of low dose irradiation. *Strahlenther Onkol* 1994;170:1–12.
30. Trott KR, Kamprad F. Radiobiological mechanisms of anti-inflammatory radio-therapy. *Radiother Oncol* 1999;51:197–203.
31. Hildebrandt G, Jahns J, Hindemith M, *et al.* Effects of low dose radiation therapy on adjuvant induced arthritis in rats. *Int J Radiat Biol* 2000;76:1143–1153.
32. Hildebrandt G, Seed MP, Freemantle CN, *et al.* Effects of low dose ionizing radiation on murine chronic granulomatous tissue. *Strahlenther Onkol* 1998;174:580–588.
33. Hildebrandt G, Seed MP, Freemantle CN, *et al.* Mechanisms of the anti-inflammatory activity of low-dose radiation therapy. *Int J Radiat Biol* 1998;74:367–378.
34. Trott KR, Parker R, Seed MP. [The effect of x-rays on experimental arthritis in the rat]. *Strahlenther Onkol* 1995; 171:534–538.
35. Kern PM, Keilholz L, Forster C, *et al.* Low-dose radiotherapy selectively reduces adhesion of peripheral blood mononuclear cells to endothelium in vitro. *Radiother Oncol* 2000;54:273–282.
36. Rubin P, Soni A, Williams JP. The molecular and cellular biologic basis for radiation treatment of benign proliferative diseases. *Semin Radiat Oncol* 1999;9:203–214.
37. Schäfer U, Micke O, Dorszewski A, *et al.* External beam irradiation inhibits neointimal hyperplasia after injury-induced arterial smooth muscle cell proliferation. *Int J Radiat Oncol Biol Phys* 1998;42:617–622.
38. Broerse JJ, Snijders-Keilholz A, Jansen JTM, *et al.* Assessment of a carcinogenic risk for treatment of Graves' ophthalmopathy in dependence on age and irradiation geometry. *Radiother Oncol* 1999;53:205–208.
39. Broerse JJ, Jansen JTM, Zoetelief J, Klein C, Seegenschmiedt MH. Calculation of effective dose for irradiation of benign diseases: Graves' ophthalmopathy, hidradenitis and heterotopic ossification. In: Seegenschmiedt MH, Makoski H, eds. Radiotherapie von gutartigen Erkrankungen—10. Kolloquium Radioonkologie/Strahlentherapie. Altenberge: Diplodocus-Verlag; 2000; p. 13–20.
40. Weintraub MI. Documentation and informed consent. *Neurol Clin* 1999;17:371–381.
41. Kosziorowski N, Seegenschmiedt MH. Radiotherapie bei gutartigen Erkrankungen: Einstelltechnik, Lagerung, Dokumentation. In: Seegenschmiedt MH, Makoski H, editors. Radiotherapie von gutartigen Erkrankungen—4. Kolloquium Radioonkologie/Strahlentherapie. Altenberge: Diplodocus-Verlag; 2000; p. 102–105.
42. Seegenschmiedt MH, Olschewski T, Guntrum F. Radiotherapy optimization in early stage Dupuytren's contracture: First results of a randomized clinical study. *Int J Radiat Oncol Biol Phys* 2000;49, in press.
43. von Pannewitz G. Röntgentherapie der Arthrosis deformans. *Strahlentherapie* 1953;92:375–382.
44. von Pannewitz G. Degenerative Erkrankungen. In: Zuppinger A, Ruckensteiner E, editors. Handbuch der Medizinischen Radiologie, Bd. XVII. Berlin: Springer; 1970. p. 73–107.
45. von Pannewitz G. Strahlentherapie der Arthrosis deformans. *Radiologe* 1970;10:51–54.
46. Cocchi U. Erfolge und Mi*β*erfolge bei Röntgenbestrahlung nichtkrebsiger Leiden. *Strahlenther* 1943;73:255–284.
47. Hess F, Bonmann KH. Die Röntgentherapie der Arthrosen, Spondylosen, der Periarthritis humeroscapularis und der Epicondylitis. *Strahlentherapie* 1955;96:75–81.
48. Jenkinson EL, Norman RC, Wilson IA. Radiation therapy of the nontraumatic painful shoulder. *Radiology* 1952;8:92.
49. Seegenschmiedt MH, Keilholz L, Katalinic A, *et al.* Heel spur: Radiation therapy for refractory pain—Results with three treatment concepts. *Radiology* 1996;200:271–276.
50. Prummel MF, Mourtis MP, Blank L, *et al*. Randomised double-blind trial of prednisone versus radiotherapy in Graves' ophthalmopathy. *Lancet* 1993;342:949–954.
51. Marcocci C, Bartalena L, Bogazzi F, *et al.* Orbital radiotherapy combined with high dose systemic glucocorticoids for Graves' ophthalmopathy is more effective than radiotherapy alone: Results of a prospective randomized study. *J Endocrinol Invest* 1991;14:853–860.
52. Schäfer U, Micke O, Glashörster M, *et al.* Strahlentherapeutische Behandlung des schmerzhaften Fersenbeinsporns. *Strahlenther Onkol* 1995;171:202–206.
53. Wagner W, Alfrink M, Micke O, *et al.* Results of prophylactic irradiation in patients with resected keloids. *Acta Oncol* 2000; 39:217–220.
54. Seegenschmiedt MH, Keilholz L. Epicondylopathia humeri (EPH) and peritendinitis humeroscapularis (PHS): Evaluation of radiation therapy long-term results and literature review. *Radiother Oncol* 1998;47:17–28.
55. Keilholz L, Seegenschmiedt MH, Kutzki D, *et al.* Periarthritis humeroscapularis: Indikation, Technik, Bestrahlungsergebnisse. *Strahlenther Onkol* 1995;171:379–384.
56. Keilholz L, Seegenschmiedt MH, Sauer R. [Radiotherapy for painful degenerative joint disorders. Indications, technique, clinical results]. *Strahlenther Onkol* 1998;174:243–250.
57. Gocht H. Therapeutische Verwendung der Röntgenstrahlen. *Fortschr Röntgenstr* 1897;1:14.
58. Canadian Medical Association. The Canadian task force on the periodic health examination. *Can Med Assoc* 1979;121: 1193–1254.
59. Cannon B, Randolph JG, Murray JE. Malignant irradiation for benign conditions. *N Engl J Med* 1959;260:197–202.
60. Jung H. Gibt es ein Strahlenrisiko bei niedrig dosierter Strahlentherapie? oder: Was sage ich Ärzten und Patienten. In: Seegenschmiedt MH, Makoski H, editors. Radiotherapie von gutartigen Erkrankungen—10. Kolloquium Radioonkologie/Strahlentherapie. Altenberge: Diplodocus-Verlag; 2000. p. 5–12.
61. Valtonen EJ, Lilius HG, Malmio K. The value of roentgen irradiation in the treatment of painful degenerative and inflammatory musculoskeletal conditions. *Scand J Rheumatol* 1975; 4:247–249.
62. Goldie I, Rosengren B, Moberg E, Hedelin E. Evaluation of radiation treatment of painful conditions of the locomotor system. *Acta Radiol Ther Phys* 1970;9:311–322.
63. Plenk HP. Calcifying tendinitis of the shoulder: A critical study of the value of X-ray therapy. *Radiology* 1952;59:384–389.
64. Jones GW, Sagar SM. No guidance is provided for situations which evidence is lacking. *BMJ* 1995;311:258.
65. Schüller P. Leaving traces in the web. *Trace Elem Electrolytes* 2000;17:190–192.

66. World Health Organization. ICD-10. International statistical classification of diseases and related health problems. 10th rev. vol. 3, Geneva, WHO; 1994.
67. Micke O, Seegenschmiedt MH, Makoski HB. Excerpt of the ICD-10 classification for radiotherapy of benign diseases. *BenigNews* 2000;1(2);2.
68. Aristizabal SA, Runyon TD. Radiotherapy of unusual benign disease. *Int J Radiat Oncol Biol Phys* 1981;7:1437–1440.
69. Gevers S. Clinical practice guidelines; legal aspects. *Med Law* 1996;15:671–675.
70. Ulsenheimer K. [Legal aspects: Nonbonding recommendations or jurisdiction on medicine?] *Z Kardiol* 2000;89:245–250.
71. Lomas J, Anderson GM, Dominik-Pierre K, *et al*. Do practice guidelines guide practice? The effect of a consensus statement on the practice of physicians. *N Engl J Med* 1989;321:1306–1311.
72. Seegenschmiedt HM, Makoski HB, Micke O. Heterotopic ossification prophylaxis about the hip joint—a multi-center study. *Int J Radiat Oncol Biol Phys* 2000;48(Suppl. 3):241–242.

APPENDIX A

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APPENDIX B

Appendix B: **Registry "Rare Benign Diseases"**

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Patient Data Record

Initials: First | Surname **Birth Date:** Day | Month | Year **Age:**

Sex: [ ] Male [ ] Female

Clinical Diagnosis:

Date of Diagnosis: Day | Month | Year

Certainty: [ ] Histology [ ] Imaging [ ] Clinically

Disease History:

Prior Treatment:

Radiation Therapy

Target Volume:

Machine: [ ] Linac [ ] Cobalt [ ] Other:

Energy keV / MeV:

Total Dose: **Gy;** **Dose / Fraction:** **Gy;** **Fractions / Week:**

Clinical Course:

Last Patient Visit / Contact Day | Month | Year

APPENDIX C

Treatment Outcome:

Clinical and / or

Imaging Studies:

Remission of Symptoms: **[ ] CR** **[ ] PR** **[ ] NC** **[ ] PD**
(if evaluable / applicable)

Radiation Side
Effects / Sequelae:

Survival: **[ ] Patient alive** **[ ] Patient died**

When?

[ ] From treated disease
[ ] From other causes

Publication:

Case already published? [ ] Yes [ ] No If yes, provide the Source

Publication in BenigNews wanted [ ] Yes [ ] No

Date, Signature

Stamp

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		

In the case of slow response repetition as a 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 – 18 Gy	1 x post interventionem	12 - 18 Gy, 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.