

PRACTICE GUIDELINES FOR RADIOTHERAPY OF NON-MALIGNANT DISORDERS:

A MULTICENTER APPROACH IN GERMANY –DEVELOPMENT,

INTRODUCTION AND GENERAL COMMENTS

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ABSTRACT

Purpose: To develop consensus guidelines for radiotherapy (RT) of benign diseases by the implementation of an S2e clinical practice guideline.

Methods: The process started with the formation of a scientific panel. The development process of these clinical guidelines followed the national and international standards: They are based on a consensus process as well as an evidence-based methodology, so that an S2e clinical guideline resulted.

The following diseases and topics were covered by the guideline: Physical and radiobiological background, radiogenic risks, lymph fistulas, bursitis trochanterica, Gorham-Stout syndrome, vertebral hemangiomas, pigmented villonodular synovitis (PVNS), heterotopic ossifications, osteoarthritis of large and small joints, Morbus Dupuytren, Morbus Ledderhose, desmoid tumors (aggressive fibromatosis), plantar fasciitis (painful heel spurs), Peyronie's disease, painful elbow syndrome and shoulder syndrome, keloids and endocrine orbitopathy.

Results: These clinical guidelines consist of the following components: (1) the physical and radiobiological basis for RT, (2) considerations regarding risks of low radiation doses, (3) general indications for the application of RT and (4) special treatment concepts for benign conditions except benign brain tumors.

Conclusions: Written evidence-based consensus guidelines have been updated in 2014 and brought into a publication consisting of four parts. These guidelines may serve as a starting point for continuous quality assessment, future clinical research including the design of prospective clinical trials, and outcome research in this important field of radiotherapy.

KEYWORDS: Non-malignant, Benign diseases, Practice guidelines, Radiotherapy & Evidence-based medicine

INTRODUCTION

Since the introduction of radiotherapy in clinical medicine in 1896 its use for the treatment of non-malignant or benign disorders has been developed in European rather than other countries [1, 2]; since the 60es of the last century its use

has been majorly practiced by radiotherapists in Central and East European countries, while in Western Europe and Anglo-American countries the use of RT to treat benign disease is not well established and up to date often regarded with great skepticism. However, the European Society for Radiation Oncology (ESTRO), despite some hesitation, still regards the wide field of non-malignant disorders as potential clinical research area [3, 4].

Nowadays in Germany, about 50.000 patients were treated for „benign” or „non-malignant diseases” resp., functional disorders “ by irradiation [5, 6, 7, 8]. The successful treatment will mostly result in a preservation or recovery of quality of life, e.g. by pain reduction and/or improvement of formerly limited function.

Depending on the type of institution (private practice, community or university hospital) and geographical position (primarily eastern or western German territories, nowadays more rural or city regions) the non-malignant indications for radiotherapy cover about 10% to 30% of all treated patients, how it was shown by different patterns of care studies [1, 5, 6, 7, 8]. Under the currently more than 300 active radiotherapy facilities in Germany, there is not a single one, which does not offer radiotherapy for benign diseases [5, 6, 7, and 8].

These developments of the last two decades must be regarded as an undoubted „Renaissance“ of a therapy, which was considered as nearly irrelevant about 25 years ago. But at the at the beginning of the 90ies and particularly after the opening of the „Iron Curtain“ between East and West Germany the radiation treatment of non-malignant disorder had a quite unexpected booming revival [1, 2, 6, 7, 9]. There was a lot of clinical experience and perception gained in years in Eastern Germany, which were systematically discussed and evaluated by modern scientific debate and justification since 1989 [1, 2, 9, 10] resulting in the demand of performing randomized clinical trials to improve the available levels of evidence [2, 9]. Recently, a number randomized clinical trials were carried out and published [11, 12, 13, 14, 15].

The autonomous development of the topic was especially promoted since 1995 by the independency German Society of Radiation Oncology (DEGRO) and by and by regular and systematic continuous education. The nowadays common radiotherapy indications in non-malignant diseases, which are quite different from the historic indications, were assured from 1996 to 2000 in the professional group by consensus-process and a guideline in the scientific society [2, 5, 6, and 7]. These clearly defined indications are definitively clinical relevant, what can be seen that the number of treated patients nearly doubled between 1999 and 2004 (Table 1) and even new investments were done in the so called „out-dated” ortho-voltage technique. Until today this trend is continuing and can be probably extrapolated to the near future. The largest share of all indications for radiation treatment is painful degenerative joint disorders [1, 5, 6, and 7].

Although RT of benign conditions is usually carried out with shorter schedules and with much lower single and total RT doses than those applied to malignant tumors, the radiation oncologist has the same duties in quality and delivery of treatment: carefully preparing, carrying through, completely documenting, and consequently following up the whole treatment process with the utmost care and attention, as it is the case with patients suffering from malignant disorders. Given this similar medical and jurisdictional background, there is also a special need for treatment guidelines for RT of benign diseases similar to those developed for most malignant disorders [1, 2, and 16].

The last written guidelines for the treatment of non-malignant diseases in Germany were developed and published by the German Cooperative Group on Radiotherapy of Benign Diseases (GCG-BD) in 1999. It was a consensus guideline based on several patterns care studies carried out by the GCG-BD [2, 5].

Table 1: Development of Radiotherapy for benign Diseases in Germany from 1999 to 2004

Non-malignant Diseases (Treatment Groups)	St&O 1999 [6]	St&O 2004 [7]	Increase
Inflammatory	456	503	10.9 %
Degenerative	12600	23754	88.5 %
Hyperproliferative	972	1252	28.8 %
Functional/Other	6099	10637	74.4%
Overall	20082	37410	86.3%

Since then, new dose concepts and treatment techniques have been introduced and well accepted in the clinical practice [1]. Thus, the update of these guidelines was a necessary, adequate and reasonable implementation process. These new guidelines on radiotherapy for benign disorders combine a national consensus process and a systematic evidence-based approach.

OBJECTIVES OF THE STUDY

To develop consensus guidelines for radiotherapy (RT) of benign diseases by the implementation of an S2e clinical practice guideline.

METHODS

The consensus process for the update of the guidelines was started in 2011 and completed in 2014. It started with the formation of a scientific panel including several experts from selected academic and non-academic radiotherapy departments and private RT practices, as well as members from the established German Cooperative Group on Radiotherapy of Benign Diseases.

The following diseases and topics were covered by the guideline: Physical and radiobiological background, radiogenic risks, lymph fistulas, bursitis trochanterica, Gorham-Stout syndrome, vertebral hemangiomas, pigmented villonodular synovitis (PVNS), heterotopic ossifications, osteoarthritis of large and small joints, Morbus Dupuytren, Morbus Ledderhose, desmoid tumors (aggressive fibromatosis), plantar fasciitis (painful heel spurs), Peyronie's disease, painful elbow syndrome and shoulder syndrome, keloids and endocrine orbitopathy.

Clearly, the guideline cannot encompass all non-malignant diseases as their number may be innumerable [1] and even the textbook of Order and Donaldson compiles more than 100, indications for RT of benign conditions [17]. But it comprehends the clinical most relevant diseases, which are most important for decision making of the radiation oncologist [16]. At the next update of the guideline, a complementation with other disease entities is planned, so it will be a growing tool for counseling. Explicitly excluded from these guidelines were benign brain tumors or other brain lesions, because recommendations for radiation treatment of these disorders are covered by other clinical guidelines.

All available data from the literature and pertinent information from clinicians and patient groups were systematically reviewed, and key articles of high scientific impact were identified. The level of evidence (LOE) for each disease entity was determined and finally graded according to the known international recommendations [2] (Table 2 and 3).

Table 2: Levels of Evidence according to the Oxford Centre of Evidence Based Medicine [18]

1a	Evidence from meta-analysis of randomized controlled trials
1b	Evidence from at least one randomized controlled trial (with narrow Confidence Interval)
1c	All or none
2a	Evidence from at least one controlled study without randomization
2b	Evidence from at least one other type of quasi-experimental study
2c	"Outcomes" Research; Ecological studies
3a	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
3b	Individual Case-Control Study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Table 3: Grades of Recommendation according to the Oxford Centre of Evidence Based Medicine [18]

A	offer (should performed)	Consistent level 1 studies
B	offer (shall performed)	consistent level 2 or 3 studies <i>or</i> extrapolations from level 1 studies
C	offer (might performed)	level 4 studies <i>or</i> extrapolations from level 2 or 3 studies
D	Decision is open	level 5 evidence <i>or</i> troublingly inconsistent or inconclusive studies of any level

There after the expert panel (Table 4) prepared a first consensus draft that was opened to propositions and comments from all participating institutions according to an established Delphi-process and during two consecutive national radiotherapy conferences related to these topics.

Table 4: Composition of Guidelines Expert Panel

Prof. Dr. med. I. A. Adamietz	Herne
Dr. rer. nat. A. Block	Dortmund
Prof. Dr. med. H. Eich	Münster
K. Galonske	Soest
PD Dr. med. R. Heyd	Frankfurt
Dr. med. I. Jacob	Traunstein
Prof. Dr. rer. nat. H. Jung	Hamburg
Prof. Dr. med. L. Keilholz	Bayreuth
Prof. Dr. med. O. Kölbl	Regensburg
Prof. Dr. med. O. Micke	Bielefeld
PD Dr. med. R. Mücke	Lemgo
Prof. Dr. rer. nat. R. Müller	Erlangen
Prof. Dr. med. M. Niewald	Homburg/Saar
PD Dr. med. O. Ott	Erlangen
Prof. Dr. med. R. Panizzon	Lausanne, CH
Prof. Dr. med. R. Panizzon	Regensburg
Dipl.-Phys. B. Reichl	Weiden
Dr. med. G. Reinartz	Münster
Prof. Dr. rer. nat. F. Rödel	Frankfurt
Prof. Dr. med. U. Schäfer	Lemgo
Prof. Dr. med. B. Schilcher	Soest
Prof. Dr. med. M. H. Seegenschmiedt	Essen
PD Dr. med. H. Weitmann	Bad Hersfeld

After completion of the discussion, a final version of the updated guideline was written by the expert panel, presented and finally approved by the executive committee of the German Society of Radiation Oncology (DEGRO).

RESULTS

These written guidelines consist of the following components: (1) the physical and radiobiological basis for RT [19], (2) considerations regarding the risks of low radiation doses, (3) general indications for the application of RT and (4) special treatment concepts for benign conditions except benign brain tumors.

The development process of these clinical guidelines followed the national and international standards [20, 21, 22, 23, 24, 25, 26, 27, 28]: They are based on a consensus process as well as an evidence-based methodology, so that an S2e guideline resulted, which were developed according to the standard of the Association of the Scientific Medical Societies in Germany (AWMF) by formal evaluated (evidence levels) statements of scientific literature by a systematic collection, selection, and review of literature [25, 26, 27, 28].

An overview of different indications, levels of evidence and resulting recommendations are given in table 5.

These practice guidelines also cover some rare benign disorders and in future updates, even more indications will be covered. This is of particular importance, because the treatment of rare disorders is a growing field in radiotherapy for benign disorders. Nevertheless, the radiotherapy for rare benign disorders are directly linked to special clinical and therapeutic problems, in particular, the low number of treated patients and low experience with the special indications. These problems lead to a special scientific uncertainty, which is typical for research on rare benign disorders.

There are over 150 published indications for radiotherapy (RT) in non-malignant disorders, which are more or less accepted in the scientific literature [17]. A large portion of these indications has a very low incidence and the number of published cases is much below 200. Therefore, decision making in radiotherapy is often difficult and prospective controlled trials are out of sight. Statistical analysis requires larger patient series to support special treatment advice.

To overcome this problem the GCG-BD established a registry for rare benign diseases to collect and to analyze RT concepts, clinical outcome and follow-up data in Germany. The aim is to create a larger database, which may serve as an open information center for clinical decision making and indication set-up, and as a source for national and international publications. A standardized documentation form was developed by a modified consensus system. Data collected include demographic data, prior, history, disease and treatment specific parameters, RT and target volume concepts, clinical outcome and long-term follow-up. The completed forms were centrally collected in the registry. In case of incongruent or incomplete data, the institutions will be directly contacted by the registry committee.

**Table 5: Levels of Evidence and Radiotherapy Recommendations
(PCS-Patterns of Care Study; ReS-Retrospective Study;
DOS-Dose Optimization-Study; RS-Randomized Study)**

Specific Disease	Number of Studies	Highest Level of Evidence	Highest Level of Recommendation	Main Indication Group
Painful Arthrosis of the Knee Joint	23	2c (PCS)	B (shall performed)	> 3 months inflammatory signs, non-responding to other therapeutic measures
Painful Arthrosis of the Hip Joint	19	4 (ReS)	C(might performed)	> 3 months inflammatory signs, non-responding to other therapeutic measures
Painful Arthrosis of Hand and Fingers	17	4 (ReS)	C(might performed)	> 3 months inflammatory signs, non-responding to other therapeutic measures
Painful Shoulder Syndrome	16	2c (DOS)	B (shall performed)	> 3 months inflammatory signs, non-responding to other therapeutic measures
Painful Elbow syndrome	22	2c (DOS)	B (shall performed)	> 3 months inflammatory signs, non-responding to other therapeutic measures
Painful Trochanteric Bursitis	2	4 (ReS)	C(might performed)	> 3 months inflammatory signs, non-responding to other therapeutic measures
Painful Plantar Fasciitis	22	1b (RS)	A(should erformed)	> 3 months inflammatory signs, non-responding to other therapeutic measures
Morbus Dupuytren	12	2c (DOS)	B (shall performed)	early stage
Morbus Ledderhose	6	4 (ReS)	C(might performed)	painful detectable or palpable lesions
Keloids	2	2c (PCS)	B (shall performed)	affected palpable lesions after surgical excision
Peyronie's Disease	21	2c (PCS)	B (shall performed)	soft localized penile plaques
Desmoid Tumors	22	4 (ReS)	C(might performed)	complete inclusion of the involved structures
Symptomatic Vertebral Hemangiomas	66	2c (PCS)	B (shall performed)	Painful vertebral hemangiomas
Pigmented Villonodular Synovitis (PVNS)	3	2c (PCS)	B (shall performed)	affected synovial cells
Gorham Stout Syndrome	6	2c (PCS)	B (shall performed)	Symptomatic cases (affected bones)
Heterotopic Ossification	5	1b (RS)	A(should erformed)	after hip joint replacement pre- or postoperative
Graves Orbitopathy	19	2c (DOS)	B (shall performed)	ophthalmologic symptoms of early and advanced inflammatory phase

In the last 15 years, a network of more than 20 closely cooperating centers has been established. Moreover, 56 other centers reported cases to the registry. Up to now the following rare non-malignant diseases have been systematically registered and evaluated: Gorham-Stout syndrome(11), giant hemangiomas(11), including Kasabach-Merritt syndrome(2), neurosaroidosis(9), gliomatosis cerebri(12) (figure 1), lymphangioliopoma(1), lymphangioma(9), systemic mastocytosis (1), aneurysmal bone cysts(10), lethal midline granuloma(1), pseudotumor orbitae(24), Schimmelpfennig-Feuerstein-Mims syndrome(1), cerebral dermoid cyst(1), Scleredema Adultorum Buschke(1), Langerhans cell histiocytosis(76), desmoid tumors (68), and giant cell tumors (45) and others.

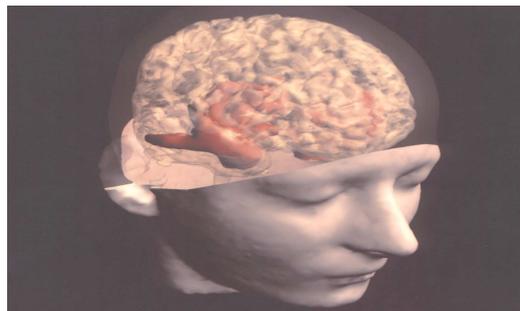


Figure 1: The Guideline also covers the Treatment of Rare Benign Disorders These Diseases are often linked to a Special Scientific Uncertainty, Due to the Low Number of Treated Patients and the Low Experience with the Special Indications

Patterns of care studies for special indications have been successfully performed to achieve a better overview of these diseases. More than 400 inquiries per year to the registry of rare benign disorders has been the word out, but it was only possible to document about one-fourth of cases with an adequate follow-up. It is crucial to improve the quantity of follow-up data to maintain the registry as a living tool for counseling in difficult rare cases. During the last 15 years, it was possible to document data of 568 patients in the registry. A close cooperation with the international rare cancer network has also been successfully established.

Therefore, the German Registry of Rare Benign Disease is a growing and a very useful tool to collect cases suffering from rare non-malignant disorders in which radiotherapy has been considered as a possible treatment. It may improve treatment decisions on the basis of larger clinical series. The use of standardized international documentation forms could broaden the access to this registry to a more international database, as the registry is open for access and data input from throughout of the world. Besides treatment details and outcome analysis, correct diagnostic assessment is of utmost importance to streamline clinical pathways and select the adequate therapy. With a growing number of rare cases, this data network will also gain new experiences and advance knowledge with regard to the best diagnostic assessment and optimal therapy.

Overall, these current clinical practice guidelines are embedded in the quality assurance approach of the German Society of Radiation Oncology (DEGRO), which is reflected by the implementation of several other clinical practice guidelines [29] and the QUIRO-Study with the evaluation of time, attendance of medical staff, and resources during radiotherapy for different disease other radiotherapy procedures [30].

DISCUSSIONS

Many factors enter into radiotherapy treatment decisions. What alternatives are available? What does the evidence suggest about the potential benefits and harms? How firm is the pertinent evidence? Is there enough reason to adjust expectations based on a particular patient's age, gender, race, co-morbidities, or other attributes? Are there any social, economic, or other practical considerations that could affect the results of a particular care option? [22, 23, 24]

The guidelines are intended to provide a systematic aid and frame work for making complex medical decisions. When rigorously developed using a transparent process that combines scientific evidence, clinician experiential knowledge, and patient values, guidelines have the potential to improve many clinician and patient healthcare decisions and enhance healthcare quality and outcomes. The present state of guideline development has yet to fully meet this promise [22, 23, and 24].

According to the Association of the Scientific Medical Societies in Germany (AWMF) a good clinical guideline is characterized by [25, 26, 27, and 28]:

- A representative developing group
 - Interdisciplinary, independent experts
- Systematic evidence-basing
 - Searching for the best available studies and knowledge
- Clinical assessment
 - Relevant impact on the daily routine
 - Practicability (e.g. extrapolation, import)
- Structures consensus process
 - Reproducible, manipulation free

Overall, it can be stated the development and the implementation of these clinical practice guidelines for

radiotherapy of benign diseases , in general, met these criteria above [2, 16].

Some further critical remarks should be taken into account when discussing guidelines and in particular, these guidelines on radiotherapy for benign diseases: Guidelines are systematically developed decision aids for an adequate medical approach to specific health problems. They represent a consensus of different experts after a defined and transparent procedure. Guidelines are scientifically based and practice-oriented recommendations. They are orientation guides in the meaning of decision corridors, from which can and must be deviated in well-founded cases. Guidelines must be regularly reviewed on their up-to-datedness and where necessary updated. The term directives must be definitively distinguished from guidelines and should be used for regulations of practice or omission, that are consented, written and published by legally authorized institutions, are obligatory for the for this institution and non-observance is followed by defined sanctions [23, 24, 25, 26, 27, 28].

At the moment, the communication level of physicians has already shifted to abstract discussions of guidelines, inducing per the preference for pre-defined clinical decisions. The inconsistencies of evidence definitions, together with the overwhelming number of guidelines and providers thereof, burden medical reasoning with superfluous complexity, and contributing to the development of cook-book mentality. In the clinical practice, it may be necessary to reduce the impact of guidelines to a degree that remains compatible with patient interests and economy. In this field, prospective controlled outcome registries may provide a control for over- and faulty regulation. Clinical professionalism should be characterized in parallel by a critical implementation of evidence-based medicine and a necessary degree of independent reasoning [31, 32].

Nevertheless, clinical practice guidelines are not intended to restrict the medical autonomy of decision and even so it is otherwise suspected, at the moment they are not legally binding [33].

CONCLUSIONS

Radiotherapy for benign, non-malignant diseases is an important and growing topic of radiotherapy.

In summary, written evidence-based consensus guidelines for RT of benign diseases have been updated in 2014 and brought into publication by means of an expert panel including all members of the German Cooperative Group on Radiotherapy of Benign Diseases.

These guidelines may serve as a starting point for continuous quality assessment, future clinical research including the design of prospective clinical trials, and outcome research in this important field of radiotherapy.

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