GUIDELINES IN RADIOTHERAPY

Radiotherapy for benign diseases

Specialist group-specific evidence-based S2e guideline of the German Society for Radiation Oncology (DEGRO)

Version 3.0 from 19.11.2022

DEGRO-AG "Radiotherapy of Benign Diseases"

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Content

1 Information and introduction

Special note

Medicine is subject to a constant process of development, so that all information in this guideline can only correspond to the state of knowledge at the time of its preparation. The greatest possible care has been taken with regard to the recommendations given on the dosage and technique of radiation therapy. Nevertheless, the person administering ionizing radiation for therapeutic purposes is ultimately responsible and should consult a specialist in case of doubt. Discrepancies that come to light while reading these guidelines can and should be reported to the guideline editors. In this guideline, registered trademarks (protected product names) are not noted as such, and an absence of a corresponding reference does not necessarily imply that the name given is the free trade name.

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1.2 Introduction

1.2.1 Foreword

The field of “radiotherapeutics” is generally associated amongst physicians and the public with the treatment of malignant diseases. This perception excludes the radiation treatment of a heterogeneous spectrum of nonmalignant diseases that originally predominated in the early days of “radiotherapeutics” and have continuously been treated in German-speaking countries over the last 100 years [561,708].

In the meantime, tens of thousands of patients are treated with radiotherapy in Germany each year for “benign” or “nonmalignant diseases” or “functional disorders” [692,693,701,705]. Taking the results of a research report on radiation protection from the German Society for Radiation Oncology (DEGRO) as a basis [636], in 2016, more than 250,000 completed treatment cycles were performed for benign diseases (including benign tumors) in Germany.

Treatment success often leads to the preservation or improvement of quality of life, e.g., through pain reduction or improvement of previously limited function(s). Depending on the type of institution and the geographic location, indications for radiotherapy comprise between 10% and 30% of the patient clientele, as shown by various patterns of care studies in Germany [693,695,701,705]. Of the more than 300 currently active radiation therapy facilities in Germany, each one offers radiation therapy for benign diseases.

This development has been promoted since 1995 through independent action as a radiation therapy professional society (DEGRO e.V.) and systematic further education and training in the field. The indications for nonmalignant diseases commonly used today were determined within the specialist group from 1996 to 2000 by a consensus process and established in a jointly developed guideline within the scientific specialist society [692,693,701]. The fact that the clearly defined clinical indications came to be viewed as a relevant basis for treatment is shown by the doubling of the number of patients receiving treatment for benign conditions from 1999 to 2004 and by new investments in orthovoltage technology. This trend continues today and is likely to continue in the near future because of the increasingly aging population in Germany and associated increase in patients with nonmalignant indications for radiation therapy. Most such indications involve degenerative painful joint diseases [692,701,705].

The uptake of ionizing radiation in low-to-medium and occasionally high doses for nonmalignant diseases represents an extremely interesting, multi-layered medical chapter. New indications have been systematically established, others have disappeared, and still others have survived from the outset [378,465,708].

1.2.2 Objective, research question, and audience of this guideline

The 2022 guideline presented here should be seen as a detailed update of the guideline first published in October 1999 and extensively updated in 2018. It takes into account the broad spectrum of indications for radiotherapy of nonmalignant diseases in 2022 in German-speaking countries.

This is a S2e guideline. It was developed from formally assessed statements in the scientific literature and deliberated and approved in a formal consensus process.

The guideline is to be regarded as specific for specialist groups and therefore primarily addressed to specialists in radiotherapy, residents undertaking further training to become specialists in radiotherapy, and radiologists involved in radiotherapy. More broadly, this guideline is also intended to offer information for therapy decisions to all groups of specialists.

After topics were assigned to experts in 2009 and 2010, open working group meetings were held in 2011 for the purpose of approving the guideline contributions. In 2013, the final guideline was published, with an update in 2018. In 2022, a call for experts was made to update the contributions again. The updated contributions are marked separately in the current version.

The guideline presented here is intended to provide the basis for action-relevant medical decision-making processes. The guideline is intended to contribute to ensuring appropriate health care with regard to radiotherapy for nonmalignant diseases and thus to form the basis for individually adapted, quality-assured, economically balanced therapy.

1.3 Methodology basics (S2e guideline)

A systematic search, selection, and evaluation of scientific evidence (‘evidence’) on the relevant clinical questions was conducted, as follows:

1. Systematic search for guidelines on the same topic and to check whether individual recommendations can be adopted or adapted from them

2. Literature search according to a largely standardized procedure (PubMed, MEDLINE, and Cochrane Library)

3. Presentation of the selection criteria for the evidence, in particular reasons for exclusion

4. Summary and evaluation of the evidence

5. Establishing the strength of the evidence (level of evidence) and the strength of the recommendation (level of recommendation)

The guideline is divided into general and specific parts.

The introductory part of this guideline includes explanations of the physical principles, radiobiological mechanisms, and radiogenic (radiation-induced cancer) risks of radiotherapy for nonmalignant diseases.

In thesite-specific guidelines the individual indications are presented. The authors followed a uniform scheme that takes into account the definition, epidemiology, etiology and pathogenesis, diagnostics and differential diagnostics, staging, and general therapy options for each disease. For each clinical picture, specific radiotherapeutic aspects, such as indication, rationale, target volume definition, dose concept, and irradiation technique, along with aspects of radiation protection, are presented.

The indications addressed in the special section represent the broad spectrum of common and rare benign diseases that the practicing radiation therapist in Germany may encounter for treatment. This selection is not claimed to be complete, and we note that the expert group decided by consensus not to include benign diseases of the central nervous system in this guideline.

The guideline is to be updated at regular intervals (e.g., every 3 or 5 years). We would like to invite interested parties to actively participate in this process.

1.4 Scheme of evidence grading

Evidence grading was based on the Oxford Centre of Evidence-Based Medicine scheme for disease therapy [470]. The scheme is presented in Table 1.

1a:	Systematic review (with homogeneity of study results) of randomized controlled trials
1b:	Single randomized controlled trial (with narrow confidence interval)
1c:	All-or-nothing principle
2a:	Systematic review (with homogeneity of study results) of cohort studies
2b:	Single cohort study or low-quality randomized controlled trial (e.g., <80% follow-up)
2c:	Outcome studies, ecological studies
3a:	Systematic review (with homogeneity of study results) of case-control studies
3b:	Single case-control study
4:	Case series (and cohort and case-control studies of low quality)
5:	Expert opinion without explicit critical evaluation or based on physiology or laboratory results

Table 1. Level of evidence based on the Oxford Centre of Evidence-Based Medicine scheme for the therapy of diseases.

1.5 Recommendations and their grading

The grading of the recommendations also was based on the Oxford Centre of Evidence-Based Medicine's scheme for the treatment of diseases [470].

Grade A	Is to be implemented	Evidence level Ia and Ib
Grade B	Should be carried out	Evidence level II or III
Degree C	Can be performed	Evidence level IV
Grade D	Decision is open	Evidence level V

Table 2. Grading of recommendations based on the Oxford Centre of Evidence-Based Medicine scheme for disease therapy.

1.6 Evidence rating

At the end of the specific articles, a level of evidence rating is followed by the level of recommendation for performing radiation therapy, for instance:

Radiotherapy should be performed, if indicated.

Evidence level 2c, recommendation level B

2 Limitations (Update 2022)

This guideline provides recommendations for radiotherapy of numerous benign diseases. Based on analysis of the available literature pool, the best available evidence was used. The authors are aware of certain limitations to this approach. For example, the gold standard in pain management research is the double-blind, placebo-controlled trial [359,740]. On the important topic of radiotherapy for pain relief in benign conditions, however, only a few studies have been conducted with this design, often with limited quality and/or number of cases [702]. Unfortunately, none of these studies has demonstrated an additional radiation-specific effect compared with sham irradiation [256,275,524,554,613,775]. Thus, the objection of some critics that, especially in osteoarthritis, low-dose pain irradiation is also a “powerful placebo effect” [54,256] still cannot be invalidated.

This limitation should not diminish the value of this guideline. Every author has worked with great care on their respective subject area and engaged in debate about it. The result is a guideline for radiation therapy of benign diseases that represents the highest available consensus within the field’s professional society. In other European countries, which so far have been rather cautious in selecting indications compared to Germany, radiotherapy of benign diseases also is increasingly coming into focus. For example, the UK’s Royal College of Radiologists updated its recommendations for radiotherapy of various benign diseases in 2022. In this regard, in an editorial published in 2022, experts from Italy and England proposed levels of evidence according to the Oxford Centre of Evidence-Based Medicine for the therapy of diseases [207].

The observation of German folklorist and poet Johann Peter Hebel, writing more than 200 years ago, is still valid: “As much as one knows, one would like to know even more.”

3 General aspects

3.1 Basic physics concepts

3.1.1 Introduction

For the treatment of inflammatory and hypertrophic processes as well as the treatment of benign tumors, ionizing radiation is used, which can be delivered in the form of X-rays, gamma rays, electron beams, or particle beams.

Processes used
The physical interaction of radiation with matter takes place in the form of the photoelectric effect, the Compton effect, and pair formation. Ionizing radiation causes changes in biological matter in the form of genetic changes, introduction of cellular defects, and changes in metabolic processes. Radiation therapy treatment of benign diseases is performed with the same equipment and according to the same principles and procedures as in radiation oncology [632,702].

An evidence level according to evidence-based medicine cannot be determined for the physical parameters of the irradiation devices. For this reason, recommendation level B is defined for the appropriate choice of irradiation device. Depending on the location of the target volume and thus the selected depth of dosage, the parameters listed in Table 3 should be used for treatment.

3.1.2 External beam radiotherapy

Radiation therapy of nonmalignant diseases can be performed by using medical electron linear accelerators (energy range 6–18 MeV), Co-60 gamma irradiation devices (1.17 and 1.33 MeV), and X-ray therapy devices.

3.1.2.1 X-ray equipment

The X-ray therapy systems are set up with kilovoltage energies – superficial and orthovoltage units generally up to 300kVand a half-depth therapy unit (from 100 kV) [157, 158]. The dose distribution in air is neither symmetrical nor uniform in X-ray therapy equipment. The largest deviation occurs in the direction parallel to the tube axis and depends on the anode angle and the heel effect. The anode angle is chosen so that these two effects are in balance, usually 30° for orthovoltage devices and 45° for surface therapy devices [426]. For an X-ray therapy device designed for a wide voltage range (50 kV to 300 kV), the anode angle is 30° [752]. To homogenize the radiation, filters made of aluminum, copper, or lead or combinations of aluminum, copper, and tin are used, which are inserted in coded filter holders.

For surface therapy, knowledge of the depth dose distribution is often of secondary interest as long as no organ at risk is located below the target volume. More often, a very uniform dose distribution is required in this region, which can be determined by measurements of the transverse profile. The penumbra must be known precisely if risk organs, such as the eye, are located in the immediate vicinity of the radiation field.

If deeper tissues are to be irradiated with the Orthovolt device, accurate information on the depth dose profile is indispensable in addition to the transverse profile analysis at these depths.

Tubes of 25 to 50 cm in length are used to better delineate the irradiation fields, which are placed on the skin. Typical tube field sizes are 4×6, 6×9, 8×10, 10×15, or 15×20 cm^2. In addition, there are open round tubes from 1 cm in diameter.

Modern X-ray therapy systems with modern switching and safety technology meet all of today's requirements in terms of handling and versatility and are suitable for both soft and hard beam therapy.

The radiation quality of an X-ray therapy system is characterized by:

a) Tube voltage
b) Total filtering
c) 1^{st}- and 2^{nd}-half thickness

The half-width thickness (HWD) is the layer thickness of a reference material (aluminum or copper) that reduces the air kerma power in the narrowly focused beam to half (s1), and the 2nd HWD reduces it to a quarter (s2). The units used are mm Al (up to 120 kV) or mm Cu. Both HWD s1 and s2 are measured in a narrow beam behind the total filter. These measurements are complex and require high-purity aluminum and copper, which are correspondingly expensive to purchase. The AAPM-TG 61 Report [490] states that the indication of the 1^{st}- and 2^{nd}-half thickness can be valid for a wider voltage range, but the same voltage level using different X-ray therapy devices can lead to different HWD. It is suggested that in addition to the HWD, the voltage level and the ratio of absorbed dose values at 2 cm and 5 cm of water depth should be given. As an alternative method of labeling radiation quality, the DGMP Report No. 15 suggests measurements in water at depths of 5 cm and 10 cm or a water-equivalent solid phantom at a constant focus-measurement distance of 50 cm and field size 125 cm^2:

QR = M10/M5

From this, the corresponding half-value thickness s1 in mm Cu can be determined for voltages above 100 kV [157].

Dosimetry should be performed with an ionization chamber calibrated to indicate absorbed dose to water or an ionization chamber calibrated freely in air to indicate air kerma in accordance with DIN 6809-4 [163]. The Farmer chamber is considered the gold standard for determination of HWD and measurement of absolute dose [490].

Scattering effects are of great importance in kV radiation. The backscatter factor (BSF) plays a specific and crucial role, which also must be considered in therapy planning. The BSF is defined as the ratio of the air kerma at the surface of a water phantom to the air kerma at the same position measured free in air [631].

BSF varies as a complex function of X-ray energy spectra, field size, source–surface distance, and different phantom materials [327]. The uncertainty around experimentally determined BSF stems from the change in the energy spectrum of the kV radiation as it transitions from air to phantom and in the energy response of the detector, as well as from perturbations in photon fluence. Theoretical data show that the energy transfer coefficient µtr, however, undergoes only a change on the order of 10% [426]. The BSF maximum is at HWD 1.0 mm Cu, which corresponds to a voltage step of 150 kV. Monte Carlo simulations for 120–200 kV of radiation resulted in deviations of less than 3% from the published RSF data of the AAPM-TG 61 report [539]. It is recommended that these BSF data be used for irradiation planning [327].

For the medical physicist (MPE) making their own measurements, care must be taken to use the correct phantom material. PMMA and RW3 as backscatter material can lead to deviations in BSF measurements of up to 7% at 50 kV, although the errors become smaller at higher beam energies.

Irradiation planning
The MPE cannot use a treatment planning system to create the physical radiation plan and needs tables that allow hand calculations for monitoring units or irradiation time.

The dose applied to the patient at a given X-ray energy depends on a number of factors [426]:

a) Depth dose value at reference point
b) Tube
c) Effective field size after shielding measures
d) Size of air gap between lower edge of tube and patient surface

Tables or graphical progressions are required for the following quantities:

a) Dosage table
b) Depth dose table
c) BSFs
d) Backscatter buildup effect

Dosing for nonmalignant disease, as in radiotherapy in general, should be based on the reference point according to ICRU 50/62 [348,350]. A maximum dose inhomogeneity of -5 to +7% is in principle desirable but often not achievable with radiotherapy equipment because of the steep dose gradients. As a rule, normalization is performed to the surface, and the radiation quality must be selected so that the target volume is still enclosed by the 90% isodose [327]. This condition can be fulfilled in the field of surface therapy for target volumes at a depth of up to 5 mm, but only to depths of about 5 cm in half-depth therapy up to 400 kV. Therefore, disease foci deeper than 5 cm below the skin should not be subjected to X-ray therapy. The dosage dose, maximum dose, reference dose, and dose minimum in the target volume should be recorded. For opposed field techniques, the contribution of both fields along the central beam must be taken into account according to the depth dose distribution and added when determining the maximum dose to the skin.

In addition, the use of shielding or collimating measures (e.g., in the form of lead shields) may be necessary, depending on the size of the target volume. For lead shielding, lead equivalent values, which are considered sufficient for radiation protection in X-ray diagnostics, should not be used as a guide [164]; instead, the specifications in megavoltage (MV) radiotherapy, which provide for shielding of 5 half-value layer thicknesses, should be applied [338]. Lead shields for limiting the useful beam should be 0.15 mm thick up to 50 kV, 0.8 mm thick from >50 kV to 100 kV, 2.0 mm thick from 120 to 200 kV, and at least 4.0 mm thick from >200 to 300 kV [791]. When very irregular field shapes are formed with lead shields, a correction factor must be introduced for the output factors, which is the ratio of the BSFs of the irregular and the open field.

Due to its high atomic number (Z=82), lead is an excellent shielding material for use with healthy tissue. However, shielding with lead leads to a reduction in backscatter and consequently a dose reduction at the surface. This dose reduction is a function of field size, lead thickness, energy, and depth of lead shielding. The largest decrease in surface dose has been observed at X-ray energies with generation voltages of about 100 kV [327]. Decreases in surface dose also are caused by deeper bones and air pockets. It is therefore recommended to estimate the dose reduction by taking into account the various influencing factors.

If lead is brought behind the target volume, e.g., in irradiations of the lip or ear, very significant perturbations in the dose distribution occur at the interfaces between water/soft tissue and materials with high atomic number. At such interfaces, changes in BSF of up to 15% may occur. In these cases, it is advisable to coat the surface of the lead with material of a lower atomic number.

In the case of field recesses with lead, the therapy beam can be contaminated with low-energy electrons, which can lead to a doubling of the dose at the surface with 150 kV radiation and even to a tripling with 300 kV. This problem can be remedied by wrapping the lead shields or the tubes with thin plastic foil.

The MPE is responsible for preparing the depth dose curves and dose tables. Dose distribution documents supplied by the manufacturer should be verified prior to use. For determining BSF and necessary correction of the backscatter build-up effect, the MPE will often have to refer to tabular works that give these values for the respective radiation quality in half-value thicknesses of aluminum and copper.

For the practical execution of irradiation planning, the MPE will need the radiation quality in half-value thicknesses of aluminum and copper. This information allows for relative depth dose values to be obtained from the tables of the BJR 25 [112] (note that it is better to use self-measured ones). The BSFs are already included if the irradiated body region is thicker than 10 cm, so that the contributions from the backscatter are saturated. The measurement regulation for calibration of an X-ray therapy device therefore also requires a minimum thickness of 10 cm for the backscattering material. At lower thicknesses, the backscattering is not yet in saturation, and the surface dose is correspondingly lower. This effect increases up to about 150 kV and then decreases again at even higher voltages. At low thicknesses of a few centimeters, the effect can lead to underdoses of up to 30% [825]. In these cases, the MPE should make a dose correction using tables [72,157]. Another possibility, e.g., for irradiations of the hand, is to place the patient with additional backscatter material under the hand [327]. Dosimetry should then also be performed with this support.

In addition to backscattering, sideways scattering occurs. For field sizes of approximately 6×6 cm and larger, sideways scattering can lead to a lack of correspondence between tube boundaries and field boundaries, according to ICRU 50 [348], but the 50% isodose is shifted about 2-3 mm outwards. The effect can be observed for all beam qualities from 50–300 kV and should be taken into account when determining the safety margin; it is particularly critical for irradiations in the immediate vicinity of the eye. It should be noted that shielding measures with lead at critical structures such as the lens of the eye considerably reduce the primary radiation, but because of scattering effects, the planned dose can increase by 25%.

Although muscle and fat tissue change the depth dose distribution by less than 5% compared with values in water, energy transfer by the photoelectric effect at photon energies up to about 200 keV leads to overexposures of bone of up to 700% [157]. The “effective photon energy” is thus required if interaction coefficients from tables for monoenergetic photons are to be used for dose and depth dose distribution corrections in the passage of X-rays through bone tissue. This energy is defined as the energy of a monoenergetic photon radiation having the same first-half thickness in copper as the polychromatic radiation present. It is obtained by calculating the average mass attenuation coefficient for copper from the following:

$$\mu/p = \ln 2/ (p * s)1$$

interpolated from corresponding tabulated mass attenuation coefficients for monoenergetic photons [631].

The linear attenuation coefficient is tabulated for the individual tissues for monoenergetic photon energies [157]. The attenuation law can be used to correct the depth dose distribution in bone by calculation or to estimate overexposure from graphical plots of relative mass energy absorption versus photon energy.

Another way to obtain the surface dose for a specific tissue (medium) from the surface dose in the Water phantom is a conversion with the following correction factor:

$$C_w^{med} = \frac{B_{med}}{B_w}\left[\left(\frac{\bar{\mu}_{en}}{\rho}\right)_{med,w}\right]_{air}$$

with $\left(\frac{\bar{\mu}_{en}}{\rho}\right)_{med,w}$ as the ratio of the mass energy absorption coefficients from the medium and water averaged over the primary photon spectrum free in air and Bmed and BW as BSFs for the medium and water, respectively [490]. Correction factors for different tissue types are listed in the AAPM-TG-61 report.

Quality control
Field control images at the linear accelerator have been standard in radiation therapy with ultrahard X-rays for decades, and for about 20 years, they have been performed mainly with electronic portal imaging systems. For irradiation of benign conditions such as Dupuytren's disease (DD), epicondylitis, fasciitis plantaris, and painful shoulder syndrome, field control images with imaging plates at different voltage levels have been attempted with humanoid phantoms on an X-ray therapy unit (20–200 kV). Voltage level had to be reduced somewhat compared with the therapeutic voltage level to obtain meaningful images for position control and documentation: from 40 kV to 20 kV for the hand and from 75 kV to 50 kV for the foot, elbow, and knee [73].

3.1.2.2 Gamma irradiation equipment
In some cases, Co-60 devices are still in use as gamma radiation devices. The energy of the gamma radiation emitted by radioactive decay of ^{60}Co is 1.17 MeV and 1.33 MeV. The procedure here is analogous to that of a linear accelerator.

3.1.2.3 Linear accelerator
In linear accelerators, electrons emitted from a cathode are accelerated in electromagnetic fields. Both the accelerated electrons themselves and the photons generated by deceleration when the electrons hit a target can be used.

Photons in the energy range of 6–18 MeV
Electrons in the energy range of 6–21 MeV

The treatment of benign diseases [632,702] is performed in keeping with the principles for treatment planning and implementation of radiation therapy of malignant diseases in radiation oncology [155,165,166,167,348,349,351,632,702,742]. The process is outlined below.

Determination of the target volume
After taking the patient's medical history and establishing the indication, the radiotherapist determines the clinical target volume (CTV). To take into account positioning inaccuracies, movement artifacts, and uncertainties in the determination of tumor volume, the planning target volume (PTV) is defined and used for radiation planning [155, 165,166,167].

Irradiation planning
Taking into account the CTV, its location, its proximity to radiation-sensitive risk organs, and available technical possibilities, an irradiation plan is prepared by a medical physics expert and a specialist in radiation therapy. Avoiding undesirable side effects in the surrounding tissue [168] requires isodose coverageof the PTV [155,166,167,168] as homogeneously as possible with the target dose at the reference dose point [156] and with as little dose as possible in adjacent risk structures and normal tissue.

This aim is achieved by selecting a suitable radiation type and energy (see Table 3), as well as a suitable irradiation technique. Depending on the disease type and target volume location, spreadsheets or computer-assisted radiation planning systems [155,347] are used. In many cases, the use of direct field techniques and opposing field techniques is sufficient in this context [156].

Nevertheless, the geometrical possibilities available through the use of linear accelerators, such as the easy-to-generate conformation of the radiation fields by means of a multi-leaf collimator or blocks, should be exploited especially when the target volume is directly adjacent to critical organs.

If necessary, other options for dose optimization, such as custom boluses, may be used.

When electron irradiation is used to treat near-surface target areas [351,702], it is necessary to fabricate special electron shields to limit the irradiation field. These shields must be appropriately dosimetrized before use on the patient.

Irradiation
To implement the irradiation plan and technique, the irradiation plan must be transferred to the patient and implemented for reproducible settings on the irradiation unit by means of removable skin markers on the patient. The following options are available for determining the isocenter of the irradiation plan and, if necessary, its field entry ports.

Setting on the device
For simple conditions, adjustments can be made according to anatomical criteria directly on the device after prior establishment of the reference dose point [155], diameter of the patient at the isocenter (if opposing techniques are used), and determination of the field size(s) to be applied. Control exposures, which check the setting accuracy (see 1.4.4 Quality control), are necessary.

Virtual simulation
Use of planning computed tomography (CT) is recommended for computer-assisted radiation planning and simultaneous determination of the isocenter of the radiation technique, using a traversable laser system and marking on the skin.

Simulation
An X-ray device can be used that has fluoroscopy capability with the same geometry and technical capabilities for setting the fields as the irradiation device. In this case, the selected irradiation technique is implemented by means of X-ray control on the simulator and appropriate markings of the space-fixed laser system, and field entry ports are applied to the patient's skin. The patient can then be adjusted and treated at the irradiation unit according to the attached markings.

Quality control
To control implementation of the irradiation plan and technique (verification [165]), it is necessary, among other things, to check the correct position of the radiation entrance ports of the individual irradiation fields and their field shape (field size and possible conformation). This quality check can be achieved by various methods using field control images, as described below.

Conventional films
This method involves recording of the individual irradiation fields on films during the irradiation session.

Portal imaging systems
Instead of films, electronic methods such as portal imaging systems can be used, which also use the radiation emitted by the accelerator during the irradiation session for imaging.

3.1.3 Brachytherapy

Objective
As a consequence of the inverse-square law, the dose falls steeply in the immediate vicinity of the radiation source. This circumstance is specifically exploited in brachytherapy to deliver a high dose directly to the target area, with good sparing of surrounding unaffected tissue [167].

One example of irradiating nonmalignant diseases is endovascular brachytherapy, in which radioactive fluids are injected into a balloon catheter, e.g., for restenosis prophylaxis. This method, which exclusively concerns vascular irradiation, is not discussed here.

Contact therapy
In contact therapy, radiation carriers are placed directly on the target area. Radiation therapists have abandoned the use of radioactive strontium derma plates for irradiations of the skin [354].

For ophthalmic applications, dome-shaped applicators with diameters from 5.2 to 12 mm are used. For irradiation planning, both the maximum dose at the surface and the first half-layer thickness in the tissue must be known. The depth extent of the superficial lesions to be treated should not exceed 10 mm.

Radionuclides
The beta emitter strontium-90 is used, which decays by emitting beta electrons with a low energy (0.546 MeV), with a long half-life of 28.7 years. High-energy beta electrons (2.27 MeV) are emitted by the daughter nuclide yttrium-90, which has a short half-life of 64 hours that is of no further significance because a decay equilibrium is established between strontium-90 and yttrium-90. The half-life layer thickness is 1.5 mm in water [250]. The final product is zirconium-90.

Another common ophthalmic applicator is ruthenium-106 (decays to rhodium-106), which has the advantage of higher beta electron energy (3.4 MeV) and greater half-layer thickness (3 mm) over strontium-90/yttrium-90 [250]. The half-life of 369 days is shorter than that of strontium-90 [157].

Palladium-103 (various gamma energies of 0.08–0.48 MeV) is used as a gamma emitter in ophthalmic applications, with a half-layer thickness of 16 mm and time of 17 days.

Irradiation planning
For irradiation planning, both the maximum dose at the surface and the first half-layer thickness in the tissue must be known. Irradiation time tables should be adjusted to radioactive decay annually for strontium-90 applicators, weekly for ruthenium-106, and daily for palladium-103.

Radiation protection
When handling beta emitters, it should be noted that although the depth of penetration into tissue is only a few millimeters, the range of the high-energy electrons in air of, e.g., strontium-90 is about 10 m. Therefore, the active sides of the applicators must never be held in the direction of a person.

3.1.4 Documentation

All parameters of radiotherapeutic treatments (irradiation plan, irradiation concept, dose, time period, and verification recordings) are recorded in the so-called irradiation protocol [166], which is documented in accordance with legal requirements [742] and must be kept for 30 years.

Equipment	Energy	Dosing depth	Recommendation level
X-ray machine, surface therapy	10–50 keV	0.1–0.15 mm	B
X-ray equipment, soft beam therapy	50–100 keV	<2 cm	B
X-ray equipment, orthovoltage therapy	100–400 keV	<5 cm	B
Cobalt device	1.17 resp. 1.33 MeV	<10 cm	B
Linear accelerator: - Photons - Electrons	6–18 MeV 6–21 MeV	All depths (if necessary, use additional build-up material, e.g., flabs)	B
Brachytherapy (Sr90 beta-radiation)	2.2 MeV β- radiation Contact therapy	<10 mm	B

Table 3. Recommended instrumentation depending on the dosing depth of the target volume to be treated.

3.2 Radiobiological mechanisms of anti-inflammatory effects of low doses of radiation

Inflammation is a basal immunological effector process in response to damage, whether infectious, chemical, or physical. The inflammatory reaction is regulated at multiple levels and is characterized by a complex of a multitude of immune cells and soluble factors that can be pathophysiological when chronic. Accordingly, it can be assumed that the clinically empirically proven anti-inflammatory and analgesic efficacy of low doses of radiation is based on the modulation of multiple components and essential inflammation-related mechanisms. Experimental studies have already demonstrated these effects.

Adhesion of mononuclear and polymorphonuclear leukocytes (monocytes and granulocytes) from peripheral blood to activated endothelial cells and subsequent migration of these immune cells into the inflamed tissue is considered an initial step of the inflammatory cascade. Regarding a mechanism of action of low-dose radiotherapy (0.3–1.0 Gy), a significant reduction in the adhesion process has been observed for either irradiated leukocytes or endothelial cells [322,407]. This characteristic coincides with increased expression and activity of the anti-adhesive cytokine transforming growth factor-beta 1 (TGF-β1) in endothelial cells, which is also a key factor for radiogenic adhesion inhibition in animal models [20,648]. Recent studies have shown that reduced adhesion is associated with discontinuous production of reactive oxygen species (ROS), the basis of which is radiation-mediated reduction in the activity of the transcription factor nuclear factor E2–related factor 2 and enzymes such as glutathione peroxidase [182,455]. Only recently, it was determined that physiological study of these processes is essential where possible [182].

Radiation can lead to cell death via stress responses. Apoptosis is a physiological suicide program of the cell induced by a variety of stimuli, including ionizing radiation [299]. It plays a central role in homeostasis during development and maintenance, as well as in the regulation of the immune response and irradiation response. After irradiation of granulocytes and monocytes, for example, a discontinuous course of apoptosis induction has been observed with a relative maximum in the dose range between 0.5 and 1.0 Gy [234,406], which may contribute to decreased recruitment of inflammatory cells through cell loss. This possibility is further supported by findings of decreased surface expression of adhesion molecules such as E-selectin on endothelial cells [322,648] and proteolytic cleavage of L-selectin on apoptotic monocytes [406]. In addition, studies show modulation of the survival-relevant enzyme AKT kinase [234] and a reduction in the release of the chemotactically active cytokine CCL20 in granulocytes after irradiation in the relevant dose range of 0.3–0.7 Gy [646]. Furthermore, apoptotic cells are eliminated in a neutral or anti-inflammatory manner, i.e., the phagocytes ingesting them secrete anti-inflammatory cytokines [789].

The subsequent effector phase of inflammation is characterized by an accumulation of monocytes and their subsequent differentiation into dendritic cells and inflammatory macrophages [774]. Macrophages, in turn, support the local inflammatory process through a variety of functions including phagocytosis, cytotoxic activity, processing/presentation of antigens, and the ability to secrete cytokines, ROS, and nitric oxide [230]. Nitric oxide regulates vascular permeability, promotes edema formation, and is involved in the development of inflammation-related pain [333]. In contrast, after irradiation of activated macrophages, a decrease in expression of inducible nitric oxide synthase and nitric oxide production is observed [325], as is ROS release [677], which may mechanistically contribute to the clinically observed analgesic effect of low-dose radiotherapy. Of note, histologically observed inhibition of disease progression in an arthritis animal model also has been associated with modulation of inducible nitric oxide synthase activity [321]. Studies have shown a reduction in migratory activity and secretion of the proinflammatory cytokine interleukin (IL)-1 in stimulated macrophages but increased expression of the anti-inflammatory factor TGF-β1 [480,829].

In addition, preliminary evidence suggests that macrophages maintain a stable phenotype (inflammatory, M1, or anti-inflammatory, M2) after irradiation, but modulation of the phenotype in the joint may arise through interaction with synovial fibroblasts [150].

A common radiobiological characteristic of the anti-inflammatory effects of low-dose radiation is a discontinuous dose–effect relationship with pronounced efficacy in the dose range of 0.3–0.7 Gy [222,643]. This behavior is confirmed in the biphasic activity of inflammation-related and anti-oxidative transcription factors such as nuclear factor kappa B and transcription factor nuclear factor E2–related factor 2 [455,480,645], the nonlinear detection of the DNA double-strand break marker γH2AX [456], and the discontinuous expression of the apoptosis regulator X-linked inhibitor of apoptosis protein in endothelial cells [642]. In addition to its anti-apoptotic effect, X-linked inhibitor of apoptosis protein can modulate nuclear factor kappa B activity and is associated with decreased adhesiveness and release of TGF-β1. The molecular mechanisms of these nonlinear relationships are still largely unknown but appear to be based on distinct effects with differential thresholds and kinetics and to act in a staggered manner (reviewed in [643]).

In addition to the increasing knowledge of underlying molecular mechanisms, the clinical anti-inflammatory effectiveness of low doses of radiation has been indicated in numerous experimental animal models (reviewed in [644]). In inducible arthritis models of the rabbit, rat, and mouse, for example, five weekly fractions of 1.0 Gy or 0.5 Gy inhibited synovial cell proliferation and synovial fluid synthesis and counteracted cartilage and bone destruction [102,208,763]. In addition, in other mouse studies, a single dose of 0.5 Gy led to a decrease in inflammation as well as a reduction inbone erosions [149]. One explanation may be local as well as systemic modulation of the immune system, as suggested by other animal model data [806] and analyses within the framework of patient studies [170]. A decrease in bone erosions can be attributable to decreased osteoclast number and activity [181, 149] and increased mineralization rate by osteoblasts [149].

To determine the lowest effective dose and optimal treatment timing, the efficacy of different fractionation regimens has been investigated. The best treatment effect was observed after daily fractionations with 5×0.5 Gy and treatment starting early in the course of the disease [471]. In recent analyses using a genetically determined polyarthritis model of tumor necrosis factor (TNF)-α transgenic mice and in an antibody-mediated osteoarthritis model, irradiation with 5×0.5 Gy showed clinical and histological prevention of arthritis progression and reduced swelling and disease progression [221,806]. Consistent with other models, the highest efficacy was found with acute inflammatory events or when applied in early disease stages.

In summary, current experimental and initial mechanistic clinical studies confirm an anti-inflammatory efficacy and immunomodulatory effect of low doses of radiation (for a summary, see [488]). The latter attenuate pre-existing inflammation and appear to have a beneficial effect on bone metabolism. Studies of the osteoimmunological effects of low-dose radiotherapy have additionally provided important insights and are the subject of current and future research [223]. Despite advances in the understanding of cellular targets and molecular mechanisms, however, important questions remain regarding (chronic) inflammatory, degenerative, and hyperproliferative diseases [641] that are based in complex (patho)physiological networks, and a large number of questions remain unresolved. Further intensive translational and clinical investigations and additional basic models are needed to elucidate additional factors and mechanisms.

3.3 Malignancy risk after low-dose radiotherapy for benign disease (Update 2022)

3.3.1 Preliminary remarks

In principle, any medical application of ionizing radiation carries a risk of undesirable stochastic treatment consequences. These risks are based in transformations or mutations of affected cells that can lead to neoplastic changes or hereditary diseases, although the latter are not considered in the following text. In general, typical low-dose radiotherapy of degenerative tendopathies or osteoarthritis poses only an extremely small individual additional risk of malignancy. This assessment is based on the comparatively advanced age of this patient population, predominantly target volumes outside the body trunk, and comparatively low total doses. However, it is not enough to exclusively consider risk to single patients. If the results of the departmental research report on radiation protection of DEGRO are taken as a basis [636], as noted in the introduction, more than 250,000 completed treatment cycles for benign diseases (including benign tumors) were performed in Germany in 2016, so that even very low, individually insignificant risks may be relevant for society as a whole.

A central component for the evaluation of ionizing radiation is radiation risk. This term should always be defined when it is used. In fact, in the frequently used terminology of the International Commission on Radiological Protection (ICRP)[1], radiation risk (detriment) is a multidimensional concept. The main components are several stochastic quantities: probability of fatal malignancy, probability of nonfatal malignancy, probability of severe heritable effects, and duration of life lost [345]. Thus, a low risk of radiation (detriment) in this context does not automatically imply a low absolute risk of radiation-induced malignancy. For example, skin cancer ranks last by far for radiation risk (detriment) but is by far the most common radiation-induced malignancy according to Table A.4.1. of ICRP Publication 103 [345]. This ranking is justified by the very low morbidity and mortality of skin malignancies. Therefore, terms and definitions, which are predominantly intended as radiation protection variables for the benefit of public health (ICRP), should be used to determine individual risk only to a very limited extent [160].

The importance of age at exposure appears to be particularly relevant to the likelihood of radiation-induced malignancies [279]. Epidemiologic data from survivors of the U.S. atomic bombing of Hiroshima and Nagasaki show a marked decrease in incidence as a function of age according to the *Life Span Study* (LSS) [448]. However, in the source data of the LSS, those who were aged ≥50 years at the time of exposure are significantly underrepresented, especially for a dose greater than 0.5 Gy [264]. Also, other epidemiologic studies of malignancy risk after radiotherapy for benign disease essentially include individuals who were children, adolescents, or young adults at the time of exposure [506]. Some authors now question whether exposure in middle age really decreases most radiation-induced malignancy risks, as is often assumed [722].

3.3.2 Procedure

The absolute probability is considered exclusively for the occurrence of malignancies after a typical low-dose radiation given for pain or as an anti-inflammatory treatment (dose range up to 6.0 Gy). Terms derived from the lexicon of radiation protection such as “radiation risk” (detriment) or “effective dose” are not used (see above).

1 International Commission on Radiological Protection

The quantitative information is taken from the column "Nominal Risk Coefficent[2]" of Table A.4.1. (Summary of sex-averaged nominal risks and detriment) of ICRP Publication 103 [345]. From this table, only values for a population aged 18 years and older at the time of exposure are used. Due to the fundamental importance of the topic, the calculated values are compared with a 2006 publication by Trott et al. with a similar approach [762]. In addition, data from further literature are included.

Finally, personal experiences from the authors' patient populations are given. As of January 2022, a total of 4294 patients had been treated since January 2010. Almost all patients received 6×1 Gy (Orthovolt). The mean age at the time of treatment was 65 years, and only a small proportion (~15%) of all patients were under age 50 years. In terms of sex distribution, women predominated (63%). After irradiation, the median life expectancy estimated according to the Kaplan–Meier method was 16 years.

For the risk assessment, it seems reasonable to distinguish three patient groups, based on body areas:

1. Irradiation of regions distant from the trunk, without blood-forming red bone marrow (RBM), such as elbows, hands/fingers, knees, or feet

2. Irradiation of regions distant from the trunk, with blood-forming RBM, such as the shoulder or hip/bursitis trochanterica (BT)

3. Radiation in the trunk, such as the sacroiliac joint or spine

Although the hematopoietic RBM in adults is distributed mainly in the spinal, thoracic, and pelvic regions, small proportions continue to be found in the shoulder and hip regions. The approximate percentage distribution is shown in Figure 1. In the case of irradiation of the trunk, in addition to a sometimes-high exposure for the hematopoietic RBM, there is exposure of organs such as the lungs, esophagus, or gastrointestinal tract. From our own data, a good 98% of all patients receive irradiation of regions distant from the trunk, of which 61% have no hematopoietic RBM and 37% have a low proportion of hematopoietic RBM. Only 2% of all patients receive target volumes in the trunk.

To estimate radiogenically induced tumor risk, a distinction should be made between solid and systemic malignancies. The clinical localization of solid malignancies is usually in the irradiation field or the peripheral area, but when MVs are used, an induction of malignancies by scattered radiation even outside the high-dose range cannot be completely excluded [502,549]. The latency period for the development of solid tumors is usually 10–60 years, with a steady increase over time [448], but may be shorter in individual cases, such as radiation-induced angiosarcomas [220]. Malignant systemic diseases (hemoblastoses) diverge from this pattern. In contrast to solid malignancies, the time interval between exposure and clinical appearance is much shorter, at least in leukemias, at 5–10 years, and subsequently also decreases significantly [867]. Of course, hemoblastoses manifest clinically outside the irradiation fields.

2 Nominal Risk Coefficient: Cases per 10,000 persons; per Sievert

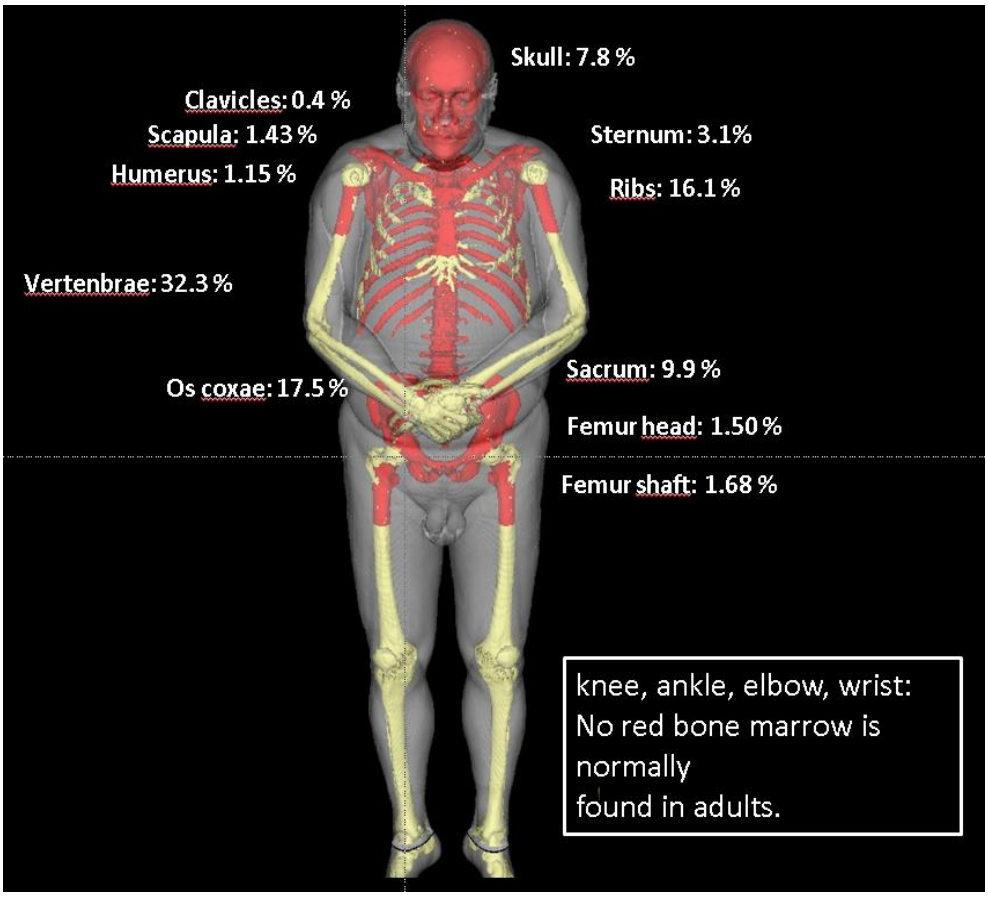

Figure 1. Distribution of active red bone marrow in adults (figure personally adapted from [368] and [344]).

3.3.3 Solid malignancies with irradiation of regions distant from the trunk of the body

When treating regions distant from the trunk, the skin, bones, and soft tissues are usually all exposed.

3.3.3.1 Skin

The spontaneous lifetime risk of a malignant skin tumor is 1 in 5 (20%) [639].

Much evidence suggests that radiation induces basal cell carcinomas of the skin, and that the risk persists throughout the lifespan. In contrast, this relationship is unclear for squamous cell carcinomas, melanomas, or Paget's disease of the skin [744]. A clear effect of age at exposure and the occurrence of radiation-induced basal cell carcinoma is described in atomic bomb victims. Thus, the additional relative risk (ERR[3]) is 15 for childhood exposure (age 0–9 years), 5.7 for adolescents (10–19 years), 1.3 for young adults (20–39 years), and almost zero for older people (aged 40+ years; from Table 3 in [744]). However, these data originating from Japan are somewhat limited because the natural rate of skin cancers in Hiroshima or Nagasaki is much lower than in Europe [744]. In addition, skin malignancies are rarely fatal and thus are either not detectable within epidemiologic studies or are deliberately not collected when only mortality is used as a criterion [506]. Below is an example of calculation of the excess relative risk, defined as the rate of disease in an exposed population divided by the rate of disease in an unexposed population, minus 1.0, and often expressed as per Gy or per Sv (ICRP Publication 103, 2007 [345]).

Example: The nominal risk coefficient for tumor induction (cases per 10,000 per 1 sievert) for persons aged 18–64 years is given in ICRP Publication 103 (Table A.4.1) as 670 (whole skin exposure) [345]. Assuming a whole-skin area of 2 m^2, a field size of 10×10 cm would give 0.5% of this proportionately. With the above-mentioned risk after total skin exposure of 670 per 10,000 per 1 Sievert (Sv), a very low skin carcinoma risk of 670×0.5% equals 3 per 10,000 persons or 0.03% per 1 Sv. Based on a linear dose-response relationship, for a typical irradiation series of 3 Gy or 6 Gy, the calculated risk for a skin tumor would be just under 0.1% (3 Gy) or 0.2% (6 Gy). These data refer to an age interval at exposure of 18–64 years, so that older patients are certainly less at risk.

Trott et al. report a risk of 0.1% for a dose of 1 Gy for sun-exposed skin areas at a 100 cm^2 field, and about an order of magnitude smaller in non–sun-exposed skin areas [762].

In our own patient population, as of January 2022, one basal cell carcinoma (patient age at exposure, 55 years) has occurred to date in the irradiation field 11 years after pain irradiation of the left shoulder with 6×1 Gy (Orthovolt).

3 Excess relative risk: the rate of disease in an exposed population divided by the rate of disease in an unexposed population, minus 1.0. This is often expressed as excess relative risk per Gy or per Sv. (ICRP Publication 103, 2007 [345])

3.3.3.2 Soft tissue and bone sarcomas

The spontaneous lifetime risk of bone sarcoma is approximately 0.07% [106].

It is well known that radiotherapy can induce malignant sarcomas. The division into soft tissue and bone sarcomas is probably similar, as is the latency period, which is reported to be between 11 and 16 years at the median [74,415], but the range can be considerable. At doses <10 Gy in the field, sarcomas are very rare [74,431]. The LSS atomic bomb studies do not provide relevant data [345].

Irradiation for ankylosing spondylitis has been associated with a significant increase in deaths from bone sarcoma after radiotherapy [141], but the total doses used in the spinal areas for the first irradiation series alone were also >10 Gy (mean 14 Gy) [802]. In 1995, Bloechle et al. described 11 patients who presented with in-field sarcoma after previous irradiation during 1975 to 1993. The total doses were also >10 Gy (12–60 Gy), with a mean of 40 Gy [74]. Studies for a low-dose range <10 Gy were not found in the literature. Below is an example of a risk calculation in this scenario:

Example: The nominal risk coefficient for induction of a malignant bone tumor for persons aged 18–64 years is given in ICRP Publication 103 as 5 cases per 10,000 persons per 1 Sv whole-body exposure [345]. For a typical irradiation of the knee joint with a field of 15 cm×10 cm, about 5% volume of the whole skeletal system is exposed[4], as calculated from a randomly selected whole-body scan from our patient data, with a total bone system volume of 5769 cm^3 and knee (bone) volume of 326 cm^3. Using the above nominal risk coefficient of 5 cases per 10,000 persons per 1 Sv (0.05%), for a typical irradiation series of a knee joint and assuming a linear dose-response relationship, the risk at doses of 3.0 Gy and 6.0 Gy for radiation-induced bone sarcoma are thus 0.008% and 0.015%, or 0.75 and 1.5 per 10,000, respectively. Similar values are likely to apply to soft tissue sarcomas.

Trott et al. report a lifetime risk of osteosarcoma of <1 in 100,000 for 1 Gy and 100 cm^2 field size (0.001%) [762].

As of January 2022, no sarcoma has occurred in the irradiation field in our own patient population.

3.3.4 Solid malignancies with radiation to the trunk

The spontaneous lifetime risk of bronchial carcinoma is approximately 7.8% in men and 6.8% in women [106].

Radiotherapy in the trunk of the body is occasionally performed to improve painful degenerative changes in the vertebral arch joints (spondylarthrosis) or in the vertebral bodies/intervertebral spaces (spondylosis deformans), as well as in chronic progressive inflammation of the sacroiliac joints (sacroiliitis). In our patient population, just under 2% of all patients received pain radiation in the trunk region. In contrast to the regions far from the trunk, other organs are exposed, mainly the thyroid gland (cervical spine), parts of the lung and esophagus (thoracic spine), or parts of the stomach and intestine parts (lumbar spine, pelvis).

Radiation-induced thyroid carcinomas are more likely to be described with childhood exposures than with adulthood exposures. From a cohort of 8144 individuals (82% aged 40–69 years) in a Swedish study with treatment to the cervical spine and an estimated average dose to the thyroid of about 1 Gy, 22 thyroid carcinomas were found versus the 13.77 that would be expected. Most thyroid cancers were diagnosed 15 years after exposure [140].

4 Own data. Calculated from a randomly-selected whole-body scan: Volume total bone system: 5769 cm3, volume knee (bone) 326 cm3.

Lung malignancies are the most common radiation-induced solid tumors after skin [361]. Radiation-induced solid carcinomas of esophagus, stomach, and colon occur less frequently than induced lung carcinomas, with nominal risk coefficients of 16, 60, and 50 per 10,000 per 1 Sv of whole-organ exposure, respectively, according to ICRP Publication 103. Parts of the lung are in the target volume during radiation therapy for ankylosing spondylitis. Darby et al. [141] observed 224 cases of death from lung tumor, compared with an expected value of 184. Lung tumors accounted for one-third of all fatal malignancies and were judged to be the most common form of radiation-induced tumor after radiotherapy for ankylosing spondylitis. The median dose to the mediastinum was 5 Gy (data taken from [762]).

Calculation example: The nominal risk coefficient for a lung malignancy for persons aged 18–64 years is given in ICRP Publication 103 as 127 per 10,000 (1.27%) for whole-body exposure [361]. This value is based on irradiation of the thoracic spine over a dorsal field of 10 cm×15 cm, 6 MV, 3.0 Gy with normalization (reference point) at 4 cm, so that FSD[5] equals 96 cm. Using our data from a randomly selected whole-body scan with a total lung volume of 2738 cm^3, the calculated mean lung exposure is about 0.9 Gy[6]. Thus, this would result in a risk of about 1.14% or 114 per 10,000. However, this value may be reduced if Orthovolt is used.

Trott et al. assumed whole-lung exposure of 1 Gy for a typical spinal irradiation and arrive at an absolute risk of radiation-induced lung tumor of approximately 1% within 25 years [762].

In our own patient population, as of January 2022, one bronchial carcinoma (patient age at exposure 53 years) has occurred in the irradiation field (paravertebral) 12 years after pain irradiation of the thoracic spine with 6×1 Gy (Orthovolt).

3.3.5 Malignant systemic diseases

The spontaneous lifetime risk of leukemia is approximately 2.1% in men and 1.2% in women [106].

It is well known that leukemia can be induced by ionizing radiation, with the exception of chronic lymphocytic leukemia [211], and has been confirmed after irradiation for benign diseases such as ankylosing spondylitis [98,141], in menorrhoeiccomplaints [662], and with gastric ulcers [477]. Radiation-induced induction also may apply to other hematologic malignancies originating in the bone marrow, such as multiple myeloma [137] or at least some subsets of non-Hodgkin lymphomas [63] may be induced by radiation. However, the relationship between radiation exposure and multiple myeloma or non-Hodgkin lymphoma remains unclear [79, 474].

Leukemias are of particular interest for estimating radiation risk in elderly patients because, unlike solid carcinomas, the assumed mean time interval between radiation exposure and clinical presentation is less than 10 years on average [395]. Because leukemias and other hematologic malignancies arise from mutant cells of the active RBM, they should be induced by radiation only when RBM-containing bones are exposed. In contrast to children, RBM in adults is found only in certain areas of the skeleton (see Chapter 3.3.2 and Figure 1).

Damber et al., in their 1995 study of 20,024 patients treated with classical low-dose pain irradiation between 1950 and 1964, found increases in standardized incidence ratios for leukemia, with ratios of 1.01 with no exposure, 1.22 with moderate exposure, and 1.40 with high exposure to RBM [139]. The risk increases significantly with irradiation of parts of the spine. In their 1987 study of just over 14,000 irradiated patients [141], Darby et al. found that 39 died of leukemia versus the expected 12.29 for a mean bone marrow dose of 1 Gy for ankylosing spondylitis. National Council on Radiation Protection & Measurements report 116 gives an overall fatal risk of leukemia of 0.5% per 1 Sv [cited in 448].

5 Focus-skin distance

6 Own data. Calculated from a randomly-selected whole-body scan with a total lung volume of 2738 cm3; own computer planning with the given data.

Calculation example: The nominal risk coefficient for leukemia (cases per 10,000 persons per 1 Sv) for persons aged 18–64 years is given in ICRP Publication 103 as 23 per 10,000 (0.23%) for whole-body exposure [351]. Shoulder irradiation is estimated to expose 2% of the active adult RBM (see Figure 1). This results in an additional risk of approximately 0.005% per 1 Gy, or 0.015% and 0.03% for 3.0 Gy and 6.0 Gy, respectively, assuming a linear dose-response relationship. Please note: For a corresponding irradiation in the spinal region, these figures may increase tenfold.

Trott et al. suggest a higher lifetime risk of leukemia of about 1% per 1 Gy of whole-body exposure [762]. Consequently, an exposure of 2% RBM would result in 0.02% for 1 Gy and an additional risk of 0.06% and 0.12% for 3 Gy and 6 Gy, respectively.

In our own patient population, 0.15% of all patients developed non-chronic lymphocytic leukemia without involvement of the hematopoietic bone marrow and 0.30% with bone marrow involvement.

3.3.6 Summary

Data on malignancy risk after low-dose radiotherapy of benign diseases are inevitably inaccurate because the absolute probabilities are relatively low and are lost in the “noise” of the natural malignancy rate. The required follow-up times are often decades long and are rarely achievable for exposures at the typical age of the affected patients, as far as solid malignancies are concerned. However, the situation is different for malignant systemic diseases, especially leukemia, which has already exceeded the incidence maximum 10 years after exposure.

In principle, irradiation of regions distant from the trunk should be separated from treatment of the pelvis or spine. In regions distant from the trunk, there is a very low absolute risk of radiation-induced solid malignancies below or in the low per thousand range. The risk is similar for hematologic malignancies if bone marrow–active regions such as the shoulder or hip are treated.

Rare irradiations of the pelvis or spine involve a higher exposure of bone marrow–active regions as well as further radiation-sensitive organs such as the lungs, so that the additional risks can approach the percentage range. Patients should be informed accordingly of these risks, and the indication should be strictly defined.

3.4 Deterministic risks (Update 2022)

In terms of content, only low-dose pain radiotherapy of benign orthopedic diseases is considered here. Antiproliferative radiotherapies, e.g., for DD or Ledderhose's disease (LD), are not addressed in this version.

3.4.1 Preliminary remarks

It may seem curious to talk about the risks of deterministic consequences in connection with low-dose pain irradiation of skeletal diseases. In general, this form of therapy in particular is considered to be well tolerated and practically free of risks. Also, commonly used patient information sheets scarcely address the risks of permanent tissue damage [619]. However, the usual total doses of 3.0–6.0 Gy are far from insignificant for the human cell: 1 Gy per cell causes approximately 1000 single-strand breaks, 50 double-strand breaks, 200 base damages, 150 DNA crosslinks, and 450 bulky lesions [302]. Repair can occur within hours, but of 100 critical double-strand breaks, 2 to 3 are repaired incorrectly and 0 to 1 are not repaired at all [668]. The spermicidal or hematotoxic effects of doses around 5.0 Gy are well known, as are radiogenic alopecia or radiation cataract of the eye lens. Deterministic effects also are conceivable in the clinical routine of low-dose pain irradiation, if, for example, the nail bed is in the radiation field during treatment of painful finger distal interphalangeal joint (DIP) osteoarthritis and there is temporary discoloration or loss of the fingernail.

Nevertheless, low-dose pain irradiation is generally considered to be free of deterministic tissue damage. However, this expectation refers only to proper and professional implementation of the treatment and to total doses of 3 Gy to 6 Gy with repetition after 6–12 weeks, if necessary (so-called second series) [796]. In the case of repeated irradiation of the same region, the relative safety becomes increasingly uncertain with the increasing number of series. For this reason, recommendations for action will be presented in this chapter.

3.4.2 Procedure

The derivation of these treatment recommendations is based on generally accessible knowledge about the biological effects of radiation. This knowledge should be acquired by every therapist who responsibly uses ionizing radiation. It is supplemented by personal experience with the authors' patient population. As of January 2022, this population consisted of 4294 patients who were treated since January 2010. Almost all patients received 6×1 Gy (Orthovolt), with many receiving a second series and some a third of the same region. Following irradiation, the mean life expectancy remained 16 years, estimated according to the Kaplan–Meier method.

The following terms are addressed in this section: tolerable risk, reference value, and tolerance value of this reference quantity.

3.4.3 Tolerable risk

Regardinglife expectancy, the diseases being treated are relatively harmless, at least compared with cancer. Therefore, there should be a claim that the treatment for them is "almost certainly" harmless. This claim sounds unusually high at first. However, with more than 250,000 completed treatment courses of radiotherapy for benign diseases per year in Germany, as an example [636], even a treatment risk of only 0.2% for expected radiation damage would mean a number of cases in the 3-digit range per year.

3.4.4 Reference value

First, a uniform reference value should be defined for which an upper limit can then be determined. This reference value should be simple and universally applicable to what may be quite different technology and dose concepts.

Frequently, the “number of series” is mentioned here. However, with the very large range of dose concepts within an irradiation series from 6×0.5 Gy to 6×1.0 Gy or 12×0.5 Gy, the pure number of series obviously is not a suitable reference value for defining an upper irradiation limit.

The use of the prescription dose to a reference point (normalization) or volume also is not suitable, however. According to Table 2 of the BfS RESFOR-173/20 [636], it can be assumed that with >250,000 outpatient treatments for benign diseases in 2016 and >140,000 applications with X-rays, more than half of all corresponding treatments are performed with Orthovolt. With the Orthovolt technique in particular, however, the reference point is selected quite differently, ranging from 0 cm to a dosing depth of 4 cm, and in individual cases even 6 cm, at least for a simple direct field. This variation can result in quite different maximum doses in organs at risk with seemingly identical prescription doses (see Figure 2).

From the above it can therefore be seen that only the **absolute dose maximum (Dmax in Gy**) in organs at risk appears suitable as a universally comparable reference value. The absolute dose maximum yields directly and simply comparable values for all different techniques and dosing concepts. The absolute dose maximum is subject to the general documentation obligation, so that pre- irradiation carried out elsewhere can be easily included.

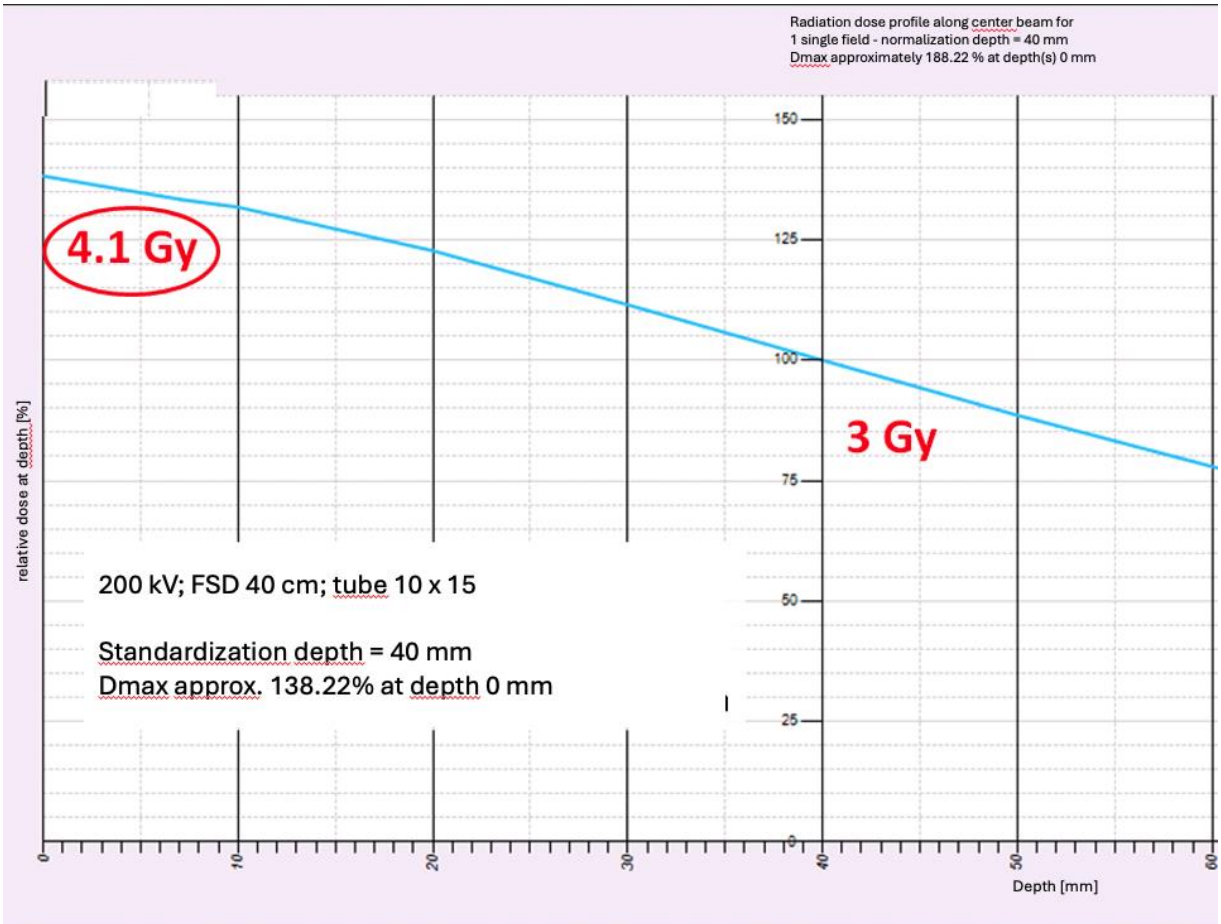

Figure 2. Dose distribution of a direct field at 200 kV Orthovolt, tube 10×15 cm, FHA 40 cm, filter 09. Prescription of a total of 3.0 Gy to 4 cm tissue depth. (Source: authors' calculation using XBeam version 1.2.0.24, calibrated for the in-house Orthovolt therapy device).

3.4.5 Tolerance doses

The classical term “tolerance dose” from radiation oncology does not seem useful for low-dose pain irradiation of benign diseases because the given dose limits deliberately include a risk of sometimes severe deterministic tissue damage of 5% [187]. This value appears prohibitively high for benign diseases (cf. chap. 3.4.3). To almost exclude tissue damage, doses used to treat benign conditions should be much lower than oncological tolerance doses.

At least when using an orthovoltage technique, the skin should be mentioned as a frequently affected risk organ for deterministic damage. For the skin, according to Turesson et al. and Emani et al., there is a risk of permanent skin changes (e.g., telangiectasia) of approximately 1% at 40 Gy and 5% at 50 Gy, both within 5 years, for normo-fractionated radiation therapy with single doses of 1.8–2.0 Gy and for a field area around 100 cm^2 [187,768]. For skin ulceration, the risk is 3% at 50 Gy and 5% at 55 Gy [187]. For field areas smaller than 100 cm^2, these risks exist only at higher total doses, and for larger field areas, at lower doses. Common risk factors such as age (reduced number of dermal stem cells) or co-morbidities such as circulatory disorders or diabetes mellitus already should be included in these values, but not rare hereditary diseases involving DNA repair defects. Admittedly, based on the authors’ calculation using a linear-quadratic model with an alpha-beta value (late) of 3.0. Gy, these tolerance doses are shifted upwards by about 20% for single doses of 1 Gy and by almost 12% for 1.4 Gy (corresponding to 1.0 Gy at 200 kV in 4 cm of tissue depth). Yet the extreme protraction of weeks, months, or years between series appears to have a major impact. CRP publication 118 (2012), chapter 2.4. “Skin,” states that “Late reactions show very little sparing from dose protraction because of the lack of any contribution from cell repopulation, which is the explanation for early-reaction sparing...” [346]).

In summary, doses used to treat benign conditions should be much lower than those used in oncology in order to achieve practically damage-free therapy and respect the wide variation in techniques and prescription modalities, including different field sizes up to 10×15 cm. Here, for reasons of practicability, half the value of the oncological tolerance dose for the organ in question is used, which for the skin is around 25 Gy, and the reference value should always be the absolute dose maximum. The typical gap between series obviously has little influence on the probability of deterministic late reactions, so this dose value can be added as the cumulative sum of all irradiation series. This upper limit is valid for life. In strong support of this statement, no deterministic tissue damage has been reported in >4000 patients from our own treatments performed while adhering to this upper limit.

3.4.6 Exceeding tolerance values

There are certainly cases where exceeding this recommendation could be considered, e.g., when repeated irradiation over a period of years achieves pain relief efficiently but always only temporarily. In this case, however, the classical low-dose pain irradiation loses its definition and becomes a risky radiotherapy, which should be made clear to the patient. Appropriate risk education should be performed and documented, as the commonly used sheets do not include it. In particular, information should be provided about the increased risk of permanent cosmetic changes, including non-healing skin ulcers, which often appear only after years. The elderly patient is particularly predisposed, as they have a significantly reduced stem cell reserve, and the use of field areas over 100 cm^2 poses a risk. Depending on the location of the cumulative dose maximum, contractures of tendons, myositides of muscles, or bone necroses are also to be considered.

7 Own calculation using linear-quadratic model with an alpha-beta value (late) of 3.0. Gy

3.4.7 Recommendation

The concept of the cumulative dose maximum as the sum of all irradiation series seems most suitable to define a uniform and practicable statement for an irradiation upper limit for all irradiation techniques and dosage concepts. Also, pre-irradiations at other clinics can be easily included. Doses used for benign conditions should be much lower than those used in oncology, with a recommendation that the lifetime tolerance dose should be approximately half the value of oncological tolerance values

4 Site-specific guidelines

4.1 Osteoarthritis

4.1.1 Recommendations for the practical implementation of low-dose irradiation of the most common musculoskeletal diseases (Update 2022)

4.1.1.1 General

Patients with benign diseases are treated on linear accelerators in most radiotherapy facilities, and an adequate definition of the target volume is becoming increasingly important [445]. In many institutions, 3D-planned irradiation is performed, necessitating precise knowledge of the respective target volume concepts. In this context, the treatment of benign diseases [632,702] is performed analogously to the principles of treating malignant diseases [155,165,166,167,348,349,351,632,702,742].

4.1.1.2 Large joints of the lower extremity

Gon- and coxarthrosis (Osteoarthritis of the knee and hip)
In osteoarthritis, the target volume should include the following structures in addition to the joint with adjacent bony and muscular structures: capsular thickening, effusion formation as well as soft tissue swelling, osteophytes, and involvement of adjacent joints as well as nerve and tendon sheaths. The gonadal region must be blocked out. In principle, care should be taken to treat the extended region and not necessarily the entire joint.

Figure 3. 3D planning coxarthrosis (property of R. Mücke).

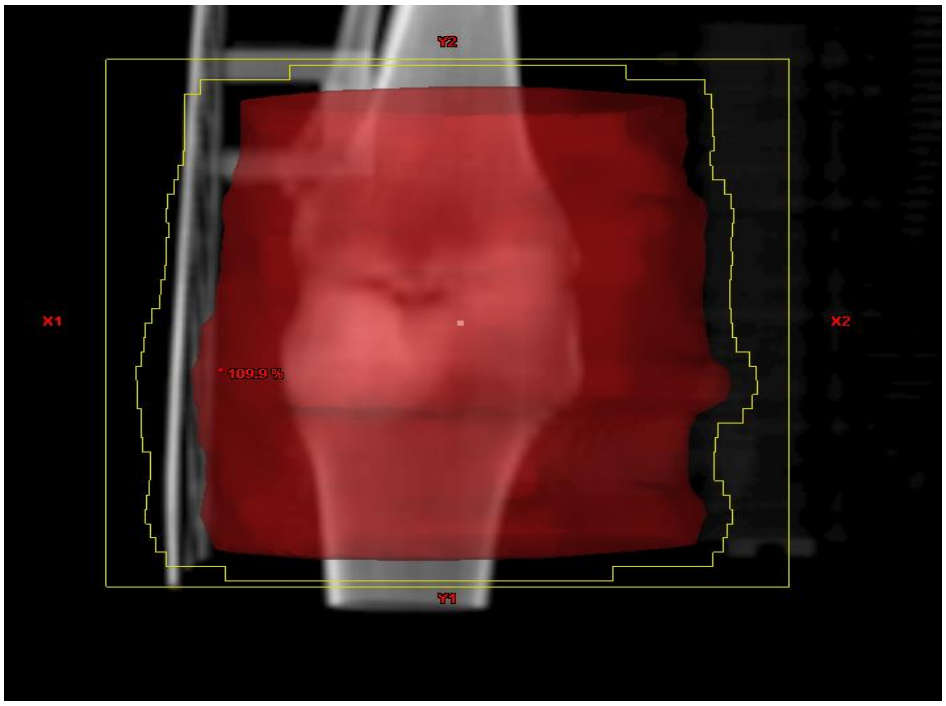

Figure 4. 3D planning gonarthrosis (property of R. Mücke).

Heterotopic ossification prophylaxis
If ossifications already exist preoperatively, the entire visible ossification in the planning CT should be included in the target volume in addition to the entire joint. If there are no ossifications yet, the entire joint with adjacent bony and muscular structures is included.

Bursitis trochanterica (BT)
The target volume should safely include the superficial and deep, as well as the primary and secondary gluteus maximus bursae. Furthermore, the gluteofemoral bursa should be included and may entail a craniocaudal extension of up to 7 cm in the presence of marked inflammation [826]. Diagnostic magnetic resonance imaging (MRI) may be helpful in defining the target volume.

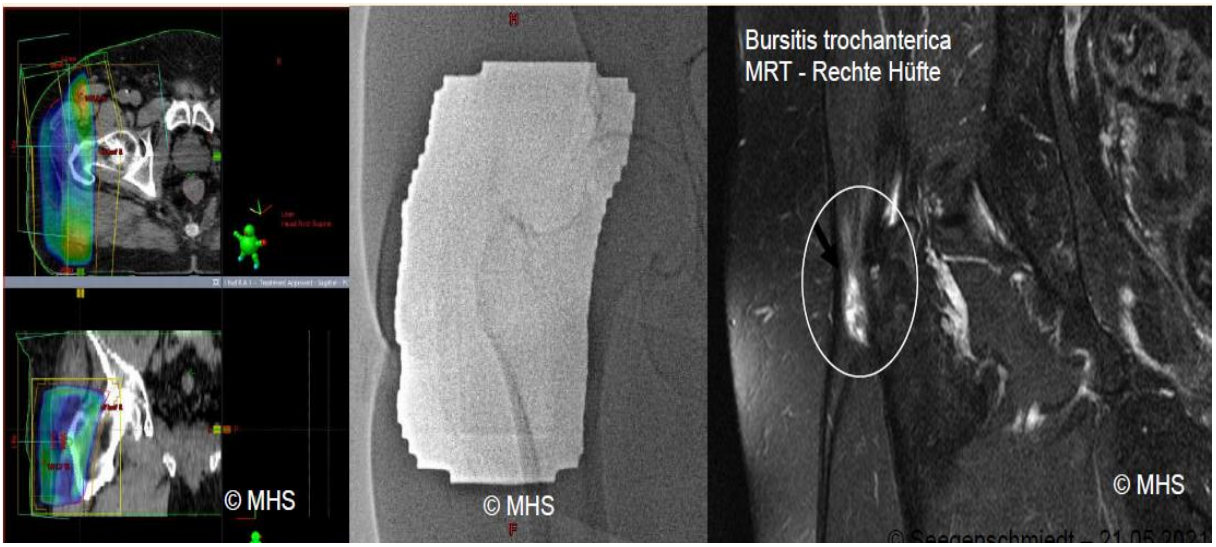

Figure 5. 3D planning of bursitis trochanterica (property of H. Seegenschmiedt).

4.1.1.3 Dorsal and Plantar Heel Pain

The term plantar heel pain includes plantar heel spur and plantar fasciitis (which is distinct from plantar fibromatosis, despite sharing the ICD-10 code of M72.2). “Dorsal heel pain” includes Achilles tendinopathy and dorsal heel spur. The radiotherapy treatment volumes for heel pain may include the entire plantar and/or dorsal calcaneus with adjacent bony and muscular structures that are relevant for the affected areas, depending on the patient’s specific symptoms.

The setting can be done clinically at the irradiation unit as well as after 3D planning. In any case, exact localization of pain by the patient is crucial for the definition of the target volume.

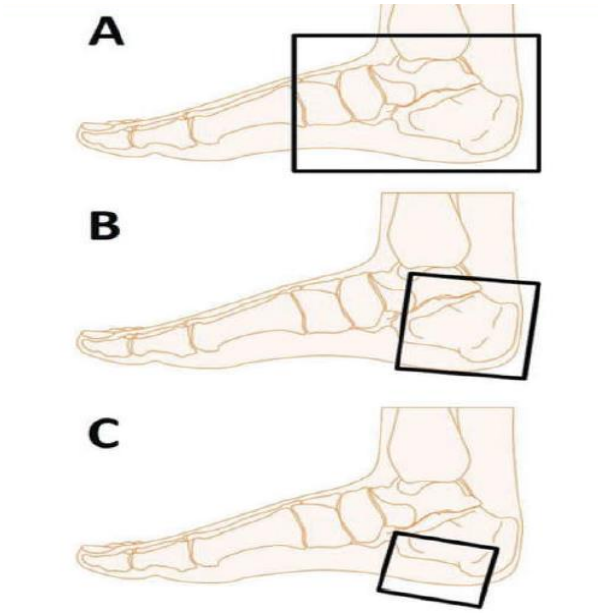

Figure 6. Clinical PTV definition with different field sizes in the irradiation of plantar heel pain according to Hermann et al. [301].

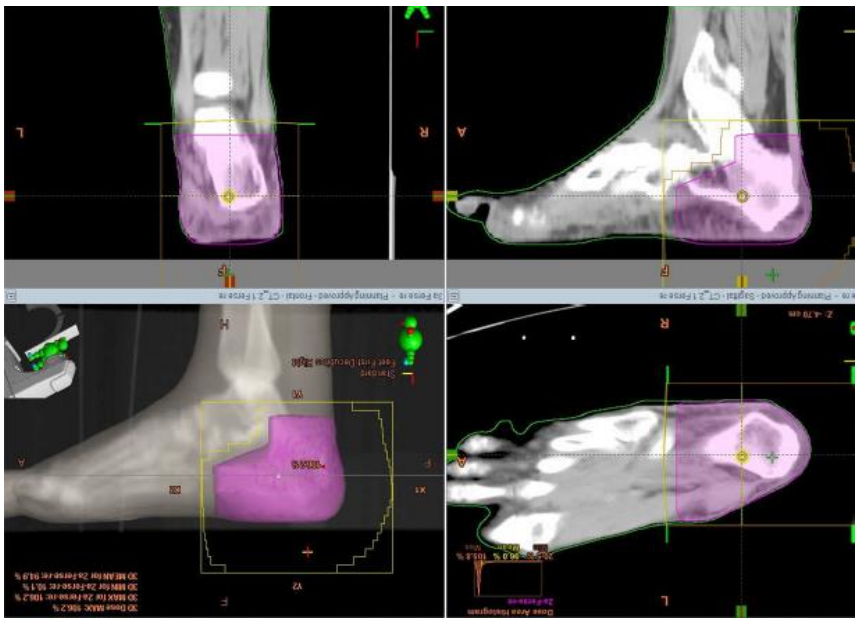

Figure 7. PTV definition and 3D planning of calcaneodynia/achillodynia (property of H. Seegenschmiedt).

In achillodynia, the entire painful tendon as well as the calcaneal tuberosityshould be targeted. The field placement can be done clinically at the irradiator as well as after 3D planning.

4.1.1.4 Large joints of the upper extremity

Painful shoulder syndrome
In principle, care should be taken to treat the extended region and not necessarily the entire joint. The adjacent lung and mammary gland must be left out of the target area. In the case of isolated supraspinatus or subdeltoid tendinitis, a smaller target volume can be selected.

Figure 8. 3D planning of omarthrosis (property of H. Seegenschmiedt).

Medial and Lateral Epicondylitis of the Elbow
In principle, care should be taken to treat the extended region and not necessarily the entire joint. The target volume should include the entire lateral or medial epicondyle with adjacent bony and muscular structures. Because of the extra-articular location of the epicondyle, it is not necessary to include the entire joint capsule. Adjustment can be performed clinically at the irradiator or after 3D planning.

Hand region and finger joints
The extent of the target volume depends on the number and pattern of joints affected. In the case of individual joints, these also can be treated locally. If several joints are affected, the entire hand maybe treated. If possible, care should be taken to ensure that the fingernails are adequately blocked out. The adjustment should be made clinically at the irradiation unit.

Figure 9. Clinical PTV definition of finger joints (PIP) (property of H. Seegenschmiedt).

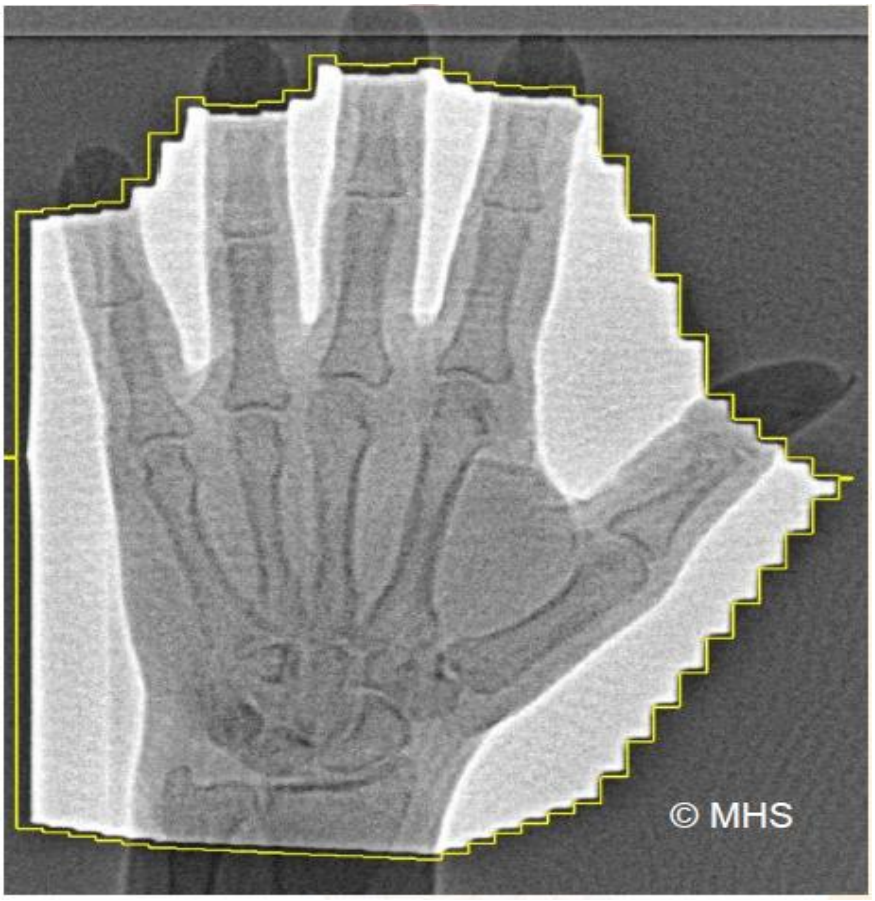

Figure 10. Clinical fielddefinition of the whole hand (property of H. Seegenschmiedt).

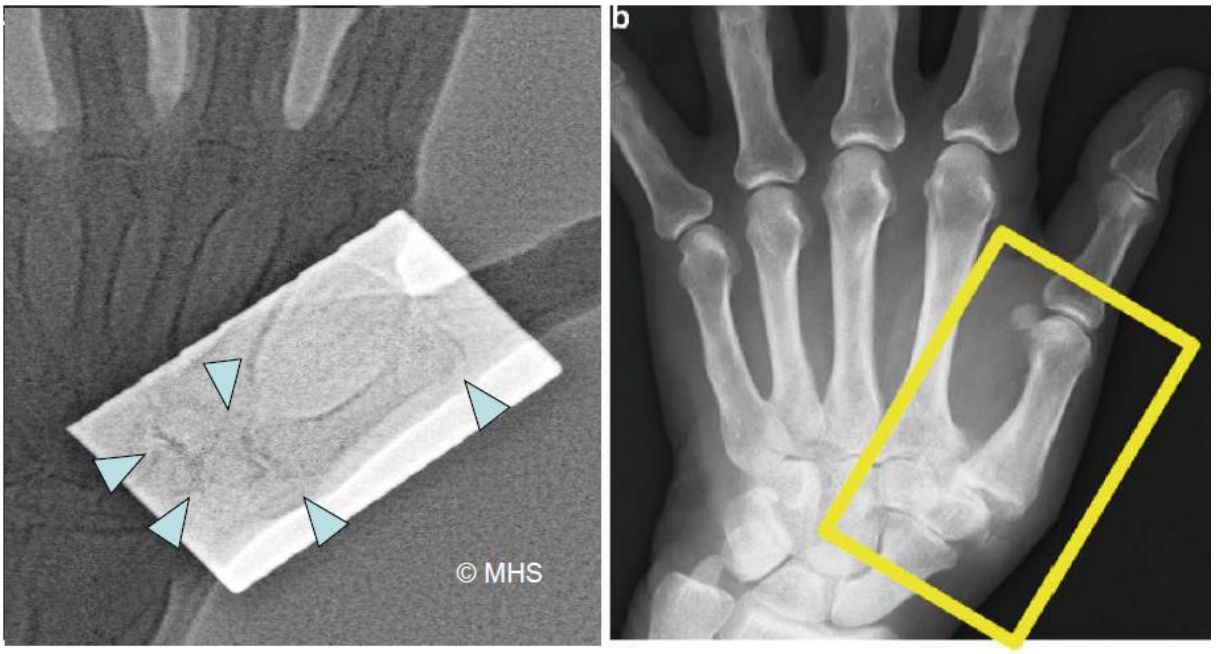

Figure 11. Clinical field definition of base of thumb osteoarthritis (property of H. Seegenschmiedt).

4.1.2 Radiotherapy for painful osteoarthritis of the large joints of the lower extremity (Update 2022)

4.1.2.1 Definition

Osteoarthritis is a chronic degenerative disease characterized by progressive destruction of articular cartilage with involvement of joint structures such as bone, the synovial and fibrous joint capsule, and periarticular musculature.

Gonarthrosis includes all degenerative diseases of the knee joint (femoro-tibial and femoro-patellar) [512].

Coxarthrosis includes all degenerative changes of the hip joint with painful reduction in function. Synonyms are the following: osteoarthritis of the hip joint, arthrosis deformans of the hip joint, arthrosis deformans coxae, osteoarthritis of the hip joint, malum coxae senile, hip arthrosis, hip joint arthrosis [374,439].

4.1.2.2 Epidemiology

The prevalence of gonarthrosis at the age of 60 is about 20%. In those aged 70 to 74 years, the proportion rises to up to 40%. If the diagnosis is based on clinical symptoms alone, the prevalence in adulthood drops to 10%. Only about 15% of patients with radiologically confirmed gonarthrosis complain of knee pain. The rate of new cases per year is estimated to be about 1% of the population over age 70 years [512].

Compared with gonarthrosis, coxarthrosis occurs less frequently, being present in approximately 3.7% of men and approximately 5.6% of women over 60 years of age, with bilateral involvement in approximately 44% of affected patients [374].

4.1.2.3 Etiology and pathogenesis

These conditions are divided into the primary (idiopathic) and secondary arthroses. Causes of secondary gonarthrosis can include axial deviations, injuries of the knee joint, arthropathies (metabolic, neurogenic, endocrine, in hemophilia, in systemic diseases), rheumatoid arthritis, bacterial arthritis, dystopias of the patella, muscular imbalances, osteochondrosis dissecans, dysplasias of the joint, osteonecrosis (e.g., Ahlbäck's disease), and chondromatosis. Causes of secondary coxarthrosis may include congenital hip dislocations, epiphyseolysis capitis femoris, rheumatoid and bacterial coxitis, Perthes disease, trauma, osteochondrosis dissecans, articular chondromatosis, idiopathic femoral head necrosis, and chronic polyarthritis.

Additional influencing factors are obesity, physical strain, and endocrine factors. The hyaline articular cartilage is considered to be the target of arthritis-causing factors and the site of disease onset [512].

Pathogenetically, damage to the chondrocytes and cartilage ground substance occurs for various reasons, which initiates osteoarthritis [5,593].

Pathophysiology [439,512]

- Release of cartilage-degrading enzymes
- Change in mechanical tissue properties
- Chondrocyte death
- Imbalance between matrix synthesis and degradation
- In the further course, phasic reactive inflammation of the synovium
- Subchondral sclerotherapy
- Osteophytes and bone cysts

4.1.2.4 Diagnostics and differential diagnostics

Clinical history for knee osteoarthritis [512]

- Pain: localization, pain radiation, daily rhythm, duration, intensity, functional limitation, pain-free walking distance
- Load capacity
- Limp
- Mobility
- Pinching, blocking, feeling of instability
- Tendency to swell, discomfort when going down stairs/downhill
- Walking aids

Clinical history for hip osteoarthritis [439]

- Pain in the hip
- Morning stiffness in the hip lasting longer than 30 minutes and shorter than 60 minutes
- Painful internal rotation
- Movement restriction
- Maximum walking distance
- Painfulness of other joints
- Previous treatment of the affected joint

Clinical examination

The clinical symptoms depend on the stage. The leading symptom is joint pain on exertion. Persistent pain at rest or during the night can be interpreted as a sign of advanced osteoarthritis. The clinical examination should include general relevant data, visual and palpatory findings, motion verification and, if necessary, special functional tests.

Special examination, knee osteoarthritis [512]

- Tape stability
- Meniscus tests
- Gait analysis

Special examination, hip osteoarthritis [439]

- Tape stability
- Pain after rest, pain on exercise, strain pain
- Low back pain in compensatory hyperlordosis due to flexion contracture of the diseased hip

Imaging and staging [439,512]
Conventional radiographs should be taken in a standardized manner in at least two planes. Depending on the problem, special functional radiographs should be performed. Radiologically, the staging of gon- and coxarthrosis is according to Kellgren and Lawrence [404]. Bone scintigraphy, CT, and especially an MRI examination to visualize the hyaline cartilage can be performed as well.

Stages of gonarthrosis according to Kellgren and Lawrence
- Grade 0 – no findings
- Grade 1 – initial osteoarthritis, incipient osteophytes
- Grade 2 – moderate joint space narrowing, moderate subchondral sclerosis
- Grade 3 – joint space narrowing >50%, flattening of the femoral condyle, extensive subchondral sclerosis, pronounced osteophytes
- Grade 4 – joint destruction, joint space completely obliterated, debris cysts in the tibial plateau and femoral condyle, subluxation position

Stages of coxarthrosis according to Kellgren and Lawrence
- Grade 0 – no findings
- Grade 1 – osteophytes
- Grade 2 – periarticular ossifications
- Grade 3 – joint space narrowing, subchondral sclerosis
- Grade 4 – cysts
- Grade 5 – bony deformities of the hip joint

Classification
For scientific comparison, the following scores are recommended in the original version:

- Knee Society Score (Insall et al. 1989) [360]
- HSS score (Ranawat and Shine 1973) [625]
- Lequesne score (1987) [468]
- WOMAC Osteoarthritis Index [55]
- Harris Hip Score [285]

Additional laboratory chemical and microbiological examinations of the blood and possibly a biopsy may be required for further differential diagnostic clarification in case of coxarthrosis [439].

4.1.2.5 General therapy options

Stage scheme of therapy for gonarthrosis [512,603]:

1. Non-drug therapy: weight reduction, orthopedic aids, physical measures and physiotherapeutic measures [46,94,97,218,342,373,660,784]

2. Drug therapy (paracetamol, non-steroidal anti-inflammatory inhibitors [NSAIDs], opioids, symptomatic slow-acting drugs for osteoarthritis, complementary medicines) [113, 203,475,759,760]

3. Intra-articular injection of corticosteroids and hyaluronic acid for effusion and severe pain [56,57]
4. Joint-preserving surgical measures [96]

5. Joint replacement surgical therapies

Stage scheme of therapy for coxarthrosis [439]:

1. General measures: lifestyle changes, physical stress in work and sports, weight reduction, exercises to eliminate muscle deficits, especially through self-exercises [46,217,373]

2. Drug therapy (paracetamol, metamizole, NSAIDs, cyclooxygenase-2 inhibitors, opioids, glucocorticoid crystal suspensions for intra-articular injections, symptomatic slow-acting drugs for osteoarthritis, vitamin E, complementary medicines) [113,203,475,759,760]

3. Physiotherapy [94,342,660,784]

4. Other conservative procedures (occupational therapy, orthopedic aids, acupuncture)

5. Joint-preserving surgical measures

6. Joint replacement surgical therapy

4.1.2.6 Radiotherapy

Previous results of radiotherapy in osteoarthritis of the hip and the knee

The recording of the results is mostly done in the literature with the help of visual analog scales and the “von Pannewitz” score [591]. A response to irradiation in the sense of a significant reduction in pain and freedom from pain has been described in 58%–91% of patients with gonarthrosis, with a total of 10,187 patients retrospectively evaluated [34,47,125,226,253, 265,287,289,305,399,403,515,527,536,591,594,612,659,669,686,758,812,813,840] (Table 4).

In 2010, the results of a Patterns of Care study in Germany were published with the finding that 78.8% of radiation therapy facilities in the country treat patients who have painful gonarthrosis [536]. A response to radiation in terms of a significant reduction in pain and freedom from pain was reported in 24%–89% of patients with coxarthrosis among a total of 741 patients evaluated retrospectively [34,125,226,241,265,289,304 305,399,473,527,594,659,686,758,812,813,840] (Table 5).

Randomized, placebo-controlled, double-blind studies also are available. Two historical studies from the 1970s with this study design had an insufficient number of patients, too short follow-up time, and radiotherapy dose-fractionations: Goldie et al. (1970) with 92 gonarthroses and 23 coxarthroses and Valtonen et al. (1975) with 16 gonarthroses and 16 coxarthroses, using dosage concepts with single doses of 1.5–2.0 Gy and a maximum follow-up time of 6 weeks [256,775]. The results should therefore be viewed with these limitations in mind. Neither group found an effect of pain irradiation beyond placebo. A 2018 placebo-controlled, double-blind study randomized a total of 55 patients with symptomatic gonarthrosis and showed no effect of pain irradiation beyond placebo. However, in that study, 45.5% of patients (n=25) had a symptom duration before radiotherapy of >5 years, which must be considered a significant flaw in study design [524].

A study by Niewald et al. published in 2021 indicated that good pain relief was achieved with either 6×0.5 Gy or 6×0.05 Gy of radiotherapy for osteoarthritis of the knee joints, with no significant difference in effect between the two doses [554]. In that study, the mean duration of pain before radiation was 56.2 and 49.6 months in the study groups, respectively. This duration was similar to that in the 2018 study described above [524].

The conclusions from the most recent randomized trials [524, 554] are that there is a need for more appropriate patient selection, which should be the goal of future studies, and that patients need to be seen much earlier in the disease course. A pain history of more than 6 months has long been associated

with a worse outcome, which should be discussed with referring physicians.

Indication, knee osteoarthritis

Based on data to date, low-dose radiation for painful Kellgren stage 2-3 knee osteoarthritis should be recommended and performed as an effective treatment option when surgical intervention is not yet indicated or not desired [536] and conservative therapies are not effective, not tolerated, or are contraindicated.

Indication, coxarthrosis
Regarding painful stage 2–4 Kellgren's coxarthrosis, low-dose irradiation may be a therapeutic option according to current data when surgical interventions are not yet indicated or not desired and conservative therapies are not effective, not tolerated, or are contraindicated.

Target volume definition
The target volume should include the entire joint with the adjacent bony and muscular structures. The gonadal region should be covered with lead if necessary.

4.1.2.7 Radiotherapy technique

Knee osteoarthritis
Antero-posterior or lateral parallel opposed fields are to be used. The dosage is to be set at a uniform depth (e.g., knee joint center). For dosimetric reasons, higher energies (≥4 MV) are suitable. Single doses of 0.5–1.0 Gy and total doses of 3.0–6.0 Gy should be used, with irradiation 2-3 times per week.

Hip osteoarhritis
Antero-posterior parallel opposed fields are to be used. The dosage is to be set at a uniform depth (e.g., center of hip joint). Regarding the radiation energy, higher energies (≥10 MV) are preferred if possible. Single doses of 0.5–1.0 Gy and total doses of 3.0–6.0 Gy should be used, with irradiation 2-3 times per week.

Evaluation of the therapy response
Functional scores (see above) or visual analog scales should be used to assess the pain situation.

From a 2010 orthopedics statement on radiation therapy for gonarthrosis: "Certainly, low-dose radiation is also indicated for painful gonarthrosis in stage 2-3 according to Kellgren" [513].

4.1.2.8 Recommendation

Gonarthrosis
Radiotherapy can be performed, if indicated.

Evidence level 2c, recommendation level C

Coxarthrosis
Radiotherapy can be performed, if indicated.

Evidence level 4, recommendation level C

Upper and lower ankle joints

The data for this indication are limited, so that no level of evidence can be determined regarding the use of radiotherapy. However, the principles described for gonarthrosis and coxarthrosis apply analogously with regard to radiation technique and dosage.

Author	Patients	Radiotherapy energy	Response rate (%)	CR (%)	PR (%)	NC (%)
Fried (1934) [226]	126	Orthovolt	90.6	30.5	60.1	9.4
Bakke (1939) [34]	148	Orthovolt	83.8	26.2	57.6	16.2
Toschke (1941) [758]	148	Orthovolt	79.0	4.7	74.3	21.0
Cocchi (1943) [125]	188	Orthovolt	70.2	25.5	44.7	29.8
Pape and Gölles (1954) [594]	190	Orthovolt	76.0	25.0	51.1	24.0
Hess and Bonmann (1955) [305]	366	Orthovolt	60.1	11.7	48.4	39.9
Pizon (1957) [612]	201	Orthovolt	87.4	43.7	43.7	12.6
Wieland and Kuttig (1965) [812]	222	Orthovolt	90.1	62.6	27.5	9.9
Wieland (1966) [813]	341	Orthovolt	89.0	62.0	27.0	11.0
Mitrov and Harbrov (1967) [527]	820	Orthovolt	91.0	57.0	34.0	9.0
Grasshoff (1970) [265]	51	Orthovolt	74.5	9.8	64.7	25.5
From Pannewitz (1970) [591]	Not specified	Orthovolt	85.0	46.0	39.0	15.0
Hartweg et al. (1973) [287]	124	Orthovolt	87.0	29.0	58.0	13.0
Zschache (1972) [840]	461	Orthovolt	84.1	18.2	65.9	15.9
Hassenstein (1976) [289]	124	Orthovolt	85.5	29.0	56.5	14.5
Keilholz (1998) [399]	49	Orthovolt	63.3	20.4	42.9	36.7
Sautter-Bihl (1993) [669]	21	Co-60	81.0	14.0	67.0	19.0
Schultze (2000) [686]	113	Orthovolt	58.4	13.3	45.1	41.6
Glatzel (2004) [253]	214	Orthovolt	68.2	9.3	58.9	31.8
Ruppert (2004) [659]	31	Orthovolt	64.0			36.0
Keller (2013) [403]	1039	Orthovolt, Caesium, Linac	79.3	10.5	68.8	20.7
Bartmann (2017) [47]	139	Orthovolt, Linac	51.0	8.8	42.2	49.0
Total	5118		77.2	25.3	51.9	22.8
PCS (2010) [536]	5069	Orthovolt, Linac, Co-60	79.5	27.8	51.7	20.5

Table 4. Literature review of radiotherapy outcomes for painful gonarthrosis, including Patterns of Care Studies results.

Author	Patients	Radiotherapy Energy	Response rate (%)	CR (%)	PR (%)	NC (%)
Fried (1934) [226]	10	Orthovolt	80.0	20.0	60.0	20.0
Bakke (1939) [34]	83	Orthovolt	82.0	18.0	64.0	18.0
Toschke (1941) [758]	26	Orthovolt	42.3	0.0	42.3	57.7
Cocchi (1943) [125]	107	Orthovolt	68.2	24.3	43.9	31.8
Pape and Gölles (1954) [594]	30	Orrthovolt	66.7	20.0	46.7	33.3
Hess and Bonmann (1955) [305]	70	Orthovolt	24.3	4.3	20.0	75.7
Wieland and Kuttig (1965) [812]	31	Orthovolt	77.4	54.8	22.6	22.6
Wieland (1966) [813]	44	Orthovolt	89.0	52.3	36.7	11.0
Mitrov and Harbrov (1967) [527]	120	Orthovolt	77.5	27.5	50.0	22.5
Grasshoff (1970) [265]	55	Orthovolt	56.4	10.9	45.5	43.6
Zschache (1972) [840]	73	Orthovolt	65.8	9.6	56.2	34.2
Hess (1974) [304]	23	Orthovolt	39.1	21.7	17.4	60.9
Hassenstein (1976) [289]	120	Orthovolt	69.2	35.9	33.3	30.8
Lindner and Freislederer (1982) [473]	53	Orthovolt	43.3	9.4	33.9	56.7
Gardener (1988) [241]	8	Orthovolt	75.0	12.5	62.5	25.0
Keilholz (1998) [399]	7	Orthovolt	71.4	28.6	42.8	28.6
Schultze (2000) [686]	31	Orthovolt	38.7	9.7	29.0	61.3
Ruppert (2004) [659]	7	Orthovolt	67.0			33.0
Total	895		62.9	21.1	41.7	37.2

Table 5. Literature review of the results of radiotherapy for painful coxarthrosis.

4.1.3 Radiotherapy for painful osteoarthritis of the small joints (Update 2022)

4.1.3.1 Definition of osteoarthritis

The primary definition of osteoarthritis is pathological manifestation in one or more joints with more or less severe joint remodeling. There may be cartilage destruction, new bone formation, and changes in the joint capsule and synovium.

4.1.3.2 Epidemiology

Almost all people over age 65 years show radiographic signs of osteoarthritis, often without clinical symptoms. Significantly more women than men are affected (75%/25%). The disease process may be accelerated and intensified by diabetes mellitus, hyperuricemia, endocrine diseases, circulatory disorders, and trauma, the disease process can be accelerated and intensified.

4.1.3.3 Etiology

Mechanical stress and physical-chemical changes over time are are important factors in the development of osteoarthritis. With age, there is a metabolic slowdown in the joint. A mismatch develops between load and load-bearing capacity [581] of cartilage and bone, which causes wear and tear.

A distinction is made between primary arthrosis deformans as a result of (over)stress, which is a disease of advanced age, and secondary arthrosis deformans as a result of inflammatory or traumatic disorders [136].

The different phases of osteoarthritis

Phase 1: The smooth cartilage surface is damaged and becomes rough.

Phase 2: There is increasing tearing of the cartilage.

Phase 3: The damaged cartilage is increasingly destroyed by microtrauma, and its elasticity is reduced; reactive osteosclerosis develops because of higher subchondral pressure; and marginal osteophytes form.

Phase 4: The subchondral bone is exposed, bone abrasion begins, synovial fluid penetrates the medullary cavity through the defects in the subchondral boundary lamella, and typical boulder cysts appear.

Phase 5: Granulation tissue covers the articular surface (in case of movement without pressure) or ankylosis (in case of no movement).

4.1.3.4 Diagnostics

Clinical picture: Arthrosis deformans can affect single joints but often occurs locally in the context of several adjacent joints also being affected. Subjectively, there is initial heaviness and stiffness of the affected joint followed by pain, swelling, and even loss of joint function. The pain is described as a deep persistent pain that increases with weight bearing and decreases with rest.

Radiological findings
Typical thickening of the joint lines appears in the X-ray image. Due to the cartilage atrophy, subchondral sclerosis and joint space narrowing are seen. Typical osteophytes arise at the joint edges, and in the late stage, typical subchondral cysts are seen. On radionuclide scintigraphy, the three-phase scintigram is a particularly sensitive but not very specific examination method; it is useful for the differential diagnosis of inflammation, neoplasia, and avascular necrosis.

CT and MRI are also used for differentiation, such as to exclude osseous metastases in a known tumor disease or to exclude osteomyelitis. By detecting synovitis, MRI can be used to diagnose incipient osteoarthritis before the appearance of bony changes. Bone marrow edema-like signal changes in the fat-suppressing sequences are pre-erosive yet potentially reversible changes without correlation in conventional radiography [634].

4.1.3.5 Therapy options

Physiotherapy
Thermotherapy in the form of heat, hyperemic substances, or cold applications can lead to pain relief. Movement treatment, massage, and physiotherapy are used. Immobilization with arthrosis splints or surgical arthrodesis also can improve symptoms.

Drug therapy
One focus of osteoarthritis treatment is certainly drug therapy. NSAIDs are predominantly used. They inhibit cyclooxygenase, which is crucially involved in the formation of prostaglandins. The synthesis of prostaglandins — the so-called pain mediators that regulate functions such as pain, inflammation, and fever — is inhibited with NSAIDs, resulting in pain relief and anti-inflammation. Glucocorticoids have good anti-inflammatory effects but can have strong diabetogenic, catabolic, and ulcerogenic side effects [88]. Ointment dressings with anti-rheumatic agents do not have as many side effects as systemic application, but the resulting analgesia is not sufficient for severe pain.

Radiosynovectomy is a local therapy that is now used very frequently. The procedure has been known for about 50 years and is based on radiogenic obliteration of the inflamed synovium using an intraarticular injection of a radionuclide in colloidal form [491]. Depending on the inflammatory activity, the inflamed synovial membrane is irradiated, the hypertrophied layers are destroyed, and subsequently fibrosis of the synovial surface develops. The maximum range is only a few millimeters, which means that this therapy reaches its limits in the case of massive thickening of the synovial membrane [194].

Other options include homeopathy, complementary medicine therapies, and acupuncture, as well as biologicals, which are thought to intervene directly in the process of the immune modulation [634]. Treatment with ultrasound also can be used with success [138].

Reconstructive surgery and prosthetic joint replacement tend to be used as a last resort.

4.1.3.6 Radiotherapy

Dosage concept
Doses of 3.0–6.0 Gy are applied in single fractions of 0.5 to 1.0 Gy twice per week. According to the DEGRO guidelines for irradiation of nonmalignant diseases [517,705], the following dosage regimen is recommended:

For acute inflammation with a duration of symptoms <3 months, a per fraction of 0.5 Gy is recommended; for a duration of symptoms >3 months, the recommendation is to use a dose of 1 Gy per fraction,

applied twice or three times per week for 6 fractions and a total dose of 3-6 Gy [704,705].

If the effect is not sufficient, a second series at the same dosage can be performed after 6–8 weeks.

X-rays of energies 100 kV and 200 kV can be used; when using 6-MV photons, a bolus of 5 mm should be applied to small joints to achieve a comparable dose distribution at a depth of 5 mm. A parallel opposed field technique is preferable to the single direct field technique.

A recent randomized, placebo-controlled, double-blind study from 2018 randomized a total of 56 patients with symptomatic osteoarthritis of the hands and concluded that there was no effect of pain radiation beyond placebo [524]. However, 39.3% of the patients (n=22) had a pre-radiotherapy symptom duration of >5 years, which must be considered a limitation [524].

A 2021 study by Niewald et al. reported that good pain relief was achieved with either 6×0.5 Gy or 6×0.05 Gy of radiotherapy for osteoarthritis of the hand, with no significant difference in effect between the two doses [554]. In that study, the mean duration of pain before radiation was 56.2 and 49.6 months, respectively, in the two study groups. This duration was similar to that in the 2018 study [524]. It may be that the reason why there was no significant difference in the outcome between the two groups was because the patients were treated too late in their disease course, and we suggest that patients are seen earlier in their disease course, in particular within 6 months of their first symptoms.

Target volume definition
Irradiation planning must comply with ICRU 50 guidelines, including that the target volume is the affected joint and that the dose reference point has been established. When irradiating the fingers and toes, the nails must be shielded with lead, if possible, to prevent growth disturbances.

The indication should be made after interdisciplinary consultation (e.g., involving orthopedists, rheumatologists, pain therapists). Radiological findings and clinical examination should be the basis. For benefit-risk analysis considerations, ionizing radiation should be used only if other therapies do not yield similarly good results or are riskier than radiation therapy. All possibilities for radiation protection should be applied (beam direction, collimators, lead protection, etc.) to minimize possible damage to organs at risk.

An explanation of possible and potential side effects must be provided prior to radiotherapy, and written informed consent must be obtained from the patient.

The documentation of the initial findings, preparation of the therapy plan, and first field setting are carried out by the radiation therapist. Further irradiations are to be carried out under the supervision of a specialist. Positioning of the patient, field setting, collimators, lead covers, etc., must be documented (e.g., in photos).

Collection and documentation of the final findings can be done according to the von Pannewitz complaint score [704]:

Category 0 = Symptom-free: The patient does not feel any pain and is therefore completely symptom free.

Category 1 = Substantially improved: There has been a marked reduction in pain with periods of complete freedom from pain alternating with mild discomfort.

Category 2 = Improved: Discomfort has decreased, with pain decreased to a tolerable level.

Category 3 = Unchanged: No change resulted from radiotherapy, or pain level has returned to the level before therapy started after temporary improvement.

Category 4 = Deteriorated: Deterioration has occurred despite irradiation.

4.1.3.7 Summary and recommendation

Irradiation of osteoarthritis of small joints is a successful, low-cost, low-risk therapy that is an alternative to other forms of therapy.

However, because of the general risk of radiation, a careful risk-benefit assessment must be made in younger patients, for instance below the age of 40 years.

A total of 75% of patients with osteoarthritis of small joints benefit from analgesic irradiation. Even after >5 years, sustained pain relief can be achieved in more than half of these patients [362].

Radiation therapy with 6.0 Gy promises good success not only after a large number of pretreatments but also for patients with a pain history of >10 years. Although radiotherapy should be started early in the course of the disease, there are no significant differences in the success of therapy with regard to the duration of symptoms. Localization, age, or sex are also not influencing factors.

A second series of irradiation leads to success in >80% of patients. Even a third can still improve pain but not to the same extent as the second series.

Considering the radiation protection, with the age distribution of the patients (median, 65 years), the tumor risk is negligible [92]. For the dose ranges used in radiotherapy of joint arthrosis, no tumor induction has been described in the literature [85,319, 324,840].

4.1.3.8 Recommendation

Radiotherapy can be performed, if indicated.

Evidence level 4, recommendation level C

4.1.4 Painful shoulder syndrome

4.1.4.1 Definition

Shoulder syndrome includes periarthritis or periathropathia humeroscapularis, as well as omarthrosis and acromioclavicular arthritis.

Periathropathia humeroscapularis includes various degenerative and inflammatory diseases of the soft tissues at the shoulder joint, such as bursitis subacromialis or subdeltoidea; tendinopathies of the various tendons (supraspinatus muscle, biceps brachii muscle, and rotator cuff); and insertional tendinopathy at the coracoid process. Initial descriptions were made by Duplay and Codman [126,176].

4.1.4.2 Epidemiology

Shoulder syndrome affects about 2%–5% of the population, predominantly people over age 40 years and menopausal women. People with diabetes have an approximately 5-fold increased risk of developing the disease. The right shoulder is more frequently affected than the left.

4.1.4.3 Etiology and pathogenesis

Often, overloading with microtrauma is considered to be the cause of the inflammatory changes in tendons and bursae.

In the chronic course, these inflammatory and scarring processes can also calcify, although calcification does not necessarily contribute to symptoms [313]. Calcification is found on X-ray in many affected individuals but can occur in unaffected individuals [238,523,614,672].

Rotator tendons distended by calcifications can cause tightness under the fornix humeri with significant restriction of abduction motion, which is called impingement syndrome [427,546].

4.1.4.4 Diagnostics and differential diagnostics

The workup for shoulder syndrome includes history, clinical examination, and radiographs of the shoulder in multiple planes. The clinical examination also includes range of motion and mobility against resistance, especially in elevation and abduction.

4.1.4.5 General therapy options

Treatment options include topical and systemic application of anti-inflammatory drugs, local cold application, electrotherapy, ultrasound and shock wave treatment, and instillation of inflammation-modulating substances to physiotherapy and surgical measures. Several Cochrane reviews are available on this subject, although none of these treatments have been shown to be very effective.

4.1.4.6 Radiotherapy

As early as 1898, Sokoloff reported on the radiation treatment of painful joint lesions. In 1925, Staunig published his experience with over 400 patients with painful shoulder lesions [729,738].

Recording of results in the literature is often performed using the von Pannewitz score [590]. The effect of the treatment is often delayed, so an assessment of the treatment success is meaningful only several weeks after therapy.

A response to irradiation in the sense of a significant reduction in pain and more freedom from pain is described in 58%–100% of patients with shoulder syndrome. Of 7928 patients who were retrospectively evaluated, 55% of the patients became pain-free and 33% experienced an improvement in symptoms; only 12% had unchanged symptoms [313].

Modern randomized, placebo-controlled and double-blinded studies unfortunately do not exist. With caution, three historical studies with low patient numbers, short follow-up time, and in some cases unusual dosing could not prove more than a placebo effect for pain irradiation [256,613,775].

Better results are obtained with acute and earlier symptomatology than with chronicized symptoms, i.e., those existing for more than 6 months [1,11,32,243,266,303,329,419,423,436,460,473, 523,602,721]. Data on a higher response rate for patients with calcification appear contradictory [11,32,115,238,424,440,473,493,504,602].

Numerous authors report that calcifications disappear after radiotherapy [1,11,23,32,34,59,80,98,423,424,427,436,440,459,483,721,739]. Regression of calcification does not correlate with clinical improvement in symptoms [32,34,59,427,436,440].

Strict eligibility criteria should improve the treatment results. This also seems reasonable because there is a small but real risk of tumor induction [98,669,674].

Indication
Based on the data, low-dose irradiation for painful shoulder syndrome should be recommended and performed as an effective and side effect–free therapeutic option before surgical interventions when conservative therapies do not lead to the desired success, show too-severe side effects, or are contraindicated and surgical interventions are quite invasive.

Target volume definition
The target volume should include the entire shoulder joint with the adjacent bony and muscular structures, leaving the adjacent lung and mammary gland out of the target area. A smaller target volume may be selected for isolated supraspinatus or subdeltoid tendinitis.

Technology
An Orthovolt device or a high-voltage device can be used for treatment. The dosage is to be set at a uniform depth (e.g., center of the shoulder joint).

Single doses of 0.5–1.0 Gy as well as total doses of 3.0–6.0 Gy should be applied, and irradiation can be performed 2–5 times a week.

Evaluation of the therapy response
Pain relief and improvement of mobility are primary treatment goals; resolution of any calcification that may be present is not a therapeutic goal.

Functional scores or visual analog scales can be used to assess mobility and pain levels.

4.1.4.7 Recommendation

Radiotherapy can be performed, if indicated.

Evidence level 4, recommendation level C

4.2 Enthesopathies

4.2.1 Trochanteric bursitis

4.2.1.1 Definition

Trochanteric bursitis is also known as “greater trochanteric pain syndrome” (GTPS), which includes elements of tendinopathy. BT is a general term capturing acute or chronic non-infectious inflammation of the bursae around the greater trochanter. In the UK/US literature, the terms “trochanteric bursitis” and GTPS are often used synonymously [129,130].

4.2.1.2 Epidemiology

It is estimated that BT is one of the most common pain syndromes of the hip region in Western industrialized countries, with an incidence of 10%–25% [818]. The age distribution shows a maximum in the fourth to sixth decades of life [472,714], with the female sex being affected more frequently in a ratio of about 3-4:1 [711,723,757]. Segal et al. [711] demonstrated a prevalence of 17.6% based on a multicenter, retrospective study including 3026 adults. Lieviense et al. [472] reported an incidence of 1.8 cases per 1000 population/year.

4.2.1.3 Etiology and pathogenesis

The development of BT is most likely multifactorial. Chronic microtraumatization of the tissues caused by continued mechanical misuse or overuse and regional muscular-ligamentous dysfunction are probably responsible. The characteristic symptom complex of BT is usually triggered by an acute event, such as an unaccustomed walking load, local trauma, or chronic pressure on the trochanter [714,818]. These abnormal loads may result from, for example, painful coxarthrosis or lumbar syndrome; the incidence with lumbar syndrome is reported to be 20%–35% [129,476,711,757]. Advanced age, female sex, ipsilateral tractus iliotibialis complaints, activated gon- or coxarthrosis, obesity, and the presence of lumbar syndrome are considered risk factors that may favor the occurrence of BT [476,711,818].

4.2.1.4 Diagnostics, differential diagnosis

BT is primarily a clinical diagnosis. The leading symptom is acute, intermittent, or chronic pain, which in about 50% of patients radiates from the trochanteric region over the lateral aspect of the thigh along the tractus iliotibialis down to the knee joint. Lying on the affected side, prolonged standing, sitting with crossed legs, stair climbing, and intensive running are frequently given as causes in the patient’s medical history. With normal walking, on the other hand, the complaints can sometimes diminish. The Patrick/FABER test often allows a provocation of pain during the clinical examination. In case of prolonged persistence, abductor weakness may manifest itself in a positive Trendelenburg sign.

Imaging can support the clinical diagnosis. In protracted courses, conventional radiology can detect nonspecific peritrochanteric soft tissue calcifications; bursa distension can be detected by joint sonography. The imaging diagnostic method of choice, especially for surgical planning, is MRI. The T2-weighted sequences reliably detect inflammatory changes of the bursae and injuries of the muscle insertions [69,434,793].

Possible differential diagnoses include acute disc herniation or other vertebral complaints, abduction fracture of the femoral neck, coxarthrosis, nonspecific coxitis, tendovaginitis, or insertional tendinopathies of the hip muscles.

4.2.1.5 Therapy options (general)

With regard to primary therapy, conservative measures are most important because spontaneous symptom regression is also possible [489]. Behavioral changes play an important role in the form of mechanical relief, weight reduction, or avoidance of stress that triggers symptoms. Furthermore, in addition to extracorporeal shock wave therapy [231], almost the entire spectrum of physical therapy measures is applied [245,372,781]. For analgesic and anti-inflammatory local therapy, cold applications, Non-steroidal anti-inflammatory drugs, and local corticosteroid infiltrations have proven effective, and their use can achieve pain remission in 60%–100% of cases [41,127,183].

A surgical approach should be reserved for those cases that are refractory to conservative therapy. A wide variety of surgical techniques have been described, including open or endoscopic-assisted bursal resections [33,196,214,688,725], trochanteric osteotomies [261], or incisions or extensions of the fascia lata [607] or of the tractus iliotibialis [119].

4.2.1.6 The role of radiotherapy

Regarding the effectiveness of low-dose radiotherapy for the treatment of BT, very limited published data are available (n=157) [47,251,386,515,519,573]. Glatzel et al. [251] reported in an abstract on 34 patients (30 women, 4 men) who had received orthovoltage therapy (175 kV, 20 mA, FHA 40 cm) during July 1996 to March 2000 for “insertional tendopathy” at the greater trochanter. A single dose of 1.0 Gy was applied three times per week, the total dose per series was 6.0 Gy, and five patients had received a second irradiation series. The median follow-up period was 14 months. Three months after completion of radiotherapy, 38% were symptom-free (complete remission), 18% had significant pain relief, 29% had moderate pain relief, and 15% had experienced no improvement or had progressive symptoms. Olschewski and Klein [573] reported 10 years later on 26 patients (20 women, 6 men) who had received radiation to a total of 27 lesions from October 2008 to September 2009. In >80%, symptoms had previously persisted for more than a year. Follow-up examinations were performed at 3-month intervals using a pain score. In total, six patients (23%) had complete pain remission, 13 (50%) had partial remission, and seven patients (27%) were unchanged with respect to pain severity. No relevant side effects were observed; only one case involved transient erythema. In 2017, Micke et al. [515] published 27 cases of patients aged ≥70 years, of whom 69.2% were pain-free or significantly pain-relieved after a median follow-up of 29 months (3–39) in terms of initial pain. Kaltenborn et al. report 60 cases with a response rate of 70% at 3 months, of whom 37% of patients were pain-free [386]. Bartmann [47] reported in the context of a dissertation on 70 patients, and at a mean follow-up of 24 months (3–40), 29.9% were pain-free, 16.4% significantly improved, 19.4% slightly improved, 29.9% unchanged, and 4.5% worsened with regard to the initial pain. The results of this dissertation also were published in 2018 [519].

Dose concept/radiotherapy technique

In analogy to the treatment of other degenerative-inflammatory diseases, single doses of 0.5 to 1.0 Gy are used; thus, the total doses per series are 3.0 to 6.0 Gy. Spontaneous remission is possible, however, so symptoms should persist for at least 3 months before initiation of radiotherapy. Because of the close proximity, care should be taken to maximize gonadal sparing, especially for those of reproductive age, and a critical indication should be required.

Regarding the irradiation technique, a safe inclusion of the superficial and deep, primary, and secondary gluteus maximus bursa should be ensured; furthermore, the gluteofemoral bursa should be included caudally, which may have an extension of up to 7 cm in the craniocaudal direction in case of pronounced inflammation [826]. In case of treatment at the linear accelerator, opposing fields are recommended, which should be adjusted at the simulator; photon energies of 6–10 MV allow for a homogeneous dose distribution. CT-guided radiation planning or prior performance of diagnostic MRI of the hip region may be considered to accurately assess the size extent of the bursa. The empirical values reported in the literature are limited to orthovoltage irradiations; to achieve the most homogeneous dose distribution possible, 2-3 fields should be used (dorsoventral + lateral).

4.2.1.7 Recommendation

Radiotherapy can be performed, if indicated.

Evidence level 4, recommendation level C

4.2.2 Radiotherapy of Plantar Heel Pain

4.2.2.1 Definition

The definition of this condition consists of inflammatory changes in the plantar aponeurosis with formation of a bony spur at the distal limit of the calcaneus, triggering pain and difficulty walking because of the inflammation itself as well as the pressure of the spur on the soft tissue structures of the sole of the foot. The terms “plantar fasciitis” and “plantar heel spur” are included.

4.2.2.2 Epidemiology

The incidence is about 8%–10%, and especially 10% of runners are affected. Women are affected more often than men, with an age peak at >40 years [520].

4.2.2.3 Etiology

The underlying mechanism is an abnormal pronation in the hindfoot. This positioning can be favored, e.g., by lower leg and foot malformations such as tibia vara, pes equinus, and a varus position in the foot, and by overweight, unsuitable sports, and unsuitable footwear [520].

4.2.2.4 Pathogenesis

The excessive stretching of the plantar aponeurosis leads to microtraumas, especially at the proximal tendon insertion of the calcaneus. Chronic inflammation develops here, which ultimately promotes the formation of the bony spur [520].

4.2.2.5 Diagnostics

Medical history

In addition to the general anamnesis, the duration of the pain, previous treatment, and sporting and occupational stress on the heel should be recorded. In particular, the patient should be asked what activities improve or worsen the pain symptoms.

Investigation

Orthopedic examination and conventional radiography are essential. Optional ultrasound, bone scintigraphy, and MRI may be added if baseline diagnostics are unclear [412].

Standardized questionnaires should be used to assess symptomatology, e.g., the corresponding questionnaire of the German Cooperative Group on Radiotherapy for Benign Diseases (GCG-BD) [556].

Classification

Here, the use of a standardized score is also recommended, e.g., the calcaneodynia score according to Rowe [556,655].

4.2.2.6 Other therapy options

A summary meta-analysis by Salvioli et al. [664] in 2017 describes positive effects of shock waves, laser, orthotics, ultrasound-guided radiofrequency treatment, needle treatment, and taping vs. placebo, with moderate to low evidence.

Individual meta-analyses (excerpted):

- Platelet-rich plasma vs. corticosteroid injections (Yang et al., 2017, [830])
- Corticosteroid injections (David et al., 2017 [142])
- Extracorporeal shockwave therapy (Sun et al., 2017, [748]; Lou et al., 2017, [484])
- Botulinum toxin A injections (Tsikopoulos et al., 2016, [765])
- Insoles/orthoses (Lee et al., 2009, [464]; Hawke et al., 2008, [295])
- Overall, the evidence is moderate to low, and the best data are found for shockwave therapy and orthoses.

4.2.2.7 Radiotherapy

Mechanism of action of radiotherapy

The mechanism is not yet fully understood. Previously, an influence on the endothelium, tissue pH, and the autonomic nervous system, as well as a release of enzymes, has been suspected. More recent work has described an influence on macrophage function, apoptosis, and cytokine secretion (especially TGF-β1). Other studies have suggested decreased adherence of macrophages to endothelium, increased activity-induced cell death in polymorphonuclear cells, and decreased adhesion of granulocytes to endothelial cells, with a maximum of these anti-inflammatory effects at a single dose of 0.3–0.7 Gy [21, 234,323,643,647,649].

Indication for radiotherapy

Indications are a painful heel spur with a history of more than 3 months. Patients under age 40 years should not be irradiated as a rule. Patients between 30 and 40 years of age may be irradiated if all conservative methods have been exhausted and were unsuccessful. Clinical and radiological evidence of calcaneal spur should be required [556].

Radiotherapy technique

Orthovolt therapy is administered with a direct plantar field. A caveat is to apply a bolus at the lateral, dorsal, and medial heel edge, with dosage set at a uniform depth.

Alternatively, it is possible to administer 4–6 MV photons of a linear accelerator via a pair of lateral opposed fields, with dosing on the heel center (MPD) according to the ICRU.

Dosage

The total reference dose is 3.0–6.0 Gy, with single doses of 0.5–1.0 Gy, with treatments given twice per week. In this context, following the aforementioned radiobiological results and in accordance with the work of Ott et al. [579], a single dose of 0.5 Gy should be preferred.

Retrospective results

Classification of results is according to von Pannewitz [589].

Freedom from pain can be achieved with this radiotherapy approach in 13%–81% of patients, with additional pain relief in 7%–70% of patients (summarized in [520]).

Recent retrospective studies

- Mücke et al. [535] in 2007 reported on positive prognostic factors, which included patients with only one treatment series, age >58 years, and high-voltage treatment.

- Badakhshi et al. in 2014 [30], Koca et al. in 2014 [428], and Uysal et al. in 2015 [773] showed freedom from pain in at least 58% of patients.

- Hermann et al. in 2013 [301] found no effect of field size on pain relief.

- Hautmann et al. in 2014 [294] reported a positive effect of reradiation after initial treatment failure.

Patterns-of-care study

- Micke et al. covered patterns of care in 2004 [516].

Randomized trials

- Heyd et al. in 2001 [319]: 3.0 Gy/0.5 vs. 6.0 Gy/1.0 Gy, each 2× per week, with no significant difference.

- Niewald et al. in 2012 [555]: with a follow-up of 48 weeks, 6.0 Gy/1.0 Gy vs. 0.6 Gy/0.1 Gy, each twice per week, with the higher dosage significantly more effective.

- Ott et al. in 2013 and 2014 [579,580]: with a median follow-up of 32 months, 6.0 Gy/1.0 Gy vs. 3.0 Gy/0.5 Gy each 2×/week, with identical results and the consequence that the majority of institutions reduced dose to 3.0/0.5 Gy.

- Niewald et al. [553] and Prokein et al. in 2017 [620]: with a follow-up of 48 weeks, 6.0 Gy/1.0Gy 2×/week vs. 6.0 Gy/0.5 Gy 3×/week, showing identical results, with influence of fractionation not detected in patients.

Randomized comparison with alternative methods

- Canyilmaz et al. in 2014 [108]: radiotherapy vs. corticosteroid injections, with a median follow-up of 12.5 months, showing radiotherapy superior.

- Gogna et al. in 2016 [255]: radiotherapy vs. platelet-rich plasma with a follow-up of 6 months and the same results.

4.2.2.8 Summary

The indication for radiotherapy is the presence of appropriate symptoms and clinical and imaging evidence. Radiation with a total reference dose of 3.0(–6.0 Gy) with single fractions of 0.5(–1.0 Gy), 2-3 times per week, is recommended.

Radiation therapy is possible by means of Orthovolt therapy or low-energy photons from a linear accelerator. Pain relief can be achieved in up to 90% of patients without side effects.

4.2.2.9 Summary and recommendation

Radiotherapy should be performed, if indicated.

Evidence level 1b, recommendation level A

4.2.3 Radiotherapy for medial and lateral epicondylitis of the elbow

4.2.3.1 Definition

Elbow syndrome is an acquired, painful, irritable condition with degenerative changes in the connective tissue at the insertion sites of the muscle tendons in the area of the epicondylus humeri radialis or the epicondylus humeri ulnaris.

Synonyms are insertional tendinopathy, tendopathy, tendinitis, and epicondylitis [62]; in the case of lateral pain symptoms, also lateral epicondylitis, writer's cramp [657], and tennis elbow; and in the medial setting, medial epicondylitis and golfer's or thrower's elbow.

4.2.3.2 Epidemiology

The prevalence of elbow syndrome is reported to be 1%–4% in the general adult population ≥40 years of age [720]. It occurs more frequently between the ages of 40 and 60 years [152,281,720, 824]. Clear differences in sex distribution are not found, but the majority of studies assume a higher probability of disease for women [200,461,719,720,824]. In direct lateral comparison, pain occurs more frequently radially as well as at the dominant elbow joint [281,314,640,718]. Socioeconomic influencing factors are not assumed [162,281].

4.2.3.3 Etiology and pathogenesis

Common pathogenetic hypotheses are based on the consideration that mechanical overloads and/or cyclic, repetitive, and intense movements under eccentric loading leads to some kind of material fatigue, submicroscopic structural damage, and either inflammatory, inflammatory-degenerative, degenerative, or microtraumatic and then reparative-degenerative changes [511].

Signs of lipoidosis, hyalinization, fragmentation of tendon fibrils, calcification, necrosis, and fibrosis have been described at the tendon insertions as a morphological correlate for the symptoms of discomfort [622,681,682]. In addition, pathognomonic vascular and cellular proliferations have been described in this context [441,616,630,667]. Tendon ruptures have been interpreted as a consequence of the degeneration process [681].

4.2.3.4 Diagnostics and differential diagnostics

Medical history

The leading symptom is load-dependent joint pain, for example when grasping or carrying and holding loads. In some cases, this pain can even go so far as to severely interfere with everyday activities, such as shaking hands or lifting a cup. In addition to load-associated pain, night and rest pain are reported less frequently. History often will include unaccustomed (e.g., carrying an infant) or repetitive activities (e.g., at a computer workstation) [652].

Clinical examination

The diagnostic landmark symptom is localized pain in the area of the epicondylus humeri radialis or ulnaris [720]. The pain symptomatology may radiate along the arm proximally and distally [116]. On clinical examination, unrestricted function is usually found with regard to flexion and extension. Pronation, especially against resistance, is typically painfully limited. Externally recognizable signs of inflammation, accompanying motor or sensory deficits, and circulatory disturbances are not typical.

Special examinations:

- Thomsen handle [314]

- Middle finger stretching test [314]

- Forced extension [314]

- Chair lift or chair test [314]

Imaging and staging
In the case of persistent pain symptoms, the conventional X-ray of the elbow in two planes is part of the basic diagnosis, not least in order not to overlook accidental neoplastic processes [123]. In most cases, however, the radiographs show normal findings corresponding to the age of the patient. Occasionally, calcifications are found at the tendon insertion. MRI is suitable for further imaging, if necessary, as it can depict inflammatory changes in addition to optimal soft tissue imaging [671,795].

There is no widely accepted staging of elbow syndrome.

4.2.3.5 Other therapy options

- Avoidance of chronic mechanical overstressing

- Extracorporeal shockwave therapy [67,679]

- Iontophoresis [67,369]

- Laser [67,68,685]

- Physiotherapeutic applications [67,571]

- Acupuncture [67,685,761]

- Bandages [67,679]

- Corticosteroid injections [661,679,824]

- Botox injections [235,384]

- NSAIDs [67,679]

- Cell therapy [132,564]

- Operative therapy [116,128,416]

4.2.3.6 Radiotherapy

Results of irradiation to date
From 1923 to 2011, outcomes after radiotherapy for elbow syndrome have been reported in more than 2000 patients. Most publications described a treatment response in ≥70% of cases. Further details are given in Table 6.

Indication
Low-dose, anti-inflammatory irradiation for elbow syndrome should be recommended and performed as an effective therapeutic option when conservative therapies do not achieve the desired outcome, have too-severe side effects, or are contraindicated, and surgical intervention is not reasonable, possible, or desirable [317,696].

Target volume definition
The target volume should include the entire lateral or medial epicondyle with the adjacent bony and muscular structures. For irradiation, the target volume is determined using a simulator or 3D planning. Because of the extra-articular location of the epicondyle, the entire joint capsule does not need to be included.

Radiotherapy technique
Depending on the pain localization, a direct field is used on the Orthovolt device in the area of the lateral or medial epicondylus humeri. The field is set clinically on the device over the lateral or medial epicondyle. At the linear accelerator, irradiation is realized via parallel opposed fields at low photon energy. The dose reference point is located in the central axis of the opposing beams at the mid-point (i.e. at MPD). The single fraction dose is 0.5 Gy, and the total dose per series is 3.0 Gy. Irradiation should be performed 2-3 times a week. Common sizes of irradiation fields are 7×7, 6×8, and 10×10 cm. In case of pain persistence, a second irradiation series is possible after 10–12 weeks.

Evaluation of the therapy response
When evaluating treatment response after radiation therapy for elbow syndrome, the primary endpoint is pain relief. Routine assessment of pain remission should be performed using a visual analog scale, and a von Pannewitz score [589,590] should be assessed. More comprehensive functional assessments, such as the Neutral-0 method [753], Thomsen handgrip [314], middle finger extension test [314], forced extension [314], chair lift or chair test [314], or a possibly modified Morrey score [531] can be helpful in the investigation of further scientific questions.

4.2.3.7 Recommendation

Radiotherapy should be performed, if indicated.

Evidence level 2c, recommendation level B

Ref.	Year	Cases (n)	Technology	Response rate [%]	CR [%]	PR [%]	NC [%]
Kind [273]	1923	15	Orthovolt	93	33	60	7
Mustakallio et al. [541]	1939	18	Orthovolt	96	82	14	4
Cocchi [125]	1943	22	Orthovolt	59	41	18	41
Canigiani [107]	1946	23	Orthovolt	87	70	17	13
Morvay [532]	1953	102	Orthovolt	94	94	-	6
Hess et al. [305]	1955	65	Orthovolt	89	54	35	11
Pizon [612]	1957	10	Orthovolt	100	80	20	-
Reinhold et al. [633]	1961	212	Orthovolt	90	58	32	10
Germ [400]	1965	4 3	Orthovolt Co-60	25 100	- -	- -	75 -
Wieland et al. [812]	1965	15	Orthovolt	87	74	13	13
Pannewitz [592]	1970	43	Orthovolt	90	52	38	10
Zschache [840]	1972	150	Orthovolt	69	5	64	31
Keinert et al. [401]	1975	639	Orthovolt	84	64	20	16
Görlitz et al. [259]	1981	50	Orthovolt	84	54	30	16
Mantell [494]	1986	30	Orthovolt	47	40	7	53
Gärtner et al. [240]	1988	26 44	Orthovolt Co-60	50 64	- -	- -	50 36
Kammerer et al. [388]	1990	299	Orthovolt	73	16	57	27
Sautter-Bihl et al. [669]	1993	11	Co-60	91	64	27	9
Schäfer et al. [674]	1996	30	Cs-137	75	57	18	25
Heyd et al. [314]	1997	45	Co-60	69	16	53	31
Seegenschmiedt et al. [696,700]	1998	85	Orthovolt	91	54	37	8
Ott et al. [577]	2012	199	Orthovolt	91	18	73	9
Ott et al. [578]	2014	199	Orthovolt	94	51	43	6
Leszek et al. [469]	2015	50	Megavolt	70	-	-	-

Table 6. Results after radiotherapy for elbow syndrome.

4.3 Hyperproliferative processes

4.3.1 Radiotherapy for Dupuytren's disease (DD)

4.3.1.1 Introduction

Dupuytren's contracture or DD is a hyperproliferative disease of the connective tissue and subcutaneous adipose tissue originating from the palmar aponeurosis of one or both hands with connective tissue induration of the palm and gradual extension to the finger areas. The condition is named after the French anatomist Baron Guillaume Dupuytren (1777–1835), although it was also described by Felix Platter (1614) and Astley Cooper (1824) [177,178]. Gradual hardening and shrinkage of the palmar aponeurosis results in the formation of coarse nodules and cords, which in the long term leads to severe functional limitations of the hand and finger function and, due to a flexion contracture, to limitations in occupation and leisure. Correspondingly, Ledderhose Disease (LD), addressed in the next main section, is a hyperproliferative disease of the connective tissue and the subcutaneous fat tissue starting from the plantar aponeurosis of one or both soles of the foot and only occasionally extending to the forefoot and toes [12,28,95,124,462,485,522,526,534,610,624,678,786,828,833].

4.3.1.2 Epidemiology and Etiology

DD manifests in multiple forms, preferentially in the catchment area of the ulnar nerve in the region of the fourth and fifth digits of the hand. However, radial and mixed polytopic forms of DD also occur. In the course of life, the disease usually manifests on both sides; approximately 10%–15% of all patients with DD also have LD, while in 25%–30% of all patients with primary presence of LD, DD is also present. It is therefore always useful to ask the patient about involvement of the hands and feet and always to inspect and palpate all extremities at the initial presentation.

Increased risk is ascribed to those with white European ancestry, but the disease also occurs outside these ethnic groups. In Western industrialized nations, the prevalence is 1%–3%. In certain regions (Ireland/certain regions of France), it is as high as 17%. In older age (from the age of 40), the risk of disease is increased. Men are usually affected up to three times more often than women. So far, no correlation with handedness is known, but in the majority of cases, bilateral involvement occurs at some point. The causes of the disease are still controversial. However, an increased risk of the disease is known with a positive family history (first-/second-degree relationship), alcohol and nicotine abuse, liver disease (especially cirrhosis), diabetes mellitus, the presence of epilepsy or the use of antiepileptic drugs, and the occurrence of other fibromatoses such as LD and Peyronie's disease, keloid formation after surgery, and "frozen shoulder" syndrome [91,485,503,522,540,698,707,828].

4.3.1.3 Pathogenesis and staging

Histopathologically and clinically, three stages of disease (according to Luck) can be distinguished, which are significant for treatability with radiotherapy [485]:

(1) In the proliferation phase, inflammatory cells and especially highly proliferating fibroblasts are initially found in greater numbers, resulting in the increased formation of type I collagen. At the same time, an increased appearance of macrophages and perivascular inflammatory cells is observed [18]. This phase of the disease is radiosensitive with respect to radiogenic influence on inflammatory cells and proliferating fibroblasts.

(2) In the involution phase, reparative processes already dominate. There is an accumulation of myofibroblasts in the fibrinous tissue of the fiber bundles, which initiates the formation of nodules and cords. This phase is only slightly radiosensitive and limited to the existing fibroblasts in the sense of proliferation inhibition.

(3) In the residual phase, fibroblast activity is suspended, the stored collagen matures, accompanied by a resulting hardening of the affected connective tissue, and finally leads to flexion contractures/increased scar formation in the respective affected fingers. This phase of the disease is not suitable for radiotherapy.

In DD, in addition to conspicuous fibroblasts, the so-called myofibroblasts represent a special feature. Gabbiani et al. detected myofibroblasts for the first time in diseased Dupuytren's tissue [232]. These cells, related to smooth muscle cells, are modified fibroblasts with intracytoplasmic myofilaments. The histogenetic origin of myofibroblasts is not clear. A proliferation of capillary endothelial cells has been discussed, which then migrate as pericytes and proliferate in the fascia, especially perivascularly [756]. The clinical stage of the disease is evaluated according to Tubiana et al. [766]. This classification, which is important for clinical practice, is based on the severity of the extension deficit in the affected metacarpophalangeal and proximal interphalangeal joints (see Table 9).

Grade 0:	no (visible) changes, possibly only early symptoms no indication for RT		
Grade N:	nodes without flexion contracture		very good indication for RT
Grade N/I:	Flexion contracture from 1° to 10°	with evidence of nodes	high effectiveness of RT
Grade I:	flexion contracture 11 to 45°	with evidence of nodes	low effectiveness of RT
Grade II:	Flexion contracture 46 to 90°.	with evidence of nodes	no effectiveness of RT
Grade III:	flexion contracture 91 to 135°	with evidence of nodes	no effectiveness of RT
Grade IV:	Flexion contracture >135°	with evidence of nodes.	no effectiveness of RT

Table 7. Clinical staging of Dupuytren's disease and significance for radiotherapy indication.

According to this classification, stage I already includes a very wide range, from only a minimal to a significant functional deficit. Therefore, to allow for a better differentiation for the indication of radiotherapy in the clinical course, the stage or grade N was further subdivided into the stages N(0) without flexion contracture and N/I with a minor flexion contracture of up to 10° [398]. To date, this classification is commonly used only by radiation oncologists. For hand surgeons, functional deficits of 30° or more are relevant for the indication of invasive measures (e.g., percutaneous needle fasciotomy).

4.3.1.4 Therapy options

Without any therapy, clinical progression rates (increase in nodules and cords, angular deficit of fingers) of more than 50% of early stages were observed after more than 6 years [51,193].

Non-surgical procedures
In addition to a purely wait-and-see approach (wait-and-see strategy) until possibly necessary surgical measures, reduction of risk factors (e.g., abstaining from nicotine and alcohol), changes in medication (e.g., abstaining from chondroitin sulfate, antiepileptic drugs), and intake of preventive drugs (such as vitamin E), if warranted, are possible in the early phase. Conservative therapy concepts in the sense of local drug treatment have so far shown no long-term effect. Systemic administration of drugs is therefore considered ineffective. Furthermore, long-term controlled randomized studies are lacking.

The efficacy of percutaneous local radiotherapy in preventing progression in early-stage DD has been demonstrated in numerous phase 1/2 clinical trials (see Table 9) [4,205,300,306,398,430,487,698,699,707,788,799], and this is well recognized, but it is adequately supported by only a few controlled phase 3 studies.

Surgical procedures
Surgical treatment concepts are considered effective because, in principle, they are used only to correct functional deficits when hand function is limited. Functional disturbances in everyday life and a functional extension deficit from 30°–45° are generally accepted indications for surgical measures. The aim is to improve function. Cure by surgical means is not yet possible. Surgical procedures are thus limited to advanced stages of the disease and lie at the end of the line of treatment options.

Two approaches for surgery are distinguished. Minimally invasive procedures include needle fasciotomy, but various extended open surgical measures are also considered, such as partial fasciectomy for limited findings and total fasciectomy for extensive findings. These procedures are considered well evaluated and established in surgery (hand and plastic surgery) [193,244,340,457,503,526]. Randomized studies comparing the different surgical procedures are not available, however. Overall, a significant overall complication rate of 15%–20% can be expected with hand surgery therapy procedures [151]. Furthermore, despite the surgical measures performed, in the long term, 30%–50% of patients experience a renewed progression or recurrence of the disease within or outside the surgical area.

Enzyme injection (collagenase)
For two decades, a non-surgical method for the treatment of DD has been developed in the United States that in the advanced stage (advanced contracture) involves injection of a connective tissue–specific enzyme (clostridial collagenase) into the Dupuytren's cord to partially dissolve it and then mechanically "break it open." The hard connective tissue cords consist predominately of collagen and can be broken down by the injected enzyme collagenase within a few hours. In most cases, the first attempt to manually and mechanically break up or cause the affected cords to rupture is made after only 24 hours, as in needle fasciotomy. Phase 1/2 controlled registration studies showed that in most cases, even severely curved fingers could be largely stretched again after one month. Enzyme injection is thus seen as an effective method and possible alternative to hand surgery. The therapy also appears to be effective in the longer term, but statistically meaningful evidence of its long-term effect is lacking to date [408]. Overall, collagenase treatment has gradually become established in the repertoire of hand surgery as a minimally invasive therapy for monotopic and oligotopic involvement of DD and also in recurrences [353].

Since 2011, treatment with collagenase has been approved in principle both in Europe and in Germany (product name: Xiapex ®). The drug has been taken off the market in Germany but can be obtained elsewhere; however, the treatment is not reimbursed by all statutory health insurers for cost reasons.

4.3.1.5 Early-stage radiotherapy
Radiation therapy for DD continues to be regarded with skepticism from a hand surgery perspective, among other things because long-term evidence from clinical studies is still lacking (36,377]. Also unknown are the mechanisms of action of ionizing radiation on proliferating fibroblasts and

myofibroblasts in the early stage, which have been demonstrated radiobiologically (641,656]. It is therefore all the more important to explain radiotherapy adequately to patients and referring physicians and to apply it only at the right stage and for clinically clear indications.

Radiation therapy, as a non-surgical treatment, can halt the progression of the disease even in the early stages (stage N and N/I). The affected areas of the palm or sole of the foot can be effectively irradiated using superficial soft X-rays (e.g., 125–150 kV) or electrons (4–6 MeV). In this process, all unaffected hand and foot regions are individually blocked out of the radiation field with lead shields.

For irradiation, different dose concepts have been established in the past. For fractionated irradiation, 2–4 Gy has been given as single doses, and for total doses, clinical experience has included 20–40 Gy, although there have been very few clinical studies with long-term results (more than 5 years follow-up) or studies with a non-treated or differently treated control group to investigate at which time point irradiation is useful and which dose concept is most effective.

Numerous standardized steps are required to perform radiation treatment.

Medical history/clinical examination
Due to the long-term course of the disease, a long-term history and clinical examination are recommended for later comparison purposes, as is systematic documentation, including photo documentation.

The corresponding documentation forms for taking medical histories and documenting findings are included in this guideline. One recommendation is to always photographically record the pattern of the affected area in relation to the selected radiation fields so that possible radiogenic acute and/or chronic radiation reactions and possible recurrences inside and outside the radiotherapy field can be precisely assigned later.

Palpable nodes and cords are usually marked directly on the skin with a colored pencil. For a 1:1 image, a photocopy can be made on a standard photocopier or digital photograph. This step ensures objective comparability of baseline findings to findings during follow-up at 3, 12, and 36 months after radiotherapy. Subjective symptoms and changes in complaints can be recorded in writing and in tabular form.

Indication
The indication for radiotherapy in early-stage DD is strictly linked to the presence of an early-stage and currently active disease. This determination should be made either on taking a clinical history, using precise information from the patient or in the further course by clinical evidence and observation over 3–6 months. The indication is based on the radiobiological rationale that proliferating fibroblasts and myofibroblasts play an essential pathogenic role in the progression of the disease.

Radiotherapy is not considered useful in the early stage without proven progression, in the “inactivity phase” when the disease has been stable for several years, or in severely advanced disease (e.g., from an angular deficit of >30°). In each case, the radiobiological targets — the proliferating fibroblasts and myofibroblasts — are not available or are not activated. Renewed stimulation of these cells by growth factors may occur, for example, after trauma or open hand surgery, which is why postoperative treatment with ionizing radiation may make sense in such instances, as has been successfully implemented in keloid treatment. Meaningful clinical studies are lacking, however, on the postoperative situation and the possible use of radiation therapy or first clinical data for a safe indication.

Documentation and radiotherapy planning
Before treatment, the patient should receive a detailed explanation about the long-term and prospective nature of the treatment. Possible risk factors (nicotine, alcohol) must be addressed,

including with regard to the potential for increased radiogenic side effects. In principle, it makes sense to also inform the patient about a slightly increased long-term local cancer risk in the region of irradiation [367]. In addition, the related need for regular follow-up examinations should be emphasized.

Radiotherapy is based on the individual extent of the objectively determined clinical findings on the palm or sole of the foot, including a sufficient safety margin. Irradiation is performed either on an Orthovolt device (with tube voltage 125–150 kV), with a 10×15–cm tube over a palmar or plantar standing field at a focus-skin distance of 30–40 cm, or on a linear accelerator, with 4–6 MeV electrons and a 5-mm bolus to adjust the depth dose effect. The unaffected areas of the palm or sole of the foot are individually shielded with lead rubber (for Orthovolt irradiation) or with a 1-cm lead absorber (for electron irradiation). The area between D1 (thumb) and D2 (index finger) is usually not irradiated because the functionality of the thumb in opposition to the fingers is functionally less important than the increasing extension deficit of the D2–D5 fingers. Exceptions are, e.g., patients needing special or highly demanding hand function, such as when playing the piano.

The guideline for determining the target volume is a safety distance of 2 cm proximal and distal and 1 cm medial and lateral to the clinically clearly recognizable nodes and cords, if possible. The field boundaries must be documented by sketch or photographically, as further therapeutic measures may be necessary later in the disease course.

Radiotherapy dose concepts
Within the framework of a Patterns of Care study of the DEGRO AG Benign Diseases, it was shown that various radiotherapy concepts are applied in Germany or have been clinically evaluated in studies. Of note, most institutions use hypofractionated concepts with relatively high single doses in the range of >3 Gy, reaching total doses of >30 Gy, which is supported by clinical studies. In contrast, another frequently applied concept with 10×2 Gy over 2 weeks, up to 20 Gy, has only weak evidence supplied from a single clinical study.

With fibroblasts/myofibroblasts as target cells or hyperproliferation as the relevant target mechanism, higher individual doses can be assumed to have a more favorable overall effect on proliferation. Corresponding radiobiological analyses by Brenner et al. confirm this idea that higher single doses and total doses are more likely to be used in fibromatous disease processes [91].

1)	3 x 10 Gy → 30 Gy	with radium moulage 1 x per month [204] (historical concept, currently not practiced).
(2)	8 x 4 Gy→ 32 Gy	(each 2 x 4 Gy/week with 4 weeks off each) over 3 months (historical concept, currently practiced by dermatologists).
(3)	7 x 3 Gy → 21 Gy	(every 2 days for a total of 14 days) (evaluated only in a randomized trial to date).
(4)	10 x 3 Gy → 30 Gy	(5 x 3 Gy in 2 series / 12 weeks off) over 3 months (frequently practiced concept that was also evaluated in a larger monocentric randomized trial).
(5)	10 x 2 Gy →20 Gy	(5 x 2 Gy/week) over 2 weeks (frequently practiced concept, not yet prospectively evaluated).

Table 8. Published radiotherapy concepts for Dupuytren's disease and clinical significance.

In this respect, results of phase 1/2 studies to date and a controlled phase 3 study play an important role in further defining so-called “standard concepts” in radiotherapy. Beyond these data, no other radiotherapeutic concept can be recommended in principle, unless it were to be tested in a controlled manner against these existing strategies.

4.3.1.6 General clinical results of radiotherapy

In numerous non-controlled monocentric phase 1/2 studies — mostly from Europe, including Germany — the concept of prophylactic radiotherapy in early-stage DD has been successfully developed [154,300,306,398,430,487,788,799,838]. Nevertheless, radiotherapy has not yet gained international acceptance [465,575,746]. This slow uptake may be the result of the absence of solid foundational data from controlled phase 3 studies, in addition to inadequate infrastructure (training, experience) [36,377]. Below, we report data from a phase 1/2 study.

In this phase 1/2 study, 206 patients (297 hands and 426 nodes and/or cords) underwent irradiation with Orthovolt beams (50 kV energy, 25 mA, 1 mm Al filter, 4 cm round tube, half depth 15 mm) and a dose schedule of 2×4 Gy per week at intervals of 3-4 weeks and a total dose of 32 Gy distributed over 8 weeks. During the long-term follow-up to 27 years (median 40 months), 93 (45%) patients showed symptom decrease, 72 (35%) had symptom stabilization, and 41 (20%) experienced progression. Average subjective satisfaction on a 10-item visual analog scale (0=dissatisfied; 10=extremely satisfied) was 7.9 points. A total of 92 (22%) nodes and/or cords disappeared after irradiation. Acute radiogenic side effects occurred as erythema in 42 (20%), skin dryness in 82 (40%), and skin desquamation in 8 (4%) patients. Chronic side effects were skin dryness in 41 (20%), skin atrophy in 7 (3%), loss of sweat gland activity in 8 (4%), telangiectasia in 6 (3%), skin desquamation in 5 (2%), and sensory disturbances in 4 (2%) patients. A shorter symptom duration with irradiation of less than 20 months was a prognostically favorable factor. No other prognostic factors for response were identified [838.]

Only long-term clinical analyses, in particular studies conducted in Erlangen and Essen, have provided convincing long-term evidence of clinical efficacy. These studies also show that the response decreases with a longer follow-up interval, however, especially for the more advanced stages I to IV, or with an extension deficit of 10°–30° because in these situations, the disease process is less amenable to influence. Thus, radiotherapy is mainly considered for stages that involve minor to no functional limitations and thus no competing treatments. This view and approach have now been adopted by some other countries/regions in Europe, such as the Royal College of Radiologists Benign Radiotherapy Guidelines [545].

Significance of the Erlangen study

The Erlangen study plays a special role in the indication and assessment of the long-term course. From 12/1982 to 02/2006, a total of 135 patients or 208 hands were recruited for treatment. Patients were consistently followed up from 1985, with controls for various patient- and disease-specific influencing variables and prognostic parameters. Regarding the radiotherapy concept, no specific question was addressed during this period; all patients/cases received the same dose concept of 10×3 Gy in two series 6–8 weeks apart, up to a total dose of 30 Gy. An Orthovolt technique with sufficient energy (120 kV; 20 mA; 4 mm Al filter) and individual collimation (lead rubber) was used. The median follow-up time was 13 years (range, 2–25 years).

Relative to baseline before treatment, 123 cases (59%) remained stable in the long term and 20 cases (10%) improved, whereas 65 (31%) developed progression. Depending on the baseline stage, in stage N, 87% of cases were stable or regressed; in stage N/I, 70% remained stable or regressed; and in advanced stages I to IV, the rate of progression increased sharply over the long-term despite radiotherapy, with 62% in stage I and 86% in stage II experiencing progression. Two-thirds of all patients benefited from a decrease in symptoms, such as burning, itching, and feelings of pressure and tension.

A minor dry skin reaction was observed in 32% of patients prior to radiotherapy and did not increase the rate of peri- or postoperative complications in case surgery was needed later. In addition, not a single case of radiation-induced cancer occurred.

Significance of the Essen study
The Essen study is currently the only prospective controlled randomized trial comparing an untreated control group with two different radiotherapy concepts in long-term follow-up. A total of 489 patients (291 men; 198 women) were recruited from 01/1997 to 12/2009 and followed up for at least 5 years (range, 5–13 years). Because of bilateral involvement, a total of 718 hands were evaluated. According to Tubiana classification, 470 (65.5%) were stage N, 124 (17%) were stage N/I (10° deficit), 106 (15%) were stage I (11°–45° deficit), and 18 (2.5%) were stage II (46°–90° deficit). After education about the different options (wait-and-see strategy versus radiotherapy), 83 patients (122 hands) chose clinical observation alone, and 406 patients (596 hands) opted for radiotherapy. This latter group was randomized to two different dose regimens:

(1) 207 patients (303 hands) received 10×3 Gy in two series of 5×3 Gy each with a break of 10–12 weeks for a total dose of 30 Gy

(2) 199 patients (297 hands) received 7×3 Gy in a series in 2 weeks, with only three fractions administered per week

Acute adverse event rates were moderately increased for the 7×3 Gy approach; an acute Common Terminology Criteria grade 1 reaction occurred in 26.5% and a grade 2 reaction in 2.5% of patients. Late reactions in the form of dry skin were observed in 14%, and cancer induction was not observed in any patients.

After a follow-up of at least 5 years (mean, 8.5 years), 119 patients (16.5%) showed remission of nodules, cords, and or symptoms, 383 (53%) remained stable, and 206 (29%) showed clinical progression (increase in nodules or cords, symptoms, or angular deficits), resulting in surgery in 97 hands (13.5%). The progression rate for the untreated control group was 60% for any form of progression and 30% for surgery. By comparison, progression rates were significantly lower in irradiated patients. In the group irradiated with 21 Gy, the progression rate was 24%, and 12% underwent surgery. In the group irradiated with 30 Gy, the progression rate was 19.5%, and 8% underwent surgery ($p<0.0001$).

These results were confirmed for all details of the disease when comparing the treatment groups with the untreated control group, such as the number of nodules and cords, angular deficit, and various symptoms ($p<0.01$). The control group experienced progression in 63 hands (52%) compared with 64 (22%) and 49 (16%) in the 21 Gy and 30 Gy irradiation groups, respectively. Overall, re-progression or recurrence occurred in 50 cases (8%) within the irradiated region and 114 cases (19%) outside the irradiated region in the irradiated patients. By comparison, these rates were 52% and 28%, respectively, in the control group. In case of progression after irradiation, surgery was possible without an increased rate of complications or side effects (wound healing disorders).

Univariate and multivariate prognostic factors for progression were determined to be the following parameters: nicotine abuse (statistical trend), symptom duration of more than 24 months before initiation of irradiation, stage of disease, angle deficit, and digital disease (all with $p<0.05$). The most important independent prognostic factor was the treatment itself, with a clear difference between irradiation and non-irradiation and slight advantages for the 30-Gy group over the 21-Gy group.

4.3.1.7 Summary statements for DD radiotherapy

If the radiobiological considerations and individual results and statements of the clinical studies to date are transferred to the definition of a “level of evidence” and a grade of recommendation or grade of recommendation for irradiation, the following statements are supported.

Indication

The indication for radiotherapy is limited to primary “prophylactic treatment” in the early stage of “nodule formation” with no or only minimal extension deficit (maximum 10° to 30°); clinical results confirm the low response in higher stages. In this respect, there is no “competition” or “overlap of indication” for radiotherapy and surgical measures. The aim of treatment is to prevent further progression of the disease in time to prevent (further) restriction of hand function and, if necessary, to avoid surgery.

Irradiation in the “inactive phase” of the disease without a detectable progression of the disease within a period of 3–6 months is not indicated. In this case, a wait-and-see strategy is always recommended, with annual subjective and objective control of the findings.

There is currently no evidence on the efficacy of radiotherapy after surgery to correct a higher grade functional deficit (stage I to IV) to prevent new early or later nodule formation or functional deficit. Neither the correct timing nor the effective dose for such a procedure is currently established. Radiotherapy is generally not recommended and should be closely coordinated with the surgeon in individual cases. Prospective randomized studies are needed in the long term.

Irradiation technology

Care must be taken to ensure that the target volume is adequately determined by careful preliminary examination, if necessary, with imaging (MRI, ultrasound), and an optimal radiation technique. The selected target volume should be neither too small nor too large. The target volume is always based on the current findings and includes an additional safety zone of 1-2 cm. Nevertheless, even with careful technique, re-progression or recurrence is possible within and outside the irradiated target volume. Both an Orthovolt technique with sufficiently high energy (at least 100–125 kV) and electrons (4–6 MeV) from a linear accelerator can be used in conjunction with a 5-mm bolus. There is no superiority of one technique over the other when used correctly. In addition, the use of individual lead shields is recommended.

Irradiation concept

Based on the clinical trials performed to date — consisting of numerous phase 1/2 trials, some of which are longer term, and one controlled phase 3 trial — the highest level of evidence currently exists for performing radiotherapy at all versus a wait-and-see strategy alone.

A direct controlled comparison between the individual dosing concepts shows a slight superiority for doses with at least a 3-Gy single dose and at least 21-Gy total dose. For lower single doses, e.g., of 2 Gy or total doses of 20 Gy, the available data are insufficient. The dosage concept with 10×3 Gy in two series at intervals of 8–12 weeks currently offers the strongest evidence.

Documentation and aftercare

The clinical studies conducted to date rely on long-term success monitoring. In this respect, careful and standardized documentation is recommended. The DEGRO AG Benign Diseases has developed appropriate templates for this purpose (see Appendix).

In particular, photo documentation before treatment and during follow-up is useful (objective assessment criteria). Pre-structured questionnaires are useful for recording symptoms and functional limitations (see Appendix).

As a minimum period for following up on radiotherapy, a period of 3 months is required, and 6 or 12 months is better still. Long-term follow-up also can be recorded annually via forms without direct patient contact. In the event of renewed progression or unusual skin reactions, a short-term follow-up visit to the radiation therapist is advisable.

Recurrence or progression is generally defined as the appearance of new nodules and/or cords and/or an increase in the extension deficit of 20°–30° per finger ray.

Importance of clinical studies
The results of the Essen study show the advantage of radiotherapy in "active disease" at an early stage. Outside this indication, the possible use of radiotherapy in the postoperative course must be evaluated, because early and late recurrences are repeatedly observed. In individual cases, after complete healing a few weeks after surgery, i.e., not immediately postoperatively as in the case of keloid, treatment with a radiation series of 5×3 Gy (15 Gy) can be attempted. However, this procedure should be performed interdisciplinarily only in cooperation with the treating surgeon. The DEGRO AG Benign Diseases therefore recommends initiating a corresponding study.

4.3.1.8 Recommendation

Radiotherapy should be performed for Dupuytren's disease only in the active early stage of "nodule formation" (stage N and N/I).

Evidence level 2 c, recommendation level B

Note: Radiation therapy after needle fasciotomy, collagenase injection, or surgery has not been evaluated to date and should be tried only in the context of individual curative trials or as part of a systematic controlled clinical trial.

Study (year)	Radiotherapy concept		Follow-up
	Single dose	Total dose	(years)
Finney (1955) [205]	1–3×1000 rad Ra-Moulage	1000–3000 rad	Unknown
Wasserburger (1956) [799]	1-3×1000 rad Ra-Moulage	1000–3000 rad	"Long term"
Lukacs et al. (1978) [487]	(2×4 Gy) ×4 every 4 weeks	32 Gy	unknown
Vogt and Hochschau (1980) [788]	(2×4 Gy) ×4 every 4 weeks	32 Gy	>3 years
Hesselkamp et al. (1981) [306]	(2×4 Gy) ×4 every 4 weeks	40 Gy	1–9 years
Köhler (1984) [430]	10×2 Gy 3–5×/week	20 Gy	1–3 years
Herbst et al. (1986) [300]	3–14×3 Gy 5×/week; 2 RT series	15 (30) 42 Gy	>1.5 years
Keilholz et al. (1996/1997) [398]	10×3 Gy 5×/wk; 2 RT series	30 Gy	1–12 years; median, 6 years
Seegenschmiedt et al. (2001 and 2012) randomized [698,699,706]	10×3 Gy versus 7×3 Gy versus observation alone	30 Gy 21 Gy	5–13 years; median, 8.5 years
Adamietz et al. (2000/2001); Betz et al. (2010) [4,64]	10×3 Gy 5×/week; 2nd radiotherapy series	30 Gy	5–25 years; median, 12 years
Schuster et al. (2015) [690]	7×3 Gy (1 series) or 10×3 Gy (2 series)	21 Gy 30 Gy	median, 30 months
Zirbs et al. (2015) [838]	(2×4 Gy) ×4 every 4 weeks	32 Gy	1–27 years; median, 40 months

Table 9. Radiotherapy concepts/single and total dose in Dupuytren's disease.

Study (year)	Patients (cases)		Follow-up	Clinical Outcomes [N (%)]		
Author (Jahr)	(Stad.)	(N)	N (%)	„Regression"	„No Change"	„Progression"
Finney (1955) [205]	43	not specified	FU: NA 25 (58%) Fälle	15 / 25 (60%) „good functional result"		
Wasserburger (1956) [799]	213	not specified	„long-term" 146 (69%) pts	„long-term cure" Stad. I: 62 of 69 (90%); Stad. II: 26 of 46 (57%); Stad. III: 10 of 31 (32%)		
Lukacs et al. (1978) [487]	106	(I: 140) (II: 18)	FU: NA 36 (23%) cases	I: 26 of 32 (81%) II: 3 of 4 (75%)	I: 6 / 32 (19%)	None
Vogt & Hochschau (1980) [788]	(I: 98) (II: 4) (III: 7)	(154)	FU > 3 years 109 (63%) pts	I: 21 of 98 (21%) II: 1 of 4 (25%) III: --	I: 73 / 98 (74%) II: 2 / 4 (50%) III: 6 / 7 (86%)	I: 4 / 98 (4%) II: 1 / 4 (25%) III: 1 / 5 (20%)
Hesselkamp et al. (1981) [306]	46	(65)	FU 1 – 9 years 46 (53%) pts	total: 24 (52%)	total: 19 (41%)	total: 3 (7%);
Köhler (1984) [430]	31	(38)	FU 1 - 3 years 33 (87%) Fälle	total: 7 (21%)	total: 20 (61%)	total: 6 (18%)
Herbst et al. (1986) [300]	33	(46)	FU > 1,5 years 46 (100%) cases	None	total: 45 (98%)	total: 1 (2%)
Keilholz et al. (1997) „Erlangen I" [398]	96 pts 142 hands	(N: 82) (N/I: 17) (I: 30) (II: 13)	FU 1 – 12 years; median: 6 years	10 (7%) improved @ 3 months, 130 (92%) stable, 2 (1%) in progression Stages: N: 99%, N/I: 88%, I: 77%, II - IV: 54% without progression 13 (23%) with progress of which 8 within RT region and 5 outside RT region.		
Adamietz et al. (2001) „Erlangen II" [4]	99 pts 176 hands	(N: 81) (N/I: 15) (I: 65) (II: 15)	FU 7 – 18 years; median: 10 years	Stage N: 84%, N/I: 67%, I: 35%, II – IV: 17% ohne Progress		
Betz et al. (2010) „Erlangen III" [64]	135 pts 208 hands	(N: 115) (N/I: 33) (I: 50) (II: 10)	FU 2 – 25 years; median: 13 years	20 (10%) improved @ last follow-up, 123 (59%) stable, 65 (31%) with progression. Stages: N 87%, N/I: 70%, I: 38%, II - IV: 14% without progression.		
Seegenschmiedt et al. (2001) „Essen I" [706]	2 arms A: 63 B: 66	(95) (103)	FU > 1 year all (100%) pts	Subjective / Objective: 55 (56%) Symptome 55 (53%) Symptome	35 (37%) 39 (38%)	7 (7%) 9 (9%)
Seegenschmiedt et al. (2012) „Essen II" [698,699]	2 arms A: 303 B: 297 C: 122	N: 470 N/I: 124 I: 106 II: 18	Minimum-FU > 5 years median: 8,5 years	A (30Gy) Progress B (21 Gy) C (0 Gy)	49 (16%) 64 (22%) 63 (52%)	OP: 25 (8%) 35 (12%) 37 (30%)
Schuster et al. (2015) [690]	33 pts, 60 regions: 45 hands, 15 feet		median: 31 months	Local progress/recurrence 14/60 (23%) regions. local control in 50 (83%) regions. Symptom improvement: pain 30 of 37 regions (81%).		
Zirbs et al. (2015) [838]	206 pts 297 hands	nn	FU 1 – 27 years median: 40 months	93 (45%) decline, 72 (35%) stabilization, and 41 (20%) progression of symptoms.		

Table 10. Literature review: previous results of radiotherapy for Dupuytren's disease.

4.3.2 Radiotherapy for Ledderhose Disease (LD)

4.3.2.1 General facts

LD belongs to the group of benign fibromatoses that includes DD. It is named after the German surgeon Georg Ledderhose and for unknown reasons occurs less frequently than DD but in association with it in 10%–20% of affected individuals. In LD, the nodules (rarely cords) usually develop in the toe ray area from D1 (big toe) to D3, i.e., on the inside of the feet or on the sole of the foot. Initially, itching, burning, and other sensations may be noted as early signs. The nodules are initially soft and elastic and usually painless, but as they progress, they become larger and harder and then painful for longer periods of time. As the nodes continue to grow, conglomerate nodes may form and also cause discomfort, sometimes significant, when walking.

Although DD contracture of the hand is typical in the long-term course (hence the name Dupuytren's contracture), in LD, contracture of the toes occurs only rarely because other stresses play a role or the tensile forces on the nodes in the sole of the foot are lower. The Ledderhose nodes can sometimes become very large, and significantly larger than the nodes on the palm of the hand, and impair walking because of their size and location.

The underlying pathogenetic mechanism, i.e., genetic disposition in conjunction with possible trauma or exposure to certain risks, is analogous to that for to DD. However, even children and adolescents can develop LD [12,111,143,180,201,254,277,370,394,453,743].

4.3.2.2 Staging and Classification

In LD, contracture (of the toes) is usually not a major problem and therefore not suitable for classification. For this reason, objectifiable and easily visible or even palpable features are used. The classification does not correspond so much to the development of the disease but rather serves to assess the indication for surgical intervention. The first classification comes from Sammarco and Mangone (2000) [665] (Table 11).

Grade 1:	FOCAL (isolated) disease (= 1 nodule) limited to a small area of the foot fascia. NO adhesion to skin, NO deep penetration into the musculature.
Grade 2:	MULTIFOCAL disease (= muliple nodules) with or without spread (distal or proximal). NO adhesion to skin, NO deep penetration into the musculature.
Grade 3:	MULTIFOCAL disease (= muliple nodules) with spread distally or proximally. EITHER adhesion to skin, OR deep penetration into the musculature.
Grade 4:	MULTIFOCAL disease (= muliple nodules) with spread distally or proximally. BOTH adhesion to skin AND deep penetration into the muscles.

Table 11. Classification of Ledderhose disease.

For the indication of radiotherapy, however, this classification has less significance than for DD because the indication for treatment is based almost exclusively on symptomatology and functional deficit. Without relevant symptomatology and a significant functional deficit, radiotherapy is not indicated. In case of doubt, imaging techniques such as MRI may help in the diagnosis and differential diagnosis, as well as in the long-term clinical course, [38] along with ultrasound.

4.3.2.3 General treatment options

Correct diagnosis of the disease is the most important step towards possible therapy because not every nodule in the sole of the foot is already a Ledderhose nodule and other therapies thus also may be considered. A specialist (orthopedic) clarification and consultation is necessary in any case before the use of radiotherapy. LD has the same or similar causes as DD, so in principle the same therapy options are available. However, the feet are subjected to considerably more stress in daily life than are the hands, and it may be easier to avoid using a hand that has just been operated on than a foot that has been operated on.

The aim of therapy is to prevent or reduce further growth of the nodules, inhibit accompanying inflammation, reduce local pain, and maintain or improve walking ability as far as possible. Therefore, to maintain the ability to walk, conservative methods are first used, such as soft insoles for shoes, or adaptable, plastic insoles to reduce pain while walking. Sometimes special perforated cushions are considered to relieve pressure on certain zones to reduce pressure on the nodes. Otherwise, the following types of treatment are available:

- Injections: Steroid injections with the corticosteroid triamcinolone can help shrink nodules and reduce pain; however, treatment must be repeated every 1–3 years, which can cause side effects locally [605].

- Cryotherapy: With this method, the nodes and surrounding tissue are deep-frozen and the growing nodes die; however, no long-term studies are available, and this method is considered experimental.

- Shockwave therapy: In individual cases, the nodes could be softened and complaints noticeably reduced with shockwave therapy, but it often is painful and ineffective in the long term. Here, too, relevant long-term studies are lacking.

- Needle fasciotomy: Needle fasciotomy is very rarely used in LD [52].

- Operation: Surgery is currently the only published measure in which large nodules are completely removed. The side effects are sometimes considerable. After the operation, it must unfortunately be assumed that walking aids will be necessary and that considerable practical losses will have to be accepted, e.g., no longer driving a car. Very often (>50%), relapses occur, some of which are worse than the primary manifestation. The outcome depends on whether only the node or the entire fascia is removed [148,797].

- N-acetylcysteine, or NAC: Long known as a drug for loosening mucus in lungs, its use in LD has been tested only in isolated cases. First results seem to be promising, but overall, it remains an experimental, non-established therapy.

- Laser therapy: This treatment with a low-energy laser can shrink the nodules and reduce pain but has not been evaluated in studies.

- X-ray irradiation (radiotherapy): This therapy can slow down progress of the disease, soften the nodules, and as in DD, likely completely dissolve small nodules in the early stages. X-ray therapy is also used when, for example, further surgery is no longer possible because of scarring from previous surgeries (recurrences) [26].

4.3.2.4 Radiotherapy options

One of the largest phases 1/2 studies of primary radiotherapy in LD with well over 100 patients/cases to date was reported by the Essen-Hamburg group at an International Symposium in 2010. They administered 10×3 Gy, analogous to the concept used in DD [698,699]. Another clinical group from Offenbach-Frankfurt also reported very good success with different dose concepts in 24 patients [308]. The follow-up time in both studies was 2–11 years. Both X-rays (Orthovolt device) and electrons were used.

The world's first publication on radiotherapy for LD was from a study in Essen and included 25 patients suffering from symptomatic LD [691]. As in DD, a dose of 10×3 Gy was applied in two series for a total dose up to 30 Gy. Patients were followed up for at least 1–5 years. About 80% experienced significant improvement of symptoms with nodal regression, and LD stabilized in the remainder. No patient required surgery.

In their 2010 study, Heyd et al. saw no progression of nodules or increase in clinical symptoms in any patient after a median follow-up of 22.5 months. Complete remission of nodules or cords occurred in only 11 cases (33.3%), with reduction or shrinkage in another 18 (54.5%), and four sites (12.1%) remained stable. Pain regression was reported in 13/19 cases (68%) and improved gait function in 11/15 (73.3%) [308].

In two other studies, radiotherapy was used after complicated surgery to preserve the outcome of surgery as much as possible [143,776]. A precise evaluation and a special control group were not implemented in these studies. In the absence of a randomized phase 3 study, only a few established studies are available in terms of patient numbers and data processing. However, a dilemma exists about the role of surgery with concerns to an even greater extent about unsatisfactory results (Table 12).

4.3.2.5 Significance of the Essen Study

From 01/1997 to 12/2009, 158 patients (91 males, 67 females; mean age, 49 years; range, 9–81 years) were referred for treatment. Among these patients, 94 feet were unaffected and 222 were affected (84 bilateral, 29 right, 25 left). A total of 91 patients (47 male, 44 female) chose radiotherapy as treatment for 136 feet; the remainder served as controls. Eighty-eight (97%) patients had developed new symptoms during the previous 6 to 12 months, 86 (95%) had gait disturbances because of discomfort, and 35 feet (26%) had progression/recurrence after surgical pretreatment. Orthovolt radiotherapy was used as in DD (125–150 kV, 4 mm Al filter). As in DD, the dose concept consisted of two radiotherapy series of 5×3 Gy each with a 10–12-week break.

After a minimum follow-up of 24 months (mean, 68 months; range, 24–144), 6 (7%) patients and 11 feet (8%) had progression; of these, 5 (6%) patients on 7 (5%) feet required recurrent surgery. Another 60 feet (44%) remained stable, and 65 (48%) had regression of nodules, cords, and/or clinical symptoms. There was complete remission in 35 feet without evidence of nodules, cords, and/or clinical symptoms. Previous symptoms and diminished function improved by up to 90% in each category. The subjective symptom score improved significantly in 81 (89%) patients. Acute Common Terminology Criteria category 1 or 2 side effects on plantar skin occurred in 29 (21%) and 7 (5%) feet, respectively. A chronic Late Effects Normal Tissue grade 1 adverse reaction (dryness of the skin, mild fibrosis) occurred in 22 (16%) feet. In the untreated control group, the rate of progression was significantly increased and symptoms were barely improved relative to treated patients. In multivariate analysis, recurrent disease, nicotine abuse, and advanced symptoms were clear prognostic factors for disease progression.

4.3.2.6 Summary statements for LD radiotherapy

Antiproliferative radiotherapy in LD is successful in both primary and recurrent treatment, although to a lesser extent in the latter. A high proportion of regression of the nodules (up to 50%) and regression of symptoms (up to 90%) can be seen. In contrast, radiotherapy has not yet become standard as a postoperative therapy. The same concepts as for DD are recommended as possible dose strategies. Instructions for the radiotherapy technique, documentation, and follow-up also correspond to those for DD and are not further elaborated here.

Overall, a wait-and-see approach appears to be reasonable in the absence of symptoms. In the case of clearly increasing symptoms, however, radiotherapy should be used at an early stage to prevent the spread of the disease and need for surgical interventions.

In the long term, DEGRO AG recommends a case-control study from all German centers analogous to the Essen study. The radiotherapy concept also could have significance with regard to a possibly effective lower single dose and total dose.

4.3.2.7 Recommendation

Radiation therapy can be performed in Ledderhose disease when symptoms are clearly increasing, both primarily and secondarily after surgery.

Evidence level 4, recommendation level C

Study (year)	Patients	Feet	Type of surgery	Recurrence rate	Complications
Parnitzke et al. (1991) [596]	6	7	PFE, SFE, TPF	5/7 (71%)	3 with wound healing problems 1 nerve lesion 1 chronic pain
Aluisio et al. (1996) [15]	30	33	PFE, SFE, TPF	13/33 (39%)	4 with wound healing problems 2 nerve lesions 2 chronic pain 1 deep vein thrombosis
Dürr et al. (1999) [180]	11	13	PFE, SFE, TPF	8/13 (62%)	4 wound healing problem
Sammarco et al. (2000) [665]	16	21	SFE	2/16 (13%)	11 with wound healing problems 1 neuroma
de Bree et al. (2004) [143]	20	26	PFE, SFE, TPF ---------- + Radiotherapy	Not stated; "best results" with radiotherapy	3/6 feet with radiotherapy had functional impairment
van der Veer et al. (2008) [776]	27	33	PFE, SFE, TPF ---------- + Radiotherapy	16 (60%); 100% PFE 25% TPF "Best results" with radiotherapy	9 with wound healing problems

Table 12. Clinical outcomes after surgery for Ledderhose disease.
PFE=partial fasciectomy; SFE=subtotal fasciectomy; TPF=total plantar fasciectomy.

4.3.3 Keloid/Hypertrophic Scars

4.3.3.1 Irradiation

Mechanism of action
The influence of ionizing radiation on the pathological development of hypertrophic scars/keloids is radiobiologically proven and has two main mechanisms, as follows:

1) A direct antiproliferative effect on fibroblasts and myofibroblasts by inhibiting new cell formation, delaying mitosis and mitosis-induced cell death, respectively. These effects depend on the single and total dose, influence of fractionation, oxygen effect, and different biological effects of the different radiation qualities (Orthovolts versus electrons versus brachytherapy).

2) An indirect anti-inflammatory effect via lymphocyte apoptosis, induction of fibroblast/fibrocyte differentiation, and effects on the cell membrane, endothelial cells, or macrophages/monocytes, as well as on leukocyte adhesion and oligonucleotides (nuclear factor kappa B). The result is a hypocellular, low-vascularized, and hypoxic tissue with less excessive fibroblast neogenesis and consequent inhibition of hypertrophic scar/keloid development. Adequate radiation dose leads to a balance between scarring and excessive cell growth without delaying wound healing.

Adverse effects
The acute undesirable effect is redness and scaling in the radiation field for a few weeks, which recedes with time. In this phase, hydrating creams and light protection are recommended as local measures. With individual doses of 3.0-4.0 Gy and total doses between 10 and 20 Gy, slight local pigmentation will occur up to one year after irradiation (requiring light protection), but it will gradually disappear. Chronic effects include hyper- and depigmentation, dryness of the skin, and telangiectasia, but these entities are very rare with fractionation up to 4.0 Gy single dose and total doses of less than 15 Gy; a higher rate of pigmentary disturbances is to be expected only with single doses of >5.0 Gy.

Indication
Radiation is usually considered only in the case of recurrence and in combination with surgical excision of the keloid/hypertrophic scar, which should be as complete as possible. Only in exceptional cases is irradiation performed alone without preceding surgery.

Response rate/Recurrence rate
In retrospective studies, some quite large, postoperative irradiation of keloids and total doses between 8 Gy to 30 Gy resulted in freedom from recurrence after 12–24 months in 79% to 92%. With irradiation of 15 keloids with 9–18 Gy alone, Doornbos et al. reported freedom from recurrence after 12 months in 73% of cases.

Implementation
Postoperative irradiation after excision of a keloid should be performed within 24 hours. A total dose of 12 Gy applied in three to four fractions daily or every 2 days is recommended. It is favorable to perform the procedure within one week, i.e., resection on Monday and performance of irradiation at some time from Tuesday to Friday. The choice of radiation quality, i.e., whether conventional radiotherapy, brachytherapy, or electron therapy or fractionation, should be decided individually and depending on the specific characteristics (shape, size, and location) of the keloid/hypertrophic scar and the available radiation technique of the treating radiation therapist [449,701].

Other
Treatment should preferably take place in specialized clinics with interdisciplinary consultation

(dermatology, plastic surgery, nuclear medicine).

After irradiation, the same postoperative precautions and special arthroplasty measures for tension-free wound care must be taken as with the other procedures for keloid prophylaxis.

4.3.3.2 Summary

Primary therapy of hypertrophic scars by irradiation is not recommended.

Therapy by irradiation of keloids as monotherapy may be recommended in individual cases when other measures cannot be considered.

Radiation postoperatively for prophylaxis of *de novo* development of Hypertrophic Scars or keloids in high- risk/predisposed patients is not recommended.

4.3.3.3 Recommendation

Radiotherapy after surgical therapy for keloid recurrence can be performed.

Evidence level 4, recommendation level C

4.3.4 Gorham-Stout Disease

4.3.4.1 Definition

Gorham-Stout Disease (GSD) is a benign proliferative disease of blood and lymphatic vessels that disrupts the physiologic equilibrium of bone formation and resorption, leading to severe osteolysis [257,258,530,550]. The synonyms “disappearing bone disease,” “vanishing bone disease,” “massive osteolysis,” or “phantom bone” are also commonly used in the US/UK literature. The disease was first described by the Boston physician John B.S. Jackson (1838), who reported on an 18-year-old patient with massive osteolysis of the humerus (“boneless arm”) [361]. After a review summarizing the histologic characteristics, pathologists L. Wittington Gorham and Arthur Purdy Stout (1955) named the condition [257].

4.3.4.2 Epidemiology

To date, a total of about 250 cases have been published, and valid epidemiologic data are quite limited because of this rarity [77,312]. With a balanced sex distribution, GSD can occur at any age and shows no familial or racial clustering. Symptoms mostly manifest before the third decade of life [213]. The initial pattern of involvement is mostly singular, whereas in protracted courses, the osseous destruction may spread to adjacent skeletal segments and involve the surrounding soft tissue mantle in up to 76% of cases. However, initial multifocal involvement has been described [583]. Most affected sites are the bony skull, especially the mandible, and the shoulder and pelvic girdles [213]. With an estimated mortality of about 13%, the prognosis is favorable overall. When the axial skeleton is involved with visceral organs or neurologic deficits, mortality increases to about 30%. It may reach 50% when the thorax is involved because of the threat of respiratory failure, especially if chylothorax occurs as a life-threatening complication due to obliteration of the thoracic duct.

4.3.4.3 Etiology and pathogenesis

Little is known about the etiology and pathogenesis of GSD, and both a neoplastic origin and autosomal dominant inheritance have been suggested as causes. The clinical course is variable; in addition to rapidly progressive courses in which lesions spread to adjacent structures within months, spontaneous remissions with regression of radiographic changes have also been described [83,105,120,209,627,733]. Histologically, abnormal hyperproliferation of thin-walled vessels is initially found in the lysis zones, whereas in the protracted courses, the bone tissue is increasingly replaced by fibrovascular connective tissue [213,257,550].

The exact pathophysiologic mechanisms leading to osteolysis are unclear [197,559,599]. A hyperemia-induced disturbance of the physiological osteoblast–osteoclast ratio [258] has been suggested, as have increased activity of hydrolytic processes triggered by local tissue acidosis [320], increased osteoclast activity associated with increases in serum IL-6 levels [153], and increased osteoclast progenitor cell activity triggered by humoral factors [328]. Recent studies show that presumably both lymphatic endothelial cells and macrophages secrete TNF-α and IL-6, stimulating osteoclasts, which promotes development of excessive osteolysis. In addition, macrophages produce vascular endothelial growth factor (VEGF)-C and VEGF-D, which in turn increases endothelial cell proliferation. Their release of VEGF-A, VEGF-C, and VEGF-D further stimulates osteoclast differentiation. Osteoblast activity and formation of new bone tissue are inhibited by TNF-α released by lymphatic endothelial cells [197].

4.3.4.4 Diagnostics, differential diagnosis

The clinical symptoms of GSD, such as pain, swelling, or weakness of the affected limb, are nonspecific, and it is not uncommon for spontaneous fractures without significant trauma to be the initial symptom. Laboratory chemistry may reveal discrete elevated serum levels of alkaline phosphatase [599]. The diagnosis is usually confirmed by biopsy and histologic confirmation after exclusion of other diseases associated with osteolysis [77,599]. The differential diagnostic considerations must include the broad field of all inflammatory, neoplastic, or endocrinologic diseases that may result in osteolysis [599]. Histopathologically, differentiation from hemangioendotheliomas, lymphangiomas, and capillary hemangiomas may be problematic [312, 550].

Diagnostic imaging can show the extent of bony destruction and soft tissue involvement, but there are no known pathognomonic findings. Conventional radiology shows subcortical and intramedullary foci in the early phase, which then result in fractures and dissolution of the bone via atrophy in the longer course [599]. CT can more sensitively visualize osseous destruction and soft tissue involvement. The signal pattern on MRI is variable and depends on the extent of vascularization and fibrosis. T1-weighted sequences typically show a low signal pattern that increases markedly after contrasting with gadolinium as a function of capillary permeability due to inflammation. T2-weighted sequences show a mixed signal pattern depending on vascularization [77,175,599,733].

4.3.4.5 Therapeutic options (non-radiotherapeutic)

Due to the rarity of GSS, no established therapeutic strategy exists. Possible treatment options include bisphosphonates, α-interferon-2b, androgens, calcium, corticosteroids, calcitonin, vitamin D, and cytostatics, surgical procedures, embolization [27,77,278,283,320,599], and radiotherapy [77,120,175,311,312,339,418]. After the use of bisphosphonates alone, as well as when combined with radiotherapy, partial long-term remissions have been reported [27,77,87,278,283,312,413,724]. Multimodality treatment approaches with sequential use of surgery, radiotherapy, and drug treatment have also been reported [171,185]. Surgical procedures range from simple resections of the lesions with or without alloplastic joint replacement to amputation [83,99,179,210,331,769]. Spontaneous resorption after placement of autologous bone material within weeks to months has been reported several times [210,827].

4.3.4.6 Special value of radiotherapy

Since the first report by King (1946) [418], who described the successful irradiation of a skeletal angiomatosis of the left femur, the use of radiotherapy for the treatment of GSD has been described in numerous, predominantly single-case or case series reports [77,120,175,312,418]. Dunbar et al. [175] described four patients, three of whom had received definitive radiotherapy with total doses ranging from 31.5 to 45.0 Gy. After follow-up periods of 77–168 months, all patients were in complete remission. The largest collective of 10 patients was pooled in the Patterns of Care study of the GCG-BD [311]. In that study, after follow-up periods of 5–204 months (median, 42 months), local control was achieved in eight cases (80.0%), although disease progression outside the irradiation volume occurred in two patients at 46 and 192 months. A literature review of 38 publications from 1958–2009, including 44 patients irradiated in 47 sites with different dose regimens, showed that after follow-up periods of 2 to 288 months (median, 24 months), local progression had occurred in 10 cases (22.7%). Stable progression was achieved in 22 cases (50.0%), associated with signs of remineralization in 12 of these 22 cases (27.3%).

Dose concept/radiotherapy technique
The total doses used as reported in the literature vary from 15 to 50 Gy, with total doses of 36–40 Gy recommended for conventional fractionated irradiation based on the above literature review. The irradiation technique should be chosen depending on the localization, with CT-based irradiation recommended with a dose prescription according to ICRU Report No. 50 because of the high rate of soft tissue involvement.

4.3.4.7 Recommendation

Radiotherapy is an effective treatment option that can improve local control in GSD, both as a stand-alone measure and in combination with alternative therapeutic options. Control rates with prevention of progression of osteolysis can be achieved in 77%–80% of cases.

Treatment is indicated only for progressive courses; conventional fractionated irradiation series (5×1.8–2.0 Gy/week) with total doses of 36 to 45 Gy have proven effective.

Because of the high rates of soft tissue involvement in approximately three-quarters of cases, CT-based 3D radiation planning and dose specification is recommended according to ICRU Report No. 50 to ensure safe inclusion of the adjacent soft tissue mantle [strength of evidence 3, recommendation grade B].

Radiotherapy should be performed, if indicated.

Evidence level 3, recommendation level B

4.3.5 Radiation therapy of induratio penis plastica (IPP, Peyronie's disease)

4.3.5.1 Definition

This condition involves stranded or nodular hardening of the tunica of the penis, causing painful deviation when erect. These factors can impair sexual activity and ultimately lead to erectile dysfunction [450]. Frequent depression has been reported in these patients [538].

4.3.5.2 Epidemiology

The incidence is approximately 1.5%–8.9% depending on age, increasing with age to 3%–7% [538,730]. In some cases, incidences of more than 20% asymptomatic Peyronie's foci are reported. The peak age is 40 to 70 years. A common association with DD and LD is to be noted. Diabetes, the use of beta-blockers, and smoking are mentioned as possible factors in the literature. A hereditary component also is possible [450,730].

4.3.5.3 Diagnostics

In consensus with urologic colleagues, clinical examination, sonography, and measurement of deviation in the erect state are considered essential [237,290].

4.3.5.4 Classification

The classification of IPP goes back to the work of Alth [14] (Table 13). A generally accepted version is that of the Committee on Peyronie's Disease and the First International Consultation of Erectile Dysfunction in 1999, as reprinted in [358]. Alternatively, the classification according to Kelami et al. [402] can be used (Table 14).

4.3.5.5 Etiology and pathophysiology

The etiology and pathophysiology of IPP are only partially understood. Recurrent microtrauma as well as a subsequent inflammatory reaction leads to scarred plaques, mostly located dorsally. The resulting inelasticity and shrinkage of the tunica albuginea causes various penile deformities. The subsequent course is undulating. A subacute inflammatory phase is distinguished from a later fibrotic phase. Spontaneous remissions are possible.

4.3.5.6 Therapy options [290,291,749]

Oral therapies (in the acute phase)

Paraaminobenzoate (Potaba®)

Phosphodiesterase inhibitors, tadalafil, vitamin E, colchicine, tamoxifen, levocarnitine (various, some low evidence)

Intralesional therapy

Collagenase, cortisone, verapamil, interferon, Clostridium histolyticum

External energy application

Iontophoresis

Extracorporeal shockwave therapy (positive meta-analysis [237])

Mechanical penis stretching

Surgical therapy (in the chronic–fibrotic stage)

4.3.5.7 Importance of radiotherapy

Treatment indication and mechanism of radiation action
Not yet fully known.

Indication
The primary indication for treatment is the presence of painful localized inflammatory plaques. The earlier stages with soft plaques should be preferred for radiotherapy over the later calcified plaques. Efficacy is probably superior in younger patients. Note that the indication has been questioned because of the lack of randomized trials (Mulhall et al. [538]).

Radiotherapy technique and dosage
The disease can be treated with Orthovolt therapy or low-energy photons or electrons. Regarding the choice of energy, please refer to the corresponding table in the general part of this text. The pubic region and scrotum are to be spared, which can be achieved, for example, by appropriate lead shielding with the penis in a horizontal position. Another possibility is the vertical alignment of the penis with the patient lying down and radiation therapy applied via laterally opposing fields [358,557].

Homogeneous irradiation of the corpus penis should be achieved. The glans should be spared to avoid extremely painful balanitis. Dosage is as follows: total dose, 10–20 Gy; single dose 2.0-3.0 Gy, once daily and five times per week.

Radiation therapy results
Based on consensus in the literature, radiation therapy leads mainly to a significant pain relief in 50% to 90% of the patients, and in 30% to 70% an additional improvement in the penile deviation is found. Published findings further suggest that softening of the indurated foci can be achieved [135,293,298,357,389,437,454,486,498,508,525,557,588,650,683, 787,803]. Randomized data are completely lacking. Key available studies are listed below:

Retrospective study:	Niewald et al., 2006 [557]
Patterns of Care Studies for Germany:	Seegenschmiedt et al., 1999 [693] Niewald et al., 2007 [558]
From Europe:	Incrocci et al., 2008 [356]
First guideline publication:	Seegenschmiedt et al., 201 [710]
Review:	Mulhall et al., 2012 [538]

Side effects include occasional mild radiogenic dermatitis or balanitis; the promotion of erectile dysfunction remains a point of discussion [355,357].

4.3.5.8 Summary

A general recommendation is difficult in the absence of randomized studies. According to the retrospective data, considerable success can be expected with regard to pain relief and reduction of penile deviation during radiotherapy. Here, the spontaneous healing rate in IPP has to be considered.

4.3.5.9 Recommendation

Radiotherapy can be performed, if indicated.

Evidence level 3b, recommendation level C

Item	Expression	Explanation
Pain	0 = missing 1 = light 2 = light 3 = moderate 4 = heavy 5 = continuous pain	 During erection During intercourse Not exclusively during intercourse
Plaque size	0 = no plaque 1 = 1 cm 2 = 2 cm 3 = 3 cm 4 = 4 cm 5 = 5 cm or more	
Deformity D = dorsal L = lateral V = ventral S = shortening	0 = none 1 = 15° 2 = 30° 3 = 45° 4 = 60° 5 = 75° or more	
Erection	0 = normal 1 = functional 2 = impaired 3 = impaired 4 = lack of hardening of the glans penis 5 = absent	 Penetration possible Penetration not possible

Table 13. Classification of IPP according to Alth [14].

Item	Expression	Explanation
Induration	I1 I2 I3	Cartilaginous Fibrous Calcified
Number	N1 N2 N3	1 plaque 2 plaques 3 plaques
Size	T1 T2 T3	<1.5 cm 1.5–3 cm >3 cm
Localization	D V Ll (r) C S B	Dorsal Ventral Lateral left (right) Corona Shaft Base
Deviation	D1 D2 D3	<30° 30–60° >60°
Pain	P- P+	No pain Pain present
Penetration	PN+ PN+/- PN-	Possible Difficult Not possible

Table 14. Classification of IPP according to Kelami [402].

4.4 Other benign diseases

4.4.1 Radiotherapy of heterotopic ossification

4.4.1.1 Definition

Heterotopic ossification (HO) refers to abnormal benign condition of bone formation in soft tissue occurring outside the original skeletal system [81]. Myositis ossificans is a similar condition that is treated in a very similar way.

4.4.1.2 Epidemiology

HO can be divided into three main groups [82]:

- traumatic HO

- non-traumatic HO

- neurological HO

The incidence of HO is highest from trauma (accident or surgery), with a rate of 25% after acetabular fracture [247], 16%–90% after endoprosthetic hip replacement (TEP) depending on the risk profile [75,653], and 50% after fracture of the elbow joint at [109,352]. The incidence of HO after knee joint dislocation is reported to be 26% [737].

HO after burns is rare and usually occurs only after burns of at least 20% of the body surface in soft tissue structures near the joints, especially near the elbow, with an incidence of 0.15%–3% [118,637].

HO occurs in up to 20% of patients with trauma-induced paraplegia [40, 670].

4.4.1.3 Etiology and pathogenesis

The etiology is not fully understood, although it is believed that an inflammatory stimulus from, e.g., bone trauma leads to the release of growth factors that cause mesenchymal undifferentiated stem cells to differentiate into osteoblasts [29,835].

The main risk factor is pre-existing ipsi- or contralateral HO [147]. Individual factors such as age and predisposing diseases such as chronic polyarthritis have been discussed as further risk factors [676].

4.4.1.4 Diagnostics

HO can be detected on radiographs at the earliest 2 weeks after trauma. In this context, the classification most commonly used to describe HO after TEP on radiographs is Brooker [93], in which, however, only grades III° and IV° with movement restriction are clinically relevant [32].

4.4.1.5 Therapy options

Except for resection, there is no definitive therapy for a pre-existing HO.

Preoperative or postoperative radiotherapy of the hip region is an effective treatment modality for reducing the incidence of HO after TEP. Radiotherapy is most effective when performed in a time window within up to 4 hours before surgery and up to 72 hours after surgery [433,585,703]. In high-risk settings, postoperative fractionated therapy is superior to preoperative radiotherapy [697]. Experience regarding repeat radiotherapy after TEP is rare but has been shown to be effective [479].

Ossification prophylaxis is successful for other fractures near the joint [586].

NSAID administration alone for at least 3–6 weeks is also effective [104,219,411].

4.4.1.6 A special place for radiotherapy

In patients with risk factors, postoperative radiotherapy can reduce the HO rate from 90% to less than 10% [703].

Dose concept/radiotherapy technique
A single dose of 7-8 Gy is efficient and effective [85,296,432], and postoperative fractionated therapy with 5×3.5 Gy is recommended for high risk cases [697].

Irradiation for, e.g., TEP of the hip joint is performed after simulation with a linear accelerator (>6 MV photons) using an opposing fields technique. The treatment field includes the typical localizations of HO [242], and risk structures in the pelvis should be blocked out [431]. Other regions should be treated in a similar way.

4.4.1.7 Summary

All patients with TEP needing removal of HO should be treated prophylactically with NSAIDs or radiotherapy. Radiotherapy should be applied within the time window of up to 4 hours before surgery or up to 72 hours after surgery. A single dose of 7-8 Gy should be applied, except in high-risk cases, which call for postoperative fractionated radiotherapy at 5×3.5 Gy.

4.4.1.8 Recommendation

Patients with TEP as well as removal of HO
Radiotherapy is to be performed.
Evidence level 1, recommendation level A

Other fractures near the joint
Radiotherapy should be performed.
Evidence level 2, recommendation level B

4.4.2 Radiotherapy for endocrine orbitopathy (EO)

4.4.2.1 Definition

Endocrine orbitopathy (EO) also known as “Graves orbitopathy” or “thyroid eye disease”, is a thyroid-associated autoimmune disease. The exact mechanism of the disease is not yet known, although it is now believed that autoantibodies against thyroid-stimulating hormone receptors in the connective tissue of the eye muscles are the cause.

4.4.2.2 Epidemiology (Incidence, Age, Sex Distribution, Characteristics)

EO occurs in 10% of all thyroid patients, in up to 90% of cases simultaneously with Graves’ disease, and in 60% of cases in conjunction with other forms of hyperthyroidism. However, there are no exact data on the frequency of Graves’ disease in Germany. In areas with sufficient iodine supply, it is reported to be 2% to 3% in women and about a tenth of that in men. The annual incidence rate of Graves’ disease is 1 per 1000 inhabitants.

4.4.2.3 Etiology and Pathogenesis (Histological Description, Staging)

The occurrence of EO is the consequence of complex autoimmune processes triggered by B and T lymphocytes and accompanied by an increased formation of antibodies (thyrotropin receptor autoantibodies, or TRAbs). There is evidence that TRAbs with stimulating properties (thyroid-stimulating antibodies, or TSAbs) particularly favor the development of EO, but the exact mechanism is not yet known. Other receptor antibodies (e.g., the insulin-like growth factors) also may play a role [103,239,337,582,597,790].

Fibroblasts in retrobulbar tissue respond particularly strongly to inflammatory-like stimuli, especially to stimulation of specific antigens, the so-called CD40 proteins, leading to the formation of new fat cells [380]. Genetic predisposition and tobacco consumption also can be factors in risk [45,717].

The immunological inflammation thus triggered leads to swelling of the muscle, fat, and connective tissue in the orbit, widens the distance between the orbital wall and the eyeball, and leads to exophthalmos and a loss of elasticity of the eye muscles with restricted movement and double vision. This process is caused by lymphocytic infiltration of the tissue and an increase in fibroblasts. In addition, there is collagen proliferation with a concomitant increase in further stored glycosaminoglycans and an excessive accumulation of water in the tissue [383]. A typical manifestation of the eye muscles and, more rarely, of the optic nerve is lipomatosis [307,442].

4.4.2.4 Diagnostics and Differential Diagnostics (Imaging, Laboratory, Clinic, Classification)

The diagnosis is primarily made clinically. In the classic case, exophthalmos occurs as part of the so-called Merseburg triad together with thyroid enlargement and tachycardia in the context of Graves’ disease [270,271].

Further diagnostic measures primarily serve to determine the degree of severity and activity of the disease, as well as impending complications. MRI examination is particularly suitable for estimating inflammatory activity [543].

Differentially, various imaging techniques (CT, MRI) should be used to exclude a tumor behind the eye as well as the clinical picture of ocular myositis [248,280,332,390,560,713].

Difficult to distinguish from EO are idiopathic orbital inflammation and isolated immunogenic orbitopathy. Both are ultimately diagnoses of exclusion in the absence of evidence of endocrine involvement [199,336].

There are various schemes for classifying disease progression and stage, but none of them have been definitively established as the standard [16]. Since 1969, the so-called NOSPECS scheme has been used, a classification of the American Thyroid Association [777]. The letter sequence is a special abbreviation for the English names of the queried symptoms. It is also known as the Werner classification [809,810]. Within this classification, a further classification is made according to the severity levels 0, A, B, and C, with which a certain point value can be determined. Together with a further parameter for disease activity, the so-called Clinical Activity Score (according to Mourits), the entire course of the disease can be evaluated.

As an extension of the NOSPECS scheme, the so-called LEMO classification (L=lid changes, E=exophthalmos, M=muscular changes, O=optic nerve involvement) has become established, and is intended to contain a more meaningful and practicable classification, as first proposed by Boergen and Pickardt in 1991. This is a so-called facet classification, using a letter associated with a number. For example, L1E2M0O2 stands for “eyelid edema only, conjunctival irritation in the morning, absent muscle changes, and peripheral visual field defects.”

These schemata are important aids before and during treatment for assessing progression or therapy-related improvement of the clinical picture in a meaningful way. In addition, they provide a clear overview of the significance of important symptoms.

4.4.2.5 Therapy options in general (overview of all options)

Although a definitive therapy is not yet identified [145], it is possible in many cases to treat the symptoms [284,364,379,397,405,443,533,817]. Cortisone preparations are considered the first-choice agents. In cases where their effect is not satisfactory, complementary measures can be taken (local irradiation, cyclosporine), but their use is not evidence-based because scientific studies are still pending [190,191].

Other conservative treatment options include local treatment with tear substitutes or ointments for mild forms associated only with dryness of the eyes or minor conjunctival irritation.

Biologics, in particular the active ingredient rituximab, are considered experimental procedures.

Surgical interventions are performed only in the inactive, chronic–fibrotic phase of the disease and after there has been a consistent finding for a period of at least 6 months. The sequence of measures in which the orbits, then the external eye muscles, and finally the eyelids are treated surgically must be followed. A few months should elapse between each operation [78,192,611].

The response to the different therapeutic modalities considering symptom duration and stages in the literature is shown in Table 15.

4.4.2.6 Radiation therapy special (special indication and rationale)

The clinical use of radiotherapy in EO is currently controversial. In Germany, radiotherapy is used as a treatment option mainly in the intermediate disease classes (2–5 according to NOSPECS), especially with manifest ocular muscle dysfunction [19,43,44,90,228,576]. Approximately 65%–75% of patients with EO show a good to excellent response after radiotherapy [202,229,435,587,779]. For response rates and success criteria, see also Table 16.

The aim is to use both the anti-inflammatory and anti-proliferative effects of radiotherapy to achieve a temporal shortening of the inflammatory phase with prevention of later complications, such as optic nerve compression with loss of visual acuity or fixation of the eye muscles in malposition [169,189,496]. A euthyroid metabolic state should be present before starting irradiation. Orbital irradiation in combination with steroid application significantly improves bulbar motility by reducing extrabulbar volume in patients with active EO [567]. Irradiation of the orbit prior to surgical orbital decompression may improve postoperative outcome in terms of decreased postoperative increase in extrabulbar muscle volume and decreased induction of postoperative diplopia [417].

Dosage concept/radiotherapy technique
Radiotherapy of EO is performed on a linear accelerator with 4–6 MV photons. After adjusting an individual mask fixation and performing a radiation planning CT, the CTV and PTV are defined: The target volume always covers the entire orbital funnel, i.e., dorsally starting from Zinn's ring at the orbital apex, covering the posterior two-thirds of the bulb to 6 mm posterior to the corneal limbus, i.e., to the attachment of the extraocular eye muscles. The distance between the corneal surface and the posterior surface of the lens is approximately 8 mm in the normal eye. Comparing the conventional and the virtual simulation in retrobulbar irradiation, it is usually confirmed that in everyday life, one can easily orient by the outer lid angle when adjusting the lateral fields. In addition, one can orient by the limbus corneae. In contrast, the lateral bony canthus is unsuitable as orientation for the ventral field border. Anatomically, certain size ratios must be taken into account during CT planning [269,343,371,393,715,727].

After 3D irradiation planning has been performed, the irradiation fields often have a minimum size of ~5×5 cm or ~6×5 cm to achieve sufficient dose in the entire target volume. In most cases, laterally opposing fields with divergence compensation are then used to optimally preserve the lenses. Other irradiation techniques include the half-field technique with center block, which eliminates the need for divergence compensation, the rotation technique, and explicit lens sparing using central shielding blocks [246,267,297,478,495,533,572,628,772,820].

General recommendations for the dosage or fractionation of radiotherapy of EO do not exist. According to a representative national survey of the "benign diseases" working group of DEGRO, most radiotherapeutic institutions in Germany perform radiotherapy of EO using a total reference dose (TRD) of 16–20 Gy and single doses of 2 Gy in five fractions per week. However, it is still unclear whether much lower doses are not isoeffective, depending on the stage of the disease. Lower total doses could further reduce the potential risk for radiogenic tumor induction [84,420,444,521,562,595,606,609,728,764,778].

Kahaly et al. performed a randomized three-group study in a total of 65 patients who had moderate EO of grades 2–5 according to NOSPECS. All patients in group A received 20 fractions of 1 Gy each, 1× weekly up to a GRD of 20 Gy (long therapy time, low single dose, high total dose). All patients in group B received 10 fractions of 1 Gy each, five times weekly up to a TRD of 10 Gy (medium therapy time, low single dose, medium total dose). All patients in group C were irradiated with a TRD of 20 Gy and single doses of 2 Gy in five fractions per week (short therapy time, high single dose, high TRD). Patients in all three groups showed comparable response rates in terms of improvement of ophthalmologic symptoms and changes on MRI. However, group A was clearly superior to groups B and C with regard to regression of soft tissue swelling and ocular motility restriction [381,382].

Another randomized trial of low-dose radiotherapy compared radiotherapy with eight fractions of 0.3 Gy each, five times weekly up to a TRD of 2.4 Gy (n=43 patients) and standard treatment with 8×2 Gy in conventional fractionation up to a TRD of 16 Gy (n=43 patients). The treatment groups were similar with respect to clinical outcomes.

Gorman et al. performed a double-blind randomized study in which one eye in the same patient was treated with standard therapy of 20 Gy in single doses of 2 Gy in five fractions per week, while the

other eye received sham irradiation only. The efficacy of both modalities was the same. However, the sham-irradiated eye had actually received “low-dose radiotherapy” as a result of a non-negligible amount of scattered radiation (approximately 0.4 Gy per fraction in the orbital funnel) [260]. This may indicate that lower radiotherapy doses may still be effective in this condition.

4.4.2.7 Summary

The above publications do not specify the timing of radiotherapy relative to the current disease phase of EO. Low-dose therapy seems to be more effective in the early inflammatory phase of EO [694,751]. In contrast, as the disease progresses, higher doses must be used to achieve the same efficacy, possibly because the target is connective tissue cells with increasing fibrosis of the soft tissues [666,709].

Percutaneous radiotherapy may also be combined with systemic administration of glucocorticoids [42,497,621,736,814]. This combined therapy is mostly used in severe cases. In a randomized study, the efficacy of irradiation of the orbit combined with systemic corticosteroids versus therapy with corticosteroids alone was investigated. The combined therapy was clearly superior to monotherapy.

For retrobulbar irradiation, use lateral parallel opposed fields while ensuring lens sparing. Dosage should be made taking into account the current phase of the disease. In the early inflammatory phase, a single dose of 0.3–2.0 Gy can be used with eight fractions and daily irradiation, for a total dose of 2.4–16 Gy. In advanced disease, the single dose should be 2.0 Gy with 8–10 fractions and daily irradiation, for a total dose 16–20 Gy.

In cases of pronounced ophthalmologic symptoms, it may be possible to improve the response to therapy by lowering the single dose to 1 Gy and prolonging the therapy period by irradiation only once a week.

4.4.2.8 Recommendation

Antiproliferative percutaneous radiotherapy for endocrine orbitopathy shouldbe performed, when ocular muscle dysfunction is manifest.

Evidence level 2, recommendation grade B

Study	Patients, n	Symptom duration	Cat. 2S (%)	Cat. 3P (%)	Cat. 4 (%)	Cat. 5C (%)	Cat. 6S (%)	Response (%)	Supplementary therapy
Bartalena et al. (1983) [42]	36 12	2.25 years (0.25–15)	97 100	56 45	93 56	-- --	100	72 25	CS + RT 100%; CS only; eye surgery 3%
Esser et al. (1995) [191]	155	0.8 years	2/3 patients (67%)	p<0.001 (55%)	p<0.01 (55%)	--	--	--	137 CS – RT Only 18 RT
Frederick et al. (1997) [228]	106 142	0.8 years (0.4-4)	56 79	62 56	70 70	-- --	-- --	78 (26 Gy) 80 (13 Gy)	106 RT only; 142 CS + RT; eye surgery 3%
Hurbli et al. (1985) [343]	62	0.6 years (0.1–1.5)	--	23	74	23	57	56	CS + RT >23%; eye surgery 34%
Konishi et al. (1986) [435]	17	1.75 years (0.2–8)	(6 patients)	(5 patients)	(8 patients)	(2 patients)	(4 patients)	59	RT – CS 18%
Lloyd et al. (1992) [478]	36	--	(22 patients)	(14 patients)	(15 patients)	(3 patients)	--	92 (*)	--
Olivotto et al. (1985) [572]	28	0.75 years (0.2–5)	93	26	43	85	100	68	CS + RT 18%; eye surgery 50%
Van Ouwerkerk et al. (1985) [779]	24	1.0 years (0.25–3)	100	(11 patients)	78	--	--	--	CS + RT 75%
Palmer et al. (1987) [587]	29	0.9 years (0.2–10)	78	52	24	--	67	48	CS + RT 34%; eye surgery 45%
Kriss/Petersen et al. (1989/1990) [444,606]	311	0.9 years	80	51	56	71	65	--	CS + RT 32%; eye surgery 29%
Pigeon et al. (1987) [611]	21	1.0 years (0–5)	76	47	32	62	--	57	CS + RT 67%
Prummel et al. (1993) [621]	28 28	-- --	64 38	-- --	43 85	-- --	-- --	50 46	CS CS + RT only
Ravin et al. (1975) [628]	37	--	"many"	32	> 11	--	89	--	CS + RT >18%; eye surgery >6%
Sandler et al.	35	0.7 years (0.1–5.8)	--	--	--	--	78	71	CS + RT 80%; eye surgery 40%

(1989) [666]									
Staar et al. (1997) [736]	225	0.7 years (0.2–3)	80	64	69	--	--	68	CS + RT 100%; eye surgery 29%
Teng et al. (1980) [751]	20	5.8 years (0.9–25)	(9 patients)	25	(1 patients)	--	--	35	CS + RT 25%
Wiersinga et al. (1988) [814]	39	1.75 years (0.4–27)	--	--	--	--	--	64	CS + RT 5%
Wilson et al. (1995) [820]	33	--	85	--	54	--	--	--	RT only
Seegenschmiedt et al. (1998) [694]	60	1.5 years (0.5–20)	50/60 83%	39/56 70%	37/54 69%	13/15 87%	8/17 47%		RT only; eye surgery 8%

CS=corticosteroid therapy; RT=radiotherapy; eye surgery=decompression or eyelid correction.

Table 15. Treatment response related to symptoms/stages in endocrine orbitopathy–literature review.

Study	Quantity (N)	Dose (Gy)	RT	Response rate (%)	Definition of the success criteria
I. Total dose <20 Gy					
Esser et al. [190] (1988)	30	10	C	7–40 82	"Improvement of individual symptoms"; "no progression"
Esser et al. [191] (1995)	155	12	K, L	--	Multiple objective ophthalmologic criteria and "improvement of individual symptoms" according to established scores
Feyerabend [202] (1989)	15	2.5–20	K	67	"Improvement of clinical symptoms"
Frederick [228] (1997)	142	13	K	80	"Very good" and "good response"
Fritsch et al. [229] (1981)	83	16	B, K	30	30% "improved," 70% "unchanged
Grauthoff et al. [267] 1980	10	≤10	K	100	"Very good success"
Heinze et al. [297] (1974)	40	8–12	B	50–68	"Improvement of individual symptoms"
Horster et al. [337] (1983)	21	<20	R	80	"No progression"
Hurbli et al. [343] (1985)	62	10.5–20	K, L, R	56	"Improvement of individual symptoms"
Pfluger et al. [609] 1990	37	10/16	L	97	"No progression"
Staar et al. [736] (1997)	225	16–19.2	L	68	"Improvement of most symptoms"
Uhlenbrock et al. [772] 1984	56	3–10	R	62	"General clinical improvement"
Wildmeister and Horster [817] (1972)	36	2.5	R	45	"General clinical improvement"
II. Total dose ≥20 Gy					
Bartalena et al. [43] (1988)	36	20	K, L	72	33% "very good", 39% "good response"
Donaldson et al. [169] (1973)	23	20	L	65	"Very good" and "good response"
Frederick [228] (1997)	106	26	K, L	78	"Very good" and "good response"
Kriss et al. [443,444] (1983/1989)	80	20	L	67	"Very good" and "good response".
Lloyd et al. [478] (1992)	36	20	L	92	"No progression"

Marcocci et al. [497] (1987)	30	20	K	60	"Very good" and "good response"
Marcocci et al. [495] (1991)	44	20	K, L	25/55	"Very good" and "good response"; "minimal response"
Olivotto et al. [572] (1985)	28	20	L	68	"Good response"
Petersen et al. [606] (1990)	311	20/30	L	90	"No progression"
Sandler et al. [666] (1989)	35	20	--	71	"No progression"
Seegenschmiedt et al. [694,709] (1995/ 1998)	60	20	L	80	Subjective statements of the patients: "very good" and "good response" and quantitative scores (ATA-, Stanford Score, OI according to Grussendorf)

Legend: Gy=Gray; ED/GD=single dose/total dose; B=betatron; C=telecesium; K=telecobalt; L=linear accelerator; R=conventional X-ray irradiation.

Table 16. Outcomes and success criteria in radiotherapy for endocrine orbitopathy.

4.4.3 Irradiation of benign lymphatic fistulas, lymphatic fistulas acquired postoperatively, and lymphatic fistulas caused by malignant primary diseases

4.4.3.1 Definition

Lymphatic fistula is the term for the opening of a lymphatic vessel, either to the body surface (external L.) or into the tissue (internal L.). A tumor or iatrogenic intervention may be the cause of this condition. Lymph fluid is secreted through this opening, the volume of which can be up to 3 L per day during a warm season. Germs and bacteria can enter the body through the fistula, which can cause erysipelas (bacterial infection of the lymphatic ducts). Injury to the thoracic duct can lead to a chylothorax. If the lymphatic fistula does not empty to the body surface, a chyloperitoneum may develop [684]. The primary therapeutic goal is to close the fistula tract to reduce or avoid sequelae such as hypoproteinemia, immunodeficiency, metabolic disturbances, or exsiccosis.

4.4.3.2 Epidemiology

Lymphatic fistulas usually occur as a complication after surgical interventions in body regions with many lymphatic channels. Their incidence is 0.5%–5.2%, depending on the region and extent of the surgical procedure. The incidence of lymphatic fistulas during initial vertebral surgery decreased by half during 1985–1997 because of improved surgical techniques and increasing surgeon routine (1985–1991: 5.2%; 1992–1997: 2.6%) [834]. Pfister et al. also noted an incidence of 2% after vascular surgery [608]. In 1991, Kalman et al. described the most comprehensive series of patients with postoperative lymphatic fistulas after infrainguinal reconstruction, and found an incidence of 1.1% for lymphatic fistulas [385]. Smaller series showed an incidence of 0.8%–6.4% after reconstructive surgery. After thyroid surgery, the incidence of lymphatic fistula is 0.5% [482]. No published data are available on the epidemiology of age and any effect of sex or gender.

4.4.3.3 Etiology and Pathogenesis

Causes of postoperative lymphatic fistula include failure to ligate the injured lymphatic vessels and inaccurate wound suturing. Furthermore, reoperation, the use of vascular canal prostheses, or excessive postoperative mobilization may contribute to the formation of a lymphatic fistula. Diabetes mellitus or increased body mass index have been discussed as factors in the incidence of lymphatic fistula. According to some authors, a body mass index above 30 is among the risk factors for postoperative lymphatic fistula formation [529]. Lymphatic leakage often occurs because of the severing of a lymphatic vessel. If lymphatic fluid accumulates in the groin, for example, wound infections or lymphocele formation may develop in the region. Poorly healing wounds, excess pressure in the wound area (surgical area), or a progressing benign tumor also are mentioned as pathogenetic causes.

4.4.3.4 Diagnostics and differential diagnostics, as well as special examinations

The leading symptom of a lymphatic fistula is the secretion of a clear yellow fluid. Laboratory chemistry can confirm that the fluid is lymphatic by determining total protein, albumin, and triglycerides [804,805]. Furthermore, redness, a local feeling of pressure, or fever may be indicative of a lymphatic fistula.

The fistula reservoir can be assessed on the basis of a sonographic examination. This procedure also is used in daily scoring. Preservation of lymphatic fluid for determination of blood count and especially lactate dehydrogenase level is indicated.

CT is performed in a standardized manner. The contrast agent (Lipiodol) is injected into the cutaneous lymphatic fistula entrance to visualize its course and origin. Detailed imaging of lymphatic vessels is essential for defect localization in cases of known or suspected lymphatic fistula. For this purpose, direct lymphography is superior to other imaging techniques. However, it is very costly and currently not in regular use.

In addition to its diagnostic application, lymphography is used as a therapeutic measure. In a series of nine patients [including those with lymphatic fistula (n=2), chylothorax (n=5), and chyloascites (n=2)], fistula closure by the contrast medium used was noted in eight patients (89%), so that further therapy was no longer indicated [804,805]. Alejandre-Lafont et al. also found that lymphatic fistula, lymphocele, chylothorax, or chylous ascites could be brought to a halt using Lipiodol in 70% of patients treated with lymphographic therapy [7].

In addition, magnetic resonance lymphography is a safe and accurate imaging modality to comprehensively evaluate the lymphatic system in patients with lymphocysts and lymphocutaneous fistulas [481].

Stages
No literature can be found on the staging of lymphatic fistulas. The secretion volume that indicates a lymphatic fistula has not yet been standardized.

Classification
No literature can be found on the classification.

4.4.3.5 Therapy options

A standard therapy for lymphatic fistula has not been established. Both conservative and invasive methods are recommended [161,376]. The first measure in the case of a severely pronounced lymphatic fistula is a tight wound dressing of the affected body region. In addition, it is advisable to elevate the adjacent limb. Bed rest or dietary measures using medium-chain triglycerides are also useful. Alternative methods include the application of fibrin glue [629], doxycycline therapy [276], vacuum-assisted closure therapy [626], radiotherapy [500], or surgical closure [146].

4.4.3.6 Radiotherapy

Dosage concept, radiotherapy technique
Few publications have addressed the topic of radiation therapy of persistent lymphatic fistulas [274]. Before 1999, radiotherapy was referred to only for lymphoceles and lymphorrhea. The mechanism of action has not been conclusively elucidated. An interaction between damaged lymphocytes and endothelium, leading to the obstruction of the lumen of the vessel, is suspected. In 1999, Neu et al. described radiation therapy of lymphatic fistulas as well as lymphoceles as an alternative to conservative and surgical treatment options. They presented the results of irradiation of 25 lymphatic fistulas and four lymphoceles, which showed the effectiveness of irradiation even after unsuccessful conservative therapy [547].

In 2000, Dietl et al. described the treatment of 28 patients whose inguinal lymphatic fistulas were treated with radiotherapy, with response assessed by secretion volume. These authors concluded that radiotherapy was a low–side effect and cost-effective therapy. The research group also concluded that

sclerotherapy with doxycycline is an inexpensive and effective treatment for lymphatic fistulas [161]. In 2005, Mayer et al. described the irradiation of 17 patients with lymphatic fistulas and found that the interval between surgery and irradiation was irrelevant to therapeutic success, but the shorter the interval, the shorter the hospital stay and the lower the cost of therapy. Low single doses of 0.3–0.5 Gy to a total dose of <3 Gy were sufficient to achieve cessation of lymphorrhea [500].

Nevertheless, individual doses in the literature vary from 0.3 and 3.0 Gy for irradiation of lymphatic fistulas, and total doses are 1.0 and 15.0 Gy, depending on the radiation quality used. Response to radiotherapy, defined as cessation of lymphatic fluid secretion, has been demonstrated in 41 of 74 reported cases (Table 17). The data suggest a better response with low doses of radiation. Low single doses (0.3–0.5 Gy) lead to better local success compared with high single doses (3.0 Gy) [500].

Target volume definition, PTV, CTV, risk organs, radiation protection/dose minimization
Neu et al. irradiated 27 patients over an electron standing field set clinically on the device (7 MeV: n=3; 10 MeV: n=4; 12 MeV: n=11; 15 MeV: n=8; and 18 MeV: n=1) with a safety margin of 4 cm. Two more were irradiated with >15 MV photon fields. The authors found that conventional fractionation with five irradiations per week compared with four irradiations resulted in no relevant differences. Recurrences did not occur, nor did wound healing disorders or wound infections [547].

Dietl et al. performed sonographic morphometry with exact length, width, and depth extent of the lesion before irradiation. The target volume included the entire course of the fistula to its origin, including a safety margin of 1 cm, with inclusion of the drainage outlet. All of the lymphatic fistulas were treated with an Orthovolt device (20 kV: n=1; 180 kV: n=2; 200 kV: n=8; 280 kV: n=1; and 300 kV: n=16) because the maximum depth extension did not exceed 4 cm. The radiation dose was applied using a lead foil collimated direct field. Irradiation was well tolerated without side effects. The reduction of secretions correlated with the measured volume, and larger lymphatic fistula volumes also showed a greater reduction of secretion volume after irradiation [161].

A patient group described by Mayer et al. was treated with photons (8 MV: n=3), electrons (4–11 MeV: n=2), or X-rays (Orthovolt devices: n=12). The target volume included the lymphatic fistula with a safety margin of 2-3 cm [500].

Depending on the localization of the lymphatic fistula, consideration should be given to organs at risk. For this reason, the 3D technique should be used if possible. A daily scoring of the secretion rate by reading the drainage secretion volume [161] or sonographic morphological assessment [500] is advisable. Irradiation can be stopped at the latest when lymphatic secretion from the fistula stops, so that total doses considered often do not have to be applied.

Response evaluation
Radiotherapy of a lymphatic fistula is considered successful when the secretion of lymphatic fluid is completely arrested. To evaluate success, at least 7 days should pass after the end of treatment. On average, a complete response of 50%–60% can be expected. If there is a partial reduction in lymphatic fluid secretion, the response should not be evaluated until 14 days after the end of radiation therapy. Physical exertion may increase pressure in the lymphatics. To prevent the induced occlusion from decreasing because of increased intravascular pressure, patients should avoid physical exertion during and for several days after radiation treatment.

4.4.3.7 Summary

Conservative therapies such as pressure dressings, repeat surgery, doxycycline treatment, or vacuum-assisted closure therapy are currently chosen as the primary treatment option, although radiation of secreting lymphatic fistulas is an effective, low-cost, low–side effect choice. Furthermore, radiation can be used after previous unsuccessful therapy and is an alternative to surgical treatment. Therapeutic strategies should be based on low single doses, which obviously promise faster response with the same efficacy. In large-volume lymphatic fistulas, radiotherapy is more beneficial than the use of fibrin glue, which is more suitable for small-volume lymphatic fistulas because of effective secretion reduction.

4.4.3.8 Recommendation

Radiotherapy can be performed.

Evidence level 4, recommendation level C

Authors	Region	RT	ED	GD	Sustaining the lymphatic secretion
Mayer et al. (2005), 17 Patients	Saphenous vein harvesting n=7 Femoropopliteal bypass n=3 Varicose vein surgery n=2 Hip replacement surgery n=3 Shunt surgery n=1 Piercing n=1	Orthovolt n=12 Electrons n=2 Photons n=3	0.3 to 2.0 Gy	1–12 Gy	13/17
Dietl (1997–2000), 28 Patients	Inguinal lymphatic fistulas	Orthovolt (120–300 kV)	3×3 Gy (n=22) 2×4 Gy (n=3) 5×3 Gy (n=3)	8–15 Gy	1/28
New (1989–1998), 29 Patients	25 lymphatic fistulas without indication of localization 4 lymphoceles, 2 located retroperitoneally	Electrons: 7–18 MeV (n=27) Photons: 15 MV (n=2)	1.0 Gy	3–12 Gy	27/29

Table 17. Results of radiotherapy for lymphatic fistulae.

4.4.4 Symptomatic vertebral body hemangiomas

4.4.4.1 Definition

Hemangiomas are nonmalignant neoplasms derived from the endothelial lining of blood conduits and can occur in all organ systems [173,318,822]. Cavernous bone hemangiomas are rare, accounting for only 0.7%–1.0% of all bone tumors [831], of which 60%–70% are localized in the cranial and axial skeleton [318]. Vertebral hemangiomas (VHs) occur mostly in the thoracic and upper lumbar spine; the pattern of involvement is predominantly singular, and diffuse is possible [215,316,318,537,598,822].

4.4.4.2 Epidemiology

VHs are the most common neoplasms of the bony axial skeleton. Although older autopsy series showed rates of incidental lesions of 10%–12% [375,623], a more recent serial study shows rates as high as 26%, 7.2% of them multifocal lesions [726]. The sex distribution is balanced, as is the involvement within the vertebral body. Of these, however, only about 0.9%–1.2% develop clinically relevant symptoms requiring treatment [315,316,598]. VHs occur more frequently beyond the fourth decade of life [318], and the average age of symptomatic cases is higher [726].

4.4.4.3 Etiology and pathogenesis

Hemangiomas are harmatomas of a dysontogenetic pathogenetic origin, presumably arising from the floor of embryonically scattered mesenchymal tissue [215,598]. Histologically, thin-walled ectatic vessels containing thrombi or hemosiderin are found embedded in hypertrophied bone bellae and adipose tissue [50,173,215,286,598]. According to morphologic criteria, cavernous VH, capillary VH, and mixed forms of both types are distinguished [173,318,551,623].

Clinically relevant symptoms are the result of epi- or intraspinal expansion of the ectatic blood conduits and, by definition, are not due to mitotic activity. Pathologic fractures, extradural hemorrhage, or ischemia of the spinal cord may aggravate symptoms [215,318]. About 10% of symptomatic cases occur premenstrually or during pregnancy. Causes are the increase of pressure in the inferior vena cava by the fetus and/or the increase of plasma volume in a range of 20%–100%.

4.4.4.4 Diagnostics, differential diagnosis

The diagnosis is made mostly on the basis of the clinical and radiological appearance, as biopsies are associated with an increased risk of bleeding [25]. Typical conventional radiologic signs include vertical striation, honeycomb-like loosening of the vertebral body internal structure, or distension of the vertebral body to loss of concave external contour (“ballooning”), predominantly in symptomatic lesions [31,249,318,598]. However, at least one-third of the vertebral body must be penetrated to detect these signs, so they are reliably detectable in only about 60% of cases, making the supplementary use of cross-sectional imaging indispensable for confirming the diagnosis and planning therapy. CT is the optimal method for evaluating stability; typically, transverse sections of the hypertrophied bone trabeculae surrounded by the dilated blood vessels of reduced density are found (i.e., “blackberry aspect,” “polka-dot appearance”) [598]. In addition, MRI can be used to better assess the width of the spinal canal and soft tissue involvement of contour-spanning findings. In T2-weighted sequences, symptomatic VHs typically show raised signal intensities because of increased vascularization [50,86,598].

The spectrum of possible differential diagnoses includes all benign and malignant spinal processes, as well as systemic diseases of the musculoskeletal system (bone metastases of malignant tumors, benign neoplasms, such as aneurysmal bone cysts, angiomas or meningiomas, Paget's disease) [173].

4.4.4.5 Therapy options (general)

The initiation of therapeutic measures is symptom-adapted on the basis of a clinical staging (Table 18) [316,318].

In cases of incidental, asymptomatic lesions (**stage 1**), no treatment is indicated, and patient monitoring is not mandatory. In cases with local or radicular symptoms without (**stage 2**) and with spinal cord compression (**stage 3**), the full range of standard conservative therapeutic options can be used alone or in combination, e.g., transarterial embolization [3,215], percutaneous vertebroplasty [3,100], intralesional ethanol injections [3,172] or radiotherapy [25,31,195,249,315,316,318, 600,623,822,832]. In the case of spinal canal involvement with acute spinal cord compression or an already manifest paraplegic syndrome (**stage 4**), prompt surgical intervention is recommended. Depending on the local extent of the processes, more complex procedures, such as vertebraectomies with alloplastic vertebral body replacement, are used in addition to simple laminectomies [3,215,286,551,598]. Preoperative embolization can reduce the intraoperative bleeding risk [3,215,568,598]. In simple decompressions, because of incomplete resection, local recurrences have been described in up to 30% at follow-up periods of ≥3 years, of which approximately 90% occur within the first 2 years [551]. With more radical resection, such as vertebraectomies, recurrence rates are lower; a literature review showed a recurrence rate of 12.5% for contour-spanning lesions [568].

4.4.4.6 Special value of radiotherapy

The treatment goal of radiotherapy is local tumor control and avoidance of neurologic deficits and pain symptomatology [249]. Due to the biological behavior of the target tissues, follow-up periods of at least 3–6 months are required to evaluate treatment success [249,822].

Since the first report from Bailey and Bucy [31], who successfully used postoperative radiation to treat a 62-year-old female patient with multilocular involvement of the thoracic spine with acute myelon compression after previous laminectomy, the value of radiation therapy has been described in numerous, predominantly case-based publications. Few reports include larger patient populations [25,249,832]. Glanzmann et al. [249] published a retrospective analysis in 1977 summarizing the treatment results of 66 cases (62 patients) from 1939–1975. After administration of total doses of 30–50 Gy, sustained symptom freedom was achieved in approximately 60% of cases. Yang et al. [832] reported on 23 patients from a period of >20 years in whom total doses of 20 to 43 Gy had been applied by orthovoltage, telecobalt, and electron irradiation. Partial or complete pain remission was found in 14/16 cases, paresthesias regressed in 4/5 cases, and improvement of a transverse syndrome was achieved in 5 of 7 cases. Asthana et al. [25] retrospectively analyzed 17 patients who had received total doses of 35 to 40 Gy by telecobalt irradiation. After follow-up periods of 1–11 years, 7 of 8 patients had complete pain remission, improvement was achieved in all 6 cases with preexisting paresthesias (4/6 complete, 2/6 partial), and remission of cross-sectional symptoms was achieved in 7 of 9 cases (6/9 complete, 1/9 partial, 2/9 none). Rades et al. [623] compared the efficacy of radiotherapy with different total doses using a collective of 117 patients (authors' data pooled with literature data) treated with radiotherapy alone. Significantly better symptom regression was seen with biologically effective total doses of ≥36 to 44 Gy. The largest series to date, with 84 patients (96 lesions), was retrospectively analyzed as part of a multicenter study. In multivariate analysis, significantly better response was found after total doses ≥34 Gy in terms of pain relief and recalcification [316].

Dose concept/radiotherapy technique

After CT-guided 3D radiation planning, simple standing fields, weighted opposing fields, oblique fields with wedge filters, or more complex techniques can be used depending on the anatomical conditions

[318,348,600,822]. Obliteration of abnormal feeding vessels is discussed as the mechanism of action of radiotherapy, assuming the endothelial cells of these vessels as the target, for which total *in vitro* doses of about 30 Gy have been shown to be successful in inhibiting proliferation [195]. Radiation doses <20 Gy were found to be ineffective [215,822, 832].

4.4.4.7 Recommendation

In clinical **stages 2** and **3,** radiotherapy is an effective treatment modality that can be used alternatively or in combination with other treatment options, resulting in long-term symptom control in approximately 80% of patients.

Conventional fractionated irradiation series (5×2.0 Gy/week) have proven effective, with significantly higher rates of pain remission and remineralization achieved with total doses ≥34 to 36 Gy.

After decompression alone with incomplete resection, postoperative radiotherapy may reduce the local recurrence rate **[strength of evidence 2c, recommendation grade B].**

Radiotherapy should be performed.

Evidence level 2c, recommendation level B

Stage	Symptoms	Indication for therapy
Stage 1	No symptoms	None
Stage 2	Local symptoms without involvement of the spinal canal	Relative (conservative: radiotherapy, embolization, vertebroplasty, etc.)
Stage 3	Local symptoms with involvement of the spinal canal without signs of myelon compression	Relative (conservative: radiotherapy, embolization, vertebroplasty, etc.)
Stage 4	Involvement of the spinal canal with signs of myelon compression	Absolute indication for surgical decompression (possibly in combination with preop embolization or postoperative radiotherapy)

Table 18. Clinical staging of symptomatic vertebral body hemangiomas

4.4.5 Pigmented villonodular synovitis (PVNS)

4.4.5.1 Definition

Pigmented villonodular synovitis (PVNS) is a benign tumor-like neoplasm [121] that derives from synovial cells of the joint capsules, bursae, and tendon sheaths [365,566]. The description goes back to Charles Marie Édouard Chassaignac (1852) [117]. Depending on the pattern of involvement and the clinical course, three forms are distinguished: the diffuse type (D-PVNS), the localized type (L-PVNS), and pigmented villonodular tenosynovitis (PVTS), which is also called giant cell tumor of the tendon sheath [365].

4.4.5.2 Epidemiology

PVNS is reported to account for 0.1% to 1% of all joint diseases, with D-PVNS accounting for about two-thirds. Incidences are reported to be 1.8 cases per year/1,000,000 for PVNS, and 9.2 cases per year/1,000,000 for PVNS [542]. A recent Danish cohort study showed an incidence rate for PVTS of 30.3 cases/1,000,000 for localized involvement and 8.4/1,000,000 for a diffuse pattern of involvement of tendon sheaths [184]. Predominantly, adults in the middle decades of life are affected with an even sex distribution; D-PVNS tends to occur at younger ages [101,365]. Rarely, the disease occurs in childhood as a differential diagnosis to juvenile arthritis [392].

4.4.5.3 Etiology and pathogenesis

The etiology of PVNS is unclear, but trauma, recurrent hemorrhage or inflammation, an abnormal humoral or cellular immune response, and local disturbances in lipid metabolism have been discussed as etiologic factors [101,499]. Furthermore, because of an association with developmental abnormalities, genetic causes have been suggested [528]. More recent studies have shown an association with chromosomal aberrations such as trisomy 5 or 7 and translocations involving colony-stimulating factor-1, most frequently (t1; 2) (p13; q37) [741].

The pattern of involvement is monoarticular in >90% of cases, with preference for the lower extremity [574]. While PVTS manifests primarily in the tendon gliding tissue of the fingers, D-PVNS preferentially affects the middle and larger joints [101]. The most frequent localization is the knee joint, but ankle, hip, elbow, and shoulder joints may also be affected in decreasing frequency; in principle, ubiquitous occurrence is possible [101,563,574].

4.4.5.4 Diagnostics, differential diagnosis

Because of the nonspecific clinical symptoms, such as recurrent joint effusions or swelling, and the rarity of the disease, confirming the diagnosis can be problematic and delayed [101,310]. Histological confirmation by biopsy is ultimately conclusive, with the characteristic hemosiderin locations allowing differentiation from malignant synovial tumors and α-mannosidase deficiency [174,365,499,528]. Diagnostic imaging usually reveals no pathognomonic signs [174,499]. Conventionally, on radiology, there may be compaction of the surrounding soft tissue mantle, subcortical erosive or cystic changes, or calcifications in 60%–70% [101,499]. CT imaging reveals these density elevations in the soft tissues with up to 130 HU [499]. MRI typically shows a hypointense signal pattern in the T2-weighted sequence with prolongation of TR and TE times and, because of hemosiderin deposition, shortening of the T2 relaxation time [499]. Skeletal scintigraphy, ultrasonography, or analysis of biopsies do not contribute decisively to confirm the diagnosis [101]. An uncharacteristically increased uptake similar to metastases of malignant diseases is also shown by PNVS formations on 18F-FDG-PET-CT [101,186].

4.4.5.5 Therapy options (non-radiotherapy)

The treatment of choice for all forms of PVNS is resection of all affected synovial tissue as completely as possible [101,310]. Based on the pattern of involvement, radical synovectomy is therefore the goal in D-PVNS, which can be performed openly or arthroscopically [282,569,783]. Infiltrations of the adjacent bony structures should be remediated by means of curettage [574]; for more extensive destruction, combinations with alloplastic joint replacement procedures must be considered [282]. The complexity of the anatomical conditions, especially at the shoulder, knee, ankle, or hip joints, sometimes requires complex surgical techniques via multiple access routes [101]. In the localized forms (L-PVNS and PVTS), simple excisions of the lesions are usually sufficient because of the circumscribed pattern of involvement [101,310]. Because of these problems with surgical repair, reported recurrence rates are 8%–56% for D-PVNS and 5%–29% for L-PVNS [310].

Postoperative recurrence rates depend on the type of disease and are significantly lower in circumscribed forms than in diffuse forms. They show a dependence on the pattern of where lesions occur. Recurrence is negligible when they affect the bursa and significantly lower in tendon sheaths compared with joints, where rates increase with increasing joint size [101].

The value of targeted therapies with monoclonal antibodies for TNF-α receptor blockade and tyrosine kinase inhibitors is currently unclear, and these therapies should be used only in the context of controlled clinical trials [71,110,118,206,446,618]. Radiofrequency ablation is experimental in nature [451].

4.4.5.6 Special value of radiotherapy

Since the first report by Friedman and Ginzler (1940) [227], the value of radiotherapy for the treatment of PVNS has been demonstrated in approximately 140 published cases in which total doses of 16–50 Gy were administered using various techniques and radiation qualities. With follow-up periods of 1–250 months, local control was achieved in an average of 85.4% [309,310]. Horoschak et al. [335] retrospectively analyzed outcomes in 17 patients (18 sites) who had received radiotherapy with total doses of 20–36 Gy after predominantly incomplete resection of recurrences. After a median follow-up of 46 months (range, 8–181 months), local control was achieved in 89% of cases. In a national pattern-of-care study, 41 evaluable cases were obtained from 14 institutions in Germany with a response rate of 83.2% of those who had received total doses of 30–50 Gy (median, 36 Gy) of irradiation. With follow-up periods ranging from 6 months to >10 years, 39 cases (95.1%) were locally controlled, and good functional outcome was achieved in 82.9% [309].

Only limited data have been published on the value of radiotherapy in the treatment of PVTS. Kotwal et al. [438] reported on a series of 48 patients with PVTS, 14 of whom had received orthovoltage irradiation of 5×2.0 Gy/week to 20 Gy due to increased mitotic rate or incomplete resections. After a mean follow-up of 52 months (range, 24–132 months), no local recurrence was reported in any case.

Dose concept/radiotherapy technique

The effects of radiotherapy in PVNS are based on proliferation inhibition. The total doses used in the literature mostly are 30–50 Gy [60,309,335,563] applied under conventional fractionation (5×1.8–2.0 Gy/week). The target volume should include the entire synovial space of the affected joint, which is most likely to be achieved at the larger joints by CT-based radiation planning [310,574]. For smaller joints or for PVTS, adjustment of the irradiation fields on the simulator is sufficient. Residual tissue after incomplete resections can best be localized with MRI, possibly in combination with arthroscopic findings. As an alternative to external radiotherapy, radiosynoviorthesis can be used [544,798], but this option can be fraught with significant complications in joints that have undergone multiple previous surgeries [310]. Calculations of radiogenic risks based on a Monte Carlo algorithm showed acceptable exposures for the surrounding organs at risk when irradiating the hip and knee joint with 36 Gy [501].

4.4.5.7 Recommendation

Radiotherapy is an effective therapeutic option for the treatment of PVNS, which can improve local control rates both in the adjuvant setting and after incomplete resections. Nevertheless, the goal should always be to achieve the most radical resection possible.

Due to the less aggressive growth behavior, progression of residual tissue can be monitored for localized involvement, especially in PVTS, even with R+ resections. In cases of involvement of bursae, postoperative irradiation is not necessary given the low recurrence rates. Especially in case of diffuse involvement of large joints, the recommendation for postoperative irradiation is stronger.

Under conventional fractionation (5×1.8–2.0 Gy/week), total doses of 36–40 Gy are recommended for D-PVNS, whereas lower total doses of 20–36 Gy are sufficient for L-PVNS and PVTS. As the target volume in joints should always include the entire synovial space, CT-based 3D radiation planning is recommended **[strength of evidence 3, recommendation grade B].**

Radiotherapy should be performed.

Evidence level 2c, recommendation level B

4.4.6 Radiotherapy for desmoid tumours

4.4.6.1 Definition

Desmoids are rare benign tumors of connective tissue arising from the deep musculo-aponeurotic structures in the region of muscle fascia, aponeuroses, tendon, and scar tissue [188,262,263]. They are referred to as “aggressive fibromatosis” in the US/UK literature [188,410]. The disease has long been known, with the first descriptions dating back to the 19th century [330,422]. The term “desmoid” or “desmoid fibroma” was coined by Johannes Müller in 1838, and its first English-language description was reported in 1932 by John McFarlane from Glasgow. In each case, neoplasms on the abdominal wall of women after childbirth were described. Similar tumors were later found in other parts of the body.

4.4.6.2 Epidemiology

Desmoid is a very rare primary benign tumor disease. The number of new cases per year is 2–4 per 1 million [262,330,422]. Differentiation by location into extra-abdominal (approximately 70%), intra-abdominal (approximately 10%), and abdominal wall desmoids (approximately 20%) may be of prognostic importance. Extra-abdominal forms are more prone to recurrence, even after apparently safe R0 resection. The intra-abdominal forms are disproportionately frequently associated with Gardner syndrome (polyposis coli), an autosomal dominant inherited disorder [58,422,425,635,716]. Only exceptionally are other genetic factors and trauma considered to be the cause of desmoids. Very rarely, desmoids develop in the area of scars after surgical interventions. Women are affected more frequently than men in a ratio of 1:1.5–2.5. The disease tends to occur in the third and fourth decades, but desmoids can also develop in young children and older people [330,422].

4.4.6.3 Etiology

The causes are largely unexplained. A hereditary predisposition is not considered to exist, except in Gardner syndrome, an association of familial adenomatous polyposis of the intestine with desmoid tumors and osteomas. Estrogen probably plays a role, as the tumor often occurs in association with pregnancy, regresses spontaneously during menopause, and sometimes responds to antihormonal therapy. In addition, the tumor is more frequently observed as a result of injury in scar tissue.

4.4.6.4 Histology

Macroscopically, the gray-white tumor has a coarse consistency and usually is >5 cm. Histologically, similar-looking fibroblasts are present in the tumor, with only minor nuclear atypia. The cells are oriented in the same direction and are located in a wave- or vortex-shaped collagen network [144,447].

4.4.6.5 Clinical

Typical of desmoid is the slow but locally aggressive and infiltrating growth and the tendency to local recurrence after local resection [2,49,58,65,526,635,716]. Some tumors show low malignancy and may spontaneously arrest in growth; others may assume huge proportions and then secondarily trigger disease-relevant symptoms. Partial and temporary remissions are possible. Desmoids can occasionally infiltrate larger organs and vessels with sometimes fatal consequences. In about 8%, desmoids lead to death [615]. Metastasis is always a rarity. Multifocal growth, e.g., multiple localizations to one limb, are known. Stage is inconsistently estimated, especially in critical localization, e.g., at the mesenteric root.

4.4.6.6 Diagnostics

MRI leads the way in assessing the extent of lesions and possible infiltration into adjacent tissues and organs [61,782]. To confirm the diagnosis, an incisional biopsy is always warranted initially to differentiate benign from malignant lesions (e.g., fibrosarcoma). Only after histological verification, a complete resection, if possible, is attempted. Histology with description of the tumor margin is obligatory and of great importance for assessing the probability of recurrence.

4.4.6.7 Therapy options

Surgery is the treatment of choice, and complete resection should be achieved with adequate safety margins. In cases of inoperability or R1 or R2 resections, as well as recurrences, radiotherapy is recommended [37,526,747]. Also discussed in cases of inoperability and recurrence are drug therapy approaches with, for example, tamoxifen, progesterone, indomethacin with vitamin C, interferon alpha, and mild chemotherapy protocols [35,366,421,425,452,467,570, 734,754,792,801,816].

4.4.6.8 Indication for radiotherapy

Radiotherapy alone

After primary radiotherapy, a high local control rate is achieved, which hardly differs from that after postoperative irradiation [37,268,326,330,387,391,409,410,422,429,466,509,561,680,687,731,732, 745,839]. Leibel et al. [466] reported a local control rate of 68% at a median follow-up of 8 years in 19 patients with residual tumor or recurrence irradiated with 50–55 Gy. Surprisingly, tumor size did not seem to have a prognostic impact on local control after radiotherapy [410,466,747].

Combined approach

In a meta-analysis, Kirschner and Sauer [422] analyzed a total of 698 cases from 13 studies. They found a 17% improvement in local control after R0 resection with postoperative radiation compared with surgery alone. For macroscopic (R2) or microscopic tumor remnants (R1), the results of postoperative radiotherapy are significantly better. The recommended total dose in the literature is 50–60 Gy for postoperative and 60–65 Gy for inoperable or recurrent tumors [25,49,262,263, 330,387,410,422, 429,466,509,561,732,745,794]. The overall position of brachytherapy in the treatment of aggressive fibromatosis is still unclear, with at least some evidence for better local control compared with surgical therapy alone [24,836].

A meta-analysis by Nuyttens et al. of 22 studies [561] showed no difference in local control between postoperative and primary radiotherapy. However, both procedures were significantly superior to surgery alone in terms of local control.

Radiotherapy technique

Radiotherapy should be performed similarly to the criteria for radiotherapy of sarcomas. Thus, CT-guided 3D-planned radiotherapy should be performed in every case.

4.4.6.9 Summary

Postoperative radiotherapy significantly improves the local control rate in desmoid compared with surgery alone. Even in primary therapy, high and long-lasting local control can be achieved with definitive radiotherapy alone. Thus, radiotherapy can be an alternative to mutilating surgery.

4.4.6.10 Recommendation

Radiotherapy can be performed, if indicated.

Evidence level 4, recommendation level C

A randomized trial is lacking to support a higher level of evidence.

4.4.7 Prophylactic radiation for prevention of gynecomastia

4.4.7.1 Definition

By definition, gynecomastia (GM) is the unilateral or bilateral enlargement of the male mammary gland due to glandular hyperplasia. It can be contrasted with pseudogynecomastia or lipomastia, which is caused by increased storage of fatty tissue. GM does not represent an independent clinical picture but is rather a symptom complex that can be triggered by a variety of different hereditary, endocrinological, metabolic, inflammatory, or neoplastic diseases [39,89,363,604,689,807,819]. Acquired forms may be paralleled by physiological types in neonates [396], during puberty [272], and in older age as so-called geriatric GM [89,689]. Fundamental here are imbalances in the regulation of sex hormones with a shift of the androgen–estrogen ratio in favor of estrogens, resulting in a proliferation stimulus of the glandular body [89,604,807].

4.4.7.2 Frequency

About 10% of all GM is caused by drug treatments [507]. Since the confirmation of androgen sensitivity of prostate carcinoma cell lines [341], endocrine therapy has become an indispensable pillar in the treatment of prostate cancer [341]. In the era of estrogen therapy, the incidence of clinically relevant GM was one of the most common side effects at approximately 90%, but with changes in hormone therapy, the incidence has decreased significantly. Reported risk is 1%–14% for orchidectomy, 1%–16% for luteinizing hormone-releasing hormone antagonists, 16%–79% for non-steroidal antiandrogens, 6% for steroidal antiandrogens, and 13%–22% for complete androgen deprivation [507]. Table 19 summarizes the relative risks for the occurrence of clinically relevant GM with other drug classes.

4.4.7.3 Pathophysiology

Up to childhood, the development of the mammary gland body of both sexes proceeds almost uniformly. At puberty, under the influence of rising estrogen and progesterone levels, the typical differentiation of the female breast begins [89], whereas the male mammary gland body undergoes only a temporary enlargement and then involutes. Nevertheless, hormone sensitivity of the rudimentary male mammary gland body persists.

The production of testicular and adrenal androgens is subject to the influence of hypothalamic and pituitary control hormones. Much of the testosterone is converted by reduction to dihydrotestosterone, the major intracellular mediator of testosterone action; the ratio to estradiol is about 100:1. Peripheral aromatization, which occurs primarily in liver, muscle, and adipose tissue, gives rise to female sex hormones from the androgens thus formed, with testosterone as a precursor for estradiol and the adrenal androstenediones as precursors for estrone. Daily testosterone production in males is about 6–8 mg/d and daily 17-ß-estradiol production is about 45 µg/d [807,819]. Free testosterone and estradiol can inhibit release of hypothalamic releasing hormones via negative feedback.

Due to the complexity of the regulatory mechanisms, numerous parameters thus can influence the testosterone–estrogen ratio. Possible causes of an increase in estrogen levels include drug intake, hormone-secreting tumors, or the persistence of placental estrogens in neonatal GM. GM in adolescents results from an earlier onset of estrogen action. Another cause is a decrease in the synthesis capacity of testosterone in geriatric GM, which also may lead to increased peripheral conversion, or in the course of cytostatic therapies [212]. Non-steroidal and steroidal antiandrogens inhibit the protective influence of androgens on male mammary gland tissue. In the case of non-steroidal antiandrogens, the feminizing effects are more pronounced because they also inhibit the mechanism of negative feedback via an additional, central attack, which in turn results in an intensification of peripheral conversion.

Histopathologic findings do not usually allow for conclusions regarding etiology or pathogenesis [17]. Histologically, the more common tubular form of GM (G. tubularis) can be distinguished from the "true" lobular form (G. lobularis), which is characterized by an increase in glandular lobules with fat synthesis in the epithelial cells and secretion [48]. Signs of increased proliferation include clustered mitoses on light microscopy, various forms and degrees of epithelial hyperplasia and metaplasia, and loss of myxoid stroma [48,288]. Transitions to atypical proliferation are found in 1.1%–6.5% [17,39]. The glandular epithelium is usually arranged in 4–6 cell layers, and in contrast to the normal male breast, the myoepithelial cells are much more prominent [288]. Positive detection of androgen, estrogen, and progesterone receptors is successful in approximately 10% of cases, more so in patients with Klinefelter syndrome or a unilateral pattern of involvement [604,617]. Younger patients more often have a more pronounced fibrotic aspect, whereas florid forms are more often found in older patients, which may be associated with an increased tendency to recurrence after resection [225].

4.4.7.4 Diagnostics, differential diagnosis

In addition to history taking and clinical examination with palpation of the glandular bodies, ultrasound examinations are of great importance [651,750,815]. Advanced diagnostics to determine the cause of GM may include mammography, radiography of the thorax, or cross-sectional imaging of various regions [675,689,821]. Typical clinical symptoms include tension and pressure tenderness, hyperesthesia of the nipple, pruritus, and less commonly, hyperpigmentation of the areola.

Laboratory determination of testosterone, estradiol, luteinizing hormone, follicle-stimulating hormone, prolactin, α-fetoprotein, ß-human chorionic gonadotropin, glutamate oxaloacetate transaminase, and creatinine may be required when appropriate [675,689,821].

The most important differential diagnosis of GM, especially in unilateral localization, is male breast carcinoma. Fibrosis, cysts, inflammatory diseases, hematomas after trauma, and lymphatic or venous outflow disorders, which may occur in thoracic tumors or retrosternal goiter, should also be distinguished [675,689,821].

4.4.7.5 Therapy options (general)

GM does not always require therapy but should be investigated, not least to exclude virile breast carcinoma [363]. In the case of physiological forms, a wait-and-see approach is recommended [821]. For the acquired forms, treatment or elimination of the causal factors should usually be pursued. The indication for treatment should depend on the severity of clinical symptoms [89,363,675,689,821] or impairment of quality of life [767]. GM in the context of hormone therapy of prostate carcinomas occupies a special position in this respect, as the cause cannot be eliminated, given the indication for the prophylactic treatment. Due to the high rate of clinically relevant GM of up to 80% of this population, patients to be treated with non-steroidal antiandrogens represent the typical target group.

In principle, various options are available for the treatment of GM in addition to drug or surgical treatment and radiotherapy [89,363,675,689, 807,821].

Drug treatment includes tamoxifen at a dosage of 10–20 mg/day, clomiphene as a partial estrogen blocker, danazol, or aromatase inhibitors such as testolactone or anastrozole [53,76,159,216,505,663,712,755,771,821]. The efficacy of local application of dihydrotestosterone is uncertain. Due to androgenic effects, danazol is not indicated in patients with prostate carcinoma.

In prospective randomized, double-blind, placebo-controlled trials, tamoxifen proved significantly superior to the use of anastrozole [76,663]. Furthermore, a daily dose of 20 mg/day was shown to have the greatest efficacy [216] and to be clearly superior to weekly doses [53]. However, possible side effects, such as thromboembolic complications, blood count changes, or lens opacities, should be weighed [821].

Surgical procedures, such as mastectomy [70,114,224,225,414,463] or liposuction [131], alone or in combination, are mostly used after failure of conservative therapeutic approaches or primarily in cases of suspected tumor.

4.4.7.6 Special value of radiotherapy

Radiosensitivity of the mammary gland body has long been described in the literature [638,767], as the target tissues are epithelia proliferating under the stimulus of excess estrogen. Fine-tissue studies after prophylactic irradiation showed rarefaction of the stroma and glandular ducts, as well as a reduction in glandular hyperplasia [458].

After the androgen dependence of prostate carcinoma cells was demonstrated [341], prophylactic radiotherapy has been regularly used in clinical routine because of the high expected rates of clinically relevant GM in the era of estrogen treatment, and its efficiency has been demonstrated in a large number of studies [8,9,10,22,66,133,134,198,233,236,292,334,458,492,510,654,658,735,800,823,837]. Larsson and Sundblom [458], in a pilot study with six patients, irradiated the right mammary gland with 1000–1500 r 14 days before initiation of estrogen treatment and applied “sham irradiation” contralaterally. After 6–9 months, four of the patients developed GM on the non-irradiated side, while only minimal hyperplasia developed contralaterally.

Meanwhile, the efficacy of radiotherapy for the use of other classes of agents also has been demonstrated in a number of prospective studies comparing control groups and sham irradiation [584,770,780,811], showing significantly lower rates of symptomatic GM. Furthermore, prospective randomized trials have demonstrated superiority of tamoxifen administration over prophylactic radiotherapy [159,785].

4.4.7.7 Dose concept/radiotherapy technique

The dose concepts described in the literature show a wide range; data from dose-comparative studies are not available for radiotherapy. A patterns-of-care study by the GCG-BD showed that the doses used in Germany for prophylactic irradiation are 9–24 Gy, but mostly consist of hypofractionated irradiation series of 12–15 Gy in 3–5 fractions [548]. Published data indicate that lower doses, such as 4×1.5 Gy, are associated with significantly worse response rates (18.4%) [654]. In patients with already symptomatic GM, higher total doses of 9–40 Gy were mostly used. For palliative irradiation of symptomatic GM, total doses of 30–40 Gy have been called for in the literature, although the value has not been established by larger case numbers [122].

In about two-thirds of the facilities, the irradiation fields were positioned clinically on the patient without further treatment planning. Mostly direct electron fields with energies of 6–18 MeV were used, but orthovoltage techniques and photon irradiation are also used.

Nieder et al. [552], in an analysis of dose-volume histograms, reported that in unfavorable anatomical conditions, parts of the left ventricle may receive up to 50%–80% of the prescribed dose at higher electron energies. The side-effect profile is usually favorable, however, with grade I erythema or hyperpigmentation in about 10% of patients [548]. A low-grade risk for induction of radiogenically induced neoplasia is present and requires patient education [6,584].

4.4.7.8 Recommendation

Prophylactic radiation treatment can significantly reduce the rate of symptomatic GM in the context of hormone therapy for prostate carcinoma. Both hypofractionated radiation series with total doses of 9–15 Gy in 3–5 fractions and single irradiations with 1×10–15 Gy have proven to be effective. The target group is primarily patients treated with non-steroidal antiandrogens. There is no evidence for use with other classes of pharmaceuticals. In cases of existing GM, radiotherapy may be considered as an alternative to mastectomy, requiring higher total doses of up to 30–40 Gy depending on the clinic.

Radiation therapy can be performed using orthovoltage, electrons, or tangential photon fields. With CT-based 3D radiation planning, the loads on relevant organs at risk (heart, lungs) can be quantified, which appears to be advantageous, at least in patients with relevant preexisting conditions and risk profiles.

Prophylactic radiotherapy should be performed, when indicated.

Evidence level 1, recommendation level A

Pharmaceutical	Relative risk*	
Verapamil	9.7	(2.6–36.0)
Spironolactone	9.3	(3.3–26.1)
Cimetidine	7.2	(4.5–11.3)
Nifedipine	2.9	(1.6–5.3)
Digoxin	2.7	(1.2–6.1)
Ranitidine	1.5	(0.8–2.6)
Omeprazole	0.6	(0.1–3.3

Table 19. Relative risks for the occurrence of clinically relevant gynecomastia.

5 Summary table

Diagnosis	Single dose	Total dose	Evidence level	Recommendation degree
Gonarthrosis	0.5 to 1 Gy	3 to 6 Gy	2c	C
Coxarthrosis	0.5 to 1 Gy	3 to 6 Gy	4	C
Arthroses of the small joints	0.5 to 1 Gy	3 to 6 Gy	4	C
Shoulder syndrome	0.5 to 1 Gy	3 to 6 Gy	4	C
Bursitis trochanterica	0.5 to 1 Gy	3 to 6 Gy	4	C
Calcaneodynia	0.5 Gy	3 Gy	1 b	A
Elbow syndrome	0.5 Gy	3 Gy	2 c	B
Dupuytren's disease (in the active stage of "node formation")	3 Gy	15 Gy (repetition of the series after 8–12 weeks)	2c	B
Ledderhose disease (increasingly symptomatic, both primary and secondary after surgery)	3 Gy	15 Gy (repetition of the series after 8–12 weeks)	4	C
Keloid	3 Gy	12 Gy	4	C
Gorham-Stout Disease	1.8 to 2 Gy	36 to 45 Gy	3	B
Induratio penis plastica	2 to 3 Gy	10 to 20 Gy	3b	C
Heterotopic ossifications	7 Gy	7 Gy	1	A
Endocrine orbitopathy (early inflammatory phase)	0.3 to 2 Gy	2.4 to 16 Gy	2	B
Endocrine orbitopathy (advanced disease)	2 Gy	16 to 20 Gy	2	B
Lymphatic fistulas	0.3 to 3 Gy	1 to 15 Gy	4	C
Vertebral body hemangiomas	2 Gy	34 to 36 Gy	2 c	B
Pigmented villonodular synovitis	1.8 to 2 Gy	36 to 40 Gy	2 c	B
Desmoid	1.8 to 2 Gy	50 to 65 Gy	4	C
Gynecomastia (prophylaxis)	3 Gy	9 to 15 Gy	1	A

Table 20. Brief overview of indications, radiation doses, levels of evidence, and grades of recommendation.

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