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ORIGINAL ARTICLE

DEGRO practical guidelines for radiotherapy of non-malignant disorders

Part I: physical principles, radiobiological mechanisms, and radiogenic risk

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Abstract
Purpose Synopsis of the introductory paragraph of the DEGRO consensus S2e-guideline recommendations for the radiotherapy of benign disorders, including physical principles, radiobiological mechanisms, and radiogenic risk.
Materials and methods This work is based on the S2e-guideline recommendations published November 14, 2013. The basic principles of radiation physics and treatment delivery, evaluation of putative underlying radiobiological mechanisms, and the assessment of genetic and cancer risk following low-dose irradiation will be presented.
Results Radiation therapy of benign diseases is performed according to similar physical principles as those governing treatment of malignant diseases in radiation oncology, using the same techniques and workflows. These methods comprise usage of orthovoltage X-ray units, gamma irradiation facilities, linear accelerators (LINACs), and brachytherapy. Experimental in vitro and in vivo models recently confirmed the clinically observed anti-inflammatory effect of low-dose X-irradiation, and implicated a multitude of radiobiological mechanisms. These include modulation of different immunological pathways, as well as the activities of endothelial cells, mono- and polymorphonuclear leukocytes, and macrophages. The use of effective dose for radiogenic risk assessment and the corresponding tumor incidence rate of 5.5 %/Sv are currently controversially discussed. Some authors argue that the risk of radiation-induced cancers should be estimated on the basis of epidemiological data. However, such data are rarely available at present and associated with high variability.
Conclusion Current radiobiological studies clearly demonstrate a therapeutic effectiveness of radiation therapy used to treat benign diseases and implicate various molecular mechanisms. Radiogenic risks should be taken into account when applying radiation treatment for benign diseases.

Keywords Inflammation · Radiation physics · Radiobiological mechanisms · Risk · Guideline

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DEGRO-S2e-Leitlinie für die Strahlentherapie von gutartigen Erkrankungen

Teil I: Physikalische Grundlagen, radiobiologische Mechanismen und radiogene Risiken

Zusammenfassung

Hintergrund Zusammenfassung des einführenden Kapitels der DEGRO-S2e-Leitlinie zur Strahlentherapie gutartiger Erkrankungen einschließlich der physikalischen Grundlagen, strahlenbiologischer Mechanismen und des radiogenen Risikos.

Material und Methoden Basis für diesen Beitrag ist die am 14. November 2013 neu aufgelegte S2e-Leitlinie zur Strahlentherapie gutartiger Erkrankungen. Dabei werden die allgemeinen Grundlagen der Strahlenphysik und Bestrahlungstechnik, zugrundeliegende radiobiologische Mechanismen und die Erfassung des genetischen und Tumorrisikos nach niedrigdosierter Bestrahlung dargestellt.

Ergebnisse Die Strahlentherapie gutartiger Erkrankungen erfolgt gemäß den gleichen physikalischen Prinzipien und Abläufen wie die Behandlung von Tumorerkrankungen in der Radioonkologie und umfasst den Einsatz von Hochvolt-Röntgentherapieanlagen, Gammabestrahlungsgeräten, Linearbeschleunigern und der Brachytherapie. Experimentelle In-vitro- und In-vivo-Modelle konnten kürzlich die klinisch beobachtete entzündungshemmende Wirkung der niedrigdosierten Strahlentherapie bestätigen und eine Vielzahl zugrundeliegender strahlenbiologischer Mechanismen aufzeigen. Diese umfassen die Modulation unterschiedlicher immunologischer Reaktionskaskaden und die Aktivität von Endothelzellen, mono- und polymorphonukleären Leukozyten und Makrophagen. Die Anwendung der effektiven Dosis zur Risikoabschätzung und entsprechende Angaben einer Tumorinzidenz von 5,5 %/Sv werden derzeit kontrovers diskutiert. Einige Autoren plädieren dafür, die Abschätzung des Risikos strahleninduzierter Krebserkrankungen auf der Basis epidemiologischer Daten vorzunehmen. Diese Daten hingegen sind derzeit noch selten und mit einer hohen Variabilität assoziiert.

Schlussfolgerung Aktuelle strahlenbiologische Studien belegen eine therapeutische Wirksamkeit und zeigen zugrundeliegende molekulare Mechanismen auf. Bei Indikationsstellung zur Therapie gutartiger Erkrankungen sollte ein mögliches radiogenes Risiko berücksichtigt werden.

Schlüsselwörter Entzündung · Strahlenphysik · Strahlenbiologische Mechanismen · Risiko · Leitlinie

Physical principles

Ionizing radiation—such as X-rays, gamma rays, photons, electrons, and charged particles—is used to treat benign inflammatory and hypertrophic diseases, as well as nonmalignant and malignant tumours.

The physical interaction of radiation and material comprises the photoelectric effect, the Compton effect, and pair production. In the case of biological structures, these effects result in genetic alterations, defects in cellular structures, and changes in molecular pathways, which are commonly referred to as the DNA damage response. Treatment of benign diseases by radiation therapy is performed according to principles similar to those governing the treatment of malignant diseases in radiation oncology, using similar equipment [48, 56].

As evidence levels (according to evidence-based medicine) cannot be applied for physical parameters, we chose evidence level B for selection of the optimal treatment unit. According to the location of the target volume and consequent depth of the radiation reference point, we recommend the use of the treatment units depicted in Table 1.

Teletherapy

Treatment can be delivered by medical electron linear accelerators (LINACs) producing electron and photon beams in an energy range of 6–18 MeV. Co-60 systems, in which the radioactive decay of Co-60 produces gamma beams of 1.17 and 1.33 MeV, are also used. In this section we focus on therapeutic kilovoltage X-ray units and LINACs.

Therapeutic kilovoltage X-ray units

Therapeutic kilovoltage X-ray units operate with peak voltages in the range of 10–400 kV. The primary clinical use

Table 1 Recommended treatment units in relation to the selected depth for the reference point of the treated target volume

Treatment unit	Energy	Reference depth	Recommendation
X-ray therapy unit; superficial	10–50 kV	Surface	B
X-ray therapy unit; low depth	50–100 kV	<2 cm	B
X-ray therapy unit; orthovoltage	100–400 kV	<5 cm	B
Cobalt radiation unit	1.17/1.33 MeV	<10 cm	B
Linear accelerator:		All depths; use of bolus material if necessary	B
Photons	6–18 MeV		
Electrons	6–21 MeV		
Brachytherapy (Sr^{90}-source)	2.2 MeV β^--radiation contact treatment	<10 mm	B

of these units is treatment of benign diseases. The different types of kilovoltage X-ray beams were classified according to their peak potential as follows:

- Grenz rays: beam potentials from 10 to 20 kV.
- Contact therapy: beam potentials of up to 50 kV.
- Superficial therapy: beam potentials of 50–100 kV [11].
- Orthovoltage or deep therapy: beam potentials from 100 to 400 kV [13].

The focus-to-window distance is short, enabling applicators of 25–50 cm length to be used. This is convenient for setting up and defining beam sizes for patients. Typical rectangular applicators have field dimensions of 4×6, 6×9, 8×10, 10×15 or 20×20 cm^2, and circular applicators have diameters of 1–10 cm. Modern orthovoltage systems are microprocessor controlled, and thus safe and easy to use according to current standards. Treatment is either dose or time controlled. However, for older X-ray units without a monitoring ionization chamber, dose delivery based on timer mode will be the only option available.

The photon spectra in these energy ranges include a huge quantity of low-energy photons, which preferentially transfer energy via the photoelectric effect. This may result in an increase of absorbed dose in the bone of up to 700% [14]. Filters of aluminum, copper and lead, or combinations of aluminum, copper, and tin are usually interposed in the beam to absorb the very soft component of the energy spectrum.

The filtering parameters (material, thickness), the first half-value layer (HVL), and the peak voltage determine beam quality and should be reported.

The HVL is defined as the thickness of absorber (typically high-purity aluminum or copper) required to reduce the air-kerma rate by a factor of 50% [40]. Due to measurement times and the effort and costs associated with highly pure thin aluminum and copper discs, the following alternative is suggested: the measurement may be conducted in water or a water-equivalent solid-state phantom at two depths, with a constant source chamber distance of 50 cm and a field size of 125 cm^2 [13]. The beam quality index can be calculated using the quotient from the read out at 10- and 5-cm depths. For the given field size (125 cm^2), the suitable HVL of copper for peak voltages exceeding 100 kV can then be determined with the help of graphs from the German Society for Medical Physics ("Deutsche Gesellschaft für Medizinische Physik", DGMP) report DGMP 15 [13].

Treatment planning At present, treatment planning for kilovoltage X-ray beams is generally performed by manual calculation of either monitor units or treatment times [28]. For manual calculations tables are required, which include at least:

- Relative output factors for any other than the reference applicator.
- Depth–dose characteristics.
- Backscatter factors (BSF).
- Buildup of backscatter effect.

In the past the dose was calculated at the surface, where the relative depth-dose value is 100%. Currently, however, it is more appropriate to follow the International Commission on Radiation Units and Measurements (ICRU) 50/62 protocols [34, 36] and to normalize the dose to a reference point within the target. The peak voltage, i.e., the beam quality, should be chosen in such a way that the target volume is surrounded by the 80% isodose (estimated from the percentage depth-dose curves). As a consequence, target volumes at depths of more than 5 cm should not be treated with X-ray units. Moreover, the radiotherapy protocol should contain the depth of dosimetry, the maximum dose, the reference dose, and the minimum dose in the target volume.

Quality control The medical physics expert (MPE) is responsible for the correctness of the depth-dose data and the dosage chart. Hence, the documents provided by the manufacturers must be checked before use. For determination of BSF and correction of buildup backscatter, the MPE will often use appropriate datasets [7]. It is always necessary to check a few samples of these data before using the published tables.

If the thickness of the irradiated tissue is less than 10 cm, buildup backscatter should be taken into consideration; otherwise, underdoses up to 30% may occur [65]. In these cases, a dose correction should be carried out by the MPE on the basis of appropriate charts [6, 13]. Cutout factors are required if a lead cutout is used to define the beam shape [28]. An inverse square law correction factor should be applied if there is a gap between the end of the applicator and the skin surface. It has been shown that bone or air cavities may result in a reduction of backscatter and, as a consequence, in a reduction of the surface dose [9].

Many datasets state the interaction coefficients in terms of effective photon energy. With the known first HVL s1 for copper, the interaction coefficients can be interpolated from datasets for the mass energy-absorption coefficients of monoenergetic photon energies [63] using the following equation: $\mu / \rho = \ln 2 / \left(\rho \cdot s1\right)$.

Linear accelerators

In a LINAC, electrons emitted by a cathode are accelerated in electromagnetic fields. These accelerated electrons (energy from 6 to 21 MeV), as well as photons (energy from 6 to 18 MeV) that are produced by electrons by hitting a target, are suitable for radiation therapy.

Benign diseases [56] are treated according to similar principles as those governing treatment planning and radiation therapy in malignant diseases [10, 14–17, 34, 35, 37, 48, 56]. These processes will be briefly outlined.

Target volume definition After evaluation of the patient's medical history and indication, the clinical target volume (CTV) is determined by a physician. Artefacts produced by patient movement and uncertainties in CTV determination are considered by adding margins, which result in the planning target volume (PTV). This PTV is used for treatment planning. Different approaches have been described for PTV generation [10, 15–17].

Treatment planning Considering the CTV, its location, and the neighbouring organs at risk, a treatment plan is produced by an MPE and a physician. In order to avoid any negative effects on normal (or noninflamed) tissue [17], the PTV should be irradiated homogenously [10, 15–17], with the planned dose normalized to the reference point [12]. This can be achieved by using suitable radiation energies and techniques (Table 1). For this purpose, spreadsheet analysis or computer-based treatment planning systems that depend on disease type and location of the target volume [10, 33] are used. Mostly, single and opposing fields fit these requirements [12]. Nevertheless, all geometric features provided by the LINACs should be applied, such as simple conformation of the treatment fields using multileaf collimators (MLC) or shielding blocks, particularly in the vicinity of the target volume next to critical organs.

Treatment delivery For correct implementation of the treatment plan and technique, the setup has to be transferred to the patient. This is to ensure a reproducible adjustment at the irradiation device using removable skin markers. Moreover, to define the isocenter of the treatment plan, and, if applicable, its field entry, the following options are available:

- Patient setup: for simple treatment the patient setup can be achieved directly at the treatment unit. Considered are anatomical factors using previous determination of the reference dose point [10, 12], diameter of the patient at the setup point (by using opposing fields), and the suitable field size(s). In this context it is necessary to use imaging techniques to control the quality of patient setup (see "quality control" below).
- Virtual simulation: computer tomography for computer-aided treatment planning and simultaneous determination of the isocenter of the intended radiation technique using a variable laser system and skin markers.
- Simulation: using an X-ray unit combined with fluoroscopy, which has the same geometrical and technical possibilities as the treatment unit for setup of the treatment fields. This will be achieved by using the unit of the simulator for controlling the patient setup, and by applying skin markers according to the laser system and the entrance of the fields to the skin.

Quality control In order to control delivery of the treatment plan and the treatment technique (verification [14]), it is necessary to check the correct localization of the entrance of the single fields to the body, as well as the field shape (field size und conformation). This can be achieved by different methods using entrance field imaging techniques:

- Portal imaging: imaging of the single treatment fields using radiographic films during radiation treatment sessions.
- Electronic portal imaging: instead of using radiographic films, electronic systems like onboard portal imaging systems can be applied. These imaging systems also use the emitted radiation of the LINAC during the radiation treatment sessions of the patient.

Brachytherapy

The major advantage of brachytherapy [16] is a very short source–target distance, which allows a high dose to be given to the target while the surrounding tissue receives lower doses. While contact therapy with strontium-90 (Sr-90) derma plates was relinquished by radiooncologists [67], ocular applications using beta-emitting radionuclides and photon emitters are still in practical use [2]. An example is the beta emitter Sr-90 (half-life 28.7 years), with a low electron energy of 0.546 MeV. The daughter nuclide yttrium-90 emits electrons with an energy of 2.27 MeV. The short half-life of yttrium-90 (64 h) is without further importance, because decay equilibrium exists between Sr-90 and Y-90. The HVL is 1.5 mm in water [22]. The final element is zirkonium-90.

Documentation

All parameters of the radiation treatment (treatment plan, dose prescription, dose, period of treatment, and verification images) are to be documented in the treatment protocol [15]. According to legal requirements, this protocol has to be stored for a period of 30 years [58].

Radiobiological mechanisms

The interrelationship between ionizing radiation and the immune system displays a dichotomous character and depends highly on the radiation dose/quality and the

immune cell population investigated. In general, X-ray treatments with single doses ≥2 Gy exert proinflammatory effects [64], while low-dose radiation therapy (LD-RT; single doses <1 Gy) has been shown to modulate a variety of inflammatory processes and clearly reveals anti-inflammatory properties [50]. This implies the involvement of complex mechanisms operating differentially at different dose levels [43, 50].

As (chronic) inflammatory and degenerative diseases are based on complex (patho)-physiological immunological networks, one may assume that the empirically proven anti-inflammatory efficacy of LD-RT [56] is based on the modulation of a multitude of inflammatory pathways and cellular components. Indeed, this has recently been demonstrated in a variety of experimental in vitro and in vivo studies.

Modulatory properties on endothelial cells

An initial event in inflammatory cascades is recruitment of peripheral blood mononuclear (PBMC) and polymorphonuclear cells (PMN, granulocytes) to the site of damaged tissue. Endothelial cells (EC) play a crucial role in the regulation of this process, both by virtue of their ability to recruit leukocytes from circulating blood, and by expressing a variety of adhesion molecules, cytokines/chemokines, and growth factors [57]. Consequently, experiments were performed on the role of EC in the anti-inflammatory effect of LD-RT. Among the first mechanisms reported to contribute to the immune modulatory effects was a significant reduction of leukocyte (PBMC and PMN) adhesion to stimulated ECs. The most pronounced effect was observed following a 0.5 Gy exposure [25, 39, 53]. This characteristic functionally coincides with nonlinear expression of the anti-inflammatory cytokine transforming growth factor β1 (TGF-β1) by EC, both in vitro and in a murine model. Likewise, neutralization of TGF-β1 restored leucocyte/EC adhesion, indicating a key role of the protein in these effects [3, 53].

Modulatory properties on leucocytes

Apoptosis, a physiological cellular suicide program, is induced by a variety of endogenous and exogenous stimuli, including ionizing irradiation [23]. Apoptosis has a significant impact on immune regulation and radiation response. In line with this, irradiation of PBMC and PMN revealed a discontinuous increase of apoptosis, with a plateau or peak following a 0.3–0.7 Gy exposure [21, 38]. This may further contribute to hampering recruitment of inflammatory cells by reducing cell numbers; a fact that is further supported by decreased surface expression of the adhesion molecule E-selectin on ECs [25, 53] and enhanced proteolytic cleavage of L-selectin from apoptotic PBMC [39]. In addition, modulation of the prosurvival mitogen-activated protein (MAP) kinases and protein kinase B (or AKT) [21], as well as reduced release of the chemotactic cytokine CCL20 from PMN following irradiation with doses below 1 Gy have been reported [52].

The major cellular elements of the immune system also include different subtypes of lymphocytes (B and T cells), as well as PMN and mononuclear leukocytes as the main components of innate host defense. In line with this, a characteristic of the effector phase of inflammation comprises accumulation of monocytes and their differentiation into dendritic cells and inflammatory macrophages [1, 61]. The latter effect supports local inflammation by a plethora of functions, such as phagocytosis and presentation of harmful antigens, secretion of cytokines, and release of reactive oxygen intermediates (ROIs) or nitric oxide (NO; [20, 45]). NO, predominantly processed by inducible nitric oxide synthase (iNOS), regulates vascular permeability, promotes edema formation, and is involved in the pathogenesis of inflammatory pain [29]. However, following irradiation of activated macrophages, decreased expression of the iNOS protein [27], as well as hampered release of ROS and superoxide production [55], have been reported. Reduced concentrations of NO and ROS may, in turn, diminish the degree of vasodilation (erythema), vascular permeability (edema), or local pain; thus perhaps contributing to the beneficial effects of LD-RT. More recent data further indicate hampered nuclear translocation of the nuclear factor-κB/p65 (NF-κB) transcription factor, lowered secretion of the proinflammatory cytokine interleukin 1 (IL-1), and increased expression of TGF-β1 by inflammation-stimulated macrophages [42], concomitant with a significantly reduced migration capability [66]. In conclusion, low-dose X-ray irradiation, most pronounced at a dose of 0.5 Gy, induces an anti-inflammatory cytokine microenvironment for macrophages, which might be accompanied by resolution of inflammation.

Mechanisms implicated in the anti-inflammatory properties

A common characteristic of the effects reported so far is a discontinuous dose–response relationship, which is shared by non-(DNA)-targeted bystander, abscopal, or adaptive effects [24]. These recent findings challenged the classical paradigm in radiation biology that deposition of energy to the nucleus and the resultant DNA damage is responsible for the biological consequences of radiation exposure [44], and take into consideration a complex intercellular communication. These results may be useful for describing radiation responses on a tissue level [5]. Mechanisms contributing to these nonlinear dose–response relationships remain, however, elusive and most likely originate from overlap of several processes that may be initiated at various threshold doses and display different kinetics (for review see [50]). These effects were further evidenced by biphasic regulation

of inflammatory transcription factor NF-κB [51] or nonlinear expression of X chromosome-linked inhibitor of apoptosis protein (XIAP) in stimulated ECs [49]. In addition to its antiapoptotic properties, XIAP regulates translocation and activity of NF-κB, and is involved in the antiadhesive properties of low-dose exposure.

Preclinical models

In addition to an increasing knowledge of the underlying cellular and molecular mechanisms, a multitude of animal arthritis models have been established to study advancements in clinical inflammatory parameters, to improve histological markers, and to confirm the anti-inflammatory effects of low-dose irradiation. In 1933, von Pannewitz was the first to report on an improvement of symptoms, joint swelling, and pain following irradiation with single doses of 1.0 Gy in a rabbit model of mechanical destruction of cartilage and bone [62]. In subsequent decades, these characteristics were confirmed in a variety of inducible inflammatory models in rabbits, rats, and, more recently, in human tumor necrosis factor α(TNF-α) transgenic mice [19]. These models convincingly indicate that low-dose irradiation inhibits proliferation of synovial cells and synthesis of synovial fluid, reduces the destruction of cartilage and bone, hampers expression of iNOS and IL-1, and increases secretion of the anti-inflammatory cytokine TGF-β1 concomitant with an increased expression of heat shock protein 70 (Hsp70) and heme oxygenase-1 (HO-1; [3, 8, 18, 26, 54, 59]). Notably, very recent in vitro data confirmed an inhibition of IL-1β-induced catenin signaling by LD-RT, with subsequent suppression of the sex-determining region Y-box 9 (Sox-9) transcription factor and NF-κB pathways in articular chondrocytes, which may well contribute to the palliation of pathophysiological processes in cartilage disorders [30]. Furthermore, the best treatment effects were evident after daily fractions of 0.5 and 1 Gy, and an early onset of treatment [19, 41].

In summary, current experimental in vitro data and in vivo models [4] have clearly confirmed anti-inflammatory effects and have proven a variety of immune modulatory effects of LD-RT, which are most pronounced at a 0.5 Gy exposure. Notably, more recent investigations further support the preclinical observation that single doses of 0.5 Gy are highly effective in the clinical setting, thus allowing total dose reduction [46, 47]. However, although considerable progress has been achieved in the understanding of cellular targets and underlying molecular mechanisms, a multitude of unresolved questions concerning (chronic) inflammatory degenerative diseases and the role of LD-RT in modulating fibrotic diseases and heterotrophic ossification still remain. Therefore, intensive basic translational and clinical research alongside with the development of suitable platforms and basic models is urgently needed.

Estimation of cancer risks

The radiation risks associated with low-dose radiation therapy result from stochastic radiation damage. They are based on transformation or mutation of affected cells, which may result in neoplastic changes or hereditary diseases. In 2007, the International Commission on Radiological Protection (ICRP) undertook a reassessment of radiation risk, which was published in 2008 [31]. The recommendations of the ICRP 60 have thus been updated and modified.

To quantify the effects of a particular radiation dose, the genetic and cancer risks must be considered. The risk of radiation-induced cancer can be estimated in two ways: on one hand by calculation of the effective dose (not without controversy) and on the other hand, by direct calculation of the risk by means of organ-related risk coefficients.

Effective dose

The effective dose is the tissue-weighted sum of the equivalent doses in all specified tissues and organs of the body. The effective dose (E) is defined as:

$$E = \sum_T w_T H_T = \sum_T w_T \sum_R w_R D_{T,R}$$

where T is the tissue or organ of interest; H_T is the equivalent dose absorbed by tissue T; w_T is the tissue weighting factor (see Table 2); w_R is the radiation weighting factor, $D_{T,R}$ is the mass-averaged absorbed dose in tissue T by radiation type R.

The unit for effective dose is Sievert (Sv). To calculate the effective dose, the absorbed organ dose is first corrected for the ionizing radiation type using a factor that gives a weighted average of the equivalent dose quantity received in the irradiated tissue (w_R). For photon beam irradiations $w_R = 1$; the values of other radiation species can be found in [31, 58]. The effective dose is further corrected for the tissues or organs being irradiated using a tissue weighting fac-

Table 2 Tissue weighting factors according to ICRP 103 (ICRP 2007)

Tissue (T)	Tissue weighting factor (W_T)	ΣW_T
Bone marrow (red), colon, lung, stomach, breast	0.12	0.72
Gonads	0.08	0.08
Bladder, esophagus, liver, thyroid	0.04	0.16
Bone surface, brain, salivary glands, skin	0.01	0.04
remaining tissues ($n = 13$)[a]	0.0092	0.12
Total	–	**1.00**

[a]Remaining tissues: adrenals, extrathoracic region, gall bladder, heart, kidneys, lymphatic nodes, muscle, oral mucosa, pancreas, prostate (♂), small intestine, spleen, thymus, uterus/cervix (♀)

tor. These tissue weighting factors have been incorporated into national radiation protection regulations ("Strahlenschutzverordnung" and "Röntgenverordnung") for medical workers and the general population.

Genetic risks

According to ICRP 1991 [32], the probability of development of severe genetic damage in any future generations is 1%/1 Sv. The risk for the first and for the second generation is estimated at 0.15%/1 Sv. For the third and subsequent generations, the genetic risk is 0.7%/1 Sv. According to ICRP 2007, the genetic risk is now estimated to be much lower [31]. However, the exposure of the gonads and thus the genetic risk is without significant importance in the majority of (low-dose) radiotherapy treatments of nonmalignant disease.

Cancer risks

The exposure to ionizing radiation is known to increase the incidence of cancer. The mechanism by which this occurs is well understood, but quantitative models predicting the level of risk remain controversial. The induction of cancer has a latent period of years or decades following exposure. According to ICRP 2007, the incidence of cancers due to ionizing radiation increases linearly and is about 5.5% per Sievert [31].

Dose and dose rate effectiveness factor

For the induction of cancer at low doses or low-dose rates, the use of a simple proportional relationship between increments of dose and increased risk is uncertain. This forms the basis of the dose and dose-rate effectiveness factor (DDREF). DDREF was introduced to extrapolate the rate of radiation risk of higher doses to the risk of a low radiation dose. In its 1990 and 2007 recommendations, the ICRP made the broad judgment that a DDREF of 2 should be applied for doses below 0.2 Sv and for dose rates of 0.1 Sv per hour [31, 32]. The use of DDREF = 2 is under discussion, also by the DEGRO and DGMP. The German Commission on Radiological Protection ("Strahlenschutzkommission", SSK) reiterated in their annual report 2014 that the DDREF and all similar parameters in radiation risk assessment need to be adjusted to reflect the current scientific knowledge. Already in 2006 the SSK did not follow the ICRP recommendations and voted for an DDREF=1. In the current report they conclude that the DDREF might be obsolete due to current scientific data.

Table 3 Organs and their tissue weighting factors taken into account for the calculation of effective dose

Tissue	Weighting factor
Bone marrow (red)	0.12
Bone surface	0.01
Skin	0.01
Lymphatic nodes	0.009
Muscle	0.009
Sum	**0.158**

Age dependence of radiation induced cancer

Radiation exposure at a younger age is associated with a higher cancer risk compared to older age [32]. This is illustrated by the following example:

The knee joint of a patient in middle or older age is irradiated with a dose of 6 × 0.5 Gy (field size 15 × 15 cm). The proportion of the exposed knee joint is estimated to be 2% (0.02) of the total body weight. The organs and their tissue weighting factors shown in table 3 are taken into account for the calculation of effective dose.

The effective dose is calculated by multiplying of the percentage of 2% (0.02), the sum of the weighting factors (0.158), the DDREF factor (2), and the dose (3 Gy), i.e.,:

Effective dose = 0.020 x 0.158 x 2 x 3 Sv = 0.019 Sv

This value corresponds approximately to the limit of radiation exposure for exposed persons per calendar year (20 mSv)—the effective dose of a CT scan of the abdomen or ten times the natural annual radiation exposure. The irradiation increases the lifetime cancer risk by about $0.019 \times 5.5\ Sv^{-1} = 0.1\%$.

Discussion

The use of the effective dose for risk assessment is not without controversy. The primary sources of data for the ICRP calculations are data from Hiroshima and Nagasaki, although this radiation exposure was evenly distributed throughout the body [32]. Therefore, some authors believe that cancer risks estimated by the effective dose method may overestimate the true risks of low-dose radiotherapy of small body parts [60]. In comparison with the effective dose method, the IRCP interpretation of the data from irradiated spondylitis patients leads to a reduction of the estimated probability of fatal cancer by a factor of about two (see chapter 3 in [32]). Alternatively, cancer risk could be determined directly from epidemiological data of patients who have undergone radiotherapy of nonmalignant diseases in the past. The present authors support this opinion, because these data would be more accurate. However, epidemiological data of low-dose radiotherapy for benign diseases are hardly available. Therefore, an own national epidemiologi-

cal study should be initiated to gain more data for calculation of cancer risks after radiotherapy for benign lesions in the locomotor system.

Conclusion

Radiation therapy of benign diseases is performed with the same methods, under the same technical conditions as the treatment of malignant diseases. In addition to medical LINACs, therapeutic kilovolt X-ray systems are widely used. Current radiobiological evidence clearly demonstrates therapeutic effectiveness and implicates a multitude of underlying molecular mechanisms. Radiogenic risks should be taken into account when assessing the indication for radiation treatment. Further studies, potentially ones based on epidemiologic data, are needed to reduce uncertainties in estimating the genetic and cancer risk.

Compliance with ethical guidelines

Conflict of interest B. Reichl, A. Block, U. Schäfer, C. Bert, R. Müller, H. Jung, and F. Rödel state that there are no conflicts of interest.

The accompanying manuscript does not include studies on humans or animals.

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