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ORIGINAL ARTICLE

DEGRO practical guidelines for the radiotherapy of non-malignant disorders – Part IV

Symptomatic functional disorders

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Abstract
Purpose To summarize the updated DEGRO consensus S2e guideline recommendations for the treatment of benign symptomatic functional disorders with low-dose radiotherapy.
Materials and methods This overview reports on the role of low-dose radiotherapy in the treatment of functional disorders in cases of heterotopic ossification (HO) and Graves orbitopathy (GO). The most relevant aspects of the DEGRO S2e Consensus Guideline "Radiation Therapy of Benign Diseases 2014" regarding diagnostics, treatment decision, dose prescription, as well as performance of radiotherapy and results are summarized.
Results For both indications (HO, GO), retrospective and some prospective analyses have shown remarkable effects in terms of symptom relief. Nevertheless, the level of evidence (LoE) and the grade of recommendation (GR) vary: LoE 1–2 and GR A-B (HO), LoE 2 and GR B (GO).
Conclusion Low-dose radiotherapy for benign symptomatic functional disorders has proven to be effective, according to different authors, for 25–100 % of the patients studied and therefore it may be a reasonable prophylactic and therapeutic option if noninvasive or invasive methods have been used without persistent success.

For HO, a single-fraction dose of 7–8 Gy or fractionated radiation with five fractions of 3.5 Gy is recommended. For GO, single-fraction doses of 0.3–2.0 Gy, and total doses of 2.4–20 Gy/series, applied in one daily fraction are recommended.

Keywords Heterotopic ossification · Graves orbitopathy · Benign functional disease · Low-dose radiotherapy · German S2e guideline

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DEGRO-S2e-Leitlinie für die Strahlentherapie von gutartigen Erkrankungen – Teil IV

Symptomatische funktionelle Erkrankungen

Zusammenfassung
Zielsetzung Zusammenfassung der Empfehlungen der DEGRO-S2e-Leitlinie zur Niedrigdosis-Radiotherapie von gutartigen symptomatischen funktionellen Erkrankungen.
Material und Methoden Die vorliegende Leitlinie berichtet über die Bedeutung der Niedrigdosis-Radiotherapie in der Behandlung von funktionellen Erkrankungen, in diesem Fall von heterotoper Ossifikation (HO) und endokriner Orbitopathie (EO). Es werden die wichtigsten Aspekte der aktuellen DEGRO-S2e-Konsensusleitlinie „Strahlentherapie gutartiger Erkrankungen 2014" bezüglich Diagnostik, Therapieentscheidungen, Dosisempfehlungen und Empfehlungen zur Durchführung der Radiotherapie zusammengefasst.
Ergebnisse Für beide Entitäten (HO, EO) wurde in zahlreichen retrospektiven und einigen prospektiven Untersuchungen ein bemerkenswerter Effekt der Niedrigdosis-Radiotherapie im Sinne einer Symptomreduktion beschrieben. Je nach Entität wurden verschiedene Evidenzlevel (LoE) fest-

gestellt, so dass unterschiedliche Empfehlungsgrade (GR) für den Einsatz der Radiotherapie ausgesprochen wurden: LoE 1–2 und GR A–B (HO), LoE 2 und GR B (EO).
Schlussfolgerung Die Niedrigdosis-Radiotherapie von benignen symptomatischen funktionellen Erkrankungen ist nach Ansicht verschiedener Autoren bei einem Anteil von 25–100 % der untersuchten Patienten effektiv und ist eine gut begründbare Therapieoption für Patienten, bei denen konservative oder operative Verfahren zu keiner anhaltenden Verbesserung geführt haben. Für die HO wird die Einzeitbestrahlung mit 7–8 Gy oder die fraktionierte Bestrahlung mit 5 × 3,5 Gy empfohlen. Für die EO werden Einzeldosen von 0,3–2,0 Gy und Gesamtdosen von 2,4–20 Gy/Serie mit täglicher Bestrahlung befürwortet.

Schlüsselwörter Heterotope Ossifikation · Endokrine Orbitopathie · Gutartige funktionelle Erkrankung · Niedrigdosis-Strahlentherapie · S2e-Leitlinie

Introduction

Heterotopic ossifications are defined as new bone formations arising in the soft tissue outside the original skeleton system [5].

"Muscle calcifications" were first reported by Goldberg in 1877 in paraplegic patients. The first attempt to classify so-called myositis ossificans was made in 1910.

Heterotopic ossifications are clinically relevant with movement restriction and pain only starting from a certain expansion. The etiology is not completely clarified, whereby it is assumed that an inflammatory stimulus, e.g., by a bone trauma, leads to the release of growth factors that cause a differentiation from undifferentiated mesenchymal stem cells or myoblasts to osteoblasts. The hypothesis for the effect of irradiation on the prophylaxis of heterotopic ossification assumes that the postulated pluripotent mesenchymal stem cells can be arrested by irradiation before entering in the differentiation phase, which takes place in the first few days after surgery. If the differentiation has already begun, it is no longer affected by the irradiation [40].

Today, several risk factors for heterotopic ossifications are recognized. A major risk factor is the already existing ipsi- or contralateral heterotopic ossification. Individual factors such as, for example, age and predisposing illnesses (e.g., chronic polyarthritis) have been reported as further risk factors.

These risk factors allow for the development of appropriate risk scores and subsequently, depending on these scores, for deciding if and when such a prophylactic therapy should be performed. Due to the frequency of occurrence of heterotopic ossifications, a primary ossification prophylaxis is indicated in the presence of one or more risk factors. Koelbl et al. [19] recommended a risk score for the development of heterotopic ossification after hip replacement surgery consisting of three different risk classes (Table 1).

Table 1 Risk factors for heterotopic ossification (HO)

Risk for HO	%	Risk factors
High risk	>90	Existing ipsi- or contralateral heterotopic ossification
Medium risk	50–90	Fractured acetabulum
		Hypertrophic osteoarthritis in the region of the hip (osteophyte extent larger than 1 cm)
		Ankylosing spondylitis (Bekhterev's disease),
		Disseminated idiopathic hyperostosis of the skeleton (Forestier disease)
		Paget's disease
Low risk	<50	Dysplasia of the hip joint
		Hypertrophic osteoarthritis in the region of the hip (osteophyte extent smaller than 1 cm)

Heterotopic ossifications can be differentiated into three main groups:

- Traumatic heterotopic ossification
- Nontraumatic heterotopic ossification
- Neurologic heterotopic ossification

The group of heterotopic ossification caused by trauma (accident or surgery) is the most frequent and rarely causes differential diagnostic problems because of the close local and temporal relationship with the traumatic event. It occurs in up to 25 % of patients following fractured acetabulum, [14], after hip joint replacement with endoprosthesis it occurs in 16–90 % of patients depending on the risk profile [31], and after fracture of the elbow joint in 50 % of patients [16]. The frequency of heterotopic ossification after knee joint dislocation is indicated to be 26 % in the literature with [37].

Nontraumatic heterotopic ossification after burns, for example, is rare and usually occurs after burns of at least 20 % of the body surface area only and in soft tissue structures close to the joints, particularly in the proximity of the elbow. Their usual frequency of occurrence lies between 0.15 and 3 % [30].

The neurologic type of heterotopic ossification occurs in the soft parts in up to 20 % of patients with traumatic paraplegia [3].

The earliest heterotopic ossifications are visible 2 weeks after trauma on a conventional radiographic image (X-ray view). The classification of the severity of heterotopic ossification is usually deduced from the visible expansion on the X-ray view, e.g., the heterotopic ossification within the range of the hip joint after hip joint replacement based on the classification of Brooker [6]. The classification of Brooker defines four degrees (Table 2). Only grades III and IV are clinically relevant with symptoms.

Table 2 Brooker grading system of heterotopic ossification

Grades	Radiographic findings
0	No soft-tissue ossification
I	Separate small foci of ossification about the hip
II	Ossification projecting from the proximal femur or pelvis with ≥1 cm between opposing bone surfaces
III	Ossification projecting from the proximal femur or pelvis with <1 cm between opposing bone surfaces
IV	Ossification completely bridging the proximal femur and pelvis

Table 3 NOSPECS scoring classification in Graves orbitopathy

Classes	Ocular signs and symptoms	Grades
0	*N*o signs or symptoms	
I	*O*nly signs, no symptoms	a = minimal, b = moderate, c = marked
II	*S*oft tissue involvement	a = minimal, b = moderate, c = marked
III	*P*roptosis	a = minimal, b = moderate, c = marked
IV	*E*xtraocular muscle involvement	a = minimal, b = moderate, c = marked
V	*C*orneal involvement	a = minimal, b = moderate, c = marked
VI	*S*ight loss	a = minimal, b = moderate, c = marked

Graves orbitopathy occurs at a rate of 10% among patients suffering thyroid diseases, over 90% of Graves orbitopathy patients exhibit Basedow's disease, and 60% of Graves orbitopathy cases are associated with hyperthyroidism. Genetic predisposition and tobacco consumption are risk factors.

Graves orbitopathy is a thyroid-associated autoimmune disorder. The precise pathomechanism is not known, but it is understood to be an inflammatory process with evidence of autoantibodies against TSH receptors (thyrotropin-receptor antibody, TRAK) in the conjunctive tissue of the eye muscles. Other receptor antibodies, such as insulin-like growth factors, are seemingly important. The immune response causes an increase in orbital muscles, fat, and connective tissue and thereby augments the distance between the orbital wall and ocular bulb. Exophthalmus, reduced eye motility, and double vision often appear. This clinical diagnosis mostly includes thyroid increase and tachycardia as part of Basedow's disease. Further diagnostic imaging allows one to assess the degree of severity of the disease; magnetic resonance imaging (MRI) serves for the evaluation of the inflammatory component. For classification of disease progression and stages, no standard is settled [1]. Since 1969 the NOSPECS scheme (*n*o signs or symptoms; *o*nly signs, no symptoms; *s*oft tissue involvement; *p*roptosis; *e*xtraocular muscle involvement; *c*orneal involvement; *s*ight loss) of the American Thyroid Association is in use (Table 3). Moreover, the LEMO classification (*l*id edema, *e*xophthalmus, *m*uscle change, *o*ptic tract involvement) is established, a practical diversification of the NOSPECS scheme and initially recommended in 1991 by Boergen and Pickardt. These two classifications play an important part before and during the course of treatment for the evaluation of response or progress of disease. They give an additional survey of the validity of significant symptoms.

More detailed information and references may be found in the complete version of the guideline, which is available on the DEGRO homepage (http://www.degro.org).

Non-radiotherapeutic treatment options

For *heterotopic ossification* a resection is the only causal therapy. Symptoms can be treated with pain medication. The objective of treatment is the prevention of a re-emergence of the heterotopic ossification after its removal or prophylactic therapy in the presence of high-risk factors.

The sole postoperative medication of nonsteroidal anti-inflammatory drugs (NSAID) over at least 3–6 weeks appears also potent. Indomethacin (Amuno®), an inhibitor of prostaglandin synthesis, was effective in different studies involving high-risk patients [8]. Prostaglandins are mediators of inflammation, i.e., prostaglandin suppresses the inflammatory reaction and the proliferation of mesenchymal cells. It is used in different dosages immediately after the operation for 3–6 weeks. However, it can frequently cause gastrointestinal side effects, so that patients with a medical history of gastric ulcer must be excluded from this therapy.

In *Graves orbitopathy* no treatment method with causal mechanism exists to date [10]. Therapy of GO in general is effective in the handling of symptoms and the application of cortisone is the treatment of choice. Other treatment options in mild cases are the use of tear substitutes or ointment. Experimental procedures include the use of biological agents, in particular rituximab.

Surgical intervention is not used until the inactive, chronic fibrotic phase of the disease is reached and the persistence of the syndrome for at least 6 months has been observed. The chronological order of and suitable intervals between appropriate surgical measures have to be respected with regard to the priorities of firstly the orbita, secondly the outer eye muscles, and finally the eyelids.

The response to different treatment methods according to the duration of symptoms and the stages found in the literature is shown in Table 4.

Antiproliferative control after low-dose radiotherapy

Pre- or postoperative radiotherapy of the hip region is one treatment modality for the reduction of the occurrence of

Table 4 Response rates in Graves orbitopathy: literature review

Study	Pts (*n*)	Symptom duration	Class II (%)	Class III (%)	Class IV (%)	Class V (%)	Class VI (%)	Response (%)	Additional therapy
Bartalena et al. 1983	36	2.25 years	97	56	93	–	100	72	CS+RT
	12	(0.25–15)	100	45	56	–		25	100%; only CS
									Eye OP 3%
Esser et al. 1995	155	0.8 years	2/3 Pts (67%)	$p<0.001$ (55%)	$p<0.01$ (55%)	–	–	–	137 CS–RT only 18 RT
Friedrich et al. 1997 [12]	106	0.8 years	56	62	70	–	–	78 (26 Gy)	106 only RT
	142	(0.4–4)	79	56	70	–	–	80 (13 Gy)	142 CS+RT
									Eye OP 3%
Hurbli et al. 1985	62	0.6 years (0.1–1.5)	–	23	74	23	57	56	CS+RT>23%
									Eye OP 34%
Konishi et al. 1986	17	1.75 years (0.2–8.0)	(6 Pts)	(5 Pts)	(8 Pts)	(2 Pts)	(4 Pts)	59	RT–CS 18%
Lloyd et al. 1992	36	–	(22 Pts)	(14 Pts)	(15 Pts)	(3 Pts)	–	92 (*)	–
Olivotto et al. 1985 [23]	28	0.75 years (0.2–5.0)	93	26	43	85	100	68	CS+RT 18%;
									Eye OP 50%
Van Ouwerkerk et al. 1985 [24]	24	1.0 years (0.25–3.0)	100	(11 Pts)	78	–	–	–	CS+RT 75%
Palmer et al. 1987 [26]	29	0.9 years (0.2–10)	78	52	24	–	67	48	CS+RT 34%
									Eye OP 45%
Kriss/ Petersen et al. 1989/1990 [20, 27]	311	0.9 years	80	51	56	71	65	–	CS+RT 32%;
									Eye OP 29%
Pigeon et al. 1987	21	1.0 years (0–5.0)	76	47	32	62	–	57	CS+RT 67%
Prummel et al. 1993 [29]	28	–	64	–	43	–	–	50	Only CS
	28	–	38	–	85	–	–	46	CS+RT
Ravin et al. 1975	37	–	"Many"	32	>11	–	89	–	CS+RT>18%
									Eye OP>6%
Sandler et al. 1989 [32]	35	0.7 years (0.1–5.8)	–	–	–	–	78	71	CS+RT 80%
									Eye OP 40%
Staar et al. 1997 [36]	225	0.7 years (0.2–3)	80	64	69	–	–	68	CS+RT 100%
									Eye OP 29%
Teng et al. 1980	20	5.8 years (0.9–25)	(9 Pts)	25	(1 Pt)	–	–	35	CS+RT 25%
Wiersinga et al. 1988	39	1.75 years (0.4–27)	–	–	–	–	–	64	CS+RT 5%
Wilson et al. 1995	33	–	85	–	54	–	–	–	Only RT
Seegenschmiedt et al. 1998 [34]	60	1.5 years (0.5–20)	50/ 60 83%	39/ 56 70%	37/ 54 69%	13/ 15 87%	8/ 17 47%		Only RT; eye OP 8%

Pts patients, *CS* corticosteroid therapy, *RT* radiotherapy, *eye OP* eye operation (decompression or lid correction)

heterotopic ossifications following hip joint replacement. Radiotherapy is most effective if applied within the time window of up to 4 h before and up to 72 h after surgery [19]. For patients with major risk factors, postoperative fractionated radiotherapy is superior to preoperative radiotherapy [25]. The rate of heterotopic ossification after hip joint replacement can be reduced from up to 90% to under 10% using pre- or postoperative radiotherapy in patients with risk factors.

Experiences concerning repeated radiotherapy after hip joint replacement are rare, but have been documented as also being effective. Because of the time interval between the first and second irradiation generally amounting to several years, the cumulative dose can be tolerated especially by older patients, accordingto Lo et al. [21]. However, some of the patients are younger people under the age of 40. Since the lifetime of a hip joint replacement is 10–15 years, one should bear in mind that the replacement has to be repeated several times.

With further fractures close to other joints, prophylactic treatment with radiotherapy to prevent heterotopic ossification is likewise successful [25].

Prophylactic radiotherapy is well tolerated, and impaired wound healing has not been reported. So far no patient was

Table 5 Results and success metrics of radiotherapy (RT) in Graves orbitopathy

Study	Year	Patients (*n*)	Dose (Gy)	RT type	Response rate (%)	Definition of response criteria
I. Total dose RT < 20Gy						
Esser et al.	1988	30	10	C	7–40 82	"Improvement of single symptoms" "No progression"
Esser et al.	1995	155	12	K, L	–	Several objective ophthalmological criteria and "improvement of single symptoms" according to established scores
Feyerabend	1989	15	2.5–20	K	67	"Improvement clinical symptoms"
Friedrich [12]	1997	142	13	K	80	"Very good" and "good response"
Fritsch et al.	1981	83	16	B, K	30	30 % "improved," 70 % "no change"
Grauthoff et.al.	1980	10	10	K	100	"Very good success"
Heinze et al.	1974	40	8–12	B	50–68	"Improvement of single symptoms"
Horster et al.	1983	21	< 20	R	80	"No progression"
Hurbli et al.	1985	62	10.5–20	K, L, R	56	"Improvement of single symptoms"
Pfluger et al. [28]	1990	37	10/16	L	97	"No progression"
Staar et al. [36]	1997	225	16–19.2	L	68	"Improvement of most symptoms"
Uhlenbrock et al. [39]	1984	56	3–10	R	62	"General clinical improvement"
Wildmeister	1972	36	2.5	R	45	"General clinical improvement"
II. Total dose RT ≥ 20Gy						
Bartalena et al.	1988	36	20	K, L	72	33 % "very good," 39 % "good response"
Donaldson et al.	1973	23	20	L	65	"Very good" and "good response"
Friedrich [12]	1997	106	26	K, L	78	"Very good" and "good response"
Kriss et al. [20]	1983/1989	80	20	L	67	"Very good" and "good response"
Lloyd et al.	1992	36	20	L	92	"no progression"
Marcocci et al. [22]	1987	30	20	K	60	"very good" and "good response"
Marcocci et al.	1991	44	20	K, L	25/55	"Very good" and "good response"; "minimal response"
Olivotto et al. [23]	1985	28	20	L	68	"Good response"
Petersen et al. [27]	1990	311	20/30	L	90	"No progression"
Sandler et al. [32]	1989	35	20	–	71	"No progression"
Seegenschmiedt et al. [33, 34]	1995/1998	60	20	L	80	Subjective statements of patients: "very good" and "good response" and quantitative scores (ATA, Stanford Score, OI according to Grußendorf)

Gy Gray, *B* betatron, *C* cesium, *K* cobalt, *L* linear accelerator, *R* radiograph X-ray

observed to develop a malignant tumor within the radiation field in the follow-up. Since radiation-induced tumors are extremely rare and only arise after latencies of 10–30 years, the risk is not relevant for most of the patients with a median age of 65 years.

The clinical use of radiotherapy in Graves orbitopathy is controversial. In Germany, radiation treatment is applied in mid-level cases (classes II–V according to NOSPECS) especially with dysfunction of the eye muscles [2, 4, 12]. About 65–75 % of patients with GO show good or excellent response rates after radiation [24, 26]. The response and success metrics are shown in Table 5. The anti-inflammatory as well as the anti-proliferative effect of radiotherapy should bring a benefit by decreasing the length of the inflammatory phase and preventing late complications (e.g., optic nerve compression with loss of vision or eye muscle fixation out of position) [11]. Before starting radiation treatment, euthyroid metabolism should be present.

Current recommendations on radiotherapy

The application of radiotherapy for avoidance of heterotopic ossification after hip joint replacement was first proven to be efficient in 48 high-risk patients using ten times a single daily dose of 2 Gy in a postoperative setting by Coventry and Scanlon in 1981 [9]. However, Lo et al. showed as early as in 1988 that a single dose of 7 Gy is also effective [21].

Preoperative irradiation could likewise reduce the rate of ossification if the prophylactic treatment is applied no longer than 4 h before surgery [19].

Based on many prospective studies, the general recommendations for dosage and fractionation in radiation pro-

phylaxis of heterotopic ossification are as follows. A single radiation dose between 7 and 8 Gy within the described time window of up to 4 h before and up to 72 h after surgery should be applied. However, for patients with major risk factors, postoperative fractionated radiotherapy applying five fractions of 3.5 Gy daily in a single dose is recommended [9, 19, 35].

The most comprehensive experience in defining the planning target volume (PTV) exists for irradiation after hip joint replacement. The PTV covers the typical localizations of heterotopic ossifications [13]. Usually the field size amounts to 14 × 14 cm. The cranial field border has to be about 3 cm above the acetabulum, the caudal field border encases about two thirds of the proximal part of the implant, offering the advantage that large parts of the prosthesis shank are not inside the irradiation volume and thus the risk of a reduced shank stability is avoided. Structures at risk in the pelvic region, like the small intestine or rectum, can be spared.

The point of dosage of the anterior-posterior—posterior-anterior field technique is at the center of the body. The radiotherapy takes place at a linear accelerator with high photon energy. Other skeletal regions should be treated accordingly to the described approach for hip joint replacement.

The radiotherapy of Graves orbitopathy is carried out at a linear accelerator with 4–6 MV photons. A mask fixation system is used for positioning and acquisition of computed tomography (CT) images.

The clinical target volume (CTV) and the PTV are determined. The PTV is defined as: dorsal margin of orbita at Zinn's zonule, including the posterior two thirds of the ocular bulb as far as 6 mm behind the corneal limbus, covering the insertion of the extraocular muscles.

During the radiation planning process, anatomical proportions in CT imaging must be considered. The distance between the cornea surface and the back face of the lens amounts to 8 mm on average. Comparison of conventional and virtual simulation demonstrates the external eyelid angle as a practical orientation for guidance of the lateral radiation field. Moreover, the corneal limbus can serve as guidance for field positioning, whereas the bony canthus is inadequate for guidance in field positioning. Three-dimensional (3D) radiation therapy planning thus results in field sizes of at least 5 × 5 cm or 6 × 5 cm for obtaining sufficient dose coverage of the entire PTV [15]. In the majority of cases, lateral opposing fields are used with compensation of divergence for optimal protection of the lenses. Further radiation techniques are: (1) half-beam technique with middle-block or (2) rotation technique with central shielding for lens protection [23, 39].

There are no general recommendations for dosage or fractionation in the radiation treatment of Graves orbitopathy. According to a representative nationwide questionnaire of the working team "benign diseases" of the DEGRO (*Deutsche Gesellschaft für Radioonkologie,* German Society for Radiation Oncology) in most radio-oncological institutions in Germany the radiotherapy of Graves orbitopathy is standard with total doses of 16–20 Gy and a fractionation of five fractions of 2 Gy per week. To date, it remains unclear if considerably lower doses are equally effective—depending on the stage of the disease. Lower total doses could reduce the potential risk for radiogenic induction of secondary tumors [7, 18, 20, 27, 28, 38].

Kahaly et al. in 2000 conducted a randomized three-armed study in a total of 65 patients, who showed moderate Graves orbitopathy of classes II–V according to NOSPECS. Patients of group A received 20 fractions of 1 Gy each, once a week up to 20 Gy: long duration of treatment, low single dose, high total dose. Patients of group B received ten fractions of 1 Gy each, five times a week up to 10 Gy: intermediate duration of treatment, low single dose, intermediate total dose. Patients of group C received ten fractions of 2 Gy each, five times a week up to 20 Gy: short duration of treatment, high single dose, high total dose. Patients of all three groups showed equal response rates with regard to the improvement of ophthalmological symptoms and changes on MRI. However, group A patients A were obviously superior to those of the two other groups concerning the reduction of swelling and eye motility [17].

Gerling et al. in 2003 in another randomized trial on low-dose radiotherapy checked two arms of patients as follows: radiotherapy with eight fractions of 0.3 Gy each, five times a week up to 2.4 Gy ($n=43$ patients) versus standard radiation with eight fractions of 2 Gy each up to 16 Gy ($n=43$ patients). The clinical results of both arms were equally effective.

Gorman et al. in 2001 conducted a double-blind randomized study, with each patient undergoing radiotherapy of one randomly selected orbit with a standard dose of 20 Gy, five times a week at 2 Gy each; whereas sham therapy (pseudo-radiation) was given to the other side. The clinical effectiveness of both modalities was the same. However, this cannot be assigned to a placebo effect solely, as the pseudo-radiated orbit received a contingent of scattered rays of approximately 0.4 Gy per fraction in the orbital cavity, constituting in fact a "low-dose radiotherapy."

In Graves orbitopathy, the use of low-dose radiotherapy seems to achieve the highest response rates in the early inflammatory phase [34]. In advanced stages of disease, higher radiation doses are required to obtain the same effectiveness [32, 33]. The external beam radiation treatment can be combined with systemic application of glucocorticoids [22, 29, 36]. Combined modality treatment is often applied in severe cases. In a randomized trial, the potency of combined treatment was superior in contrast to glucocorticoid therapy alone [22, 29, 36].

Summary

To avoid heterotopic ossification, a single radiation dose of 7–8 Gy respecting the described time window is effective; in patients with major risk factors the postoperative fractionated radiotherapy with five fractions of 3.5-Gy daily single doses is recommended. The level of evidence (LoE) and the grade of recommendation (GR) vary: patients with *endoprosthesis or resection of HO* should get radiotherapy with LoE 1 and GR A; *fractures close to joints* should get radiotherapy with LoE 2 and GR B.

In Graves orbitopathy, retrobulbar radiotherapy is carried out using lateral opposing fields with protection of the lenses. The dosage should be adapted to the individual phase of disease: in the *early inflammatory phase,* single dose of 0.3–2.0 Gy, eight fractions, daily radiation, total dose 2.4–16 Gy; in *advanced inflammatory phase,* single dose 2.0 Gy, eight to ten fractions, daily radiation, total dose 16–20 Gy. To avoid severe ophthalmologic symptoms, the efficacy of radiation could be improved by the use of a reduced single dose of 1 Gy and the prolongation of therapy duration with radiation only once a week. In Graves orbitopathy with manifest dysfunction of the eye muscles, antiproliferative external beam radiotherapy is recommended with LoE 2 andGR B.

Compliance with ethical guidelines

Conflict of interest G. Reinartz, H.T. Eich, F. Pohl, and the German Cooperative Group on Radiotherapy for Benign Diseases state that there are no conflicts of interest.

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