

Radiotherapy in the treatment of Graves ophthalmopathy—to do it or not?

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Abstract To the objective of this study is to evaluate the role and toxicity of radiotherapy in the treatment of Graves ophthalmopathy. In the years 2000–2003, 121 patients with malignant exophthalmos were treated with radiotherapy of the retrobulbar area to the total dose of 20 Gy in ten fractions with a 6 MeV photon beam. The treatment was performed by the team of the Clinic of Oncology of the Jagiellonian University Medical College in Cracow. The radiotherapy was preceded by intravenous steroid therapy: methylprednisolone acetate administered at the dose of 2 g/week for four consecutive weeks. The highest efficacy, expressed as improvement of all ocular symptoms, was observed for the combined treatment. Female and non-diabetic patients responded positively to the combined treatment. Radiotherapy combined with steroid therapy in the treatment of Graves ophthalmopathy seems to be an effective treatment for strictly defined indications. In the treatment of Graves–Basedow disease, radiotherapy is a well-tolerated treatment modality. Diabetes is a factor that worsens prognosis in Graves ophthalmopathy and female sex is a favourable factor for this condition.

Keywords Graves ophthalmopathy · Radiotherapy · Combined treatment

Introduction

Graves ophthalmopathy is a complex of ocular symptoms accompanying autoimmune thyroid diseases. In 90% of cases, it is associated with hyperthyreosis. In the other 10% of

cases, it is diagnosed in euthyreotic patients, and is called ocular Graves disease, or in hypothyreotic patients (and then it is most frequently associated with Hashimoto disease) [40]. Modern imaging techniques revealed that ocular symptoms occur in almost all patients with hyperthyreosis [11, 12, 69, 73, 74]. These are usually benign lesions (non-infiltrative ophthalmopathy) that subside totally after normal thyroid function is restored [11, 18, 49, 70, 73]. About 5–10% of patients with hyperthyreosis develop Graves ophthalmopathy of a progressive course that may lead to severe ocular complications [28, 73, 74]. Sometimes only involvement of oculomotor muscles is found without exophthalmos. Optic neuropathy, corneal ulcerations and perforations with consequent blindness may occur [21, 28, 73, 74].

In the treatment of infiltrative ophthalmopathy, irrespective of thyroid function control, there is a necessity to reduce the volume of oedematous swollen intraorbital tissues to expand free space inside the orbit. To achieve the above glycocorticosteroid treatment, radiotherapy, combination of both methods or surgical orbital decompression are used [1, 7, 11, 35, 36, 42, 65, 71, 72, 73]. Surgical decompression reduces only mechanical effects of exophthalmos and usually, sooner or later, requires subsequent glycocorticosteroid therapy. Effectiveness of glycocorticosteroids (recently administered in the form of pulses of methylprednisolone acetate) is found to be 60% [11, 37, 58, 64, 73].

Starting from the year 1983, high doses of glycocorticosteroid are combined with orbital radiotherapy [5]. Glycocorticosteroid therapy provides quick improvement of ocular symptoms and prevents transient worsening of these symptoms as the result of radiotherapy [11, 16, 29, 42, 53, 67]. Irradiation consolidates the effects of steroid therapy and decreases the risk of ocular symptoms relapse [9, 11, 16, 57, 73]. Radiotherapy has unspecific anti-inflammatory and specific immunosuppressive effects on

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both mediators (lymphocytes) and effectors (fibroblasts) of the immune reaction in the orbit [56, 74]. The optimal irradiation dose in the treatment of Graves ophthalmopathy is 20 Gy in ten fractions administered within 2 weeks [11, 27, 30, 31, 39, 56, 62, 73–75].

This paper summarizes my own experience in the treatment of Graves ophthalmopathy.

Materials and methods

From January 2000 to December 2003, the team of the Clinic of Oncology of the Jagiellonian University Medical College performed radiotherapy of the retrobulbar area in 121 patients (91 female—75.2% and 30 males—24.8%). Mean age was 55.1 years (range, 32–85). One hundred sixteen out of 121 (95.9%) patients received previously in the Clinic of Endocrinology intravenous treatment with methylprednisolone acetate at the dose of 2 g/week for four consecutive weeks.

Five patients (4.1%) did not receive glycocorticosteroids due to: contraindications (two patients), improvement of ocular symptoms after treatment with methimazole (except persistent symptoms within the peribulbar soft tissue; two patients) and due to refusal of consent for steroid treatment (one patient).

Twelve months after the treatment was completed, in 106/121 patients ophthalmologic examination and orbital CT scan were performed. Three out of the remaining 15 patients died before the follow-up visit and 12 refused to undergo the follow-up procedures. Clinical characteristics of 101 patients subject to further analysis are presented in Table 1.

As shown in the table above, mean age in the combined treatment group was 52 years. Female patients, non-smokers and non-diabetics predominated. Mean time from the onset of ocular symptoms to the treatment start was 16 months. The majority of patients was previously treated for hyperthyreosis (61/101 i.e. 60.4%) and was hyperthyreotic at the time of exophthalmos onset. However, at the moment of referral for radiotherapy, the majority of patients had normal fT4 and thyroid-stimulating hormone (TSH) levels.

The subsequent analysis will involve two groups of patients:

1. One hundred one/101 patients previously treated with intravenous steroids (assessed before radiotherapy),
2. Ninety-three patients out of 101 patients in group A treated with the combined method, i.e., with steroid therapy with subsequent radiotherapy to the total dose of 20 Gy in ten fractions (assessed after radiotherapy).

Irradiation technique

Before the start of radiotherapy assessed individual celone moulds were done for all patients. In all patients, orbital CT

Table 1 Characteristics of 101 patients treated with the combined method

Mean age	52.3 years (32–81)
Sex	
Males	26 (25.7%)
Females	75 (74.3%)
Time from the onset of ocular symptoms to the start of the combined treatment	16.8 months (4–116 months)
Smoking	
No	50 (49.5%)
Yes	49 (48.5%)
Unknown	2 (2%)
Diabetes	
No	89 (88.1%)
Yes	12 (11.9%)
Thyroid status at the moment of exophthalmos diagnosis	
Normal	16 (15.8%)
Hyperthyreosis	74 (73.3%)
Unknown	11 (10.9%)
Treatment of hyperthyreosis	
No	17 (16.8%)
Yes	84 (83.2%)
Pre-treatment fT4 level (normal range, 11–22 pmol/l)	
Normal	74 (73.3%)
Elevated	5 (5%)
Lowered	16 (15.8%)
No data	6 (5.9%)
Pre-treatment TSH level: (normal range, 0.2–6.5 μU/mol)	
Normal	70 (69.3%)
Elevated	7 (6.9%)
Lowered	24 (23.8%)

scans were done for treatment planning. CT slice thickness was 3 mm. Two opposite isocentric beam techniques were used to cover the retrobulbar area. Beam angles were adjusted for divergence to form coincident plane behind lenses (Fig. 1). Extraorbital structures were individually shielded with Wood alloy shields. Irradiation was performed with a 6 MeV photon beam emitted by the Mevatron Primus accelerator. The planned irradiation dose was 20 Gy in ten fractions. Treatment planning was done in a 3D treatment planning system—TMS Helax.

Assessment of treatment efficacy

The following methods were used to assess the efficacy of the treatment: medical history, ophthalmologic examination and CT scan of the retrobulbar areas. Ophthalmologic examination was done before the start of the treatment and

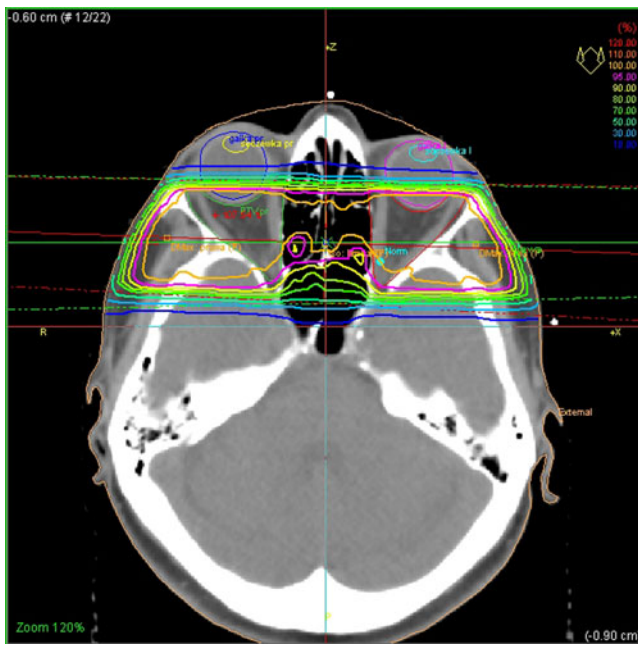


Fig. 1 The arrangement of beams and the dose distribution during irradiation of the retrobulbar area in Graves-Basedow disease

12 months after treatment completion. During the examination the NOSPECT score system was used to define severity of ophthalmopathy based on such parameters as: soft tissues (i.e., conjunctiva, eyelids), exophthalmos, oculomotor muscle dysfunction, condition of the cornea and vision. These symptoms were attributed scores: 1–2–3, depending on symptom severity. Eyelids and conjunctiva: 1—minor reddening of conjunctiva or moderate eyelid oedema, 2—significant reddening of conjunctiva or major eyelid oedema, 3—severe inflammatory condition of the above structures. Exophthalmos was measured with exophthalmometer: 20–24 mm scored—1, 24–27 mm—2, above 27 mm—3. Oculomotor muscle involvement: eye globe mobility impairment in extreme eye positions—1, significant impairment of eye globe mobility—2, immobilisation of one or both eye globes—3. Cornea: single epithelial defects (with fluorescein staining)—1, moderate epithelial defects—2, extensive epithelial defects—3. Snellen chart was used for vision assessment. Vision defect ranging from 0.67–0.33 scored 1, 0.32–0.10—2, below 0.10—3. CT scan of retrobulbar areas was performed in all patients before the start the treatment and after 12 months of treatment completion. Based on CT of retrobulbar area the following parameters were assessed: thickness of the recti muscles and lacrimal glands, volume of the retrobulbar fat and optic nerve condition.

Statistical analysis

Qualitative parameters were characterised by percentage distribution. Relationships between qualitative parameters, including assessment of the treatment effect, were evaluated

with chi square independent test. To compare particular treatment stages the case–control method and Fisher test was used. *p* value was calculated for all tests.

Results

Evaluation of the treatment with steroids

Treatment results as assessed by ophthalmologic examination in the group of patients treated previously with intravenous steroids (situation before radiotherapy) are presented in Tables 2 and 3.

Based on the above table, significant improvement within right peribulbar soft tissues following intravenous steroid therapy may be shown ($p < 0.05$). Nevertheless, this observation is weakened by the fact that in half of the patients, post-treatment ophthalmologic assessment is missing.

Based on the above table, significant improvement within left peribulbar soft tissues following intravenous steroid therapy may be shown ($p < 0.05$). Nevertheless, this observation is weakened by the fact that in half of the patients, post-treatment ophthalmologic assessment is missing.

Treatment results as assessed by computed tomography (CT) of the retrobulbar areas 12 months after treatment completion in the group of patients treated previously with intravenous steroid therapy.

Treatment results are presented in Table 4.

As shown in the table above, no improvement was found within the right eye as assessed with computed tomography. Only slight improvement of the left eye condition was observed, in terms of reduction of the retrobulbar fat tissue.

Evaluation of efficacy of the combined treatment

Treatment results as assessed by ophthalmologic examination.

The results are presented in Tables 5 and 6.

Based on the table, no effect of intravenous steroid therapy followed by radiotherapy was found within the right eye, as assessed by ophthalmologic examination (no statistical significance).

Based on the table, no effect of intravenous steroid therapy followed by radiotherapy was found within the left eye, as assessed by ophthalmologic examination (no statistical significance).

Treatment results as assessed by computed tomography (CT) of the retrobulbar areas.

Treatment efficacy measured with CT of retrobulbar areas is presented in Table 7.

As shown in the table, no improvement was achieved within the right eye after the combined treatment, as assessed by computed tomography. Some improvement

Table 2 Treatment results as assessed by ophthalmologic examination in the group of patients treated previously with intravenous steroids ($n=101$)—the right eye

	NOSPECT	The right eye before steroid treatment	The right eye after steroid treatment	p (Mc Nemara test)
Soft tissues	Normal	15/101 (14.8%)	15/42 (35.7%)	0.0059
	Grade 3	1/101 (1.0%)	0/42 (0.0%)	0.5165
	Grade 2	33/101 (32.7%)	0/42 (0.0%)	
	Grade 1	52/101 (51.5%)	27/42 (64.3%)	
	Not examined	0/101 (0.0%)	59/101 (58.4%)	
Exophthalmos	Normal	46/101 (45.5%)	18/42 (42.8%)	0.7678
	Grade 3	2/101 (2.0%)	1/42 (2.4%)	0.8799
	Grade 2	12/101 (11.9%)	5/42 (11.9%)	
	Grade 1	41/101 (40.6%)	18/42 (42.8%)	
	Not examined	0/101 (0.0%)	59/101 (58.4%)	
Oculomotor muscles	Normal	23/101 (22.8%)	12/42 (28.6%)	0.4639
	Grade 3	6/101 (5.9%)	0/42 (0.0%)	0.1101
	Grade 2	35/101 (34.7%)	11/42 (26.2%)	
	Grade 1	37/101 (36.6%)	19/42 (45.2%)	
	Not examined	0/101 (0.0%)	59/101 (58.4%)	
Cornea	Normal	88/101 (87.2%)	36/42 (85.7%)	0.8099
	Grade 3	0/101 (0.0%)	0/42 (0.0%)	1.0000
	Grade 2	0/101 (0.0%)	0/42 (0.0%)	
	Grade 1	13/101 (12.8%)	6/42 (14.3%)	
	Not examined	0/101 (0.0%)	59/101 (58.4%)	
Visual acuity	Normal	8/101 (7.9%)	1/42 (2.4%)	0.2191
	Grade 3	0/101 (0.0%)	0/42 (0.0%)	1.0000
	Grade 2	0/101 (0.0%)	0/42 (0.0%)	
	Grade 1	93/101 (92.1%)	41/42 (97.6%)	
	Not examined	0/101 (0.0%)	59/101 (58.4%)	

was achieved within the left eye in terms of fat tissue reduction and decrease of optic nerve oedema. However, this observation is based on a relatively small group of patients.

Comparison of treatment results

Improvement after the treatment of malignant exophthalmos was mostly of subjective nature. Therefore, evaluation of efficacy of particular treatment methods was limited to the patient self-reported results (Table 8).

As demonstrated in the table above, the highest efficacy with respect to improvement of all ocular symptoms was found after the combined treatment. Taking into consideration the fact that the combined treatment of ophthalmopathy was the most effective one, the effect of prognostic factors on the results of this treatment was studied. It was shown that females and non-diabetic patients respond favourably to the combined treatment (Tables 9 and 10). Such factors as patient age, ocular symptoms duration, smoking and thyroid function did not affect treatment results (no statistical significance was demonstrated).

Toxicity of radiotherapy

Acute reaction occurred in 11/121 patients (9.1%) during radiotherapy. Symptoms of acute reactions are presented in Table 11.

Acute reaction symptoms were mild to moderate and transient. Acute reaction in the diabetic group was not worse than average.

During follow-up after treatment completion in the group of 106 patients, three cases of cataract were diagnosed that were rather related to physiological ageing process than to radiotherapy. No diabetic retinopathy was found in the diabetic group.

Symptoms of late post-irradiation reaction are presented in Table 12.

Discussion

Aetiology of ophthalmopathy is not fully understood; therefore, its treatment is usually of palliative nature and

Table 3 Treatment results as assessed by ophthalmologic examination in the group of patients treated previously with intravenous steroids ($n=101$)—the left eye

	NOSPECT	The left eye before steroid treatment	The left eye after steroid treatment	p (Mc Nemara)
Soft tissues	Normal	14/101 (13.8%)	16/42 (38.1%)	0.0014
	Grade 3	1/101 (1.0%)	0/42 (0.0%)	0.5165
	Grade 2	32/101 (31.7%)	0/42 (0.0%)	
	Grade 1	54/101 (53.5%)	26/42 (61.9%)	
	Not examined	0/101 (0.0%)	59/101 (58.4%)	
Exophthalmos	Normal	54/101 (53.5%)	23/42 (54.8%)	0.8873
	Grade 3	4/101 (3.9%)	0/42 (0.0%)	0.1965
	Grade 2	12/101 (11.9%)	6/42 (14.3%)	
	Grade 1	31/101 (30.7%)	13/42 (30.9%)	
	Not examined	0/101 (0.0%)	59/101 (58.4%)	
Oculomotor muscles	Normal	15/101 (14.9%)	9/42 (21.4%)	
	Grade 3	5/101 (4.9%)	0/42 (0.0%)	0.3454
	Grade 2	37/101 (36.6%)	12/42 (28.6%)	0.1465
	Grade 1	44/101 (43.6%)	21/42 (50.0%)	
	Not examined	0/101 (0.0%)	59/101 (58.4%)	
Cornea	Normal	88/101 (87.1%)	33/42 (78.6%)	0.2017
	Grade 3	1/101 (1.0%)	0/42 (0.0%)	0.5165
	Grade 2	1/101 (1.0%)	0/42 (0.0%)	
	Grade 1	11/101 (10.9%)	9/42 (21.4%)	
	Not examined	0/101 (0.0%)	59/101 (58.4%)	
Visual acuity	Normal	6/101 (5.9%)	0/42 (0.0%)	0.1101
	Grade 3	2/101 (2.0%)	0/42 (0.0%)	0.3576
	Grade 2	0/101 (0.0%)	0/42 (0.0%)	
	Grade 1	93/101 (92.1%)	42/42 (100.0%)	
	Not examined	0/101 (0.0%)	59/101 (58.4%)	

the purpose of this treatment is to inhibit progression of the disease and of functional eye disorders as well as improvement of patient’s appearance [11, 36, 73]. Diagnostic criteria, selection of the treatment method as well as Graves ophthalmopathy treatment results are still the matter of controversy [12, 18, 22, 25, 38, 48, 51, 57, 63, 64].

Diagnosis is based mainly on clinical data [4, 12, 33, 54, 62, 64]. In the analysed material, the most common complaints (most 95% of patients) were related to exophthalmos and in 75% of patients (89/121) ocular symptoms were accompanied by hyperthyreosis. In the remaining 25% of patients, orbital CT scan was necessary to explain the

Table 4 Treatment results as assessed by computed tomography (CT) of the retrobulbar areas in the group of patients treated previously with intravenous steroid therapy ($n=101$)

	Left eye after treatment completion—improvement	Right eye after treatment completion—improvement
Thickness of the superior rectus muscle	0/43 (0.0%)	0/43 (0.0%)
Thickness of the inferior rectus muscle	0/54 (0.0%)	0/48 (0.0%)
Thickness of the lateral rectus muscle	0/33 (0.0%)	0/28 (0.0%)
Thickness of the median rectus muscle	0/71 (0.0%)	0/68 (0.0%)
Fat tissue	1/21 (4.8%)	0/18 (0.0%)
Optic nerve	0/1 (0.0%)	0/0 (0.0%)
Lacrimal gland	0/1 (0.0%)	0/2 (0.0%)

numerator the number of patients with improvement, *denominator* the number of patients with particular symptoms at baseline

Table 5 Treatment results as assessed by ophthalmologic examination in the group of patients treated with steroids and full-dose radiotherapy 20 Gy/10 fractions ($n=93$)—the right eye

	NOSPECT	Right eye before treatment	Right eye 12months after treatment	p (Mc Nemara)
Exophthalmos	Normal	42/93 (45.2%)	42/87 (48.3%)	0.2561
	Grade 3	2/93 (2.1%)	0/87 (0.0%)	
	Grade 2	11/93 (11.8%)	12/87 (13.8%)	
	Grade 1	38/93 (40.9%)	33/87 (37.9%)	
	Not examined	0/93 (0.0%)	6/93 (6.45%)	
Soft tissues	Normal	14/93 (15.1%)	48/83 (57.8%)	0.1945
	Grade 3	1/93 (1.1%)	0/83 (0.0%)	
	Grade 2	30/93 (32.3%)	2/83 (2.4%)	
	Grade 1	47/93 (50.5%)	33/83 (39.8%)	
	Not examined	0/93 (0.0%)	10/93 (10.8%)	
Oculomotor muscles	Normal	21/93 (22.6%)	43/83 (46.2%)	0.8200
	Grade 3	6/93 (6.4%)	0/83 (0.0%)	
	Grade 2	33/93 (35.5%)	4/83 (4.3%)	
	Grade 1	34/93 (36.6%)	36/83 (38.7%)	
	Not examined	0/93 (0.0%)	10/93 (10.8%)	
Cornea	Normal	80/93 (86.0%)	79/83 (95.2%)	0.8816
	Grade 3	0/93 (0.0%)	0/83 (0.0%)	
	Grade 2	0/93 (0.0%)	0/83 (0.0%)	
	Grade 1	13/93 (14.0%)	4/83 (4.8%)	
	Not examined	0/93 (0.0%)	10/93 (10.8%)	
Visual acuity	Normal	7/93 (7.5%)	4/83 (4.8%)	0.1046
	Grade 3	0/93 (0.0%)	0/83 (0.0%)	
	Grade 2	0/93 (0.0%)	0/83 (0.0%)	
	Grade 1	86/93 (92.5%)	79/83 (95.2%)	
	Not examined	0/93 (0.0%)	10/93 (10.8%)	

cause of ocular symptoms. The most important for diagnosis of Graves ophthalmopathy is evaluation of the oculomotor muscles diameters with maximum normal values of 4.9 mm ($-/+0.5$ mm) [64].

The decision concerning the treatment of malignant exophthalmos must be based on assessment of two elements: severity of the symptoms and the level of disease control [3, 11]. An obvious reflection of disease severity is a significantly limited field of vision related to infiltration of the optic nerve, as well as significant exophthalmos [11]. A separate problem is the level of disease activity. It seems that after a period of progression, malignant exophthalmos enters the phase of partial remission followed by a stationary period. Additionally, exophthalmos activity level does not correlate with symptoms severity [11].

Glycocorticosteroids may be used in the oral (prednisone), retrobulbar/subconjunctival or intravenous (methylprednisolone acetate) forms [11, 29, 44, 64, 73]. The intravenous route seems to be the most effective one, particularly with respect to the soft tissue symptoms and optic neuropathy [9–11]. The effect of steroid therapy on

exophthalmos and eye globe mobility is only a minor one [11]. Improvement is found in about 60% of patients with infiltrative ophthalmopathy [11, 64, 73]. Additionally, this treatment is associated with numerous side effects [11, 26, 29, 42, 44, 51, 53, 73].

The efficacy of radiotherapy alone in the treatment of Graves ophthalmopathy is assessed to be about 60% [6, 20, 27, 30, 57, 58, 62, 64, 73]. In the discussed material, only five patients were treated with radiotherapy alone. The above treatment was mostly effective in elimination of eye burning sensation and lacrimation, peribulbar tissue oedema and pain and/or eye pushing-out sensation. The follow-up ophthalmologic examination suggests improvement of vision acuity and CT scan, improvement of optic nerve condition. It could be accordant with literature data but the relatively low number of the observed patients makes it difficult to draw any conclusions [2, 19, 50].

In the discussed material, acute reaction to radiotherapy occurred in 11/121 patients (9.1%) and it was transient in nature. Radiation sequent reported in the literature such as: palpebral erythema, periorbital and conjunctival oedema,

Table 6 Treatment results as assessed by ophthalmologic examination in the group of patients treated with steroids and full-dose radiotherapy 20 Gy/10 fractions (*n*=93)—the left eye

	NOSPECT	Left eye before treatment	Left eye 12months after treatment	p (Mc Nemara)
Exophthalmos	Normal	49/93 (52.7%)	48/86 (55.8%)	0.0698
	Grade 3	3/93 (3.2%)	0/86 (0.0%)	
	Grade 2	12/93 (12.9%)	6/86 (7.0%)	
	Grade 1	29/93 (31.2%)	32/86 (37.2%)	
	Not examined	0/93 (0.0%)	7/93 (7.5%)	
Soft tissues	Normal	14/93 (15.0%)	41/74 (55.4%)	0.2942
	Grade 3	1/93 (1.1%)	0/74 (0.0%)	
	Grade 2	29/93 (31.2%)	1/74 (1.4%)	
	Grade 1	49/93 (52.7%)	32/74 (43.2%)	
	Not examined	0/93 (0.0%)	19/93 (20.4%)	
Oculomotor muscles	Normal	15/93 (16.1%)	35/83 (42.2%)	0.3332
	Grade 3	5/93 (5.4%)	0/83 (0.0%)	
	Grade 2	32/93 (34.4%)	5/83 (6.0%)	
	Grade 1	41/93 (44.1%)	43/83 (51.8%)	
	Not examined	0/93 (0.0%)	10/93 (10.8%)	
Cornea	Normal	80/93 (86.0%)	76/82 (92.7%)	0.8216
	Grade 3	1/93 (1.1%)	0/82 (0.0%)	
	Grade 2	1/93 (1.1%)	0/82 (0.0%)	
	Grade 1	11/93 (11.8%)	6/82 (7.3%)	
	Not examined	0/93 (0.0%)	11/93 (11.8%)	
Visual acuity	Normal	6/93 (6.4%)	5/83 (6.0%)	0.1696
	Grade 3	1/93 (1.1%)	1/83 (1.2%)	
	Grade 2	0/93 (0.0%)	0/83 (0.0%)	
	Grade 1	86/93 (92.5%)	77/83 (92.8%)	
	Not examined	0/93 (0.0%)	10/93 (10.7%)	

headache, hair loss, blurred vision were also transient and mild in nature [14, 17, 34, 47, 52, 55, 60, 65, 73, 74].

Late complications following radiotherapy of retrobulbar area include: retinopathy, cataract and radiation-induced tumours [9, 13–15, 17, 23, 24, 26, 29, 42, 43, 45, 46, 51, 59, 61, 65, 66, 68, 73]. In the presented material, three cases of cataract (three out of 106=2.8%) were reported that

however might have been related to the physiological ageing process and not to radiotherapy. In the group of diabetic patients (12/93=12.9%) no diabetic retinopathy was found after the combined treatment. Until now, no secondary tumours were found within the previously irradiated area.

At least two controlled studies showed that combination of high-dose steroid therapy with radiotherapy is the most

Table 7 Treatment results as assessed by computed tomography (CT) of the retrobulbar areas in the group of patients treated with steroids and full-dose radiotherapy 20 Gy/10 fractions (*n*=93)

	Left eye after treatment completion—improvement	Right eye after treatment completion—improvement
Thickness of the superior rectus muscle	0/41 (0.0%)	0/41(0.0%)
thickness of the inferior rectus muscle	0/51 (0.0%)	0/45 (0.0%)
Thickness of the lateral rectus muscle	0/30 (0.0%)	0/26 (0.0%)
Thickness of the median rectus muscle	0/68 (0.0%)	0/63 (0.0%)
Fat tissue	2/21 (9.5%)	0/18 (0.0%)
Optic nerve	1/1 (100%)	0/0 (0.0%)
Lacrimal gland	0/1 (0.0%)	0/2 (0.0%)

numerator the number of patients with improvement, *denominator* the number of patients with particular symptoms before the treatment

Table 8 Patient self-reported eye symptoms improvement by treatment method

Symptom	Steroid therapy n=101 A	Combined therapy n=93 B	p (Fisher test)
Unilateral or bilateral exophthalmos	49/97 (50.5%)	71/89 (79.8%)	A/B 0.0000
Oedema of the peribulbar soft tissue	39/96 (40.6%)	56/88 (63.7%)	A/B 0.0020
Diplopia	50/93 (53.8%)	47/85 (55.3%)	A/B 0.8809
Eye burning/lacrimation	35/91 (38.5%)	61/84 (72.6%)	A/B 0.0000
Pain and/or eye pushing-out sensation	27/81 (33.3%)	56/76 (73.7%)	A/B 0.0000
Visual acuity	26/50 (52.0%)	26/47 (55.3%)	A/B 0.8392
Colour vision	4/7 (57.1%)	5/6 (83.3%)	A/B 0.5594

numerator the number of patients with improvement, *denominator* the number of patients reporting particular symptoms at baseline

Table 9 Improvement of ocular symptoms by sex in the group of patients treated with the combined method (n=93)

numerator the number of patients with improvement, *denominator* the number of patients (by sex) with particular symptoms at baseline

^a Statistically significant difference ($p < 0.05$)

Symptom	Men improvement	Women improvement	Chi square
Exophthalmos	16/22 (72.7%)	54/67 (80.6%)	0.4345
Oedema	15/22 (68.2%)	40/66 (60.6%)	0.5250
Diplopia	8/22 (36.4%)	38/63 (60.3%)	0.0523
Eye burning/tearing	10/20 (50.0%)	50/64 (78.1%)	0.0151 ^a
Pain/eye pushing-out sensation	13/17 (76.5%)	41/58 (70.7%)	0.6406
Visual acuity	4/12 (33.3%)	22/35 (62.8%)	0.0759
Colour vision	0/0 (0.0%)	5/5 (100%)	

Table 10 Improvement of ocular symptoms in diabetic and non-diabetic patients in the group treated with the combined method (n=93)

Symptom	Diabetics improvement	Non-diabetics improvement	Chi square
Exophthalmos	6/11 (54.6%)	65/78 (83.3%)	0.0261 ^a
Oedema	6/12 (50.0%)	50/76 (65.8%)	0.2907
Diplopia	2/11 (18.2%)	44/73 (60.3%)	0.0089 ^a
Eye burning/tearing	5/12 (41.7%)	56/72 (77.8%)	0.0094 ^a
Pain/eye pushing-out sensation	5/9 (55.6%)	51/67 (76.1%)	0.1884
Visual acuity	3/6 (50.0%)	23/41 (56.1%)	0.7790
Colour vision	1/2 (50.0%)	4/4 (100%)	0.1213

numerator the number of patients with improvement, *denominator* the number of non-diabetics/diabetics with particular symptoms

^a Statistically significant difference ($p < 0.05$)

Table 11 Symptoms of acute reaction in the group of 121 patients with Graves ophthalmopathy occurring during radiotherapy of retrobulbar areas

Acute post-irradiation reaction	n=121
Significant tearing and eyelid oedema	3 (2.5%)
Erythema in high-dose areas	3 (2.5%)
Slight tearing	2 (1.6%)
Erythema and eye burning sensation	1 (0.8%)
Aggravation of diplopia and worsening of visual acuity	1 (0.8%)
Aggravation of tearing and worsening of visual acuity	1 (0.8%)

Table 12 Symptoms of late post-irradiation reaction found during follow-up after treatment completion in the group of 101 patients with Graves ophthalmopathy

Late post-irradiation reaction	n=101
Retinopathy	0 (0.0%)
Cataract	3 (2.8%)
Radiation-induced tumours	0 (0.0%)

effective treatment of malignant exophthalmos [5, 11, 41, 75]. In the analysed material, the vast majority of patients were treated with the combined method (93/101). Based on the follow-up ophthalmologic examination, it was shown the intravenous steroid therapy followed by radiotherapy is effective with respect to normalisation of soft tissue and oculomotor muscles condition as well as exophthalmos improvement.

The following factors are considered to worsen the prognosis of ophthalmopathy: patient age above 50–60 years, male sex, smoking, symptom duration, concomitant diabetes, hyperthyreosis [2, 5, 8, 9, 13, 14, 25, 26, 30, 32, 45, 49, 51, 52, 58, 59, 70]. The effect of these factors was analysed in the group of patients treated with the most effective method, i.e. with the combined method. Patient age, symptom duration, smoking, TSH and FT4 levels did not affect significantly the results of the malignant exophthalmos treatment—in contrast to concomitant diabetes and male sex.

Graves ophthalmopathy treatment available at present is not fully satisfactory. Its efficacy is assessed to be about 60–80% [46, 51]. Therefore, new treatment methods are tested. Use of cytokine antagonists, in particular, pentoxifylline, somatostatin analogues and colchicine seems to be the most promising among them [10, 36, 64, 73].

However, the majority of centres consider combined steroid and radiotherapy treatment to be, at present, the best treatment method for Graves ophthalmopathy [31, 57, 64, 67, 73, 75].

Conclusions

1. Radiotherapy combined with steroid therapy in the treatment of Graves ophthalmopathy seems to be an effective treatment of malignant exophthalmos symptoms at strictly defined indications.
2. Radiotherapy is a well-tolerated treatment modality in Graves ophthalmopathy.
3. Diabetes mellitus is a factor worsening prognosis in Graves ophthalmopathy.
4. Female sex is a favourable prognostic factor in Graves ophthalmopathy.

Conflict of interest statement There is no conflict of interest related to this paper.

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