Efficacy and toxicity of radiotherapy for Graves’ ophthalmopathy: the University of Athens experience

V Kouloulias1,*, J Kouvaris3, A Zygogianni2, E Mosa1, J Georgakopoulos1, P Theodosiadis3, C Antypas2, K Platoni1, M Tolia2, I Beli1, D Alonistiotis3, M Dilvoi1, G Patatoukas1, C Asimakopoulos1, E Efstathopoulos1, N Kelekis1

Abstract

Aim
To evaluate the efficacy, the feasibility as well as the acute and late toxicity of orbital radiotherapy in patients with Graves’ ophthalmopathy.

Materials and methods
Between 2002 and 2011, we retrospectively evaluated 17 patients (7 males, 10 females) diagnosed with Graves’ orbitopathy that were treated with external three-dimensional conformal radiotherapy. The median age of the patients was 58 years. Patient symptoms included pain (17/17), proptosis (14/17), redness of the eyelid (17/17) and extracocular muscle dysfunction with decreased eye movements (16/17). The mean clinical activity score (CAS) was 8.65 ± 1.87. Corticosteroids were used in all the patients. A dose of 20 Gy in 10 daily fractions was prescribed. The primary endpoints were the assessment of the therapeutic impact, the safety of the treatment and the acute toxicity of irradiation.

Results
The median follow-up was 15 months. Stabilization of the disease without recurrence was achieved in 12/17 patients. At the end of radiotherapy, the CAS regressed to 4.82 ± 2.24 (P < 0.001, Wilcoxon test). However, in smokers, the CAS decreased significantly slower and to a lower extent than that in non-smokers (P = 0.008, log-rank test). Extraocular motility and pain behind the globe were improved in 14/17 and 16/17 patients, respectively. Five patients developed recurrent signs and symptoms and they underwent surgical decompression, all of them being smokers. However, mortality was not reported. None of the patients developed retinopathy, while cataract and chronic dry eyes were observed in 2/17 and 6/17 patients, respectively.

Conclusion
Orbital radiotherapy for Graves’ disease is a well-established treatment option, even if patients have failed previously with other treatment modalities such as corticosteroids and surgical decompression.

Introduction
Thyroid ophthalmopathy is usually the main sign of Graves’ disease, but can also arise in association with Hashimoto’s thyroiditis or myxedema without previous thyreotoxicosis. It rarely occurs in patients without a history of thyroid dysfunction. It refers to an inflammatory fibrosing disease of the predominantly retro-orbital contents. Graves’ orbitopathy (GO) is considered an autoimmune disease due to the T-cell predominant lymphocytic infiltration of orbital tissues and the appearance of glycosaminoglycans in peribulbar fat and extraocular muscles1,2. The symptomatic presentation of GO is a direct result of the inflammatory and fibrotic reactions in the retro–orbit space and can occur as exophthalmos, impaired muscle involvement, diplopia, blurred vision, peribulbar oedema, chemosis, lid retraction and compressive optic neuropathy. Typical presentation symptoms may include proptosis, pain, tearing, visual impairment and rarely blindness.

Management of Graves’ ophthalmopathy is a challenging procedure, based on individualized data after thorough evaluation of each patient and which also requires a multidisciplinary approach from a team of physicians including endocrinologists, ophthalmologists, radiologists, radiation oncologists and orbital surgeons3.

There are several important variables that should always be considered when making a treatment plan for GO. First, thyroid function should be taken into account, since euthyroidism is necessary when treating GO. Second, severity classification of GO is of major importance. The European Group of Graves’ Orbitopathy (EUGOGO) classifies GO severity based on subjective symptoms and objective signs into three categories: mild, moderate to severe and sight-threatening4. The last category is of major importance as these patients are at a risk of vision loss.

Patients of sight-threatening GO appear to have dysthyroid optic neuropathy or corneal breakdown and need immediate intervention4. On the other hand, the activity of GO refers to the presence of inflammatory signs. It can be measured through the clinical activity score (CAS) based on the classical features of inflammation. In this way, one point is given for each of the classical features of inflammation: oedema, chemosis, lid retraction, compressive optic neuropathy, pseudotumorous swelling, and thrombosis of an extraorbital artery (0–5 points). A CAS ≥ 4 indicates a sight-threatening GO and requires urgent intervention5.
the following features: spontaneous retrobulbar pain, pain of attempted up- or down gaze, conjunctival redness, redness of the eyelid, swelling of the caruncle or plica, swelling of the eyelid and chemosis. A score ≥3 represents active GO. Orbital radiotherapy (RT) for GO is a well-established treatment modality for patients, as a sole therapy or in combination with glucocorticosteroids. The aims of this study, in terms of primary endpoints, was to report in a retrospective manner the efficacy and the acute as well as the late toxicity of an irradiated scheme of 20 Gy administered in 10 fractions of 2 Gy per fraction. The secondary endpoint was the impact of smoking on the treatment outcome of orbital irradiation. In general, the manuscript reports on the experience of the two University Radiotherapy Units of the Medical School of Athens.

Methods and materials

Patient characteristics

Between 2002 and 2011, 17 patients with bilateral GO were enrolled into this retrospective study. Of these, 7 were males and 10 were females. The median age at the time of enrolment was 58 years (range: 45–74). All patients were evaluated before initiation of treatment by a multidisciplinary team of physicians including endocrinologists, ophthalmologists, radiologists, radiation oncologists and orbital surgeons.

According to the EUGOGO criteria, patients were categorized in three categories. Patients with mild GO only had a minor impact on daily life, insufficient to justify immunosuppressive or surgical treatment. They presented with one or more of the following: minor lid retraction (<2 mm), mild soft tissue involvement, exophthalmos <3 mm above normal for race and gender, transient or no diplopia and corneal exposure responsive to lubricants. Patients with moderate-to-severe GO suffered from eye disease with sufficient impact on daily life, justifying the risks of immunosuppression (if active) or surgical intervention (if inactive), and they usually presented with one or more of the following: lid retraction ≥2 mm, moderate or severe soft tissue involvement, exophthalmos ≥3 mm above normal for race and gender and inconstant or constant diplopia.

The complete pre-treatment evaluation at presentation apart from the physical examination included pathology review, laboratory studies with complete blood count, chemistries and thyroid function tests, radiological imaging with computed tomography (CT) and/or magnetic resonance imaging (MRI) of the orbits and measurement of proptosis with Hertel exophthalmometer.

If GO was estimated as mild or stable and there was no threat of impending vision loss, the aim of the treatment was to correct the underlying thyroid disorder. If GO was moderately symptomatic with signs of progression and refractory symptoms the treatment strategy included orbital RT with systemic immunosuppressive agents, especially IV corticosteroids and oral steroids. In this case, the RT scheme comprised 20 Gy in 10 fractions in 2 weeks’ time. When vision loss was diagnosed, decompressive surgery was the standard of care. Patients included in the present study were those diagnosed with moderate-to-severe and sight-threatening GO, according to the EUGOGO criteria, and with a CAS ≥4. Patients with mild thyroid-associated ophthalmopathy (TAO) (CAS <4), psychological disorders or those who were very elderly and unfit for immobilization during RT were excluded. Patients were also excluded if they had history of previous RT for GO and if they had suffered from diabetes mellitus and hypertension. All patients were subjected to treatment with glucocorticoids. Patient characteristics are summarized in Table 1.

Patients were referred either to ATTIKO University Hospital of Athens or Aretaieio University Hospital to undergo radical RT as a treatment for GO. All patients were required to sign an informed consent form, concerning the side effects of irradiation.

RT treatment and radiobiological assessments

CT scan images (3-mm slice thickness) were acquired and transferred to the treatment planning system. Patients were treated in a neutral supine position, while being immobilized with a thermoplastic head mask. Pretreatment planning included orbital CT. Patients were instructed not to move during CT scan and simulation and during the complete treatment course. CT datasets were transferred either to the Prosoma® Virtual simulation or Plato® contouring system through a DICOM III network. Contouring of clinical target volume (CTV), planning target volume (PTV) and normal structures (organs at risk, OARs) was performed according to the International Commission on Radiation Units and Measurements (ICRU) criteria. Dose calculations were performed using either the treatment planning system Eclipse (Varian Associates, Palo Alto, CA) or PLATO (Nucletron, The Netherlands) to deliver the prescribed dose to the ICRU reference point. Treatment planning consisted of three-dimensional (3D) conformal planning to the bilateral retro-orbital contents. Each patient’s globe, lens, extraocular muscles and brain were contoured. Anterior blocking shielded the anterior chamber and lens of the eye, whereas posterior and superior blocking shielded the brain, sella turcica and lacrimal gland. Each portal field was designed to cover all enlarged rectus muscles and retro-orbital tissues during treatment planning. When necessary, the beams were angled 5° posteriorly or they were shielded by a half-beam block of the anterior edge of the field to minimize the contralateral lens exit dose (Figure 1). Weighted beams and wedges were used as necessary to improve dose homogeneity.
In general, the fields were placed iso-centrically. We kept the dose range between 95% and 107% of prescribed dose\textsuperscript{10}. Wedge compensation was used to ensure uniform dose distribution throughout the target volume. To evaluate the dose constraints for normal tissues, we used the QUANTEC trial\textsuperscript{12}.

RT was delivered once daily with a 2 Gy dose per fraction, five times a week for a period of 10 days. For the treatment technique, histograms were generated; a number of parameters—including mean, median and maximum dose—were evaluated. Patient set-up was monitored weekly using portal films obtained in the treatment position with therapeutic beam to confirm adequate coverage. Patients were treated with megavoltage equipment, either on a VARIAN CLINAC 600 C Linac with 6 MV photons or on an ELECTA 6 MV Linac.

**Follow-up**

All patients were evaluated to determine RT response and toxicity at the beginning of the treatment, once a week during treatment and at completion of radiation course. Post-RT follow-up was performed by radiation oncologists and ophthalmologists monthly, bimonthly and biannually later on. Symptoms occurring in the intervals between the start of RT and 90 days after this time point were classified as “acute”. “Late” radiation complications were defined as those appearing 3 months from the end of the treatment. The evaluation of acute and late radiation-induced toxicity was done with the EORTC/RTOG toxicity criteria\textsuperscript{13}. Median follow-up duration was 12 months (range, 10–15).

**Statistical analysis**

The response to treatment in terms of CAS regression and stabilization was presented via life table analysis according to Kaplan–Meier, while the differences between smokers and non-smokers were tested with the log-rank test 12 months post-RT. Failure after RT was considered an event when calculating the response to treatment. Surgical control after RT was not considered in this study. Difference in the incidence of CAS before and after RT was evaluated using the Chi\textsuperscript{2} test. The significance in CAS regression after RT was assessed with the Wilcoxon non-parametric test. The significance level was set at 0.05. The analysis was performed with SPSS ver. 10 software (IL, USA).

**Results**

All patients completed the planned 3D-conformal RT (3DCRT) with none experiencing acute treatment reactions necessitating a break in the treatment. All patients completed the irradiation schedule with 20 Gy in 10 daily fractions. Stabilization of the disease without recurrence was

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics (n = 17)</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age median (range)</td>
<td>58 (45–74)</td>
</tr>
<tr>
<td>Male/female</td>
<td>7/10</td>
</tr>
<tr>
<td>Severity classification in GO (CAS)</td>
<td></td>
</tr>
<tr>
<td>Moderate-to-severe (CAS: 3–5)</td>
<td>2/17</td>
</tr>
<tr>
<td>Sight-threatening (CAS &gt;5)</td>
<td>15/17</td>
</tr>
<tr>
<td>Smokers</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11/17</td>
</tr>
<tr>
<td>No</td>
<td>6/17</td>
</tr>
<tr>
<td>Median duration of GT (range) in months</td>
<td>36 (13–60)</td>
</tr>
<tr>
<td>Median duration of TAO (range) in months</td>
<td>9 (3–12)</td>
</tr>
</tbody>
</table>

**Figure 1:** A 3D-conformal treatment planning with two oppose fields with shielding of the lenses.

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achieved in 12/17 patients. At the end of RT, the CAS regressed to 4.82 ± 2.24 (P < 0.001, Wilcoxon test). The CAS before and after RT is detailed in Table 2. As shown in Figure 2, the mean CAS regressed from 9.1 ± 1.3 to 6.0 ± 1.9 and 7.9 ± 2.0 to 3.1 ± 1.7, respectively, for smokers and non-smokers. Moreover, in smokers, the CAS decreased significantly to a lower extent than that in non-smokers (P < 0.01). Time to response, together with smokers versus non-smokers, is shown in Figure 3. Response to treatment was slower in smokers than in non-smokers (P = 0.008, log-rank test). Three patients failed to present a decrease of more than 2 in the CAS, all being smokers. Extraocular motility and pain behind the globe were improved in 14/17 and in 16/17 patients, respectively. In a time range of 5–7 months after the establishment of any response, five patients developed recurrent signs and symptoms followed by surgical decompression, all of them being smokers. However, mortality was not reported. No patients developed retinopathy. Late toxicity was noted in 6/17 patients that developed chronic dry eyes and in 2/17 that developed cataract. No patients experienced retinopathy, concerning the presence of ≥1 haemorrhages and/or microaneurysms on standardized 50° red-free, black and white retina photographs.

**Table 2 CAS before RT and after the establishment of a stable response**

<table>
<thead>
<tr>
<th>Items</th>
<th>Description</th>
<th>Before RT N (%)</th>
<th>Post-RT N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Painful, oppressive feeling on or behind the globe during the last 4 weeks</td>
<td>17/17</td>
<td>1/17</td>
</tr>
<tr>
<td></td>
<td>Pain on attempted up, side or down gaze during the last 4 weeks</td>
<td>17/17</td>
<td>1/17</td>
</tr>
<tr>
<td>Redness</td>
<td>Redness of the eyelid(s)</td>
<td>17/17</td>
<td>14/17</td>
</tr>
<tr>
<td></td>
<td>Diffuse redness of the conjunctiva, covering at least one quadrant</td>
<td>15/17</td>
<td>15/17</td>
</tr>
<tr>
<td>Swelling</td>
<td>Swelling of the eyelid(s)</td>
<td>13/17</td>
<td>13/17</td>
</tr>
<tr>
<td></td>
<td>Chemosis</td>
<td>15/17</td>
<td>13/17</td>
</tr>
<tr>
<td></td>
<td>Swollen caruncle</td>
<td>15/17</td>
<td>12/17</td>
</tr>
<tr>
<td></td>
<td>Increase of proptosis of ≥2 mm during a period of 1–3 months</td>
<td>14/17</td>
<td>6/17</td>
</tr>
<tr>
<td>Impaired function</td>
<td>Decrease of eye movements in any direction ≥5° during a period of 1–3 months</td>
<td>16/17</td>
<td>3/17</td>
</tr>
<tr>
<td></td>
<td>Decrease of visual acuity of 1 line(s) on the Snellen chart (using a pinhole) during a period of 1–3 months</td>
<td>8/17</td>
<td>4/17</td>
</tr>
<tr>
<td>Mean total CAS (±SD)</td>
<td>The sum of all items scored by 1 each</td>
<td>8.65 ± 1.87</td>
<td>4.82 ± 2.24</td>
</tr>
</tbody>
</table>

**Figure 2:** Mean CAS before and after the establishment of a response to RT. Vertical lines represent standard deviation.

**Discussion**

GO is an autoimmune disease characterized by an inflammatory swelling of...
10 daily fractions. However, there are cases where acute or chronic treatment with steroids can provoke major side effects, especially when people suffer from diabetes mellitus, hypertension, cardiovascular disorders, obesity and gastrointestinal diseases. Additionally, the usage of corticosteroids can provoke major side effects, especially when people suffer from diabetes mellitus, hypertension, cardiovascular disorders, obesity and gastrointestinal diseases. Additionally, chronic treatment with steroids can lead to acute liver damage (cytotoxic, autoimmune or viral), liver steatosis and autoimmune hepatitis-related autoantibodies. However, the usage of corticosteroids can provoke major side effects, especially when people suffer from diabetes mellitus, hypertension, cardiovascular disorders, obesity and gastrointestinal diseases. Additionally, chronic treatment with steroids can lead to acute liver damage (cytotoxic, autoimmune or viral), liver steatosis and autoimmune hepatitis-related autoantibodies.

The advantage of RT over glucocorticosteroids is that it is well tolerated with usually no side effects. However, the usage of corticosteroids can provoke major side effects, especially when people suffer from diabetes mellitus, hypertension, cardiovascular disorders, obesity and gastrointestinal diseases. Additionally, chronic treatment with steroids can lead to acute liver damage (cytotoxic, autoimmune or viral), liver steatosis and autoimmune hepatitis-related autoantibodies.

The advantage of RT over glucocorticosteroids is that it is well tolerated with usually no side effects. However, the usage of corticosteroids can provoke major side effects, especially when people suffer from diabetes mellitus, hypertension, cardiovascular disorders, obesity and gastrointestinal diseases. Additionally, chronic treatment with steroids can lead to acute liver damage (cytotoxic, autoimmune or viral), liver steatosis and autoimmune hepatitis-related autoantibodies.

Studies that suggest that doses <20 Gy are sufficient for patients with only soft tissue signs, without ocular dysmotility. It is a fact that the duration of symptoms before RT has been found to be of great importance. Matthiesen et al. reported that patients treated for <6 months from the onset of symptoms had worse results than those treated in the 6–12 month duration of the presence of orbitopathy. In our study, the median time of irradiation after the onset of GO was 9 months.

A correct management of GO should include adequate patient counselling, concerning therapy outcomes, risks related to treatments, timing and the need for a long lasting follow-up. Radiation-induced tumours have so far not been reported in follow-up studies, even in the setting of reirradiation for GO. On the contrary, radiation-induced retinopathy has been documented in low quality in terms of technique treatments and with the coexistence of diabetes mellitus.

Cataract as late radiation toxicity is rarely seen when lens receive <10% of the prescribed radiation dose. Table 3 summarizes the results from several controlled-randomized trials that have studied the efficacy of RT in the treatment of GO. In all cases, a significant response to RT was noted, while the highest incidence of radiation-induced cataract was 27%. Our own study is in accordance with these results by means of treatment efficacy, while the acute and late toxicity were quite minimal. In general, RT improves extraocular motility. However, radiation-induced retinopathy, although rare, is a potential side effect of orbital RT. In our study, no patients presented with orbital retinopathy. It is worth mentioning that smoking is associated with an increased risk of GO development and/or progression, while at the same time, it may decrease the effectiveness of GO treatment, something which was profound in our study as the CAS was significantly better in non-smokers. (Figures 2 and 3).

Last but not the least, all patients were thoroughly checked histologically by pathologists in case of simultaneous presence of thyroid carcinoma or mediastinal disease and other autoimmune diseases. It is also important to mention that the follow-up of patients who have undergone orbital RT should be as extended as much as possible. Retinopathy is a severe radiation-induced toxicity that is presented as a late effect of RT and would be confirmed after a minimum of six months post-RT. Studies with more patients, more extended follow-ups and modern intensity-modulated RT techniques are required.

**Conclusions**

Our retrospective study shows that external RT with 3DCRT is a safe modality for patients with ocular symptomatology derived from Graves’ thyroid eye disease. The majority of patients achieve clinical improvement, without progression. Our study is in complete agreement with these results by means of treatment efficacy, while the acute and late toxicity were quite minimal. In general, RT improves extraocular motility. However, radiation-induced retinopathy, although rare, is a potential side effect of orbital RT. In our study, no patients presented with orbital retinopathy. It is worth mentioning that smoking is associated with an increased risk of GO development and/or progression, while at the same time, it may decrease the effectiveness of GO treatment, something which was profound in our study as the CAS was significantly better in non-smokers. (Figures 2 and 3).

Figure 3: Decrease of CAS >2 by time (%) in a Kaplan–Meier curve for all patients together with smokers versus non-smokers (P = 0.008, log-rank test). Bold line represents all patients; slim line represents non-smokers and dotted line represents smokers.
according with studies in the literature, which suggest that a combination of 3DCRT and glucocorticosteroids is a well-established treatment modality that can be safely prescribed with good results for the treatment of GO.

**References**


**Table 3 Randomized-controlled studies with irradiation for GO concerning the efficacy and toxicity of RT**

<table>
<thead>
<tr>
<th>Study, N (patients)</th>
<th>Intervention</th>
<th>Severity/Activity of GO</th>
<th>Age (median)</th>
<th>Primary study outcome</th>
<th>Radiation-induced toxicity</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartalena et al.20, N = 24</td>
<td>RT + prednisone vs. prednisone alone</td>
<td>Active GO</td>
<td>44</td>
<td>Mean decrease OI: 4.8, 10/12 patients good response</td>
<td>None</td>
<td>19</td>
</tr>
<tr>
<td>Antonelli et al.21, N = 14</td>
<td>Orbital radiation IVIG vs. IVIG alone</td>
<td>OI &gt; 4</td>
<td>46</td>
<td>Mean decrease OI: 3.2, 4/12 good response</td>
<td>None</td>
<td>6</td>
</tr>
<tr>
<td>Prummel et al.15, N = 59</td>
<td>Sham RT + prednisone vs. OR (10 × 2 Gy) + placebo</td>
<td>Moderate</td>
<td>47</td>
<td>NOSPECTS: 18.5° to 21.8° for RT (P = 0.003)</td>
<td>1 headache</td>
<td>6</td>
</tr>
<tr>
<td>Prummel et al.22, N = 88</td>
<td>Orbital RT (10 × 2 Gy) vs. sham RT</td>
<td>Mild motility impairment, mild or moderate lid swelling, proptosis ≤24</td>
<td>45</td>
<td>Major and minor criteria 52% response in RT vs. 27% in sham RT</td>
<td>No significant changes in quality of life in both groups</td>
<td>12</td>
</tr>
<tr>
<td>Wakelkamp et al.4, N = 245</td>
<td>Orbital RT(10 × 2 Gy) + GC vs. GC</td>
<td>Active GO</td>
<td>48</td>
<td>Major and minor criteria</td>
<td>15% possible retinopathy, 2% definitive retinopathy, RT: 29% cataract</td>
<td>132</td>
</tr>
<tr>
<td>Ng et al.23, N = 16</td>
<td>Orbital RT (10 × 2 Gy) + GC vs. GC alone</td>
<td>Moderate to severe</td>
<td>56</td>
<td>Change in NOSPECS</td>
<td>37% had mild exacerbation of periorbital swelling, 37% had temporal hair loss</td>
<td>12</td>
</tr>
<tr>
<td>Current study</td>
<td>Orbital RT (10 × 2 Gy) + GC</td>
<td>Moderate to severe</td>
<td>58</td>
<td>Mean decrease of CAS: 3.83</td>
<td>Cataract: 2/17, chronic dry eyes: 6/17</td>
<td>15</td>
</tr>
</tbody>
</table>

OI, Ophthalmopathy index as proposed by Donaldson et al.26; IVIG, Intravenous immunoglobulin; NOSPECTS, Classification of eye disease related to Graves’; GC, Glycol-corticosteroids.

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