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# Invited article

# Graves' disease with special reference to radiation therapy

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*Graves' disease, although not malignant, nevertheless can lead to serious events such as permanent loss of vision if it remains untreated. This review article describes the clinical symptoms of the disease, includes a commentary on the Graves' disease subgroup of thyroid-associated orbitopathy (TAO), and defines clinical activity scoring systems which grade the severity of the disease in patients (clinical activity, NOSPECS and LEMO scoring). An overview of radiotherapy in the 1980s is followed by a summary of the 2003 German national survey on radiotherapy for Graves' disease. Radiation therapy technique is then described and discussed. Case histories are from the Alfred Krupp Hospital in Essen.*

**Key words:** Graves' disease, opthalmopathy, orbitopathy, radiotherapy

## Introduction

Robert James Graves (1796-1853) was an Irish physician who is best remembered for his description of exophthalmic goitre in 1833* [1]. The son of a Dublin clergyman, he enjoyed a colourful start to his career. For example, during a continental tour his remarkable expertise as a linguist led to his arrest as a German spy in Austria; while another adventure saw him quelling a mutiny during a storm in the Mediterranean, and then saving the ship by taking command. In later life, in 1821, he became chief physician to the Meath Hospital in Dublin [2]

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* Previously, when the discovery of Graves' disease is mentioned in the literature, the year 1835 is given for the discovery and the reference 'Clinical lectures. *London Med & Surg J* 1835; 7: 516-7'. This journal was consulted at the Royal Society of Medicine, London, and it was found that in reality, Graves' discovery was in 1833, two years earlier. During 1833 he published a series of 'Clinical lectures' and in Lecture XIX reported the new disease. The incorrect reference for 1835 is for a lecture by Broussais M & Gully JM, 'Course of general pathology and therapeutics'.

The disease has several other names besides Graves' disease. These alternative names/classifications include the following: Graves' opthalmopathy, Basedow's disease, cachexia exophthalmica, diffuse toxic goitre, exophthalmic goitre, Flajani's disease, Parry's disease and tachycardia strumosa exophthalmica [3].

The disease can be defined [4] as 'exophtalamos caused by increased water content of retroocular orbital tissues; associated with thyroid disease, usually hyperthyroidism. An alternative definition [3] is 'a disorder of the thyroid of unknown but probably autoimmune aetiology, occurring most often in women, characterised by thyrotoxicosis with diffuse goitre, exophthalmos, or pretibial myxoedema, or any combination of the three. Signs and symptoms include fatigue, heat intolerance and increased sweating, weight loss, palpitation, and tremor of the hands and tongue. Some patients have varying degrees of exophthalmos, Most patients have thyroid-stimulating immunogloblins (TSI) that cause excessive secretion of thyroid hormones by binding to TSI receptors on thyroid cells'. Also [5], 'the primary tissues involved are the intraocular muscles and indications for therapy include corneal exposure secondary to proptosis and optic nerve compression, which may lead to permanent visual loss. The diagnosis is aided by computed tomography (CT), which may demonstrate thickening of muscles. Steroid use is first-line therapy, but radiation therapy can be beneficial when steroids fail'.

## Incidence of clinical symptoms

Table I presents the distribution of clinical symptoms, after a report on 120 patients from Bartley & Gorman [6] of the Mayo Clinic.

**Table I. Incidence of clinical symptoms [6]**

| Symptom | Incidence (%) |
|---|---|
| Retraction of upper eyelid (pathognomonic) | 90 |
| Involvement of intraorbital soft tissues: exophthalmus (proptosis) | 62 |
| Involvement of eye muscles (double vision) | 43 |
| Involvement of cornea (erosions) | 10 |
| Involvement of optic nerve (vision loss) | 6 |

## Thyroid-associated orbitopathy

Graves' disease is an organ-specific autoimmune disorder which is often characterised by the triad, hyperthyroidism, orbitopathy and pretibial myxoedema [7]. The thyroid-associated orbitopathy (TAO) is apparent in 20-50% of patients [8]. In 90% of the cases, it is associated with hyperthyroidism; it usually occurs within 18 months after the onset of hyperthyroidism [9]. Table II summarises the annual case workload for Graves' disease in German centres, 1995-1998. Taking the mean workload as 10 cases per centre per year, then 90% of 20-50% are only 2-5 cases per centre per year calculated as an estimated incidence of TAO. Therefore, because of this relatively low incidence of Graves' disease, if clinical trials are to be organised, then probably the only subgroup available for such study is TAO: but a clinical trial would definitely have to be organised nationally for results to be obtained in a reasonable number of years..

**Table II. Annual case workload in selected radiotherapy centres in Germany 1995-1998 [10]**

| Parameter | 1995 | 1996 | 1997 | 1998 |
|---|---|---|---|---|
| No. of centres | 138 | 141 | 144 | 145 |
| Total no. cases | 1154 | 1314 | 1423 | 1518 |
| Mean cases per centre | 8.3 | 9.3 | 9.9 | 10.5 |
| Range of cases per centre | 0-50 | 0-75 | 0-100 | 0-100 |

## Clinical activity score classification

Clinical activity score assessed in the range 1-10, adapted from Mourits et al [11] and Weetman [12], is illustrated in Figure 1. Patients with serious inflammatory Graves' opthalmopathy should be treated with anti-inflammatory drugs or radiation therapy, in order to prevent complications such as fibrosis. Those with non-inflammatory opthalmopathy may be treated immediately by surgery. However, it is often difficult to distinguish inflammatory from non-inflammatory Graves' disease. We therefore present a simple clinical classification, Figure 1, to distinguish between these two conditions.

This classification is based on the classical signs of inflammation: pain, redness, swelling and impaired function. After two consecutive clinical examinations an activity score can be determined in the range 0-10. In a retrospective study testing the efficacy of this classification, we found that patients with a score of 3 or greater at the start of therapy, responded well to anti-inflammatory drugs, while those with a lower activity score mostly did not respond well.

Comparing the pre-treatment activity score with the degree of enlargement of the extraocular muscles on the CT scan we found a significant correlation between these two parameters. The higher the activity score, the greater the enlargement of the muscles. We conclude that this

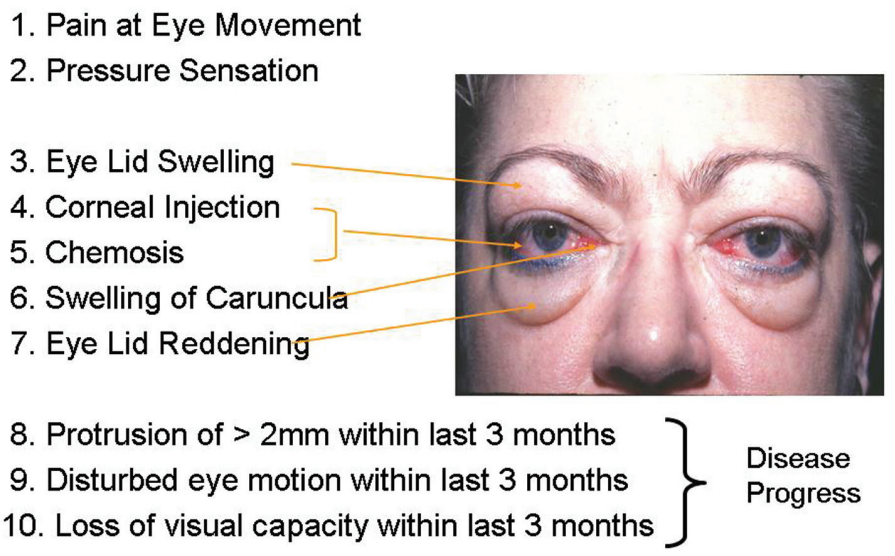


**Figure 1.** Clinical activity score adapted from Mourits et al [11] and Weetman [12]

classification facilitates the proper selection of patients for treatment.

## NOSPECS and LEMO grading schemes

The NOSPECS scheme, which was first proposed in 1969 and later modified by Werner in 1977 [13] is given in Table III. Within classes 1-6 the physicians must differentiate between the severity grades 0, A, B and C. Although this scheme is widely used it unfortunately suffers from numerous ambiguities. A more modern and unambiguous grading scheme is the LEMO classification [14, 15]. LEMO is intended to complement NOSPECS and four categories, Table IV, are associated with integer values between 0 and 4 depending on the severity of the disease. Thus L1 E1 M2 O0 denotes endocrine opthalmopathy with lid oedema, exothalmus, and pseudoparesis of the external eye muscles, but with no optic nerve involvement.

**Table III. NOSPECS scheme for grading endocrine ophthalmology**

| Class | Endocrine opthalmopathy |
|---|---|
| 0 | N = No signs or symptoms |
| 1 | O = Only signs, no symptoms (e.g., lid retraction) |
| 2 | S = Soft tissue involvement (swelling of eyelid) |
| 3 | P = Proptosis (position of eyeball relative to the nose) |
| 4 | E = Extraocular muscle involvement (muscle vision) |
| 5 | C = Corneal involvement (inflammation, reddening) |
| 6 | S = sight loss (doe to optic nerve damage) |

Figure 2 is an example of a patient who had an exothalmometry using CT and was graded NOSPECS class 3.

Figure 3 is a patient with more advanced Graves' disease, involving the optic nerve, with NOSPECS class 6. This case shows optic nerve compression caused by massive thickening of the eye muscles within the orbital pyramidal cone. The consequences were visual deterioration (sight loss at the perimeter of vision),

**Table IV. LEMO scheme categories and severity grades.**

| Category | Severity grade |
|---|---|
| L =Lid | |
| | 0 = Absent |
| | 1 = Lid oedema only |
| | 2 = Real retraction (impaired lid closure) |
| | 3 = Retraction and upper lid oedema |
| | 4 = Retraction and global lid oedema |
| E = Exophalmus | |
| | 0 = Absent |
| | 1 = Eyelid closure not impaired |
| | 2 = Conjunctival injection required each morning |
| | 3 = Perssistent conjunctival injections required |
| | 4 = Corneal complications |
| M = Muscular | |
| | 0 = Absent |
| | 1 = Detectable only in imaging |
| | 2 = Pseudoparesis |
| | 3 = Pseudoparalysis |
| O = Optical nerve | |
| | 0 = Absent |
| | 1 = Colour vision only, or detectable via VEP |
| | 2 = Peripheral scotoma |
| | 3 = Central scotoma |

reduced colour vision, pathogenic VECP (visual evoked cortical potentials, to register nerve activity), and dilatation of the conjunctival veins. A patient such as this, with NOSPECS class 6, is often a contraindication for radiation therapy.

## Radiotherapy overview, 1980s

A brief overview in the late 1980s [5] of the radiation dose required for Graves' disease quoted radiation therapy treatment being usually given by a direct single lateral portal with shielding of the lens; with a dose of 15-20 Gy in 10 fractions usually sufficient to alleviate symptoms [16-20]. In addition, 12-15 MeV electrons were considered to be ideal for treatment but it was

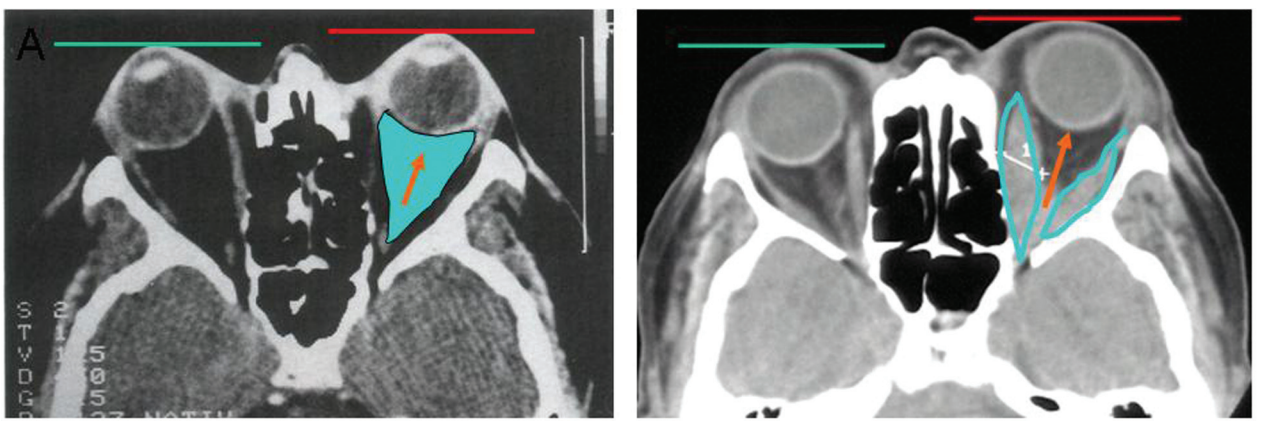


**Figure 2.** Exothalmometry using CT scanning, which shows (left) expansion of the retro-orbital fatty tissue and (right) swelling of the intraorbital eye muscles. This patient was graded as NOSPECS 3

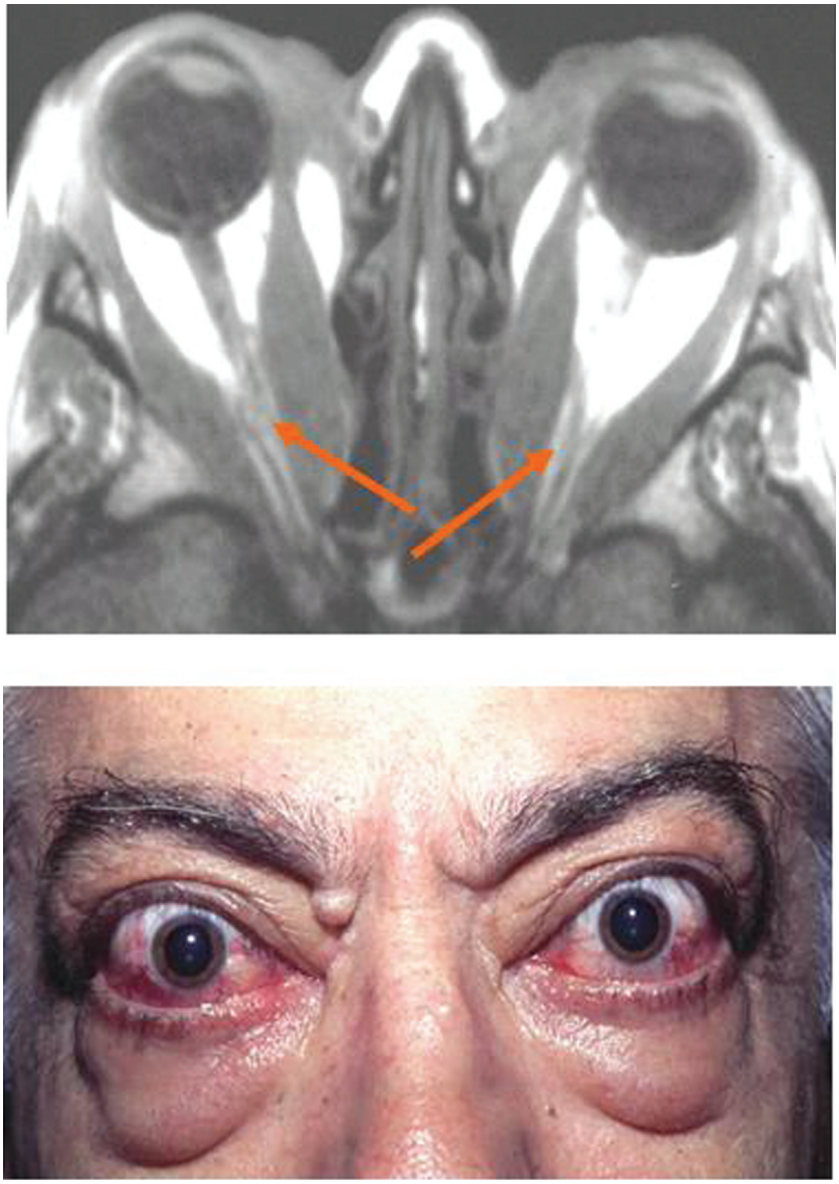

**Figure 3.** Graves' disease patient with involvement of the optic nerve: NOSPECS class 6

emphasised that special care is required when using photons should be taken not to irradiate the optic nerve or the contralateral eye excessively [5]. The response of normal orbital structures to irradiation is given in Table V [21].

**Table V. Response of normal orbital structures to irradiation, adapted from Moss & Cox [21]**

| Structure | Safe dose range | Toxic dose |
|---|---|---|
| Eyelashes | | > 20 Gy in 2 weeks |
| Eyelid | 40-50 Gy in 4-5 weeks | |
| Lacrimal gland | 30-40 Gy | |
| Cornea | 30-50 Gy | > 60 Gy |
| Lens | < 2 Gy single dose or<br>< 4 Gy over 3-12 weeks or<br>< 5.5 Gy over 12 weeks | |
| Retina | < 40-50 Gy over time | > 20 Gy single dose |
| Optic nerve | < 50-60 Gy | |

## German national survey on radiotherapy, 2003

The most recent extensive survey on radiotherapy for Graves' disease for the period 1995-1998 is a German national survey from 152 institutions (not all replied for all years in the range 1995-1998), organised by the German Cooperative Group on Radiotherapy for Benign Diseases (GCG-BD) of the German Society of Radiation Oncology (DEGRO) [10]. Table II has already described the workload statistics. Only 135/152 centres provided data on radiotherapy technique and the results are summarised in Tables VI and VII.

Simultaneous steroid medication was routinely administered by 14% of centres with the initial steroid dose in the range 20-100 mg. In 75% of centres the decision whether to prescribe steroids depended on the previous treatment or occurred as an overlap with the start of radiotherapy.

**Table VI. Details of radiotherapy techniques used in 135 centres: data presented as percentages [10].**
**[X] 23% applied both techniques and 30% used additional lead block shielding around the orbit to shield adjacent parts of brain and soft tissue**

| Parameter | Use by centres (%) |
|---|---|
| Face mask immobilisation system | 82 |
| Simple head support | 17 |
| No immobilisation | 1 |
| CT treatment planning | 67 |
| Simulator-based portal positioning | 27 |
| No pre-treatment planning | 7 |
| 1-5° angular rotation towards the posterior of the linear accelerator gantry for protection of the lens[X] | 60 |
| Asymmetric ventral borders of the portals or half-beam blocking for lens protection[X] | 60 |

**Table VII. Dose-fractionation and total dose data. The standard field sizes were in the range 2.5 x 2.5 cm² to 6.0 x 8.0 cm² [10]. Dose-fraction data was provided by 128 centres and total dose data by 129 centres**

| Parameter | Use by centres (%) |
|---|---|
| *Fractionation schedule* | |
| 5 x 2.0 Gy | 50 |
| 5 x 1.0 Gy | 11 |
| 5 x 1.8 Gy | 7 |
| 5 x 1.5 Gy | 6 |
| 3 x 1.0 Gy | 6 |
| 4 x 2.0 Gy | 5 |
| Other | 15 |
| *Total dose* | |
| 20 Gy | 30 |
| 16 Gy | 29 |
| 15 Gy | 8 |
| Other | 33 |

## Radiation therapy technique

### Orbital pseudotumour

Because pseudotumor may involve any area of the orbital space, and multifocal occurrence is possible, a highly individualised irradiation technique is recommended using CT-based 3D treatment planning. In the case of superficial anterior involvement, electron beam irradiation can be used and permit sufficient dose distribution and optimal protection of the lens. Furthermore, the disease is often localised to a unilateral orbit and may be treated with a single photon field which is split beam or angled posteriorly to protect the contralateral lens. The standard dose is 20 Gy given in 10 fractions of 2.0 Gy over two weeks, applied to the 100% isodose line, with the 95% isodose encompassing the target volume.

### Graves' orbitopathy

The target volume for radiotherapy in TAO involves the posterior two-thirds of the eye globe of both orbits and should include the complete involved extraocular muscles (5-6 mm behind the vertex of the lens curvature). Unilateral irradiation is uncommon. To achieve an optimal lens protection, a split beam technique or posterior angling of the lateral opposing treatment portals are routinely used. CT-based 3D treatment planning is recommended in order to assess asymmetry in proptosis. Block shielding techniques permit a reduction of possible radiation risks of the surrounding tissue. Irradiation of the pituitary gland which has been recommended in the past, is now obsolete and plays no role in the current technique of orbital radiotherapy. The standard dose is a total dose of 20.0 Gy applied in 10 fractions of 2.0 Gy over two weeks.

### Treatment planning

Figure 4 is an example of a treatment plan for Graves' orbitopathy and Figure 5 shows the method of immobilisation used in Essen.

### Before & after treatment

Figure 6 shows a 42-year old female patients with TAO before and after treatment of 16 Gy radiation therapy plus corticosteroids.

## Discussion

Orbital irradiation has become an integral component of the interdisciplinary treatment of TAO. Most common is the prescription of radiation therapy in the ATA stages II-V after an inadequate response to systemic corticoid administration and an immediate treatment onset is recommended.

The efficacy of radiation therapy has been investigated in numerous papers and the reported rates of symptom control varies from 30% to 97% with a mean of 69.5%. Usually, follow-up periods of 6-12 months are necessary in order to evaluate a definitive result.

Even in cases with muscle involvement, prospective randomised trials comparing radiation therapy versus sham-irradiation [22] and versus systemic corticoid administration [23] have demonstrated a significant advantage after the use of radiation therapy.

Severe initial symptom expression, smoking, a delay of symptom onset and initiation of radiation therapy of more than 6-7 months, male gender, advanced age, and insufficient suppression of hyperthyroidism have been proven to be prognostic factors influencing the treatment outcome.

Whereas the radiation technique is standardised to a large degree, the optimal dose-fractionation schedule is not completely clear. As the national survey in Germany demonstrated [12] total doses usually in the

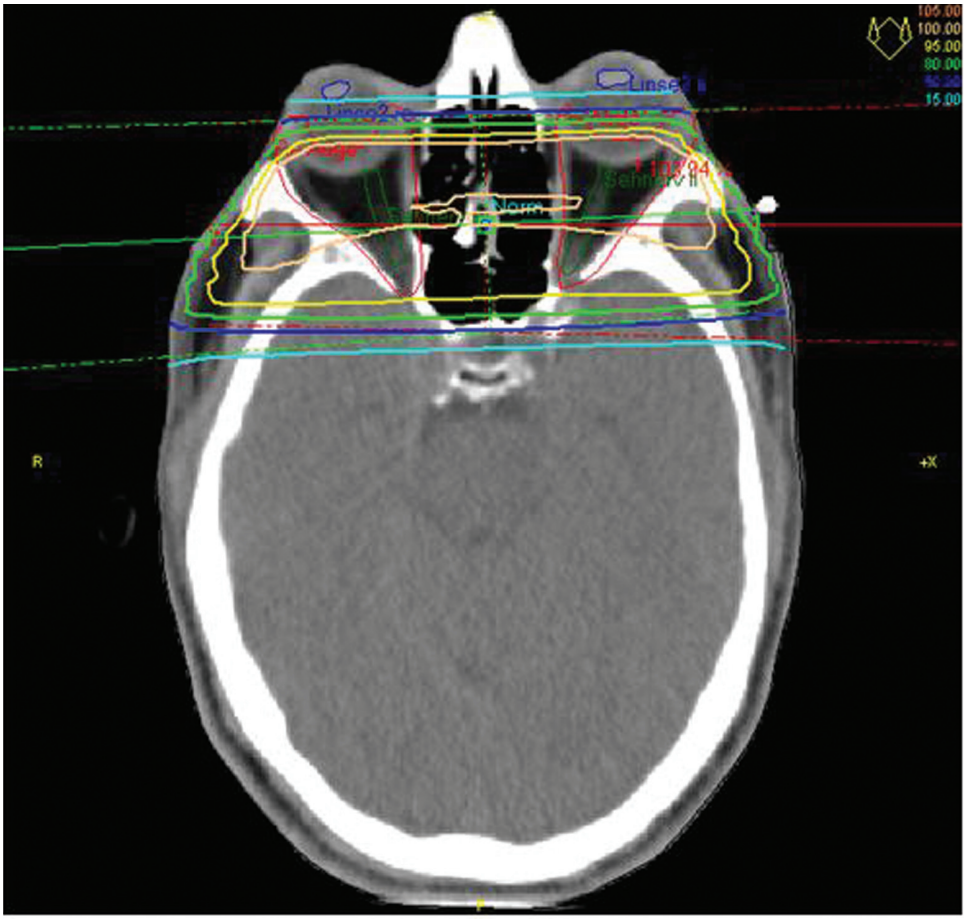


**Figure 4.** 3D-CT treatment plan. In the top right-hand corner of the figure are the colour codes for the six sodose contours shown: 105 cGy, 100 cGy, 95 cGy, 80 cGy, 50 cGy and 15 cGy

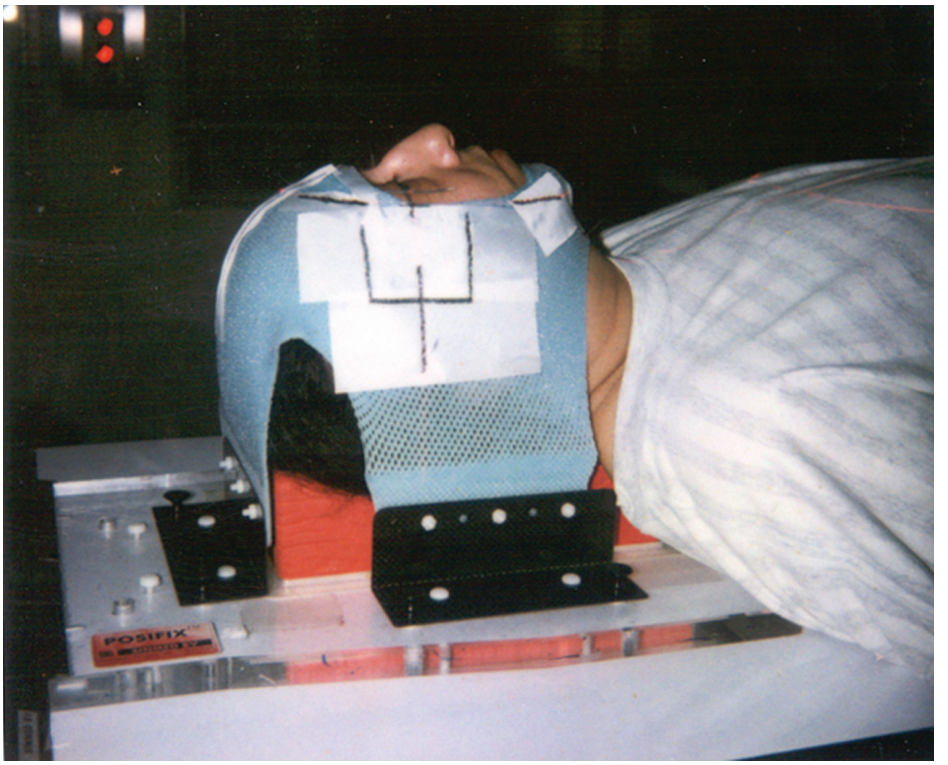


**Figure 5.** Immobilisation of the patient with the treatment fields marked on the cast

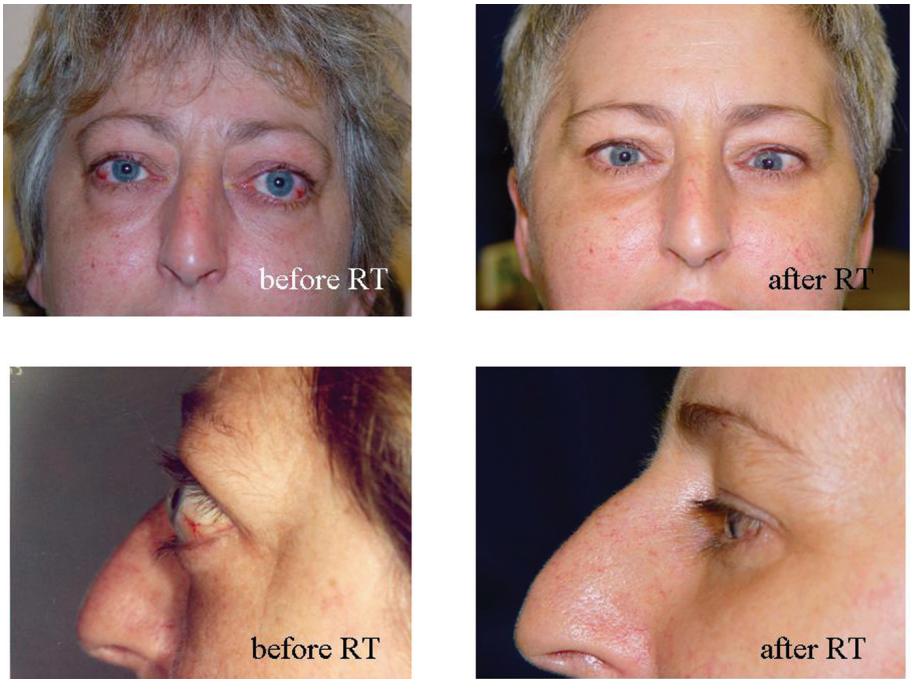


**Figure 6.** A patient with Graves' disease before and after radiation therapy

range of 16.0-20.0 Gy are applied using 10 weekly fractions of 1.6-2.0 Gy.

The precise cellular target of radiation therapy is still not defined and lymphocytes as well as mesenchymal cells are stil under discussion. Hence *in vitro* or *in vivo* models which could permit an experimental dose study are not available. Furthermore, because of the lack of studies including an adequate number of patients it is still unclear whether the combination of radiation therapy with systemic corticoids result in a better clinical outcome than the use of radiation therapy alone.

## Conclusions

Our conclusions are those following the German national survey [10]. We strongly recommend a review of national patterns of care for treatment of benign and malignant disease on a regular basis and implementation of a quality assurance programme on both national and international levels. Prospective and technical and clinical trials should be performed to improve the applied radiotherapy techniques and the long-term outcome in thyroid associated orbitopathy (TAO). Patients who have been treated with ionising radiation.

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