NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of retrobulbar irradiation for thyroid eye disease

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

- This overview was prepared in April 2005.

Procedure name

- Orbital radiotherapy for thyroid eye disease.
- Low dose orbital radiation for thyroid eye disease.
- Orbital radiotherapy for dysthyroid eye disease.
- Orbital radiotherapy for Graves' ophthalmopathy

Specialty societies

- Royal College of Radiologists.
- British Oculoplastic Surgery Society.

Description

Indications

Thyroid eye disease (also known as dysthyroid eye disease, Graves' eye disease, Graves' ophthalmopathy, or thyroid orbitopathy) is a disease that predominantly affects the extraocular muscles. It affects an estimated 400 000 people in the UK assuming a 37.5 % prevalence of thyroid eye disease in Graves' disease (1). It is the most common cause of unilateral or bilateral proptosis (prominent or staring eyes) in adults, due to enlarged eye muscles and an increase in the fatty tissue behind the eyes.

Other symptoms include diplopia (double vision), soreness and grittiness of the eyes with increased watering, and photophobia. In more severe cases the lids may not close properly which can result in corneal exposure and ulceration. In addition the increased orbital tissue may cause optic nerve compression with resultant damage to the sight.

Current treatment and alternatives

Many of the symptoms related to thyroid eye disease can be treated quite easily. For feeling of dryness in the eyes 'artificial tears' preparations can be used as often as needed. With respect to the appearance of bulging or protruding eyes, tinted glasses may be all that is needed in the majority of cases but surgery is sometimes used to improve the appearance in severe cases. If double vision is present, the addition of corporation of prisms onto spectacle lenses may be used, and in severe cases surgery to the ocular muscles may be required.

Steroid medication is the most commonly used treatment for thyroid eye disease. These work by decreasing the inflammation in the eye muscles and orbital tissue. Often, high dose systemic corticosteroids are required but these have significant side effects. Recurrence of active eye disease after treatment requires other therapeutic options being considered

Surgical orbital decompression is an important method of relieving severe pressure on the optic nerve, which threatens vision, and may also be used. Various surgical procedures are used to make room in the eye socket for the swollen and thickened orbital tissue. This allows the bulging eye to relax back to its normal position.

Radiation therapy targeted at the tissue behind the eyeball aims to decrease orbital inflammation. Orbital radiotherapy may be used alone or in combination with steroids.

What the procedure involves

Patients are commonly treated on an outpatient basis. The patient is placed in a supine position, and the head fixed with a full head shell. Irradiation is given with photons generated by a linear accelerator targeted at the retobulbar content of the orbit, and the full dose delivered in about 10 fractions over a two week period.

Efficacy

A randomised controlled trial of radiotherapy versus sham therapy in 88 patients with mild, untreated, Graves' ophthalmopathy found a greater response rate with the active therapy, using a composite outcomes measure of eye function and physical properties (relative risk [RR] 1.9; 95% confidence interval [CI] 1.1 to 3.4; $p = 0.02$). Radiotherapy also improved diplopia score compared with sham irradiation, a difference of -0.3 (95% CI -0.1 to -0.5; $p < 0.05$) at 12 months.

In another randomised controlled study of 60 patients with moderately severe Graves' ophthalmopathy, a successful treatment outcomes was achieved more often with radiotherapy than with sham treatment (RR 1.9; 95% CI 1.0 to 3.6; $p = 0.04$). Improvement in eye motility was achieved in 82% (14/17) of patients following radiotherapy and in 27% (4/15) of sham therapy patients ($p = 0.004$). At 24 weeks eye elevation was improved by 4.9° more in radiotherapy treated patients ($p = 0.01$). There were no significant differences in proptosis or eyelid swelling between the study arms.

Where radiotherapy and prednisolone were compared in a randomised controlled trial there were no significant differences between the treatment arms in eye function as measured by NOSPECS class, proptosis, visual acuity or lid aperture size. Similarly, self-reported eye-evaluation scores were similar between the two groups at 24 weeks.

A randomised cross-over trial of 42 patients with either left or right eye treated first found no significant differences between eyes treated with radiotherapy and those

receiving sham treatment in outcomes of muscle volume, and proptosis at 3 months following treatment.

Safety

Two case series with long-term follow-up of 7.2 and 11 years recorded the incidence of cataracts to be between 10% (21/204) and 12% (22/197), and retinopathy to occur in 1% (2/197 and 2/204) of cases. One series found tumours in 5% (10/197) of patients treated with radiotherapy, but none of these were located within the area treated. Another case series found no incidence of secondary tumour in the head or neck following up 204 patients for 11 years. However, mucosal thickening or polyps in the paranasal tissue was recorded in 34% (53/157) of patients by CT scans.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to orbital radiation therapy. Searches were conducted via the following databases, covering the period from their from commencement to 05/04/2005 MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and Science Citation Index. Trial registries and the Internet were also searched. No language restriction was applied to the searches.

The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	People with thyroid eye disease.
Intervention/test	Orbital radiation therapy with or without corticosteroid therapy.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on four randomised controlled trials (three comparing radiotherapy with sham treatment and one with steroid therapy) and two case series

Existing reviews on this procedure

No existing systematic reviews or evidence-based guidelines were found on the topic of radiotherapy for thyroid eye disease during the electronic literature search.

Table 1 Summary of key efficacy and safety findings on irradiation in thyroid eye disease

Abbreviations used: GO – Graves' ophthalmopathy, TSI – thyroid-stimulating immunoglobulin, CI – confidence interval, SD – standard deviation

Study details	Key efficacy findings	Key safety findings	Comments

Abbreviations used: GO – Graves' ophthalmopathy, TSI – thyroid-stimulating immunoglobulin, CI – confidence interval, SD – standard deviation

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Prummel M F (2004) (3)

Randomised controlled trial

Holland

n = 88 (44 radiation therapy 44 sham therapy)

Patients with untreated mild GO who were euthyroid for a minimum 2 months. Diagnosis by typical signs and symptoms, and CT scan

Age = 45 years
Male = 20%
Duration of hyperthyroidism = 2 years
Duration of GO = 16 months

Radiotherapy administered with a 5-meV accelerator in 10 fractions of 2 Gy over 2 weeks

Follow-up by the same ophthalmologist at 3, 6 and 12 months.</td>
<td>Primary outcome measure of treatment success
12 month outcome was assessed against the following criteria

<u>Major</u>
Change of 8 degrees or more in monocular duction
Change in one or more grade in diplopia score
Change in visual acuity of 1 or more lines on Snellen chart
<u>Minor</u>
Change of 2 mm or more in proptosis
Change of 2 mm or more in lid aperture
Change of 1 or more grades in soft tissue involvement

Very good response — improvement in two major
Good response — improvement in one major
Fair response — improvement in two minor
No change — no change or one minor
Worse — deterioration in one major or two minor

Response rate in the radiotherapy arm was 52% (23/44) and in the sham arm it was 27% (12/44). Relative risk 1.9 (95% CI 1.1 to 3.4) (p = 0.02)

<table>
<tr><th>Response</th><th>Sham therapy (n=44)</th><th>Radiotherapy (n=44)</th></tr>
<tr><td>Very good</td><td>1</td><td>12</td></tr>
<tr><td>Good</td><td>7</td><td>8</td></tr>
<tr><td>Fair</td><td>4</td><td>3</td></tr>
<tr><td>No changes</td><td>25</td><td>15</td></tr>
<tr><td>Worse</td><td>7</td><td>6</td></tr>
</table>

The rate of worsening was similar in each arm

Clinical variables
The range of motion at 12 months over baseline increased more in the radiotherapy group 552 mm^2 (SD 787) than in the sham therapy group 171 mm^2 (SD 956), a difference of 370 mm^2 (95% CI 1 to 739) ($p < 0.05$)

Diplopia score was reduced further in the radiotherapy group -0.4 (SD 0.6) than in the sham therapy group -0.1 (SD 0.4), difference -0.3 (95% CI -0.1 to -0.5) ($p < 0.05$)</td>
<td>None presented</td>
<td>Block randomisation, using coded sealed envelopes for allocation to intervention therapy or sham. Patients and outcome assessors blind to allocation.

There were no significant differences in patient demographics, thyroid function, or GO severity between the groups at baseline.

Two patients withdrew from the study (one from each arm) and the 'last value carried forward' principle is used for these patients.

Assessment of function of extraocular eye muscles may be more relevant to the patient than changes in volumes of orbital tissue.</td>
</tr>
</table>

Abbreviations used: GO – Graves' ophthalmopathy, TSI – thyroid-stimulating immunoglobulin, CI – confidence interval, SD – standard deviation

Study details	Key efficacy findings	Key safety findings	Comments
Prummel M F (2004) cont.	**Quality of life** All patients completed the disease specific Graves ophthalmopathy quality of life questionnaire This outcome was not assessed in 42% of the patients and at 12 months showed no differences between the two groups **Further treatment** In the radiotherapy group 34% (15/44) of patients required no further therapy compared with 16% (7/44) of patients in the sham therapy group (p = 0.049) **Subgroup analysis of outcomes** Among patients who had eye disease for less than 18 months there was a successful therapeutic outcome in 58% (15/26) of irradiated patients and 20% (5/25) successful outcome in sham treated patients. Relative risk 2.9 (95% CI 1.2 to 6.8) (p = 0.01)		

Abbreviations used: GO – Graves' ophthalmopathy, TSI – thyroid-stimulating immunoglobulin, CI – confidence interval, SD – standard deviation

Study details	Key efficacy findings	Key safety findings	Comments
Mourtis M P (2000) (4) Randomised controlled trial Holland n = 60 (30 radiation therapy 30 sham therapy) Patients with moderately severe Graves' orbitopathy, based on clinical features and CT scan of intraorbital fat. All patients had not been treated for their orbitopathy except for local measures. Excluded: patients with mild eye disease or symptoms of optic nerve compression Age = 49 years Male = 15% Duration of orbitopathy = 14 months Proptosis = 20 mm Subjective eye score = 4.3 (1-10 scale, 10 best) Radiotherapy administered with a 6 MV photon beam, dose of 20 Gy in 10 fractions over 12 days Follow-up to 24 weeks	**Primary outcome measure of treatment success** 24 week outcome was assessed against the following criteria <u>Major</u> Change of 8 degrees or more in eye movement Improvement in diplopia grade, no diplopia, diplopia in extreme gaze only, or improvement in diplopia in all directions <u>Minor</u> Change of 2 mm or more in Hertel readings Change of 2 mm or more in lid aperture Change in eyelid swelling Successful response – improvement in one major or two minor No success – no change There was a successful treatment outcome in 60% (18/30) of irradiated patients and 31% (9/29) of patients in the sham arm. Relative risk 1.9 (95% CI 1.0 to 3.6) (p = 0.04) **Quantitative evaluation** Motility was improved in 82% (14/17) of patients recievign radiotherapy compared to 27% (4/15) of those in the sham arm. Relative risk 3.1 (95% CI 1.3 to 7.4) (p = 0.004) There was a 4.9 degree difference in eye elevation in favour of the radiotherapy group (95% CI 1.1 to 8.7) (p = 0.010) at 24 weeks follow-up. There were no significant differences in outcomes for proptosis, or eyelid swelling at 24 weeks **Subjective eye evaluation** There was no significant difference in self-reported eye score between the two groups at 24 weeks. **Further treatment** There was no significant difference between the radiotherapy and sham groups in the number of additional treatments required following the trial	**Adverse events** There were no serious side effects associated with treatment Transient redness of skin 10% (3/30) Transient local hair loss 7% (2/30)	Sham-controlled double-blind trial with randomisation at an external office. No details of concealment given. There were no differences in characteristics of the groups at baseline. 34% (31/91) of suitable patients refused to participate, these had similar characteristics at baseline. One patient from the radiotherapy arm withdrew at week 12 and last result was carried forward, one patient in the sham group withdrew before therapy and was excluded. Sham irradiation dose undetectable above background level.

Abbreviations used: GO – Graves' ophthalmopathy, TSI – thyroid-stimulating immunoglobulin, CI – confidence interval, SD – standard deviation

Study details	Key efficacy findings	Key safety findings	Comments
Prummel M F (1993) (5) Randomised controlled trial Holland n = 56 (28 radiotherapy, 28 prednisolone) Patients with moderately severe GO based on clinical features and CT scan of extraocular eye muscles, who had no previous treatment for ophthalmopathy Age = 47 years Male = 16% Duration of eye disease = 14 months Duration of thyroid disease = 19.5 months Subjective eye score = 5.2 (1-10 scale, 10 best) Radiation therapy administered by 5 meV linear accelerator, dose 20 Gy in 10 fractions over 2 weeks Prednisone given at 60 mg for 2 weeks, 40 mg for 2 weeks, 30 mg for 4 weeks, 20 mg for 4 weeks, then tapered by 2.5 mg per week Follow up 12 months	**Primary treatment outcome** At 24 weeks there was a similar change in the highest NOSPECS class (a 7 factor scale from 0 = no signs or symptoms to 6 = sight loss, with increments within each factor) with 50% (14/28) of the prednisone treated patients and 46% (13/29) of the radiotherapy group responding successfully Treatment was classified as having failed in 14% (4/28) of patients in both groups **Quantitative evaluation** There were no significant differences between the groups in outcomes relating to proptosis, eye muscle score, visual acuity, elevation, or lid aperture size **Subjective eye evaluation** There was no significant difference in self-reported eye score between the two groups at 24 weeks **Further treatment** Following the completion of the study 25% (7/28) of irradiated patients and 21% (6/28) of the prednisone group required no further therapy or had minor lid surgery only	**Treatment side effects** There was a significant increase in mean body weight in the prednisone group from a mean 71kg (95% CI 67 to 75) at baseline to 73 kg (95% CI 68 to 78) at 24 weeks (p = 0.002) In total major, moderate, and minor side effects were more common in the prednisone group than the radiotherapy group (p < 0.001) Event / steroids / radiotherapy **Major** Severe depression: 4% (1/28) / 0% Herpes zoster: 4% (1/28) / 0% **Moderate** / steroids / radiotherapy hypertension: 7% (2/28) / 0% Severe pyrosis: 18% (5/28) / 7% (2/28) Hirsutism: 7% (2/28) / 0% Behavioural change: 11% (3/28) / 0% Weight gain > 2 kg: 43% (12/28) / 11% (3/28) Cushingoid face: 50% (14/28) / 0% **Minor** Transient hair loss: 0% / 14% (4/28) Transient increase in soft tissue involvement: 7% (2/28) / 14% (4/28)	Randomisation by list (not fully described). Double blinded with sham radiotherapy or placebo capsules. There were no differences in thyroid function or severity of eye disease between groups at baseline. Single assessor carried out all baseline assessment. Trial powered to detect 25% difference in therapeutic outcome. Minimal difference in compliance between steroid and placebo groups.

Abbreviations used: GO – Graves' ophthalmopathy, TSI – thyroid-stimulating immunoglobulin, CI – confidence interval, SD – standard deviation

Study details	Key efficacy findings	Key safety findings	Comments
Gorman C A (2001) (2) Randomised controlled crossover trial USA n = 42 (84 eyes) Patients with mild to moderate ophthalmopathy with positive TSI levels who were euthyroid with or without replacement therapy Excluded: patients who had received systemic steroids in previous 2 weeks, had previous head or neck external beam radiotherapy, or were diabetic Age = 48 years Male = 14% Time from eye symptom onset to study entry = 1.3 years Diagnosis of hyperthyroidism to study entry = 2.8 years Radiation therapy by 6-MV photons, delivering 20 Gy in 10 fractions over 12 days Follow-up = 6 months after each phase of crossover trial Standardised clinical assessment of the eye were made at baseline and follow-up, and quantitative assessment of muscle and fat volume in the retrobulbar space made by CT scans	**Eye function and quantitative assessment** There were no clinically or statistically significant differences between outcomes for treated and untreated eyes at 3 or 6 months The mean difference in fat and muscle volume from baseline to 6 months was -0.1 ml (SD 1.0) for untreated eyes and 10.3 ml (SD 1.1) for treated eyes (p = 0.10) The mean change in proptosis from baseline to 6 months was 0.0 mm (SD 1.0) for untreated eyes, and -0.1 mm (SD 1.3) for treated eyes (p = 0.46) The mean change in lid fissures from baseline to 6 months was 0.0 mm (SD 2.0) for untreated eyes and -0.1 mm (SD 1.7) for treated eyes (p = 0.42) **Diplopia fields** There was a slight reduction in area of diplopia from baseline to 12 months in treated eyes, mean 10cm^2 (SD 27) (p = 0.02). However, there was no control for this outcome in untreated eyes and the effect may be due to spontaneous remission **Qualitative assessment of eye appearance** Six independent reviewers studied side-by-side photographs of the treated and untreated eyes, but could not identify the treated eye any more regularly than would be expected by chance alone **Subgroup analysis of outcomes** There were no statistically significant differences in outcomes for patients when analysed for clinical activity, length of eye symptoms, or previous treatment with corticosteroids	**Spill over radiation** The maximum dose of radiation in the untreated orbit was approximately 2 Gy **Further surgery** Following the end of the study protocol 12% (5/42) of the patients underwent orbital decompression for proptosis or soft tissue congestion, 19% (8/42) of patients had extraocular muscle surgery for diplopia, and 38% (16/42) of patient underwent eyelid surgery for retraction or lagophthalmos	Cross-over design on first and second treated orbit allowed for comparison of active or sham radiation therapy while the hormonal and immunologic status of the patient remained constant. For sham treatment the jaws of the linear accelerator were closed. The first orbit to be treated was selected by computer generated random numbers. There was a statistically higher average muscle volume and proptosis in the orbits treated first, but the difference was not considered clinically significant. Three patients broke protocol, all available data included in outcome assessments. All outcomes were evaluated by assessors unaware of which orbit had been treated. Thyroid hormone levels adjusted to maintain a euthyroid state throughout the study. Too few patients treated within 6 months of symptom onset to assess efficacy in early cases.

Abbreviations used: GO – Graves' ophthalmopathy, TSI – thyroid-stimulating immunoglobulin, CI – confidence interval, SD – standard deviation

Study details	Key efficacy findings	Key safety findings	Comments
Marquez S D (2001) (6) Case series USA n = 197 Patients treated for Graves' ophthalmopathy Age = 53 years (median) Male = 28% 20 or 30 Gy delivered by a 4-6 MV linear accelerator in 2 Gy fractions 5 days a week Follow-up 7.2 years (mean)	**Ophthalmic index** The SPECS scoring system was used, with assessment of five clinical parameters; soft tissue findings, proptosis, extraocular muscle dysfunction, corneal abnormalities, and sight. Each scored from 1 to 3 with a total of 15 points (low scores better). Treatment failure was defined as a increase in SPECS score, and response as scores decreasing or remaining stable The mean ophthalmic index improved from 5.4 before treatment to 2.0 following irradiation ($p < 0.00001$) 19% (35/188) of patients achieved a complete response at final follow-up point There was significant improvement in all factors in the composite SPECS outcome Subgroup analysis found that baseline SPECS score was a predictor of response to radiotherapy **Patient satisfaction** 84% (150/178) patients reported a subjective improvement in symptoms at 1 year following radiotherapy, 14% (25/178) were stable , and 2% (3/178) were symptomatically worse.	**Complications following irradiation** Cataracts 12% (22/197) Tumours 5% (10/197) (none within the treated field) Retinopathy 1% (2/197) (20 and 10 years following treatment) **Subsequent interventions** 33% (65/197) of patients underwent further surgery following radiotherapy 16% (≈32/197) of patients required surgery to preserve vision or correct diplopia	Consecutive prospective series. 33% (65/197) had previously had radiotherapy. 15% (30/197) of patients received corticosteroids during study period. Authors state that final response to radiation therapy may take longer to plateau than they had expected. Retrospective study might be following up patients treated with outdated equipment.

Abbreviations used: GO – Graves' ophthalmopathy, TSI – thyroid-stimulating immunoglobulin, CI – confidence interval, SD – standard deviation

Study details	Key efficacy findings	Key safety findings	Comments
Marcocci C (2003) (7) Case series (historical cohort study) Italy n = 204 Patients treated between 1972 and 1996 Median age (at irradiation) = 47 years Male = 25% 20 Gy delivered in 10 fractions over 2 weeks. Generated by a cobalt unit (CU) from '72 to '85, and with a linear accelerator (LA) from '86 to '96. Follow-up with complete medical history, physical examination, and ophthalmologist assessment (blind) in all cases. 157 patients (77%) had CT scan of the orbit, and results compared with 86 patients with GO who were yet to receive radiotherapy Median follow-up 11 years	None reported	**Cataract** All cataracts 10% (21/204) Mature cataract 5% (10/204) There was no significant difference in the prevalence of cataract in patients treated with CU or LA **Retinopathy** Retinal changes 7% (15/204) Minimal signs of hypertensive retinopathy 6% (13/204) Retinopathy 1% (2/204) (both patients had hypertension, and one diabetes mellitus also) **CT scan assessment** Secondary tumour in head or neck region 0% (0/157) Mucosal thickening or polyps of paranasal tissue 34% (53/157) The prevalence of these changes was significantly higher in 157 radiotherapy treated patients than 86 controls with GO (p = 0.02)	Retrospective study might be following up patients treated with outdated equipment. 34% (106/310) of study sample are yet to reach the minimum 5-year follow-up and outcomes not presented. Authors state that preliminary assessment suggests similar frequency of cataract and retinopathy to the 204 cases reported here. The median age at time of therapy was not statistically different but the CU patients were significantly older at follow-up than LA patients (p = 0.005) due to this modality being used first.

Validity and generalisability of the studies

- Natural history of the condition means that patients at different stages of their disease may derive different benefit from therapy.
- Spontaneous recovery without treatment makes outcome assessment difficult.
- There is considerable variation in evaluation of outcomes – looking at different efficacy parameters.

Specialist advisors' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

- Two advisors questioned whether irradiation should be used alone or with steroids.
- All advisors suggested that the procedure is established but there remain concerns regarding efficacy and long term safety.
- Theoretical adverse events include short terms exacerbation of thyroid eye disease, dry eyes, cataracts, retinopathy (particularly in diabetic patients), and late carcinogenesis.
- Patients should be selected in conjunction with a consultant ophthalmologist, and treated in a radiotherapy unit.
- There are only a limited number of suitable cases treated each year for this disease and will only probably be used in a minority of UK hospitals.

Issues for consideration by IPAC

- This is a long-established procedure notified because of concerns regarding safety.
- There is a natural course for symptoms to improve in Graves disease which makes evaluation of efficacy outcomes difficult
- Radiation therapy may be considered as an alternative or an adjunct to systemic steroid therapy.
- The timing of therapy following onset of symptoms may affect efficacy.
- Patient selection for therapy in terms of disease severity needs to be established.

References

(1) Cawood T, Moriarty P, O'Shea D. Recent developments in thyroid eye disease. BMJ 2004; 329(7462):385-390.

(2) Gorman CA, Garrity JA, Fatourechi V, Bahn RS, Petersen IA, Stafford SL et al. A prospective, randomized, double-blind, placebo-controlled study of orbital radiotherapy for Graves' ophthalmopathy. Ophthalmology 2001; 108(9):1523-1534.

(3) Prummel MF, Terwee CB, Gerding MN, Baldeschi L, Mourits MP, Blank L et al. A randomized controlled trial of orbital radiotherapy versus sham irradiation in patients with mild Graves' ophthalmopathy.[see comment]. Journal of Clinical Endocrinology & Metabolism 2004; 89(1):15-20.

(4) Mourits MP, Kempen-Harteveld ML, Garcia MB, Koppeschaar HP, Tick L, Terwee CB. Radiotherapy for Graves' orbitopathy: randomised placebo-controlled study. Lancet 2000; 355(9214):1505-1509.

(5) Prummel MF, Mourits MP, Blank L, Berghout A, Koornneef L, Wiersinga WM. Randomized double-blind trial of prednisone versus radiotherapy in Graves' ophthalmopathy.[see comment]. Lancet 1993; 342(8877):949-954.

(6) Marquez SD, Lum BL, McDougall IR, Katkuri S, Levin PS, MacManus M et al. Long-term results of irradiation for patients with progressive Graves' ophthalmopathy. International Journal of Radiation Oncology, Biology, Physics 2001; 51(3):766-774.

(7) Marcocci C, Bartalena L, Rocchi R, Marino M, Menconi F, Morabito E et al. Long-term safety of orbital radiotherapy for Graves' ophthalmopathy. Journal of Clinical Endocrinology & Metabolism 2003; 88(8):3561-3566.

Appendix A Additional papers on selective international radiation therapy not included in the summary tables

Article title	Number of patients/follow-up	Comments	Direction of conclusions
Abalkhail S, Doi SAR, Al Shoumer KAS. The use of corticosteroids versus other treatments for Graves' ophthalmopathy: A quantitative evaluation. Medical Science Monitor 2003; 9(11).	Total of 813 patients from 14 studies. Follow up varied between studies	Results only summarised as 'better' or 'worse'	Combination radiotherapy and steroids better than oral corticosteroids alone in treating graves ophthalmopathy
Akmansu M, Dirican B, Bora H, Gurel O. The risk of radiation-induced carcinogenesis after external beam radiotherapy of Graves' orbitopathy. Ophthalmic Research 2003; 35(3):150-153.	The number of cases and length of follow up are not stated	No relevant clinical outcomes are reported	There is a 0.7& risk of developing fatal radiation induced cancer
Bartalena L, Marcocci C, Chiovato L, Laddaga M, Lepri G, Andreani D et al. Orbital cobalt irradiation combined with systemic corticosteroids for Graves' ophthalmopathy: comparison with systemic corticosteroids alone. Journal of Clinical Endocrinology & Metabolism 1983; 56(6):1139-1144.	n=12 cases follow up = 18 months	A controlled study without randomisation	Combination radiotherapy and steroids better than corticosteroids alone
Gerling J, Kommerell G, Henne K, Laubenberger J, Schulte-Monting J, Fells P. Retrobulbar irradiation for thyroid-associated orbitopathy: double-blind comparison between 2.4 and 16 Gy. International Journal of Radiation Oncology, Biology, Physics 2003; 55(1):182-189.	n=86 cases Follow up = 6 months	A dose comparison study.	No difference found between 2.4 Gy and 16 Gy dose. Both may be ineffective
Gorman CA, Garrity JA, Fatourechi V, Bahn RS, Petersen IA, Stafford SL et al. The aftermath of orbital radiotherapy for graves' ophthalmopathy. Ophthalmology 2002; 109(11):2100-2107.	n=42 Follow up = 3 years	A small case series. Larger series with longer follow up are included in table 1	Limited evidence for a clinically significant improvement following radiotherapy which may be due to treatment or natural progression
Kahaly GJ, Rosler H-P, Pitz S, Hommel G. Low- versus high-dose radiotherapy for Graves' ophthalmopathy: A randomized, single blind trial. Journal of Clinical Endocrinology & Metabolism 2000; 85(1).	n=65 Follow up = 24 weeks	A dose comparison study.	In patients with moderately severe GO there were similar response rates for low and high doses, but the 1 GY / week protocol was better tolerated than daily regimens
Ohtsuka K, Sato A, Kawaguchi S, Hashimoto M, Suzuki Y. Effect of steroid pulse therapy with and without orbital radiotherapy on Graves' ophthalmopathy. American Journal of Ophthalmology 2003; 135(3):285-290.	n=39 (20 radiotherapy arm) Follow up = 6 months	A controlled study without randomisation	Irradiation therapy had no therapeutic effect on muscle hypertrophy or proptosis
Wakelkamp IM, Tan H, Saeed P, Schlingemann RO, Verbraak FD, Blank LE et al. Orbital irradiation for Graves' ophthalmopathy: Is it safe? A long-term follow-up study. Ophthalmology 111(8):1557-62, 2004.	n=157 Follow up = 11years	A case series. Larger series are included in table 1	Radiotherapy is a safe treatment for GO except possibly for diabetic patients

Appendix B Literature search for orbital radiotherapy for thyroid eye disease

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in EMBASE, Current Contents, PredMedline and all EMB databases.

For all other databases a simple search strategy using the key words in the title was employed.

#	Search History	Results	Display
1	exp RADIOTHERAPY/	75161	Display
2	exp Graves' Disease/	10064	Display
3	exp ORBIT/re, ra [Radiation Effects, Radiography]	1516	Display
4	2 and 3	142	Display
5	1 and 4	22	Display
6	(retrobulbar adj2 irradiation).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]	39	Display
7	(orbit$ adj2 radio$).ti.	117	Display
8	7 not lymphoma$.mp.	103	Display
9	limit 8 to yr=1996 - 2005	36	Display
10	5 or 6 or 9	89	Display