0021-972X/04/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 89(1):15–20

doi: 10.1210/jc.2003-030809

A Randomized Controlled Trial of Orbital Radiotherapy *Versus* Sham Irradiation in Patients with Mild Graves' Ophthalmopathy

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Radiotherapy is often used in Graves' ophthalmopathy, but its efficacy has been doubted. We compared its efficacy with sham irradiation in mild ophthalmopathy. In a double-blind randomized trial, 44 patients received orbital irradiation, and 44 were sham-irradiated. The primary outcome was assessed using major and minor criteria. As secondary outcome, we used a disease-specific quality of life questionnaire (the GO-QoL) and compared cost-effectiveness and need for follow-up treatment. The primary outcome was successful in 23 of 44 (52%) irradiated patients *vs.* 12 of 44 (27%) sham-irradiated patients at 12 months after treatment (relative risk, 1.9; 95% confidence interval, 1.1–3.4; $P = 0.02$). Radiotherapy was effective in improving eye muscle motility and decreasing the severity of diplopia. However, quality of life improved similarly in both groups. In the radiotherapy group there was less need for follow-up treatment; 66% *vs.* 84% of the patients needed further treatment ($P = 0.049$). Retrobulbar irradiation did not prevent worsening of ophthalmopathy, which occurred in 14% of the irradiated and 16% of the sham-irradiated patients. Radiotherapy is an effective treatment in mild ophthalmopathy. However, the improvement upon irradiation may not be associated with an increase in quality of life or a reduction in treatment costs. (*J Clin Endocrinol Metab* 89: 15–20, 2004)

ORBITAL IRRADIATION IS a frequently used treatment modality in patients with Graves' ophthalmopathy (GO) (1, 2). Its mode of action is not entirely clear, but apart from having a nonspecific antiinflammatory effect, irradiation probably affects the radiosensitive lymphocytes and fibroblasts in the orbital tissues (3). It is mainly used in patients with moderate to severe GO, either alone or in combination with corticosteroids (4). Previous randomized clinical trials have shown that orbital irradiation is equally effective as oral prednisone, (5) and that the combination of these treatment modalities is more effective than either treatment alone (6, 7). Combining the results of all available studies, an overall response rate of 59% was found, with favorable effects mainly on soft tissue signs, motility disorders, and optic neuropathy (3).

Recently, two placebo-controlled trials have been published with conflicting results. Mourits *et al.* (8) irradiated 30 patients with moderately severe GO and found a positive response rate of 60%, significantly more than the 31% response rate seen in the sham-irradiated patients. Gorman *et al.* (9) irradiated only 1 orbit in 42 patients with mild to moderate GO and used the other orbit as an internal control. They could not find any significant difference between the treated and untreated orbits at 6 months after the start of therapy. Since the publication of this last paper, a sometimes heated debate has started on the efficacy of radiotherapy for this thyroid-related eye disease (10–19).

We have performed a double-blind, randomized, clinical trial comparing radiotherapy and sham irradiation in 88 patients with mild and previously untreated GO. In contrast to the above-mentioned studies, we selected patients with mild eye disease to determine whether radiotherapy is a better option than the "wait and see" policy that is usually adopted in these patients (20). Outcome was assessed not only by changes in clinical measurements, but also using a validated disease-specific quality of life questionnaire (21, 22), as advocated by an ad hoc committee of the sister thyroid associations (23). In addition, a cost-effectiveness analysis was performed.

Patients and Methods

Patients

We included consecutive patients seen at the Academic Medical Center in Amsterdam or at the University Medical Center Utrecht with untreated mild GO, aged 18–75 yr, who had been euthyroid for at least 2 months, as indicated by normal values for plasma free T_4 (0.78–1.71 ng/dl; 10.0–22.0 pmol/liter) and T_3 (85–160 ng/dl; 1.30–2.45 nmol/liter) in the absence of an elevated plasma TSH level (0.4–4.0 μU/ml). Suppressed TSH values (in the presence of normal free T_4 and T_3 levels) were accepted, because this is frequently seen during treatment of Graves' hyperthyroidism and is probably an effect of TSH receptor-stimulating immunoglobulins binding to the pituitary TSH receptor (24). Most patients (n = 58) were taking antithyroid drugs with or without T_4, 21 received T_4 supplementation after thyroid surgery or radioactive iodine

Abbreviations: CI, Confidence interval; GO, Graves' ophthalmopathy; GO-QOL, GO quality of life; MOS, Medical Outcomes Study; SIP, Sickness Impact Profile.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

(the latter was given >6 months before inclusion), 3 patients were euthyroid after radioiodine treatment, and in 6 there was no evidence of Graves' thyroid disease.

The diagnosis of GO was based on a combination of typical clinical signs and symptoms with enlarged extraocular eye muscles on a coronal computed tomography scan of the orbits. We wanted to include patients with mild ophthalmopathy and to use an objective criterion. Mild disease was defined as having a mild extraocular eye muscle motility disturbance (mostly elevation) using an age-specific nomogram (Fig. 1) derived from the references values for monoocular ductions (25) with or without mild or moderate eyelid swelling, as assessed clinically. At inclusion, eye lid swelling was assessed subjectively by the ophthalmologist, but for assessment of the therapeutic outcome, color slides were used (see below). Proptosis values of 24 mm or less were arbitrarily defined as mild ophthalmopathy.

All patients were untreated for their eye disease, except for local measures such as eye drops. We did not include patients with more severe GO, defined as having severe periorbital swelling (assessed clinically), proptosis of 25 mm or more, moderate or severe motility disturbances, or any sign of optic nerve involvement. Excluded were patients with contraindications for radiotherapy (mostly diabetes), with severe concomitant disease, or who did not give informed consent.

The study was approved by the medical ethics committees of the Academic Medical Center in Amsterdam and the University Medical Center Utrecht, and all patients gave their informed consent.

Treatment

Patients were treated on an out-patient basis. Randomization was performed by the radiotherapist (who was not involved in the outcome assessments) using coded sealed opaque envelopes containing the treatment allocation. Block randomization with blocks of four patients was used to ensure near-equal distribution of patients over the two groups. The patient as well as the treating ophthalmologist and endocrinologist were kept blind for the treatment allocation until after the final outcome assessments.

Retrobulbar radiotherapy was administered with a 5-meV linear accelerator in 10 divided fractions of 2 Gy daily over 2 wk. Localization and verification films with lead markers on the canthus of each eye were performed for each patient on a simulator. The dose was calculated at the midline and was given by two 3° anterior angled lateral portals of 5×5 cm, with the patient's head fixed with a full head shell. Patients allocated to sham irradiation underwent the same procedures, and the sound of the accelerator was simulated.

Clinical outcome assessment

All patients were examined by the same ophthalmologist before and at 3, 6, and 12 months after the start of therapy. At each visit the eye manifestations were assessed using the following measures. Eyelid aperture in millimeters was measured as the distance between the upper and lower eyelids in the midline with a ruler. Soft tissue involvement was assessed in grades (0–3) using standardized frontal and lateral color slides (26) by an independent observer who assessed all color slides in one session after completion of the trial. Proptosis was measured in millimeters using the same Hertel exophthalmometer. Monoocular eye muscle motility was measured in degrees using a modified hand perimeter in all four directions of gaze (25), and from these measurements a range of motion was calculated as the surface in square millimeters of the square made up by the ductions in the four directions of gaze (1° = 1 mm). Diplopia was assessed subjectively using in four grades: 1 = no diplopia, 2 = intermittent, 3 = inconstant, and 4 = constant diplopia (27). Pinhole visual acuity was assessed using the Snellen chart and was expressed as a decimal (*e.g.* 20/20 = 1.0; 20/30 = 0.67) (28). Because the orbits are not always equally affected, we chose to report these measurements in the most affected eye. Disease activity was assessed using the clinical activity score (29, 30). In addition, the treating ophthalmologist assessed the need for further treatment after completion of the study for each patient. Only data on the first additional therapy modality are given.

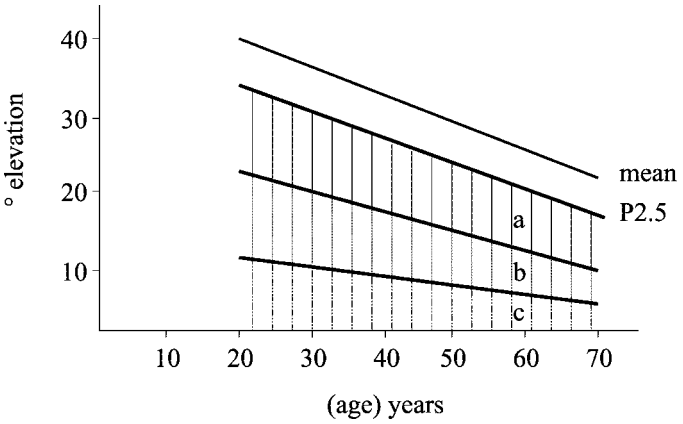

FIG. 1. Nomogram to assess severity of impairment of elevation in grades a–c, using age-dependent reference values obtained in 40 healthy subjects (25). P 2.5 represents the upper limit of normal; below this level three degrees (a = mild; b = moderate; c = severe) of progressively impaired elevation are denoted.

Treatment efficacy at 12-month follow-up was used as the primary outcome measure. As the definition of outcome we used major and minor criteria, slightly modified from others (8, 31). Major criteria were a change of 8° or more in monoocular duction in the most affected direction of gaze (mostly elevation), a change of one or more grades in the diplopia score, and a change in pinhole visual acuity of one or more lines on the Snellen chart. Minor criteria were a change of 2 mm or more in lid aperture, a change of 2 mm or more in proptosis, and a change of one or more grades in soft tissue involvement on the color slides. A response to treatment was defined as very good in the case of an improvement in at least two major criteria, as good in the case of an improvement in one major criterion, as fair in the case of an improvement in two minor criteria, as no change in the case of no changes or a change in only one minor criteria, and as worse in the case of a deterioration in at least one major or two minor criteria. The primary outcome thus was the difference between the groups in the percentage of patients with a favorable response at 12 months.

Quality of life assessment

At baseline and 12 months, the patients were asked to complete the disease-specific Graves' ophthalmopathy quality of life (GO-QOL) questionnaire, (21) that was specifically developed for this trial to be used as an outcome measure. It measures limitations in visual functioning as a consequence of diplopia and/or decreased visual acuity (eight questions) and limitations in psychosocial functioning as a consequence of a changed appearance (eight questions). Its validity, reproducibility, and longitudinal validity have been established in three external GO patient populations (22, 32). In addition, the patients completed four other health-related quality of life questionnaires: the Medical Outcomes Study Short-Form General Health Survey (MOS-24) (33, 34), three subscales from the Sickness Impact Profile (SIP subscales social interaction, household management, and leisure pastimes and recreation) (35), and the EuroQol 5D (36). All questionnaire subscales were transformed to 0–100 scales, with higher scores indicating better health.

Assessment of costs

Costs were calculated from a societal perspective as the number of resource units used multiplied by the cost per unit (37). All costs are given in euros. Costs were estimated for three categories of care: 1) the costs of radiotherapy and the preceding out-patient visits and diagnostic procedures; 2) the costs of care during the first year after radiotherapy, including out-patient visits, traveling costs, visits to the general practitioner, home care, and out of pocket costs (*e.g.* sunglasses and make-up); and 3) the costs of immunosuppressive treatment and surgeries received in the first year after the end of the trial. Costs during follow-up were estimated based on individual patient data about health care resources used obtained with a questionnaire that all patients included after the first 2 months of the study completed at each follow-up visit (four questionnaires in total). The number of immunosuppressive treatment and surgeries received in the first year after the end of the trial was retrieved from the medical records. Direct medical costs were estimated

as real costs using detailed information from the financial accounts of the Academic Medical Center in Amsterdam to allocate overhead costs to divisions, departments, and procedures. Costs of a computed tomography scan, traveling, visits to the general practitioner, and home care were based on guidelines of the Institute for Medical Technology Assessment in Rotterdam (38). Out of pocket costs were based on real costs reported by the patients.

Statistical analyses

A sample size of 44 patients in each group was estimated to be sufficient to detect a difference in percentage of response to treatment of 60% in the radiotherapy group *vs.* 30% in the sham irradiation group, with an α of 0.05 and a power of 74%. All data were analyzed according to the intention to treat principle. When a patient was prematurely withdrawn from the study, in the case of a decrease in visual acuity of two or more Snellen lines, an increase in proptosis of 3 mm or more, or a decrease in eye muscle motility of 10° or more, all outcomes measures were assessed at that time, and the patient was analyzed according to the last value carried forward principle.

The primary outcome was assessed using the relative risk. A relative risk with 95% confidence interval was calculated as the percentage of patients with a response to treatment in the radiotherapy group divided by the percentage of patients with a response to treatment in the sham irradiation group. Differences between the two groups in dichotomous data were expressed as relative risks with 95% confidence intervals. Differences in continuous data are expressed as mean differences with 95% confidence intervals. Dichotomous data were compared with use of the χ^2 statistic. Continuous data were expressed as the mean ± SD and compared using unpaired *t* test or Mann-Whitney *U* test in the case of not normally distributed data.

Results

Patients

We included 88 patients in the trial. Forty-four patients received radiotherapy, and 44 received sham irradiation. There were no significant differences in general patient characteristics, thyroid function, or GO severity between the 2 groups (Table 1).

All patients remained euthyroid during the study. One patient in each group was prematurely withdrawn from the study because of a severe decrease in visual acuity. Both were retained in the final analysis. The radiotherapy was well tolerated by the patients.

Treatment efficacy

In the radiotherapy group the response at 12 months after the start of treatment was 52% (23 of 44), compared with 27% (12 of 44) in the sham irradiation group [relative risk, 1.9; 95% confidence interval (CI), 1.1–3.4; $P = 0.02$; Table 2]. Essentially similar results were seen at 6 months. Worsening of the ophthalmopathy could not be prevented by radiotherapy, as the rate of worsening was similar in both groups. Significant differences after 12 months were found between the 2 groups for changes in eye muscle motility and diplopia (Table 3). The need for further treatment was lower in the radiotherapy group than in the sham-irradiated patients. In the radiotherapy patients, 15 of 44 needed no further therapy compared with 7 of 44 in the sham-irradiated group ($\chi^2 = 3.879$; $P = 0.049$; Table 4).

When we only considered patients with a duration of the eye disease of 18 months or less (taken from the history by the patients), a successful therapeutic outcome was observed in 15 of 26 (58%) irradiated and in 5 of 25 (20%) sham-irradiated patients (relative risk, 2.9; 95% CI, 1.2–6.8; $P = 0.01$). Smoking had no effect on the outcome of radiotherapy; the relative risk for response to treatment was 1.9 in both smokers (95% CI, 0.9–3.8) and nonsmokers (95% CI, 0.7–4.7).

TABLE 1. Baseline characteristics of patients in the radiotherapy group and the sham irradiation group

	Sham irradiation (n = 44)	Radiotherapy (n = 44)
Age (yr)[a]	45.1 (12.8)	45.2 (12.0)
Sex (F/M)	37/7	33/11
No. of smokers	22	25
Thyroid function		
Duration GH (months)[b]	26 (0–276)	21 (0–144)
Total T_3 (ng/dl)[a]	143 (54)	146 (45)
TSH (μU/ml)[b]	1.15 (<0.01–9.70)	0.21 (<0.01–8.70)
Free T_4 (ng/dl)[a]	1.24 (0.37)	1.27 (0.27)
TBII (U/liter)[b]	17 (<5–209)	27 (<5–400)
GO severity (worst eye)		
Duration GO (months)[b]	15 (5–156)	17 (5–144)
Lid aperture (mm)[a]	12.2 (2.1)	13.0 (2.0)
Soft tissue involvement[c] (none/mild/moderate/severe)	1/24/18/1	1/16/23/4
Proptosis (mm)[a]	20.1 (3.4)	20.7 (2.8)
EOM motility in degrees (mean eye)		
Adduction[a]	43.1 (5.9)	41.7 (5.4)
Abduction[a]	42.5 (7.6)	40.3 (7.2)
Elevation[a]	28.4 (6.3)	26.7 (7.6)
Depression[a]	52.7 (11.0)	49.0 (10.3)
Most affected duction (worst eye)[a]	27.1 (7.4)	26.2 (8.0)
Range of motion (mm^2)[a,d]	3553 (1070)	3174 (1020)
Diplopia (none/intermittent/inconstant/constant)	7/14/19/4	8/14/16/6
Clinical activity score[a]	3.3 (1.5)	3.0 (1.3)
GO-QoL visual functioning score	62.5 (23.1)	60.4 (23.2)
GO-QoL appearance score	53.0 (25.9)	53.2 (27.5)

GH, Graves hyperthyroidism; EOM, extraocular muscle. Normal values: free T_4, 0.78–1.71 ng/dl (conversion factor for Systeme International units, multiply by 12.87; T_3, 85–160 ng/dl (conversion factor for Systeme International units, multiply by 0.01536); TSH, 0.4–4.0 μU/ml. Upper normal limits: proptosis, 20 mm; lid aperture, 10 mm.

[a] Mean (SD).

[b] Median (range).

[c] Assessed using color slides.

[d] Calculated from the four ductions above (see text).

TABLE 2. Treatment efficacy after 12 months of follow-up in patients treated with radiotherapy and in sham-irradiated patients with mild GO

Response	Sham irradiation (n = 44)	%	Radiotherapy (n = 44)	%
Very good	1		12	
Good	7	27	8	52
Fair	4		3	
No change	25	59	15	34
Worse	7	16	6	14

By χ^2, $P = 0.02$.

Quality of life outcomes

Quality of life could not be assessed in the first 23 patients. In the remaining 65 patients, the response rate was 92% (60

TABLE 3. Mean (SD) changes in clinical variables (worst eye) between baseline and 12 months after treatment in patients treated with radiotherapy and in the sham-irradiated patients

	Sham irradiation (n = 44)	Radiotherapy (n = 44)	Difference (95% CI)
Lid aperture (mm)	−0.16 (1.5)	−0.70 (1.8)	−0.55 (−1.25 to 1.06)
Soft tissue involvement (none/mild/moderate/severe)[a]	3/21/17/2	3/12/26/3	
Proptosis (mm)	0 (1.5)	−0.6 (1.5)	−0.6 (−1.2 to 0.1)
EOM motility in degrees			
Adduction	2.1 (6.0)	1.6 (5.0)	0.5 (−1.8 to 2.9)
Abduction	1.3 (7.2)	2.2 (6.2)	0.8 (−2.1 to 3.7)
Elevation	1.2 (6.1)	2.5 (5.8)	1.3 (−1.2 to 3.9)
Depression	−0.2 (8.9)	5.8 (10.1)	6.1 (2.0 to 10.1)[b]
Most affected duction	2.4 (6.8)	5.5 (7.5)	3.0 (0.01 to 6.1)[b]
Range of motion (mm^2)	171 (956)	552 (787)	370 (1 to 739)[b]
Diplopia (none/intermittent/inconstant/constant)[a]	10/13/17/4	14/16/11/3	
Diplopia score[c]	−0.1 (0.4)	−0.4 (0.6)	−0.3 (−0.1 to −0.5)[b]
Clinical activity score	−1.19 (1.53)	−0.84 (1.15)	−0.3 (−0.2 to 0.9)

[a] Grades scored 12 months after start of treatment.
[b] $P < 0.05$.
[c] Mean of the four grades of diplopia.

TABLE 4. Additional treatment needed after completion of the study in patients treated with radiotherapy and in sham-irradiated patients

	Sham irradiation (n = 44)	%	Radiotherapy (n = 44)	%
No further treatment	7	16	15	34
Further immunosuppression	7		2	
Decompression	17		17	
Eye muscle surgery	3		1	
Lid surgery and/or blepharoplasty	10	84	9	66

χ^2, 3.879; $P = 0.049$.

of 65) at baseline and 85% (55 of 65) for the 12 month follow-up questionnaire. In total, 51 of 88 (58%; 26 in the radiotherapy group and 25 in the sham irradiation group) completed the baseline as well as the 12 month follow-up questionnaire. Because quality of life changes could not be assessed in 42% of the patients, this part of our study lacks sufficient power for statistical comparison between the 2 groups. At the 12 month follow-up, the changes on all quality of life subscales between the 2 treatment groups were similar (Table 5). The mean scores on the visual functioning subscale of the GO-QOL improved 8.2 points in the radiotherapy group compared with 10.5 points in the sham irradiation group. The mean scores on the appearance subscale of the GO-QOL improved 6.7 points in the radiotherapy group compared with 5.5 points in the sham irradiation group. Mean changes in MOS-24 subscales varied from −3.8 points for mental health in the sham irradiation group to 6.7 points for role functioning in the radiotherapy group. Mean changes in SIP subscales varied from 0.8 points for household management in the radiotherapy group to 7.4 points for leisure pastimes in the radiotherapy group. Mean changes in EuroQol rating scale were 1.2 points in the radiotherapy group and 3.2 points in the sham irradiation group.

Costs

Sixty-five patients were included in the assessments of health care use. The response rate varied from 69% (45 of 65) for the second follow-up questionnaire to 85% (55 of 65) for the last questionnaire. The total costs of radiotherapy were estimated to be 2779 euros/patient (Table 6). The total costs of health care, traveling, home care, and out of pocket costs during the first year of follow-up were similar in both groups: 2071 euros/patient in the sham irradiation group *vs.* 2088 euros/patient in the radiotherapy group (Table 6). The mean costs of treatments in the first year after the trial were slightly higher in the sham irradiation group than in the radiotherapy group (2394 *vs.* 1840 euros), leading to the total of 4465 euros in the sham irradiation group *vs.* 5007 euros in the radiotherapy group.

Discussion

Our results show that orbital radiotherapy is effective in patients with mild GO. In agreement with other prospective studies (5, 8), irradiation mainly improves eye muscle motility, resulting in less diplopia. Its effect on proptosis is insignificant, just as is the case with other forms of immunosuppression, such as corticosteroids (2). Apparently these treatment modalities have little effect on the total retrobulbar volume. Nevertheless, radiotherapy does improve the function of the extraocular muscles, presumably by killing the cells infiltrating these muscles. In this study we saw no beneficial effect on soft tissue involvement. On the other hand, 15 of 44 irradiated patients (34%) did not need further treatment of the eye disease compared with 7 of the 44 sham-irradiated patients (16%; $P = 0.049$).

This study thus supports the results of two other prospective, controlled studies in patients with more severe GO (5, 8), but is in disagreement with one further trial (9). One of the reasons for this discrepancy is the selection of patients in these studies. Whereas the three studies showing a beneficial effect of radiotherapy only included untreated GO patients, the study by Gorman *et al.* (9) also included 19 of 42 (45%) patients previously treated with corticosteroids. The other obvious difference is the randomization method. We and others used placebo-treated patients as controls, whereas in the study by Gorman *et al.* (9) only one orbit was irradiated, and the contralateral orbit was used as a control. This study design has been criticized because the contralateral orbit received a small radiation dose of up to 2 Gy (39), and lower

TABLE 5. Mean (SD) changes in quality of life subscales between baseline and 12 months after treatment

	Sham irradiation (n = 25)	Radiotherapy (n = 26)	Difference (95% CI)
GO-QOL visual functioning	10.5 (16.8)	8.2 (15.8)	−2.3 (−11.5 to 6.7)
GO-QOL appearance	5.5 (16.6)	6.7 (17.2)	1.2 (−8.4 to 10.7)
MOS-24 physical functioning	−1.4 (19.4)	−0.3 (11.2)	1.1 (−7.8 to 9.9)
MOS-24 role functioning	2.0 (20.3)	6.7 (18.1)	4.7 (−6.1 to 15.5)
MOS-24 social functioning	−3.2 (23.6)	−1.5 (23.9)	1.7 (−11.7 to 15.0)
MOS-24 mental health	−3.8 (17.1)	2.3 (19.1)	6.1 (−1.4 to 16.4)
MOS-24 general health perceptions	−3.4 (16.3)	0.2 (16.0)	3.6 (−5.5 to 12.7)
MOS-24 bodily pain	−1.0 (31.9)	−1.0 (32.8)	0.04 (−18.2 to 18.2)
MOS-24 vitality	−0.4 (17.4)	3.3 (13.3)	3.7 (−5.0 to 12.4)
SIP social interaction	1.2 (14.3)	3.5 (12.8)	2.4 (−5.3 to 10.0)
SIP household management	3.8 (19.3)	0.8 (12.4)	−3.1 (−12.2 to 6.0)
SIP leisure pastimes and recreation	5.0 (22.2)	7.4 (16.3)	2.4 (−8.6 to 13.4)
EuroQol rating scale	3.2 (14.3)	1.2 (14.5)	−2.0 (−11.9 to 7.9)

TABLE 6. Costs of radiotherapy and care during the first year after radiotherapy and costs of follow-up treatments

	Sham irradiation		Radiotherapy	
	Average resource use	Costs per patient	Average resource use	Costs per patient
Radiotherapy				
CT scan			1	145
Visit outpatient clinic			3	219
Radiotherapy			10 sessions	2415
Total				2779
Care during follow-up				
Visits outpatient clinic	14.8	1041	15.2	1070
Travel		95		98
General practitioner	2	32	2	32
Glasses and make-up		43		41
Home care (h)	37.7	860	37.1	847
Total		2071		2088
Treatments after trial				
Immunosuppression	7/44	442	2/44	1
Orbital decompression	17/44	1587	17/44	1587
Eye muscle surgery	3/44	138	1/44	46
Eyelid lengthening	10/44	227	9/44	206
Total (all patients)		2394		1840
Overall total		4465		5007

Costs (euros) of follow-up treatments per patient: radiotherapy, 2779; prednisone, 33; orbital decompression, 4.107; eye muscle surgery, 2.024; eyelid lengthening, 1.007. CT, Computed tomography.

doses of irradiation may also be effective (40). In addition, during the irradiation of one orbit, the lymphocytes from the other orbit may travel through the body and home in the irradiated orbit, where they are subsequently killed. A final difference concerns the method used to assess the therapeutic outcome. Whereas Gorman *et al.* (9) relied heavily on changes in the volumes of orbital tissues measured on computed tomography scan, we measured changes in the functionality of the eye muscles, which improved in both quantitative and qualitative (less diplopia) terms. Because no immunosuppressive therapies are known to reduce proptosis in a clinically significant manner (2), we believe that assessment of the function of the extraocular eye muscles is more relevant for the patient.

The results in the sham-irradiated group are remarkably in line with a study on the natural history of patients with mild GO (41). In that study with 1 yr of follow-up in 59 patients, an improvement was seen in 22% (we observed this in 27%), no change was seen in 62% (57% in our study), and worsening occurred in 14% (we saw this in 16%). Mourits *et al.* (8) also found an improvement of eye signs in sham-irradiated patients with moderate GO in 31% of patients. A rate of approximately 25% of spontaneous improvement thus seems a reliable figure to be used in sample size calculations of future clinical trials.

The aim of our study was to evaluate whether radiotherapy is a better option than a wait and see policy in patients with milder forms of GO. Although radiotherapy was effective in our study, it did not improve the quality of life of our patients, which improved equally in the treated and sham-irradiated patients. It is unlikely that this lack of effect is due to an insufficient power of this instrument, because the improvement in GO-QoL scores in both groups was between 5.5–10.5 points, whereas a change of 6 points has been found to be clinically relevant (32). Also, radiotherapy did not prevent worsening of the eye disease, which occurred in 7 sham-irradiated and 6 treated patients. Lastly, radiotherapy did not reduce the total costs of treatment in this study.

Radiotherapy is thus an effective form of treatment of mild GO, but in view of the apparent lack of effect on the patient's

quality of life or on total treatment costs, careful observation of patients is a good alternative strategy.

Acknowledgments

Received May 9, 2003. Accepted October 15, 2003.

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This work was supported by a grant from the Dutch Health Care Insurance Board (OG 94/038).

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