

Low- Versus High-Dose Radiotherapy for Graves' Ophthalmopathy: A Randomized, Single Blind Trial

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ABSTRACT

Orbital radiotherapy (Rx) is a commonly used treatment for Graves' ophthalmopathy (GO), but controlled clinical trials evaluating different Rx doses and application forms have not been performed. In euthyroid patients with moderately severe GO, we randomly compared the efficacy and tolerability of three Rx protocols. Orbital Rx (telecobalt) was administered either in 20 divided fractions of 1 Gy (Gy) weekly over 20 weeks (group A) or in 10 fractions of 1 Gy (B) and 2 Gy (C) daily over 2 weeks. Before and 24 weeks after starting Rx, ophthalmic investigation and magnetic resonance imaging were performed. Response to therapy, defined as a significant amelioration of three objective parameters, was noted in 12 A (67%), 13 B (59%), and 12 C (55%) subjects (*C vs. A*, $P = 0.007$). Ophthalmic symptoms and signs regressed most in group A; changes in lid fissure width were -1.5 , -0.5 , and 0 mm in the A, B, and C groups, respectively (*A vs. C*, $P = 0.005$), whereas changes in intraocular pressure (upgaze) were -3 , $+1$, and -1.5 mm Hg, respectively (*A vs. B*, $P = 0.002$). The

median decreases in proptosis were -2 mm (*A*, $P = 0.0001$), -1.5 mm (*B*, $P = 0.02$), and -1 mm (*C*, $P = 0.007$; *A vs. C*, $P = 0.0380$). Visual acuity ($+0.15$; $P = 0.02$) and eye muscle motility (bulbar elevation, 30° vs. 37° , $P = 0.03$, *A vs. C*, $P = 0.0020$; abduction, 45 vs. 49° , $P = 0.02$; *A vs. C*, $P = 0.017$) improved in group A only. A significant change in all rectus muscle areas was noted in 14 A (78%), 12 B (55%), and 9 C (41%) subjects (*C vs. A*, $P = 0.002$). A decrease in the NOSPECS classes was observed in 12 A (67%), 13 B (59%), and 13 C (59%) patients (*A vs. B/C*, $P = 0.01$). Rx-induced conjunctivitis was not observed in group A, but was seen in 4 B (18%) and 8 C (36%) subjects (*C vs. A*, $P = 0.003$). At 24 weeks, satisfaction rates were 67%, 59%, and 55% in the A, B, and C groups, respectively (*C vs. A*, $P = 0.008$). Thus, in patients with moderately severe GO, similar response rates were observed for low and high Rx doses, but the 1 Gy/week protocol was more effective and better tolerated than the short arm regimens. (*J Clin Endocrinol Metab* 85: 102–108, 2000)

THE RATIONALE for the use of orbital radiotherapy (Rx) in patients with Graves' ophthalmopathy (GO) resides in the well established radiosensitivity of lymphocytes, which are considered important effectors in this disorder (1–4). Activated orbital T lymphocytes secrete various cytokines, which in a paracrine manner induce glycosaminoglycan production by fibroblasts (5, 6). Excessive secretion of these hydrophilic molecules results in tissue edema, which, besides lymphocyte infiltration, causes the marked swelling of the orbital tissue in GO (7–10).

There have been many uncontrolled and/or retrospective studies of Rx as second line treatment in GO (11–17), and the natural course toward improvement of eye changes could have influenced the findings because of a long interval between treatment and assessment of results. Some patients were simultaneously treated with glucocorticoids (18) or included despite an abnormal thyroid function, which can affect the severity of the eye changes. In most countries, a total Rx dose of 20 Gray (Gy) is delivered over 2 weeks [higher doses do not provide further benefit (16)], whereas in Germany, markedly lower doses, e.g. 4–10 Gy, are administered (19). Clinical and experimental data strongly suggest that low dose Rx (single fractions of 1 Gy or less) is sufficient to achieve a pronounced antiphlogistic effect on

inflammatory processes (20) despite the lack of understanding of the biological mechanisms involved. Even if limited comparability is taken into account, the data fail to provide evidence for the superiority of the higher dose with respect to response rates. As it is important to reduce the radiation burden for the patient, it seems attractive to reduce the total dose, especially if similar effectiveness could be proved. Although Rx is a commonly used treatment for GO (21), controlled trials evaluating different doses and application forms have not been performed. Thus, in patients with moderately severe GO, we randomly compared the efficacy and tolerability of three protocols for orbital Rx. We speculated that during the same treatment period, a low dose would be as effective as a high one. We hypothesized that repeated administration of an antiinflammatory low dose may inhibit activated, radiation-sensitive, orbital T cells more than the application of equal or higher doses during a shorter period of time.

Subjects and Methods

Subjects

Sixty-five subjects with untreated and clinically congestive and inflamed GO classes 2–5, were enrolled (April to September, 1995). Inclusion criteria were mild to moderate eye disease, euthyroidism, over the age of 18 yr, willingness to omit all but local treatment measures for 24 weeks, and informed consent. Patients had to exhibit the following criteria: swollen eyelids or red swollen conjunctiva of the eye, staring or bulging eyes, involvement of both eyes, pain or excessive watering, and muscle enlargement on magnetic resonance imaging. Exclusion criteria were previous specific treatment (steroids

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or radiotherapy) or surgical decompression, pregnancy, diabetes mellitus, and optic neuropathy. The following measures before and after orbital Rx were performed: lid fissure width (measured at its widest vertical dimension), proptosis (measured by a Hertel exophthalmometer), range of extraocular motion in degrees on a perimeter, area and constancy of diplopia (intermittent, present only when fatigued; inconstant, present in secondary positions of gaze; constant, present in primary and reading positions = normgaze), intraocular pressure in norm- and upgaze (rise in intraocular pressure on actual or attempted upward gaze, compared to gaze in the primary position) measured using an applanation tonometer, optic nerve function was assessed by recording of the corrected visual acuity and funduscopy, the cornea was inspected for the presence of exposure keratitis with a slit lamp, and the NOSPECS classification was graded (22–25). Data were also obtained for subjective symptoms (orbital pain, blurred vision, satisfaction rate of the patients at week 24). All subjects were examined by the same ophthalmologist on the day before and at 24 weeks after the start of treatment. Thyroid medication was not changed during the study period (methimazole, 2.5–20 mg/day). The type of therapy was not known to either the ophthalmologist or the radiologist who assessed treatment results. To determine the overall response to treatment, therapeutic outcome at week 24 was used as the end point of the study. As previously reported (26), response to therapy was defined as a significant amelioration of at least three objective signs [change (Δ) in lid fissure width >2 mm, Δ proptosis >2 mm, Δ intraocular pressure (upgaze) >3 mm Hg, Δ eye muscle area >5 mm², or absence of diplopia in primary position (normgaze)]. No response was indicated by the absence of change in objective signs or by treatment failure if an increase in class or grade occurred. Written informed consent was obtained from all subjects, and the trial received local ethical committee approval. At week 24, patients left the study, and further therapy could be initiated, tailored to the needs of the individual patient. The type of further treatment after completing the trial was noted for all patients. Thyroid hormones (Roche Molecular Biochemicals, Mannheim, Germany) and TSH receptor autoantibodies (radioreceptor assay, Brahms, Berlin, Germany) were measured using commercially available kits.

Orbital radiotherapy

A randomization list was used to assign each GO patient to receive either 20 divided fractions of telecobalt 60, 1 Gy weekly over 20 weeks (protracted protocol; total or cumulative dose, 20 Gy; group A), or 10 fractions of 1 Gy daily, 5 days a week over 2 weeks (short arm regimen; total dose, 10 Gy; group B), or 10 fractions of 2 Gy daily over 2 weeks (short arm; total dose, 20 Gy; group C). The patient's head was stabilized using a head holder or bite block. Simulation films were taken with a lead marker on the lateral fleshy cantos of each eye and with a contact lens containing a radiopaque marker on each cornea. All patients were treated using opposed lateral fields. The fields were defined by the bony limits of the orbit, incorporating the entire retrobulbar tissues and extraocular muscles. Shaped blocks were used to delineate the fields, which were usually 5×6 cm in size. Radiation dose was calculated at the midline, giving a uniform dose to both retrobulbar regions. The dose to the opposite lens was reduced by angling the lateral beams 3° posteriorly.

Magnetic resonance imaging (MRI) of the orbits with a 0.28-T magnet (BMT 1100, Bruker, Erlangen, Germany) was performed, and the T2-weighted relaxation time (T2) was measured in a coronal section of 5 mm thickness. Squares containing nine pixels were chosen for T2 determination within the extraocular rectus muscles. Calculations of T2 were performed with a Carr-Purcell-Meiboom-Gill sequence with eight consecutive echoes (800/34–272, repetition time second/echo time second). The normal range of T2 within the extraocular rectus muscles was 92 ms (80–97 ms). All MRI images were interpreted in a blinded fashion and in random order at the end of the study.

Statistical analysis was performed using SAS software (27). For detailed description of the results, the median, minimum, and maximum values recorded for affected eyes of the investigations 6 months after the beginning of therapy were calculated for the quantitative parameters. For representation of the qualitative parameters, the relative frequencies in the three groups were compared and contrasted after 24 weeks. To examine whether there is a significant difference in the results of therapy

among the 3 groups, the 2-sided Wilcoxon rank sum test for independent groups (probability of error $\alpha = 0.05\%$) was carried out for the quantitative parameters. A sample size of at least 60 patients was required, with a power of 80% and a significance level of 5%. The Mann-Whitney U test for multiple comparison was used as appropriate, and paired comparisons of more than 2 proportions were analyzed using the Bonferroni adjustment. To compare percentages, we used the χ^2 test. The correlation coefficients were generated with the Pearson bivariate correlation test. Correlations among various parameters were calculated using Spearman's test.

Results

Seventy patients with moderately severe GO met the inclusion criteria; 5 subjects chose not to participate. Twenty-one patients (of whom 3 were excluded because of insufficient follow-up and poor compliance) were assigned to receive the protracted protocol (group A, 1 Gy/week), and 22 each were assigned to receive the short arm regimens (groups B and C, 1 or 2 Gy/day). There were no differences in thyroid function or severity of eye disease among the 3 groups (Table 1). All patients remained euthyroid during the study period. As predefined, therapeutic outcome at week 24 was observed in 12 A (67%), 13 B (59%), and 12 C (55%) patients (C vs. A, $P = 0.007$). Of the 6 A (33%), 9 B (41%), and 10 C (45%) subjects in whom treatment was unsuccessful, 4 A (22%), 3 B (14%), and 3 C (14%), showed no change, and 2 A (11%), 6 B (27%), and 7 C (31%) were classified as treatment failures. Response to therapy was independent of duration of eye and/or thyroid disease. When responders were compared with nonresponders for all groups, there were no differences in baseline characteristics, e.g. age, gender, or thyroid-related parameters. Seven of 12 A (58%), 8 of 13 B (62%), and 7 of 12 C (58%) responders were smokers. Among nonresponders, 3 of 6 A (50%), 4 of 9 B (45%), and 6 of 10 C (60%) were smokers.

Ophthalmic symptoms and signs regressed most in group A. The Δ lid fissure widths were -1.5 , -0.5 , and 0 mm in groups A, B, and C, respectively, whereas Δ intraocular pressures (upgaze) were -3 , $+1$, and -1.5 mm Hg (Table 2). The median decreases in proptosis were -2 mm (A), -1.5 mm (B), and -1 mm (C). At 24 weeks, visual acuity improved in group A only, in groups B and C no changes were observed, but only a few patients had a vision below 0.8. As for eye muscle motility, abnormalities in adduction and depression were seen in only a few, whereas most patients had impaired bulbar elevation and abduction. Elevation and abduction of the globe significantly improved in group A only, and the number of patients without diplopia in normgaze slightly changed in groups A and C only. Sixth months after starting therapy, congestive signs were present in nearly half of the A patients and to a lesser extent in B patients, whereas no changes were noted in group C. Seven of the 12 A patients who responded to the 1 Gy/week protocol had an improvement in soft tissue signs compared with none of the 12 C responders. A decrease in the NOSPECS classification of eye changes (Table 3) was observed in 12 A (67%), 13 B (59%), and 13 C (59%) patients (A vs. B/C, $P = 0.01$). Rx-induced conjunctivitis was not observed in group A, but was seen in 4 B (18%) and 8 C (36%) patients (C vs. A, $P = 0.003$).

TABLE 1. Baseline clinical and laboratory variables in patients according to randomization to treatment with three orbital irradiation schedules

Study group	A	B	C
Fraction dose	1 Gray/week	1 Gray/day	2 Gray/day
Total dose	20 Gray	10 Gray	20 Gray
Irradiation time	20 weeks	2 weeks	2 weeks
No.	18	22	22
Female	13 (72)	21 (95)	17 (77)
Male	5 (28)	1 (5)	5 (23)
Graves' thyroidal disease	17 (94)	22 (100)	21 (95)
Hashimoto's thyroiditis	1 (6)	0	1 (5)
Smokers	10 (56)	12 (55)	13 (59)
Age (yr)	48	47	49
Duration of ophthalmopathy (months)	31-79	24-67	30-72
	7	12	12
	2-15	3-16	2-14
Duration of thyroid disease (months)	15	14	15
	2-23	1-19	4-20
TSH receptor antibodies (mU/L)	52	38	29
	6-128	4-99	0-101
Baseline TSH (mU/L)	1.3	0.9	1.1
	0.2-3.4	0.1-2.5	0.2-2.9
Free T ₃ (2-5 pg/mL)	2.8	3.5	3.1
	2.1-4.7	2.0-5.0	2.2-3.9
Free T ₄ (1-2 ng/dL)	1.4	1.5	1.3
	1.1-1.9	1.0-1.8	1.1-1.9
Thyroid vol (mL)	32	27	28
	12-44	14-35	12-39
Lid fissure width (mm)	12.5	12	12
Visual acuity	0.8	0.9	0.8
Proptosis (mm)	24	22	23
Intraocular pressure (mm Hg)	17	17	16

Data are given as the median and range, except where indicated. The only statistical significant differences were among the three orbital radiotherapy groups for gender (B vs. A, $P = 0.038$ and B vs. C, $P = 0.043$, respectively). Percentages are given in parentheses.

The areas of extraocular rectus muscles decreased in all groups, significantly more in group A (Table 4). In this group, 14 of 18 patients (78%) showed significant changes in all four rectus muscles compared with 12 of 22 B (55%) and 9 of 22 C (41%) patients, respectively (C vs. A, $P = 0.002$). In group C, significant changes in muscle area were noted for the medial and superior rectus only. The decrease in T2 time of the eye muscles correlated with the decrease in muscle area ($P = 0.01$). T2 of orbital connective tissue decreased most in group A.

After completion of the study, 23 of 62 (37%) patients (8 A, 44%; 8 B, 36%; 7 C, 32%; A vs. C, $P = 0.01$) needed no further therapy or had minor lid surgery (1 A, 5.5%). Of the remaining 39 subjects, 11 (2 A, 11%; 4 B, 18%; 5 C, 23%; A vs. C, $P = 0.04$) still had congestive eye disease and were further treated with prednisolone. Four patients (2 B, 9%; 2 C, 9%) were submitted to decompressive orbital surgery, and 8 (3 A, 17%; 3 B, 14%; 2 C, 9%) subjects had surgery for squint. Thus, within the follow-up period of 6 months, 24 of the 62 subjects (39%) received further specific ophthalmic therapy.

Discussion

In this randomized single blind trial, for the first time different Rx doses and application forms were compared in GO. This study showed that when delivered over 2 weeks in patients with moderately severe GO, the low (1 Gy/day) and high (2 Gy/day) irradiation doses were equally effective. In these two groups, we did not detect any significant difference in the degree of improvement,

as judged from changes in ophthalmic symptoms and signs as well as eye muscle enlargement on MRI. More crucial and clinically relevant is the finding that the application modality seems to be more important than the dose. There was a tendency for the 1 Gy/week scheme to have a greater effect on soft tissue swelling, to have significantly lower rates of Rx-induced conjunctivitis, and for Rx to be more effective in improving eye muscle motility. However, all three treatments, especially the short arm protocols, had only a slight effect on proptosis, in accordance with previous studies (3, 4). As the majority of the GO subjects at the trial start had almost normal vision, a significant improvement in visual acuity was detected only in the 1 Gy/week regimen. In this study and as previously shown in patients with congestive GO (28), quantitative MRI allowed noninvasive detection of edematous changes in orbital tissue. Further, the predicted probability of response to treatment increased with enhanced T2 relaxation time of the eye muscles before therapy. Therefore, measurement of elevated T2 might play a role in the prediction of the reversibility of muscle thickening and could favor the choice of antiinflammatory therapy in these patients.

In accordance with a recent publication (29), less than 60% of our patients were smokers. Although extensively informed, patients kept smoking during the trial. With respect to response rate and clinical amelioration, there was no difference between smokers and those who did not. In the study from Pisa (29), a similar number of responders to orbital Rx

TABLE 2. Ophthalmic signs and symptoms at baseline and 24 weeks after starting orbital radiotherapy

Study group Irradiation scheme Week	A 1 Gy/wk:20 wk 0 24		B 1 Gy/day:2 wk 0 24		C 2 Gy/day:2 wk 0 24		P	C vs. A
Lid fissure width (mm)	12.5	11	12	11.5	12	12	0.691	0.489
Normgaze	10-19	8-14	11-20	8-17	9-18	8-14		
Downgaze	5.5	3.5	5	4	5.5	4	0.03	0.01
Proptosis (mm)	2-9	1-5	3-10	1-6	2-11	1-8	0.02	0.007
24	24	22	22	20.5	23	22		
19-28	19-28	18-25	18-28	17-26	19-28	17-26	0.03	0.562
17	17	15	17	16	16	15		
Intraocular pressure (mm Hg)	13-28	11-21	12-26	10-20	12-24	12-19	0.002	0.006
Normgaze	21	18	18	19	20	18.5	0.315	0.02
Upgaze	17-28	13-26	12-35	14-26	13-31	12-25	0.244	0.076
30	30	37	36	39	37	39		
Bulbar elevation (degree)	5-40	10-40	5-40	15-40	5-40	5-40	0.846	0.698
45	45	49	46	48	46	47		
20-50	20-50	30-50	25-50	40-50	15-50	25-50		
Diplopia (n)	12	9	14	12	15	12	0.094	0.03
Constant	3	5	3	6	3	5		
Intermittent	2	1	3	2	1	1		
Absent	1	3	2	2	3	4		
Visual acuity	0.8	0.95	0.9	0.95	0.8	0.9	0.06	0.311
0.4-1	0.4-1	0.5-1	0.1-1	0.1-1	0.3-1	0.3-1		
30	30	14	26	14	30	30	0.004	0.107
34	34	14	25	21	30	30	0.03	0.139
Chemosis (eyes)	7	1	8	2	9	5	0.001	0.004
Conjunctivitis (eyes)	9	5	7	4	8	5	0.01	0.001
Orbital pain (no.)	5.5	2.5	5	3	5.5	4	0.002	0.01
Blurred vision (no.)	3-7	1-4	3-6	2-5	3.5-7	3-5	0.009	0.001
Clinical activity score								
Satisfaction rate (no., %)		12 (67)		13 (59)		12 (55)		0.008

Data are given as the median and range, except where indicated. The only significant differences were between groups C and B for chemosis and conjunctivitis $P = 0.002$ and $P = 0.012$, respectively). Gy, Gray; wk, week.

TABLE 3. Grades within NOSPECS classes at baseline and at the end of the study (week 24) in patients treated with orbital radiotherapy

Study group Fraction Dose Total dose Irradiation period Week	A 1 Gray/week 20 Gray 20 weeks		B 1 Gray/day 10 Gray 2 weeks		C 2 Gray/day 20 Gray 2 weeks	
	0	24	0	24	0	24
	n=18		n=22		n=22	
Class and grade	n=18		n=22		n=22	
Soft tissue involvement with symptoms and signs						
0: absent	0	1	0	0	0	0
a: minimal	0	6	3	8	3	6
b: moderate	3	5	6	7	4	2
c: marked	15	6	13	7	15	14
Proptosis (mm)						
0: <23	2	4	3	4	2	3
a: 23–24	7	10	8	11	9	10
b: 25–27	5	3	9	6	7	7
c: >27	4	1	2	1	4	2
Extraocular muscle involvement						
0: absent	3	4	5	4	4	5
a: limitation of motion at extremes of gaze	3	5	3	6	3	5
b: evident restriction of motion	12	9	14	12	15	12
c: fixation of a globe or globes	0	0	0	0	0	0
Corneal involvement						
0: absent	10	16	15	12	15	8
a: erosion	7	2	6	8	5	10
b: ulceration	1	0	1	2	2	4

NOSPECS classification of eye changes in Graves' ophthalmopathy adapted from Werner (22).

(20 Gy) was found in the smoker ($n = 58$) and nonsmoker ($n = 61$) groups, but there were significantly more smokers ($n = 27$) than nonsmokers ($n = 4$) in the nonresponder group. Of note, several smokers had excellent or good responses to orbital Rx. This implies that cigarette smoking is only one of many risk factors involved in the progression of GO. Identification of such risk factors should be a goal of future research so that therapy may be improved and disease may be prevented.

Ophthalmic symptoms and signs decreased most in group A (1 Gy/week). In comparison, Ravin *et al.* (30) treated 37 GO patients with 10 fractionated doses of 1 Gy, only. Muscle function in subjects with eye muscle abnormalities ameliorated, but did not return to normal; visual function improved in all 9 patients with optic neuropathy, although 1 still required decompression. There is experimental evidence that the clinically observed antiinflammatory effects of low dose protracted Rx are due to the functional alteration of cells involved in the inflammatory response (20, 31). A dose-dependent modulation of the nitric oxide pathway, which plays a central role in inflammation, was observed with a significant inhibition by a low Rx dose, whereas a high dose resulted in stimulation. In rat models of arthritis, a fractionated dose schedule of four times 1 Gy every 4 days had a therapeutic effect, with significant reductions in bone resorption and cartilage glycosaminoglycan (32). Thus, the suppressive interference of low and protracted doses of Rx with the nitric oxide pathway may be one of the radiobiological mechanisms that underlies the clinically documented efficacy of antiinflammatory Rx.

By the 6 month follow-up after completion of the study (especially in the short arm regimens), approximately 40% of our patients needed further ophthalmic therapy. This finding underscores the fact that the benefits of Rx are modest, as judged from the results of the objective oph-

thalmic signs. During the period of orbital inflammation in GO, rehabilitative surgery is considered difficult. Because the duration of the active stage can vary from months to several years, one of the goals of Rx is to inactivate the autoimmune process, thus permitting surgery to be performed successfully at an earlier stage. It is conceivable that Rx, by suppressing the radiosensitive lymphocytes and fibroblasts, inactivates inflammation (33); improvement is therefore to be expected only in congestive GO. This was illustrated by Petersen *et al.*, who found a 91% response rate in patients with a recent exacerbation of GO (17). Ideally, therefore, treatment should not be given to patients with clinically inactive disease.

In the 1 Gy/week and 1 Gy/day groups, orbital Rx was well tolerated. As preexisting diabetes mellitus potentates the onset of retinopathy (34, 35), we excluded diabetics from this trial. Risk for Rx-induced retinopathy can usually be ascribed to doses exceeding 20 Gy (36–41). In a study with 14 treated subjects, 6 of whom developed retinopathy, 4 received 30 Gy and 1 received 23 Gy; all who did not develop retinopathy had doses less than 21 Gy (40). The Stanford group described 242 patients treated with 20 or 30 Gy, none of whom developed retinopathy after a median follow-up of either 16 or 34 months (16, 17). On the other hand, transitory blindness has been reported shortly after Rx with 20 Gy (42), and retinopathy has occurred after safe doses as low as 11 and 12 Gy (43, 44). Thus, retinopathy may be a complication of Rx even at radiation levels previously thought to be safe.

In conclusion, in patients with moderately severe GO, similar response rates were observed for low and high irradiation doses, but the protracted Rx protocol was more effective and better tolerated than the short arm regimens. As it is important to reduce the radiation burden for the patient, it seems attractive to fractionate and protract the Rx protocol

TABLE 4. Quantitative MR imaging at baseline and 24 weeks after starting orbital radiotherapy

Study group Schedule Week	A 1 Gy/wk		P	B 1 Gy/day		P	C 2 Gy/day		P	C us. A
	0	24		0	24		0	24		
Rectus eye muscle area (mm ²)										
Medial	35 20-120	28 12-85	0.0005	35 19-99	29 15-91	0.0009	34 20-86	31 18-77	0.004	0.028
Inferior	37 20-111	29 15-87	0.009	40 19-92	36 16-65	0.03	40 18-119	39 14-100	0.139	0.0004
Lateral	31 16-55	21 12-38	0.006	28 18-49	22 13-37	0.001	25 15-57	23 12-35	0.155	0.0006
Superior	42 21-94	29 16-81	0.009	36 20-93	28 18-47	0.001	38 22-78	30 17-49	0.02	0.001
T2 relaxation time (ms)										
Rectus eye muscles										
Medial	99 70-140	64 50-99	0.0001	89 60-162	69 48-98	0.003	100 61-200	79 50-124	0.02	0.005
Inferior	89 60-170	79 45-110	0.0003	86 70-194	77 48-120	0.02	98 68-202	83 52-137	0.03	0.001
Lateral	80 64-137	69 48-95	0.0001	71 60-118	64 49-90	0.315	79 63-131	75 58-110	0.437	0.0001
Superior	84 62-129	78 53-118	0.059	76 64-113	73 54-91	0.681	82 63-124	75 45-103	0.086	0.536
Connective tissue	135 90-151	108 79-116	0.0008	129 89-140	107 81-113	0.006	127 90-138	110 84-121	0.03	0.0014

Data are given as the median and range, except where indicated. Significant differences were between groups C and B for both areas of the inferior and lateral rectus eye muscles ($P = 0.022$ and $P = 0.013$, respectively). Gy, Gray; wk, week.

as well as reduce the total dose, especially if similar efficacy can be achieved.

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