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OCULOPLASTICS AND ORBIT

Efficacy of combined orbital radiation and systemic steroids in the management of Graves' orbitopathy

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Abstract
Purpose To compare the efficacy and safety of combination therapy with orbital irradiation and systemic steroids versus steroid monotherapy in the management of active Graves' orbitopathy (GO).
Methods The clinical charts of 127 patients with active inflammation due to GO who received intravenous steroid pulse therapy as a first-line treatment with or without orbital radiotherapy between 2010 and 2014 were reviewed. Patients were divided into two treatment groups: 1) combined orbital radiotherapy and steroid pulse therapy (SRT group) and 2) steroid pulse therapy only (ST group). Primary outcome measures included clinical activity score (CAS); NOSPECS classification; ocular motility impairment; and exophthalmos at 1, 3, 6, and 12 months after treatment. The secondary outcome measure was the change in orbital, extraocular muscle (EOM), and fat volume after treatment measured by orbit computed tomography.
Results Sixty-eight patients were included in the SRT group, and 59 patients were in the ST group. In both treatments, CAS and NOSPECS were significantly reduced. In the comparison of the degree of change from baseline between the groups, the SRT group demonstrated more improvement in NOSPECS and scores of ocular motility. Orbital, EOM, and fat volume significantly decreased in the SRT group; however, only fat volume was reduced in the ST group. Compressive optic neuropathy after treatment developed in 0 % of the SRT group and 3.4 % (2/59) of the ST group. Reactivation of inflammation occurred in 11.8 % (8/68) of the SRT group and 28.8 % (17/59) of the ST group.
Conclusions Orbital radiotherapy in combination with steroid treatment significantly improved ocular motility by reducing EOM volume in patients with active GO.

Keywords Orbital radiation · Systemic steroids · Graves' orbitopathy · Thyroid-associated orbitopathy

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Introduction

Graves' orbitopathy (GO) is an inflammatory condition of the orbit that is closely associated with autoimmune thyroid disease. During the course of the disease, severe disability occurs in 3–5 % of patients [1, 2]. GO follows a biphasic course in which an initial active phase of progression is followed by a subsequent partial regression and a static inactive phase. In the active phase, activated T lymphocytes produce many cytokines that induce activation and proliferation of fibroblasts and, thus, further aggravate the inflammatory reaction. Extraocular muscle (EOM) and periorbital tissue volumes increase as a result of orbital inflammation, causing a variety of symptoms such as proptosis, ocular motility impairment, diplopia, and compressive optic neuropathy (CON). Currently,

the most effective treatment for GO in the active phase is corticosteroid and orbital radiotherapy (RT), and prompt treatment during this period is critical because early interventions can prevent serious ocular complications and the need for invasive surgical measures [1].

High-dose intravenous (IV) corticosteroid treatment is effective as a primary therapy for GO; however, there is a chance, although rare, of severe adverse events and a high rate of recurrence occurs during steroid tapering or after withdrawal [3–5]. In some patients, steroid resistance may also occur [6–10]. In such cases, RT has provided a suitable alternative treatment for GO patients for almost a decade [11]. Despite numerous clinical studies conducted to demonstrate the efficacy of RT on GO patients, the actual therapeutic benefit is still debatable [12, 13]. However, previous studies have indicated that a combination of systemic corticosteroids and orbital RT is more effective than either individual treatment [14]. Therefore, we compared the efficacy and safety of combination therapy with orbital irradiation and systemic steroids versus steroid-alone therapy in the management of active GO.

Patients and methods

This was a retrospective, non-randomized, controlled study. Subjects were patients with GO who visited the Department of Ophthalmology at Severance Hospital, Yonsei University College of Medicine between January 2010 and March 2015. During their visit at the clinic, information regarding age, smoking history, duration of Graves' disease (GD) and GO, and treatment history were collected. Also, serum concentrations of free thyroxine (FT4), thyroid-stimulating hormone (TSH), thyroid-stimulating immunoglobulin (TSI), and TSH receptor antibody were measured in addition to a complete blood cell count, electrolyte battery, and renal and liver function tests. All subjects were selected for participation in the study according to the following inclusion criteria: 1) the duration of GO ocular symptoms at initial diagnosis was no longer than 6 months, 2) the clinical activity score (CAS) was three or greater, 3) treatments included intravenous steroid pulse therapy as a first anti-inflammatory treatment with or without orbital radiation, and 4) regular follow-ups at 3-month intervals were conducted for more than 12 months by a single ophthalmologist. Exclusion criteria included pregnancy, active peptic ulcer, sepsis, age under 20 or older than 80 years, previously treated with oral steroids, a history of other diseases treated with steroid therapy and a past medical history of other eye diseases such as glaucoma, diabetic retinopathy, or maculopathy. Best corrected visual acuity and intraocular pressure were measured, and exophthalmometry was conducted using a Hertel exophthalmometer. The binocular single vision test was done and the monocular excursion was evaluated by performing the Hess screen test. Computed tomography (CT) was performed before and after treatment. The modified CAS was used to assess GO activity [15]. The modified CAS was evaluated by assigning a point to each of the following seven signs: retrobulbar pain, pain on eye movements, eyelid erythema, conjunctival injection, chemosis, swelling of the caruncle, and eyelid edema. The modified NOSPECS score was used to assess GO severity and to measure ocular motility impairment. (0; no EOM involvement, 2;>20° upgaze, 35° abduction, 3; ≤20° upgaze, 35° abduction; Table S) [16]. A single examiner (YJS) evaluated the patient CAS and NOSPECS scores. Contiguous 1-mm sections of the orbital CT scans of the subjects were obtained. Volumetric measurements of orbits were taken using the technique described by Regensburg et al. [17]. Regensburg et al. used both region-growing and manual segmentation simultaneously in axial, coronal, and sagittal images of orbital CT scans with control of the 3D reconstruction, applying commercially available software. Orbital soft tissue CT numbers were set at −200 to +100 Hounsfield units (HU) for bony orbital volume, −200 to −30 HU for fat tissue, and −30 to +100 HU for muscle tissue. The borders of the orbital aditus were determined by the frontal bone, frontozygomatic suture, inferior orbital rim and the anterior orbital crest. The entrance of the optic nerve in the orbital canal, the fossa pterygopalatina, and the orbital fissures were used for the cut-off point of the orbital end. The orbital volume was defined as the difference between the volumes of the bony orbital volume and the eyeball. Extraorbital fat was erased by deleting the fat tissue in the skin of the eyelids and the fat in the superior and inferior orbital fissures.

Patients were divided into two study groups according to their treatment regimen. The SRT group consisted of patients who received combined orbital radiotherapy and steroid pulse therapy. The ST group received steroid pulse therapy only. Indications for corticosteroid treatment were: 1) periocular soft tissue inflammation (CAS 3 or greater), 2) CON, and 3) strabismus. The steroid regimen comprised methylprednisolone administered intravenously at a daily dose of 500 mg for 3 days and 500 mg weekly for 6 weeks (for a total of 4.5 g). Thereafter, oral prednisolone at 1 mg/kg was administered daily until tapering over a 2- or 3-month period, depending on the GO activity and severity. The primary indications for combination treatment with orbital radiotherapy were: 1) the development of significant restriction in ocular motility, 2) total cumulative dose of corticosteroids reaching unsafe levels over 8 g, 3) intolerance to corticosteroids, and 4) inadequate control of disease activity with corticosteroids. Orbital irradiation was given within 2 weeks after the corticosteroid pulse therapy. The dose of orbital irradiation was 20 Gy (2000 rad) in 10 fractions over a 2-week period. The location of the isocenter was determined by CT imaging during pretreatment planning. The beam arrangement consisted of a 60-degree wedged pair, ±45° from the lateral side. In the comparison

of volumetric values, the opposite normal eyes in age- and sex-matched controls who had undergone orbital CT scans at 1-year intervals for other oculoplastic disorders such as anopthalmos, orbital wall fracture, disorder of lacrimal system, etc. without any treatment were included in the non-GO control group.

Data analysis was performed using SPSS statistical software (version 20.0). Independent t tests were used to compare ages between study groups, and sex, smoking history, treatment for GD, and recurrence rate between the study groups were compared using Chi-square tests. The Mann–Whitney test was applied to compare the medians of duration of GO and GD between the study groups. Changes in CAS, NOSPECS, ocular motility impairment, and proptosis before and after treatment were compared between the two groups using a linear mixed model. A comparison of orbital, EOM, and fat volume among groups was performed using independent *t* tests, and paired *t* tests were used for comparing 1-year values with baseline values.

Results

After evaluating 321 patients with GO who received steroid therapy during the indicated study period, 127 patients fit the inclusion criteria. Sixty-eight patients received both orbital radiotherapy and steroid pulse therapy (SRT group), and 59 received steroid pulse therapy only (ST group). There were no significant differences in the mean age, sex ratio, smoker proportion, duration of GO and GD, and types of GD treatment between the SRT and ST groups (Table 1).

The change in the CAS during the 12-month follow-up period after treatment was analyzed using a linear mixed model. The average initial CAS values between the SRT (4.10 ± 0.14) and the ST (3.86 ± 0.15) groups showed no statistical difference ($p = 0.240$). Both groups showed a significant decrease in CAS over time, and there was no difference in overall reduction between the two groups at the end of the follow up (Fig. 1a, Table 2). NOSPECS also showed a similar pattern of decrease after treatment. The initial NOSPECS values (SRT group 6.71 ± 0.26, ST group 5.92 ± 0.27) were significantly greater in the SRT group ($p = 0.035$); however, 12 months following treatment there was no significant difference in NOSPECS between the two groups ($p = 0.372$; Fig. 1b, Table 2). The changes from baseline levels were significantly greater in the SRT group at 6 and 12 months ($p < 0.01$ at 6, 12 months).

The baseline EOM involvement prior to treatment was more significant in the SRT group (1.88 ± 0.15) compared to the ST group (1.44 ± 0.16; $p = 0.040$). However, the changes from baseline levels were significantly greater in the SRT group at 6 and 12 months ($p < 0.01$ at 6,12 months), and after 12 months, there was no significant difference in values between the two groups (SRT1.18 ± 0.14, ST 1.27 ± 0.15; $p = 0.652$; Fig. 1c, Table 2). The SRT group (19.59 ± 0.34) also showed a significantly greater baseline measurement for exophthalmos compared to the ST group (18.53 ± 0.37; $p = 0.037$). The changes from baseline were significantly greater in the SRT group at 6 months ($p = 0.010$); however,

Table 1 Comparison of demographics between the SRT group and the ST group

	SRT group	ST group	*p* value
Number of patients	68	59	
Age, mean ± SD	50.85 ± 9.88	48.25 ± 11.38	0.171[a]
Sex, female (%)	41 (60.3 %)	43 (72.9 %)	0.135[b]
Smoker, number (%)	29 (42.6 %)	19 (32.2 %)	0.226[b]
Duration of GO, median (IQR), months	4 (2–6)	3 (1–5)	0.088[c]
Duration of GD, median (IQR), months	7 (4–12)	5.50 (2–12)	0.114[c]
Treatment of GD	85.3/4.4/10.3	93.2/1.7/5.1	0.342[b]
(ATD/RAI/Surgery,%)			
Thyroid function	55.9/16.2/27.9	71.2/8.5/20.3	0.161[b]
(Hyper/Hypo/Euthyroidism,%)			
Total T3 (0.9–2.4 pmol/l), mean ± SD	1.44 ± 0.98	1.79 ± 1.70	0.166[a]
FT4 (9–19.1 pmol/l), mean ± SD	1.45 ± 1.02	1.7 5 ± 1.26	0.135[a]
TSH (0.35–4.94 μIU/ml), mean ± SD	2.14 ± 4.91	2.01 ± 7.39	0.904[a]

SRT orbital radiotherapy and steroid pulse therapy, *ST* steroid pulse therapy, *SD* standard deviation, *IQR* interquartile range, *GO* Graves' orbitopathy, *GD* Graves' disease, *ATD* antithyroid drug, *RAI* radioiodine therapy, *hyper* hyperthyroidism, *hypo* hypothyroidism, *TSH* thyroid-stimulating hormone, *FT4* free thyroxine

[a] Independent *t* test

[b] Chi-squared test

[c] Mann–Whitney test

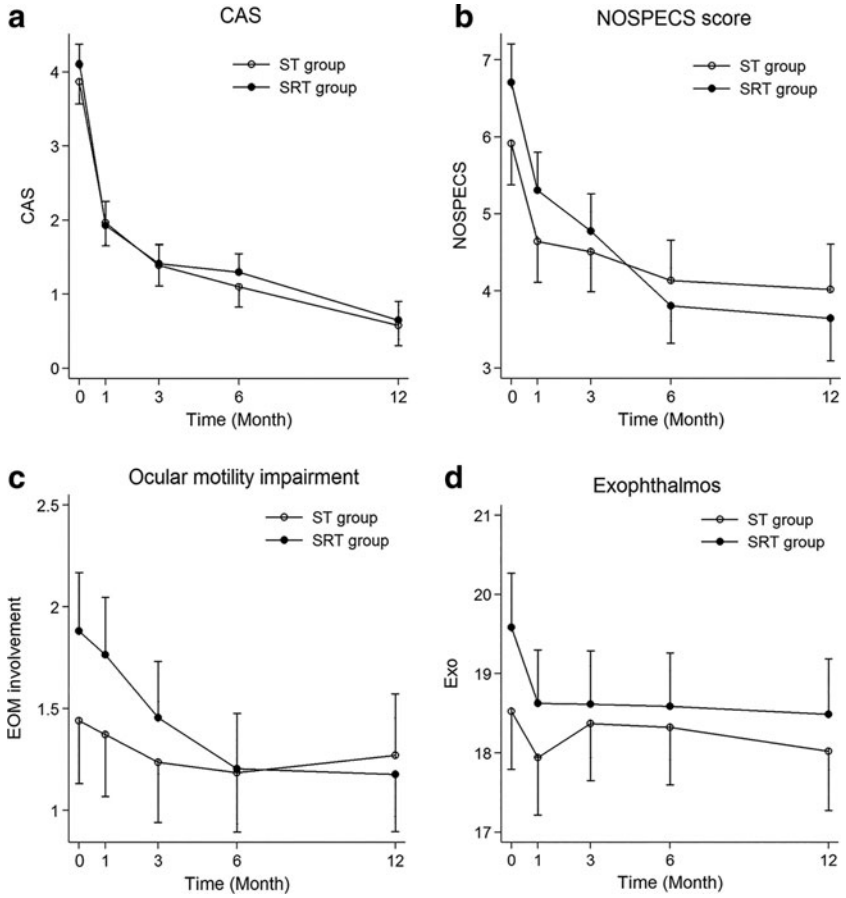

Fig. 1 Linear mixed model analysis of the change in CAS, NOSPECS score, ocular motility impairment, exophthalmos during a 12-month follow-up period after treatment. **a** Both groups showed a similar pattern of significant decrease in CAS throughout the follow-up period. No significant difference existed between the groups. **b** The SRT group showed a significantly greater baseline measurement of NOSPECS score compared to the ST group ($p = 0.048$). Both groups showed a significant decrease in the score at follow-up, but no significant difference between the groups was present. **c** Ocular motility impairment also showed a significant difference between the groups at the baseline measurement ($p = 0.044$). The SRT group showed significant decrease in EOM involvement at each 3-month interval, but no difference between the groups was observed throughout the follow-up. **d** The baseline measurement of exophthalmos between SRT and ST showed a significant difference ($p = 0.042$). No significant difference between the measurements was observed at follow-up

no statistically significant difference between the two groups was found in the changes from baseline at 12 months ($p = 0.078$). At the end of the 12-month follow-up period, there was no significant difference between the groups (SRT18.49 ± 0.35, ST18.02 ± 0.38; $p = 0.376$; Fig. 1d, Table 2). In addition, no statistically significant difference between the SRT and ST groups was found in the percentage of patients with over 2-mm decreases in exophthalmometer values for 12 months (SRT 34.3 %, ST 32.2 %; $p = 0.801$).

Eleven patients were diagnosed with CON prior to treatment, and nine of these patients received combined IV steroid and RT treatment, while two patients received only IV steroids. All patients who received combined treatment showed regression of CON. The two patients who received only steroid treatment also had improved symptoms. There were no recurrences of optic neuropathy after either treatment. However, among the 59 patients in the ST group, two newly developed cases of CON following steroid treatment and had to receive emergency decompression. The two cases occurred at 3 and 6 weeks following withdrawal. There were no cases of newly developed CON in the SRT group.

The percentages of patients who showed reactivation of inflammation within 1 year of treatment were 11.8 % (8/68) for the SRT group and 28.8 % (17/59) for the ST group. There was a significant difference in the ratio between the two groups ($p = 0.018$). The average duration of the disease-free state until reactivation was 6.38 ± 3.50 months for the SRT group and 3.82 ± 4.23 months for the ST group. Twenty-five patients who experienced reactivation did not have any history of clinical events such as ophthalmologic surgery or trauma during the follow-up that might have caused the relapse (Fig. 2).

A quantitative subgroup analysis was performed to evaluate the changes in orbital, EOM and fat volume for patients who received a CT scan before and 1 year

Table 2 The change in CAS, NOSPECS score, EOM involvement, and exophthalmos from baseline in the SRT group and the ST group during a 12-month follow-up period

Time (month)	SRT group		ST group		*p* value[b] (SRT vs ST)
	Means ± SE	*p* value[a]	Means ± SE	*p* value[a]	
CAS					
Baseline	4.10 ± 0.14	Reference	3.86 ± 0.15	Reference	0.240
1	1.93 ± 0.14	**<0.01**	1.97 ± 0.15	**<0.01**	0.843
3	1.41 ± 0.13	**<0.01**	1.39 ± 0.14	**<0.01**	0.911
6	1.29 ± 0.13	**<0.01**	1.10 ± 0.14	**<0.01**	0.313
12	0.65 ± 0.13	**<0.01**	0.58 ± 0.14	**<0.01**	0.711
Δ(6 -Baseline)*	−2.81 ± 1.39		−2.76 ± 1.18		0.842[c]
Δ(12-Baseline)*	−3.46 ± 1.26		−3.29 ± 1.15		0.437[c]
NOSPECS					
Baseline	6.71 ± 0.26	Reference	5.92 ± 0.27	Reference	**0.035**
1	5.31 ± 0.25	**<0.01**	4.64 ± 0.27	**<0.01**	0.072
3	4.78 ± 0.25	**<0.01**	4.51 ± 0.27	**<0.01**	0.455
6	3.81 ± 0.25	**<0.01**	4.14 ± 0.27	**<0.01**	0.372
12	3.65 ± 0.28	**<0.01**	4.02 ± 0.30	**<0.01**	0.372
Δ(6 -Baseline)*	−2.90 ± 2.64		−1.78 ± 1.76		**<0.01[c]**
Δ(12-Baseline)*	−3.06 ± 2.59		−1.90 ± 2.12		**<0.01[c]**
EOM involvement					
Baseline	1.88 ± 0.15	Reference	1.44 ± 0.16	Reference	**0.040**
1	1.76 ± 0.14	0.79	1.37 ± 0.15	1.00	0.064
3	1.46 ± 0.14	**<0.001**	1.24 ± 0.15	0.08	0.290
6	1.21 ± 0.14	**<0.001**	1.19 ± 0.15	0.33	0.924
12	1.18 ± 0.14	**<0.001**	1.27 ± 0.15	1.00	0.652
Δ(6 -Baseline)*	−0.68 ± 0.89		−0.25 ± 0.63		**<0.01[c]**
Δ(12-Baseline)*	−0.71 ± 0.96		−0.17 ± 0.72		**<0.01[c]**
Exophthalmos (mm)					
Baseline	19.59 ± 0.34	Reference	18.53 ± 0.37	Reference	**0.037**
1	18.63 ± 0.33	**<0.01**	17.94 ± 0.37	**<0.01**	0.177
3	18.62 ± 0.33	**<0.01**	18.37 ± 0.37	1.00	0.627
6	18.59 ± 0.35	**<0.01**	18.32 ± 0.37	1.00	0.598
12	18.49 ± 0.35	**<0.01**	18.02 ± 0.38	0.20	0.376
Δ(6 -Baseline)*	−1.00 ± 1.76		−0.20 ± 1.82		**0.010[c]**
Δ(12-Baseline)*	−1.10 ± 1.82		−0.5 ± 1.97		0.078[c]

Data presented as means ± standard error. *SRT* combination of steroid and radiotherapy, *ST* steroid only, *SE* standard error, *CAS* clinical activity score, *EOM* extraocular muscle

Bold values denote statistical significance, $p < 0.05$

*Change from baseline

[a] Linear mixed model, *p* value compared with values at baseline

[b] Linear mixed model, *p* value compared between two groups

[c] Independent *t* test, *p* value compared between two groups

after treatment (non-GO $n = 20$, SRT $n = 44$, ST $n = 37$). At baseline, all measured values in the GO group, including orbital, EOM, and fat volume, were significantly greater than those in the non-GO group (Table 3). However, there was no significant difference between the SRT group and the ST group. In a repeated analysis after 1 year, there was no significant difference in volumetric values between baseline and after 1 year in the non-GO group. In the comparison of the GO group with combined treatment or systemic steroid alone between baseline and after 1 year, orbital, EOM, and fat volume significantly decreased in the combined treatment group ($p = 0.046$ orbit, $p = 0.008$ EOM, $p = 0.010$ fat). In the systemic steroid alone group, orbital, EOM, and fat volume were reduced, but the change was only significant in fat volume ($p = 0.065$ orbit, $p = 0.533$ EOM, $p = 0.029$

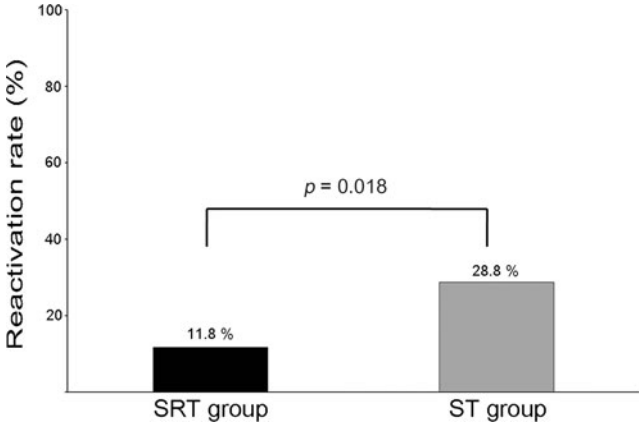

Fig. 2 Comparison of the percentage of patients with reactivation of inflammation between the SRT group and the ST group. The SRT group showed 11.8 % (8/68) of patients with relapse within 1 year after treatment and the ST group showed 28.8 % (17/59) relapse. The percentages showed a significant difference between the two groups ($p = 0.018$)

fat). No patients in the SRT group developed orbital radiotherapy-induced retinopathy, optic neuropathy, or orbital malignancy up to the time of final follow-up. The proportions of patients in each group with side effects associated with an IV steroid pulse therapy were similar; overall, 38 % (48/127) of both groups reported side effects. These included moon face (6 %, 8/127), insomnia (5 %, 6/127), glucose intolerance (2 %, 3/127), paresthesia (2 %, 3/127), gastrointestinal symptoms (4 %, 5/127), facial flushing (2 %, 2/127), liver dysfunction (2 %, 3/127), weight gain (2 %, 2/127), alopecia (1 %, 1/127), fatigue (1 %, 1/127), osteoporosis (1 %, 1/127), acne (2 %, 2/127), foreign body sensation in eye (3 %, 4/127), epiphora (4 %, 5/127), and cataract (2 %, 2/127).

Discussion

In this study, SRT showed a greater efficacy in reducing GO severity than ST when evaluated by NOSPECS. In particular, ocular motility impairment was greatly improved with SRT treatment compared with ST. Previous studies have reported that in GO patients, RT is more efficient in improving ocular motility impairment than at improving proptosis or soft tissue involvement [11]. Mourits et al. also reported that RT is more effective in the treatment of motility impairment and diplopia than in the treatment of proptosis or eyelid swelling [18]. Prummel et al. suggested RT as the treatment of choice in the management of moderately severe GO because RT demonstrated the same therapeutic benefit as steroid therapy, but with fewer adverse events and, therefore, better tolerability [19]. A recent review further proposed that the combination of orbital RT and corticosteroids is superior to steroid treatment alone in the management of ocular impairment in GO patients [20]. Nonetheless, most RT in clinical practice is still only recommended as a secondary treatment for recurrence after steroid therapy. In this study, we compared cases in which RT was included in the primary treatment to cases in which steroids were used alone. The investigation revealed that the inflammation-reducing effects were similar between the two treatment modalities; however, the rate at which the clinical severity decreased over a 1-year follow-up period was significantly greater with the combination therapy. A significant decline in the recurrence rate of inflammation was also noted.

Aggressive anti-inflammatory treatment during the early stage of GO is critical because the ocular movement restriction that occurs after the disease has progressed into the fibrotic stage is very difficult to treat without invasive surgical intervention. Because SRT demonstrated a superior effect in reducing NOSPECS and improving EOM involvement in this

Table 3 Change of EOM muscle volume between baseline and 1-year follow-up in non-GO and GO patients

Volume	Baseline						After 1 year					
	Non-GO ($n=20$)	GO		p [a] Non-GO vs SRT	p [a] Non-GO vs ST	p [a] SRT vs ST	Non-GO ($n=20$)	p [b]	GO (after treatment)			
		SRT ($n=44$)	ST ($n=37$)						SRT ($n=44$)	P [b]	ST ($n=37$)	P [b]
Orbital	18.1 ± 1.7	23.5 ± 1.8	23.1 ± 1.7	**<0.001**	**<0.001**	0.113	18.3 ± 1.9	0.658	22.2 ± 2.0	**0.046**	22.8 ± 1.4	0.065
EOM	4.0 ± 1.1	5.3 ± 1.2	4.9 ± 1.2	**<0.001**	**<0.001**	0.223	3.98 ± 1.1	0.640	4.95 ± 1.3	**0.008**	4.80 ± 1.4	0.533
Fat	14.6 ± 1.1	18.2 ± 3.3	18.0 ± 2.8	**<0.001**	**<0.001**	0.134	14.9 ± 1.4	0.599	17.2 ± 2.4	**0.010**	17.3 ± 2.5	**0.029**

Data presented as means ± standard deviation (cm^3)

GO Graves' orbitopathy, *EOM* extraocular muscle, *SRT* combination of steroid and radiotherapy, *ST* steroid only

Bold values denote statistical significance, $p < 0.05$

[a] Independent *t* test comparing non-GO vs SRT, non-GO vs ST, SRT vs ST

[b] Paired *t* test comparing 1-year value to baseline value

study, we recommend SRT during the early stages of GO to better decrease pathological severity. Ng et al. conducted a similar prospective study involving active moderate to severe GO patients. They reported that the combination of orbital irradiation and systemic steroids versus steroids alone resulted in a greater improvements in symptoms such as soft tissue swelling, ocular motility, and visual acuity. Further, the treatment was better tolerated by the study patients [21]. Furthermore, the results showed that the SRT group had a significantly lower rate of recurrence after treatment and a longer disease-free duration until relapse. Hahn et al. investigated a group of 86 GO patients who received RT and reported no reactivation throughout the 18-month follow-up period, and they proposed that RT can shorten treatment duration and reduce therapeutic dosage, which, in turn, minimizes potential adverse effects [22]. When inflammation is reactivated, patients must frequently resume a high-dose steroid regimen, which increases the risk of severe adverse events and can result in a deterioration in the patient's general condition. Therefore, implementation of RT in the early stage of treatment should be considered to improve the quality of life of GO patients with severe myopathy.

Here, a volumetric analysis of orbital, EOM, and fat was performed as an objective quantitative evaluation index for the therapeutic effect of RT on extraocular motility impairment and proptosis. Our results showed that orbital, EOM, and fat volume significantly decreased in the SRT group following treatment, thus making the clinical results of reducing GO severity and improving ocular motility impairment more persuasive. Considering that there was no significant difference in volumetric values between baseline and after 1 year in the non-GO group, the volumetric changes in the SRT group were attributable to therapy, not physiological variation. These results contradict those of Gorman et al. previously reported in which RT did not affect EOM volume [13]. However, in another study published by the same authors, there was a decrease in muscle volume after 3 years [23]. Wu et al. also recently published a study in which a significant decrease in EOM volume and T2 signal intensity ratio (inferior rectus muscle/ipsilateral temporal muscle) was observed after RT [24].

Combined steroid and radiotherapy lowers the risk of CON [25]. Shams et al. observed study participants for an average of 3.2 years and reported that 25 out of 144 in the ST group and 0 out of 105 in the SRT group developed CON. In the present study, we found that no patients in the SRT group and two out of 59 in the ST group developed CON.

A maximum of 20 Gy is typically applied in orbital RT, a dose that is generally well-tolerated and at which adverse effects in the orbit are generally avoided [26]. A previous long-term study demonstrated that this specific dose showed no increase in the risk of secondary malignancy or decrease in overall survival [27]. Bartalena et al. reported that unusual adverse events, such as the development of cataracts and radiation retinopathy, occur in 10 % and 1 % of cases, respectively [28]. In the present study, RT was applied at a total dose of 20 Gy, 2 Gy per day, and only 3 % of the patients developed cataracts, while no radiation retinopathy occurred.

This present retrospective study was limited in that SRT was more likely to be considered as a treatment for patients with greater clinical severity and ocular motility impairment. Also, the medical cost of RT was not considered in this study despite its substantial influence in decision-making. At Severance Hospital, RT costs an additional US $1000–1500. The price is relatively reasonable compared to the cost in the USA, where it is 3–10 times greater ($3500–15,000) [12]. A low medical cost allows patients more affordability and accessibility to the treatment; however, the effects of cost were not assessed in this study.

In this present study, the therapeutic safety and efficacy of combined orbital RT and steroid treatment versus steroid pulse therapy alone were compared. The combination therapy showed a more significant improvement in clinical severity and motility impairment. A quantitative analysis of the therapeutic effect of RT was demonstrated by the reduction in EOM volume after treatment. This research is notable for its validation of therapeutic RT with objective and evidence-based evaluation of the treatment modality.

Compliance with ethical standards For this type of study, formal consent is not required.

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Conflict of interest All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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