Orbital Radiotherapy in Graves' Ophthalmopathy for 1 week versus 2 weeks:

A Phase II Randomized Controlled Trial (ORaGO-1 Trial)

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Backgrounds

Graves' ophthalmopathy (GO) is an autoimmune disease primarily affecting orbital fibroblasts. The severity of GO is classified as mild, moderate to severe, or sight-threatening by the European Group of Graves' Orbitopathy (EUGOGO), based on subjective and objective criteria. Moderate to severe GO presents with specific signs, including eyelid retraction, soft tissue involvement, and exophthalmos. Disease activity is assessed using the Clinical Activity Score (CAS), with active GO defined as CAS $\geq$ 3. Treatment typically begins with intravenous methylprednisolone (IVMP), with orbital radiotherapy (RT) considered as a second-line option for non-responsive or intolerant patients. Low Dose Radiotherapy (LD-RT) is hypothesized to exert anti-inflammatory, anti-proliferative, and immunomodulatory effects. Studies have shown efficacy of combined LD-RT and IVMP in improving clinical severity. Concerns regarding long-term side effects and treatment access exist. Various RT dosing regimens have been explored, with differing effects on ocular symptoms [1-8]. Our study aims to reduce radiation doses by minimizing fractions, aiming to maintain effectiveness while enhancing patient quality of life.

Study Objectives

This phase II prospective randomized controlled trial aims to compare standard orbital radiotherapy fractionation (2 Gy per fraction, 1 fraction per day, total 20 Gy over 2 weeks) with reduced-dose orbital radiotherapy (2 Gy per fraction, 1 fraction per day, total of 10 Gy over 1 week) in combination with intravenous methylprednisolone (IVMP) for patients with active Grave's ophthalmopathy.

Primary Objective

To assess the non-inferiority of outcomes in terms of the proportion of patients transitioning from active (CAS > 4) to inactive eye disease (CAS <3) with a CAS drop > 2 points following orbital radiotherapy combined with IVMP, comparing standard dose and reduced-dose orbital radiotherapy.

Secondary Objectives

1. To compare the change in volume of extra-ocular muscles and retrobulbar fat after orbital radiotherapy, comparing standard with reduced-dose orbital radiotherapy
2. To evaluate the efficacy in reducing diplopia, by measuring the difference in prism deviation in primary gaze after standard and reduced-dose orbital radiotherapy
3. To assess differences in quality of life, using the Graves' ophthalmopathy quality of life (GO-QOL) scores (Thai version) after standard and reduced-dose orbital radiotherapy.

4. To compare the incidence of the RTOG radiation toxicities after standard and reduced-dose orbital radiotherapy.
5. To examine other ophthalmologic evaluations including visual acuity (VA) and visual fields (VF) between standard dose and reduced-dose orbital radiotherapy.

Inclusion criteria

1. Patient with active moderate to severe thyroid eye disease with a CAS $\geq$ 4 with/ without diplopia before starting IVMP
2. Patient with poor response to 3 doses of IVMP (CAS drop $\leq$ 1) or CAS score $\geq$ 3 after 3 doses of IVMP
3. Patients with diplopia after 3 doses of IVMP
4. Patients with Graves' Ophthalmopathy who have maintained euthyroidism for a minimum of three months.
5. Non-pregnant adults (aged 35 years or older

Exclusion criteria

1. Individuals with severe hypertension or diabetic retinopathy

All patients required full written informed consent.

Withdrawal criteria

1. Graves' Ophthalmopathy with the potential to cause vision-threatening complications.
2. Severe complications, such as severe eye inflammation (Grade 3-4) or severe skin complications (Grade 3-4), as defined by RTOG criteria, or instances of complicating infections necessitating additional treatment.
3. Instances of intolerance will be treated according to the intention-to-treat principle.
4. Patients experiencing complications due to receiving IVMP.

Sample size calculation

The Standard improvement of eye symptoms, as reported in the literature, ranges from 62-85 % after treatment [6,8]. During the protocol development phase, a one-sided approach was defined. The non-inferiority margin was set at 23%, providing 80% statistical power with a one-side α of 0.023. The total sample size calculated by Stata (College Station, TX, USA) was 136 eyes (68 eyes in each arm) and shown below. Considering an expected 15% loss follow-up rate, the estimated sample size would be 136 eyes (68 eyes per arm).

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. power twoproportions 0.85 0.62, m1(2) m2(2) onesided

Estimated numbers of clusters for a two-sample proportions test
Cluster randomized design, Pearson's chi-squared test
H0: p2 = p1  versus  Ha: p2 < p1

Study parameters:

        alpha =    0.0500
        power =    0.8000
        delta =   -0.2300  (difference)
           p1 =    0.8500
           p2 =    0.6200

Cluster design:

           M1 =         2
           M2 =         2
          rho =    0.5000

Estimated numbers of clusters and sample sizes:

           K1 =        34
           K2 =        34
           N1 =        68
           N2 =        68
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The research project is scheduled to span a total of 4 years, covering the entire project duration. The data collection period will also extend over this 4 year, and the researchers affirm the initial schedule.

Throughout the project, data for all N participants will be consistently gathered until the predetermined sample size is attained.

Statistical analysis plan

Primary outcome;

The proportion of changes from active to inactive eye disease.

- Proportion of CAS drop $\geq$ 2 (Before IVMP – week 24th (end of study)

- Using the Chi-squared test

Secondary outcomes

Using a mixed model or analyzed as repeated measurements over various time points.

The comparison of mean changes between the treatment groups will be conducted using the t-test.

- The measurement of the volume of extra-ocular muscles [9] and retro bulbar fat

- Assessment of diplopia (the difference in prism deviation in primary gaze)

- Assessment of Graves' ophthalmopathy Quality of life (Thai version) [11] scores

- Summation of radiation side effects scores (RTOG criteria) [10]

- Visual acuity (VA) and visual fields (VF) (mean deviation of Humphrey visual field)

Study Flow

week 0		- Diagnosis of Active moderate to severe Graves' ophthalmopathy - Preparation of patients for the commencement of systemic high-dose corticosteroid therapy	- Blood for CBC BUN Cr Electrolyte Anti-HIV - CAS Score - Eye examination - QOL
week 1	1st IVMP	- administration of 500 mg IVMP	
week 2	2nd IVMP	- administration of 500 mg IVMP	
week 3	3rd IVMP	- administration of 500 mg IVMP	
Week 4	4th IVMP	- administration of 500 mg IVMP - Evaluation of inclusion and exclusion criteria. - RT consultation	After the completion of three doses of steroids. - CAS Score - Eye examination
week 5	5th IVMP	- administration of 500 mg IVMP - Re-evaluation of inclusion and exclusion criteria. - CT SIMULATION for RT planning	- RT planning - Measure volume/diameter of extra-ocular muscles and retrobulbar fat
week 6	6th IVMP	- administration of 500 mg IVMP - Randomization before starting radiation therapy	- CAS Score - Eye examination - QOL - Acute/Late RT Side effects
week 7	7th IVMP	- administration of 250 mg IVMP - RT completion ARM short course: 10 Gy/5F	- CAS Score - Eye examination - Acute/Late RT Side effects.
week 8	8th IVMP	- administration of 250 mg IVMP - RT completion ARM standard course: 20 Gy/10F	- CAS Score - Eye examination - Acute/Late RT Side effects
week 9	9th IVMP	- administration of 250 mg IVMP	
week 10	10th IVMP	- administration of 250 mg IVMP	

week 11	11th IVMP	- administration of 250 mg IVMP	
week 12	12th IVMP	- administration of 250 mg IVMP Stop IVMP	
week 13-14	-	-	-
week 15		1st Follow up	- CAS Score - Eye examination - QOL - Acute/Late RT Side effects
week 16-23	-	-	-
week 24 END of the study		2nd Follow up CT SIMULATION (Non-contrast)	- CAS Score - Eye examination - QOL - Measure volume/diameter of extraocular muscles and retro bulbar fat - Acute/Late RT Side effects

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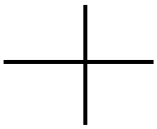
Initial CAS Score item 1-7		
1.Pain or pressure in a periorbital or retroorbital distribution	☐ YES	☐ NO
2.Pain with upward, downward, or lateral eye movement	☐ YES	☐ NO
3.Swelling of the eyelids	☐ YES	☐ NO
4.Redness of the eyelids	☐ YES	☐ NO
5.Conjunctival injection	☐ YES	☐ NO
6.Chemosis	☐ YES	☐ NO
7.Inflammation of the caruncle or plica	☐ YES	☐ NO
Total Score	____ /7	
Follow up after 1-3 months score items including 8-10		
8. increase of > 2 mm proptosis	☐ YES	☐ NO
9. decrease in uniocular ocular excursion in any one direction of > 8 degrees	☐ YES	☐ NO
10.decrease of acuity equivalent to 1 Snellen line	☐ YES	☐ NO
Total Score	____ /10	

Eye assessment		
Hertel's Exophthalmometry Base :_____ mm.	RE _____ .mm	LE _____ .mm
VA Pinhole	RE _____. RE _____.	LE _____. LE _____.
RAPD	RE Present /Absent	LE Present /Absent
Color vision	RE Normal /Abnormal	LE Normal /Abnormal
Motility	RE Ductions (degrees) Restriction 	LE Ductions (degrees) Restriction
Lid retraction	☐ YES	☐ NO
Eyelid measurement	RE upper (MRD-1) _____mm (inferior sclera show) _____ mm Lagophthalmos _____mm	LE upper (MRD-1) _____mm (inferior sclera show) _____ mm Lagophthalmos _____mm
Corneal stain	RE _____ sec.	LE _____ sec.

Radiological assessment

CT SIMULATION

	RE	LE
Extraocular muscle diameters	- Inferior rectus_____cm - Medial rectus_____cm - Lateral rectus_____cm - Superior group_____cm	- Inferior rectus_____cm - Medial rectus_____cm - Lateral rectus_____cm - Superior group_____cm
Extraocular muscle volume	- Inferior rectus_____cm^3 - Medial rectus_____cm^3 - Lateral rectus_____cm^3 - Superior group_____cm^3	- Inferior rectus_____cm^3 - Medial rectus_____cm^3 - Lateral rectus_____cm^3 - Superior group_____cm^3
Proptosis	_____ cm	_____ cm
Retrobulbar fat volume	_____ cm3	_____ cm3

Grave's Ophthalmopathy Quality of Life (GO-QOL) (Thai version) (Lumyongsatien M

	0 (never)	1 Seriously limited	2 A little limited	3 Not limited at all
Functioning				
1. Bicycling				
2. Driving				
3. Moving around the house				
4. Walking outside the house				
5. Reading				
6. Watching TV				
7. Enjoying hobby or pastime				
8. Prevented from doing what you want to do				
Appearance				
9. Changed physical appearance				
10. Stared at on the streets				
11. People have a negative reaction				
12. Influence on self-confidence				
13. Social isolation				
14. Effect on making friends				
15. Reluctance to be photographed				
16. Hide or conceal physical changes				
			Raw score _____	Total Score ___ /100

Total score = (raw score – Y)/ (2 x Y) x 100

Y; number of completed question items

RTOG Radiation side effects

Tissue	Gr .0	Gr .1	Gr .2	Gr .3	Gr .4
Dry eye	☐ None	☐ Asymptomatic clinical or diagnostic observations only; symptoms relieved by lubricants	☐ Symptomatic moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	☐ Symptomatic with marked - decrease in visual acuity , limiting self-care ADL	
Eye pain	☐ None	☐ Mild pain	☐ Moderate pain; limiting instrumental ADL	☐ Severe pain; limiting self-care ADL	
Keratitis	☐ None	☐ Asymptomatic	☐Moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	☐Symptomatic with marked decrease in visual acuity limiting self-care ADL	☐Perforation; best corrected visual acuity of 20/200 or worse in the affected eye
Eyelids	☐ None	☐Erythema ☐Loss of eye lashes	☐Tender ☐Bright erythema	☐Moist desquamation	☐ Visual loss
Conjunctiva	☐ None	☐Mild conjunctivitis	☐Moderate conjunctivitis		☐ Visual loss
Lacrimal gland system	☐ None	☐ Increased Tearing	☐Need artificial tear		☐ Visual loss
Cornea	☐ None	☐ Scleral injection	☐ Keratitis ☐ Need steroid / ATB	☐ Server keratitis with corneal ulcer	☐ Visual loss
IRIS	☐ None		☐ Iritis ☐ Photophobia		☐ Visual loss
Skin	☐ None	☐ Faint erythema, mild tight skin	☐ Bright erythema /dry desquamation, Itchy ☐ Moist desquamation	☐ confluent moist desquamation , Soreness with edema	☐ Ulceration , hemorrhage , Necrosis
					Total scores _____/ 34