TABLE e4. SUMMARY OF RANDOMIZED CONTROLLED TRIALS COMPARING DIFFERENT ORBITAL RADIOTHERAPY REGIMENTS AND ORBITAL RADIOTHERAPY TO PLACEBO OR CORTICOSTEROIDS

Study	***Treatment Groups***	***Primary Outcome Measure***	***Primary Positive Outcome Results (n, %)***	***Comments***
Bartalena et al 1983[98]	12 pts po steroid [a] 12 pts ORT+ po steroid	OI	po steroid group: 4/12 (33%) ORT+ po steroid group: 10/12 (83%)	Active TED 24 of the total 48 patients were randomized Mean decrease in OI: 4.8 vs 3.2 in favor of ORT+ po steroid group (p=0.005)
Marcocci et al 1991[99]	15 pts ORT [b] 15 pts ORT+ po steroid	OI	ORT group: 5/15 (38%) ORT+ po steroid group: 9/15 (69%)	Active TED 12/13 pts in ORT+ po steroid group had improvement in soft tissue changes. 6/13 pts in ORT group had improvement in soft tissue changes The 1 pt in ORT+ po steroid group had improvement in optic neuropathy. The 1 pt in the ORT group with optic neuropathy had no improvement in optic neuropathy

Prummel et al. 1993[100]	28pts ORT [c] 28 pts po steroid	OI	ORT group: 13/28 (46%) po steroid group:14/28 (50%)	Moderately severe TED 4% in each group considered treatment failures Steroid group improved quicker than ORT group. Side effects more common in steroid group ORT group had more improvement in ocular motility. Steroid group had more improvement in soft tissue. No significant improvement in proptosis in either group
Mourtis et al. 2000[96]	30 pts ORT [d] 30 pts sham	CAS Major and minor clinical criteria (diplopia, lid retraction, proptosis, eyelid swelling)	ORT group: 2 (12%) Sham group: 4 (21%)	Moderately severe TED Greatest improvement was in diplopia. No difference in proptosis or eyelid swelling
Kahaly et al 2000[105]	18 pts group A [e] 22 pts group B 22 pts group C	Response to therapy: significant amelioration of at least three objective signs [*]	Group A: 12/18 (67%) Group B: 13/22 (59%) Group C: 12/22(55%)	Moderately severe TED Decrease in proptosis and ocular motility was noted only in group A. 11% group A, 18% group B and 23% group C required steroids after ORT. 0% group A, 9% group B and 9% group C required orbital decompression after ORT 17% group A, 14% group B and 9% group C required strabismus surgery after ORT

Marcocci et al 2001[101]	41 pts ORT+ po steroid [f] 41 pts ORT+ iv steroid	Changes in at least two major criteria (variations in proptosis and lid width of 2 mm or greater, appearance, disappearance, or change in the degree of diplopia, changes in the CAS 2 points or more, and changes on one tenth or more in visual acuity) and change in one minor criterion (soft tissue changes, self-assessment evaluation)	ORT+ po steroid group: 26/41 (63.4%) ORT+ iv steroid group: 36/41 (87.8%)	Moderately severe TED Significant reduction in proptosis, lid retraction and diplopia in both groups. iv group had a greater % of pts with complete resolution of double vision (48.1% vs 36.4%). Final CAS score was lower in the iv group. Greater % of pts in the iv group had improvement in optic neuropathy (11/14 vs 3/9)
Gorman et al 2002[97]	42 pts: First ORT randomized to one orbit. Six months later fellow orbit treated with ORT. [g]	Volume of extraocular muscle and fat Ocular movement and diplopia Lid retraction	See comment section	Moderate TED At 6 months there was no difference in any of the clinical parameters measured between the ORT treated and sham treated orbits.
Gerling et al 2003[106]	41 pts 2.4 Gy ORT [h] 40 pts 16 Gy ORT	Appearance of eye region Exophthalmos Range of vertical eye motility Eye muscle thickness Patient complaints.	See comment section.	Active TED At 6 months there was no statistical difference between the two groups in any of the 5 outcome criteria All outcome measures in both groups improved

Prummel et al 2004[94]	44 pts ORT [i] 44 pts sham	Major criteria (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 $\geq$ 1 lines on the Snellen chart) and 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 if improvement in at least two major criteria, good if improvement in one major criterion, fair if improvement in two minor criteria, no change if no changes or a change in only one minor criteria, and worse if deterioration in at least one major or two minor criteria.	ORT group: 23/44 (52%) Sham group: 12/44 (27%)	Mild TED Quality of life was improved in both groups. ORT group had a lower rate of follow-up treatment (66% vs 84%). No difference in progression of mild disease between ORT or sham (14% vs 16%, respectively)
Ng et al 2005[102]	8 pts ORT+ steroid [j] 7 pts steroid	NOSPECS	ORT+ steroid group: 7/8 (87.5%) Steroid group: 4/7(57%)	Moderately severe TED Greatest improvement in ocular motility and soft tissue signs No significant change of proptosis in either group No significant change in vision between the 2 groups

[*] change in lid fissure width >2 mm, proptosis >2 mm, eye muscle area > 5mm^2, or absence of diplopia in primary position (normgaze)

ABBREVIATIONS

TED: thyroid eye disease
ORT: orbital radiotherapy
CAS: clinical activity score
OI: Ophthalmology index
pts: patients
iv: intravenous
po: oral

N/A: not available

TREATMENT PROTOCOLS

[a] ORT: cobalt radiotherapy (10 daily doses of 200 Gy/day, total 2000 Gy/orbit);
Steroids: 70-80 mg/day oral methylprednisolone for 3 weeks. Dose gradually tapered by 5 mg/week until daily dosage of 20 mg, then the dose was subsequently reduced by 2.5-5 mg every 2-3 weeks. Treatment discontinued after 5-6 months.

[b] ORT: Linear accelerator (10 daily doeses of 2 Gy/day over 2 weeks)
Steroids: 100 mg/day oral prednisone for 7 days followed by gradual weekly reduction until a daily dose of 25 mg reached, then dose reduced by 5 mg every 2 weeks till discontinuation.

[c] ORT: Linear accelerator (10 daily doses of 2 Gy/day over 2 weeks);
Steroids: 60 mg/day po prednisone for 2 weeks, 40 mg/day 2 weeks, 30 mg/day 2 weeks, 20 mg/day 2 weeks, taper by 2.5 mg/week until zero.

[d] ORT: Linear accelerator (20 Gy in 10 fractions over 12 days)

[e] ORT: Linear accelerator
Group A= 20 fractions of 1 Gy weekly over 20 weeks (protracted protocol; total or cumulative dose, 20 Gy)
Group B= 10 fractions of 1 Gy daily, 5 days a week over 2 weeks (short arm regimen; total dose, 10 Gy)
Group C= 10 fractions of 2 Gy daily over 2 weeks (short arm; total dose, 20 Gy)

[f] ORT: Linear accelerator (total of 20 Gy was delivered to each orbit in 10 fractions over 2 wks);
Steroids: 100 mg/day po prednisone for 7 days followed by gradual weekly reduction until a dose of 25 mg was reached; the dose was then tapered by 5 mg every 2 wk or iv methylprednisolone 15 mg/kg body weight for four cycles and then 7.5 mg/kg body weight for four cycles; each cycle consisted of two infusions on alternate day at 2 wk intervals. The duration of treatment was 14 weeks.

[g] ORT: Linear accelerator (total of 20 Gy to each orbit in 10 fractions over 12 days).

[h] ORT: Linear accelerator (8 divided fractions of 0.3 Gy daily over 16 days (total of 2.4 Gy) or 8 divided fractions of 2.0 Gy daily over 16 days (total of 16 Gy))

[i] ORT: Linear accelerator (10 divided fractions of 2 Gy daily over 2 wks)

[j] ORT: Linear accelerator (total of 20 Gy to each orbit in 10 fractions over 2 weeks);
Steroids: iv methylprednisolone 500 mg/day for 3 days followed by 0.7 mg/kg oral prednisolone daily for 4 weeks. From week 5, the dose was reduced by

5 mg per week until it reached 5 mg per day and was then further reduced to 2.5 mg daily for 1 more week and then stop