

1 Combined immunosuppression & radiotherapy in thyroid eye disease (CIRTED): a multi-  
2 centre, factorial randomised controlled trial

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50

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52 **Abstract**

53 *Background*

54 Thyroid eye disease is a disabling inflammatory orbital condition causing visual dysfunction  
55 and psychological morbidity. The additional benefit of concomitant orbital radiotherapy and  
56 antiproliferative immunosuppression is unclear.

57

58 *Methods*

59 Participants all received a 24 week course of oral prednisolone and were also randomised to  
60 receive radiotherapy or sham-radiotherapy, and azathioprine or placebo, in a 2x2 factorial  
61 design. The primary outcomes were a binary composite clinical outcome score and  
62 ophthalmopathy index at 48 weeks and clinical activity score at 12 weeks. (ISRCTN 22471573).

63

64 *Findings*

65 126 patients were randomized of which 103 (82%) provided outcome data. In those providing  
66 data 39 (80)% of these randomised to radiotherapy remained in the study long enough to  
67 complete it. Pre-specified intention-to-treat analysis of improvement in the binary clinical  
68 composite outcome measure was observed for azathioprine  $OR_{(adj)}=2.56$  (95% CI 0.98, 6.66;  
69  $p=0.05$ ) but not radiotherapy  $OR_{(adj)}=0.89$  (95% CI 0.36, 2.23;  $p=0.80$ ). In a post hoc analysis  
70 of patients completing their allocated therapy, improvement was more frequent on azathioprine  
71 ( $OR_{(adj)}=6.83$ ; 95% CI 1.66, 28.1;  $p=0.008$ ) than radiotherapy ( $OR_{(adj)}=0.71$ ; 95% CI 0.26, 1.95;  
72  $p=0.50$ ). The ophthalmopathy index, clinical activity score and also number of adverse events  
73 (azathioprine N=161, radiotherapy N=156) did not differ between treatment groups.

74

75 *Interpretation*

76 In patients receiving oral prednisolone for 24 weeks, the addition of radiotherapy was not  
77 beneficial. Regarding azathioprine, our conclusions are limited by a high number of  
78 withdrawals from treatment. However, these results suggest that disease severity at 48 weeks  
79 was reduced in participants who completed azathioprine treatment.

80

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82 *National Eye Research Centre, Moorfields Eye Charity, NIHR infrastructural investment*  
83 *support.*

84

85

**Research in Context**

Active moderate-to-severe thyroid eye disease is currently treated with systemic corticosteroids, but outcomes are often sub-optimal. Corticosteroids are most effective when administered intravenously, but this is inconvenient, and oral administration remains common in global clinical practice. However, uncertainty remains about the additional benefit of orbital radiotherapy and antiproliferative immunosuppressive drugs.

**Evidence before this study**

Previous retrospective case series have reported that the antiproliferative immunosuppressive drug azathioprine reduces disease severity and the need for rehabilitative surgery, but no prior RCTs have been completed. The evidence base for orbital radiotherapy is stronger, but conflicting, especially in the context of systemic corticosteroid treatment.

**Added value of this study**

Eighty per cent of subjects completed radiotherapy, but no significant short (12 week) or longterm (48 week) benefit resulted over and above the improvement seen with a 24-week tapering course of oral corticosteroids. Less strong conclusions can be drawn with regard to azathioprine, as many patients did not complete treatment due to abnormalities in monitoring blood tests or side-effects, but those that continued azathioprine for more than 24 weeks benefitted, predominantly due to a prevention of deterioration after the end of corticosteroid treatment.

**Implications of all the available evidence**

These results do not support the use of radiotherapy in thyroid eye disease in patients also treated with systemic corticosteroids. They also provide evidence in favour of the use of anti-proliferative immunosuppressive agents such as azathioprine beyond the period of corticosteroid therapy to improve long-term clinical outcomes.

87 **Introduction**

88 Active moderate-to-severe thyroid eye disease, also known as Graves' orbitopathy or thyroid  
89 associated orbitopathy) occurs in 5-10% of cases of Graves' disease(1). It can be both visually  
90 disabling and cosmetically disfiguring and substantially impairs quality of life(1-3). The aim  
91 of treatment is to suppress orbital inflammation and reduce consequent tissue re-modelling in  
92 extraocular muscles, orbital fat and other periocular soft tissues(4, 5). Immunosuppressive  
93 therapies, in particular corticosteroids(1, 4, 6), are the mainstay of treatment for active  
94 moderate-to-severe thyroid eye disease (1). However, they are typically withdrawn after 24  
95 weeks of treatment to limit cumulative toxicity regardless of whether they are administered via  
96 the oral or intravenous route(7), and given that active disease lasts 1–2 years, recurrence at the  
97 time of withdrawal often occurs(1, 7-9).

98

99 Consequently, the avoidance of corticosteroid side-effects, improvement in treatment efficacy  
100 and maintenance of long-term disease control are major goals for the field of thyroid eye  
101 disease as a whole. However, efforts to use monoclonal antibody therapies to more selectively  
102 suppress disease are still either early in their route to market(10), or have failed to demonstrate  
103 definitive treatment benefit(11, 12). Hence, given the proven short-term efficacy of  
104 corticosteroids in the treatment of active moderate-to-severe thyroid eye disease , it is likely  
105 that they will remain the gold-standard first-line treatment for several years to come, and the  
106 need to find adjunctive therapies to augment and sustain their benefit remains very real.

107

108 To date, the only non-corticosteroid conventional immunosuppressant drug to have been  
109 evaluated in RCTs is cyclosporine A(13, 14), which was found to be beneficial, but its use has  
110 not been widely adopted because of concerns about side-effects(6). An alternative strategy is  
111 to use an antiproliferative agent such as azathioprine as it is better tolerated than cyclosporine  
112 A(15, 16) and although ineffective as monotherapy(17), retrospective data indicates that in  
113 combination with corticosteroids it reduces disease severity and the need for rehabilitative  
114 surgery(18). In addition to immunosuppression, non-pharmaceutical treatment of active  
115 thyroid eye disease with orbital radiotherapy has been advocated for decades, and older RCTs

116 demonstrated that this was more effective when used in combination with corticosteroids(19,  
117 20). . However, subsequent studies either questioned the role of orbital radiotherapy or  
118 concluded that its benefit was limited to improvement in oculomotility(21-23). This has  
119 generated significant controversy, in particular due to concerns about the entry criteria, trial  
120 design and radiotherapy administration in Gorman et al's paper(22), which has led to disparity  
121 in practice. Orbital radiotherapy has now been largely abandoned in North America, whereas  
122 in European centres, including the UK, it is still routinely used(6, 23-25). As it is administered  
123 daily over 2-3 weeks and patients are typically of working age, this also has significant  
124 implications for the use of healthcare resources and patients' time. Furthermore, only two  
125 relatively small studies have evaluated the additional effect of radiotherapy when combined  
126 with a high-dose course of systemic corticosteroids(19, 20), and clinical outcomes beyond 24  
127 weeks have rarely been reported for any intervention in thyroid eye disease. **We therefore**  
128 **sought to evaluate the long-term benefit of orbital radiotherapy and low-cost antiproliferative**  
129 **immunosuppression with azathioprine** in the context of sustained systemic corticosteroid  
130 treatment for active moderate-to-severe thyroid eye disease .

131

## 132 **Methods**

### 133 *Study design and participants*

134 We undertook this **factorial design multicentre RCT in 6 centres in the UK**. Patients were  
135 recruited to receive either azathioprine or placebo, *plus* either orbital radiotherapy or sham-  
136 radiotherapy, in *combination* with a standardised 24-week tapering oral prednisolone regime  
137 **(Supplementary Table 1 and Supplementary Figure 1)**. In brief, all patients received an  
138 initial oral prednisolone dose of 80mg / day, which reduced to 20mg / day by 6 weeks, 10mg /  
139 day by 15 weeks and 5mg / day by 21 weeks. In accordance with the factorial design, study  
140 recruits were then randomly allocated into 4 groups 2 weeks after starting corticosteroids:  
141 azathioprine plus orbital radiotherapy, azathioprine plus sham-radiotherapy, placebo plus  
142 orbital radiotherapy, or placebo plus sham-radiotherapy. Full protocol details, including pre-  
143 specified primary and secondary outcome measures and statistical analyses, have been  
144 previously peer-reviewed, published and are openly available(26).

145

146 Eligible patients had a clinical activity score(27)  $\geq 4$  (worst eye) OR  $\geq 2$  (worst eye) with a  
147 history of proptosis or motility restriction of less than 6 months duration. They were also  
148 required to have a past or present history of abnormal thyroid function or a clinical diagnosis  
149 of thyroid eye disease made and confirmed by  $\geq 2$  muscle involvement on computed  
150 tomography or magnetic resonance imaging scan. The clinical activity score was scored out of  
151 7 at the enrolment visit as its last 3 items (decreasing proptosis, decreasing visual acuity and  
152 decreasing eye movement) require a change in consecutive measurements to be calculated.  
153 This therefore cannot be done at the first assessment, but at all subsequent visits clinical activity  
154 score was scored out of 10. If study recruits *either* had a  $< 6$  month history of thyroid eye  
155 disease (defined as time since first symptom) *or* an improvement in any item of clinical activity  
156 score 2 weeks after starting the trial prednisolone regime, they were considered to have active  
157 disease and were randomised at the second trial visit. Key exclusion criteria included age  $< 20$   
158 or  $> 75$  years, dysthyroid optic neuropathy, abnormal thiopurine methyltransferase activity and  
159 use of radioiodine or any immunomodulatory or cytotoxic drugs within the last 3 months  
160 (thyroidectomy was permitted).

161

#### 162 *Randomisation and masking*

163 Patients were allocated to treatment groups by remote computerised randomization.  
164 Minimisation was used to reduce baseline disparities in potential confounding variables  
165 between trial interventions. These included smoking status at the time of thyroid eye disease  
166 diagnosis, thyroid status on enrolment, previous corticosteroid use, gender, disease  
167 severity, study centre, disease duration, age greater than 60 years and disease activity.

168

#### 169 *Procedures*

##### 170 *Orbital radiotherapy*

171 Twenty gray (Gy) of radiation was administered to the retrobulbar orbit in 10-12 fractions over  
172 2 to 3 weeks. Subjects receiving sham-radiotherapy also attended and underwent all the same  
173 procedures other than no radiation being delivered. Extensive effort was used across trial

174 centres to ensure participants were unable to identify if they were receiving sham therapy,  
175 including use of a noise emitting device to simulate treatment administration(26) (for details  
176 of the radiotherapy procedures at each trial centre see **Supplementary Text 2)**

177

#### 178 *Azathioprine*

179 Treatment dose varied between 100mg and 200mg daily (dispensed as 50 mg tablets),  
180 depending on body weight. Matched placebo tablets and packaging were used and the dose  
181 was adjusted according to a standard algorithm dependent on patients' blood test results. Again,  
182 extensive effort was taken to ensure participants were unaware if they were receiving placebo,  
183 including identical blood tests and random placebo dose adjustments. To reduce the risk of  
184 serious adverse events, patients with abnormal thiopurine methyltransferase activity who are  
185 at increased risk of developing bone marrow suppression (low activity) or hepatotoxicity (high  
186 activity) with azathioprine were not enrolled.

187

#### 188 *Follow-up and withdrawals*

189 Follow-up continued for a minimum of 48 weeks. Withdrawn subjects were returned to their  
190 referring ophthalmologist, however they were invited to attend assessment visits at the early  
191 (co-primary) and late (primary) outcome measure assessment times of 12 and 48 weeks to  
192 obtain data in accordance with the planned intention-to-treat analyses. Withdrawal criteria  
193 included worsening of disease (defined as a 2 point increase in clinical activity score or  
194 development of optic neuropathy) and sustained blood test abnormalities (leucopenia,  
195 lymphopenia or abnormal liver function tests despite dose adjustment of azathioprine or  
196 placebo).

197

#### 198 *Ethical approval and Trial Oversight*

199 The trial protocol was given a favourable opinion by the UK's National Health Service South  
200 West Central Bristol Research Ethics Committee (REC reference: 05/Q2006/62). Clinical Trial  
201 Authorisation was given by the Medicines and Healthcare products Regulatory Agency  
202 (MHRA, reference: 03299/0003/001-0001; ISRCTN22471573) with the University of Bristol



203 acting as the legal sponsor. Research governance and local Research and Development  
204 approvals were obtained across all sites prior to the start of recruitment. All participants gave  
205 written informed consent.

206

### 207 *Outcomes*

208 As the principle objective of the trial was to evaluate treatment success and failure at the late  
209 time-point of 48 weeks, our primary outcome measures of disease severity binary clinical  
210 composite outcome measure (**BOX 1**) and Ophthalmopathy Index (**Supplementary Table 2**)  
211 were selected to quantify the change in ocular deformity and visual dysfunction. An early, 12-  
212 week, assessment of disease activity using the clinical activity score score was given lower  
213 priority and designated as a co-primary outcome (we expected that all participants would have  
214 a significant improvement in clinical activity score by 48 weeks in accordance with the natural  
215 history of the disease(28)). Secondary outcome measures included Total Eye Score  
216 (**Supplementary Table 3**) as an additional assessment of disease severity, and the patient-  
217 reported Graves' Ophthalmopathy Quality of Life score.

#### **Box 1 Calculation of the Binary Clinical Composite Outcome Measure**

##### ***Major Criteria***

- An improvement of  $\geq 1$  grade in diplopia score
- An improvement of  $>8$  degrees of eye movement in any direction
- A reduction of  $\geq 2$  mm in proptosis

##### ***Minor Criteria***

- A reduction of  $\geq 2$  mm in lid aperture
- An improvement of  $\geq 1$  grade in soft tissue involvement
- An improvement in best-corrected visual acuity of  $\geq 1$  line on the Snellen chart
- Subjective improvement

***All items refer to the worst eye***

***Response to treatment is calculated as follows***

*Improved* = improvement in  $\geq 1$  major criteria or  $\geq 2$  minor criteria

*No Change* = improvement or deterioration in  $\leq 1$  minor criterion

*Worse* = deterioration in  $\geq 1$  major or  $\geq 2$  minor criteria (even if other criteria improve)

218

219 *Statistical analyses*

220 Planned statistical analyses were pre-specified in our protocol paper, based on a sample size of  
221 100 complete datasets at 48 weeks(26). These were undertaken according to CONSORT  
222 guidelines for RCTs. **As required by the factorial design, the primary intention-to-treat** analysis  
223 (ITT) combined the treatment groups to compare radiotherapy versus sham-radiotherapy and  
224 azathioprine versus placebo for each of the two primary outcomes at 48 weeks follow up. This  
225 analysis was made using multivariable regression models, adjusting for minimisation variables,  
226 the factorial design, and the value of the outcome variable at baseline. Statistical significance  
227 was defined in advance as a p-value of <0.05. Patients who had no outcome data for the primary  
228 analyses had data imputed using last observation carried forward if they had data available  
229 between 24-48 weeks. Analysis was performed for all primary outcomes (binary clinical  
230 composite outcome, Ophthalmopathy Index and Clinical Activity Score) Patients who withdrew  
231 from treatment due to side-effects, disease progression or personal preference, were  
232 encouraged to continue to attend for follow-up assessments and their data included in the  
233 **intention-to-treat analyses**. Since there were a large number of withdrawals from treatment  
234 (although most trial subjects still returned for assessment at the primary endpoint visit), **a post-**  
235 **hoc** as-per-protocol analysis was conducted including only patients who had not withdrawn  
236 and continued to receive their assigned treatment. Testing for interaction was performed using  
237 likelihood ratio tests. Additional sensitivity analyses were performed for the binary clinical  
238 composite outcome measure including recoding those who withdrew due to deterioration,  
239 irrespective of their final status at 48 weeks (as they may have received alternative rescue  
240 therapy). **Secondary patient-reported health economic analyses were planned but not**  
241 **completed due to insufficient data**. All statistical analyses were undertaken using STATA  
242 version 12 (STATA CORP, College Station, TX, USA).

243

244 *Study Sponsor and role of the funding source*

245 The study sponsor was the University of Bristol. Funding was provided by the UK's National  
246 Eye Research Centre and Moorfields Eye Charity supported by infrastructural investment from

247 the National Institute for Health Research. The sponsor and funders had no role in the study  
248 design, in the collection, analysis, and interpretation of data, in the writing of the report or in  
249 the decision to submit the paper for publication. In addition, the corresponding author had full  
250 access to all of the data and the final responsibility to submit for publication.

## 251 **Results**

### 252 *Study Population*

253 126 people were recruited and randomised in this study between February 2006 and October  
254 2013 (71 patients from Moorfields Eye Hospital, 34 from Bristol Eye Hospital, 7 from  
255 Manchester Eye Hospital, 5 from the Western Eye Hospital, 4 from University College London  
256 Hospital, 4 from Gartnavel General Hospital and 1 from the University Hospital of Wales).  
257 The flow of study participants is shown in **Figure 1**. Data on both the primary outcomes was  
258 provided by 103 participants. Baseline characteristics of the minimisation variables by group  
259 are shown in **Table 1**. Individuals allocated to azathioprine had a relatively lower proportion  
260 of non-caucasian patients (not a criterion used for minimisation).

261

### 262 *Intention-to-treat analysis*

#### 263 *Binary Clinical Composite Outcome Measure (primary outcome)*

264 The difference in the binary clinical composite outcome measure between individuals  
265 randomised to azathioprine versus placebo tablets was on the threshold of our pre-specified  
266 significant p-value of  $<0.05$ , but did not meet this (the adjusted odds ratio [ $OR_{adj}$ ] of the **binary**  
267 **clinical composite outcome measure's improvement** on azathioprine was 2.56; 95%CI 0.98,  
268 6.66;  $p=0.05$ , **Table 2 Figure 2A**). In contrast, there was no improvement with orbital  
269 radiotherapy ( $OR_{adj} = 0.89$ , 95%CI 0.36, 2.23,  $p=0.80$ ). **Also with** regard to the factorial  
270 design, there was no evidence of interaction between azathioprine and radiotherapy ( $p_{int} = 0.86$ )  
271 and the combination of azathioprine and orbital radiotherapy did not offer additional advantage  
272 over azathioprine alone. An overview of the impact on the binary clinical composite outcome  
273 measure of azathioprine and orbital radiotherapy is shown in **Supplementary Figure 2A+2B**.  
274 Furthermore, additional sensitivity analyses in which withdrawn patients were coded to  
275 unfavourable outcomes regardless of their status at 48 weeks enhanced rather than lessened the

276 improvement observed with azathioprine treatment ( $OR_{adj}$  3.65; 95%CI 1.34, 9.86;  $p=0.01$ ,  
277 **Supplementary Table 4**).

278

279 *Ophthalmopathy Index (primary outcome)*

280 Analysis of all patients revealed that the ophthalmopathy index fell between week 12 (mean  
281 9.15, SD 0.39) and week 48 (mean 8.43, SD 0.38,  $p=0.04$ ). No additional benefits were seen  
282 with either azathioprine or orbital radiotherapy. Individuals randomised to azathioprine had an  
283 adjusted Beta ( $B_{(adj)}$ ) of 0.46 (95%CI -1.04, 1.95;  $p=0.55$ ) and in those randomised to orbital  
284 radiotherapy  $B_{(adj)}$  was -0.89 (95%CI -2.34, 0.56;  $p=0.23$ ) (**Table 2**). There was also no  
285 evidence of an interaction between azathioprine and radiotherapy in their effect on  
286 ophthalmopathy index ( $p_{int} = 0.51$ ).

287

288 *Clinical Activity Score (co-primary outcome)*

289 Across all subjects, substantial improvement in median clinical activity score was seen over  
290 the study period from 5 (IQR 4 - 5) at baseline to 3 (IQR 2- 4;  $p<0.0001$ ) at week 12, and 2  
291 (IQR 1-3;  $p<0.0001$ ) at week 48 (**Figure 2B, 2C**). The majority of patients  $n=97$  (70.0%)  
292 improved their clinical activity score by week 12 and 96 (98%) of the 98 patients with clinical  
293 activity score data at 48 weeks showed improvement in their clinical activity score versus  
294 baseline. No difference in the change in clinical activity score at 12 weeks was observed  
295 between individuals who received treatment with azathioprine versus not receiving  
296 azathioprine, or who received radiotherapy versus sham radiotherapy  $B_{(adj)} = -0.01$  (95%CI -  
297 0.69, 0.68;  $p=0.99$  – **Table 2**). There was no interaction between azathioprine and radiotherapy  
298 in their effect on clinical activity score ( $p_{int} = 0.48$ ). There was also no evidence that  
299 azathioprine or orbital radiotherapy improved clinical activity score score at week 48  
300 (**Supplementary Table 5**).

301

302 *Total Eye Score (secondary outcome)*

303 Total eye score improved considerably over the study period with a mean at baseline of 15.1  
304 (95%CI 13.8, 16.3) falling to a mean of 9.36 (95%CI 8.12, 10.6;  $p < 0.0001$ ), but this was not

305 affected by the addition of either azathioprine or orbital radiotherapy (**Supplementary Table**  
306 **6**).

307

308 *Graves Ophthalmopathy Quality of Life (secondary outcome)*

309 Across all subjects, mean Graves ophthalmopathy quality of life visual function was higher  
310 (improved) at 12 weeks than at baseline (71.5 - 95%CI 66.1, 76.9 vs 64.1 - 95%CI 58.5, 70.0;  
311  $p=0.002$ ), and at week 48 (75.5 - 95%CI 70.3, 80.7;  $p<0.001$  versus baseline). GO-QoL visual  
312 appearance was also higher at 12 weeks than at baseline (58.0 - 95%CI 52.5, 63.5 vs 53.2 -  
313 95%CI 47.9, 58.6;  $p=0.007$ ) and at week 48 (61.3 - 95%CI 55.6, 67.1;  $p=0.001$  versus  
314 baseline). Individuals who had an improvement in the binary clinical composite measure at  
315 week 48 had a higher Graves ophthalmopathy quality of life visual function ( $B=17.9$  - 95%CI  
316 7.07, 28.6;  $p<0.001$ ) and a higher Graves ophthalmopathy quality of life visual appearance  
317 ( $B_{(adj)}=11.5$  - 95%CI 0.60, 23.6;  $p=0.06$ ). There was no clear benefit from the addition of either  
318 azathioprine or orbital radiotherapy with regard to long-term Graves ophthalmopathy quality of  
319 life visual function or visual appearance (**Supplementary Table 7, Supplementary Figure**  
320 **3**).

321

322 *As-per-protocol (APP) analysis*

323 Sixty individuals did not withdraw from study treatment before 48 weeks, completed their  
324 therapy period as allocated and were included in the APP analysis. Ten of these patients were  
325 randomised to azathioprine and sham-radiotherapy, 17 were randomised to orbital radiotherapy  
326 and placebo alone, 12 were randomised to azathioprine and orbital radiotherapy and 21 were  
327 randomised to sham-radiotherapy and placebo. Individuals in the APP analysis appeared  
328 similar at baseline to those who were withdrawn from study treatment, although there was a  
329 higher percentage of non-caucasians in those recruited from the larger study centres  
330 (**Supplementary Table 8**).

331

332 In the APP analysis, individuals randomised to receive azathioprine ( $n=22$ ) had a higher odds  
333 ratio of improvement in their disease severity measured by the **primary** binary clinical

334 composite outcome measure at 48 weeks ( $OR_{(adj)}=6.83$ , 95%CI 1.66, 28.1;  $p=0.008$ ). No  
335 benefit was seen in individuals randomised to receive orbital radiotherapy ( $OR_{(adj)}$  1.32,  
336 95%CI 0.36, 4.84;  $p=0.67$ , **Table 3 Figure 2A**). To assess the effect of the duration of  
337 exposure to azathioprine we also conducted a comparative analysis of patients who continued  
338 to receive their allocated treatments at 12 weeks ( $n=84$ ), 24 weeks ( $n=79$ ) and 36 weeks  
339 ( $n=68$ ). This indicated that benefit was observed with  $\geq 24$  weeks of azathioprine exposure  
340 (**Figure 2A, Supplementary Table 9 and Supplementary Figure 2A**). Individuals receiving  
341 azathioprine also had a modest improvement in TES ( $B_{(adj)}=-3.23$ , 95%CI -6.42, 0.03;  
342  $p=0.05$ , **Supplementary Table 6**). However, the APP analysis did not reveal any benefit in  
343 ophthalmopathy index, clinical activity score or Graves ophthalmopathy quality of life of being  
344 randomised to receive either azathioprine or orbital radiotherapy (**Table 3**).

345

#### 346 *Withdrawals from the study*

347 **There** was a high number of patients who withdrew from their allocated treatment ( $n=66$ ,  
348 52.4%) (**Figure 1**), but the majority of these ( $n=45$ , 68.2%) returned for primary outcome  
349 evaluation. Twenty-five withdrawals were within the first 12 weeks (**Figure 3**). Withdrawals  
350 were less in non-caucasians and in participants at two of the study centres (Moorfields and  
351 Bristol Eye Hospitals). Before 48 weeks there were 40 withdrawals in those randomised to  
352 receive azathioprine and 34 withdrawals in those randomised to receive orbital radiotherapy.  
353 Overall, participants randomised to receive azathioprine had increased odds of withdrawal  
354 compared to those who did not  $OR_{(adj)}=2.82$  (95%CI 1.23, 6.45)  $p=0.01$  (**Supplementary**  
355 **Table 10**). The reasons for withdrawal are presented in **Supplementary Figure 4**. Patients  
356 receiving azathioprine had an increased odds of withdrawal due to precautionary blood test  
357 abnormalities or side effects  $OR=9.10$  (95%CI 2.60, 31.9)  $p=0.001$  (**Supplementary Table**  
358 **11**). However, unlike patients receiving placebo, patients taking azathioprine did not withdraw  
359 due to deterioration following cessation of steroid treatment at 24 weeks (**Figure 3C**). No  
360 baseline characteristics predicted withdrawal due to either azathioprine or orbital radiotherapy  
361 although the highest odds of withdrawal for disease deterioration was in the sham-radiotherapy  
362 and placebo group (**Supplementary Table 12**). There was no evidence of bias between

363 treatment groups with regard to failure to provide data at 48 weeks (**Supplementary Table 13**  
364 **and Supplementary Table 14**).

365

366 *Rescue therapy (including surgery) and adverse events*

367 Twenty-one (47%) of the trial subjects who withdrew from study treatment but provided  
368 outcome data were documented to have received additional therapy (**Supplementary Table**  
369 **15**). In most cases this was additional steroid therapy continuing until the endpoint of the study  
370 (week 48). Surgery was however required in 5 individuals, 3 of whom were in the azathioprine  
371 group (3 orbital decompressions, 1 lid surgery and 1 strabismus correction). The number of  
372 individuals experiencing an adverse event did not differ across the treatment groups  
373 (**Supplementary Table 16 and Supplementary Table 17**).

374

## 375 **Discussion**

376 CIRTED fulfilled its target sample size, with more than 100 complete data sets at 48 weeks.  
377 Improvement in our primary, co-primary and secondary outcome measures (binary clinical  
378 composite outcome measure, clinical activity score and Graves ophthalmopathy quality of life)  
379 across all groups confirmed the previously reported benefits of high dose systemic  
380 corticosteroid therapy in active moderate-to-severe thyroid eye disease (**Figures 2B and 2C**).  
381 In this context, orbital radiotherapy did not confer additional patient benefit in any pre-  
382 specified outcome measure either in the short (12-week) or longer term (48-week).  
383 Radiotherapy was delivered early in the treatment (before 12 weeks), and 80.2% (101 subjects)  
384 remained in the study up to this point; hence it is unlikely that this result is significantly  
385 confounded by the high withdrawal rate later in the treatment course.

386

387 Less strong conclusions can be drawn with regard to azathioprine as comparatively few patients  
388 completed the full course of treatment. Nonetheless, the improvement in the binary clinical  
389 composite outcome measure observed in the azathioprine-treated group of subjects that was on  
390 the threshold of statistical significance in our intention-to-treat analysis ( $p=0.05$ ) is likely to be  
391 real as the effect was sustained or enhanced in our sensitivity analyses (**Supplementary Table**

392 **4, Supplementary Table 9**). This is reinforced by the **post-hoc as-per-protocol** analysis results  
393 which showed substantial benefit in favour of azathioprine ( $OR_{(adj)}=6.83$   $p=0.008$ ). Of note,  
394 patient outcomes improved particularly in those receiving azathioprine for 24 weeks or more  
395 (figure 3A). Since steroid therapy was stopped at 24 weeks (as is common practice in thyroid  
396 eye disease), this suggests that the key benefit of azathioprine is to prevent relapse after  
397 withdrawal of steroids. This observation is consistent with the generally recognised role of  
398 azathioprine as a steroid-sparing agent, used to prevent relapse in other autoimmune conditions  
399 and the findings of the MINGO study using an alternative antiproliferative agent  
400 (mycophenylate sodium) (REF). Furthermore, this view is supported by analysis of the binary  
401 clinical composite outcome measure components indicating that azathioprine did not increase  
402 major improvement rates overall but did reduce major deterioration in the binary clinical  
403 composite outcome measure ( $p=0.004$ , **Supplementary Figure 2A**), plus the observation that  
404 late withdrawal (after 24 weeks) due to deterioration was not seen in patients treated with  
405 azathioprine (**Figure 3C**).

406

407 A major feature of this study was the high rate of withdrawal from patients' allocated treatment.  
408 In all study groups, early withdrawals (before 24 weeks) due to disease deterioration were seen  
409 as the steroid dose was reduced and this was not mitigated by orbital radiotherapy (**Figure 3C**).  
410 Our masked protocol necessarily set strict thresholds for withdrawal due to abnormal  
411 monitoring blood tests (white cell counts and liver function), which together with treatment  
412 side-effects led to more common withdrawals in those allocated to azathioprine (**Figure 3B**).  
413 Hence, it is likely that in usual clinical practice azathioprine treatment would be continued in  
414 a higher percentage of patients. Importantly, many of those withdrawing from treatment still  
415 completed their study follow-up visits until the primary endpoint (48 weeks), resulting in the  
416 outcomes for over 80% of randomised subjects being available for **our intention-to-treat**  
417 analysis.

418

419 The other key methodological point to consider is our use of two primary outcome measures  
420 at 48 weeks. As we have previously published(26), this was because of the lack of fully



421 validated long-term disease severity measures in thyroid eye disease. We also wished to  
422 mitigate the theoretical limitations of composite binary scoring systems, in particular with  
423 regard to baseline variability between treatment groups, by using a continuous variable with  
424 regression analyses in mind. However, our minimisation strategy was successful in balancing  
425 baseline features across trial arms and the binary clinical composite outcome measure has since  
426 become the preferred end-point for thyroid eye disease studies as it is more sensitive to  
427 change(21, 23). We have therefore focused on this rather than the ophthalmopathy index which  
428 has not been a primary endpoint in other recent trials.

429

430 The key strengths of this RCT include the use of minimisation, low rates of loss-to-follow-up  
431 (including of withdrawn patients) and the extensive efforts that were made to mask both  
432 azathioprine and radiotherapy treatment allocation to both the patients and clinicians (including  
433 the use of sham radiotherapy). In addition, we observed no evidence of interaction between the  
434 two interventions (radiotherapy and azathioprine), which is supportive of our choice of a  
435 factorial design. Conversely, a major limitation of our study was the high withdrawal rate,  
436 particularly for those randomised to receive azathioprine. Therefore our conclusions with  
437 regard to the efficacy of this treatment need to be interpreted with caution. We also permitted  
438 patients to enrol in the trial and start systemic corticosteroid therapy before their thyroid  
439 function tests were normalised. This potentially confounds the interpretation of our data with  
440 the benefit of returning to euthyroidism, but we judged intervening with immunosuppression  
441 in the early active phase of disease to outweigh this risk. Furthermore, given that demonstration  
442 of clinical improvement following a 2 week course of high-dose oral steroids was a key entry  
443 criterion, our results cannot be extrapolated to infer the value of radiotherapy or azathioprine  
444 in patients with steroid refractory disease. Oral steroid therapy was used in this study and given  
445 to all study participants as this was the **standard of care in the study centres at the time of trial**  
446 **initiation** and remains commonly prescribed in many regions **including North America(29).**

447

448 In summary, our results suggest that low-dose orbital radiotherapy confers no additional short  
449 or long-term treatment benefit when combined with a six-month reducing course of oral

450 corticosteroids. Our findings with regard to azathioprine are less definitive, but taken together  
451 indicate that, if tolerated, azathioprine improves 48-week clinical outcomes in patients with  
452 active moderate-to-severe thyroid eye disease. This supports the use of long-term  
453 antiproliferative treatments in combination with systemic corticosteroids for the treatment of  
454 active moderate-to-severe thyroid eye disease, consistent with established practice in other  
455 autoimmune conditions.

456

457

458

459

460 **Table and figure headings**

461	Table 1	Characteristics of the 4 trial groups
462	Table 2	Intention to treat analysis Binary Composite Clinical Outcome Measure,
463		Ophthalmopathy Index and Change in Clinical Activity Score
464	Table 3	As per protocol analysis Binary Composite Clinical Outcome Measure,
465		Ophthalmopathy Index and Change in Clinical Activity Score
466	Figure 1	Consort Diagram
467	Figure 2A	Odds ratio of having an improved Binary Composite Clinical Outcome
468		Measure score by treatment and duration in study
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473	Figure 3A	Kaplan Meier survival showing withdrawals from treatment (all reasons)
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475		abnormal blood results)
476	Figure 3C	Kaplan Meier survival showing withdrawals from treatment (deterioration)
477		

478

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504

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507

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518

519 **Declaration of Interest**

520 The authors report no declarations of interest

521

522

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- 610



**Table 1 Characteristics of the Four Trial Groups**

<b>Variable</b>	<b>RT + Aza</b>	<b>Sham + Aza</b>	<b>RT + Placebo</b>	<b>Sham + Placebo</b>
Number of patients	31	31	32	32
Age at enrollment	50·4 (10·4)	51·4 (9·53)	46·1 (11·5)	49·2 (11·7)
Age ≥ 60 years (%)	16·1	12·9	18·8	15·6
Disease Duration (months)	6·01 (11·4)	5·01 (4·39)	5·50 (9·41)	7·29 (12·6)
Duration > 6 months	35·5	22·6	34·4	28·1
Ethnicity (% Non Caucasian)	12·9	22·6	40·6	34·4
% Male	29·0	22·5	28·1	25
% Smoker	54·8	48·4	34·4	46·9
Thyroid State (%)				
Euthyroid	9·7	12·9	9·7	6·3
Hyperthyroid	83·9	74·2	80·7	81·3
Hypothyroid	6·5	12·9	9·7	12·5
Previous steroid use (%)	16·1	6·5	12·5	15·6
Study Centre (%) Moorfields or Bristol vs the other centres)	83·9	83·9	81·3	84·4
CAS Score				
2-3	17·9	16·7	24·1	9·4
4-5	53·6	70·0	55·2	68·9
6-7	28·6	13·3	20·7	21·9
TES Score				
<22	77·4	83·3	81·3	90·6
>22	22·5	16·7	18·8	9·4

**Aza = Azathioprine, RT = Radiotherapy**

**CAS = Clinical Activity Score TES = Thyroid Eye Score**

**Table 2 Intention to treat analysis Binary Composite Clinical Outcome, Ophthalmopathy Index and Change in Clinical Activity Score**

	Outcome	OR	B	95%CI	P	OR*	B*	95%CI*	P*
Aza	Binary Clinical Composite Outcome <sup>1</sup> (N=103) <sup>†</sup>	1.99	-	(0.88, 4.51)	0.10	2.56		0.98, 6.66	0.05
RT		1.07	-	(0.47, 2.39)	0.87	0.89		0.36, 2.23	0.80
AzaRT		2.16	-	(0.85, 5.47)	0.11	2.52		0.87, 7.29	0.09
Aza	Ophthalmopathy Index Week 48 <sup>2</sup> N=109	-	0.50	(-1.00, 2.00)	0.51	-	0.46	-1.04, 1.95	0.55
RT		-	-0.41	(-1.91, 1.09)	0.59	-	-0.89	-2.34, 0.56	0.23
AzaRT		-	-0.43	(-2.21, 1.35)	0.63	-	-0.78	-2.52, 0.96	0.37
Aza	Change in Clinical Activity Score <sup>3</sup>	-	-0.48	(-1.17, 0.21)	0.17	-	-0.54	-1.25, 0.16	0.13
RT	Week 12	-	-0.08	(-0.78, 0.62)	0.82	-	-0.01	-0.69, 0.68	0.99
AzaRT	(N=107)	-	-0.71	(-1.52, 0.10)	0.09	-	-0.64	-1.46, 0.18	0.13

\* Adjusted for age group, ethnicity, smoking status, gender, thyroid state, disease duration, study centre, recent steroid use, baseline CAS score, baseline TES score. For Azathioprine and Radiotherapy, this analysis is also adjusted for the other treatment option (but not the combined Azathioprine-Radiotherapy group)

OR= Odds ratio, B = Beta Coefficient

95% CI = 95% confidence interval

p = p value against the null hypothesis of no association

Aza = Randomised to Azathioprine, RT = Randomised to Radiotherapy,

AZART = Randomised to Azathioprine and Radiotherapy

<sup>1</sup> 6 individuals with last data carried forward

<sup>2</sup> 8 individuals with last data carried forward

<sup>3</sup> 10 individuals with last data carried forward

<sup>†</sup> Absolute values 22/50 patients who received azathioprine improved versus 16/54 who did not receive azathioprine. 19/50 patients who received orbital radiotherapy improved vs 19/54 who did not receive orbital radiotherapy.

**Table 3 As per protocol analysis Binary Composite Clinical Outcome, Ophthalmopathy Index and Change in Clinical Activity Score**

	<b>Outcome</b>	<b>OR/B</b>	<b>95%CI</b>	<b>P</b>	<b>OR/B*#</b>	<b>95%CI*</b>	<b>P*</b>	
Aza	Binary Clinical Composite Outcome <sup>†</sup> Week 48 (N=58) <sup>†</sup>	5.21	(1.62, 16.8)	0.006	6.83	(1.66, 28.1)	0.008	
RT		1.49	(0.53, 4.21)	0.45	1.32	(0.36, 4.84)	0.67	
AzaRT		7.24	(1.40, 37.4)	0.02	16.1	(2.03, 127.6)	0.009	
Aza	Ophthalmopathy Index Week 48 (N=59)	-0.16	(-2.12, 1.80)	0.87	-0.85	(-2.65, 0.95)	0.35	
RT		-0.20	(-2.10, 1.69)	0.83	-0.79	(-2.52, 0.94)	0.36	
AzaRT		-1.34	(-3.66, 0.99)	0.26	-2.02	(-4.13, 0.09)	0.06	
Aza	Change in Clinical Activity Score	-0.63	(-1.37, 0.12)	0.10	-0.54	(-1.29, 0.20)	0.15	
RT		Week 12	-0.03	(-0.79, 0.73)	0.94	0.10	(-0.66, 0.85)	0.80
AzaRT		(N=88)	-0.86	(-1.73, 0.002)	0.05	-0.66	(-1.55, 0.22)	0.14

\*\* Adjusted for age group, ethnicity, smoking status, gender, thyroid state, disease duration, study centre, recent steroid use, baseline CAS score, baseline TES score. For Azathioprine and Radiotherapy, this analysis is also adjusted for the other treatment option (but not the combined Azathioprine-Radiotherapy group)

OR= Odds ratio, B = Beta Coefficient

95% CI = 95% confidence interval

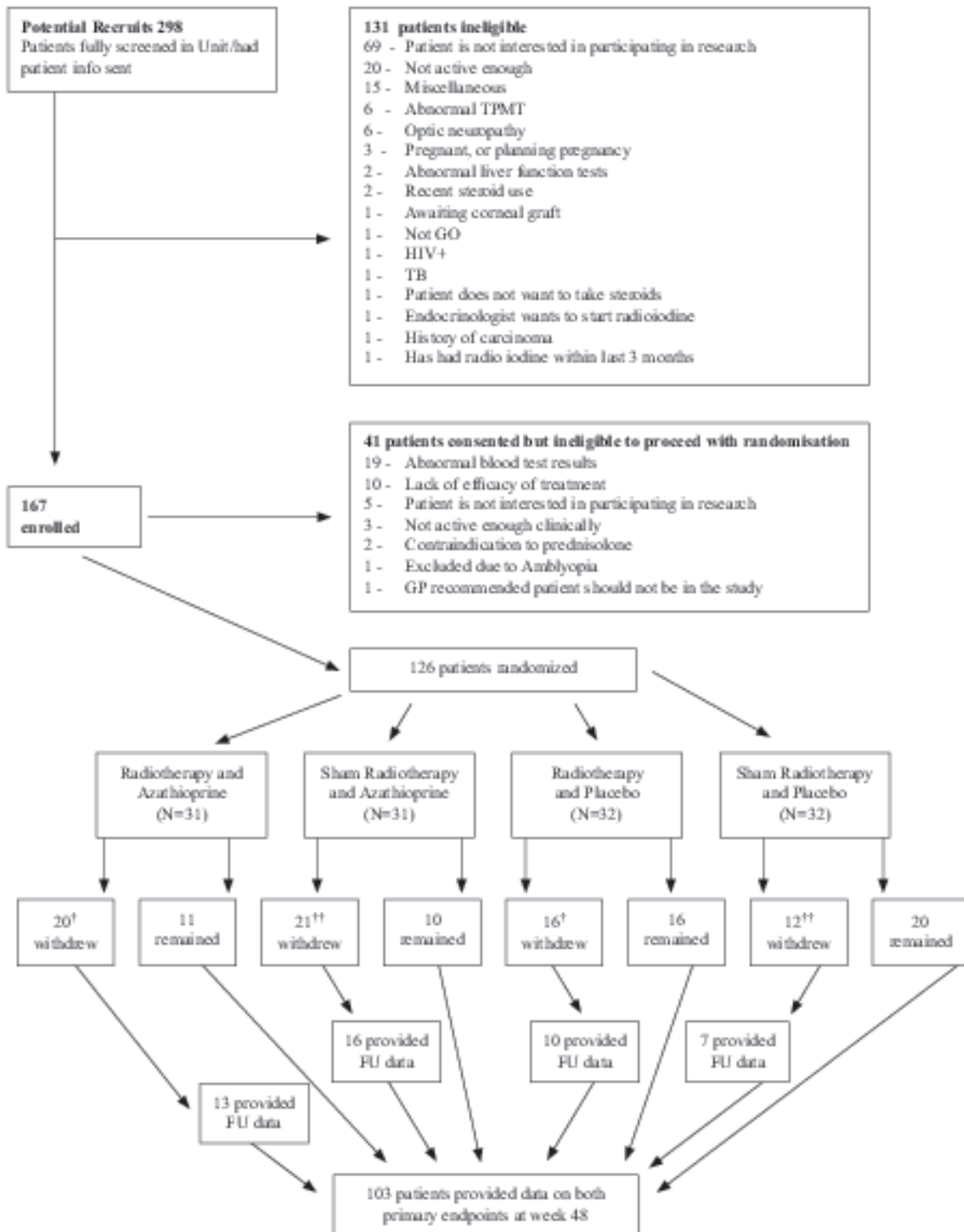
p = p value against the null hypothesis of no association

Aza = Randomized to Azathioprine, RT = Randomized to Radiotherapy,

AZART = Randomized to Azathioprine and Radiotherapy

<sup>†</sup>Absolute Values 15/21 patients who completed protocol on azathioprine improved vs 12/37 who did not receive azathioprine  
14/27 patients who completed protocol on orbital radiotherapy improved vs 13/31 who did not receive orbital radiotherapy

**Figure 1 Consort Diagram**



† 1 patient provided data for OI but not BCCOM

†† 2 patients provided data for OI but not BCCOM

Figure 2A Odds ratio of having an improved BCCOM score by treatment and duration in study

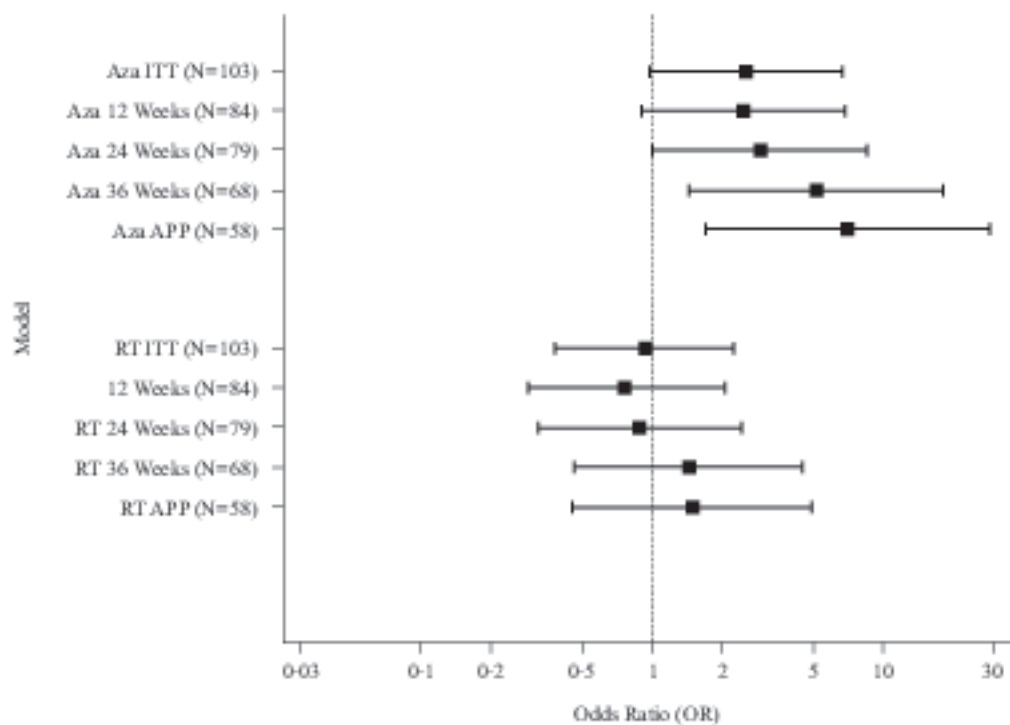


Figure 2C Boxplot of CAS at baseline, week 12 and week 48 by whether a participant was randomised to radiotherapy

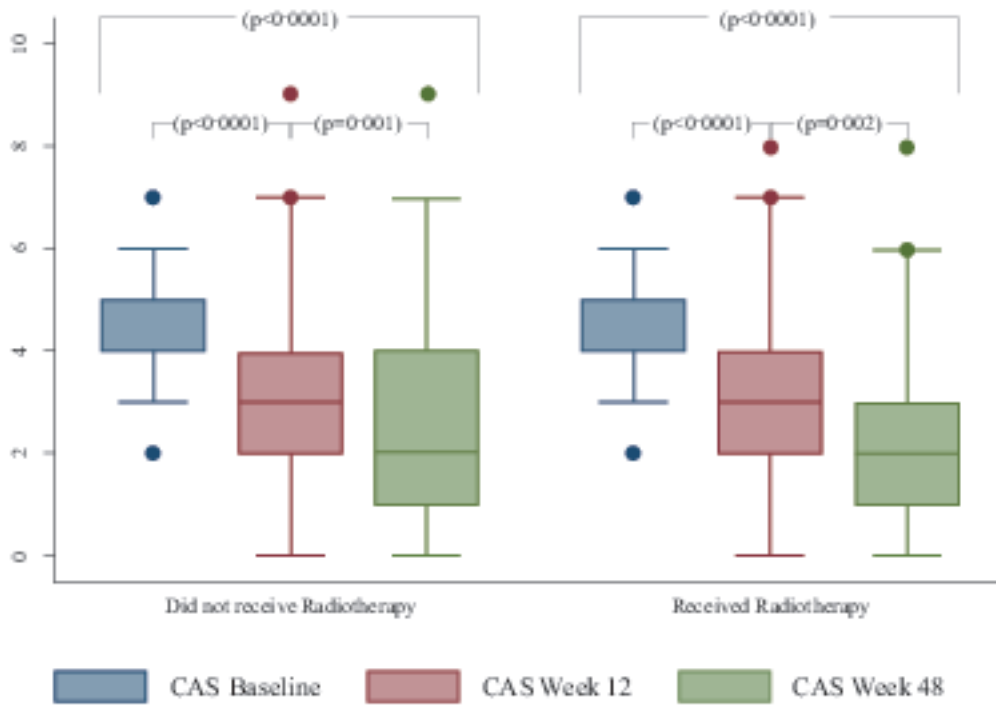
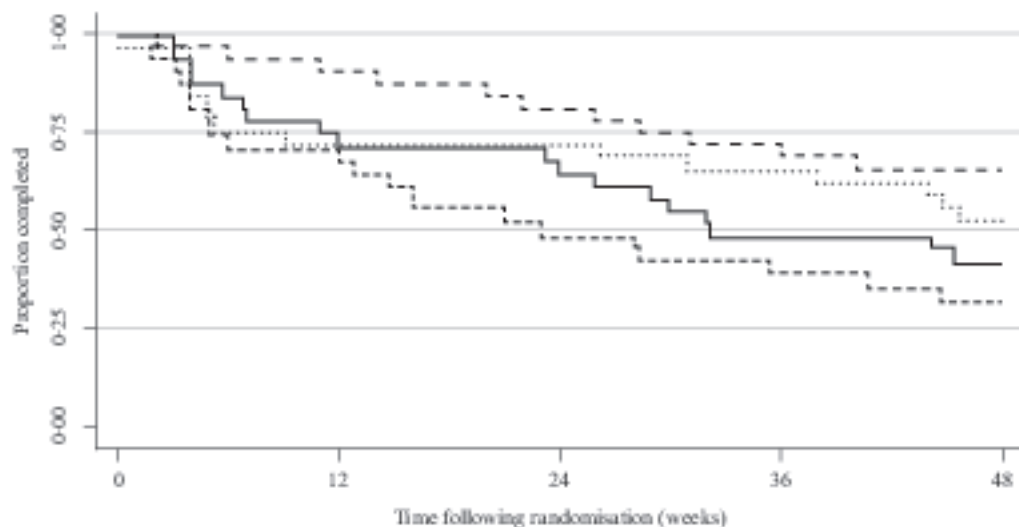


Figure 3A Kaplan Meier showing withdrawals from treatment (all reasons)

Withdrawal Overall



Number at risk					
	0	12	24	36	48
RT and AZA	31	23	20	15	13
RT and Placebo	32	23	23	20	16
Sham and AZA	31	22	15	12	10
Sham and Placebo	32	29	26	23	21

— RT and AZA                      ····· RT and Placebo  
 - · - · Sham and AZA                - - - - Sham and Placebo

Figure 3B Kaplan Meier showing withdrawals from treatment (side effects and abnormal blood test results)

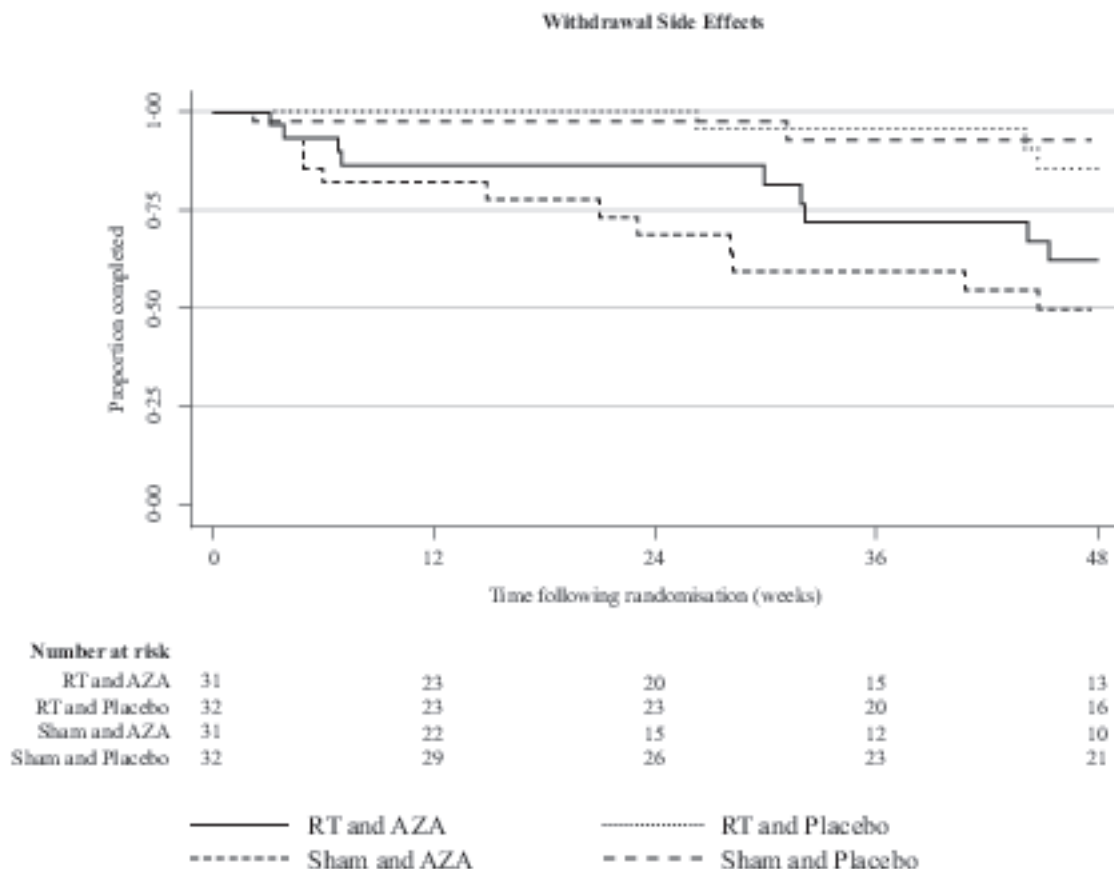
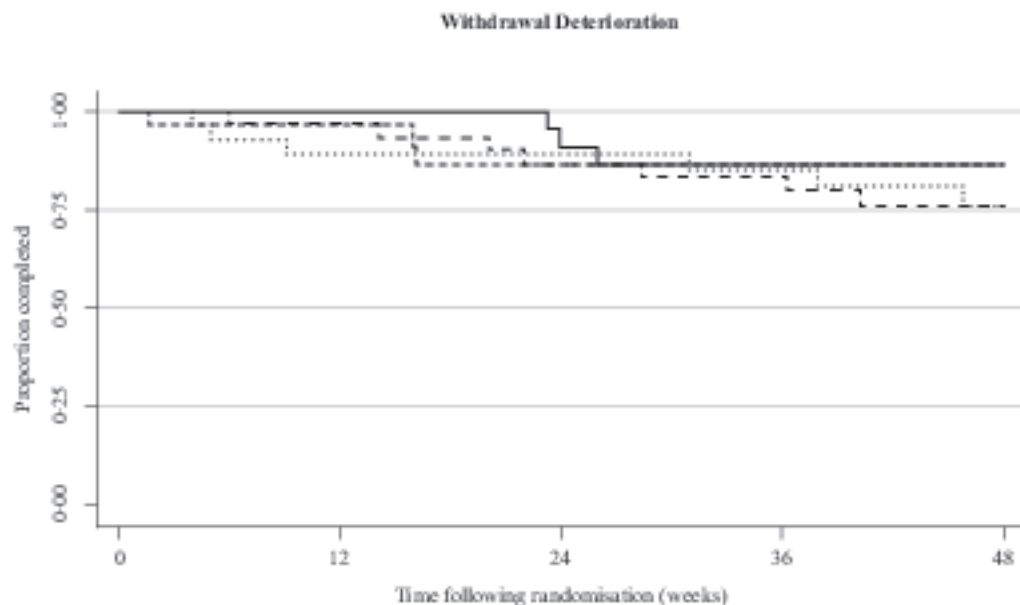




Figure 3C Kaplan Meier showing withdrawals from treatment (deterioration)



Number at risk					
	0	12	24	36	48
RT and AZA	31	23	20	15	13
RT and Placebo	32	23	23	20	16
Sham and AZA	31	22	15	12	10
Sham and Placebo	32	29	26	23	21

— RT and AZA                      ····· RT and Placebo  
 - · - · - Sham and AZA              - - - - Sham and Placebo