4 Gy versus 24 Gy radiotherapy for follicular and marginal zone lymphoma (FoRT): long-term follow-up of a multicentre, randomised, phase 3, non-inferiority trial

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Summary

Background The optimal radiotherapy dose for indolent non-Hodgkin lymphoma is uncertain. We aimed to compare 24 Gy in 12 fractions (representing the standard of care) with 4 Gy in two fractions (low-dose radiation).

Methods FoRT (Follicular Radiotherapy Trial) is a randomised, multicentre, phase 3, non-inferiority trial at 43 study centres in the UK. We enrolled patients (aged >18 years) with indolent non-Hodgkin lymphoma who had histological confirmation of follicular lymphoma or marginal zone lymphoma requiring radical or palliative radiotherapy. No limit on performance status was stipulated, and previous chemotherapy or radiotherapy to another site was permitted. Radiotherapy target sites were randomly allocated (1:1) either 24 Gy in 12 fractions or 4 Gy in two fractions using minimisation and stratified by histology, treatment intent, and study centre. Randomisation was centralised through the Cancer Research UK and University College London Cancer Trials Centre. Patients, treating clinicians, and investigators were not masked to random assignments. The primary endpoint was time to local progression in the irradiated volume based on clinical and radiological evaluation and analysed on an intention-to-treat basis. The non-inferiority threshold aimed to exclude the chance that 4 Gy was more than 10% inferior to 24 Gy in terms of local control at 2 years (HR 1·37). Safety (in terms of adverse events) was analysed in patients who received any radiotherapy and who returned an adverse event form. FoRT is registered with ClinicalTrials.gov, NCT00310167, and the ISRCTN Registry, ISRCTN65687530, and this report represents the long-term follow-up.

Findings Between April 7, 2006, and June 8, 2011, 614 target sites in 548 patients were randomly assigned either 24 Gy in 12 fractions (n=299) or 4 Gy in two fractions (n=315). At a median follow-up of 73·8 months (IQR 61·9–88·0), 117 local progression events were recorded, 27 in the 24 Gy group and 90 in the 4 Gy group. The 2-year local progression-free rate was 94·1% (95% CI 90·6–96·4) after 24 Gy and 79·8% (74·8–83·9) after 4 Gy; corresponding rates at 5 years were 89·9% (85·5–93·1) after 24 Gy and 70·4% (64·7–75·4) after 4 Gy (hazard ratio 3·46, 95% CI 2·25–5·33; p<0·0001). The difference at 2 years remains outside the non-inferiority margin of 10% at –13·0% (95% CI –21·7 to –6·9). The most common events at week 12 were alopecia (19 [7%] of 287 sites with 24 Gy *vs* six [2%] of 301 sites with 4 Gy), dry mouth (11 [4%] *vs* five [2%]), fatigue (seven [2%] *vs* five [2%]), mucositis (seven [2%] *vs* three [1%]), and pain (seven [2%] *vs* two [1%]). No treatment-related deaths were reported.

Interpretation Our findings at 5 years show that the optimal radiotherapy dose for indolent lymphoma is 24 Gy in 12 fractions when durable local control is the aim of treatment.

Funding Cancer Research UK.

Introduction

Current guidelines[1,2] for radiotherapy of indolent lymphoma recommend a dose of 24 Gy in 12 fractions, which was defined in a randomised trial[3] comparing 40 Gy with 24 Gy and showing no difference between the two doses. Subsequently, based on findings of several small cohort studies[4,5] and a phase 2 study showing durable response to only 4 Gy,[6] FoRT (Follicular Radiotherapy Trial) was initiated to compare 24 Gy in 12 fractions with 4 Gy in two fractions in a multicentre, randomised, phase 3, non-inferiority study. The initial analysis of FoRT,[7] with a median follow-up of 26 (range 0·4–75·4) months, showed that time to local progression with 4 Gy was not non-inferior to 24 Gy (hazard ratio [HR] 3·42, 95% CI 2·09–5·55, p<0·0001). Thus, 24 Gy remains the standard of care in this setting, although in the palliative setting (in which durable control might not be paramount), 4 Gy offers a simple short option for local control and symptom relief. Based on findings of cohort studies,[8,9] it has been proposed that orbital indolent lymphoma might need no more than 4 Gy, and despite evidence supporting use of 24 Gy, sporadic series using 4 Gy continue to be reported.[10–14] Here, we report the long-term follow-up results of FoRT.

Research in context

Evidence before this study

No formal systematic review has addressed radiation dose for follicular lymphoma. At the time of developing the protocol in 2004, we did a formal literature search using MEDLINE and the terms "follicular lymphoma", "lymphoma", "indolent lymphoma", "low grade lymphoma", and "radiotherapy". We also hand-searched abstracts from meeting proceedings of European Society for Radiotherapy and Oncology (ESTRO), American Society for Radiation Oncology (ASTRO), and the Lugano International Lymphoma Meetings. These searches were updated at the time of this analysis (April 9, 2020). Our search identified several small phase 2 studies showing efficacy for 4 Gy, but no comparative trials using standard doses as control. No relevant randomised trials were found in the Cochrane Central Register of Controlled Trials.

Added value of this study

The results of this trial confirm that, with long-term follow-up, 4 Gy in two fractions is not non-inferior to 24 Gy in 12 fractions for local control when treating follicular lymphoma, in both the radical and palliative setting. Exploratory analyses show the same effect for marginal zone lymphoma and orbital lymphoma.

Implications of all the available evidence

In the palliative setting, 4 Gy of radiotherapy might provide a pragmatic treatment for local symptom control, but, for durable local control of follicular and marginal zone lymphoma, 24 Gy should be used.

Methods

Study design and participants

FoRT is a randomised, phase 3, non-inferiority trial at 43 study centres in the UK (appendix pp 1–2). Patients older than 18 years with histologically confirmed follicular lymphoma or marginal zone lymphoma who required local radiotherapy for either palliative or radical intent were eligible for the trial. Entry was based on initial histological diagnosis at the treating centre; tissue blocks were sent for independent central review. Assessment of the treated site was based on clinical and radiological assessment using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. No limit on performance status was stipulated, and previous chemotherapy or radiotherapy to another site was permitted. Exclusion criteria included systemic chemotherapy within 4 weeks of randomisation and a predicted life expectancy of less than 3 months.

FoRT was approved by the East of England—Cambridge South research ethics committee and all patients gave written informed consent. The protocol for this trial is available in the appendix.

Randomisation and masking

Central randomisation was through the Cancer Research UK and University College London Cancer Trials Centre using the MINIM6 program.[15] Radiotherapy target sites were randomly assigned (1:1) either 4 Gy in two fractions or 24 Gy in 12 fractions using minimisation and stratified by histology (follicular lymphoma *vs* marginal zone lymphoma), treatment intent (palliative *vs* curative), and study centre. Randomisation was by target site rather than patient, so an individual patient could contribute more than one site to the trial. Masking would have required sham radiotherapy and, since this was not used, patients, treating clinicians, and investigators were aware of random assignments.

Procedures

Radiotherapy was delivered using standard megavoltage involved-field techniques, as previously described,[7] and a formal quality assurance programme was enforced. The two fractionation schedules were 24 Gy in 12 fractions of 2 Gy, treating daily Monday to Friday, and 4 Gy in two fractions of 2 Gy, on consecutive days. No dose reductions were allowed. Acute toxicity was assessed before treatment, weekly during radiotherapy, and at 4 weeks after completion. Late toxicity was assessed at 12 weeks, 6 months, and every 6 months thereafter. We used Radiation Therapy Oncology Group acute radiation morbidity scoring criteria and European Organisation for Research and Treatment of Cancer late radiation morbidity scoring criteria, and Common Toxicity Criteria for Adverse Events (version 3.0) for late effects. Quality of life was measured using the EQ-5D questionnaire. Local control was assessed at the same timepoints as for toxicity using clinical examination and appropriate imaging (usually CT). No central review of response assessments was done. Patients could withdraw from trial therapy for progression within the irradiated field, toxicity, intercurrent illness, any other change in condition thought to be clinically relevant, or withdrawal of consent. Withdrawal from trial follow-up was only stopped by withdrawal of consent.

See Online for appendix

Outcomes

The primary outcome was time to local progression (local control) in the irradiated volume, based on clinical and radiological evaluation, assessed by the investigators as the local progression-free interval. Secondary endpoints were response (assessed using RECIST 1.1 and reported elsewhere), overall survival (time from randomisation to date of death of any cause), toxicity, and quality of life. A health economic assessment was also included and will be reported separately. Quality of life was not assessed at this long-term analysis because of limited additional data.

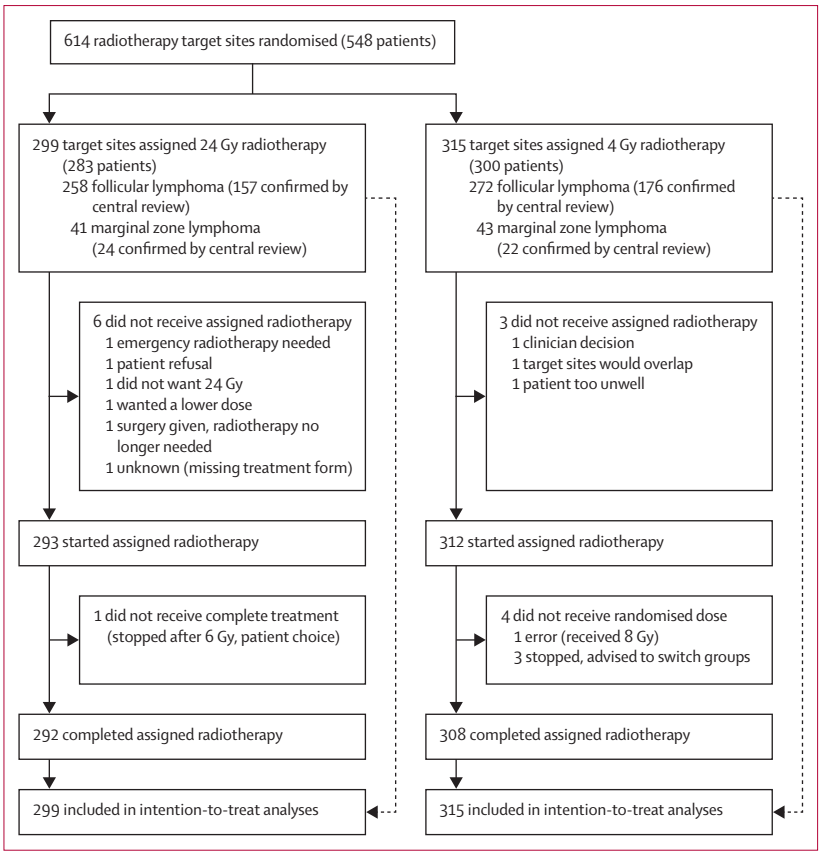

Figure 1: **Trial profile**

Statistical analysis

The study was designed as a non-inferiority trial to exclude the chance that 4 Gy was more than 10% inferior to 24 Gy in terms of local control at 2 years (HR 1·37). We assumed that 60% of radiotherapy target sites would be progression free at 2 years and, using a one-sided alpha of 5% and 90% power, we calculated that 364 events (650 target sites) would be needed to exclude this difference. The trial closed after randomisation of 614 sites (94% recruitment) at the recommendation of the independent data monitoring committee (IDMC) based on the observed difference between treatment groups at this point.

Local progression-free interval was measured from the date of randomisation until the first progression within the irradiated field. Progression was measured by recurrence or an increase in size after partial or minimal response. Target sites without progression within the field were censored at the patient's date of death or date last seen. A secondary local progression-free interval analysis was done, censoring at the treatment date any target site that received further therapy before local progression. This analysis was done based on the observance that patients were often given additional treatment before progression. It censored time at the date of any systemic or further local treatment to the trial-randomised site, but not if local treatment was given to other sites.

We estimated overall survival and local progression-free interval distributions using Kaplan-Meier curves, and we analysed differences in survival with the log-rank test. We used a Cox proportional hazards model to estimate the HR (and 95% CIs) between the two groups and checked the proportionality assumption using Schoenfeld residuals.

Numbers of target sites experiencing each event are presented at 12 weeks, 6 months, 1 year, and yearly up until year 5. Sites were excluded from each subsequent timepoint if local progression had occurred or if additional to-target or systemic anticancer treatment had been given. Total numbers of sites experiencing any event and response rates were compared using the χ^2 test or Fisher's exact test.

All analyses were by intention to treat in the first instance, except response and toxicity, which were restricted to sites that received the assigned treatment.

The primary analysis used all randomised target sites; however, sensitivity analyses were done using the first site randomised, patients randomised only once, and six randomly chosen samples with one site per patient. One of these random samples (the final sample) was used for the primary analysis of overall survival, but this endpoint was also analysed with each of the cohorts mentioned above. In addition to this sensitivity analysis, we did a post-hoc analysis of local progression-free interval using a Cox shared-frailty model, including patient as a random effect. Post-hoc exploratory analyses included the effect of histology (follicular *vs* marginal zone), treatment intent, follicular lymphoma international prognostic index (FLIPI) score, tumour bulk, target site (orbital *vs* others and extranodal *vs* others), serum lactate dehydrogenase, previous treatment, and initial response. These analyes were done in the whole population and in the population with confirmed follicular lymphoma. Subgroup analyses for histology and treatment intent were also done for overall survival.

All analyses were done using Stata (version 15.1). A p value of 0·05 was considered significant for all analyses. Interaction p values were calculated using a likelihood ratio test comparing a model with and without the interaction term.

FoRT is registered with ClinicalTrials.gov, NCT00310167, and the ISRCTN Registry, ISRCTN65687530.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between April 7, 2006, and June 8, 2011, 614 target sites in 548 patients were randomly assigned radiotherapy of either 24 Gy in 12 fractions (299 target sites) or 4 Gy in two fractions (315 target sites; figure 1). Median age of

patients was 66 (IQR 59–74) years (table 1). 530 (86%) of 614 target sites were recorded as follicular lymphoma and 84 (14%) as marginal zone lymphoma. On central review, this histology was confirmed for 328 (62%) of 530 sites and 32 (38%) of 84 sites (328 [88%] of 373 sites reviewed and 32 [76%] of 42 sites reviewed), respectively. An additional 19 target sites were confirmed eligible but were reclassified as marginal zone lymphoma (14 randomised as follicular lymphoma) or follicular lymphoma (five randomised as marginal zone lymphoma). Treatment intent was curative for 248 (40%) sites and palliative for 366 (60%) sites (table 1). 20 (7%) patients in the 24 Gy group and 23 (7%) in the 4 Gy group had completely excised disease before radiotherapy.

Median follow-up was 73·8 (IQR 61·9–88·0) months. 117 local progression events were recorded, 27 in the 24 Gy group and 90 in the 4 Gy group. The 2-year local progression-free rate was 94·1% (95% CI 90·6–96·4) after 24 Gy and 79·8% (74·8–83·9) after 4 Gy. Corresponding rates at 5 years were 89·9% (95% CI 85·5–93·1) and 70·4% (64·7–75·4), respectively (HR 3·46, 95% CI 2·25–5·33; p<0·0001; figure 2A). The difference at 2 years remains outside the non-inferiority level of 10% at –13·0% (95% CI –21·7 to –6·9). Median time to local progression has not been reached, but for sites that had local progression, these occurred at a median time of 19·3 months (IQR 12·0–31·0) for sites treated with 24 Gy and 12·3 months (7·1–27·5) for sites treated with 4 Gy. Sensitivity analyses, with one site per patient, and an analysis using a Cox shared-frailty model were also done, with no changes to the conclusion (appendix p 8).

155 target sites had further treatment reported before local progression. Use of systemic treatment was similar for both groups (appendix p 6). When patients were censored at the time of either additional local treatment to the target site or systemic treatment, the proportion of patients without local progression at 2 years was 94·5% (95% CI 90·9–96·7) after 24 Gy and 79·2% (73·8–83·7) after 4 Gy. At 5 years, corresponding values were 89·4% (95% CI 84·5–92·8; 25 events) after 24 Gy and 69·0% (62·6–74·6; 78 events) after 4 Gy (HR 3·49, 95% CI 2·22–5·47; p<0·0001; figure 2B).

These results were mirrored in a post-hoc exploratory analysis comparing sites treated with radical intent and those with palliative intent for both the whole trial population and the confirmed follicular lymphoma group (table 2). Although both treatment intents showed a significant benefit with 24 Gy compared with 4 Gy, the relative effect was bigger in the group treated with curative intent than in the group treated with palliative intent, although the interaction was not significant (p=0·20).

Post-hoc subgroup analyses were done for a range of factors that might have affected the outcome, including FLIPI score, previous treatments, target lesion size, and response. These subgroup analyses were done for the whole trial population (figure 3) and the confirmed

	24 Gy group (n=299)	4 Gy group (n=315)
Age, years	66 (59–74)	66 (59–74)
Time from diagnosis to randomisation, months	11·6 (2·4–57·7)	7·0 (2·6–47·2)
Sex		
Female	150 (50%)	154 (49%)
Male	149 (50%)	161 (51%)
Diagnosis		
Follicular lymphoma	258 (86%)	272 (86%)
Marginal zone lymphoma	41 (14%)	43 (14%)
Reason for radiotherapy		
Curative	119 (40%)	129 (41%)
Palliative	180 (60%)	186 (59%)
Karnofsky performance status score, %		
50	2 (1%)	2 (1%)
60	2 (1%)	4 (1%)
70–80	53 (17%)	41 (13%)
90–100	242 (81%)	268 (85%)
Radiological stage		
I	125 (42%)	137 (43%)
II	55 (18%)	53 (17%)
III	54 (18%)	57 (18%)
IV	34 (11%)	30 (10%)
Missing	31 (10%)	38 (12%)
Target site maximum diameter, cm		
<5	190 (64%)	189 (60%)
≥5	108 (36%)	118 (37%)
Missing	1 (<1%)	8 (3%)
Lactate dehydrogenase at randomisation		
Normal	210 (70%)	221 (70%)
Abnormal	51 (17%)	46 (15%)
Missing	38 (13%)	48 (15%)
Extranodal site		
No	174 (58%)	209 (66%)
Yes	125 (42%)	106 (34%)
Histology confirmed by central review		
Follicular lymphoma*	157 (53%)	176 (56%)
Marginal zone lymphoma*	24 (8%)	22 (7%)
Other	18 (6%)	18 (6%)
Other, chronic lymphocytic leukaemia	1	1
Other, classical Hodgkin lymphoma	0	1
Other, DLBCL	9	9
Other, DLBCL with underlying follicular lymphoma	5	4
Other, diffuse follicle centre lymphoma	1	2
Other, lymphocyte predominant nodular Hodgkin lymphoma	1	0
Other, multiple myeloma	1	1
Histology tested, no diagnosis	35 (12%)	32 (10%)
Insufficient or unsuitable sample	25	23
No definitive evidence of lymphoma	5	6
Reactive changes only	5	3
Histology not centrally reviewed	65 (22%)	67 (21%)

(Table 1 continues on next page)

	24 Gy group (n=299)	4 Gy group (n=315)
(Continued from previous page)		
FLIPI score†		
Low (0–1)	144 (48%)	160 (51%)
Intermediate (2)	83 (28%)	70 (22%)
High (≥3)	42 (14%)	54 (17%)
Missing	30 (10%)	31 (10%)
FLIPI score (confirmed follicular lymphoma only)†		
Low (0–1)	74 (47%)	89 (51%)
Intermediate (2)	46 (29%)	40 (23%)
High (≥3)	21 (13%)	33 (19%)
Missing	16 (10%)	14 (8%)
Previous radiotherapy		
No	222 (74%)	241 (77%)
Yes	77 (26%)	74 (23%)
Previous chemotherapy		
No	201 (67%)	205 (65%)
Yes	97 (32%)	110 (35%)
Missing	1 (<1%)	0
Number of randomised radiotherapy sites		
1	241 (81%)	254 (81%)
2	40 (13%)	48 (15%)
3	11 (4%)	7 (2%)
4	4 (1%)	4 (1%)
5	3 (1%)	2 (1%)

Data are n (%) or median (IQR). DLBCL=diffuse large B-cell lymphoma. FLIPI=Follicular Lymphoma International Prognostic Index. *14 patients who were entered as follicular lymphoma were confirmed as marginal zone lymphoma, and five patients entered as marginal zone lymphoma were confirmed as follicular lymphoma; these patients were not included in the confirmed by central review percentages, but were eligible for the trial. †Calculated at randomisation.

Table 1: **Baseline characteristics**

follicular lymphoma group (appendix p 3). No significant interaction was noted between treatment and any subgroup.

Although marginal zone lymphoma (comprising 84 [14%] of 614 target sites) is considered an indolent lymphoma, it might differ from follicular lymphoma in its radiotherapy responsiveness. In a post-hoc analysis, the local progression-free interval was compared between marginal zone and follicular histologies (as recorded at randomisation; appendix p 4). The group with marginal zone lymphoma reported good local control with both 24 Gy and 4 Gy, but the same conclusion (inferiority of 4 Gy *vs* 24 Gy) can be drawn. Six of 43 target sites treated with 4 Gy reported local progression compared with none of 41 in the 24 Gy treated group. At 5 years, local progression-free rates were 100% (95% CI not estimable) with 24 Gy and 88·0% (73·6–94·8) with 4 Gy (HR not calculable; log-rank p=0·015). Within the group with follicular lymphoma, the difference in local progression-free interval between treatment groups was similar to that in the overall population, with local progression-free rates at 5 years of 88·2% (95% CI 83·2–91·9; 27 events) with 24 Gy and 67·5% (61·1–73·0; 84 events) with 4 Gy (HR 3·25, 95% CI 2·10–5·01; p<0·0001). These results also hold when patients are censored for further treatment (data not shown).

The intention-to-treat analysis of the primary endpoint was based on declared histology by local teams at randomisation. Only 379 (62%) of 614 target sites had central review with histological confirmation of follicular lymphoma (333 sites) or marginal zone lymphoma (46 sites). 14 patients who were entered as follicular lymphoma were confirmed as marginal zone lymphoma (six in the 24 Gy group and eight in the 4 Gy group), and five patients entered as marginal zone lymphoma were confirmed as follicular lymphoma (one in the 24 Gy group and four in the 4 Gy group; table 1). For confirmed follicular lymphoma sites, this analysis showed no difference in the effect of dose fractionation (difference at 2 years for confirmed follicular lymphoma only, –15·4%, 95% CI –28·7 to –6·7; 16 of 157 events in the 24 Gy arm *vs* 57 of 176 events in the 4 Gy arm; HR 3·58, 95% CI 2·06–6·24; p<0·0001). Although the number of events precluded calculation of an HR for the groups with confirmed marginal zone lymphoma, two relapses at 22 sites occurred after 4 Gy, with none occurring at 24 sites after 24 Gy (p=0·18).

An exploratory, post-hoc analysis was done in the subgroup with orbital follicular lymphoma (35 orbital sites, 21 assigned 24 Gy and 14 assigned 4 Gy). 33 sites received the allocated treatment (17 follicular lymphoma and 16 marginal zone lymphoma). No progressions were reported at 20 sites treated with 24 Gy, and two progressions were noted at 13 sites treated with 4 Gy. One of these progressions was in follicular lymphoma and the other in marginal zone lymphoma, and both progressions were late (at 5 years and 6 years; appendix p 5). Five non-progressing sites in each treatment group also received further systemic anticancer therapy.

No difference in overall survival was recorded, with 67 deaths in the 24 Gy group (33 lymphoma, 34 non-lymphoma) and 77 in the 4 Gy group (40 lymphoma, 37 non-lymphoma; HR 1·03, 95% CI 0·74–1·43; p=0·86; appendix p 7). 2-year overall survival was 89·0% (95% CI 84·8–92·1) in the 24 Gy group and 90·4% (86·5–93·2) in the 4 Gy group; 5-year overall survival was 75·1% (69·6–79·8) with 24 Gy and 77·6% (72·4–81·9) with 4 Gy. Sensitivity analyses gave similar results (appendix p 8), as did subgroup analyses by treatment intent in both the whole trial population and within confirmed follicular lymphoma sites only (table 2).

Acute toxicity at week 4 was reported previously; here, we report late-term toxicity from week 12 onwards. At week 12, more adverse events were reported for target sites treated with 24 Gy than with 4 Gy (appendix pp 9–11). However, the numbers of adverse events in both treatment groups were low, with 29 (10%) of 287 patients experiencing a grade 2 or above event in the 24 Gy group (27 grade 2, two grade 3 [one mucositis and one constipation]) and 11 (4%) events in 301 patients in the 4 Gy

group (nine grade 2, two grade 3 [both fatigue]; p=0·0029 for difference between groups in grade 2 and 3 events). The most common events at week 12 were alopecia (19 [7%] of 287 sites with 24 Gy *vs* six [2%] of 301 sites with 4 Gy), dry mouth (11 [4%] *vs* five [2%]), fatigue (seven [2%] *vs* five [2%]), mucositis (seven [2%] *vs* three [1%]), and pain (seven [2%] *vs* two [1%]). At later timepoints (from week 12 up to 5 years), event rates decreased further, with one grade 3 event in the 24 Gy group (musculoskeletal pain) and no grade 4 events. No differences in the frequency of adverse events of grade 2 or worse were recorded between treatment groups during the study period (5% [13 of 248] *vs* 2% [five of 215] at 1 year; 2% [three of 170] *vs* 0% [none of 144] at 3 years, and 1% [one of 134] *vs* 0% [none of 102] at 5 years). No treatment-related deaths were reported.

Discussion

This long-term follow-up analysis of FoRT confirms the previously published results[7] showing that 4 Gy is inferior to 24 Gy in terms of duration of local control. With mature follow-up (median 73·8 months), a continuous reduction in local control was noted with 4 Gy, with the rate of freedom from local progression falling from 79·8% at 2 years to 70·4% at 5 years. By contrast, the rate of freedom from local progression after 24 Gy only fell from 94·1% to 89·9%. This finding suggests that lymphoma cells are surviving with 4 Gy radiotherapy, and these cells are either viable or able to repair damage and subsequently manifest as local recurrence, which accords with the difference in complete response rate seen between the two dose levels.

However, it is remarkable that durable control is achieved in two-thirds of patients with such small doses of radiotherapy. Findings of the TROG study of combination treatment for stage I–II follicular lymphoma,[16] delivering rituximab, cyclophosphamide, and vincristine after 30 Gy radiotherapy (median follow-up 9·6 years), showed an improvement in progression-free survival with use of adjuvant chemotherapy (HR 0·57, 95% CI 0·34–0·95; p=0·033). 10-year progression-free survival was only 41% in the control group after 30 Gy radiotherapy, but local control was high, with only 11 relapses in the radiation volume of 148 target sites. It is feasible that, when using combined modality treatment, lower doses of radiation could be equally effective as higher doses, but this idea requires formal testing. It has also been suggested that, since many patients have adequate response with 4 Gy, this dose should be given initially and retreatment offered for limited response or later relapse. However, it should be noted that patients treated with 4 Gy with a complete response still have more than double the risk of relapse. This approach requires closer surveillance, increases anxiety for patients, and assumes salvage has a high success rate. On balance, in view of the low toxicity of 24 Gy, this dose should remain the preferred option for radical local treatment, and 4 Gy should be restricted to the palliative setting. Even in this setting, in view of the long and unpredictable natural history of indolent lymphoma, and with a median time to relapse after 4 Gy of only 11 months, this low dose should be used only in conjunction with other potentially effective systemic treatments or when the outlook is for no more than a few months of life.

Findings of cohort studies have suggested that orbital follicular lymphoma could be adequately controlled using 4 Gy.[8,9] However, in our study, two of 13 orbital sites treated with 4 Gy had local progression. Of the 11 sites

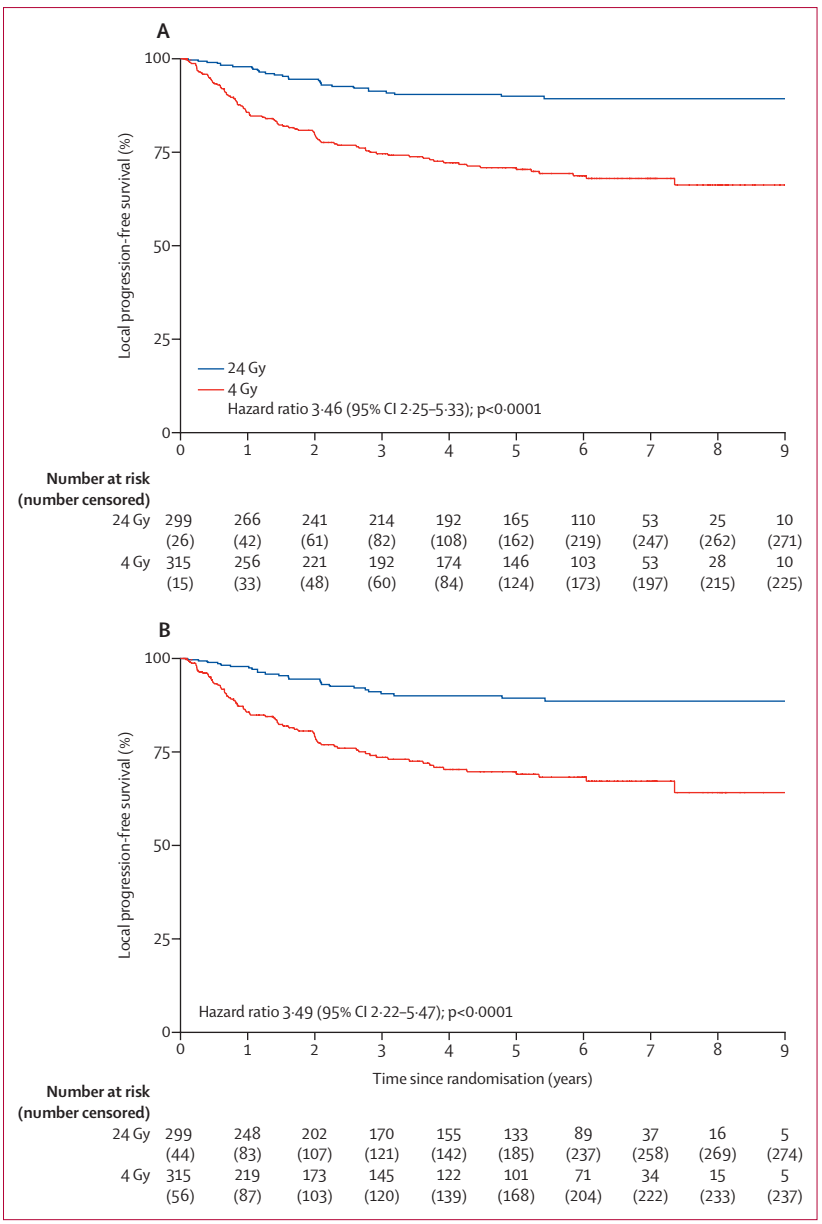

***Figure 2*: Time-to-event plots**
Time to local progression (A), and time to local progression with censoring for additional to-target or systemic therapy given before local progression (B).

	Time to local progression*			Overall survival (primary analysis population)*		
	Events/N	Hazard ratio (95% CI)	p value	Events/N	Hazard ratio (95% CI)	p value
All sites						
Curative intent	..	..	..	..	..	..
24 Gy	5/119	1 (ref)	..	12/118	1 (ref)	..
4 Gy	29/129	5·80 (2·25–14·99)	<0·0001	15/124	1·14 (0·53–2·44)	0·74
Palliative intent	..	..	..	..	..	..
24 Gy	22/180	1 (ref)	..	55/146	1·00	..
4 Gy	61/186	2·97 (1·83–4·84)	<0·0001	62/160	0·98 (0·69–1·43)	0·98
Follicular lymphoma confirmed by central review						
Curative intent	..	..	..	..	..	..
24 Gy	1/58	1 (ref)	..	7/57	1·00	..
4 Gy	19/76	15·99 (2·14–119·46)	<0·0001	9/74	0·95 (0·35–2·56)	0·92
Palliative intent	..	..	..	..	..	..
24 Gy	15/99	1 (ref)	..	29/86	1·00	..
4 Gy	38/100	2·92 (1·61–5·31)	<0·0001	34/90	1·08 (0·66–1·77)	0·76

*Denominators for time to local progression and overall survival differ because time to local progression is analysed for all sites but overall survival is restricted to one site per patient.

***Table 2*: Time to local progression and overall survival, by treatment intent**

	24 Gy		4 Gy		2-year difference (95% CI)	HR (95% CI)	Interaction p value
	Events (n)	Sites (N)	Events (n)	Sites (N)			
Intent							
Curative	5	119	29	129	−4·2% (−11·8 to −1·1)	5·80 (2·25–14·99)	0·20
Palliative	22	180	61	186	−15·9% (−28·4 to −7·1)	2·97 (1·83–4·84)	
FLIPI score							
Low	11	144	42	160	−14·6% (−30·0 to −5·2)	3·74 (1·93–7·27)	0·81
Intermediate	9	83	22	70	−10·1% (−24·8 to −2·1)	3·18 (1·46–6·90)	
High	3	42	21	54	−26·0% (−66·5 to −4·9)	6·23 (1·86–20·91)	
Bulk							
<5cm	15	190	41	189	−9·1% (−19·0 to −3·1)	2·94 (1·63–5·31)	0·48
≥5cm	12	108	46	118	−19·4% (−37·2 to −7·8)	4·01 (2·13–7·58)	
Target site							
Nodal	21	174	68	209	−15·1% (−27·3 to −6·6)	2·92 (1·79–4·76)	0·35
Extranodal	6	125	22	106	−6·2% (−16·8 to −1·6)	4·72 (1·92–11·65)	
Lactate dehydrogenase							
Normal	19	210	63	221	−9·1% (−19·0 to −3·1)	3·55 (2·13–5·94)	0·54
Abnormal	4	51	17	46	−23·2% (−58·5 to −4·6)	5·13 (1·73–15·25)	
Previous treatment							
None	9	161	40	166	−7·3% (−16·1 to −2·6)	4·87 (2·36–10·04)	0·07
Radiotherapy	5	40	11	38	−11·3% (−41·3 to 3·2)	2·08 (0·72–5·99)	
Chemotherapy	11	60	29	75	−15·5% (−36·0 to −2·3)	2·38 (1·19–4·76)	
Radiotherapy and chemotherapy	2	37	10	36	−23·6% (−74·0 to −1·2)	5·47 (1·20–24·96)	
Response							
Complete response	17	183	30	147	−5·3% (−12·2 to −1·2)	2·38 (1·31–4·32)	0·29
Partial response or stable disease	8	84	47	136	−22·6% (−46·3 to −7·3)	3·97 (1·87–8·40)	
Overall	**27**	**299**	**90**	**315**	**−13·0% (−21·7 to −6·9)**	**3·46 (2·25–5·33)**	
Heterogeneity between groups: p=0·995							
Overall (I^2=0·0%, p=0·931)							

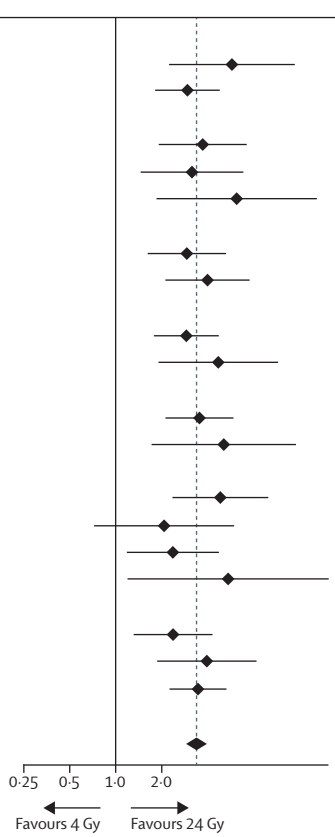

***Figure 3*: Subgroup analyses of time to local progression, all randomised sites**
FLIPI=Follicular Lymphoma International Prognostic Index. HR=hazard ratio.

without local progression, five had also received additional systemic therapy within the first 5 years, so we cannot be sure that radiotherapy alone provided disease control. By contrast, none of the 20 sites treated with 24 Gy relapsed.

Most patients in our study had follicular lymphoma and our results are applicable to this subgroup of indolent lymphoma. The same advantage of 24 Gy was seen in patients recorded as having marginal zone lymphoma. However, since this analysis was not prespecified, and with only a few events recorded in patients with marginal zone lymphoma (and no events in the 24 Gy group with confirmed marginal zone lymphoma), caution must be used in extrapolating these results to this histological subgroup. Marginal zone lymphoma differs from follicular lymphoma in several important ways. It has a different natural history and is characterised by three subtypes—extranodal (which is most prevalent), splenic, and nodal.[17] It is associated with previous chronic bacterial infections, associated inflammatory reactions, and autoimmune conditions (eg, Sjögren's syndrome). The mutational landscape for each histological subgroup of lymphoma is different. Deregulation of genes associated with the NF-κB pathway, including *MALT1*, *BIRC3*, and *BCL10*, are prominent in marginal zone lymphoma, whereas in follicular lymphoma the hallmark is the *BCL2* translocation, with changes in histone-modifying genes, and NF-κB activation is also common.[18] The observation that 24 Gy is superior to 4 Gy in the marginal zone lymphoma cohort is not definitive, but does pave the way for a future trial in this histological subgroup.

The mechanisms of low-dose radiotherapy in follicular lymphoma remain an area of uncertainty. Apoptosis after BCL2 inactivation and macrophage activation remain likely events leading to cell death after low-dose radiation.[19] Low-dose radiation has been shown to upregulate the *BBC3*, *BAX*, and *PMAIP1* pathways, and the so-called death receptor genes *TRAIL-R2* (also known as *TNFRSF10B*) and *FAS*, and to result in significant overexpression of CASP8 and CASP9.[20] With increasing recognition of the role of the immune system in controlling malignant cells, the importance of radiation in enhancing cancer cell antigenicity and induction of viral mimicry with production of type I interferon and other proinflammatory cytokines offers a further mechanism for the effects of low-dose radiation.[21] Therefore, there is a strong biological rationale for the efficacy of 4 Gy in follicular lymphoma.

In the earlier report of this trial,[7] quality-of-life data were presented, and no difference was noted between treatment groups, with no suggestion of any further separation at later timepoints. Because we had sparse long-term quality-of-life data, we have not updated this analysis.

The limitations of our study have been stated previously[7] and have not changed. The study design, which allowed multiple sequential randomisations in one patient, with each target site being used for events, has been criticised, but defended by the robust means of data collection per site and additional analyses, which all drew the same conclusion. The premature closure by the IDMC at 614 target sites is mitigated by the prolonged difference emerging with additional events on mature follow-up, as presented here. Other considerations are that less than two-thirds of the target sites had central histological confirmation, although the result is no different when these patients are excluded. Heterogeneity within treatment groups with respect to treatment intent (palliative *vs* curative) and receipt of other therapies was recorded, but these are well balanced. We have done several subgroup analyses and these do not suggest a different conclusion within any subgroup. The trial was a non-inferiority design, aiming to exclude a 10% decrease in local progression-free survival (ie, a lower CI above –10%). As subgroups are smaller, we would not be powered to exclude a 10% difference and, in some cases, because local progression-free interval rates are higher, this difference might be less appropriate. For instance, a 10% difference with a control local progression-free interval rate of 60%, as assumed in this design, is an HR of 1·36, but with a control rate of 90%, this HR is 2·1. In all cases, the estimate of the 2-year difference was below –10% or an HR greater than 2 was seen, suggesting that no subgroup had an acceptable reduction in efficacy and that a larger sample size would not have changed these conclusions.

These mature results from FoRT, to our knowledge the only randomised trial to have addressed the role of low-dose radiotherapy in indolent non-Hodgkin lymphoma, provide level 1 evidence for use of 24 Gy in 12 fractions in patients for whom durable local control is the aim of treatment. No subgroup has been identified in which this conclusion does not apply. Responses are seen with 4 Gy in two fractions, and around two-thirds of patients have local control for several years, and this low dose schedule could be considered in patients requiring palliation or in whom definitive systemic treatment is planned.

Contributors

PH was chief investigator and was responsible for trial design and protocol writing. AAK was the trial statistician and did the data analysis. PH and AAK wrote the report. PH, IS, MR, EG-E, KM, and CB were members of the trial management group and local principal investigators responsible for patient recruitment, data collection, data interpretation, and writing and review of the report. BP and OS were trial coordinators responsible for data collection, data analysis, data interpretation, and writing of the report. LC-H was responsible for central data management. TI and AMB were principal investigators, patient recruiters, and involved in interpretation and writing of the report. PH and AAK have accessed and verified the data. All authors had access to the data presented in this report, and AAK, BP, OS, and LC-H had access to the raw data. All authors reviewed and approved the final report and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

There was no data sharing plan for this study, but specific requests will be considered by the chief investigator (PH).

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