4 Gy versus 24 Gy radiotherapy for follicular and marginal zone lymphoma (FoRT): long-term follow-up results 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. The aim of the study was to compare 24Gy in 12 fractions representing the standard of care with low dose radiation (4Gy in 2 fractions) .

Methods: FORT is a randomised multicentre non-inferiority trial comparing 24Gy in 12 fractions with 4Gy in 2 fractions in indolent non-Hodgkin lymphoma. Eligible patients had histological confirmation of follicular or marginal zone lymphoma requiring radical or palliative radiotherapy. No limit on age or performance status was stipulated and previous chemotherapy or radiotherapy to another site was permitted. Randomisation was by irradiated site ("target site") using minimisation stratified by histology, treatment intent and centre. The primary endpoint was time to local progression in the irradiated volume based on clinical and radiological evaluation analysed by ITT in this final analysis. The trial was registered with ClinTrials.gov NCT 00310167 and the International Standardised Controlled Trial ISRCTN 65687530.

Findings: A total of 614 target sites in 548 patients (299-24Gy; 315-4Gy) were randomized between April 7th 2006 and June 8th 2011.

This mature analysis has a median follow up of 73.8 months. The 2-year local progression free rate is 94.1% (95% CI: 90.6 – 96.4) after 24Gy and 79.8% (74.8 – 83.9) after 4Gy; the corresponding rates at 5 years are 89.9% (85.5 – 93.1) after 24Gy and 70.4% (64.7 – 75.4) after 4Gy (HR: 3.46 (95% CI: 2.25 – 5.33, p<0.001). Toxicity rates were low with no difference seen in Grade ≥2 events between 24Gy and 4Gy. The most common events were dry mouth, 11(3.8%) vs 5(1.7%); mucositis, 7(2.4%) vs 3(1.0%); fatigue 7(2.4%) vs 5(1.7%). . There were no treatment related deaths.

Interpretation: The optimal radiotherapy dose for indolent lymphoma is 24Gy when durable local control is the aim of treatment.

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Introduction: Current guidelines [1,2] for radiotherapy of indolent lymphoma recommend a dose of 24Gy in 12 fractions which was defined in a prospective randomised trial comparing 40Gy with 24Gy and showing no significant difference between the two. [3]Subsequently, based on several small cohort studies[,4, 5] and a phase II study showing durable response to only 4Gy [6], the FoRT trial compared 24 Gy in 12 fractions with 4 Gy in 2 fractions in a prospective multi-centre non-inferiority study. The initial analysis, with a median follow-up of 26 months, showed that 24Gy resulted in a significantly better local progression free interval than 4Gy [7]. Thus 24Gy remains the standard of care in this setting, although in the palliative setting where durable control may not be paramount, 4Gy offers a simple short option for local control and symptom relief. Based on cohort studies it has been proposed that orbital indolent lymphoma may require no more than 4Gy[,8,9]. and despite the above evidence sporadic series of 4Gy continue to be reported [10,11,12.13,14]

In this paper the long-term results of the FORT trial are reported with a median follow up of 73.8 months.

Methods:

Study design and participants

FORT is a prospective randomised non-blind multicentre study.

Patients over 18 years of age with no upper limit requiring local radiation therapy with histologically confirmed follicular lymphoma (FL) with either palliative or radical intent were eligible. Patients with marginal zone lymphoma (MZL) were also included later in the study. Entry was based on initial histological diagnosis at the treating centre; subsequently tissue blocks were forwarded for central review. Assessment of treated site was based on clinical and radiological evaluation using RECIST criteria. Exclusion criteria included systemic chemotherapy within 4 weeks of randomisation and a predicted prognosis of <3 months.

The study was approved by the East of England – Cambridge South Research Ethics committee and all patients gave written informed consent. The trial was registered with ClinTrials.gov NCT 00310167 and the International Standardised Controlled Trial ISRCTN 65687530. The protocol for this study is available in the supplementary appendix

Randomisation

Central randomisation was through the Cancer Research UK and University College London Cancer Trials Centre using the MINIM6 program. Sites were randomly assigned (1:1) to either 4Gy or 24Gy radiotherapy using minimisation stratified by histology (follicular lymphoma vs marginal zone lymphoma), treatment intent (palliative vs curative) and centre. Randomisation was by irradiated site ("target site") rather than patient so that an individual patient could contribute more than one site to the study. Since blinding would have required sham radiotherapy this was not used.

Procedures

Radiotherapy was delivered using standard megavoltage involved field techniques as previously described and a formal quality assurance programme was enforced. The two fractionation schedules were 24Gy in 12 fractions of 2Gy treating daily Monday to Friday and 4Gy in 2 fractions of 2Gy on consecutive days. No dose reductions were allowed. Acute toxicity was assessed prior to treatment, weekly during radiotherapy and at 4 weeks after completion. Late toxicity was assessed at week 12, 6 months and 6 monthly thereafter. The Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring Criteria and European Organisation for Research and Treatment of cancer (EORTC) Late radiation Morbidity scoring criteria were used as well as the Common Toxicity Criteria for Adverse Events (CTC AE) v3.0 for late effects. Quality of life was measured using the equation-5D (EQ-

5D) questionnaire. Local control was assessed at the same time points using clinical examination and appropriate imaging, usually CT scan. There was no central review of response assessments. 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.

Outcomes

The primary outcome was local control within the irradiated volume by intention to treat. Secondary endpoints were response, overall survival, toxicity and quality of life. A health economic assessment was also included and will be reported separately.

Statistical considerations and analysis

The study was designed as a non-inferiority trial aiming to exclude the chance that 4Gy was more than 10% inferior to 24Gy in terms of local control at 2-years (hazard ratio (HR) of 1.37). It was assumed that 60% of RT sites would be progression-free at 2 years and using a 1-sided 5% alpha and 90% power we would require 364 events (650 target sites) to exclude this difference. The primary analysis used all randomised target sites, however sensitivity analyses were conducted 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 also performed a post-hoc analysis of the LPFI using a Cox shared-frailty model including patient as a random effect.

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 the arms at this point.

The local progression free interval (LPFI) 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 their date last seen. A secondary LPFI analysis was performed censoring LPFI times for any target site receiving further therapy before local progression. This censored the 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.

Overall survival was measured from the date of randomisation until death or the date last seen. We estimated overall survival and LPFI distributions using Kaplan-Meier curves, and analysed differences in survival with the log-rank test. We used a Cox proportional hazards model to estimate the hazard ratio between the two groups and checked the proportionality assumption using the Schoenfeld residuals.

Late toxicity was assessed at week 12 and at each designated follow-up appointment. Numbers of target sites experiencing each event are presented at week 12, 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 anti-cancer treatment had been given. Total numbers of sites experiencing any event and response rates were compared using Fisher's exact tests. All analyses were intention to treat (ITT) in the first instance except response and toxicity which were limited to patients who received their randomised treatment and all were performed using Stata version 15.1.

Post hoc exploratory analyses included the impact of histology (follicular vs marginal zone), treatment intent, FLIPI score, tumour bulk, target site (orbital vs others and extra nodal vs others), serum LDH, previous treatment and initial response. A p-value of 0.05 was considered significant for all analyses.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report, All authors had access to this data presented in this report. AAK, BP, OS and LC-H had access to the raw data. The corresponding author (PH) had full access to all of the data and the final responsibility to submit for publication

Results: A total of 614 target sites in 548 patients were randomized between April 7th 2006 and June 8th 2011 (Figure 1). 299 were randomized to receive 24Gy and 315 to 4Gy. The demographic details of the population are shown in table 1. Median age was 66 years; 530/614 (86.3%) were recorded as FL and the remaining 84/614 (13.7%) were MZL. On histology review this was confirmed in 328/530 (61.9%) and 32/84 (38%) respectively (328/373 (87.9%) and 32/42 (76.2%) of those reviewed). Treatment intent was curative in 248/614 (40.4%) and palliative in 366/614 (59.6%). Twenty (6.7%) patients in the 24Gy arm and 23 (7.3%) in the 4Gy arm had completely excised disease prior to RT.

Overall response rate (ORR) and complete response rate (CR) were both higher in sites treated with 24Gy than 4GY (236/260 (90.8%) vs 227/281 (80.8%), p = 0.00093 and 176/260 (67.7%) vs 137/281 (48.8%) p<0.0001, see supplement page 4).

Time to local progression, the primary end point, is shown in figure 2A; with a median follow up of 73.8 months (IQR: 61.9 - 88.0 months) we have recorded 117 local progression events,

27 in the 24Gy arm and 90 in the 4Gy arm and we now observe 2-year local progression free rates of 94.1% (95% CI: 90.6 - 96.4) after 24Gy and 79.8% (74.8 – 83.9) after 4Gy; the corresponding rates at 5 years are 89.9% (95% CI: 85.5 – 93.1) after 24Gy and 70.4% (95% CI: 64.7 – 75.4) after 4Gy (HR: 3.46 (95% CI: 2.25 – 5.33, p<0.0001). The difference at 2 years remains well outside the non-inferiority level of 10% at -13.0% (-21.7% to -6.9%).

Median time to local progression has not been reached, but for patients who had local progression, these occurred at a median time of 19.3 months (IQR: 12.0 – 31.0) for sites treated with 24Gy and 12.3 months (IQR: 7.1 – 27.5) for sites treated with 4Gy.

One-hundred and fifty-five target sites had further treatment reported before local progression. The use of systemic treatment was similar with 73/299 (24.4%) after 24Gy and 68/315 (21.6%) after 4Gy (see supplement page 5). Figure 2B shows time to local progression when patients were censored at the time of either additional local treatment to the target site or systemic treatment. The percentages of patients without local progression at 2 and 5 years were 94.5% (95% CI: 90.9 – 96.7) and 89.4% (95% CI: 84.5 – 92.8) after 24Gy and 79.2% (95% CI: 73.8 – 83.7) and 69.0% (95% CI: 62.6 – 74.6) after 4Gy; HR: 3.49 (2.22 – 5.47), p<0.0001.

These results are mirrored in a pre-planned subgroup analysis comparing those treated with radical intent and those with palliative intent shown in table 2, although both groups showed a significant benefit, for 24Gy the relative effect was bigger in the group treated with curative intent, though the interaction was not significant, p=0.20.

Non-prespecified subgroup analyses were conducted for a range of factors which might have influenced outcome including the follicular lymphoma international prognostic index (FLIPI),

previous treatments, target lesion size and response; these were performed for the whole trial population and the confirmed FL group (see figure 3 and supplement page 1). There was no significant interaction between treatment and any subgroup.

Although MZL is considered an indolent lymphoma and was included, accounting for 84/614 (14%) of the entire population, it may differ from FL in its radioresponsiveness and therefore, although again not prespecified, supplement page 2 shows the LPFI comparing marginal zone and follicular histologies as recorded on randomisation. The MZL group reported better local control in both arms, but the same conclusion (inferiority of 4Gy compared to 24Gy) can be drawn. The HR within the FL group was similar to that in the total population; 3.25 (2.10 – 5.01), p<0.0001 with rates of 88.2% (95% CI: 83.2 – 91.9) and 67.5% (95% CI: 61.1 – 73.0) at 5 years. In the MZL group, 6 of the 43 sites treated with 4Gy reported local progression compared to 0/41 in the 24Gy treated group; the rates at 5 years were 100% and 88.0% (95% CI: 73.6 - 94.8) and log-rank p=0.015. These results also hold when patients are censored for further treatment (data not shown).

The ITT analysis for primary end point was performed based on declared histology by local teams at randomisation. Only 379 of the 614 target sites (62%) had central review with histological confirmation of FL (333 sites) or MZL (46 sites). For confirmed FL this analysis shows no difference in the effect of dose fractionation: HR (95% CI) 3.58 (2.06 – 6.24), p<0.0001, although the number of events precludes the calculation of an HR for confirmed MZL, both relapses occurred within the 4Gy arm; 0/24 relapses after 24Gy and 2/22 relapses after 4Gy (log-rank p = 0.18).

As cohort studies have suggested that in orbital FL durable control is achieved in virtually all patients after 4Gy, we performed an exploratory non-prespecified subgroup analysis within

this group. Thirty-five orbital sites were randomised in FoRT (21 to 24Gy, 14 to 4Gy). Thirty-three patients were given their randomised treatment, 17 were FL and 16 MZL. No progressions were reported in the 20 treated with 24Gy and 2 progressions in the 13 treated with 4Gy. One of the progressions was in FL and the other in MZL and both progressions were late (at 5 and 6 years, supplement page 3). Five patients with non-progressing sites in each arm also received further systemic anti-cancer therapy.

There remains no difference in overall survival, with 67 deaths (supplement page 6) in the 24Gy arm (33 lymphoma, 34 non-lymphoma) and 77 in the 4Gy arm (40 lymphoma and 37 non-lymphoma); HR: 1.03 (0.74 – 1.43, p=0.86). Sensitivity analyses gave very similar results and can be seen in supplement page 7-8.

At week 12 significantly more adverse events were reported for target sites treated with 24Gy than 4 Gy (all events shown in supplement page 9-10), however numbers in both arms were low; 29 (10.1%), 27 grade 2, 2 grade 3 (one mucositis and one constipation) vs 11 (3.7%), 9 grade 2 and 2 grade 3 (both fatigue), p=0.0029. At later timepoints event rates decreased further with only one grade 3 musculoskeletal pain event in the 24Gy arm and no grade 4 events. The most common events were dry mouth, 11(3.8%) vs 5(1.7%); mucositis, 7(2.4%) vs 3(1.0%); fatigue 7(2.4%) vs 5(1.7%). There were no significant differences between the arms (5.3% vs 2.3% at 1 year, 1.8% vs 0% at 3 years and 0.8% vs 0% at 5 years). There were no treatment-related deaths. The earlier publication of this trial [7] presented quality of life data in which there was no difference between the arms with no suggestion of any further separation at later timepoints. As we have limited long term QOL data this has not been updated.

Discussion :

This analysis confirms the previously published results demonstrating that 4Gy is inferior to 24Gy in terms of response and duration of local control. With a median follow up of 73.8 months the initial results are confirmed showing superiority of 24Gy over 4Gy with an HR of 3.46 (previously 3.42 (95%CI: 2.10 – 5.57)). With mature follow up a continuous reduction in local control is observed, the freedom from local progression rate (FFLPR) falling from 79.8% at 2 years to 70.4% at 5 years. In contrast the FFLPR after 24Gy only falls from 94.1% to 89.9%. This suggests that with 4Gy there are surviving lymphoma cells which are viable or able to repair damage and subsequently manifest as local recurrence and is consistent with the difference in complete response rate seen between the two dose levels.

Despite this, it is remarkable that durable control is achieved in two-thirds of patients with such small doses. Recent publication of the TROG study of combination treatment for stage I-II FL delivering rituximab, cyclophosphamide and vincristine (RCVP) after radiotherapy delivering 30Gy has shown with a median follow up of 9.6 years an improvement in progression free survival with the use of adjuvant chemotherapy with an HR of 0.57 (95% CI, 0.34 to 0.95; P = .033) [15] . Ten year progression free survival was only 41% in the control arm but local control was very high with only 11/148 relapses in the radiation volume. It is feasible that using combined modality treatment lower doses of radiation could be equally effective given the significant local control rate of 4Gy alone but clearly this requires formal testing. It has also been suggested that since many patients have adequate treatment with 4Gy this should be given initially and retreatment offered for limited response or later relapse. It should however be noted that even in 4Gy patients achieving CR there is a more than doubling

in the risk of relapse. This approach requires closer surveillance, increases anxiety for patients and assumes salvage has a high success rate. On balance, given the low toxicity of 24Gy, this should remain the preferred option for radical local treatment and 4Gy should be limited to the palliative setting. Even here given the long and unpredictable natural history of indolent lymphoma, and with a median time to relapse after 4Gy of only 11 months, it should be used only in conjunction with other potentially effective systemic treatment or where the outlook is for no more than a few months of life.

Cohort studies have suggested that orbital FL could be adequately controlled using 4Gy [8, 9], however we found that 2/13 orbital sites treated with 4Gy experienced local progression. In the 11 without local progression, 5 had also received additional systemic therapy within the first 5 years so we cannot be sure that the RT alone provided disease control. In contrast none of the 20 sites treated with 24Gy relapsed.

The majority of patients in this study had FL and clearly the results are applicable to this group of indolent lymphoma. The same advantage for 24Gy was seen in the patients recorded as having MZL however since this analysis was not prespecified and there were a small number of events, with no events in the 24Gy arm confirmed MZL group, caution must be used in extrapolating these results. MZL has a number of important differences from FL. It has a different natural history and is characterised by three subtypes: the extranodal type which is most prevalent, splenic and nodal [16]. It is associated with previous chronic bacterial infections, associated inflammatory reactions and autoimmune conditions such as Sjogrens syndrome. The mutational landscape for each is different. Deregulation of genes associated with the NF-

κB pathway including MALT1, BIRC3 and BCL10 are prominent in MZL whilst in FL the hallmark is the BCL2 translocation with changes in histone modifying genes and NF-κB activation is also relatively common [17]. The inclusion of MZL in this trial was not prespecified and therefore the observation that 24Gy appears superior to 4Gy in this cohort is not definitive but does pave the way for a future trial in MZL.

The mechanisms of low dose radiotherapy in FL remain an area of uncertainty. Apoptosis following BCl2 inactivation and macrophage activation remain likely events leading to cell death after low dose radiation [18]. Low dose radiation has been shown to upregulate BBC3, BAX, PMAIP1 pathways as well as the 'death receptor' genes TRAIL-R2 and FAS and to result in a significant over-expression of caspase 8 and caspase 9 [Knoops et al 2007]. 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 IFN and other pro-inflammatory cytokines offer a further mechanism for the effects of low dose radiation [19]. There is therefore a strong biological rationale for the efficacy of 4Gy in FL.

Limitations of this study were noted in the original report and have not changed. The design which allowed multiple sequential randomisations in one patient with each 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 histologic confirmation, although the result is no different when these patients are excluded. There was within the treatment arms heterogeneity in

treatment intent (palliative vs curative) and receipt of other therapies but these are well balanced. We have performed multiple subgroup analyses which 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 i.e. a lower confidence interval above -10%. As subgroups are smaller, we would not be powered to exclude a 10% difference, and in some cases, as LPFI rates are higher, this difference may be less appropriate i.e. a 10% difference with a control LPFI rate of 60%, as assumed in this design, is an HR of 1.36 i.e. an increase in risk of 36%. But with a control rate of 90% this HR is 2.1 i.e. a more than doubling of the risk. In all cases, the estimate of the 2-year difference was below -10% or an HR of >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 the only randomised trial to have addressed the role of low dose radiotherapy in indolent non-Hodgkin lymphoma provide level 1 evidence for the use of 24Gy in 12 fractions in patients for whom durable local control is the aim of treatment. No subgroup has been identified where this conclusion does not apply. Responses are seen with 4Gy in 2 fractions and around two-thirds of patients may have local control for several years and this low dose schedule may be considered in patients requiring palliation or in whom definitive systemic treatment is planned.

Author Contributions

PH was chief investigator, responsible for trial design, protocol writing and lead author. AK was the trial statistician who did the data analysis and, with PH, wrote the report. PH and AK have accessed and verified the data. 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, interpretation and manuscript writing and review. BP and OS were trial coordinators responsible for data

collection, data analysis, and interpretation, and writing the paper. 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. All authors reviewed and approved the final manuscript.

Conflict of Interest

We declare no competing interests

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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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Figures

Figure 1: Consort diagram

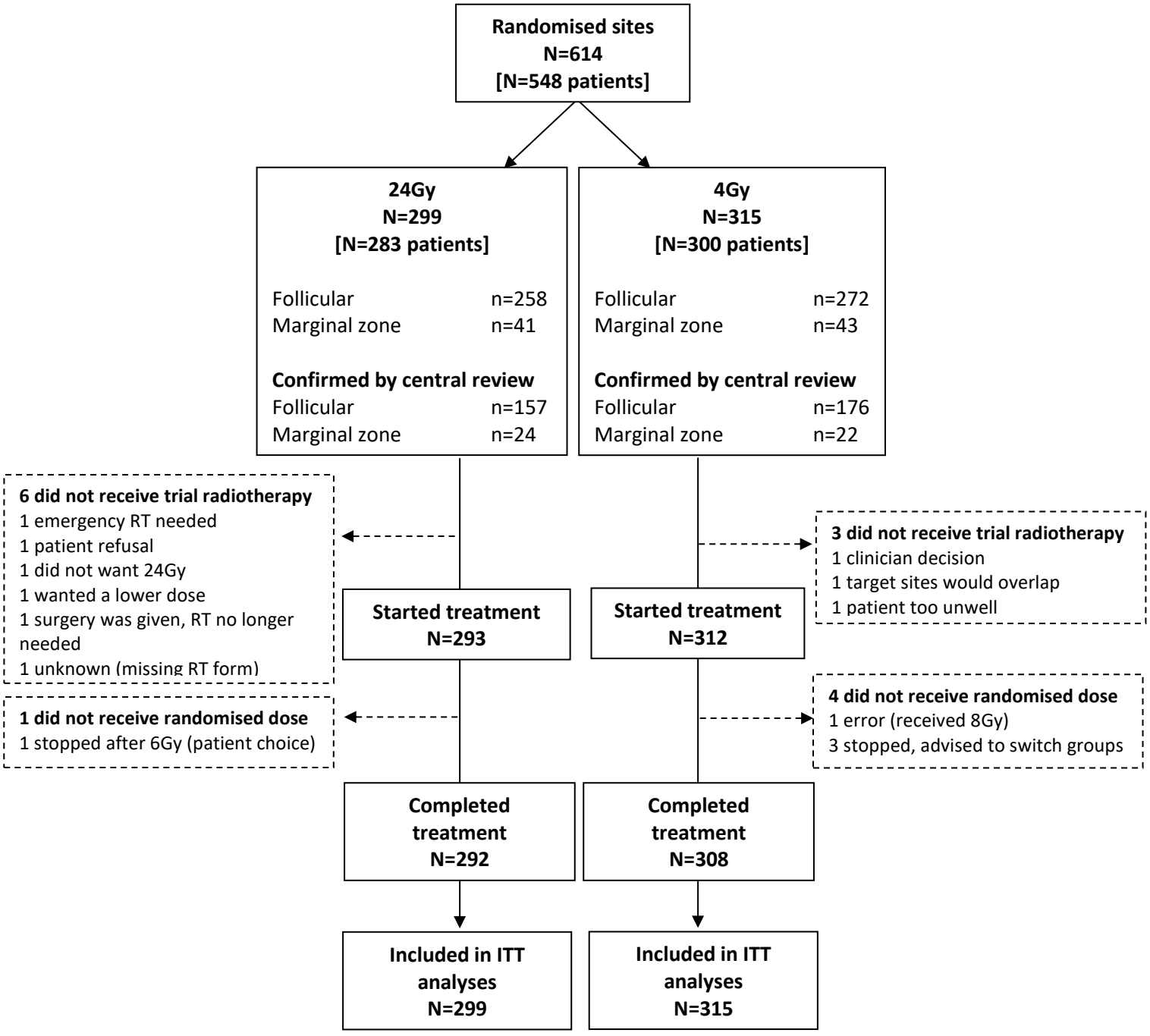

Figure 2A and 2B

Figure 2A Time to local progression

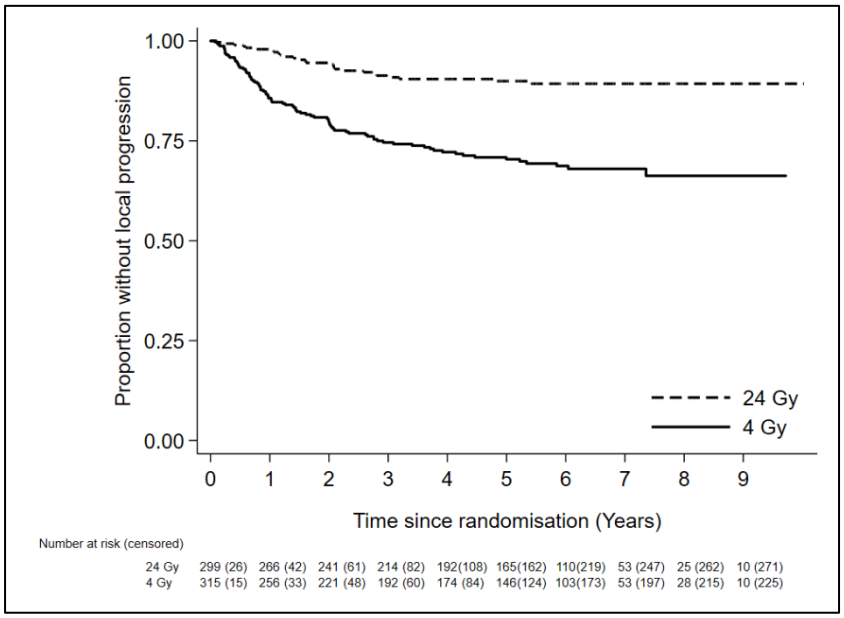

Figure 2B: Time to local progression with censoring for additional to-target or systemic therapy given before local progression.

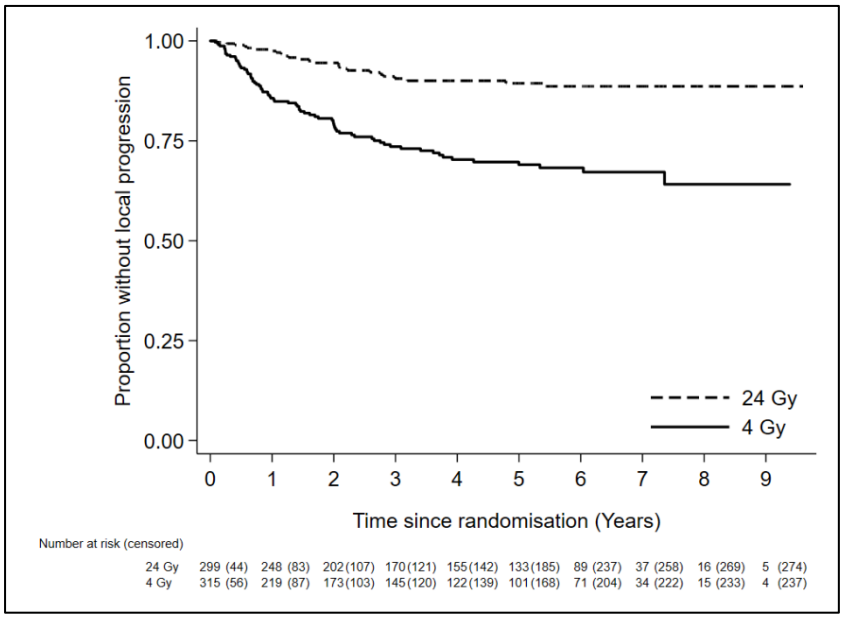

Figure 3 Subgroup analyses: all randomised sites