The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials

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Summary

Background 5-year results of the UK Standardisation of Breast Radiotherapy (START) trials suggested that lower total doses of radiotherapy delivered in fewer, larger doses (fractions) are at least as safe and effective as the historical standard regimen (50 Gy in 25 fractions) for women after primary surgery for early breast cancer. In this prespecified analysis, we report the 10-year follow-up of the START trials testing 13 fraction and 15 fraction regimens.

Methods From 1999 to 2002, women with completely excised invasive breast cancer (pT1–3a, pN0–1, M0) were enrolled from 35 UK radiotherapy centres. Patients were randomly assigned to a treatment regimen after primary surgery followed by chemotherapy and endocrine treatment (where prescribed). Randomisation was computer-generated and stratified by centre, type of primary surgery (breast-conservation surgery or mastectomy), and tumour bed boost radiotherapy. In START-A, a regimen of 50 Gy in 25 fractions over 5 weeks was compared with 41·6 Gy or 39 Gy in 13 fractions over 5 weeks. In START-B, a regimen of 50 Gy in 25 fractions over 5 weeks was compared with 40 Gy in 15 fractions over 3 weeks. Eligibility criteria included age older than 18 years and no immediate surgical reconstruction. Primary endpoints were local-regional tumour relapse and late normal tissue effects. Analysis was by intention to treat. Follow-up data are still being collected. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN59368779.

Findings START-A enrolled 2236 women. Median follow-up was 9·3 years (IQR 8·0–10·0), after which 139 local-regional relapses had occurred. 10-year rates of local-regional relapse did not differ significantly between the 41·6 Gy and 50 Gy regimen groups (6·3%, 95% CI 4·7–8·5 *vs* 7·4%, 5·5–10·0; hazard ratio [HR] 0·91, 95% CI 0·59–1·38; p=0·65) or the 39 Gy (8·8%, 95% CI 6·7–11·4) and 50 Gy regimen groups (HR 1·18, 95% CI 0·79–1·76; p=0·41). In START-A, moderate or marked breast induration, telangiectasia, and breast oedema were significantly less common normal tissue effects in the 39 Gy group than in the 50 Gy group. Normal tissue effects did not differ significantly between 41·6 Gy and 50 Gy groups. START-B enrolled 2215 women. Median follow-up was 9·9 years (IQR 7·5–10·1), after which 95 local-regional relapses had occurred. The proportion of patients with local-regional relapse at 10 years did not differ significantly between the 40 Gy group (4·3%, 95% CI 3·2–5·9) and the 50 Gy group (5·5%, 95% CI 4·2–7·2; HR 0·77, 95% CI 0·51–1·16; p=0·21). In START-B, breast shrinkage, telangiectasia, and breast oedema were significantly less common normal tissue effects in the 40 Gy group than in the 50 Gy group.

Interpretation Long-term follow-up confirms that appropriately dosed hypofractionated radiotherapy is safe and effective for patients with early breast cancer. The results support the continued use of 40 Gy in 15 fractions, which has already been adopted by most UK centres as the standard of care for women requiring adjuvant radiotherapy for invasive early breast cancer.

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Introduction

The local cancer control and overall survival benefits of adjuvant radiotherapy for women with early breast cancer have been established by a systematic review of 17 randomised trials involving more than 10 000 patients.[1] In most studies, a total dose of 50 Gy was delivered in 25 fractions of 2 Gy over 5 weeks. This standard regimen is based on a historical assumption that breast cancer is less sensitive to changes in the dose per fraction than dose-limiting healthy normal tissues. If true, a sequence of small (2 Gy) fractions to a high total dose (≥50 Gy) spares the healthy tissues relative to the cancer, and for that reason is beneficial to the patient.

However retrospective analysis of clinical data raised the suggestion that breast cancer might be much more sensitive to changes in radiotherapy dose per fraction than most other cancers.[2,3] Supporting data were reported by a UK pilot trial (n=1410) begun in 1986 and by a Canadian

trial (n=1234) begun in 1993.[4–7] The Standardisation of Breast Radiotherapy (START) trials began in 1998, on the basis of results of the UK START pilot trial that assessed two doses (39 Gy and 42·9 Gy) of a 13 fraction regimen delivered over 5 weeks compared with 50 Gy in 25 fractions.[6,7] START-A maintained the 5-week overall treatment time across all randomised groups and included two doses of a 13 fraction regimen, enabling the investigators to make unconfounded estimates of the sensitivity to fraction size. 5-year results for local tumour control and late-occurring normal tissue effects assessed by patients and from photographs were consistent with the hypothesis that breast cancer tissue and the dose-limiting normal tissues are similarly sensitive to fraction size.[8,9] START-B had a pragmatic design, with 5-year results suggesting that local tumour control and safety of normal tissue effects are as good after 40 Gy in 15 fractions over 3 weeks (used in the UK and Canada for decades) as with 50 Gy in 25 fractions over 5 weeks.[9,10] The 5-year results of the START trials had a large effect on breast cancer radiotherapy practice both in the UK and worldwide. START results have subsequently informed National Institute for Health and Care Excellence (NICE) and American Society for Radiation Oncology (ASTRO) guidelines for breast radiotherapy fractionation.[11,12] A 2010 Cochrane review concluded that hypofractionation did not seem to compromise safety and efficacy, but that longer follow-up was needed for a more complete assessment.[13] We here present a 10-year update of START-A and START-B, including assessment of long-term efficacy and adverse effects.

Methods

Study design and participants

The START trials were two randomised, unmasked trials of women recruited between 1999 and 2002, from UK radiotherapy centres—17 centres for START-A and 23 for START-B. Patients were recruited after complete excision of primary invasive breast cancer (pT1–3a, pN0–1, M0) and referred for radiotherapy as part of standard treatment. When patients were given adjuvant chemotherapy, a 2-week interval was required before the start of radiotherapy. Patients in START-A were randomly assigned to either 50 Gy in 25 fractions (control group) or 41·6 Gy in 13 fractions or 39 Gy in 13 fractions over 5 weeks, and START-B patients to either 50 Gy in 25 fractions (control group) over 5 weeks or 40 Gy in 15 fractions over 3 weeks. Randomisation method was computer-generated, and stratified by centre, type of primary surgery (breast-conservation surgery or mastectomy), and tumour bed boost radiotherapy. Both START trials permitted prescription of a sequential tumour bed boost dose of 10 Gy in five fractions, which needed to be planned before randomisation to ensure that the independent effect of tumour bed boost radiotherapy on adverse effects did not affect the comparisons of fractionation schedules. The study design, eligibility criteria, randomisation procedures, and details of the radiotherapy planning, delivery, and verification protocols have been previously reported.[8–10] The START trials were approved by the South Thames Multi-Research Ethics Committee in September, 1998, and by the local ethics committees of all participating centres. Written informed consent was obtained for all patients.

The principal endpoints were local-regional relapse—defined as relapse in breast or chest wall, ipsilateral axilla, or supraclavicular fossa within an irradiated target volume—and late normal tissue effects. Normal tissue effects in the breast, arm, and shoulder were assessed by physician, photographic comparison with baseline, and patient self-reports. Patients were assessed every year for tumour relapse and radiotherapy-induced normal tissue effects. Physician assessments of normal tissue effects in the treated breast compared with the contralateral breast were scored on a four-point scale ("none", "a little", "quite a bit", or "very much"). Results of the photographic assessments and patient self-assessments of late normal tissue effects up to 5 years (the final timepoint for these endpoints) have been published.[8–10]

Secondary endpoints were local relapse (relapse in breast or chest wall), distant relapse (relapse in non-irradiated organs), disease-free survival (survival from any breast cancer-related event including local, regional, or distant relapse, breast cancer death, or contralateral breast cancer), and overall survival.

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See **Online** for appendix

	Events (n/patients; %)	Estimated proportion of patients with event by 5 years (%; 95% CI)	Estimated proportion of patients with event by 10 years (%; 95% CI)	Crude hazard ratio (95% CI)	p value*
Local relapse					
50 Gy	40/749 (5·3%)	3·4% (2·3–5·1)	6·7% (4·9–9·2)	1·00	..
41·6 Gy	37/750 (4·9%)	3·1% (2·0–4·7)	5·6% (4·1–7·8)	0·90 (0·57–1·40)	0·63
39 Gy	47/737 (6·4%)	4·4% (3·1–6·2)	8·1% (6·1–10·7)	1·20 (0·79–1·83)	0·39
Local-regional relapse					
50 Gy	45/749 (6·0%)	4·0% (2·8–5·7)	7·4% (5·5–10·0)	1·00	..
41·6 Gy	42/750 (5·6%)	3·8% (2·6–5·5)	6·3% (4·7–8·5)	0·91 (0·59–1·38)	0·65
39 Gy	52/737 (7·1%)	5·1% (3·7–7·1)	8·8% (6·7–11·4)	1·18 (0·79–1·76)	0·41
Distant relapse					
50 Gy	100/749 (13·3%)	9·8% (7·9–12·3)	14·7% (12·2–17·7)	1·00	..
41·6 Gy	110/750 (14·7%)	9·5% (7·6–11·9)	16·8% (14·0–20·0)	1·08 (0·82–1·41)	0·58
39 Gy	121/737 (16·4%)	11·8% (9·7–14·4)	18·0% (15·1–21·2)	1·24 (0·95–1·61)	0·11
Any breast cancer-related event†					
50 Gy	154/749 (20·6%)	14·0% (11·6–16·7)	22·6% (19·5–26·1)	1·00	..
41·6 Gy	149/750 (19·9%)	11·7% (9·5–14·2)	22·7% (19·5–26·3)	0·94 (0·75–1·17)	0·57
39 Gy	163/737 (22·1%)	15·5% (13·0–18·3)	24·3% (21·1–28·0)	1·08 (0·87–1·35)	0·48
All-cause mortality					
50 Gy	130/749 (17·4%)	10·5% (8·5–13·0)	19·8% (16·8–23·2)	1·00	..
41·6 Gy	128/750 (17·1%)	10·7% (8·7–13·2)	18·4% (15·7–21·6)	0·96 (0·75–1·22)	0·74
39 Gy	134/737 (18·2%)	9·9% (8·0–12·4)	20·3% (17·3–23·7)	1·05 (0·82–1·34)	0·69

*Assessed with Wald test comparing each schedule with 50 Gy. †Local, regional, or distant relapse, breast cancer death, contralateral breast cancer.

Table 1: **Relapse and mortality according to fractionation schedule in START-A**

Statistical analysis

We predicted a 5-year local-regional tumour relapse rate of 10% in the 50 Gy schedule group (control), on the basis of the START pilot trial.[7] START-A had a target sample size of 2000 patients to provide 80% power to detect a difference of 5% in the local-regional relapse rate between the control and each test schedule (two-sided α=0·05). START-B had a target of 1840 patients to provide 95% power to exclude an increase of 5% in the local-regional relapse rate in the 40 Gy schedule compared with control (one-sided α=0·025).

We used survival analysis methods to compare endpoint occurrences between fractionation schedules. Length of follow-up was calculated as time from randomisation until time of first event or last follow-up assessment, whichever occurred first. Patients were still evaluable for local-regional relapse after distant relapse. For the physician assessments of normal tissue effects, an event was defined as the first occurrence of a moderate or marked symptom (graded as "quite a bit" or "very much"). We calculated Kaplan-Meier estimates of 10-year rates (with 95% CIs) and used the Wald test to compare schedules. We used Cox proportional hazards regression models to obtain crude hazard ratios (HRs) and 95% CIs. Both one-sided and two-sided 95% CIs were calculated for the absolute difference in local-regional relapse rates because the upper limit is of greater clinical interest, in view of concern about a possible excess risk caused by hypofractionated schedules. We plotted Kaplan-Meier survival curves and cumulative hazard rates according to fractionation schedule, censoring at the median length of follow-up.

We obtained direct estimates of the α/β value for breast cancer and the dose-limiting normal tissues from Cox proportional hazards regression models containing terms for total dose, and total dose multiplied by dose per fraction as well as known prognostic factors (appendix). The α/β value is derived from an empirical model that describes sensitivity of a normal or malignant tissue to fraction size; α/β values less than 10 Gy indicate relative sensitivity to fraction size. We carried out meta-analyses of START-A, START-B, and the START pilot trial by fitting the Cox proportional hazards regression models to all individual patient data from the three trials. We stratified the analyses by trial to enable baseline hazards to vary according to trial but assuming equal treatment effects. The analyses included all enrolled patients on an intention-to-treat basis. Analyses were done with SPSS (version 19) and Stata (version 9).

The trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN59368779.

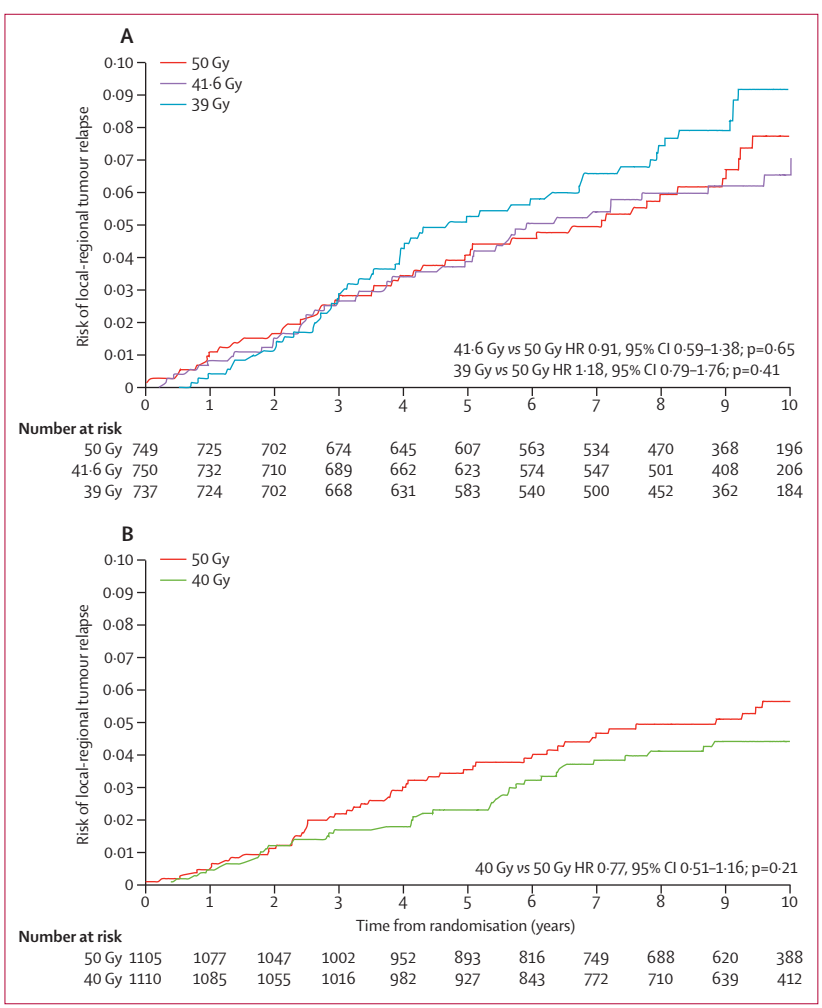

Figure 1: **Cumulative risk of local-regional tumour relapse**
In START-A (A) and START-B (B).

Role of the funding source

The funders of the study provided peer-reviewed approval for the trials and had no role other than as representatives (as observers) on the trial steering committee. The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data, and had final responsibility for the decision to submit for publication.

Results

2236 women were recruited into START-A between Jan 20, 1999, and Dec 20, 2002; median age was 57 years (range 25–85) (appendix). 1900 (85%) had received breast-conserving surgery, 1138 (51%) had tumours smaller than 2 cm, 643 (29%) had positive lymph nodes, 1572 (70%) had grade 1 or 2 disease, 793 (35%) received adjuvant chemotherapy, 1758 (79%) received tamoxifen, and 318 (14%) received lymphatic radiotherapy. 1152 of 1900 (61%) patients who had breast-conserving surgery had tumour bed boost radiotherapy. The appendix shows baseline characteristics by treatment schedule. At a median follow-up in survivors of 9·3 years (IQR 8·0–10·0, maximum 12·4 years), 1700 of 2236 patients (76·0%) were alive and without relapse, 57 (2·5%) were

alive with local-regional relapse (without distant relapse), 78 (3·5%) were alive with distant relapse (including 16 with local-regional relapse), 392 (17·5%) had died (including 66 with local-regional relapse), and nine (0·4%) had had no follow-up.

At the time of analysis (Feb 20, 2012), 139 of 2236 (6·2%) patients in START-A had local-regional tumour relapse. The HRs for local-regional relapse relative to the 50 Gy schedule were 0·91 (95% CI 0·59–1·38) for the 41·6 Gy schedule and 1·18 (0·79–1·76) for the 39 Gy schedule (table 1). The estimated absolute differences in the proportion of patients with local-regional relapses at 10 years compared with 50 Gy were –0·6% (95% CI –3·0 to 2·7) for 41·6 Gy and 1·3% (–1·5 to 5·2) for 39 Gy. The upper limits of the one-sided 95% CI for the absolute difference in 10-year local-regional relapse rates indicated an estimated maximum 2·0% excess risk with 41·6 Gy and 4·5% with 39 Gy compared with 50 Gy. There were few local-regional relapses in START-A (figure 1, appendix). The estimated α/β value for local-regional relapse in START-A was 4 Gy (95% CI 0·0–8·9), adjusting for age, tumour size, type of primary surgery, use of adjuvant chemotherapy, use of tamoxifen, lymphatic radiotherapy, and tumour bed boost radiotherapy. Meta-analysis of START-A and the START pilot trial (349 events, 3646 women), provided an adjusted α/β value for local-regional relapse of 3·5 Gy (95% CI 1·2–5·7).

At the time of analysis, 273 of 392 deaths (69·6%) in START-A were from breast cancer (92 with 50 Gy, 86 with 41.6 Gy, and 95 with 39 Gy), 26 (6·6%) were related to cardiac disease only (seven with 50 Gy, 13 with 41·6 Gy, and six with 39 Gy), 34 (8·7%) were from other cancers (nine with 50 Gy, ten with 41·6 Gy, and 15 with 39 Gy), 44 (11·2%) were from other non-cancer causes (16 with 50 Gy, 16 with 41·6 Gy, and 12 with 39 Gy), and 15 (3·8%) were from unknown cause (six with 50 Gy, three with 41·6 Gy, and six with 39 Gy). 15 (57·7%) of the 26 deaths from cardiac disease in START-A were in women with left-sided primary tumours (four of seven with 50 Gy, ten of 13 with 41·6 Gy, and one of six with 39 Gy). Distant relapses, disease-free survival, and overall survival were not significantly different between schedules in START-A, with no evidence of a clinically significant detriment for either of the hypofractionated schedules compared with 50 Gy (table 1, figure 2).

Breast shrinkage and induration were the most common normal tissue effects at 10 years in START-A (table 2). Moderate or marked breast induration, telangiectasia, and breast oedema were significantly less common in the 39 Gy regimen patients group than in the 50 Gy regimen group (table 2, figure 3). Moderate or marked normal tissue effects did not differ significantly between 41·6 Gy and 50 Gy groups (table 2, figure 3). α/β estimates for normal tissue endpoints in START-A (adjusting for age, breast size, surgical deficit, lymphatic radiotherapy, and tumour bed boost radiotherapy) were 3·5 Gy (95% CI 0·7–6·4) for breast shrinkage,

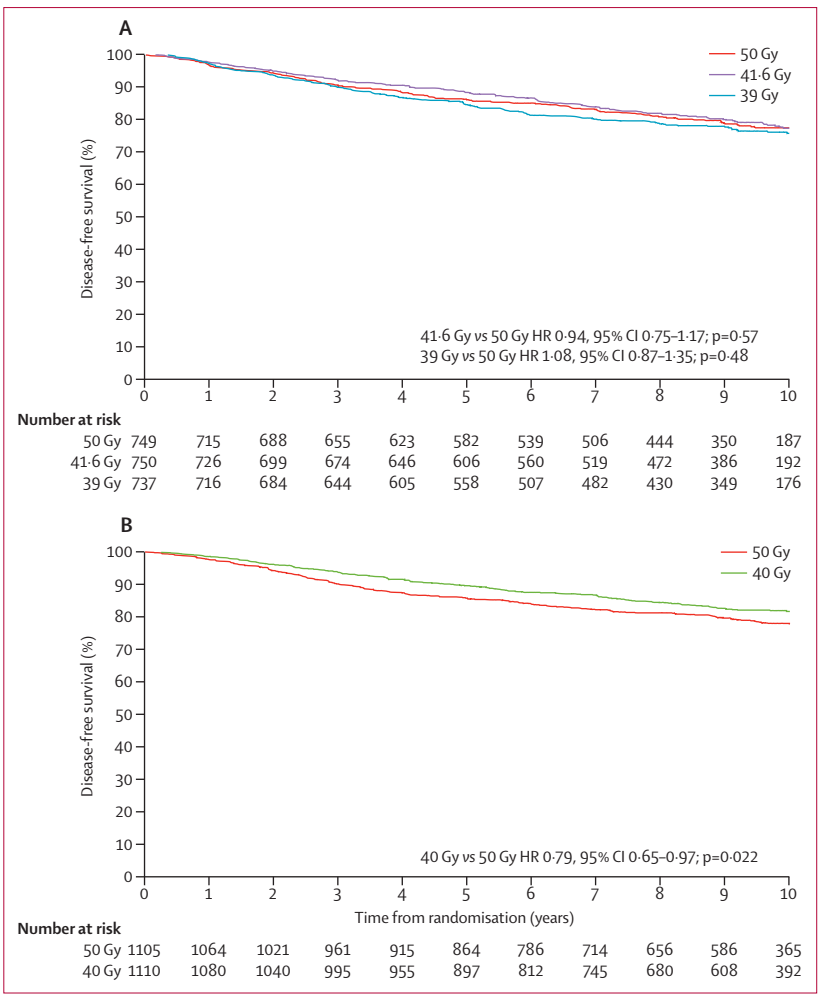

Figure 2: **Kaplan-Meier analysis of disease-free survival**
In START-A (A) and START-B (B).

4 Gy (2·3–5·6) for breast induration, 3·8 Gy (1·8–5·7) for telangiectasia, and 4·7 Gy (2·4–7·0) for breast oedema. Ischaemic heart disease, symptomatic rib fracture, and symptomatic lung fibrosis were rare at 10 years (table 3) and occurred in much the same proportions with each treatment schedule.

2215 women were recruited into START-B between Jan 4, 1999, and Oct 12, 2001. Median age was 57 years (range 23–86). 2038 of 2215 (92%) patients had received breast-conserving surgery, 1412 (64%) had tumours smaller than 2 cm, 504 (23%) had positive lymph nodes, 1667 (75%) had grade 1 or 2 disease, 491 (22%) received adjuvant chemotherapy, 1928 (87%) received tamoxifen, and 161 (7%) received lymphatic radiotherapy (appendix). 868 of 2038 (43%) patients who had breast-conserving surgery received tumour bed boost radiotherapy. The appendix shows baseline characteristics in each treatment group. At a median follow-up in survivors of 9·9 years (IQR 7·5–10·1, maximum 12·5 years), 1732 of 2215 (78·2%) patients were alive and without relapse, 50 (2·3%) were

	Moderate or marked events (n/patients; %)	Estimated proportion of patients with event by 5 years (%; 95% CI)	Estimated proportion of patients with event by 10 years (%; 95% CI)	Crude hazard ratio (95% CI)	p value*
Breast shrinkage†					
50 Gy	165/616 (26·8%)	14·1% (11·5–17·2)	34·2% (29·8–39·2)	1·00	..
41·6 Gy	168/627 (26·8%)	17·8% (14·9–21·1)	31·4% (27·2–36·0)	0·98 (0·79–1·21)	0·83
39 Gy	140/617 (22·7%)	14·7% (12·0–18·0)	30·0% (25·7–34·8)	0·86 (0·69–1·08)	0·19
Breast induration (tumour bed)†					
50 Gy	142/616 (23·0%)	18·5% (15·6–21·9)	27·1% (23·3–31·3)	1·00	..
41·6 Gy	150/627 (23·9%)	18·9% (16·0–22·3)	28·2% (24·2–32·7)	1·01 (0·80–1·27)	0·95
39 Gy	110/617 (17·8%)	15·0% (12·3–18·3)	21·6% (18·1–25·7)	0·76 (0·59–0·98)	0·034
Telangiectasia					
50 Gy	42/730 (5·7%)	4·3% (3·0–6·1)	7·2% (5·2–9·8)	1·00	..
41·6 Gy	43/733 (5·9%)	4·9% (3·5–6·8)	7·1% (5·2–9·5)	1·00 (0·65–1·53)	0·99
39 Gy	18/723 (2·5%)	1·3% (0·6–2·5)	3·0% (1·8–5·0)	0·43 (0·25–0·75)	0·003
Breast oedema†					
50 Gy	78/616 (12·7%)	12·1% (9·7–15·0)	13·5% (10·9–16·6)	1·00	..
41·6 Gy	67/627 (10·7%)	9·2% (7·1–11·7)	11·8% (9·3–14·8)	0·82 (0·59–1·14)	0·24
39 Gy	43/617 (7·0%)	7·3% (5·5–9·7)	7·3% (5·5–9·7)	0·54 (0·37–0·78)	0·001
Shoulder stiffness‡					
50 Gy	14/117 (12·0%)	8·8% (4·7–16·4)	17·5% (10·2–29·1)	1·00	..
41·6 Gy	10/95 (10·5%)	7·1% (3·3–15·2)	14·8% (8·0–26·6)	0·85 (0·38–1·90)	0·69
39 Gy	8/92 (8·7%)	7·5% (3·4–16·0)	11·0% (5·6–21·0)	0·74 (0·31–1·76)	0·49
Arm oedema‡					
50 Gy	15/117 (12·8%)	12·8% (7·6–21·2)	16·3% (9·9–26·2)	1·00	..
41·6 Gy	16/95 (16·8%)	11·9% (6·6–21·0)	22·5% (14·1–34·7)	1·31 (0·65–2·66)	0·45
39 Gy	6/92 (6·5%)	6·4% (2·7–14·7)	8·2% (3·7–17·6)	0·50 (0·20–1·30)	0·16
Other					
50 Gy	18/729 (2·5%)	1·3% (0·7–2·6)	3·4% (2·1–5·4)	1·00	..
41·6 Gy	20/733 (2·7%)	2·0% (1·2–3·4)	3·7% (2·3–6·1)	1·09 (0·58–2·06)	0·79
39 Gy	24/724 (3·3%)	2·3% (1·4–3·8)	3·9% (2·6–5·9)	1·37 (0·74–2·52)	0·31

*Assessed by Wald test, comparing each schedule with 50 Gy. †Only assessed in women who had breast-conserving surgery. ‡Restricted to women who received lymphatic radiotherapy (to axilla or supraclavicular fossa).

Table 2: **Physician-assessed normal tissue effects by fractionation schedule in START-A**

alive with local-regional relapse (without distant relapse), 63 (2·8%) were alive with distant relapse (including ten with local-regional relapse), 351 (15·8%) had died (including 35 with local-regional relapse), and 19 (0·9%) had no follow-up.

At the time of the analysis, 95 of 2215 (4·3%) patients in START-B had had local-regional tumour relapse, a lower proportion than in START-A, which is probably a result of the slightly better prognosis of patients recruited into START-B compared with START-A. The HR for local-regional relapse for the 40 Gy schedule compared with the 50 Gy schedule was 0·77 (95% CI 0·51–1·16; table 4). The estimated absolute difference in the proportion of patients with 10-year local-regional relapse for 40 Gy compared with 50 Gy was –1·2% (95% CI –2·6% to 1·0%). The upper limit of the one-sided 95% CI for the absolute difference in 10-year local-regional relapse rates suggested an estimated 0·4% excess risk associated with the 15 fraction schedule. The Kaplan-Meier and cumulative hazard rate plots for local-regional relapse according to fractionation schedule (figure 1, appendix) show the low number of recurrences in both randomised groups in START-B.

236 of 351 (67·2%) deaths in START-B were from breast cancer (130 with 50 Gy and 106 with 40 Gy), 17 (4·8%) were related to cardiac disease only (12 with 50 Gy and five with 40 Gy), 48 (13·7%) were from other cancers (25 with 50 Gy and 23 with 40 Gy), 40 (11·4%) were from other non-cancer causes (21 with 50 Gy and 19 with 40 Gy), and ten (2·8%) were from unknown cause (four with 50 Gy and six with 40 Gy). 11 (64·7%) of the 17 deaths from cardiac disease were in women with left-sided primary tumours (eight of 12 with 50 Gy and three of five with 40 Gy). There were significantly fewer distant relapses up to 10 years in the 40 Gy group (HR 0·74, 95% CI 0·59–0·94), which contributed to the significantly higher rates of disease-free survival and overall survival in the 40 Gy group compared with the 50 Gy group (table 4, figure 2).

Breast shrinkage and induration were the most common late normal tissue effects at 10 years in

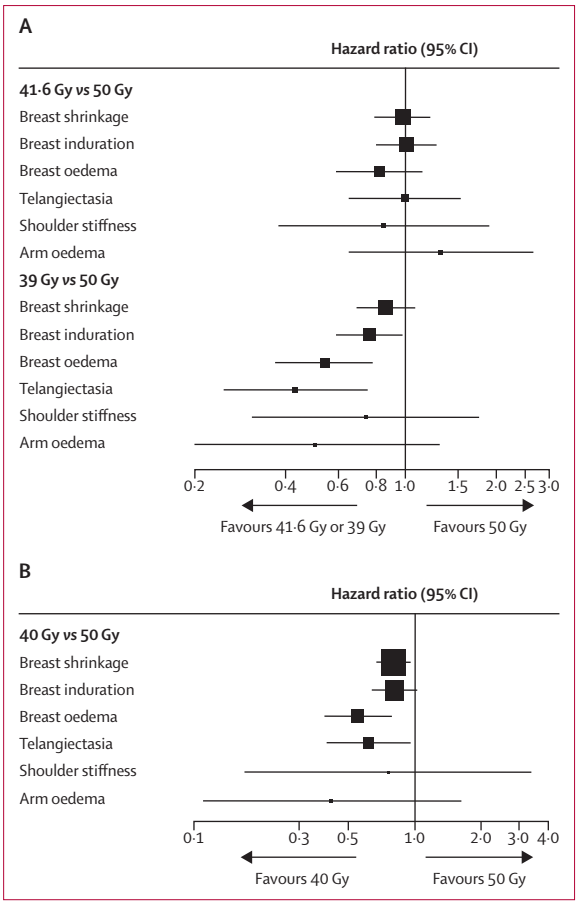

Figure 3: **Late normal tissue effects**
In START-A (A) and START-B (B). Assessed as moderate or marked by physicians.

START-B (table 5). Moderate or marked breast shrinkage, telangiectasia, and breast oedema were significantly lower with 40 Gy than with 50 Gy (figure 3, table 5). Ischaemic heart disease, symptomatic rib fracture, and symptomatic lung fibrosis were rare and occurred in much the same proportions with each treatment schedule (table 3).

Post-hoc subgroup analyses of the combined hypofractionated regimens versus the control groups for local-regional relapse in START-A, START-B, and the pilot trial (n=5861) showed that the treatment effect was not significantly different irrespective of age, type of primary surgery, axillary node status, tumour grade, adjuvant chemotherapy use, or use of tumour bed boost radiotherapy (figure 4). In a post-hoc analysis, the incidence of any moderate or marked physician-assessed normal tissue effects in the breast (shrinkage, induration, oedema, or telangiectasia) for the 4660 women with data available from START-A, START-B, and the pilot trial showed that the treatment effect was similar irrespective of age, breast size, use of tumour bed boost radiotherapy, adjuvant chemotherapy, or tamoxifen (figure 5).

	START-A				START-B		
	50 Gy (n=749)	41·6 Gy (n=750)	39 Gy (n=737)	Total (n=2236)	50 Gy (n=1105)	40 Gy (n=1110)	Total (n=2215)
Symptomatic rib fracture*							
Reported	5 (0·7%)	8 (1·1%)	9 (1·2%)	22 (1·0%)	17 (1·5%)	24 (2·2%)	41 (1·9%)
Confirmed†	0	0	1 (0·1%)	1 (<0·1%)	3 (0·3%)	3 (0·3%)	6 (0·3%)
Symptomatic lung fibrosis							
Reported	6 (0·8%)	9 (1·2%)	8 (1·1%)	23 (1·0%)	19 (1·7%)	19 (1·7%)	38 (1·7%)
Confirmed†	0	2 (0·3%)	1 (0·1%)	3 (0·1%)	2 (0·2%)	8 (0·7%)	10 (0·5%)
Ischaemic heart disease‡							
Reported	14 (1·9%)	11 (1·5%)	8 (1·1%)	33 (1·5%)	23 (2·1%)	17 (1·5%)	40 (1·8%)
Confirmed†							
Total	7 (0·9%)	5 (0·7%)	6 (0·8%)	18 (0·8%)	16 (1·4%)	8 (0·7%)	24 (1·1%)
Left sided	4 (0·5%)	1 (0·1%)	4 (0·5%)	9 (0·4%)	5 (0·5%)	4 (0·4%)	9 (0·4%)
Brachial plexopathy	0	1 (0·1%)	0	1 (<0·1%)	0	0	0

Data are n (%). *Reported cases include seven after trauma (five in START-A, two in START-B), and ten after metastases (five in START- A and five in START-B). †After imaging and further investigations. ‡26 patients in START-A and 22 in START-B had pre-existing heart disease at enrolment and were excluded.

Table 3: **Incidence of other late adverse effects according to fractionation schedule**

	Events (n/patients; %)	Estimated proportion of patients with event by 5 years (%; 95% CI)	Estimated proportion of patients with event by 10 years (%; 95% CI)	Crude hazard ratio (95% CI)	p value*
Local relapse					
50 Gy	50/1105 (4·5%)	3·3% (2·4–4·6)	5·2% (3·9–6·9)	1·00	..
40 Gy	36/1110 (3·2%)	1·9% (1·2–3·0)	3·8% (2·7–5·2)	0·70 (0·46–1·07)	0·10
Local-regional relapse					
50 Gy	53/1105 (4·8%)	3·5% (2·5–4·8)	5·5% (4·2–7·2)	1·00	..
40 Gy	42/1110 (3·8%)	2·3% (1·5–3·4)	4·3% (3·2–5·9)	0·77 (0·51–1·16)	0·21
Distant relapse					
50 Gy	158/1105 (14·3%)	10·5% (8·8–12·5)	16·0% (13·8–18·5)	1·00	..
40 Gy	121/1110 (10·9%)	7·5% (6·0–9·2)	12·3% (10·3–14·6)	0·74 (0·59–0·94)	0·014
Any breast cancer-related event†					
50 Gy	222/1105 (20·1%)	14·3% (12·3–16·5)	22·2% (19·7–25·0)	1·00	..
40 Gy	182/1110 (16·4%)	10·4% (8·7–12·4)	18·3% (16·0–20·9)	0·79 (0·65–0·97)	0·022
All-cause mortality					
50 Gy	192/1105 (17·4%)	10·9% (9·1–12·9)	19·2% (16·8–21·9)	1·00	..
40 Gy	159/1110 (14·3%)	7·9% (6·4–9·6)	15·9% (13·7–18·4)	0·80 (0·65–0·99)	0·042

*Assessed with log-rank test compared with 50 Gy. †Local, regional, or distant relapse, breast cancer death, contralateral breast cancer.

Table 4: **Relapse and mortality according to fractionation schedule in START-B**

Discussion

Although the absolute numbers of events have increased over time, the relative differences between the hypofractionated and control schedules at 10 years remain similar to those at 5 years, confirming that appropriately dosed hypofractionated radiotherapy for women with early breast cancer is safe and effective.[8–10] In START-A, 41·6 Gy in 13 fractions over 5 weeks remains a safe and effective alternative to 50 Gy in 25 fractions—the two regimens have much the same anti-tumour and adverse effects. Use of a 5-week treatment time across all

	Moderate or marked events (n/patients; %)	Estimated proportion of patients with event by 5 years (%; 95% CI)	Estimated proportion of patients with event by 10 years (%; 95% CI)	Crude hazard ratio (95% CI)	p value*
Breast shrinkage†					
50 Gy	256/1003 (25·5%)	15·8% (13·6–18·3)	31·2% (27·9–34·9)	1·00	..
40 Gy	221/1006 (22·0%)	11·4% (9·5–13·6)	26·2% (23·1–29·6)	0·80 (0·67–0·96)	0·015
Breast induration (tumour bed)†					
50 Gy	153/1003 (15·3%)	12·1% (10·2–14·4)	17·4% (14·9–20·3)	1·00	..
40 Gy	129/1006 (12·8%)	9·6% (7·9–11·6)	14·3% (12·1–16·9)	0·81 (0·64–1·03)	0·084
Telangiectasia					
50 Gy	52/1081 (4·8%)	3·8% (2·8–5·2)	5·8% (4·4–7·7)	1·00	..
40 Gy	34/1094 (3·1%)	1·8% (1·1–2·8)	4·2% (2·9–5·9)	0·62 (0·40–0·96)	0·032
Breast oedema†					
50 Gy	86/1003 (8·6%)	8·1% (6·6–10·1)	9·0% (7·3–11·0)	1·00	..
40 Gy	49/1006 (4·9%)	4·7% (3·5–6·2)	5·1% (3·9–6·7)	0·55 (0·39–0·79)	0·001
Shoulder stiffness‡					
50 Gy	4/73 (5·5%)	2·9% (0·7–11·0)	8·2% (2·9–21·8)	1·00	..
40 Gy	3/81 (3·7%)	3·1% (0·8–11·9)	3·1% (0·8–11·9)	0·76 (0·17–3·39)	0·71
Arm oedema‡					
50 Gy	7/73 (9·6%)	6·0% (2·3–15·3)	13·5% (6·4–27·0)	1·00	..
40 Gy	3/81 (3·7%)	2·8% (0·7–10·7)	4·7% (1·5–14·0)	0·42 (0·11–1·63)	0·21
Other					
50 Gy	77/1082 (7·1%)	5·6% (4·3–7·2)	8·1% (6·5–10·2)	1·00	..
40 Gy	53/1095 (4·8%)	3·3% (2·4–4·6)	6·4% (4·8–8·4)	0·65 (0·46–0·93)	0·018

*Assessed by Wald test compared with 50 Gy. †Only assessed in women who had breast-conserving surgery. ‡Restricted to women who received lymphatic radiotherapy (to axilla or supraclavicular fossa).

Table 5: **Physician-assessed normal tissue effects by fractionation schedule in START-B**

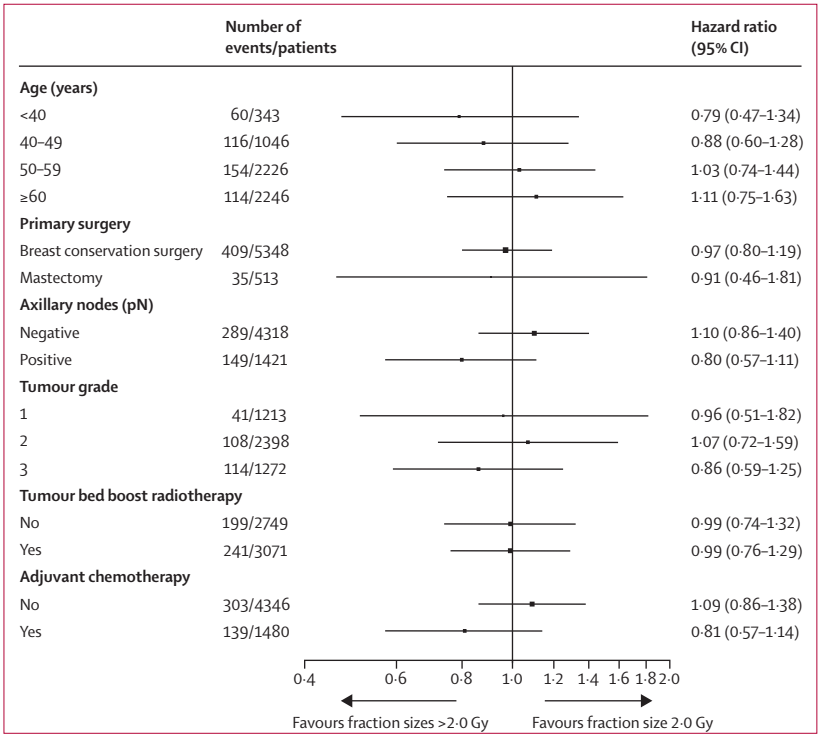

Figure 4: **Meta-analysis of local-regional relapse comparing hypofractionated regimens versus 50 Gy in 25 fractions**
Includes 5861 patients from the START pilot trial, START-A, and START-B.

treatment groups enabled an unconfounded test of sensitivity to fraction size. The CIs around the α/β estimate for breast cancer become narrower as more data are collected, and the low value is supported by the evidence from the combined hypofractionation trials.[14] The average estimate describes an underlying distribution of α/β that can be narrow or broad: its characterisation is a challenge for correlative research. The 10-year results of START-B confirm that 40 Gy in 15 fractions over 3 weeks is at least as safe and effective as 50 Gy in 25 fractions over 5 weeks. Some normal tissue effects were less common after the 15 fraction regimen than the control schedule (breast shrinkage, telangiectasia, and breast oedema). Application of an α/β value of 3·5 Gy for breast shrinkage—as obtained from START-A—and assuming no effect of treatment time on late normal tissue effects, 40 Gy in 15 fractions corresponds to 45 Gy in 2 Gy equivalents. The 15 fraction regimen is less harmful to normal tissues, and there is no suggestion that it is less effective in treating the cancer.

The data from the START trials are consistent with the 10-year results of the Ontario trial, which reported that local tumour control and breast cosmesis were no worse with a regimen of 42·5 Gy in 16 fractions over 3·2 weeks compared with 50 Gy in 25 fractions over 5 weeks.[5] The START pilot trial, Ontario trial, and START-A and START-B trials, considered together, present robust evidence that hypofractionation is a safe and effective approach to breast cancer radiotherapy (panel).[15] The corollary is that the continued use of small (2 Gy) fractions spares the cancer as much as the normal tissues, thereby bringing no benefit to patients. The unexpected survival benefit with the 40 Gy schedule at 5 years in START-B still exists at 10 years. The proportion of patients who had distant metastases differed after the first few years of follow-up, which translated into an overall survival benefit (table 4). This effect did not occur in START-A and it occurs too early to be a result of better local control, in which case the survival benefit would not be apparent until after 15 years. Similarly, it is unlikely to be caused by baseline differences in patient and treatment characteristics, which were well balanced between schedules, and unknown factors are unlikely to be imbalanced in randomised trials of this size. Following publication of the START trials' 5-year results, most UK centres pragmatically adopted the 15 fraction schedule as standard of care, as recommended by NICE guidelines in 2009.[11] The 15 fraction schedule was already in widespread use in the UK and elsewhere before the START trials, but had not been formally tested in a randomised controlled setting.

Controversy remains about generalising trial findings to all patients satisfying the eligibility criteria of the START trials.[12] To address this concern, we did unplanned subgroup meta-analyses of the START-A and START-B trials and the START pilot trial comparing all

hypofractionated schedules combined versus the control schedules. Although direct comparisons of results across the different trials are inadvisable because of the different patient populations, our subgroup analyses lend no support to a conservative approach with respect to patient age, breast size, tumour grade, axillary node status, type of surgery, cytotoxic chemotherapy, tumour bed boost radiotherapy, and lymphatic radiotherapy, although numbers are small in some groups. Along with other investigators,[16] we have found no suggestion of a detrimental effect of hypofractionated radiotherapy on risk of local relapse in grade 3 tumours, which does not support a subgroup analysis of the Ontario trial.[5] Whether or not a tumour bed boost radiotherapy was given did not alter the effect of hypofractionation on risk of late normal tissue effects, and tumour bed boost radiotherapy could not have a confounding effect because it was prescribed before randomisation and was given to similar proportions of patients in each treatment schedule group. A meta-analysis of many thousands of patients would be needed to assess individual prognostic subgroups more precisely. One exclusion criterion from the START trials was immediate breast reconstruction, and a conservative approach might be to defer from using a 15 fraction regimen in such patients, despite the very high likelihood, in our opinion, that the 15 fraction schedule would reduce normal tissue effects and provide equivalent local-regional control. Treatment of the supraclavicular fossa and axilla is another aspect that is often approached conservatively, despite the fact that even a dose of 40 Gy in 15 fractions at the level of the brachial plexus delivers the equivalent of 46·7 Gy, 47·6 Gy, and 48·9 Gy in 2·0 Gy equivalents, assuming α/β values of 2·0 Gy, 1·5 Gy, and 1.0 Gy, respectively.[17] In other words, 40 Gy in 15 fractions is less damaging to the brachial plexus than is 50 Gy in 25 fractions, even under extreme assumptions about the fractionation sensitivity of the nervous system. Although only a small proportion of women in the START trials received lymphatic radiotherapy, the assessments of arm and shoulder effects showed no evidence of a detrimental effect for the hypofractionated schedules. Finally, concerns have been raised about doses to the heart with hypofractionated schedules.[12] Our results showed that although follow-up was still short for cardiac events, there was no major difference between the schedules for the number of cases of heart disease in women with left-sided primary tumours. Some research suggests that hypofractionated breast radiotherapy might be safer for the heart than are conventional regimens.[18] Although such findings are reassuring, the heart is sensitive to radiation whatever fractionation is used, with no lower dose threshold for adverse effects.[19] Thus, the heart should be protected irrespective of the dose fractionation regimen used.

Other ongoing or planned trials of hypofractionation for whole breast radiotherapy aim to validate the findings from the START trials in different populations. Meanwhile, the UK FAST-Forward trial (ISRCTN19906132; aiming to recruit 4000 participants) is testing the safety and efficacy of five-fraction schedules delivered in a week,

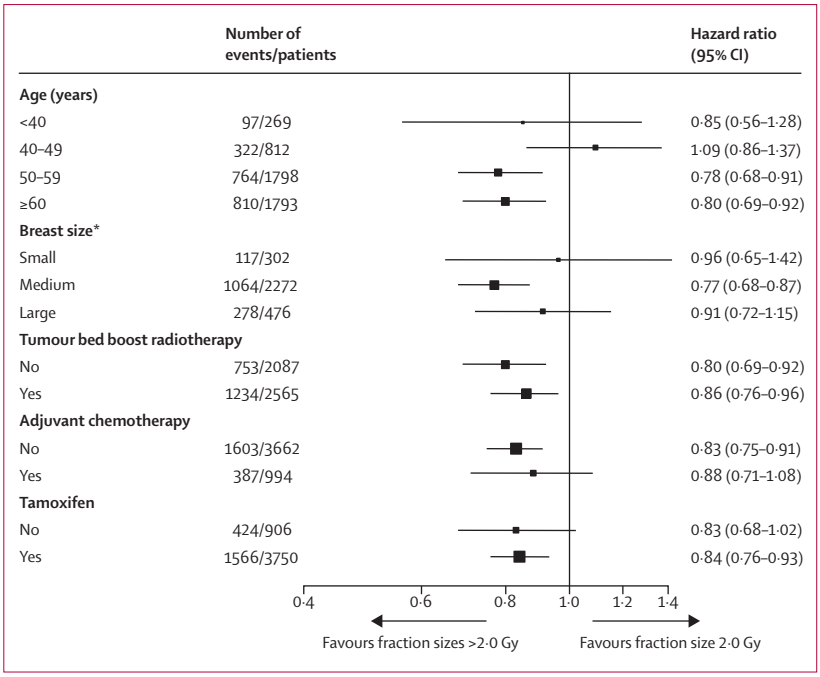

Figure 5: **Meta-analysis of any moderate or marked physician-assessed normal tissue effects in the breast comparing hypofractionated regimens versus 50 Gy in 25 fractions**
Includes 4672 patients from START pilot trial, START-A, and START-B. *Assessed from baseline photographs.

Panel: Research in context

Systematic review

The START trials began with the pilot study in 1986, at which time there was no evidence available from randomised trials comparing alternative fractionation schedules for breast cancer radiotherapy. Alternative shorter fractionation schedules were in use at some UK centres and in Canada, but the only evidence available for these schedules was from case series and cohort studies. The need for the START trials was shown by a survey of fractionation practices done by the UK Royal College of Radiologists in 1993. A similar trial to START-B began in Ontario in 1993. 5-year results of the START trials were published in 2008, and in 2002 for the Ontario trial, which suggested that the hypofractionated regimens were as safe and effective as the historical standard control schedule of 50 Gy in 25 fractions. However, confirmation after long-term follow-up was needed, especially because late normal tissue effects continue to occur for many years after radiotherapy. 10-year follow-up results of the Ontario trial were published in 2010, and an updated Cochrane systematic review was published in 2010.

Interpretation

Following publication of 5-year results from the Ontario and START trials, long-term follow-up was needed to confirm the safety and efficacy of the hypofractionated schedules. The 10-year START trial results presented here, together with the long-term results of the Ontario trial, confirm the earlier findings and strengthen the evidence in favour of using hypofractionated schedules for breast cancer radiotherapy. They support the continued use of 40 Gy in 15 fractions as the UK standard of care as recommended by the National Institute for Health and Care Excellence, and contribute further to the worldwide debate about breast cancer radiotherapy hypofractionation.

informed by the results of the pilot FAST trial (n=915).[20] In conclusion, long-term follow-up of the START trials confirms that appropriately dosed hypofractionated radiotherapy is safe and effective for patients with early breast cancer.

Contributors

JRY was chief investigator and chair of the Trial Management Group. All other authors were members of the Trial Management Group. JRY and JMB were responsible for the trial design, trial management, data interpretation, and writing the report. JSH did the statistical analyses, interpreted data, and wrote the report. JRO and JAD contributed to trial design, trial management, data interpretation, and wrote the report. SS and MAS coordinated the trial and collected data. PH and JM did the quality-of-life study and contributed to trial management. KV designed and carried out the radiotherapy quality assurance programme and contributed to the trial management. RKA, JB, PJB-L, HJD, PAL, and BJM contributed to trial design, trial management, data interpretation, and commented on the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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