Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 10-year efficacy and late normal tissue effects from a multicentre, open-label, non-inferiority, phase 3, randomised controlled trial and 5-year efficacy results from a randomised axillary substudy

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Summary

Background FAST-Forward aimed to identify a 1-week adjuvant radiotherapy schedule for early-stage breast cancer that was as safe and efficacious as the standard 3-week schedule of 40 Gy in 15 fractions over 3 weeks. Primary analysis showed non-inferiority of 5-year ipsilateral breast recurrence for 26 Gy and 27 Gy in five fractions over 1 week, with 26 Gy also having similar results to 40 Gy for normal tissue effects. Here, we report 10-year outcomes of the FAST-Forward trial and 5-year efficacy outcomes of a substudy assessing the approach in patients requiring axillary treatment.

Methods FAST-Forward is a multicentre, open-label, non-inferiority, phase 3, randomised controlled trial done at 97 hospitals (47 radiotherapy centres and 50 referring hospitals) in the UK. Patients aged 18 years or older with invasive carcinoma of the breast (pT1–3, pN0–1, M0) after breast conservation surgery or mastectomy were eligible. We randomly allocated patients (in a 1:1:1 ratio with random permuted blocks, stratified by radiotherapy centre) to either 40 Gy in 15 fractions (over 3 weeks), 27 Gy in five fractions (over 1 week), or 26 Gy in five fractions (over 1 week) to the whole breast or chest wall. Allocation was not masked because of the nature of the intervention. The primary endpoint was non-inferiority of ipsilateral breast recurrence at 5 years. Here, we report the planned 10-year analysis assessed in the intention-to-treat population (all participants who were randomly assigned and consented for use of data). We also report a planned intention-to-treat analysis of a subsequent substudy assessing 5-year efficacy of the same schedules in patients meeting the study criteria but requiring axillary treatment. The clinical trial was registered with ISRCTN (ISRCTN19906132); the main trial is complete, follow-up of the substudy cohort is ongoing.

Findings Between Nov 24, 2011, and June 19, 2014, 4110 participants were enrolled in the main FAST-Forward trial. 23 withdrew consent for data use and were excluded and 4087 participants were included in the intention-to-treat population for this 10-year analysis. Participants were randomly assigned to 40 Gy (n=1358), 27 Gy (n=1362), or 26 Gy (n=1367). Median follow-up was 10·1 years (IQR 10·0–10·2). Ipsilateral breast recurrence was reported for 116 participants (45 in the 40 Gy group, 41 in the 27 Gy group, and 30 in the 26 Gy group), with 10-year cumulative incidence of 3·6% (95% CI 2·7–4·9) for the 40 Gy group, 2·9% (2·1–4·0) for the 27 Gy group, and 2·1% (1·5–3·1) for the 26 Gy group. 10-year clinician-reported moderate or marked breast or chest wall effects occurred in 100 (13·1%) of 765 participants in the 40 Gy group, 157 (19·3%) of 814 in the 27 Gy group, and 111 (14·4%) of 770 in the 26 Gy group. Between April 11, 2016, and Oct 2, 2018, 469 participants enrolled in the nodal substudy, 466 of which were included in intention-to-treat analyses. Median follow-up was 7·0 years (IQR 6·2–7·1) and 32 locoregional recurrences were reported.

Interpretation Long-term follow-up confirms that 26 Gy in five fractions over 1 week is safe and efficacious for adjuvant radiotherapy to the breast or chest wall, supporting its use as a standard of care. Efficacy data for this schedule in the axillary nodal radiotherapy setting are reassuring; however, sample size limits precision of estimation for this subgroup on its own.

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Introduction

Radiotherapy after primary surgery in people with early-stage breast cancer reduces locoregional cancer recurrence and breast cancer mortality.[1,2] Historically, adjuvant radiotherapy was delivered as 25 fractions of 2 Gy over 5 weeks. Multiple, large randomised controlled

Research in context

Evidence before this study

In the context of radiotherapy after primary surgery for breast cancer, to the best of our knowledge, there have been four large, randomised, phase 3 clinical trials with 10-year follow-up (totalling 7000 participants across the four trials) that have shown that delivering radiotherapy daily over 3 weeks (in 15 or 16 daily treatments or fractions) is as effective at reducing risk of recurrence as the traditional 5-week schedules (25 fractions). In 2008, Bentzen and colleagues showed that a schedule of 40 Gy in 15 fractions over 3 weeks reduced adverse effects on normal tissues than a schedule of 50 Gy in 25 fractions over 5 weeks and became an international standard of care from 2009. Outcomes from a five-fraction schedule delivered over 5 weeks (FAST trial) suggested further scope for reducing the burden of curative radiotherapy for people with early breast cancer. Evidence to inform the FAST-Forward trial design was based on a PubMed search done in 2009 using the search terms breast cancer, radiotherapy, fractionation, and trials, as well as direct communication with international researchers; no formal meta-analysis was done. The trial was designed to compare two 1-week schedules (26 Gy in five fractions over 1 week and 27 Gy in five fractions over 1 week) against the standard of care 40 Gy in 15 fractions over 3 weeks schedule for adjuvant radiotherapy to the breast or chest wall after primary breast surgery (breast conservation or mastectomy).

Added value of this study

The 10-year outcomes from the FAST-Forward trial support that both 1-week schedules (26 Gy in five fractions over 1 week and 27 Gy in five fractions over 1 week) are as effective as a 40 Gy in 15 fractions over 3 weeks schedule in terms of 10-year cumulative incidence of ipsilateral breast recurrence. At 10 years, incidence of moderate or marked patient-reported and clinician-reported breast or chest wall side-effects were similar for the 40 Gy in 15 fractions and 26 Gy in five fractions. As seen in the primary analysis, incidences of these effects were slightly higher with 27 Gy in five fractions over 1 week, suggesting this schedule is suboptimal. Although not powered for efficacy outcomes, 5-year data from the nodal substudy reported here show that, for those receiving axillary radiotherapy, incidence of locoregional recurrence was low with both 26 Gy in five fractions over 1 week and 40 Gy in 15 fractions over 3 weeks schedules, consistent with main trial results.

Implications of all the available evidence

The 10-year outcomes from FAST-Forward support a 26 Gy in five fractions over 1 week schedule as the international standard of care for adjuvant radiotherapy to the breast or chest wall in early breast cancer. 5-year results from the axillary nodal substudy show the 26 Gy schedule is safe and efficacy data are reassuringly consistent with the main trial. However, sample size limits the precision of efficacy estimates for this subgroup on its own. This uncertainty should be part of shared decision making for those patients considering 26 Gy axillary radiotherapy. Shorter radiotherapy schedules reduce the burden of breast cancer treatment on patients, health services, and the environment.

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trials have shown that hypofractionation (fewer treatments in higher doses per fraction, equating to a lower total dose) can deliver comparable efficacy and safety alongside shorter treatment times.[3–10] In 2009, a 3-week schedule of 40 Gy in 15 fractions became the UK standard of care for adjuvant local and locoregional radiotherapy, with mature trial data confirming the safety and non-inferiority of 15 fractions of approximately 2·7 Gy (giving a total dose of 40·0 Gy) or 16 fractions of approximately 2·7 Gy (giving a total dose of 42·5 Gy).[5,8] These schedules have since been adopted internationally.[11–13] Data from these trials,[3–10] however, suggested that the 3-week schedule was unlikely to represent the limit of hypofractionation.

The FAST-Forward trial was designed to evaluate whether a 1-week course of adjuvant radiotherapy (five fractions of 26 Gy or 27 Gy) to the breast or chest wall for early-stage breast cancer was non-inferior to the international standard of 40 Gy in 15 fractions over 3 weeks. At 5 years, 26 Gy in five fractions was non-inferior for local recurrence,[14] with comparable normal tissue effects and reduced early skin toxicity.[15] Since disease recurrence and normal tissue effects can occur many years after treatment, this preplanned 10-year analysis reports longer-term efficacy alongside patient-reported and clinician-reported adverse events, providing, to our knowledge, the most robust evidence to date on use of a 1-week, five-fraction schedule in this setting.

The FAST-Forward nodal substudy evaluates the same schedules in people requiring axillary radiotherapy; recently published normal tissue effect data showed that 26 Gy in five fractions over 1 week to the axilla is non-inferior to 40 Gy in 15 fractions over 3 weeks in terms of 5-year incidence of patient-reported arm or hand swelling.[16] Here, we report efficacy data from the substudy in a planned meta-analysis with the main trial.

Methods

Study design and participants

The trial design has been published previously;[14] the schema and protocol are provided in the appendix (p 7). An updated statistical analysis plan was created for this analysis of 10-year follow-up data from the main trial, including the prespecified analysis of 5-year efficacy data from the nodal substudy (appendix). FAST-Forward is a multicentre, open-label, non-inferiority, phase 3,

See Online for appendix

randomised controlled trial, done at 97 hospitals (47 radiotherapy centres and 50 referring hospitals) in the UK, assessing the safety and efficacy of five-fraction schedules of adjuvant radiotherapy to the whole breast or chest wall delivered in 1 week compared with a 15-fraction, 3-week schedule (UK standard at trial initiation). After the main trial recruitment, a randomised substudy opened assessing the same schedules for people requiring axillary radiotherapy (levels 1–4) with a safety primary endpoint of 5-year patient-reported arm or hand swelling, which was reported previously.[16]

The primary 5-year analysis of the main trial, published in 2020, showed non-inferiority of the 1-week schedules for ipsilateral breast recurrence.[14] The current analysis was planned for 10 years after enrolment of the last main trial participant. Efficacy data from the nodal substudy was also preplanned to be analysed at this time (>5 years after last enrolment), in conjunction with main trial data, since the substudy alone was underpowered for these outcomes.

The main trial included people aged 18 years or older with histologically confirmed invasive carcinoma of the breast (pT1–3, pN0–1, M0) after complete microscopic excision of primary tumour by breast-conservation surgery or mastectomy (reconstruction allowed). A protocol amendment (approved Feb 15, 2013) excluded the lowest risk patients (aged 65 years or older with pT1 grade 1 or 2, oestrogen receptor [ER] positive, HER2 negative, pN0, M0 disease) to avoid over recruitment of this population, which might lead to the trial being underpowered. Concurrent endocrine therapy or trastuzumab were permitted, as was chemotherapy completed 2 weeks or more before radiotherapy (but not concurrent chemotherapy). All participants had axillary surgery (sentinel node biopsy or axillary dissection). In the main trial, nodal radiotherapy was not allowed.

The nodal substudy eligibility criteria were as for the main trial except that participants required radiotherapy to levels 1–4 of the axilla. Patients who required internal mammary node radiotherapy were excluded since indications were unclear at the time of recruitment.

FAST-Forward was approved by the national South East Coast Kent Research Ethics Committee (11/LO/0958), sponsored by The Institute of Cancer Research, and conducted in accordance with principles of Good Clinical Practice. Patient advocates contributed throughout, from study design through to dissemination. Participants provided written informed consent. The trial is registered with ISRCTN (ISRCTN19906132); the main trial is complete, follow-up of the substudy cohort is ongoing.

Randomisation and masking

Participants were randomly assigned (1:1:1) to receive either 40 Gy in 15 fractions of 2·67 Gy over 3 weeks (control group), 27 Gy in five fractions of 5·4 Gy over 1 week, or 26 Gy in five fractions of 5·2 Gy over 1 week. Allocation used random permuted blocks (block size 6 and 9), stratified by radiotherapy centre. In the main trial, participants were additionally stratified by risk group (high risk [age <50 years or grade 3] *vs* low risk [age ≥50 years and grade 1 or 2]) and, in the nodal substudy, by whether axillary clearance had been performed. Clinicians or patients were not masked to allocation. While recruitment to the nodal substudy was ongoing, main trial 3-year normal tissue effect data suggested that the 27 Gy schedule was suboptimal[17] and recruitment to the substudy 27 Gy group was stopped early (Dec 12, 2017). Allocation continued (1:1) to the remaining groups.

Procedures

Details of radiotherapy outlining, planning, and verifying have been published previously (with planning guidelines included as appendices for those publications).[14,16] Radiotherapy planning guidelines were developed with the UK Radiotherapy Trials Quality Assurance Group who oversaw a comprehensive quality assurance programme across all treatment centres.

Test dose levels represented the upper and lower estimates of isoeffect with 40 Gy in 15 fractions for late normal tissue effects based on historical data.[6,18] The two-test dose strategy facilitates interpolation to estimate isoeffect with control in terms of late normal tissue effects. A sequential tumour bed boost to the conserved breast was allowed, with boost intention and dose (10 Gy or 16 Gy in 2 Gy fractions) specified before randomisation.

The treatment plan was optimised with 3D dose compensation to reach the following planning target volume (PTV) dose distribution: more than 95% of the PTV received 95% of prescribed dose, less than 5% of the PTV received 105% or more, less than 2% of the PTV received 107% or more, and global maximum of less than 110%. Dose constraints for the control group were less than 15% of ipsilateral lung volume receiving 12 Gy, less than 30% of heart volume receiving 2 Gy, and less than 5% of heart volume receiving 10 Gy. Dose constraints for the five-fraction schedules were less than 15% of ipsilateral lung volume receiving 8 Gy, less than 30% of heart volume receiving 1·5 Gy, and less than 5% of heart volume receiving 7 Gy. Tumour bed boost was delivered sequentially via photons or electrons. Verification was done by use of electronic portal imaging with MV or kV x-rays.

In the nodal substudy, axillary lymph node levels 1–4 to be irradiated, established before randomisation, were CT-delineated as lymph node clinical and planning target volumes. The lymph node clinical target volume landmarks and margins were from European Society for Radiotherapy and Oncology (ESTRO) guidelines.[19] The lymph node PTV margins were 5–10 mm as appropriate, with 5 mm maximum level 4 medially.

Participants were assessed for disease recurrence and late effects once per year until year 7 with a final

assessment at year 10 (assessments at year 8 and 9 were optional), including mammograms done once per year up to and including year 5 (or until screening age according to UK guidelines, if younger). Patients were followed up regardless of whether radiotherapy was received as planned, unless consent was explicitly withdrawn. Reported data for ipsilateral breast recurrence (including angiosarcomas) and deaths were centrally reviewed by AMB, DAW, or AMK. For the ipsilateral breast recurrence, data collection did not systematically distinguish between angiosarcoma and other new primaries; however, where identified from reported histology, these angiosarcomas are also presented separately. For clinician-reported and patient-reported late normal tissue effects, clinicians assessed breast shrinkage, distortion, induration in the tumour bed, induration outside the tumour bed, telangiectasia, breast or chest wall oedema and breast or chest wall discomfort by use of four-point scales (ie, not at all, a little, quite a bit, or very much), comparing to the contralateral breast where relevant. A composite breast or chest wall late effect endpoint was defined as the worst score across these symptoms (excluding discomfort, since this relies on asking the patient rather than independent clinician assessment). For analysis, scores were dichotomised to identify moderate or marked effects (ie, quite a bit or very much), but are also presented graphically according to the original categorisation. Clinicians also reported symptomatic rib fracture, symptomatic lung fibrosis, ischaemic heart disease, and any specialist referral for management of radiotherapy-related adverse effects. 10-year patient-reported outcome assessment, co-developed with trial participants, included the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQ) BR23 (breast cancer) and EORTC QLQ SURV100 (survivorship), as well as the Body Image Scale (BIS) questionnaire. Breast symptoms scored on a four-point scale (ie, none, a little, quite a bit, very much) were dichotomised, as for clinician assessments, to report moderate or marked effects. Symptom and function scale scores were calculated as per published guidelines.[20–23] All main trial participants were given the opportunity to complete 10-year patient-reported outcome questionnaires. Sex was clinician-reported and race or ethnicity data were not recorded as these data were not routinely collected in trials at the time of initiation.

Outcomes

Terminology for efficacy outcomes in the original protocol and primary analysis was updated to align with current standards.[24] The primary endpoint of the main trial was ipsilateral breast recurrence, defined as invasive carcinoma or ductal carcinoma in situ presenting anywhere in the ipsilateral breast parenchyma, overlying skin, or post-mastectomy chest wall, whether considered local recurrence or new primary, including angiosarcoma. The primary endpoint for the nodal substudy assessed in the intention-to-treat population at 5 years was patient-reported arm or hand swelling (reported as quite a bit or very much on Q18 of the EORTC QLQ BR23) and is reported elsewhere.[16]

Ipsilateral breast recurrence was a secondary endpoint in the nodal substudy. Other secondary disease-related endpoints in the main trial and substudy were: locoregional recurrence (ie, ipsilateral breast recurrence or nodal recurrence in ipsilateral axilla, supraclavicular fossa, or internal mammary regions), recurrence-free interval (ie, ipsilateral breast recurrence, locoregional recurrence, distant recurrence, or death from breast cancer), distant recurrence-free interval (ie, distant recurrence or death from breast cancer), breast cancer-free interval (ie, ipsilateral breast recurrence, locoregional recurrence, distant recurrence, ductal carcinoma in situ or invasive contralateral cancer, or death from breast cancer), new contralateral primaries, non-breast second primary cancers, and overall survival. Although not specified as endpoints in the protocol, locoregional recurrence, breast cancer-free interval, and non-breast second primary cancers were prespecified in the statistical analysis plan, and align with the primary analysis of the trial and with current recommendations.[24]

Further secondary endpoints for the main trial included clinician-reported and patient-reported late normal tissue effects. The health economics endpoint (main trial) was cost per quality adjusted life-year (QALY) gained over a lifetime horizon based on a decision model incorporating patient-reported health resource usage and health status (EQ-5D-5L questionnaire).[25]

Statistical analysis

The main trial sample size of 4000 participants provided 80% power, with one-sided α of 0·025, to exclude an absolute increase of 1·6% in 5-year incidence of ipsilateral breast recurrence with a 1-week schedule, assuming 2% incidence with the 3-week schedule and 10% lost to follow-up. Non-inferiority was shown in the primary efficacy analysis. Formal testing against a prespecified non-inferiority margin was not planned for this 10-year analysis. Instead, focus was on estimation of effects; hence, p values are not presented. The target sample size for the nodal substudy (172 participants in both the 26 Gy group and control group) was based on the patient-reported outcome primary endpoint[16] and was not powered for disease-related endpoints. Hence, analyses focused on consistency of results with the main trial.

Comparisons were made between each test group and the control group; for the nodal substudy, the 27 Gy group were only compared with the control group participants who were randomised during the period when recruitment to the 27 Gy group was open. Efficacy

analyses were done in the intention-to-treat population including all participants who were randomly assigned, analysed according to allocated treatment. Ipsilateral breast recurrence was also analysed in the per-protocol population (including participants who completed their protocol-defined radiotherapy regimen without major deviation, such as ineligibility or receipt of non-allocated treatment). Analysis of clinician-reported adverse effects was done in the modified intention-to-treat population, including all randomly assigned participants with available data for each endpoint, analysed according to allocated treatment.

Except for new contralateral and second primary cancers (reported as frequencies), disease and survival endpoints were analysed as time-to-event, with times measured from randomisation and censored for event-free patients at last follow-up or death (where death was not an event). Participants remained evaluable for local recurrence after distant recurrence. For ipsilateral breast recurrence and other time-to-event disease-related endpoints, Kaplan–Meier estimates of 10-year incidence (or proportion event-free) are reported with 95% CIs and corresponding plots (Kaplan–Meier or Nelson–Aelen plots as applicable). Treatment effect hazard ratios (HRs) were estimated from unadjusted Cox regression models. Absolute treatment differences (and 95% CIs) were calculated from the control group Kaplan–Meier estimate and the HR.

Supplementary prespecified analyses considered adjustment for prespecified factors: receipt of adjuvant

	Cumulative number of events	10-year cumulative incidence (95% CI)	Hazard ratio* (95% CI)	Estimated absolute difference *vs* 40 Gy at 10 years (95% CI)†	Adjusted hazard ratio (95% CI)‡
Intention-to-treat analysis					
Ipsilateral breast recurrence§					
40 Gy	45	3·6% (2·7 to 4·9)	1 (ref)	..	1 (ref)
27 Gy	41	2·9% (2·1 to 4·0)	0·90 (0·59 to 1·37)	−0·4% (−1·5 to 1·3)	0·91 (0·59 to 1·39)
26 Gy	30	2·1% (1·5 to 3·1)	0·66 (0·41 to 1·04)	−1·2% (−2·1 to 0·2)	0·65 (0·41 to 1·03)
Locoregional recurrence					
40 Gy	56	4·5% (3·5 to 5·8)	1 (ref)	..	1 (ref)
27 Gy	54	4·0% (3·0 to 5·2)	0·95 (0·65 to 1·37)	−0·2% (−1·5 to 1·6)	0·96 (0·66 to 1·39)
26 Gy	47	3·4% (2·6 to 4·6)	0·83 (0·56 to 1·22)	−0·8% (−2·0 to 1·0)	0·78 (0·53 to 1·15)
Distant recurrence					
40 Gy	99	7·7% (6·3 to 9·3)	1 (ref)	..	1 (ref)
27 Gy	99	7·6% (6·3 to 9·2)	1·00 (0·76 to 1·32)	0·1% (−1·8 to 2·4)	1·05 (0·79 to 1·39)
26 Gy	103	7·8% (6·5 to 9·4)	1·03 (0·79 to 1·37)	0·3% (−1·6 to 2·7)	1·04 (0·79 to 1·38)
Any recurrence					
40 Gy	138	10·7% (9·2 to 12·6)	1 (ref)	..	1 (ref)
27 Gy	131	9·8% (8·3 to 11·6)	0·95 (0·74 to 1·20)	−0·6% (-2·7 to 2·0)	0·98 (0·77 to 1·25)
26 Gy	130	9·7% (8·2 to 11·4)	0·93 (0·73 to 1·19)	−0·8% (−2·8 to 1·8)	0·94 (0·73 to 1·19)
Any breast cancer event					
40 Gy	170	13·0% (11·2 to 15·0)	1 (ref)	..	1 (ref)
27 Gy	163	12·4% (10·7 to 14·4)	0·96 (0·77 to 1·19)	−0·6% (−2·9 to 2·2)	0·99 (0·80 to 1·23)
26 Gy	160	12·1% (10·4 to 14·0)	0·94 (0·76 to 1·17)	−0·7% (−3·0 to 2·0)	0·94 (0·75 to 1·16)
All-cause mortality					
40 Gy	197	14·8% (12·9 to 16·8)	1 (ref)	..	1 (ref)
27 Gy	217	15·7% (13·9 to 17·8)	1·09 (0·89 to 1·32)	1·2% (−1·4 to 4·3)	1·12 (0·92 to 1·36)
26 Gy	208	14·9% (13·0 to 16·9)	1·05 (0·86 to 1·28)	0·7% (−1·9 to 3·7)	1·06 (0·87 to 1·29)
Per-protocol analysis					
Ipsilateral breast recurrence§					
40 Gy	44	3·6% (2·7 to 4·8)	1 (ref)	..	1 (ref)
27 Gy	39	2·8% (2·0 to 3·9)	0·88 (0·57 to 1·35)	−0·4% (−1·5 to 1·2)	0·89 (0·58 to 1·37)
26 Gy	30	2·1% (1·5 to 3·1)	0·68 (0·43 to 1·07)	−1·1% (−2·0 to 0·3)	0·68 (0·42 to 1·08)

Data are n (%) unless otherwise specified. 1358 patients were included in the 40 Gy group, 1362 in the 27 Gy group, and 1367 in the 26 Gy group in the intention-to-treat analysis and 1350, 1349, and 1344 patients in each respective group in the per-protocol analysis. *Hazard ratio of less than 1 favours five-fraction schedules. †Estimated absolute difference at 10 years for each five-fraction group versus 40 Gy group obtained from the hazard ratio and Kaplan–Meier estimate of cumulative 10-year incidence in 40 Gy group. ‡Hazard ratio from adjusted model where a hazard ratio of less than 1 favours five-fraction schedules; adjusted for adjuvant chemotherapy (yes *vs* no), risk group (age ≥50 years and grade 1 or 2; age <50 years, grade 3, or both), oestrogen receptor (ER) and HER2 status (HER2 positive, ER positive and HER2 negative, or ER negative and HER2 negative). §Includes 11 cases of angiosarcoma in ipsilateral breast (four in the 40 Gy group, two in the 27 Gy group, and five in the 26 Gy group).

Table 1: **Recurrence and survival endpoints in the main trial**

chemotherapy, risk group, and ER and HER2 status. Prespecified exploratory subgroup analyses considered effects of schedule on ipsilateral breast recurrence risk within each subgroup defined by these factors, using HRs with 99% CIs to account for multiple testing. Subgroups defined by tumour grade, histology, and presence of lymphovascular invasion were also considered. A Fine–Gray competing risks regression was also fitted with two competing event types: non-ipsilateral breast recurrence breast cancer events (ie, regional recurrence, distant recurrence, or breast cancer death); and non-breast cancer deaths and second primaries (including contralateral breast). Methods for analysis of other main trial secondary endpoints are described in the appendix (p 8). As a prespecified exploratory analysis, estimates of fractionation sensitivity (α/β values with 95% CIs and equivalent dose in 2 Gy fractions [EQD_2]) were obtained for both ipsilateral breast recurrence and clinician-reported normal tissue effects using methodology from the START and FAST trials as described previously.[3,14]

For the nodal substudy, disease-related endpoints were analysed in the intention-to-treat population similarly to the main trial but focussing on 5-year outcomes. For ipsilateral breast recurrence, recurrence-free interval, breast cancer-free interval, and overall survival, results from the nodal substudy and main trial were combined by use of a meta-analytic approach, focusing on the 26 Gy versus 40 Gy comparison. Pooled estimates with 95% CIs were generated with fixed-effects models, reflecting the assumption that the intervention effect is the same in the two cohorts, and presented in forest plots. Heterogeneity tests were performed. An independent data monitoring committee was used. Analyses were based on a database snapshot from June 20, 2025, and used Stata version 17.0.

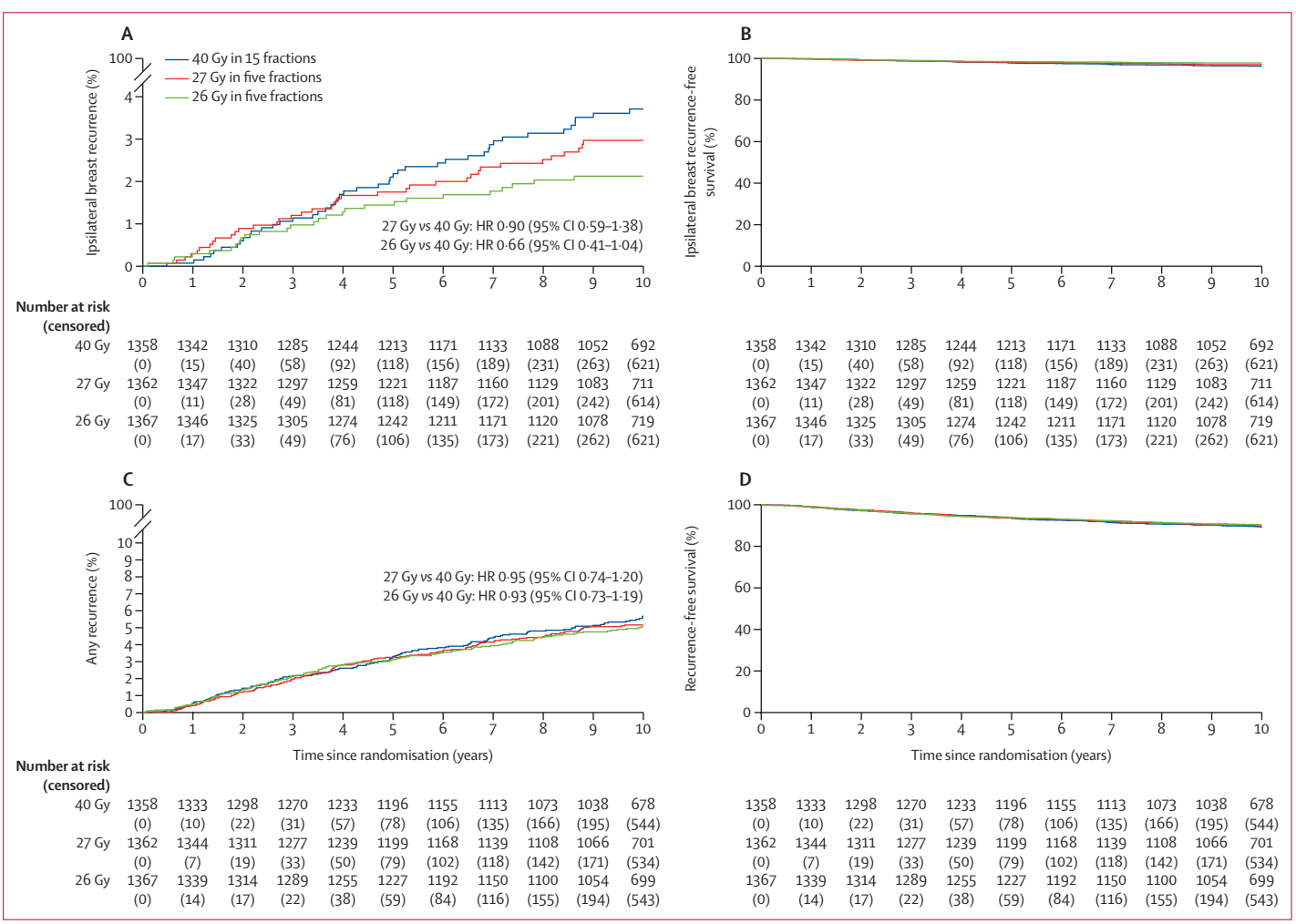

Figure: **Ipsilateral breast recurrence and any recurrence by treatment group in the intention-to-treat population of the main trial**
Nelson–Aalen cumulative hazard plot for risk of ipsilateral breast recurrence (A) and corresponding Kaplan–Meier plot for ipsilateral breast recurrence-free interval (B). Nelson–Aalen cumulative hazard plot for risk of any recurrence (C) and corresponding Kaplan–Meier plot for recurrence-free interval (D). X-axes are shown to 10 years; although a small number of events were reported beyond this timepoint, these events could be subject to reporting bias as they were not recorded as part of a scheduled follow-up, and so are not shown. HR=hazard ratio.

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.

Results
Between Nov 24, 2011, and June 19, 2014, 4110 participants enrolled in the main FAST-Forward trial. 23 withdrew consent for data use and were excluded after randomisation (nine withdrew since the primary analysis). Thus, 4087 were included in the current intention-to-treat analyses (1358 assigned to 40 Gy in 15 fractions, 1362 assigned to 27 Gy in five fractions, and 1367 assigned to 26 Gy in five fractions; appendix p 9). Baseline characteristics (appendix pp 10–12) and treatment compliance were reported previously.[14] The per-protocol population comprised 4043 participants (1350 in the 40 Gy group, 1349 in the 27 Gy group, and 1344 in the 26 Gy group; appendix p 9). Median follow-up was 10·1 years (IQR 10·0–10·2), with last follow-up on Feb 23, 2025. 10-year visit forms were available for 3137 (76·8%) of 4087 participants in the intention-to-treat population, including clinician-reported normal tissue effects for 2354 (57·6%) and patient-reported data for 1748 (42·8%).

	40 Gy in 15 fractions (n=1358)	27 Gy in five fractions (n=1362)	26 Gy in five fractions (n=1367)
Contralateral breast second primary	38 (2·8%)	36 (2·6%)	34 (2·5%)
Invasive	30 (2·2%)	31 (2·3%)	28 (2·0%)
Ductal carcinoma in situ	7 (0·5%)	5 (0·4%)	5 (0·4%)
Unknown	1 (0·1%)	0	1 (0·1%)
Non-breast second primary	78 (5·7%)	81 (5·9%)	91 (6·7%)
Bladder	3 (0·2%)	2 (0·1%)	3 (0·2%)
Brain	3 (0·2%)	0	0
Cancer of unknown primary	1 (0·1%)	2 (0·1%)	1 (0·1%)
Colorectal	19 (1·4%)	12 (0·9%)	17 (1·2%)
Head and neck	2 (0·1%)	1 (0·1%)	4 (0·3%)
Leukaemia	3 (0·2%)	2 (0·1%)	4 (0·3%)
Lung	9 (0·7%)	26 (1·9%)	15 (1·1%)
Melanoma	2 (0·1%)	3 (0·2%)	3 (0·2%)
Myeloma	1 (0·1%)	3 (0·2%)	2 (0·1%)
Oesophagus	0	4 (0·3%)	1 (0·1%)
Ovary or other gynaecological	10 (0·7%)	9 (0·7%)	20 (1·5%)
Pancreas	9 (0·7%)	7 (0·5%)	4 (0·3%)
Renal	4 (0·3%)	2 (0·1%)	3 (0·2%)
Non-Hodgkins lymphoma	3 (0·2%)	3 (0·2%)	4 (0·3%)
BCC or SSC (skin)	2 (0·1%)	0	5 (0·4%)
SSC (anal)	1 (0·1%)	1 (0·1%)	0
Thyroid	1 (0·1%)	0	3 (0·2%)
Other*	5 (0·4%)	4 (0·3%)	2 (0·1%)
Death	197 (14·5%)	217 (15·9%)	208 (15·2%)
Breast cancer	77 (5·7%)	78 (5·7%)	73 (5·3%)
Second primary cancer	22 (1·6%)	34 (2·5%)	29 (2·1%)
Cardiac	21 (1·5%)	22 (1·6%)	19 (1·4%)
Other cause	77 (5·7%)	82 (6·0%)	86 (6·3%)
Unknown	0	1 (0·1%)	1 (0·1%)

BCC=basal cell carcinoma. SCC=squamous cell carcinoma. *Other includes cholangiocarcinoma, kidney, prostate, sarcoma, stomach, and ampulla.

Table 2: **Second primary cancers and deaths by treatment group in the intention-to-treat population of the main trial**

Between April 11, 2016, and Oct 2, 2018, 469 participants enrolled in the nodal substudy (309 were enrolled before 27 Gy group closure). Three participants subsequently withdrew consent for data use; thus, 466 were included in intention-to-treat analyses (180 participants assigned to 40 Gy in 15 fractions, 104 assigned to 27 Gy in five fractions, and 182 assigned to 26 Gy in five fractions; appendix p 13). Demographic and clinical characteristics for the substudy and combined cohorts are provided in the appendix (pp 14–17); treatment compliance was reported previously.[16] Median follow-up for participants enrolled in the substudy was 7·0 years (IQR 6·2–7·1), with last follow-up on June 4, 2025.

In the main trial intention-to-treat population, 116 participants had ipsilateral breast recurrence events (45 in the 40 Gy group, 41 in the 27 Gy group, and 30 in the 26 Gy group) with cumulative 10-year incidence of 3·6% (95% CI 2·7 to 4·9) in the 40 Gy group, 2·9% (2·1 to 4·0) in the 27 Gy group, and 2·1% (1·5 to 3·1) in the 26 Gy group. Estimated absolute differences in ipsilateral breast recurrence compared with the 40 Gy group were –0·4% (–1·5 to 1·3) for the 27 Gy group and –1·2% (–2·1 to 0·2) for the 26 Gy group (table 1; figure A, B). Results were similar for the per-protocol analysis (table 1) and competing risks modelling (appendix p 18); 106 ipsilateral breast recurrence events occurred before any competing event. 11 ipsilateral breast recurrence events were angiosarcomas (four in the 40 Gy group, two in the 27 Gy group, and five in the 26 Gy group; appendix p 19), with five of 11 angiosarcomas diagnosed 7–12 years after randomisation. The unadjusted α/β estimate for ipsilateral breast recurrence was 3·4 Gy (1·6–5·2), with EQD_2 estimates of 45·0 Gy for the 40 Gy group, 44·0 Gy for the 27 Gy group, and 41·4 Gy for the 26 Gy group without correction for treatment time (appendix p 20). No differences in ipsilateral breast recurrence risk by schedule were observed across subgroups in exploratory analysis (appendix pp 21–22). Three ipsilateral breast recurrence events occurred post-mastectomy (two in the 40 Gy group and one in the 27 Gy group). 5-year estimates of cumulative ipsilateral breast recurrence incidence based on the dataset used in this analysis were similar to those reported previously (appendix p 23).[14]

In the main trial, 157 participants had locoregional recurrence (56 in the 40 Gy group, 54 in the 27 Gy group, and 47 in the 26 Gy group; table 1); 301 had distant recurrence (99 in the 40 Gy group, 99 in the 27 Gy group, and 103 in the 26 Gy group; table 1); and 108 (2·6%) developed contralateral breast primary cancers (38 in

the 40 Gy group, 36 in the 27 Gy group, and 34 in the 26 Gy group), of which 89 were invasive (table 2). Non-breast second primary cancers were reported for 250 (6·1%) participants (78 in the 40 Gy group, 81 in the 27 Gy group, and 91 in the 26 Gy group; table 2). Recurrence at any site occurred in 399 participants, with a 10-year recurrence-free interval in 89·3% (87·4–90·8) of participants in the 40 Gy group, 90·2% (88·4–91·7) for the 27 Gy group, and 90·4% (88·6–91·9) for the 26 Gy group (table 1; figure C, D). Cumulative incidence of distant recurrence and any breast cancer event are also reported in table 1, with breast cancer-free interval shown in appendix (p 24).

In the main trial, 622 participants died (197 in the 40 Gy group, 217 in the 27 Gy group, and 208 in the 26 Gy group); 228 deaths were due to breast cancer, 62 were cardiac-related, 85 were due to second cancers, and 247 were due to other or unknown causes (table 2). 10-year overall survival was 85·2% (83·2–87·1) in the 40 Gy group, 84·3% (82·2–86·1) in the 27 Gy group, and 85·1% (83·1–87·0) in the 26 Gy group (table 1; appendix p 24).

Cross-sectional analysis of clinician-reported normal tissue effects shows symptoms that persisted to 10 years (table 3). In the modified intention-to-treat population of the main trial, moderate or marked breast or chest wall effects were reported at 10 years for 100 (13·1%)

	Cross-sectional analysis of moderate or marked normal tissue effects at 10 years		Time-to-event analysis of moderate or marked normal tissue effects		
	Number of participants with effects	Estimated absolute difference *vs* 40 Gy at 10 years (95% CI)*	Cumulative number of participants with effects	10-year cumulative incidence (95% CI)†	Hazard ratio (95% CI)‡
Any adverse event in breast or chest wall§					
40 Gy	100/765 (13·1%)	..	467/1311	38·6% (35·8 to 41·6)	1 (ref)
27 Gy	157/814 (19·3%)	6·2% (2·6 to 9·8)	556/1338	43·0% (40·2 to 45·9)	1·23 (1·09 to 1·39)
26 Gy	111/770 (14·4%)	1·3% (–2·1 to 4·8)	464/1329	37·2% (34·5 to 40·1)	0·98 (0·86 to 1·12)
Breast distortion¶					
40 Gy	37/712 (5·2%)	..	183/1232	16·2% (14·1 to 18·5)	1 (ref)
27 Gy	50/759 (6·6%)	1·4% (–1·0 to 3·8)	229/1264	19·5% (17·3 to 22·0)	1·24 (1·02 to 1·51)
26 Gy	40/719 (5·6%)	0·4% (–2·0 to 2·7)	189/1252	15·5% (13·5 to 17·7)	1·02 (0·83 to 1·25)
Breast shrinkage¶					
40 Gy	65/714 (9·1%)	..	269/1234	23·4% (20·9 to 26·2)	1 (ref)
27 Gy	110/761 (14·5%)	5·4% (2·1 to 8·6)	321/1264	26·1% (23·6 to 28·8)	1·18 (1·01 to 1·39)
26 Gy	73/718 (10·2%)	1·1% (–2·0 to 4·1)	251/1252	20·8% (18·5 to 23·4)	0·90 (0·76 to 1·07)
Breast induration (in tumour bed)¶					
40 Gy	30/711 (4·2%)	..	174/1232	15·0% (13·0 to 17·3)	1 (ref)
27 Gy	56/755 (7·4%)	3·2% (0·8 to 5·6)	235/1265	19·9% (17·7 to 22·5)	1·35 (1·11 to 1·64)
26 Gy	36/719 (5·0%)	0·8% (–1·4 to 3·0)	182/1252	16·0% (13·9 to 18·4)	1·02 (0·83 to 1·26)
Breast induration (outside tumour bed)¶					
40 Gy	10/708 (1·4%)	..	57/1232	5·1% (3·8 to 6·6)	1 (ref)
27 Gy	26/752 (3·5%)	2·1% (0·5 to 3·6)	121/1265	10·0% (8·4 to 12·0)	2·09 (1·53 to 2·86)
26 Gy	10/719 (1·4%)	–0·2 (–1·2 to 1·2)	67/1252	5·5% (4·3 to 7·0)	1·15 (0·81 to 1·64)
Telangiectasia					
40 Gy	12/758 (1·6%)	..	52/1310	4·2% (3·2 to 5·6)	1 (ref)
27 Gy	16/804 (2·0%)	0·4% (–0·9 to 1·8)	74/1336	5·8% (4·6 to 7·3)	1·38 (0·97 to 1·97)
26 Gy	19/768 (2·5%)	0·9% (–0·5 to 2·3)	67/1327	5·5% (4·3 to 7·0)	1·26 (0·88 to 1·81)
Breast or chest wall oedema					
40 Gy	4/760 (0·5%)	..	85/1311	6·9% (5·6 to 8·6)	1 (ref)
27 Gy	9/805 (1·1%)	0·6% (–0·3 to 1·5)	147/1338	11·6% (9·9 to 13·5)	1·73 (1·32 to 2·26)
26 Gy	4/719 (0·6%)	0·0% (–0·7 to 0·7)	113/1329	9·1% (7·7 to 10·9)	1·32 (0·99 to 1·74)
Breast or chest wall discomfort					
40 Gy	31/761 (4·1%)	..	213/1311	18·0% (15·8 to 20·4)	1 (ref)
27 Gy	41/807 (5·1%)	1·0% (–1·1 to 3·1)	237/1337	18·7% (16·6 to 21·1)	1·08 (0·90 to 1·30)
26 Gy	23/771 (3·0%)	–1·1% (–2·9 to 0·8)	200/1330	16·5% (14·5 to 18·8)	0·91 (0·75 to 1·11)

Data are n/N (%) unless otherwise specified. Analyses were done on a modified intention-to-treatment basis, including all randomly assigned patients with data available for the specific endpoint, grouped according to their allocated schedule; denominators might vary if there are missing assessments for specific effects. *Differences calculated as proportion of test group (27 Gy group or 26 Gy group) minus proportion of control group (40 Gy group). †All events up to 10·5 years are included to allow for scheduling of 10-year assessment. ‡Hazard ratio of less than 1 favours five-fraction schedules. §Includes breast distortion, breast shrinkage, breast induration (inside or outside tumour bed), telangiectasia, and breast or chest wall oedema. ¶Not applicable after mastectomy (unless reconstructive surgery done).

***Table 3*: Clinician-reported late adverse effects in the breast or chest wall in the modified intention-to-treat analysis of the main trial**

of 765 participants in the 40 Gy group, 157 (19·3%) of 814 participants in the 27 Gy group, and 111 (14·4%) of 770 participants in the 26 Gy group, of which 15 (2·0%), 31 (3·8%), 14 (1·8%) participants had marked effects, respectively. Higher incidence of breast shrinkage and induration (inside and outside tumour bed) contributed towards the higher rate of symptoms overall with 27 Gy. Across all groups, the most common effect was breast shrinkage.

	40 Gy in 15 fractions (n=572)	27 Gy in five fractions (n=601)	26 Gy in five fractions (n=575)
Breast appearance changed			
Response category			
None	106/556 (19·1%)	79/580 (13·6%)	110/558 (19·7%)
A little	243/556 (43·7%)	246/580 (42·4%)	234/558 (41·9%)
Quite a bit	113/556 (20·3%)	138/580 (23·8%)	120/558 (21·5%)
Very much	94/556 (16·9%)	117/580 (20·2%)	94/558 (16·8%)
Participants reporting moderate or marked events	207/556 (37·2%)	255/580 (44·0%)	214/558 (38·4%)
Estimated absolute difference *vs* 40 Gy at 10 years (95% CI)	..	6·7% (1·0 to 12·4)	1·1% (–4·6 to 6·8)
Breast smaller			
Response category			
None	172/550 (31·3%)	159/573 (27·7%)	172/555 (31·0%)
A little	191/550 (34·7%)	176/573 (30·7%)	190/555 (34·2%)
Quite a bit	91/550 (16·5%)	114/573 (19·9%)	88/555 (15·9%)
Very much	96/550 (17·5%)	124/573 (21·6%)	105/555 (18·9%)
Participants reporting moderate or marked events	187/550 (34·0%)	238/573 (41·5%)	193/555 (34·8%)
Estimated absolute difference *vs* 40 Gy at 10 years (95% CI)	..	7·5% (1·9 to 1·3)	0·7% (–4·8 to 6·4)
Breast harder or firmer to touch			
Response category			
None	308/551 (55·9%)	254/571 (44·5%)	295/552 (53·4%)
A little	153/551 (27·8%)	163/571 (28·5%)	153/552 (27·7%)
Quite a bit	54/551 (9·8%)	86/571 (15·1%)	54/552 (9·8%)
Very much	36/551 (6·5%)	68/571 (11·9%)	50/552 (9·1%)
Participants reporting moderate or marked events	90/551 (16·3%)	154/571 (27·0%)	104/552 (18·8%)
Estimated absolute difference *vs* 40 Gy at 10 years (95% CI)	..	10·6% (5·9 to 15·4)	2·5% (–2·0 to 7·0)
Skin appearance changed			
Response category			
None	303/559 (54·2%)	300/584 (51·4%)	292/558 (52·3%)
A little	193/559 (34·5%)	209/584 (35·8%)	190/558 (34·1%)
Quite a bit	38/559 (6·8%)	42/584 (7·2%)	49/558 (8·8%)
Very much	25/559 (4·5%)	33/584 (5·7%)	27/558 (4·8%)
Participants reporting moderate or marked events	63/559 (11·3%)	75/584 (12·8%)	76/558 (13·6%)
Estimated absolute difference *vs* 40 Gy at 10 years (95% CI)	..	1·6% (–2·2 to 5·3)	2·3% (–1·6 to 6·2)

(Table 4 continues on next page)

At 10 years, the most common patient-reported moderate or marked breast symptoms were change in breast appearance and breasts being smaller (table 4). 10-year scores for breast symptoms, body image and other functional and symptom scales were similar across groups (appendix pp 25–27).

10-year cumulative incidence of moderate or marked breast or chest wall normal tissue effects was 38·6% (95% CI 35·8–41·6) in the 40 Gy group, 43·0% (40·2–45·9) in the 27 Gy group, and 37·2% (34·5–40·1) in 26 Gy group (table 3; appendix pp 28–29). Cumulative incidences of individual symptoms were generally higher in the 27 Gy group, particularly for induration outside tumour bed and oedema.

Longitudinal modelling of normal tissue effects indicates where symptoms are persistently reported across follow-up assessments (appendix pp 30–32). Numbers of individual reports of symptoms were consistently higher with 27 Gy, compared with 40 Gy. Models also suggest more individual reports of induration (outside tumour bed) and oedema with 26 Gy (*vs* 40 Gy), but for induration the numbers of patients with these symptoms were similar. The unadjusted α/β estimate for any breast or chest wall moderate or marked normal tissue effects was 2·1 Gy (95% CI 1·6–2·6), giving EQD_2 estimates of 46·5 Gy for 40 Gy in 15 fractions, 49·4 for 27 Gy in five fractions, and 46·3 Gy for 26 Gy in five fractions (appendix p 20). Symptomatic rib fracture, symptomatic lung fibrosis, ischaemic heart disease, and specialist referrals were rare across all groups (appendix p 33).

In health economic analysis, 10-year data produced only minor adjustments to survival analysis coefficients from the 5-year analysis,[25] and correspondingly produced only negligible changes in estimated costs and QALYs, leaving dominance hierarchies and cost-effectiveness probabilities essentially unchanged (appendix p 34).

In the nodal substudy, five participants in each of the 40 Gy and 26 Gy groups had ipsilateral breast recurrence events, with cumulative 5-year incidence of 1·8% (95% CI 0·6–5·4) and 1·2% (0·3–4·8; appendix p 35). Locoregional recurrences were reported for ten participants in the 40 Gy group and 13 participants in the 26 Gy group; 5-year cumulative incidence was 4·1% (95% CI 2·0–8·5) for the 40 Gy group and 4·2% (2·0–8·6) for the 26 Gy group. Combining substudy and main trial data, the pooled unadjusted HR for ipsilateral breast recurrence for 26 Gy in five fractions compared with 40 Gy in 15 fractions was 0·70 (95% CI 0·45–1·08) and for any recurrence was 0·98 (0·79–1·21), with no evidence of heterogeneity between cohorts (appendix p 36). Pooled results were consistent with main trial results for other disease-related endpoints. In the nodal substudy 27 Gy group, there were nine locoregional events, including three ipsilateral breast recurrence events; in control participants who were concurrently randomly assigned, six locoregional events (including

three ipsilateral breast recurrence events) were reported (appendix p 37). Details of deaths and second cancers in the nodal substudy are provided in the appendix (p 38).

Discussion

10-year incidence of ipsilateral breast recurrence and locoregional recurrence in the FAST-Forward main trial builds on 5-year findings showing that both five-fraction schedules are non-inferior to the standard 40 Gy in 15 fractions over 3 weeks regimen for disease control. At 10 years, the locoregional recurrence for the 40 Gy group of 4·5% (95% CI 3·5–5·8) closely mirrors the outcomes observed in the UK START-B trial (4·3%, 95% CI 3·2–5·9), which recruited a clinically and demographically similar population and established 40 Gy in 15 fractions over 3 weeks against the historical 50 Gy in 25 fractions over 5 weeks standard.[8] 10-year incidences of ipsilateral breast recurrence (2·1%, 95% CI 1·5–3·1) and locoregional recurrence (3·4%, 2·6–4·6) with the 26 Gy in five fractions over 1 week schedule are reassuringly low. There was also no evidence of a difference according to schedule for any subgroups, including younger patients and those with higher grade disease.

Assuming no time effect, the unadjusted 10-year α/β estimate of 3·4 Gy for tumour control was consistent with the 5-year estimate (3·7 Gy)[14] and the combined START-P and START-A trials estimate of 3·5 Gy based on 10-year data,[3,6,8] providing a radiobiological explanation for the outcome data.[26] In the FAST-Forward main trial, 10-year overall survival was approximately 85% across all groups, with breast cancer deaths contributing just under 40% of deaths. Updated health economic analysis shows that the five-fraction schedules remain cost-effective in the longer term, reinforcing existing UK National Health Service recommendations.

Although the nodal substudy was not powered for efficacy outcomes, meta-analysis pooling main trial and substudy data suggested that these were consistent with the main trial. 5-year incidence in the substudy of 1·2% (95% CI 0·3–4·8) ipsilateral breast recurrence and 4·2% (2·0–8·6) locoregional recurrence with 26 Gy in five fractions are reassuringly low and similar to 40 Gy in 15 fractions. However, relatively wide confidence intervals reflect the smaller cohort size. With primary endpoint data having previously shown the safety of this schedule for axillary radiotherapy,[16] 26 Gy in five fractions can be considered an option for patients requiring axillary treatment, with appropriate discussion around the remaining uncertainty. As expected with a higher-risk population, 5-year cumulative incidence of locoregional recurrence was more common in the nodal substudy (4·2% [95% CI 2·0–8·6] with 26 Gy and 4·1% [2·0–8·5] with 40 Gy) than in the main trial (1·9% with 26 Gy and 2·7% with 40 Gy).

In the main trial, for patient-reported and clinician-reported normal tissue effects persisting at 10 years, the 26 Gy schedule was similar to the standard 40 Gy schedule. The proportion with any clinician-reported breast or chest wall moderate or marked effects was 13·1% for 40 Gy and 14·4% for 26 Gy. Results were also similar between these two groups for the

	40 Gy in 15 fractions (n=572)	27 Gy in five fractions (n=601)	26 Gy in five fractions (n=575)
(Continued from previous page)			
Breast pain			
Response category			
None	306/565 (54·2%)	319/591 (54·0%)	319/568 (56·2%)
A little	202/565 (35·8%)	200/591 (33·8%)	182/568 (32·0%)
Quite a bit	36/565 (6·4%)	37/591 (6·3%)	49/568 (8·6%)
Very much	21/565 (3·7%)	35/591 (5·9%)	18/568 (3·2%)
Participants reporting moderate or marked events	57/565 (10·1%)	72/591 (12·2%)	67/568 (11·8%)
Estimated absolute difference vs 40 Gy at 10 years (95% CI)	..	2·1% (–1·5 to 5·7)	1·7% (–1·9 to 5·3)
Breast swollen			
Response category			
None	499/565 (88·3%)	503/590 (85·3%)	492/564 (87·2%)
A little	53/565 (9·4%)	55/590 (9·3%)	56/564 (9·9%)
Quite a bit	5/565 (0·9%)	18/590 (3·1%)	11/564 (2·0%)
Very much	8/565 (1·4%)	14/590 (2·4%)	5/564 (0·9%)
Participants reporting moderate or marked events	13/565 (2·3%)	32/590 (5·4%)	16/564 (2·8%)
Estimated absolute difference vs 40 Gy at 10 years (95% CI)	..	3·1% (0·9 to 5·3)	0·5% (–1·3 to 2·4)
Breast oversensitive			
Response category			
None	349/564 (61·9%)	351/587 (59·8%)	356/566 (62·9%)
A little	162/564 (28·7%)	159/587 (27·1%)	147/566 (26·0%)
Quite a bit	27/564 (4·8%)	43/587 (7·3%)	37/566 (6·5%)
Very much	26/564 (4·6%)	34/587 (5·8%)	26/566 (4·6%)
Participants reporting moderate or marked events	53/564 (9·4%)	77/587 (13·1%)	63/566 (11·1%)
Estimated absolute difference vs 40 Gy at 10 years (95% CI)	..	3·7% (0·1 to 7·4)	1·7% (–1·8 to 5·3)
Skin problems on breast			
Response category			
None	443/565 (78·4%)	470/591 (79·5%)	442/567 (78·0%)
A little	92/565 (16·3%)	85/591 (14·4%)	82/567 (14·5%)
Quite a bit	19/565 (3·4%)	21/591 (3·6%)	27/567 (4·8%)
Very much	11/565 (1·9%)	15/591 (2·5%)	16/567 (2·8%)
Participants reporting moderate or marked events	30/565 (5·3%)	36/591 (6·1%)	43/567 (7·6%)
Estimated absolute difference vs 40 Gy at 10 years (95% CI)	..	0·7% (–1·9 to 3·5)	2·3% (–0·6 to 5·1)

Data are n/N (%) unless otherwise specified. Analyses were done on a modified intention-to-treatment basis, including all randomly assigned patients with data available for the specific endpoint, grouped according to their allocated schedule; denominators might vary if there are missing assessments for specific effects.

Table 4: **Patient-reported breast symptoms at 10 years in the modified intention-to-treat analysis of the main trial**

six individually assessed adverse effects. Notably, the low and similar rate in these groups for induration outside the tumour bed provides reassurance that a relative difference observed at 5 years was attributable to low absolute event numbers.[14] Cumulative incidence, across the 10-year follow-up, was also similar in the 26 Gy and 40 Gy groups for the different symptoms, with the exception of a small absolute difference in breast or chest wall oedema. Longitudinal modelling identified higher numbers of individual reports of induration (outside tumour bed) and oedema with 26 Gy than with 40 Gy; however, absolute numbers of participants with these symptoms are low and, for induration in particular, the number is similar in the two groups. Furthermore, there is an increased chance of false-positive results associated with multiple testing of different symptoms across different timepoints. As previously reported, acute (clinician-reported) skin reactions are milder with 26 Gy compared with 40 Gy.[15,27]

There was an increase in clinician-reported 10-year moderate or marked normal tissue effects with 27 Gy compared with 40 Gy, particularly for the composite endpoint of any adverse event in breast or chest wall, and individually for breast shrinkage and breast induration, both in the tumour bed and outside the tumour bed. Consistent with 5-year data, this suggests that the 27 Gy in five fractions over 1 week schedule is similar to 50 Gy in 25 fractions over 5 weeks for adverse effects. Updated α/β estimates and corresponding EQD_2 estimates for clinician-reported normal tissue effects reflect the same pattern and are consistent with direct estimates generated by START-P,[3] START-A,[6] and FAST trials.[28] In START-B, breast shrinkage, telangiectasia, and breast oedema were favourable for the 40 Gy group over the 50 Gy group.[8]

Patient-reported moderate or marked effects at 10 years were higher than clinician-reported effects across all treatment groups, as seen in START.[29] However, key patient-reported outcomes were similar between the 40 Gy and 26 Gy groups; change in breast appearance, reduction in breast size, and breast harder or firmer to touch. Importantly, despite little concordance between patient and clinician assessments in the START trials, α/β estimates based on patient-reported and clinician-reported changes in breast appearance at 10 years in START-A were similar.[29] As for clinician assessments, participants receiving 27 Gy reported all individual effects more often than those in the 40 Gy group.

We report 11 cases of secondary angiosarcoma, which occurred throughout follow-up, with five of 11 participants diagnosed 7–12 years after randomisation. Incidence of radiation-induced secondary breast angiosarcoma is difficult to ascertain, with many publications being case reports. A rate of one case of secondary breast angiosarcoma per 1000 patients with breast cancer was reported from the Netherlands Cancer Registry (184 823 patients received radiation, median follow-up was 7·7 years (range 0·0–29·1), median latency from treatment was 8 years [range 3–20]);[30] and a secondary sarcoma rate of 0·9 cases per 1000 patients with breast cancer after 15 years in the SEER database (82 296 patients received radiation; 24 of 26 cases of secondary sarcoma occurred 3–7 years after primary breast cancer diagnosis).[31] Our cohort adds to the current evidence-base for this rare outcome, with robust long-term follow-up (which might explain slightly higher case numbers), and no evidence of an increase with hypofractionated schedules.

There are some limitations to the data presented. Some subgroups were small and underpowered to show differences between schedules; nevertheless, subgroup analyses have shown consistency of effects and adequately powered trials of less common subgroups are not likely to be feasible. Both clinician-reported and patient-reported 10-year normal tissue effect data are incomplete due to drop-out and missed assessments. Although inevitable with long-term follow-up, obtaining 10-year data appeared more challenging compared with previous large breast cancer trials; in part, assumed to be due to a post-COVID pandemic environment. Patients with missing data tended to have higher grade disease and were more likely to have comorbidities. Nevertheless, extent of missing data was similar across treatment groups and analyses considering trends over time (incorporating earlier follow-up data) showed consistent results in terms of comparisons between the groups. For less common late events (eg, cardiac events or second cancers), sample size and extent of follow-up would not be sufficient to show differences between schedules. Furthermore, only the first occurrence of a second cancer was recorded. However, no differences are expected between radiotherapy schedules and the data are reassuring in this respect.

The IMPORT LOW trial was designed with the same 40 Gy in 15 fractions whole breast control group as FAST-Forward and 10-year results from IMPORT LOW support partial-breast radiotherapy for patients at low-risk of local recurrence.[32] When considered together with the FAST-Forward results, partial-breast radiotherapy can be delivered by the 26 Gy in five fractions over 1 week schedule. FAST-Forward provides no data on internal mammary node irradiation or use of simultaneous integrated boost within a five-fraction schedule, since these were not standard care at trial initiation. For patients requiring a boost, the option for simultaneous integrated boost with a 40 Gy schedule will impact the comparison of costs with a 26 Gy schedule where simultaneous integrated boost cannot yet be recommended. Other ongoing trials, including FAST-Forward Boost (NIHR157800),[33] will help to address these remaining questions.

The 5-year primary data from the FAST-Forward main trial[14] led to 26 Gy in five fractions being incorporated into guidelines for adjuvant irradiation of the breast, partial breast, or chest wall, including consensus statements from the UK Royal College of Radiologists

(2021)[34] and the ESTRO Advisory Committee in Radiation Oncology Practice.[13] However, in many countries, 26 Gy in five fractions has not yet been adopted as standard.

The 5-year nodal substudy shows safety of the schedule for axillary radiotherapy, and the analysis of efficacy in the combined main and substudy cohorts is reassuring. However, sample size limits the precision of efficacy estimates for the nodal subgroup alone. This uncertainty should be part of shared decision making for those patients considering 26 Gy in five fractions axillary radiotherapy. By contrast, the 10-year data on efficacy, normal tissue effects, and cost-effectiveness support widespread adoption of the 26 Gy in five fractions over 1 week schedule for radiotherapy to the whole or partial breast or chest wall.

Contributors

AMB is the current chief investigator and JRY is the previous chief investigators. DAW is the chief clinical coordinator. JMB is the scientific lead for the study within The Institute of Cancer Research Clinical Trials and Statistics Unit and provided oversight and guidance for trial management and statistical analysis throughout. JRY, JMB, and JSH were responsible for the study design. JP, FHC, JSH, and CLG were responsible for statistical analysis and contributed to data interpretation. JP and FHC directly accessed and verified the data reported in the manuscript. SG and CChi were responsible for health economics analysis and interpretation. AMB, AMK, JMB, and FHC wrote the first draft of the manuscript. MAS managed the study and data collection. HF is a patient advocate member of the trial management group and provided guidance and input from a patients' perspective throughout the trial. ZN was responsible for radiotherapy quality assurance. DJB, CCha, CEC, SC, AG, AMK, CCK, ES, NS, IS, and KV are members of the trial management group who contributed to study design, were responsible for oversight throughout the trial, and contributed to data interpretation. All authors reviewed and approved the manuscript, had full access to all data in the study, and had final responsibility for the decision to submit for publication.

Declaration of interests

JMB reports research grants from Novartis (previously GlaxoSmithKline), AstraZeneca, Janssen-Cilag, Merck Sharpe and Dohme, Puma Biotechnology, Pfizer, Eli Lilly, Kortuc, Versatem, Breast Cancer Now, and Breast International Group outside the submitted work. DJB reports payment of honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca and Daiichi Sankyo outside the submitted work. JMB reports membership of ATNEC (University of Warwick) and POSNOC (University of Nottingham) data safety monitoring boards. AMK was President of the European Society of Radiotherapy and Oncology from May, 2022 to May, 2024 (unpaid). All other authors declare no competing interests.

Data sharing

Trial documentation, including the protocol and radiotherapy planning pack have been published previously and are provided as supplementary material. The Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU) supports the wider dissemination of information from its research and increased cooperation between investigators. Trial data are collected, managed, stored, shared, and archived according to ICR-CTSU standard operating procedures to ensure the enduring quality, integrity, and utility of the data. De-identified individual participant data, together with a data dictionary defining each field in the set, will be made available to other researchers on request to ICR-CTSU. Formal requests for data sharing are considered in line with ICR-CTSU procedures with due regard given to funder and sponsor guidelines. Requests are via a standard proforma describing the nature of the proposed research and extent of data requirements. Data recipients are required to enter a formal data sharing agreement that describes the conditions for release and requirements for data transfer, storage, archiving, publication, and intellectual property. Requests are reviewed by the trial management group in terms of scientific merit and ethical considerations including patient consent. Data sharing is undertaken if proposed projects have a sound scientific or patient benefit rationale as agreed by the trial management group and approved by the independent data monitoring and steering committee as required. Restrictions relating to patient confidentiality and consent will be limited by aggregating and anonymising identifiable patient data.

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