FAST-Forward phase III multi-centre non-inferiority randomised controlled trial of 1- versus 3-week hypofractionated breast radiotherapy: 5-year results for efficacy and late normal tissue effects

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Research in context

Evidence before this study

Radiotherapy (radiation therapy) after primary surgery for early breast cancer has historically been delivered in 5 daily doses (fractions) of 1.8-2Gy per week over at least 5 weeks, but randomised phase III clinical trials conducted in Canada, UK and subsequently China and Denmark have confirmed the safety and efficacy of 15- or 16-fraction schedules using daily fractions of 2.7Gy. Four of these trials published 10-year follow-up data on a total of 7,000 patients, and 3-week schedules have replaced traditional regimens in many countries over the last decade for most, if not all, patients prescribed local or locoregional radiation therapy after breast conservation surgery or mastectomy. Most recently, long term outcome data for a 5-fraction schedule delivered by once-weekly treatments has been reported which suggests further scope for simplifying curative radiotherapy for women with early breast cancer.

Added value of this study

Fifteen or 16 fractions over 3 to 3.2 weeks are unlikely to represent the limits of this approach, called hypofractionation. The FAST-Forward trial shows that 26Gy in 5 fractions of 5.2Gy to the conserved breast or post-mastectomy chest wall after primary surgery is non-inferior in terms of 5-year ipsilateral local tumour relapse to 40Gy in 15 fractions over 3 weeks within an absolute 1.6% non-inferiority margin compared with 2% incidence following 40Gy. The 5-day schedule causes milder early skin reaction and comparable rates of late adverse effects. When mature, a randomised FAST-Forward sub-study will report the safety of the 5-fraction regimen for patients prescribed radiotherapy to breast/chest wall combined with axilla and/or supraclavicular fossa.

Implications of all the available evidence

FAST-Forward results confirm that 26Gy in 5 fractions is as effective and safe as an international standard 15-fraction regimen after primary surgery for early breast cancer. The 1-week schedule has major benefits compared with 3- or 5-week regimens in terms of convenience and cost for patients and for health services globally.

ABSTRACT

Background

FAST-Forward aims to identify a 5-fraction (Fr) schedule of adjuvant radiotherapy (radiation therapy) delivered in 1 week which is non-inferior for local cancer control and as safe as an international standard 15Fr regimen after primary surgery for early breast cancer. Five-year results are presented.

Methods

FAST-Forward (ISRCTN19906132) is a non-inferiority randomised controlled trial that allocated (1:1:1) patients with invasive carcinoma of the breast (pT1-3 pN0-1 M0) after breast conservation surgery or mastectomy to 40Gy in 15Fr (3 weeks), 27Gy or 26Gy in 5Fr (1 week) to whole breast/chest wall. Allocation was not blinded due to the nature of the intervention. Primary endpoint was ipsilateral breast tumour relapse (IBTR); assuming 2% 5-year incidence for 40Gy, non-inferiority was pre-defined as $\leq$1.6% excess for 5Fr schedules (critical hazard ratio HR=1.81). Normal tissue effects (NTE) were assessed by clinicians, patients and photographs.

Findings

4096 consenting patients (1361 40Gy, 1367 27Gy, 1368 26Gy) were recruited November 2011-June 2014 from 97 UK centres. At 71 months median follow-up, 79 IBTR events were reported (40Gy: 31, 27Gy: 27, 26Gy: 21); HRs (95%CI) versus 40Gy/15Fr were 27Gy/5Fr: 0.86 (0.51,1.44), 26Gy/5Fr: 0.67 (0.38,1.16). Five-year incidence of IBTR after 40Gy was 2.1% (1.4,3.1); estimated absolute differences versus 40Gy/15Fr were -0.3% (-1.0,0.9) for 27Gy/5Fr (probability of incorrectly accepting an inferior 5-fraction schedule versus 40Gy/15Fr, p=0.0022) and -0.7% (-1.3,0.3) for 26Gy/5Fr (p=0.00019 versus 40Gy/15Fr).

5-year prevalence of any clinician-assessed moderate/marked breast NTE after 40Gy: 98/986 (10%), 27Gy: 155/1005 (15%), 26Gy: 121/1020 (12%). Across all clinician assessments from 1-5 years, odds ratios versus 40Gy/15Fr were 1.55 (1.32,1.83, p<0.0001) for 27Gy/5Fr and 1.12 (0.94,1.34, p=0.20) for 26Gy/5Fr. Patient and photographic assessments showed higher NTE risk for 27Gy versus 40Gy but not for 26Gy.

Interpretation

26Gy/5Fr in 1 week is non-inferior to 40Gy/15Fr in 3 weeks for local tumour control and as safe in terms of NTE up to 5 years for patients prescribed adjuvant local radiotherapy after primary surgery for early stage breast cancer.

Funding

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BACKGROUND

The Early Breast Cancer Trialists' Collaborative Group systematic overview confirms that radiotherapy after primary surgery in women with early stage cancers reduces locoregional cancer recurrence and breast cancer deaths, including patients with positive lymph nodes

treated by mastectomy and axillary clearance[1,2]. For many decades, schedules of adjuvant radiotherapy for these patients delivered 25 fractions of 2Gy in 5 weeks. Randomised controlled trials with long-term follow-up have since confirmed that fewer, larger fractions giving a lower total dose are at least as safe and effective as the previously-used international standard[3-10]. Specifically, mature data confirm the safety and non-inferiority of 15 or 16 fractions of ~2.7Gy to total doses of 40.0Gy or 42.5Gy, respectively[5,8]. A 3-week schedule of 15 fractions has been the UK standard of care for adjuvant locoregional radiotherapy for early breast cancer since 2009 and is now an international standard for adjuvant local radiotherapy[11,12]. There is no reason to assume that 15 fractions represent the lower limits of this hypofractionated and accelerated approach. We report outcomes of a randomised phase III trial testing 2 dose levels of a 5-fraction regimen delivered in 1 week against 40Gy in 15 fractions in 3 weeks for patients prescribed local radiotherapy after breast conservation surgery or mastectomy for early breast cancer. The objectives are to identify a 1-week schedule non-inferior to a standard 3-week regimen for 5-year local tumour control and comparable in terms of late adverse effects. FAST-Forward was informed by the FAST trial that tested 2 dose levels of 5 once-weekly fractions[13,14]; FAST trial results to 10-year follow-up are in press. The trial design used dose levels estimated to be the upper and lower bounds isoeffective with the control schedule in terms of tumour control and normal tissue effects.

METHODS

Study design

FAST-Forward (https://www.icr.ac.uk/fastforward (last accessed 07/04/2020); protocol in appendix) is a multicentre, non-blinded phase III randomised controlled non-inferiority trial testing the safety and efficacy of 5-fraction (Fr) schedules of adjuvant radiotherapy to the

whole breast/chest wall delivered in one week compared with the UK standard 15-fraction schedule. Sub-studies included a published acute toxicity study[15], photographic assessments of late adverse effects and patient-reported outcomes (PRO); not all centres participated in the sub-studies. Following recruitment into the main trial a further sub-study opened testing the same fractionation schedules for patients requiring radiotherapy to the axilla and/or supraclavicular fossa (SCF) lymph nodes after sentinel node biopsy or SCF only (levels 3-4) after axillary dissection with a primary endpoint focussing on safety. Patients and results from this sub-study are not reported here since follow-up is not mature. FAST-Forward was approved by the national South East Coast Kent Research Ethics Committee (11/LO/0958) and local Research and Development offices of all participating centres. The trial was sponsored by The Institute of Cancer Research and is registered as ISRCTN19906132. All patients provided written informed consent.

Patients

Eligible patients were women or men aged ≥18 years with invasive carcinoma of the breast (pT1-3 pN0-1 M0) following complete microscopic excision of primary tumour by breast conservation surgery or mastectomy (reconstruction allowed), recruited in the UK from 47 radiotherapy centres and 50 referral centres. A protocol amendment in February 2013 excluded the lowest risk patients (aged ≥65 years pT1 G1/G2 ER+ HER2- pN0 M0) to increase the overall primary event rate. All patients had axillary surgery (sentinel node biopsy and/or axillary dissection); nodal radiotherapy was not allowed in the main study. Concurrent endocrine therapy and/or trastuzumab were permitted but not concurrent chemotherapy. For the PRO sub-study all patients at participating centres were eligible. All patients who had breast conservation surgery were eligible for the photographic sub-study at participating centres. A small number of post-mastectomy patients were recruited into the photographic

sub-study to validate the scoring method in chest wall patients but are not reported here as photographs were only available for 76 patients.

Randomisation and masking

Patients were randomised (1:1:1) to receive 40Gy in 15 fractions of 2.67Gy, 27Gy in 5 fractions of 5.4Gy or 26Gy in 5 fractions of 5.2Gy. A sequential tumour bed radiotherapy boost to the conserved breast was allowed, with centres required to specify boost intention and dose (10Gy or 16Gy in 2Gy fractions) before randomisation. Randomisation was performed by telephone or fax from the recruiting centre to the Clinical Trials and Statistics Unit, Institute of Cancer Research (ICR-CTSU), London, and used an in-house bespoke trial-specific randomisation system set-up by the ICR-CTSU IT team. Computer-generated random permuted blocks were used (block sizes 6 and 9), stratified by radiotherapy centre and risk group (high: age <50 years or grade 3 versus low: age ≥50 years and grade 1 or 2). Treatment allocation was not blinded to clinicians or patients.

Test dose levels were informed by START and FAST trials generating α/β values for late normal tissue effects (NTE)[8,15]. Assuming α/β=3Gy and no effect of overall time on outcomes, 27Gy/5Fr of 5.4Gy was predicted to match late NTE of 40Gy/15Fr of 2.7Gy or 46Gy/23Fr of 2Gy. Allowance for a possible effect of treatment time informed the choice of the slightly lower 26Gy dose level.

Radiotherapy

The whole breast clinical target volume (CTV) including the soft tissues from 5mm below the skin surface to the deep fascia was either determined from field-based tangential fields or volumed prospectively. Post-mastectomy chest wall CTV encompassed post-surgical skin

flaps and underlying soft tissues to the deep fascia; both excluded underlying muscle and rib cage. Surgeons were strongly encouraged to mark the tumour cavity walls with titanium clips or gold seeds at the time of breast conservation surgery in order to aid placement of tangential fields and delineation of tumour bed. A typical margin of 10mm was added around the breast/chest wall CTV accounting for set-up error, breast swelling and breathing to create a planning target volume (PTV). For all patients a full 3D CT set of outlines covering the whole breast and organs at risk was collected with a slice separation up to 5mm and organs at risk were outlined prospectively. A tangential opposing pair beam arrangement encompassed the whole breast/chest wall PTV, minimising the ipsilateral lung and heart exposure. The treatment plan was optimised with 3D dose compensation to achieve the following PTV dose distribution: >95% received 95% of prescribed dose, <5% received ≥105%, <2% received ≥107% and global maximum <110%. Dose constraints for the control group were: volume of ipsilateral lung receiving 12Gy <15%, and volume of heart receiving 2Gy and 10Gy <30% and <5% respectively. Dose constraints for the 5-fraction schedules were: volume of ipsilateral lung receiving 8Gy <15%, and volume of heart receiving 1.5Gy and 7Gy <30% and <5% respectively. X-ray beam energies for treatment were 6 megavoltage (MV) or 10MV, but a mixture of energies e.g. 6MV and 10-15MV was allowed for larger patients. Tumour bed boost was delivered via electrons or photons. Verification was carried out using electronic portal imaging using MV or kV x-rays. Control group treatment verification was required for at least 3 fractions in the first week with correction for any systematic error and then once weekly with a tolerance of 5mm. The 5-fraction schedules required verification imaging for each fraction with recommendations to correct all measured displacements. A comprehensive quality assurance programme involved every radiotherapy centre before trial activation and continued throughout trial accrual; this was co-ordinated by the UK

Radiotherapy Trials Quality Assurance team based at Mount Vernon Hospital, UK. The radiotherapy planning pack is in the appendix.

Assessments

Patients were assessed by clinicians for ipsilateral breast tumour relapse (IBTR) and late NTE at annual follow-up visits. Starting 12 months after trial entry, late-onset NTE in ipsilateral breast/chest wall (breast distortion, shrinkage, induration and telangiectasia; breast/chest wall oedema and discomfort) were graded by clinicians on a 4-point scale (none, a little, quite a bit or very much), interpreted as none, mild, moderate or marked. Symptomatic rib fracture, symptomatic lung fibrosis and ischaemic heart disease were recorded. Clinical assessments of acute skin toxicity have been previously reported[15].

In the PRO sub-study, questionnaires were administered at baseline (pre-randomisation), 3, 6, 12, 24 and 60 months, including the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-BR23 breast cancer module, body image scale and protocol-specific questions relating to changes to affected breast following treatment (including breast appearance changed, smaller, harder/firmer, skin appearance changed). Patient assessments used a 4-point scale (not at all, a little, quite a bit, very much).

In the photographic sub-study, photographs were taken at baseline, 2 and 5 years after radiotherapy. Change in photographic breast appearance compared with the post-surgical (pre-radiotherapy) baseline was scored on a 3-point scale (none, mild or marked) based on changes in breast size and shape relative to the contralateral breast. Patients were ineligible for further photographic assessments following breast reconstruction surgery and further ipsilateral disease. Digital photographs were scored by three observers blind to patient

identity and treatment allocation following scoring procedures established in the START trials[16]. Breast size and surgical deficit were assessed from the baseline photographs on a 3-point scale (small, medium, large).

Outcomes

The primary endpoint was IBTR, defined as invasive carcinoma or ductal carcinoma in situ presenting anywhere in the ipsilateral breast parenchyma and/or overlying skin or post-mastectomy chest wall whether considered local recurrence or new primary tumour. Data on first regional relapse (axilla, supraclavicular fossa and internal mammary chain), distant metastases, new primary cancer and death were collected. Key secondary endpoints were late NTE assessed by clinicians, patients and from photographs, and other disease-related and survival outcomes.

Statistical considerations

The target sample size was 4000 patients (balanced allocation between groups). This provided 80% power (1-sided α=0.025 allowing for non-inferiority hypothesis and a simple Bonferroni correction taking into account comparisons between each test schedule and the control group[17]) to exclude an absolute increase of 1.6% in 5-year IBTR incidence for a 5-fraction schedule compared with control, assuming 2% 5-year incidence in the 40Gy group (START data[7] and allowing for reduced IBTR due to evolution of surgical techniques and systemic therapy). The 1.6% absolute non-inferiority margin was defined at the trial design stage by the protocol development group that included clinicians and patient advocates, and was considered to be acceptable and appropriate. Binary proportions were used for the sample size calculations as event rates are so low. Estimates allowed for 10% loss to follow-

up or unevaluable, expected to be largely due to development of metastatic disease. 2196 patients (732 per group) was estimated for the photographic and PRO sub-studies to provide 80% power to detect an 8% difference in the 5-year prevalence of late NTE between the 5-fraction schedules (assuming 35% with 5-year mild/marked change in photographic breast appearance from START-B 40Gy results[7]), allowing for 10% loss to follow-up or unevaluable.

Kaplan-Meier estimates (with 95% confidence intervals, CI) of 5-year IBTR incidence were calculated, and hazard ratios (HR, 95%CI) comparing fractionation schedules obtained from Cox proportional hazards (PH) regression, censoring patients at date of death or last follow-up. Absolute differences (95%CI) in 5-year IBTR incidence were estimated by applying the HRs (and CI) to the control group 5-year event-free estimate[18]. Primary assessment of non-inferiority was based on whether the upper limit of the 2-sided 95%CI (corresponding to 1-sided 97.5%CI) for the absolute difference in 5-year IBTR was <1.6%. Non-inferiority of each 5-fraction schedule versus control was also tested using the *a priori* critical HR of 1.81 (ln0.964/ln0.98, from protocol-specified incidence); $p<0.025$ was deemed statistically significant (probability of incorrectly accepting an inferior 5-fraction schedule). An exploratory competing risks analysis was done for IBTR, with death from any cause as a competing event in a Fine-Gray competing risks regression model.

Clinician and patient assessments of late NTE were analysed as follows: (i) 5-year cross-sectional analyses compared prevalence of moderate/marked effects versus none/mild between groups using risk ratios and risk differences (95%CI), and Fisher's exact test; (ii) longitudinal analyses of moderate/marked effects (versus none/mild) using generalised estimating equations (GEE)[19] including all assessments, comparing groups across the whole follow-up period using odds ratios (OR, 95%CI) and the Wald test; GEE models included a

term representing years of follow-up, enabling time trends to be modelled. Additionally, to enable comparison of clinician-assessed NTE with results reported from other trials, survival analysis methods analysed time to first moderate/marked event, including Kaplan-Meier estimates of cumulative incidence, and groups compared using HR (95%CI) from Cox PH regression and the pairwise log-rank test.

Scores for change in photographic breast appearance at 2 and 5 years were modelled using GEE. Categories of mild and marked change in photographic breast appearance were combined for analysis as there were very few with marked change. Pairwise comparisons of mild/marked change at 2 and/or 5 years between groups were described by OR (95%CI) obtained from the GEE models and the Wald test. Due to multiple testing a significance level of 0.005 was used for the clinician and patient NTE assessments; all hypotheses for the NTE endpoints were 2-sided.

Estimates of fractionation sensitivity (α/β values, 95%CI) in FAST-Forward were obtained for the primary endpoint of IBTR and late NTE as per methodology in the START and FAST trials[3]. The α/β estimate for breast cancer was obtained from a Cox PH regression model of time to first IBTR, and for late NTE from GEE models including all follow-up assessments (separate models for photographic and clinician assessments). Each model included terms for total dose and total dose multiplied by fraction size; the α/β ratio was calculated by dividing the 2 parameter estimates respectively, with a 95%CI estimated from the model using the covariance of the two estimates (lower confidence limits were truncated at zero). Isoeffect doses in 2Gy equivalents (EQD_2) were calculated for the 5-fraction schedules, together with

an estimate of the 5-fraction schedule isoeffective with 40Gy in 15 fractions in terms of local tumour control and late NTE. No correction was made for difference in treatment time.

There were no formal interim analyses; accumulating data were monitored annually by the Independent Data Monitoring Committee. All analyses were performed on an intention-to-treat basis that included all patients according to their allocated treatment regardless of what was actually received. As the main hypothesis was non-inferiority the primary endpoint was also tested in the per protocol population, which excluded patients for whom a major deviation was reported. The database snapshot was taken on 22/11/2019; Stata version 15 (StataCorp) was used for analyses.

Role of the funding source

The funding source provided peer-reviewed approval for the trial but had no role in study design, collection, analysis, interpretation of data, or writing the report. The corresponding author had full access to all trial data and had final responsibility for the decision to submit for publication.

RESULTS

Between November 2011 and June 2014, 4110 patients were enrolled in the FAST-Forward trial. Fourteen withdrew consent for use of data and were removed from the intention-to-treat population; hence results are reported for 4096 consenting participants. Nine patients were found to be ineligible after randomisation; 3 in the control group received 40Gy in 15 fractions

as standard and 6 in the test groups did not receive the allocated schedule. Twenty eligible patients received a non-allocated schedule, and 6 received no radiotherapy. Compliance with allocated treatment was 99% (Figure 1). Demographic and clinical characteristics at baseline were well-balanced between groups (Table 1). Overall, 2551/4096 (62%) were classified as low risk (age $\geq$50 and grade 1 or 2); the majority were ER positive/HER2 negative (3335/4077 with data, 82%), and 407/4077 with data (10%) were HER2 positive. 3832 (93%) had breast conservation surgery, 1011 (25%) received a radiotherapy boost to tumour bed, 1174 (29%) had neo- or adjuvant chemotherapy, 3512/3649 (96%) ER positive patients had endocrine therapy, and 311/407 (76%) HER2 positive patients received trastuzumab. Five-year visit forms were available for 3563 (93%) patients out of 3830 still in follow-up (not died, withdrawn or lost).

After a median follow-up of 71.5 months (IQR 71.3, 71.7), IBTR was recorded in 79 patients (40Gy: 31, 27Gy: 27, 26Gy: 21). Estimated cumulative incidence of IBTR up to five years was 2.1% (95%CI 1.4, 3.1) for 40Gy (expected incidence 2%), 1.7% (1.2, 2.6) for 27Gy and 1.4% (0.9, 2.2) for 26Gy (Table 2, Figure 2). Estimated absolute differences in IBTR versus 40Gy were -0.3% (-1.0, 0.9) for 27Gy and -0.7% (-1.3, 0.3) for 26Gy. Since the upper confidence limits excluded an increase in IBTR of $\geq$1.6%, non-inferiority can be claimed for both 5-fraction schedules compared with 40Gy in 15 fractions. This is confirmed by a test against the critical HR>1.81, with p=0.0022 for 27Gy and p=0.00019 for 26Gy compared with 40Gy. Analyses in the per protocol population were consistent (estimated absolute difference versus 40Gy -0.4%; (-1.0,0.8), p=0.0017 for 27Gy and -0.6% (-1.2,0.4), p=0.00037 for 26Gy; full data for per-protocol analyses not shown as 99% treatment compliance). Comparing the 5-fraction schedules, the estimated absolute difference in IBTR cumulative incidence up to five years was -0.4% (-1.0, 0.6) for 26Gy versus 27Gy. The unadjusted α/β estimate for IBTR was

3.7Gy (0.3, 7.1Gy), with EQD_2 estimates of 44.7Gy for 40Gy, 43.1Gy for 27Gy and 40.6Gy for 26Gy with no correction for treatment time. Adjusting for risk group and ER/HER2 status made minimal difference (adjusted α/β estimate 3.7Gy; 0.4, 6.9). Hazard ratios obtained from a competing risks analysis of IBTR with death from any cause as a competing event were almost identical to those from the primary analysis reported in Table 2 (HRs from competing risks model: 0.85 (95%CI 0.51, 1.43) for 27Gy versus 40Gy; 0.67 (0.38, 1.16) for 26Gy versus 40Gy).

Regional relapses occurred in 34/4096 (1%) patients (40Gy: 13, 27Gy: 11, 26Gy: 10; Table 3), 6 of which were concurrent with IBTR. Incidence of locoregional relapse, distant relapse, disease-free and overall survival were similar between groups, with no statistically significant differences (Table 2, Figures A1 and A2). No formal subgroup analyses were done due to the low number of primary events, but frequencies of IBTR, regional and distant relapse were tabulated according to age, grade and ER/HER2 status for descriptive purposes; as expected, there were more IBTR in the patients with higher grade primary tumours (Table A1). Invasive contralateral breast cancer was reported for 55/4096 (1%) patients (40Gy: 18, 27Gy: 17, 26Gy: 20; Table 3), and non-breast second primary cancers for 123/4096 (3%) patients (40Gy: 42, 27Gy: 37, 26Gy: 44; Table 3), the most common being colorectal cancer with 25 cases in total.

A total of 287/4096 (7%) patients died, 151 (4%) from breast cancer, 125 (3%) from other causes (including 38 (1%) from second cancers and 27 (1%) cardiac-related), and 11 (0.3%) with unknown cause of death and no evidence of disease relapse (Table 3). Of 27 patients with a cardiac-related death (40Gy: 10, 27Gy: 9, 26Gy: 8), 15 (40Gy: 7, 27Gy; 4, 26Gy: 4)

had a history of cardiac disease reported at randomisation or was a current/ex-smoker in past year.

At least one annual clinical assessment of NTE was available for 3975/4096 (97%) patients. At 5 years, any moderate/marked clinician-assessed NTE in the breast/chest wall was reported for 98/986 (10%) patients in the 40Gy group, 155/1005 (15%) for 27Gy and 121/1020 (12%) for 26Gy (Table A2, Figure A3), with a statistically significant difference between 40Gy and 27Gy (p=0.0003) but not between 40Gy and 26Gy (p=0.17). Breast shrinkage was the most prevalent moderate/marked effect at 5 years, reported in 50/916 (6%) for 40Gy, 78/948 (8%) for 27Gy and 65/954 (7%) for 26Gy (Table A2). Longitudinal analysis of all annual clinical assessments of NTE over follow-up showed a statistically significant increased risk of any moderate/marked effect in the breast/chest wall for the 27Gy group compared with 40Gy (OR 1.55; 1.32, 1.83; p<0.0001), with no statistically significant difference between 26Gy and 40Gy (OR 1.12; 0.94, 1.34; p=0.20); Table 4. This pattern was similar for the individual effects of breast distortion, shrinkage, induration and breast/chest wall oedema, with statistically significant higher risk for 27Gy compared with 40Gy but not for 26Gy (Table 4, Figure A3). Comparing the two 5-fraction schedules, 26Gy had statistically significantly lower risk of any moderate/marked breast/chest wall NTE (p=0.0001) and breast shrinkage (p=0.0018) compared with 27Gy. Estimates of 5-year cumulative incidence of any moderate/marked clinician-assessed NTE in the breast/chest wall were 26.8% (95%CI 24.4, 29.4) for 40Gy, 35.1% (32.4, 37.9) for 27Gy and 28.5% (26.0, 31.1) for 26Gy (Table A3). Results for comparison of schedules from the analyses of time to first moderate/marked effect were similar to those from the longitudinal modelling of all annual clinical assessments (Table A3).

1796 patients consented to the PRO sub-study, 18 of whom withdrew consent immediately after randomisation or were not given the baseline booklet. Questionnaires returned from those expected (patients alive and well, not withdrawn) totalled 1771/1778 (99%) at baseline, 1668/1733 (96%) at three months, 1622/1722 (94%) at six months, 1599/1707 (94%) at one year, 1531/1669 (92%) at two years and 1334/1589 (84%) at five years. Of the 1774 patients with at least one completed questionnaire, 1634 had breast conservation surgery and 140 mastectomy. Change in breast appearance had the highest 5-year prevalence, with moderate/marked change reported in 140/432 (32%) for 40Gy, 158/440 (36%) for 27Gy and 136/429 (32%) for 26Gy. There were no statistically significant differences in 5-year prevalence of patient-reported adverse effects between the schedules (Table A4, Figure A3). There was some evidence of an increase in patient-reported moderate/marked breast hardness/firmness at 5 years for 27Gy compared with 40Gy and more breast swelling in both 5-fraction schedules, but these were not statistically significant at the pre-specified cut-off of p=0.005. Longitudinal analyses of all patient assessments from baseline to 5 years showed a statistically significantly higher risk of moderate/marked breast hardness/firmness for 27Gy compared with 40Gy (OR 1.42, 1.17, 1.72, p=0.0003), and less change in breast appearance for 26Gy compared with 27Gy (p=0.0018), but no statistically significant differences between schedules for the other NTE (Table 5, Figure A3).

Of the 1737 patients (breast conservation surgery and post-mastectomy) who consented to the photographic sub-study, baseline photographs were received for 1634 (94%), and 2 and/or 5-year photographs were available for 1385 (80%). The vast majority (1309) were patients who had breast conservation surgery; for these patients, 2 and 5-year photographs were assessed in 1267 and 875 respectively (Table A5). A total of 226 patients died or withdrew from the photographic sub-study by year 5, for the remainder the most common

reasons for photographs not being taken were appointments not made due to clerical errors at the centres, patients not attending clinic visits, and patients withdrawing consent from the sub-study. At 2 years, mild/marked change in photographic breast appearance was reported in 35/411 (8%) for 40Gy, 67/429 (16%) for 27Gy and 46/427 (11%) for 26Gy; corresponding figures at 5 years were 34/283 (12%) for 40Gy, 83/308 (27%) for 27Gy and 37/284 (13%) for 26Gy (Table A5). Modelling 2- and 5-year photographic assessments together, 27Gy had a statistically significantly increased risk of mild/marked change in breast appearance compared with 40Gy (OR 2.29; 1.60, 3.27; $p<0.0001$), with no statistically significant difference between 26Gy and 40Gy (OR 1.26; 0.85, 1.86; $p=0.24$; Table A5). 26Gy had a statistically significantly lower risk of change in photographic breast appearance compared with 27Gy ($p=0.0006$).

The unadjusted α/β estimate for any moderate/marked clinician-assessed NTE in the breast/chest wall was 1.7Gy (1.2, 2.3), giving EQD_2 estimates of 47.1Gy for 40Gy/15Fr, 51.6Gy for 27Gy/5Fr and 48.3Gy for 26Gy/5Fr; adjusting for prognostic factors (age, boost, whole-breast planning treatment volume as a proxy for breast size) made very little difference. α/β estimated from the photographic endpoint (adjusting for breast size and surgical deficit evaluated from the baseline photographs) was very similar (1.8Gy; 1.1, 2.4). The unadjusted α/β estimate for patient-reported change in breast appearance was 2.3Gy (1.8, 2.9), resulting in EQD_2 estimates of 46.1Gy, 48.2Gy and 45.2Gy for the 40Gy, 27Gy and 26Gy schedules respectively; as above, adjusting for covariates made minimal difference.

The most common specialist referral for radiotherapy-related adverse effects during follow-up was to lymphoedema clinics (Table A6). Incidence of ischaemic heart disease,

symptomatic rib fracture and symptomatic lung fibrosis was very low at this stage of follow-up (Table A7).

DISCUSSION

Non-inferiority in terms of IBTR of 5-fraction schedules compared with 40Gy in 15 fractions is demonstrated at 5 years' follow-up for patients with early breast cancer, the majority of whom were treated by local tumour excision and sentinel node biopsy for node negative disease. NTE up to 5 years for 26Gy in 5 fractions were comparable with 40Gy in 15 fractions. Extremely low rates of IBTR and of moderate/marked late NTE can be attributed to improvements in all diagnostic and treatment modalities and to the commitment of patients to early diagnosis and randomised trials[20].

The 10-year analyses of IBTR and NTE reported by earlier Canadian and UK trials confirm that although NTE continue to accumulate beyond 5 years, there is evidence that relative differences between test and control groups change very little over time[3-8,21]. In START-B trial, the hazard ratio (95%CI) for clinician-assessed breast shrinkage after 40Gy in 15 fractions compared with 50Gy in 25 fractions was 0.83 (0.66-1.04) at 5 years and 0.80 (0.67-0.96) at 10 years, by which time the proportion of patients with breast shrinkage increased from 11.4% (9.5-13.6) at 5 years to 26.2% (23.2-29.6)[8]. The findings of FAST-Forward can be applied to different prognostic groups in view of the very low overall IBTR incidence, a conclusion consistent with meta-analysis of 5861 patients entered into the three START trials, which identified no inconsistency of effect in terms of NTE or recurrence risk across any of the prognostic or treatment subgroups investigated[8].

The lack of a detectable dose response for local tumour control between 26Gy and 27Gy in 5 fractions is a potential limit to precision, but this feature reflects the shallowness of the dose response curve for subclinical breast cancer around the 98% control level, so the -0.4% estimated difference in absolute levels of IBTR between 27Gy and 26Gy likely reflects random sampling variability in the IBTR rate and/or chance imbalances in unmeasured prognostic factors between test groups. For late NTE the dose response is much steeper, enabling detection of clinically and statistically significant differences in event rates between 26Gy and 27Gy in 5 fractions. The 5-fraction schedule isoeffective with 40Gy in 15 fractions allows direct estimation of α/β for late NTE, which is consistent with values generated from our other trials. The α/β value of 3.7Gy (0.3-7.1) for tumour control in FAST-Forward is similar to 3.5Gy (1.2–5.7) estimated from the START pilot and START-A trials[8]. Point estimates of α/β, assuming no effect of time, for late NTE in FAST-Forward scored by clinicians, patients and photographic assessments are closer to 2Gy than the 3Gy estimated in the earlier START[8] and FAST trials[14], but 95%CI overlap for each endpoint in all trials. In FAST, 915 women were randomised after breast conservation surgery for node negative disease to 50Gy in 25 fractions versus 2 dose levels of a 5-fraction regimen delivered once-weekly, thereby ensuring complete repair between fractions and controlling for overall treatment time[13,14]. The α/β value for change in photographic breast appearance in FAST was 2.6Gy (1.4–3.7). Uncertainty about biological processes, which include a time factor in FAST-Forward, does not interfere with clinical evaluation and decisions on implementation of FAST-Forward results in comparable patient groups.

The 5-fraction regimen is relevant to partial breast radiotherapy, the preferred alternative to whole breast radiotherapy for many women after recent phase III trials[22-25]. Beyond its safety and effectiveness, the 26Gy FAST-Forward schedule is convenient and substantially less

expensive for patients and for health services. It is also likely to be safe for patients requiring regional radiotherapy, an approach currently under formal evaluation in a randomised FAST-Forward sub-study comparing 40Gy in 15 fractions and 26Gy in 5 fractions. Assuming no effect of time, 26Gy in 5 fractions is equivalent to 46.8Gy and 53.7Gy in 2Gy fractions assuming α/β values 2 and 1Gy, respectively, dose intensities well within the limits of tolerance for these structures[26,27]. Finally, there is no reason to consider the heart more sensitive to fraction size than most other soft tissues, but it is undoubtedly sensitive to total dose[28]. Any heart exposure is potentially harmful, so the priority is to exclude the heart from the treatment volume as far as possible using deep inspiration breath hold or comparable technique[29,30].

In conclusion, 5-year IBTR incidence after a 1-week course of adjuvant breast radiotherapy delivered in 5 fractions is non-inferior to the standard 3-week schedule according to the pre-defined inferiority threshold. The 26Gy dose level is comparable to 40Gy in 15 fractions in terms of patient-assessed NTE, clinician-assessed NTE, and photographic change in breast appearance, and is comparable to NTE expected after 46-48Gy in 2Gy fractions. The consistency of FAST-Forward results with earlier hypofractionation trials supports the adoption of 26Gy in 5 daily fractions as a new standard for women with operable breast cancer requiring adjuvant radiotherapy to partial or whole breast.

Contributors

AMB and JRY are the current and previous chief investigators respectively, and DAW is the chief clinical co-ordinator for the trial. JMB is the trials methodology lead within the Institute of Cancer Research - Clinical Trials and Statistics Unit (ICR-CTSU) and provided oversight

and guidance for trial management throughout the trial. JRY, JMB and JSH were responsible for the study design. AMB, JRY and JSH wrote the first draft of the manuscript. JSH was responsible for statistical analyses and contributed to data interpretation. AA, DJB, CC, MC, SC, CEC, AG, AH, PH, AMK, CCK, CM, ZN, ES, NS, IS are members of the FAST-Forward Trial Management Group (TMG), which contributed to study design, was responsible for oversight throughout the trial and contributed to data interpretation and manuscript preparation. MAS, and LS managed the study and data collection at ICR-CTSU. CM is a patient advocate member of the TMG and provided guidance for study documentation and reports. PH was the lead for the PRO sub-study. ZN was responsible for radiotherapy quality assurance. All authors reviewed and approved the manuscript.

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Declaration of interests

JMB reports grants from NIHR HTA and grants from Cancer Research UK during the conduct of the study, and grants and non-financial support from Novartis (previously GSK), grants and non-financial support from Astra Zeneca, grants and non-financial support from Clovis Oncology, grants and non-financial support from Janssen-Cilag, grants and non-financial support from Merck Sharpe & Dohme, grants and non-financial support from Puma Biotechnology, grants and non-financial support from Pfizer, grants and non-financial support from Roche, grants from Medivation, outside the submitted work. DAW reports travel grants from Roche Pharmaceuticals, outside the submitted work. JSH, MAS and LS report grants from NIHR HTA and grants from Cancer Research UK, during the conduct of the study. CCK reports personal fees from Roche Pharmaceutical, outside the submitted work. AA, AMB, DJB, CC, CEC, MC, AG, PH, CM, ZN, NS, IS, JRY declare no competing interests.

Data sharing

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. Trial documentation including the protocol are available at https://www.icr.ac.uk/fastforward (last accessed 07/04/2020). The Institute of Cancer Research – Clinical Trials and Statistics Unit (ICR-CTSU) supports wider dissemination of information from the research it conducts and increased cooperation between investigators. Trial data are obtained, managed, stored, shared, and archived according to ICR-CTSU standard operating procedures to ensure the enduring quality, integrity, and utility of the data. 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, which describes the conditions for release and requirements for data transfer, storage,

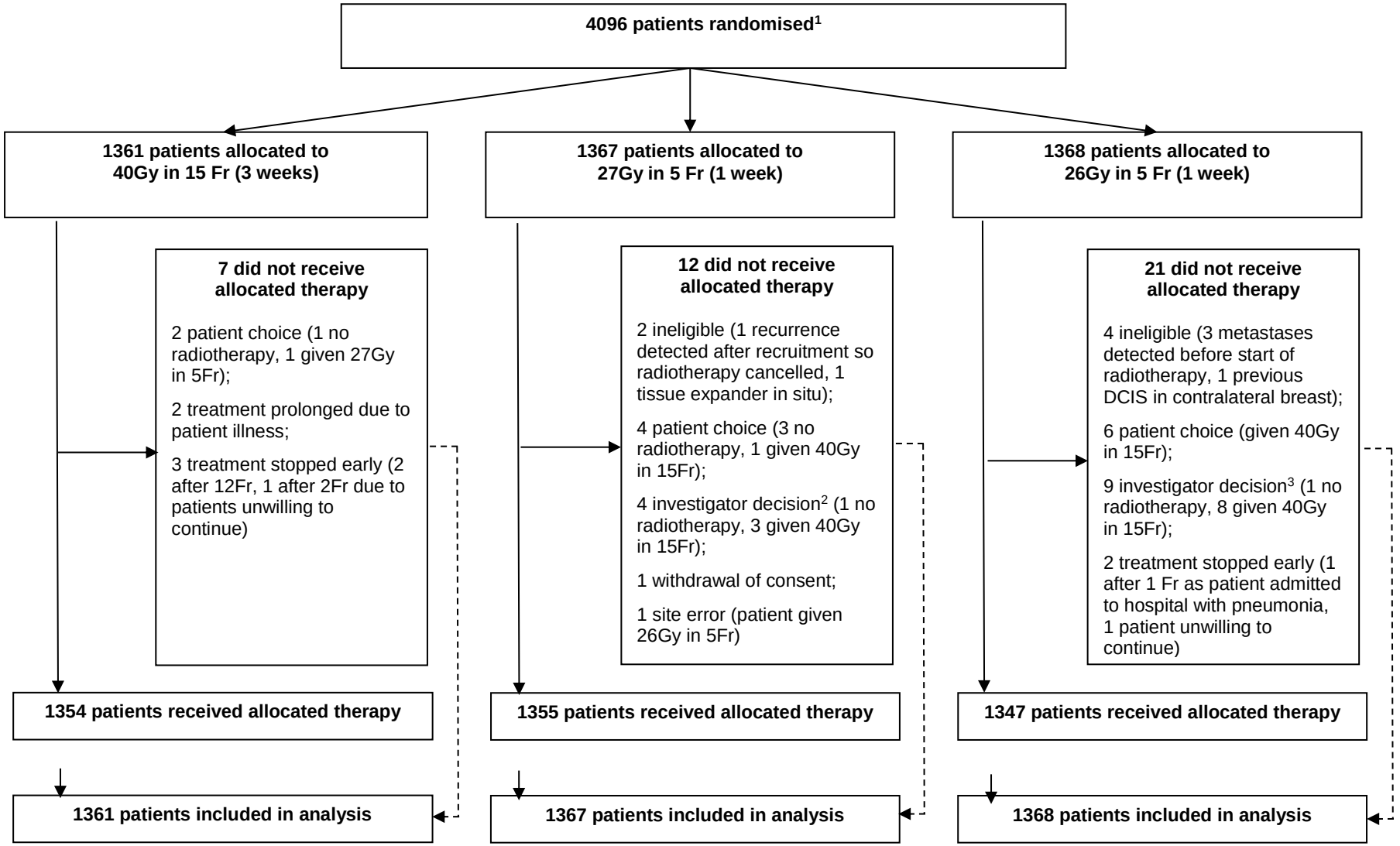
archiving, publication, and intellectual property. Requests are reviewed by the Trial Management Group (TMG) in terms of scientific merit and ethical considerations, including patients' consent. Data sharing is undertaken if proposed projects have a sound scientific or patients' benefit rationale, as agreed by the TMG and approved by the Independent Data Monitoring and Steering Committee, as required. Restrictions relating to patients' confidentiality and consent will be limited by aggregating and anonymising identifiable patients' data. Additionally, all indirect identifiers that could lead to deductive disclosures will be removed in line with ICR-CTSU data sharing guidelines.

Figure legends

Figure 1: FAST-Forward trial profile

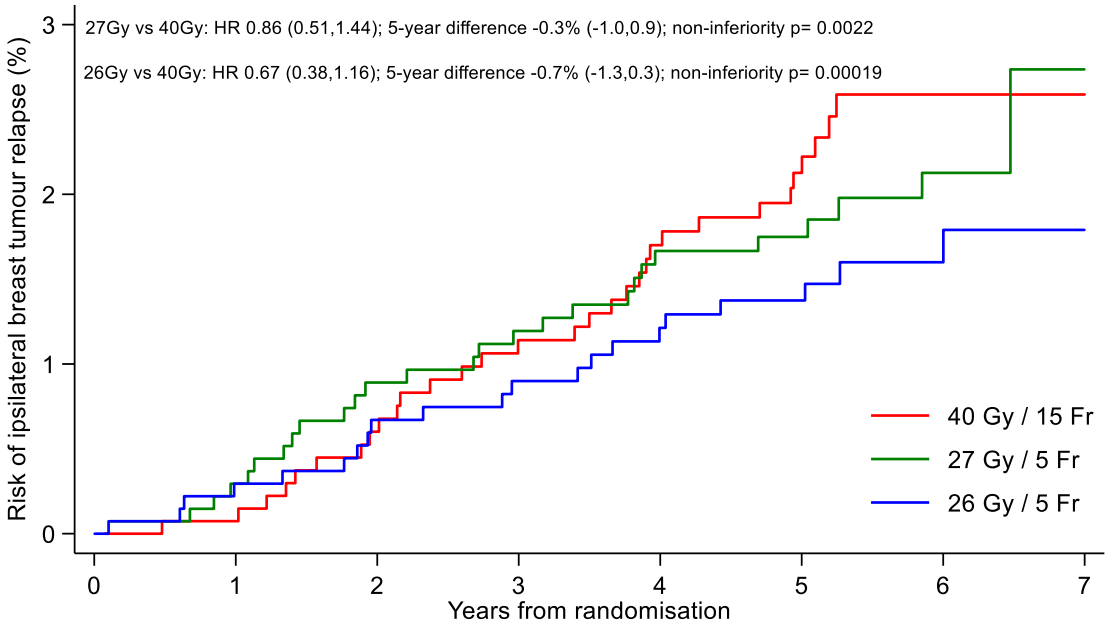
Figure 2: Cumulative risk of ipsilateral breast tumour relapse by fractionation schedule

Figure 1: FAST-Forward Trial profile



[1] 14 patients withdrew consent for any of their data to be used in the analysis (7 x 40Gy, 3 x 27Gy, 4 x 26Gy); [2] 1 no radiotherapy given as patient unable to get into stable position for RT; 3 given 40Gy in 15Fr: 1 concern for brachial plexus, 1 decided on different treatment plan, 1 constraints of treatment planning); [3] 1 no radiotherapy given as patient diagnosed with pemphigoid; 8 given 40Gy in 15Fr: 1 dose constraints not met, 1 unable to plan within protocol constraints due to tumour bed position, 1 poor PTV coverage, 1 technical difficulties in planning, 1 transferred to direct electron field, 1 simulator plan as 3D images not possible, 1 small pericardial effusion found at planning, 1 reason not given)

Figure 2: Cumulative risk of ipsilateral breast tumour relapse by fractionation schedule



No. at risk (40Gy)	1361	1347	1307	1281	1230	1045	486	91
censored	0	13	46	65	109	289	844	1239
event	0	1	8	15	22	27	31	31
No. at risk (27Gy)	1367	1352	1328	1303	1255	1066	508	90
censored	0	11	27	48	90	278	833	1250
event	0	4	12	16	22	23	26	27
No. at risk (26Gy)	1368	1347	1325	1302	1257	1070	524	89
censored	0	17	34	54	95	280	824	1258
event	0	4	9	12	16	18	20	21

Table 1: Demographic, clinical and treatment characteristics at randomisation of the 4096 patients consenting to the FAST-Forward trial[1]

	40 Gy / 15 Fr N=1361 (%)	27 Gy / 5 Fr N=1367 (%)	26 Gy / 5 Fr N=1368 (%)
Age (years)			
Median (IQR)	60 (53-66)	61 (53-67)	61 (52-66)
[range]	29-89	25-90	25-89
<40	12 (0.9)	16 (1.2)	28 (2.0)
40-49	186 (13.7)	173 (12.7)	189 (13.8)
50-59	440 (32.3)	423 (30.9)	414 (30.3)
60-69	506 (37.2)	511 (37.4)	524 (38.3)
70-79	175 (12.9)	197 (14.4)	172 (12.6)
≥80	42 (3.1)	47 (3.4)	41 (3.0)
Sex			
Female	1355 (99.6)	1365 (99.9)	1362 (99.7)
Male	6 (0.4)	2 (0.1)	4 (0.3)
Not known	0	0	2
Tumour grade			
1	315 (23.1)	315 (23.0)	300 (21.9)
2	660 (48.5)	663 (48.5)	690 (50.4)
3	386 (28.4)	389 (28.5)	378 (27.6)
Risk group			
Low (age ≥50 & grade 1 or 2)	843 (61.9)	854 (62.5)	854 (62.4)
High (age <50 and/or grade 3)	518 (38.1)	513 (37.5)	514 (37.6)
Primary surgery			
Breast conservation surgery	1270 (93.3)	1278 (93.5)	1284 (93.9)
BCS with oncoplastic technique	*42*	*33*	*42*
Mastectomy	91 (6.7)	89 (6.5)	84 (6.1)
Mastectomy with immediate reconstruction	*8*	*11*	*7*
Type of reconstruction (mastectomy patients):			
Autologous reconstruction	*5*	*7*	*3*
Implant-based reconstruction	*2*	*4*	*4*
Reconstruction type not specified	*1*	*0*	*0*
Side of primary			
Left	726 (53.3)	674 (49.3)	662 (48.5)
Right	635 (46.7)	693 (50.7)	704 (51.5)
Not known	0	0	2
Maximal extent of axillary staging			
Sentinel node biopsy/guided axillary sampling	1157 (85.0)	1184 (86.6)	1164 (85.2)
Axillary clearance	200 (14.7)	181 (13.2)	201 (14.7)
Other	4 (0.3)	2 (0.1)	1 (0.1)
Not known	0	0	2
Pathological node status			
Positive	257 (18.9)	243 (17.8)	256 (18.7)
Negative	1103 (81.1)	1124 (82.2)	1110 (81.3)
Not known	1	0	2
Histological type			
Infiltrating ductal	1084 (79.6)	1096 (80.2)	1086 (79.6)
Lobular	144 (10.6)	139 (10.2)	127 (9.3)

	40 Gy / 15 Fr N=1361 (%)	27 Gy / 5 Fr N=1367 (%)	26 Gy / 5 Fr N=1368 (%)
Mixed	51 (3.7)	63 (4.6)	65 (4.8)
Other	82 (6.0)	69 (5.0)	87 (6.4)
Not known	0	0	3
Pathological tumour size (cm)			
Median (IQR)	1.6 (1.1-2.2)	1.6 (1-2.2)	1.6 (1.1-2.4)
pT stage			
T1mi	4 (0.3)	5 (0.4)	6 (0.4)
T1a	69 (5.1)	68 (5.0)	51 (3.7)
T1b	258 (19.0)	270 (19.8)	256 (18.8)
T1c	612 (45.1)	601 (44.1)	602 (44.1)
T2	394 (29.0)	389 (28.5)	424 (31.1)
T3	21 (1.5)	30 (2.2)	25 (1.8)
Not known	3	4	4
ER / HER2 status			
ER+ / HER2+	103 (7.6)	103 (7.6)	93 (6.8)
ER+ / HER2-	1108 (81.8)	1130 (82.9)	1097 (80.7)
ER- / HER2+	32 (2.4)	34 (2.5)	42 (3.1)
ER- / HER2-	111 (8.2)	96 (7.0)	128 (9.4)
Not known	7	4	8
PgR status			
Positive	577 (73.1)	541 (70.3)	566 (69.8)
Negative	212 (26.9)	229 (29.7)	245 (30.2)
Not done	571	596	555
Missing on form	1	1	2
Lymphovascular invasion			
Present	186 (14.2)	178 (13.7)	202 (15.4)
Absent	1085 (83.1)	1084 (83.3)	1055 (80.7)
Uncertain	34 (2.6)	40 (3.1)	51 (3.9)
Not known	56	65	60
Neo-adjuvant chemotherapy received			
Yes	48 (3.5)	56 (4.1)	43 (3.1)
No	1312 (96.5)	1311 (95.9)	1323 (96.9)
Not known	1	0	2
Adjuvant therapy received[2]			
All patients:			
Chemotherapy[3]	333/1360 (24.5)	324/1367 (23.7)	370/1366 (27.1)
HER2 + patients:			
Trastuzumab	100/135 (74.1)	98/137 (71.5)	113/135 (83.7)
Chemotherapy & trastuzumab	*84*	*85*	*100*
Trastuzumab, no chemotherapy	*16*	*13*	*13*
Chemotherapy, no trastuzumab	*2*	*2*	*0*
No chemotherapy, no trastuzumab	*33*	*37*	*22*
ER+ patients:			
Endocrine therapy	1169/1216 (96.1)	1186/1237 (95.9)	1157/1196 (96.7)
Boost given			
Yes	342 (25.2)	337 (24.7)	332 (24.4)
No	1017 (74.8)	1027 (75.3)	1031 (75.6)
Not known	2	3	5
Boost dose	N=342	N=337	N=332

	40 Gy / 15 Fr N=1361 (%)	27 Gy / 5 Fr N=1367 (%)	26 Gy / 5 Fr N=1368 (%)
10Gy/5fr	260 (76.0)	273 (81.0)	257 (77.4)
16Gy/8fr	80 (24.0)	64 (19.0)	75 (22.6)
Not known	2	0	0

IQR = interquartile range; BCS = breast conservation surgery

[1] 14 patients withdrew consent for any of their data to be used in analysis

[2] Patients could have more than one type of adjuvant systemic therapy

[3] Chemotherapy type (for those specified): anthracyclines (N=584), taxane + anthracycine (N=348), taxane + other; e.g. TCH, TCarbo (N=83), other (N=3)

Table 2: Relapse and mortality by fractionation schedule: results of time to event analyses for 4096 patients consenting to the FAST-Forward trial

	Cumulative no. of events / total (%)	KM estimate (95%CI) of cumulative incidence by 5 years, %	Hazard ratio[1] (95% CI); p-value[2]	Estimated absolute difference vs 40 Gy at 5 years[3] (95%CI), %
Ipsilateral breast tumour (local) relapse[4]				
40 Gy	31/1361 (2.3)	2.1 (1.4, 3.1)	1	
27 Gy	27/1367 (2.0)	1.7 (1.2, 2.6)	0.86 (0.51, 1.44); 0.56	-0.3 (-1.0, 0.9)
26 Gy	21/1368 (1.5)	1.4 (0.9, 2.2)	0.67 (0.38, 1.16); 0.15	-0.7 (-1.3, 0.3)
Locoregional relapse[5]				
40 Gy	43/1361 (3.2)	2.8 (2.0, 3.9)	1	
27 Gy	35/1367 (2.6)	2.3 (1.6, 3.3)	0.80 (0.51, 1.25); 0.33	-0.5 (-1.4, 0.7)
26 Gy	29/1368 (2.1)	1.8 (1.2, 2.7)	0.66 (0.41, 1.06); 0.083	-0.9 (-1.6, 0.2)
Distant relapse				
40 Gy	59/1361 (4.3)	3.8 (2.9, 5.0)	1	
27 Gy	69/1367 (5.0)	4.7 (3.7, 6.0)	1.16 (0.82, 1.64); 0.41	0.6 (-0.7, 2.3)
26 Gy	76/1368 (5.6)	5.1 (4.0, 6.4)	1.27 (0.90, 1.79); 0.17	1.0 (-0.4, 2.9)
Any breast cancer-related event[6]				
40 Gy	119/1361 (8.7)	7.8 (6.5, 9.4)	1	
27 Gy	112/1367 (8.2)	7.2 (5.9, 8.7)	0.93 (0.71, 1.20); 0.56	-0.6 (-2.2, 1.5)
26 Gy	114/1368 (8.3)	7.5 (6.2, 9.0)	0.94 (0.73, 1.22); 0.65	-0.4 (-2.1, 1.6)
All-cause mortality				
40 Gy	92/1361 (6.8)	5.4 (4.3, 6.8)	1	
27 Gy	105/1367 (7.7)	6.9 (5.7, 8.4)	1.12 (0.85, 1.48); 0.42	0.6 (-0.8, 2.5)
26 Gy	90/1368 (6.6)	5.6 (4.5, 7.0)	0.96 (0.72, 1.28); 0.78	-0.2 (-1.5, 1.5)

KM = Kaplan-Meier, 95%CI = 95% confidence interval; IBTR = ipsilateral breast tumour relapse

[1] Hazard ratio <1 favours 5-fraction schedules;

[2] Log-rank test (2-sided), for each 5-fraction schedule compared with 40Gy/15fr (control);

[3] Estimated absolute difference at 5 years for each 5-fraction schedule versus 40Gy obtained from hazard ratio and KM estimate of cumulative incidence in 40Gy group;

[4] Includes 3 with angiosarcoma in ipsilateral breast (1 in 40Gy, 2 in 26Gy);

[5] Locoregional relapse defined as IBTR or regional relapse (axilla, supraclavicular fossa and internal mammary chain);

[6] Breast cancer-related events: local, regional or distant relapse, breast cancer death, contralateral breast cancer (disease-free survival)

Table 3: Relapses, second primary cancers and deaths by fractionation schedule, in 4096 patients consenting to the FAST-Forward trial

Event	40 Gy / 15 Fr N=1361 (%)	27 Gy / 5 Fr N=1367 (%)	26 Gy / 5 Fr N=1368 (%)
Local tumour control event (primary endpoint)[1,2]	**31 (2.3)**	**27 (2.0)**	**21 (1.5)**
Local relapse	*23*	*22*	*17*
Ipsilateral breast new primary	*6*	*3*	*4*
Cannot differentiate	*2*	*2*	*0*
Regional relapse	**13 (1.0)**	**11 (0.8)**	**10 (0.7)**
Distant relapse	**59 (4.3)**	**69 (5.0)**	**76 (5.5)**
Contralateral breast second primary	**23 (1.7)**	**20 (1.5)**	**23 (1.7)**
Invasive	*18*	*17*	*20*
DCIS	*5*	*3*	*2*
Unknown	*0*	*0*	*1*
Non-breast second primary	**42 (3.1)**	**37 (2.7)**	**44 (3.2)**
Death	**92 (6.8)**	**105 (7.7)**	**90 (6.6)**
Breast cancer[3]	*47*	*51*	*53*
Second cancer	*12*	*16*	*10*
Cardiac	*10*	*9*	*8*
Other cause	*17*	*27*	*16*
Unknown	*6*	*2*	*3*

NB: Patients reporting events of more than one type are included in each relevant row

[1] Includes angiosarcoma in ipsilateral breast (1 in 40Gy, 2 in 26Gy)

[2] Includes 6 patients with ductal carcinoma in situ, DCIS (3 in 40Gy, 2 in 27Gy, 1 in 26Gy)

[3] Includes 13 patients with distant relapse before death from other causes (4 in 40Gy, 4 in 27Gy, 5 in 26Gy)

Table 4: Longitudinal analysis of moderate/marked clinician-assessed late normal tissue effects including all annual follow-up assessments for 3975 patients with at least one annual clinical assessment

Normal tissue effect	No. moderate/marked events / total no. of assessments over follow-up (%)	Odds ratio for schedule[2] (95%CI)	Comparison with 40 Gy; p-value[3]	Comparison between 27 Gy & 26 Gy; p-value[3]	Odds ratio for years of follow-up (95%CI); p-value[3]
Any AE in the breast/chest wall[1+]					0.98 (0.96,1.00);
40 Gy	651/6121 (10.6)	1			0.055
27 Gy	1004/6303 (15.9)	1.55 (1.32,1.83)	<0.0001		
26 Gy	774/6327 (12.2)	1.12 (0.94,1.34)	0.20	0.0001	
Breast distortion*					0.99 (0.95,1.02);
40 Gy	232/5724 (4.0)	1			0.38
27 Gy	363/5953 (6.1)	1.51 (1.15,1.97)	0.0028		
26 Gy	299/5945 (5.0)	1.20 (0.91,1.60)	0.19	0.083	
Breast shrinkage*					1.03 (1.00,1.06);
40 Gy	330/5728 (5.8)	1			0.023
27 Gy	503/5944 (8.5)	1.50 (1.20,1.88)	0.0004		
26 Gy	369/5943 (6.2)	1.05 (0.82,1.33)	0.71	0.0018	
Breast induration (tumour bed)*					1.00 (0.96,1.04);
40 Gy	185/5713 (3.2)	1			0.95
27 Gy	304/5948 (5.1)	1.56 (1.19,2.05)	0.0013		
26 Gy	236/5937 (4.0)	1.19 (0.90,1.59)	0.23	0.047	
Breast induration (outside tumour bed)*					0.96 (0.90,1.02);
40 Gy	45/5712 (0.8)	1			0.17
27 Gy	137/5943 (2.3)	2.79 (1.74,4.50)	<0.0001		
26 Gy	97/5930 (1.6)	1.90 (1.15,3.14)	0.013	0.059	
Telangiectasia+					1.21 (1.14,1.29);
40 Gy	63/6087 (1.0)	1			<0.0001
27 Gy	100/6272 (1.6)	1.68 (1.07,2.65)	0.025		
26 Gy	102/6300 (1.6)	1.53 (0.96,2.43)	0.070	0.65	

Normal tissue effect	No. moderate/marked events / total no. of assessments over follow-up (%)	Odds ratio for schedule[2] (95%CI)	Comparison with 40 Gy; p-value[3]	Comparison between 27 Gy & 26 Gy; p-value[3]	Odds ratio for years of follow-up (95%CI); p-value[3]
Breast / chest wall oedema+					0.73 (0.69,0.78);
40 Gy	89/6097 (1.5)	1			<0.0001
27 Gy	217/6287 (3.4)	2.18 (1.57,3.03)	<0.0001		
26 Gy	155/6318 (2.4)	1.47 (1.03,2.09)	0.032	0.0097	
Breast / chest wall discomfort+					0.93 (0.89,0.97);
40 Gy	234/6086 (3.8)	1			0.0003
27 Gy	269/6285 (4.3)	1.10 (0.86,1.40)	0.44		
26 Gy	250/6309 (4.0)	0.98 (0.76,1.26)	0.86	0.35	

[1] Any AE in breast includes shrinkage, induration, telangiectasia, oedema; [2] OR estimated from GEE model including all follow-up data, and represents relative odds of moderate/marked AE (versus none/mild) for each pairwise comparison of fractionation schedules across all follow-up assessments; [3] p-value from Wald test. * BCS and mastectomy patients; + BCS patients and mastectomy patients with reconstruction

Table 5: Longitudinal analysis of moderate/marked patient-assessed late normal tissue effects from baseline to 5 years for 1774 patients with at least one completed questionnaire

Normal tissue effect	No. patients reporting moderate / marked event at baseline / total (%)	No. moderate/marked events / total no. of assessments over 3-60 months follow-up (%)	Odds ratio for schedule[2] (95%CI)	Comparison with 40 Gy; p-value[3]	Comparison between 27 Gy & 26 Gy; p-value[3]	Odds ratio for years of follow-up (95%CI); p-value[3]
Protocol-specific items						
Breast appearance changed						1.03 (1.01, 1.05); 0.0010
40 Gy	170/573 (29.7)	778/2480 (31.4)	1			
27 Gy	177/583 (30.4)	929/2550 (36.4)	1.22 (1.02, 1.46)	0.033		
26 Gy	155/581 (26.7)	770/2563 (30.0)	0.91 (0.75, 1.10)	0.33	0.0018	
Breast smaller						1.11 (1.09, 1.13); <0.0001
40 Gy	96/560 (17.1)	585/2445 (23.9)	1			
27 Gy	106/576 (18.4)	606/2520 (24.0)	1.05 (0.85, 1.29)	0.67		
26 Gy	90/574 (15.7)	515/2542 (20.3)	0.81 (0.65, 1.00)	0.053	0.017	
Breast harder/firmer						0.95 (0.93, 0.97); <0.0001
40 Gy	94/558 (16.8)	499/2446 (20.4)	1			
27 Gy	105/572 (18.4)	690/2512 (27.5)	1.42 (1.17, 1.72)	0.0003		
26 Gy	95/566 (16.8)	626/2534 (24.7)	1.22 (1.00, 1.48)	0.048	0.1007	
Skin appearance changed						0.96 (0.93, 0.99); 0.0080
40 Gy	78/577 (13.5)	345/2505 (13.8)	1			
27 Gy	61/586 (10.4)	392/2571 (15.2)	1.03 (0.83, 1.28)	0.77		
26 Gy	67/580 (11.5)	338/2576 (13.1)	0.90 (0.72, 1.13)	0.37	0.23	
EORTC QLQ-BR23 items						
Breast pain						0.96 (0.94, 0.99); 0.011
40 Gy	53/583 (9.1)	338/2538 (13.3)	1			
27 Gy	42/590 (7.1)	428/2601 (16.5)	1.23 (0.98, 1.54)	0.068		
26 Gy	53/588 (9.0)	417/2597 (16.1)	1.23 (0.98, 1.53)	0.074	0.96	

Normal tissue effect	No. patients reporting moderate / marked event at baseline / total (%)	No. moderate/marked events / total no. of assessments over 3-60 months follow-up (%)	Odds ratio for schedule[2] (95%CI)	Comparison with 40 Gy; p-value[3]	Comparison between 27 Gy & 26 Gy; p-value[3]	Odds ratio for years of follow-up (95%CI); p-value[3]
Breast swollen						0.84 (0.80, 0.89);
40 Gy	56/583 (9.6)	122/2538 (4.8)	1			<0.0001
27 Gy	43/589 (7.3)	236/2597 (9.1)	1.46 (1.10, 1.94)	0.0080		
26 Gy	47/589 (8.0)	192/2599 (7.4)	1.27 (0.95, 1.69)	0.11	0.22	
Breast oversensitive						0.96 (0.93, 0.99);
40 Gy	57/579 (9.8)	283/2528 (11.2)	1			0.0097
27 Gy	42/584 (7.2)	334/2596 (12.9)	1.10 (0.87, 1.40)	0.43		
26 Gy	62/586 (10.6)	319/2587 (12.3)	1.11 (0.88, 1.41)	0.37	0.91	
Skin problems in breast						0.96 (0.92, 1.01);
40 Gy	26/582 (4.5)	156/2539 (6.1)	1			0.11
27 Gy	24/290 (4.1)	209/2596 (8.0)	1.25 (0.95, 1.65)	0.11		
26 Gy	18/590 (3.0)	164/2592 (6.3)	0.98 (0.73, 1.31)	0.90	0.084	
Arm / shoulder pain						1.00 (0.97, 1.03);
40 Gy	66/582 (11.3)	401/2537 (15.8)	1			>0.99
27 Gy	78/591 (13..2)	441/2601 (17.0)	1.12 (0.91, 1.37)	0.29		
26 Gy	81/589 (13.7)	455/2599 (17.5)	1.14 (0.93, 1.40)	0.2006	0.83	
Arm / hand swollen						1.06 (1.00, 1.11);
40 Gy	24/582 (4.1)	101/2536 (4.0)	1			0.031
27 Gy	17/588 (2.9)	103/2600 (4.0)	0.95 (0.66, 1.36)	0.77		
26 Gy	22/590 (3.7)	124/2592 (4.8)	1.14 (0.80, 1.62)	0.46	0.31	
Difficulty raising arm						1.04 (0.99, 1.08);
40 Gy	27/582 (4.6)	171/2533 (6.7)	1			0.089
27 Gy	36/589 (6.1)	209/2599 (8.0)	1.24 (0.94, 1.63)	0.12		

Normal tissue effect	No. patients reporting moderate / marked event at baseline / total (%)	No. moderate/marked events / total no. of assessments over 3-60 months follow-up (%)	Odds ratio for schedule[2] (95%CI)	Comparison with 40 Gy; p-value[3]	Comparison between 27 Gy & 26 Gy; p-value[3]	Odds ratio for years of follow-up (95%CI); p-value[3]
26 Gy	37/587 (6.3)	188/2596 (7.2)	1.12 (0.85, 1.48)	0.42	0.46	

[2] OR estimated from GEE model including all questionnaires (baseline to 5 years), and represents relative odds of moderate/marked AE (versus none/mild) for each pairwise comparison of fractionation schedules across all questionnaires; [3] p-value from Wald test

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