One versus three weeks hypofractionated whole breast radiotherapy for early breast cancer treatment: the FAST-Forward phase III RCT

Adrian Murray Brunt,[1,2*] Joanne S Haviland,[2] Duncan A Wheatley,[3] Mark A Sydenham,[2] David J Bloomfield,[4] Charlie Chan,[5] Suzy Cleator,[6] Charlotte E Coles,[7] Ellen Donovan,[8] Helen Fleming,[9] David Glynn,[10] Andrew Goodman,[11] Susan Griffin,[10] Penelope Hopwood,[2] Anna M Kirby,[12] Cliona C Kirwan,[13] Zohal Nabi,[14] Jaymini Patel,[2] Elinor Sawyer,[15] Navita Somaiah,[12] Isabel Syndikus,[16] Karen Venables,[14] John R Yarnold[12] and Judith M Bliss[2] on behalf of the FAST-Forward Trial Management Group

[1]School of Medicine, University of Keele and University Hospitals of North Midlands, Staffordshire, UK
[2]Clinical Trials and Statistics Unit (ICR-CTSU), The Institute of Cancer Research, London, UK
[3]Department of Oncology, Royal Cornwall Hospital NHS Trust, Truro, UK
[4]Sussex Cancer Centre, Brighton and Sussex University Hospitals, Brighton, UK
[5]Women's Health Clinic, Nuffield Health Cheltenham Hospital, Cheltenham, UK
[6]Department of Oncology, Imperial Healthcare NHS Trust, London, UK
[7]Department of Oncology, University of Cambridge, Cambridge, UK
[8]Centre for Vision, Speech and Signal Processing, University of Surrey, Guildford, UK
[9]Clinical and Translational Radiotherapy Research Group, National Cancer Research Institute, London, UK
[10]Centre for Health Economics, University of York, York, UK
[11]Oncology Unit, Torbay Hospital, Devon, UK
[12]Department of Radiotherapy, The Royal Marsden NHS Foundation Trust, Sutton, UK and Division of Radiotherapy and Imaging, The Institute of Cancer Research, London, UK
[13]Division of Cancer Sciences, University of Manchester, Manchester, UK
[14]RTQQA, Mount Vernon Cancer Centre, Middlesex, UK
[15]Comprehensive Cancer Centre, King's College London, London, UK
[16]Clatterbridge Cancer Centre, Clatterbridge Hospital NHS Trust, Cheshire, UK

[*]Corresponding author m.brunt@keele.ac.uk and fastforward-icrctsu@icr.ac.uk

Declared competing interests of authors

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Scientific summary

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Scientific summary

Background

Breast cancer is the most common malignancy in women and the second leading cause of cancer death. After a diagnosis of early breast cancer, a combination of treatments is planned by a multidisciplinary team. This usually involves surgery to remove the cancer with additional radiotherapy (RT) and systemic therapies tailored to the stage and biology of the cancer, and to the individual patient's characteristics and wishes.

Meta-analyses confirm that RT after surgery for early breast cancer reduces local cancer relapse and breast cancer deaths. Randomised controlled trials involving over 8000 patients with long-term follow-up confirmed that hypofractionated RT [fewer larger fractions (Fr; daily doses)] can be at least as safe and effective as the historic standard of 50 Gray (Gy) in 25 fractions (5 weeks) if a lower total dose is used. The UK START trials contribute much of the global data for moderate hypofractionation. START-A maintained the 5-week treatment time across all randomised groups and included two doses of a 13-fraction regimen, enabling the investigators to make unconfounded estimates of the sensitivity to fraction size. START-B tested 40 Gy in 15 fractions over 3 weeks against 50 Gy in 25 fractions over 5 weeks. Five- and ten-year results for local tumour control and late-occurring normal tissue effects (NTE) assessed by patients, clinicians and from photographs were consistent with the hypothesis that breast cancer tissue and the dose-limiting normal tissues are similarly sensitive to fraction size.

The START trials had a large effect on breast cancer RT practice in the UK and worldwide. A 15-fraction schedule has been the UK standard-of-care recommended by the National Institute for Health and Care Excellence since 2009, but was thought unlikely to represent the useful limits of hypofractionation for whole breast RT.

The UK FAST trial compared 28.5 Gy in 5 fractions of 5.7 Gy or 30 Gy in 5 fractions of 6 Gy, both delivered once weekly over 5 weeks, to 50 Gy in 25 fractions. The first results of the FAST trial, subsequently confirmed with the 10-year results, identified a 5-fraction schedule estimated to be radiobiologically equivalent to the 25-fraction standard in terms of late NTE. This gave impetus to the investigation of 1-week 5-fraction schedules in the phase III FAST-Forward Trial.

Objectives

Main Trial: to identify a 5-fraction schedule of curative RT delivered in once-daily fractions (1 week) that is at least as effective and safe as the current UK standard 15-fraction (3-week) regimen after primary surgery for early breast cancer, in terms of local tumour control, adverse effects, patient-reported outcomes (PRO) and health economic (HE) consequences.

Nodal Sub-Study: to show that a 5-fraction schedule of adjuvant RT to level I–III axilla and/or level IV axilla [supraclavicular fossa (SCF)] is non-inferior to a 15-fraction standard in terms of patient-reported arm swelling and function, and to contribute additional information to the endpoints of the Main Trial.

Methods

FAST-Forward is a UK-wide phase III randomised non-inferiority trial testing two 1-week schedules against the 3-week regimen. Patients with early breast cancer requiring adjuvant RT were randomly

allocated (1 : 1 : 1) to 40 Gy in 15 fractions over 3 weeks, 27 Gy or 26 Gy in 5 fractions over 1 week to the whole breast or chest wall (Main Trial) plus the regional lymph nodes (Nodal Sub-Study). A sequential tumour bed RT boost to the conserved breast was allowed, with centres required to specify boost intention before randomisation. Primary endpoints were local relapse (Main Trial) and patient-reported arm/hand swelling (Nodal Sub-Study). Secondary endpoints were late NTE assessed by patients and clinicians, cancer and survival outcomes.

The Main Trial target sample size was 4000 patients, providing 80% power (one-sided α = 0.025) to exclude an absolute increase of 1.6% in 5-year ipsilateral breast tumour relapse (IBTR) incidence for a 5-fraction schedule compared with control, assuming 2% 5-year incidence in the 40 Gy group.

Eligibility for the Main Trial was patients with complete microscopic resection of early invasive breast cancer, following breast conservation surgery or mastectomy, prescribed local RT. Inclusion criteria was age ≥ 18 years, axillary staging and/or dissection, pT1-3 pN0-1 M0 disease, written informed consent, able to comply with follow-up; concurrent anti-human epidermal growth factor receptor-2 (HER-2) therapy and/or endocrine therapies were allowed. Age ≥ 65 years with pT1 G1/2 ER+ve/HER-2−ve pN0 M0 invasive disease was excluded from protocol v2.0 due to the very low risk of local cancer relapse. Exclusions included ipsilateral microinvasive disease and/or non-gradeable tumours, contralateral and/or previous ipsilateral breast cancer, concurrent cytotoxic chemotherapy (sequential neoadjuvant or adjuvant cytotoxic therapy allowed if ≥ 2 weeks between chemotherapy and RT) and RT to any regional lymph node area (excepting lower axilla included in standard tangential fields to breast/chest wall).

The whole breast clinical target volume (CTV) was either determined retrospectively 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; underlying muscle and rib cage excluded. The lymph node CTV included the axillary chain and/or the SCF (level IV axilla) either in entirety or levels specified by the clinician. The treatment plan was optimised with 3D dose compensation to achieve the dose constraints. A comprehensive quality assurance programme involved every RT centre before trial activation and continued throughout trial accrual. The RT planning packs for the Main Trial and Nodal Sub-Study are available from www.icr.ac.uk/fastforward.

Patients were assessed by clinicians for IBTR and late NTE at annual follow-up visits. Late-onset NTE in ipsilateral breast or chest wall (breast distortion, shrinkage, induration and telangiectasia; and breast or chest wall oedema and discomfort) were graded by clinicians on a 4-point scale, interpreted as none, mild, moderate, or marked. Symptomatic rib fracture, symptomatic lung fibrosis, and ischaemic heart disease were recorded.

In the PRO sub-study, questionnaires were administered at baseline (pre-randomisation), 3, 6, 12, 24 and 60 months. Patient assessments used a 4-point ordinal scale, as for the clinical assessments. In the photographic sub-study, photographs were taken at baseline (pre-RT), 2 and 5 years after RT and scored on a 3-point ordinal scale.

In the acute toxicity sub-study, patients were assessed pre-treatment, then weekly for 6 weeks, or longer if there was higher than grade 1 toxicity still present. Two acute toxicity studies were performed; in the first study the scoring system included oedema, which is usually related to recent surgery, and also included patients with a boost. A second study was done without these confounding issues to more accurately assess the acute toxicity of the 1-week schedules compared with the 3-weekly standard. Acute reactions of the treated breast skin were graded using Radiation Therapy Oncology Group (RTOG) criteria for the first sub-study and standard common toxicity criteria for adverse effects (CTCAE) criteria for the second.

The Nodal Sub-Study inclusion criteria required pT1-3 pN1-3a M0 disease and histological involvement of axillary lymph nodes with an indication for RT to level I-III axilla and/or level IV axilla. From 2018 the

Nodal Sub-Study design was amended to a 2-group trial, with no further randomisation to Test Group 1 (27 Gy). All patients in the Nodal Sub-Study were asked to consent to the PRO sub-study and photographic assessments. The following additional PRO were included in the Nodal Sub-Study: shoulder stiffness, upper limb pain, sensorimotor symptoms and arm function.

A HE evaluation was conducted to assess the cost-effectiveness of whole breast RT with 26 Gy/5 fractions over 1 week compared with the 3-week schedule of 40 Gy/15 fractions.

We report the 5-year primary analysis of the Main Trial and a descriptive interim analysis of the Nodal Sub-Study up to 3 years' follow-up; formal analysis of the Nodal Sub-Study will await 5 years' follow-up.

Results

Between November 2011 and June 2014, 4110 patients were enrolled in the FAST-Forward Main Trial from 97 UK centres (47 RT and 50 referring centres); 14 patients subsequently withdrew consent. One hundred and ninety patients were recruited into acute toxicity study 1, 161 patients into acute toxicity study 2, 1798 patients into the PRO sub-study, 1737 patients into the photographic assessment sub-study, 3878 patients consented to donate a blood sample and 4077 patients consented to donate their primary tissue sample. Four hundred and sixty-nine patients were recruited to the Nodal Sub-Study. The demographic and clinical characteristics at baseline were well balanced between groups.

In the Main Trial, after a median follow-up of 71.5 months IBTR was recorded in 79 patients (31 in the 40 Gy group, 27 in the 27 Gy group and 21 in the 26 Gy group); hazard ratios (HRs) versus 40 Gy in 15 fractions were 0.86 (95% confidence interval 0.51 to 1.44) for 27 Gy/5 fractions and 0.67 (0.38 to 1.16) for 26 Gy/5 fractions. Estimated 5-year cumulative incidence of IBTR was 2.1% for 40 Gy (expected incidence 2%), 1.7% for 27 Gy and 1.4% for 26 Gy. Estimated absolute differences in IBTR versus 40 Gy were −0.3% (−1.0 to 0.9) for 27 Gy and −0.7% (−1.3 to 0.3) for 26 Gy. As the upper confidence limits excluded an increase in IBTR of 1.6% or more so non-inferiority can be claimed for both 5-fraction schedules compared with 40 Gy/15 fractions.

At least one annual clinical assessment of NTE was available in the Main Trial for 3975 (97.0%) of 4096 patients. At 5 years, any moderate or marked clinician-assessed NTE in the breast or chest wall was reported for 98 of 986 (9.9%) 40 Gy patients, 155 (15.4%) of 1005.27 Gy patients, and 121 of 1020 (11.9%) 26 Gy patients, with a significant difference between 40 Gy and 27 Gy (0.0003) but not between 40 Gy and 26 Gy (p = 0·17). Breast shrinkage was the most prevalent moderate or marked effect at 5 years, reported in 50 (5.5%) of 916.40 Gy patients, 78 (8.2%) of 948.27 Gy patients, and 65 (6.8%) of 954.26 Gy patients. Longitudinal analysis of all annual clinical assessments of NTE over follow-up showed a significantly increased risk of any moderate or marked effect in the breast or chest wall for the 27 Gy group compared with 40 Gy with no significant difference between 26 and 40 Gy. Comparing the two 5-fraction schedules, 26 Gy had significantly lower risk of any moderate or marked breast or chest wall NTE and breast shrinkage compared with 27 Gy. Estimates of 5-year cumulative incidence of any moderate or marked clinician-assessed NTE in the breast or chest wall were 26.8% for 40 Gy, 35.1% for 27 Gy and 28.5% for 26 Gy.

Retrospective subgroup analyses in the Main Trial comparing IBTR in 26 Gy versus 40 Gy provide no evidence of a differential effect according to age, grade, pathological tumour size, nodal status, tumour bed boost, treatment with adjuvant chemotherapy, HER-2 status or in triple-negative patients. Confidence intervals for the HR overlap for the subgroups, although the number of events in these analyses was small, hence results should be interpreted with caution as the statistical power is low. Subgroup analysis in the Main Trial according to type of primary surgery was not possible as there was only one IBTR event post-mastectomy in a control group patient (out of 91) and none in the 173 patients treated with 5 fractions.

The two acute toxicity sub-studies comprised a total of 350 patients. Incidence of grade 3+ acute skin toxicity according to RTOG criteria was 14% for 40 Gy/15 fractions, 10% for 27 Gy/5 fractions, and 6% for 26 Gy/5 fractions in sub-study 1. For sub-study 2, acute toxicity grade 3+ according to CTCAE was 0%, 2.4% and 0%, respectively. Grade 2 toxicity was more common in 40 Gy/15 fractions compared with the two 5-fraction schedules.

Four hundred and sixty-nine patients from 28 RT and 22 referral centres (183 for 40 Gy/15 fractions, 104 for 27 Gy/5 fractions and 182 for 26 Gy/5 fractions) were entered into the Nodal Sub-Study. Compared with the Main Trial, as expected more patients had higher-grade disease and nearly half had a mastectomy. Axillary clearance was performed in around 50% of patients, with the remainder having some form of nodal sampling. At this interim review at 2 years patients reported moderate or marked hand/arm swelling in 10% (40 Gy), 7% (26 Gy) and 13% (27 Gy). Prevalence of clinician-assessed lymphodema at 3 years was 8% (40 Gy), 12% (26 Gy) and 11% (27 Gy).

In the cost-effectiveness work the base case analysis, mean costs and quality-adjusted life-years (QALYs) for 40 Gy/15 fractions were £31,640 and 11.08 QALYs; for 26 Gy/5 fractions these were £29,638 and 11.12 QALYs. Therefore the 26 Gy/5 fractions regimen was expected to dominate with expected cost savings of £2002 (95% interval £1245 to £2804) and higher expected QALYs: 0.04 (95% interval −0.01 to 0.09). Across simulations there was a 99.9% chance that 26 Gy/5 fractions either dominated 40 Gy/15 fractions or had an incremental cost-effectiveness ratio below £15,000/QALY.

Conclusion

The 26 Gy/5 fractions 1-week schedule is non-inferior to 40 Gy/15 fractions over 3 weeks for IBTR. The 26 Gy dose level is comparable to 40 Gy/15 fractions in terms of NTE assessed by patients, clinicians and from photographs, and is comparable to NTE expected after 46–48 Gy in 2 Gy fractions. The 27 Gy/5 fractions regimen was non-inferior for IBTR but had statistically significantly higher levels of many late NTE compared with the 40 and 26 Gy schedules, with late NTE rates of comparable magnitude to 50 Gy/25 fractions, the historic standard schedule.

Acute skin reactions reported within the trial are low, whichever regimen is used. Prevalence rates suggest that erythema after the 1-week schedule came on slightly quicker, is less intense and settles about 2 weeks earlier than after the 3-week schedule although no formal statistical analysis of this was performed. The mildness of the acute skin toxicity associated with the 5-fraction regimens was expected.

Interim results from the Nodal Sub-Study at 2–3 years' follow-up indicate no cause for concern of an excess in NTE for 26 Gy/5 fractions compared with 40 Gy/15 fractions.

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. Beyond its safety and effectiveness, the 26 Gy/5 fractions schedule is convenient and less expensive for patients and for health services. The 26 Gy/5 fractions schedule reduces the estimated healthcare fiscal cost of breast RT by over 50%. The 5-fraction regimen reduces the machine time required for breast RT patients, thus improving patient access for other groups of cancer patients within the NHS.

Study registrations

FAST-Forward is registered at www.isrctn.com, ISRCTN19906132. The Main Trial is published in *Lancet* 2020;**395**:1613–26. See the NIHR Journals Library website for further project information.

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