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

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GLOSSARY OF ABBREVIATIONS

ΔAE – Difference in Adverse Event

AE – Adverse Effects/Event

ASTRO – American Society for Radiation Oncology

BCS – Breast Conservation Surgery

BIS – Body Image Scale

CI – Confidence Interval or Chief Investigator

CIN – Cervical Intra-epithelial Neoplasia

CONSORT – Consolidated Standards of Reporting Trials

PH – Proportional Hazards

CRF – Case Report Form

CT – Computerised Tomography

CTCAE – Common Toxicity Criteria for Adverse Effects

CTV – Clinical target volume

DCIS – Ductal Carcinoma In Situ

EORTC – European Organisation for Research and Treatment of Cancer

EQ-5D-5L – EuroQol 5D-5L

EQD2 – Equivalent Dose in 2 Gy fractions

ER – Estrogen Receptor

Fr – Fraction

GEE – General Estimating Equations

GI COPD – Gastro-Intestinal Chronic Obstructive Pulmonary Disease

Gy – Gray (units)

HER2 – Human Epidermal Growth Factor Receptor 2

HR – Hazard Ratio

IBTR – Ipsilateral Breast Tumour Relapse

ICR-CTSU – The Institute of Cancer Research Clinical Trials and Statistics Unit

IDMC – Independent Data Monitoring Committee

IMC – Internal Mammary Chain

IQR – Inter Quartile Range

KM – Kaplan Meier

NCRI – National Cancer Research Institute

NICE – National Institute for Clinical Excellence

NIHR HTA - National Institute for Health Research Health Technology Assessment Programme

NTE – Normal Tissue Effects

OCOG – Ontario Clinical Oncology Group

OR – Odds Ratio

PPI – Patient and Public Involvement

PR – Progesterone Receptor

PRO – Patient Reported Outcome

PTV – Planning Target Volume

RT – Radiotherapy

RTOG – Radiation Therapy Oncology Group

RT QA – Radiotherapy Quality Assurance

RTTQA – Radiotherapy Trials Quality Assurance

SCF – supraclavicular fossa

TMG – Trial Management Group

TSC - Trial Steering Committee

ABSTRACT

Background

FAST-Forward aimed to identify a 5-fraction schedule of adjuvant radiotherapy delivered in 1 week that was non-inferior in terms of local cancer control and as safe as the standard 15-fraction regimen after primary surgery for early breast cancer. Published acute toxicity and 5-year results are presented here with other aspects of the trial.

Design

Multi-centre phase III non-inferiority trial. Patients with invasive carcinoma of the breast (pT1-3pN0-1M0) after breast conservation surgery or mastectomy randomised (1:1:1) to 40Gy in 15 fractions (3 weeks), 27Gy or 26Gy in 5 fractions (1 week) whole breast/chest wall (Main Trial). Primary endpoint was ipsilateral breast tumour relapse (IBTR); assuming 2% 5-year incidence for 40Gy, non-inferiority pre-defined as <1.6% excess for 5-fraction schedules (critical hazard ratio HR=1.81). Normal tissue effects (NTE) were assessed independently by clinicians, patients and photographs.

Sub-studies

Two acute skin toxicity sub-studies were undertaken to confirm safety of the test schedules. Primary endpoint was proportion of patients with grade ≥3 acute breast skin toxicity any time from the start of radiotherapy to 4 weeks after completion.

Nodal sub-study patients had breast/chest wall plus axillary radiotherapy testing the same three schedules, reduced to the 40Gy and 26Gy groups on amendment, with the primary endpoint of 5-year patient-reported arm/hand swelling.

Limitations

A sequential hypofractionated or simultaneous integrated boost has not been studied.

Participants

97 UK centres recruited 4096 patients (1361 40Gy, 1367 27Gy, 1368 26Gy) into the Main Trial November 2011-June 2014. The Nodal Sub-Study recruited an additional 469 patients from 50 UK centres. 190 and 162 Main Trial patients were included in the acute toxicity sub-studies.

Results

Acute toxicity sub-studies evaluable patients: 1) acute grade 3 RTOG toxicity reported in 40Gy/15Fr 6/44 (13.6%); 27Gy/5Fr 5/51 (9.8%); 26Gy/5Fr 3/52 (5.8%). 2) grade 3 CTCAE toxicity reported for one patient.

At 71 months median follow-up in the Main Trial, 79 IBTR events (40Gy:31, 27Gy:27, 26Gy:21); HRs (95%CI) versus 40Gy were 27Gy:0.86 (0.51,1.44), 26Gy:0.67 (0.38,1.16). With 2.1% (1.4,3.1) 5-year incidence IBTR after 40Gy, estimated absolute differences versus 40Gy (non-inferiority test) were -0.3% (-1.0,0.9) for 27Gy (p=0.0022) and -0.7% (-1.3,0.3) for 26Gy (p=0.00019).

5-year prevalence of any clinician-assessed moderate/marked breast NTE was 40Gy:98/986 (9.9%), 27Gy:155/1005 (15.4%), 26Gy:121/1020 (11.9%). Across all clinician assessments from 1-5 years, odds ratios versus 40Gy were 1.55 (1.32,1.83,p<0.0001) for 27Gy and 1.12 (0.94,1.34,p=0.20) for 26Gy. Patient and photographic assessments showed higher NTE risk for 27Gy versus 40Gy but not for 26Gy.

Nodal Sub-Study reported no arm/hand swelling in 80% and 77% in 40Gy and 26Gy at baseline, and 73% and 76% at 24 months. The prevalence of moderate/marked arm/hand swelling at 24 months was 10% versus 7% for 40Gy compared with 26Gy.

Interpretation

5-year local tumour incidence and NTE prevalence show 26Gy in 5 fractions in 1 week is a safe and effective alternative to 40Gy in 15 fractions for patients prescribed adjuvant local radiotherapy after primary surgery for early-stage breast cancer.

Future Work

10-year Main Trial follow-up essential. Inclusion in hypofractionation meta-analysis on-going. A future hypofractionated boost trial strongly supported.

Trial Registration

FAST-Forward was sponsored by The Institute of Cancer Research and was registered as ISRCTN19906132.

Trial Funding

The FAST-Forward trial was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme 09/01/47

PLAIN ENGLISH SUMMARY

Patients diagnosed with early breast cancer are often recommended to have radiotherapy after surgery because research has shown that it lowers the risk of the cancer returning. However, it may cause some short- and long-term side-effects. Previous clinical trials showed that the same, or even better, outcomes with a lower total dose of radiotherapy given in fewer, larger daily doses compared with older historical treatment schedules. The NIHR HTA-funded FAST-Forward trial aimed to see whether the number of doses could be reduced further without reducing the beneficial effects of radiotherapy.

Between November 2011 and June 2014, 4096 patients agreed to take part in the FAST-Forward Main Trial testing 3 schedules of radiotherapy to the breast. Standard treatment given on 15 days over 3 weeks (Control Group) was compared with 2 different lower dose schedules where treatment was given on 5 days over 1 week (lower dose Test Groups). An additional 469 patients entered a sub-study where the gland area under the arm also received radiotherapy (Nodal Sub-Study).

Main Trial 5-year results reported in April 2020 showed that the number of patients whose cancer had returned in the treated breast was low in all groups: around 2 in 100 (2.1%) for the Control Group, and 1.7% in the higher dose and 1.4% in the lower dose Test Groups. The majority of reported side-effects assessed by patients and doctors up to 5 years after radiotherapy were mild for all treatment groups. Patients in the Control Group and in the lower dose Test Group experienced similar levels of side-effects. More side-effects were reported in the higher dose Test Group, although differences were small.

Overall, the FAST-Forward findings suggest that the lower dose 1-week schedule gave similar results in terms of the cancer returning and side-effects to the standard 3-week treatment and this schedule can now be used to help treat future patients.

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 25Fr (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 15Fr over 3 weeks against 50 Gy in 25Fr over 5 weeks. 5- and 10-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 Clinical 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 5Fr of 5.7 Gy or 30 Gy in 5Fr of 6 Gy, both delivered once weekly over 5 weeks, to 50 Gy in 25Fr. 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 15Fr over 3 weeks, 27 Gy or 26 Gy in 5Fr 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 & clinicians, cancer & survival outcomes.

The Main Trial target sample size was 4000 patients, providing 80% power (one-sided $\alpha=0\cdot025$) to exclude an absolute increase of $1\cdot6\%$ 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-HER2 therapy and/or endocrine therapies were allowed. Age ≥65 years with pT1 G1/2 ER+ve / HER2-ve pN0 M0 invasive disease was excluded from protocol v2.0 due 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 radiotherapy) 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 clinical target volumes 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 https://www.icr.ac.uk/fastforward.

Patients were assessed by clinicians for ipsilateral breast tumour relapse 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 four-point scale, interpreted as none, mild, moderate, or marked. Symptomatic rib fracture, symptomatic lung fibrosis, and ischaemic heart disease were recorded.

In the patient reported outcome (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 one-week schedules compared with the three-weekly standard. Acute reactions of the treated breast skin were graded using RTOG criteria for the first sub-study and standard 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 health economic evaluation was conducted to assess the cost-effectiveness of whole breast RT with 26 Gy/5Fr over one week compared with the 3-week schedule of 40 Gy/15Fr.

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. 190 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. 469 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 (HR) versus 40 Gy in 15 fractions were 0·86 (95% CI 0·51 to 1·44) for 27 Gy/5Fr and 0·67 (0·38 to 1·16) for 26 Gy/5Fr. Estimated 5-year cumulative incidence of ipsilateral breast tumour relapse 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 five-fraction schedules compared with 40 Gy/15Fr.

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 Gy and 40 Gy. Comparing the two five-fraction schedules, 26 Gy had significantly lower risk of any moderate or marked breast or chest wall normal tissue effects 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, HER2 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 1 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/15Fr, 10% for 27 Gy/5r, and 6% for 26 Gy/5Fr 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/15Fr compared with the two 5-fraction schedules.

469 patients from 28 RT and 22 referral centres (183 for 40 Gy/15Fr, 104 for 27 Gy/5Fr and 182 for 26 Gy/5Fr) 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/15Fr were £31,640 and 11.08 QALYs; for 26 Gy/5Fr these were £29,638 and 11.12 QALYs. Therefore the 26 Gy/5Fr regimen was expected to dominate with expected cost savings of £2,002 (95% interval £1,245 to £2,804) and higher expected QALYs: 0.04 (95% interval -0.01 to 0.09). Across simulations there was a 99.9% chance that 26 Gy/5Fr either dominated 40 Gy/15Fr or had an incremental cost effectiveness ratio below £15,000/QALY.

Conclusion

The 26 Gy/5Fr 1-week schedule is non-inferior to 40 Gy/15Fr over 3 weeks for IBTR. The 26 Gy dose level is comparable to 40 Gy/15Fr 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/5Fr regimen was non-inferior for IBTR but had statistically significantly higher levels of many late NTE compared with the 40 Gy and 26 Gy schedules, with late NTE rates of comparable magnitude to 50 Gy/25Fr, 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/5Fr compared with 40 Gy/15Fr.

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

Funding details

Study registrations

FAST-Forward is registered at https://www.isrctn.com, ISRCTN19906132. The Main Trial is published in The Lancet 2020;395:1613-1626. See the NIHR Journals Library website for further project information.

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CHAPTER 1: INTRODUCTION

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Background

Breast cancer and the multidisciplinary team

Breast cancer is globally the most commonly occurring cancer in women with over 2 million new cases in 2018, including 58,000 in the UK. It is rare in men, with around 300-400 cases per year in the UK. Since the early 1990s, breast cancer incidence rates in females have increased by around a quarter (24%) [5]. Despite increased incidence, UK mortality rates from breast cancer have fallen, due to advances in all aspects of breast cancer diagnosis and treatment, including radiotherapy.

Breast cancer usually presents as symptoms such as a lump, nipple changes or a finding of an abnormal mammogram. Patients are generally assessed in a specific Breast clinic where they have a triple assessment involving clinical assessment, imaging (mammography/ ultrasound) and a biopsy. A plan for treatment is then made in a multidisciplinary meeting which nearly always involves surgery to resect the cancer. In the modern era this is a wide local excision (breast conserving therapy), or a mastectomy, along with nodal surgery. The resected tissue is examined by a pathologist to determine the size, grade, type, receptor profile and resection margins of the cancer along with other features. The lymph nodes may be selectively sampled (sentinel node biopsy) or all removed if involved (axillary clearance).

In larger, or more biologically aggressive cancers (triple negative and HER-2 positive) chemotherapy is now often given prior to surgery to downstage the cancer in the breast and the

axilla, and to assess response to therapy, which may well alter subsequent treatment, including surgery, post-operative drug therapy and radiotherapy. Similarly in larger hormone receptor positive HER-2 negative cancers, upfront antihormonal therapy may be given with similar intent. However surgery is still used after the neoadjuvant therapy to remove any remaining cancer and to assess residual cancer burden.

Benefits and adverse effects of radiotherapy for patients with breast cancer

Radiotherapy uses high energy x-rays to destroy cancer cells remaining in the breast after the main lump has been removed. Many studies have shown that this treatment substantially reduces the risk of the cancer recurring in the breast and or lymph glands and improves overall survival. A meta-analysis from the Early Breast Cancer Trials Collaborative Group (EBCTCG) showed that after breast-conserving surgery, radiotherapy reduces relapse and breast cancer death [6]. Increased risk of local relapse is associated with age under 50 years and grade 3 cancers. Other risk factors include cancer size, cancer biology, negative hormonal receptor status, HER-2 positive status, the presence of lymphovascular invasion and axillary node involvement. The absolute benefits of radiotherapy are greatest in those with the highest risk factors. The EBCTCG meta-analysis included individual patient data for 10,801 women in 17 randomised trials of radiotherapy versus no radiotherapy after breast-conserving surgery, 8337 of whom had pathologically confirmed node-negative (pN0) or node-positive (pN+) disease. Overall, radiotherapy reduced the 10-year risk of any (i.e., locoregional or distant) first relapse from 35·0% to 19·3% (absolute reduction 15·7%, 95% CI 13·7–17·7, 2p<0·00001) and reduced the 15-year risk of breast cancer death from 25·2% to 21·4% (absolute reduction 3·8%, 1·6–6·0, 2p=0·00005). In women with pN0 disease (n=7287), radiotherapy reduced the first relapse risk from 31·0% to 15·6% (absolute relapse reduction 15·4%, 13·2–17·6, 2p<0·00001) and risk of breast cancer death from 20·5% to 17·2% (absolute mortality reduction 3·3%, 0·8–5·8, 2p=0·005), respectively. In these women with pN0 disease, the absolute relapse reduction varied according to age, grade, oestrogen-receptor status, tamoxifen use and the extent of surgery. These characteristics were used to predict large (≥20%), intermediate (10–19%), or lower (<10%) absolute reductions in the 10-year relapse risk. The absolute reductions in 15-year risk of breast cancer death in these three prediction categories were 7·8% (95% CI 3·1–12·5), 1·1% (–2·0 to 4·2), and 0·1% (–7·5 to 7·7) respectively (trend in absolute mortality reduction 2p=0·03). In the smaller number of women with pN+ disease (n=1050), radiotherapy reduced the 10-year relapse risk from 63·7% to 42·5% (absolute reduction 21·2%, 95% CI 14·5–27·9, 2p<0·00001) and the 15-year risk of breast cancer death from 51·3% to 42·8% (absolute reduction 8·5%, 1·8–15·2, 2p=0·01). Overall, about one breast cancer death was avoided by year 15 for every four relapses avoided by year 10. The mortality reduction did not differ significantly from this overall relationship in any of the three prediction categories for pN0 disease or for pN+ disease.

Stepwise improvements in many aspects of patient management have led to a steady reduction in the absolute risk of relapse and death for patients over the decades. This reduction is due to many factors such as improved screening, better surgery with closer adherence to guidelines on achieving negative margins and advances in systemic therapy and radiotherapy techniques. A local relapse risk of around 2% at 5 years is a reasonable target to aim for in the current era, although the absolute risk will be higher in younger patients with grade 3 tumours and may be lower in elderly patients with grade 1 tumours. Currently patients at extremely low-risk of relapse following surgery, are commonly recommended no adjuvant radiotherapy based on studies such as PRIME [7].

The absolute benefit of radiotherapy for each patient are considered by the multidisciplinary team based on the biological and pathological staging of the tumour, type of surgery, and patient factors, including age and comorbidities. The main short-term side-effects of radiotherapy are tiredness, skin colour changes, discomfort and swelling (oedema). Long-term side-effects may develop over many years following radiotherapy and these are thought to be due to damage to the small blood vessels supplying tissue that has been irradiated. Long-term side-effects include the following: (a) Skin changes, where the treatment area appears permanently tanned after treatment has finished, although this is not harmful. Later, the skin might appear to have very tiny broken veins in the skin called telangiectasia. (b) Breast shrinkage or distortion; radiotherapy can make the breast tissue contract so that the breast gradually gets smaller. This can happen to natural breast tissue or a reconstructed breast. An implant in a reconstructed breast can become hard (capsular contracture) and may need replacing. (c) Breast induration, where the breast feels hard and less stretchy; this is due to a side-effect called radiation fibrosis. (d) Cough and breathlessness may occur in some patients who have radiotherapy to the chest area although this is not common. The problems are due to changes in the lung tissue called chronic radiation pneumonitis. They might start many months or a few years after treatment. The chances of this happening increase if the volume of lung irradiated increases, or if the patient has pre-existing lung conditions. (e) Irradiation of the ribs or clavical may lead to radiation osteitis or rarely to osteoradionecrosis which may cause non-healing fractures. (f) Radiotherapy may cause nerve damage in the arm on the treated side, which can develop many years after treatment. Symptoms include tingling, numbness, pain, and weakness, and in some people it may cause some loss of movement in the arm and shoulder. This is extremely rare with modern radiotherapy. (g) Radiotherapy treatment may cause another type of cancer in many years' time. These include lung cancers, especially in smokers, and the rare angiosarcoma.

Partial breast radiotherapy in low relapse risk patient subgroups

Instead of irradiating the whole breast, partial-breast radiotherapy restricted to the region of the original tumour in low relapse risk patients reduces the morbidity of radiotherapy without compromising its ability to cure the cancer. This technique is based on international reports of reductions in local relapse incidence, and the recognition that the majority of ipsilateral local relapses occur close to the region of the index tumour (the so-called tumour bed). Several studies have assessed partial-breast radiotherapy compared with whole-breast radiotherapy [8-12] . Most of them show comparable rates of local control in patients receiving partial-breast radiotherapy compared with whole-breast radiotherapy. However, most of the studies not only compared partial versus whole breast-radiotherapy, but also used differing radiotherapy techniques and doses in the treatment groups, making toxicity comparisons difficult.

IMPORT LOW was a multicentre, randomised, controlled, phase 3, non-inferiority trial comparing the safety and efficacy of standard whole-breast radiotherapy (control, whole-breast group) with experimental schedules of radiotherapy to the whole breast and partial breast (reduced-dose group), and to the partial breast only (partial-breast group) [12]. Patients assigned to whole-breast radiotherapy (control) received 40 Gy in 15 fractions (daily doses) to the whole breast. Those assigned to the reduced-dose group received 36 Gy in 15 fractions to the whole breast and 40 Gy in 15 fractions to the partial breast containing the tumour bed, and those assigned to the partial-breast group received 40 Gy in 15 fractions to the partial breast only. Women who were aged 50 years or older who had breast-conserving surgery for unifocal invasive ductal adenocarcinoma (excluding invasive carcinoma of classical lobular type) of any grade (1–3) were recruited. Other inclusion criteria were pathological tumour size of 3 cm or less (pT1–2), axillary lymph-node negative or one to three positive lymph nodes (pN0–1), and a minimum microscopic margins of non-cancerous tissue of 2 mm or more. A total of 2018 patients were randomly assigned to the three groups, with around 670 patients per group. Patients were clinically assessed yearly for local relapse and toxicity, and around half completed questionnaires included self-assessments of side-effects and health-related quality of life. After a median follow-up of 72·2 months, local relapse had been reported for 18 patients, nine (1%) of whom were in the whole-breast group, three (<1%) in the reduced-dose group, and six (1%) in the partial-breast group. The 5-year estimated cumulative incidence of local relapse was 1·1% (95% CI 0·5–2·3) in the whole-breast group, 0·2% (95% CI 0·02–1·2) in the reduced-dose group, and 0·5% (95% CI 0·2–1·4) in the partial-breast group. At 5 years patients reported fewer moderate or marked normal tissue effects in terms of skin change, change in overall breast appearance, breast being smaller, and breast being harder or firmer to touch in the partial-breast group than in the whole-breast group although this reduction was statistically significant for change in breast appearance only (p<0·0001). At 5 years, change in breast appearance had the highest cumulative incidence of items reported as moderate or marked

by patients in all groups. Reports of breast becoming harder or firmer were significantly reduced in both the reduced-dose group (p=0·002) and partial-breast group (p<0·0001) compared with the whole-breast group. The conclusions from IMPORT LOW were that for patients over 50, with smaller, generally lymph node-negative breast cancer, partial-breast radiotherapy was non-inferior to whole-breast radiotherapy with regards local control and had less toxicity. Reduced-volume breast cancer treatment will also reduce lung and cardiac doses. Follow- up to 10 years is ongoing in the IMPORT LOW trial to collect data on longer-term efficacy and toxicity outcomes.

The control arm in IMPORT LOW was 40 Gy in 15 fractions to whole breast, which has been adopted as the standard of care for partial-breast radiotherapy. The control arm for the FAST-Forward trial was the same. Therefore, if the 40 Gy/15Fr schedule was found to be isoeffective for either of the test arms, then it was deemed that this would also be the same for partial-breast radiotherapy. It would make no biological sense to have different fractionation schedules with reduced-field radiotherapy (partial-breast). For FAST-Forward whole-breast radiotherapy was still the standard-of-care when the study was conceived and recruiting.

Simplifying radiotherapy dose schedules for patients with breast cancer

For many years, and still in some countries, the international standard regimen for whole-breast radiotherapy delivers a total dose of 50 Gy in 25 fractions over 5 weeks following surgical resection of primary tumour in women with early breast cancer. Attempts to reduce the number of fractions in the 1970s made inadequate downward adjustments to total dose, resulting in unacceptable rates of late complications [13]. These miscalculations inhibited further research in breast radiotherapy fractionation for decades, but interest in fewer larger fractions delivered over a shorter overall treatment time has been rekindled by randomised clinical trials based on a better understanding of normal tissue and tumour responses (radio-biology). Fractionation sensitivity describes responses of normal and malignant tissues to radiotherapy fraction size and is quantified in terms of the α/β ratio, expressed in Gy. The lower the α/β ratio, the greater the effect on normal and malignant tissues of changes in fraction size.

Four randomised trials involving a total of greater than 8000 women have compared a lower total dose in fewer larger fractions against 50 Gy in 25 fractions, and all have reported favourable results in terms of local tumour control and late adverse effects [14-18]. The Royal Marsden Hospital/Gloucestershire Oncology Centre (now sometimes referred to as START-P) and Ontario (OCOG) trials totalling 2644 women with mainly axillary lymph node-negative tumours < 5 cm diameter were the subject of a 2008 Cochrane review of altered radiotherapy fractionation in early breast cancer [19]. Radiotherapy fractions larger than 2.0 Gy did not appear to affect: a) local-relapse free survival (absolute difference 0.4%, 95% CI -1.5% to 2.4%), b) breast appearance (risk

ratio (RR) 1.01, 95% CI 0.88 to 1.17; p = 0.86), c) survival at five years (RR 0.97, 95% CI 0.78 to 1.19; p = 0.75), d) late skin toxicity at five years (RR 0.99, 95% CI 0.44 to 2.22; p = 0.98, or e) late radiation toxicity in subcutaneous tissue (RR 1.0, 95% CI 0.78 to 1.28; p = 0.99). The review concluded that the use of unconventional fractionation regimens did not affect breast appearance or toxicity, nor appear to affect local cancer relapse. The results of the UK START trials (N = 4451) were published too late to be included in the overview but were consistent with the findings. The START Trials tested the effects of radiotherapy schedules using fraction sizes larger than 2.0 Gy. The START-A Trial tested two dose levels of a 13-fraction regimen delivered over 5 weeks in order to measure the sensitivity of normal and malignant tissues to fraction size. Patients in START-A were randomly assigned to either 50 Gy in 25 fractions (control group) or 41·6 Gy in 13 fractions or 39 Gy in 13 fractions over 5 weeks. Patients in the START-B trial were randomly assigned to either 50 Gy in 25 fractions (control group) over 5 weeks or 40 Gy in 15 fractions over 3 weeks. The START-A trial (N=2236) showed that the estimated absolute differences in 5-year local-regional relapse rates compared with the control schedule of 50 Gy in 2.0 Gy fractions were 0.2% (95% CI -1.3% to 2.6%) after 41.6 Gy and 0.9% (95% CI -0.8% to 3.7%) after 39 Gy. In START A, photographic and patient self-assessments suggested lower rates of late adverse effects after 39 Gy than with 50 Gy, with a hazard ratio for late change in photographic breast appearance of 0.69 (95% CI 0.52 to 0.91, p=0.01). In the START-B trial (N = 2215) the estimated absolute difference in 5-year local-regional relapse rates for 40.05 Gy compared with 50 Gy was -0.7% (95% CI -1.7% to 0.9%), and the hazard ratio for late change in photographic breast appearance was 0.83 (95% CI 0.66 to 1.04). Therefore, the START trials reported similar local tumour control with some evidence of lower rates of late adverse effects after schedules with fraction sizes larger than 2.0 Gy compared with the international standard 25-fraction regimen [18].

A 15-fraction schedule has been the UK standard-of-care recommended by the National Institute for Health and Clinical Excellence (NICE) since 2009, but it was thought to be unlikely to represent the useful limits of hypofractionation for whole breast radiotherapy. There is a history of prescribing once-weekly fractions of whole-breast radiotherapy for women too frail or otherwise unable to attend for conventional schedules. In a French series of 115 patients undergoing primary radiotherapy without surgery for non-metastatic breast cancer from 1987 to 1999, the whole breast was treated with two tangential fields and received 5 once-weekly fractions of 6.5 Gy [20]. 101 were given additional tumour bed boost doses, 7 with 1 fraction, 69 with 2 fractions and 25 with 3 once-weekly fractions of 6.5 Gy using electrons. Kaplan-Meier estimates of late effects in the breast were 24% grade 1, 21% grade 2 and 6% grade 3 at 48 months. The 5-year local progression-free rate was 78% (95% CI: 66.6-88.4). In a separate French series, 5 once-weekly fractions of 6.5 Gy to the whole breast with no boost were given to 50 women after local tumour

excision [21]. Grade 1 or 2 induration was reported in 33% of the patients at a median follow-up of 93 months (range 9-140). The 7-year local relapse free survival was 91%.

The UK FAST Trial (N = 915) tested two dose levels of a 5-fraction regimen delivering 1 fraction per week against a control schedule of 50 Gy in 25 fractions, defining radiotherapy adverse effects as the primary endpoint [22]. The two test dose levels delivered 5 fractions of 5.7 Gy or 6.0 Gy (total dose 28.5 Gy or 30 Gy), estimated to be iso-effective with the control regimen assuming α/β values of 3.0 Gy or 4.0 Gy, respectively. 915 patients were recruited from October 2004 - March 2007. The mean age of participants was 62.7 years. Only 17 patients (5.2%) developed moist desquamation (12 after 50 Gy, 3 after 30 Gy, 2 after 28.5 Gy) out of 327 with RTOG skin toxicity data available. At a median follow-up of 28.3 months (IQR 24.1-33.6), 729 patients had 2-year photographic assessments available, with mild and marked change in breast appearance in 19.3% and 1.7% after 50 Gy, 26.2% and 9.3% after 30 Gy, and 20.3% and 3.7% after 28.5 Gy. Risk ratios for mild and marked change for 30 Gy vs. 50 Gy were 1.48 (95%CI 1.06 -2.05) and 6.06 (2.14 -17.20), p<0.001 for trend, favouring 50 Gy; and for 28.5 Gy vs. 50 Gy were 1.07 (0.75 -1.54) and 2.25 (0.70 -7.18), p=0.26 for trend, favouring 50 Gy. Any clinically-assessed moderate or marked adverse effects in the breast were increased for 30 Gy compared with 50 Gy (hazard ratio, HR 2.19, 95%CI 1.46 - 3.29, p<0.001), but similar for 28.5 Gy (HR 1.33, 95%CI 0.86 -2.08, p=0.19). At a median follow-up of 37.3 months 2 local tumour relapses had been recorded.

The ten-year results from the FAST trial were subsequently published in 2020 [23], confirming that as far as late toxicity is concerned, the 28.5 Gy schedule was isoeffective to the 50 Gy schedule. The 30 Gy schedule had an increased rate of late toxicity compared with 50 Gy. Any moderate or marked physician-assessed normal tissue effects (NTE) in the breast (shrinkage, induration, telangiectasia, oedema) was reported for 92/774 (11.9%) at 5 years and 55/392 (14.0%) at 10 years. The most prevalent individual effect was breast shrinkage. Five-year prevalence of any moderate or marked breast NTE was estimated to be 10% higher (95% CI, 5% to 16%) for 30 Gy versus 50 Gy (p<0.001), with no statistically significant difference between 28.5 Gy and 50 Gy (2%; 95% CI, −2% to +7%; p=0.349). At 5 years, risk ratios for moderate or marked breast shrinkage versus 50 Gy were 2.03 (95% CI, 1.15 to 3.58; p = 0.017) for 30 Gy and 1.20 (95% CI, 0.63 to 2.27; p=0.604) for 28.5 Gy. There were no statistically significant differences between schedules in 5-year prevalence of moderate or marked breast induration, telangiectasia, and breast oedema, nor in 10-year prevalence of any moderate/marked effects, with few marked events. At 10 years, the estimated absolute differences in prevalence of any moderate or marked breast NTE compared with 50 Gy were 9% (95% CI, 1% to 18%: p= 0.032) for 30 Gy and 5% (95% CI, −2% to +13%; p=0.184) for 28.5 Gy.

Five- and 10-year cumulative incidence rates of moderate or marked NTE in the breast were higher for 30 Gy compared with 50 Gy, with statistically significant differences for any NTE in the breast, breast shrinkage, breast induration, and breast oedema. Cumulative incidence rates of any moderate or marked NTE in the breast and breast induration were significantly higher for 28.5 Gy versus 50 Gy. Modeling all annual physician assessments over follow-up, rates of moderate or marked effects were statistically significantly higher for 30 Gy compared with 50 Gy (odds ratio [OR] for any breast NTE, 2.12; 95% CI, 1.55 to 2.89; p<0.001), but with no significant difference between 28.5 Gy and 50 Gy (OR, 1.22; 95% CI, 0.87 to 1.72; p=0.248; Statistically significant differences between the test schedules were found for breast shrinkage, telangiectasia, and breast oedema, with higher rates for 30 Gy compared with 28.5 Gy. The prevalence of breast shrinkage and telangiectasia increased over time, with a decline in breast oedema.

By the time of the 10-year analysis of the FAST trial only 11 local relapses had been reported (50 Gy: 3, 30 Gy: 4, 28.5 Gy: 4), hence analysis of tumour control outcomes would be underpowered.

A gain in local tumour control due to shortening treatment time to 1 week from longer 3-5 week schedules is theoretically possible. Evidence based on retrospective studies for an influence of treatment time on local tumour control is conflicting with recent systematic reviews drawing different conclusions [24, 25] (Hebert-Croteau, Freeman et al. 2002, Huang, Barbera et al. 2003). Even without a gain in tumour control, accelerated radiotherapy is likely to be more convenient for patients, and may ease scheduling with other treatment modalities. A pilot study (N = 30) tested 30 Gy in 5 fractions of 6.0 Gy in 15 days to the whole breast in terms of acute adverse effects and late effects at 2 years [26]. In this series, 23/30 (77%) patients scored no change in post-operative photographic breast appearance at 2 years, 7/30 (23%) scored mild change and none scored marked change. The acute skin reactions were mild, with no reaction more severe than grade 2 erythema, scored in 9/30 (27%) patients. In conclusion, it is fair to say that after decades of resistance to evaluating larger radiotherapy fraction sizes in breast cancer, expert opinion is responding to an accumulating body of evidence supporting the safety and effectiveness of this approach.

Against this background, the FAST-Forward phase III randomised trial was designed, with the primary aim of testing local tumour control in women with early breast cancer following a 5-fraction schedule of adjuvant radiotherapy delivered in 1 week.

Lymph node radiotherapy for breast cancer

This sub-study to the Main Trial tested the safety of 5-fraction regimens in the context of lymphatic radiotherapy. The model of breast cancer spread that was dominant in earlier decades envisaged a limited role for regional therapy beyond protection of quality of life, typically secured by surgery.

Systematic overviews of radiotherapy effects by the Early Breast Cancer Trialists Collaborative Group (EBCTG) provides level 1A evidence that prevention of local-regional relapse has a major impact on breast cancer mortality [6, 27]. An important conclusion to be drawn is that even heavily axillary lymph node-positive axillary patients can be cured by effective local-regional treatment, whether this is achieved by surgery, radiotherapy or systemic therapy [27]. The traditional model of breast cancer spread still has some adherents. The Z11 trial randomised 891 out of a planned 1900 patients with clinically lymph node negative, sentinel lymph node positive disease to axillary clearance versus no further axillary treatment [28]. Twenty-seven percent allocated axillary clearance had additional positive lymph nodes. The axillary relapse rate at 5 years was 0.5% after axillary clearance and 0.9% after no axillary clearance, and there was no difference in breast cancer mortality. For some, this result reinforces the traditional model of breast cancer spread that discounts a role of nodal metastases in determining cancer spread. This interpretation fails to take account that standard post-operative tangential beam RT includes at least lower axillary lymph nodes and may be needed to eradicate residual disease. The same issue has been raised in discussion of the IBCSG 23-01 trial that compared axillary dissection versus no further axillary surgery in 929 sentinel lymph node-positive patients, 91% of whom were treated by breast conservation followed by whole-breast radiotherapy [29]. The disease-free survival events, including axillary relapses, were non-inferior in the group spared axillary dissection, where standard whole-breast radiotherapy will have included at least level I axillary lymph nodes. Although this remains a contested area, there is a wide consensus that control of axillary disease, whether by surgery, systemic therapy or radiotherapy, is an important component of curative therapy.

The AMAROS trial is informative in determining the role of surgery or radiotherapy for axillary management [30]. The study randomised 1425 patients with positive sentinel lymph nodes to either axillary lymph node dissection in 744 patients or axillary radiotherapy including photon beams to axillary apex and medial supraclavicular fossa (SCF) in 681 patients. The axillary relapse rates were low in both groups; 1.19% after radiotherapy and 0.43% after surgery, too low to assess non-inferiority. The main difference is that clinically reported arm swelling was less of a problem after radiotherapy than after surgery; 13.6% vs 28.0%, respectively, at 5 years; p<0.0001. The implication is that lymphatic radiotherapy may increasingly be used as an alternative to surgery in this context.

Very little internal mammary chain (IMC) radiotherapy has been given in the UK in recent decades, but a modest reduction in breast cancer mortality is suggested by the NCIC MA20 trial and confirmed by the EORTC 229922 trial [6, 31]. Both tested IMC and supraclavicular fossa (SCF) radiotherapy, so it is possible that therapeutic effects are attributable solely to the SCF component. This does not seem likely since, if SCF radiotherapy is needed in order to enhance cure of patients with positive IMC nodes, it is reasonable to assume that the latter require

managing too. The same argument might apply to the infraclavicular (ICF) lymph nodes (level III axilla), which are usually included in unshielded (rectangular) fields to the SCF. In the EORTC trial, 4004 patients with axillary lymph node-positive disease or had cancers that were centrally or medially situated but axillary lymph node-negative were randomised to receive IMC/medial SCF radiotherapy or not. At a median of 10.9 years of follow up, the primary endpoint of overall survival improved from 80.75% to 82.3% with the addition of IMC/SCF RT (HR=0.87; CI 0.76-1.00; p=0.0556; p=0.0496 after adjustment). It is not currently clear how these results will impact on practice. In conclusion, there was a need to test the safety of a 5-fraction schedule of lymphatic radiotherapy if the FAST-Forward Trial is to remain relevant to the 25% of patients referred for treatment with lymph node-positive disease. Whereas most are currently referred following axillary dissection, international and UK practices are changing, and more patients are likely to be referred in future for radiotherapy to axillary, SCF/ICF and perhaps IMC lymph node groups. When hypofractionation for breast cancer was first introduced in the 1960s, inappropriate dose regimens and uncertain dosimetry combined to cause unacceptably high rates of brachial plexopathy in patients with early breast cancer [32-44]. Even with hindsight, it is difficult to be sure how much of the morbidity was related to technical factors, especially beam overlap, and how much to dose-time factors. The only series describing brachial plexopathy after total dose ≤50 Gy delivered in 1.8-2.0 Gy fractions to breast and axilla/SCF reported 3/724 (0.6%) affected patients treated between 1968-85, of whom 2 resolved and 1 progressed at 6.5 years median follow-up [44]. All patients were treated at the Joint Center, Boston, in a supine treatment position using a 3-field technique with hanging block. A review of all published evidence available in 2005, suggested that brachial plexopathy after local-regional radiotherapy for early breast cancer is uncommon (<1%) at doses <55 Gy in 2.0 Gy equivalents [45]. Dose regimens were normalised using a linear quadratic model, assuming α/β value of 2.0 Gy.

The dose-response relationships are not difficult to reconcile with current practices in head and neck cancer, where total doses of 60 Gy in 30 fractions are standard. One recent example modelled the relationship between total dose in 2.0 Gy fractions and probability of brachial plexopathy in 330 patients systematically screened for evidence of sensorimotor symptoms a median of 56 months (range 6-135) after radical radiotherapy for head and neck cancer. Patients treated with definitive radiotherapy received a median dose of 70 Gy, and for those treated post-operatively the median dose was 60 Gy. Intensity modulated radiotherapy (MRT) was used on 62% cases, and 40% had concurrent chemotherapy, usually cisplatin. The brachial plexus was outlined using RTOG criteria on x-ray CT scans [46].

Against this background, the FAST-Forward Trial was extended beyond its original target accrual in order to test the safety of hypofractionated lymphatic radiotherapy. It is realistic to test only the common dose-limiting adverse effects, including arm swelling and overall arm function. Very

uncommon adverse effects, including brachial plexopathy, cannot be formally tested in such a protocol, since a non-inferiority trial wishing to exclude an excess 1% risk with standard statistical power would require tens of thousands of patients.

Aims and objectives

Main Trial: to identify a 5-fraction schedule of curative radiotherapy delivered in once-daily fractions, that is at least as effective and safe as the current UK standard 15-fraction 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 (from Protocol v3.0, 08/07/2015): to show that a 5-fraction (1 week) schedule of adjuvant radiotherapy to level I-III axilla and/or level IV axilla (supraclavicular fossa, SCF) is non-inferior to a 15-fraction (3 weeks) standard in terms of patient reported arm swelling and function, and to contribute additional information to the endpoints of the Main Trial.

CHAPTER 2: METHODS

Trial Design

FAST-Forward was a multi-centre, three-group, non-blind, phase III randomised controlled non-inferiority clinical trial addressing the hypothesis that a 1-week course of curative whole breast radiotherapy would be at least as effective and safe as the UK standard 3-week regimen after primary surgery for early breast cancer. Patients were allocated in a 1:1:1 ratio to either 40.05 Gy in 15 fractions of 2.67 Gy over 3 weeks (Control group; labelled 40 Gy throughout the reminder of this report); 27.0 Gy in 5 fractions of 5.4 Gy over 1 week (Test group 1) or 26.0 Gy in 5 fractions of 5.2 Gy over 1 week (Test group 2). Dose prescriptions are summarised in Appendix 2, Table 33

A sequential tumour bed radiotherapy boost following breast conservation surgery was allowed, with centres required to state boost intention and dose (10 Gy or 16 Gy in 2.0 Gy fractions, or radiobiological equivalent from Protocol v4.0) prior to randomisation.

The Nodal Sub-Study (from Protocol v3.0 08/07/2015) was an extension to the FAST-Forward Main Trial, maintaining the original design as a phase III randomised clinical trial but restricted to patients prescribed radiotherapy to level I-III axilla and/or level IV axilla (SCF) in addition to the breast/chest wall area. Trial schemas for the Main Trial and the Nodal Sub-Study are shown in Figures 1 and 2 respectively.

Test dose levels were informed by α/β estimates describing the fractionation sensitivity of late normal tissues obtained from the START and FAST trials [17] [47]. Assuming $\alpha/\beta=3$ Gy and no effect of overall time on outcomes, 27 Gy/5Fr of 5.4 Gy was predicted to match late normal tissue effects (NTE) of 40 Gy/15Fr of 2.7 Gy or 46 Gy/23Fr of 2 Gy. Allowance for a possible effect of treatment time informed the choice of the slightly lower 26 Gy dose level. A 3-group design was used for the trial to allow interpolation between the two test doses in order to estimate the 5-fraction dose equivalent to 40 Gy in 15 fractions in terms of local tumour control, and late NTE.

From Protocol v5.0 (14/12/2017) onwards the trial design of the Nodal Sub-Study was amended to a 2-group trial, with no further randomisation to Test group 1 (27 Gy in 5 fractions of 5.4 Gy). This amendment was on the advice of the Independent Data Monitoring Committee (IDMC) and Trial Steering Committee (TSC). Further details are presented in the Study Conduct section (Chapter 2).

Figure 1: FAST-Forward Schema: Main Trial

FAST-Forward Trial Schema

Patient Population
Female or male, age ≥ 18; primary breast conservation surgery or mastectomy of invasive carcinoma (pT1-3 pN0-1 M0) with complete microscopic resection; whole breast/chest wall radiotherapy +/- tumour bed boost dose.

↓

Exclusion Criteria
- Patients aged 65 and over with pT1 G1/G2 ER+HER2- pN0 M0 invasive disease.
- Ipsilateral microinvasive disease and/or non-gradeable tumours
- Previous malignancy (other than basal cell skin cancer and CIN cervix uteri), or 5 years disease free following treatment with curative intent.
- Contralateral and/or previous ipsilateral breast cancer, including DCIS, irrespective of date of diagnosis.
- Concomitant chemotherapy (sequential chemotherapy allowed).
- Radiotherapy to lymphatic pathways.

Patient eligible for FAST-Forward and consents to participate

↓

*Baseline Patients Reported Outcome Measures questionnaires – **prior to randomisation**
*Baseline health economics questionnaires – **prior to randomisation**
*Baseline photographs of breast/chest wall following surgery – **prior to radiotherapy**
Blood sample collection/family history questionnaire – **at any time**

↓

Randomise to one of three treatments

↓

Control Group	**Test Group 1**	**Test Group 2**
40.05Gy / 15 Fr	27.0 Gy / 5 Fr	26.0 Gy / 5 Fr
3 weeks	1 week	1 week
2.67 Gy/Fr	5.4 Gy/Fr	5.2 Gy/Fr

16 Gy or 10 Gy in 2 Gy fractions sequential electron or photon boost to the tumour bed is allowed in all 3 treatment arms (boost decision to be declared before randomisation for each individual patient)

↓

Follow up
Acute toxicity study I – assessed the first 190 patients weekly during and for 4 weeks post
(completed)   radiotherapy, then weekly until RTOG ≤1 if symptoms persist
Acute toxicity study II – assess 150 patients, who are not receiving a boost dose, weekly
               during and for 4 weeks post radiotherapy. If moist desquamation persists
               then continue weekly assessments until CTCAE (moist desquamation) ≤1
Annual clinical assessment follow up for 10 years post radiotherapy
* Patient Reported Outcome Measures questionnaires at 3 & 6 months post radiotherapy and 1, 2, 5 and 10 years post randomisation
* Health economics questionnaires at 3 & 6 months post radiotherapy and 1, 2, 5 and 10 years post randomisation
* Photographs of breast/chest wall at 2, 5 and 10 years post radiotherapy
Tissue collection from primary and recurrence/new primary in either breast

* - to start after the first acute toxicity study has completed

Figure 2: FAST-Forward Schema: Nodal Sub-Study

Patient Population

Female or male, age ≥ 18; primary breast conservation surgery or mastectomy of invasive carcinoma (pT1-3 pN1-3a M0[#]) with complete microscopic resection; axillary staging and/or dissection; histological involvement of axillary lymph nodes; whole breast/chest wall radiotherapy +/- tumour bed boost dose; indication for radiotherapy to level I-III axilla +/- level IV axilla (SCF)[#].

↓

Exclusion Criteria

• patients with N0 disease[#]; known macroscopic residual nodal disease[#]; any positive level IV (SCF) nodes[#]; any requirement for IMC RT (these patients are excluded because indications for IMC RT are currently unclear)[#]

• ipsilateral microinvasive disease and/or non-gradeable tumours; Previous malignancy (other than basal cell skin cancer and CIN cervix uteri) or 5 years disease free following treatment with curative intent; Contralateral and/or previous ipsilateral breast cancer, including DCIS, irrespective of date of diagnosis; Concomitant chemotherapy (sequential chemotherapy allowed).

↓

Patient eligible for FAST-Forward and consents to participate

↓

[$]Baseline Patients Reported Outcome Measures questionnaires – **mandatory[Δ] prior to randomisation**
[$]Baseline health economics questionnaires – **prior to randomisation**
[$]Baseline photographs of breast/chest wall following surgery – **prior to radiotherapy**
Blood sample collection/family history questionnaire – **at any time**

↓

Randomise to one of three treatments

↓ ↓ ↓

Control Group	**Test Group 1**	**Test Group 2**
40.05Gy / 15 Fr	27.0 Gy / 5 Fr	26.0 Gy / 5 Fr
3 weeks	1 week	1 week
2.67 Gy/Fr	5.4 Gy/Fr	5.2 Gy/Fr

16 Gy or 10 Gy in 2 Gy fractions (or radiobiological equivalent[Δ]) sequential electron or photon boost to the tumour bed is allowed in all 3 treatment arms (boost decision to be declared before randomisation for each individual patient)

↓

Follow up

Acute toxicity study I* – assessed the first 190 patients weekly during and for 4 weeks post
(completed)   radiotherapy, then weekly until RTOG ≤1 if symptoms persist

Acute toxicity study II* – assess 150 patients, who are not receiving a boost dose, weekly
during and for 4 weeks post radiotherapy. If moist desquamation persists then continue weekly assessments until CTCAE (moist desquamation) ≤1

Annual clinical assessment follow up for 10 years post radiotherapy

[$] Patient Reported Outcome Measures questionnaires at 3 & 6 months post radiotherapy and 1, 2, 5 and 10 years post randomisation

[$] Health economics questionnaires at 3 & 6 months post radiotherapy and 1, 2, 5 and 10 years post randomisation

[$] Photographs of breast/chest wall at 2, 5 and 10 years post radiotherapy

Tissue collection from primary and recurrence/new primary in either breast

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* up to and including protocol version 2.2; [$] from protocol version 2.1; [#] from protocol version 3; [Δ] from protocol version 4

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Embedded sub-studies

Acute toxicity

Acute skin reactions are more related to the total dose and less sensitive to fraction size than late-reacting normal tissues. Therefore the lower total doses under test in the trial are expected to reduce their severity and duration, despite the shorter overall treatment time. In order to confirm these relationships two acute toxicity sub-studies were undertaken during 2011 and 2013 in patients entered into the Main Trial from a subset of centres. Details of the acute toxicity sub-studies are presented in the separate chapter.

Patient-reported outcomes (PRO)

There is evidence that radiotherapy causes long-term effects on quality of life in terms of altered breast appearance, breast, arm and shoulder symptoms, as well as a possible impact on some general aspects such as fatigue. Results from the START trial highlighted the value of patients' self-reported post–radiotherapy symptoms in discriminating between radiotherapy regimens in favour of hypofractionation [48]. The PRO sub-study within FAST-Forward aimed to provide subjective views of key breast symptoms and body image following treatment, to add supportive data in the comparison of a trade-off between local tumour control and adverse effects of treatment. A subset of Main Trial centres participated in the PRO sub-study. For the Nodal Sub-Study PROs were mandatory since the primary outcome was patient-assessed. Details of the PRO methods are included later on in this chapter.

Photographic assessments

Photographic assessments of change in breast appearance following radiotherapy as used in other trials including START, IMPORT LOW and HIGH, and FAST, provide an objective assessment of late adverse effects, since they are scored by independent observers blinded to treatment allocation and patient identity. The same centres involved in the PRO sub-study also participated in the photographic assessments. Details of the photographic assessment methods are included later on in this chapter.

Health economics

The health economic evaluation aimed to establish the cost-effectiveness of a 5-fraction schedule of curative radiotherapy compared with current UK practice using quality of life and health resource data, and health states including cancer relapse. Quality of life and health resource use data were collected on the PRO questionnaires for those patients participating in the PRO sub-study. Details of the health economics evaluation are presented in the separate chapter.

Blood & tissue collection

All patients were asked to consent to donate a single blood sample and complete a family history questionnaire; these were collected at any point during the trial. All patients were also asked to consent to the donation of a tissue sample from their original tumour and to the donation of a tissue sample should a relapse occur. The consent ensured that the samples remain a resource for future use, pending separate funding for translational research.

Participants

Patient Selection

Women and men with complete microscopic resection of early invasive breast cancer following breast conservation surgery or mastectomy prescribed local radiotherapy.

Eligibility for Main Trial

Eligibility criteria for the Main Trial from protocol version 2.3 (11/11/2013; last version of Main Trial protocol before addition of Nodal Sub-Study) are as follows:

Main Trial inclusion criteria[1]

- Age ≥18 years
- Female or male
- Primary invasive carcinoma of the breast
- Breast conservation surgery or mastectomy (reconstruction allowed, providing port of a tissue expander positioned outside the breast)
- Complete microscopic excision of primary tumour
- Axillary staging &/or dissection
- pT1-3 pN0-1 M0 disease
- Written informed consent
- Able to comply with follow-up

[1] Concurrent anti-HER2 therapy and/or endocrine therapies are allowed

Main Trial exclusion criteria

- Age ≥65 years with pT1 G1/2 ER+ve / HER2-ve pN0 M0 invasive disease (from protocol v2.0)
- Ipsilateral microinvasive disease and/or non-gradeable tumours
- Past history of malignancy except (i) basal cell skin cancer, (ii) CIN cervix uteri or (iii) non-breast malignancy allowed if treated with curative intent and >5 years disease-free

- Contralateral and/or previous ipsilateral breast cancer, including DCIS, irrespective of date of diagnosis
- Concurrent cytotoxic chemotherapy (sequential neoadjuvant or adjuvant cytotoxic therapy allowed with ≥2 weeks between therapy and radiotherapy)
- Radiotherapy to any regional lymph node area (excepting lower axilla included in standard tangential fields to breast/chest wall)

Eligibility for Nodal Sub-Study

Protocol Version 3.0 onwards included additional requirement for lymphatic radiotherapy. Typical examples of indications for lymphatic radiotherapy include (a) Patients with positive lymph nodes removed by axillary clearance who require radiotherapy to level I-III axilla and/or level IV axilla (supraclavicular fossa, SCF). (b) Patients with sentinel node positive axillary disease not proceeding to axillary dissection and who require radiotherapy to level I-III axilla and/or level IV axilla (SCF). (c) Patients treated by pre-operative systemic therapy who are recommended postoperative radiotherapy to level I-III axilla and/or level IV axilla (SCF).
Eligibility criteria for the Nodal Sub-Study from protocol version 4.0 (24/02/2017) onwards are as follows:

Nodal Sub-Study inclusion criteria[*]

- Age ≥18 years
- Female or male
- Primary invasive carcinoma of the breast
- Breast conservation surgery or mastectomy (reconstruction allowed, providing port of a tissue expander positioned outside the breast)
- Complete microscopic excision of primary tumour
- Axillary staging &/or dissection
- pT1-3 pN1-3a M0 disease
- Histological involvement of axillary lymph nodes
- Indication for radiotherapy to level I-III axilla and/or level IV axilla (SCF)
- Written informed consent
- Able to comply with follow-up

[*] Concurrent anti-HER2 therapy and/or endocrine therapies are allowed

Nodal Sub-Study exclusion criteria

- Ipsilateral microinvasive disease and/or non-gradeable tumours
- Past history of malignancy except (i) basal cell skin cancer, (ii) CIN cervix uteri or (iii) non-breast malignancy allowed if treated with curative intent and >5 years disease- free
- Contralateral and/or previous ipsilateral breast cancer, including DCIS, irrespective of date of diagnosis
- Concurrent cytotoxic chemotherapy (sequential neoadjuvant or adjuvant cytotoxic therapy allowed with ≥2 weeks between therapy and radiotherapy)
- Patients with N0 disease
- Known residual macroscopic nodal disease
- Any positive level IV (SCF) nodes
- Requirement for IMC radiotherapy[*]

* Excluded because indications for internal mammary chain (IMC) radiotherapy were unclear at the time of the protocol

The eligibility criteria of Fast-Forward Main Trial were amended in versions 2.0 (13/02/2013), 2.2 (02/05/2013) and for the Nodal Sub-Study in versions 3.0 (08/07/2015) and 4.0 (24/02/2017) of the study protocol, as shown in Appendix 2, Table 34.

Eligibility for PRO and photographic assessment sub-studies

For the PRO sub-study all the patients at those centres participating were eligible (and all patients in the Nodal Sub-Study). All patients who had breast conservation surgery were eligible for the photographic sub-study at participating centres, with the intention that the same group of patients were included in the PRO and photographic studies.

Protocol amendments

Protocol amendments for the FAST-Forward are summarised in Appendix 2, Table 35. The current approved version of the protocol is v5.1 (05/02/2018).

Trial procedures

Participating centres

All hospitals in the UK were invited to participate in the trial and were designated as treating (radiotherapy) and referring (non-radiotherapy) centres. All centres had to obtain the necessary regulatory approvals and radiotherapy centres completed a rigorous radiotherapy quality assurance (RT QA) approval process (see Chapter 3 for details of RT QA programme). A site initiation visit was performed either in person or by telephone prior to opening to recruitment. Radiotherapy centres identified eligible patients, obtained informed consent, treated patients and

performed assessments according to the schedule. Non-radiotherapy hospitals performed the same activities except for the radiotherapy and acute toxicity assessments. Centre staff are listed in Table 30.

Patient information and informed consent

Eligible patients (see eligibility criteria) were identified during breast cancer multidisciplinary meetings or from clinic lists at participating sites. Patients were invited to participate in the FAST-Forward trial during consultations in oncology clinics, where treatment options were discussed. Here the local principal investigator, co-investigator or other trained health care professionals, discussed the trial with the patient and provided them with a copy of the patient information sheet. Patients were given at least 24 hours to consider participation in the trial, to discuss this with their family and friends and to ask questions of the clinical team. Patients who were willing to participate were asked to provide written informed consent to the principal investigator, co-investigator or other trained individual. All patients from the start of the trial were asked to provide consent for the tissue and blood sub-studies. Other optional sub-studies were included in subsequent versions of the consent form.

There were 2 consent forms available at the start of the trial:
1. For centres participating in the acute toxicity sub-studies (seven centres)
2. For centres participating in the PROMS and photographic sub-studies

There were 2 consent forms available from Protocol v2.1:
1. For centres opting to participate in the PRO and photographic assessment sub-studies
2. For all other centres

There was only 1 consent form from Protocol v3.0 (inclusion of Nodal Sub-Study) as the PRO assessments were mandatory, since the primary endpoint of this sub-study was patient-assessed arm / hand swelling.

Randomisation

Patients in the Main Trial and Nodal Sub-Study were allocated to 40.05 Gy in 15 fractions, 27.0 Gy in 5 fractions or 26.0 Gy in 5 fractions in a 1:1:1 ratio. The 27.0 Gy group in the Nodal Sub-Study was closed to recruitment from Protocol v5.0 (14/12/2017) onwards (as described in Protocol amendments and Study Conduct sections). Treatment allocation was not blinded to patients or clinicians. Randomisation was performed by recruiting centres contacting ICR-CTSU by telephone or fax. The randomisation allocation method was computer-generated random permuted blocks (mixed block sizes 6 and 9 [changed to 4 and 6 following the amendment of Nodal Sub-Study to 2-

group design] to avoid predictability). Patients in the Main Trial were stratified according to radiotherapy centre and risk group (high: <50 years or grade 3 versus low: ≥50 years and grade 1 or 2). Patients in the Nodal Sub-Study were stratified according to radiotherapy centre and whether or not the patient had a level II/III axillary clearance. A unique trial identifier was assigned to each patient comprising components for centre number, patient number and designated stratification.

Radiotherapy procedures

The whole breast clinical target volume (CTV) including the soft tissues from 5mm below the skin surface to the deep fascia 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; 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). 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. A tangential opposing pair beam arrangement encompassed the whole breast/chest wall PTV, minimising the ipsilateral lung and heart exposure.

The lymph node clinical target volumes included the axillary chain and/or the supraclavicular nodes (level IV axilla). The axilla could be treated in its entirety, i.e., levels I-IV, or only the levels specified by the clinician. For the level IV axilla (SCF) PTV a maximum of 5 mm margin was applied medially in order to limit the dose to midline structures.

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 12 Gy <15%, and volume of heart receiving 2 Gy and 10 Gy <30% and <5% respectively. Dose constraints for the 5-fraction schedules were: volume of ipsilateral lung receiving 8 Gy <15%, and volume of heart receiving 1.5 Gy and 7 Gy <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 (see RT QA Chapter 3).

The radiotherapy planning packs for the Main Trial and Nodal Sub-Study are available on the ICR-CTSU FAST-Forward trial webpage at https://www.icr.ac.uk/fastforward.

Trial assessments

Table 1 shows the schedule of assessments for all patients participating in the trial.

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 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 ordinal scale (none, a little, quite a bit or very much), interpreted as none, mild, moderate or marked. In addition, patients in the Nodal Sub-Study were assessed annually for the presence of breast lymphoedema, arm lymphoedema and sensori-motor symptoms. 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, including the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 core questionnaire, EORTC QLQ-BR23 breast cancer module, EORTC QLQ-FA13 fatigue 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 ordinal scale (not at all, a little, quite a bit, very much). The EQ-5D-5L was also included in the PRO questionnaire booklets and healthcare service use questions.

All patients in the Nodal Sub-Study were asked to consent to the patient-reported outcomes (PRO) sub-study and photographic assessments. The following PRO were included in the Nodal Sub-Study (but not the Main Trial): patient assessments of shoulder stiffness, upper limb pain, sensorimotor symptoms and arm function.

In the photographic sub-study, photographs were taken at baseline, 2 and 5 years after radiotherapy. At each visit two frontal views of the chest were taken, one with hands on the hips and the other with hands raised as far as possible above the head; photographs excluded the patient's head. Change in photographic breast appearance and distortion compared with the post-surgical (pre-radiotherapy) baseline were scored on a 3-point ordinal 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 [49]. Breast size and surgical deficit were assessed from the baseline photographs on a 3-point scale (small, medium, large).

Table 1: Schedule of assessments

Event		Prior to randomisation	Post randomisation pre RT	**Treatment** wk 1	wk 2	wk 3	**Follow up** (all taken from date of randomisation except where shown) weekly for 4 weeks post RT	mth 3 Post RT	mth 6 Post RT	yr 1	yr 2	yr 3	yr 4	yr 5	yr 6	yr 7	yr 8	yr 9	yr 10
Eligibility checklist		x																	
Informed consent		x																	
Randomisation checklist		x																	
Radiotherapy QA		**Prior to centre initiation and throughout the trial recruitment period**																	
3D radiotherapy planning			x																
Radiotherapy treatment				x	x[1]	x[1]													
Radiotherapy verification				**Up to daily during treatment**															
Serious Adverse Event (if applicable)				x	x	x	x	x											
Acute toxicity assessments#	Study I (first 190 patients)		x	x	x[1]	x[1]	✶												
	Study II (150 patients, no boost)		x	x	x[1]	x[1]	✶												
Follow up - annual clinical assessment (all patients)										x	x	x	x	x	x	x	x	x	x
Sub studies																			
PROMS [2]		x (baseline*)						x	x	x	x			x					x
Photographic assessment [2]			x								x			x					x
Health economics - annual assessment		x (baseline*)						x	x	x	x	x	x	x	x	x	x	x	x
Lymphatic radiotherapy including PROMS[3]		x (baseline*)						x	x	x	x	x	x	x	x	x	x	x	x
Blood sample collection and family history questionnaire		**At any time during the trial, ideally by the end of RT**																	
CT scan if recurrence				**At the time of recurrence**															
Tissue collection - 1º tumour - recurrence/new 1º tumour		**As requested during the trial**																	

up to and including Protocol version 2.2; *Follow up booklets will be sent by post from the ICR-CTSU office; [1] Control group only; CRFs to be completed throughout the trial as indicated in the Trial Guidance Notes; [2] PROMS and photographic assessments are to be offered to the same set of patients; [3] from Protocol version 3

Data management

Data collection

All participating centres were supplied with NCR Case Report Form (CRF) booklets and paper copies of the baseline PRO booklets. Site staff were trained in trial procedures during the site initiation visit which was performed either in person or by telephone. Data were collected according to the schedule in Table 1 and used to populate the CRFs. All CRFs and baseline PRO booklets were returned to the ICR-CTSU where they were logged into a tracking database. The clinical data were entered into a clinical database (MACRO).

Data queries

Visual checks were performed on all CRFs received at ICR-CTSU consistency checks of the data were written into the clinical database to identify any discrepancies in the data entered. Data queries were raised for these anomalies, discrepancies and omissions and were sent to centres on a regular basis. Queries were resolved by centres and returned to ICR-CTSU.

Central statistical data monitoring

Details of data monitoring were described in the FAST-Forward Central Statistical Data Monitoring Plan (v1.0 May 2018). Checks of the data stored on the MACRO database were performed regularly and on an ongoing basis, including prior to each analysis for an IDMC report, and queries raised with the study sites. In addition, a formal comparison between FAST-Forward CRFs received (clinical CRFs and PRO booklets) and data entered onto the MACRO database was done for 5% of Main Trial patients for all CRFs from baseline up to and including year 5 follow-up. The error rate found in this data quality control exercise was very low (0.2% of items checked).

Site monitoring

The quality of the data received from sites was assessed on a regular basis by the number of data queries generated per centre. Early intervention with the centre was initiated to discuss the queries and to avoid repeat of the errors. Central statistical monitoring of the data was also performed on a regular basis as described above. No centres were identified as needing an on-site monitoring visit.

Data assumptions / coding

Adverse effects reported under "other" on the annual follow-up forms were reviewed (blind to randomised treatment schedule) by the Chief Investigator and coded according to whether they were likely to be radiotherapy-related. Prior to the Main Trial primary analysis all reported local and regional relapses were reviewed (blind to randomised treatment schedule) along with pathology reports to check coding of the relapses, including location and whether invasive or DCIS.

Endpoints

Efficacy endpoints

The protocol specified that ipsilateral tumour relapse and contralateral primary tumour must be confirmed by cytological/histological assessment. Distant relapse was to be determined by an appropriate combination of clinical, haematological, imaging and pathological assessment, recognising that pathological confirmation was not always possible. Patients remained evaluable for local relapse after distant relapse. Patients without an event were censored at the last follow-up assessment or death. Patients were to have annual clinical assessments for 10 years and annual mammograms for 5 years or until screening age if younger (as per NICE guidelines) [50].

Primary endpoint (Main Trial)

- **Ipsilateral local tumour control**, where an event was defined as any tumour relapse (invasive or non-invasive) or a new primary tumour in the ipsilateral breast unless confirmed by pathology to represent nodal relapse, in which case classified as regional, see below. Analyses used the date an event was confirmed.

Secondary disease-related and survival endpoints (Main Trial and Nodal Sub-Study)

- **Contralateral breast tumours** (invasive and non-invasive)
- **Relapse-free survival**, defined as time from randomisation until local relapse, regional relapse (axilla, supraclavicular fossa or other regional) or distant relapse (originating from the primary breast tumour).
- **Disease-free survival**, defined as time from randomisation to first confirmed occurrence of local relapse, regional relapse, distant relapse, contralateral breast cancer or death due to breast cancer.
- **Time to distant metastases**, defined as time from randomisation to the first confirmed occurrence of any distant metastases originating from the original breast cancer. For

patients with second cancers reported and metastases, centres were asked to confirm that the metastases had originated from the primary breast cancer.

- **Overall survival**, defined as time from randomisation to death from any cause.
- **Other second primary cancers**, reported as incidence of other second primary cancers.

Endpoints of late adverse effects of radiotherapy

Patient questionnaires were to be completed at baseline, 3, 6, 12, 24 and 60 months after randomisation. Clinical assessments of radiotherapy-related late adverse effects were carried out annually from the date of randomisation up to at least 5 years.

Primary endpoint (Nodal Sub-Study)

- Patient-assessed arm/hand swelling from EORTC QLQ-BR23 breast cancer module (Q18: Did you have a swollen arm or hand?). Scored on a 4-point ordinal scale: 'not at all', 'a little', 'quite a bit', 'very much'.

Secondary adverse effect endpoints (Main Trial and Nodal Sub-Study)

Patient and clinician assessments of late radiotherapy adverse effects were scored on a 4-point scale: 'not at all' (none), 'a little', 'quite a bit', 'very much'.

- Patient self-assessments of late adverse effects: These were assessed using the EORTC QLQ-BR23 breast cancer module, Body Image Scale (BIS) and additional protocol-specific items relating to adverse effects in the breast and arm/shoulder/hand. Key adverse effects specific to the Nodal Sub-Study included shoulder stiffness, upper limb pain, sensorimotor symptoms and arm function.

- Clinician assessments of late adverse effects: The following late adverse effects were assessed on a 4-point ordinal scale: breast distortion, breast shrinkage, breast induration (tumour bed), breast induration (outside tumour bed), telangiectasia, breast/chest wall oedema, and breast/chest wall discomfort. A composite endpoint of any clinician-assessed late adverse effect in the breast was defined as the worst grade reported for breast distortion, breast shrinkage, breast induration, telangiectasia and breast oedema. Breast discomfort was not included in the composite endpoint as it was not an external assessment by the clinician (scored by asking the patient), unlike the other assessments. Adverse effects reported under 'other' were classified according to whether they were likely to be radiotherapy-related and analysed separately from the other clinician-assessed adverse effects listed above (not included in the composite endpoint as some effects reported under 'other' on the CRF were indicated as having resolved prior to the follow-up

visit and so were no longer present, unlike the other clinician-assessed effects). Clinical assessments for the Nodal Sub-Study included the following additional adverse effects reported as present/absent (with laterality): breast lymphoedema, arm lymphoedema, and sensori-motor symptoms. A separate sensori-motor symptoms CRF was completed if symptoms were noted on the follow-up form.

- Incidence of symptomatic rib fracture, symptomatic lung fibrosis and ischaemic heart disease.

- Specialist referral for management of radiotherapy-related adverse effects.

Statistical considerations

Sample size

Main Trial

The target sample size for the Main Trial was 4000 patients, with numbers balanced between randomised groups. This provides 80% power (1-sided α=0.025 to allow for 1-sided hypothesis and a Bonferroni correction accounting for comparisons between each test group and the control group) to exclude an absolute increase of 1.6% in 5-year IBTR incidence for a 5-fraction schedule versus control. A 5-year rate of 2% in the 40 Gy schedule was assumed (using START trial data and allowing for reduction in IBTR due to evolution of systemic therapy and surgical techniques). The 1.6% absolute non-inferiority margin was defined at the trial design stage by the protocol development group including clinicians and patient advocates and was considered to be acceptable. Binary proportions were used for the sample size calculations due to the low expected event rates. Estimates allowed for 10% loss to follow-up or unevaluable (primarily due to development of metastatic disease). A total of 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 40 Gy results), allowing for 10% loss to follow-up or unevaluable.

Nodal Sub-Study

The sample size for the Nodal Sub-Study was based on the primary endpoint of patient-assessed arm swelling at 5 years. The original design of the sub-study had 3 groups that mirrored the Main Trial design but was revised to a 2-group design in Protocol v5.0 (14/12/2017), when accrual into

Test group 1 (27 Gy) was closed. The original and revised sample size justifications for the Nodal Sub-Study are given below.

Original target sample size for Nodal Sub-Study

The target sample size was 627 patients with numbers balanced equally in each of the three randomised groups. This provided 90% power (1 sided α=0.025 to allow for 1-sided hypothesis and multiple testing) to exclude an arm swelling rate at 5 years of 20% in each of the test groups compared to an assumed rate in the control group of 10%, (allowing for 10% attrition due to illness or death based on experience from the START trial).

Revised target sample size for Nodal Sub-Study

From Protocol v5.0 onwards the target sample size for the Nodal Sub-Study was reduced to 344 (172 in each of the Control group and Test group 2). This provided 90% power (1 sided α = 0.05) to exclude an arm swelling rate of 20% in Test group 2 compared with an assumed rate of 10% in the Control group at 5 years (allowing for 10% attrition). With the numbers recruited into Test group 1 up until Protocol v5.0, comparison of arm swelling between Test group 1 and the Control group would have approximately 73% power using the same assumptions as above.

Statistical methods

Baseline characteristics

Baseline patient, clinical and treatment characteristics were described according to randomised group using summary statistics, with no formal comparative tests as these data would be expected to be balanced between the groups due to randomisation.

Primary endpoint (Main Trial)

The number of IBTR primary endpoint events were tabulated by treatment group. Survival analysis methods compared IBTR between treatment groups, censoring patients at date of death or last follow-up. Kaplan Meier methods were used to estimate event rates and graphically display local control rates and cumulative incidence in each treatment group. Kaplan-Meier estimates of 5-year IBTR cumulative incidence were presented along with 95% confidence intervals (CI) for each group and each Test group separately compared with the Control group using the log-rank test.

Crude estimates of treatment effect for each Test group compared with the Control group were described by Hazard Ratios (HR, with 95%CI) obtained from an unadjusted Cox regression model. All comparisons were expressed relative to the Control group so that a HR less than one indicates

a decreased risk of the event in the Test group. Absolute treatment differences were calculated (by applying the HRs to the control group 5-year event-free estimate) along with both one- and two-sided 95% CI (calculated from the CIs for the HRs and the control group 5-year event-free estimate). As the protocol-defined non-inferiority margin is an absolute excess of 1.6%, the primary assessment of non-inferiority was whether the upper limit of the two-sided 95% CI for the absolute difference in 5-year local tumour control (calculated as above) is less than 1.6%.

Additionally, non-inferiority of each Test group versus Control was tested using the *a priori* critical HR of 1.8 (ln0.964 / ln0.98, derived from the absolute rates specified in the protocol); a p-value of less than 0.025 will be deemed statistically significant (the probability of incorrectly accepting an inferior test group treatment). Assessment of non-inferiority using the HR, a measure of relative rather than absolute treatment effect, will aid interpretation of the primary endpoint results particularly if the 5-year rate of ipsilateral disease events in the control group is less than the 2% assumed in the protocol, in which case relative excess may be deemed important to consider. If non-inferiority in terms of the *a priori* critical HR of 1.8 was not shown, a sensitivity analysis would be carried out using methods stated above to test the critical hazard ratio calculated from the observed (rather than protocol-specified) 5-year event-free rate in the control group and 1.6% absolute excess in the test groups. 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.

Primary endpoint (Nodal Sub-Study)

The primary outcome of patient-assessed arm/hand swelling ("Did you have a swollen arm or hand?" Q18 from EORTC QLQ-BR23 breast cancer module) was summarised at each time-point from baseline up to 2 years using frequencies and percentages of each response category ('not at all', 'a little', 'quite a bit', 'very much') according to treatment group.

Secondary endpoints

Other efficacy outcomes were tabulated in the Main Trial according to treatment group, with deaths presented according to whether or not breast cancer-related or cardiac-related. Analyses of other efficacy outcomes including regional relapse, distant metastases, disease-free survival and overall survival used survival analysis methods as described for IBTR above. Analysis of efficacy outcomes in the Nodal Sub-Study will await 5-year follow-up, when a meta-analysis will be conducted with data from the Main Trial.

Clinician and patient assessments of late NTE were tabulated for each treatment group and time point separately for the Main Trial and the Nodal Sub-Study. Descriptive data are shown for the Nodal Sub-Study up to 2 years for PRO and to 3 years for clinical assessments. Formal statistical analysis of primary and secondary endpoints for the Nodal Sub-Study will await 5-year follow-up (as specified in the protocol).

NTE endpoints in the Main Trial were dichotomised as 'not at all'/'a little' (none/mild) vs 'quite a bit'/'very much' (moderate/marked) and analysed as follows: (i) cross-sectional analyses at key time points compared prevalence of moderate/marked effects versus none/mild between groups using risk differences (95%CI), and Fisher's exact test; (ii) longitudinal regression analyses of moderate/marked effects (versus none/mild) using generalised estimating equations (GEE), comparing groups across the whole follow-up period including assessments from all timepoints using odds ratios (OR, 95%CI) and the Wald test; GEE models included a term representing years of follow-up to assess time trends. Risk ratios are not presented in this report for the 5-year cross-sectional analyses of clinician and patient-assessed NTE since they may be open to over-interpretation given the low absolute event rates for many of the endpoints, as reflected by the wide confidence intervals. Survival analysis methods analysed time to first moderate/marked clinician-assessed NTE; Kaplan-Meier estimates of cumulative incidence were obtained and groups compared using HR (95%CI) from Cox PH regression and the pairwise log-rank test. The proportional hazards assumption was not met for patient-assessed NTE endpoints, and so time to event analyses were not performed.

For the Main Trial photographic assessments 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.

For the Nodal Sub-Study comparisons between the Control group and Test group 1 only included Control group patients randomised concurrently (i.e., up to end of 2017 prior to protocol amendment dropping Test group 1).

For all patient and clinician-assessed NTE endpoints a significance level of 0.005 was used for Main Trial analyses, to allow for multiple testing. No formal testing is done for the Nodal Sub-Study at this stage of follow-up.

Estimates of fractionation sensitivity (α/β values, 95%CI) were obtained for the Main Trial primary endpoint of IBTR and late NTE using methodology from the START and FAST trials [17, 47]. 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 clinician and photographic assessments). Terms for total dose (D) and total dose multiplied by fraction size (Dxd) were included in each model; the α/β ratio was calculated by dividing the two parameter estimates (D / Dxd), with an estimated 95%CI derived using the covariance of the two estimates (lower confidence limits truncated at zero). Isoeffect doses in 2 Gy equivalents (EQD_2) were calculated for both 5-fraction schedules, together with an estimate of the 5-fraction schedule isoeffective in terms of local control and late NTE with 40 Gy in 15 fractions.

There were no pre-planned subgroup analyses for the Main Trial specified in the protocol. Exploratory post-hoc subgroup analyses were conducted in the Main Trial for the primary endpoint according to risk factors including age, grade, pathological tumour size, pathological node status, ER/PR/HER2 status, tumour bed boost and adjuvant chemotherapy. Additionally, exploratory post-hoc analyses of NTE in the Main Trial were done according to age, breast size, surgical deficit, tumour bed boost and adjuvant chemotherapy.

There were no formal interim analyses other than for the acute toxicity studies; accumulating data were monitored annually by the IDMC. 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 for the Main Trial was non-inferiority the primary endpoint was also tested in the per protocol population excluding patients for whom a major treatment deviation was reported.

The database snapshot for the Main Trial was taken on 22/11/2019 and Stata version 15 (StataCorp) used for analyses. For the 3-year descriptive analysis of the Nodal Sub-Study the database snapshot was taken on 01/12/2021; Stata version 17 (StataCorp) was used for the Nodal Sub-Study analyses.

Study conduct

Patient and Public Involvement (PPI)

FAST-Forward was part of a broader portfolio of patient centred ICR-CTSU and National Cancer Research Institute (NCRI) Breast Group trials where patient representatives with lived experience of breast cancer have been partners from concept, formalising their role as members of the protocol working group and TMG. In FAST-Forward patient representatives helped shape the trial with active involvement from trial concept, through recruitment, reviewing trial documents, discussing trial results prior to publication and helping to write lay summaries of the results for trial participants. A link to the lay summary of the Main Trial results that was distributed to trial

participants following publication of the primary analysis in 2020 can be found on the ICR-CTSU FAST-Forward webpage (https://www.icr.ac.uk/fastforward). Our PPI partnerships enabled design of an efficient and cost-effective follow-up schedule that truly reflects the patient experience with minimal burden and patient-centred.

In addition, ongoing links have been forged with local (Royal Marsden) and national (Independent Cancer Patients' Voice, UK Breast Intergroup, NCRI) patient advocate groups, embedding patient representation in the whole clinical trial lifecycle. PPI work in breast RT trials co-ordinated by ICR-CTSU has included development of alternative patient information formats, focus groups where patients emphasised the need for information on risks/benefits of RT at all stages of treatment and recovery, and future plans to collaborate within a PhD project optimising data capture of adverse effects from trial participants.

The TMG had preferentially at least 2 patient representatives which enabled mutual support and empowerment. All TMG members were included in any email discussions, encouraging PPI input at all times. A mentoring programme for new TMG members was also initiated which included conversations with the Chief Investigator and PPI lead at ICR-CTSU.

Trial oversight committees

The Trial Management Group (TMG), Trial Steering Committee (TSC) and Independent Data Monitoring Committee (IDMC) each worked to a charter issued by ICR-CTSU and met annually until the time of Main Trial publication, with the TMG and TSC continuing to meet thereafter.

Trial Management Group

The FAST-Forward Trial Management Group was responsible for day-to-day trial conduct. Membership included the Chief Investigator, additional Principal Investigators from recruiting sites across the UK, physics and radiographer staff from recruiting sites, members of the NCRI Radiotherapy Trials Quality Assurance group, key ICR-CTSU staff and patient representatives. Members are listed in the Acknowledgements section.

Trial Steering Committee

The ICR-CTSU Breast RT Trials Steering Committee (Chair Prof Malcolm Mason) provided strategic oversight of the study on behalf of the Funder and Sponsor and met annually from the start of the trial. The independent membership comprised 4 members (listed in Acknowledgements).

Independent Data Monitoring Committee

The Independent Data Monitoring Committee (Chair Prof Matthew Sydes) reviewed emerging trial data on an annual basis. Following each meeting, the IDMC reported their recommendations to the TSC. There were no stopping rules for the Main Trial (only the acute toxicity sub-studies), and no formal interim analyses were done. Following review of the report prepared for the IDMC meeting in October 2016 the IDMC recommended to the TSC that the 27 Gy/5Fr group be dropped from the Nodal Sub-Study, which was recruiting at the time. The IDMC reviewed emerging results of the Main Trial at a median follow-up of 3 years and recommended presentation or publication of the 3-year NTE data to inform the worldwide e   vidence base [51]. The IDMC noted that previous breast radiotherapy trials (START, FAST and IMPORT LOW) confirmed that normal tissue effect rates at 3 years had been shown to predict 5 and 10-year comparisons. Absolute rates of moderate/marked NTE in the Main Trial were reassuringly low at 3 years, but there was evidence of increased late toxicity for Test group 1 compared with the control schedule, which although statistically significant was not felt by the TSC and TMG to be clinically significant, as the rate of normal tissue effects was comparable to that after 50-52 Gy in 2.0 Gy fractions. Data were shared confidentially with the TSC following further discussions with the IDMC in 2016/2017, and the TMG produced a guidance document for the IDMC to aid interpretation of differences in late NTE between the schedules. It was concluded that Test group 1 was no longer needed in the Nodal Sub-Study, given that the optimal 5-day schedule was highly unlikely to involve fraction sizes >5.2 Gy. This allowed simplification of the trial design for the Nodal Sub-Study, allowing a 2-group design to test the safety of 26 Gy in 5 fractions against the Control schedule of 40 Gy in 15 fractions. The design of the Nodal Sub-Study was revised to a 2-group trial in December 2017. IDMC members are listed in the Acknowledgements section.

Approvals, reporting & compliance

FAST-Forward was sponsored by The Institute of Cancer Research and was registered as ISRCTN19906132.

FAST-Forward was approved by the London-Brighton and Sussex Research Ethics Committee (REC) (previously named South East Coast - Kent REC then South East Coast - Brighton and Sussex REC) on 2nd September 2011 (11/LO/0958). Local Research and Development department approval was obtained at each participating NHS trust before patients were randomised. The trial was conducted in accordance with the principles and guidelines of Good Clinical Practice, UK legislation, The Institute of Cancer Research-Clinical Trials and Statistics Unit (ICR-CTSU) Standard Operating Procedures and the REC and MHRA approved protocol. All patients provided written informed consent.

The current trial protocol is available online at the ICR-CTSU website
https://www.icr.ac.uk/fastforward.

CHAPTER 3: RADIOTHERAPY QUALITY ASSURANCE

As stated in the Methods (Chapter 2), all participating centres in the Fast-Forward Trial underwent a comprehensive radiotherapy quality assurance (RT QA) programme.

Background

The complex nature of modern radiotherapy carries inherent problems both in ensuring reproducibility and accuracy within a radiotherapy unit and, more particularly, when carried out on a multi-centre basis. Specific issues in the treatment of the breast/chest wall and nodal region arise from the geometry and proximity of the associated treatment volumes, with important radiation sensitive structures underlying the breast, chest wall and nodal region including the lung, heart and brachial plexus.

Careful localisation, computerised planning, accurate verification of beam position and meticulous attention to alignment and matching during treatment are essential.

A QA programme is "a mandatory prerequisite when aiming at high dose, high precision radiotherapy" and is an integral component of any radiotherapy trial as defined by the EORTC guidelines for trial protocols in radiotherapy [52, 53].

In this multi-centre randomised trial, the RT QA programme enabled confirmation that technical guidelines within the protocol were understood and implemented correctly by participants and that the dose prescription was delivered according to protocol, together with appropriate documentation of technique and patient related data. This ensured that clinical observations in terms of tumour control and normal tissue damage reflect differences in the randomised schedules rather than departures from trial protocol. Techniques used have been documented and these data are available should differences in observed outcomes emerge.

In this way the definition of RT QA as "all those planned and systematic actions necessary to provide adequate confidence that a product will satisfy given requirements of quality" [54] can be satisfied and the scientific worth of the parent trial be validated.

The RT QA programme for the Fast-Forward trial was built on the foundations of the START and IMPORT trials. This has provided an element of consensus in radiotherapy techniques amongst radiotherapy centres. FAST-Forward helped with the implementation of new technology in some centres where the use of intensity-modulated radiotherapy (IMRT) or image-guided radiotherapy (IGRT) had not been used previously.

Plan of investigation

The RT QA programme followed the guidelines set out by the EORTC [53] and the RT QA component of the trial was coordinated by the National Radiotherapy Trials Quality Assurance (RTTQA) Group based at Mount Vernon Cancer Centre [55, 56]. A total of 47 radiotherapy centres took part in the UK over a three-year period 2011-4. Protocol Versions 1.0-2.2 of the RT QA programme applied to whole breast/chest wall radiotherapy and, from version 3.0 onwards, centres had to gain additional QA approval for nodal radiotherapy.

The RT QA programme included both pre-trial and on-trial components. It was completed by all participating centres, unless streamlined through the IMPORT trial, and is detailed below:

Pre-trial QA

i)   A facility questionnaire and process document collating details of techniques, equipment and processes to be used within the centre for FAST-Forward patients.

ii) A dummy-run (centre-selected sample patient) plan containing target and organ-at-risk (OAR) structures outlined by the principal investigator and used to create a clinical plan, was assessed to ensure adherence to the trial protocol.

iii) Once the nodal study was introduced through Protocol v3.0, each centre was required to undergo credentialing for lymphatic nodal outlining & planning through completion of an outlining and a planning benchmark case (RTTQA Group provided cases). Centres were also asked to submit an amended process document detailing additional information in relation to treatment of patients randomised to the nodal study.

A visit by the RTTQA Group was also performed prior to centre participation to validate, independently, the technique used against the information given in the process document. In particular, the following parameters were assessed:

i)   Target volume and treatment technique used.

ii) Confirmation of plan modulation – implementation e.g. IMRT forward planning.

iii) Planning of dose distribution across the treatment volume for homogeneity and prescription points.

iv) Assessment of routine quality checks (QC) performed by the centre compared with current IPEM guidelines [57].

v)   Dose measurements across the treatment volume within a purpose-made phantom, if not performed for the same technique within the last 3 years.

vi) Assessment of imaging verification protocol and technique

<u>On-trial QA</u>

i) A prospective review of the outlines and radiotherapy plan was performed for the first breast and first chest wall patients recruited from each centre prior to the patient starting treatment. On introduction of the nodal study a prospective review of the nodal CTV outlines and radiotherapy plan was conducted for the first patient recruited at each centre. Feedback was provided to the investigator site within 48 hours of receipt of data. If any major protocol variations were identified, additional reviews were requested.

ii) All patients' radiotherapy planning CT, plan file, dose file, structure set and plan assessment forms were anonymised by the centre and submitted electronically to the RTTQA Group.

iii) Retrospective outlining and planning reviews were performed to monitor continued protocol compliance. Any protocol variations were reported and discussed with the Chief Investigator (CI) and The Institute of Cancer Research-Clinical Trials and Statistics Unit (ICR-CTSU).

Quality control by department for IMRT

Where a centre had an established IMRT programme that had been previously credentialled by the RTTQA Group for an equivalent trial, some aspects of the FAST-Forward RT QA programme were streamlined. Where an established IMRT programme was not set up, additional QA was required such as verification of fluence maps for each field.

Analysis of the RT QA programme

The data from the RT QA programme have been analysed separately from the Main Trial. Any major variations from trial protocol would have been notified to the ICR-CTSU, the CI and participating centres. These included:

i) Discrepancies in documentation, dose prescription and dose recording.

ii) Failure to meet upper and lower dose limits for treatment volumes.

iii) Systematic errors of technique in any stage of treatment from planning through to implementation.

Detailed analysis of the RT QA data has produced quality information covering the following areas:

i) Variations in breast radiotherapy practice in participating centres

ii) A comparison of methods used for IMRT (multiple static fields, dynamic fields)

iii)   An assessment of the emerging technologies and their quality control

iv)   Quantification of dose uniformity during the treatment period

Results

A number of studies were carried out by the RTTQA Group evaluating the data collected within FAST-Forward. These are summarised below:

(i)   Field-based and volume-based PTVs as plan evaluation structures in the UK FAST-Forward breast trial [58]

Centres were initially given the option of reporting either a field-based or volume-based breast PTV. Analysis of the initial 338 plans from 8 centres showed that the majority of centres were using a field-based technique (7 centres). This study also showed that in some patients there were significant areas of high dose (105% of prescription) outside of the reported volume-based PTV. In order to ensure consistency in reporting across all patients and to ensure that all regions of high dose was captured within the reported PTV, field-based PTV reporting was used for all patients within the trial. Field-based PTVs were added by the RTTQA Group for any patients that were submitted with volume-based PTV.

(ii)   Interim analysis of treatment plans in the FAST-Forward hypofractionation breast radiotherapy trial [59]

This study analysed the RT treatment plans collected and evaluated their compliance with the trial protocol. An interim analysis was performed when the first 504 plans were available. This demonstrated that 95.6% of these plans complied with the dose requirements of the FAST-Forward protocol, but highlighted differences in OAR doses and PTV coverage related to the treatment technique used. Centres using field-based planning (the majority) included less lung and heart in the field compared to volume-based planning.

(iii)   Results from the radiotherapy quality assurance programme for the FAST-Forward breast trial [60]

Additional work was carried out to analyse the radiotherapy (RT) treatment plans collected in the FAST-Forward trial to monitor consistency of treatment across all centres and compliance with trial protocol.

The review performed on 3600 plans submitted as part of the FAST-Forward trial demonstrated that, overall, the quality of the radiotherapy treatment plans had been maintained across centres. The majority of plans (97.3%) complied with the dose objectives specified in the protocol, with only

2.7% of all reviewed data not achieving one or more of the dose objectives. On further examination more than half of these variations were either unavoidable or not significant. Unavoidable variations (1.5%) included complex cases where a clinical compromise was deemed necessary for example 8 plans exceeded the V105% and V107% tolerances with higher doses to a non clinically significant volume. Avoidable variations (0.8% of plans) included misinterpretation of the DVH information at the investigator site and/or inaccurate contouring of evaluation structures.

(iv)   Variability of contouring using the ESTRO guideline for elective breast cancer radiotherapy [61]

As part of the FAST-Forward Nodal Sub-Study, inter-observer variability of nodal contouring was evaluated against the ESTRO consensus guideline for elective breast cancer radiotherapy.

It was concluded that contouring of the regional lymph nodes using the ESTRO consensus guidelines reduced interobserver variability in volumes contoured [62]. Results suggested that experience and/or training is associated with less inter-observer variability, promoting the role of RT QA when adopting new outlining guidelines as part of a multicentre trial. In addition, the methodology developed helped to inform evaluation of nodal contouring within the trial as part of prospective and retrospective analyses.

Discussion

RT QA plays an important role in ensuring trial protocol compliance and consistency in delivery of radiotherapy across multiple centres; establishing best practice and improving radiotherapy standards. The benefits of of RT QA has been shown by numerous clinical trials in ensuring that clinical outcomes reflect differences in randomisation schedules rather than departures from trial protocol [63]. It is particularly important when introducing novel techniques and frequently centres use clinical trial participation to implement new techniques supported by trial protocol and comprehensive RT QA programmes. The pre-trial and on-trial RT QA programme implemented for the FAST-Forward trial monitored the radiotherapy planning and delivery with the aim to deliver precise radiation dose to the target, maximizing the dose to the tumour and minimizing the dose to surrounding organs at risk, in order to improve the therapeutic index [64]. A particular benefit of the detailed QA programme for this trial was that it gave confidence in adopting IGRT in breast cancer radiotherapy - which was not common, and often regarded as a low priority. This has benefits for patients both within and outside of the trial

Findings from the RT QA studies provided reassurance that all FAST-Forward participating centres could comply with the standards required by the trial protocol. The first study examined the use of field-based and volume-based PTV to assess the suitability as breast plan evaluation structures. This informed centres on the difference between the two techniques and enabled centres to make a more informed choice [58-61]. Further studies looked to monitor the consistency of radiotherapy treatment across all centres and compliance with the trial protocol. The majority of the plans were protocol compliant and any deviations were explored for future guidance [60]. The variability of contouring using the ESTRO consensus guidelines was reviewed as the FAST-Forward Nodal Sub-Study required delineation of axillary nodal CTV comprising of levels 1-4 [61] and nodal outlining was not routine practice across UK centres. The study helped to identify systematic regions of variance and informed the continued development of the radiotherapy planning and delivery guidelines in order to improve conformity. These studies demonstrate the importance of a robust RT QA process, particularly when introducing new techniques, either in clinical studies or in routine care.

CHAPTER 4: ACUTE TOXICITY SUB-STUDIES

Background

Acute or short-term effects of radiotherapy occur during and shortly after radiotherapy. Acute effects are commonly reddening of the skin, usually mild, but occasionally leading to severe redness, or blistering of the skin. They can also include discomfort, swelling and fatigue. The severity of acute side-effects are related to total dose given, rather than dose per fraction. In FAST-Forward, the severity of acute side-effects were not expected to be worse with the one week schedules, but actually to be milder, and shorter-lived due to the lower total dose. This was supported from previous studies such as START and FAST, where in a subset of patients, acute toxicity was evaluated and found to be milder in patients having hypofractionated schedules, compared to the standard 50 Gy in 25 fractions. However, despite this, many clinicians and patients assume that the higher dose per fraction would lead to much more severe reactions, quoting that it would cause severe reactions, or 'burns'. It was therefore decided to carry out a detailed assessment of acute side-effects in the first cohort of patients recruited at a subset of centres participating in the FAST-Forward Main Trial.

Methods

Patients and centres

The acute toxicity sub-studies were conducted in a subset of centres (Royal Marsden Hospital, Royal Cornwall Hospital, University Hospitals of North Midlands, Derriford Hospital Plymouth, Norfolk and Norwich University Hospitals and Addenbrookes Hospital) that had the infrastructure necessary to carry out weekly toxicity assessments. The same centres participated in both sub-studies, with the addition of Torbay Hospital in the second sub-study. Patients receiving a radiotherapy tumour bed boost were eligible for the first acute toxicity sub-study but were excluded from the second acute toxicity sub-study since the objective of this sub-study was to quantify the toxicity of 5-fraction schedules relative to control, effects that are independent and additive to those of the boost. At centres participating in the acute toxicity sub-studies, consecutive eligible patients were invited to participate at the time of consent to the Main Trial.

Assessments

Acute reactions of the skin of the treated breast were graded using RTOG criteria for the first sub-study (Protocol version 1.0). Following discussions with both the FAST-Forward Independent Data Monitoring Committee and Trial Steering Committee, it was agreed that this may not be the most appropriate scoring system in this context due to the inclusion of oedema in the RTOG system, since the primary concern was to score moist desquamation. Therefore, it was agreed that a

second sub-study would be undertaken using standard CTCAE criteria (v4.03) (Protocol versions 2.1 and 2.2). Toxicity assessments were made by a healthcare professional at each participating centre using predesigned forms. The assessments were scheduled to be carried out weekly during treatment and for 4 weeks following the end of radiotherapy. In the second sub-study, if moist desquamation beyond skin folds or creases (CTCAE grade 3) were seen during this time, weekly assessments were to continue until the reaction resolved to CTCAE grade 1 or less. If any assessment was missed, the centre contacted the patient by telephone to assess and grade acute skin reactions by asking the patient to describe the skin appearance and supplementing this by direct questions. In the first acute toxicity substudy patient self-assessments of acute adverse effects (breast soreness, reddening, swelling and blistering) were recorded using patient diary cards completed weekly during radiotherapy and for at least 4 weeks post-radiotherapy. The scores were recorded as "none", "a little", "quite a bit" or "very much". If symptoms persisted, patients were asked to continue scoring their adverse effects on a weekly basis until all scores were graded as "none" or "a little". The submitted patient diaries showed low data completion to the extent that the results were not considered of value to be included in the submitted manuscript.

Acute skin reactions scoring scales

Modified RTOG scale (acute toxicity study I)

Grade 0: No visible change

Grade 1: Faint/dull erythema

Grade 2: Tender/bright erythema +/- dry desquamation

Grade 3: Patchy moist desquamation, moderate oedema

Grade 4: Confluent moist desquamation, pitting oedema

CTCAE version 4.03 (acute toxicity study II)

Grade 1: Faint erythema or dry desquamation

Grade 2: Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin fold and creases; moderate oedema

Grade 3: Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion

Grade 4: Life threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated

Grade 5: Death

Endpoints

The primary endpoint for each of the sub-studies was the proportion of patients within each treatment group with grade $\geq$3 toxicity (RTOG and CTCAE respectively) at any time from the start of radiotherapy to 4 weeks after completion of radiotherapy. The secondary endpoints were clinical assessment of (i) any acute skin toxicity, defined as the worst grade reported from the start of radiotherapy to 4 weeks post-radiotherapy, (ii) acute skin toxicity during radiotherapy, defined as the worst grade reported from the start to the end of radiotherapy, (iii) acute skin toxicity post radiotherapy, defined as the worst grade reported at completion of radiotherapy until at least 4 weeks post radiotherapy and (iv) adherence to the acute toxicity assessments.

Statistical considerations

Each sub-study aimed to recruit approximately 150 evaluable patients (50 per group) in order to exclude a within-group rate of grade $\geq$3 acute skin reactions of over 11% compared to target rate of under 3% (89% power and one-sided 7.9% significance level). The sample size was informed by data from the FAST pilot trial [26] .

Principal analyses were based on the evaluable population, defined as all patients randomised into the study receiving at least one fraction of radiotherapy (regardless of whether they were later found to be ineligible or a protocol violator) and with complete data, or, at most, one missing toxicity assessment. For the first sub-study which included some patients receiving a boost, only non-boost assessments were used to define inclusion in the evaluable population. The required number of assessments for a 40 Gy/15Fr patient was 7 (3 during and 4 post-radiotherapy) and 5 for 27 Gy/5Fr and 26 Gy/5Fr patients (1 during and 4 post-radiotherapy). Given the focus of the sub-studies on safety patients who switched to receive a different trial treatment after randomisation were analysed according to treatment received rather than randomised treatment.

For the primary endpoint, the proportion of patients within each treatment group with grade $\geq$3 RTOG toxicity (first sub-study) or grade $\geq$3 CTCAE toxicity (second sub-study) was estimated with associated upper one-sided 95% confidence interval. Secondary endpoints were estimated as frequencies and percentages, with the prevalence of grades $\geq$1, $\geq$2 and $\geq$3 toxicity at each time-point presented graphically. Adherence to toxicity assessments was estimated as frequencies and percentages. Toxicity data were included as reported, there were no restrictions based on the date of assessment. The acute toxicity sub-study was designed to be non-comparative so no statistical comparisons were made across the treatment groups.

Results

Recruitment to the first acute toxicity sub-study opened in November 2011 and closed in May 2012. Of 194 potentially eligible patients recruited in sub-study centres, 190 patients consented (63, 63 and 64 in the 40 Gy/15Fr, 27 Gy/5Fr and 26 Gy/5Fr groups, respectively). Recruitment was performed at 7 treating centres across the UK with the infrastructure to carry out weekly toxicity assessments.

Recruitment to the second acute toxicity sub-study opened in April 2013 and closed in February 2014. Of 269 potentially eligible patients recruited in the 8 sub-study centres, 162 patients consented (55, 44 and 63 in the 40 Gy/15Fr, 27 Gy/5Fr and 26 Gy/5Fr groups, respectively). Two patients subsequently withdrew consent for all data to be used. The number of patients potentially eligible, consented, receiving allocated radiotherapy and evaluable for the primary endpoint for each sub-study is given in Figure 3.

Figure 3: Flow diagram of participation in the first and second acute toxicity sub-studies

Reproduced from Brunt et al (2016) (CC BY 4.0)[3]
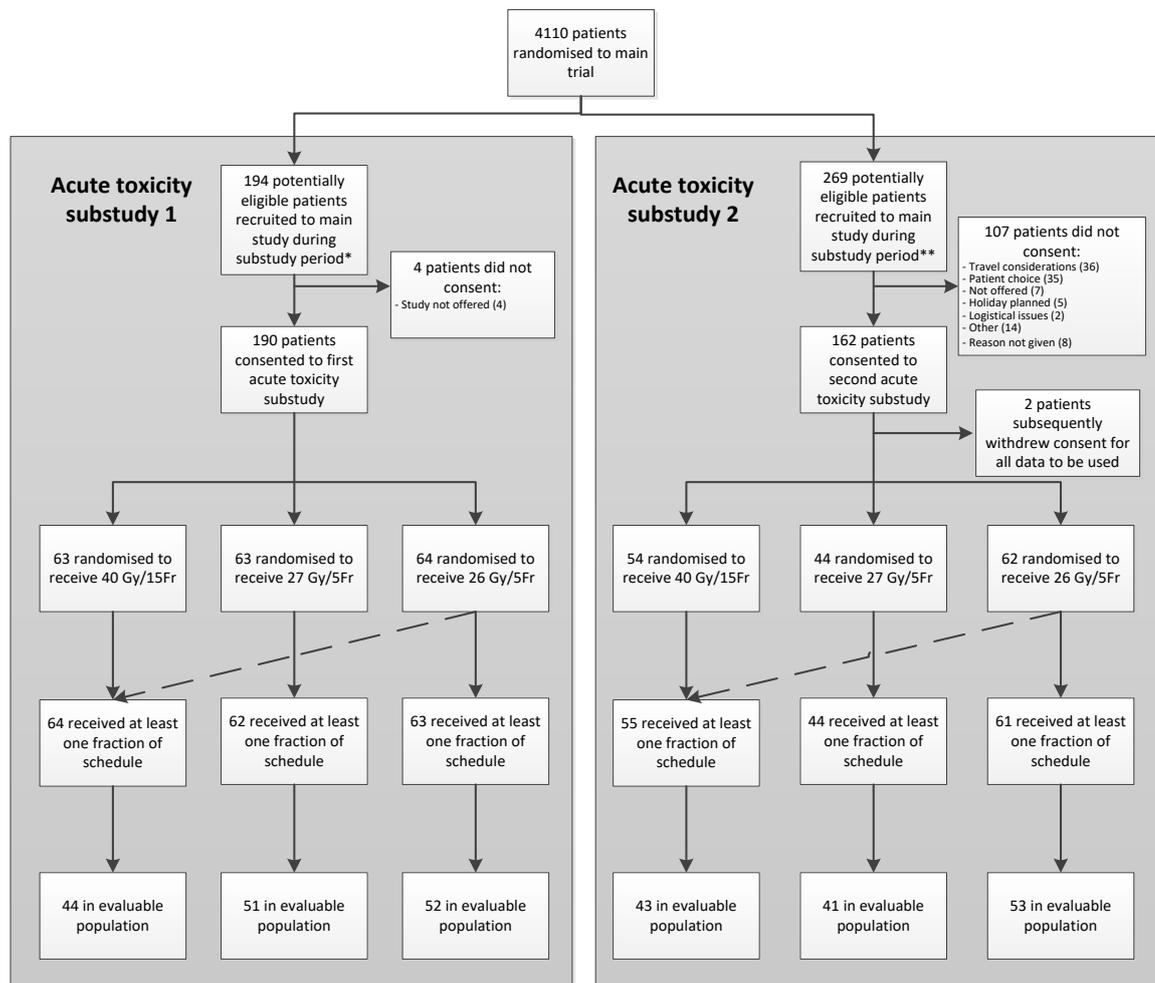
*- All patients recruited at sub-study centres during sub-study period
**- All patients recruiting at sub-study centres during sub-study period for whom a boost was not planned

Patients recruited to the sub-studies were broadly comparable with those of the whole trial population [3]. Radiotherapy treatment characteristics (for each sub-study separately) are presented in Appendix 2, Table 36, suggesting no significant imbalances between groups. Compliance to toxicity assessments by treatment group is shown in Appendix 2, Table 37. For the first acute toxicity sub-study, worst RTOG grade experienced by treatment received is reported in Table 2. The proportions of evaluable patients with grade 3 RTOG toxicity during the acute phase were as follows: 40 Gy/15Fr 6/44 (13.6%); 27 Gy/5Fr 5/51 (9.8%); 26 Gy/5Fr 3/52 (5.8%). Twenty-nine patients in the first sub-study received a boost to their treatment, of which 22 were evaluable. No evidence of a higher rate of grade 3 toxicity was observed in this subset of patients (40 Gy/15Fr 1/9 (11.1%); 27 Gy/5Fr 0/10; 26 Gy/5Fr 0/3).

For the second acute toxicity sub-study, worst CTCAE grade experienced by treatment received is reported in Table 3. The proportions of evaluable patients with a grade 3 CTCAE toxicity during the acute phase were as follows: 40 Gy/15Fr 0/43; 27 Gy/5Fr 1/41 (2.4%); 26 Gy/5Fr 0/53. Grade 2 toxicity was largely due to moderate to brisk erythema, with only 3 patients with moderate oedema (two 40 Gy/15Fr and one 26 Gy/5Fr patient), see Appendix 2, Table 38. CTCAE toxicity score reported at each time point is presented graphically during radiotherapy and post radiotherapy (Figure 4). A single patient in the second cohort randomised to the 27 Gy/5Fr group after mastectomy, adjuvant cytotoxic chemotherapy and chest wall radiotherapy with bolus was assessed as a CTCAE grade 3 toxicity recorded after a missed assessment by telephone appointment 36 days after start of treatment, having been assessed as grade 2 seven days before and assessed with grade 1 erythema seven days later.

Table 1: Acute toxicity sub-study 1 - Acute skin toxicities reported

Worst RTOG grade (on or post RT)	40 Gy/15Fr N=44 N (%)[1]	27 Gy/5Fr N=51 N (%)[1]	26 Gy/5Fr N=52 N (%)[1]
0	0	2 (4)	3 (6)
1	14 (32)	24 (47)	32 (62)
2	24 (55)	20 (39)	14 (27)
3	6 (14)	5 (10)	3 (6)
4	0	0	0
Percentage of RTOG grade 3+ (upper limit of 1-sided 95% CI)	13.6 (25.2%)	9.8 (19.5%)	5.8 (14.2%)

[1]Percentages calculated from those evaluable

Table 2: Acute toxicity sub-study 2 - Worst acute CTCAE score according to treatment

CTCAE grade	40 Gy/15Fr N=43 N (%)[1]	27 Gy/5Fr N=41 N (%)[1]	26 Gy/5Fr N=53 N (%)[1]
0	0	3 (7)	3 (6)
1	21 (49)	26 (63)	31 (58)
2	22 (51)	11 (27)	19 (36)
3	0	1 (2)[2]	0
4	0	0	0
Proportion grade 3+ (upper limit of 1-sided 95% CI)	0 (6.7%)	2.4 (11.1)%	0 (5.5)%

[1]Percentages calculated from those evaluable
[2]Grade 3 toxicity reported at 4 weeks post-RT resolved to grade 1 one week later

Figure 4: Acute toxicity sub-study 2 – Prevalence of grade 1+, grade 2+ and grade 3+ CTCAE toxicity.

Reproduced from Brunt et al (2016) (CC BY 4.0)[3]
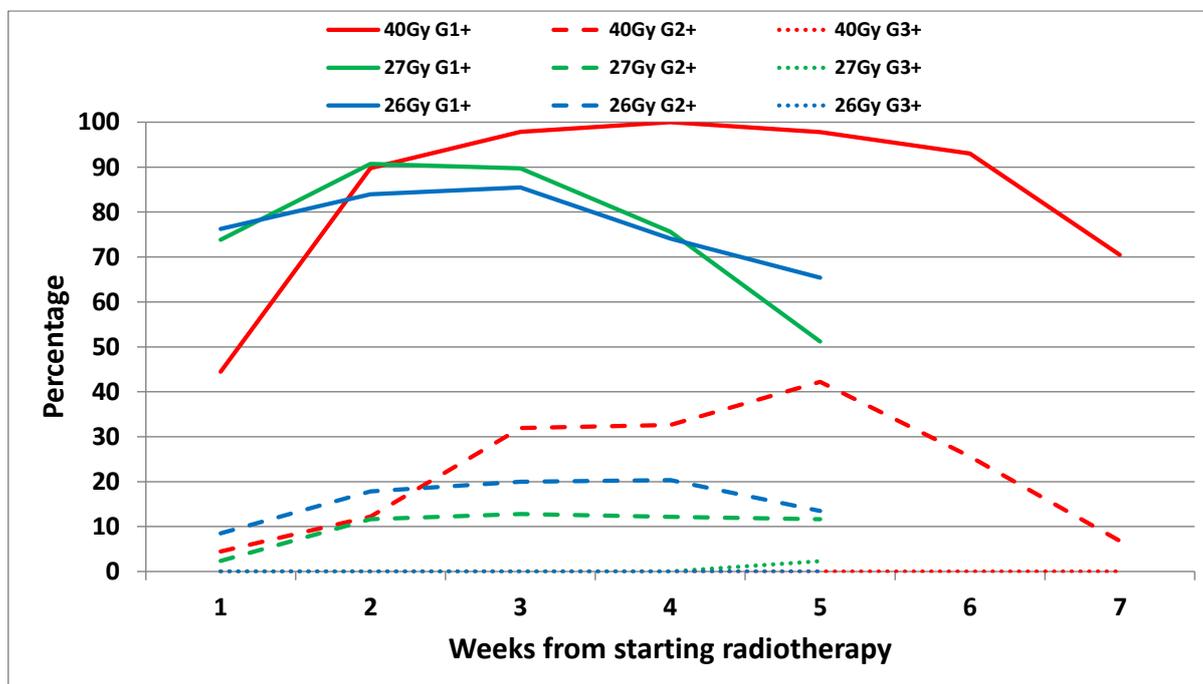
Grade 3 toxicity reported at 4 weeks post-RT in 27 Gy in 5 Fr patient resolved to grade 1 one week later

Discussion

The acute skin toxicity sub-studies were not designed to involve statistical hypothesis testing across treatment groups, but to confirm low incidence rates of clinically significant acute skin toxicity associated with each schedule. On this basis, the results raised no concerns that the 5-day schedules led to more severe or longer-lasting acute skin reactions compared with 40 Gy in 15 fractions. The prevalence rates suggested that erythema after the 1-week schedule was less intense and settled about 2 weeks earlier than after the 3-week schedule. An imbalance in numbers in the 27 Gy group was attributed to the play of chance, since consent to participate in the sub-study was obtained prior to allocation of randomised treatment. Overall compliance with the toxicity assessments was high, making it unlikely that patients developing severe skin reactions were under-reported. No suggestion of a dose response was noted between the 2 dose levels of the 5-fraction test regimens. The results of the first toxicity sub-study were consistent with those from the second sub-study, despite the unhelpful inclusion of oedema with erythema and desquamation in the RTOG system used for scoring early skin reactions.

The mildness of the acute skin toxicity associated with the 5-fraction regimens was expected. A series of classic studies investigating the dependence of acute skin reactions on total dose, fraction size, inter-fraction interval and overall treatment time was undertaken in the 1980s and 1990s by Turesson and colleagues, using reflectance spectrophotometry to quantify erythema and clinical grading to score moist desquamation [65-67]. These confirmed the absence of a treatment time effect for the first 4 weeks of radiotherapy delivered using fraction sizes of 2.0 Gy and 4.0 Gy delivered using 12 MeV electrons to the internal mammary chain daily or twice per week [65]. Using the same experimental system, whereby different fractionation regimens were delivered to the right and left internal mammary chains of the same patient, weak dependence of erythema and desquamation on fraction size was demonstrated, with estimates of α/β ratios between 7.5 and 11.2 Gy [66]. In the context of the FAST-Forward trial, the reductions in total dose, from 40 Gy to 27 Gy and 26 Gy appear to compensate for increased dose per fraction where acute skin reactions are concerned. In conclusion, the acute skin toxicity sub-studies conducted in patients entered into the FAST-Forward trial raised no concerns and showed that short-term effects are if anything milder, and shorter lasting.

CHAPTER 5: MAIN TRIAL

Recruitment

Between November 2011 and June 2014, 4110 patients were enrolled in the FAST-Forward trial from 97 UK centres (47 radiotherapy centres and 50 referring hospitals; Appendix 2 Table 31). The trial completed recruitment 17 months ahead of schedule (Figure 5). 190 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.

Figure 5: Target and actual recruitment for FAST-Forward Main Trial
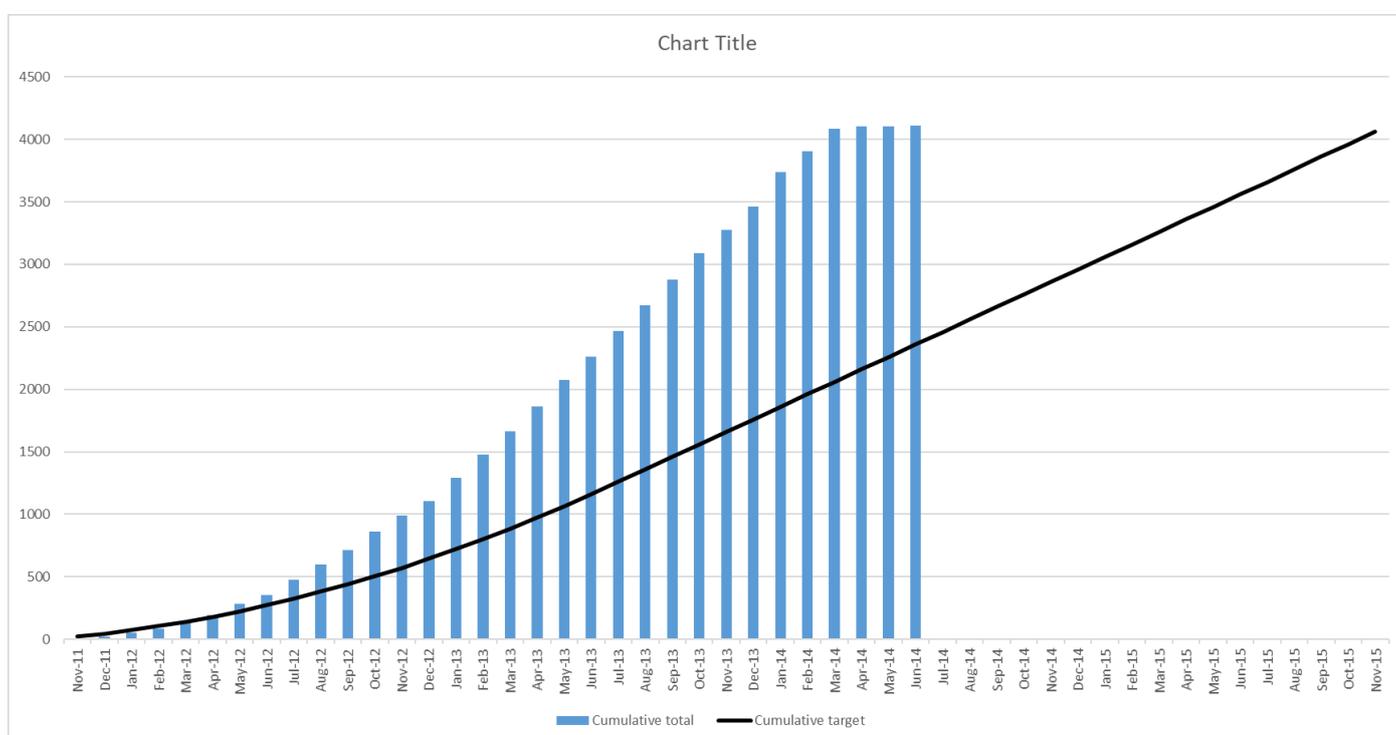
The original target for recruitment was based on 5 centres opening to recruitment once the trial opened with a further 1 centre expected to open per month until a total of 25 centres were open to recruitment. Each centre was predicted to recruit 4 patients per month. Using these figures it was predicted that recruitment would take 54 months to attain. Appendix 3, Figure 20 shows that over 100 centres opened to recruitment which allowed the target to be reached 17 months early. 72 centres recruited at a rate of at least one patient a month.

Deviations and withdrawals

Fourteen patients withdrew consent for use of data and were removed from the intention-to-treat population, therefore results are reported for 4096 consenting participants. A total of 40 patients (7 in 40 Gy, 12 in 27 Gy, 21 in 26 Gy) did not receive the allocated therapy (Figure 6); compliance with allocated treatment was therefore 99% (4056/4096). These 40 patients included 6 found to be ineligible after randomisation: 2 in the 27 Gy group (1 with relapse detected after recruitment so radiotherapy cancelled, and 1 with tissue expander in situ) and 4 in the 26 Gy group (3 with metastases detected before start of radiotherapy, and 1 with previous DCIS in contralateral breast).

A total of 22 patients withdrew from clinical follow-up before 5 years, and 1 was lost to follow-up. Of the 1798 patients who consented to participate in the PRO sub-study, 181 had withdrawn from the PRO questionnaires by 5 years.

Data returns

Baseline forms were received for 100% out of those expected. Data return rates of annual follow-up forms were over 90%, with 5-year visit forms available for 3733 (98%) patients out of 3798 still in follow-up (not died, withdrawn or lost). Data returns for individual forms are shown in Appendix 2, Table 39 and are correct up to 1st March 2022.

Figure 6: **FAST-Forward Main Trial Profile (CONSORT flow diagram)** *(Reproduced from Brunt et al. (2020) (CC BY 4.0)[1]*
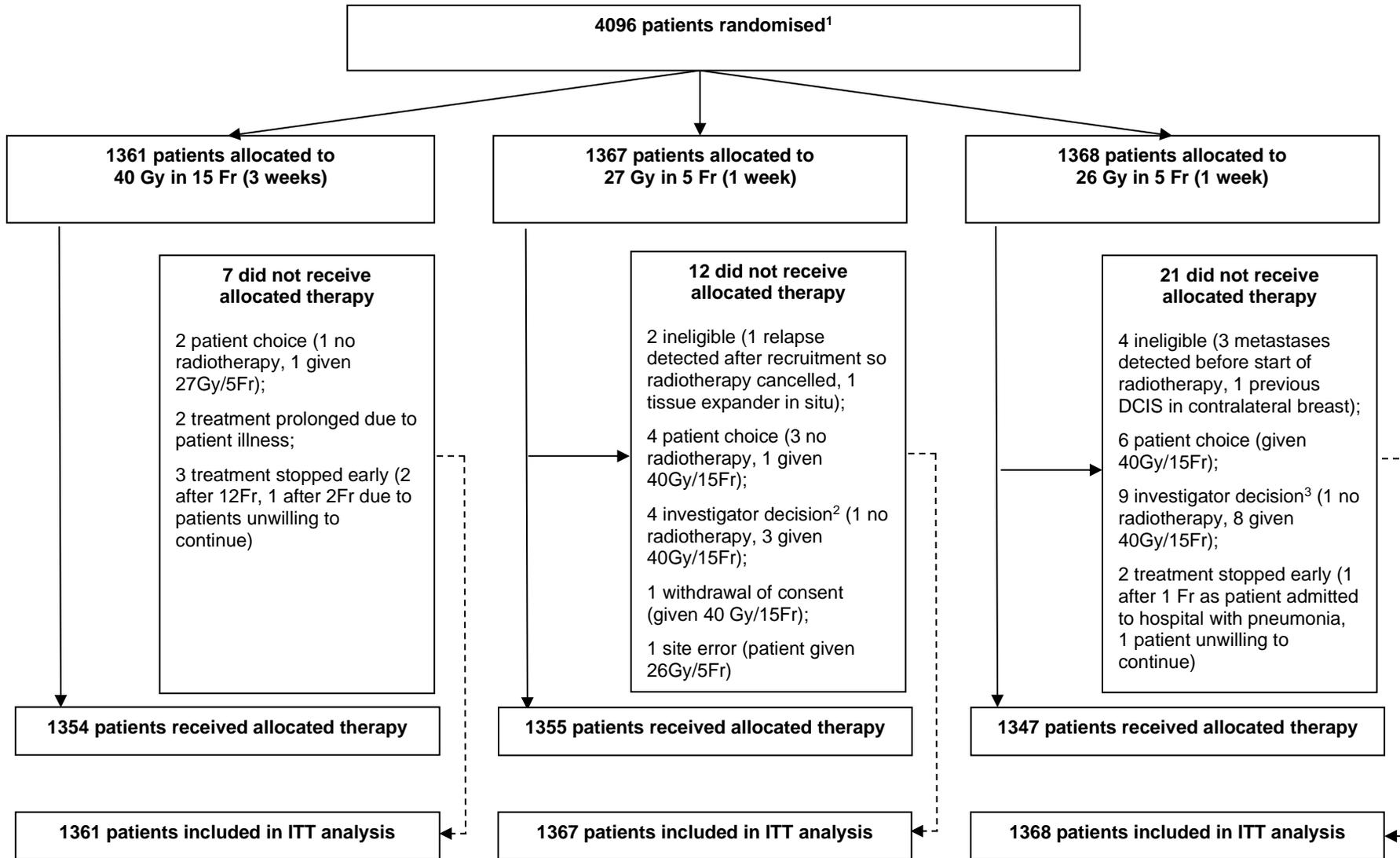
Baseline data

Demographic and clinical characteristics at baseline were well-balanced between groups (Table 4). Overall, 2551/4096 (62%) were classified as low-risk (age >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-adjuvant or adjuvant chemotherapy, 3512/3649 (96%) ER positive patients had endocrine therapy, and 311/407 (76%) HER2 positive patients received trastuzumab. Medical history details at randomisation are presented in Appendix 2, Table 40 and radiotherapy details are in Table 5.

Table 3: Demographic, clinical and treatment characteristics at randomisation of the 4096 patients consenting to the FAST-Forward Main Trial[1]

Reproduced from Brunt et al. (2020) (CC BY 4.0)[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 (1)	16 (1)	28 (2)
40-49	186 (14)	173 (13)	189 (14)
50-59	440 (32)	423 (31)	414 (30)
60-69	506 (37)	511 (37)	524 (38)
70-79	175 (13)	197 (14)	172 (13)
≥80	42 (3)	47 (3)	41 (3)
Sex			
Female	1355 (99)	1365 (99)	1362 (99)
Male	6 (<1)	2 (<1)	4 (<1)
Not known	0	0	2
Tumour grade			
1	315 (23)	315 (23)	300 (22)
2	660 (48)	663 (48)	690 (50)
3	386 (28)	389 (28)	378 (28)
Risk group			
Low (age ≥50 & grade 1 or 2)	843 (62)	854 (62)	854 (62)
High (age <50 and/or grade 3)	518 (38)	513 (37)	514 (38)
Primary surgery			
Breast conservation surgery	1270 (93)	1278 (94)	1284 (94)
BCS with oncoplastic technique	*42*	*33*	*42*
Mastectomy	91 (7)	89 (6)	84 (6)
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)	674 (49)	662 (48)
Right	635 (47)	693 (51)	704 (51)
Not known	0	0	2
Maximal extent of axillary staging			

	40 Gy / 15 Fr N=1361 (%)	27 Gy / 5 Fr N=1367 (%)	26 Gy / 5 Fr N=1368 (%)
Sentinel node biopsy/guided axillary sampling	1157 (85)	1184 (87)	1164 (85)
Axillary clearance	200 (15)	181 (13)	201 (15)
Other	4 (<1)	2 (<1)	1 (<1)
Not known	0	0	2
Pathological node status			
Positive	257 (19)	243 (18)	256 (19)
Negative	1103 (81)	1124 (82)	1110 (81)
Not known	1	0	2
Histological type			
Infiltrating ductal	1084 (80)	1096 (80)	1086 (80)
Lobular	144 (11)	139 (10)	127 (9)
Mixed	51 (4)	63 (5)	65 (5)
Other	82 (6)	69 (5)	87 (6)
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 (<1)	5 (<1)	6 (<1)
T1a	69 (5)	68 (5)	51 (4)
T1b	258 (19)	270 (20)	256 (19)
T1c	612 (45)	601 (44)	602 (44)
T2	394 (29)	389 (28)	424 (31)
T3	21 (1)	30 (2)	25 (2)
Not known	3	4	4
ER / HER2 status			
ER+ / HER2+	103 (8)	103 (8)	93 (7)
ER+ / HER2-	1108 (82)	1130 (83)	1097 (81)
ER- / HER2+	32 (2)	34 (2)	42 (3)
ER- / HER2-	111 (8)	96 (7)	128 (9)
Not known	7	4	8
PgR status			
Positive	577 (73)	541 (70)	566 (70)
Negative	212 (27)	229 (30)	245 (30)
Not done	571	596	555
Missing on form	1	1	2
Lymphovascular invasion			
Present	186 (14)	178 (14)	202 (15)
Absent	1085 (83)	1084 (83)	1055 (81)
Uncertain	34 (3)	40 (3)	51 (4)
Not known	56	65	60
Neo-adjuvant chemotherapy received			
Yes	48 (3)	56 (4)	43 (3)
No	1312 (97)	1311 (96)	1323 (97)
Not known	1	0	2
Adjuvant therapy received[2]			
All patients:			
Chemotherapy[3]	333/1360 (24)	324/1367 (24)	370/1366 (27)
HER2 + patients:			
Trastuzumab	100/135 (74)	98/137 (71)	113/135 (84)
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:			

	40 Gy / 15 Fr N=1361 (%)	27 Gy / 5 Fr N=1367 (%)	26 Gy / 5 Fr N=1368 (%)
Endocrine therapy	1169/1216 (96)	1186/1237 (96)	1157/1196 (97)
Boost given			
Yes	342 (25)	337 (25)	332 (24)
No	1017 (75)	1027 (75)	1031 (76)
Not known	2	3	5
Boost dose	N=342	N=337	N=332
10 Gy/5fr	260 (76)	273 (81)	257 (77)
16 Gy/8fr	80 (24)	64 (19)	75 (23)
Not known	2	0	0

%s calculated out of those with data available; 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 + anthracycline (N=348), taxane + other; e.g. TCH, TCarbo (N=83), other (N=3)

Table 4: Radiotherapy details for the 4090 treated patients in the FAST-Forward Main Trial[1]

Radiotherapy (RT) details	40 Gy/15Fr N=1360 (%)	27 Gy/5Fr N=1363 (%)	26 Gy/5Fr N=1367 (%)
Days from randomisation to starting RT			
N	1358	1362	1361
Median (IQR)	22 (17-29)	22 (18-29)	22 (18-29)
Range	3-219	3-155	3-281
Days of RT with no boost (including weekends and bank holidays)			
N	1017	1025	1029
Median (IQR)	21 (21-22)	7 (5-7)	7 (5-7)
Range	2[3]-51	5-22	1[3]-33
Days of RT with a boost (including weekends and bank holidays)			
N	341	337	332
Median (IQR)	29 (28-31)	14 (12-15)	14 (14-16)
Range	14-43	5-35	5-29
Methods used to localise tumour bed[2]			
Surgical clips	1203 (90)	1184 (88)	1192 (89)
Gold seeds	2 (<1)	2 (<1)	0 (0)
Other	114 (8)	153 (11)	137 (10)
None	23 (2)	14 (1)	15 (1)
Not known	18	10	23
Volume of breast/chest wall PTV (cc)			
N	1353	1350	1343
Median (IQR)	908 (568-1281)	942 (584-1352)	875 (570-1287)
Range	1-9642	20-3331	3-8908
Bolus used (mastectomy patients only)	N=91	N=89	N=84
Yes	62 (68)	58 (66)	55 (66)
No	29 (32)	30 (34)	28 (34)
Not known	0	1	1
Dose homogeneity constraints achieved			
Yes	1299 (96)	1311 (96)	1298 (96)
No	58 (4)	49 (4)	60 (4)
Not known	3	3	9
Organs at risk dose constraints achieved			
Yes	1332 (98)	1335 (98)	1338 (98)
No	24 (2)	25 (2)	20 (2)
Not known	4	3	9
Was patient re-planned during radiotherapy?			
Yes	25 (2)	12 (1)	10 (1)
No	1333 (98)	1349 (99)	1352 (99)
Not known	2	2	5
Whole breast RT extended by >3 days			
Yes	23 (2)	5 (<1)	7 (<1)
No	1335 (98)	1357 (99)	1355 (99)
Not known	2	1	5
Reasons[3]:			
Bank holidays	*15*	*1*	*4*

Radiotherapy (RT) details	40 Gy/15Fr N=1360 (%)	27 Gy/5Fr N=1363 (%)	26 Gy/5Fr N=1367 (%)
Machine service or breakdown	*4*	*0*	*0*
Patient illness	*9*	*2*	*1*
Other	*4*	*1*	*1*

[1] 14 patients withdrew consent for any of their data to be used in analysis & 6 patients received no RT

[2] >1 method of localisation of tumour bed possible

[3] >1 reason for extension of RT possible

Follow-up

Calculating length of follow-up as the time between randomisation and date last seen (censoring at date of death or withdrawal of consent from follow-up where applicable), median follow-up in Main Trial patients at the time of the primary analysis data snapshot (22/11/2019) was 71.5 months (IQR 71.3 - 71.7). Five-year visit forms were available for 3733 (98%) patients out of 3798 still in follow-up (not died, withdrawn or lost).

5-year cancer outcomes in the Main Trial

After a median follow-up of 71.5 months (IQR 71.3, 71.7), ipsilateral breast tumour relapse (IBTR) was recorded in 79 patients (40 Gy: 31, 27 Gy: 27, 26 Gy: 21) Table 6. Estimated cumulative incidence of IBTR up to five years was 2.1% (95%CI 1.4, 3.1) for 40 Gy (expected incidence 2%), 1.7% (1.2, 2.6) for 27 Gy and 1.4% (0.9, 2.2) for 26 Gy (Table 7, Figures 7 and 8). Estimated absolute differences in IBTR versus 40 Gy were -0.3% (-1.0, 0.9) for 27 Gy and -0.7% (-1.3, 0.3) for 26 Gy. Since the upper confidence limits excluded an increase in IBTR of >1.6%, non-inferiority can be claimed for both 5-fraction schedules compared with 40 Gy in 15 fractions. This is confirmed by a test against the critical HR>1.81, with p=0.0022 for 27 Gy and p=0.00019 for 26 Gy compared with 40 Gy. Analyses in the per protocol population were consistent (estimated absolute difference versus 40 Gy -0.4%; (-1.0,0.8), p=0.0017 for 27 Gy and -0.6% (-1.2,0.4), p=0.00037 for 26 Gy; 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 26 Gy versus 27 Gy. The unadjusted α/β estimate for IBTR was 3.7 Gy (0.3, 7.1 Gy), with EQD2 estimates of 44.7 Gy for 40 Gy, 43.1 Gy for 27 Gy and 40.6 Gy for 26 Gy with no correction for treatment time. Adjusting for risk group and ER/HER2 status made minimal difference (adjusted α/β estimate 3.7 Gy; 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 19 (HRs from competing risks model: 0.85 (95%CI 0.51, 1.43) for 27 Gy versus 40 Gy; 0.67 (0.38, 1.16) for 26 Gy versus 40 Gy).

Regional relapses occurred in 34/4096 (1%) patients (40 Gy: 13, 27 Gy: 11, 26 Gy: 10; Table 6), 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 7, Figures 9-10, Appendix 3, Figures 21-26). Invasive contralateral breast cancer was reported for 55/4096 (1%) patients (40 Gy: 18, 27 Gy: 17, 26 Gy: 20; Table 18), and non-breast second primary cancers for 123/4096 (3%) patients (40 Gy: 42, 27 Gy: 37, 26 Gy: 44; Table 18), 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 6). Of 27 patients with a cardiac-related death (40 Gy: 10, 27 Gy: 9, 26 Gy: 8), 15 (40 Gy: 7, 27 Gy; 4, 26 Gy: 4) had a history of cardiac disease reported at randomisation or was a current/ex-smoker in past year.

Table 5: Relapses, second primary cancers and deaths by fractionation schedule, in 4096 patients consenting to the FAST-Forward Main Trial *Reproduced from Brunt et al. (2020) (CC BY 4.0)[1]*

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 40 Gy, 2 in 26 Gy)

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

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

Table 6: Relapse and mortality by fractionation schedule: results of time to event analyses for 4096 patients consenting to the FAST-Forward trial *Reproduced from Brunt et al. (2020) (CC BY 4.0)[1]*

	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 40 Gy/15fr (control);

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

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

[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)

Figure 7: Kaplan-Meier plot of ipsilateral breast tumour relapse in Main Trial

Number at risk (events)

40Gy	1361	(1)	1347	(7)	1307	(7)	1281	(7)	1230	(5)	1046	(4)	486
27Gy	1367	(4)	1352	(8)	1328	(4)	1303	(6)	1255	(1)	1066	(3)	508
26Gy	1368	(4)	1347	(5)	1325	(3)	1302	(4)	1257	(2)	1070	(2)	524
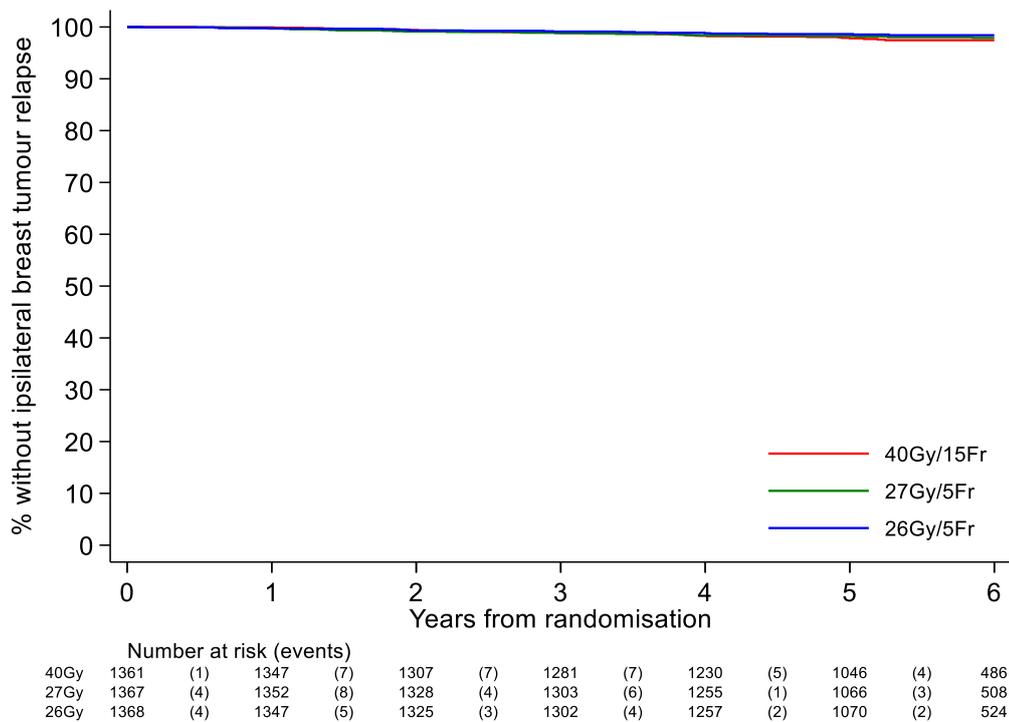
Figure 8: Cumulative risk of ipsilateral breast tumour relapse in Main Trial

Number at risk (events)

40Gy	1361	(1)	1347	(7)	1307	(7)	1281	(7)	1230	(5)	1046	(4)	486
27Gy	1367	(4)	1352	(8)	1328	(4)	1303	(6)	1255	(1)	1066	(3)	508
26Gy	1368	(4)	1347	(5)	1325	(3)	1302	(4)	1257	(2)	1070	(2)	524
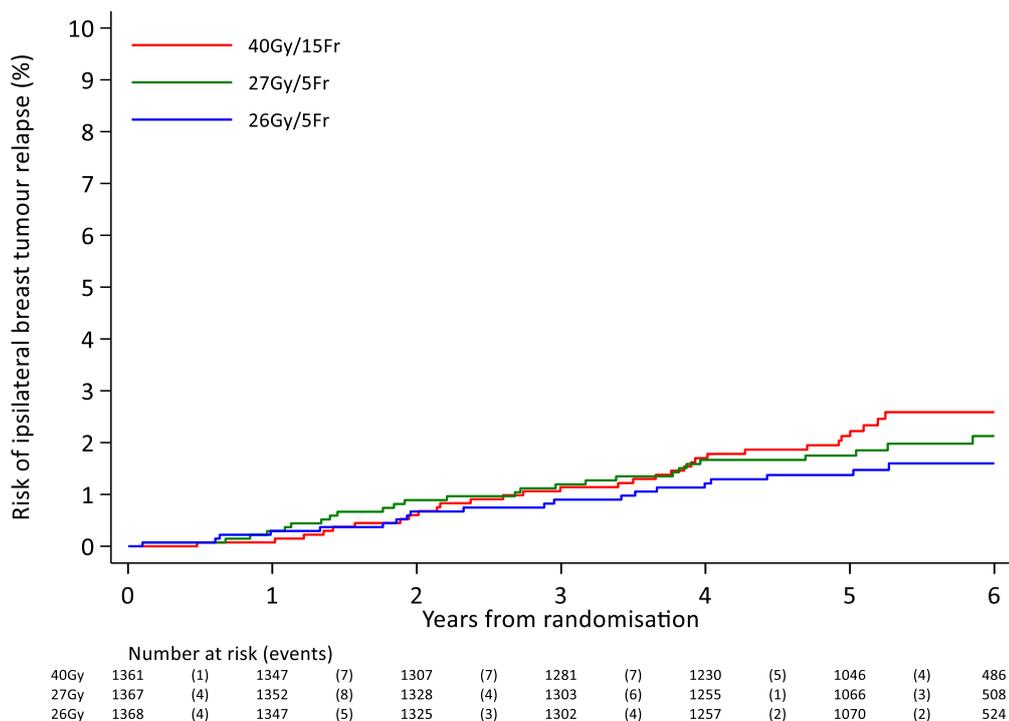
Figure 9: Kaplan-Meier plot of disease-free survival in Main Trial

Number at risk (events)												
40Gy	1361	(18)	1335	(22)	1292	(28)	1253	(15)	1204	(20)	1017	(12)	475
27Gy	1367	(12)	1348	(24)	1313	(23)	1277	(21)	1229	(16)	1038	(10)	493
26Gy	1368	(18)	1336	(27)	1305	(26)	1270	(20)	1220	(9)	1044	(10)	513
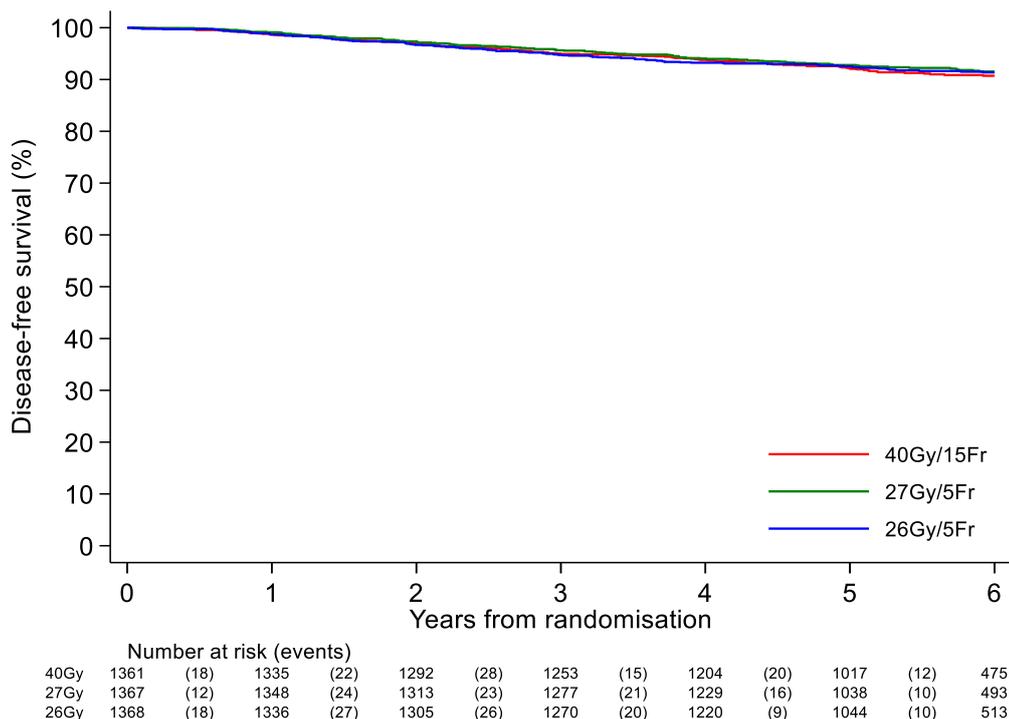
Figure 10: Cumulative risk of any breast cancer-related event* in Main Trial

Number at risk (events)												
40Gy	1361	(18)	1335	(22)	1292	(28)	1253	(15)	1204	(20)	1017	(12)	475
27Gy	1367	(12)	1348	(24)	1313	(23)	1277	(21)	1229	(16)	1038	(10)	493
26Gy	1368	(18)	1336	(27)	1305	(26)	1270	(20)	1220	(9)	1044	(10)	513
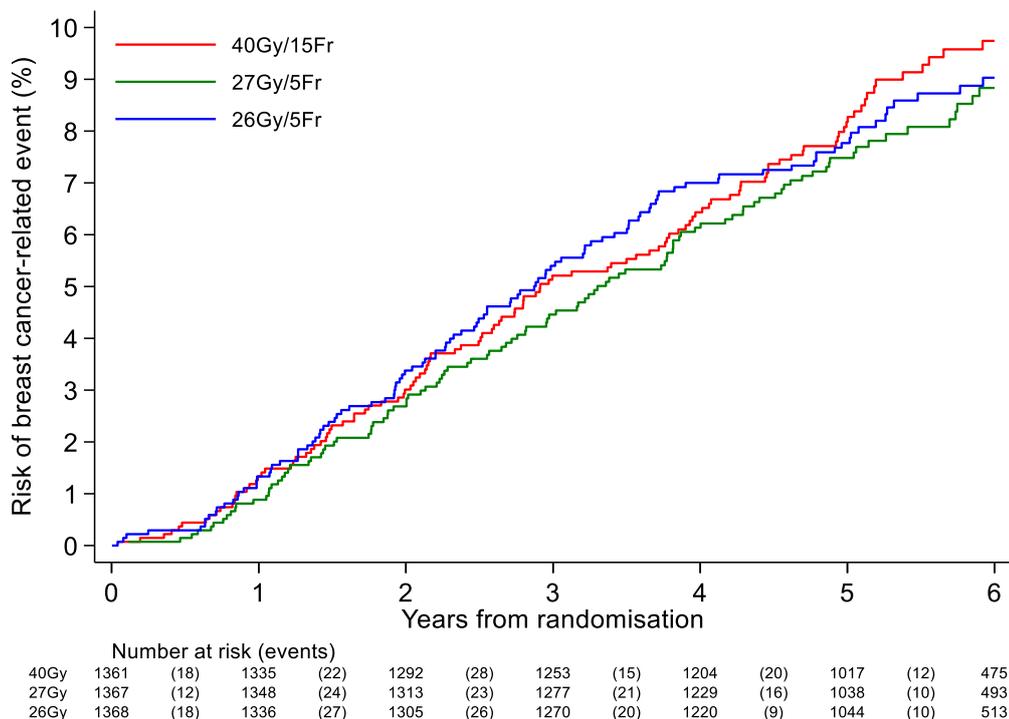
* Any breast cancer-related event includes local, regional or distant relapse, breast cancer death, contralateral breast cancer

Late normal tissue effects up to 5 years' follow-up in the Main Trial

Clinician assessments

At least one annual clinical assessment of NTE was available for 3975/4096 (97%) patients. Frequencies of clinician-assessed NTE according to year of follow-up (from 1-4 years) and fractionation schedule are shown in Appendix 2, Table 41. Bar charts of clinician-assessed NTE from 1-5 years are presented in Appendix 3, Figures 27-33. Cross-sectional analyses of clinician-assessed NTE at 5 years are in Table 8. At 5 years, any moderate/marked clinician-assessed NTE in the breast/chest wall was reported for 98/986 (10%) patients in the 40 Gy group, 155/1005 (15%) for 27 Gy and 121/1020 (12%) for 26 Gy (Table 8, Figure 11), with a statistically significant difference between 40 Gy and 27 Gy (p=0.0003) but not between 40 Gy and 26 Gy (p=0.17). Breast shrinkage was the most prevalent moderate/marked effect at 5 years, reported in 50/916 (6%) for 40 Gy, 78/948 (8%) for 27 Gy and 65/954 (7%) for 26 Gy (Table 8). 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 27 Gy group compared with 40 Gy (OR 1.55; 1.32, 1.83; p<0.0001), with no statistically significant difference between 26 Gy and 40 Gy (OR 1.12; 0.94, 1.34; p=0.20); Table 9. This pattern was similar for the individual effects of breast distortion, shrinkage, induration and breast/chest wall oedema, with statistically significant higher risk for 27 Gy compared with 40 Gy but not for 26 Gy (Table 9, Appendix 3, Figures 34-40). Comparing the two 5-fraction schedules, 26 Gy had statistically significantly lower risk of any moderate/marked breast/chest wall NTE (p=0.0001) and breast shrinkage (p=0.0018) compared with 27 Gy. 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 40 Gy, 35.1% (32.4, 37.9) for 27 Gy and 28.5% (26.0, 31.1) for 26 Gy (Table 10). 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 7: Cross-sectional analysis of clinician-assessed late normal tissue effects at 5 years according to fractionation schedule for 3626 patients with 5-year assessments

| | 40 Gy N=1197 (%) | 27 Gy N=1220 (%) | 26 Gy N=1209 (%) | Moderate/Marked vs. None/Mild | | | | | |
| | | | | 27 Gy vs. 40 Gy | | 26 Gy vs. 40 Gy | | 27 Gy vs. 26 Gy | |
				Risk difference (95%CI), %	p-value[1]	Risk difference (95%CI), %	p-value[1]	Risk difference (95%CI), %	p-value[1]
Any AE in breast / chest wall[2]				5.5 (2.6, 8.4)	0.0003	1.9 (-0.8, 4.6)	0.17	3.6 (0.6, 6.5)	0.020
None	504 (51)	464 (46)	535 (52)						
Mild	384 (39)	386 (38)	364 (36)						
Moderate	93 (9)	132 (13)	105 (10)						
Marked	5 (<1)	23 (2)	16 (2)						
Not assessed	211	215	189						
Breast distortion[3]				3.1 (1.2, 5.1)	0.0022	2.1 (0.2, 3.9)	0.035	1.0 (-1.0, 3.2)	0.34
None	669 (73)	680 (72)	717 (75)						
Mild	215 (23)	206 (22)	185 (19)						
Moderate	30 (3)	58 (6)	45 (5)						
Marked	2 (<1)	5 (<1)	8 (<1)						
N/A	67	63	59						
Not assessed	214	208	195						
Breast shrinkage[3]				2.8 (0.5, 5.0)	0.022	1.3 (-0.8, 3.5)	0.25	1.4 (-0.9, 3.8)	0.26
None	645 (70)	642 (68)	670 (70)						
Mild	221 (24)	228 (24)	219 (23)						
Moderate	48 (5)	69 (7)	56 (6)						
Marked	2 (<1)	9 (1)	9 (1)						
N/A	67	63	59						
Not assessed	214	209	196						
Breast induration (tumour bed)[3]				2.9 (1.1, 4.8)	0.0018	1.3 (-0.3, 3.0)	0.13	1.6 (-0.3, 3.5)	0.11
None	717 (78)	712 (75)	754 (79)						
Mild	172 (19)	183 (19)	163 (17)						
Moderate	24 (3)	49 (5)	35 (4)						
Marked	1 (<1)	5 (<1)	4 (<1)						
N/A	67	63	59						
Not assessed	216	208	194						
Breast induration (outside tumour bed)[3]				2.0 (1.1, 2.9)	<0.0001	2.0 (1.0, 2.9)	<0.0001	0.0 (-1.3, 1.3)	>0.99
None	859 (94)	878 (93)	879 (92)						
Mild	51 (6)	50 (5)	56 (6)						
Moderate	1 (<1)	14 (1)	17 (2)						
Marked	0	6 (<1)	3 (<1)						
N/A	67	63	59						
Not assessed	219	209	195						
Telangiectasia				1.0 (-0.2, 2.2)	0.14	0.2 (-0.8, 1.3)	0.72	0.7 (-0.5, 1.9)	0.27
None	893 (91)	878 (87)	913 (90)						
Mild	78 (8)	102 (10)	88 (9)						
Moderate	13 (1)	18 (2)	15 (1)						
Marked	1 (<1)	6 (<1)	2 (<1)						

| | 40 Gy N=1197 (%) | 27 Gy N=1220 (%) | 26 Gy N=1209 (%) | Moderate/Marked vs. None/Mild | | | | | |
| | | | | 27 Gy vs. 40 Gy | | 26 Gy vs. 40 Gy | | 27 Gy vs. 26 Gy | |
				Risk difference (95%CI), %	p-value[1]	Risk difference (95%CI), %	p-value[1]	Risk difference (95%CI), %	p-value[1]
Not assessed	212	216	191						
Breast / chest wall oedema				1.1 (0.1, 2.1)	0.042	1.0 (0.0, 1.9)	0.063	0.1 (-1.0, 1.3)	0.87
None	931 (94)	918 (92)	950 (93)						
Mild	47 (5)	66 (6)	51 (5)						
Moderate	6 (<1)	16 (2)	13 (1)						
Marked	1 (<1)	2 (<1)	4 (<1)						
Not assessed	212	218	191						
Breast / chest wall discomfort				-0.2 (-1.8, 1.5)	0.90	0.0 (-1.7, 1.6)	>0.99	-0.2 (-1.8, 1.5)	0.90
None	816 (83)	802 (80)	825 (81)						
Mild	131 (13)	167 (17)	153 (15)						
Moderate	29 (3)	31 (3)	29 (3)						
Marked	7 (<1)	4 (<1)	8 (<1)						
Not assessed	214	216	194						
Other RT-related				0.0 (-0.7, 0.8)	>0.99	0.3 (-0.5, 1.1)	0.63	-0.2 (-1.0, 0.6)	0.81
None	967 (98)	984 (98)	996 (97)						
Mild	12 (1)	17 (2)	17 (2)						
Moderate	6 (<1)	4 (<1)	7 (<1)						
Marked	1 (<1)	4 (<1)	3 (<1)						
Not assessed	211	211	186						

Denominators in column headings show the total number of questionnaires returned at each time-point. Denominators for individual symptoms may vary due to missing items on the questionnaire; percentages are calculated out of totals with data available for each item. [1] p-value for Fisher's exact test; [2] Any AE in breast /chest wall includes breast distortion, breast shrinkage, breast induration (in & outside tumour bed), telangiectasia, breast / chest wall oedema; [3] Applicable following breast conservation surgery or reconstruction. N/A: not applicable (primary surgery mastectomy without immediate reconstruction). Risk ratios not shown as confidence intervals wide, due to low absolute event rates.

Table 8: 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); 0.055
40 Gy	651/6121 (10.6)	1			
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); 0.38
40 Gy	232/5724 (4.0)	1			
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); 0.023
40 Gy	330/5728 (5.8)	1			
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); 0.95
40 Gy	185/5713 (3.2)	1			
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); 0.17
40 Gy	45/5712 (0.8)	1			
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); <0.0001
40 Gy	63/6087 (1.0)	1			
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 9: Survival analyses of moderate/marked clinician-assessed late normal tissue effects by fractionation schedule for 3975 patients in Main Trial with at least one annual clinical assessment *Reproduced from Brunt et al. (2020) (CC BY 4.0)[1]*

Normal tissue effect	Moderate/ Marked events / total[2] (%)	KM estimate (95%CI) of cumulative incidence (%) of moderate/marked events by 5 years[3]	Hazard ratio (95%CI)	Comparison with 40 Gy; p-value[4]	Comparison between 27 Gy & 26 Gy; p-value[4]
Any NTE in the breast / chest wall[1]					
40 Gy	344/1307 (26.3)	26.8 (24.4, 29.4)	1		
27 Gy	468/1339 (34.9)	35.1 (32.4, 37.9)	1.41 (1.23, 1.62)	<0.0001	
26 Gy	380/1326 (28.7)	28.5 (26.0, 31.1)	1.09 (0.95, 1.27)	0.22	0.0002
Breast distortion[5]					
40 Gy	126/1225 (10.3)	10.8 (9.1, 12.7)	1		
27 Gy	190/1265 (15.0)	15.2 (13.2, 17.4)	1.50 (1.20, 1.88)	0.0004	
26 Gy	159/1249 (12.7)	12.8 (11.0, 14.9)	1.25 (0.99, 1.57)	0.066	0.083
Breast shrinkage[5]					
40 Gy	185/1227 (15.1)	14.9 (12.9, 17.1)	1		
27 Gy	247/1265 (19.5)	19.1 (16.9, 21.5)	1.34 (1.11, 1.62)	0.0026	
26 Gy	189/1249 (15.1)	146 (12.7, 16.9)	0.99 (0.81, 1.21)	0.95	0.0018
Breast induration (tumour bed)[5]					
40 Gy	125/1225 (10.2)	10.3 (8.6, 12.2)	1		
27 Gy	178/1266 (14.1)	14.0 (12.1, 16.2)	1.42 (1.13, 1.78)	0.0027	
26 Gy	133/1249 (10.6)	9.9 (8.3, 11.8)	1.04 (0.81, 1.32)	0.78	0.0062
Breast induration (outside tumour bed)[5]					
40 Gy	36/1225 (2.9)	2.9 (2.1, 4.1)	1		
27 Gy	87/1266 (6.9)	6.7 (5.4, 8.3)	2.40 (1.63, 3.54)	<0.0001	
26 Gy	52/1249 (4.2)	4.3 (3.2, 5.7)	1.42 (0.93, 2.17)	0.11	0.0024
Telangiectasia					
40 Gy	36/1305 (2.8)	3.0 (2.1, 4.2)	1		
27 Gy	59/1337 (4.4)	4.8 (3.7, 6.2)	1.61 (1.06, 2.44)	0.023	
26 Gy	52/1324 (3.9)	3.5 (2.6, 4.8)	1.41 (0.92, 2.16)	0.11	0.49
Breast / chest wall oedema					
40 Gy	72/1306 (5.5)	5.5 (4.3, 6.9)	1		
27 Gy	140/1339 (10.5)	10.5 (8.9, 12.3)	1.95 (1.47, 2.59)	<0.0001	
26 Gy	99/1326 (7.5)	7.5 (6.2, 9.2)	1.36 (1.01, 1.85)	0.045	0.0060
Breast / chest wall discomfort					
40 Gy	156/1306 (11.9)	12.2 (10.5, 14.3)	1		
27 Gy	178/1337 (13.3)	13.4 (11.6, 15.5)	1.12 (0.90, 1.39)	0.308	
26 Gy	159/1327 (12.0)	11.8 (10.1, 13.8)	0.99 (0.79, 1.24)	0.94	0.27

KM = Kaplan-Meier, 95%CI = 95% confidence interval;

[1] Any AE in the breast /chest wall = breast distortion, breast shrinkage, breast induration (in & outside tumour bed), telangiectasia and breast / chest wall oedema

[2] Follow-up AE data available for 3978 patients (40 Gy: 1309, 27 Gy: 1340, 26 Gy: 1329), denominators may vary due to missing clinician assessments for some events

[3] Rate estimated at 5 years and 3 months to allow for visits occurring up to 3 months after the due date

[4] p-value for pairwise logrank test

[5] Not applicable after mastectomy (unless reconstructive surgery done)

Figure 11: Kaplan-Meier plot of any moderate / marked clinician-assessed NTE in breast / chest wall (Main Trial)

Number at risk (events)

40Gy/15Fr	1307	(62)	1239	(107)	1099	(49)	1003	(48)	891	(47)	697	(18)	325
27Gy/5Fr	1339	(58)	1276	(192)	1054	(82)	926	(40)	828	(43)	641	(33)	286
26Gy/5Fr	1326	(58)	1258	(123)	1115	(63)	1010	(46)	899	(44)	686	(30)	314
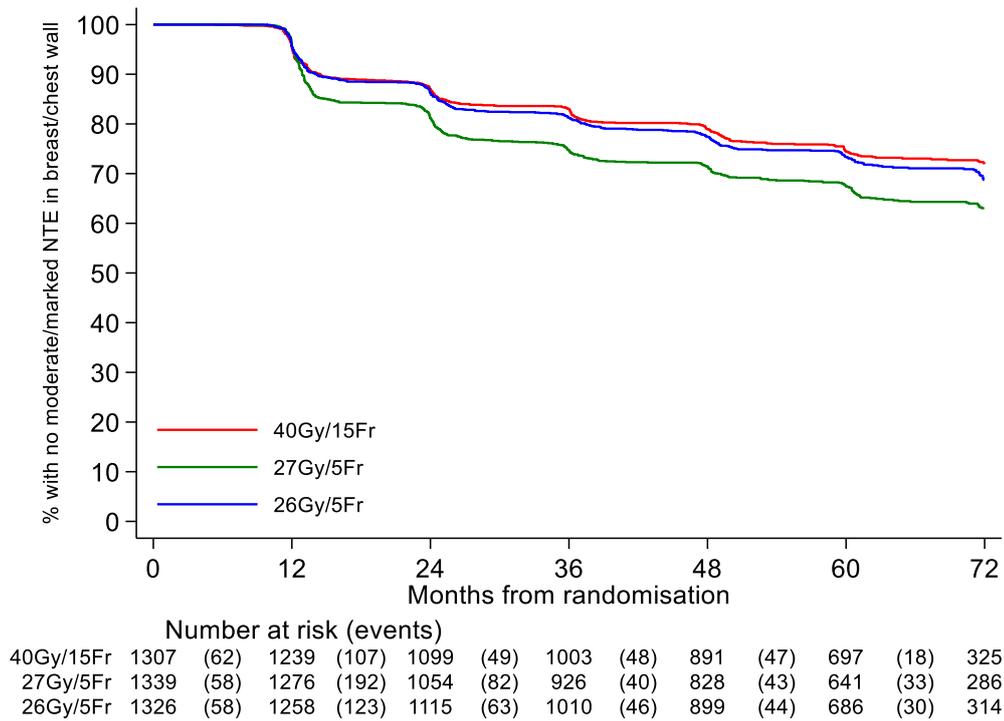
Patient self-assessments

1796 patients consented to the PRO sub-study, of whom 10 withdrew consent immediately after randomisation and 8 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.

Frequencies of patient-assessed breast/chest wall and arm/shoulder/hand symptoms are shown for each time-point from baseline to 2 years and according to fractionation schedule in Appendix 2, Table 42. Cross-sectional analyses of patient-assessed symptoms at 5 years are in Table 11. Bar charts of patient-assessed late adverse effects up to 5 years are presented in Appendix 3. Figures 41-51.

Change in breast appearance had the highest 5-year prevalence, with moderate/marked change reported in 140/432 (32%) for 40 Gy, 158/440 (36%) for 27 Gy and 136/429 (32%) for 26 Gy. There were no statistically significant differences in 5-year prevalence of patient-reported adverse effects between the schedules (Table 11). There was some evidence of an increase in patient-reported moderate/marked breast hardness/firmness at 5 years for 27 Gy compared with 40 Gy 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 27 Gy compared with 40 Gy (OR 1.42, 1.17, 1.72, p=0.0003), and less change in breast appearance for 26 Gy compared with 27 Gy (p=0.0018), but no statistically significant differences between schedules for the other NTE (Table 12).

Table 10: Cross-sectional analysis of patient-assessed late normal tissue effects at 5 years according to fractionation schedule for 1338 patients in the Main Trial with 5-year questionnaire data available *Reproduced from Brunt et al. (2020) (CC BY 4.0)[1]*

| | 40 Gy N=444 (%) | 27 Gy N=450 (%) | 26 Gy N=444 (%) | Moderate/Marked vs. None/Mild | | | | | |
| | | | | 27 Gy vs. 40 Gy | | 26 Gy vs. 40 Gy | | 27 Gy vs. 26 Gy | |
				Risk difference (95%CI), %	p-value[1]	Risk difference (95%CI), %	p-value[1]	Risk difference (95%CI), %	p-value[1]
Protocol-specific items									
Breast appearance changed				3.5 (-2.8, 9.8)	0.28	-0.7 (-6.9, 5.5)	0.83	4.2 (-2.1, 10.5)	0.20
None	77 (18)	79 (18)	86 (20)						
Mild	215 (50)	203 (46)	207 (48)						
Moderate	86 (20)	100 (23)	79 (18)						
Marked	54 (12)	58 (13)	57 (13)						
Missing	12	10	15						
Breast smaller				-0.7 (-6.7, 5.3)	0.88	-4.5 (-10.4, 1.4)	0.14	3.9 (-2.0, 9.6)	0.21
None	145 (14)	153 (35)	166 (39)						
Mild	161 (38)	161 (37)	160 (37)						
Moderate	72 (17)	67 (15)	52 (12)						
Marked	50 (12)	54 (12)	51 (12)						
Missing	16	15	15						
Breast harder/firmer				7.0 (2.0, 12.1)	0.0075	3.2 (-1.7, 8.0)	0.22	3.9 (-1.4, 9.2)	0.17
None	239 (56)	196 (45)	209 (49)						
Mild	128 (30)	144 (33)	142 (33)						
Moderate	38 (9)	54 (12)	47 (11)						
Marked	23 (5)	38 (9)	27 (6)						
Missing	16	18	19						
Skin appearance changed				1.1 (-3.2, 5.4)	0.68	-1.8 (-5.9, 2.3)	0.44	2.9 (-1.3, 7.0)	0.20
None	251 (58)	238 (54)	226 (52)						
Mild	133 (31)	150 (34)	163 (38)						
Moderate	32 (7)	37 (8)	26 (6)						
Marked	18 (4)	19 (4)	16 (4)						
Missing	10	6	13						
EORTC QLQ-BR23 items									
Breast pain				-1.1 (-5.3, 3.1)	0.67	0.4 (-3.9, 4.7)	0.92	-1.5 (-5.7, 2.8)	0.53
None	198 (45)	205 (46)	193 (44)						
Mild	191 (43)	195 (43)	189 (43)						
Moderate	35 (8)	40 (9)	39 (9)						
Marked	18 (4)	9 (2)	15 (3)						
Missing	2	1	8						
Breast swollen				3.3 (1.0, 5.6)	0.0072	2.8 (0.5, 5.0)	0.017	0.5 (-2.2, 3.3)	0.75
None	383 (87)	362 (81)	356 (82)						
Mild	50 (11)	63 (14)	60 (14)						
Moderate	2 (<1)	18 (4)	17 (4)						
Marked	5 (1)	4 (1)	2 (<1)						
Missing	4	3	9						
Breast oversensitive				-0.4 (-4.2, 3.3)	0.90	1.9 (-2.1, 5.8)	0.37	-2.3 (-6.2, 1.6)	0.26
None	253 (58)	252 (56)	252 (58)						
Mild	144 (33)	157 (35)	136 (31)						

| | 40 Gy N=444 (%) | 27 Gy N=450 (%) | 26 Gy N=444 (%) | Moderate/Marked vs. None/Mild | | | | | |
| | | | | 27 Gy vs. 40 Gy | | 26 Gy vs. 40 Gy | | 27 Gy vs. 26 Gy | |
				Risk difference (95%CI), %	p-value[1]	Risk difference (95%CI), %	p-value[1]	Risk difference (95%CI), %	p-value[1]
Moderate	23 (5)	24 (5)	31 (7)						
Marked	16 (4)	14 (3)	16 (4)						
Missing	8	3	9						
Skin problems on breast				1.5 (-1.4, 4.4)	0.36	0.5 (-2.2, 3.3)	0.75	1.0 (-2.0, 3.9)	0.55
None	347 (79)	338 (75)	351 (81)						
Mild	75 (17)	84 (19)	62 (14)						
Moderate	9 (2)	19 (4)	18 (4)						
Marked	10 (2)	7 (2)	3 (<1)						
Missing	3	2	10						
Arm/shoulder pain				-3.0 (-7.6, 1.6)	0.21	0.4 (-4.5, 5.2)	0.93	-3.4 (-8.0, 1.3)	0.18
None	230 (52)	230 (51)	236 (54)						
Mild	141 (32)	162 (36)	130 (30)						
Moderate	51 (12)	43 (10)	50 (11)						
Marked	18 (4)	14 (3)	20 (5)						
Missing	4	1	8						
Arm/hand swollen				-1.2 (-3.9, 1.5)	0.42	0.0 (-2.8, 2.9)	>0.99	-1.2 (-4.0, 1.5)	0.41
None	370 (84)	375 (84)	365 (84)						
Mild	48 (11)	54 (12)	48 (11)						
Moderate	18 (4)	11 (2)	16 (4)						
Marked	4 (1)	6 (1)	6 (1)						
Missing	4	4	9						
Difficulty raising arm				-0.6 (-4.1, 3.0)	0.80	-1.3 (-4.8, 2.2)	0.52	0.7 (-2.7, 4.1)	0.70
None	326 (74)	336 (75)	321 (74)						
Mild	79 (18)	77 (17)	85 (19)						
Moderate	23 (5)	24 (5)	21 (5)						
Marked	13 (3)	10 (2)	9 (2)						
Missing	3	3	8						

Denominators may vary due to missing items on the questionnaire; percentages are calculated out of totals with data available for each item; [1] p-value for Fisher's exact test. Risk ratios not shown as confidence intervals wide, due to low absolute event rates. Pre-specified cut-off for statistical significance for normal tissue effect analyses was p=0.005.

Table 11: Longitudinal analysis of moderate/marked patient-assessed late normal tissue effects from baseline to 5 years for 1774 patients in the Main Trial with at least one completed questionnaire *Reproduced from Brunt et al. (2020) (CC BY 4.0)[1]*

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); <0.0001
40 Gy	56/583 (9.6)	122/2538 (4.8)	1			
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); 0.0097
40 Gy	57/579 (9.8)	283/2528 (11.2)	1			
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); 0.11
40 Gy	26/582 (4.5)	156/2539 (6.1)	1			
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); >0.99
40 Gy	66/582 (11.3)	401/2537 (15.8)	1			
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); 0.031
40 Gy	24/582 (4.1)	101/2536 (4.0)	1			
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); 0.089
40 Gy	27/582 (4.6)	171/2533 (6.7)	1			
27 Gy	36/589 (6.1)	209/2599 (8.0)	1.24 (0.94, 1.63)	0.12		
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. Pre-specified cut-off for statistical significance for normal tissue effect analyses was p=0.005.

Photographic assessments of late adverse effects in the Main Trial

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 13). 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 40 Gy, 67/429 (16%) for 27 Gy and 46/427 (11%) for 26 Gy; corresponding figures at 5 years were 34/283 (12%) for 40 Gy, 83/308 (27%) for 27 Gy and 37/284 (13%) for 26 Gy (Table 13). Modelling 2- and 5-year photographic assessments together, 27 Gy had a statistically significantly increased risk of mild/marked change in breast appearance compared with 40 Gy (OR 2.29; 1.60, 3.27; p<0.0001), with no statistically significant difference between 26 Gy and 40 Gy (OR 1.26; 0.85, 1.86; p=0.24; Table 13). 26 Gy had a statistically significantly lower risk of change in photographic breast appearance compared with 27 Gy (p=0.0006).

At 2 years, mild/marked retraction / distortion was reported in 14/411 (3.4%) for 40 Gy, 27/429 (6.3%) for 27 Gy and 14/427 (3.3%) for 26 Gy; corresponding figures at 5 years were 3/283 (1.1%) for 40 Gy, 25/308 (8.1%) for 27 Gy and 14/284 (4.9%) for 26 Gy (Table 14). Modelling 2- and 5-year photographic assessments together, 27 Gy had a statistically significantly increased risk of mild/marked change in breast appearance compared with 40 Gy (OR 2.83; 1.50, 5.34; p=0.001), with no statistically significant difference between 26 Gy and 40 Gy (OR 1.59; 0.79, 3.18; p=0.190; Table 14). There was no statistically significantly difference in risk of retraction / distortion for 26 Gy compared with 27 Gy (p=0.056).

Table 12: Change in photographic breast appearance at 2 and 5 years (breast conservation surgery patients) by fractionation schedule: results of longitudinal analysis for 1309 patients in the Main Trial with photographic assessments at 2 and/or 5 years *Reproduced from Brunt et al. (2020) (CC BY 4.0)[1]*

	2 years				5 years				OR for mild / marked change vs 40 Gy (95%CI)	Comparison with 40 Gy; p-value[1]	Comparison between 27 Gy & 26 Gy; p-value[1]
	N	None (%)	Mild (%)	Marked (%)	N	None (%)	Mild (%)	Marked (%)			
40 Gy / 15Fr	411	376 (91.5)	33 (8.0)	2 (0.5)	283	249 (88.0)	33 (11.7)	1 (0.3)	1	-	-
27 Gy / 5Fr	429	362 (84.4)	48 (11.2)	19 (4.4)	308	225 (73.1)	70 (22.7)	13 (4.2)	2.29 (1.60, 3.27)	<0.0001	-
26 Gy / 5Fr	427	381 (89.2)	33 (7.7)	13 (3.0)	284	247 (87.0)	28 (9.9)	9 (3.2)	1.26 (0.85, 1.86)	0.24	0.0006

[1] p-value from Wald test; OR = odds ratio (estimated from GEE model including 2 and 5-year data); 95%CI=95% confidence interval

Table 13: Retraction / distortion at 2 and 5 years (breast conservation surgery patients) by fractionation schedule: results of longitudinal analysis for 1309 patients in the Main Trial with photographic assessments at 2 and/or 5 years

	2 years				5 years				OR for mild / marked change vs 40 Gy (95%CI)	Comparison with 40 Gy; p-value[1]	Comparison between 27 Gy & 26 Gy; p-value[1]
	N	None (%)	Mild (%)	Marked (%)	N	None (%)	Mild (%)	Marked (%)			
40 Gy / 15Fr	411	397 (96.6)	14 (3.4)	0	283	280 (98.9)	3 (1.1)	0	1	-	-
27 Gy / 5Fr	429	402 (93.7)	21 (4.9)	6 (1.4)	308	283 (91.9)	19 (6.2)	6 (1.9)	2.83 (1.50, 5.34)	0.001	-
26 Gy / 5Fr	427	413 (96.7)	12 (2.8)	2 (0.5)	284	270 (95.1)	11 (3.9)	3 (1.1)	1.59 (0.79, 3.18)	0.190	0.056

[1] p-value from Wald test; OR = odds ratio (estimated from GEE model including 2 and 5-year data); 95%CI=95% confidence interval

Severe late adverse effects and specialist referrals for radiotherapy-related adverse effects in the Main Trial

The most common specialist referral for radiotherapy-related adverse effects during follow-up was to lymphoedema clinics (Table 15). Incidence of ischaemic heart disease, symptomatic rib fracture and symptomatic lung fibrosis was very low at this stage of follow-up (Table 16).

Table 14: Specialist referrals for radiotherapy-related late adverse effects during follow-up in the Main Trial

Specialist referral type[*]	40 Gy N=1361 (%)	27 Gy N=1367 (%)	26 Gy N=1368 (%)
Lymphoedema	90 (6.6)	122 (8.9)	106 (7.7)
Breast surgery / breast surgeon	13 (0.9)	13 (0.9)	17 (1.2)
Cardiology	5 (0.4)	10 (0.7)	7 (0.5)
Pulmonary/Respiratory	4 (0.3)	6 (0.4)	3 (0.2)
Dermatology	4 (0.3)	2 (0.1)	3 (0.2)
Pain	6 (0.4)	5 (0.4)	2 (0.1)
Other	3 (0.2)	6 (0.4)	4 (0.3)

[*] Where patients had more than one type of referral, each is listed separately

Table 15: Incidence of other late adverse effects in the Main Trial

	40 Gy N=1361 (%)	27 Gy N=1367 (%)	26 Gy N=1368 (%)
Symptomatic rib fracture			
Reported[1]	14 (1.0)	25 (1.8)	20 (1.5)
Confirmed[2]	6 (0.4)	13 (1.0)	12 (0.9)
Ipsilateral side	*5 (0.4)*	*11 (0.8)*	*8 (0.6)*
Symptomatic lung fibrosis			
Reported[3]	9 (0.7)	10 (0.7)	10 (0.7)
Confirmed[2]	6 (0.4)	9 (0.7)	7 (0.5)
Ipsilateral side	*4 (0.3)*	*8 (0.6)*	*5 (0.4)*
Ischaemic heart disease			
Reported[4]	13 (1.0)	17 (1.2)	24 (1.7)
Confirmed[2]	12 (0.9)	11 (0.8)	10 (0.7)
Left-sided	*6 (0.4)*	*8 (0.6)*	*3 (0.2)*

[1] Reported cases of symptomatic rib fracture include 8 not radiotherapy-related (5 trauma, 1 metastases, 1 osteopenia, 1 reason not given but stated to be not due to radiotherapy); [2] After imaging and further investigations; excluding cases not radiotherapy-related; [3] Reported cases of symptomatic lung fibrosis include 2 not radiotherapy-related (1 secondary to infection and 1 GI COPD); [4] Reported cases of ischaemic heart disease include 17 patients with pre-existing heart disease at randomisation

Estimation of radiobiology parameters for late adverse effects

The unadjusted α/β estimate for any moderate/marked clinician-assessed NTE in the breast/chest wall was 1.7 Gy (1.2, 2.3), giving EQD2 estimates of 47.1 Gy for 40 Gy/15Fr, 51.6 Gy for 27 Gy/5Fr and 48.3 Gy for 26 Gy/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 (1.8 Gy; 1.1, 2.4). The unadjusted α/β estimate for patient-reported change in breast appearance was 2.3 Gy (1.8, 2.9), resulting in EQD2 estimates of 46.1 Gy, 48.2 Gy and 45.2 Gy for the 40 Gy, 27 Gy and 26 Gy schedules respectively; as above, adjusting for covariates made minimal difference.

Assuming no clinically significant time effect for late adverse effects between 1 and 3 weeks, complete sublethal damage repair between fractions and an α/β of 2.8 Gy for late NTE, the last assumption based on the combined estimates of α/β in START-A and FAST. On this basis, the relative EQD of the FAST-Forward schedules to 50 Gy in 25 fractions are shown in Table 17, where negative values indicate estimated AE rates lower than 50 Gy in 25 fractions.

Table 16: Relative EQD in 2 Gy fractions of FAST-Forward schedules and the absolute % difference in adverse events (ΔAE) expected compared to 50 Gy in 25 fractions assuming i) α/β=2.8 Gy as per START-A and FAST, ii) complete repair of sublethal damage between fractions and iii) a dose response gradient corresponding to γ=1.4 as per START-A trial

Reproduced from Brunt et al. (2021) (CC BY 4.0)[2]

Fractionation regimen	EQD$_{2/2.8}$ (Gy)	ΔAE (%)*
50 Gy / 25Fr / 5 weeks	50.0	Reference
40.05 Gy / 15Fr / 3 weeks	45.6	-12.3
27 Gy / 5Fr / 1 week (5.4 Gy/Fr)	46.1	-11.1
26 Gy / 5Fr / 1 week (5.2 Gy/Fr)	43.3	-18.8

*Negative values indicate estimated NTE rates lower than after 50 Gy in 25 fractions.

5-year subgroup analyses in the Main Trial

As stated in the Statistical Methods section in Chapter 2, the Main Trial protocol did not include pre-specified subgroup analyses, but exploratory post-hoc subgroup analyses of the primary endpoint and of NTE were carried out.

Risk group was a stratification factor for the Main Trial at randomisation, with low-risk defined as age ≥50 and grade 1 or 2, and high-risk defined as age <50 and / or grade 3; 1545 (37.8%) patients were in the high-risk category. Retrospective subgroup analyses 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, adjuvant chemotherapy, HER2 status and in triple negative patients (Figure 12). Confidence intervals for the hazard ratios overlap for the subgroups, although the number of events in these analyses was small (52), hence results should be interpreted with caution as the statistical power is low. Subgroup analysis according to type of primary surgery was not possible as there was only 1 IBTR event post-mastectomy in a control group patient (out of 91) and none in the 173 patients treated with 5 fractions. Subgroup analyses of IBTR for 27 Gy/5Fr versus 40 Gy/15Fr are shown in Figure 13. Table 18 and Appendix 2, Table 43 show the frequencies and number of patients according to subgroups defined by age, grade, primary surgery type and receptor status. No evidence to signal concern was seen for the 5-fraction schedules. The use of boost and dose/fractionation, both declared prior to randomisation, were balanced between the 3 treatment groups minimising risk of bias in dose intensity between trial groups.

Table 17: Ipsilateral breast tumour relapse by higher risk subgroup in the Main Trial

Reproduced from Brunt et al. (2021) (CC BY 4.0)[2]

Subgroup	Event/Number	40 Gy/15Fr	27 Gy/5Fr	26 Gy/5Fr
Age under 50 years at randomisation	Events	3	7	4
	Number at risk	198	189	217
Grade 3	Events	20	15	8
	Number at risk	386	389	378
Mastectomy	Events	1	0	0
	Number at risk	91	89	84
ER negative/HER2 negative[1]	Events	10	5	3
	Number at risk	111	96	128
HER2 positive	Events	4	7	2
	Number at risk	135	137	135

[1]PR status was not mandatory in the UK or the trial but when ER/HER2 were negative PR status was negative/positive/unknown in 265/18/52 respectively

Figure 12: Subgroup analyses of time to ipsilateral breast tumour relapse for 26 Gy/5Fr versus 40 Gy/15Fr in the Main Trial *Reproduced from Brunt et al. (2021) (CC BY 4.0)[2]*

	Hazard ratio (95% CI)	Events	Total
Age <50yrs	1.23 (0.28, 5.51)	7	419
Age 50-59yrs	0.48 (0.19, 1.17)	22	856
Age 60-69yrs	0.67 (0.25, 1.75)	17	1027
Age >=70yrs	1.03 (0.21, 5.11)	6	427
Grade 1	2.04 (0.37, 11.15)	6	615
Grade 2	0.96 (0.38, 2.42)	18	1350
Grade 3	0.40 (0.18, 0.91)	28	764
Path tumour size <=1cm	0.60 (0.18, 2.06)	11	644
Path tumour size 1-2cm	0.75 (0.35, 1.58)	28	1213
Path tumour size >2cm	0.57 (0.19, 1.74)	13	864
Node negative	0.73 (0.39, 1.36)	40	2213
Node positive	0.56 (0.16, 1.92)	11	513
No tumour bed boost	0.72 (0.38, 1.34)	40	2048
Tumour bed boost	0.52 (0.16, 1.72)	12	674
No adjuvant chemotherapy	0.78 (0.38, 1.60)	30	2023
Adjuvant chemotherapy	0.51 (0.21, 1.21)	22	703
HER2 +ve	0.51 (0.09, 2.81)	6	270
HER2 -ve	0.69 (0.38, 1.24)	46	2444
HER2/ER/PR -ve: no	0.48 (0.20, 1.20)	21	1405
HER2/ER/PR -ve: yes	0.39 (0.10, 1.51)	10	191

Favours 26Gy/5Fr   Favours 40Gy/15Fr

Hazard Ratio (95% CI)

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Figure 13: Subgroup analyses of time to ipsilateral breast tumour relapse for 27 Gy/5Fr versus 40 Gy/15Fr in the Main Trial *Reproduced from Brunt et al. (2021) (CC BY 4.0)[2]*

	Hazard ratio (95% CI)	Events	Total
Age <50yrs	2.43 (0.63, 9.40)	10	393
Age 50-59yrs	0.27 (0.09, 0.81)	19	861
Age 60-69yrs	0.98 (0.41, 2.35)	20	1014
Age >=70yrs	1.79 (0.45, 7.16)	9	460
Grade 1	1.48 (0.25, 8.85)	5	630
Grade 2	1.00 (0.40, 2.52)	18	1323
Grade 3	0.72 (0.37, 1.41)	35	775
Path tumour size <=1cm	0.69 (0.22, 2.17)	12	674
Path tumour size 1-2cm	0.81 (0.39, 1.68)	29	1212
Path tumour size >2cm	1.11 (0.43, 2.87)	17	834
Node negative	1.10 (0.63, 1.93)	49	2227
Node positive	0.15 (0.02, 1.22)	8	500
No tumour bed boost	0.85 (0.47, 1.55)	43	2044
Tumour bed boost	0.63 (0.21, 1.92)	13	679
No adjuvant chemotherapy	1.04 (0.53, 2.01)	35	2070
Adjuvant chemotherapy	0.64 (0.28, 1.49)	23	657
HER2 +ve	1.81 (0.53, 6.18)	11	272
HER2 -ve	0.73 (0.41, 1.30)	47	2445
HER2/ER/PR -ve: no	1.08 (0.52, 2.24)	29	1390
HER2/ER/PR -ve: yes	0.66 (0.19, 2.25)	11	167

Favours 27Gy/5Fr   Favours 40Gy/15Fr

Hazard Ratio (95% CI)

Retrospective subgroup analyses comparing time to first clinician-assessed moderate or marked adverse effect in the breast or chest wall for 26 Gy versus 40 Gy provided no evidence of a differential effect of the 5-fraction schedule according to age, breast size, surgical deficit, tumour bed boost, or adjuvant chemotherapy, as confidence intervals for subgroups overlap, although power for these retrospective subgroup analyses is low (Figure 14). The corresponding figure for 27 Gy/5Fr versus 40Gy/15Fr is shown in Figure 15.

Figure 14: Subgroup analyses of time to first moderate or marked clinician-assessed adverse event in breast / chest wall for 26 Gy/5Fr versus 40 Gy/15Fr in the Main Trial

Reproduced from Brunt et al. (2021) (CC BY 4.0)[2]

	Hazard ratio (95% CI)	Events	Total
Age <50yrs	1.57 (1.06, 2.34)	103	401
Age 50-59yrs	1.02 (0.78, 1.33)	214	829
Age 60-69yrs	1.00 (0.79, 1.26)	278	999
Age >=70yrs	1.15 (0.81, 1.63)	129	404
Breast size: small *	1.39 (0.95, 2.02)	110	413
Breast size: medium *	1.04 (0.69, 1.57)	93	315
Breast size: large *	0.95 (0.48, 1.88)	33	101
Surgical deficit: small *	1.16 (0.83, 1.62)	140	599
Surgical deficit: medium *	1.41 (0.86, 2.31)	64	178
Surgical deficit: large *	0.61 (0.29, 1.27)	29	48
No tumour bed boost	1.05 (0.88, 1.25)	519	1978
Tumour bed boost	1.25 (0.95, 1.65)	204	652
No adjuvant chemotherapy	1.09 (0.92, 1.29)	544	1957
Adjuvant chemotherapy	1.10 (0.82, 1.48)	180	676

Favours 26Gy/5Fr   Favours 40Gy/15Fr

Hazard Ratio (95% CI)

* Assessed from baseline photographs

Figure 15: Subgroup analyses of time to first moderate or marked clinician-assessed adverse event in breast / chest wall for 27 Gy/5 Fr versus 40 Gy/15 Fr in the Main Trial

Reproduced from Brunt et al. (2021) (CC BY 4.0)[2]

	Hazard ratio (95% CI)	Events	Total
Age <50yrs	1.83 (1.22, 2.75)	99	379
Age 50-59yrs	1.47 (1.15, 1.89)	256	836
Age 60-69yrs	1.34 (1.07, 1.68)	313	988
Age >=70yrs	1.19 (0.85, 1.65)	144	443
Breast size: small *	1.41 (0.97, 2.06)	109	413
Breast size: medium *	1.54 (1.05, 2.26)	110	309
Breast size: large *	1.56 (0.85, 2.85)	47	112
Surgical deficit: small *	1.55 (1.13, 2.13)	158	594
Surgical deficit: medium *	1.97 (1.24, 3.14)	78	188
Surgical deficit: large *	0.45 (0.21, 0.97)	27	49
No tumour bed boost	1.42 (1.21, 1.67)	593	1983
Tumour bed boost	1.42 (1.08, 1.86)	218	662
No adjuvant chemotherapy	1.44 (1.23, 1.69)	631	2009
Adjuvant chemotherapy	1.32 (0.99, 1.77)	181	637

Favours 27Gy/5Fr   Favours 40Gy/15Fr

Hazard Ratio (95% CI)

* Assessed from baseline photographs

Discussion of Main Trial results is in the main Discussion section (Chapter 8)

CHAPTER 6: MAIN TRIAL COST-EFFECTIVENESS ANALYSIS

Introduction

An economic evaluation was conducted to assess the cost-effectiveness of whole breast radiotherapy with 26 Gy delivered in five fractions (5Fr) over one week compared to the international standard 3-week schedule of 40 Gy in 15 fractions (15Fr). The target population was UK adults who have undergone breast conserving surgery or mastectomy for early breast cancer (stage I/II/IIIa).

A decision analytic model was constructed to estimate the costs and benefits of each option over a lifetime time horizon. The analysis followed the reference case outlined by the National Institute for Health and Care Excellence (NICE) in which health effects and costs which fall on the NHS were considered [68]. The economic analysis excludes the trial arm schedule of 27 Gy delivered in five fractions over one week as this was associated with higher normal tissue effect risk compared to 40 Gy and 26 Gy, and is not considered a relevant comparator for future clinical practice.

Methods

Lifetime costs and health outcomes were estimated for each treatment using a Markov model. A discount rate of 3.5% per year was used for costs and health effects. Costs were set to a base year of 2019, adjusting for inflation [69]. Quality adjusted life years (QALYs) were used to capture health impacts.

R Statistical programming language and was used to build the model and coding principle from the DARTH modelling group were followed [70, 71].

Model structure and patient population

The target population was UK adults who have undergone breast conserving surgery or mastectomy for early breast cancer (stage I/II/IIIa). The patient population for the model matched the inclusion criteria for FAST-Forward as described in Chapter 2. This included individuals with tumour grades 1-3, estrogen receptor positivity and negativity, HER2 positivity and negativity and those with or without regional lymph node metastasis.

A Markov model was built to estimate the total QALYs and costs for each treatment alternative. The structure of the economic model is illustrated in Figure 16. Circular arrows indicate the possibility of staying in the same state for multiple cycles, linear arrows represent the possible transitions between states. The model structure was developed in discussion with clinical experts. A single health state was used to capture locoregional relapse, which includes local relapse and regional relapse as these relapses have similar prognostic and cost implications. The Markov

model cycle length was one year as outcomes occur over a long period. A half-cycle correction was applied.

Figure 16: Markov model structure of early breast cancer
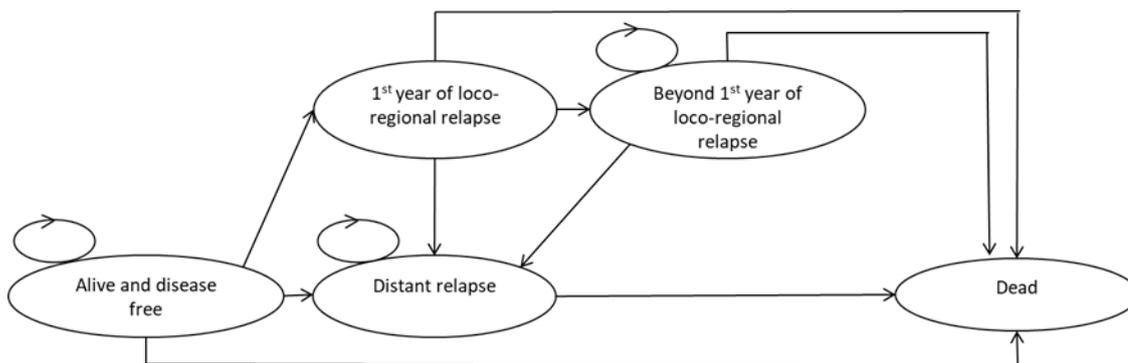
Patients entered the model following local tumour excision and received radiotherapy in either 15 fractions or 5 fractions. The radiotherapy schedules differed in terms of resource use and the likelihood of inducing acute skin reactions. Following radiotherapy, patients began in the "alive and disease free" health state and over time were at risk of locoregional relapse, distant (metastatic) relapse or death. Radiotherapy modality determined how patients move through states over time.

Radiotherapy treatment period

This section concerns costs of delivering radiotherapy and the costs of managing acute side-effects. Patients were assumed to receive treatment as specified in the FAST-Forward protocol [2]. Radiotherapy costs were applied at model entry and are calculated as shown in Table 19. As radiotherapy delivery resource activity was not recorded in the trials, resource use was informed by expert opinion. A proportion of patients are instructed to follow breath hold techniques while receiving radiotherapy in order to protect the heart. This extends the duration of the radiotherapy appointment, and we estimated the consequent increase in cost.

We included costs relating to treating acute adverse skin reactions during treatment. These were assumed to be one-off costs which depend on the severity of adverse effects as measured by worst RTOG score observed during treatment [72]. Preference based measures of health-related quality of life were collected at baseline and at three months, but not during receipt of radiotherapy when acute skin reactions would be present. Literature review did not identify any studies that linked health-related quality of life measures to RTOG scores. Quality of life was assumed to be the same across 5 and 15 fractions during the treatment period due to an absence of preference-based quality of life data for this period. This assumption was viewed to be conservative towards the 26 Gy schedule given the numerically lower number of events compared to 40 Gy.

Table 18: Radiotherapy costs

Input	Value	Source
Radiotherapy delivery		
Radiotherapy planning cost	£315	[73]
Cost of delivering one fraction of RT	£124	[73]
Percentage receiving breath hold with whole breast radiotherapy	25%	Expert opinion
Increase in fraction costs associated with breath hold	30%	Expert opinion, [74, 75]
Treatment	**Formula: (unit cost) x (units per patient) x (proportion of patients)**	**Cost**
WB15F		
Planning cost		£315.00
RT without breath hold	£124 x 15 x 75%	£1,395.00
RT with breath hold	(£124 x 1.3) x 15 x 25%	+ £604.50
Total		£2,314.50
WB5F		
Planning cost		£315.00
RT without breath hold	£124 x 5 x 75%	£465.00
RT with breath hold	(£124 x 1.3) x 5 x 25%	+ £201.50
Total		£981.50

RT = Radiotherapy

Post radiotherapy period

Time to locoregional relapse, distant relapse and some maintenance costs and health related quality of life parameters were estimated from FAST-Forward individual patient data. Stata 16 was used to carry out all individual patient data analysis [76]. The remaining model parameters were informed by searching the wider literature. All model inputs for this period are presented in Table 20.

Transition probabilities

Transition probabilities estimated from FAST-Forward

The rate of loco-regional relapse and distant relapse outcomes were estimated using separate models. This is the approach used in the clinical analyses in which separate Cox models are fit to loco-regional and distant relapse (see Chapter 5). To choose an appropriate statistical model, the algorithm outlined in DSU guidance (2013) was used [77]. It was found that an exponential survival model fit the data best for both loco-regional relapse and distant relapse. Data from patients receiving 40 Gy and 26 Gy arm was used to fit the model (n = 2,723) with a dummy to indicate the treatment schedule.

In the trial 45% would be considered at lower than average risk of local relapse and eligible for partial breast radiotherapy according to Royal College of Radiologists guideline [78]. Our economic model estimates outcomes for the combined FAST-Forward population but allows for a separate analysis of low and high-risk populations [12, 78]. A subgroup dummy was included in the survival analysis to reflect differences in baseline risk of local relapse based on patient characteristics. The average ages in subgroups 1 and 2 were 63 and 60 respectively.

Definition of low and high-risk subgroups

Subgroup 1: Lower risk of local relapse (eligible for partial breast radiotherapy under RCR guidelines). All of the following criteria: 50+ years old, and tumour grade 1-2, and tumour size <=3cm, and estrogen receptor positive (ER+), and HER2 negative, and with no regional lymph node metastasis (N0).

Subgroup 2: Higher risk of local relapse (not eligible for partial breast radiotherapy). Any of the following criteria: Less than 50 years old, or tumour grade 3, or tumour size > 3cm or estrogen receptor negative (ER-), or HER2 positive or with regional lymph node metastasis (N1 or greater).

In the dataset, some individuals were recorded as having a distant relapse and locoregional relapse at the same time point. As a sensitivity analysis, we estimated the time to first event (either distant or locoregional), censoring individuals that experience more than one type of relapse (each participant only contributes their 1st event). For this we used a log-normal survival model which also fit the data well.

Estimated parameters for all survival analyses are reported in Tables 44-51 (Appendix 2).

Transition probabilities for the remaining model states

The assumption was made that individuals who have not experienced a distant relapse have the same rate of all-cause mortality as the age and sex matched general population [79]. Patients who developed distant relapse were at increased risk of death. This risk was based on a French study of metastatic breast cancer. In the base case, mortality with distant relapse was adjusted for age and based on the hormone receptor positive and HER2 negative molecular subtype. This was chosen as it is the most common subtype in FF. The impact of using alternative molecular subtypes was investigated in sensitivity analyses [80]. The assumption was made that increased mortality from breast cancer occurs by first experiencing distant relapse. Therefore, the UK rate of breast cancer mortality was removed from all-cause mortality to avoid double counting [12].

The rate of transition from locoregional to distant relapse was taken from a Dutch study of breast cancer [81]. It was assumed that radiotherapy modality did not affect the rate of transition from locoregional to distant relapse or the mortality risk with distant relapse.

Treatment effects

To model the rates of locoregional relapse for 5 fractions relative to 15 fractions, we applied the hazard ratio for locoregional relapse estimated in FF to the baseline rate of locoregional relapse estimated in the survival model. For both 5 fractions and 15 fractions, a common rate of transition from alive and disease free to distant relapse was assumed. This assumption was based on the clinical rationale that radiotherapy is a local treatment and therefore it's causal impact on developing distant relapse (if any) can only occur through reducing locoregional relapses. The impact of this assumption was explored in a sensitivity analysis. For the base case, treatment effects were assumed to persist over time.

Costs

Costs for the alive and disease-free state estimated from FAST-Forward

The resource use questionnaire collected in FAST-Forward covered activities related and unrelated to breast cancer such as general practitioner costs, nursing costs and hospitalisations. To construct per patient costs, unit costs were applied to resource use, see Table 52 (Appendix 2).

A panel of cost data was constructed for each data collection time period. Individuals only contributed data if there were classified as being in the alive and disease-free state. Summary statistics are shown in Table 53 (Appendix 2).

A generalised estimating equation (GEE) model was fit to the 3 month cost data [76]. This model had an exchangeable within-individual correlation structure. A gamma family distribution was chosen to reflect the non-negativity and skewed distribution of cost data. A log link was chosen given the typical structure of cost data. The GEE model utilises all available observations of the dependent variable. This is equivalent to a complete case analysis (CCA). CCA was chosen as the degree of missing data in the study was low, less than 25% at any timepoint. This implies a missing completely at random assumption (MCAR) i.e. missingness is independent of both observed and unobserved values [82]. When fitting the models, baseline costs were discarded as it is the post treatment costs that are to be estimated.

Plotting the data revealed a large drop between costs in the first 6 months after treatment and the costs from 6 months onward. This discontinuity was modelled by defining a binary covariate indicating 6 months pre and post treatment. A dummy for high vs low-risk was also included in the

analysis. Age and treatment were found not to be statistically significant and so were not included in the model.

The following values were estimated after scaling costs up from average costs over 3 months to 12 months:

- Yearly costs in subgroup 1: low-risk = £1216, with SE = £82.

- Yearly costs in subgroup 2: high-risk = £1412, with SE = £68.

- Additional costs associated with first year after treatment = £402 with SE £64.

Costs for the remaining model states

These costs were sourced from the wider literature as there was insufficient observations to estimate them from FAST-Forward. Locoregional relapse was associated with one off mastectomy costs in addition to supportive care costs in the first year of the event [50, 83-85]. Following this first year supportive care was assumed to consist of one GP visit and one mammogram per year [50]. A UK study was used to estimate supportive care and treatment costs for distant relapse [86].

To make them consistent with the inclusion of related and unrelated costs in the FAST-Forward resource use questionnaire, costs unrelated to breast cancer were added to the breast cancer costs for locoregional and distant relapse health states [87].

Health related quality of life (HRQoL)

HRQoL for the alive and disease-free state estimated from FAST-Forward

Quality of life (QoL) was captured in FAST-Forward by the EuroQol EQ-5D 5 level questionnaire. NICE's current advice is to map 5L scores to 3L using the method described by van Hout et al., (2012) [88].

Data was collected in the PRO sub-study (n=1,179) at baseline (before randomisation or radiotherapy), 3, 6 months post treatment and 1, 2 and 5 years post randomisation.

A panel of QoL data was constructed for each data collection time period. Individuals only contributed data if there were classified as being in the alive and disease-free state. Summary statistics are shown in Table 54 (Appendix 2).

A generalised liner model (GLM) based on the wave of data closest to treatment was used for simplicity as time was found to have no statistical impact on results. A gamma distribution for disutility was used as this fits the range utility data. An identity link was chosen.

A complete case analysis (CCA) was chosen as the degree of missing data in the study was low at less than 25% at any timepoint. This implies a missing completely at random assumption (MCAR) i.e. missingness is independent of both observed and unobserved values (Faria et al., 2014) [82].

Using the full sample (6,143 observations on 1,044 patients), we estimated a GLM model. This model estimated disutilities (1 – EQ5D score). It included a dummy for the alive and disease-free state, for high vs low-risk, a time dummy equal to one for all post-treatment time points, all possible interactions between the previous dummies and a dummy for the treatment arm. The average EQ-5D score for patients in the alive and disease-free state in subgroup 1 was 0.788 (SE=0.013, p-value<0.001), for subgroup 2 this was 0.773 (SE=0.006, p-value<0.001).

HRQoL for the remaining model states

HRQoL post locoregional relapse was assumed to be the same as for the alive and disease-free state. The decrement in HRQoL with distant relapse was taken from a previous radiotherapy decision model [89]. A Health Survey for England study was used to model the decline in HRQoL with age [90].

Table 19: Summary of base case input values for post radiotherapy period

Input	Mean	Standard Error	Distribution	Source
Population characteristics				
Average age at beginning of model				
Subgroup 1	63 years	-	-	FF
Subgroup 2	60 years	-	-	FF
Acute side-effects during treatment				
Costs of treating adverse skin reactions for states: RTOG0, RTOG1, RTOG2a, RTOG2b, RTOG3	£0, £0, £132, £132, £136	-	-	Expert opinion, [91]
Probability of RTOG states: RTOG0, RTOG1, RTOG2a, RTOG2b, RTOG3				
15 Fraction radiotherapy	0%, 32%, 27.5%, 27.5%, 14%	-	Dirichlet	[72]
5 Fraction radiotherapy	6%, 62%, 13.5%, 13.5%, 6%	-	Dirichlet	[72]
Transition rate between states				
Alive disease free to locoregional relapse: 15Fr				
Subgroup 1	0.0038	0.0014	Exponential	FF
Subgroup 2	0.0073	0.0014	Exponential	FF
Alive disease free to distant relapse: 15Fr				
Subgroup 1	0.0024	0.0007	Exponential	FF
Subgroup 2	0.0128	0.0018	Exponential	FF
Alive and disease free to death	Variable - dependant on age	-	-	[79]
Locoregional relapse to distant relapse	0.0515	0.0045	Exponential	[81]

Input	Mean	Standard Error	Distribution	Source
Locoregional relapse to death	Variable - dependant on age	-	-	[79]
Distant relapse to death				
Subgroup 1	0.2196	0.5102	Exponential	[80]
Subgroup 2	0.21	0.5102		
Relative treatment effect estimates				
Alive disease free to locoregional relapse: 5Fr vs 15Fr	0.66	0.167	Log normal	[23]
Health care costs				
Alive and disease free (annual)				
Subgroup 1	£1,216	£82	Gamma	FF
Subgroup 2	£1,412	£68	Gamma	FF
Additional costs of 1st year alive and disease free	£402	£64	Gamma	FF
1st year of locoregional relapse				
Treatment costs	£4,241	±20%	Gamma	[83-85, 87]
Supportive care costs	£2,995	±20%	Gamma	[50, 87]
Beyond 1st year locoregional relapse (annual)	£2,139	±20%	Gamma	[50, 87]
Distant relapse (annual)	£13,426	±20%	Gamma	[86, 87]
Health related quality of life				
Alive and disease free				
Subgroup 1	0.7880	0.0130	Gamma	FF
Subgroup 2	0.7730	0.0060	Gamma	FF
Locoregional relapse				
Subgroup 1	0.7880	0.0130	Gamma	FF
Subgroup 2	0.7730	0.0060	Gamma	FF

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Input	Mean	Standard Error	Distribution	Source
Decrement for distant relapse relative to alive and disease free	0.3030	0.1550	Gamma	[89]
Quality of life decrement with age	Variable - dependant on age	-	-	[90]

RTOG = Radiation Therapy Oncology Group;15Fr = 15 Fractions; 5Fr = 5 fractions; WB = whole breast; PB = partial breast

Uncertainty analyses

The distributions described in Table 20 were applied to each of the parameters to represent uncertainty in the model. A probabilistic sensitivity analysis (PSA) was used to reflect the impact of this joint uncertainty on outcomes. This involved taking 10,000 draws from the distributions and calculating model outcomes for each iteration. One-way sensitivity analysis was used to explore the sensitivity of results to one at a time changes in individual inputs and assumptions, see Table 21.

Cost-effectiveness analysis

Discounted costs and QALYs were calculated for each treatment option taking account of outcomes over the patient lifetime. Incremental cost effectiveness ratios (ICERs) were calculated with whole breast 15 fractions as the comparator treatment. The ICER was calculated as the mean additional costs divided by the mean additional health gained for 5 fractions compared to 15 fractions. The ICER was compared to a cost-effectiveness threshold of £15,000/QALY. This was chosen as it is the value used by the Department of Health in the UK to represent the marginal rate at which NHS activities generate QALYs [92, 93]. Sensitivity analysis used the threshold values commonly used in NICE decision making: £20,000 - £30,000/QALY [68].

Validation

Model validation was carried out using the TECH-VER checklist [94].

Subgroup analyses

FAST-Forward contained a combination of individuals who were both high and low-risk. The model allowed for these subgroups to be analysed separately or as a combined population. The primary analysis reports results for the combined population. Secondary analysis reports results for each population separately.

Results

For the base case analysis, mean costs and QALYs for 15 fractions were £31,640 and 11.08 QALYs respectively. For 5 fractions these were £29,638 and 11.12 QALYs. Therefore, 5 fraction therapy was expected to dominate with expected cost savings of £2,002 (95% interval £1,245 to £2,804) and higher expected QALYs: 0.04 (95% interval -0.01 to 0.09). Across simulations there was a 99.9% chance that 5 fractions either dominated WB15F or had an ICER below £15,000/QALY. The probabilistic results are shown in the incremental cost-effectiveness plane in Figure 17. The dashed line represents the cost effectiveness threshold of £15,000 per QALY. The

points below this line represent simulations in which 5 fractions is cost effective relative to 15 fractions. This diamond indicates mean costs savings and expected gains in health.

Figure 17: Base case cost effectiveness plane comparing 5 fractions to 15 fractions
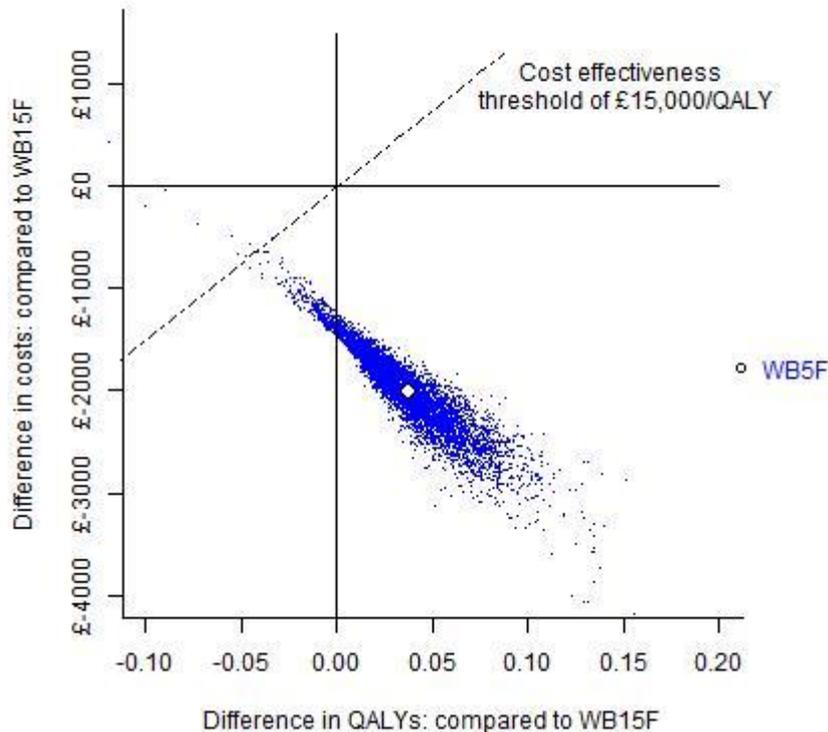
WB15F = whole breast 15 fractions; WB5F = whole breast 5 fractions; QALYs = quality adjusted life years.

Subgroups

For the low-risk population (subgroup 1), 5 fraction therapy was expected to dominate with expected cost savings of £1,881 (95% interval £1,252 to £2,648) and higher expected QALYs: 0.03 (95% interval -0.01 to 0.07). Across simulations there was a 99.9% chance that 5 fractions either dominated WB15F or had an ICER below £15,000/QALY.

For the high-risk population (subgroup 2), 5 fraction therapy was expected to dominate with expected cost savings of £2,102 (95% interval £1,230 to £3,093) and higher expected QALYs: 0.05 (95% interval -0.01 to 0.11). Across simulations there was a 99.9% chance that 5 fractions either dominated WB15F or had an ICER below £15,000/QALY.

Sensitivity analysis

Based on expected outcomes, 5 fractions dominated all other options except when using the distant relapse hazard ratio results estimated in the trial (see Table 21). In this one scenario, 5

fractions compared with 15 fractions was expected to be less expensive with incremental costs of -£908 (95% interval -£2,689 to £975) but less effective, with -0.14 incremental QALYs (95% interval -0.43 to 0.12). This placed the expected ICER in the south west quadrant. With a threshold of £15,000/QALY 5 fractions was expected to have 33.8% chance of being cost effective in this scenario.

Table 20: Results for base case and sensitivity analyses in FAST forward population. All analyses are based on 10000 probabilistic simulations.

Scenario	FAST-Forward population	
	Whole breast 15 Fractions	Whole breast 5 Fractions
	ICER (probability treatment ICER < Threshold)	
Base case (£15,000/QALY)	Dominated (0.1%)	£0 (99.9%)
Threshold £20,000/QALY	Dominated (0.2%)	£0 (99.8%)
Threshold £30,000/QALY	Dominated (0.4%)	£0 (99.6%)
Distant relapse hazard ratio estimated in FAST-Forward	£0 (66.2%)	£6,271 (33.8%)
All treatment effects maintained for 10 years	Dominated (0.1%)	£0 (99.9%)
All treatment effects maintained for 5 years	Dominated (0.1%)	£0 (99.9%)
Mortality rate following distant relapse based on HER2+ population [80]	Dominated (0.1%)	£0 (99.9%)
Mortality rate following distant relapse based on TNBC (HR- & HER2-) population [80]	Dominated (0.1%)	£0 (99.9%)
Distant relapse costs reduced to £8,934 per year [95]	Dominated (0.1%)	£0 (99.9%)
Distant relapse costs increased to £16,111 per year (20% increase)	Dominated (0.1%)	£0 (99.9%)
Disutility resulting from distant relapse reduced to 0.26 [96]	Dominated (0.1%)	£0 (99.9%)
Disutility resulting from distant relapse increased to 0.3636 (20% increase)	Dominated (0.1%)	£0 (99.9%)
Use of breath hold assumed to not increase cost to deliver one fraction of radiotherapy (£124)	Dominated (0.1%)	£0 (99.9%)
Use of breath hold assumed to double the cost to deliver one fraction of radiotherapy (£248)	Dominated (0.1%)	£0 (99.9%)
Rate of adverse skin reactions set equal across all treatment options	Dominated (0.1%)	£0 (99.9%)
Health related quality of life weight during radiotherapy set to zero	Dominated (0.1%)	£0 (99.9%)
Log normal survival model in which each participant only contributes their 1st event	Dominated (12%)	£0 (88%)

Discussion

Across a range of scenarios, 5 fraction radiotherapy were expected to be cost effective at a threshold of £15,000/QALY. 5 fractions was expected to provide more QALYs and have lower costs compared to 15 fractions. The expected cost savings were primarily due to reducing the number of fractions of radiotherapy. The improvement in QALYs was driven by the modest expected reduction in locoregional relapses. Figure illustrates how 5 fractions is associated with lower costs and greater QALYs. The figure also illustrates that the spread of points for 5 fractions lies almost completely to the south east of the £15,000/QALY cost effectiveness threshold. This indicates that the cost effectiveness of 5 fractions was associated only with minimal parametric uncertainty.

Resource savings from reduced fractionation may enable the same number of patients to be treated with lower linear accelerator capacity therefore freeing capacity to treat breast and other cancers. The increased capacity could also be used to introduce the many improvements in the quality of therapy, such as cardiac-sparing breath hold if not fully implemented. Further, the benefits to patients would immediately be realised in terms of reduced burden of treatment and hospital-footfall, and this may have added benefits such as reduced exposure to COVID-19 [97].

The sensitivity analyses reported in Table 21 illustrated that these overall conclusions were robust to alternative inputs and assumptions. Across all scenarios the 5Fr regimens remained the least costly alternative. Using different molecular subtype populations to model mortality following distant relapse did not impact results [80]. This was because in this scenario *relative* rates of distant relapse were assumed common across arms. In the scenario in which relative rates of distant relapse were calculated using the hazard ratio estimated in FAST-Forward, 5 fractions was associated with fewer expected QALYs. With a cost effectiveness threshold of £15,000/QALY, 5 fractions was not expected to be the cost-effective alternative. The relatively lower QALYs associated with 5 fractions in these scenarios was due to the hazard ratio for distant relapse for 5 vs 15 fractions estimated in FAST-Forward. This estimate indicated a higher rate of distant relapse with 5 fractions, HR = 1.27 (0.90 to 1.80) which in absolute terms is equivalent to an increase of 1% (-0.4% to 2.9%). Though this was not statistically significant (p = 0.17) distant relapse had a large impact on both morbidity and mortality in the economic model and so drove differences in expected QALYs between treatment options.

The key assumption in the base case analysis is that there was a common pattern of transition from alive and disease free to distant relapse across treatment options. This assumption was based on the clinical argument that radiotherapy is a local treatment and therefore has local effects. One alternative approach to capture treatment effects in the model would be to estimate

the rate of any relapse (distant or local or regional). This approach could be used to estimate baseline and relative effects across radiotherapy modalities. This alternative approach was not carried out here so that the economic analysis followed the analysis in the published trial [23]. Additionally, estimating the difference in any relapse between arms would imply a common treatment effect on local, distant and regional relapses which may not be clinically plausible. Even if this approach was used, it would remain necessary to separate out the different relapse types has they have different costs and health consequences. A fully comprehensive approach may require a multi-state modelling framework and thus a different approach to both data collection and modelling [98, 99]. This approach would need to take account of recognised issues with effect identification [100, 101]. Further research is required in this area.

Other limitations of the analysis are described here. The HRQoL impact of acute skin reactions was not captured due to lack of EQ-5D data during the treatment period, only treatment costs were included. Including HRQoL impacts into the analysis would likely improve the relative benefits of 5 fraction therapy as this was observed to have fewer severe acute adverse reactions than 15 fractions in Brunt et al., (2016) [72].

To our knowledge, no other studies have examined the cost-effectiveness of 5 fraction radiotherapy in a UK context. For the US system, Deshmukh et al., (2017) compared whole breast radiotherapy delivered over 5-7 weeks to radiotherapy delivered over 3-4 weeks and found that reducing fractionation (and therefore duration of radiotherapy) dominated higher fractionation [102]. This is in line with our base case results.

Based on the results presented, 5 fraction radiotherapy offers potentially significant benefits to the UK health system compared to 15 fractions.

CHAPTER 7: NODAL SUB-STUDY

Recruitment

The original target accrual for the Nodal Sub-Study was 627 patients to be recruited over 2 years. The first patient was recruited into the sub-study on 11/04/2016. Accrual was suspended from 06/12/2017 until 23/01/2018 whilst the substantial protocol amendment to close accrual into Test Group 1 (27 Gy/5Fr) for the sub-study was being processed for approval. At this stage a total of 109, 104 and 97 patients had been recruited into the 40 Gy/15Fr, 27 Gy/5Fr and 26 Gy/5Fr groups respectively. In Protocol v5.0 (14/12/2017) target recruitment for the sub-study was changed to 344 patients (172 in each of the Control Group and Test Group 1). Including the additional 104 patients randomised to Test Group 1 before the protocol amendment the revised overall target sample size was 448. Having reached the revised target accrual into the Nodal Sub-Study, centres were contacted on 29/08/2018 and asked not to approach any new patients regarding the trial. A few additional patients were subsequently randomised who had been previously approached and given information about the trial prior to this date, and the last patient was randomised on 02/10/2018.

The final number of patients entered into the Nodal Sub-Study was 469 from 28 radiotherapy centres and 22 referral centres (183 for 40 Gy/15Fr, 104 for 27 Gy/5Fr and 182 for 26 Gy/5Fr). 416 patients were recruited into the photographic assessment sub-study, 442 patients consented to donate a blood sample and 465 patients consented to donate their primary tissue sample. Recruitment figures according to centre are presented in Table 32 (Appendix 2). Cumulative recruitment over time compared with the target recruitment rate is shown in Figure 18.

Figure 18: Target and actual recruitment for Nodal Sub-Study
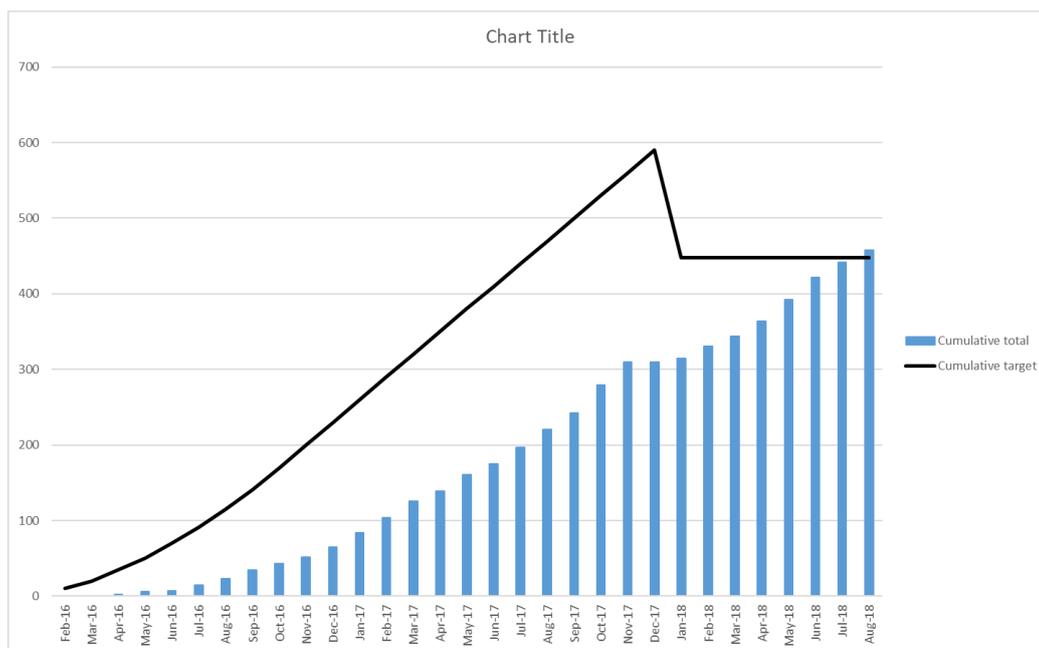
The original target for recruitment was based on 5 centres opening to recruitment once the Nodal Sub-Study opened with a further 2 centres expected to open per month until a total of 49 radiotherapy centres were open to recruitment. Each centre was predicted to recruit 2 patients per month with a maximum of 30 patients per month. Using these figures it was predicted that recruitment would take 24 months to attain. Radiotherapy centres were asked to obtain and additional QA approval procedure and only 32 centres undertook this. 52 centres opened to recruitment to the Nodal Sub-Study with a maximum of 31 patient recruited in any one month. 2 centres did not recruit any patients.

Deviations and withdrawals

Two patients withdrew consent for use of data and were removed from the intention-to-treat population, therefore Nodal Sub-Study results are reported for 467 consenting patients. A total of 18 patients (8 in 40 Gy, 4 in 27 Gy, 6 in 26 Gy) did not receive the allocated therapy (Figure 19); compliance with allocated treatment was therefore 96% (449/467). These 18 patients included 2 found to be ineligible after randomisation: 1 in the 40 Gy group (Non-Hodgkins lymphoma), and 1 in 26 Gy (no axillary staging due to co-morbidities).

By 3 years' follow-up 10 patients had withdran from clinical follow-up (9 in 40 Gy and 1 in 26 Gy), and 49 had died (19 in 40 Gy, 10 in 27 Gy, 20 in 26 Gy).

Data returns

Data return rates were calculated as % of CRFs or questionnaires received at ICR-CTSU out of those expected (expected numbers exclude patients who have died or withdrawn). Baseline CRFs were available for 99% of patients. As of 24/01/2022, annual clinical follow-up forms had been returned to the trials office for 98% (441 received out of 451 expected) for year 1, 99% (433/435) for year 2, and 90% (376/420) for year 3. As of the date of this report, all Nodal Sub-Study patients have reached the 3-year time-point and further follow-up is ongoing, hence the CONSORT diagram and results for the Nodal Sub-Study presented in this report include data up to 3 years. Analysis of follow-up beyond 3 years in the Nodal Sub-Study will be done in the future once data collection is complete.

Return rates for the patient self-completed questionnaires up to 2 years' follow-up were 98% (460 received out of 467 expected) at baseline, 89% (386/434) at 3 months, 89% (379/427) at 6 months, 87% (359/415) at 1 year and 89% (367/414) at 2 years. As of the date of this report, collection of 5-year questionnaires is underway, with the last one due in October 2023.

Figure 19: FAST-Forward Nodal Sub-Study profile (CONSORT diagram)

	467 patients randomised[1]	
181 patients allocated to 40 Gy in 15 Fr (3 weeks)	**104 patients allocated to 27 Gy in 5 Fr (1 week)**	**182 patients allocated to 26 Gy in 5 Fr (1 week)**

8 did not receive allocated therapy

1 ineligible (Non-Hodgkins lymphoma)

1 given 50Gy/25Fr + 10Gy concomitant boost

2 patients died after randomisation

3 patients radiotherapy forms are missing

1 patient withdrew after first RT session

4 did not receive allocated therapy

1 patient choice (given 40Gy/15 Fr)

2 clinical decisions; given 40Gy/15Fr (toxicities noticed in previous patient who suffered flap failure of DIEP reconstruction; test treatment withdrawn & clinician decided to give control treatment)

1 site error (given 40Gy/15Fr)

6 did not receive allocated therapy

1 ineligible (no axillary staging due to comorbidities

1 given 26Gy/5Fr without nodal RT

3 No RT given (clinician choice); (1 restricted movement, 1 5Fr unacceptable due to hotspots, 1 clinical incident at 1st Fr)

1 dose constraint not met (given 40Gy/15Fr)

173 patients received allocated therapy

100 patients received allocated therapy

176 patients received allocated therapy

181 patients included in ITT analysis

104 patients included in ITT analysis

182 patients included in ITT analysis

[1] 2 patients withdrew consent for any of their data to be used in the analysis (1 x 40 Gy, 1 x 26 Gy); ITT = intention to treat

Baseline data

Baseline demographic, clinical and treatment characteristics according to treatment group are shown in Table 22, enabling the following comparisons: (a) all patients randomised to 40 Gy versus all those randomised to 26 Gy, and (b) patients randomised to 40 Gy up to end 2017 versus all those randomised to 27 Gy. The median age of all Nodal Sub-Study patients was 60 years (IQR 51-70; overall range 31-89), and it included 4 men. A total of 250 (53%) were grade 2 and 182 (39%) grade 3. Just over half (255, 55%) had breast conservation surgery, and 43/212 (20%) mastectomy patients had an immediate breast reconstruction. The majority of patients had axillary clearance (254/467, 54%). Median pathological tumour size was 2.6 cm (IQR 0.9-7.2). The majority of patients were ER positive, HER2 negative (325, 70%). A total of 113 (24%) received neo-adjuvant chemotherapy, and 216 (46%) received adjuvant chemotherapy; 13 patients received both neo-adjuvant and adjuvant chemotherapy.

Radiotherapy details for the 458 patients who received radiotherapy are shown in Table 23. Deviations from allocated treatment are described above. A tumour bed boost was prescribed for 117/458 (25%) of patients, most commonly to a dose of 10 Gy in 5Fr (58/117, 50%). For the overall trial cohort the median breast/chest wall planning target volume (PTV) was 870 cc (IQR 269-1954), and median nodal PTV was 134.6 cc (IQR 41.5 – 357.2). Bolus was used for 89 of the 209 (43%) mastectomy patients who received radiotherapy.

Table 21: Demographic, clinical and treatment characteristics at randomisation of the 467 patients consenting to the FAST-Forward Nodal Sub-Study[1]

	40 Gy/15Fr All randomised N=181 (%)	26 Gy/5Fr N=182 (%)	40 Gy/15Fr Randomised concurrently with 27 Gy/5Fr N=108 (%)	27 Gy/5Fr N=104 (%)
Age (years)				
Median (IQR)	61 (51-72)	60 (51-70)	60 (49-72)	57 (49-67)
[range]	34-89	34-86	36-89	30-84
<40	7 (4)	14 (8)	6 (6)	4 (4)
40-49	31 (17)	28 (15)	22 (20)	23 (22)
50-59	47 (26)	49 (27)	26 (24)	28 (27)
60-69	43 (24)	45 (25)	23 (21)	29 (28)
70-79	42 (23)	32 (18)	25 (23)	13 (12)
$\geq$80	11 (6)	14 (8)	6 (6)	7 (7)
Sex				
Female	180 (99)	180 (99)	107 (99)	103 (99)
Male	1 (1)	2 (1)	1 (1)	1 (1)
Tumour grade				
1	15 (8)	12 (7)	13 (12)	8 (8)
2	95 (52)	97 (53)	50 (46)	58 (56)
3	71 (39)	73 (40)	45 (42)	38 (36)
Primary surgery				
Breast conservation surgery	95 (52)	106 (58)	60 (56)	54 (52)
BCS with oncoplastic technique	*2*	*2*	*2*	*1*
Mastectomy	86 (48)	76 (42)	48 (44)	50 (48)
Mastectomy with immediate reconstruction	*15*	*17*	*8*	*11*
Type of reconstruction (mastectomy patients):				
Autologous reconstruction	*5/15*	*3/17*	*2/8*	*3/11*
Implant-based reconstruction	*10/15*	*13/17*	*6/8*	*7/11*
Reconstruction type not specified	*0*	*1/17*	*0*	*1/11*
Side of primary				
Left	87 (48)	104 (57)	50 (46)	55 (53)
Right	94 (52)	78 (43)	58 (54)	49 (47)
Maximal extent of axillary staging				
Sentinel node biopsy/guided axillary sampling	74 (41)	90 (50)	41 (38)	48 (46)
Axillary clearance	107 (59)	91 (50)	67 (62)	56 (54)
Not known	0	1	0	0
Post-op infection requiring antibiotics				
Yes	21 (12)	21 (12)	12 (11)	14 (13)
No	155 (86)	157 (86)	94 (87)	87 (84)
Not known	5 (3)	4 (2)	2 (2)	3 (3)
Post-op haematoma requiring surgical evacuation				
Yes	1 (<1)	1 (<1)	0	3 (3)
No	174 (96)	176 (97)	106 (98)	97 (93)
Not known	6 (3)	5 (3)	2 (2)	4 (4)
Post-op seroma requiring aspiration				
Yes	45 (25)	41 (22)	30 (28)	19 (18)
No	132 (73)	136 (75)	77 (71)	80 (77)
Not known	4 (2)	5 (3)	1 (1)	5 (5)

	40 Gy/15Fr All randomised N=181 (%)	26 Gy/5Fr N=182 (%)	40 Gy/15Fr Randomised concurrently with 27 Gy/5Fr N=108 (%)	27 Gy/5Fr N=104 (%)
Histological type				
Infiltrating ductal	136 (75)	143 (79)	86 (80)	85 (82)
Lobular	33 (18)	25 (14)	13 (12)	12 (11)
Mixed	9 (5)	7 (4)	7 (6)	5 (5)
Other	3 (2)	6 (3)	2 (2)	2 (2)
Not known	0	1	0	0
Pathological tumour size (cm)				
Median (IQR)	3 (1 – 7)	3 (1 – 8)	3 (1 – 7)	3 (1 – 7)
pT stage				
T1mi	2 (1)	2 (1)	1 (1)	1 (1)
T1a	2 (1)	2 (1)	2 (2)	
T1b	6 (3)	7 (4)	3 (3)	6 (6)
T1c	49 (27)	42 (23)	33 (31)	31 (30)
T2	92 (51)	100 (55)	54 (50)	50 (48)
T3	29 (16)	27 (15)	14 (13)	15 (14)
Not known	1	2	1	1
ER / HER2 status				
ER+ / HER2+	29 (16)	27 (15)	22 (20)	13 (12)
ER+ / HER2-	124 (68)	122 (68)	72 (67)	79 (76)
ER- / HER2+	7 (4)	6 (3)	3 (3)	4 (4)
ER- / HER2-	21 (12)	24 (13)	11 (10)	8 (8)
Not known	0	2	0	0
PgR status				
Positive	80 (44)	71 (40)	51 (48)	48 (47)
Negative	36 (20)	44 (25)	19 (18)	17 (16)
Not done	64 (36)	63 (35)	37 (34)	38 (37)
Missing on form	1	3	1	1
Lymphovascular invasion				
Present	75 (41)	77 (43)	47 (44)	48 (46)
Absent	90 (50)	86 (47)	48 (44)	46 (44)
Uncertain	9 (5)	11 (6)	8 (7)	6 (6)
Not known	7 (4)	7 (4)	5 (5)	4 (4)
Neo-adjuvant chemotherapy received				
Yes	43 (24)	44 (24)	27 (25)	26 (25)
No	137 (76)	137 (76)	80 (75)	78 (75)
Adjuvant therapy received[2]				
All patients:	169 (94)	170 (94)	102 (95)	99(95)
Chemotherapy[3]	80 (47)	87 (51)	48 (47)	49 (49)
HER2 + patients:				
Trastuzumab	26 (72)	28 (85)	19 (76)	16 (94)
Chemotherapy & trastuzumab	14 (82)	14 (100)	8 (89)	9 (100)
Trastuzumab, no chemotherapy	12 (67)	14 (82)	11 (69)	7 (88)
Chemotherapy, no trastuzumab				
No chemotherapy, no trastuzumab	12 (67)	14 (82)	11 (69)	7 (88)
ER+ patients:				
Endocrine therapy	153 (85)	151 (83)	94 (87)	92 (88)

IQR = interquartile range; BCS = breast conservation surgery; [1] 2 patients withdrew consent for any of their data to be used in analysis

Table 22: Radiotherapy details for the 458 treated patients in the FAST-Forward Nodal Sub-Study[1]

Radiotherapy details	40 Gy/15Fr All randomised N=175 (%)	26 Gy/5Fr N=179 (%)	40 Gy/15Fr Randomised concurrently with 27 Gy/5Fr N=107 (%)	27 Gy/5Fr N=104 (%)
Days from randomisation to starting RT N	174	178	107	104
Median (IQR)	27 (21-37)	26 (21-34)	27 (20-36)	25.5 (20-33)
Range	7-90	8-86	7-90	6-116
Dose delivered to whole breast / chest wall / nodes				
40 Gy/15Fr	173 (99)	1 (<1)	107 (100)	4 (4)
26 Gy/5Fr	0	176 (99)	0	0
27 Gy/5Fr	0	0	0	100 (96)
2 Gy/1Fr	0	1 (<1)	0	0
50 Gy/25Fr	1 (1)	0	0	0
Missing on form	1	1	0	0
Boost given				
Yes	46 (26)	46 (26)	30 (28)	25 (24)
No	128 (74)	132 (74)	77 (72)	79 (76)
Missing on form	1	1	0	0
Boost dose received	N=46	N=46	N=30	N=25
10 Gy/5Fr	19 (42)	24 (52)	15 (50)	15 (60)
16 Gy/8Fr	5 (11)	8 (17)	5 (17)	6 (24)
12.5 Gy/5Fr	2 (4)	0 (0)	2 (7)	0
13.35 Gy/5Fr	9 (20)	7 (15)	6 (20)	2 (8)
14 Gy/5Fr	3 (7)	2 (4)	2 (7)	1 (4)
16 Gy/5Fr	0 (0)	0 (0)	0 (0)	1 (4)
12 Gy/4Fr	4 (9)	4 (9)	0 (0)	0 (0)
10 Gy/4Fr	3 (7)	0 (0)	0 (0)	0 (0)
9 Gy/3Fr	0 (0)	1 (2)	0 (0)	0 (0)
Not known	1	0	0	0
Volume of breast/chest wall PTV (cc) N	173	177	105	103
Median (IQR)	850 (566-1114)	876 (547-1277)	870 (583-1140)	915 (552-1368)
Range	64-4911	69-7338	64-4911	119-2794
Nodal areas irradiated				
Axillary level I	80 (46)	91 (51)	47 (45)	46 (45)
Axillary level II	89 (51)	95 (54)	52 (50)	51 (50)
Axillary level III	121 (70)	126 (71)	76 (72)	66 (64)
Level IV (SCF)	159 (92)	163 (92)	93 (89)	95 (92)
IMC	0	1 (<1)	0	0
Missing on form	2	2	2	1
Volume of nodal PTV (cc)				
N	172	177	104	103
Median (IQR)	129 (85-207)	140 (92-213)	133 (86-223)	139 (97-211)
Range	13-1257	10-635	13-1257	14-803

Radiotherapy details	40 Gy/15Fr All randomised N=175 (%)	26 Gy/5Fr N=179 (%)	40 Gy/15Fr Randomised concurrently with 27 Gy/5Fr N=107 (%)	27 Gy/5Fr N=104 (%)
Bolus used (mastectomy patients only)	N=83	N=76	N=47	N=50
Yes	33 (41)	30 (43)	17 (38)	26 (54)
No	48 (59)	40 (57)	28 (62)	22 (46)
Missing on form	2	6	2	2
Dose homogeneity constraints achieved				
Yes	163 (94)	162 (91)	100 (94)	98 (95)
No	11 (6)	16 (9)	6 (6)	5 (5)
Missing on form	1	1	1	1
Organs at risk dose constraints achieved				
Yes	161 (93)	161 (90)	96 (91)	95 (92)
No	13 (7)	17 (10)	10 (9)	8 (8)
Missing on form	1	1	1	1
Was patient re-planned during radiotherapy?				
Yes	5 (3)	6 (3)	3 (3)	0
No	169 (97)	172 (97)	103 (97)	103 (100)
Missing on form	1	1	1	1
RT extended by >3 days				
Yes	1 (<1)	2 (1)	1 (1)	0
No	173 (99)	176 (99)	105 (99)	103 (100)
Missing on form	1	1	1	1
Reason:				
Bank holidays	*0*	*1*	*0*	*0*
Patient illness	*1*	*0*	*1*	*0*
Other	*0*	*1*	*0*	*0*

RT = radiotherapy; SCF = supraclavicular fossa; IMC = internal mammary chain

[1] 2 patients withdrew consent for any of their data to be used in analysis & 9 patients received no RT

Follow-up

As of the data snapshot on 01/12/2021, median follow-up in each treatment group was 36 months (IQR 31-48) for all 40 Gy/15Fr patients, 37 months (IQR 31-48) for 26 Gy/5Fr, and 48 months (IQR 37-49) for 27 Gy/5Fr. Median follow-up in 40 Gy/15Fr patients randomised prior to the December 2017 protocol amendment (i.e. concurrently with 27 Gy/5Fr) was 47 months (IQR 34-48). Centres were requested to schedule annual follow-up assessments as close to the due date as possible, which was calculated from date of randomisation. Some leeway was permitted within the trial to accommodate local hospital policy that schedules follow-up based on date of surgery rather than date of trial randomisation. Annual clinical follow-ups occurred within 3 months of the due date in 86% of cases (1054 of 1220 clinical follow-ups).

Annual clinical follow-ups were primarily conducted in person at sites prior to the COVID-10 pandemic. On 01/04/2020 sites were advised that these could be done via telephone by a health care professional, and guidance was provided regarding the clinical assessments to be carried out at each visit.

Late normal tissue effects in Nodal Sub-Study

As stated in the Statistical Methods section (Chapter 2), formal comparisons of NTE in the Nodal Sub-Study will await 5-year follow-up. Descriptive data for PRO up to 2 years and for clinical assessments up to 3 years are included in this report.

Patient-reported outcomes (PRO)

PRO were available at baseline for 180 patients in the 40 Gy group, 181 in 26 Gy and 103 in 27 Gy, and at 24 months for 127, 135 and 89 respectively.

Symptoms in arm, shoulder or hand

Frequencies of PRO relating to arm / shoulder / hand symptoms from baseline to 24 months are shown in Table 24 for 40 Gy compared with 26 Gy (all randomised patients), and in Table 25 for 40 Gy and 27 Gy patients randomised up to the end of 2017. For all outcomes relating to arm, shoulder or hand, the number of patients reporting marked effects was small at all time-points in all treatment groups. Table 55 (Appendix 2) shows baseline arm / shoulder / hand symptoms according to maximal extent of axillary surgery and fractionation schedule.

The majority of patients reported no arm / hand swelling (primary outcome of the Nodal Sub-Study) from baseline up to 24 months, with 80% and 77% in 40 Gy and 26 Gy at baseline and 73% and 76% at 24 months (Table 24). For the comparison of 40 Gy and 27 Gy, 81% and 84% reported no arm / hand swelling at baseline, and 74% and 66% at 24 months (Table 25). Most of those reporting arm / hand swelling had mild symptoms (graded as "a little" on the questionnaires). The prevalence of moderate or marked arm / hand swelling at 24 months (corresponding to "quite a bit" or "very much") was 10% versus 7% for 40 Gy compared with 26 Gy, and 8% versus 14% for 40 Gy compared with 27 Gy.

The most frequently reported effect in the arm, shoulder or hand across all time-points was pain in the arm or shoulder, with symptoms (any grade) reported at baseline by 64% in 40 Gy, 60% in 26 Gy and 67% in 27 Gy. However, most of these were mild symptoms, with moderate or marked arm or shoulder pain reported at baseline by 15%, 22% and 20% in 40 Gy, 26 Gy and 27 Gy respectively. At 24 months moderate or marked arm or shoulder pain was reported by 18%, 14% and 25% in 40 Gy, 26 Gy and 27 Gy respectively.

The prevalence of moderate/marked neuropathic symptoms was low (Tables 24 and 25). Pins and needles of any grade were reported at baseline by 28% in 40 Gy, 28% in 26 Gy and 28% in 27 Gy on the affected side and by 15% in 40 Gy, 18% in 26 Gy and 15% in 27 Gy on the non-affected side. Pins and needles of any grade were reported at 24 months by 34% in 40 Gy, 35% in 26 Gy

and 44% in 27 Gy on the affected side and by 21% in 40 Gy, 18% in 26 Gy and 28% in 27 Gy on the non-affected side. However, most of these were mild symptoms, with moderate or marked pins and needles reported at baseline by 7%, 5% and 3% in 40 Gy, 26 Gy and 27 Gy respectively on the affected side and by 5%, 3% and 2% in 40 Gy, 26 Gy and 27 Gy respectively on the non-affected side. At 24 months moderate or marked pins and needles was reported by 9%, 9% and 6% in 40 Gy, 26 Gy and 27 Gy respectively on the affected side and by 4%, 5% and 9% in 40 Gy, 26 Gy and 27 Gy respectively on the non-affected side.

Symptoms in breast or chest wall

Frequencies of PRO relating to breast / chest wall symptoms from baseline to 24 months are shown in Table 26 for 40 Gy compared with 26 Gy (all randomised patients), and in Table 27 for 40 Gy and 27 Gy patients randomised up to the end of 2017. For outcomes relating to breast or chest wall symptoms, the number of patients reporting marked effects was generally small at all time-points in all treatment groups.

The most frequently reported moderate or marked effect at 24 months was change in overall appearance of breast (as a result of any of the breast cancer treatments), which was reported by 47%, 38% and 58% of 40 Gy, 26 Gy and 27 Gy respectively. Prevalence of moderate or marked effects were higher for the protocol-specific items than for the breast symptoms from the EORTC QLQ-BR23 breast module, which generally improved over time from 3 to 24 months following radiotherapy. Compared with PRO in the Main Trial, prevalence of symptoms from the EORTC QLQ-BR23 breast module for patients in the Nodal Sub-Study were similar, but frequencies of moderate or marked effects on the protocol-specific breast items were higher than reported in the Main Trial (Chapter 5).

Table 23: Patient-reported effects in arm / shoulder / hand: baseline to 24 months for 40 Gy vs 26 Gy (all randomised patients) in Nodal Sub-Study

Arm / shoulder / hand effect	Baseline 40 Gy N=180 (%)	Baseline 26 Gy N=181 (%)	3 months 40 Gy N=141 (%)	3 months 26 Gy N=153 (%)	6 months 40 Gy N=137 (%)	6 months 26 Gy N=151 (%)	12 months 40 Gy N=130 (%)	12 months 26 Gy N=142 (%)	24 months 40 Gy N=127 (%)	24 months 26 Gy N=135 (%)
Swollen arm or hand (EORTC QLQ-BR23)										
Not at all	144 (80)	140 (77)	100 (71)	112 (73)	95 (70)	104 (69)	98 (75)	95 (67)	93 (73)	102 (76)
A little	29 (16)	26 (14)	29 (20)	33 (22)	27 (20)	37 (25)	22 (17)	35 (25)	21 (17)	22 (16)
Quite a bit	4 (2)	8 (5)	7 (5)	3 (2)	9 (7)	5 (3)	6 (5)	8 (6)	7 (5)	7 (5)
Very much	3 (2)	7 (4)	5 (4)	5 (3)	5 (3)	4 (3)	4 (3)	3 (2)	6 (5)	3 (2)
Missing	0	0	0	0	1	1	0	1	0	1
Pain in arm or shoulder (EORTC QLQ-BR23)										
Not at all	65 (36)	72 (40)	46 (33)	38 (25)	40 (30)	43 (28)	46 (35)	47 (33)	50 (39)	53 (40)
A little	89 (49)	68 (38)	52 (37)	67 (44)	57 (42)	69 (46)	55 (42)	59 (42)	54 (43)	61 (46)
Quite a bit	20 (12)	27 (15)	29 (21)	34 (22)	29 (21)	28 (19)	21 (16)	19 (13)	14 (11)	15 (11)
Very much	6 (3)	13 (7)	13 (9)	13 (9)	10 (7)	11 (7)	8 (6)	17 (12)	9 (7)	5 (3)
Missing	0	1	1	1	1	0	0	0	0	1
Difficult to raise arm or move it sideways (EORTC QLQ-BR23)										
Not at all	113 (63)	106 (58)	76 (54)	67 (44)	66 (49)	65 (43)	76 (58)	68 (48)	78 (61)	74 (55)
A little	51 (28)	52 (29)	47 (33)	61 (40)	49 (36)	68 (45)	37 (28)	53 (38)	34 (27)	50 (38)
Quite a bit	12 (7)	16 (9)	10 (7)	15 (10)	12 (9)	9 (6)	11 (8)	8 (6)	8 (6)	6 (4)
Very much	3 (2)	7 (4)	8 (6)	10 (6)	9 (7)	8 (5)	6 (5)	11 (8)	7 (6)	4 (3)
Missing	1	0	0	0	1	1	0	2	0	0
Shoulder stiffness										
Not at all	123 (69)	115 (64)	69 (50)	67 (44)	61 (45)	62 (41)	64 (50)	61 (44)	70 (56)	67 (52)
A little	49 (27)	49 (27)	47 (34)	58 (38)	50 (37)	58 (39)	47 (37)	56 (40)	43 (34)	46 (36)
Quite a bit	6 (3)	12 (7)	13 (9)	17 (11)	17 (13)	22 (15)	9 (7)	14 (10)	7 (6)	12 (9)
Very much	2 (1)	3 (2)	8 (6)	11 (7)	7 (5)	7 (5)	7 (6)	8 (6)	5 (4)	4 (3)
Missing	0	2	3	0	2	2	3	3	2	6
Pins & needles in arm/hand on affected side (protocol-specific item[1])										
Not at all	128 (72)	128 (72)	83 (60)	100 (65)	92 (68)	89 (59)	86 (67)	85 (61)	82 (66)	84 (65)
A little	38 (21)	41 (23)	39 (28)	32 (21)	28 (21)	40 (27)	31 (24)	41 (30)	31 (25)	34 (26)
Quite a bit	7 (4)	6 (3)	9 (7)	16 (11)	8 (6)	14 (10)	5 (4)	10 (7)	8 (6)	10 (8)
Very much	6 (3)	3 (2)	7 (5)	5 (3)	7 (5)	6 (4)	6 (5)	3 (2)	4 (3)	1 (1)
Missing	1	3	3	0	2	2	2	3	2	6
Pins & needles in arm/hand on non-affected side (protocol-specific item[1])										
Not at all	152 (85)	146 (82)	106 (77)	119 (78)	117 (87)	115 (77)	105 (82)	111 (80)	99 (79)	106 (82)
A little	18 (10)	26 (15)	25 (18)	20 (13)	15 (11)	21 (14)	17 (13)	19 (14)	22 (17)	17 (13)
Quite a bit	3 (2)	6 (3)	4 (3)	9 (6)	1 (<1)	8 (5)	3 (2)	6 (4)	2 (2)	4 (3)
Very much	6 (3)	0	3 (1)	5 (3)	2 (1)	5 (3)	3 (2)	3 (2)	2 (2)	3 (2)

Arm / shoulder / hand effect	Baseline		3 months		6 months		12 months		24 months	
	40 Gy N=180 (%)	26 Gy N=181 (%)	40 Gy N=141 (%)	26 Gy N=153 (%)	40 Gy N=137 (%)	26 Gy N=151 (%)	40 Gy N=130 (%)	26 Gy N=142 (%)	40 Gy N=127 (%)	26 Gy N=135 (%)
Missing	1	3	2	0	2	2	2	3	2	5
Numbness in fingers on affected side (protocol-specific item[1])										
Not at all	145 (81)	137 (77)	98 (71)	107 (70)	97 (72)	98 (66)	91 (71)	92 (66)	90 (72)	87 (67)
A little	16 (9)	33 (19)	26 (19)	26 (17)	28 (21)	36 (24)	30 (23)	39 (28)	28 (22)	34 (26)
Quite a bit	10 (6)	8 (4)	10 (7)	15 (10)	6 (4)	9 (6)	2 (2)	6 (4)	2 (2)	8 (6)
Very much	8 (4)	0	4 (3)	5 (3)	4 (3)	6 (4)	5 (4)	2 (1)	5 (4)	1 (1)
Missing	1	3	3	0	2	2	2	3	2	5
Numbness in fingers on non-affected side (protocol-specific item[1])										
Not at all	146 (82)	149 (84)	112 (81)	124 (81)	108 (81)	118 (79)	103 (81)	110 (79)	106 (85)	111 (85)
A little	14 (7)	22 (12)	17 (12)	17 (11)	19 (14)	22 (15)	19 (15)	22 (16)	15 (12)	13 (10)
Quite a bit	10 (6)	6 (3)	6 (4)	7 (5)	5 (4)	3 (2)	3 (2)	5 (4)	2 (2)	5 (4)
Very much	9 (5)	1 (1)	3 (2)	5 (3)	2 (1)	6 (4)	2 (2)	2 (1)	2 (2)	1 (1)
Missing	1	3	3	0	3	2	3	3	2	5
Weakness in arm/hand on affected side (protocol-specific item[1])										
Not at all	112 (63)	118 (67)	66 (48)	74 (48)	62 (46)	63 (43)	63 (49)	63 (45)	57 (46)	69 (53)
A little	51 (28)	46 (26)	48 (35)	52 (34)	47 (35)	61 (41)	45 (35)	60 (43)	40 (32)	48 (37)
Quite a bit	12 (7)	9 (5)	15 (11)	22 (15)	21 (16)	17 (12)	15 (12)	12 (9)	18 (14)	11 (8)
Very much	4 (2)	4 (2)	9 (6)	5 (3)	4 (3)	6 (4)	5 (4)	4 (3)	10 (8)	2 (2)
Missing	1	4	3	0	3	2	2	3	2	5
Weakness in arm/hand on non-affected side (protocol-specific item[1])										
Not at all	159 (89)	155 (87)	107 (78)	120 (78)	102 (76)	117 (79)	106 (83)	113 (82)	97 (78)	102 (78)
A little	14 (8)	20 (11)	26 (19)	24 (16)	23 (17)	22 (15)	16 (13)	18 (13)	18 (14)	23 (18)
Quite a bit	4 (2)	2 (1)	3 (2)	8 (5)	7 (5)	5 (3)	3 (2)	6 (4)	5 (4)	4 (3)
Very much	2 (1)	1 (<1)	1 (1)	1 (1)	2 (1)	4 (3)	3 (2)	1 (1)	5 (4)	1 (1)
Missing	1	3	3	0	3	3	2	4	2	5

[1] Questions relating to pins and needles, numbness and weakness in arm and hands were adapted from similar questions in the EORTC Quality of Life Item Library

Table 24: Patient-reported effects in arm / shoulder / hand: baseline to 24 months for 40 Gy vs 27 Gy (patients randomised up to end 2017) in Nodal Sub-Study

Arm / shoulder / hand effect	Baseline 40 Gy N=108 (%)	Baseline 27 Gy N=103 (%)	3 months 40 Gy N=88 (%)	3 months 27 Gy N=94 (%)	6 months 40 Gy N=82 (%)	6 months 27 Gy N=93 (%)	12 months 40 Gy N=79 (%)	12 months 27 Gy N=87 (%)	24 months 40 Gy N=72 (%)	24 months 27 Gy N=89 (%)
Swollen arm or hand (EORTC QLQ-BR23)										
Not at all	87 (81)	87 (84)	58 (66)	65 (70)	59 (72)	65 (70)	59 (74)	57 (65)	53 (74)	59 (66)
A little	15 (13)	13 (13)	21 (24)	23 (25)	14 (17)	18 (20)	14 (18)	23 (26)	13 (18)	18 (20)
Quite a bit	3 (3)	3 (3)	6 (7)	4 (4)	6 (7)	6 (7)	3 (4)	4 (5)	3 (4)	8 (9)
Very much	3 (3)	0 (0)	3 (3)	1 (1)	3 (4)	3 (3)	3 (4)	3 (3)	3 (4)	4 (5)
Missing	0	0	0	1	0	1	0	0	0	0
Pain in arm or shoulder (EORTC QLQ-BR23)										
Not at all	36 (33)	36 (33)	30 (35)	26 (28)	25 (30)	27 (29)	25 (32)	23 (26)	26 (36)	29 (32)
A little	51 (47)	51 (47)	27 (31)	41 (45)	28 (34)	37 (40)	35 (44)	39 (45)	32 (44)	38 (43)
Quite a bit	17 (16)	17 (16)	20 (23)	20 (22)	22 (27)	22 (24)	12 (15)	16 (18)	8 (11)	15 (17)
Very much	4 (4)	4 (4)	10 (11)	5 (5)	7 (9)	7 (7)	7 (9)	9 (10)	6 (8)	7 (8)
Missing	0	0	1	2	0	0	0	0	0	0
Difficult to raise arm or move it sideways (EORTC QLQ-BR23)										
Not at all	61(57)	54 (52)	46 (52)	48 (52)	35 (43)	42 (45)	46 (58)	47 (54)	38 (53)	51 (57)
A little	37 (34)	37 (36)	30 (34)	30 (32)	33 (40)	34 (37)	22 (28)	31 (35)	26 (36)	25 (28)
Quite a bit	8 (8)	10 (10)	7 (8)	11 (12)	8 (10)	14 (15)	5 (6)	4 (5)	5 (7)	8 (9)
Very much	1 (1)	2 (2)	5 (6)	4 (4)	6 (7)	3 (3)	6 (8)	5 (6)	3 (4)	5 (6)
Missing	1	0	0	1	0	0	0	0	0	1
Shoulder stiffness										
Not at all	75 (69)	59 (57)	44 (51)	36 (39)	35 (43)	41 (44)	40 (50)	41 (47)	36 (51)	42 (48)
A little	29 (27)	34 (33)	29 (33)	44 (47)	31 (38)	29 (32)	27 (34)	34 (39)	27 (38)	31 (35)
Quite a bit	3 (3)	9 (9)	8 (9)	10 (11)	11 (13)	19 (21)	6 (8)	6 (7)	6 (8)	10 (11)
Very much	1 (1)	1 (1)	6 (7)	3 (3)	5 (6)	3 (3)	6 (8)	6 (7)	2 (3)	5 (6)
Missing	0	0	1	1	0	1	0	0	1	1
Pins & needles in arm/hand on affected side (protocol-specific item[1])										
Not at all	78 (72)	74 (72)	52 (59)	46 (50)	53 (65)	53 (58)	52 (66)	53 (61)	48 (68)	47 (55)
A little	21 (19)	26 (25)	27 (31)	35 (38)	18 (22)	27 (29)	20 (25)	26 (30)	18 (25)	33 (38)
Quite a bit	3 (3)	1 (1)	6 (7)	6 (7)	7 (8)	11 (12)	2 (3)	6 (7)	3 (4)	3 (3)
Very much	6 (6)	2 (2)	3 (3)	5 (5)	4 (5)	1 (1)	5 (6)	2 (2)	2 (3)	3 (3)
Missing	0	0	0	2	0	1	0	0	1	3
Pins & needles in arm/hand on non-affected side (protocol-specific item[1])										
Not at all	94 (87)	88 (85)	68 (77)	72 (77)	71 (87)	68 (74)	64 (81)	68 (78)	59 (83)	62 (72)
A little	8 (7)	13 (13)	16 (18)	12 (13)	10 (12)	19 (21)	12 (15)	14 (16)	12 (17)	16 (19)
Quite a bit	1 (1)	1 (1)	3 (3)	7 (8)	0 (0)	4 (4)	1 (1)	4 (5)	0 (0)	5 (6)
Very much	5 (5)	1 (1)	1 (1)	2 (2)	1 (1)	1 (1)	2 (3)	1 (1)	0 (0)	3 (3)

Arm / shoulder / hand effect	Baseline		3 months		6 months		12 months		24 months	
	40 Gy N=108 (%)	27 Gy N=103 (%)	40 Gy N=88 (%)	27 Gy N=94 (%)	40 Gy N=82 (%)	27 Gy N=93 (%)	40 Gy N=79 (%)	27 Gy N=87 (%)	40 Gy N=72 (%)	27 Gy N=89 (%)
Missing	0	0	0	1	0	1	0	0	1	3
Numbness in fingers on affected side										
Not at all	86 (80)	72 (70)	61 (69)	52 (56)	60 (72)	56 (61)	53 (67)	60 (69)	51 (72)	55 (63)
A little	10 (9)	24 (23)	18 (21)	27 (29)	16 (20)	26 (28)	21 (27)	21 (24)	17 (24)	26 (30)
Quite a bit	7 (6)	3 (3)	8 (9)	8 (9)	3 (4)	6 (7)	1 (1)	5 (6)	1 (1)	3 (3)
Very much	5 (5)	4 (4)	1 (1)	6 (6)	3 (4)	4 (4)	4 (5)	1 (1)	2 (3)	3 (3)
Missing	0	0	0	1	0	1	0	0	1	2
Numbness in fingers on non-affected side (protocol-specific item[1])										
Not at all	89 (82)	79 (77)	71 (81)	70 (75)	68 (84)	71 (77)	63 (81)	68 (78)	61 (86)	67 (77)
A little	9 (8)	20 (19)	12 (14)	14 (15)	10 (12)	14 (15)	13 (17)	16 (18)	9 (13)	12 (14)
Quite a bit	5 (5)	1 (1)	4 (5)	6 (7)	2 (2)	6 (7)	0 (0)	2 (2)	1 (1)	6 (7)
Very much	5 (5)	3 (3)	0 (0)	3 (3)	1 (1)	1 (1)	2 (2)	1 (1)	0 (0)	2 (2)
Missing	0	0	0	1	1	1	1	0	1	2
Weakness in arm/hand on affected side (protocol-specific item[1])										
Not at all	64 (59)	70 (68)	41 (47)	40 (43)	35 (43)	35 (38)	35 (44)	42 (48)	33 (47)	34 (39)
A little	32 (30)	26 (25)	29 (33)	33 (35)	27 (33)	36 (39)	31 (39)	34 (39)	22 (31)	41 (47)
Quite a bit	8 (7)	5 (5)	12 (13)	14 (15)	16 (20)	16 (17)	9 (11)	6 (7)	13 (18)	9 (10)
Very much	4 (4)	2 (2)	6 (7)	6 (7)	3 (4)	5 (4)	4 (5)	5 (6)	3 (4)	3 (4)
Missing	0	0	0	1	1	1	0	0	1	2
Weakness in arm/hand on non-affected side (protocol-specific item[1])										
Not at all	93 (86)	91 (88)	65 (76)	74 (80)	59 (73)	69 (75)	66 (84)	71 (82)	56 (79)	68 (78)
A little	9 (8)	8 (8)	17 (20)	12 (13)	16 (20)	15 (16)	9 (11)	13 (15)	10 (14)	12 (14)
Quite a bit	4 (4)	3 (3)	2 (2)	4 (4)	5 (6)	5 (6)	1 (1)	3 (3)	3 (4)	5 (6)
Very much	2 (2)	1 (1)	2 (2)	3 (3)	1 (1)	3 (3)	3 (4)	0 (0)	2 (3)	2 (2)
Missing	0	0	0	1	1	1	0	0	1	2

[1] Questions relating to pins and needles, numbness and weakness in arm and hands were adapted from similar questions in the EORTC Quality of Life Item Library

Table 25: Patient-reported effects in breast / chest wall: baseline to 24 months for 40 Gy vs 26 Gy (all randomised patients) in Nodal Sub-Study

Breast / chest wall effect	Baseline		3 months		6 months		12 months		24 months	
	40 Gy N=180 (%)	26 Gy N=181 (%)	40 Gy N=141 (%)	26 Gy N=153 (%)	40 Gy N=137 (%)	26 Gy N=151 (%)	40 Gy N=130 (%)	26 Gy N=142 (%)	40 Gy N=127 (%)	26 Gy N=135 (%)
Pain in area of affected breast (EORTC QLQ-BR23)										
Not at all	88 (49)	77 (42)	38 (27)	41 (27)	47 (35)	36 (24)	53 (41)	56 (39)	61 (48)	56 (42)
A little	80 (44)	87 (48)	75 (53)	83 (54)	66 (48)	90 (60)	54 (41)	67 (47)	50 (39)	58 (43)
Quite a bit	9 (5)	12 (7)	21 (15)	22 (14)	18 (13)	16 (11)	17 (13)	14 (10)	12 (9)	14 (10)
Very much	3 (2)	5 (3)	7 (5)	7 (5)	5 (4)	8 (5)	6 (5)	5 (4)	4 (3)	6 (5)
Missing	0	0	0	0	1	1	0	0	0	1
Swelling in area of affected breast (EORTC QLQ-BR23)										
Not at all	123 (69)	119 (65)	98 (70)	92 (60)	95 (70)	91 (61)	100 (77)	97 (68)	98 (78)	103 (77)
A little	42 (24)	51 (28)	31 (22)	37 (24)	33 (24)	42 (28)	22 (17)	32 (23)	27 (21)	23 (17)
Quite a bit	10 (5)	6 (3)	10 (7)	17 (11)	3 (2)	13 (9)	6 (5)	9 (6)	1 (1)	4 (3)
Very much	3 (2)	5 (3)	2 (1)	7 (5)	5 (4)	3 (2)	2 (1)	4 (3)	0	4 (3)
Missing	2	0	0	0	1	2	0	0	1	1
Oversensitivity in area of affected breast (EORTC QLQ-BR23)										
Not at all	106 (59)	105 (58)	71 (51)	61 (40)	65 (48)	63 (42)	71 (55)	80 (57)	82 (65)	66 (50)
A little	62 (35)	61 (34)	48 (34)	64 (42)	53 (39)	64 (43)	37 (28)	42 (30)	35 (28)	48 (36)
Quite a bit	6 (3)	9 (5)	13 (9)	19 (13)	14 (10)	13 (9)	17 (13)	12 (8)	9 (7)	13 (10)
Very much	5 (3)	6 (3)	8 (6)	8 (5)	4 (3)	9 (6)	5 (4)	7 (5)	0 (0)	5 (4)
Missing	1	0	1	1	1	2	0	1	1	3
Skin problems on or in area of affected breast (EORTC QLQ-BR23)										
Not at all	142 (79)	137 (76)	89 (64)	95 (63)	97 (72)	113 (75)	92 (71)	107 (75)	96 (76)	100 (75)
A little	31 (17)	36 (20)	39 (28)	39 (26)	26 (20)	27 (18)	27 (21)	31 (22)	23 (18)	27 (20)
Quite a bit	0 (0)	6 (3)	8 (6)	8 (5)	9 (6)	10 (7)	8 (6)	4 (3)	6 (5)	6 (5)
Very much	7 (4)	2 (1)	4 (3)	10 (6)	3 (2)	1 (<1)	3 (2)	0 (0)	2 (1)	1 (<1)
Missing	0	0	1	1	2	0	0	0	0	1
Change in appearance of skin in area of affected breast (protocol-specific item)										
Not at all	97 (55)	86 (48)	44 (32)	52 (35)	55 (43)	57 (39)	56 (45)	64 (47)	71 (61)	74 (59)
A little	51 (29)	60 (34)	55 (41)	56 (38)	51 (39)	62 (43)	42 (34)	47 (34)	31 (26)	40 (32)
Quite a bit	14 (8)	21 (12)	20 (15)	28 (20)	11 (9)	17 (12)	13 (10)	19 (14)	9 (8)	3 (2)
Very much	14 (8)	10 (6)	16 (12)	11 (7)	12 (9)	9 (6)	13 (10)	7 (5)	6 (5)	8 (7)
Missing	4	4	6	5	8	6	6	5	10	10
Change in overall appearance of breast (protocol-specific item)										
Not at all	27 (17)	33 (19)	17 (13)	24 (18)	15 (13)	16 (12)	19 (17)	24 (19)	20 (18)	28 (23)
A little	58 (35)	57 (34)	49 (39)	39 (28)	48 (40)	48 (37)	41 (36)	43 (34)	38 (35)	47 (39)
Quite a bit	24 (15)	40 (24)	22 (18)	34 (24)	20 (17)	35 (27)	19 (17)	30 (24)	24 (22)	20 (17)
Very much	55 (33)	40 (23)	37 (30)	41 (30)	37 (30)	31 (24)	34 (30)	30 (24)	27 (25)	25 (21)

Breast / chest wall effect	Baseline		3 months		6 months		12 months		24 months	
	40 Gy N=180 (%)	26 Gy N=181 (%)	40 Gy N=141 (%)	26 Gy N=153 (%)	40 Gy N=137 (%)	26 Gy N=151 (%)	40 Gy N=130 (%)	26 Gy N=142 (%)	40 Gy N=127 (%)	26 Gy N=135 (%)
Missing	16	11	16	15	17	21	17	15	18	15
Breast smaller (protocol-specific item)										
Not at all	55 (35)	59 (36)	47 (41)	56 (42)	41 (37)	49 (40)	41 (40)	53 (44)	37 (37)	48 (43)
A little	37 (24)	47 (29)	31 (27)	35 (26)	28 (26)	27 (22)	29 (29)	20 (17)	30 (30)	28 (25)
Quite a bit	21 (14)	21 (13)	14 (12)	13 (10)	16 (15)	24 (20)	10 (10)	20 (17)	16 (16)	24 (21)
Very much	42 (27)	37 (25)	23 (20)	30 (22)	24 (22)	22 (18)	21 (21)	26 (22)	17 (17)	13 (12)
Missing	25	17	26	19	28	29	29	23	27	22
Breast harder / firmer to touch (protocol-specific item)										
Not at all	64 (43)	79 (48)	38 (33)	37 (29)	40 (37)	31 (26)	35 (35)	28 (24)	55 (57)	37 (34)
A little	48 (32)	35 (21)	30 (26)	37 (29)	31 (28)	35 (29)	37 (37)	38 (33)	22 (23)	43 (39)
Quite a bit	19 (13)	26 (16)	23 (20)	23 (18)	22 (20)	34 (28)	13 (13)	27 (23)	8 (8)	20 (18)
Very much	18 (12)	24 (15)	24 (21)	32 (24)	16 (14)	20 (17)	16 (16)	23 (20)	12 (12)	10 (9)
Missing	31	17	26	24	28	31	29	26	30	25
Position of nipple of affected breast different from other side (protocol-specific item)										
Not at all	56 (44)	72 (48)	39 (39)	43 (36)	34 (34)	44 (41)	39 (43)	46 (44)	34 (40)	55 (53)
A little	29 (23)	26 (18)	25 (25)	30 (25)	31 (32)	25 (23)	24 (27)	23 (22)	30 (35)	20 (19)
Quite a bit	7 (5)	9 (6)	13 (13)	10 (9)	7 (7)	15 (14)	9 (10)	14 (13)	3 (3)	12 (12)
Very much	36 (28)	41 (28)	23 (24)	35 (30)	28 (28)	23 (22)	18 (20)	21 (20)	19 (22)	16 (16)
Missing	52	33	41	35	37	44	40	38	36	32
Problems getting a bra to fit (protocol-specific item)										
Not at all	110 (70)	113 (68)	68 (54)	72 (52)	63 (51)	64 (48)	68 (58)	74 (57)	56 (51)	68 (55)
A little	22 (14)	26 (16)	22 (18)	39 (28)	35 (28)	40 (30)	22 (19)	29 (23)	30 (28)	33 (27)
Quite a bit	10 (6)	8 (5)	20 (16)	7 (5)	14 (11)	14 (11)	12 (10)	13 (10)	12 (11)	13 (11)
Very much	16 (10)	19 (11)	15 (12)	21 (15)	12 (10)	15 (11)	15 (13)	12 (9)	11 (10)	9 (7)
Missing	19	15	16	14	13	18	13	14	18	12

Table 26: Patient-reported effects in breast / chest wall: baseline to 24 months for 40 Gy vs 27 Gy (patients randomised up to end 2017) in Nodal Sub-Study

Breast / chest wall effect	Baseline		3 months		6 months		12 months		24 months	
	40 Gy N=108 (%)	27 Gy N=103 (%)	40 Gy N=88 (%)	27 Gy N=94 (%)	40 Gy N=82 (%)	27 Gy N=93 (%)	40 Gy N=79 (%)	27 Gy N=87 (%)	40 Gy N=72 (%)	27 Gy N=89 (%)
Pain in area of affected breast (EORTC QLQ-BR23)										
Not at all	47 (43)	46 (45)	22 (25)	22 (24)	29 (35)	20 (22)	27 (34)	30 (34)	29 (40)	38 (43)
A little	52 (48)	47 (46)	48 (55)	45 (48)	37 (45)	54 (58)	37 (47)	41 (47)	34 (47)	37 (42)
Quite a bit	6 (6)	9 (8)	13 (15)	21 (23)	13 (16)	13 (14)	11 (14)	10 (12)	8 (11)	11 (12)
Very much	3 (3)	1 (1)	5 (5)	5 (5)	3 (4)	6 (6)	4 (5)	6 (7)	1 (1)	3 (3)
Missing	0	0	0	1	0	0	0	0	0	0
Swelling in area of affected breast (EORTC QLQ-BR23)										
Not at all	68 (64)	68 (67)	61 (69)	49 (53)	59 (72)	47 (51)	58 (73)	55 (63)	52 (72)	63 (71)
A little	30 (28)	22 (21)	17 (19)	24 (26)	17 (20)	28 (30)	14 (18)	18 (21)	19 (26)	21 (23)
Quite a bit	6 (5)	9 (9)	8 (9)	16 (17)	2 (3)	14 (15)	5 (6)	7 (8)	1 (1)	5 (6)
Very much	3 (3)	3 (3)	2 (2)	4 (4)	4 (5)	4 (4)	2 (3)	7 (8)	0	0
Missing	1	1	0	1	0	0	0	0	0	0
Oversensitivity in area of affected breast (EORTC QLQ-BR23)										
Not at all	59 (54)	63 (62)	42 (48)	35 (38)	42 (51)	39 (42)	43 (55)	43 (50)	47 (66)	46 (52)
A little	41 (38)	29 (28)	30 (34)	38 (41)	26 (32)	37 (40)	20 (25)	32 (37)	21 (30)	35 (39)
Quite a bit	4 (4)	9 (9)	9 (10)	14 (15)	11 (13)	10 (11)	12 (15)	7 (8)	3 (4)	7 (8)
Very much	4 (4)	1 (1)	7 (8)	6 (6)	3 (4)	6 (7)	4 (5)	4 (5)	0	1 (1)
Missing	0	1	0	1	0	1	0	1	1	0
Skin problems on or in area of affected breast (EORTC QLQ-BR23)										
Not at all	81 (75)	71 (69)	55 (63)	48 (52)	58 (71)	53 (57)	54 (68)	55 (63)	52 (72)	66 (74)
A little	21 (19)	19 (18)	26 (29)	24 (26)	16 (20)	27 (29)	15 (19)	25 (29)	14 (20)	15 (16)
Quite a bit	0 (0)	10 (10)	3 (3)	17 (18)	4 (5)	8 (9)	7 (9)	3 (3)	6 (8)	4 (5)
Very much	6 (6)	3 (3)	4 (5)	4 (4)	3 (4)	5 (5)	3 (4)	4 (5)	0	4 (5)
Missing	0	0	0	1	1	0	0	0	0	0
Change in appearance of skin in area of affected breast (protocol-specific item)										
Not at all	62 (58)	50 (49)	23 (27)	20 (22)	30 (38)	23 (26)	29 (39)	24 (29)	40 (60)	34 (40)
A little	29 (27)	35 (34)	34 (41)	45 (49)	31 (40)	39 (44)	27 (36)	39 (47)	16 (24)	28 (33)
Quite a bit	7 (7)	9 (9)	16 (19)	18 (20)	8 (10)	16 (18)	9 (12)	13 (16)	5 (8)	11 (13)
Very much	8 (8)	8 (8)	11 (13)	8 (9)	9 (12)	10 (12)	10 (13)	7 (8)	5 (8)	11 (13)
Missing	2	1	4	3	4	5	4	4	6	5
Change in overall appearance of breast (protocol-specific item)										
Not at all	19 (19)	16 (17)	7 (9)	8 (9)	8 (11)	10 (12)	6 (9)	10 (13)	10 (16)	8 (10)
A little	36 (37)	30 (31)	31 (40)	34 (39)	32 (43)	23 (28)	28 (40)	21 (28)	29 (47)	25 (32)
Quite a bit	15 (15)	19 (20)	19 (25)	13 (15)	13 (17)	17 (20)	11 (16)	17 (23)	11 (18)	16 (20)
Very much	28 (29)	31 (32)	20 (26)	32 (37)	22 (29)	33 (40)	25 (36)	27 (36)	12 (19)	30 (38)

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Breast / chest wall effect	Baseline		3 months		6 months		12 months		24 months	
	40 Gy N=108 (%)	27 Gy N=103 (%)	40 Gy N=88 (%)	27 Gy N=94 (%)	40 Gy N=82 (%)	27 Gy N=93 (%)	40 Gy N=79 (%)	27 Gy N=87 (%)	40 Gy N=72 (%)	27 Gy N=89 (%)
Missing	10	7	11	7	7	10	9	12	10	10
Breast smaller (protocol-specific item)										
Not at all	35 (37)	40 (45)	31 (42)	28 (36)	27 (40)	29 (38)	23 (36)	21 (30)	20 (36)	27 (38)
A little	24 (26)	15 (17)	18 (25)	20 (25)	16 (24)	14 (18)	20 (32)	16 (23)	21 (38)	14 (20)
Quite a bit	15 (16)	7 (8)	11 (15)	12 (15)	8 (12)	10 (13)	5 (8)	11 (16)	7 (12)	11 (15)
Very much	20 (21)	27 (30)	13 (18)	19 (24)	16 (24)	23 (31)	15 (24)	21 (31)	8 (14)	19 (27)
Missing	14	14	15	15	15	17	16	18	16	18
Breast harder / firmer to touch (protocol-specific item)										
Not at all	37 (40)	31 (36)	25 (34)	18 (23)	27 (40)	11 (15)	20 (32)	10 (14)	33 (59)	20 (29)
A little	32 (35)	23 (27)	16 (21)	23 (30)	20 (30)	22 (30)	24 (38)	23 (33)	12 (21)	22 (31)
Quite a bit	13 (14)	13 (15)	18 (24)	23 (30)	9 (14)	18 (25)	6 (10)	21 (30)	7 (13)	15 (21)
Very much	10 (11)	19 (22)	16 (21)	13 (17)	11 (16)	22 (30)	13 (21)	16 (23)	4 (7)	13 (19)
Missing	16	17	13	17	15	20	16	17	16	19
Position of nipple of affected breast different from other side (protocol-specific item)										
Not at all	39 (50)	39 (51)	30 (46)	25 (37)	21 (35)	25 (40)	22 (40)	20 (34)	21 (43)	25 (40)
A little	15 (19)	13 (17)	13 (20)	15 (22)	18 (30)	11 (17)	15 (27)	12 (20)	17 (35)	13 (21)
Quite a bit	3 (4)	0 (0)	7 (11)	5 (8)	3 (5)	8 (13)	4 (7)	7 (12)	1 (2)	6 (10)
Very much	21 (22)	24 (32)	15 (23)	22 (33)	18 (30)	19 (30)	14 (25)	20 (34)	10 (20)	18 (29)
Missing	30	27	23	27	22	30	24	28	23	27
Problems getting a bra to fit (protocol-specific item)										
Not at all	67 (70)	49 (51)	43 (56)	43 (47)	35 (47)	39 (45)	39 (54)	35 (42)	33 (55)	30 (36)
A little	12 (13)	20 (21)	16 (21)	22 (24)	23 (31)	18 (21)	14 (19)	24 (29)	13 (22)	26 (32)
Quite a bit	7 (7)	16 (17)	10 (13)	12 (13)	9 (12)	14 (16)	7 (10)	9 (11)	8 (13)	8 (10)
Very much	10 (10)	11 (11)	8 (10)	15 (16)	8 (11)	16 (18)	12 (17)	15 (18)	6 (10)	18 (22)
Missing	12	7	11	2	7	6	7	4	12	7

Clinician assessments of normal tissue effects

Frequencies of clinician assessments of radiation-related adverse effects in the breast / chest wall and arm from 1-3 years following radiotherapy are shown in Table 28 for 40 Gy compared with 26 Gy (all randomised patients), and in Table 29 for 40 Gy and 27 Gy patients randomised up to the end of 2017.

The prevalence of clinician-reported arm lymphoedema remained relatively stable from 1-3 years following radiotherapy, with 8%, 12% and 11% in 40 Gy, 26 Gy and 27 Gy respectively at year 3. Clinician-reported breast lymphoedema declined from 1-3 years, with 4%, 10% and 5% in 40 Gy, 26 Gy and 27 Gy respectively at year 3. Frequencies of marked clinician-assessed adverse effects in the breast or chest wall (graded as "very much") were low across 1-3 years' follow-up. The most frequently reported adverse effect graded as moderate or marked by clinicians was breast distortion, with 20%, 8% and 14% in 40 Gy, 26 Gy and 27 Gy respectively at 3 years.

Table 27: Clinician-assessed radiotherapy-related adverse effects in Nodal Sub-Study: 1-3 years' follow-up for 40 Gy vs 26 Gy (all randomised patients)

	Year 1		Year 2		Year 3	
	40 Gy **N=166 (%)**	**26 Gy** **N=169 (%)**	**40 Gy** **N=166 (%)**	**26 Gy** **N=159 (%)**	**40 Gy** **N=135 (%)**	**26 Gy** **N=134 (%)**
Arm lymphoedema						
No	149 (93)	147 (89)	147 (92)	138 (89)	119 (92)	108 (88)
Yes	11 (7)	19 (11)	13 (8)	17 (11)	11 (8)	15 (12)
Ipsilateral side	*11*	*19*	*13*	*17*	*11*	*15*
Missing	6	3	6	4	5	11
Breast lymphoedema						
No	147 (92)	141 (85)	153 (96)	137 (89)	126 (96)	113 (90)
Yes	12 (8)	24 (15)	7 (4)	17 (11)	5 (4)	12 (10)
Ipsilateral side	*12*	*24*	*7*	*16*	*5*	*11 (1 NK)*
Missing	7	4	6	5	4	9
Breast distortion[1]						
None	58 (70)	62 (64)	51 (66)	39 (53)	35 (57)	36 (59)
A little	15 (18)	23 (24)	16 (21)	26 (35)	14 (23)	20 (33)
Quite a bit	10 (12)	10 (10)	8 (10)	6 (8)	11 (18)	4 (6)
Very much	0 (0)	2 (2)	2 (3)	3 (4)	1 (2)	1 (2)
N/A[2]	50	45	45	36	27	26
Not assessed	33	27	44	49	47	47
Breast shrinkage[1]						
None	57 (69)	61 (62)	48 (63)	43 (59)	38 (62)	34 (56)
A little	20 (24)	24 (25)	18 (23)	19 (26)	13 (22)	17 (28)
Quite a bit	6 (7)	12 (12)	11 (14)	10 (14)	10 (16)	9 (15)
Very much	0 (0)	1 (1)	0 (0)	1 (1)	1 (2)	1 (1)

	Year 1		Year 2		Year 3	
	40 Gy N=166 (%)	**26 Gy N=169 (%)**	**40 Gy N=166 (%)**	**26 Gy N=159 (%)**	**40 Gy N=135 (%)**	**26 Gy N=134 (%)**
N/A[2]	50	45	45	36	27	26
Not assessed	33	26	44	50	46	47
Breast induration (tumour bed)[1]						
None	60 (72)	66 (68)	50 (65)	41 (56)	38 (66)	39 (64)
A little	13 (16)	19 (20)	17 (22)	25 (34)	13 (22)	17 (28)
Quite a bit	9 (11)	9 (9)	8 (10)	6 (8)	5 (9)	5 (8)
Very much	1 (1)	3 (3)	2 (3)	1 (1)	2 (3)	0
N/A[2]	50	45	45	36	27	26
Not assessed	23	27	44	50	50	47
Breast induration (outside tumour bed)[1]						
None	68 (82)	75 (77)	64 (83)	62 (85)	47 (80)	54 (89)
A little	8 (10)	17 (18)	8 (10)	8 (11)	7 (12)	5 (8)
Quite a bit	6 (7)	4 (4)	3 (4)	2 (3)	4 (6)	2 (3)
Very much	1 (1)	1 (1)	2 (3)	1 (1)	1 (2)	0 (0)
N/A[2]	50	45	45	36	27	26
Not assessed	33	27	44	50	49	47
Telangiectasia						
None	126 (96)	137 (97)	108 (88)	102 (93)	78 (92)	78 (87)
A little	5 (4)	4 (3)	11 (9)	5 (5)	7 (8)	6 (7)
Quite a bit	0 (0)	0 (0)	4 (3)	3 (3)	0 (0)	5 (6)
Very much	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Not assessed	35	28	43	49	50	45
Breast / chest wall oedema						
None	108 (82)	111 (79)	107 (86)	93 (84)	78 (91)	76 (85)
A little	21 (16)	22 (16)	14 (11)	13 (12)	8 (9)	9 (10)
Quite a bit	2 (2)	7 (5)	2 (2)	5 (4)	0 (0)	3 (3)
Very much	1 (<1)	1 (<1)	1 (1)	0 (0)	0 (0)	1 (1)
Not assessed	34	28	42	48	49	45
Breast / chest wall discomfort						
None	101 (75)	100 (69)	90 (73)	83 (74)	61 (69)	72 (79)
A little	24 (18)	36 (25)	27 (22)	27 (24)	20 (23)	15 (17)
Quite a bit	9 (7)	6 (4)	7 (6)	3 (2)	5 (6)	3 (3)
Very much	0 (0)	2 (1)	0 (0)	0 (0)	2 (2)	1 (1)
Not assessed	32	25	42	46	47	43

[1] Applicable following breast conservation surgery or reconstruction
[2] N/A: not applicable; primary surgery was mastectomy without immediate reconstruction

Table 28: Clinician-assessed radiotherapy-related adverse effects in Nodal Sub-Study: 1-3 years' follow-up for 40 Gy vs 27 Gy (patients randomised to end 2017)

	Year 1		Year 2		Year 3	
	40 Gy N=99 (%)	27 Gy N=103 (%)	40 Gy N=97 (%)	27 Gy N=101 (%)	40 Gy N=85 (%)	27 Gy N=90 (%)
Arm lymphoedema						
No	87 (92)	84 (85)	83 (91)	86 (87)	73 (91)	76 (89)
Yes	8 (8)	15 (15)	8 (8)	13 (13)	7 (9)	9 (11)
Ipsilateral side	*8*	*13*	*8*	*13*	*7*	*9*
Missing	4	4	6	2	5	5
Breast lymphoedema						
No	87 (92)	79 (80)	86 (95)	90 (90)	78 (96)	81 (95)
Yes	8 (8)	20 (20)	5 (5)	9 (9)	3 (4)	4 (5)
Ipsilateral side	*8*	*18*	*5*	*9*	*3*	*4*
Missing	4	4	6	2	4	5
Breast distortion[1]						
None	32 (64)	40 (68)	29 (63)	30 (58)	21 (58)	21 (50)
A little	11 (22)	14 (24)	10 (22)	17 (33)	8 (22)	15 (36)
Quite a bit	7 (14)	3 (5)	7 (15)	4 (8)	7 (20)	4 (9)
Very much	0 (0)	2 (3)	0 (0)	1 (2)	0 (0)	2 (5)
N/A[2]	26	32	27	32	12	21
Not assessed	23	12	24	17	37	27
Breast shrinkage[1]						
None	32 (64)	35 (59)	29 (63)	37 (70)	23 (64)	20 (47)
A little	16 (32)	18 (31)	10 (22)	11 (21)	6 (17)	14 (32)
Quite a bit	2 (4)	5 (8)	7 (15)	4 (8)	7 (19)	6 (14)
Very much	0 (0)	1 (2)	0 (0)	1 (2)	0 (0)	3 (7)
N/A[2]	26	32	27	32	12	21
Not assessed	23	12	24	16	37	26
Breast induration (tumour bed)[1]						
None	37 (74)	43 (73)	27 (59)	37 (70)	25 (72)	27 (66)
A little	8 (16)	12 (20)	14 (30)	11 (21)	6 (17)	10 (24)
Quite a bit	5 (10)	3 (5)	5 (11)	4 (8)	4 (11)	2 (5)
Very much	0 (0)	1 (2)	0 (0)	1 (2)	0 (0)	2 (5)
N/A[2]	26	32	27	32	12	21
Not assessed	23	12	24	16	38	28
Breast induration (outside tumour bed)[1]						
None	39 (78)	51 (86)	36 (78)	45 (87)	29 (83)	32 (78)
A little	7 (14)	6 (10)	7 (15)	5 (10)	5 (14)	7 (17)
Quite a bit	4 (8)	2 (3)	3 (7)	2 (4)	1 (3)	2 (5)
Very much	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
N/A[2]	26	32	27	32	12	21
Not assessed	23	12	24	17	38	28
Telangiectasia						
None	76 (97)	84 (92)	67 (89)	79 (92)	43 (93)	58 (92)
A little	2 (3)	7 (8)	7 (9)	5 (6)	3 (7)	5 (8)
Quite a bit	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)

	Year 1		Year 2		Year 3	
	40 Gy N=99 (%)	**27 Gy N=103 (%)**	**40 Gy N=97 (%)**	**27 Gy N=101 (%)**	**40 Gy N=85 (%)**	**27 Gy N=90 (%)**
Very much	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Not assessed	21	12	22	16	39	27
Breast / chest wall oedema						
None	63 (80)	62 (68)	62 (82)	72 (85)	42 (91)	59 (92)
A little	13 (16)	19 (21)	12 (16)	13 (15)	4 (9)	5 (8)
Quite a bit	2 (3)	8 (9)	1 (1)	0 (0)	0 (0)	0 (0)
Very much	1 (1)	2 (2)	1 (1)	0 (0)	0 (0)	0 (0)
Not assessed	20	12	21	16	39	26
Breast / chest wall discomfort						
None	61 (77)	57 (63)	56 (74)	60 (68)	34 (71)	37 (58)
A little	12 (15)	25 (17)	16 (21)	22 (25)	12 (25)	19 (30)
Quite a bit	6 (8)	8 (9)	4 (5)	4 (5)	2 (4)	5 (7)
Very much	0 (0)	1 (1)	0 (0)	2 (2)	0 (0)	3 (5)
Not assessed	20	12	21	13	37	26

[1] Applicable following breast conservation surgery or reconstruction
[2] N/A: not applicable; primary surgery was mastectomy without immediate reconstruction

Discussion of Nodal Sub-Study results is in the main Discussion section (Chapter 8).

CHAPTER 8: DISCUSSION

Opening statements

Previous trials, particularly the UK START trials, have confirmed the feasibility and benefits of hypofractionation such that 40 Gy in 15 fractions was adopted as the UK standard schedule in 2009 [50] and subsequently internationally [103] but there is no reason why the concept of hypofractionation should be limited to 15 fractions. The UK FAST trial [104] was planned in the early 2000s when 50 Gy in 25 fractions over five weeks was considered standard. The FAST trial compared 28.5 Gy in 5 fractions of 5.7 Gy or 30 Gy in 5 fractions of 6 Gy with 50 Gy in 25 fractions, with the 5-fraction regimens delivered once weekly over five weeks to reduce overall time as a variable. The primary endpoint was photographic assessment at two and five years. A low-risk patient population was deliberately chosen, excluding patients requiring a breast boost or systemic chemotherapy for instance. Two test groups were used, as in the START-pilot and START-A trials, to allow interpolation to estimate an iso-effective dose to control if necessary. The FAST trial identified a 5-fraction schedule estimated to be radiobiologically equivalent to the 25-fraction standard in terms of late NTE.

The 5-year results from the START trials [17, 18], with the change in standard UK fractionation to 40 Gy/15Fr (NICE 2009), the first results of the FAST trial [104], plus the acute toxicity and 2-year adverse-effects from a pilot study delivering 30 Gy in 5 fractions over 15 days [26] gave impetus to the investigation of 1-week 5-fraction schedules in a phase III study. With these results the FAST-Forward trial was developed to test two 5-fraction schedules over a week against the standard of 40 Gy in 15 fractions over 3 weeks, specifically to be non-inferior for local relapse and without an increase in late adverse effects.

FAST-Forward Local relapse

FAST-Forward is a non-inferiority trial with ipsilateral breast tumour relapse (IBTR or local relapse) as the primary endpoint. Based on START trial data [18] and incorporating subsequent improvements in surgical technique and systemic therapy, it was anticipated that 5-year IBTR rate in the FAST-Forward control group given 40 Gy in 15 fractions would be 2%. Applying a non-inferiority margin of 1.6% at 5 years required a sample size of 4,000 patients. This provided 80% power (one-sided α of 0·025 allowing for non-inferiority hypothesis and a simple Bonferroni correction taking into account comparisons between each test schedule and the control group) to exclude an absolute increase of 1·6% in 5-year ipsilateral breast tumour relapse incidence for a five-fraction schedule compared with control. Estimated 5-year IBTR after 40 Gy in 15 fractions was 2.1% (95% CI 1.4-3.1), after 27 Gy was 1.7% (1.2-2.6) and after 26 Gy was 1.4%

(0.2-2.2). The upper confidence limits (CI) excluded an increase in IBTR of >1.6% after both 5-fraction schedules with p=0.0022 and p-0.00019 for non-inferiority of 27 Gy and 26 Gy schedules respectively compared with 40 Gy in 15 fractions.

Therefore, it can be said emphatically that non-inferiority in terms of IBTR of 5-fraction schedules compared with 40 Gy in 15 fractions was 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. The lack of a detectable dose response for local tumour control between 26 Gy and 27 Gy 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 27 Gy and 26 Gy likely reflects random sampling variability in the IBTR rate and/or chance imbalances in unmeasured prognostic factors between test groups.

Longer follow-up is well recognised as having added value for radiotherapy trials. IBTR continues to present beyond 5 years, but trials of hypofractionation have so far reported almost identical hazard ratios (HR) for IBTR between test and control groups at 5 and 10 years, the relevant metric for comparisons of effect. For example, START-B[18] incidence rates of IBTR at 5/10 years after 50 Gy in 25 fractions vs. 40 Gy in 15 fractions were 3.3%/5.2% and 1.9%/3.8%, respectively, reflecting crude HR of 0.72 (95% CI 0.43-1.21) and 0.70 (95% CI 0.46-1.07) at the respective time points i.e., barely changed between 5 and 10 years. The Ontario Clinical Oncology Group (OCOG) reported IBTR rates at 5/10 years after 50 Gy in 25 fractions vs. 42.5 Gy in 16 fractions of 3.2%/6.7% and 2.8%/6.2%, respectively, giving an absolute difference of 0.4% (95% CI -1.5-2.4%) and 0.5% (95% CI -2.5-3.5%) respectively.[105] This is reassuring but the 10-year IBTR rates will be reported when the data matures to address any remaining concerns over efficacy of five daily fractions.

Application of FAST-Forward to partial breast radiotherapy

IMPORT LOW tested 40 Gy/15Fr over 3 weeks PBI compared with 40 Gy/15Fr over 3 weeks to whole-breast (control) [106]. This is the only PBI RCT worldwide where irradiated volume is the only variable and all other factors including dose / fractionation are constant. The reduced volume of breast tissue treated with PBI was associated with non-inferior local control and reduced late normal tissue toxicity. Given that we know that reduced volume (PBI) results in reduced late normal tissue toxicity for a constant dose/fractionation as per IMPORT LOW, then it is logical that 26 Gy/5Fr is also adopted for PBI given that both trials used the same dose/fractionation for control. It would be counter-intuitive to state that 26 Gy/5Fr can be used for whole breast RT with

excellent local control and minimal toxicity, but not for PBI given that IMPORT LOW has shown (i) reduced volume is non-inferior for local control (ii) reduced volume has less toxicity, i.e. it would be illogical (and possibly unethical) to have a greater treatment burden for the lower risk group of patients eligible for PBI.

Use of hypofractionation in the post-mastectomy setting

Wang et al.[107] reported on 810 patients in a single institution randomised non-inferiority trial of moderate hypofractionated radiotherapy post-mastectomy. All patients underwent axillary dissection and were at least 4-node positive or T3-4, unless they received neoadjuvant chemotherapy in which case either clinical stage III or pathological axillary node positive patients were eligible. The hypofractionated schedule was 43.5 Gy in 15 fractions over 3 weeks vs. 50 Gy in 25 fractions over 5 weeks as standard. The radiotherapy target volume included the chest wall, level 3 axilla and supraclavicular fossa. The 5-year locoregional relapse rate was 8.3% (90% CI 5.8-10.7) with the 15-fraction schedule and 8.1% (90% CI 5.4-10.6) with the 25-fraction schedule. With a $p<0.0001$ for non-inferiority they concluded that the hypofractionated regimen was non-inferior to standard.

In the FAST-Forward Main Trial there were 264 patients who had had a mastectomy and only one of these had a local relapse. 173 patients received chest wall only radiotherapy with one of the 5-fraction schedules with no local relapse reported. Whilst this is too few events to make any firm statements the data raise no concerns regarding the efficacy or safety of the 5-fraction schedules. There is no logical reason why a 5-fraction schedule would not be as effective when irradiating the chest wall as opposed to the intact breast.

Breast cancer subgroups and local relapse

Commentators have suggested that hypofractionation may be less applicable in certain patient and pathological subgroups. The initial 2011 American Society for Radiation Oncology (ASTRO) evidence-based guidelines [108] were unable to confirm agreement on hypofractionation in patients <50 years. The small number of patients and the increased risk of IBTR at young age were cited, but no evidence of an adverse outcome by age after hypofractionation has been reported. A post-hoc analysis of tumour grade in the OCOG trial [105] suggested an interaction of grade and randomisation group, but subsequent central analysis of tumour blocks reported no trend for patients with high-grade tumours to be disadvantaged after 42.5 Gy in 16 fractions [105] as compared to 50Gy in 25 fractions. OCOG also found that tumour grade and molecular subtype did

not predict response to hypofractionation. A sub-group meta-analysis of locoregional relapse was performed of the START-P, START-A and START-B trials in 5861 patients reporting 10-year results [109]. Treatment effects of hypofractionation were not significantly different from 50 Gy in 25 fractions when examined by age, type of primary surgery, axillary node status, tumour grade, use of adjuvant chemotherapy or boost radiotherapy. The HR for locoregional control and the patient numbers for the combined hypofractionation schedules against 50 Gy in 25 fractions were 0.79 (95% CI 0.47-1.34) in 343 patients aged under 40 years, 0.88 (95% CI 0.60-1.28) in 1046 patients aged 40-49 years, 0.86 (95% CI 0.59-1.25) in 1272 patients with grade 3 tumours, 0.91 (95% CI 0.59-1.25) in 513 patients following mastectomy and 0.81 (95% CI 0.46-1.81) in 1480 patients after adjuvant chemotherapy. The 2018 ASTRO evidence-based guidelines subsequently approved hypofractionated breast radiotherapy with 40/42.5 Gy in 15/16 fractions over 3 weeks irrespective of age, tumour grade or receptor status [103].

FAST-Forward reported non-inferior IBTR for both 5-fraction schedules and given the preceding arguments inferiority in any subgroups would not be expected. 1545 (37.8%) patients were in the high-risk category as defined by age <50 years (604 patients), grade 3 tumour (1153 patients) or both, and this was a stratification factor at randomisation. Formal subgroup analysis was not performed due to the low number of IBTR events but descriptive data according to age, grade, and receptor status showed no signals of concern for the 5-fraction schedules. The use of boost and dose/fractionation, both declared prior to randomisation, were balanced between the 3 treatment groups so there is no risk of bias in dose intensity between trial groups.

Disease-free survival and overall survival

The EBCTCG meta-analysis reports 10-year relapse and 15-year mortality effect of radiotherapy after breast-conserving surgery [6]. After breast-conserving surgery the results from 10,801 women showed that 15-year all-cause mortality was 3·0% (95% CI 0·6–5·4, 2p=0·03) better following radiotherapy; it was only 0.8% after 5 years. The trials included in the meta-analysis came from a different era when local relapse rates and risk of metastases were much higher than is currently the case. Thus, one would not anticipate any differences according to radiotherapy schedule after 5 years in FAST-Forward. Incidence of distant relapse, disease-free survival and overall survival were similar between the fractionation schedules, with no evidence of statistically significant differences between groups.

Normal tissue effects (NTE)

For late NTE the dose response curve is much steeper than for IBTR, enabling detection of clinically and statistically significant differences in event rates between 26 Gy and 27 Gy in 5

fractions. The 5-fraction schedule isotoxic for late NTE with 40 Gy 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 3.7 Gy (0.3-7.1) for tumour control in FAST-Forward is similar to 3.5 Gy (1.2–5.7) estimated from the START pilot and START-A trials[110]. 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 2 Gy than the 3 Gy estimated in the earlier START and FAST trials, 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 50 Gy 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. The α/β value for change in photographic breast appearance in FAST was 2.6 Gy (1.4–3.7). There is uncertainty about biological processes, such as possible influence of a time factor in FAST-Forward. However this does not interfere with clinical evaluation and thus decisions on implementation of FAST-Forward results in comparable patient groups.

In FAST-Forward, late NTE assessed by clinicians, patients and photographs were key secondary endpoints. On the basis of the similarity between NTEs for the 26 Gy in 5 daily fractions schedule and for the 40 Gy in 15 fractions schedule, 26Gy in 5 fractions is the regimen recommended for clinical implementation. By 'similar' we mean that NTE were not statistically or clinically significantly different from 40 Gy in 15 fractions with respect to clinician- or patient-assessed NTE including external photographic assessments conducted blind to treatment allocation. In contrast, the 27 Gy 5-fraction schedule *was* significantly different to the 40 Gy standard for many late NTE and also to the 26 Gy schedule, confirming the sensitivity of trial outcome measures to a difference in dose intensity corresponding to 3 Gy in 2 Gy equivalents assuming $\alpha/\beta=2$ Gy (see below). The 27 Gy 5-fraction regimen exhibited late NTE rates of comparable magnitude to 50 Gy in 25 daily fractions, defended for so long as standard and still in use by many practitioners outside the UK. To provide some perspective for the late NTE after 5-fraction regimens, 40 Gy in 15 fractions is equivalent to about 46 Gy in 2 Gy fractions in terms of late NTE compared to 50 Gy in 25 fractions according to START trial outcomes [110]. In FAST-Forward, the 26 Gy regimen is comparable to 47 Gy in 2 Gy equivalents in terms of late NTE.

Early NTE are much less responsive to fraction size than late NTE, the contribution of total dose to early NTE being relatively more important. FAST-Forward offers a good example in that breast erythema was less intense and also settled a fortnight earlier after 5-fraction than 15-fraction schedules [3]. In this context, the milder erythema was due to 26 & 27 Gy *total dose* levels much more than to *fraction sizes* of 5.2 & 5.4 Gy. Acute reactions were also milder in both 5-fraction schedules (total doses 27 & 30 Gy) of the FAST trial than the 50 Gy schedule [26].

Induration is a key late NTE that is expected to increase with the passage of time irrespective of radiation schedule. Other factors contributing to breast appearance include fat necrosis and oedema, particularly in the early years. Table 56 (Appendix 2) reproduces results already presented in Chapter 5, but shows clinical and patient assessments together, for the longitudinal FAST-Forward moderate or marked assessments that equate to fibrosis (including clinician-assessed distortion, shrinkage and induration outside the tumour bed) as well as patient-assessed breast appearance change (smaller and harder or firmer). The odds ratios do not tell the whole story, the absolute level of events also being very important. For example, for breast shrinkage, the most frequent of any clinician-assessed effects, the rate at 5 years was 5.1% in the 40 Gy and 6.3% in the 26 Gy schedule. Also, it should be noted that, for all clinician-assessed events documented in the moderate/marked categories, most were moderate rather than marked in severity. For the patient assessments, in which there was a baseline post-surgery but pre-radiotherapy assessment, the number of longitudinal events is generally not much higher than that post-surgery baseline. This is likely to be the same event rather than a distinct event. These late effect results are very important in terms of giving patients realistic expectations. With regard to increasing late NTE with time, stability of the HR at later timepoints is clinically relevant as discussed earlier for IBTR. In START-B the breast shrinkage HR for test to control arm was 0.83 (95% CI 0.66-1.04) at 5 years and 0.80 (95% CI 0.67-0.96) at 10 years. For 5-fractions we are now able to investigate the FAST 5- and 10-year results noting the same principle but with confidence limits which are wider given the smaller number of patients compared to START [23]. For breast shrinkage the test to control arm HR at 5 and 10 years respectively was 2.03 (95% CI 1.15-3.58) and 1.83 (95% CI 0.88-3.81) for the 30 Gy schedule and 1.20 (95% CI 0.63-2.27) and 1.83 (95% CI 0.88-3.81) for 28.5 Gy schedule. For 'any NTE' the test to control arm at 5 and 10 years respectively was 2.40 (95% CI 1.45-3.97) and 2.03 (95% CI 1.06-3.89) for the 30 Gy schedule and 1.32 (95% CI 0.75-2.34) and 1.61 (95% CI 0.81-3.18) for 28.5 Gy schedule. The principle of the relative difference between test and control arm changing little with time can therefore be applied to FAST-Forward, again noting the low absolute levels of marked and moderate events.

The Danish-led HYPO trial of 1864 patients was designed to determine whether 40 Gy in 15 fractions would not increase induration of the breast at 3 years compared to 50 Gy in 25 fractions. Results confirmed no increase in induration with moderate hypofractionation [111]. Breast size was a stratification at randomisation and they reported that induration at 3 years was significantly increased for large compared with small breasted patients but that at no time-point was the hypofractionated schedule worse than control for this NTE. Shaitelman et al.[112] conducted a randomised non-inferiority trial due to low uptake of hypofractionated whole-breast radiotherapy in the United States, the low uptake being attributed to to concerns of safety for patients receiving a

tumour bed boost, chemotherapy or having large breast size. The standard arm was 50 Gy in 25 daily fractions with a 10-14 Gy boost in 5-7 fractions and hypofractionation was 42.56 Gy in 16 daily fractions with a 10-12.5 Gy boost in 4-5 fractions. Primarily they investigated the proportion of patients with adverse patient-reported cosmetic outcome at three years. 106 patients (36.9%) of the 287 patients were defined as large breast size with a bra cup size of at least D. Adverse patient-reported cosmetic outcome was 5.4% lower (8.2% vs 13.6%, p=0.002 for inferiority) in the hypofractionated group overall and 18.6% lower (90% upper confidence limit 8% lower) for large breasted patients. They conclude that this offers strong reassurance for hypofractionation not compromising cosmetic outcome based on large breast size.

Tsang et al [113] looked at dose heterogeneity with regards to the FAST trial and the risk of 'triple trouble' [114]. 390 full CT-planning data sets were reviewed for patients where there was a baseline and 2-year photographic assessment, the primary endpoint of FAST. The two 5-fraction groups were combined for analysis and there was no significant difference between these and control for breast volume or for patient tumour and treatment characteristics from the whole FAST population. Multiple logistic regression analyses show that after adjusting for breast size (and surgical deficit) there was no evidence of late NTE associated with dose inhomogeneity using various definitions of hotspots. The effect of inhomogeneity was not significantly different for any of the dosimetric parameters between control and 5-fraction schedules. In FAST-Forward the α/β estimate for any clinician-assessed moderate or marked NTE was barely different unadjusted or when adjusted for breast size, using whole-breast planning treatment volume as the proxy for breast size. The same lack of difference was found with photographic-assessment and breast size. We can conclude that breast size is an established factor for increased NTE following breast radiotherapy but that hypofractionation, including 5-fraction schedules, is not an additional concern for larger breasted patients.

What about other organs at risk? The heart is often mentioned and, given that very long follow-up is required to detect late cardiac events, is cited as a reason to wait for longer-term data before adopting hypofractionation as standard of care. However, there is no specific reason to expect an increased cardiac sensitivity to hypofractionation. Darby et al have shown that there is no safe dose to the heart and therefore the effort is to reduce or eliminate cardiac dose [115]. At this early stage, after imaging and further investigation, excluding cases confirmed not to be radiotherapy-related, for left-sided radiotherapy there are 6 cases of ischaemic heart disease in the 40 Gy arm and 3 cases in the 26 Gy arm.

The most frequent specialist referral we have seen is to lymphoedema clinics for breast lymphoedema, 90 (6.6%) following 40 Gy and 106 (7.7%) after 26 Gy. Breast oedema is

predominantly an early side effect which we have seen settling such that at 5 years the moderate/marked incidence on clinician-assessment is 9 (0.7%) patients after 40 Gy and 17 (1.7%) patients after 26 Gy with none at all in 94% and 93% respectively. These rates are low and not significantly different. These low rates are also encouraging for patients.

Tumour control and radiobiology

In a review of the linear-quadratic model and implications for practice, Brand and Yarnold present FAST-Forward as an example of a trial evaluating of 5-fraction hypofractionated accelerated radiotherapy [116]. To make sense of FAST-Forward in terms of fraction size effects, the START trials offer a good entry point. The START-P/-A trials (1986-2003) each compared 50 Gy in 25 fractions over 5 weeks (control) with 2 test dose levels of a 13-fraction regimen over 5 weeks (5 fractions per fortnight). By controlling for time-related effects, repopulation being the likeliest mechanism in tumours, and assuming complete repair of sub-lethal damage between fractions in all groups, an unconfounded estimate of sensitivity to fraction size is possible. This simply involves identifying the total dose in 13 fractions matching the IBTR rate in the control group by interpolation between test dose levels if needed. The START-A test dose level of 41.6 Gy in 13 fractions of 3.2 Gy was the closest, from which the α/β estimate of 3.5 Gy (95% CI 1.2-5.7) was derived based on a 10-year total of 349 IBTR events in 3646 women. The reduction from 50 Gy to 41.6 Gy (around 8 Gy) total dose needed to match anti-tumour effects of 13 fractions of 3.2 Gy and 25 fractions of 2.0 Gy is a vivid example of increasing fraction size sensitivity at play.

To our knowledge, START-P/-A generated the only direct clinical estimate of α/β for a cancer, others being based on non-randomised or randomised comparisons that do not control for one or more variables, especially time. START-B is a good example of the latter, testing 50 Gy in 25 fractions over 5 weeks against 40 Gy in 15 fractions of 2.7 Gy over 3 weeks. Applying the $\alpha/\beta=3.5$ generated by START-P/-A, the equivalent total dose in 2.0 Gy fractions ($EQD_{2/3.5}$) of the 3-week schedule is only 45 Gy, yet based on 95 IBTR events in 2215 patients (4.3%), the test schedule was non-inferior to 50 Gy (HR 0.77 95% CI 0.51-1.16, p=0.21). In fact, the point estimate 10-year IBTR rate of the 3-week regimen was about 1% superior 50 Gy.

A post hoc analysis asked the question "If this difference is real, what would it tell us about the impact of treatment time?" We know that in laryngeal carcinomas at least 0.5 Gy/day can be 'wasted' compensating for accelerated repopulation from the fourth week of treatment onwards, first described by Withers in patients treated with primary radiotherapy and confirmed by

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Overgaard et al in a randomised clinical trial comparing 60 Gy in 30 fractions delivered 5 versus 6 times per week [117, 118]. Breast cancers have relatively low mitotic rates at presentation, but they might be in an accelerated phase of repopulation by the time radiotherapy starts several weeks or months after primary surgery &/or cytotoxic chemotherapies. In the context of the START-B result, the post hoc analysis estimated 0.6 Gy/day (95% CI 0.1-1.8, p=0.02) 'wasted' dose in control group patients during weeks 4 & 5. If true, it implies roughly 14 x 0.6 = 8 Gy of the control regimen (50 Gy) 'wasted', leaving an $EQD_{2/3.5}$ of 42 Gy against 45 Gy for the 3-week schedule. The HYPO trial offers an independent test of START-B regimens in a comparable group of patients, in whom the 9-year risk of locoregional relapse was 3.3% (95% CI, 2.0- 5.0) in the 50 Gy in 25 fractions group compared to 3.0% (95% CI, 1.9-4.5) in the 40- Gy in 15 fractions group (risk difference, 20.3%; 95% CI, 22.3-1.7)[8], a result almost identical to START-B.

What have we seen in FAST-Forward? The trial generated an α/β estimate for IBTR of 3.7 Gy (95% CI 0.3-7.1), the CI reflecting very low IBTR rates. The analysis plan did not incorporate a hypothetical time correction, so the α/β estimate of 3.7 Gy necessarily incorporates a putative time effect by contributing to the efficacy of the shorter test regimens. Regardless of whether or not there is a time effect, the clinically effective $EQD_{2/3.7}$ of 26 Gy in 5 fractions is 41 Gy in 2 Gy fractions, see Table 3. The difference between this EQD and the 45 Gy of 40 Gy in 15 fractions at such high levels of local control may be just too small to detect clinically, but the most important clinical conclusion that can be robustly drawn is that the 5-fraction regimen has demonstrated non-inferiority in relation to the predefined ≤1·6% excess IBTR boundary set in the protocol. Questions have been raised whether 26 Gy in 5 fractions has any anti-tumour effect at all [111]. With 5-year IBTR rate of 2.1% (95% CI 1.4-3.1) after 40 Gy in 15 fractions, the rate would be expected to be about 6% at 5 years and perhaps 10% at 10 years without any radiotherapy according to systematic overviews of radiotherapy effects [6]. The observed 5-year IBTR rates after 26 Gy in 5 fractions are hardly consistent with an absence of effect.

To take the 0.6 Gy/day 'wasted' dose further a hypothesis could be generated with regard to 26 Gy in 5 daily fractions. If the 'wasted dose' continues down to a week, 40 Gy in 15 fractions is 14 days longer and an $EQD_{2/3.7}$ of 37 Gy is calculated as opposed to an $EQD_{2/3.7}$ of 41 Gy for 26 Gy in 5 fractions. The same calculation for 50 Gy in 25 daily fractions gives an $EQD_{2/3.7}$ of 33 Gy. These are all hypothesis-generating.

Normal tissue effects and radiobiology

Turning to late adverse effects (AE), meticulous data generated in human skin are consistent with minimal measurable effect of time on probability of late NTE; Turesson reported a tiny time effect

for telangiectasia associated with complete absence of mitotic figures in capillary endothelium on serial skin biopsies over many weeks of radiotherapy, the lack of mitoses excluding repopulation as a mechanism [66]. The effect was thought more likely to represent a very slow component of repair decaying with a $T_{1/2}$ of around 40 days.[66] The same post hoc analysis of time in START-B described above examined late AE as a negative control, yielding an estimate of 0.14 Gy/day (95%CI -0.09 to 0.34 Gy/day, p = 0.29) for change in photographic breast appearance, consistent with the absence of a time effect for AE between 3 and 5 weeks of breast radiotherapy [119].

The reason for going into this amount of detail is that FAST-Forward test dose levels of 27 and 26 Gy assumed firstly no clinically significant time effect for late AE between 1 and 3 weeks, secondly complete sublethal damage repair between fractions and thirdly an α/β of 2.8 Gy for late NTE, the last assumption based on the combined estimates of α/β in START-A and FAST. On this basis, the relative EQD of the FAST-Forward schedules to 50 Gy in 25 fractions were calculated (Table 31, Chapter 5).

Although the 5-fraction regimen *predicted* to be iso-effective with 40 Gy in 15 fractions was 27 Gy the *observed* iso-effect at 5 years was closer to 26 Gy, suggesting a slightly lower α/β value, see Table 3. The α/β point estimates are all around 2 Gy, corresponding to $EQD_{2/2}$ of 46.8 Gy for 26 Gy in 5 fractions compared to $EQD_{2/2.8}$ = 45.6 Gy for 40 Gy in 15 fractions, the latter using α/β=2.8, a combined estimate based on START-A and FAST. The confidence intervals of α/β values generated for a wide range of AE in the FAST-Forward trial are all consistent with the α/β values of all late AE generated by FAST and START-P/-A. One interpretation, and statistically-speaking the most likely, is that they are all internally consistent with each other, as reflected by wide confidence intervals associated with individual point estimates. The implication is that for mean α/β values for specific late AE endpoints are the same across all trials and fraction sizes in the range 2.0-6.0 Gy. A combined estimate based on all trials would likely be somewhere between 2.0 and 2.5 Gy.

In conclusion, the slightly reduced α/β values in FAST and FAST-Forward relative to START-P/-A might be real, in which case, one potential explanation includes a time effect related to a slow component of repair. These somewhat esoteric considerations should not obscure the all-important clinical conclusion that 26 Gy in 5 daily fractions offers patients comparable AE rates and non-inferior IBT to 40 Gy in 15 fractions.

Resource implications

The economic analysis demonstrated that 5 fraction radiotherapy is expected to be cost effective. When compared to 15 fractions, 5 fraction radiotherapy is expected to result in a reduction in direct treatment costs from £2,315 to £982 per person treated. Total costs are also expected to reduce from £31,640 to £29,638, where these resource savings are primarily due to reductions in direct treatment costs. The implications of these resource savings for the health system are complex and depend on how the extra capacity is used. The same number of individuals may be treated with lower radiotherapy capacity, freeing up these resources for other uses. The additional capacity may also be used to drive quality, for instance increasing the use of cardiac sparing breath hold technique where that is not fully utilised for breast cancer patients. The capacity and technical advances may be utilised for cancers other than breast cancer.

COVID-19

Dissemination of the Main Trial primary results was expedited due to the Covid-19 pandemic. In March 2020 emergency guidelines for radiotherapy were published by the National Institute for Healthcare and Clinical Excellence (NICE) [120] and the RCR created an online resource of clinical advisory documents containing risk mitigation approaches for radiotherapy [121]. The aim was to reduce footfall in radiotherapy departments and hospitals to reduce person-to-person contact to minimise the spread of COVID-19. The breast cancer RCR guidance cited FAST-Forward 3-year NTE outcomes, recommending the 26 Gy/5Fr schedule for adjuvant treatment of early breast cancer, stating that the 5-year local relapse publication was imminent [51]. This schedule was rapidly adopted nationwide, since FAST-Forward involved most UK radiotherapy centres who therefore had the required quality assurance measures already in place. From the National Radiotherapy Dataset, 60.6% of breast radiotherapy courses used 26 Gy/5Fr in April 2020 versus only 0.2% in April 2019 [97].

Breast consensus/guidelines and moving forward

The UK held a breast fractionation consensus meeting under the auspices of the Royal College of Radiologists and included an in-depth look at the FAST-Forward data. Lewis et al.[122] explain the Royal College of Radiologists consensus statement program and the explicit methodology that is used. There was very strong support to *offer* 26 Gy in 5 fractions over 1 week for whole breast, chest wall and partial breast radiotherapy. Where there had been a mastectomy and breast reconstruction there was strong support to *consider* 26 Gy in 5 fractions over a week. Using the 10-year FAST data there was very strong support to consider 28.5 Gy in 5 fractions over 5 weeks instead of 26 Gy in 5 fractions over 1 week for patients with significant co-morbidities and/or frailty that make daily radiotherapy difficult. For patients requiring a boost there was strong support to

offer 26 Gy in 5 fractions whole breast radiotherapy plus either a sequential normofractionated boost or a hypofractionated boost (delivered in no more than 5 fractions RCR Consensus Guidance, 2016) or 15 fraction simultaneous integrated boost (SIB), e.g. 48 Gy to boost volume and 40 Gy to rest of breast all over 3 weeks.

European Society for Radiotherapy and Oncology (ESTRO) Advisory Committee in Radiation Oncology Practice (ACROP) consensus recommendations on patient selection and dose/fractionation for external beam radiation therapy in early breast cancer were developed due to a lack of agreement persisting in the radiation oncology community on radiation dose/fractionation/volume selection in early-stage breast cancer. These were published in 2022 [123]. Most of the evidence was on moderate hypofractionation (15- 16- fraction regimens) but the FAST-Forward trial on "ultra-(5-fraction-) hypofractionation" was included. Concentrating on the statements on 26 Gy in 5 fractions in a week there was consensus that whole breast or chest wall irradiation without breast reconstruction can be offered as (i) standard-of-care or (ii) within a randomised controlled trial or prospective registration cohort. There was strong consensus that moderate hypofractionation (40 Gy in 15 fractions) and ultra-hypofractionation (26-30 Gy in 5 fractions) represent acceptable schedules for external beam partial breast irradiation.

The St Gallen 2021 International consensus guidelines, produced bi-annually, cover local and systemic therapies for early breast cancer [124]. Regarding 5-fractions, FAST and FAST-Forward schedules, the panel did not endorse these as standard treatment as yet but stated that there was growing interest [124]. The National Comprehensive Cancer Network clinical practice guidelines in oncology (NCCN guidelines [125]), probably the most used in the USA, recommend either 25-28 Fr or preferably hypofractionation with 15/16 Fr for whole breast RT. For the chest wall 25-28 Fr are recommended. The current guidelines thus show a mixed picture with the 5-year FAST-Forward results not enough to produce universal change.

Global health

Breast cancer is the commonest cancer worldwide, both in terms of incidence and prevalence and is the leading cause of death from any cancer in women with around 2.3 million cases and 700, 000 deaths in 2020 [126]. It is predicted that by 2040 there will be around 3 million cases annually with the majority occurring in low- and middle-income countries (LMICs) [127]. In addition, 70% of the predicted 1 million deaths will also be in lower income settings if there is no intervention in the current mortality trends [127].

Radiotherapy is an important component of the multi-modality treatment of breast cancer and contributes to improving both local control and survival [128, 129]. However, radiotherapy infrastructure is severely under resourced in many low- and middle-income countries with some regions having no access to radiotherapy at all [130]. Compounding this is the relative lack of uptake of hypofractionated radiotherapy in LMICs compared with higher income countries [131]. Furthermore, these regions also have a very high rates of patients who do not initiate or abandon breast cancer treatment for a variety of reasons [132].

Five-fraction radiotherapy over 1 week would go some way to helping this disparity. Mature results of the FAST-Forward Nodal Sub-Study will be particularly relevant, given that many people in LMIC's present with more advanced disease. This shortened fractionation would help alleviate health system costs and limit the potential financial toxicity for patients who would have received 3-5 weeks of radiotherapy. Access to and completion of good quality multi-modality treatment, including radiotherapy would prevent premature breast cancer deaths currently seen in many LMICs [132].

Other trials and areas of future research and collaboration

FAST-Forward provides the only published randomised controlled trial evidence for 1-week 5Fr schedules. There are several other studies either in set-up or open to recruitment evaluating the 26 Gy 1-week schedule in early breast cancer; effectively almost a decade behind FAST-Forward. However it will be many years until any results of these are known, and FAST-Forward has more patients enrolled than all of the other studies combined. The Indian HYPORT-Adjuvant trial opened in 2019 with a recruitment target ~2100 (NCT03788213) and randomises patients requiring adjuvant RT to the breast/chest wall +/- regional lymph nodes to 40 Gy/15Fr over 3 weeks versus 26 Gy/5Fr in 1 week. The use of a simultaneous integrated boost (dose of 8Gy and 6Gy, respectively) is allowed in patients who have undergone breast conservation. Another Indian trial HYPART; NCT04472845) is testing 26 Gy/5Fr in 1 week versus 34Gy/10Fr in 2 weeks in high-risk patients; the trial opened in March 2020 with a target sample size of 1018. The Canadian RHEAL trial (NCT04228991) has a similar design to the FAST-Forward Nodal Sub-Study; the target sample size is 588 patients and the estimated trial completion date is end of 2027. There are four other studies involving between 36 and 100 patients investigating the 26 Gy/5Fr schedule that are currently recruiting and will have no long-term data for many years. The UK is therefore best placed to maximise the knowledge already gained from the testing of 5Fr schedules.

FAST-Forward will contribute to future collaborations such as the planned EBCTCG meta-analysis breast RT fractionation trials. Another potential collaboration is the CONFLUENCE project. This

National Cancer Institute (USA) funded initiative aims to use genome-wide association studies (GWAS) to improve knowledge of breast cancer genetics. This research resource of different races/ethnicities will include at least 300,000 cases of both breast cancer and controls. The confluence of existing GWAS and new genome-wide genotyping data generated through this project will achieve this aim.

Limitations of the trial

The boost policy for each patient (yes or no) and dose prescription (10 Gy in 5 daily fractions or 16 Gy in 8 daily fractions) had to be declared to the CTSU ahead of randomisation. In the planning stage of the trial we debated the sequential normofraction boost against a hypofractionated boost. There was logic in using a hypofractionated boost for a trial of hypofractionation. To limit variables it was decided to continue with the established schedules for boost at the time. Boost is therefore treated as a randomly distributed variable that impacts (randomly) across all groups and contributes, like excision volume, breast size, smoking and genetic factors, to likelihood of adverse events. The reason for retaining sequential boost was to avoid having to commit to synchronous boost dose levels considered most likely to be iso-effective with control before knowing the outcome of the trial. That involves making an assumption about the likely α/β value (testing 2 values to cover upper and lower estimates would have made things very complex and prone to error). The limitation is that we used standard of care 5- or 8- fraction boost schedules in the Main Trial and not hypofractionated boosts. The boost policy was changed via an amendment for the nodal substudy to allow a hypofractionated boost in no more than 5 fractions. The trial will not contribute to information on a hypofractionated boost.

Confirmation that the 5Fr schedule is as safe as 15Fr for patients also receiving axillary RT is more important than ever as a higher proportion of node positive patients who require axillary treatment are now having nodal RT rather than surgery than when the FAST-Forward Nodal Sub-Study was conceived. This shift in practice followed publication of the AMAROS study which showed non-inferiority of nodal RT to axillary nodal dissection, with halved lymphoedema rates in the irradiated group [30]. Contemporary practice means there is also increasing use of neoadjuvant chemotherapy in patients with bulky or involved axillary nodes at presentation, especially in the HER2-positive and triple negative breast cancer sub-types, where high complete pathological responses are observed. The need for subsequent axillary surgery in these patients is being questioned, and is diminishing, being replaced by axillary RT or no treatment (NIHR ATNEC trial; NCT04109079). Lymphoedema (highlighted in a Living With and Beyond Cancer (LWBC) priority setting workshop) is the focus of the FAST-Forward Nodal Sub-Study which provides the best

opportunity to quantify these effects and further funding will supplement the shorter current follow-up currently available since it started midway through the Main Trial.

For some, the long-term results are essential to change practice, long-term meaning at least 10 years. Whilst the START trial 5-year outcomes were published in 2008 and 10-year outcomes in 2013, international guidelines were slow to adopt the 15Fr schedule that has been the UK standard-of-care since 2009. US guidelines were updated to encompass broader adoption of hypofractionation for breast cancer only in 2018 [103], and a number of countries still use the historic standard 25Fr schedule. Lack of long-term safety data is often cited as a reason for remaining cautious regarding adoption of new standards of radiotherapy treatment. To understand this caution in adoption it is worth emphasising what long-term follow-up means for radiotherapy trials, and the continued relevance and importance of reporting on outcomes, up to and even beyond 10 years. In the START-B trial of 15Fr vs 25Fr moderate/marked breast shrinkage increased from 11.4% at 5 years to 26.2% at 10 years after 40 Gy/15Fr. Outcomes for local relapse were 1.9% and 3.8% respectively. Similar increases in prevalence of outcomes after 5 years were seen in other trials [105, 111]. Other trials have continued to report outcomes to 15 years [133, 134].

There is caution regarding effectiveness of the 5Fr schedule in higher risk patients, as mentioned above [135, 136]. There are no data to support this concern but the lack of events per biological sub-group at 5 years is the argument used. Again, as stated above there are concerns over late toxicities emerging with longer term follow-up, such as cardiac and respiratory toxicity, that are not obviously apparent now. Some are concerned that early adoption may lead to long-term irreversible changes for patients and are sticking to their current 15-25Fr schedules. Particular emphasis has been placed on statistically rather than clinically significant values, such as a 1-2% increase in breast hardening outside the tumour bed with the 1-week schedule. We expect the cumulative effects of long-term toxicity and relapses to go up over time, but do not expect the relative differences between the groups to change. However, we need to demonstrate this.

Long-term follow-up of patients in cancer trials is recognised as essential to understanding recovery from treatment and its long-term effects and limitations as well as developing optimal management strategies for patients. Patients have shown high compliance with long term follow-up questionnaires, and this will provide important additional data in the planned 10-year outcomes study. This is particularly pertinent for RT where adverse effects continue to occur and progress years after treatment completion. Trial follow-up is essential in order to measure long-term outcomes since in the UK most breast cancer patients are now discharged from routine clinical follow-up within 12 months. Long-term safety data from FAST-Forward, only available with continued trial follow-up, will be invaluable for future patients in order to support fully informed consent and shared decision-making regarding treatment. UK health data systems do not routinely

collect the type of data that is required to assess breast-related radiation toxicity. Even serious toxicity such as lung/heart damage and second malignancies, would be difficult to routinely and accurately attribute in a comprehensive and timely manner. In the earliest studies of breast radiotherapy the benefits of reducing relapse were at least counterbalanced if not outweighed by long-term excess of deaths from cardiac causes. Although this is avoided or reduced by heart sparing techniques in the modern era, we need to be sure that there is no excess of these rare events with the 5Fr schedule. Although relapses and deaths could be collected from UK databases, they are not always complete, potentially indistinguishable from new primary breast cancer (contralateral) and are subject to a time-lag in availability. With relapse rates so low, it is important to collect as accurately and comprehensively as possible all of these occurrences. National breast RT consent forms developed by the RCR state expected rates of long-term risks after 15Fr and will need to be updated for 5Fr in future [121].

Survivorship issues are especially relevant for breast cancer; an estimated 600,000 people are alive in the UK after a diagnosis of breast cancer currently, predicted to rise to 1.2 million by 2030 [137]. Given the increasing incidence and low local relapse rates with increasing survival rates in breast cancer the issue of survivorship is magnified. If 50% of patients undergo RT and a side-effect was 10% more prevalent then by 2030 60,000 people will be affected. In the recent debate held at the San Antonio breast conference (December 2021), it was argued by some that in the long-term, if the 5Fr regimen led to more rare but expensive complications this could be detrimental. The FAST-Forward trialists do not believe this will be the case, but it is vital to be able to evidence this with long-term data.

Evaluation of progressive long-term and late side-effects occurring many years after cancer treatment are highlighted in the James Lind Alliance Top 10 priorities for LWBC [138]. Data collection beyond 5 years in FAST-Forward is the only available source to provide robust estimates of these effects for 5Fr schedules contributing significantly to worldwide knowledge in the field of breast RT extreme hypofractionation. Collection of patient-reported outcomes (PRO) finished at 5 years in our previous UK trials; the planned collection of 10-year data in FAST-Forward will enable a unique comparison of patient and clinician assessments of adverse effects and wider survivorship issues at this time-point. Reports published since START-B have illustrated that this is particularly important given that patients and clinicians have different perspectives of symptoms with patients' ratings of symptomology consistently higher than ratings by clinicians [139].

Future plans

The NIHR HTA has approved new funding for follow-up in the Main Trial to 10 years, and to at least 5 years in the Nodal Sub-Study. This proposal contained details for crucial long-term follow-up of breast cancer patients and was developed by the TMG including patient views via a strong PPI partnership. In Q2 2021 hospitals were asked to share a flyer with FAST-Forward patients giving them the chance to work with the trial team to optimise the future plans for the trial. Given that participants were on annual follow-up it was reassuring to have 146 responses within a month. Due to the larger number of people responding than had been anticipated a two-stage consultation was established, firstly to complete an online survey and secondly the establishment of focus groups to gauge participant opinion. In spite of a time-lag in sending out the survey due to the need to get appropriate approvals, 82 responses were received (56% response rate). Of these, 39 also attended one of two focus group meetings held in Q4 2021. Survey respondents appeared to be representative for both geographical region and treatment allocation 58/82 (71%) having received hypofractionated treatment (expected 2/3rds).

Participants were unanimous in endorsing the continuation of follow-up to 10 years and largely supportive of the pragmatic approach to reduce burden of data collection at sites during year 8 & 9 whilst focussing on getting complete data from face-to-face clinical visits at year 10. In the focus groups the emerging themes were the reassurance provided by the annual visits and the recognition that side-effects continue to emerge in later years. Some felt that they had signed up for 10 years and that this should be honoured if possible. NHS resource constraints were also noted.

They also confirmed their support for collecting patient views on their health and treatment at 10 years using a PRO questionnaire. Opinions were sought on the aspects of quality of life, toxicity and well-being that should be included. Concerns about continued changes in the treated breast, pain and physical functioning were highlighted but also fear of relapse, psychological wellbeing, fatigue and impact of other life events and comorbidities (previously reported in[140]. The views expressed led the trial team to seek out a variation to the original questionnaires to extend data collection to cover survivorship issues and to offer the PRO assessment to all patients not just those who had previously been in the PRO sub-study.

46 Main Trial sites opted to participate in the PRO Sub-Study, which was offered to all of their eligible patients (1796 consented to PRO). All Nodal Sub-Study patients were asked to consent to PRO collection since the primary endpoint is patient-assessed arm / hand swelling. We propose to offer all Main Trial patients still in follow-up involvement in the PRO study at 10 years, as this would greatly increase the number evaluable for PRO assessment. The trial provided a unique opportunity to capture extremely valuable PRO assessments of the long-term effects of living with and beyond breast cancer and capturing longer-term outcomes of hypofractionated RT. In reality

due to timings this assessment would be collected between follow-up years 10 and 11. Given the chronic nature of RT related effects this is considered a pragmatic solution and is endorsed by our participant involvement groups which had been retained as an ongoing patient representative collaborative resource.

Our participant focus groups have already demonstrated the huge value of engaging with, listening to and actively involving patients with lived experience of breast cancer. The focus groups may assist with other PPI issues that arise during the trial as the focus group members are keen to continue working with us.

Research recommendations

Future research with regard to hypofractionation of 26 Gy/5Fr in a week would include confirmation of our results in other geographic populations. The HYPORT-adjuvant trial is open to recruitment in India (NCT03788213). This is a 2-arm multicentre RCT aiming to recruit 2100 patients. The control arm is 40 Gy/15Fr over 3 weeks and is being compared to 26 Gy/5Fr in a week. The inclusion criteria are described as 'non-restrictive' to enable the results to be applicable to an Indian population. The OCOG group in Canada is recruiting to the RHEAL trial of locoregional radiotherapy also with a control arm of 40 Gy/15Fr over 3 weeks compared to 26 Gy/5Fr in a week (ClinicalTrials.gov Identifier: NCT04228991). There are other trials in the planning phase.

The appropriate boost dose, ideally delivered using a synchronous integrated boost (SIB), needs to be determined. The HYPORT trial is using either a sequential or SIB boost for both the trial and test arms of the study. This is a topic that would be appropriate for further study to build on both the IMPORT High and FAST-Forward trials. For instance the 15-fraction SIB dose of 48 Gy/15Fr from IMPORT High as the standard schedule could be compared with two 5FR SIB doses over a week.

The FAST-Forward Nodal Sub-Study will provide information on axillary radiotherapy in 5Fr. Evidence on the safety of a hypofractionated approach in patients requiring IMC radiotherapy also needs to be gathered. There will be some data from centres that used 5 fractions at the height of the Covid-19 pandemic but trial-based evidence is required. Both the HYPORT and RHEAL trials include patients having IMC radiotherapy.

Is 5-fraction hypofractionation the limit for external beam radiotherapy, might 2 fractions be an option? We are unaware of any trials examining this question.

Equality, diversity and inclusion for study participants

The study recruited from nearly 100 centres (RT and referring centres) across the whole of the UK. The inclusion criteria were very broad to allow easy access to the study regardless of where the patient lived. The study was attractive to many patients because of the usual reasons to help with research, but also because of the 2/3 chance of a 1-week radiotherapy schedule, thus completing treatment more quickly and with less expense and incursion. The trial included all the subtypes of breast cancer, which were broadly represented as per the incidence that they occur in the UK. The age of patients in FAST-Forward ranged from 25-90 years with 16.4% aged 70+ years. Men were eligible although being a rare disease in men, only 12 were entered. Ethnicity data has been collected (for those who donated a blood sample for genetic research) and will be reported with the 10-year results.

The study is in the follow-up stage, so no more patients will be recruited. However, extension of the PRO sub-study to all available Main Trial participants will provide a broader, all-encompassing view of patient outcomes at 10 years.

Patient and public involvement

Patient advocate involvement has been integral to ICR-CTSU breast RT trials for over 25 years as demonstrated by the involvement of the RAGE consortium in the START trials. Such involvment is from trial concept to protocol review and membership of the TMG, the patient advocates are a constant guide to ensure that the trialists are acting on patients' best interests and answering the questions they want answering. Patient advocates have also been integrally involved in discussions at TMG meetings regarding the trade-off between toxicity and efficacy and in advising on content of PRO questionnaires. Other essential discussions with patient advocates have included differentiating between what is statistically significant with what is clinically relevant to patients. Issues such as does an increase incidence of 1% of breast hardening at 5 years matter to patients, with a trade-off of a week's treatment with generally low toxicity.

In November 2021 around 80 FAST-Forward trial participants completed an online questionnaire seeking their feedback on plans for further follow-up in the trial including content of a PRO questionnaire at 10 years. Over 40 of these patients then participated in participant involvement group discussions organised by ICR-CTSU in December 2021 that further explored patients' views on long-term follow-up in the trial and issues important to them at 10 years following cancer

treatment. Outputs from the online survey and the discussion meetings have informed the future plans of FAST-Forward.

Conclusions

Extremely low rates of IBTR and of clinically-assessed 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. The 26 Gy dose level has been shown to be comparable to 40 Gy in 15 fractions in terms of patient-assessed NTE, clinician-assessed NTE, and NTE photographic change in breast appearance, and to NTE expected after 46-48 Gy in 2 Gy fractions.

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

The reduced number of patient attendances in a 5 fraction schedule places less burden on patients and the carers. In some geographically large countries, where travel times to radiotherapy centres are prohibitive, fewer women choose breast conservation for early breast cancer. Reducing the travel and personal financial burden may allow more women to choose breast conservation rather than mastectomy.

In response to global warming, it is important that healthcare systems respond in an environmentally conscious manner. Reducing the number of patient visits to only 5 fractions will reduce the carbon footprint for patient travel. Furthermore, the impact of a 5-fraction regimen on improving access times for other cancer patients will lead to more efficient use of linear accelerators and hence reduce carbon footprint for each radiotherapy centre.

It is also likely to be safe for patients requiring regional radiotherapy, an approach currently under formal evaluation in our randomised FAST-Forward Nodal Sub-Study comparing 40 Gy in 15 fractions and 26 Gy in 5 fractions. Areas of future research with regard to hypofractionation of 5 fractions would include confirmation of our results in other geographic populations, trials are both on-going and in set-up. The appropriate boost dose, ideally delivered using a synchronous integrated boost (SIB), needs to be determined. Evidence on the safety of a hypofractionated approach in patients requiring IMC radiotherapy is being trialled. Is 5-fraction hypofractionation the limit for external beam radiotherapy, might 2 fractions be an option? FAST-Forward can and is influencing both practice and future research.

ACKNOWLEDGEMENTS

Table 29: Centre staff who participated in the FAST-Forward trial - Current principal investigators, past principal investigators, main co-investigators and trials teams (including physicists, radiographers, nurses and data managers)

Centre No	Centre Name	Centre Staff
01	Royal Marsden Hospital Sutton	**Dr N Somaiah***, Dr A Kirby*, Dr I Locke, Dr D Tait, **_Prof J Yarnold_***, R Colgan, L Gothard, C Lucy
02	Royal Cornwall	**Dr D Wheatley***, Prof D Radstone, Dr A Thomson, n Ashley, S Eloi, A Griffiths, J Kingston, N Simpson
03	University Hospital of North Midlands	**Prof AM Brunt***, Dr D Gahir, Dr A Jegannathen, L Contoret, M Evans, K Glover, A Myatt, R Smith
03a/10c	Stafford General Hospital	**Dr A Jegannathen**, Dr L Pettit, Dr C Brammer, C Harvey, A Myatt, L Verueco
04	Derriford Hospital, Plymouth	**Dr U Panwar**, Dr S Dubey, **_Dr S Kelly_** (RIP), N Blacker, L Cadmore, H Congdon, I Harvey
05*	Norfolk and Norwich Hospital	**Dr D Geropantas**, Dr A Bulman, **_Dr A Harnett_***, S Barber, M Bloomfield, E Malone, J Platt
05a*	James Paget Hospital	**Dr S Down**, **_Dr A Harnett_***, A Brooks, J Harman
05b/09b*	Queen Elizabeth Hospital, Kings Lynn	**Dr M Daly**, R Lee, H Webb
06*	Bristol Haematology and Oncology	**Dr C Comins**, **_Dr A Bahl_**, Dr S Masson, Dr N Thanvi, H Appleby, A Lowe, H Saldanha, V Lee
06a*	Weston General Hospital	**Dr T Wells**, **_Dr M Tomlinson_**, K Owens, H Lloyd-Jones, G Saunders
07*	Royal Shrewsbury Hospital	**Dr L Pettit**, **_Dr R Agrawal_**, Dr H Abel Gadir, **_Dr S Khanduri_**, S Jose, S Potts, A Welsh
08	Royal Devon + Exeter Hospital	**Dr J Forrest**, Dr A Goodman*, **_Dr A Hong_**, Dr D Hwang, K Baines, A Betts, T Lawless, S Scrutton
08a*	North Devon District Hospital	**Dr J Forrest**, **_Dr D Hwang_**, R Holbrook, S Ley, L Van Koutrik

09*	Addenbrookes Hospital	**Prof C Coles***, Dr L Hughes-Davies, ***Dr C Wilson,*** A Bates, C Philpott, C Spain, B Stratton, N Twyman, J Wilkinson;
09a*	Hinchingbrooke Hospital	**Dr S Russell**, V Goss, R Kurian, S Miller
09c*	West Suffolk Hospital	**Dr M Moody**, Dr C Woodward, S Hale
09d*	Bedford Hospital	**Dr S Smith,** V Bastion, G Lubimbi, A Willis, J Valentine
10	New Cross Hospital	**Dr R Allerton**, Dr C Brammer, ***Dr M Churn***, Dr L Pettit, Dr P Ramachandran, R Horton, M James-King
10a/50a	Kidderminster Hospital	**Dr M Churn***, S Stringer, H Tranter
10b*	Russell's Hall	**Dr R Allerton**, Dr G Georgiev, Dr P Ramachandra, K Kanyi, K McGarry, A Watts
11*	Southend University Hospital	**Dr H Algurafi**, Dr W Ella, ***Dr A Robinson***, T Davies, A McPherson, L Romero, S Shibu-Thomas
11a*	Basildon Hospital	**Dr H Swinburn**, ***Dr W Ella***, C McCormick
12	Clatterbridge Cancer Centre	**Dr S Tolan**, ***Dr I Syndikus***, Dr N Thorp, S Green, K Hughes, H Mayles
12a*	Warrington Hospital	**Dr I Syndikus***, L Lee, C Lowthian, R Madew
12c*	St Helens + Whiston	**Dr R Sripadam**, N Hornby
12d	University Hospital, Aintree	**Dr P Robson**, L Beresford
12e*	Countess of Chester	**Dr A Hall**, S Bennett, E Gallimore, M Moffit, J Prince
13	Velindre Cancer Centre	**Dr H Passant***, Dr J Abraham, ***Prof P Barrett-Lee***, Dr A Borley, Dr T Howe, Dr R Stevens, M Jenkins, S Slade, A Weaver, O Woodley
14*	Royal Surrey County Hospital	**Dr R Laing**, Dr A Franklin, Dr A Neal, Dr S Whittaker, L Adams, M Flavin, B Moloney-Oates, A Tindall
15*	Essex County Hospital	**Dr M Mukesh**, Dr V Loo, ***Dr P Murray***, K Cooke, C Driscoll
16	Beatson West of Scotland Cancer Centre	**Dr A Alhasso***, Prof P Canney, Dr G Fraser, Dr G Lumsden, Dr M Rizwanullah, A Armstrong, J Fleming, T Ibotoye, A Leonard, M McJury, C Seager, V Withers
16a	Royal Alexandra Hospital	**Dr A Alhasso***, P Eaddy, E MacLeod
16b	Forth Valley Hospital	**Dr H Marashi**, Dr I Rabnawaz, F Johnston, L Prentice, A Scott
16c	Wishaw Hospital	**Dr J Hicks**, ***Dr M Rizwanullah***, K Douglas
16d*	New Victoria ACH	**Dr D Ritchie**, Dr J Ansari, E Moody
16e	Hairmyres Hospital	**Dr J Hicks**, ***Dr G Dunn***, L Devlin, L Glass
16f*	Crosshouse Hospital, Kilmarnock	**Dr G Lumsden**, K Bain, C Burns, P Cannon
17*	Singleton Hospital, Swansea	**Dr M Rolles**, Dr C Askill, ***Dr D Pudney***, Dr R Taylor, E Brinkworth, H Cheley, S Foyle, E Harris, N Viney, J Williams
18	Cheltenham General Hospital	**Dr J Bowen***, Dr K Benstead, Dr R Counsell, Dr S Elyan, R Bakawala, N Bulmer, J Chittock, J Kukielska, A Skelton, M Tan
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18b*	Hereford County Hospital	Dr D Nelmes, *Dr S Guglani*, J Birch, M Evans, G Horsfield
19	Royal Preston	Dr M Hogg
19c	Blackpool Victoria Infirmary	Dr F Danwata, *Dr A Hindley*, Dr S Susnerwala, E Davies, S Lancaster, L Smith
19d	Royal Lancaster Infirmary	Dr D Williamson, *Dr G Skailes*, C Bartlett, A Fielding
20*	Queens Hospital, Romford	Dr E Sims, Dr C Bridgewater, *Dr M Quigley*, Dr E Staples, T Mills-Baldock, J Cook
21	Peterborough Hospital	Dr C Jephcott, Dr C Round, Dr S Treece, K Cavanagh, C Chisenga, M Cowen
22	Weston Park Hospital, Sheffield	Dr M Hatton, Dr O Din, Dr C Lee, G Brown, J Conway, L Fiorentino, J Swinscoe
23*	Royal Sussex County Hospital	Dr D Bloomfield*, Dr S Mitra, Dr A Nikapota, Dr R Simcock, Dr S Westwell, P Frattaroli, A Hewines, J Tremlett
23a*	Worthing Hospital	Dr SY Sham, *Dr A Nikapota*, *Dr S Mitra*, S Funnell, J Gilbert
23b*	Eastbourne Hospital	Dr S Westwell, K Jones-Skipper
24	Guys Hospital	Prof E Sawyer*, Dr L Brazil, Dr S Harris, Prof A Tutt, G Keunzig, C Thomas
25*	Ipswich Hospital	Dr R Venkitaraman, *Dr L Sherwin*, C Mackenzie, P Ridley, M Riley
26*	Glan Clwyd Hospital	Dr J Bishop, G Davies, S Owen, V Saul
26a*	Wrexham Maelor Hospital	Dr W Soe, Dr J Bishop, Dr N Ghosal, J Stockport
26b*	Ysbyty Gwynedd Hospital	Dr J Bishop, D Thomas, L Williams.
27	Queen Elizabeth Hospital, Birmingham	Dr A Stevens, *Dr MS Anwar*, Dr D Spooner, S Manolopoulos, R Shingler
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27b*	City Hospital. Birmingham	Dr D Spooner, D Devonport, B Gammon
27c	Manor Hospital, Walsall	Dr S Yaha, *Dr MS Anwar*, J Fletcher
28	Charing Cross Hospital	Dr S Cleator*, *Dr C Lowdell*, P Dunn, S McInerney
28a*	Ealing Hospital	Dr O Hatcher, *Dr C Lewanski*, S Magwaro, D Murati, K Watson
28b	West Middlesex Hospital	Dr P Riddle, Dr R Ahmad, J Swallow
29	Mount Vernon Hospital	Dr C Westbury, *Dr M Ah-See*, Dr A Makris, Dr P Ostler, Dr N Shah, Dr N Thanvi, T Chalk, S Hasan, E Windmill
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30*	Royal United Hospital, Bath	Dr M Beresford, Dr A Jenner, Dr S Mancero, Dr S Manson, Dr H Newman, T Allen, C Milsom, T Tylee, S Whittle
31	Queen Alexandra Hospital, Portsmouth	Dr K Bradley, Dr JD Dubois, Dr A Suovuori, R Baker, K Haselip, N Rivington
32	Torbay District General Hospital	Dr A Goodman*, Dr P Bliss, M Allison, P Bowen, S Chamberlain, I Koehler
33	Southampton General Hospital	Dr C Crowley, Dr J Marshall, Dr S Raj, C Britton, E Cooper, K Meeking, K Stevens

33a*	Salisbury Hospital	**Dr C Crowley**, J Attlee, S Strong-Sheldrake
33b*	Royal Hampshire County Hospital	**Dr S Raj**, J Conti, V Corner, J Smith
34	Royal Berkshire	**Dr R Davis**, Dr J Adams, ***Dr J Barrett***, Dr C Charlton, J Jones, P Pabari, E Vowell
34a*	Wexham Park Hospital	**Dr R Davis**, ***Dr J Adams***, Dr S Inayat, N Barnes, S Das, D Mciver, J Weerasinghe
35	St Bartholomew's Hospital	**Dr V Wolstenholme**, Dr C Cottrill, Dr N Patel, Dr K Tipples, F Bibi, H Payne, A Pena-Remorin, A Sivajothi, E Tutor
36	St James' University Hospital, Leeds	**Dr S Kumar**, Dr I Chaudhuri, S Hartup, A Henson, J Lilley, P Shuttleworth
36a^	Pinderfields Hospital, Wakefield	**Dr S Kumar**, J Ball, S Buckley, C Hirst
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36c^	Huddersfield Royal Infirmary	**Dr N Roberts**, M Brady, S Dale, D Melia, S Mellor
37	University Hospital of Coventry and Warwickshire	**Dr D Hrouda**, Dr L Fresco, Dr C Irwin, ***Dr N Walji***, Dr J Wordling, S Manolopoulos, K Sanders
37a*	George Eliot Hospital, Nuneaton	**Dr S Lupton**, Dr L Fresco, J Lake
37b*	Warwick Hospital	**Dr N Walji**, J Harris, L Maher
37c/50b	Alexandra Hospital, Redditch	**Dr M Churn***, Dr D Hrouda, Dr C Irwin, H Hodson, A Morgan
38	Musgrove Park, Taunton	**Dr M Varughese**, ***Dr J Graham***, S Mahoney
38a	Yeovil District Hospital	**Dr U Barthakur**, J McCrory, K Rennie
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40	Northampton General Hospital	**Dr R Agrawal**, Prof H Eldeeb, ***Dr C Macmillan***, A Kempa, M Polnik, R Tighe, N Whilde
41	James Cook University Hospital	**Dr B Sethugavalar**, ***Dr J Hardman***, Dr JCM Van der Voet, H Curtis, E Thompson
41a	University Hospital of North Tees	**Dr E Thompson**, ***Dr N Storey***, Dr A Rathmell, L Poole
42	Western General Hospital, Edinburgh	**Dr C Bedi**, Dr T Evans, Prof I Kunkler, Dr F Yuille, R Allan, L Carruthers, L Primrose
42a	Borders General Hospital	**Dr C Bedi**, M Tolson
42b	Dumfries and Galloway Hospital	**Dr A Hennessy**, ***Dr T Evans***, J Duignan
42c	Queen Margaret Hospital, Dunfermline	**Dr M MacLennan***, Dr A Stillie, ***Dr T Evans***, F Adam
42d	St John's Hospital, Livingstone	**Dr F Yuille**, R Allen, A Clark
43	Belfast City Hospital	**Dr H McCarty**, Dr J Clarke, ***Dr G Hanna***, Dr L Mulholland, D Irvine, O Stewart, G Totton
44*	University College London Hospitals	**Dr G Blackman**, Dr A Cassoni, Dr M Gaze, ***Dr M McCormack***, Dr J Tobias, R Patel, S Wickers
45*	Poole Hospital	**Dr J Brady**, Dr A Chakrabarti, Dr P Crellin, N Gurung, D Forster, F Mellor, B Troke, L Varnham
46	Leicester Royal Infirmary	**Dr K Kancherla**, C Belcher, J Potterton, S Wright
47*	Churchill Hospital, Oxford	**Dr S Oliveros**, ***Dr B Lavery***, N Ann, C Hector, M Flavin, G Samkange

48**	Ninewells Hospital, Dundee	**Dr D Adamson,** A Black, G Georgiev
49**	Nottingham City Hospital	**Dr P Lawton**, Dr M Griffin, P Dawson, S Dennis, S Fleet
49a**	Kings Mill Hospital,	**Dr M Griffin**, D Nash

*Recruited to Main Trial only

^Recruited to Nodal Sub-Study only

**Did not recruit

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AM Brunt, JR Yarnold and D Wheatley (Chief Investigators / Chief Clinical Co-ordinator) - Contributed to the conception and design of the study, responsible for oversight throughout the trial, interpretation of the results and writing of the report

JM Bliss (Trial methodology lead) - Contributed to the conception and design of the study, provided oversight and guidance for trial management and analyses throughout the trial, interpretation of the results and writing of the report

JS Haviland (Principal Statistician) - Contributed to the conception and design of the study, conduct of the trial, responsible for the analysis and interpretation of the results and writing of the report

J Patel (Trial Statistician) - responsible for the analysis and interpretation of some of the results and contributed to the writing of the report

M Sydenham (Trial Manager) - Contributed to the design of the study, managed the study and data collection at ICR-CTSU, conduct of the trial, interpretation of the results and writing of the report

DJ Bloomfield, C Chan, S Cleator, CE Coles, E Donovan, A Goodman, P Hopwood, AM Kirby, CC Kirwan, E Sawyer, N Somaiah, and I Syndikus (Trial Management Group members) - Contributed to the design of the study, conduct of the trial, interpretation of the results and writing of the report

D Glynn and S Griffin (Health Economics team) - Contributed to the conception, design and analysis of the health economics study and the writing of the health economics chapter.

Z Nabi and K Venables (RTTQA team) – contributed to the design, conduct and analysis of the QA programme and the writing of the QA chapter

H Fleming (Patient and Public Involvement) - patient advocate member of the TMG, provided guidance for study documentation and reports and writing of the report.

All authors reviewed and approved the final report

Publications and presentations

Zotova R, Tsang YM, Conibear J, Miles E. Field-based and volume-based PTVs as plan evaluation structures in the UK FAST-Forward breast trial. Poster presentation, ECCO conference, Amsterdam, September 2013. Radiother Oncol. 2013; 106(S2):S122 (PD-0317).

A.M. Brunt, J.R. Yarnold, D. Wheatley, N. Somaiah, S. Kelly, A. Harnett, C. Coles, A. Goodman, R. Zotova, M.A. Sydenham, C.L. Griffin, J.M. Bliss on behalf of the FAST-Forward Trial Management Group. Acute skin toxicity reported in the FAST-Forward trial (HTA 09/01/47): a phase III randomised trial of 1-week whole breast radiotherapy compared to standard 3 weeks in patients with early breast cancer. Poster presentation at NCRI conference, Liverpool, 2-5 Nov 2014.

Zotova R, Yarnold JR, Wheatley D, Griffin C, Brunt M. Results from the radiotherapy quality assurance programme for the FAST-Forward breast trial. Abstract submission for ESTRO 2015 conference. Radiother Oncol. 2015;115(S1):S209-S210(PD-0430)

A.M. Brunt, D. Wheatley, J.R. Yarnold, N. Somaiah, S. Kelly, A. Harnett, C.E. Coles, A. Goodman, A. Bahl, M. Churn, R. Zotova, M.A. Sydenham, C.L. Griffin, J. Morden, J.M. Bliss. Acute skin toxicity associated with a 1-week schedule of whole breast radiotherapy compared with a standard 3-week regimen delivered in the UK FAST-Forward Trial. Radiother Oncol 2016 Jul:120(1): 114–118. Epub 2016 Apr 1.

D. Megias, M. Sydenham, D. Wheatley, M. Maclennan, E. Spezi, A.M. Brunt. Variability of contouring using the ESTRO guideline for elective breast cancer radiotherapy. Oral presentation at ESTRO conference, Vienna, May 2017. Radiother Oncol. 2017;123(S1):S136-S137(OC-0265).

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FAST-Forward phase 3 RCT of 1-week hypofractionated breast radiotherapy: 3-year normal tissue effects. Oral presentation at NCRI conference, Glasgow, UK, 5th November 2018.

Hypofractionation for Whole Breast Irradiation in 5 days (Fast Forward Trial). Oral presentation at ASTRO conference, US, 22nd October 2018.

Hypofractionated Whole Breast Radiation Regimens. Oral presentation at ASTRO conference, US, 18th September 2019.

AM Brunt, JS Haviland, DA Wheatley, MA Sydenham, A Alhasso, D Bloomfield, C Chan, M Churn, S Cleator, CE Coles, A Goodman, A Harnett, P Hopwood, AM Kirby, CC Kirwan, C Morris, Z Nabi, E Sawyer, N Somaiah, L Stones, I Syndikus, JM Bliss, JR Yarnold on behalf of the FAST-Forward Trial Management Group. 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. The Lancet 2020; 395: 1613–26. https://doi.org/10.1016/S0140-6736(20)30932-6.

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Paradigm shift: the role of hypofractionated breast radiotherapy. Oral presentation at UK Association of Breast Surgeons hypofractionation webinar, UK, 26th May 2020.

Hypofractionated breast radiotherapy for 1-week versus 3-weeks (FAST-Forward). Oral presentation at Virtual Oncology Global webinar Conference organised by Memorial Sloan Kettering, US, 28th May 2020.

FAST-Forward and beyond. Oral presentation at the CONNECT SENATURK meeting on "Hypofractionated radiotherapy in breast cancer: now even shorter" on 13th June 2020.

NCRI Virtual Webinar titled - Radiotherapy research in the UK: What's new? Oral presentation of FAST-Forward trial results, 16th July 2020.

Update on FAST-Forward Trial: Oral presentation at UK Association of Breast Surgeons Webinar Series titled "Interesting perspective on patient management since Covid-19 and update on radiotherapy changes" on 22nd September 2020.

FAST-Forward phase 3 RCT of 1-week hypofractionated breast radiotherapy: 5-year results for efficacy and late normal tissue effects. Oral presentation at UK Royal College of Radiologists consensus meeting, 15th October 2020.

[FAST-Forward phase 3 RCT of 1-week hypofractionated breast radiotherapy: 5-year results](#). Invited speaker presentation by Murray Brunt in the 'Cancer Breakthough' session at ASTRO 2020 on 25th October 2020. Selected from best of ESTRO 2020.

Who should have the FAST-FORWARD 5 Fraction Radiotherapy Schedule? Oral presentation at virtual 8th UKBCG annual meeting, 20th November 2020.

FAST-Forward phase 3 RCT of 1-week hypofractionated breast radiotherapy: 5-year results for efficacy and late normal tissue effects. Oral presentation at virtual ESTRO 39 conference, 30th November 2020. Abstract number E20-2292/ OC-0610.

Shortening breast radiotherapy to one week, FAST-Forward to implementation. Oral presentation at Edinburgh Breast Cancer Special Symposium, 27th Feb 2021.

Oral presentation of FAST-Forward trial results at annual international BIR Annual Radiotherapy and Oncology Meeting 2021, 26th March 2021.

Oral presentation of FAST-Forward trial results in the Breast Cancer Session at the Virtual UK Oncology Forum 2021, 21st October 2021.

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Ethics approval

FAST-Forward was approved by the London-Brighton and Sussex Research Ethics Committee (REC) (previously named South East Coast - Kent REC then South East Coast - Brighton and Sussex REC) on 2nd September 2011 (11/LO/0958).

DATA SHARING

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review. Trial documentation including the protocol are available at https://www.icr.ac.uk/fastforward (last accessed 20/05/2022).

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APPENDICES

Appendix 1: Centre recruitment to Main Trial and Nodal Sub-Study

Table 30: Recruitment by centre to FAST-Forward Main Trial

Centre No	Centre	Principal Investigator(s)*	Date site opened	Date first patient	Total
1	RMH Sutton	Dr N Somaiah, *Prof J Yarnold*	*25/11/2011*	*09/12/2011*	**185**
2	Royal Cornwall	Dr D Wheatley	*09/01/2012*	*10/01/2012*	**248**
3	University Hospital of North Staffordshire	Prof AM Brunt	*23/11/2011*	*24/11/2011*	**298**
3a	Stafford General Hospital	Dr A Jegannathen	*16/01/2012*	*25/01/2012*	**87**
4	Derriford Hospital, Plymouth	Dr U Panwar, *Dr S Kelly*	*17/01/2012*	*24/01/2012*	**144**
5	Norfolk and Norwich Hospital	Dr D Geropantas, *Dr A Harnett*	*02/04/2012*	*10/04/2012*	**100**
5a	James Paget Hospital	Dr S Down, *Dr A Harnett*	*02/04/2012*	*04/05/2012*	**33**
6	Bristol Haematology and Oncology	Dr C Comins, *Dr A Bahl*	*07/02/2012*	*14/03/2012*	**47**
6a	Weston General Hospital	Dr T Wells, *Dr M Tomlinson*	*30/04/2012*	*01/05/2012*	**22**
7	Royal Shrewsbury Hospital	Dr L Pettit, *Dr R Agrawal, Dr S Khanduri*	*28/02/2012*	*09/03/2012*	**126**
8	Royal Devon + Exeter Hospital	Dr J Forrest, *Dr A Hong*	*02/05/2012*	*16/05/2012*	**70**
8a	North Devon District Hospital	Dr J Forrest, *Dr D Hwang*	*10/05/2012*	*17/05/2012*	**46**
9	Addenbrookes Hospital	Prof C Coles	*07/03/2012*	*20/03/2012*	**99**
9a	Hinchingbrooke Hospital	Dr S Russell	*07/09/2012*	*09/10/2012*	**17**
9b	Queen Elizabeth Hospital, Kings Lynn	Dr M Daly	*26/10/2012*	*10/12/2012*	**5**
9c	West Suffolk Hospital	Dr M Moody	*28/11/2012*	*07/02/2013*	**10**
9d	Bedford Hospital	Dr S Smith	*29/05/2013*	*05/07/2013*	**2**
10	New Cross Hospital	Dr R Allerton, *Dr M Churn*	*09/03/2012*	*04/04/2012*	**67**
10a	Kidderminster Hospital	Dr M Churn	*12/03/2012*	*10/05/2012*	**47**
10b	Russell's Hall	Dr R Allerton	*25/05/2012*	*25/05/2012*	**21**
11	Southend University Hospital	Dr H Algurafi, *Dr A Robinson*	*27/04/2012*	*15/05/2012*	**37**
11a	Basildon Hospital	Dr H Swinburn, *Dr W Ella*	*18/07/2012*	*25/07/2012*	**25**
12	Clatterbridge Cancer Centre	Dr S Tolan, *Dr I Syndikus*	*18/05/2012*	*26/07/2012*	**22**
12a	Warrington Hospital	Dr I Syndikus	*18/05/2012*	*07/06/2012*	**27**
12c	St Helens + Whiston	Dr R Sripadam	*21/05/2012*	*28/09/2012*	**4**
12d	University Hospital, Aintree	Dr P Robson	*28/06/2012*	*15/05/2013*	**8**
12e	Countess of Chester	Dr A Hall	*25/07/2012*	*15/08/2012*	**12**
13	Velindre Cancer Centre	Dr H Passant, *Prof P Barrett-Lee*	*20/06/2012*	*25/06/2012*	**167**
14	Royal Surrey County Hospital	Dr R Laing	*08/05/2012*	*02/08/2012*	**40**
15	Essex County Hospital	Dr M Mukesh, *Dr P Murray*	*14/05/2012*	*22/08/2012*	**19**
16	Beatson West of Scotland Cancer Centre	Dr A Al-Hasso	*25/05/2012*	*25/07/2012*	**24**
16a	Royal Alexandra Hospital	Dr A Al-Hasso	*25/05/2012*	*31/05/2012*	**41**
16b	Forth Valley Hospital	Dr H Marashi	*24/07/2013*	*19/11/2013*	**13**
16c	Wishaw Hospital	Dr J Hicks, *Dr M Rizwanullah*	*28/06/2012*	*14/08/2012*	**25**
16d	New Victoria ACH	Dr D Ritchie	*17/07/2012*	*15/08/2012*	**7**
16e	Hairmyres Hospital	Dr J Hicks, *Dr G Dunn*	*25/02/2014*	*13/03/2014*	**1**
16f	Crosshouse Hospital, Kilmarnock	Dr G Lumsden	*06/08/2012*	*07/08/2012*	**30**

Centre No	Centre	Principal Investigator(s)*	Date site opened	Date first patient	Total
17	Singleton Hospital, Swansea	Dr M Rolles, *Dr D Pudney*	*28/05/2012*	*29/06/2012*	**72**
18	Cheltenham General Hospital	Dr J Bowen	*27/06/2012*	*09/07/2012*	**48**
18a	Worcester Royal Infirmary	Dr M Churn, *Dr J Bowen*	*25/07/2012*	*12/10/2012*	**19**
18b	Hereford County Hospital	Dr D Nelmes, *Dr S Guglani*	*27/06/2012*	*19/11/2012*	**18**
19c	Blackpool Victoria Infirmary	Dr F Danwata, *Dr A Hindley*	*12/09/2012*	*21/09/2012*	**38**
19d	Royal Lancaster Infirmary	Dr D Williamson, *Dr G Skailes*	*16/07/2012*	*25/07/2012*	**92**
20	Queens Hospital, Romford	Dr E Sims, *Dr M Quigley*	*27/06/2012*	*08/10/2012*	**52**
21	Peterborough Hospital	Dr C Jephcott	*13/07/2012*	*12/09/2012*	**36**
22	Weston Park Hospital, Sheffield	Dr M Hatton	*02/07/2012*	*20/08/2012*	**86**
23	Royal Sussex County Hospital	Dr D Bloomfield	*05/07/2012*	*25/07/2012*	**116**
23a	Worthing Hospital	Dr SY Sham, *Dr A Nikapota, Dr S Mitra*	*14/01/2013*	*23/01/2013*	**59**
23b	Eastbourne Hospital	Dr S Westwell	*03/12/2012*	*12/12/2012*	**35**
24	Guys Hospital	Prof E Sawyer	*07/09/2012*	*03/12/2012*	**25**
25	Ipswich Hospital	Dr R Venkitaraman, *Dr L Sherwin*	*25/07/2012*	*24/10/2012*	**18**
26	Glan Clwyd Hospital	Dr J Bishop	*10/01/2013*	*28/01/2013*	**31**
26a	Wrexham Maelor Hospital	Dr W Soe	*10/01/2013*	*11/02/2013*	**24**
26b	Ysbyty Gwynedd Hospital	Dr J Bishop	*23/01/2013*	*12/06/2013*	**10**
27	Queen Elizabeth Hospital, Birmingham	Dr A Stevens, *Dr MS Anwar*	*03/08/2012*	*21/08/2012*	**66**
27a	Sandwell Hospital	Dr D Spooner	*26/10/2012*	*23/11/2012*	**4**
27b	City Hospital. Birmingham	Dr D Spooner	*26/10/2012*	*14/11/2012*	**31**
27c	Manor Hospital, Walsall	Dr S Yaha, *Dr MS Anwar*	*23/05/2013*	*02/08/2013*	**6**
28	Charing Cross Hospital	Dr S Cleator, *Dr C Lowdell*	*13/09/2012*	*19/09/2012*	**62**
28a	Ealing Hospital	Dr O Hatcher, *Dr C Lewanski*	*24/06/2013*	*11/10/2013*	**7**
28b	West Middlesex Hospital	Dr P Riddle	*07/02/2013*	*26/02/2013*	**17**
29	Mount Vernon Hospital	Dr C Westbury, *Dr M Ah-See*	*21/09/2012*	*24/09/2012*	**108**
29a	Luton and Dunstable University Hospital	Dr A Vinayan, *Dr M Ah-See*	*10/05/2013*	*25/09/2013*	**23**
30	Royal United Hospital, Bath	Dr M Beresford	*14/12/2012*	*03/01/2013*	**45**
31	Queen Alexandra Hospital, Portsmouth	Dr K Bradley	*14/11/2012*	*29/11/2012*	**92**
32	Torbay District General Hospital	Dr A Goodman	*14/11/2012*	*27/11/2012*	**62**
33	Southampton General Hospital	Dr C Crowley	*11/12/2012*	*19/12/2012*	**50**
33a	Salisbury Hospital	Dr C Crowley	*21/12/2012*	*04/03/2013*	**21**
33b	Royal Hampshire County Hospital	Dr S Raj	*10/05/2013*	*01/07/2013*	**10**
34	Royal Berkshire	Dr R Davis, *Dr J Barrett*	*10/01/2013*	*21/01/2013*	**91**
34a	Wexham Park Hospital	Dr R Davis, *Dr J Adams*	*31/05/2013*	*06/08/2013*	**12**
35	St Bartholomew's Hospital	Dr V Wolstenholme	*14/01/2013*	*25/01/2013*	**55**
36	St James' University Hospital, Leeds	Dr S Kumar	*29/01/2013*	*12/02/2013*	**24**
37	University Hospital of Coventry and Warwickshire	Dr D Hrouda, *Dr N Walji*	*11/02/2013*	*10/04/2013*	**40**
37a	George Eliot Hospital, Nuneaton	Dr S Lupton	*11/02/2013*	*26/02/2013*	**35**
37b	Warwick Hospital	Dr N Walji	*11/02/2013*	*06/03/2013*	**56**
37c	Alexandra Hospital, Redditch	Dr M Churn	*11/02/2013*	*03/06/2013*	**12**
38	Musgrove Park, Taunton	Dr M Varughese, *Dr J Graham*	*03/05/2013*	*29/05/2013*	**39**

Centre No	Centre	Principal Investigator(s)*	Date site opened	Date first patient	Total
38a	Yeovil District Hospital	Dr U Barthakur	24/05/2013	22/08/2013	8
39	Lincoln County Hospital	Dr A Chaudhuri, *Dr E Murray*	17/05/2013	29/05/2013	50
39a	Pilgrim Hospital, Boston	Dr A Chaudhuri, *Dr E Murray*	17/05/2013	20/06/2013	9
40	Northampton General Hospital	Dr R Agrawal, *Dr C Macmillan*	03/07/2013	13/08/2013	19
41	James Cook University Hospital	Dr B Sethugavalar, *Dr J Hardman*	01/08/2013	01/10/2013	22
41a	University Hospital of North Tees	Dr E Thompson, *Dr N Storey*	18/10/2013	21/10/2013	8
42	Western General Hospital, Edinburgh	Dr C Bedi	23/09/2013	21/01/2014	13
42a	Borders General Hospital	Dr C Bedi	27/09/2013	26/11/2013	5
42b	Dumfries and Galloway Hospital	Dr A Hennessy, *Dr T Evans*	24/12/2013	12/02/2014	3
42c	Queen Margaret Hospital, Dunfermline	Dr M MacLennan, *Dr T Evans*	21/01/2014	04/02/2014	4
42d	St John's Hospital, Livingstone	Dr F Yuille	27/09/2013	19/12/2013	7
43	Belfast City Hospital	Dr H McCarty, *Dr G Hanna*	08/01/2014	20/01/2014	9
44	University College London Hospitals	Dr G Blackman, *Dr M McCormack*	07/08/2013	28/08/2013	16
45	Poole Hospital	Dr J Brady	24/12/2013	03/02/2014	8
46	Leicester Royal Infirmary	Dr K Kancherla	14/01/2014	24/01/2014	5
47	Churchill Hospital, Oxford	Dr S Oliveros, *Dr B Lavery*	04/02/2014	13/03/2014	1
Total					**4110**

* Past PI(s) in italics

Table 31: Recruitment by centre to FAST-Forward Nodal Sub-Study

Centre No	Centre	Principal Investigator(s)*	Date site opened	Date first patient	Total
01	RMH Sutton	Dr N Somaiah, *Prof J Yarnold*	21/10/2016	02/12/2016	37
02	Royal Cornwall	Dr D Wheatley	08/04/2016	26/07/2016	36
03	University Hospital of North Midlands	Dr D Gahir *Prof AM Brunt*	16/02/2016	08/04/2016	63
03a	Stafford General Hospital	Dr A Jegannathen	23/05/2016	01/09/2017	1
04	Derriford Hospital, Plymouth	Dr U Panwar, *Dr S Kelly*	20/02/2018	01/05/2018	17
08	Royal Devon + Exeter Hospital	Dr J Forrest, *Dr A Hong*	11/04/2016	27/04/2016	10
09	Addenbrookes Hospital	Prof C Coles	15/04/2016	*Did not recruit*	0
10	New Cross Hospital	Dr R Allerton, *Dr M Churn*	12/08/2016	04/01/2017	5
12	Clatterbridge Cancer Centre	Dr S Tolan, *Dr I Syndikus*	05/06/2017	*Did not recruit*	0
12d	University Hospital, Aintree	Dr P Robson	05/06/2017	28/03/2018	1
13	Velindre Cancer Centre	Dr H Passant, *Prof P Barrett-Lee*	18/08/2017	11/10/2017	1
16	Beatson West of Scotland Cancer Centre	Dr A Al-Hasso	05/12/2016	18/01/2017	12
16a	Royal Alexandra Hospital	Dr A Al-Hasso	05/12/2016	12/12/2016	21
16b	Forth Valley Hospital	Dr H Marashi	05/12/2016	22/05/2018	2
16c	Wishaw Hospital	Dr J Hicks, *Dr M Rizwanullah*	06/02/2017	12/05/2017	5
16e	Hairmyres Hospital	Dr J Hicks, *Dr G Dunn*	06/02/2017	12/05/2017	5
18	Cheltenham General Hospital	Dr J Bowen	13/07/2016	06/10/2016	10
18b	Hereford County Hospital	Dr D Nelmes, *Dr S Guglani*	07/12/2016	06/09/2017	2
19	Royal Preston	Dr M Hogg	19/05/2017	*Did not recruit*	0
19c	Blackpool Victoria Infirmary	Dr F Danwata, *Dr A Hindley*	19/05/2017	23/04/2018	2
19d	Royal Lancaster Infirmary	Dr D Williamson, *Dr G Skailes*	13/11/2017	09/03/2018	7
21	Peterborough Hospital	Dr C Jephcott	14/06/2016	08/09/2016	2
22	Weston Park Hospital, Sheffield	Dr M Hatton	24/05/2016	05/10/2016	8
24	Guys Hospital	Prof E Sawyer	06/09/2016	06/10/2016	2
27	Queen Elizabeth Hospital, Birmingham	Dr A Stevens, *Dr MS Anwar*	14/12/2016	10/03/2017	7
27c	Manor Hospital, Walsall	Dr S Yaha, *Dr MS Anwar*	06/06/2017	01/02/2018	1
28	Charing Cross Hospital	Dr S Cleator, *Dr C Lowdell*	08/07/2016	01/08/2016	17
28b	West Middlesex Hospital	Dr P Riddle	11/07/2017	11/07/2017	7
31	Queen Alexandra Hospital, Portsmouth	Dr K Bradley	10/08/2016	10/02/2017	2
32	Torbay District General Hospital	Dr A Goodman	02/11/2016	11/01/2017	13
33	Southampton General Hospital	Dr C Crowley	08/07/2016	01/08/2017	7
34	Royal Berkshire	Dr R Davis, *Dr J Barrett*	09/02/2017	01/08/2017	14
35	St Bartholomew's Hospital	Dr V Wolstenholme	21/07/2016	22/09/2016	3
36	St James's University Hospital, Leeds	Dr S Kumar	20/12/2016	09/02/2017	15
36a	Pinderfields Hospital, Wakefield	Dr S Kumar	21/06/2017	09/08/2017	4
36b	Bradford Royal Infirmary	Dr E Thomas	21/11/2017	29/11/2017	4
36c	Huddersfield Royal Infirmary	Dr N Roberts	25/01/2018	23/02/2018	3
37	University Hospital of Coventry and Warwickshire	Dr D Hrouda, *Dr N Walji*	27/03/2017	31/10/2017	2
38	Musgrove Park, Taunton	Dr M Varughese, *Dr J Graham*	11/02/2017	24/01/2017	14
38a	Yeovil District Hospital	Dr U Barthakur	22/03/2017	07/06/2017	9

Centre No	Centre	Principal Investigator(s)*	Date site opened	Date first patient	Total
39	Lincoln County Hospital	Dr A Chaudhuri, *Dr E Murray*	08/06/2017	10/07/2017	18
39a	Pilgrim Hospital, Boston	Dr A Chaudhuri, *Dr E Murray*	28/06/2017	09/08/2017	5
40	Northampton General Hospital	Dr R Agrawal, *Dr C Macmillan*	20/07/2016	*Did not recruit*	0
41	James Cook University Hospital	Dr B Sethugavalar, *Dr J Hardman*	15/11/2016	23/03/2017	15
41a	University Hospital of North Tees	Dr E Thompson, *Dr N Storey*	19/12/2016	10/05/2017	3
42	Western General Hospital, Edinburgh	Dr C Bedi	13/04/2016	05/07/2016	11
42a	Borders General Hospital	Dr C Bedi	13/04/2016	23/12/2016	7
42b	Dumfries and Galloway Hospital	Dr A Hennessy, *Dr T Evans*	25/05/2016	06/09/2016	2
42c	Queen Margaret Hospital, Dunfermline	Dr M MacLennan, *Dr T Evans*	13/04/2016	07/03/2017	7
42d	St John's Hospital, Livingstone	Dr F Yuille	13/04/2016	*Did not recruit*	0
43	Belfast City Hospital	Dr H McCarty, *Dr G Hanna*	05/06/2017	04/10/2017	4
46	Leicester Royal Infirmary	Dr K Kancherla	08/03/2017	24/03/2017	7
50	Worcester Royal Infirmary	Dr M Churn	17/08/2016	03/02/2017	5
50a	Kidderminster Hospital	Dr M Churn	17/08/2016	24/08/2016	9
50b	Alexandra Hospital, Redditch	Dr M Churn	17/08/2016	23/03/2017	5
Total					**469**

* Past PI(s) in italics

Appendix 2: Additional tables

Methods

Table 32: Dose prescriptions to whole breast/chest wall, level I-III axilla and/or level IV axilla (SCF)

Trial group	Total dose (Gy)	Dose per fraction (Gy)	Number of fractions	Fractions per week	Treatment time (weeks)
Control Group	40.05	2.67	15	5	3
Test Group 1	27.0	5.4	5	5	1
Test Group 2	26.0	5.2	5	5	1

Table 33: Amendments to eligibility criteria

Eligibility Criteria						
Exclusion Criteria		**Version 1** 27/05/2011	**Version 2** 13/02/2013	**Version 2.2** 02/05/2013	**Version 3** 08/07/2015(Nodal Sub-Study)	**Version 4** 24/02/2017(Nodal Sub-Study)
1	Past history of malignancy except (i) basal cell skin cancer and CIN cervix uteri or (ii) non-breast malignancy allowed if treated with curative intent and at least 5 years disease free	✓	✓	✓	✓	✓
2	Contralateral breast cancer, including DCIS, irrespective of date of	✓	N/A	N/A	N/A	N/A

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Eligibility Criteria						
Exclusion Criteria		**Version 1** **27/05/2011**	**Version 2** **13/02/2013**	**Version 2.2** **02/05/2013**	**Version 3** **08/07/2015(Nodal Sub-Study)**	**Version 4** **24/02/2017(Nodal Sub-Study)**
	diagnosis (superseded)					
2	Ipsilateral and contralateral breast cancer, including DCIS, irrespective of date of diagnosis (superseded)	N/A	✓	N/A	N/A	N/A
2	Contralateral and/or previous ipsilateral breast cancer, including DCIS, irrespective of date of diagnosis	N/A	N/A	✓	✓	✓
3	Breast reconstruction using implants	✓	N/A	N/A	N/A	N/A
4	Concurrent cytotoxic chemotherapy (sequential neoadjuvant or adjuvant cytotoxic therapy allowed as long as there is ≥ 2 weeks between therapy and radiotherapy)	✓	✓	✓	✓	✓
5	Radiotherapy to any regional lymph node areas (excepting lower axilla included in standard tangential fields to	✓	✓	✓	N/A	N/A

Eligibility Criteria						
Exclusion Criteria		**Version 1** **27/05/2011**	**Version 2** **13/02/2013**	**Version 2.2** **02/05/2013**	**Version 3** **08/07/2015(Nodal Sub-Study)**	**Version 4** **24/02/2017(Nodal Sub-Study)**
	breast/chest wall)					
6	Age ≥65 years and pT1G1/G2 ER+HER2-pN0 M0 invasive disease	N/A	✓	✓	N/A	N/A
7	Ipsilateral microinvasive disease and/or non-gradeable tumours	N/A	✓	✓	✓	✓
8	Any patient with N0 disease	N/A	N/A	N/A	✓	✓
9	Known residual macroscopic nodal disease	N/A	N/A	N/A	✓	✓
10	≥10 positive axillary nodes	N/A	N/A	N/A	✓	N/A
11	Any positive level IV (SCF) nodes	N/A	N/A	N/A	✓	✓
12	Any requirement for internal mammary chain (IMC) RT because indications for IMC RT are currently unclear	N/A	N/A	N/A	✓	✓

Table 34: Summary of FAST-Forward protocol amendments

Protocol version	Summary of changes
Version 2.0 (13/02/2013)	Change to eligibility criteria to exclude patients with very low-risk of relapse from the trial (defined as age ≥65 years and pT1G1/G2 ER+HER2-pN0 M0 invasive disease) Inclusion of the Health Economics sub-study Inclusion and renaming of the Quality of life sub-study to Patient Reported Outcome Measures (PRO) study Addition of the second short-term side-effects study Updates to the PIS and consent forms due to reflect the opening of the sub-studies
Version 2.1 (13/03/2013)	Minor formatting changes to main protocol and minor changes to PIS
Version 2.2 (02/05/2013)	Correction to the fourth exclusion criteria – insertion of the word "previous" Update to the PIS and consent form to removing text stating "breast conservation patients only", so that mastectomy patients as well will be eligible for the photographic sub-study.
Version 3.0 (08/07/2015)	Substantial amendment to include the Nodal Sub-Study
Version 3.1 (15/06/2016)	Minor wording change to one exclusion criterion – removal of word "no" so exclusion reads "known residual macroscopic nodal disease".
Version 4.0 (24/02/2017)	Inclusion of patients with >9 positive nodes provided the treatment intention is adjuvant (curative intent) Hypofractionated boost is now permitted & needs to be declared prior to randomisation.
Version 5.0 (14/12/2017)	Change of design of Nodal Sub-Study to a 2-group randomisation (removal of Test Group 1) Revised target sample size for the Nodal Sub-Study
Version 5.1 (05/02/2018)	Minor amendment to include statement regarding the presentation and publication of the analysis of normal tissue effect data up to 3 years' follow-up.

Acute toxicity sub-studies

Table 35: Radiotherapy details of patients in first and second acute toxicity sub-studies

Reproduced from Brunt (2016) (CC BY 4.0)[3]

Radiotherapy (RT) details	Acute toxicity sub-study 1			Acute toxicity sub-study 2		
	40 Gy/15Fr N=64[1] N (%)	27 Gy/5Fr N=62 N (%)	26 Gy/5Fr N=63 N (%)	40 Gy/15Fr N=55[2] N (%)	27 Gy/5Fr N=44 N (%)	26 Gy/5Fr N=61 N (%)
Radiotherapy received						
Yes	64 (100)	62 (100)	63 (100)	54 (98)	44 (100)	61 (100)
No	0	1 (2)[3]	0	1 (2)[4]	0	0
Boost received						
Yes	11 (17)	11 (18)	7 (11)	0	0	0
No	53 (83)	51 (82)	56 (89)	54 (100)	44 (100)	61 (100)
Treatment duration in patients receiving no boost (including weekends and bank holidays)[5]						
Median (IQR)	22 (21-23)	5 (5-7)	7 (5-7)	21 (20-22)	6 (5-7)	6 (5-7)
Range	15-25	5-11	5-9	15-23	5-8	5-8
Treatment duration in patients receiving boost (including weekends and bank holidays)						
Median (IQR)	30 (26-33)	18 (12-20)	14 (12-17)	-	-	-
Range	22-35	7-20	7-21	-	-	-
Whole breast – total fractions						
5	0	62 (100)	63 (100)	0	44 (100)	61 (100)
15	63 (98)	0	0	54 (100)	0	0
Other[6]	1 (2)	0	0	0	0	0
Whole breast – total dose (Gy)						
26	0	0	63 (100)	0	0	61 (100)
27	0	62 (100)	0	0	44 (100)	0
40	63 (98)	0	0	54 (100)	0	0
Other[6]	1 (2)	0	0	0	0	0
Bolus used (mastectomy patients only)						
Yes	1 (100)	1 (33)	3 (50)	2 (40)	1 (50)	5 (100)
No	0	2 (67)	3 (50)	3 (60)	1 (50)	0
Dose homogeneity constraints achieved						
Yes	62 (97)	61 (98)	60 (95)	53 (98)	44 (100)	60 (98)
No	2 (3)	1 (2)	3 (5)	1 (2)	0	1 (2)
Organs at risk dose constraints achieved						
Yes	64 (100)	61 (98)	62 (98)	53 (98)	44 (100)	61 (100)
No	0	1 (2)	1 (2)	1 (2)	0	0
Any deviations from RT[7]						
Yes	1 (2)	0	0	1 (2)	0	0
No	63 (98)	62 (100)	63 (100)	53 (98)	44 (100)	61 (100)
Whole breast RT extended by >3 days						
Yes	0	0	0	0	0	0
No	64 (100)	62 (100)	63 (100)	54 (100)	44 (100)	61 (100)

[1] Includes one patient randomised to receive 26 Gy/5Fr who was treated with 40 Gy/15Fr due to patient choice, this patient is included in 40 Gy/15Fr group for all subsequent analyses

[2] Includes one patient randomised to receive 26 Gy/5Fr who was treated with 40 Gy/15Fr due to coverage issues, this patient is included in 40 Gy/15Fr group for all subsequent analyses

[3] Patient refused any radiotherapy after randomisation

[4] Patient withdrew consent prior to radiotherapy

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Table 36: Overall compliance to toxicity assessments during and post radiotherapy

Reproduced from Brunt (2016) (CC BY 4.0)[3]

Total number of acute toxicity assessments during and post treatment	Acute toxicity sub-study 1			Acute toxicity sub-study 2		
	40 Gy/15Fr N=64 N (%)	27 Gy/5Fr N=62 N (%)	26 Gy/5Fr N=63 N (%)	40 Gy/15Fr N=55 N (%)	27 Gy/5Fr N=44 N (%)	26 Gy/5Fr N=61 N (%)
Expected number of assessments	7	5	5	7	5	5
Number of completed assessments[1]						
0	2 (3)	0	1 (2)	6 (11)	0	1 (2)
1	3 (5)	3 (5)	4 (6)	0	0	1 (2)
2	2 (3)	3 (5)	0	0	1 (2)	1 (2)
3	5 (8)	5 (8)	6 (10)	1 (2)	2 (5)	5 (8)
4	1 (2)	16 (26)	14 (22)	1 (2)	5 (11)	7 (11)
5	7 (11)	35 (56)	38 (60)	4 (7)	36 (82)	46 (75)
6	14 (22)	-	-	9 (16)	-	-
7[2]	30 (47)	-	-	34 (62)	-	-
Total number evaluable	44	51	52	43	41	53

[1] Only includes non-boost assessments (First sub-study)
[2] Includes one patient with 4 on-treatment assessments + 4 post-treatment assessments

Table 37: Acute toxicity sub-study 2 - Nature of grade 1 and 2 toxicities according to treatment

CTCAE grade 1 and 2 symptoms	40 Gy/15Fr N (%)[1]	27 Gy/5Fr N (%)[1]	26 Gy/5Fr N (%)[1]
Total Evaluable	43	41	53
Grade 1			
Faint erythema	42 (98)	38 (93)	47 (89)
Dry desquamation	7 (16)	1 (2)	8 (15)
Grade 2			
Moderate to brisk erythema	20 (47)	11 (27)	16 (30)
Patchy moist desquamation confined to skin folds/creases	8 (19)	2 (5)	6 (11)
Moderate oedema	2 (5)	0	1 (2)

[1]Percentages calculated from those evaluable

Main Trial

Table 38: Return rates of baseline and follow-up forms in FAST-Forward Main Trial

Form	Expected	Received	Percentage received
Randomisation Checklist	4107	4107	100
Medical History	4104	4104	100
Baseline Pathology	4104	4104	100
Primary Surgery	4104	4104	100
Planned Systemic Treatment	4103	4103	100
Radiotherapy	4099	4099	100
Year 1 follow up	4051	4045	99.8
Year 2 follow up	3995	3984	99.7
Year 3 follow up	3937	3850	99.2
Year 4 follow up	3901	3723	98.7
Year 5 follow up	3798	3733	98.0
Year 6 follow up	3661	3486	95.2
Year 7 follow up	3570	3273	91.7

Number of expected forms calculated as number of patients who have not died, withdrawn or are lost to follow-up

Table 39: Medical history details at randomisation for the 4096 patients consenting to the FAST-Forward Main Trial[1]

Medical history	40 Gy / 15Fr N=1361 (%)	27 Gy / 5Fr N=1367 (%)	26 Gy / 5Fr N=1368 (%)
Current smoker			
Yes	201 (15)	206 (15)	203 (15)
No	1159 (85)	1161 (85)	1162 (85)
Not known	1	0	3
Previous smoker (in past year)	N=1159	N=1161	N=1162
Yes	83 (7)	81 (7)	69 (6)
No	1073 (93)	1077 (93)	1086 (94)
Not known	3	3	7
History of cardiovascular disease			
Yes	94 (7)	123 (9)	87 (6)
No	1267 (93)	1244 (91)	1279 (94)
Not known	0	0	2
Diabetes			
Yes	88 (6)	95 (7)	99 (7)
No	1273 (94)	1272 (93)	1267 (93)
Not known	0	0	2
Hypertension			
Yes	360 (26)	404 (29)	407 (30)
No	1000 (74)	963 (71)	959 (70)
Not known	1	0	2
Statin use			
Yes	220 (16)	250 (18)	259 (19)
No	1140 (84)	1117 (82)	1106 (81)
Not known	1	0	3
ACE inhibitor use			
Yes	147 (11)	162 (12)	172 (13)
No	1214 (89)	1204 (88)	1193 (87)
Not known	0	1	3

%s calculated out of those with data available

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

Table 40: Cross-sectional frequencies of clinician-assessed late normal tissue effects at 1-4 years according to fractionation schedule

NTE	Year 1			Year 2			Year 3			Year 4		
	40 Gy N=1341 (%)	27 Gy N=1350 (%)	26 Gy N=1351 (%)	40 Gy N=1319 (%)	27 Gy N=1336 (%)	26 Gy N=1327 (%)	40 Gy N=1285 (%)	27 Gy N=1300 (%)	26 Gy N=1309 (%)	40 Gy N=1243 (%)	27 Gy N=1260 (%)	26 Gy N=1261 (%)
Any AE in breast / chest wall[1]												
None	592 (51)	510 (43)	587 (49)	618 (54)	547 (46)	586 (50)	587 (54)	548 (49)	581 (52)	569 (54)	497 (46)	554 (51)
Mild	421 (36)	479 (40)	465 (39)	411 (36)	445 (37)	436 (37)	383 (35)	414 (37)	405 (36)	368 (35)	412 (38)	414 (38)
Moderate	135 (12)	175 (14)	133 (11)	114 (10)	178 (15)	115 (10)	104 (10)	140 (12)	108 (10)	101 (10)	134 (13)	108 (10)
Marked	12 (1)	34 (3)	18 (1)	8 (<1)	29 (2)	26 (2)	7 (1)	25 (2)	24 (2)	6 (1)	28 (3)	18 (2)
Not assessed	181	152	148	168	137	164	204	173	191	199	189	167
Breast distortion[2]												
None	834 (77)	837 (74)	874 (77)	818 (76)	811 (72)	816 (74)	772 (76)	780 (73)	808 (77)	723 (74)	729 (72)	776 (75)
Mild	205 (19)	218 (19)	196 (17)	203 (19)	246 (22)	225 (21)	197 (19)	228 (22)	198 (19)	210 (22)	222 (22)	208 (20)
Moderate	38 (3)	67 (6)	54 (5)	54 (5)	63 (6)	46 (4)	43 (4)	46 (4)	35 (3)	36 (4)	46 (5)	38 (4)
Marked	4 (<1)	9 (1)	6 (<1)	3 (<1)	8 (<1)	10 (1)	2 (<1)	9 (1)	11 (1)	3 (<1)	12 (1)	8 (1)
N/A	79	72	73	75	71	70	71	69	68	71	65	64
Not assessed	181	147	148	166	137	160	200	168	189	200	186	167
Breast shrinkage[2]												
None	802 (74)	795 (70)	835 (74)	776 (72)	783 (69)	801 (73)	717 (71)	765 (72)	767 (73)	682 (70)	691 (69)	721 (70)
Mild	218 (20)	230 (20)	239 (21)	241 (22)	248 (22)	228 (21)	238 (23)	207 (20)	218 (21)	234 (24)	233 (23)	250 (24)
Moderate	56 (5)	87 (8)	49 (4)	59 (5)	81 (7)	59 (5)	56 (5)	79 (7)	58 (5)	54 (6)	70 (7)	53 (5)
Marked	5 (<1)	17 (2)	8 (1)	3 (<1)	15 (1)	7 (<1)	4 (<1)	9 (1)	9 (1)	2 (<1)	13 (1)	6 (<1)
N/A	79	72	73	75	71	70	71	69	68	71	65	64
Not assessed	181	149	147	165	138	162	199	171	189	199	188	167
Breast induration (tumour bed) [2]												
None	828 (77)	824 (73)	875 (78)	857 (80)	856 (76)	858 (79)	822 (82)	828 (78)	852 (81)	795 (82)	783 (78)	816 (79)
Mild	211 (19)	242 (21)	210 (19)	184 (17)	215 (19)	185 (17)	150 (15)	187 (18)	164 (16)	150 (15)	180 (18)	177 (17)
Moderate	40 (4)	59 (5)	34 (3)	32 (3)	47 (4)	39 (4)	33 (3)	36 (3)	27 (3)	27 (3)	39 (4)	33 (3)
Marked	2 (<1)	4 (<1)	8 (<1)	2 (<1)	11 (1)	10 (<1)	3 (<1)	8 (1)	9 (<1)	1 (<1)	7 (<1)	3 (<1)
N/A	79	72	73	75	71	70	71	69	68	71	65	64
Not assessed	181	149	151	169	136	165	206	172	189	199	186	168
Breast induration (outside tumour bed)[2]												
None	986 (91)	990 (88)	1005 (90)	1012 (94)	1031 (91)	1014 (93)	943 (93)	976 (92)	969 (92)	909 (93)	922 (92)	935 (91)
Mild	84 (8)	103 (9)	96 (9)	52 (5)	73 (7)	66 (6)	53 (5)	64 (6)	68 (6)	59 (6)	62 (6)	74 (7)
Moderate	10 (1)	30 (3)	16 (1)	11 (1)	16 (1)	10 (1)	11 (1)	14 (1)	8 (1)	5 (<1)	18 (2)	16 (2)
Marked	1 (<1)	5 (<1)	5 (<1)	0 (0)	9 (1)	3 (<1)	2 (<1)	4 (<1)	6 (1)	1 (<1)	5 (<1)	3 (<1)
N/A	79	72	73	75	71	70	71	69	68	71	65	64
Not assessed	181	150	156	169	136	164	205	173	190	198	188	169
Telangiectasia												
None	1107 (96)	1130 (95)	1143 (96)	1090 (95)	1092 (92)	1074 (93)	990 (93)	1005 (90)	1026 (92)	963 (93)	951 (89)	1000 (92)
Mild	38 (3)	53 (4)	48 (4)	50 (4)	80 (7)	68 (6)	71 (7)	94 (8)	61 (5)	57 (5)	93 (9)	67 (6)

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NTE	Year 1			Year 2			Year 3			Year 4		
	40 Gy N=1341 (%)	27 Gy N=1350 (%)	26 Gy N=1351 (%)	40 Gy N=1319 (%)	27 Gy N=1336 (%)	26 Gy N=1327 (%)	40 Gy N=1285 (%)	27 Gy N=1300 (%)	26 Gy N=1309 (%)	40 Gy N=1243 (%)	27 Gy N=1260 (%)	26 Gy N=1261 (%)
Moderate	5 (<1)	6 (<1)	5 (<1)	6 (<1)	17 (1)	13 (1)	8 (1)	17 (2)	22 (2)	16 (2)	23 (2)	17 (2)
Marked	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	3 (<1)	0 (0)	1 (<1)	4 (<1)	3 (<1)	2 (<1)	3 (<1)
Not assessed	191	161	155	172	146	169	216	183	196	204	191	174
Breast / chest wall oedema												
None	969 (84)	900 (75)	970 (81)	1030 (90)	994 (83)	1005 (86)	995 (93)	962 (86)	1001 (89)	973 (93)	938 (88)	996 (91)
Mild	146 (13)	217 (18)	174 (15)	96 (8)	155 (13)	130 (11)	67 (6)	127 (11)	97 (9)	60 (6)	103 (10)	74 (7)
Moderate	38 (3)	70 (6)	50 (4)	20 (2)	41 (3)	24 (2)	8 (1)	27 (2)	16 (1)	9 (1)	22 (2)	16 (1)
Marked	4 (<1)	9 (1)	8 (<1)	0 (0)	7 (1)	4 (<1)	0 (0)	6 (1)	4 (<1)	0 (0)	5 (<1)	2 (<1)
Not assessed	184	154	149	173	139	164	215	178	191	201	192	173
Breast / chest wall discomfort												
None	837 (73)	832 (70)	869 (73)	888 (77)	890 (74)	895 (77)	857 (80)	854 (76)	881 (79)	833 (80)	830 (78)	864 (79)
Mild	251 (22)	286 (24)	267 (22)	207 (18)	255 (21)	224 (19)	185 (17)	225 (20)	202 (18)	172 (17)	195 (18)	186 (17)
Moderate	52 (4)	65 (5)	48 (4)	41 (4)	42 (3)	39 (3)	26 (2)	44 (4)	32 (3)	26 (2)	43 (4)	36 (3)
Marked	11 (1)	3 (<1)	10 (1)	10 (1)	8 (1)	6 (1)	6 (1)	4 (<1)	5 (<1)	5 (<1)	2 (<1)	3 (<1)
Not assessed	190	164	157	173	141	163	211	173	189	207	190	172
Other RT-related												
None	1116 (95)	1147 (95)	1156 (95)	1107 (96)	1151 (96)	1137 (97)	1049 (96)	1103 (97)	1098 (97)	1015 (97)	1049 (97)	1058 (97)
Mild	39 (3)	46 (4)	40 (3)	37 (3)	35 (3)	23 (2)	25 (2)	15 (1)	17 (1)	20 (2)	18 (2)	25 (2)
Moderate	14 (1)	11 (1)	13 (1)	8 (1)	8 (1)	7 (<1)	8 (1)	10 (1)	7 (1)	10 (1)	6 (1)	9 (1)
Marked	3 (<1)	7 (<1)	3 (<1)	4 (<1)	7 (<1)	2 (<1)	5 (<1)	5 (<1)	4 (<1)	4 (<1)	3 (<1)	3 (<1)
Not assessed	169	139	139	163	135	158	198	167	183	194	184	166

Denominators in column headings show the total number of questionnaires returned at each time-point. Denominators for individual symptoms may vary due to missing items on the questionnaire; percentages are calculated out of totals with data available for each item.

[1] Any AE in breast /chest wall includes breast distortion, breast shrinkage, breast induration (in & outside tumour bed), telangiectasia, breast / chest wall oedema; [2] Applicable following breast conservation surgery or reconstruction. N/A: not applicable (primary surgery mastectomy without immediate reconstruction)

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Table 41: Cross-sectional frequencies of patient-assessed breast/chest wall and arm/shoulder symptoms from baseline to 2 years in the Main Trial

	Baseline			3 months			6 months			12 months			24 months		
	40 Gy N=584	27 Gy N=594	26 Gy N=591	40 Gy N=541	27 Gy N=563	26 Gy N=562	40 Gy N=530	27 Gy N=542	26 Gy N=552	40 Gy N=527	27 Gy N=532	26 Gy N=540	40 Gy N=506	27 Gy N=521	26 Gy N=514
Protocol-specific items															
Breast appearance changed															
None	96 (17)	133 (23)	133 (23)	78 (15)	85 (15)	95 (17)	73 (14)	60 (11)	94 (17)	62 (12)	55 (11)	86 (16)	75 (15)	83 (16)	105 (21)
Mild	307 (54)	273 (47)	293 (50)	287 (54)	276 (50)	291 (53)	278 (54)	274 (52)	277 (51)	293 (57)	266 (51)	291 (55)	264 (54)	240 (47)	261 (52)
Moderate	104 (18)	104 (18)	86 (15)	107 (20)	120 (22)	107 (19)	94 (18)	110 (21)	117 (21)	95 (19)	121 (23)	105 (20)	99 (20)	108 (21)	83 (16)
Marked	66 (11)	73 (12)	69 (12)	57 (11)	71 (13)	61 (11)	70 (14)	86 (16)	57 (11)	63 (12)	77 (15)	47 (9)	53 (11)	78 (15)	56 (11)
Missing	11	11	10	12	11	8	15	12	7	14	13	11	15	12	8
Breast smaller															
None	249 (44)	264 (46)	290 (50)	211 (41)	272 (50)	276 (50)	201 (40)	239 (46)	255 (47)	179 (35)	210 (41)	234 (45)	171 (35)	202 (40)	225 (45)
Mild	215 (38)	206 (36)	194 (34)	206 (40)	172 (32)	182 (33)	182 (36)	165 (31)	178 (33)	204 (40)	175 (34)	180 (34)	200 (41)	165 (33)	171 (34)
Moderate	49 (9)	64 (11)	41 (7)	58 (11)	57 (10)	51 (9)	76 (15)	64 (12)	62 (12)	65 (13)	72 (14)	65 (12)	65 (13)	77 (15)	54 (11)
Marked	47 (8)	42 (7)	49 (9)	43 (8)	43 (8)	40 (7)	48 (9)	57 (11)	44 (8)	57 (11)	56 (11)	45 (9)	51 (11)	59 (12)	51 (10)
Missing	24	28	17	23	19	13	23	17	13	22	19	16	19	18	13
Breast harder/ firmer															
None	246 (44)	255 (44)	249 (44)	168 (32)	176 (32)	178 (33)	170 (33)	135 (26)	160 (30)	188 (37)	141 (27)	174 (33)	217 (45)	194 (39)	223 (44)
Mild	218 (39)	212 (37)	222 (39)	227 (44)	220 (41)	233 (43)	219 (43)	209 (40)	209 (39)	205 (41)	209 (41)	202 (39)	186 (39)	198 (39)	178 (35)
Moderate	70 (13)	78 (14)	64 (11)	86 (17)	89 (16)	79 (14)	78 (15)	106 (20)	108 (20)	73 (15)	107 (21)	97 (19)	55 (11)	65 (13)	68 (13)
Marked	24 (4)	27 (5)	31 (5)	39 (7)	57 (11)	56 (10)	43 (8)	70 (13)	61 (11)	39 (8)	58 (11)	48 (9)	25 (5)	46 (9)	35 (7)
Missing	26	22	25	21	21	16	20	22	14	22	17	19	23	18	10
Skin appearance changed															
None	246 (43)	284 (48)	270 (46)	203 (38)	204 (37)	211 (38)	201 (38)	200 (38)	218 (40)	214 (41)	217 (41)	245 (46)	263 (53)	253 (49)	271 (54)
Mild	253 (44)	241 (41)	243 (42)	237 (44)	265 (48)	257 (46)	236 (45)	244 (46)	239 (44)	234 (45)	220 (42)	222 (42)	188 (38)	188 (37)	186 (37)
Moderate	62 (11)	46 (8)	50 (9)	67 (13)	59 (11)	59 (11)	55 (11)	60 (11)	63 (11)	48 (9)	66 (13)	53 (10)	31 (6)	52 (10)	32 (6)
Marked	16 (3)	15 (3)	17 (3)	28 (5)	28 (5)	31 (5)	31 (6)	29 (5)	26 (5)	22 (4)	23 (4)	14 (3)	13 (3)	19 (4)	18 (4)
Missing	7	8	11	6	7	4	7	9	6	9	6	6	11	9	7

	Baseline			3 months			6 months			12 months			24 months		
	40 Gy N=584	27 Gy N=594	26 Gy N=591	40 Gy N=541	27 Gy N=563	26 Gy N=562	40 Gy N=530	27 Gy N=542	26 Gy N=552	40 Gy N=527	27 Gy N=532	26 Gy N=540	40 Gy N=506	27 Gy N=521	26 Gy N=514
EORTC QLQ-BR23 items															
Breast pain															
None	223 (38)	250 (42)	220 (37)	130 (24)	124 (22)	130 (23)	154 (29)	137 (26)	142 (26)	182 (35)	176 (33)	189 (35)	205 (41)	198 (38)	193 (38)
Mild	307 (53)	298 (51)	315 (54)	318 (59)	315 (56)	313 (56)	300 (57)	287 (53)	302 (55)	281 (53)	279 (53)	269 (50)	241 (48)	257 (50)	260 (51)
Moderate	44 (7)	36 (6)	45 (8)	73 (14)	100 (18)	93 (17)	59 (11)	91 (17)	88 (16)	51 (10)	61 (11)	65 (12)	47 (9)	46 (9)	46 (9)
Marked	9 (2)	6 (1)	8 (1)	17 (3)	23 (4)	24 (4)	14 (3)	27 (5)	20 (4)	12 (2)	15 (3)	15 (3)	12 (2)	16 (3)	12 (2)
Missing	1	4	3	3	1	2	3	0	0	1	1	2	1	4	3
Breast swollen															
None	360 (62)	375 (64)	360 (61)	375 (70)	344 (61)	359 (64)	369 (70)	319 (59)	352 (64)	418 (79)	362 (68)	388 (72)	428 (85)	379 (74)	406 (79)
Mild	167 (29)	171 (29)	182 (31)	120 (22)	151 (27)	138 (25)	125 (24)	156 (29)	138 (25)	83 (16)	120 (23)	127 (24)	65 (13)	105 (20)	83 (16)
Moderate	40 (7)	35 (6)	42 (7)	31 (6)	51 (9)	39 (7)	19 (4)	50 (9)	49 (9)	14 (3)	34 (6)	19 (3)	9 (2)	23 (4)	18 (4)
Marked	16 (3)	8 (1)	5 (1)	12 (2)	16 (3)	24 (4)	14 (3)	17 (3)	13 (2)	12 (2)	14 (3)	5 (1)	4 (1)	9 (2)	6 (1)
Missing	1	5	2	3	1	2	3	0	0	0	2	1	0	5	1
Breast oversensitive															
None	307 (53)	312 (53)	283 (48)	238 (44)	213 (38)	214 (38)	238 (45)	197 (37)	224 (41)	268 (51)	247 (47)	253 (47)	265 (53)	255 (49)	268 (52)
Mild	215 (37)	230 (39)	241 (41)	216 (40)	262 (47)	256 (46)	225 (43)	257 (48)	244 (44)	209 (40)	216 (41)	224 (42)	189 (38)	206 (40)	197 (39)
Moderate	41 (7)	29 (5)	53 (9)	67 (13)	61 (11)	61 (11)	50 (9)	62 (11)	59 (11)	34 (6)	55 (10)	42 (8)	32 (6)	40 (8)	34 (7)
Marked	16 (3)	13 (2)	9 (2)	15 (3)	26 (5)	27 (5)	15 (3)	23 (4)	21 (4)	14 (3)	13 (2)	17 (3)	17 (3)	16 (3)	11 (2)
Missing	5	10	5	5	1	4	2	3	4	2	1	4	3	4	4
Skin problems on breast															
None	457 (78)	471 (80)	462 (78)	360 (67)	374 (66)	373 (67)	369 (70)	379 (70)	396 (72)	387 (73)	369 (70)	408 (76)	403 (80)	389 (75)	417 (82)
Mild	99 (17)	95 (16)	110 (19)	134 (25)	140 (25)	142 (25)	121 (23)	106 (20)	112 (20)	109 (21)	118 (22)	96 (18)	78 (15)	90 (17)	71 (14)
Moderate	21 (4)	18 (3)	11 (2)	30 (6)	36 (6)	31 (6)	22 (4)	38 (7)	30 (5)	20 (4)	29 (5)	23 (4)	14 (3)	22 (4)	16 (3)
Marked	5 (1)	6 (1)	7 (1)	15 (3)	13 (2)	13 (2)	16 (3)	16 (3)	14 (3)	11 (2)	14 (3)	9 (2)	9 (2)	15 (3)	7 (1)
Missing	2	4	1	2	0	3	2	3	0	0	2	4	2	5	3
Arm/ shoulder pain															
None	279 (48)	296 (50)	290 (49)	224 (42)	217 (39)	218 (39)	229 (43)	212 (39)	212 (38)	250 (48)	253 (48)	262 (49)	254 (50)	261 (50)	255 (50)

	Baseline			3 months			6 months			12 months			24 months		
	40 Gy N=584	27 Gy N=594	26 Gy N=591	40 Gy N=541	27 Gy N=563	26 Gy N=562	40 Gy N=530	27 Gy N=542	26 Gy N=552	40 Gy N=527	27 Gy N=532	26 Gy N=540	40 Gy N=506	27 Gy N=521	26 Gy N=514
Mild	237 (41)	217 (37)	218 (37)	213 (40)	233 (42)	239 (43)	212 (40)	221 (41)	241 (44)	206 (39)	206 (39)	185 (34)	177 (35)	165 (32)	166 (32)
Moderate	43 (7)	63 (11)	63 (11)	78 (14)	83 (15)	81 (14)	65 (12)	80 (15)	75 (14)	52 (10)	60 (11)	64 (12)	55 (11)	63 (12)	68 (13)
Marked	23 (4)	15 (2)	18 (3)	24 (4)	27 (5)	23 (4)	20 (4)	29 (5)	24 (4)	18 (3)	12 (2)	26 (5)	20 (4)	30 (6)	24 (5)
Missing	2	3	2	2	3	1	4	0	0	1	1	3	0	2	1
Arm/hand swollen															
None	501 (86)	516 (88)	507 (86)	451 (84)	473 (84)	477 (85)	447 (85)	446 (82)	464 (84)	448 (85)	449 (85)	445 (83)	428 (85)	430 (83)	431 (84)
Mild	57 (10)	55 (9)	61 (10)	68 (13)	67 (12)	58 (10)	61 (11)	72 (13)	61 (11)	61 (12)	65 (12)	64 (12)	53 (11)	66 (13)	55 (11)
Moderate	14 (2)	11 (2)	19 (3)	15 (3)	19 (3)	20 (4)	12 (2)	19 (4)	16 (3)	6 (1)	12 (2)	16 (3)	15 (3)	18 (3)	17 (3)
Marked	10 (2)	6 (1)	3 (1)	5 (1)	3 (1)	4 (1)	9 (2)	4 (1)	9 (2)	10 (2)	5 (1)	11 (2)	7 (1)	6 (1)	9 (2)
Missing	2	6	1	2	1	3	1	1	2	2	1	4	3	1	2
Difficulty raising arm															
None	429 (74)	443 (75)	422 (72)	354 (66)	361 (64)	379 (68)	345 (65)	313 (58)	347 (63)	381 (73)	376 (71)	383 (71)	379 (75)	363 (70)	375 (74)
Mild	126 (22)	110 (19)	128 (22)	143 (27)	155 (28)	137 (24)	142 (27)	171 (32)	160 (29)	118 (22)	125 (24)	117 (22)	95 (19)	113 (22)	104 (20)
Moderate	15 (3)	25 (4)	28 (5)	29 (5)	36 (6)	37 (7)	28 (5)	40 (7)	38 (7)	17 (3)	27 (5)	29 (5)	22 (4)	28 (5)	21 (4)
Marked	12 (2)	11 (2)	9 (1)	9 (2)	8 (1)	7 (1)	13 (3)	17 (3)	7 (1)	9 (2)	3 (1)	9 (2)	8 (2)	16 (3)	10 (2)
Missing	2	5	4	6	3	2	2	1	0	2	1	2	2	1	4

Denominators in column headings show the total number of questionnaires returned at each time-point. Denominators for individual symptoms may vary due to missing items on the questionnaire; percentages are calculated out of totals with data available for each item.

Table 42: Locoregional and distant relapses by patient subgroups at randomisation and fractionation schedule in the Main Trial

Subgroup	Ipsilateral breast tumour relapse			Regional relapse			Distant relapse		
	40 Gy / 15 Fr N=31	27 Gy / 5 Fr N=27	26 Gy / 5 Fr N=21	40 Gy / 15 Fr N=13	27 Gy / 5 Fr N=11	26 Gy / 5 Fr N=10	40 Gy / 15 Fr N=59	27 Gy / 5 Fr N=69	26 Gy / 5 Fr N=76
Age at randomisation									
<50	3	7	4	6	4	2	8	20	18
≥50	28	20	17	7	7	8	51	49	58
Grade									
1	2	3	4	1	0	0	2	2	2
2	9	9	9	7	3	4	20	24	30
3	20	15	8	5	8	6	37	43	44
ER / HER2 status									
ER+ / HER2+	3	4	1	0	2	1	6	7	9
ER+ / HER2-	17	15	16	9	3	4	36	44	42
ER- / HER2+	1	3	1	0	3	0	0	5	5
ER- / HER2-	10	5	3	3	3	5	16	13	18
Unknown	0	0	0	1	0	0	1	0	2

Denominators representing numbers at risk for subgroups are in Table 4.

Main Trial Cost-Effectiveness Analysis

Table 43: Loco-regional relapse coefficients for exponential survival model. All results are on the log scale.

Model	Constant		Subgroup 2		Treatment	
	Mean	SE	Mean	SE	Mean	SE
Exponential	-4.9097	0.1736	-0.6557	0.2566	-0.3878	0.2414

SE = standard error.

Table 44: Loco-regional relapse variance covariance matrix for exponential survival model. All results are on the log scale.

Exponential variance-covariance matrix			
	Treatment	Subgroup 2	Constant
Treatment	0.0582923		
Subgroup 2	0.00001	0.065863	
Constant	-0.023813	0.020412	0.030136

Table 45: Loco-regional relapse coefficients for log-normal survival model. All results are on the log scale.

Model	Constant		Subgroup 2		Treatment		Sigma	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Log-normal	5.7267	0.5110	0.7109	0.2649	0.4814	0.2533	0.8032	0.1141

SE = standard error.

Table 46: Loco-regional relapse variance covariance matrix for log-normal survival model. All results are on the log scale.

	Log-normal variance-covariance matrix			
	Treatment	Subgroup 2	Constant	Sigma
Treatment	0.064143	-	-	-
Subgroup 2	0.0038388	0.070187	-	-
Constant	0.0030285	0.007884	0.2611	-
Sigma	0.0066437	0.007125	0.0546	0.01302

Table 47: Distant relapse coefficients for exponential survival model. All results are on the log scale.

Model	Constant		Subgroup 2		Treatment	
	Mean	SE	Mean	SE	Mean	SE
Exponential	-4.3506	0.1347	-1.6704	0.2475	0.2429	0.1735

SE = standard error.

Table 48: Distant relapse variance covariance matrix for exponential survival model. All results are on the log scale.

Exponential variance-covariance matrix

	Treatment	Subgroup 2	Constant
Treatment	0.0301071		
Subgroup 2	-0.00007	0.061252	
Constant	-0.01694	-0.008583	0.018152

Table 49: Distant relapse coefficients for log-normal survival model. All results are on the log scale.

Model	Constant		Subgroup 2		Treatment		Sigma	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Log-normal	5.0030	0.3101	1.5875	0.2485	-0.2730	0.1862	0.7769	0.0775

SE = standard error.

Table 50: Distant relapse variance covariance matrix for log-normal survival model. All results are on the log scale.

	Log-normal variance-covariance matrix			
	Treatment	Subgroup 2	Constant	Sigma
Treatment	0.034668	-	-	-
Subgroup 2	-0.00332	0.061755	-	-
Constant	-0.0242	0.019531	0.096166	-
Sigma	-0.00162	0.008413	0.021288	0.006011

Table 51: FAST-Forward costing of resource use

Resource use questionnaire			
Question	**Unit cost**	**Explanation**	**Source**
How many times have you been visited by your GP for any reason?	£167.99	GP visit unit cost is £134.89 which includes travel time. Curtis et al., 2010 (PSSRU) used as not reported in more recent publications. Add to this average prescription cost per consultation £33.10 (Curtis et al., 2019).	[141] p167 (inflated), [69] p119
How many times have you visited your GP for any reason?	£72.10	GP surgery consultation unit cost £39 plus average prescription costs per visit £33.10.	[69] p119
How many times have you been visited by a district nurse?	£32.50	District Nurse cost £44.22 per hour according to Curtis et al., 2018 (PSSRU) (inflated), Curtis et al., 2010 (PSSRU) reports face to face home visit for community nurse (includes district nurse) takes 20 minutes. Ratio of indirect to direct time for home visits is reported to be 1:1.21 resulting in total time 44.2 mins and cost £30.76 (this includes travel time). Curtis et al., 2010 (PSSRU) also reported travel costs of £1.74 (inflated) per visit.	[142] p18; [141] p159
How many times have you been visited by a MacMillan nurse?	£23.10	Nurses cost £29 per hour according to MacMillan (2019) costing document. Curtis et al., 2010 (PSSRU) reports face to face home visit for community nurse takes 20 minutes. Ratio of indirect to direct time for home visits is reported to be 1:1.21 resulting in total time 44.2 mins and cost £21.36 (this includes travel time). Curtis et al., 2010 (PSSRU) also reported travel costs of £1.74 (inflated) per visit.	[143] [141] p159
How many days have you spent in hospital related to your breast cancer?	£378.90	Activity weighted average of elective and non-elective cost per day for Malignant Breast Disorders with and without Interventions reported in 2018/19 reference costs. Includes Elective Inpatients, Non Elective Inpatients, Non-Elective Short Stay, Day Case and Regular Day or Night Admissions.	[80] JA12D, JA12E, JA12F, JA12G, JA12H, JA12J, JA12K, JA12L
How many days have you spent in hospital for other reasons?	£568.88	Activity weighted average of elective and non-elective inpatient costs per day reported in 2018/19 reference costs.	[73]
How many hospital outpatient visits have you had related to breast cancer?	£94.93	Activity weighted average of outpatient procedure costs in clinical oncology (previously radiotherapy) reported in 2018/19 reference costs.	[73]
How many hospital outpatient visits have you had for other reasons?	£148.00	Weighted average of cost for all outpatient attendances reported in 2018/19 reference costs.	[73]

Table 52: Descriptive statistics for alive and disease-free health state

Variable	Alive and disease free				
	Obs	Mean	Std Err	Min	Max
3 month total costs					
Month 6	1,035	£556	£1,293	£0	£24,255
Year 1	1,030	£340	£445	£0	£4,682
Year 2	972	£329	£638	£0	£13,720
Year 5	821	£295	£533	£0	£7,991

Std Err=standard error. All results pertain to average costs over a 3 month period to adjust for differences in recall period.

Table 53: Summary statistics for quality of life in alive and disease free health state.

Variable	Alive and disease free				
	Obs	Mean	SE	Min	Max
EQ-5D-3L utility score (cross-walked)					
Baseline	1,146	0.800	0.174	-0.209	1
Month 3	1,044	0.778	0.180	-0.181	1
Month 6	1,052	0.770	0.186	-0.594	1
Year 1	1,050	0.788	0.191	-0.594	1
Year 2	974	0.777	0.196	-0.161	1
Year 5	811	0.782	0.215	-0.594	1

SE=standard error.

Nodal Sub-Study

Table 54: Patient-reported effects in arm / shoulder / hand at baseline by maximal extent of axillary surgery in Nodal Sub-Study

Arm / shoulder / hand effect	All randomised patients				Patients randomised up to end 2017			
	40 Gy N=181		26 Gy N=182		40 Gy N=108		27 Gy N=103	
	Axillary sampling N=74 (%)	Axillary clearance N=107 (%)	Axillary sampling N=90 (%)	Axillary clearance N=91 (%)	Axillary sampling N=41 (%)	Axillary clearance N=67 (%)	Axillary sampling N=48 (%)	Axillary clearance N=56 (%)
Swollen arm or hand (EORTC QLQ-BR23)								
Not at all	61 (84)	83 (78)	78 (87)	61 (68)	34 (83)	53 (79)	39 (83)	48 (86)
A little	9 (12)	20 (19)	6 (7)	20 (22)	5 (12)	10 152)	6 (13)	7 (13)
Quite a bit	1 (1)	3 (3)	3 (3)	5 (6)	0 (0)	3 (4)	2 (4)	1 (2)
Very much	2 (3)	1 (<1)	3 (3)	4 (4)	2 (5)	1 (1)	0 (0)	0 (0)
Missing	1	0	0	1	1	0	1	0
Pain in arm or shoulder (EORTC QLQ-BR23)								
Not at all	38 (52)	27 (25)	41 (46)	31 (35)	21 (52)	15 (22)	22 (47)	16 (29)
A little	27 (37)	62 (58)	33 (37)	34 (38)	14 (34)	37 (55)	15 (32)	30 (54)
Quite a bit	5 (7)	15 (14)	11 (12)	16 (18)	4 (10)	13 (19)	10 (21)	7 (13)
Very much	3 (4)	3 (3)	5 (6)	8 (9)	2 (5)	2 (3)	0 (0)	3 (5)
Missing	1	0	0	2	0	0	0	0
Difficult to raise arm or move it sideways (EORTC QLQ-BR23)								
Not at all	60 (82)	53 (50)	60 (67)	45 (50)	33 (80)	28 (42)	28 (60)	26 (46)
A little	9 (12)	42 (40)	27 (33)	28 (31)	6 (15)	31 (47)	13 (28)	24 (43)
Quite a bit	4 (5)	8 (8)	4 (4)	12 (13)	2 (5)	6 (9)	6 (13)	4 (7)
Very much	0 (0)	3 (3)	2 (2)	5 (6)	0 (0)	1 (2)	0 (0)	2 (4)
Missing	1	1	0	1	0	1	1	0
Shoulder stiffness								
Not at all	63 (86)	60 (56)	62 (70)	53 (60)	36 (88)	39 (58)	30 (64)	29 (52)
A little	9 (12)	40 (37)	23 (26)	25 (28)	5 (12)	24 (36)	12 (26)	22 (39)
Quite a bit	1 (1)	5 (5)	4 (4)	8 (9)	0 (0)	3 (4)	5 (11)	4 (7)
Very much	0 (0)	2 (2)	0 (0)	3 (3)	0 (0)	1 (1)	0 (0)	1 (2)
Missing	1	0	1	2	0	0	1	0
Pins & needles in arm/hand on affected side (protocol-specific item[1])								
Not at all	66 (92)	62 (58)	69 (78)	59 (67)	36 (88)	42 (63)	37 (79)	37 (66)
A little	3 (4)	35 (33)	14 (16)	26 (30)	3 (7)	18 (27)	9 (19)	17 (30)
Quite a bit	2 (3)	5 (5)	6 (8)	0 (0)	1 (2)	2 (3)	0 (0)	1 (2)
Very much	1 (1)	5 (5)	0 (0)	3 (3)	1 (2)	5 (7)	1 (2)	1 (2)
Missing	2	0	1	3	0	0	1	0
Pins & needles in arm/hand on non-affected side (protocol-specific item[1])								

Arm / shoulder / hand effect	All randomised patients				Patients randomised up to end 2017			
	40 Gy N=181		26 Gy N=182		40 Gy N=108		27 Gy N=103	
	Axillary sampling N=74 (%)	Axillary clearance N=107 (%)	Axillary sampling N=90 (%)	Axillary clearance N=91 (%)	Axillary sampling N=41 (%)	Axillary clearance N=67 (%)	Axillary sampling N=48 (%)	Axillary clearance N=56 (%)
Not at all	68 (94)	84 (79)	73 (82)	72 (81)	38 (93)	56 (84)	37 (79)	51 (91)
A little	1 (1)	17 (16)	14 (16)	12 (14)	1 (2)	7 (10)	8 (17)	5 (9)
Quite a bit	2 (3)	1 (<0)	2 (2)	4 (5)	1 (2)	0 (0)	1 (2)	0 (0)
Very much	1 (1)	5	0 (0)	0 (0)	1 (2)	4 (6)	1 (2)	0 (0)
Missing	2	0	1	3	0	0	1	3
Numbness in fingers on affected side (protocol-specific item[1])								
Not at all	65 (90)	80 (75)	72 (81)	64 (73)	37 (90)	49 (73)	37 (79)	35 (63)
A little	3 (4)	13 (12)	11 (12)	22 (25)	3 (7)	7 (10)	8 (17)	16 (29)
Quite a bit	3 (4)	7 (7)	6 (7)	2 (2)	1 (2)	6 (9)	0 02)	3 (5)
Very much	1 (1)	7 (7)	0 (0)	0 (0)	0 (0)	5 (7)	2 (4)	2 (4)
Missing	2	0	1	3	0	0	1	0
Numbness in fingers on non-affected side (protocol-specific item[1])								
Not at all	63 (88)	83 (76)	73 (82)	75 (85)	36 (88)	53 (79)	38 (81)	41 (73)
A little	4 (6)	10 (9)	11 (12)	17 (13)	4 (10)	5 (7)	8 (17)	12 (21)
Quite a bit	4 (6)	6 (6)	5 (6)	1 (1)	1 (2)	4 (6)	0 (0)	1 (2)
Very much	1 (1)	8 (7)	0 (0)	1 (1)	0 (0)	5 (7)	1 (2)	2 (4)
Missing	2	0	1	3	0	0	1	0
Weakness in arm/hand on affected side (protocol-specific item[1])								
Not at all	58 (81)	54 (50)	67 (75)	51 (59)	31 (76)	33 (49)	32 (68)	38 (68)
A little	9 (13)	42 (39)	18 (20)	27 (31)	6 (15)	26 (39)	12 (26)	14 (25)
Quite a bit	5 (6)	7 (7)	2 (2)	7 (8)	4 (10)	4 (6)	2 (4)	3 (5)
Very much	0 (0)	4 (4)	2 (2)	2 (2)	0 (0)	4 (6)	1 (2)	1 (2)
Missing	2	0	1	4	0	0	1	0
Weakness in arm/hand on non-affected side (protocol-specific item[1])								
Not at all	62 (86)	97 (91)	74 (83)	80 (91)	35 (85)	58 (87)	39 (83)	52 (93)
A little	6 (8)	8 (7)	12 (13)	8 (9)	2 (5)	7 (10)	6 (13)	2 (4)
Quite a bit	4 (6)	0 (0)	2 (2)	0 (0)	4 (10)	0 (0)	1 (2)	2 (4)
Very much	0 (0)	2 (2)	1 (1)	0 (0)	0 (0)	2 (3)	1 (2)	0 (0)
Missing	2	0	1	3	0	0	1	0

Discussion

Table 55: Breast clinician and patient assessments in FAST-Forward

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Normal tissue effect	Clinician or patient assessed	Moderate or marked events in 40 Gy at 5 years (%)	Moderate or marked events in 26 Gy at 5 years (%)	Odds ratio comparison with 40 Gy across follow-up[1] (95% CI)	P-value comparison with 40 Gy[2]
Breast distortion	Clinician	32/916 (3.5)	53/955 (5.5)	1.20 (0.91-1.60)	0.19
Breast shrinkage	Clinician	50/916 (5.5)	65/954 (6.8)	1.05 (0.82-1.33)	0.71
Breast induration outside tumour bed	Clinician	1/911 (0.1)	20/955 (2.1)	1.90 (1.15-3.14)	0.013
Breast appearance changed	Patient	140/432 (32.4)	136/429 (31.7)	0.91 (0.75-1.10)	0.33
Breast smaller	Patient	122/428 (28.5)	103/429 (24.0)	0.81 (0.65-1.00)	0.053
Breast harder or firmer	Patient	61/428 (14.2)	74/425 (17.4)	1.22 (1.00-1.48)	0.048

[1]Clinician assessment is longitudinal all years. Patient assessment is longitudinal 3 months to 5 years, adjusting for baseline assessment. [2]Statistical significance defined in the statistical analysis plan for normal tissue endpoints as p<0.005 to allow for multiple testing.

Appendix 3: Additional figures

Main Trial

Figure 20: Recruitment by centre in FAST-Forward Main Trial
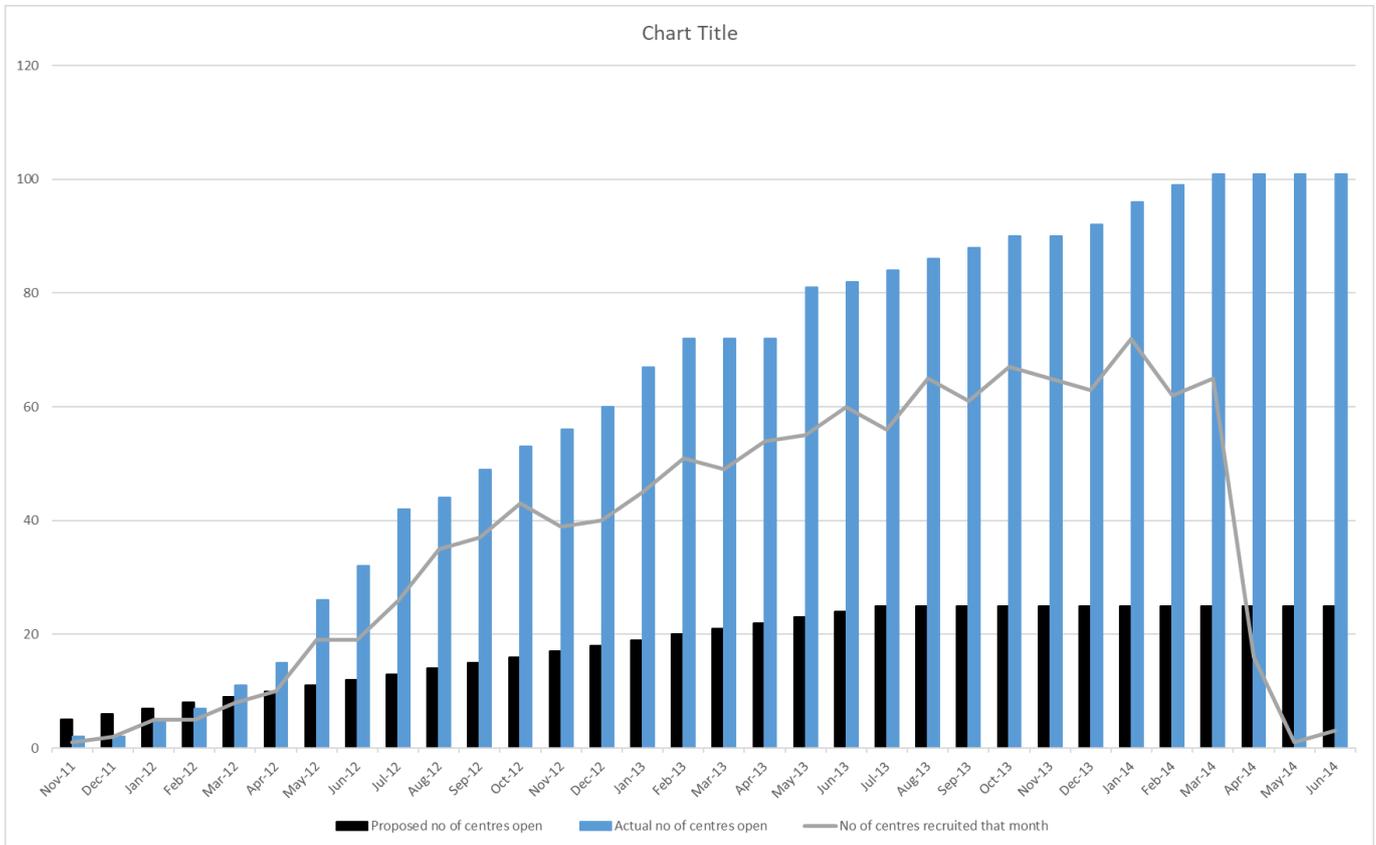
Figure 21: Kaplan-Meier plot of locoregional relapse in Main Trial

Number at risk (events)													
40Gy	1361	(2)	1347	(9)	1306	(9)	1279	(8)	1228	(8)	1043	(5)	485
27Gy	1367	(5)	1351	(8)	1328	(6)	1301	(10)	1249	(2)	1062	(3)	507
26Gy	1368	(5)	1346	(7)	1322	(6)	1298	(4)	1255	(2)	1070	(3)	524
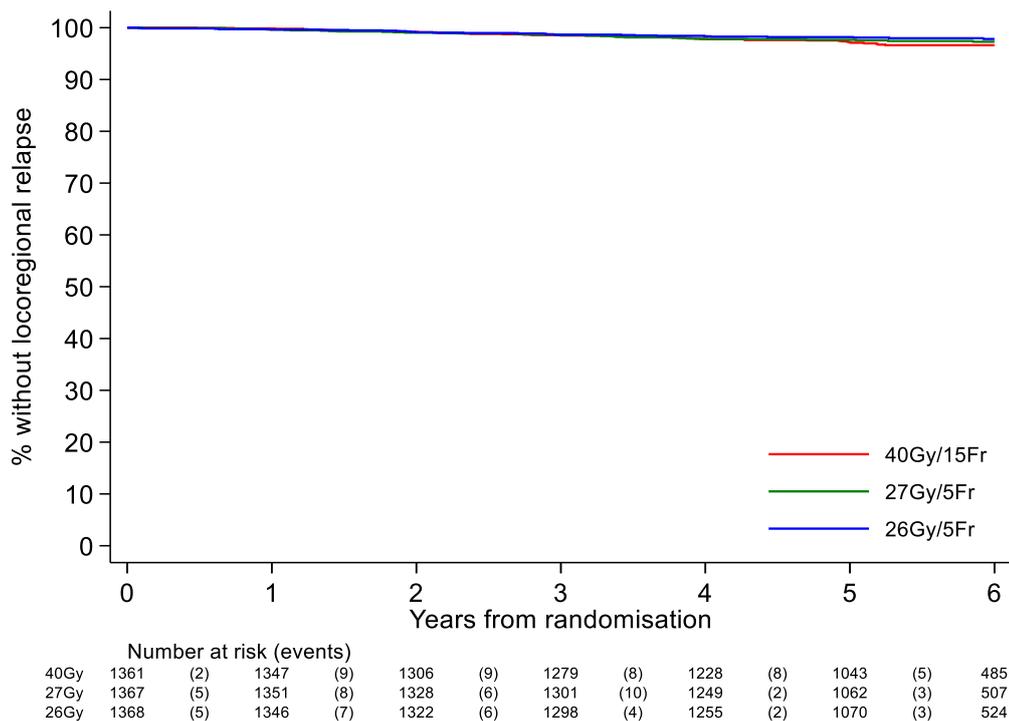
Figure 22: Cumulative risk of locoregional relapse in Main Trial

Number at risk (events)													
40Gy	1361	(2)	1347	(9)	1306	(9)	1279	(8)	1228	(8)	1043	(5)	485
27Gy	1367	(5)	1351	(8)	1328	(6)	1301	(10)	1249	(2)	1062	(3)	507
26Gy	1368	(5)	1346	(7)	1322	(6)	1298	(4)	1255	(2)	1070	(3)	524
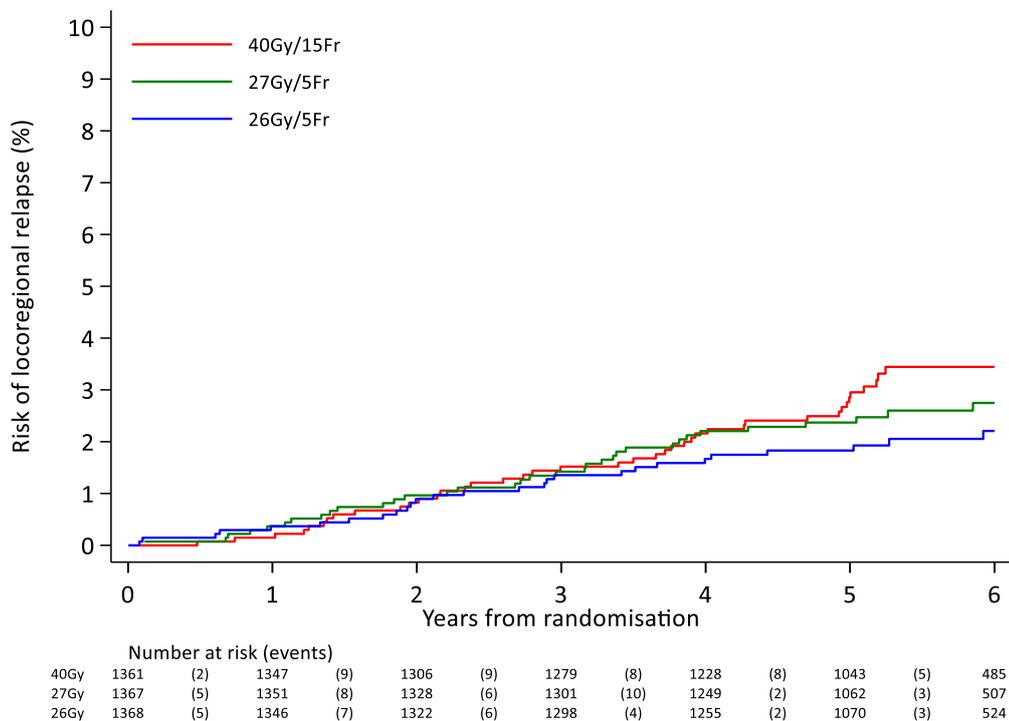
Figure 23: Kaplan-Meier plot of distant relapse in Main Trial

Number at risk (events)

40Gy	1361	(12)	1340	(15)	1301	(10)	1278	(3)	1236	(10)	1050	(6)	491
27Gy	1367	(7)	1353	(16)	1324	(16)	1294	(13)	1250	(11)	1056	(4)	501
26Gy	1368	(10)	1344	(17)	1322	(20)	1292	(16)	1245	(5)	1064	(5)	525
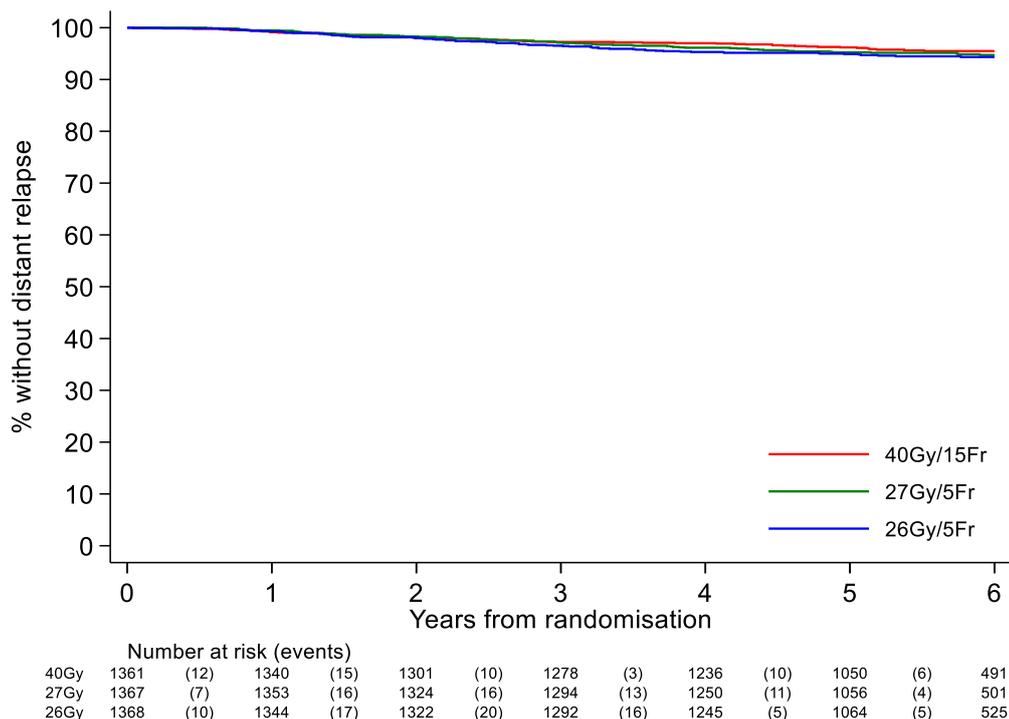
Figure 24: Cumulative risk of distant relapse in Main Trial

Number at risk (events)

40Gy	1361	(12)	1340	(15)	1301	(10)	1278	(3)	1236	(10)	1050	(6)	491
27Gy	1367	(7)	1353	(16)	1324	(16)	1294	(13)	1250	(11)	1056	(4)	501
26Gy	1368	(10)	1344	(17)	1322	(20)	1292	(16)	1245	(5)	1064	(5)	525
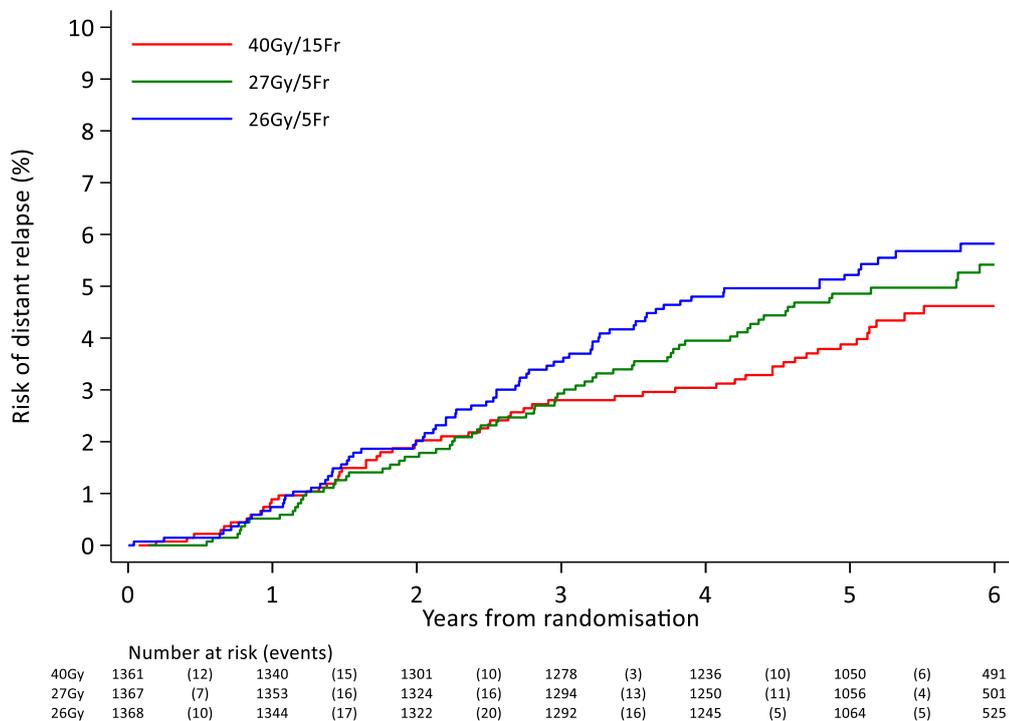
Figure 25: Kaplan-Meier plot of overall survival in Main Trial

Number at risk (events)												
40Gy	1361	(5)	1348	(22)	1312	(12)	1291	(18)	1245	(15)	1062	(15)	494
27Gy	1367	(10)	1356	(18)	1337	(18)	1314	(24)	1271	(23)	1075	(8)	511
26Gy	1368	(5)	1351	(16)	1332	(14)	1310	(20)	1266	(20)	1077	(7)	531
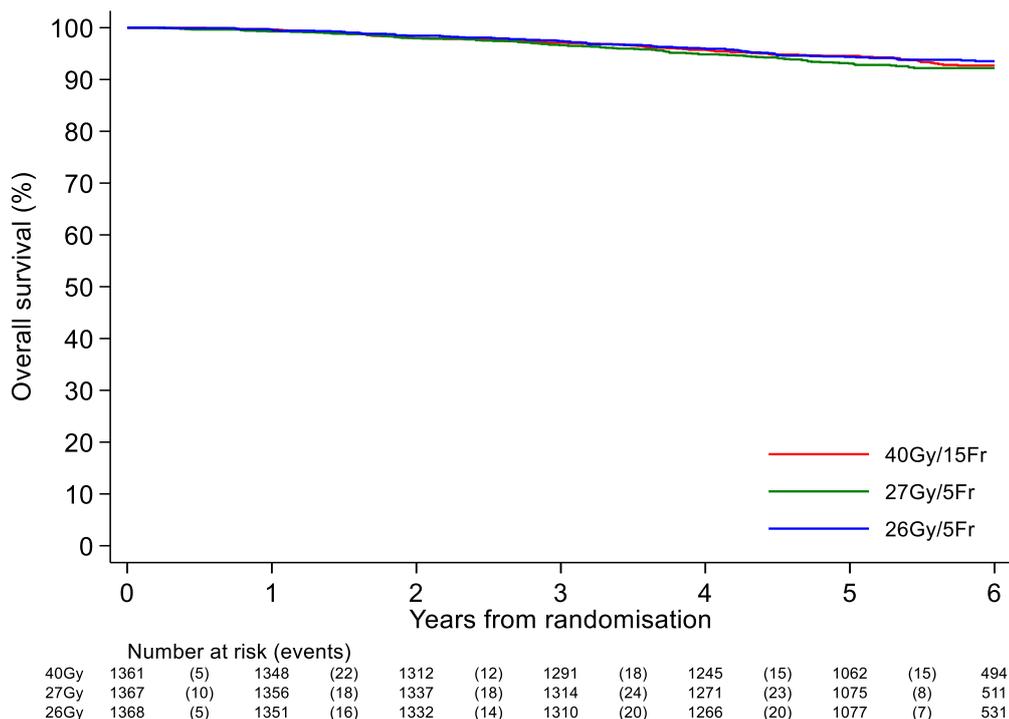
Figure 26: Cumulative risk of death from any cause in Main Trial

Number at risk (events)												
40Gy	1361	(5)	1348	(22)	1312	(12)	1291	(18)	1245	(15)	1062	(15)	494
27Gy	1367	(10)	1356	(18)	1337	(18)	1314	(24)	1271	(23)	1075	(8)	511
26Gy	1368	(5)	1351	(16)	1332	(14)	1310	(20)	1266	(20)	1077	(7)	531
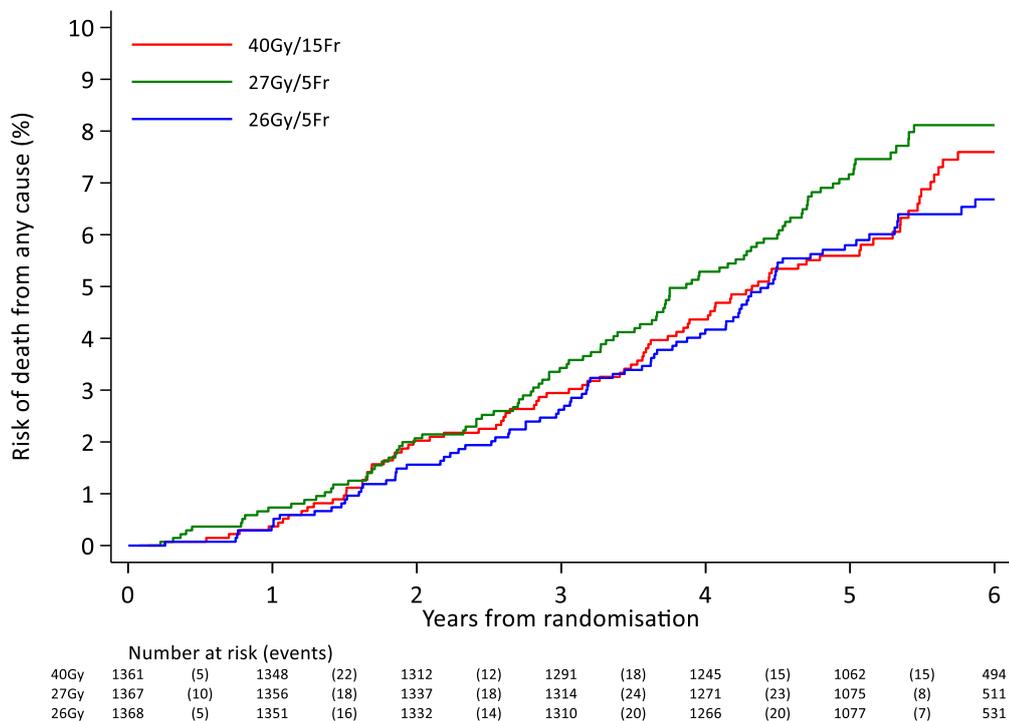
Bar charts of clinical assessments of late normal tissue effects to 5 years

Reproduced from Brunt (2020) (CC BY 4.0)[1]

Figure 27: Clinician-assessed breast distortion from 1-5 years in Main Trial

Number of patients					
40Gy	1081	1078	1014	972	916
27Gy	1131	1128	1063	1009	949
26Gy	1130	1097	1052	1030	955
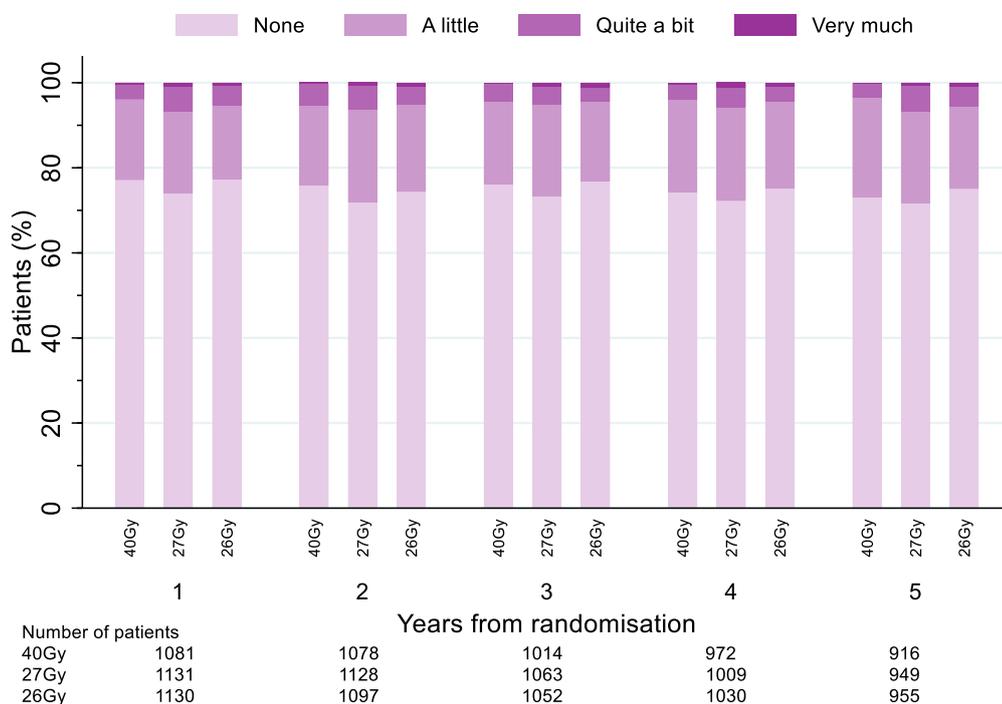
Figure 28: Clinician-assessed breast shrinkage from 1-5 years in Main Trial

Number of patients					
40Gy	1081	1079	1015	973	916
27Gy	1129	1127	1060	1007	948
26Gy	1131	1095	1052	1030	954
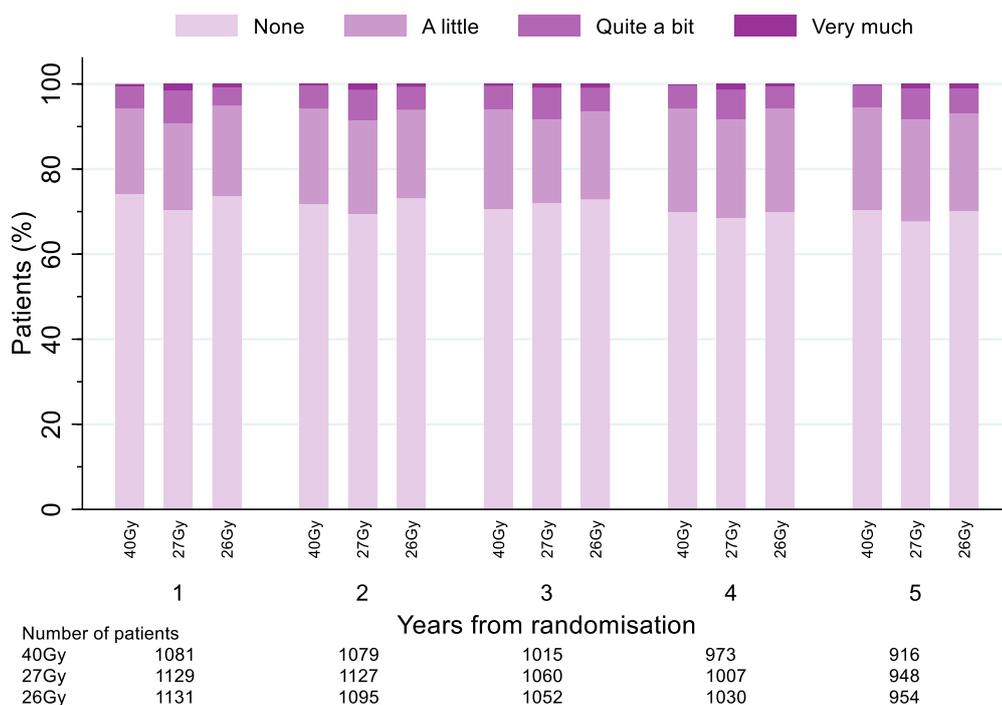
Figure 29: Clinician-assessed breast induration (tumour bed) from 1-5 years in Main Trial

Legend: None | A little | Quite a bit | Very much

Y-axis: Patients (%)
X-axis: Years from randomisation (1, 2, 3, 4, 5)
Each year shows bars for 40Gy, 27Gy, 26Gy

Number of patients

	1	2	3	4	5
40Gy	1081	1075	1008	973	914
27Gy	1129	1129	1059	1009	949
26Gy	1127	1092	1052	1029	956
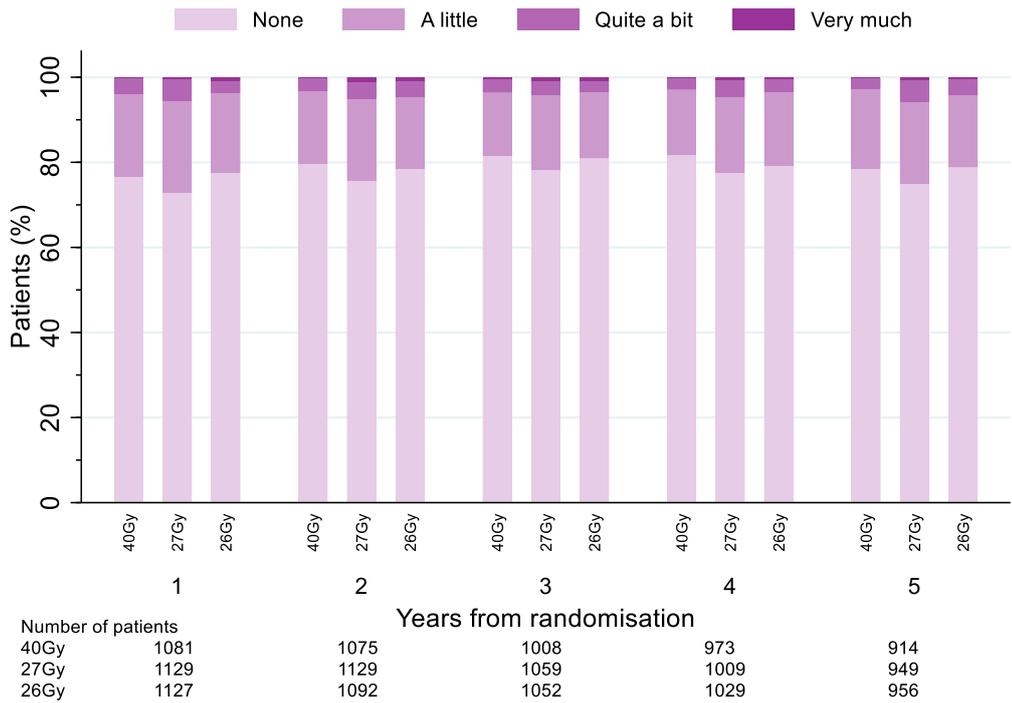
Figure 30: Clinician-assessed breast induration (outside tumour bed) from 1-5 years in Main Trial

Legend: None | A little | Quite a bit | Very much

Y-axis: Patients (%)
X-axis: Years from randomisation (1, 2, 3, 4, 5)
Each year shows bars for 40Gy, 27Gy, 26Gy

Number of patients

	1	2	3	4	5
40Gy	1081	1075	1009	974	911
27Gy	1128	1129	1058	1007	948
26Gy	1122	1093	1051	1028	955
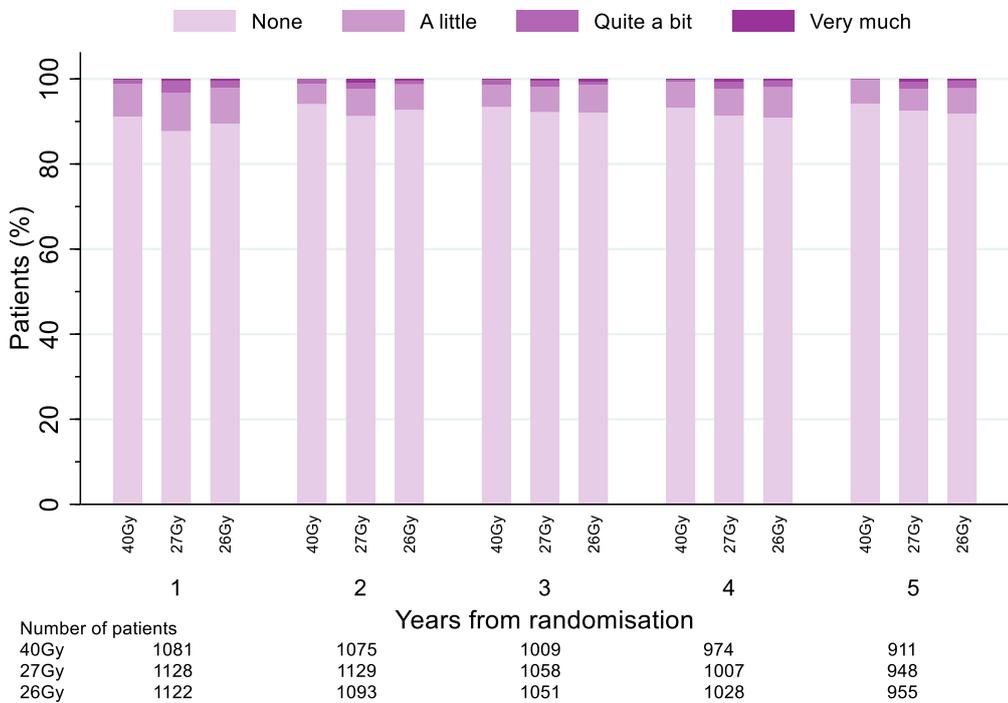
Figure 31: Clinician-assessed telangiectasia from 1-5 years in Main Trial

Legend: None | A little | Quite a bit | Very much

Y-axis: Patients (%)
X-axis: Years from randomisation

Number of patients

	Year 1	Year 2	Year 3	Year 4	Year 5
40Gy	1150	1147	1069	1039	985
27Gy	1189	1190	1117	1069	1004
26Gy	1196	1158	1113	1087	1018
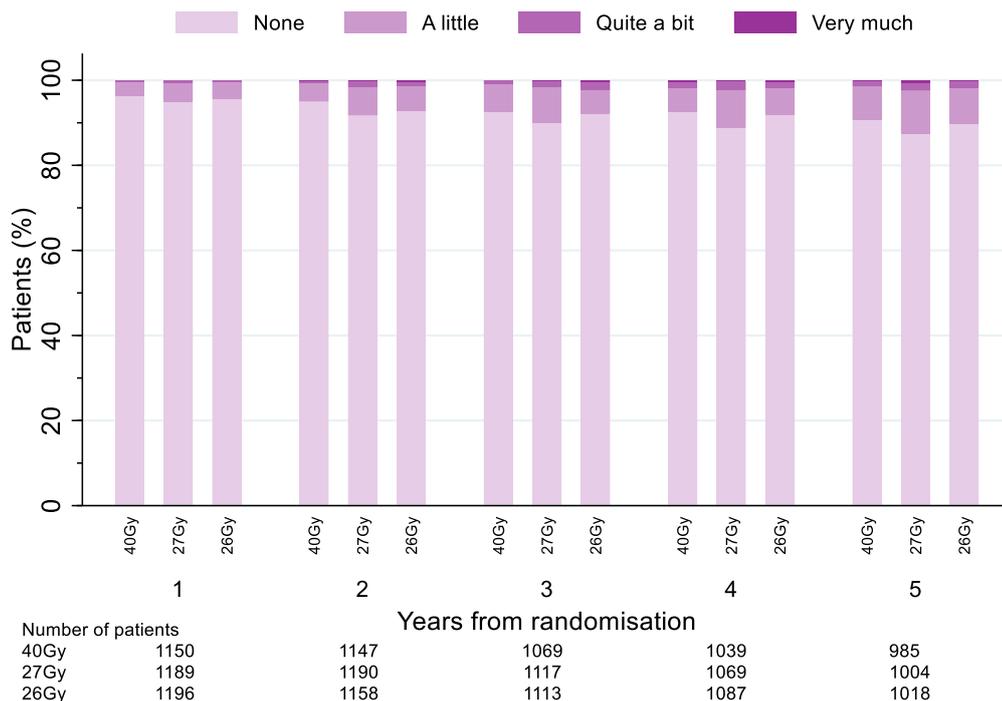
Figure 32: Clinician-assessed breast / chest wall oedema from 1-5 years in Main Trial

Legend: None | A little | Quite a bit | Very much

Y-axis: Patients (%)
X-axis: Years from randomisation

Number of patients

	Year 1	Year 2	Year 3	Year 4	Year 5
40Gy	1157	1146	1070	1042	985
27Gy	1196	1197	1122	1068	1002
26Gy	1202	1163	1118	1088	1018
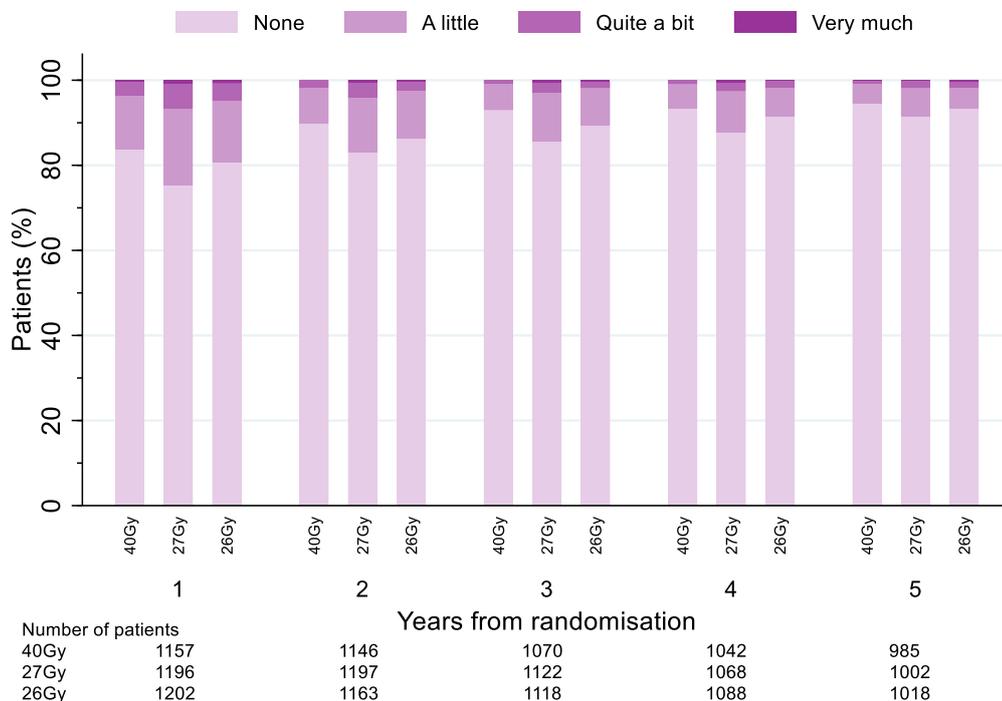
Figure 33: Clinician-assessed breast / chest wall discomfort from 1-5 years in Main Trial

Number of patients
40Gy	1151	1146	1074	1036	983
27Gy	1186	1195	1127	1070	1004
26Gy	1194	1164	1120	1089	1015
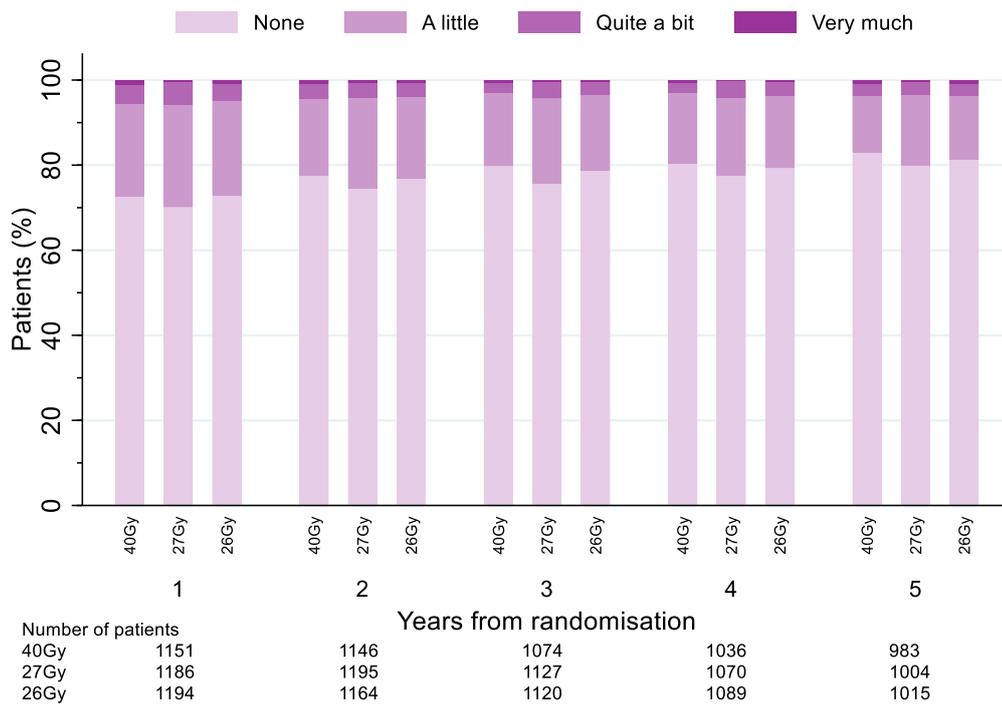
Kaplan-Meier plots for clinician-assessed NTEs in FAST-Forward Main Trial

Reproduced from Brunt (2020) (CC BY 4.0)[1]

Figure 34: Kaplan-Meier plot of clinician-assessed breast distortion (Main Trial)

Number at risk (events)													
40Gy/15Fr	1225	(21)	1199	(29)	1136	(31)	1058	(21)	969	(16)	787	(7)	385
27Gy/5Fr	1265	(27)	1234	(68)	1137	(29)	1058	(18)	968	(21)	775	(19)	361
26Gy/5Fr	1249	(22)	1217	(53)	1146	(27)	1082	(23)	989	(16)	798	(14)	380
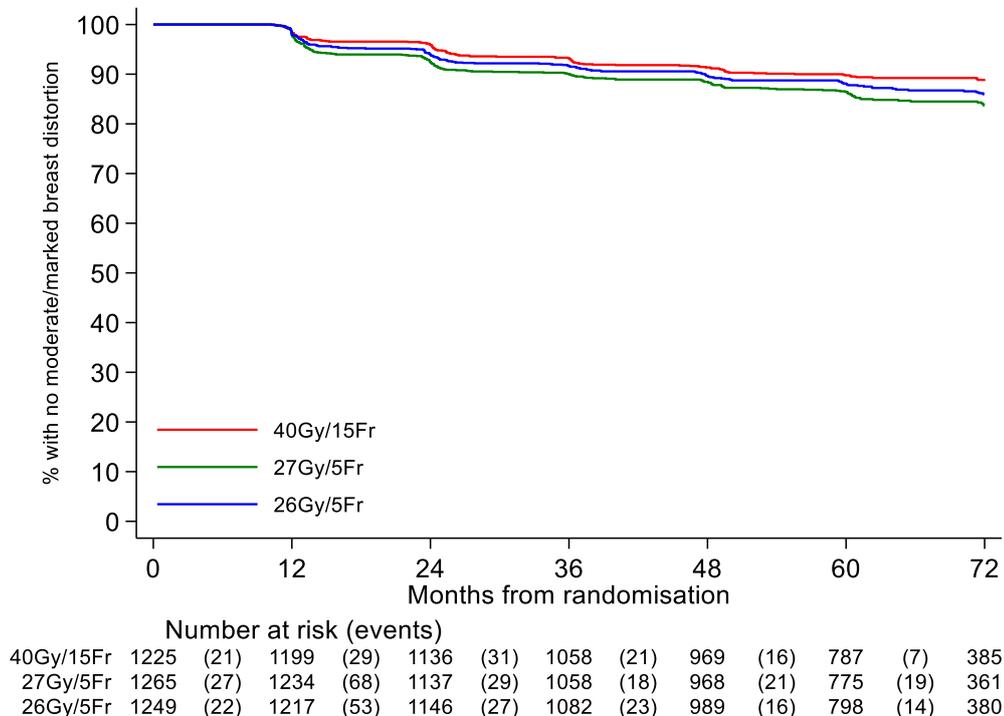
Figure 35: Kaplan-Meier plot of clinician-assessed breast shrinkage (Main Trial)

Number at risk (events)													
40Gy/15Fr	1227	(25)	1195	(51)	1110	(33)	1031	(27)	939	(27)	754	(11)	363
27Gy/5Fr	1265	(30)	1229	(87)	1115	(44)	1022	(23)	932	(23)	745	(23)	350
26Gy/5Fr	1249	(19)	1220	(53)	1149	(30)	1081	(24)	985	(25)	781	(23)	365
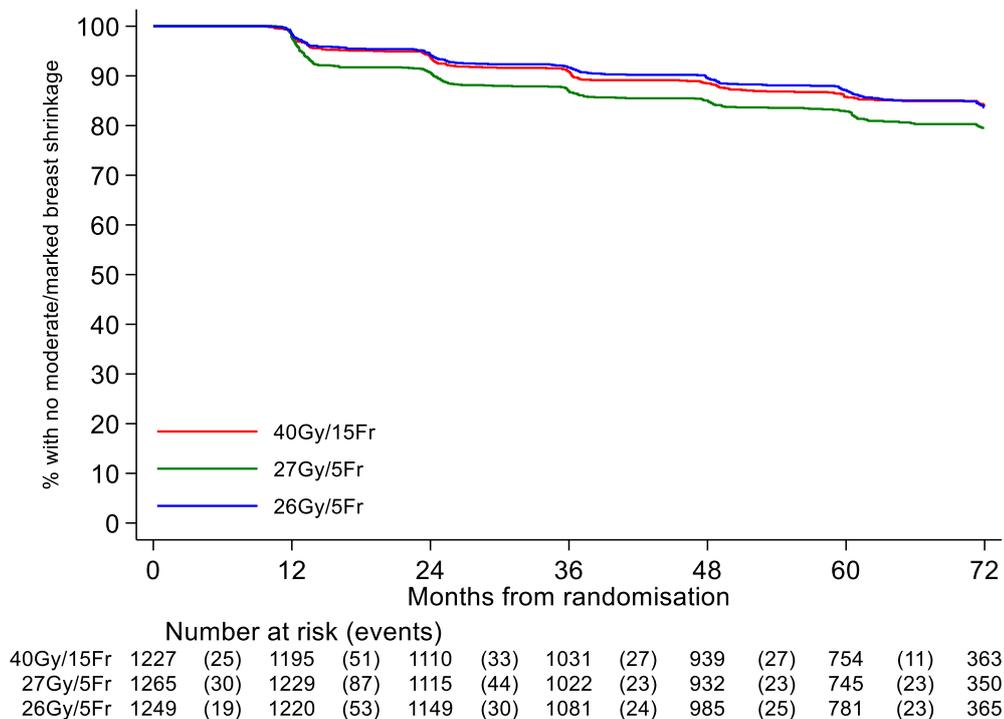
Figure 36: Kaplan-Meier plot of clinician-assessed breast induration (tumour bed) (Main Trial)

Number at risk (events)

40Gy/15Fr	1225	(18)	1201	(35)	1133	(17)	1069	(19)	979	(18)	798	(10)	383
27Gy/5Fr	1266	(15)	1245	(62)	1153	(34)	1067	(18)	975	(21)	778	(19)	363
26Gy/5Fr	1249	(18)	1221	(37)	1165	(22)	1104	(19)	1010	(12)	817	(14)	393
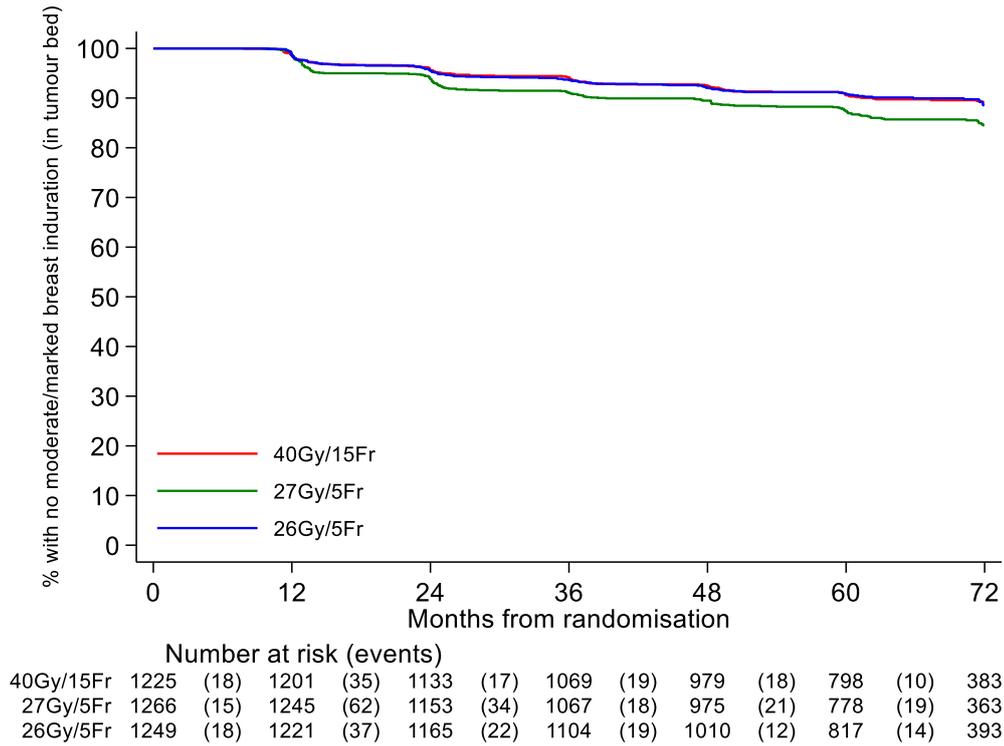
Figure 37: Kaplan-Meier plot of clinician-assessed breast induration (outside tumour bed) (Main Trial)

Number at risk (events)

40Gy/15Fr	1225	(6)	1213	(8)	1170	(8)	1114	(7)	1032	(3)	854	(2)	413
27Gy/5Fr	1266	(11)	1249	(28)	1191	(14)	1124	(8)	1041	(11)	842	(8)	400
26Gy/5Fr	1249	(7)	1232	(16)	1196	(8)	1147	(4)	1066	(8)	869	(7)	418

223
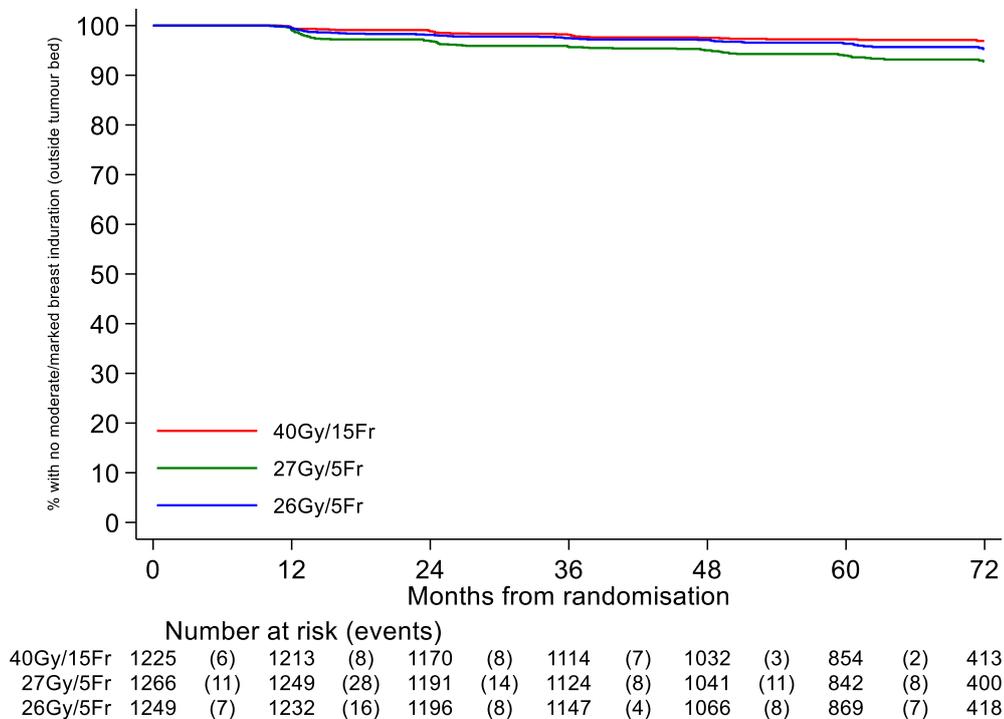
Figure 38: Kaplan-Meier plot of clinician-assessed telangiectasia (Main Trial)

Number at risk (events)

40Gy/15Fr	1305	(2)	1296	(4)	1251	(7)	1190	(9)	1102	(10)	901	(3)	422
27Gy/5Fr	1337	(1)	1329	(11)	1284	(16)	1210	(10)	1119	(12)	907	(8)	432
26Gy/5Fr	1324	(2)	1312	(7)	1281	(16)	1219	(11)	1126	(5)	916	(7)	440
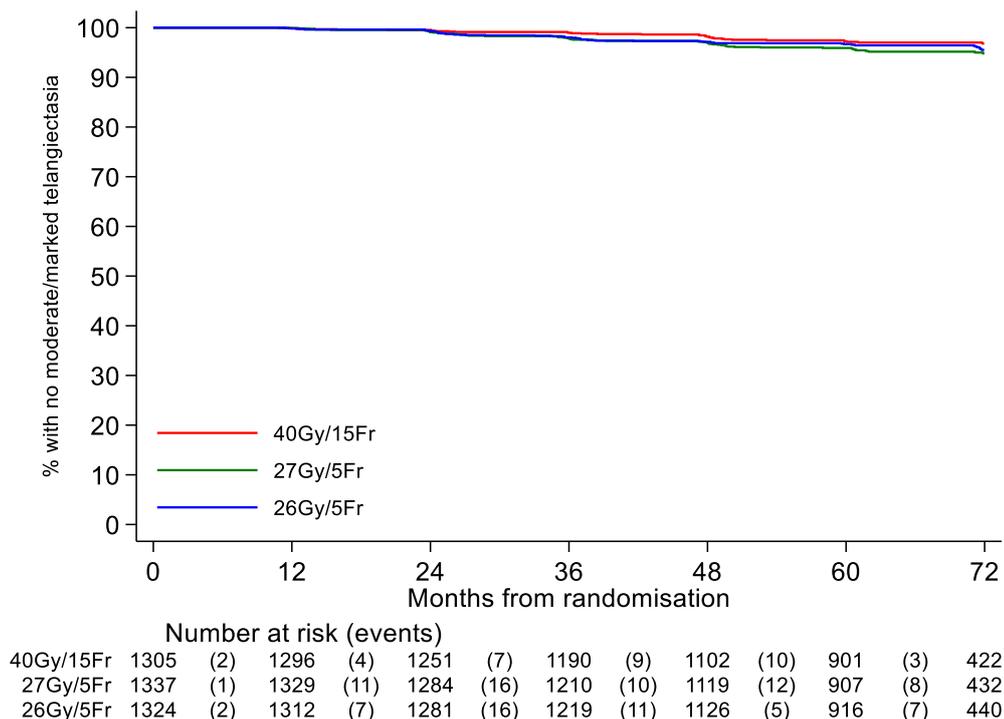
Figure 39: Kaplan-Meier plot of clinician-assessed breast / chest wall oedema (Main Trial)

Number at risk (events)

40Gy/15Fr	1306	(22)	1278	(26)	1216	(8)	1157	(5)	1074	(6)	883	(2)	419
27Gy/5Fr	1339	(25)	1308	(64)	1211	(23)	1135	(10)	1047	(10)	841	(6)	396
26Gy/5Fr	1326	(23)	1293	(40)	1230	(10)	1174	(10)	1087	(8)	882	(5)	427
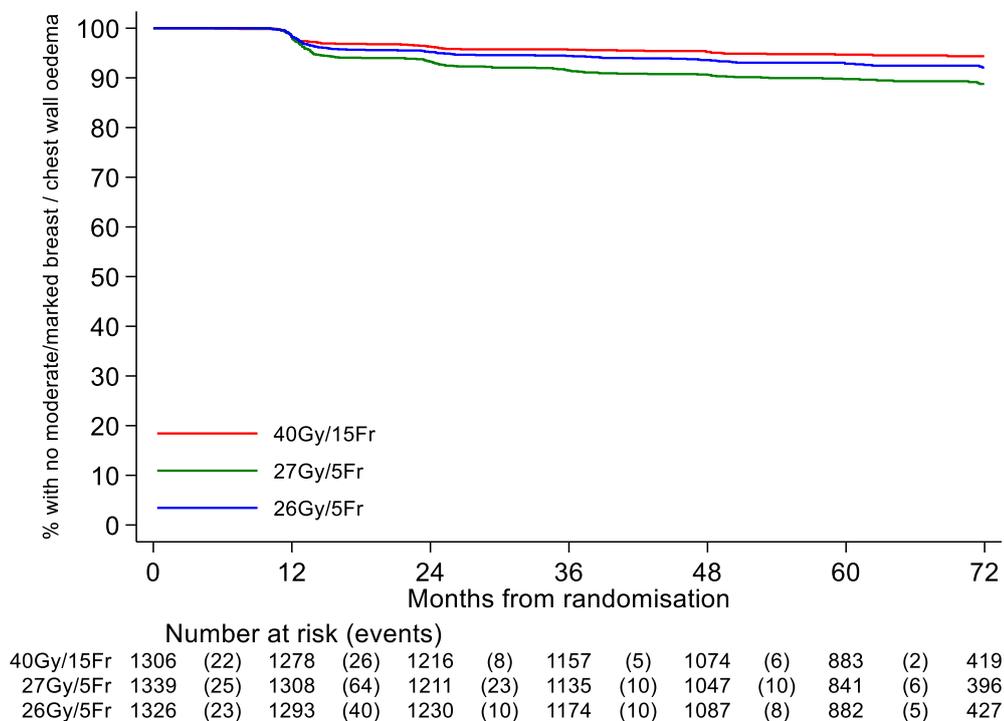
Figure 40: Kaplan-Meier plot of clinician-assessed breast / chest wall discomfort (Main Trial)

Number at risk (events)

40Gy/15Fr	1306	(32)	1268	(46)	1185	(26)	1109	(19)	1013	(18)	822	(12)	388	
27Gy/5Fr	1337	(21)	1311	(59)	1221	(31)	1136	(28)	1036	(21)	824	(14)	388	
26Gy/5Fr	1327	(22)	1296	(51)	1221	(23)	1152	(27)	1046	(20)	839	(7)	409	
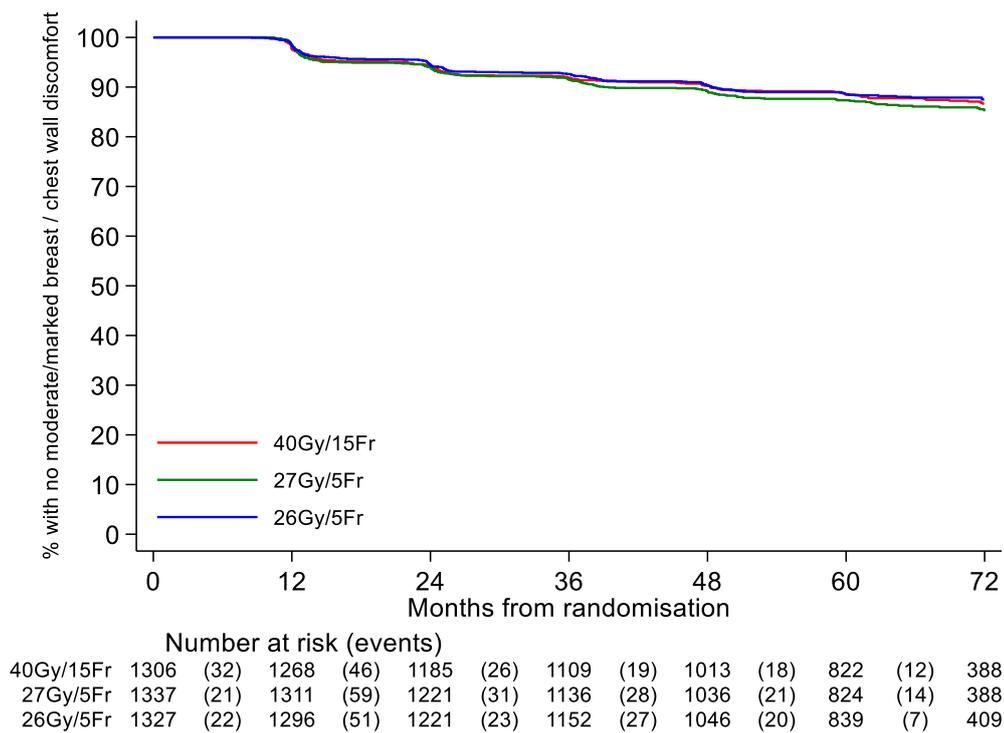
Bar charts for patient-assessed adverse effects to 5 years in the Main Trial

Reproduced from Brunt (2020) (CC BY 4.0)[1]

Figure 41: Patient-assessed pain in arm or shoulder up to 5 years in the Main Trial

Number of patients

	Baseline	3m	6m	12m	24m	60m
40Gy	582	539	526	526	506	440
27Gy	591	560	542	531	519	449
26Gy	589	561	552	537	513	436
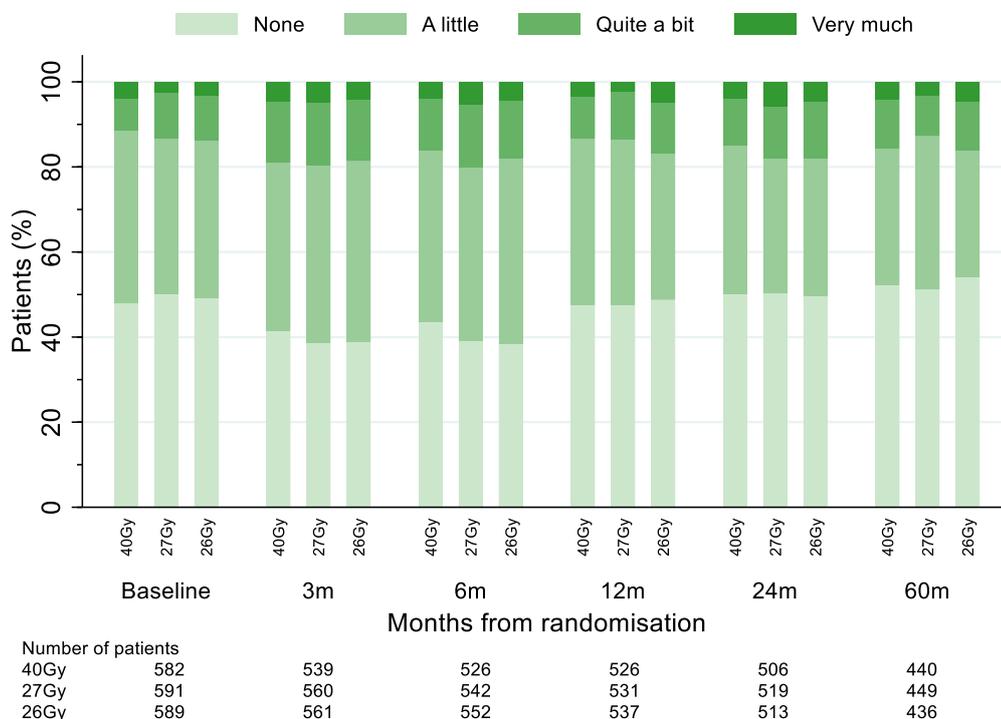
Figure 42: Patient-assessed swollen arm or hand up to 5 years in the Main Trial

Number of patients

	Baseline	3m	6m	12m	24m	60m
40Gy	582	539	529	525	503	440
27Gy	588	562	541	531	520	446
26Gy	590	559	550	536	512	435
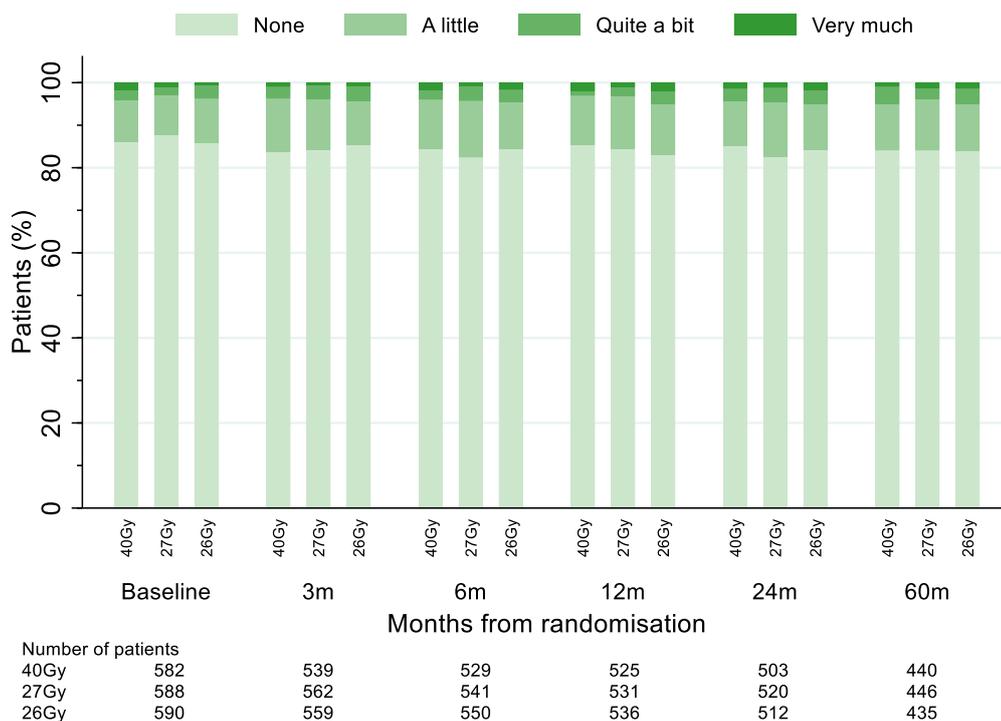
Figure 43: Patient-assessed difficulty raising arm/moving it sideways up to 5 years in the Main Trial

Legend: None | A little | Quite a bit | Very much

Patients (%) — y-axis
Months from randomisation — x-axis

Baseline: 40Gy, 27Gy, 26Gy
3m: 40Gy, 27Gy, 26Gy
6m: 40Gy, 27Gy, 26Gy
12m: 40Gy, 27Gy, 26Gy
24m: 40Gy, 27Gy, 26Gy
60m: 40Gy, 27Gy, 26Gy

Number of patients

	Baseline	3m	6m	12m	24m	60m
40Gy	582	535	528	525	504	441
27Gy	589	560	541	531	520	447
26Gy	587	560	552	538	510	436
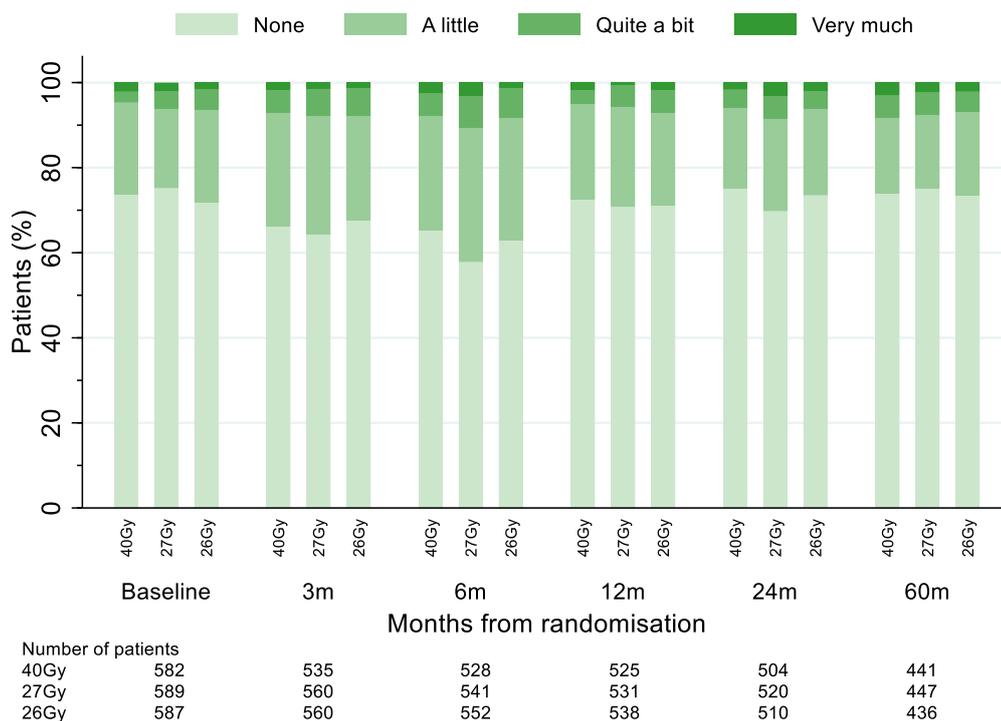
Figure 44: Patient-assessed breast pain up to 5 years in the Main Trial

Legend: None | A little | Quite a bit | Very much

Patients (%) — y-axis
Months from randomisation — x-axis

Baseline: 40Gy, 27Gy, 26Gy
3m: 40Gy, 27Gy, 26Gy
6m: 40Gy, 27Gy, 26Gy
12m: 40Gy, 27Gy, 26Gy
24m: 40Gy, 27Gy, 26Gy
60m: 40Gy, 27Gy, 26Gy

Number of patients

	Baseline	3m	6m	12m	24m	60m
40Gy	583	538	527	526	505	442
27Gy	590	562	542	531	517	449
26Gy	588	560	552	538	511	436
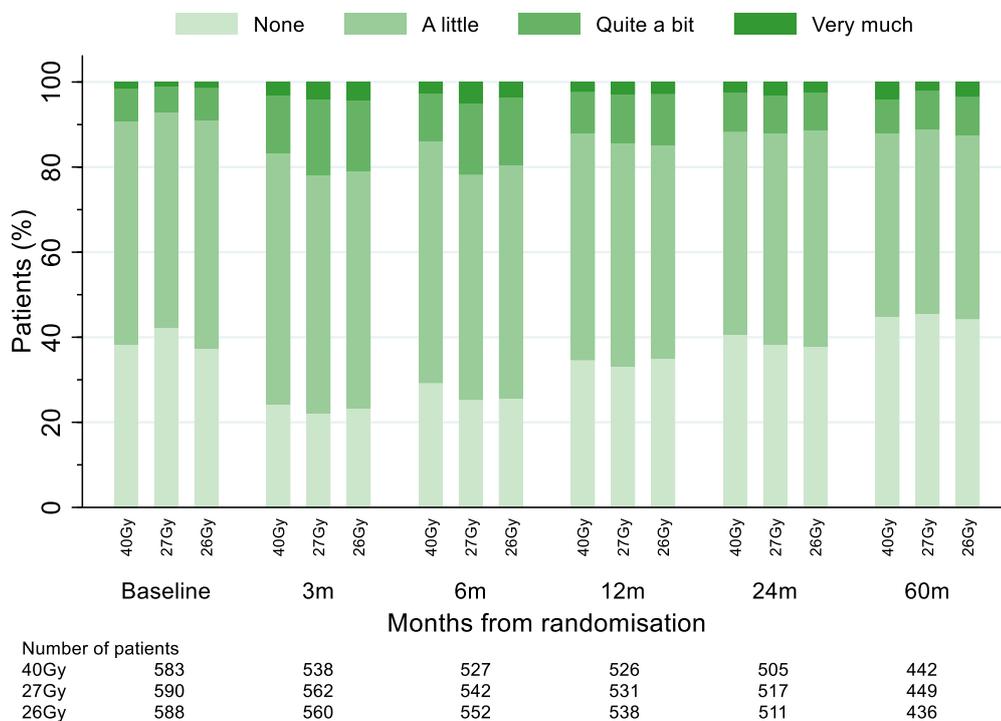
Figure 45: Patient-assessed breast swelling up to 5 years in the Main Trial

Number of patients						
	Baseline	3m	6m	12m	24m	60m
40Gy	583	538	527	527	506	440
27Gy	589	562	542	530	516	447
26Gy	589	560	552	539	513	435
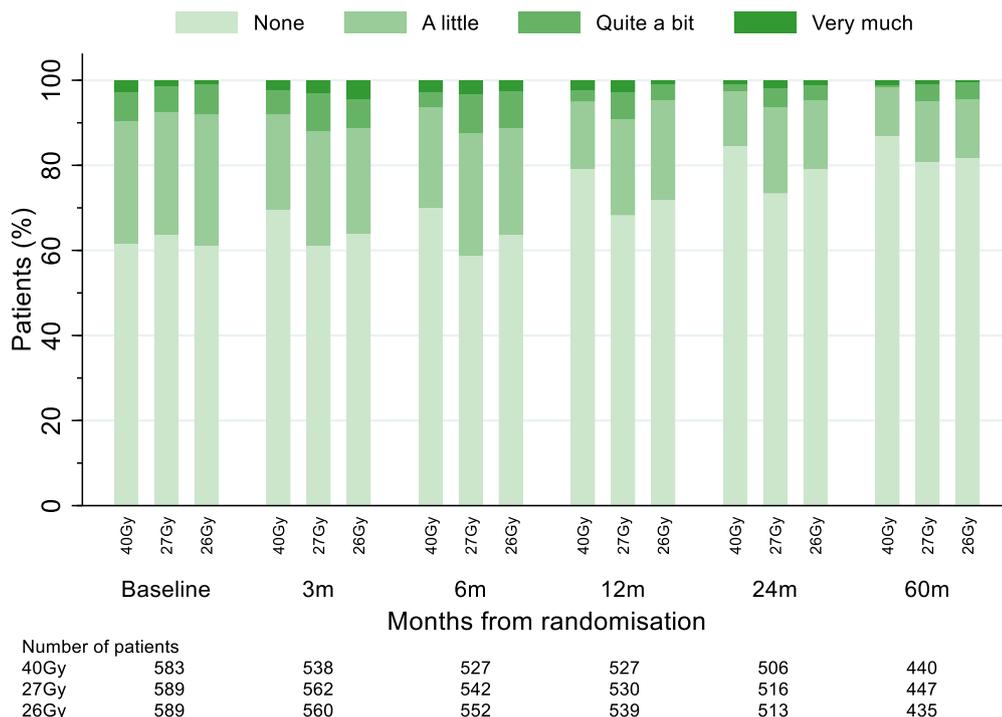
Figure 46: Patient-assessed breast oversensitivity up to 5 years in the Main Trial

Number of patients						
	Baseline	3m	6m	12m	24m	60m
40Gy	579	536	528	525	503	436
27Gy	584	562	539	531	517	447
26Gy	586	558	548	536	510	435
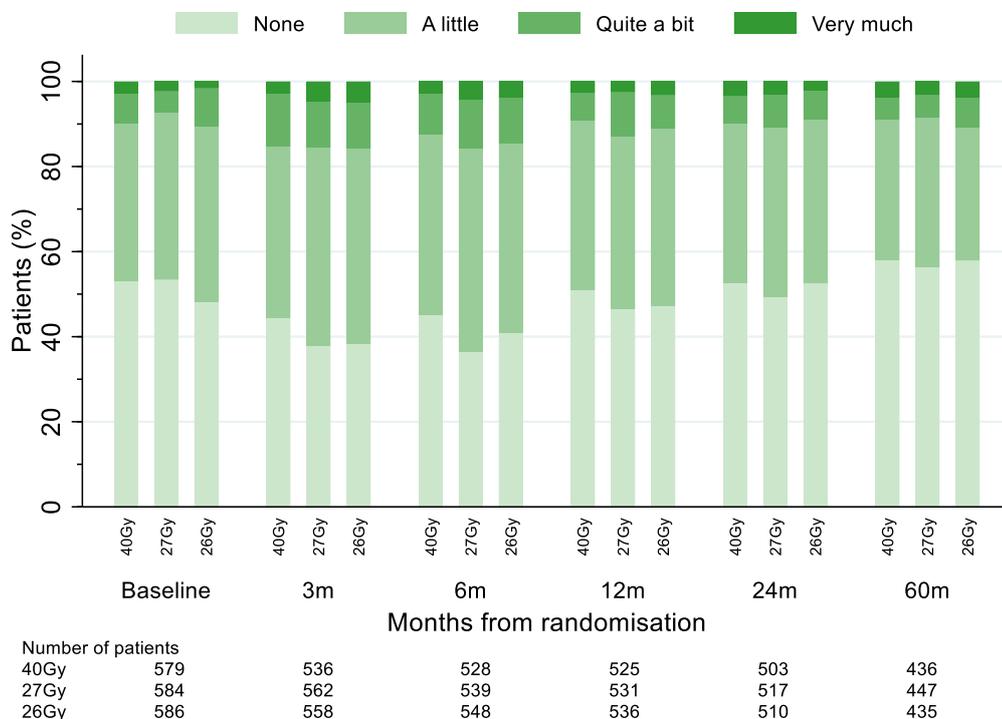
Figure 47: Patient-assessed skin problems on affected breast up to 5 years in the Main Trial

Number of patients

	Baseline	3m	6m	12m	24m	60m
40Gy	582	539	528	527	504	441
27Gy	590	563	539	530	516	448
26Gy	590	559	552	536	511	434
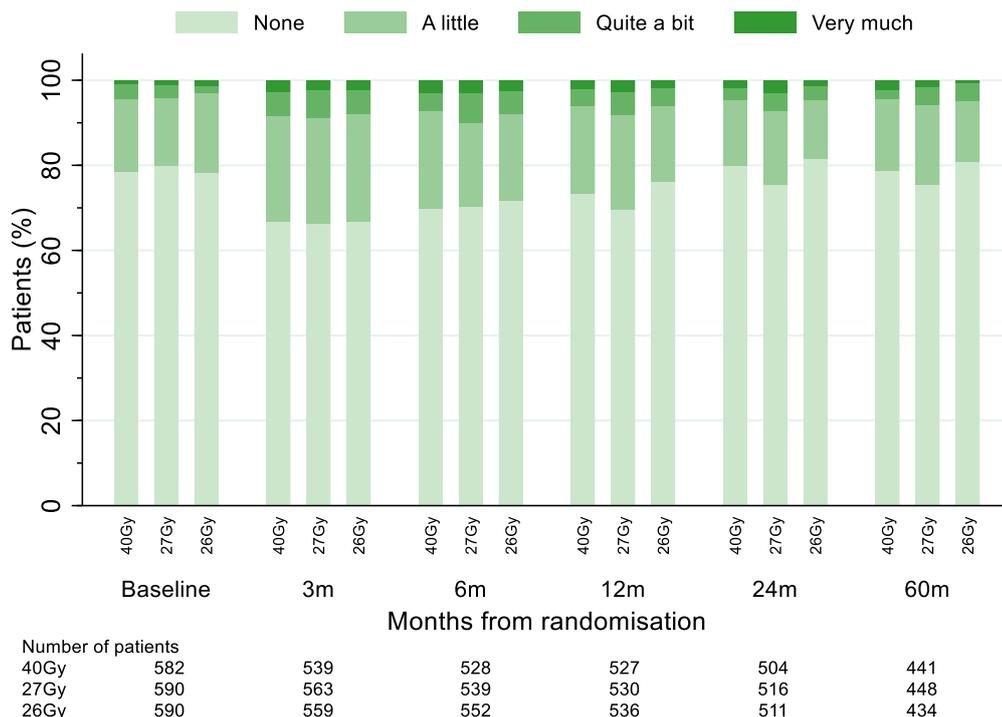
**Figure 48: Patient-assessed change in skin appearance on affected breast up to 5 years in the Main Trial**

Number of patients

	Baseline	3m	6m	12m	24m	60m
40Gy	577	535	523	518	495	434
27Gy	586	556	533	526	512	444
26Gy	580	558	546	534	507	431
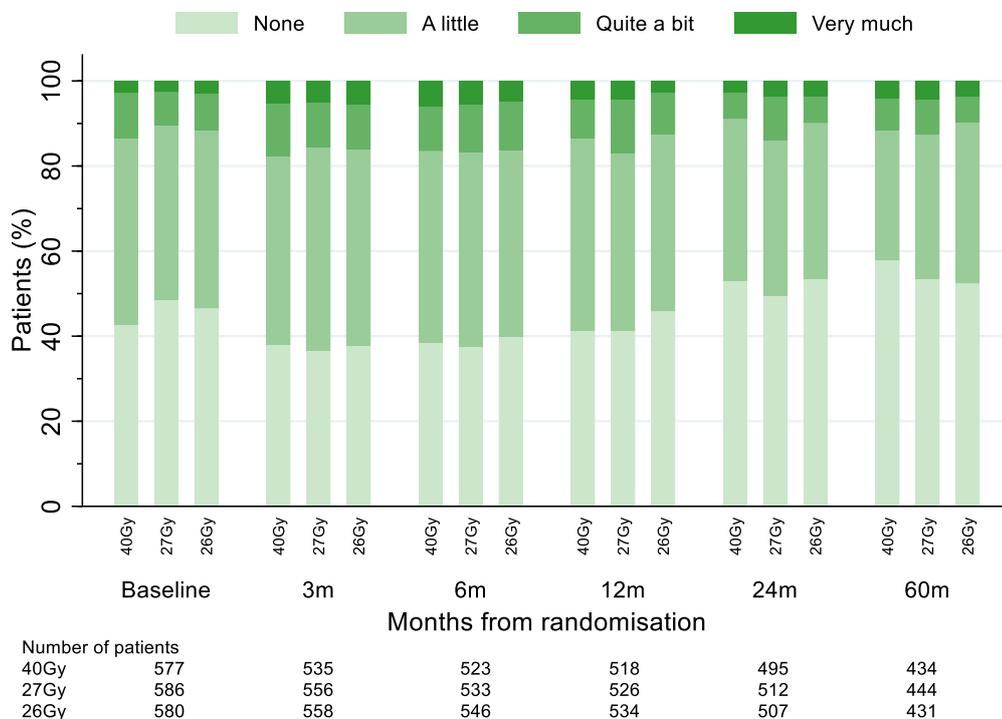
Figure 49: Patient-assessed change in overall breast appearance up to 5 years in the Main Trial

Number of patients						
40Gy	573	529	515	513	491	432
27Gy	583	552	530	519	509	440
26Gy	581	554	545	529	506	429
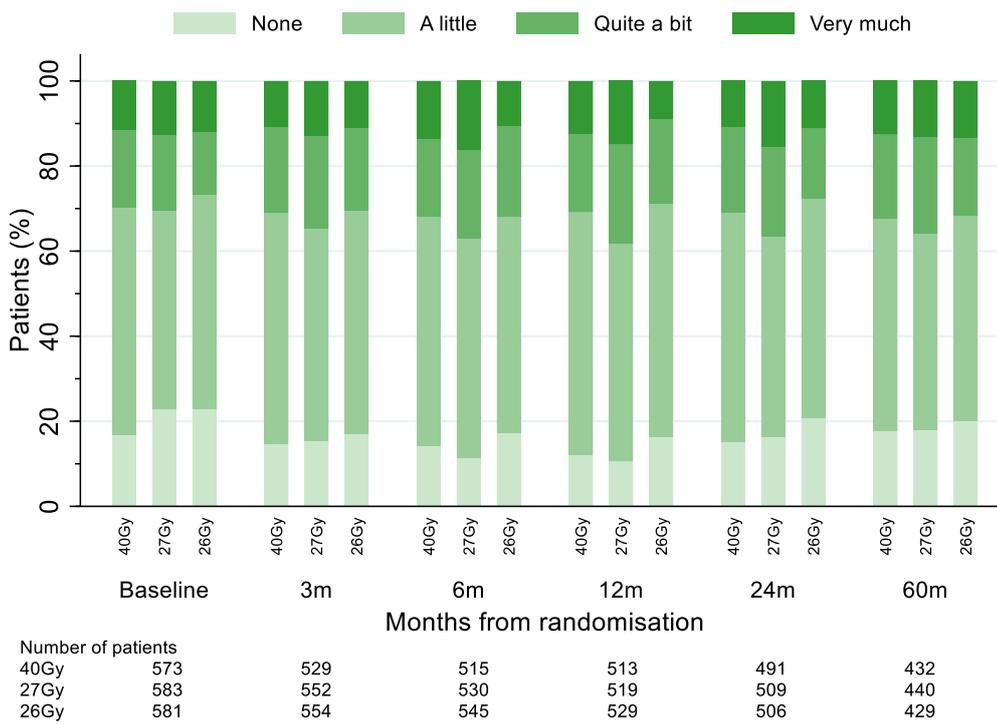
Figure 50: Patient-assessed breast shrinkage up to 5 years in the Main Trial

| Number of patients						
40Gy	560	518	507	505	487	428
27Gy	576	544	525	513	503	435
26Gy	574	549	539	524	501	429

230
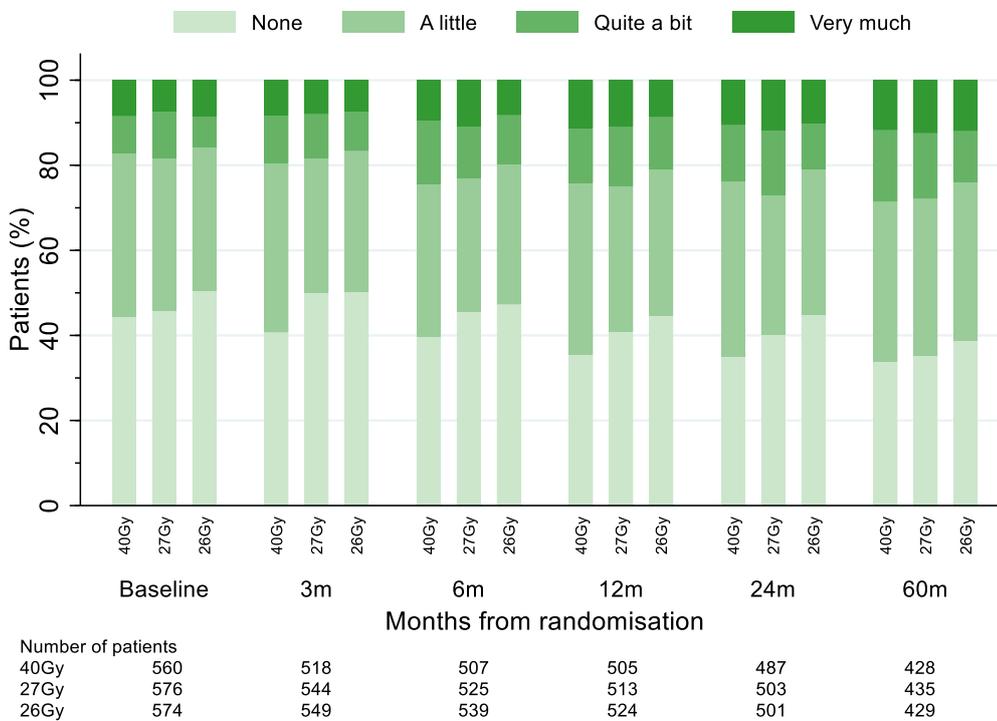
Figure 51: Patient-assessed breast hardness up to 5 years in the Main Trial

Number of patients

40Gy	558	520	510	505	483	428
27Gy	572	542	520	515	503	432
26Gy	566	546	538	521	504	425