Ten-year results of FAST: a randomised controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer

Adrian Murray Brunt* FRCR[1], Joanne S Haviland* MSc[2], Mark Sydenham BSc Hons[2], Rajiv K Agrawal FRCR[3], Hafiz Algurafi FRCR[4], Abdulla Alhasso FRCR[5], Peter Barrett-Lee FRCR[6], Peter Bliss FRCR[7], David Bloomfield FRCR[8], Joanna Bowen FRCR[9], Ellen Donovan[10], Andy Goodman FRCR[11], Adrian Harnett FRCR[12], Martin Hogg FRCR[13], Sri Kumar FRCR[14], Helen Passant FRCR[6], Mary Quigley FRCR[15], Liz Sherwin FRCR[16], Alan Stewart FRCR[17], Isabel Syndikus FRCR[18], Jean Tremlett[8], Yat Tsang PhD[19], Karen Venables[19], Duncan Wheatley FRCR[20], Judith M Bliss[+] MSc[2], John R Yarnold[+] FRCR[21]

* Joint first authors; [+] Joint senior authors

Affiliations:

1. Cancer Centre, University Hospitals of North Midlands NHS Trust & Keele University, Stoke-on-Trent, Staffordshire
2. Institute of Cancer Research - Clinical Trials and Statistics Unit, Sutton, Surrey
3. Oncology Centre, Lingen Davies Centre, Royal Shrewsbury Hospital, Shrewsbury, Shropshire
4. Oncology Department, Southend University Hospital, Southend, Essex
5. Radiotherapy, Beatson West of Scotland Cancer Centre, Glasgow, Scotland
6. Velindre Cancer Centre, Velindre Hospital, Cardiff, Wales
7. Oncology, Torbay Hospital, Torquay, Devon
8. Sussex Cancer Centre, Royal Sussex County Hospital, Brighton, Sussex
9. Oncology Centre, Cheltenham General Hospital, Cheltenham, Gloucestershire
10. Centre for Vision, Speech and Signal Processing CVSSP, University of Surrey, Guildford, Surrey
11. Exeter Oncology Centre, Royal Devon and Exeter Hospital, Exeter, Devon
12. Oncology and Haematology Department, Norfolk and Norwich University Hospital, Norwich, Norfolk
13. The Cancer Centre, Royal Preston Hospital, Preston, Lancashire
14. Leeds Cancer Centre, St James' University Hospital, Leeds, Yorkshire
15. Oncology Department, Queen's Hospital, Romford, Essex
16. Department of Oncology and Haematology, Ipswich Hospital, Ipswich, Suffolk
17. Radiotherapy Department, The Christie Hospital. Manchester, Lancashire
18. The Clatterbridge Cancer Centre, Clatterbridge Hospital, Bebington, Wirral, Cheshire
19. RTTQA, Mount Vernon Hospital, Rickmansworth, Middlesex
20. The Sunrise Centre, Royal Cornwall Hospital, Truro, Cornwall
21. Institute of Cancer Research and Royal Marsden Hospital NHS Foundation Trust, Sutton, Surrey

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Corresponding author: Professor A M Brunt, Royal Stoke University Hospital & Keele University, University Hospitals of North Midlands NHS Trust, Newcastle Road, Stoke-on-Trent, Staffordshire, ST4 6QG

Tel: 0208 722 4104; Email: fastforward-icrctsu@icr.ac.uk

Running head: FAST hypofractionated breast radiotherapy trial: 10-year results

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Key points:

- **Key objective**: To test the reduction in total dose of adjuvant whole breast radiotherapy delivered by 5 once-weekly fractions needed to match the late adverse effects of a standard 25-fraction schedule.
- **Knowledge generated:** A once-weekly 5-fraction schedule of 28Gy is estimated to be radiobiologically equivalent to 50Gy in 25 fractions in terms of late adverse effects at 10 years of follow-up.
- **Relevance**: Alpha/beta estimates for late adverse effects are consistent with historical estimates of fraction size sensitivity in patients prescribed adjuvant whole breast

radiotherapy and can be used to inform further trials of accelerated hypofractionation. Whilst results from the UK FAST-Forward trial are needed to confirm the efficacy of a 5-fraction schedule in terms of local tumour control, our findings may nevertheless be relevant to the needs of patients who are unable to comply with or gain access to standard 25-, 16- or 15-fraction schedules.

ABSTRACT

Purpose: Previous studies of hypofractionated adjuvant whole-breast radiotherapy for early breast cancer established a 15- or 16-fraction (fr) regimen as standard. The FAST Trial (CRUKE/04/015) evaluated normal tissue effects (NTE) and disease outcomes following 5-fraction regimens. Ten-year results are presented.

Patients and methods: Women ≥50 years with low-risk invasive breast carcinoma (pT1-2 pN0) were randomised to 50Gy/25fr (5 weeks), 30 or 28.5Gy in 5fr of 6.0 or 5.7Gy (1 week). Primary endpoint was change in photographic breast appearance at 2 and 5 years; secondary endpoints were physician assessments of NTE and local tumour control. Odds ratios (OR) from longitudinal analyses compared regimens.

Results: 915 women were recruited from 18 UK centres (2004-2007). Five-year photographs were available for 615/862 (71%) eligible patients. OR for change in photographic breast appearance were 1.64 (95%CI 1.08-2.49, p=0.019) for 30Gy and 1.10 (0.70-1.71, p=0.686) for 28.5Gy versus 50Gy. α/β estimate for photographic endpoint was 2.7Gy (1.5, 3.9), giving a 5-fraction schedule of 28Gy (26, 30) estimated to be isoeffective with 50Gy/25fr. OR for any moderate/marked physician-assessed breast NTE (shrinkage, induration, telangiectasia, oedema) were 2.12 (1.55-2.89, p<0.001) for 30Gy and 1.22 (0.87-1.72, p=0.248) for 28.5Gy

versus 50Gy. With 9.9 years median follow-up, 11 ipsilateral breast cancer events (50Gy: 3, 30Gy: 4, 28.5Gy: 4) and 96 deaths (50Gy: 30, 30Gy: 33, 28.5Gy: 33) have occurred.

Conclusion: At 10 years, there was no significant difference in NTE rates after 28.5Gy/5fr compared with 50Gy/25fr, but NTE were higher after 30Gy/5fr. Results confirm the published 3-year findings that a once-weekly 5-fraction schedule of whole breast radiotherapy can be identified that appears to be radiobiologically comparable for NTE to a conventionally-fractionated regimen.

BACKGROUND

Ten-year results of four randomised trials totalling >7000 patients confirm the safety and efficacy of hypofractionated radiotherapy after primary surgery for early breast cancer[1-4]. The UK START-B and Ontario trials established 15- and 16-fraction schedules as new standards of care delivered over 21-22 days[5-7]. Sensitivity to fraction size was tested in the START pilot and START-A trials by controlling for treatment time, generating an α/β estimate of 3.5Gy (95% CI 1.2,5.7) for tumour control, comparable to that for late adverse effects[2,4,8]. Fifteen- or 16-fraction regimens are unlikely to represent the clinical limits of hypofractionation, and 3-year adverse effects of 5-fraction schedules in the UK FAST trial were reported in 2011[9]. In FAST, 5.7 or 6.0Gy once-weekly were tested against 50Gy in 25 fractions, the standard of care at the time. The explanatory trial design allowed interpolation between two 5-fraction schedules that suggested a schedule equivalent to 50Gy in 25 fractions in terms of late adverse effects. Five fractions of 5.7 and 6.0Gy were predicted to be radiobiologically equivalent to 25 fractions of 2.0Gy, assuming α/β values of 3.0 and 4.0Gy for late normal tissue responses and tumour control, respectively[10]. At a median follow up of 3 years, 28.5Gy in 5 fractions was comparable to 50Gy in 25 fractions and milder than 30Gy in 5 fractions in terms of adverse effects in the breast[9]. This manuscript presents the 5-year results for change

in photographic breast appearance, and physician assessments of breast normal tissue effects (NTE) up to 10 years following radiotherapy, as well as breast cancer disease events.

METHODS

Patients

FAST is a multicentre, phase III randomised controlled trial. Full details of trial design, eligibility criteria, radiotherapy planning and delivery, and study procedures have been presented previously[9]. Eligible patients were women having invasive early breast cancer aged ≥50 years, pathological tumour size <3cm, axillary node negative, breast conserving surgery with complete microscopic resection and whole breast radiotherapy. Patients requiring mastectomy, lymphatic radiotherapy, tumour bed boost or cytotoxic therapy were ineligible.

Patients were randomised (1:1:1) to receive 50Gy in 25 fractions of 2.0Gy, 30Gy in 5 once-weekly fractions of 6.0Gy or 28.5Gy in 5 once-weekly fractions of 5.7Gy. Randomisation was performed by telephone or fax from the recruiting centre to the Clinical Trials and Statistics Unit, Institute of Cancer Research (ICR-CTSU), London. Computer-generated random permuted blocks stratified by participating centre were used. Treatment allocation was not blinded due to the nature of the intervention.

All patients provided written informed consent. FAST (CRUKE/04/015) was approved by the national South-West Multicentre Research Ethics Committee (04/MRE06/17) and the local ethics committees of participating centres. FAST was sponsored by The Institute of Cancer

Research and is registered as an International Standard Randomised Controlled Trial (ISRCTN62488883).

Radiotherapy

Patients lay supine on an inclined plane in a position that remained unchanged during imaging/simulation and treatment, verified by orthogonal laser beams. Clinical target volume included soft tissues of the whole breast down to deep fascia, but not including underlying muscle, ribcage, overlying skin or excision scar. Planning target volume included entire breast with 1cm margins to palpable breast tissue. Medial and lateral borders did not normally extend beyond the anterior midline or the mid-axilla. Margins were reduced in selected patients if the tumour bed did not encroach, to exclude or reduce the volume of heart and/or lung within the high dose volume. The deep margin extended down to the deep fascia.

Transverse cross-sections of the patient were taken through the centre of the planning target volume; a minimum of five slices was recommended, spaced appropriately. Sixteen out of 18 centres used full dose compensation with computerised tomography; others used optical outlining devices capturing the central external contour supplemented by two further outlines collected 1cm inside the superior field border and 1cm superior to the infra-mammary fold[11]. The maximum thickness of lung included in the tangential field was 2cm; cardiac shielding used multileaf collimator (MLC) or other technique. The dose distribution across the target volume was modified to ensure homogeneity within ICRU50/62 guidelines[12]. Doses were prescribed to the reference point at/near the centre of the target volume. Maximum and minimum doses were $\leq$10% of doses on the central plane after full dose compensation; where full dose compensation was not possible, maximum doses in the superior plane and plane through the infra-mammary fold were recorded. Three main dose compensation methods were used to improve dose homogeneity: (i) physical breast compensators, (ii) simple

forward-planned intensity-modulated radiation therapy (IMRT) MLC segment fields/field-in-field technique and (iii) inverse-planned IMRT MLC segment fields[13].

Outcome assessment

The primary endpoint was change in photographic breast appearance. Secondary endpoints were physician assessments of radiation-induced breast changes and ipsilateral disease in the breast (relapse or new primary).

Photographs were taken at baseline, 2 and 5 years following radiotherapy. Change in photographic breast appearance compared with the post-surgical (pre-radiotherapy) baseline was scored on a qualitative 3-point scale (none, mild or marked change), based on changes in size, shrinkage and shape. Patients were ineligible for further photographic assessments following breast reconstructive surgery and after further ipsilateral disease. All photographs were scored by at least two observers blind to patient identity and treatment allocation following procedures established in the START Trials[14] (Appendix). As a number of years had elapsed since the scoring of the 2-year photographs for the previous publication[9], these were rescored along with the 5-year photographs to ensure consistency of assessment criteria (Appendix). Breast size and surgical deficit were assessed from the baseline photographs using a qualitative 3-point scale (small, medium, large), with surgical deficit expressed relative to the contralateral breast size.

Late-onset NTE in the breast (shrinkage, induration, telangiectasia, oedema) were assessed by physicians at annual follow-up and graded on a 4-point scale for the treated breast relative to the contralateral breast (none, a little, quite a bit or very much; interpreted as none, mild, moderate or marked). Incidence of symptomatic rib fracture, symptomatic lung fibrosis and

ischaemic heart disease were recorded. Physicians were not blinded to randomised treatment allocation. No patient-reported outcomes were assessed within the FAST trial. Clinical assessments of acute skin toxicity have been previously reported[9].

Ipsilateral disease was defined as a malignancy (invasive or DCIS) presenting anywhere in the ipsilateral breast parenchyma and/or overlying skin, whether considered ipsilateral breast relapse or new primary tumour. Data on first regional relapse (axilla, supraclavicular fossa and internal mammary chain), distant metastases, new primary cancer and death were also collected.

Statistical considerations

Using START pilot trial results[2], an average 2-year rate of mild or marked change in photographic breast appearance for the test groups of 20% was assumed, allowing a sample size of 900 to detect a 10% difference in the prevalence of change in photographic breast appearance between test dose levels with 90% power, 2-sided $\alpha=0.05$, allowing for 10% loss to follow-up/unevaluable. The trial was not statistically powered to test for differences in local tumour control.

Scores for change in photographic breast appearance at 2 and 5 years were modelled using generalised estimating equations (GEE)[15]. Mild and marked categories were combined as marked change was rare. Pairwise comparisons of mild/marked change between schedules were described by odds ratios (OR, with 95% confidence intervals, CI) obtained from the GEE models, and the Wald test.

Cross-sectional analyses of physician-assessed breast NTE at 5 and 10 years compared frequencies of moderate/marked effects versus none/mild between pairs of schedules using risk ratios and risk differences (with 95%CI), and Fisher's exact test. Longitudinal analyses of moderate/marked physician-assessed NTE (versus none/mild) used GEE models including all annual assessments, comparing schedules across the whole follow-up period using OR (with 95%CI) and the Wald test; a term representing years of follow-up was included, enabling time trends to be modelled. Survival analysis methods analysed time to first moderate/marked physician-assessed NTE, including Kaplan-Meier plots and estimates of cumulative incidence rates. Hazard ratios (HR, with 95%CI) were obtained from Cox proportional hazards regression, and schedules compared using the log-rank test. Inconsistencies between the GEE and Cox models for some endpoints appeared to be due to more patients in the 28.5Gy group having only 1 event, which has a greater influence on the time-to-event analysis (where only 1 event is needed) compared with the longitudinal models including all events over follow-up.

Kaplan-Meier estimates (with 95% CI) of 5- and 10-year cumulative incidence of ipsilateral disease in the breast were calculated, and HR (with 95%CI) comparing schedules obtained from Cox proportional hazards regression, with patients censored at date of distant metastases, new primary cancer (contralateral breast or non-breast), death, or date of last follow-up.

Estimates of the α/β ratio for late NTE were obtained by fitting GEE models to all follow-up assessments (photographic and physician), including terms for total dose and total dose multiplied by fraction size. The α/β ratio was calculated as estimate for total dose/estimate

for total dose x fraction size, with 95%CI estimated from the model (lower confidence limits were truncated at zero when the calculated limit was negative). Isoeffect doses in 2.0Gy equivalents (EQD_2) were calculated for the experimental schedules, and the 5-fraction schedule estimated to be isoeffective with 50Gy/25fr was derived.

All analyses were performed on an intention-to-treat basis, from a database snapshot taken on 17th July 2018; Stata version 15 (StataCorp) was used.

Role of the funding source

The funding source provided peer-reviewed approval for the trial but had no role in study design, collection, analysis, interpretation of data, or writing of the report.

RESULTS

915 women were recruited October 2004-March 2007 from 18 UK radiotherapy centres. Baseline clinical and demographic details were reported previously[9]; (Table A1). Mean age at randomisation was 62.9 years (range 50-88), mean pathological tumour size was 1.3cm (range 0.1–3.0), 34% of patients had a grade 1 tumour and 88.4% of patients were scheduled to receive adjuvant endocrine therapy. At the time of analysis, median follow-up was 9.9 years (interquartile range 8.3-10.1). Of patients alive and disease-free, assessments of change in photographic breast appearance were available for 732/901 (81%) patients at 2 years and 615/862 (71%) at 5 years (Figure A1).

At 5 years, 489/615 (79.5%) patients had no change in photographic breast appearance, 109 (17.7%) mild change and 17 (2.8%) marked change. Rates of mild/marked change in photographic breast appearance at 2 or 5 years were statistically significantly higher for 30Gy compared with 50Gy (OR 1.64, 95%CI 1.08,2.49, p=0.019) but not significantly different for 28.5Gy and 50Gy (1.10, 0.70,1.71, p=0.686); Table 1. Rates of mild/marked change in photographic breast appearance were slightly higher for 30Gy compared with 28.5Gy (p=0.052).

Any moderate/marked physician-assessed 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 (Table 2). The most prevalent individual effect was breast shrinkage (Figure 1). Five-year prevalence of any moderate/marked breast NTE was estimated to be 10% higher (95%CI 5,16%) for 30Gy versus 50Gy (p<0.001), with no statistically significant difference between 28.5Gy and 50Gy (2%, -2,+7%, p=0.349). At 5 years, risk ratios for moderate/marked breast shrinkage versus 50Gy were 2.03 (1.15,3.58, p=0.017) for 30Gy and 1.20 (0.63,2.27, p=0.604) for 28.5Gy. There were no statistically significant differences between schedules in 5-year prevalence of moderate/marked breast induration, telangiectasia and breast oedema, nor in 10-year prevalence of any moderate/marked effects, with very few marked events (Table 2). At 10 years, the estimated absolute differences in prevalence of any moderate/marked breast NTE compared with 50Gy were 9% (1,18, p=0.032) for 30Gy and 5% (-2,+13, p=0.184) for 28.5Gy.

Five and 10-year cumulative incidence rates of moderate/marked NTE in the breast were higher for 30Gy compared with 50Gy, with statistically significant differences for any NTE in

the breast, breast shrinkage, breast induration and breast oedema (Figure 1, Table A2). Cumulative incidence rates of any moderate/marked NTE in the breast and breast induration were significantly higher for 28.5Gy versus 50Gy.

Modelling all annual physician assessments over follow-up, rates of moderate/marked effects were statistically significantly higher for 30Gy compared with 50Gy (OR for any breast NTE 2.12, 1.55,2.89, $p<0.001$), but with no significant difference between 28.5Gy and 50Gy (1.22, 0.87,1.72, $p=0.248$); Table 3. Statistically significant differences between the test schedules were found for breast shrinkage, telangiectasia and breast oedema, with higher rates for 30Gy compared with 28.5Gy. The prevalence of breast shrinkage and telangiectasia increased over time, with a decline in breast oedema (Figure 1).

Change in photographic breast appearance gave an unadjusted α/β estimate of 2.7Gy (1.5,3.9); adjusting for breast size and surgical deficit made little difference (Table 4). Using an α/β of 2.7Gy, the isoeffect doses expressed in 2.0Gy equivalents for 30 and 28.5Gy in 5 fractions were approximately 56 and 51Gy, respectively, and the once-weekly 5-fraction schedule estimated to be isoeffective with 50Gy/25fr was 28Gy (26,30). Estimates of α/β for physician-assessed NTE were consistent with the photographic endpoint (Table 4).

A total of 123 patients (13.4%) were referred to a specialist for radiotherapy-related adverse effects, most frequently lymphoedema, with similar rates between the schedules (Table A3). Symptomatic rib fracture was reported for 11 patients (1.2%), symptomatic lung fibrosis for 8 (0.9%) and ischaemic heart disease for 17 (1.9%), including 7 cases in patients treated for left-sided breast cancer (Table A4).

Ipsilateral breast events were reported for 11/915 (1.2%) patients (50Gy; 3, 30Gy: 4, 28.5Gy: 4), with estimated cumulative incidence rates of 0.7% (0.3,1.6) at 5 years and 1.3% (0.7,2.3) at 10 years (Table 5). A total of 96 patients (10.5%) have died (50Gy; 30, 30Gy: 33, 28.5Gy: 33), including 25 (2.7%) breast cancer deaths (50Gy: 7, 30Gy: 8, 28.5Gy: 10). Schedules appeared similar regarding breast cancer-related events, new primary cancers or deaths, although numbers were small (Table A5).

DISCUSSION

The FAST Trial tested once-weekly 5-fraction schedules of whole breast radiotherapy in terms of late NTE against a standard regimen of 50Gy in 25 fractions. Patient eligibility focused on factors associated with a low absolute risk of local tumour relapse, as experienced by an older patient age group with early stage pathologically node negative disease.

Change in photographic breast appearance was the primary endpoint of late NTE as in the START trials, since breast appearance following breast cancer treatment is of importance to women and photographs allow external assessors to control for baseline surgical deficit and to score post-radiotherapy changes blind to treatment allocation[14]. Marked change in photographic breast appearance in the FAST trial was rare. The low rates of change recorded in the FAST trial after 50Gy incorporate the benefits of 3D dosimetry compared with 2D dosimetry used in the START and Ontario trials, as well as fewer women with large breast size included in FAST. Physician assessments, whilst not blinded to allocated treatment and hence potentially subject to bias, nevertheless provide a valuable assessment of late NTE

from a different perspective to the photographs, and both sets of results contribute to the overall evidence from the trial. Annual physician assessments identified very few moderate or marked effects over 10 years. The prevalence of breast shrinkage and telangiectasia increased over follow-up in FAST, as shown in other studies[4,16], while breast oedema declined, consistent with patient-reported outcomes of the IMPORT LOW trial of partial breast radiotherapy[17]. Incident cases of ischaemic heart disease were rare but longer follow-up is required in order to adequately monitor cardiac risk following breast radiotherapy.

The α/β estimates from FAST are consistent with the 10-year analysis of the START-A trial, which generated estimates around 3-4Gy for late NTE in the breast[4]. This consistency supports the validity of the linear-quadratic model for fraction sizes as high as 5.0-6.0Gy. However, fractionation sensitivity might be slightly higher (α/β value slightly lower) than predicted by the model due to much lower rates of moist desquamation and later consequential late skin damage when larger fractions are used. Rates of patchy/confluent moist desquamation in the FAST trial after 50.0Gy, 30.0Gy and 28.5Gy were 11.7%, 2.7% and 2.8%, respectively (including only one confluent case), confirming the well-established insensitivity of early reacting self-renewal tissues to fraction size and the importance of total dose[9,18].

The FAST trial was not powered for formal statistical comparison of local tumour control; the 10-year cumulative incidence estimate was 1.3%, in keeping with the low risk population for which the trial was designed. The extremely low number of local tumour events reflects the patient demographics, tumour characteristics, careful attention to microscopic excision

margins, the use of adjuvant endocrine therapy and high quality radiotherapy. Deaths from other causes were the most frequent consequential event.

The FAST trial was conceived in the early 2000s and since then the UK[5] and international standard[7] has become 40Gy in 15 fractions over 3 weeks or similarly hypofractionated. Based on an α/β value of 2.7Gy, the 15-fraction regimen is equivalent to 45.7Gy in 2.0Gy equivalents. In response to 10-year results of the START and Ontario trials, 15- or 16-fraction regimens are the preferred dose-fractionation options for whole breast radiotherapy according to the American Society of Radiation Oncology[7]. FAST informed the design of the UK phase III FAST-Forward trial testing 2 dose levels of a 5-fraction schedule delivered in 1 week compared with 40Gy in 15 fractions in women prescribed adjuvant radiotherapy to whole breast or post-mastectomy chest wall after primary surgery for early breast cancer. FAST-Forward will report on the primary endpoint of 5-year ipsilateral tumour control in 2020; 3-year results showed similar rates of late NTE after 26Gy in 5 fractions compared with 40Gy in 15 fractions[19]. A sub-study within FAST-Forward tests the same dose schedules as the main trial in patients who also require radiotherapy to the axilla and/or supraclavicular fossa.

In conclusion, the FAST trial identifies a 5-fraction schedule estimated to be radiobiologically equivalent to the 25-fraction standard in terms of late NTE. Identification of a 5-fraction schedule equivalent with respect to tumor control is being evaluated in the UK FAST-Forward trial. Although not powered for tumour control, the FAST trial suggests that for patients at low risk of relapse and for whom daily visits over 3 or 5 weeks are not possible due to frailty or co-morbidities, 28Gy in 5 fractions as a once-weekly schedule might be an appropriate alternative to no treatment.

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REFERENCES

1. Yarnold J, Ashton A, Bliss J, Homewood J, Harper C, Hanson J, Haviland J, Bentzen S, Owen R. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial. Radiother Oncol 2005; 75: 9-17.
2. Owen JR, Ashton A, Bliss JM, Homewood J, Harper C, Hanson J, Haviland J, Bentzen S, Yarnold JR. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. Lancet Oncol 2006; 7: 467-471.
3. Whelan T, Pignol J-P, Levine M, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010; 362: 513–20.
4. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee P, Dobbs HJ, Hopwood P, Lawton PA, Magee BJ, Mills J, Simmons S, Sydenham MA, Venables K, Bliss JM and Yarnold JR on behalf of the START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) randomised trials of radiotherapy hypofractionation for treatment of early breast cancer; 10-year follow-up results (CRUK/96/001). Lancet Oncol 2013; 14: 1086-94.
5. National Institute for Health and Clinical Excellence. NICE clinical guideline 101: Early and locally advanced breast cancer: diagnosis and management. Published July 2018, updated from 2009. http://www.nice.org.uk/guidance/ng101 (accessed 30th April 2019).
6. Royal College of Radiologists clinical guideline. Dose fractionation. https://www.rcr.ac.uk/system/files/publication/field_publication_files/brfo193_radiotherapy_dose_fractionation_third-edition.pdf (accessed 30th April 2019).

7. Smith BD, Bellon JR, Blitzblau R, et al. Radiation therapy for the whole breast: executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Pract Radiat Oncol 2018; 8 (3): 145–52.
8. START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol 2008; 9(4): 331-41.
9. FAST Trialists' Group. First results of the randomised UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015). Radiother Oncol 2011; 100(1): 93-100.
10. Jones, L., P. Hoban, and P. Metcalfe, The use of the linear quadratic model in radiotherapy: a review. Australas Phys Eng Sci Med 2001; 24(3): 132-46.
11. Venables, K., Tsang, Y., Ciurlionis, L., Coles, C. and Yarnold, J. Does Participation in Clinical Trials Influence the Implementation of New Techniques? A Look at Changing Techniques in Breast Radiotherapy in the UK. Clin Oncol (R Coll Radiol) 2012; 24(8): e100-e105.
12. Landberg T, Chavaudra J, Dobbs J, Hanks G, Johansson K-A, Möller T, Purdy J. Report 50, Journal of the International Commission on Radiation Units and Measurements, Volume os26, Issue 1, 1 September 1993, Page NP, https://doi.org/10.1093/jicru/os26.1.Report50
13. Tsang Y, Venables K, Yarnold J. Quality assurance analysis of participating centres' protocol compliance to a UK multicentre hypofractionated breast (FAST) trial. The British Journal of Radiology. 2012;85(1017):e647-e653.
14. Haviland, J.S., et al., Evaluation of a method for grading late photographic change in breast appearance after radiotherapy for early breast cancer. Clin Oncol (R Coll Radiol) 2008; 20(7): 497-501.

15. Hanley JA, Negassa A, Edwardes MD, et al. Statistical analysis of correlated data using generalized estimating equations: An orientation. Am J Epidemiol 2003; 157: 364-375.
16. Bentzen SM, Turesson I, Thames HD. Fractionation sensitivity and latency of telangiectasia after postmastectomy radiotherapy: a graded-response analysis. Radiother Oncol 1990; 18(2): 95-106.
17. Bhattacharya IS*, Haviland JS*, Kirby AM, Kirwan CC, Hopwood P, Yarnold JR, Bliss JM, Coles CE on behalf of the IMPORT Trialists. Patient-Reported Outcomes Over 5 Years After Whole- or Partial-Breast Radiotherapy: Longitudinal Analysis of the IMPORT LOW (CRUK/06/003) Phase III Randomized Controlled Trial. J Clin Oncol. 2019; 37(4): 305-317. https://doi.org/10.1200/JCO.18.00982
18. Dorr, W. and J.H. Hendry, Consequential late effects in normal tissues. Radiother Oncol 2001; 61(3): 223-31.
19. Brunt AM, Haviland JS, Sydenham MA, Alhasso A, Bloomfield D, Chan C, Churn M, Cleator S, Coles CE, Emson M, Goodman A, Griffin C, Harnett A, Hopwood P, Kirby A, Kirwan C, Morris C, Sawyer E, Somaiah N, Syndikus I, Wilcox M, Wheatley D, Zotova R, Bliss JM, Yarnold JR. OC-0595: FAST-Forward phase 3 RCT of 1-week hypofractionated breast radiotherapy: 3-year normal tissue effects. Radiotherapy and Oncology 2018; (127) Suppl 1: S311-S312.

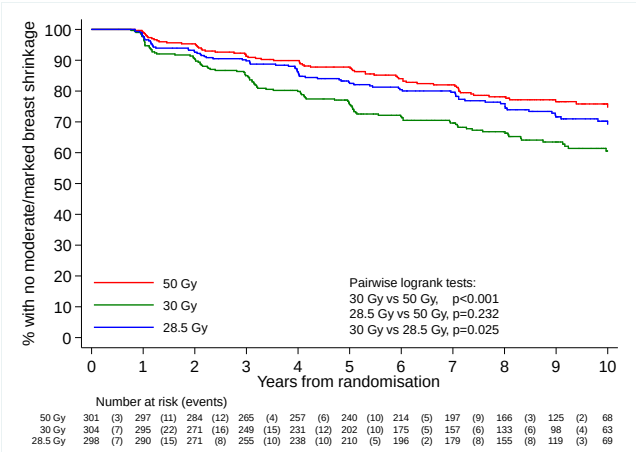
Figure legends

Figure 1: Physician assessments of late normal tissue effects; (a) Breast shrinkage to 10 years, (b) Time to first reported moderate/marked breast shrinkage, (c) Breast induration to 10 years, (d) Time to first reported moderate/marked breast induration, (e) Breast oedema to 10 years, (f) Time to first reported moderate/marked breast oedema, (g) Telangiectasia to 10 years, (h) Time to first reported moderate/marked telangiectasia

Figure 1: Physician assessments of late normal tissue effects

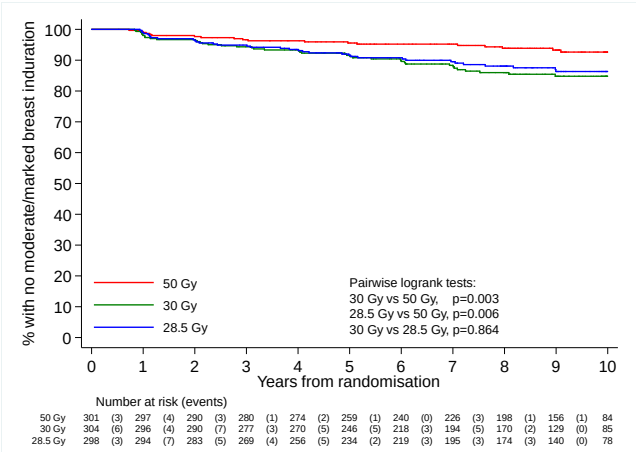
(a) Breast shrinkage to 10 years

(b) Time to first reported moderate/marked breast shrinkage



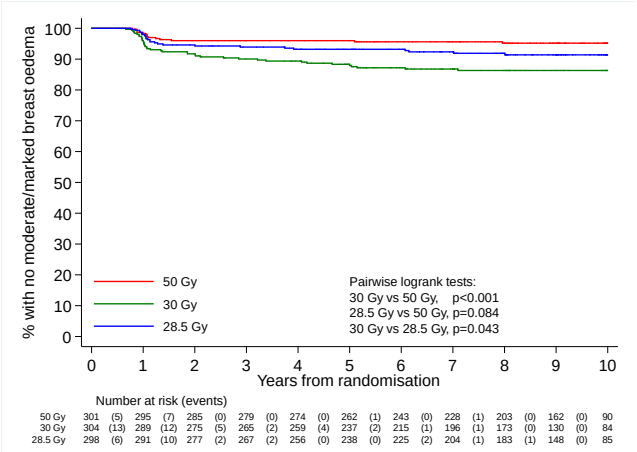
(c) Breast induration to 10 years

(d) Time to first reported moderate/marked breast induration



(e) Breast oedema to 10 years

(f) Time to first reported moderate/marked breast oedema



(g) Telangiectasia to 10 years

(h) Time to first reported moderate/marked telangiectasia

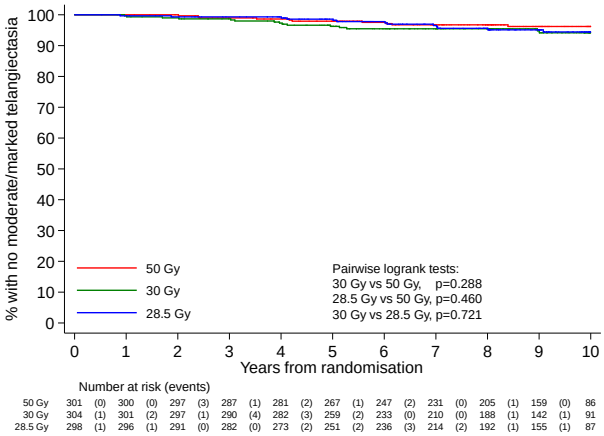


Table 1: Change in photographic breast appearance at 2 and 5 years

Fractionation schedule	2 years			5 years			OR for mild/marked change (95%CI)	Comparison with 50 Gy; p-value[1]	Comparison between 30Gy & 28.5Gy; p-value[1]
	None (%)	Mild (%)	Marked (%)	None (%)	Mild (%)	Marked (%)			
50 Gy	217 (90.4)	20 (8.3)	3 (1.3)	163 (82.3)	31 (15.7)	4 (2.0)	1		
30 Gy	205 (82.7)	36 (14.5)	7 (2.8)	160 (75.5)	44 (20.8)	8 (3.8)	1.64 (1.08, 2.49)	0.019	
28.5 Gy	215 (88.1)	27 (11.1)	2 (0.8)	166 (81.0)	34 (16.6)	5 (2.4)	1.10 (0.70, 1.71)	0.686	0.052

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

Table 2: Cross-sectional analyses of physician-assessed late normal tissue effects at 5 and 10 years according to fractionation schedule

	50 Gy N (%)	30 Gy N (%)	28.5 Gy N (%)	Moderate/Marked vs. None/Mild								
				30Gy vs. 50Gy			28.5Gy vs. 50Gy			30Gy vs. 28.5Gy		
				Risk ratio (95%CI)	Risk difference (95%CI), %	p-value[1]	Risk ratio (95%CI)	Risk difference (95%CI), %	p-value[1]	Risk ratio (95%CI)	Risk difference (95%CI), %	p-value[1]
At 5 years:												
Any NTE in breast[2]	N=254	N=267	N=253	2.40 (1.45, 3.97)	10 (5, 16)	<0.001	1.32 (0.75, 2.34)	2 (-2, 7)	0.349	1.82 (1.16, 2.86)	8 (2, 14)	0.008
None	160 (63.0)	152 (56.9)	155 (61.3)									
Mild	75 (29.5)	67 (25.1)	73 (28.8)									
Moderate	15 (5.9)	40 (15.0)	24 (9.5)									
Marked	4 (1.6)	8 (3.0)	1 (0.4)									
Breast shrinkage	N=254	N=266	N=252	2.03 (1.15, 3.58)	6 (1, 11)	0.017	1.20 (0.63, 2.27)	1 (-3, 6)	0.604	1.69 (0.99, 2.89)	5 (0.1, 10)	0.059
None	176 (69.3)	180 (67.7)	169 (67.1)									
Mild	62 (24.4)	52 (19.5)	64 (25.4)									
Moderate	14 (5.5)	29 (10.9)	19 (7.5)									
Marked	2 (0.8)	5 (1.9)	0 (0)									
Breast induration	N=254	N=266	N=253	3.18 (0.89, 11.43)	3 (-0.1, 5)	0.089	1.67 (0.40, 6.93)	1 (-1, 3)	0.504	1.90 (0.66, 5.49)	2 (-1, 5)	0.297
None	235 (92.5)	219 (82.3)	223 (88.1)									
Mild	16 (6.3)	37 (13.9)	25 (9.9)									
Moderate	3 (1.2)	9 (3.4)	4 (1.6)									
Marked	0 (0)	1 (0.4)	1 (0.4)									
Telangiectasia	N=254	N=267	N=253	2.85 (0.78, 10.42)	2 (-0.3, 5)	0.143	0.67 (0.11, 3.97)	-0.4 (-2, 1)	>0.99	4.26 (0.93, 19.54)	3 (0.2, 5)	0.064
None	242 (95.3)	243 (91.0)	236 (93.3)									
Mild	9 (3.5)	15 (5.6)	15 (5.9)									
Moderate	1 (0.4)	9 (3.4)	2 (0.8)									
Marked	2 (0.8)	0 (0)	0 (0)									
Breast oedema	N=254	N=267	N=253	6.66 (0.82, 53.74)	2 (0.2, 4)	0.069	0	-0.4 (-1, 0.4)	>0.99	NC	3 (1, 4)	0.015
None	246 (96.8)	246 (92.1)	248 (98.0)									
Mild	7 (2.8)	14 (5.2)	5 (2.0)									
Moderate	1 (0.4)	5 (1.9)	0 (0)									
Marked	0 (0)	2 (0.8)	0 (0)									
Other RT-related	N=254	N=266	N=252	2.86 (0.58, 14.06)	1 (-1, 3)	0.286	1.01 (0.14, 7.10)	0.01 (-1, 1)	>0.99	2.84 (0.58, 13.95)	1 (-1, 3)	0.287
None	245 (96.5)	250 (94.0)	247 (98.0)									
Mild	7 (2.8)	10 (3.8)	3 (1.2)									
Moderate	2 (0.8)	5 (1.9)	2 (0.8)									
Marked	0 (0)	1 (0.4)	0 (0)									
At 10 years:												
Any NTE in breast[2]	N=132	N=130	N=130	2.03 (1.06, 3.89)	9 (1, 18)	0.032	1.61 (0.81, 3.18)	5 (-2, 13)	0.184	1.26 (0.73, 2.19)	4 (-5, 13)	0.505
None	90 (68.2)	66 (50.8)	72 (55.4)									
Mild	30 (22.7)	40 (30.8)	39 (30.0)									
Moderate	11 (8.3)	18 (13.8)	17 (13.1)									
Marked	1 (0.8)	6 (4.6)	2 (1.5)									

	50 Gy N (%)	30 Gy N (%)	28.5 Gy N (%)	Moderate/Marked vs. None/Mild								
				30Gy vs. 50Gy			28.5Gy vs. 50Gy			30Gy vs. 28.5Gy		
				Risk ratio (95%CI)	Risk difference (95%CI), %	p-value[1]	Risk ratio (95%CI)	Risk difference (95%CI), %	p-value[1]	Risk ratio (95%CI)	Risk difference (95%CI), %	p-value[1]
Breast shrinkage	N=132	N=130	N=130	1.83	6	0.113	1.83	6	0.113	1.00	0	>0.99
None	97 (73.5)	79 (60.8)	79 (60.8)	(0.88, 3.81)	(-1, 14)		(0.88, 3.81)	(-1, 14)		(0.54, 1.83)	(-8, 8)	
Mild	25 (18.9)	33 (25.4)	33 (25.4)									
Moderate	9 (6.8)	15 (11.5)	17 (13.1)									
Marked	1 (0.8)	3 (2.3)	1 (0.8)									
Breast induration	N=132	N=130	N=130	1.01	0.02	>0.99	3.05	3	0.170	0.33	-3	0.281
None	118 (89.4)	108 (83.1)	112 (86.1)	(0.14, 7.10)	(-3, 3)		(0.63, 14.82)	(-1, 7)		(0.07, 1.62)	(-7, 1)	
Mild	12 (9.1)	20 (15.4)	12 (9.2)									
Moderate	2 (1.5)	2 (1.5)	5 (3.8)									
Marked	0 (0)	0 (0)	1 (0.8)									
Telangiectasia	N=132	N=130	N=130	6.09	4	0.065	0	-1	>0.99	NC	5	0.029
None	128 (96.7)	119 (91.5)	123 (94.6)	(0.74, 49.90)	(-0.04, 8)			(-2, 1)			(1, 8)	
Mild	3 (2.3)	5 (3.8)	7 (5.4)									
Moderate	1 (0.8)	3 (2.3)	0 (0)									
Marked	0 (0)	3 (2.3)	0 (0)									
Breast oedema	N=132	N=130	N=130	NC	1	0.496	NC	0	NC	NC	1	>0.99
None	131 (99.2)	125 (96.1)	129 (99.2)		(-1, 2)			(0, 0)			(-1, 2)	
Mild	1 (0.8)	4 (3.1)	1 (0.8)									
Moderate	0 (0)	1 (0.8)	0 (0)									
Marked	0 (0)	0	0 (0)									
Other RT-related	N=134	N=129	N=131	2.08	1	0.616	0	-1	>0.99	NC	1	0.245
None	128 (95.5)	127 (98.4)	125 (95.4)	(0.19, 22.63)	(-2, 3)			(-2, 1)			(-1, 4)	
Mild	5 (3.7)	0 (0)	6 (4.6)									
Moderate	0 (0)	2 (1.6)	0 (0)									
Marked	1 (0.8)	0 (0)	0 (0)									

[1] p-value for Fisher's exact test; [2] Any NTE in breast includes shrinkage, induration, telangiectasia, oedema; NC = not possible to calculate due to zeros in denominator

Table 3: Longitudinal analysis of moderate/marked physician-assessed late normal tissue effects including all follow-up assessments

Normal tissue effect endpoint	No. moderate/marked events / total no. of assessments over follow-up (%)	Odds ratio for RT schedule[2] (95%CI)	Comparison with 50Gy; p-value[3]	Comparison between 30Gy & 28.5Gy; p-value[3]	Odds ratio for years of follow-up (95%CI); p-value[3]
Any NTE in the breast[1]					1.04 (1.01, 1.06) p=0.002
50Gy	202/2255 (9.0)	1			
30Gy	392/2313 (16.9)	2.12 (1.55, 2.89)	<0.001		
28.5Gy	233/2269 (10.3)	1.22 (0.87, 1.72)	0.248	<0.001	
Breast shrinkage					1.09 (1.06, 1.22) p<0.001
50Gy	160/2252 (7.1)	1			
30Gy	284/2311 (12.3)	1.88 (1.32, 2.67)	<0.001		
28.5Gy	175/2266 (7.7)	1.11 (0.76, 1.64)	0.589	0.002	
Breast induration					1.00 (0.94, 1.05) p=0.924
50Gy	33/2254 (1.5)	1			
30Gy	78/2310 (3.4)	2.39 (1.31, 4.35)	0.004		
28.5Gy	54/2265 (2.4)	1.67 (0.89, 3.16)	0.112	0.169	
Telangiectasia					1.15 (1.07, 1.23) p<0.001
50Gy	21/2254 (0.9)	1			
30Gy	52/2313 (2.3)	2.68 (1.33, 6.34)	0.025		
28.5Gy	16/2267 (0.7)	0.78 (0.26, 2.35)	0.656	0.009	
Breast oedema					0.68 (0.62, 0.76) p<0.001
50Gy	16/2253 (0.7)	1			
30Gy	67/2311 (2.9)	3.70 (1.86, 7.35)	<0.001		
28.5Gy	30/2266 (1.3)	1.92 (0.91, 4.07)	0.087	0.027	

[1] Any NTE 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 NTE (versus none/mild) for each pairwise comparison of fractionation schedules across all annual assessments over follow-up; [3] p-value from Wald test

Table 4: Estimates of α/β and isoeffect doses in 2.0Gy equivalents (EQD_2) for late normal tissue effects

Normal tissue effect endpoint	α/β estimate (95%CI), Gy	EQD_2 for 30Gy schedule[3], Gy	EQD_2 for 28.5Gy schedule[3], Gy
Photographic assessments			
Mild/marked change in photographic breast appearance	2.7 (1.5, 3.9)	55.7 (50.3, 64.3)	51.0 (46.4, 58.6)
Mild/marked change in photographic breast appearance, adjusted for breast size and surgical deficit	2.5 (1.1, 3.9)	56.4 (50.3, 68.7)	51.7 (46.4, 62.5)
Physician-assessed moderate/marked NTE			
Any NTE in the breast[1]	2.5 (1.8, 3.3)	56.4 (52.8, 61.4)	51.7 (48.5, 56.1)
Breast shrinkage	2.7 (1.9, 3.5)	55.5 (51.8, 60.8)	50.9 (47.6, 55.6)
Breast induration	1.6 (0, 4.4)[2]	63.7 (48.9, 90.0)	58.1 (45.1, 81.2)
Telangiectasia	3.1 (2.3, 3.9)	53.5 (50.2, 58.1)	49.1 (46.2, 53.2)
Breast oedema	1.9 (0.4, 3.5)	60.3 (51.9, 79.2)	55.2 (47.8, 71.7)

[1] Any NTE in the breast = shrinkage, induration, telangiectasia and oedema; [2] Lower limit truncated at 0; [3] EQD_2 calculated for the 30 Gy and 28.5 Gy schedules as: {Total Dose * (Dose per fraction + α/β)} / (2 + α/β)

Table 5: Survival analysis of ipsilateral disease in the breast overall and by fractionation schedule

	Ipsilateral breast event[1] / total (%)	KM estimate (95%CI) of cumulative incidence (%) by:		Hazard ratio (95%CI)
		5 years	10 years	
All patients	11/915 (1.2)	0.7 (0.3-1.6)	1.3 (0.7-2.3)	-
50 Gy	3/302 (1.0)	0.7 (0.2-2.8)	0.7 (0.2-2.8)	1
30 Gy	4/308 (1.3)	1.0 (0.3-3.2)	1.4 (0.5-3.8)	1.36 (0.30-6.06)
28.5 Gy	4/305 (1.3)	0.4 (0.05-2.6)	1.7 (0.6-4.4)	1.35 (0.30-6.05)

KM = Kaplan-Meier, 95%CI = 95% confidence interval; [1] Includes one patient with angiosarcoma in the ipsilateral breast (30 Gy)

Supplementary Appendix

Principal and main co-investigators according to centre (Number of patients recruited)

Cheltenham General Hospital, Cheltenham (2), K Benstead, JR Owen; Gloucester Royal Hospital, Gloucester (2), K. Benstead; Worcestershire Royal Infirmary, Worcester (6), J. Bowen, R. Counsell; Christie Hospital, Manchester (12), A. Stewart; Clatterbridge Centre for Oncology, Bebington (6), I. Syndikus; Warrington and Halton Hospitals, Warrington (18), I. Syndikus; Ipswich Hospital, Ipswich (17), E. Sherwin; Leeds General Hospital, Leeds (5), S. Kumar Mid-Yorks Hospitals, Wakefield (4), S. Kumar, F. Roberts; Norfolk and Norwich University Hospital, Norwich (27), A. Harnett, A. Bulman; James Paget, Norfolk and Norwich (25), A. Harnett, A. Bulman; University Hospital of North Staffordshire, Stoke-on-Trent (112), A.M. Brunt, A. Al Niaimi; Royal Marsden Hospital, Sutton (75), J.R. Yarnold, D. Tait, A. Rostom, M. Dryzmala; Royal Cornwall Hospital, Truro (109), D. Wheatley, A. Thomson, T. Hurst; Royal Devon and Exeter Hospital, Exeter (61), A. Goodman, A. Hong, P. Bliss; North Devon Hospital, (20), A. Hong; Burnley General Hospital, Burnley (14), M Hogg, W Appel Blackpool Royal Infirmary, Blackpool (6), Royal Preston, A. Hindley, S. Susnerwala; Royal Shrewsbury Hospital, Shrewsbury (36), R.K. Agrawal; Southend General Hospital, Southend (66), A. Robinson; Basildon University Hospital, Basildon (3), C. Trask; Torbay District General Hospital, Torbay (58), P. Bliss, A. Goodman; Velindre Hospital, Cardiff (42), J. Abraham, C. Gaffney, P.J. Barrett-Lee; Royal Gwent Hospital (7), J. Abraham, C. Gaffney, P.J. Barrett-Lee; Royal Glamorgan Hospital, (4), J. Abraham; Royal Sussex County Hospital, Brighton (34), D. Bloomfield, R. Simcock; Worthing Hospital, Worthing (41), S. Mitra; Eastbourne Hospital, Eastbourne (2), A. Robinson; Queens Hospital, Romford (9), M. Quigley, E. Sims; Beatson Oncology Centre,

Glasgow (85), A. Alhasso, D. Ritchie; Victoria Infirmary, Glasgow (2), A. Alhasso; Crosshouse Hospital, Kilmarnock (5), A. Alhasso, D. Ritchie.

Figure A1: FAST Trial profile

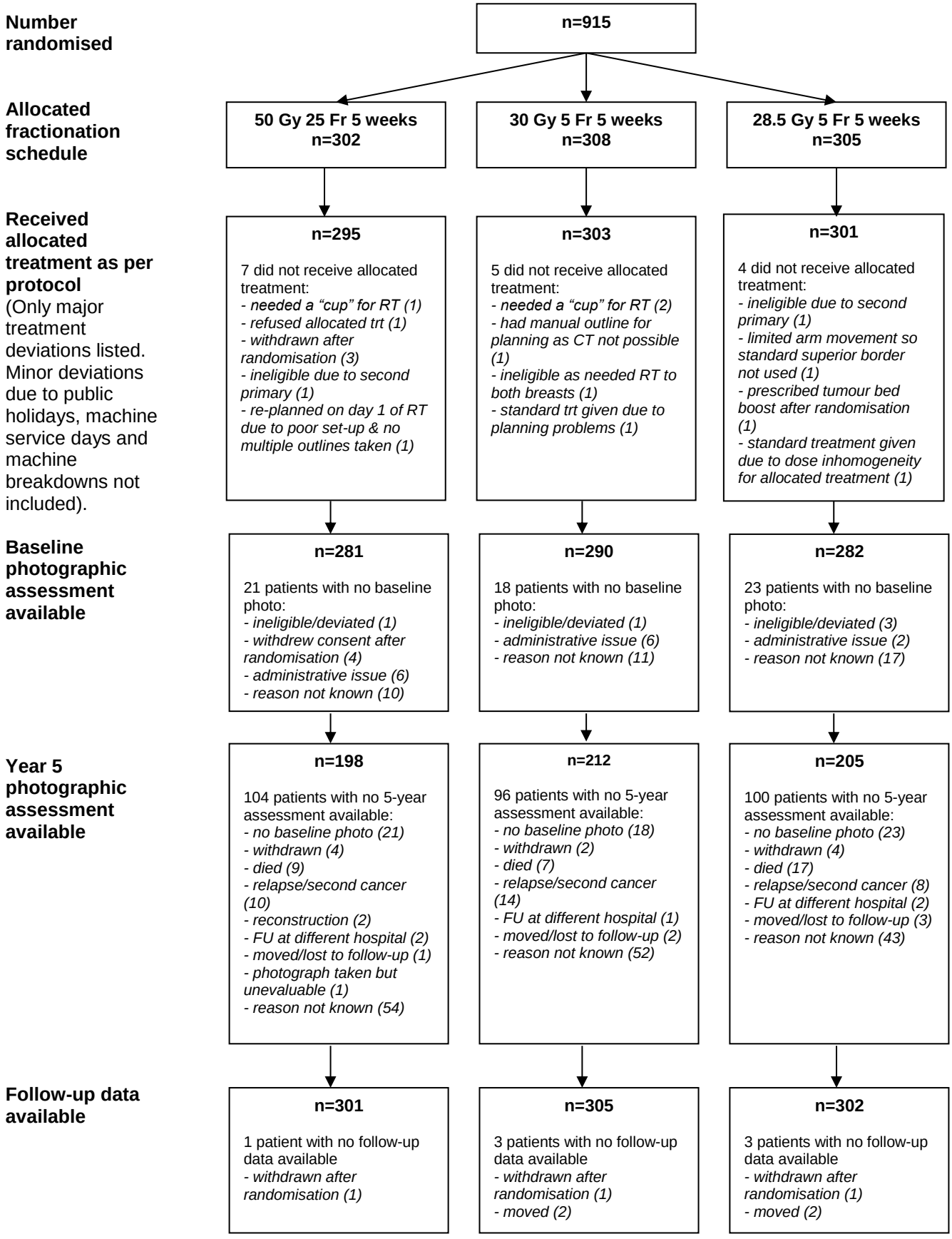


Table A1 – Baseline characteristics by fractionation schedule

	50 Gy	30 Gy	28.5 Gy
	N=302 (%)	N=308 (%)	N=305 (%)
Age (years)			
50-59	112 (37.1)	112 (36.4)	110 (36.1)
60-69	143 (47.4)	145 (47.1)	153 (50.2)
70-79	44 (14.6)	42 (13.6)	39 (12.8)
80-	3 (1.0)	9 (2.9)	3 (1.0)
Mean (SD)	*63.1 (7.2)*	*62.9 (7.5)*	*62.7 (6.8)*
[range]	*[50.0-88.4]*	*[50.1-84.9]*	*[50.0-82.3]*
Time from surgery to randomisation (weeks):			
Median (interquartile range)	6.0 (4.4-7.6)	5.7 (4.1-7.2)	6.0 (4.1-7.6)
[range]	[1.3-22.1]	[0.4-21.1]	[0.7-19.0]
Histological type			
Ductal	230 (76.2)	241 (78.2)	229 (75.1)
Lobular	36 (11.9)	29 (9.4)	30 (9.8)
Special type	22 (7.3)	31 (10.1)	29 (9.5)
Mixed	10 (3.3)	7 (2.3)	15 (4.9)
DCIS	3 (1.0)	0 (0.0)	1 (0.3)
Other	1 (0.3)	0 (0.0)	1 (0.3)
Axillary surgery			
None	1 (0.3)	0	3 (1.0)
SNB	49 (16.2)	52 (16.9)	57 (18.7)
Sampling	140 (46.0)	133 (43.2)	134 (43.9)
Clearance	85 (28.1)	85 (27.6)	80 (26.2)
SNB & sampling	24 (7.9)	35 (11.4)	28 (9.2)
SNB & clearance	1 (0.3)	2 (0.6)	2 (0.6)
Other	2 (0.7)	1 (0.3)	1 (0.3)
Pathological tumour size (cm)			
<1	90 (29.8)	84 (27.3)	87 (28.5)
1 - 2	166 (55.0)	165 (53.6)	160 (52.5)
≥ 2	46 (15.2)	59 (19.2)	58 (19.0)
Mean (SD)	*1.3 (0.6)*	*1.3 (0.6)*	*1.3 (0.7)*
[range]	*[0.05-3.0]*	*[0.13-3.0]*	*[0.1-3.0]*
Tumour grade			
1	94 (31.1)	113 (36.7)	102 (33.4)
2	176 (58.3)	159 (51.6)	168 (55.1)
3	29 (12.9)	35 (11.4)	34 (11.1)
Not known	3 (1.0)	1 (0.3)	1 (0.3)
Adjuvant therapy			
None	39 (12.9)	37 (12.0)	30 (9.8)
Tamoxifen	227 (75.2)	243 (78.9)	224 (73.4)
AI	31 (10.3)	26 (8.4)	45 (14.8)
Tamoxifen -> AI	4 (1.3)	2 (0.6)	4 (1.3)
Unknown type	1 (0.3)	0 (0.0)	2 (0.7)
Breast size			
Small	154 (51.0)	172 (55.8)	163 (53.4)
Medium	89 (29.5)	87 (28.2)	93 (30.5)
Large	38 (12.6)	31 (10.1)	24 (7.9)
Unknown[1]	21 (7.0)	18 (5.8)	23 (7.5)
Surgical deficit			
Small	156 (51.7)	148 (48.1)	154 (50.5)
Medium	68 (22.5)	83 (26.9)	77 (25.2)

	Large	57 (18.9)	59 (19.2)	51 (16.7)
	Unknown[1]	21 (7.0)	18 (5.8)	23 (7.5)

[1] Breast size and surgical deficit scored from baseline photographs. Unknown indicates no baseline photograph available

Table A2: Survival analyses of moderate/marked physician-assessed late normal tissue effects by fractionation schedule

NTE endpoint	Moderate/Marked events / total[2] (%)	KM estimate (95%CI) of cumulative incidence (%) of moderate/marked events by:		Hazard ratio (95%CI)	Comparison with 50Gy; p-value[5]	Comparison between 30Gy & 28.5Gy; p-value[5]
		5 years[3]	10 years[4]			
Any NTE in the breast[1]						
50Gy	88/301 (29.2)	20.1 (15.9-25.1)	33.6 (27.5-40.8)	1		
30Gy	134/304 (44.1)	37.2 (31.9-43.0)	50.4 (44.0-57.1)	1.79 (1.37-2.34)	<0.001	
28.5Gy	116/298 (38.9)	27.9 (23.1-33.6)	47.6 (40.6-55.2)	1.45 (1.10-1.91)	0.008	0.099
Breast shrinkage						
50Gy	69/301 (22.9)	13.7 (10.2-18.2)	28.5 (22.2-36.1)	1		
30Gy	104/304 (34.2)	27.4 (22.7-33.0)	40.5 (34.3-47.4)	1.71 (1.26-2.32)	<0.001	
28.5Gy	79/298 (26.5)	17.9 (13.9-22.9)	33.4 (27.0-40.9)	1.22 (0.88-1.68)	0.232	0.025
Breast induration						
50Gy	19/301 (6.3)	4.8 (2.9-8.0)	7.4 (4.7-11.4)	1		
30Gy	40/304 (13.2)	9.2 (6.4-13.1)	15.2 (11.3-20.3)	2.22 (1.29-3.84)	0.003	
28.5Gy	38/298 (12.7)	9.2 (6.3-13.2)	18.6 (12.7-26.7)	2.14 (1.23-3.71)	0.006	0.864
Telangiectasia						
50Gy	10/301 (3.3)	2.1 (1.0-4.5)	3.8 (2.0-7.0)	1		
30Gy	15/304 (4.9)	4.1 (2.4-7.2)	5.8 (3.5-9.7)	1.55 (0.70-3.45)	0.288	
28.5Gy	13/298 (4.4)	2.2 (1.0-4.8)	5.5 (3.2-9.5)	1.35 (0.59-3.09)	0.460	0.721
Breast oedema						
50Gy	14/301 (4.6)	4.4 (2.6-7.4)	4.8 (2.9-8.0)	1		
30Gy	40/304 (13.2)	12.8 (9.5-17.2)	13.7 (10.2-18.2)	2.98 (1.62-5.48)	<0.001	
28.5Gy	24/298 (8.0)	6.8 (4.4-10.3)	8.6 (5.8-12.6)	1.78 (0.92-3.43)	0.084	0.043
Other						
50Gy	14/301 (4.6)	3.5 (1.9-6.4)	6.5 (3.4-12.5)	1		
30Gy	37/304 (12.2)	8.1 (5.5-11.8)	14.1 (10.4-19.1)	2.80 (1.51-5.18)	<0.001	
28.5Gy	25/298 (8.4)	6.4 (4.0-9.9)	9.9 (6.7-14.4)	1.88 (0.98-3.62)	0.054	0.123

KM = Kaplan-Meier, 95%CI = 95% confidence interval; [1] Any NTE in the breast = shrinkage, induration, telangiectasia and oedema; [2] Follow-up NTE data available for 903/915 patients; [3] Rate estimated at 5 years and 3 months; [4] Rate estimated at 10 years and 3 months; [5] p-value for pairwise logrank test

Table A3: Specialist referral during follow-up, by fractionation schedule

Specialist referral type*	50 Gy N=302 (%)	30 Gy N=308 (%)	28.5 Gy N=305 (%)	Total N=915 (%)
Lymphoedema	15 (5.0)	31 (10.1)	7 (2.3)	53 (5.8)
Breast surgery / breast surgeon	2 (0.7)	11 (3.6)	4 (1.3)	17 (1.9)
Cardiology	6 (2.0)	2 (0.6)	2 (0.6)	10 (1.1)
Pulmonary/Respiratory	3 (1.0)	4 (1.2)	1 (0.3)	8 (0.9)
Biopsy	0	1 (0.3)	2 (0.6)	3 (0.3)
Dermatology	1 (0.3)	2 (0.6)	0	3 (0.3)
GP	1 (0.3)	0	1 (0.3)	2 (0.2)
Pain	1 (0.3)	0	2 (0.6)	3 (0.3)
Other	4 (1.4)	9 (2.9)	11 (3.6)	24 (2.6)

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

Table A4: Incidence of other late adverse effects, by fractionation schedule

	50 Gy N=302 (%)	30 Gy N=308 (%)	28.5 Gy N=305 (%)	Total N=915 (%)
Symptomatic rib fracture	4 (1.3)	5 (1.6)	2 (0.7)	11 (1.2)
Symptomatic lung fibrosis	3 (1.0)	3 (1.0)	2 (0.7)	8 (0.9)
Ischaemic heart disease Total Left-sided	 8 (2.6) 4 (1.3)	 6 (1.9) 2 (0.6)	 3 (1.0) 1 (0.3)	 17 (1.9) 7 (0.8)

Table A5: Relapses, second primary cancers and deaths, by fractionation schedule

	Fractionation schedule			Total
	50 Gy N=302 (%)	30 Gy N=308 (%)	28.5 Gy N=305 (%)	N=915 (%)
Relapses				
Local (breast skin or parenchyma)	3 (1.0)	3 (1.0)	4 (1.3)	10 (1.1)
Regional (axilla or supraclavicular fossa)	2 (0.7)	0	3 (1.0)	5 (0.5)
Distant	17 (5.6)	15 (4.9)	15 (4.9)	47 (5.1)
Second primary cancer	23 (7.6)	21* (6.8)	25 (8.2)	69* (7.5)
Deaths	30 (9.9)	33 (10.7)	33 (10.8)	96 (10.5)
Breast cancer	7 (2.3)	8 (2.6)	10 (3.3)	25 (2.7)
Other cause	23 (7.6)	25 (8.1)	23 (7.5)	71 (7.8)
Second cancer	*13*	*5*	*9*	*27*
Cardiovascular	*2*	*6*	*6*	*14*
Pulmonary	*2*	*8*	*2*	*12*
Other	*6*	*6*	*6*	*18*

* Includes one patient with angiosarcoma in the ipsilateral breast

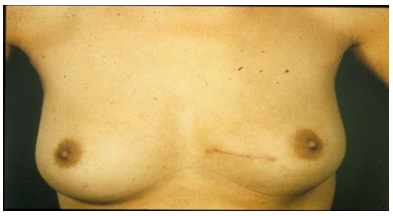
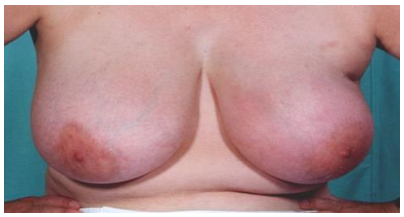
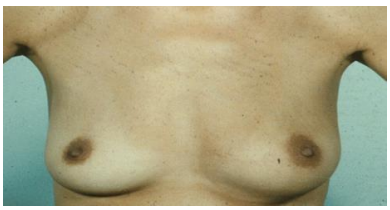
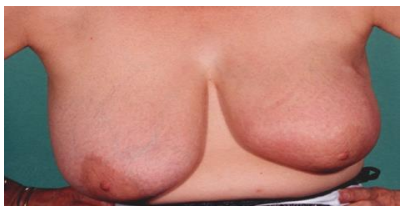
Scoring photographic assessments of change in breast appearance: further details of methods and update of published 2-year results

Methods

Photographs were scored by a team comprising two-three observers (two consultant clinical oncologists including JRY, Chief Investigator of FAST Trial, and a research manager in the CI's research team). Each scoring session began with a review of photographs previously scored, followed by scoring of the new photographs; sessions generally lasted for one day. As previously described[12], observers conferred and agreed a score by consensus. The same processes were followed for the 5-year photographs as for the original 2-year photograph scoring, with one change of personnel (clinical oncologist).

The categories of mild and marked change were assessed qualitatively as it was not possible to quantitatively measure breast shrinkage from the photographs. Examples of no change and marked change in photographic breast appearance are shown in Figure A2.

Figure A2: Examples of no change and marked change in photographic breast appearance

	No change	Marked change
After surgery, before radiotherapy:		
Years later:		

Update of 2-year results

Three additional 2-year photographs were scored since the 2011 publication[9], taking the total at year 2 to 732.

When the year 5 photographs were scored, it was noted that the overall prevalence of mild and marked changes was unexpectedly lower than reported at 2 years in the 2011 publication. Marked changes in particular would not be expected to reverse except for some cases with marked breast oedema. Since there was no objective measure used, such as a quantitative measurement of breast shrinkage for example, it is considered more likely that perceptions of radiotherapy-related changes changed over the long time period since the 2-year photographs were originally scored, causing discrepancies between the published 2-year results and the 5-year results reported here. Hence it was decided to rescore all 2-year photographs originally scored as mild

or marked change, together with a random sample of those originally scored as no change.

Overall 472 paired scores (original and rescore) were available for year 2. Scores where the rescore is the same as the original are highlighted in the table below. The number of scores expected to agree by chance have been calculated, along with the weighted Kappa statistic to test agreement between the pairs.

Table A6: Comparison of original scores and rescores for change in photographic breast appearance at 2 years

Original score	Rescore			Total
	No change	Mild change	Marked change	
No change	277 (98.6%)	4 (1.4%)	0 (0%)	**281**
Mild change	103 (66.0%)	52 (33.3%)	1 (0.6%)	**156**
Marked change	2 (5.7%)	23 (65.7%)	10 (28.8%)	**35**
Total	**382**	**79**	**11**	**472**

There were less mild and marked changes in the rescores at year 2. The number of pairs of scores expected to agree by chance were 227 (no change), 26 (mild), 0.8 (marked); i.e. observed agreement for mild and marked changes was higher than would be expected by chance (weighted Kappa=0.46 (“moderate” agreement), SE 0.03).

In summary, although the observed agreement between the original scores and the rescores for mild and marked changes was higher than would be expected by chance, it was decided to use the rescores for all analyses presented in this manuscript as the level of agreement overall was only “moderate”. The number of patients with mild/marked change in photographic breast appearance at 2 years reported here is less than in the 2011 manuscript, but conclusions regarding differences between the fractionation schedules are as before[9].