Title page

5-fraction radiotherapy for breast cancer: FAST Forward to implementation.

Authors:

Brunt AM, Haviland JS, Kirby AM, Somaiah N, Wheatley D, Bliss JM, Yarnold JR.

Corresponding author**:** Professor A M Brunt, University Hospitals of North Midlands NHS Trust & Keele University, c/o ICR

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

Affiliations:

Adrian Murray Brunt, David Weatherall Building, School of Medicine, University of Keele, Keele, Staffordshire ST5 5BG
m.brunt@keele.ac.uk

Joanne Susan Haviland, Clinical Trials and Statistics Unit (ICR-CTSU), The Institute of Cancer Research, Sutton, London, UK
jo.haviland@icr.ac.uk

Anna M Kirby, Department of Radiotherapy, Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Downs Road, Sutton, Surrey SM2 5PT UK
anna.kirby@rmh.nhs.uk

Navita Somaiah, Division of Radiotherapy and Imaging, Institute of Cancer Research and Royal Marsden NHS Foundation Trust, Downs Road, Sutton, Surrey SM2 5PT UK

navita.somaiah@icr.ac.uk

Duncan A Wheatley, Sunrise Centre, Royal Cornwall Hospital, Truro, Cornwall, TR1 3LJ
duncanwheatley@nhs.net

Judith M Bliss, Clinical Trials and Statistics Unit (ICR-CTSU), The Institute of Cancer Research, Sutton, London, UK
Judith.bliss@icr.ac.uk

John R Yarnold, Emeritus Professor of Clinical Oncology, Division of Radiotherapy and Imaging, The Institute of Cancer Research, London, UK
John.Yarnold@icr.ac.uk

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We are all authors of the FAST-Forward 2020 publication in The Lancet and have continued roles in the FAST-Forward trial.

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Research highlights

5-year local control after 26 or 27Gy 5-fractions non-inferior to 40Gy 15 fractions

No evidence that 5-fraction regimens inferior for any subgroup

26Gy 5-fractions side-effects, including subgroups, similar to 40Gy 15-fractions

26Gy 5-fractions for breast radiotherapy ready for implementing now

Key words

breast cancer; radiotherapy; hypofractionation; radiobiology; non-inferiority-RCT; tumour-control.

Abstract

Introduction

The phase 3 FAST-Forward trial reported outcomes for 26 and 27Gy schedules delivered in 5 fractions over 1 week versus 40 Gy in 15 fractions over 3 weeks in 4000 patients. We discuss concerns raised by the radiotherapy community in relation to implementing this schedule.

Ipsilateral Breast Tumour Relapse (IBTR)

Published estimated 5-year IBTR with 95% CI after 40Gy in 15 fractions was 2.1% (95% CI 1.4-3.1), 1.7% (1.2-1.6) after 27Gy and 1.4% (0.2-2.2) after 26Gy, emphatically showing non-inferiority of the 5-fraction regimens. Subgroup analyses comparing IBTR in 26Gy versus 40Gy show no evidence of differential effect regarding age, grade, pathological tumour size, nodal status, tumour bed boost, adjuvant chemotherapy, HER2 status and triple negative status. The number of events in these analyses is small and results should be interpreted with caution. There was only 1 IBTR event post-mastectomy.

Normal tissue effects

The 26Gy schedule, on the basis of similar NTE to 40Gy in 15 fractions, is the recommended regimen for clinical implementation. There is a low absolute rate of moderate/marked NTE, these are predominantly moderate not severe change. Subgroup analyses comparing clinician-assessed moderate or marked adverse effect for 26Gy versus 40Gy show no evidence of differential effects according to age, breast size, surgical deficit, tumour bed boost, or adjuvant chemotherapy.

Radiobiological considerations

The design of the FAST-Forward trial does not control for time-related effects, and the ability to interpret clinical outcomes in terms of underlying biology is limited. There could conceivably be a time-effect for tumour control. A slight reduction in α/β estimate for the late normal tissue effects of test regimens might be a chance effect, but if real could reflect fewer consequential late effects due to lower rates of moist desquamation.

Conclusion

The 26Gy 5-fraction daily regimen for breast radiotherapy can be implemented now.

Introduction

Over the last 30 years breast radiotherapy fractionation has been systematically investigated and debated. Moderate hypofractionation, using 15 or 16 fractions over three weeks delivering total doses in the range 40 to 42.5 Gy, has become the widespread international standard[1,2,3]. Recent published studies of 5-fraction breast radiotherapy describe safe, effective and simpler regimens likely to become a new standard of care. The phase 3 randomised FAST-Forward trial[4] reported outcomes, in relation to both tumour control and normal tissue effects, for 26 and 27 Gy in 5 fractions over 1 week versus 40 Gy in 15 fractions over 3 weeks in >4000 patients. Selection of total doses for the 5-fraction schedules was informed by earlier trials including the FAST trial of 915 patients testing 28.5 and 30 Gy in 5 fractions delivered once-weekly vs. 50 Gy in 25 fractions over 5 weeks, which has now published 10-year results[5].

At a consensus meeting held in October 2020 under the auspices of The Royal College of Radiologists the UK breast cancer radiotherapy community voted for 5-fraction breast radiotherapy as its new national standard for breast radiotherapy. Some commentators however suggest caution in adopting the schedule now. In the editorial accompanying the FAST-Forward results[6], Levy and Rivera agree that results are practice-changing for low-risk patients but want longer-term disease outcomes and clinically defined subgroup analyses. Offersen and Overgaard[7] argue that 26 Gy in 5 fractions is expected to be less effective than 40 Gy in 15 fractions based on conventional α/β estimates. We explore these issues along with recurring themes that have come up when presenting the data since publication.

Ipsilateral Breast Tumour Relapse (IBTR)

FAST-Forward is a non-inferiority trial with IBTR as the primary endpoint. Based on START trial data[8,9] and incorporating subsequent improvements in surgical technique and systemic therapy, it was anticipated that the incidence of IBTR by 5 years in the FAST Forward control group giving 40 Gy in 15 fractions would be 2%. Following discussions with clinicians and patient advocates, a non-inferiority margin of 1.6% was pre-specified in the protocol, which required a sample size of 4,000 patients. Estimated 5-year incidence of IBTR after 40

Gy in 15 fractions was 2.1% (95% CI 1.4-3.1), 1.7% (1.2-1.6) after 27 Gy and 1.4% (0.2-2.2) after 26 Gy. These 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.

These results on IBTR are definitive. However, one requirement proposed by commentators is longer follow-up as IBTR continues beyond 5 years. Other trials of hypofractionation have reported almost identical hazard ratios (HR) for IBTR at 5 and 10 years, the relevant metrics for comparisons of effect. For example, START-B[10] incidence rates of IBTR at 5/10 years after 40 Gy in 15 fractions vs. 50 Gy in 25 fractions were 1.9%/3.8% vs. 3.3%/5.2% respectively, reflecting crude HR of 0.72 (95% CI 0.43-1.21) and 0.70 (95% CI 0.46-1.07) i.e. unchanged between 5 and 10 years. The Ontario Clinical Oncology Group (OCOG) reported[11] 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%) at 5- and 10-year timepoints.

Commentators refer to subgroups for whom hypofractionation may not be so effective but the empirical data are reassuring. The 2011 American Society for Radiation Oncology (ASTRO) evidence-based guidelines[12] were unable to confirm agreement on hypofractionation in patients <50 years. The small number of patients included in trials and 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[11] suggested 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[13]. They 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[14], -A[8] and -B[9] trials in 5861 patients reporting 10-year results[10]. Treatment effects of hypofractionation in terms of tumour control 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 2018 ASTRO evidence-based guidelines approved

hypofractionated breast radiotherapy with 40/42.5 Gy in 15/16 fractions over 3 weeks irrespective of age, tumour grade or receptor status[1].

Wang et al[15] reported on 810 patients in a single institution randomised non-inferiority trial of 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 recurrence 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.

FAST-Forward reported non-inferior IBTR for both 5-fraction schedules and given the preceding arguments we would not expect inferiority to be observed in any subgroups, but what did we find? 1545 (37.8%) patients were in the high-risk category as defined by age <50 years, grade 3 tumour or both, and this was a stratification factor at randomisation. 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 1). Confidence intervals for the hazard ratios overlap for the subgroups, although the number of events in these analyses is 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. Table 1 shows the frequencies and number of patients in each category of age <50 years, grade 3, post-mastectomy, triple negative and HER2 positive tumours. No evidence to signal concern is 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.

Normal tissue effects (NTE)

In FAST-Forward late NTE assessed by clinicians, patients and photographs were key secondary endpoints. The 26 Gy in 5 daily fractions schedule, on the basis of similar NTE to 40 Gy in 15 fractions, is the recommended regimen for clinical implementation. By 'similar' we mean that NTE were neither statistically nor clinically significantly different from 40 Gy in 15 fractions with respect to clinician- or patient-assessed outcomes, including photographic assessments conducted blind to treatment allocation. The 27 Gy 5-fraction schedule was statistically 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 detect a difference in dose intensity corresponding to 3 Gy in 2 Gy equivalents assuming α/β=2 Gy (see below). The 27 Gy 5-fraction regimen exhibited late NTE rates of comparable magnitude to 50 Gy in 25 daily fractions. 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[11]. 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 being relatively more important[16]. 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[17]. In this context, the milder erythema was a response 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 arms (total doses 28.5 & 30 Gy) of the FAST trial than the 50 Gy schedule[18].

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[19]. Table 2 shows FAST-Forward breast assessments recorded separately by patients and clinicians. It is important to consider the absolute frequencies of events as well as the relative comparisons between schedules. For example, for breast shrinkage, the most frequent of the clinician-assessed

effects, the prevalence of moderate or marked effects at 5 years was 5.5% in 40 Gy and 6.8% in 26 Gy, and the 5-year prevalence of moderate or marked induration outside the tumour bed was only 0.1% and 2.1% in 40Gy and 26Gy respectively. For all clinician-assessed events documented in the moderate/marked change categories, most were moderate rather than marked in severity.

With regard to increasing frequency of late NTE with time, stability of the HR at longer timepoints is clinically relevant, as shown for START-B[10] and FAST[5] in table 3. The principle of the relative difference between test and control group 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 tested the non-inferiority of 40 Gy in 15 fractions in terms of breast induration at 3 years compared with 50 Gy in 25 fractions[7]. This important study reproduced the START-B results with 3-year rates of induration 11.8% (95% CI, 9.7% to 14.1%) in the 50 Gy group and 9.0% (95% CI, 7.2% to 11.1%) in the 40 Gy group (risk difference, 22.7%; 95% CI, 25.6% to 0.2%; p= .07). Low uptake of hypofractioned whole-breast radiotherapy in the United States, due in part to concerns of safety for patients receiving a tumour bed boost, chemotherapy or having large breast size, led to a randomised non-inferiority trial[20]. The standard treatment of 50 Gy in 25 daily fractions with a 10-14 Gy boost in 5-7 fractions was tested against 42.56 Gy in 16 daily fractions with a 10-12.5 Gy boost in 4-5 fractions. 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, the primary endpoint, was 5.4% lower (8.2% vs 13.6%, p=0.002 for non-inferiority) in the hypofractionated arm 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 looked at dose heterogeneity with regards to the FAST trial and the risk of 'triple trouble[21]. 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 showed 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 change 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.

In FAST-Forward, 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 provides 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 2).

What about other organs at risk? The heart is often mentioned particularly as very long follow-up is required to assess full risk, though 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[22]. 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 group and 3 cases in the 26 Gy group. The most frequent specialist referral we have seen is to lymphoedema clinics for breast lymphoedema, 90 patients (6.6%) following 40 Gy, 122 (8.9%) after 27 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 7 (0.7%) patients after 40 Gy, 18

(1.8%) after 27 Gy and 17 (1.7%) patients after 26 Gy with no oedema in 94%, 92% and 93% respectively. These rates are low and not clinically or statistically significantly different.

Some radiobiological considerations: Tumours

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[23]. 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[8,10,14] (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 and assuming complete repair of sub-lethal damage between fractions in all groups, an unconfounded estimate of sensitivity to fraction size (α/β) is possible. This simply involves identifying the total dose in 13 fractions matching the IBTR rate in the 25-fraction group, sometimes involving interpolation between test dose levels. In START-A, IBTR after 13 fractions of 3.2 Gy was closer than 13 fractions of 3.0 Gy to IBTR after 25 fractions of 2.0 Gy, from which a direct α/β estimate of 3.5 Gy (95% CI 1.2-5.7) was based on the 10-year total of 349 IBTR events in 3646 women[24]. The 8.4 Gy reduction from 50 Gy to 41.6 Gy needed to match the IBTR of 3.2 Gy fractions with 25 fractions of 2.0 Gy is a vivid measure of fraction size sensitivity at play.

To our knowledge, START-P/-A trials 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 α/β=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 (table 4), 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 1% *lower* than the 5-week control regimen (ns). A post hoc analysis asked the question "If this difference is real, what would it tell us about the impact of treatment time?"[24] 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[25] in patients treated with primary radiotherapy and confirmed by Lyhne et al[26] in a randomised clinical trial comparing 60 Gy in 30 fractions delivered 5 versus 6 times per week. 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 and/or chemotherapy. In the context of the START-B result, if the post hoc analysis (hypothesis generating) estimated 0.6 Gy/day (95% CI 0.1-1.8, p=0.02) 'wasted' dose in control group patients during weeks 4 & 5 is true, it implies roughly 14 x 0.6 = 8 Gy of the control regimen (50 Gy) 'wasted'. This implies a time-corrected $EQD_{2/3.5}$ of 42 Gy for the 5-week regimen compared to 45 Gy for the 3-week schedule. The Danish-led HYPO trial[7] offers an independent test of START-B in a comparable group of patients, in whom the 9-year risk of locoregional recurrence is 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), a result very similar 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 wide CI reflecting very low incidence of IBTR. The analysis plan did not incorporate a hypothetical time correction, so the α/β estimate of 3.7 Gy necessarily incorporates all underlying biology, including fraction size sensitivity, completeness of repair and putative time effects. 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 4. The difference in estimated anti-tumour effect between this $EQD_{2/3.7}$=41 for the 5-fraction schedule and $EQD_{2/3.7}$ =45 Gy of 40 Gy in 15 fractions would be too small to detect at such high levels of local control. Nevertheless, a robust clinical conclusion can be drawn, namely 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[27]. With a 5-year incidence of IBTR of 2.1% (95% CI 1.4-3.1) after 40 Gy in 15 fractions, the incidence without any radiotherapy would be expected to be about 6% at 5 years and 10% at 10 years according to systematic overviews of radiotherapy effects[28] The observed 5-year incidence IBTR after 26 Gy in 5 fractions are hardly consistent with an absence of effect.

Some radiobiological considerations: Late reacting normal tissues

The discussion of tumour responses above has a lot to say about the potential impact of time on IBTR. Turning to late NTE, meticulous data generated in human skin are consistent with minimal measurable effect of time. Turesson[29] 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. The effect was thought more likely to represent a very slow component of repair decaying with a $T_{1/2}$ of around 40 days. The same post hoc investigation of a time effect in breast cancer in START-B described above included analysing effect of time on late NTE 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[26].

The reason for providing this level of detail is that the selection of FAST-Forward test dose levels 27 and 26 Gy assumed, firstly, no clinically significant time effect for late NTE 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 $EQD_{2/2.8}$ of all FAST-Forward schedules relative to 50 Gy in 25 fractions are shown in Table 5, where negative values indicate estimated NTE rates lower than 50 Gy in 25 fractions.

Although the 27 Gy test dose level was predicted to be iso-effective for NTE with 40 Gy in 15 fractions, the observed iso-effect for NTE at 5 years was closer to 26 Gy, suggesting a slightly lower α/β value, see Table 4. The α/β point estimates are all around 2 Gy, corresponding to $EQD_{2/2}$ of about 47 Gy for 26 Gy in 5 fractions. This compares to $EQD_{2/\mathbf{2.8}}$ of about 46 Gy for 40 Gy in 15 fractions, the latter using the combined estimate of α/β=2.8 for this regimen based on START-A and FAST.

The 95% confidence intervals of α/β point estimates for all NTE scored in the FAST-Forward trial fall within the confidence intervals of α/β estimates for all late NTE in the FAST and START-P/-A trials. One interpretation, and statistically-speaking the likeliest, is that they are all internally consistent with each other. Alternatively, the differences in α/β estimates is real, and late NTE are truly slightly more likely after 26 Gy in 5 fractions. If so, we exclude repopulation for the reasons described above, leaving slow (>24hr) repair between daily fractions reported by Turesson and modelled in Appendix 2 of the FAST Forward trial protocol as the likely explanation[4]. Alternatively, lower rates of moist desquamation (high α/β) after 5-fraction regimens may cause less consequential late NTE (same high α/β), enough to reduce the α/β estimate of late NTE compared to conventional fractionation. These somewhat esoteric considerations should not obscure the all-important clinical conclusion that 26 Gy in 5 daily fractions offers patients comparable NTE rates and non-inferior IBTR to 40 Gy in 15 fractions.

<u>UK consensus and recommendations for implementation</u>

The UK consensus meeting[2] included an in-depth review of the FAST-Forward results, including many of the clinical aspects examined in this manuscript. The results of FAST-Forward were planned to be taken together with those of IMPORT LOW[30], which had the same control regimen of 40 Gy in 15 fractions to the whole breast, and therefore are applicable to partial breast radiotherapy. There is no clinical rationale for excluding groups which were underrepresented unless there is a logical argument for doing so. The decisions taken at the consensus meeting were to adopt 26 Gy in 5 daily fractions of 5.2 Gy for whole-breast, partial-breast and chest wall radiotherapy as the standard regimen.

The coronavirus pandemic has unexpectedly given clinicians and centres all over the world experience of 26 Gy in 5 daily fractions. Audit of that experience by centre, region or country should aid confidence in incorporating it into national or international guidelines. The original publication[4] and appendices include links to the trial protocol as a resource, the UK consensus weblink in this document is also a resource and the FAST-Forward team have provided advice both to individual centres and via webinars to international groups over the

last year. The START trials[8,9] 5-year outcomes were published in 2008 and the 40 Gy in 15 fractions schedule was adopted as UK standard of care in 2009 (https://www.nice.org.uk/guidance/ng101) as a result albeit that the 10-year outcomes[10] gave clinicians and patients confidence that regimen was safe and effective in the longer term. Similarly, the 26 Gy 5-fraction schedule is ready for adoption globally, and indeed is already going through that process in some countries. Whilst, based on the START[10] and FAST[5] data, it is anticipated that outcomes will remain non-inferior at 10 years, it is important to continue collecting data to the 10-year timepoint to provide reassurance around the longer-term safety and efficacy of the 5 daily fraction schedule.

Conclusions

We conclude that 26 Gy in 5 daily fractions for breast radiotherapy is an effective regimen for tumour control. There is no evidence or scientific rationale to argue against it for any subgroup. With regard to adverse effects it is as well tolerated as moderate hypofractionation over 3 weeks of daily radiotherapy. Furthermore, it is convenient for patients and less burdensome for radiotherapy departments. We recommend that 26 Gy in 5 daily fractions for all indications of whole-breast, partial-breast and chest wall radiotherapy be adopted as the standard of care.

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References

1. Smith BD, Bellon JR, Blitzblau R, Freedman G, Haffty B, Hahn C, 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: 145–52. doi: 10.1016/j.prro.2018.01.012
2. Lewis P, Griffin S, Coles C, Brunt AM, Locke I and Roques T. Moving forward fast with FAST-Forward. Clin Oncol 2021
3. Marta GN, Coles C, Kaidar-Person O, Meattini I, Hijal T, Zissiadis Y et al. The use of moderately hypofractionated post-operative radiation therapy for breast cancer in clinical practice: A critical review. Crit Rev Oncol Hematol. 2020; 156: 103090. https://doi.org/10.1016/j.critrevonc.2020.103090
4. Brunt AM, Haviland JS, Wheatley DA, Sydenham MA, Alhasso A, Bloomfield DJ, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet 2020; 395: 1613–26. https://doi.org/10.1016/S0140-6736(20)30932-6
5. Brunt AM, Haviland JS, Sydenham M, Agrawal RK, Algurafi H, Alhasso A, et al. Ten-year results of FAST: A randomized controlled trial of 5-fraction whole breast radiotherapy for early breast cancer. J Clin Oncol. 2020; 38: 3261-3272. DOI: 10.1200/JCO.19.02750
6. Levy A and Rivera S. 1-week hypofractionated adjuvant whole-breast radiotherapy: towards a new standard? 28 Apr 2020, 395(10237):1588-1589 https://doi.org/10.1016/S0140- 6736(20)30978-8

7. Offersen BV, Alsner J, Nielsen HM, Jakobsen EH, Nielsen MH, Krause M, et al: Hypofractionated versus standard fractionated radiotherapy in patients with early breast cancer or ductal carcinoma in situ in a randomized phase III trial: The DBCG HYPO trial. J Clin Oncol 2020; 38: 3615-25. doi:10.1200/JCO.20.01363
8. Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, Bliss JM, et al. 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: 331–41. doi: https://doi.org/10.1016/S1470-2045(08)70077-9
9. Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, Bentzen SM, et al. The UK standardisation of breast radiotherapy (START) trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet 2008; 371: 1098–107.
10. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK standardisation of breast radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol 2013; 14: 1086-94. doi: https://doi.org/10.1016/S1470-2045(13)70386-3
11. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010; 362: 513–20. doi: https://doi.org/10.1056/NEJMoa0906260
12. Smith BD, Bentzen SM, Correa CR et al. Fractionation for whole breast irradiation: an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Int J Radiat Oncol Biol Phys 2011; 81: 59–68.
13. Bane AL, Whelan TJ, Pond GR, Parpia S, Gohla G, Fyles AW, et al: Tumor factors predictive of response to hypofractionated radiotherapy in a randomized trial following breast conserving therapy. Ann Oncol 2014; 25: 992-8. Doi: https://doi.org/10.1093/annonc/mdu090
14. Owen JR, Ashton A, Bliss JM, Homewood J, Harper C, Hanson J, et al. 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. doi: 10.1016/S1470-2045(06)70699-4.

15. Wang S-L, Fang H, Hu C, Song Y-W, Wang W-H, Hu C, et al. Hypofractionated versus conventional fractioned postmastectomy radiotherapy for patients with high-risk breast cancer: a randomized, non-inferiority, open-label, phase 3 trial. Lancet Oncol 2019; 20: 352-60. http://dx.doi.org/10.1016/S1470-2045(18)30813-1.
16. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol 1989; 62:679-94.
17. Brunt AM, Wheatley D, Yarnold J, Somaiah N, Kelly S, Harnett A, et al. 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; 120: 114–8. doi: https://doi.org/10.1016/j.radonc.2016.02.027
18. Agrawal RK, Alhasso A, Barrett-Lee PJ, Bliss JM, Bliss P, Bloomfield D, et al. First results of the randomised UK FAST trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015). Radiother Oncol 2011; 100:93-100. doi: https://doi.org/10.1016/j.radonc.2011.06.026
19. Yarnold J, Bentzen SN, Coles C and Haviland J. Hypofractionated whole-breast radiotherapy for women with early breast cancer: myths and realities. Int J Radiat Oncol Biol Phys 2011; 89: 1-9.
20. Shaitelman SF, Lei X, Thompson A, Schlembach P, Bloom ES, Arzu IY, et al. Three-year outcomes with hypofractionated versus conventionally fractionated whole-breast irradiation: Results of a randomized, noninferiority clinical trial. J Clin Oncol. 2018; 36: 3495-3503.
21. Tsang Y, Haviland J, Venables K, Yarnold J on behalf of the FAST trial management group. The impact of dose heterogeneity on late normal tissue complication risk after hypofractionated whole breast radiotherapy. Radiother Oncol 2012; 104: 143-147.
22. Darby SC, Ewertz M, McGale P, Bennett AM, Blom-Goldman U, Bronnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013; 368: 987–998.
23. Brand DH and Yarnold JR. The linear-quadratic model and implications for fractionation. Clin Oncol 2019; 31: 673-677.
24. Haviland JS, Bentzen SM, Bliss JM, Yarnold JR, on behalf of the START Trial Management Group. Prolongation of overall treatment time as a cause of treatment

failure in early breast cancer: an analysis of the UK START (Standardisation of Breast Radiotherapy) trials of radiotherapy fractionation. Radiother Oncol 2016; 121:420-423.

25. Withers HR, Taylor JMG, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol 1988; 27, 131-146. DOI: 10.3109/02841868809090333
26. Lyhne NM, Primdahl H, Kristensen CA, Andersen E, Johansen J, Andersen LJ, et al. The DAHANCA 6 randomized trial: Effect of 6 vs 5 weekly fractions of radiotherapy in patients with glottic squamous cell carcinoma. Radiother Oncol 2015; 117: 91-98.
27. Offersen BV and Overgaard J. Breast cancer radiation therapy. Lancet 2020; 396: 1558.
28. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011; 378: 1707-1716.
29. Turesson I and Thames HD. Repair capacity and kinetics of human skin during fractionated radiotherapy: Erythema, desquamation, and telangiectasia after 3 and 5 year's follow-up. Radiother Oncol 1989; 15: 169-188.
30. Coles CE, Griffin CL, Kirby AM, Titley J, Agrawal RK, Alhasso A, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. Lancet 2017;390: 1048-1060.

Figure legends

Figure 1a: Subgroup analyses of time to ipsilateral breast tumour relapse (IBTR) for 26 Gy in 5 fractions versus 40 Gy in 15 fractions

Figure 1b: Subgroup analyses of time to ipsilateral breast tumour relapse (IBTR) for 27 Gy in 5 fractions versus 40 Gy in 15 fractions

Figure 2a: Subgroup analyses of time to first moderate or marked clinician-assessed adverse event in breast / chest wall for 26 Gy in 5 fractions versus 40 Gy in 15 fractions

Figure 2b: Subgroup analyses of time to first moderate or marked clinician-assessed adverse event in breast / chest wall for 27 Gy in 5 fractions versus 40 Gy in 15 fractions

Figure 1a: Subgroup analyses of time to ipsilateral breast tumour relapse (IBTR) for 26 Gy in 5 fractions versus 40 Gy in 15 fractions

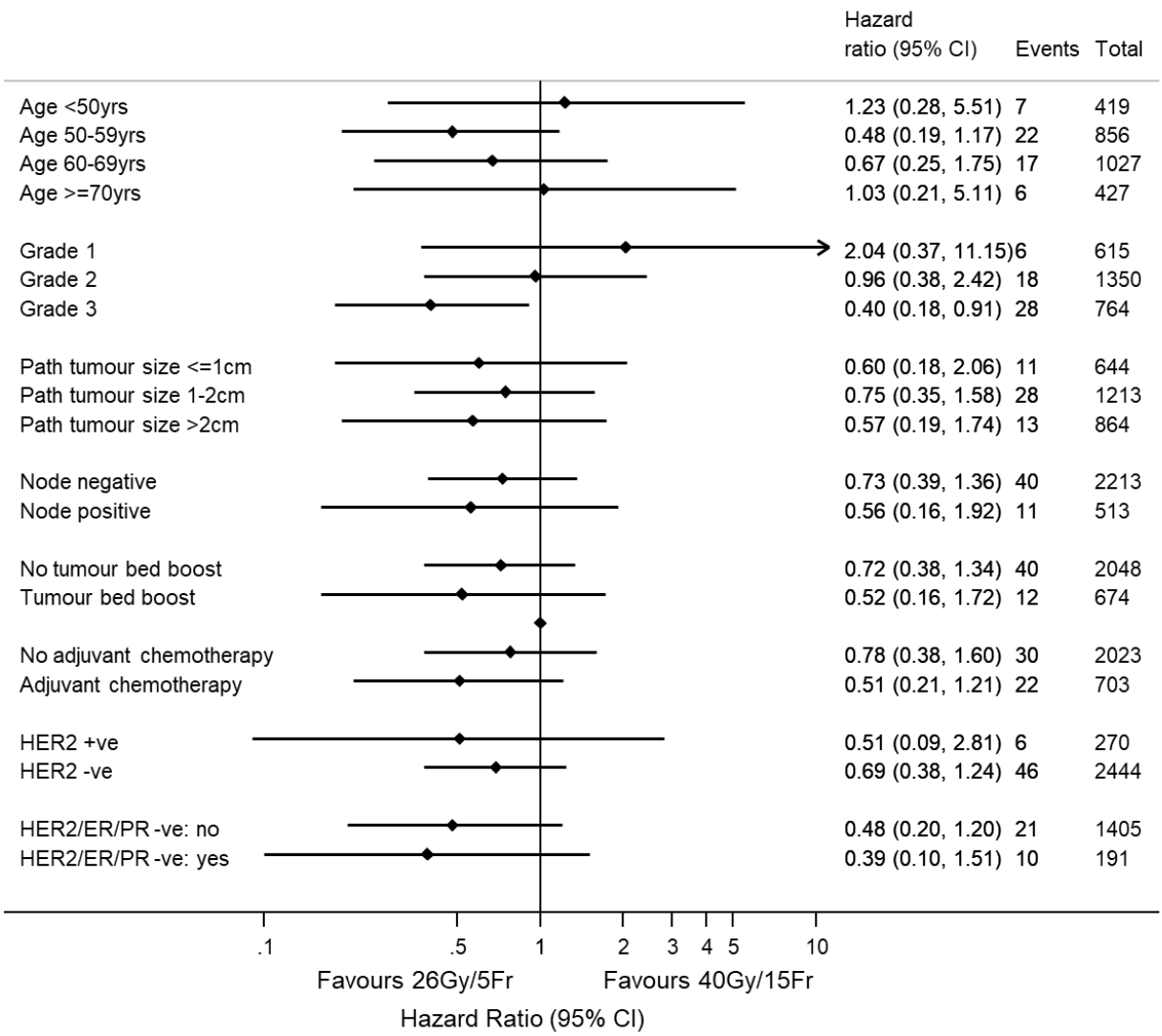


Figure 1b: Subgroup analyses of time to ipsilateral breast tumour relapse (IBTR) for 27 Gy in 5 fractions versus 40 Gy in 15 fractions

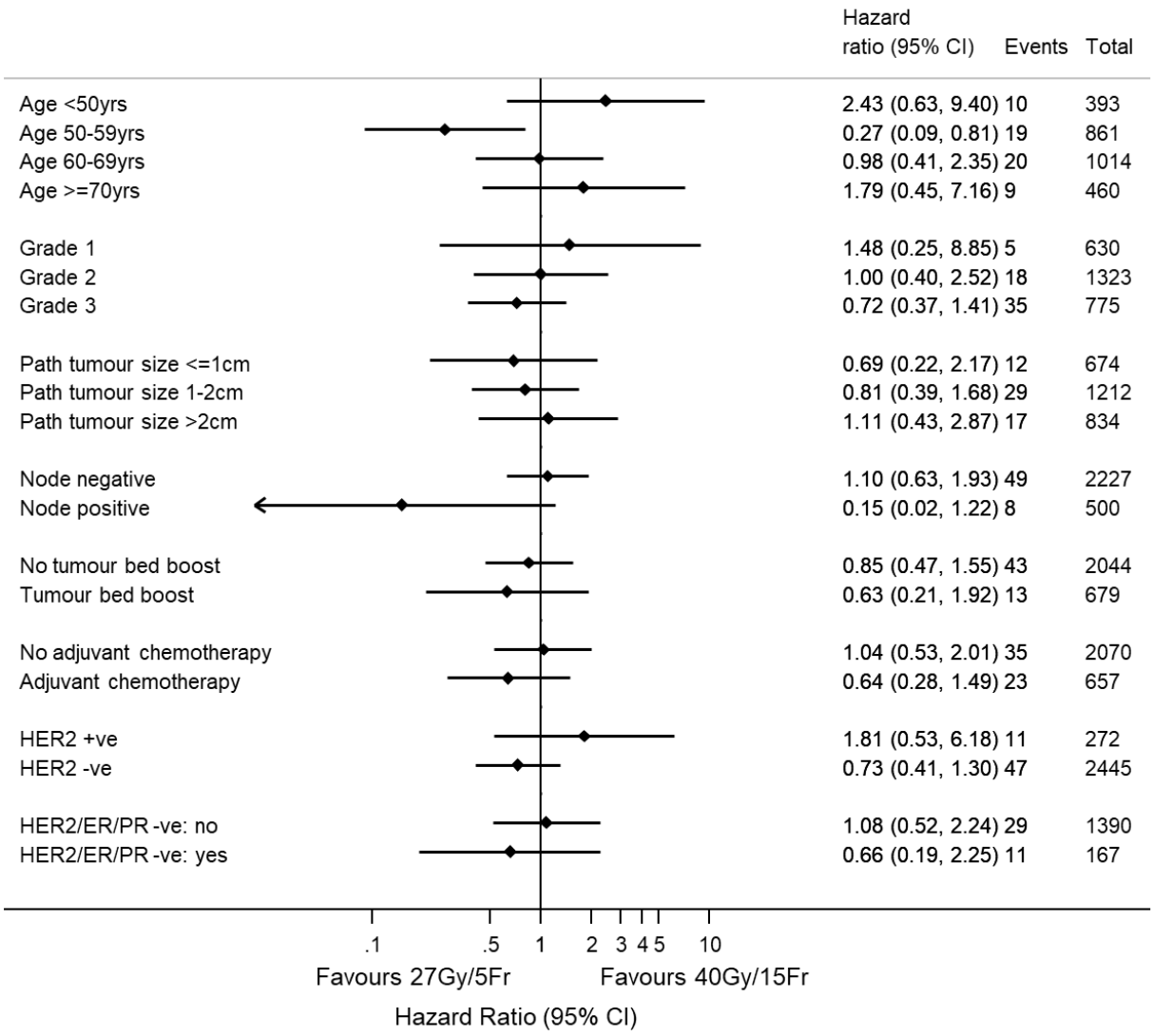
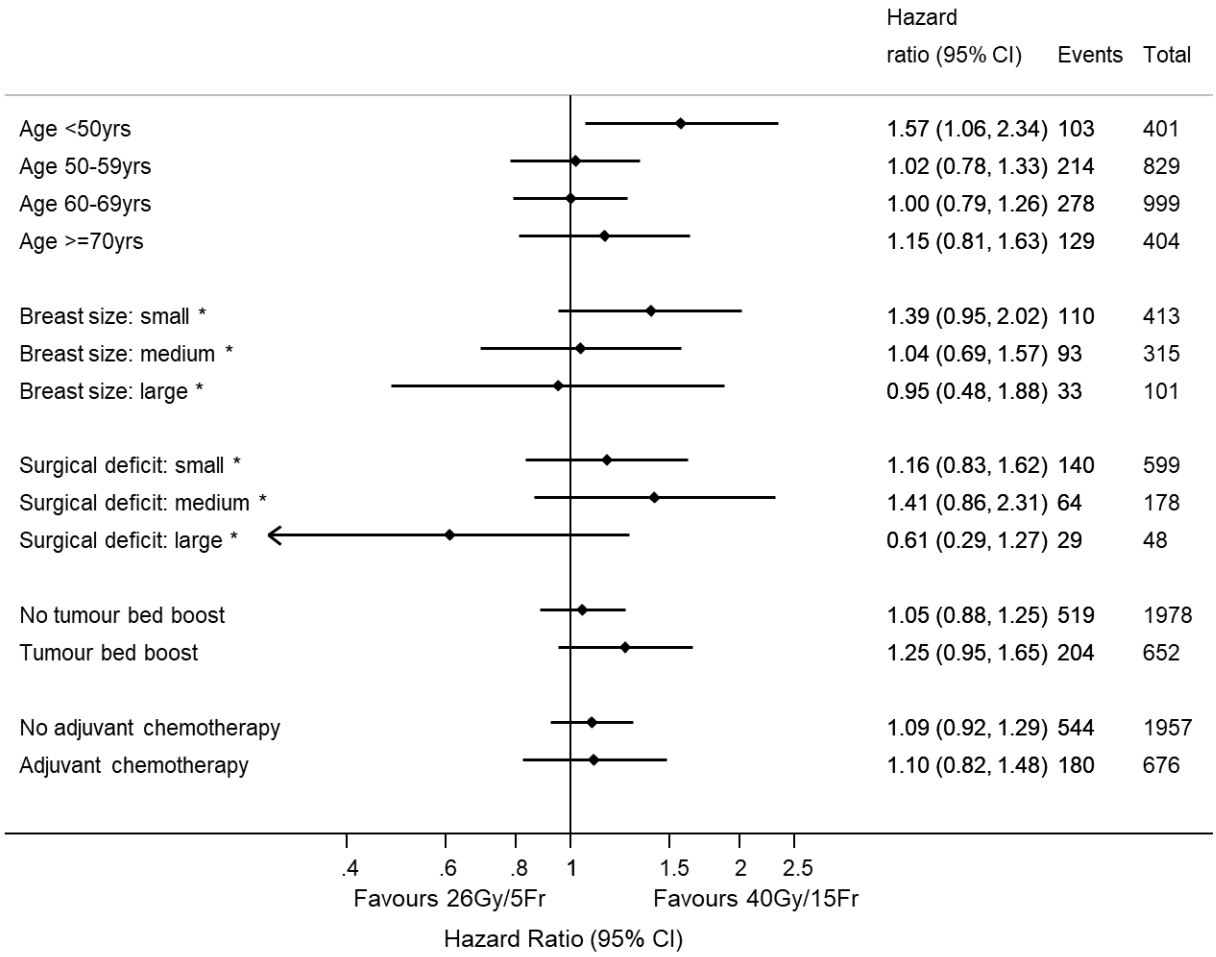
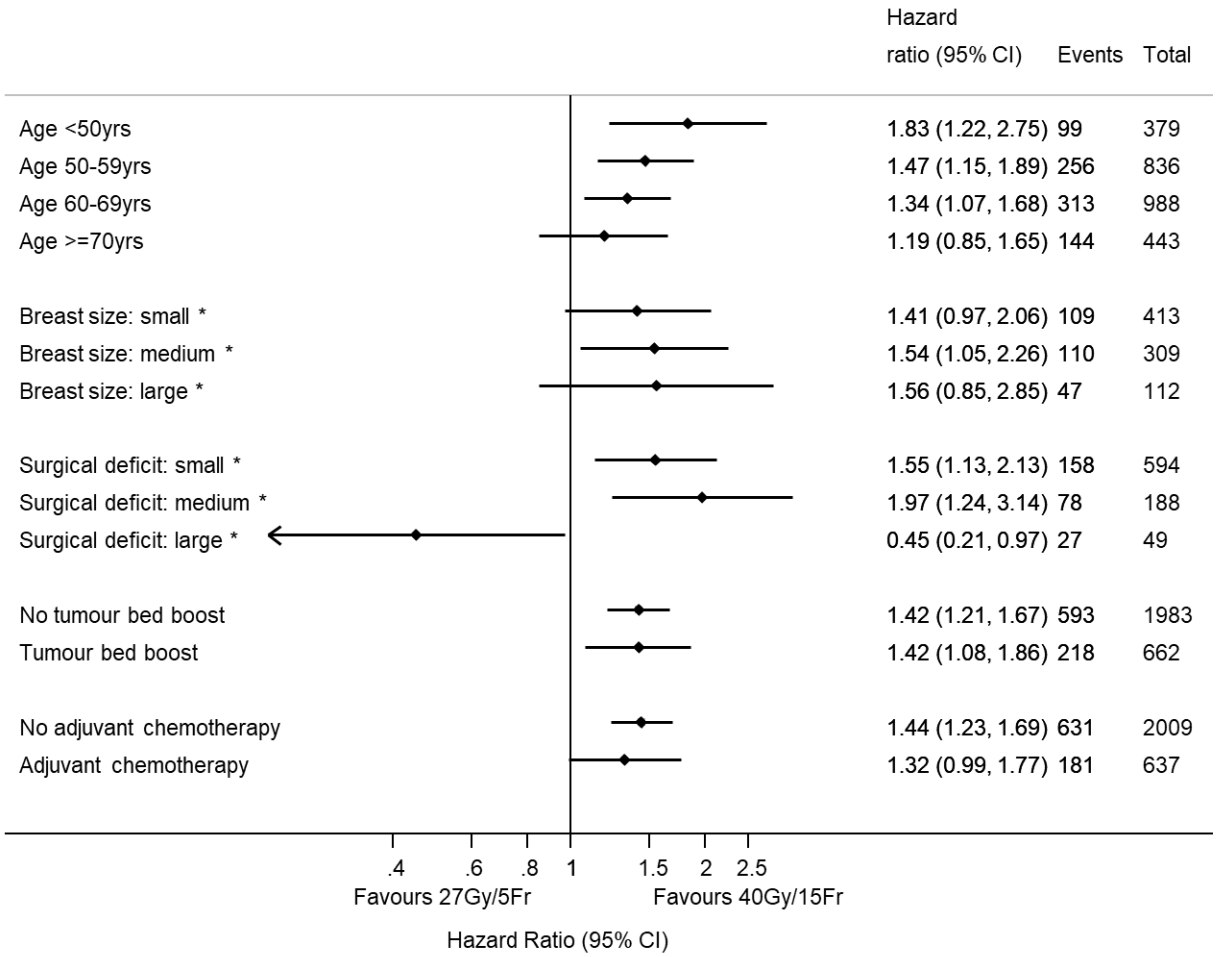


Figure 2a: Subgroup analyses of time to first moderate or marked clinician-assessed adverse event in breast / chest wall for 26 Gy in 5 fractions versus 40 Gy in 15 fractions



* Assessed from baseline photographs

Figure 2b: Subgroup analyses of time to first moderate or marked clinician-assessed adverse event in breast / chest wall for 27 Gy in 5 fractions versus 40 Gy in 15 fractions



* Assessed from baseline photographs

Table legends

Table 1. Ipsilateral breast tumour relapse by higher risk subgroup in FAST-Forward.

Table 2. Breast clinician and patient assessment in FAST-Forward.

Table 3. Treatment comparisons for moderate or marked breast shrinkage at 5 & 10 years' follow-up in previous breast RT trials

Table 4. 2 Gy equivalents (EQD2) for regimens (referenced) with relevant α/β point values from manuscript text.

Table 1. Ipsilateral breast tumour relapse by higher risk subgroup in FAST-Forward.

Subgroup	**Event/Number**	**40 Gy/15 fractions**	**27 Gy/5 fractions**	**26 Gy/5 fractions**
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

Table 2. Breast clinician and patient assessment in FAST-Forward.

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.

Table 3. Treatment comparisons for moderate or marked breast shrinkage at 5 & 10 years' follow-up in previous breast RT trials

Trial	Risk ratio (95%CI) at 5 years	Risk ratio (95%CI) at 10 years
START-B:		
40Gy/15Fr vs 50Gy/25Fr	0.77 (0.56-1.07)	0.87 (0.59-1.26)
FAST:		
30Gy/5Fr vs 50Gy/25Fr	2.03 (1.15-3.58)	1.83 (0.88-3.81)
28.5Gy/5Fr vs 50Gy/25Fr	1.20 (0.63-2.27)	1.83 (0.88-3.81)

Table 4. 2 Gy equivalents (EQD2) for regimens (referenced) with relevant α/β point values from manuscript text.

α/β Gy $\rightarrow$ Regimen/reference $\downarrow$	3.7	3.5	3.0	2.8	2.3	2.0	1.8	1.7
50 Gy/25 Fr	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
43.5 Gy/15 Fr[16]	50.4	50.6	51.3	51.7	52.6	53.3	53.8	54.1
42.9 Gy/13 Fr[15]	52.7	53.0	54.0	54.5	55.9	56.8	57.6	58.0
42.5 Gy/16 Fr[12]	47.4	47.6	48.1	48.3	49.0	49.5	49.9	50.1
41.6 Gy/13 Fr[9]	50.4	50.7	51.6	52.0	53.2	54.1	54.7	55.1
40 Gy/15 Fr[4,8,10]	44.7	44.9	45.4	45.6	46.2	46.7	47.0	47.2
39 Gy/13 Fr[9,15]	45.9	46.1	46.8	47.1	48.1	48.7	49.3	49.5
30 Gy/5 Fr[5]	51.1	51.8	54.0	55.0	57.9	60.0	61.6	62.4
28.5 Gy/5 Fr[5]	47.0	47.7	49.6	50.5	53.0	54.9	56.3	57.0
27 Gy/5 Fr[4]	43.1	43.7	45.4	46.1	48.4	50.0	51.2	51.8
26 Gy/5 Fr[4]	40.6	41.1	42.6	43.3	45.3	46.8	47.9	48.5

Table 5. 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 (https://www.icr.ac.uk/our-research/centres-and-collaborations/centres-at-the-icr/clinical-trials-and-statistics-unit/clinical-trials/fast_forward_page/)

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

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