Dose escalated simultaneous integrated boost radiotherapy in early breast cancer: results of the IMPORT HIGH multi-centre phase III randomised controlled trial (ISRCTN47437448)

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ABSTRACT

Background

A tumour bed boost delivered after whole-breast radiotherapy increases local cancer control rates but requires more patient visits and can increase breast hardness. IMPORT HIGH tests simultaneous-integrated-boost (SIB) against sequential-boost aiming to reduce treatment duration whilst maintaining excellent local control and similar/reduced toxicity.

Methods

IMPORT HIGH (ISRCTN47437448) is a non-inferiority open-label randomised controlled trial allocating women after breast-conserving surgery for pT1-3pN0-3aM0 invasive carcinoma between 40Gy/15F to whole-breast (WB) + 16Gy/8F sequential photon tumour bed (TB) boost ("40+16Gy"; control), 36Gy/15F to WB, 40Gy to partial-breast + 48Gy ("48Gy") or + 53Gy ("53Gy") in 15F SIB to TB (1:1:1). Boost clinical target volume was the clip-defined TB. Primary endpoint was ipsilateral breast tumour relapse (IBTR); assuming 5% 5-year incidence with 40+16Gy, non-inferiority was pre-defined as $\leq$3% absolute excess in test groups (upper limit of 2-sided 95%CI). Adverse events (AE) were assessed by clinicians, patients and photographs.

Findings

2617 patients (871: 40+16Gy, 874: 48Gy, 872: 53Gy) were recruited 03/2009-09/2015 from 76 UK centres. Median boost CTV was 13cm^3 (IQR 7, 22). At 74-months median follow-up there were 76 IBTR events (40+16Gy: n=20, 48Gy: n=21, 53Gy: n=35). Five-year IBTR incidence was 1·9% (95% CI 1·2, 3·1) for 40+16Gy, 2·0% (1·2, 3·2) for 48Gy, 3·2% (2·2, 4·7) for 53Gy, with estimated absolute differences versus 40+16Gy: 0·1% (-0·8, 1·7) for 48Gy, 1·4% (0·03, 3·8) for 53Gy. Upper confidence limit for 48Gy versus 40+16Gy indicated non-inferiority for 48Gy. Cumulative 5-year incidence of clinician-reported moderate/marked breast induration was 11·5% for 40+16Gy, 10·6% for 48Gy (p=0·40 versus 40+16Gy) and 15·5% for 53Gy (p=0·015 versus 40+16Gy).

Interpretation

In all groups five-year IBTR incidence was lower than the 5% originally expected regardless of boost sequencing. Dose-escalation is not advantageous. 5-year moderate/marked AE rates were low using small boost volumes. IMPORT HIGH-SIB is safe and reduces patient visits. 297/300

Funding

Cancer Research UK (CRUK/06/003)

RESEARCH IN CONTEXT

Evidence before this study

A comprehensive literature search was carried out before the trial opened using PubMed and Medline to review all publications addressing (i) pathological and clinical studies investigating patterns of ipsilateral breast tumour relapse following radiotherapy (RT) (ii) breast tumour bed boost studies (iii) methods of tumour bed definition and localisation for breast boost. It was concluded that most ipsilateral breast tumour relapses occur in and around the tumour bed; all published breast boost trials used sequential boost RT, and historical methods of breast boost localisation and treatment were suboptimal – large volumes were needed to reduce risk of tumour bed "miss", which could also cause increased normal tissue toxicity. It was hypothesised that dose intensity modulation using simultaneous integrated boost (SIB) offers a novel and effective alternative to conventional sequential boost techniques with a reduction in number of treatments.

Added value of this study

IMPORT HIGH is the first phase III randomised trial to publish 5-year outcome data using hypofractionated SIB and is substantially larger than any other reported SIB studies. In addition, as far as the authors are aware, it is the first breast boost trial to use smaller, more targeted boost volumes with intensity modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) in all groups, including the control group. This ensured consistent boost volumes across the treatment groups, leaving timing of boost (synchronous versus sequential) as the main variable in the trial. At 5 years, hypofractionated SIB (48Gy) shows non-inferiority in terms of ipsilateral local relapse compared with sequential boost with incidence of relapse much lower than anticipated, and with low late adverse effect rates in all groups. There was no advantage for escalating to 53Gy SIB, which was associated with increased breast induration. In contrast, 48Gy SIB showed similar or reduced normal tissue toxicity compared with control. Follow-up is on-going and reporting of 10-year results is envisaged.

Implications of all the available evidence

Standard linear accelerators can deliver both IMRT and IGRT, making it possible to deliver SIB in most countries worldwide using existing resources. Breast-boost radiotherapy usually consists of 4-6 weeks of treatment, so a reduction to just 3 weeks SIB would be beneficial for patients and healthcare systems. For those centres who have adopted 1-week whole breast RT followed by 1 week boost, 3-week SIB is still an important treatment for patients requiring 3-week nodal RT, including internal mammary irradiation. The results of IMPORT HIGH will also facilitate new studies to investigate 1-week SIB to include patients needing nodal radiotherapy.

INTRODUCTION 4863/4500

Data from pathological breast specimens and clinical studies suggest that most ipsilateral breast tumour relapses occur close to the original site of resection - the tumour bed (TB) (1-3). Furthermore, randomised trials of breast conserving surgery (BCS) followed by whole-breast radiotherapy with or without a TB boost demonstrated that a boost roughly halves the risk of breast tumour relapse (4, 5). Although individual boost trials have not shown an overall survival advantage over whole-breast radiotherapy alone, breast tumour relapse should be minimised as it is a significant life-event for patients often requiring mastectomy and systemic therapy. Independent prognostic factors for local relapse include young age and high tumour grade (6). In the EORTC boost versus no boost trial, risk of local failure at 10-years with boost was 13·5% and 8·7% in patients <40-years and 41-50-years respectively.

The potential local control gain with boost is offset by an increased risk of late normal tissue toxicity, including an approximate doubling of breast fibrosis (7) which increases with irradiated volume (8). Boost is traditionally delivered sequentially after whole-breast radiotherapy in 5-8 treatments (fractions) thereby increasing treatment burden for patients and health care systems.

IMPORT HIGH builds on results of previous UK breast radiotherapy trials (9, 10) and uses newer radiation techniques (intensity-modulated-radiotherapy (IMRT) and image-guided-radiotherapy (IGRT)) to address the challenges of boost radiotherapy. Using IMRT, dose-intensity can be modulated throughout the breast to better reflect risk of relapse. Dose per fraction can be increased to the tumour bed and this is known as a simultaneous integrated boost (SIB). The boost volume is minimised by targeting titanium clips (or gold seeds) placed in the TB during surgery (11, 12). This enables escalation of radiation dose to the TB whilst delivering a standard dose to nearby breast tissue and a slightly lower dose to peripheries of breast tissue where risk of relapse is lowest. IMPORT HIGH is the largest randomised trial to date testing dose-escalated SIB against standard sequential boost. Five-year efficacy and normal tissue toxicity results are reported.

METHODS

Study design

IMPORT HIGH is a multicentre randomised phase III non-inferiority trial that tested the safety and efficacy of dose-escalated IMRT after BCS for early breast cancer in women with higher than average local relapse risk. IMPORT HIGH was originally designed as a phase II trial with the primary endpoint of palpable induration inside the boost volume. It was anticipated that these results would inform the design of a subsequent practice-changing phase III trial evaluating ipsilateral breast tumour relapse (IBTR). However, additional funding from Cancer Research UK was obtained via a competitive peer-reviewed process to increase the sample size to allow robust statistical evaluation of IBTR. This amendment endorsed by the Independent Data Monitoring Committee (IDMC) and the Trial Steering Committee, enabled an efficient and streamlined evaluation of toxicity and cancer outcomes within one trial.

Participants

Women aged ≥18-years receiving BCS for invasive adenocarcinoma T1-3, pN0-pN3a, M0 at presentation, with clear microscopic resection margins (minimum clear margin not specified) were eligible. Patients were ineligible if they had a previous malignancy (except basal cell skin cancer and cervical intraepithelial neoplasia or non-breast malignancy and ≥5 years disease-free), had undergone mastectomy, had ipsilateral breast implant, or received concurrent chemo-radiotherapy. Eligibility for IMPORT HIGH and IMPORT LOW (13) did not overlap. All patients in IMPORT HIGH were deemed suitable to receive a tumour bed boost, whereas no boosts were given in IMPORT LOW. The study was approved by the Cambridgeshire Research Ethics Committee 4 (08/H0305/13), sponsored by The Institute of Cancer Research and conducted in accordance with the principles of Good Clinical Practice. All patients provided written informed consent. The trial is registered as ISRCTN47437448.

Randomisation and masking

Women were randomly assigned (1:1:1) to receive (i) 40Gy in 15-fractions to whole-breast plus 16Gy in 8-fractions sequential photon boost to the TB (control), or (ii) 36Gy in 15-fractions to low-dose-breast -volume with 40Gy in 15-fractions to standard-dose-breast-volume and 48Gy in 15-fractions concomitant photon boost to TB (Test group 1), or (iii) as for (ii) but 53Gy in 15-fractions concomitant photon boost to TB (Test group 2); Figure A1. In all groups, the dose to lymph node regions in patients requiring nodal radiotherapy was 40Gy in 15-fractions. To randomise a patient, centres telephoned The Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU; London, UK). Computer-generated random permuted blocks (mixed size 6 and 9) were used to stratify patients by radiotherapy treatment centre. Treatment allocation was unmasked for patients and clinicians.

Procedures

The TB was localised with titanium surgical clips or gold seeds to enable radiotherapy planning and aid IGRT verification. IMPORT HIGH was recruiting when TB clip insertion was still being implemented into routine practice. Participants were CT-imaged supine for radiotherapy planning. Most patients were scanned in free-breathing, with deep-inspiratory breath-hold techniques introduced only towards the end of the trial. A TB clinical target volume (CTV_{boost}) was defined as clips plus surrounding architectural distortion. It was recommended that the CTV_{boost} be ≤5% of the whole-breast planning target volume (PTV). The CTV_{boost} was grown by 5mm to create the boost PTV (PTV_{boost}). For patients randomised to the test groups, the CTV_{boost} was expanded by 15mm to create a partial breast CTV (CTV_{PB}) which was edited to be within whole-breast CTV (CTV_{WB}) including cropping 5mm from the skin. A 10mm margin was added to each of CTV_{PB} and CTV_{WB} to create PTV_{PB} and PTV_{WB} respectively. Either forward or inverse-planned IMRT was allowed (14). Where nodal radiotherapy was recommended, a single anterior field matched to the superior aspect of the tangents

was used for most patients with moderately hypofractionated radiotherapy as per UK guidelines and more recently international guidelines (15-16). Additional details are described in the radiotherapy planning pack, which was developed with the National Institute for Health Research and Care Radiotherapy Trials Quality Assurance (NIHR-RTTQA) team. The protocol and radiotherapy planning pack are available online (https://www.icr.ac.uk/our-research/centres-and-collaborations/centres-at-the-icr/clinical-trials-and-statistics-unit/clinical-trials/import_high). The trial quality assurance included facility questionnaires, contouring and planning benchmark cases, process documents, dosimetry audits, prospective and retrospective case reviews. All radiotherapy planning data were requested and stored electronically at the RTTQA repository.

After radiotherapy, patients were scheduled for annual follow-up to 10 years. Late adverse effects (AE) were assessed independently by clinicians, patients and using photographs. Clinicians assessed AE annually for all patients. Centres could opt into patient-reported outcomes (PRO) and photographic substudies; all patients at these centres were offered participation into both of the substudies. Photographs were taken at baseline (post-surgery and pre-radiotherapy), 3 and 5-years. PRO questionnaires were administered at baseline (before randomisation), 6 months, 1, 3 and 5-years. PRO included the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-BR23 breast cancer module, Body Image Scale, and protocol-specific questions relating to ipsilateral breast changes following treatment.

Outcomes

IBTR was defined as invasive carcinoma or ductal carcinoma in situ presenting anywhere in the ipsilateral breast parenchyma and/or overlying skin whether considered local relapse or new primary tumour. IBTR was localised as follows: (a) Breast parenchyma/skin within boost volume (all groups); (b) Breast parenchyma/skin within volume receiving 40+16Gy in 15-fractions (all groups); (c) Breast parenchyma/skin within volume receiving 36Gy in 15-fractions (test groups only); (d) Marginal relapse in skin or subcutaneous tissue/breast on border or just outside (within 2cm) of whole breast volume (all groups).

Secondary efficacy outcomes included location of local tumour relapse, time to first regional relapse (axilla, supraclavicular fossa and internal mammary chain), distant relapse, disease-free and overall survival. Secondary outcomes relating to late AE were assessed by patients, photographs and clinicians. Clinicians assessed breast shrinkage, distortion, induration, breast oedema, breast tenderness on palpation, breast discomfort and telangiectasia using a 4-point ordinal scale (“not at all”, “a little”, “quite a bit” or “very much”, interpreted as none, mild, moderate or marked), comparing the ipsilateral versus contralateral breast where relevant. Symptomatic rib fracture, symptomatic lung fibrosis, ischaemic heart disease and pneumonitis were recorded. Results for PRO relating to breast and arm/shoulder symptoms (scored on a 4-point ordinal scale as for the clinical assessments) are reported in this manuscript; further analysis of PRO will be reported separately. Digital photographs were scored on a 3-point ordinal scale representing none, mild or marked change in breast appearance at 3 and 5-years compared with baseline by 3 observers (17). Observers were blind to treatment allocation but not year of follow-up.

Acute toxicity was not recorded in the trial as the we have shown previously that acute normal tissue effects are mild even with boost using hypofractionated radiotherapy and that acute toxicity is not associated with development of late normal tissue events (18).

Statistical methods

This was a non-inferiority design. Assuming 5% IBTR cumulative incidence rate by 5-years for control group, 856 patients per group (2568 total) were required to exclude an IBTR rate of ≥8% in either test group (≥3% increase) with 80% power and 1-sided α=0·025 (allowing for comparison of each test group versus control), assuming 7% unevaluable at 5 years. Sample size justification for original primary endpoint of palpable induration inside the boost volume is in the Appendix.

Survival analysis methods compared efficacy outcomes between each test group and the control group, with time measured from randomisation and censoring at death or last follow-up for those who remained event-free. Kaplan-Meier and cumulative hazard functions were plotted by treatment group and estimates of 5-year cumulative incidence with 95% confidence intervals (CI) obtained. Treatment effects for each test group versus control were summarised using hazard ratios (HR, with 95%CI) from Cox proportional hazards (PH) regression models and pairwise logrank tests. Absolute differences (95%CI) in 5-year IBTR were estimated by applying the HRs (and CI) to the control group 5-year event-free estimate. The principal assessment of non-inferiority for IBTR for each test group versus control was whether the upper limit of 2-sided 95%CI (corresponding to 1-sided 97·5%CI) for the absolute difference in 5-year IBTR was <3%. Following confidential review of the trial results, the IDMC proposed that a range of hypothetical scenarios be presented to the Trial Management Group (TMG) without disclosing observed event rates. The TMG discussions including patient advocates agreed that absolute rather than relative risk was more pertinent. As specified in the protocol and statistical analysis plan, non-inferiority was also tested using the *a priori* critical HR of 1·63 derived from the expected 5-year IBTR rate in the control group and absolute difference of 3%; p<0·025 was deemed statistically significant for the non-inferiority test (probability of incorrectly accepting an inferior test group). The proportional hazards assumption of the Cox regression model for each efficacy outcome was tested and found to hold for all relapse and survival endpoints. An exploratory competing risks analysis was done for IBTR, with death from any cause as a competing event in a Fine-Gray competing risks regression model.

A composite endpoint of any clinician-assessed AE in the breast was derived using the worst score for distortion, shrinkage, induration, telangiectasia and oedema separately for each time point. Clinician and patient assessments of late AE were dichotomised as none/mild versus moderate/marked and analysed as follows: (i) 5-year cross-sectional analyses compared prevalence between groups using risk ratios (RR) and risk differences, and Fisher's exact test. (ii) Survival analysis of time to first moderate/marked event, including Kaplan-Meier estimates of cumulative incidence, and groups compared using HR from Cox PH regression and the pairwise logrank test. Patients not experiencing an event were censored at last AE assessment (by clinician or patient as appropriate) or death. For PRO the Cox model was adjusted for baseline scores. (iii)

Longitudinal analyses accounting for within-patient correlations between repeated measurements using generalised estimating equations (GEE) including all assessments compared treatment groups across the whole follow-up period using odds ratios (OR) and the Wald test; GEE models included a term representing years of follow-up. GEE models compared mild/marked change in photographic breast appearance between treatment groups. Due to multiple testing a significance level of 0·01 was used for the clinician and patient AE assessments, except for clinician-assessed breast induration that used p=0·05 as per the original trial design.

Dosimetric data were summarised for each treatment group using descriptive statistics, with no formal statistical testing. Two-sided 95%CI were calculated for all estimates. Analyses were by intention to treat (ITT). A sensitivity analysis of the primary outcome excluded patients with major treatment deviations. There were no planned formal subgroup analyses due to low numbers of IBTR events anticipated in subgroups. Analyses were based on a database snapshot taken on 11th January 2021 and used Stata version 16.1 (StataCorp).

Role of funding source

Cancer Research UK provided peer-reviewed approval but had no role in study design, collection, analysis, interpretation of data, or report writing. CEC had final responsibility to submit for publication; JSH and JMB had full access to study data.

RESULTS

Baseline characteristics and follow-up

From January 2009-September 2015, 2621 patients were recruited from 39 UK radiotherapy centres and 37 referral centres (Table A1); 4 patients withdrew consent for use of their data and were excluded from analyses, leaving 2617. A total of 181 patients (6·9% of 2617) did not receive their allocated treatment, predominantly due to difficulties outlining the TB due to lack of surgical clips (Figure 1). The PRO sub-study recruited 1070 participants; 1052 consented to photographic assessments. Demographic and clinical characteristics were well balanced across treatment groups (Table 1). Five-year follow-up forms were available for 2335/2411 (96·8%) expected (i.e. not died or withdrawn). Median follow-up was 74·0 months (IQR 73·4, 75·6). Patient ethnicity was 75.8% white, 1.3% black, 1.6% Asian or Indian, 0.5% mixed race, 0.3% other and 20.5% not reported.

Radiotherapy plan assessment forms were available in 77·5% of cases; all mandatory dosimetric constraints were met in 95·9%, 96·4%, and 95·2% of these in 40+16Gy, 48Gy and 53Gy groups respectively. Median CTV_{TB} volume was 12·8cm^3 and median CTV_{TB}/PTV_{WB} ratio was 0·015; CTV_{TB} volume was $\leq$5% of the PTV_{WB} in 95·6%. The number of patients treated with DIBH is not known, but this would have been a very small number. Further details on radiotherapy planning techniques and dosimetry are in Appendix Tables A2-7.

Ipsilateral breast tumour relapse

IBTR was recorded in 76 patients (40+16Gy: 20, 48Gy: 21, 53Gy: 35; Table 2). Estimated 5-year cumulative incidence of IBTR was 1·9% (95%CI 1·2, 3·1) for 40+16Gy, 2·0% (1·2, 3·2) for 48Gy and 3·2% (2·2, 4·7) for 53Gy (Table 2, Figures 2a and 2b). IBTR 5-year event rates were lower than anticipated; upper confidence limits for 5-year IBTR rate in all treatment groups were <5% (anticipated rate in control group). Estimated absolute differences in IBTR versus 40+16Gy were 0·1% (-0·8, 1·7) for 48Gy and 1·4% (0·03, 3·8) for 53Gy, indicating non-inferiority in absolute terms according to the pre-specified difference of 3% for 48Gy versus control but not for 53Gy. Non-inferiority was tested in terms of relative treatment effects: HRs were 1·04 (0·56, 1·92) for 48Gy and 1·76 (1·02, 3·04) for 53Gy versus 40+16Gy (Table 2). As upper confidence limits were greater than the protocol-specified critical HR of 1·63, non-inferiority could not be claimed in terms of relative treatment effects (non-inferiority tests against critical HR>1·63: p=0·076 for 48Gy and p=0·61 for 53Gy versus 40+16Gy). Since the IBTR rate was lower than expected, non-inferiority tests were carried out against the post-hoc critical HR>2·59 (obtained using the observed 1·9% control rate and assuming 3% absolute non-inferiority above this), with p=0·002 for 48Gy and p=0·082 for 53Gy, confirming non-inferiority for 48Gy.

Most IBTR events were considered to be a relapse by treating clinicians (66/76, 86·8%) rather than a new primary (7/76, 9·2%); 3 events could not be differentiated (Table A8). Location of the local relapse/new primary reported showed that 34/76 (44·7%) were inside the tumour bed PTV, 12/76 (15·8%) were inside the partial breast PTV but outside the tumour bed PTV, and 12/76 (15·8%) were inside the whole breast PTV but outside the partial breast PTV (Table A8). Results of per protocol and competing risks analyses are in the Appendix.

Secondary efficacy endpoints

Regional relapses occurred in 53 (2·0%) patients, 9 of which were concurrent with IBTR (Table A8). No statistically significant differences were seen in locoregional relapse, distant relapse, any relapse, disease-free and overall survival (Table 2, Figures A2a and 2b, A3a and 3b). Invasive contralateral breast cancer was reported for 34 (1·3%) patients, and non-breast second primary cancers for 63 (2·4%) (Table A8). A total of 206 (7·9%) patients died, 163 from breast cancer, 40 from other causes, and 3 from unknown cause with no evidence of disease relapse (Table A8).

Adverse effects: clinicians, patients, photographs

Clinical AE assessments were available at one or more years of follow-up for 2496/2617 (95·4%) patients. Prevalence of clinician-assessed moderate/marked effects were low across all groups (Figure A4a, Figure A5a-h). Five-year prevalence of moderate/marked breast induration was 6% (36/600) for 40+16Gy, 5·2% (34/653) for 48Gy and 8·9% (56/627) for 53Gy (Table A9). Comparisons between groups were broadly similar from 5-year cross-sectional, time to event and longitudinal analyses, with similar levels of moderate/marked

AE for 48Gy versus 40+16Gy and increased risk of AE for 53Gy versus 48Gy (Tables 3, A9 and A10). Cumulative incidence of moderate/marked breast induration was similar for 48Gy and 40+16Gy (HR 0·90, 95%CI 0·71-1·14, p=0·40), and higher for 53Gy versus 40+16Gy (HR 1·31, 95%CI 1·05-1·63, p=0·015) (Table 3, Figure A4a). Except for breast oedema and discomfort that declined over time, there were significant increases in risk of AE with longer follow-up (Table A10).

At least one questionnaire was completed by 1063/1070 (99·3%) patients. Change in overall breast appearance was the item patients most frequently reported as moderate/marked (Figure A6a-l, Tables 4 and A11). Five-year patient-reported moderate/marked breast hardness/firmness was significantly lower for 48Gy versus 40+16Gy (RR 0·54, 95%CI 0·38-0·78, p=0·001) and higher after 53Gy versus 48Gy (RR 1·61, 95%CI 1·10-2·35, p=0·008) (Table A11). There were no statistically significant differences between treatment groups in time-to-event and longitudinal analyses of patient-reported moderate/marked breast hardness/firmness and other PROs relating to breast, arm and shoulder AE up to 5-years (Tables 4 and A12, Figure A4b).

Photographic assessments were available at 3 or 5-years for 698/918 (76·0%) patients with a baseline photograph. At 3-years, mild or marked change in photographic breast appearance was observed in 35/218 (16·1%), 25/210 (11·9%) and 36/213 (16·9%) for 40+16Gy, 48Gy and 53Gy respectively. Five-year prevalence of mild/marked changes increased in all treatment groups (40+16Gy: 36·8% (60/163), 48Gy: 24·4% (42/172) and 53Gy: 27·5% (49/178)). There were no statistically significant differences in mild/marked change in photographic breast appearance between groups, but some indication of reduced risk for 48Gy versus 40+16Gy (OR for mild/marked change at 3 and/or 5 years 0·61, 95%CI 0·41, 0·93; p=0·021) (Table A13).

Severe late AEs were rare, with 11, 7, 6 and 6 confirmed reports of symptomatic rib fracture, symptomatic lung fibrosis, ischaemic heart disease and pneumonitis respectively (Table A14). A total of 103/2617 patients (3·9%) were referred to lymphoedema clinics (39/871, 4·3% for 40+16Gy, 36/874, 4·1% for 48Gy, and 28/872, 3·2% for 53Gy).

DISCUSSION

This trial demonstrated lower than anticipated IBTR incidence by 5-years across all treatment groups within a population at higher risk of relapse. Observing lower than anticipated event rates adds complexity to interpretation of non-inferiority trials given that the relative effect threshold is defined according to the original absolute risk estimates. Therefore, the pre-defined critical HR translates to a smaller absolute difference leading to dialogue around the importance of absolute versus relative treatment differences. In IMPORT HIGH, the TMG, including patient advocates, discussed this specific dilemma whilst still blinded to the observed results. It was agreed that the absolute 3% difference between groups and confirmation that event rates were low (compared with anticipated 5% IBTR) were of importance. There was no evidence of a difference in efficacy endpoints between groups. Within the two SIB test groups there was no evidence of benefit in escalating boost dose beyond current biologically equivalent standard of care doses. Prevalence of moderate/marked late normal tissue adverse events was low in all groups for clinician-reported, patient-

reported and photographic assessments, with no statistically significant differences in rates between trial groups. In comparison with control, 48Gy was milder for clinician-reported oedema on time-to-event analysis, and for breast hardness/firmness on patient-reported cross-sectional analysis. There was also a suggestion of decreased mild/marked adverse events on photographic assessment for 48Gy compared with control. In contrast, 53Gy showed increased clinician-reported breast induration compared to control for both time-to-event and longitudinal analyses. 48Gy SIB delivered in 3-weeks demonstrated similar efficacy to sequential boost delivered over 4·5 weeks, with similar/milder rates of AEs. A 53Gy SIB gave no additional benefit in local cancer control but a higher risk of moderate/marked breast induration.

The slightly higher IBTR rate with 53Gy is difficult to explain. Within the context of a very low overall event rate (lower than the anticipated 5% control group IBTR rate at 5-years), it is most likely to be a chance finding. It cannot be explained by a higher relapse rate in the lower dose region as most relapses were within the index quadrant. Distribution of higher risk pathological characteristics at diagnosis appear balanced across all groups (Table A15). The 48Gy group also had a reduced dose region and showed similar IBTR rates to control. The EORTC “boost versus no boost” trial had a substudy randomising patient with microscopically incomplete surgical margins to low boost dose (10Gy) or high boost dose (26Gy) both carried out in 2Gy daily factions (19). The study failed to recruit its planned sample size of 660 patients and only 251 were recruited. A significant difference in local control could not be demonstrated at 10 years, but the high boost dose significantly increased the risk of fibrosis. Taken with the results of IMPORT HIGH, this could suggest that there is a dose-response boost threshold for improvement in local control and increasing the boost dose beyond an EQD2 of around 60Gy causes increased fibrosis with no benefit. It is possible other strategies are required to overcome tumour radioresistance. We await the local control results of the Young Boost Trial (YBT) (20) that randomised patients ≤50-years to 16Gy (standard boost group) or 26Gy (high boost group) following BCS. The IMPORT HIGH authors are evaluating molecular clonality and spatial mapping of index tumours and local relapses to help understand relapse patterns.

Whilst direct comparisons of AEs within other breast radiotherapy trials cannot be made due to differences in trial populations, protocols and assessments, there is a suggestion that AEs in IMPORT HIGH may be lower than observed in YBT (AEs have been reported and the primary local control endpoint is awaited (20). Boost techniques in YBT included photons, electrons and interstitial brachytherapy and, although most patients received sequential boosts, some had SIB. Moderate/marked breast fibrosis as scored by clinicians at 4-years was 19% and 39% in the standard and high-boost groups respectively, with 27% and 45% cumulative incidence. Important risk factors for poor cosmesis were photon rather than electron boost, higher boost dose, large boost volume, poor cosmesis before radiotherapy, and adjuvant chemotherapy. The IMPORT HIGH team only used photon boosts and limited boost volumes based on a pre-trial dosimetry study which showed that tumour bed coverage was often worse with electrons compared with photons. The TMG were concerned that photon planning with more generous tumour bed coverage could produce larger irradiated boost volumes and increased toxicity. Therefore, the CTV was limited to TB clips/ seroma with no additional margin. The CTV-PTV margin was 5mm with IGRT determined by the GOLDSEED study (11). This may account for the differences in fibrosis/induration rates seen between the two trials.

The YBT publication also suggested that SIB increased the risk of adverse normal tissue events. However, the authors state that a possible explanation was that the YBT SIB had a higher equivalent dose in 2Gy fractions (EQD2) compared with the sequential boosts: EQD2 68·2Gy versus 66Gy and 79·5Gy versus 76Gy, α/β of 3Gy. The slightly milder induration seen with 48Gy in IMPORT HIGH could be a result of an EQD2 of 60Gy to tumour bed using an α/β of 3Gy for normal tissue late effects compared, with 62Gy in the control.
A strength of IMPORT HIGH is use of photon boosts only to standardise boost volume across all trial groups. Therefore, the only variables were SIB, dose escalation in the 53Gy group and modest dose reduction distant from the index quadrant in both test groups. A second strength was the stringent radiotherapy quality assurance. An embedded mechanistic substudy determined the utility of clip-based image-guided boost IMRT (12). In addition, participation of 39 UK radiotherapy centres demonstrated the ability to implement image-guided SIB in multiple radiotherapy departments.

IMPORT HIGH is the largest randomised study of SIB, increasing precision of confidence limits for study outcomes. The only previously published SIB study with a local control primary endpoint is the IMRT-MC2 trial, which randomised 502 patients to 50·4Gy in 1·8Gy daily fractions with a SIB to a total dose of 64·4Gy delivered over 5·5 weeks compared with a control group with sequential boost delivered over 7 weeks (21). Non-inferiority for local control was reported at 2-year median follow-up with no statistically significant difference in cosmesis. The NRG RTOG 1005 randomised trial (22) was similar to IMPORT HIGH 48Gy group, but had 2 dose levels (40Gy whole breast and 48Gy SIB). The study population had a higher median age of 55 versus 49 years and included some patients with high grade DCIS. 48Gy SIB was non-inferior for local relapse and toxicity and cosmetic outcome appeared similar. The DBCG Skagen trial 1 (NCT02384733) (23) had a primary endpoint of arm lymphoedema 3 years after radiotherapy. Randomisation was between 50Gy/25 fractions and 40Gy/15 fractions, 5 fractions weekly and simultaneous integrated boosts were used. At 3 years median follow up, there was no difference in arm lymphoedema, loco-regional or distant recurrence or overall survival.

SIB is less burdensome for patients and their families, reducing travel costs and enabling return to work sooner. It is an efficient use of resource for health care providers whereby radiotherapy “slots” can be used for other patients. The same level of technology is required for SIB as a CT-planned sequential photon boost, but a single integrated radiotherapy plan is resource-saving. Most centres would recommend daily image-guidance with hypofractionated radiotherapy even without SIB, as there is less opportunity to correct on-treatment variations.

Limitations of IMPORT HIGH include the unmasked AE reporting by clinicians and patients that could lead to bias. It is not possible to mask treatment groups as they can determine this based on number of treatments received. However, previous UK breast radiotherapy trials with similar designs have all demonstrated that clinician and patient reported outcomes are sensitive and can differentiate between dose and volume differences between trial groups (9, 10, 13, 24). A further limitation is changing regional node irradiation during the lifetime of IMPORT HIGH. During the recruitment phase, most node positive breast cancer was

treated with surgical axillary clearance. Most commonly supraclavicular fossa radiotherapy was used and the internal mammary chain was not treated. Several practice-changing trials have since reported resulting in increased use of axillary radiotherapy as an alternative to surgery and resurgence of internal mammary chain irradiation (25-28). Regional nodal irradiation using 40Gy would be challenging to integrate with the reduced dose to the peripheries of breast tissue and the effect of 36Gy on regional nodes is unknown. IMPORT HIGH results may not be completely generalisable to sequential boosts using different dose-fractionations, which may have different cosmetic outcomes and relapse rates when compared to 16Gy in 8F.

UK standard of care for boost radiotherapy is now either a 3-week 48Gy SIB (two dose levels) or 1-week of 26Gy whole-breast radiotherapy with a 1-week hypofractionated sequential boost (29). Choice of approach depends on patient and radiotherapy centre planning preference: some departments favour SIB as target coverage and organs at risk doses can be assessed in a single plan. The ultimate goal is 1-week SIB based on results of FAST-Forward and IMPORT HIGH. This is a UK trial proposal under development and will also test 1-week internal mammary chain irradiation. A 200-patient Belgian randomised trial is testing a 31Gy SIB in 5-fractions over 10-12 days with 28·5Gy to whole-breast (30). The group have reported favourable acute toxicity (30) as expected given that acute side-effects are related to total dose (31). An Indian multicentre randomised trial HYPORT-Adjuvant is currently recruiting and tests 32Gy SIB in 5-fractions over 1 week with 26Gy to whole breast and aims to recruit 2100 patients (32). 1-week SIB is especially attractive for low-middle-income countries, whereby many people would otherwise forego treatment due to travelling and accommodation costs for longer radiotherapy courses.

Conclusions

IBTR rates are low in this higher-risk breast cancer group treated with small boosts, whether boost is delivered sequentially or simultaneously with the upper limit of the 95%CI excluding the 5-year 5% rate originally predicted for the control group. Non-inferiority for IBTR was achieved in absolute terms according to the pre-specified difference of 3% for 48Gy versus control but not for 53Gy. This highlights the challenges of assessing non-inferiority when primary outcome events rates become very low. Rates of 5-year moderate/marked AE are low and 48Gy SIB showed similar/reduced toxicity compared with control. SIB is a safe treatment with reduced patient visits and further escalation of boost dose does not appear advantageous.

Author contributions

CEC and JRY are the current and previous chief investigators respectively and AMK is the chief clinical coordinator for the trial. JMB is the trials methodology lead within the Institute of Cancer Research-Clinical Trials and Statistics Unit (ICR-CTSU) and provided oversight and guidance for trial management throughout the trial. JRY, CEC, JMB, and JSH were responsible for the study design. CEC, AMK and JSH wrote the first

draft of the manuscript. JSH and CLG was responsible for statistical analyses and contributed to data interpretation. SL, IB, AMB, CC, EMD, ES, IS AND NIT are members of the IMPORT HIGH trial management group (TMG), which contributed to study design, was responsible for oversight throughout the trial and contributed to data interpretation and manuscript preparation. JCT, MAS and ME managed the study and data collection at ICR-CTSU and contributed to the manuscript preparation. MLJ is a patient advocate member of the TMG and provided guidance for study documentation and reports. PH was the lead for the patient-reported outcomes substudy. YT and DJE were responsible for radiotherapy quality assurance. All authors reviewed and approved the manuscript

Declaration of interests

JMB, EMD, ME, CLG, JSH, PH, MAS, JCT, YT report grants from Cancer Research UK during the conduct of the study. SVL reports PhD funding from Cancer Research UK. JMB reports grants and non-financial support from AstraZeneca, Clovis Oncology, Eli Lilley, Janssen-Cilag, Merck Sharpe and Dohme, Novartis (previously GlaxoSmithKline), Pfizer, Puma Biotechnology and Roche outside the submitted work. CEC reports grants from National Institute for Health Research Efficacy and Mechanism Evaluation, RADNET, Lancet Breast Cancer Commission and Addenbrooke's Charitable Trust outside the submitted work. CEC also reports membership of 5 external Independent Monitoring Committees and Chair of the Lancet Breast Cancer Commission. AMK reports President of the European Society of Radiation Oncology. All other authors declare no competing interests.

Data sharing

Deidentified individual participant data, together with a data dictionary defining each field in the set, will be made available to other researchers on request. Trial documentation including the protocol are available online. The Institute of Cancer Research-Clinical Trials and Statistics Unit (ICR-CTSU) supports wider dissemination of information from the research it conducts and increased cooperation between investigators. Trial data are obtained, managed, stored, shared, and archived according to ICR-CTSU standard operating procedures to ensure the enduring quality, integrity, and utility of the data. Formal requests for data sharing are considered in line with ICR-CTSU procedures, with due regard given to funder and sponsor guidelines. Requests are via a standard proforma describing the nature of the proposed research and extent of data requirements. Data recipients are required to enter a formal data sharing agreement, which describes the conditions for release and requirements for data transfer, storage, archiving, publication, and intellectual property. Requests are reviewed by the trial management group in terms of scientific merit and ethical considerations, including patients' consent. Data sharing is undertaken if proposed projects have a sound scientific or patients' benefit rationale, as agreed by the trial management group and approved by the independent data monitoring and steering committee, as required. Restrictions relating to patients'

confidentiality and consent will be limited by aggregating and anonymising identifiable patients' data. Additionally, all indirect identifiers that could lead to deductive disclosures will be removed in line with ICR-CTSU data sharing guidelines.

Acknowledgments

This work uses data provided by patients and collected by the NHS as part of their care and support. We thank the patients who participated in this study and all investigators and research support staff, past and present, at participating centres (Appendix). Recognition goes to all trials unit staff at The Institute of Cancer Research Clinical Trials and Statistics Unit who contributed to the central coordination of the study, especially Ronald Kaggwa who died in January 2022. We thank the members of the trial oversight committees (Appendix) especially Maggie Wilcox who died in December 2021.

The IMPORT HIGH trial is funded by Cancer Research UK (C1491/A16831), with a programme grant from Cancer Research UK to support the work of ICR-CTSU (C1491/A25351). We acknowledge NHS funding to the NIHR Biomedical Research Centre at the Royal Marsden NHS Foundation Trust (London, UK) and The Institute of Cancer Research (London, UK). In addition, Professor Charlotte Coles is funded by the National Institute of Health and Social Care Research (NIHR) and supported by the NIHR Cambridge Biomedical Research Centre. The views expressed are those of the author and not necessarily those of the NIHR or the Department of Health and Social Care.

We are grateful to the NCRI Radiotherapy Trials Quality Assurance (RTTQA) group at Mount Vernon Hospital for overseeing the radiotherapy planning and delivery throughout the study. The IMPORT Trialists' Group consists of the Trial Management Group, Trial Steering Committee, Independent Data Monitoring Committee and the principal and main co-investigators at the participating centres.

IMPORT HIGH is sponsored by The Institute of Cancer Research, London.

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Figure legends

Figure 1: IMPORT HIGH trial profile (CONSORT diagram)

Figure 2: Ipsilateral breast tumour relapse (IBTR) by treatment group: (a) Kaplan-Meier plot, (b) Cumulative risk plot

Appendix:

Figure A1: IMPORT HIGH trial schema

Figure A2: Disease-free survival by treatment group: (a) Kaplan-Meier plot, (b) Cumulative risk plot

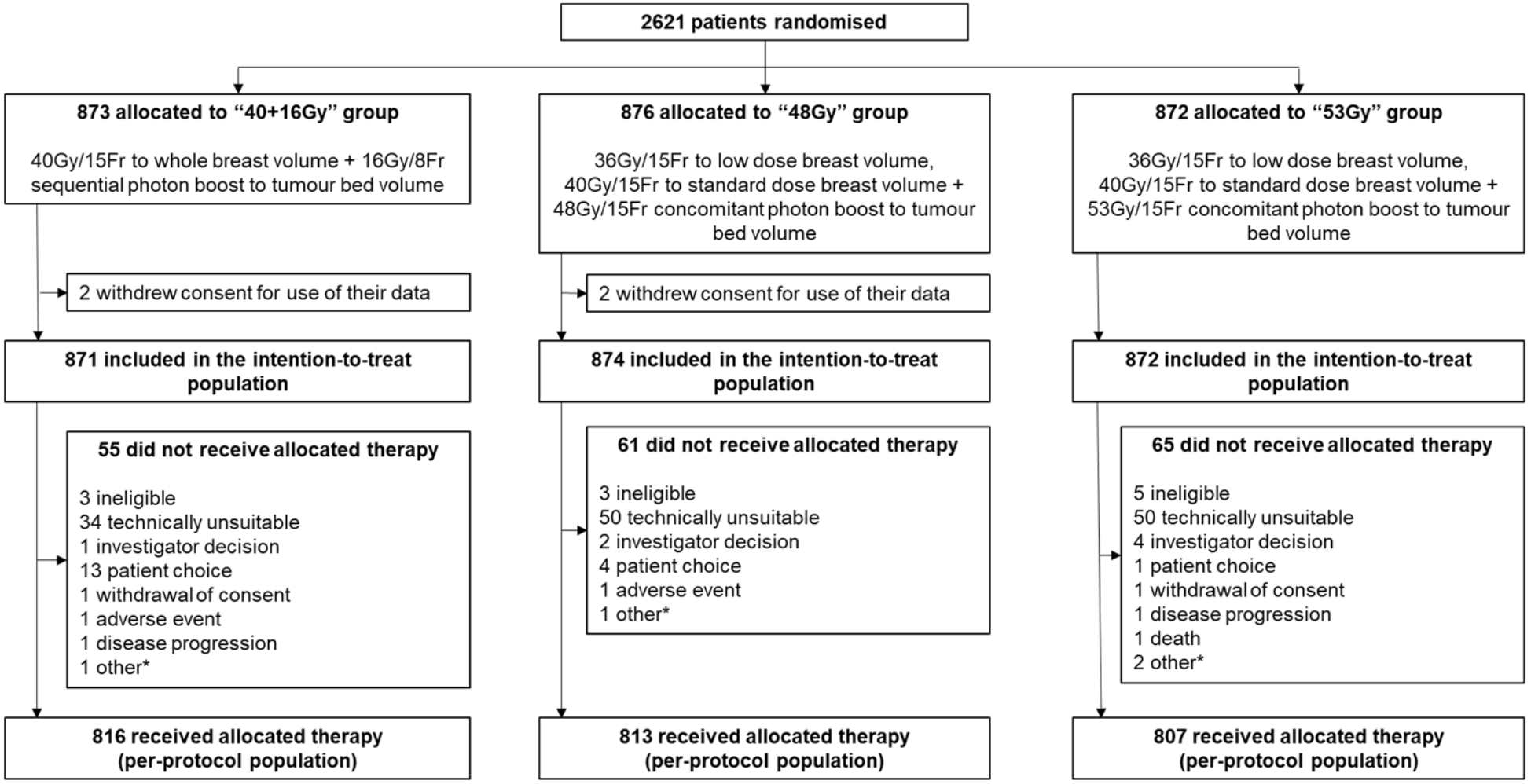
Figure A3: Overall survival by treatment group: (a) Kaplan-Meier plot, (b) Cumulative risk plot

Figure A4: Breast induration (moderate / marked) by treatment group: (a) Clinician-assessed breast induration (in index quadrant), (b) Patient-assessed breast hardness / firmness

Figure A5: Clinician assessments of late normal tissue effects up to 8 years, by treatment group: (a) Any breast adverse effect, (b) Breast distortion, (c) Breast shrinkage, (d) Breast induration (index quadrant), (e) Telangiectasia, (f) Breast oedema, (g) Breast tenderness on palpation, (h) Breast discomfort

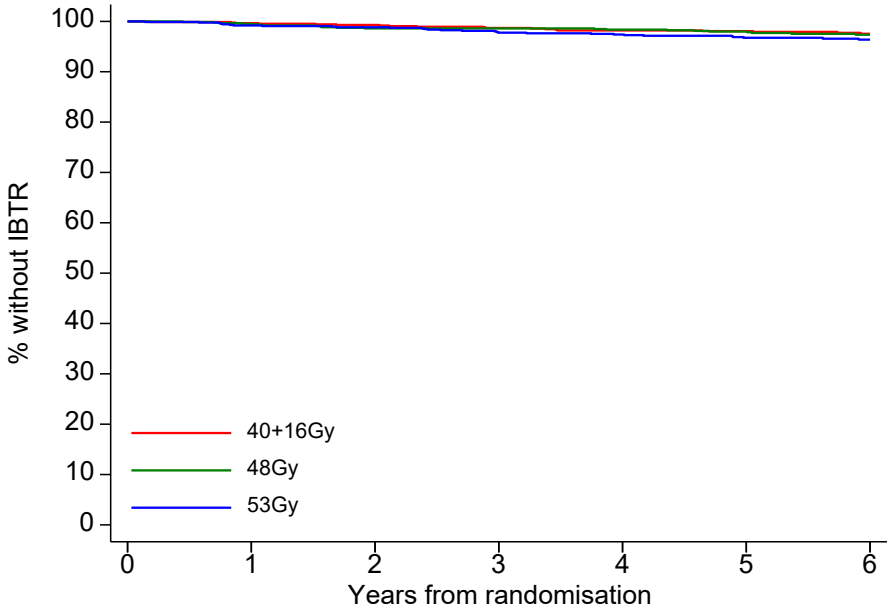
Figure A6: Patient assessments of late normal tissue effects up to 5 years, by treatment group: (a) Change in overall breast appearance, (b) Breast smaller, (c) Breast hardness / firmness, (d) Change in skin appearance on affected breast, (e) Shoulder stiffness, (f) Breast pain, (g) Breast swollen, (h) Breast oversensitive, (i) Skin problems on breast, (j) Arm / shoulder pain, (k) Arm / hand swollen, (l) Difficulty raising arm or moving it sideways

Figure 1: IMPORT HIGH trial profile



* 40+16Gy: No CT information for 3rd field as patient simulated, department standard treatment given; 48Gy: Breakdown of kv imaging devices on 2 machines therefore no appropriate verification, standard treatment given; 53Gy: 1 x Departmental planning problem, unable to fulfil trial criteria, standard treatment given; 1 x bolus required.

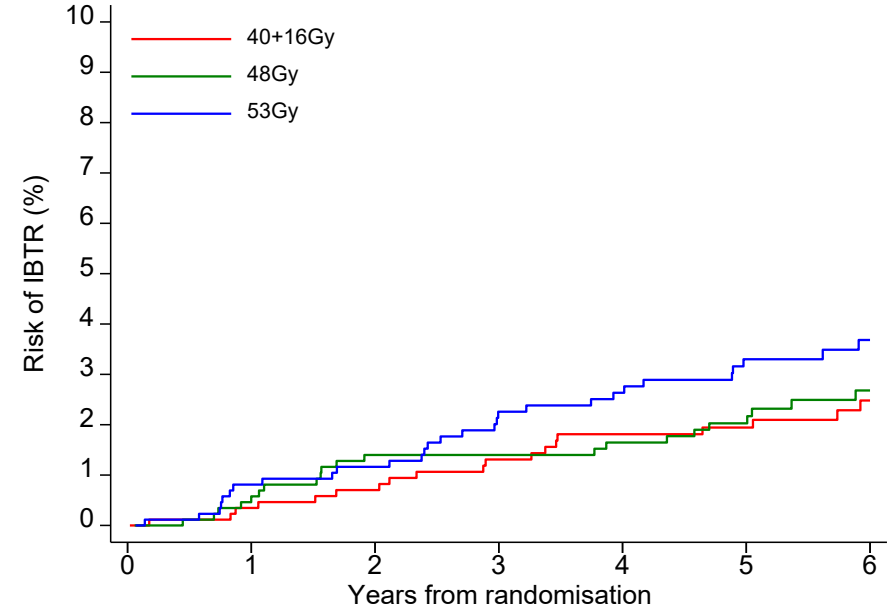
Figure 2a: Ipsilateral breast tumour relapse (IBTR)-free survival by treatment group



Number at risk (events)

40+16Gy	871	(3)	857	(3)	830	(5)	809	(4)	784	(1)	696	(3)	465
48Gy	874	(5)	861	(7)	842	(0)	828	(2)	799	(3)	712	(4)	465
53Gy	872	(7)	857	(3)	840	(9)	809	(3)	788	(5)	693	(2)	473

Figure 2b: Cumulative risk of ipsilateral breast tumour relapse (IBTR) by treatment group



Number at risk (events)

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48Gy	874	(5)	861	(7)	842	(0)	828	(2)	799	(3)	712	(4)	465
53Gy	872	(7)	857	(3)	840	(9)	809	(3)	788	(5)	693	(2)	473

Table 1: Baseline demographic, clinical and treatment characteristics in the IMPORT High trial

Characteristic	40+16Gy N=871 (%)	48Gy N=874 (%)	53Gy N=872 (%)	Total N=2617 (%)
Age (years) Median (IQR)	49·4 (45·2-56·4)	48·9 (44·6-55·2)	49·2 (43·5-57·1)	49·2 (44·4-56·1)
Side of primary				
Left	429 (49)	423 (48)	445 (51)	1297 (50)
Right	439 (50)	450 (51)	426 (49)	1315 (50)
Unknown	3 (<1)	1 (<1)	1 (<1)	5 (<1)
Location of primary tumour bed				
Central	174 (20)	177 (20)	163 (19)	514 (20)
Upper outer	395 (45)	425 (49)	406 (47)	1226 (47)
Upper inner	147 (17)	124 (14)	149 (17)	420 (16)
Lower outer	88 (10)	97 (11)	103 (12)	288 (11)
Lower inner	62 (7)	48 (5)	45 (5)	155 (6)
Unknown	5 (<1)	3 (<1)	6 (<1)	14 (<1)
Pathological tumour size (cm) Median (IQR)	2·0 (1·5-2·8)	2·0 (1·5-2·7)	2·0 (1·5-2·7)	2·0 (1·5-2·7)
Unknown	2	1	1	4
Tumour grade				
1	83 (10)	71 (8)	71 (8)	225 (9)
2	340 (39)	310 (35)	329 (38)	979 (37)
3	445 (51)	492 (56)	470 (54)	1407 (54)
Unknown	3 (<1)	1 (<1)	2 (<1)	6 (<1)
Re-excision				
Yes	185 (21)	185 (21)	179 (20)	549 (21)
No	683 (78)	688 (79)	692 (79)	2063 (79)
Unknown	3 (<1)	1 (<1)	1 (<1)	5 (<1)
Axillary surgery				
Yes	852 (98)	858 (98)	854 (98)	2564 (98)
No	15 (2)	15 (2)	17 (2)	47 (2)
Unknown	4 (<1)	1 (<1)	1 (<1)	6 (<1)
Pathological node status				
Positive	260 (30)	268 (31)	251 (29)	779 (30)
Negative	608 (70)	605 (69)	620 (71)	1833 (70)
Unknown	3 (<1)	1 (<1)	1 (<1)	5 (<1)
Histological type				
Infiltrating ductal	774 (89)	772 (88)	772 (88)	2318 (89)
Mixed	30 (3)	28 (3)	29 (3)	87 (3)
Other	66 (8)	71 (8)	70 (8)	207 (8)
Unknown	1 (<1)	3 (<1)	1 (<1)	5 (<1)
Lymphovascular invasion				
Yes	126 (14)	116 (13)	124 (14)	366 (14)
No	307 (35)	307 (35)	306 (35)	920 (35)
Uncertain	19 (2)	25 (3)	10 (1)	54 (2)
Not reported[1]	419 (48)	426 (49)	432 (50)	1277 (49)
ER status				
Positive	683 (78)	657 (75)	652 (75)	1992 (76)
Poor	188 (22)	216 (25)	219 (25)	623 (24)
Unknown	0	1 (<1)	1 (<1)	2 (<1)
PR status				
Positive	304 (35)	289 (33)	289 (33)	882 (34)
Poor	195 (22)	214 (24)	207 (24)	616 (24)

Characteristic	40+16Gy N=871 (%)	48Gy N=874 (%)	53Gy N=872 (%)	Total N=2617 (%)
Unknown	4 (<1)	12 (1)	5 (<1)	21 (<1)
Not done	368 (42)	359 (41)	371 (43)	1098 (42)
HER2 status				
Positive	157 (18)	139 (16)	165 (19)	461 (18)
Negative	710 (81)	731 (84)	705 (81)	2146 (82)
Unknown	4 (<1)	4 (<1)	2 (<1)	10 (<1)
ER and HER2 status				
ER + / HER2 +	121 (14)	104 (12)	111 (13)	336 (13)
ER + / HER2 -	558 (64)	550 (63)	540 (62)	1648 (63)
ER - / HER2 +	36 (4)	35 (4)	54 (6)	125 (5)
ER - / HER2 -	152 (17)	181 (21)	165 (19)	498 (19)
Unknown	4 (<1)	4 (<1)	2 (<1)	10 (<1)
Adjuvant therapy received: all patients				
Chemotherapy	564/869 (65)	574/873 (66)	578/872 (66)	1716/2614 (66)
Unknown	2/869 (<1)	1/873 (<1)	0	3/2614 (<1)
Adjuvant therapy received: HER2-positive patients				
Chemotherapy & trastuzumab	88/157 (56)	74/139 (53)	102/165 (62)	264/461 (57)
Trastuzumab, no chemotherapy	6/157 (4)	1/139 (<1)	5/165 (3)	12/461 (3)
Chemotherapy, no trastuzumab	42/157 (27)	48/139 (35)	40/165 (24)	130/461 (28)
No chemotherapy, no trastuzumab	15/157 (10)	15/139 (11)	15/165 (9)	45/461 (10)
Unknown	6/157 (4)	1/139 (<1)	3/165 (2)	10/461 (2)
Adjuvant therapy received: ER-positive patients				
Endocrine therapy	665/683 (97)	640/657 (97)	636/652 (98)	1941/1992 (97)
Unknown	2 (<1)	0	0	2 (<1)
Radiotherapy to lymph nodes*				
Yes	93/869 (11)	90/871 (10)	87/871 (10)	270/2611 (10)
SCF	*85*	*87*	*77*	*249*
Axilla	*7*	*3*	*10*	*20*
Unknown	*1*	*0*	*0*	*1*
No	775/869 (89)	778/871 (89)	781/871 (90)	2334/2611 (89)
Unknown	0/869	3/871 (<1)	2/871 (<1)	5/2611 (<1)

* Denominator is 2611 as 6 patients received no radiotherapy (details in Figure 1)

Table 2: Relapse and mortality by treatment group: results of time to event analyses

Efficacy endpoint	Cumulative no. of events / total (%)	KM estimate (95%CI) of cumulative incidence by 5 years, %	Hazard ratio[1] (95% CI); p-value[2]	Estimated absolute difference vs 40+16Gy at 5 years[3] (95%CI), %
Ipsilateral breast tumour (local) relapse[4]				
40+16Gy	20/871 (2·3)	1·9 (1·2, 3·1)	1	-
48Gy	21/874 (2·4)	2·0 (1·2, 3·2)	1·04 (0·56, 1·92); 0·91	0·1 (-0·8, 1·7)
53Gy	35/872 (4·0)	3·2 (2·2, 4·7)	1·76 (1·01, 3·04); 0·041	1·4 (0·03, 3·8)
Local-regional relapse[5]				
40+16Gy	32/871 (3·7)	3·0 (2·0, 4·4)	1	-
48Gy	32/874 (3·7)	3·1 (2·1, 4·5)	0·99 (0·60, 1·61); 0·96	-0·04 (-1·2, 1·8)
53Gy	48/872 (5·5)	4·7 (3·4, 6·3)	1·50 (0·96, 2·35); 0·072	1·5 (-0·1, 3·9)
Distant relapse				
40+16Gy	66/871 (7·6)	6·6 (5·1, 8·5)	1	-
48Gy	67/874 (7·7)	6·5 (5·1, 8·4)	1·00 (0·71, 1·41); 0·99	0·02 (-1·8, 2·6)
53Gy	74/872 (8·5)	7·8 (6·2, 9·8)	1·12 (0·80, 1·55); 0·52	0·7 (-1·3, 3·5)
Any relapse (local, regional, distant)				
40+16Gy	84/871 (9·6)	8·5 (6·8, 10·6)	1	-
48Gy	81/874 (9·3)	7·6 (6·0, 9·6)	0·95 (0·70, 1·29); 0·74	-0·4 (-2·5, 2·3)
53Gy	103/872 (11·8)	10.4 (8·6, 12·7)	1·23 (0·92, 1·64); 0·16	1·8 (-0·6, 5·0)
Any breast cancer-related event[6]				
40+16Gy	94/871 (10·8)	9·2 (7·4, 11·4)	1	-
48Gy	94/874 (10·8)	8·5 (6·8, 10·6)	0·99 (0·74, 1·31); 0·92	-0·1 (-2·3, 2·7)
53Gy	117/872 (13·4)	11·9 (9·9, 14·3)	1·25 (0·95, 1·64); 0·10	2·2 (-0·4, 5·5)
All-cause mortality				
40+16Gy	71/871 (8·1)	6·1 (4·7, 8·0)	1	-
48Gy	59/874 (6·7)	5·0 (3·7, 6·7)	0·82 (0·58, 1·16); 0·27	-1·1 (-2·5, 0·9)
53Gy	76/872 (8·7)	6·7 (5·2, 8·6)	1·06 (0·77, 1·47); 0·71	0·4 (-1·4, 2·8)

KM = Kaplan-Meier, 95%CI = 95% confidence interval; IBTR = ipsilateral breast tumour relapse
[1] Hazard ratio >1 favours 40+16Gy;
[2] Log-rank test (2-sided), for each test group compared with 40+16Gy (control);
[3] Estimated absolute difference at 5 years for each test group versus 40+16Gy obtained from hazard ratio and KM event-free estimate in 40+16Gy group;
[4] Ipsilateral breast tumour relapse (IBTR) includes local relapse and ipsilateral new primary;
[5] Locoregional relapse defined as IBTR or regional relapse (axilla, supraclavicular fossa, other);
[6] Breast cancer-related events: local, regional or distant relapse, breast cancer death, contralateral breast cancer (disease-free survival)

Table 3: Clinician-assessed late adverse effects by treatment group for 2496 patients with at least one annual clinical assessment: results of time to event analyses

Adverse effect	Moderate/ Marked events / total[2] (%)	KM estimate (95%CI) of cumulative incidence (%) of moderate/marked events by 3 years[3]	KM estimate (95%CI) of cumulative incidence (%) of moderate/marked events by 5 years[3]	Comparison with 40+16Gy Hazard ratio (95%CI); p-value[4]	Comparison between 53Gy & 48Gy Hazard ratio (95%CI); p-value[4,5]
Any AE in the breast [1]					
40+16Gy	283/817 (34·6)	23·5 (20·7, 26·7)	33·1 (29·8, 36·7)	1	-
48Gy	271/836 (32·4)	20·8 (18·2, 23·8)	29·9 (26·8, 33·3)	0·90 (0·76, 1·06); 0·21	1
53Gy	302/834 (36·2)	25·8 (23·0, 29·0)	34·5 (31·2, 38·0)	1·06 (0·90, 1·24); 0·50	1·18 (1·00, 1·39); 0·026
Breast distortion					
40+16Gy	126/814 (15·5)	8·.6 (6·8, 10·8)	13·8 (11·5, 16·6)	1	-
48Gy	108/834 (12·9)	8·4 (6·7, 10·5)	12·2 (10·1, 14·8)	0·82 (0·63, 1·06); 0·13	1
53Gy	140/833 (16·8)	10·3 (8·3, 12·6)	15·7 (13·3, 18·5)	1·11 (0·87, 1·41); 0·39	1·36 (1·05, 1·74); 0·008
Breast shrinkage					
40+16Gy	145/813 (17·8)	9·4 (7·5, 11·6)	15·7 (13·2, 18·6)	1	-
48Gy	143/834 (17·1)	8·9 (7·1, 11·0)	15·2 (12·8, 18·0)	0·93 (0·74, 1·17); 0·56	1
53Gy	142/832 (17·1)	9·5 (7·7, 11·7)	15·7 (13·3, 18·6)	0·95 (0·76, 1·20); 0·70	1·02 (0·81, 1·29); 0·42
Breast induration (index quadrant)					
40+16Gy	143/814 (17·6)	11·5 (9·5, 14·0)	16·6 (14·1, 19·5)	1	-
48Gy	134/834 (16·1)	10·6 (8·6, 12·9)	14·3 (12·0, 16·9)	0·90 (0·71, 1·14); 0·40	1
53Gy	183/832 (22·0)	15·5 (13·1, 18·2)	20·0 (17·3, 23·0)	1·31 (1·05, 1·63); 0·015	1·45 (1·16, 1·81); <0·001
Telangiectasia					
40+16Gy	17/815 (2·1)	1·2 (0·6, 2·2)	1·9 (1·1, 3·2)	1	-
48Gy	14/835 (1·7)	0·6 (0·3, 1·5)	1·0 (0·5, 2·0)	0·80 (0·40, 1·63); 0·56	1
53Gy	14/834 (1·7)	0·8 (0·3, 1·7)	1·6 (0·9, 2·9)	0·82 (0·41, 1·67); 0·56	1·02 (0·49, 2·14); 0·48
Breast oedema					
40+16Gy	70/814 (8·6)	7·8 (6·1, 9·9)	8·6 (6·8, 10·8)	1	-

Adverse effect	Moderate/ Marked events / total[2] (%)	KM estimate (95%CI) of cumulative incidence (%) of moderate/marked events by 3 years[3]	KM estimate (95%CI) of cumulative incidence (%) of moderate/marked events by 5 years[3]	Comparison with 40+16Gy Hazard ratio (95%CI); p-value[4]	Comparison between 53Gy & 48Gy Hazard ratio (95%CI); p-value[4,5]
48Gy	44/836 (5·3)	4·6 (3·4, 6·3)	5·2 (3·9, 7·0)	0·59 (0·41, 0·87); 0·006	1
53Gy	54/834 (6·5)	5·3 (3·9, 7·1)	5·7 (4·3, 7·6)	0·74 (0·52, 1·05); 0·091	1·24 (0·83, 1·85); 0·14
Breast tenderness on palpation					
40+16Gy	112/804 (13·9)	9·4 (7·5, 11·7)	13·6 (11·3, 16·3)	1	-
48Gy	111/821 (13·5)	8·3 (6·6, 10·4)	11·9 (9·8, 14·5)	0·96 (0·73, 1·24); 0·74	1
53Gy	142/813 (17·5)	10·5 (8·.6, 12·9)	15·0 (12·6, 17·8)	1·26 (0·98, 1·62); 0·066	1·32 (1·03, 1·69); 0·014
Breast discomfort					
40+16Gy	112/796 (14·1)	9·7 (7·8, 12·.0)	13·6 (11·3, 16·3)	1	-
48Gy	114/811 (14·1)	8·6 (6·8, 10·8)	13·1 (10·9, 15·8)	0·98 (0·76, 1·28); 0·91	1
53Gy	153/804 (19·0)	12·4 (10·3, 15·0)	17·0 (14·5, 19·9)	1·39 (1·09, 1·77); 0·008	1·41 (1·10, 1·79); 0·002

KM = Kaplan-Meier, 95%CI = 95% confidence interval;
[1] Any AE in the breast = distortion, shrinkage, induration, telangiectasia, oedema; [2] AE data available for 2496 patients (40+16Gy: 820, 48Gy: 837, 53Gy: 839), denominators may vary due to missing clinician assessments for some events; [3] Rate estimated at 3 (or 5) years and 3 months to allow for visits occurring up to 3 months after the due date; [4] p-value for pairwise log-rank test; [5] 1-sided p-value

Table 4: Patient-assessed late adverse effects by treatment group for 1063 patients with at least one completed questionnaire: results of time to event analyses

Adverse effect	Moderate/ marked events over follow-up / total[1] (%)	KM estimate (95%CI) of cumulative incidence (%) of moderate/ marked events by 3 years	KM estimate (95%CI) of cumulative incidence (%) of moderate/ marked events by 5 years	Comparison with 40+16Gy Hazard ratio[2,3] (95%CI); p-value[4]	Comparison between 53Gy & 48Gy Hazard ratio[2,3] (95%CI); p-value[5,6]
Protocol-specific items					
Breast appearance changed					
40+16Gy	187/348 (53·7)	46·8 (41·6, 52·4)	52·8 (47·4, 58·4)	1	-
48Gy	161/324 (49·7)	42·6 (37·3, 48·3)	48·0 (42·4, 53·9)	0·98 (0·78, 1·22); 0·26	1
53Gy	174/343 (50·7)	44·3 (39·1, 49·9)	49·9 (44·5, 55·7)	0·91 (0·73, 1·12); 0·42	0·92 (0·73, 1·15); 0·624
Breast smaller					
40+16Gy	136/348 (39·1)	31·7 (26·9, 37·0)	38·4 (33·1, 44·1)	1	-
48Gy	126/324 (38·9)	28·8 (24·0, 34·2)	39·6 (34·0, 45·8)	1·11 (0·86, 1·43); 0·72	1
53Gy	137/343 (39·9)	30·9 (26·2, 36·2)	38·1 (32·9, 43·8)	1·03 (0·80, 1·32); 0·83	0·92 (0·72, 1·19); 0·674
Breast harder/firmer					
40+16Gy	165/348 (47·4)	42·7 (37·5, 48·2)	49·5 (44·0, 55·3)	1	-
48Gy	139/324 (42·9)	37·6 (32·5, 43·2)	44·1 (38·5, 50·0)	0·85 (0·67, 1·07); 0·26	1
53Gy	162/343 (47·2)	39·6 (34·6, 45·1)	48·1 (42·6, 53·8)	0·97 (0·77, 1·22); 0·77	1·15 (0·91, 1·47); 0·197
Skin appearance changed					
40+16Gy	104/348 (29·9)	27·9 (23·4, 33·0)	29·1 (24·5, 34·4)	1	-
48Gy	84/323 (26·0)	22·4 (18·2, 27·5)	24·0 (19·5, 29·1)	0·85 (0·62, 1·15); 0·27	1
53Gy	92/343 (26·8)	21·1 (17·1, 26·0)	26·7 (22·1, 32·0)	0·89 (0·66, 1·19); 0·27	1·02 (0·74, 1·41); 0·491
Shoulder stiffness					
40+16Gy	72/348 (20·7)	16·5 (12·9, 21·0)	21·3 (17·1, 26·4)	1	-
48Gy	84/324 (25·9)	19·9 (15·9, 24·8)	25·5 (20·9, 31·0)	1·40 (1·01, 1·95); 0·079	1
53Gy	76/343 (22·2)	16·3 (12·7, 20·8)	20·9 (16·7, 25·9)	1·10 (0·79, 1·53); 0·66	0·78 (0·57, 1·08); 0·915
EORTC QLQ-BR23 items					

Adverse effect	Moderate/ marked events over follow-up / total[1] (%)	KM estimate (95%CI) of cumulative incidence (%) of moderate/ marked events by 3 years	KM estimate (95%CI) of cumulative incidence (%) of moderate/ marked events by 5 years	Comparison with 40+16Gy Hazard ratio[2,3] (95%CI); p-value[4]	Comparison between 53Gy & 48Gy Hazard ratio[2,3] (95%CI); p-value[5,6]
Breast pain					
40+16Gy	113/348 (32·5)	30·8 (26·2, 36·1)	33·4 (28·5, 38·9)	1	-
48Gy	100/324 (30·9)	29·1 (24·4, 34·5)	31·7 (26·8, 37·3)	1·02 (0·76, 1·35); 0·74	1
53Gy	113/343 (32·9)	28·1 (23·6, 33·2)	32·4 (27·6, 37·8)	1·05 (0·80, 1·38); 0·98	1·03 (0·78, 1·37); 0·36
Breast swollen					
40+16Gy	59/348 (16·9)	15·5 (12·0, 19·9)	16·7 (13·1, 21·2)	1	-
48Gy	50/324 (15·4)	15·6 (12·0, 20·2)	16·0 (12·4, 20·6)	0·88 (0·59, 1·31); 0·64	1
53Gy	42/343 (12.2)	10·7 (7·8, 14·6)	12·0 (8·9, 16·2)	0·74 (0·49, 1·12); 0·093	0·83 (0·54, 1·28); 0·89
Breast oversensitive					
40+16Gy	87/348 (25·0)	23·0 (18·9, 27·9)	25·8 (21·4, 31·0)	1	-
48Gy	90/324 (27·8)	24·1 (19·7, 29·2)	29·1 (24·2, 34·7)	1·11 (0·82, 1·50); 0·40	1
53Gy	97/343 (28·3)	23·4 (19·2, 28·3)	28·3 (23·6, 33·6)	1·16 (0·86, 1·57); 0·38	1·02 (0·76, 1·38); 0·50
Skin problems on breast					
40+16Gy	58/348 (16·7)	14·2 (10·9, 18·4)	16·8 (13·1, 21·3)	1	-
48Gy	46/324 (14·2)	12·8 (9·6, 17·1)	14·4 (10·9, 18·9)	0·85 (0·57, 1·29); 0·42	1
53Gy	40/343 (11·7)	10·6 (7·7, 14·4)	12·4 (9·3, 16·6)	0·78 (0·51, 1·18); 0·063	0·89 (0·57, 1·40); 0·85
Arm / shoulder pain					
40+16Gy	133/348 (38·2)	31·1 (26·5, 36·3)	37·3 (32·2, 43·0)	1	-
48Gy	118/324 (36·4)	28·9 (24·2, 34·3)	34·6 (29·5, 40·4)	0·97 (0·75, 1·26); 0·65	1
53Gy	113/343 (32·9)	26·5 (22·1, 31·7)	32·3 (27·4, 37·9)	0·87 (0·67, 1·13); 0·17	0·90 (0·69, 1·18); 0·81
Arm / hand swollen					
40+16Gy	48/348 (13·8)	11·1 (8·2, 15·0)	13·9 (10·5, 18·3)	1	-
48Gy	41/323 (12·7)	10.0 (7·1, 13·9)	13·2 (9·7, 17·8)	0·89 (0·57, 1·38); 0·75	1
53Gy	48/343 (14·0)	10·2 (7·3, 14·0)	14·6 (11·1, 19·1)	1·00 (0·66, 1·50); 0·95	1·12 (0·72, 1·73); 0·35
Difficulty raising arm					
40+16Gy	68/348 (19·5)	16·0 (12·5, 20·4)	18·9 (15·0, 23·7)	1	-

Adverse effect	Moderate/ marked events over follow-up / total[1] (%)	KM estimate (95%CI) of cumulative incidence (%) of moderate/ marked events by 3 years	KM estimate (95%CI) of cumulative incidence (%) of moderate/ marked events by 5 years	Comparison with 40+16Gy Hazard ratio[2,3] (95%CI); p-value[4]	Comparison between 53Gy & 48Gy Hazard ratio[2,3] (95%CI); p-value[5,6]
48Gy	61/324 (18·8)	13·5 (10·1, 17·8)	17·7 (13·7, 22·6)	1·05 (0·73, 1·50); 0·95	1
53Gy	56/343 (16·3)	12·1 (9·0, 16·1)	14·9 (11·3, 19·4)	0·84 (0·58, 1·21); 0·31	0·80 (0·55, 1·17); 0·82

KM = Kaplan-Meier, 95%CI = 95% confidence interval;
[1] Follow-up questionnaires available for 1015 patients (40+16Gy: 348, 48Gy: 324, 53Gy: 343), denominators may vary due to missing assessments for some endpoints; [2] Adjusted for baseline assessment of adverse effect; [3] HR>1 favours 40+16Gy; [4] 2-sided p-value for logrank test; [5] HR>1 favours 48Gy; [6] 1-sided p-value for logrank test

APPENDIX

IMPORT HIGH recruitment by centre

Table A1: IMPORT HIGH recruitment by centre

Centre	Date opened	Principal Investigator(s)*	Other recruiting consultants	Accrual	RT centre total
Addenbrooke's (RT)	23/07/2009	Prof C Coles	Dr L Hughes-Davies, Dr C Wilson	191	333
QEH, King's Lynn	23/12/2010	Dr M Daly		31	
Bedford	04/05/2011	Dr S Aslam	*Dr S Smith*	43	
West Suffolk	14/09/2011	Dr C Woodward	Dr M Moody	68	
Hinchingbrooke	10/01/2012	Dr S Russell		0	
RMH, Sutton (RT)	05/03/2009	Dr A Kirby	Dr I Locke, Dr N Somaiah, Dr D Tait	165	206
St Georges, Tooting	27/10/2009	Dr A Kirby		3	
Croydon University Hospital	30/09/2010	Miss C Pogson	Mr S Ebbs, Dr N Somaiah	38	
Ipswich (RT)	23/01/2009	Dr E Sherwin	Dr R Venkitaraman	219	219
Clatterbridge (RT)	04/06/2009	Dr R Sripidam	Dr K Hayat, *Dr I Syndikus*, Dr N Thorp	92	222
Warrington/Halton	04/06/2009	Dr S Tolan	*Dr I Syndikus*		
Royal Liverpool	04/06/2009	Dr N Thorp	Dr S Tolan	17	
St Helen's (Whiston)	04/06/2009	Dr R Sripadam		54	
Aintree	30/06/2010	Dr P Robson		49	
Southport General	16/09/2011	Dr K Hayat		10	
Christie (RT)	10/01/2014	Dr J Loncaster		18	30
Macclesfield	20/05/2014	Dr L Barraclough		5	
North Manchester General	17/01/2014	Dr J Loncaster		1	
Tameside, Ashton Under Lyne	24/04/2014	Dr C Blake	*Dr L Bhatt*	3	
Stepping Hill, Stockport	18/03/2014	Dr A Chittalia		0	
Leighton Hospital, Crewe	14/07/2014	Dr S Hignett	*Dr P Burt*	2	
Royal Albert Edward, Wigan	01/07/2014	Dr N Bayman	Dr C Anandadas	1	
Royal Stoke (RT)	22/01/2010	Dr D Gahir	*Prof AM Brunt*	90	90
St James's Institute of Oncology, Leeds (RT)	07/02/2012	Dr S Kumar		42	59
Bradford	22/02/2012	Dr E Thomas		17	
Leeds General Infirmary	07/02/2012	Dr S Kumar			
Guy's and St Thomas' (RT)	11/05/2011	Prof E Sawyer	Dr L Brazil, Dr S Harris, Prof A Tutt	27	27
Cheltenham General (RT)	03/11/2010	Dr P Jenkins	Dr K Benstead, Dr J Bowen, Dr R Counsell, Dr S Elyan	201	311
Worcester Royal	04/11/2010	Dr R Counsell	*Dr J Bowen*	55	
Hereford County	04/11/2010	Dr D Nelmes	*Dr S Guglani*	50	
Royal Gloucester	03/11/2010	Dr P Jenkins		5	
Norfolk and Norwich (RT)	02/07/2010	Dr D Geropantas	Dr A Bulman, *Dr A Harnett*	84	84
James Paget	02/07/2010	Dr S Down	*Dr A Harnett*		
Bristol Haematology and Oncology Centre (RT)	18/07/2011	Dr C Comins	*Dr A Bahl*, Dr M Tomlinson	44	63
Weston General	20/12/2011	Dr T Wells	*Dr M Tomlinson*	19	
Royal Free (RT)	28/06/2010	Dr S Needleman	*Dr K Pigott*	52	52
University College London (RT)	01/08/2011	Dr M MacCormack	Dr G Blackman, Dr A Cassoni, Dr M Gaze, Dr J Tobias	137	137
Charing Cross (RT)	20/02/2012	Dr S Cleator	Dr C Lowdell	19	27
St Mary's Hospital, Paddington	20/02/2012	Dr S Cleator			
Ealing Hospital	11/02/2013	Dr O Hatcher	*Dr C Lewanski*	4	
West Middlesex University Hospital	20/08/2012	Dr P Riddle		4	
Derriford Hospital, Plymouth (RT)	13/09/2011	Dr U Panwar	Dr S Dubey, *Dr S Kelly (RIP)*	38	38
Weston Park, Sheffield (RT)	21/03/2011	Dr O Din	Dr K Dunn, Dr M Hatton, Dr C Lee, Dr O Prakash Purohit	160	160
Queen's, Romford (RT)	18/09/2014	Dr M Quigley		7	7
Southampton General (RT)	03/01/2012	Dr S Raj	Dr C Crowley	14	32
Royal Hampshire County	05/01/2012	Dr S Raj		18	
James Cook, Middlesbrough (RT)	23/09/2011	Dr E Thompson	Dr E Aynsley, Dr J Hardman, *Dr N Storey*	28	28
Mount Vernon (RT)	07/10/2011	Dr C Westbury	*Dr M Ah-See*	18	18
Northampton General Hospital (RT)	17/07/2012	Dr R Agarwal	Prof H Eldeeb, *Dr C Macmillan*	42	42
Royal Surrey County (RT)	01/11/2011	Dr R Laing	Dr A Franklin, Dr A Neal, *Dr S Whitaker*	67	67
Peterborough (RT)	30/08/2011	Dr C Jephcott	Dr S Treece	29	29

Centre	Date opened	Principal Investigator(s)*	Other recruiting consultants	Accrual	RT centre total
Beatson WoS Cancer Centre (RT)	16/03/2012	Dr A Alhasso		37	41
Royal Alexandra, Paisley	16/03/2012	Dr A Alhasso			
Wishaw General Hospital	14/01/2015	Dr M Rizwanullah		4	
Crosshouse Hospital	20/01/2016	Dr G Lumsden			
Lincoln County (RT)	21/02/2012	Dr A Chaudhuri	Dr E Murray, Dr V Sivoglo, Dr T Sreenivasan	59	65
Pilgrim Hospital, Boston	21/02/2012	Dr A Chaudhuri	Dr E Murray, Dr A Papkostidi, Dr V Sivoglo	5	
Grantham and District	21/02/2012	Dr A Chaudhuri		1	
Royal Preston (Rosemere Centre) (RT)	10/05/2012	Dr M Hogg		5	46
The Royal Blackburn	10/05/2012	Dr M Hogg	Wiebke Appel	6	
Burnley General	10/05/2012	Dr M Hogg	Wiebke Appel	35	
Royal Cornwall (RT)	27/03/2015	Dr D Wheatley		3	3
Queen Alexandra, Portsmouth (RT)	30/06/2014	Dr A Suovuori	Dr K Bradley, Dr JD Dubois, Dr G Khoury	62	62
Churchill Hospital, Oxford (RT)	04/09/2012	Dr B Lavery	Dr S Oliveros	42	42
Nottingham University Hospital (RT)	30/06/2014	Dr S Hosni	*Dr P Lawton*	3	3
Torbay Hospital (RT)	23/11/2012	Dr P Bliss	Dr A Goodman	31	31
Velindre Cancer Centre (RT)	08/10/2014	Dr H Passant	Dr A Borley	8	8
Belfast City Hospital (RT)	06/03/2015	Dr G Hanna		0	0
Royal Devon and Exeter (RT)	09/09/2014	Dr J Forrest	Dr D Hwang	5	5
University Hospital of Coventry (RT)	03/10/2014	Dr S Lupton		3	17
George Eliot Hospital, Nuneaton	03/10/2014	Dr S Lupton		3	
Alexandra Hospital, Redditch	03/10/2014	Dr C Irwin	*Dr D Hrouda*	0	
Warwick Hospital	03/10/2014	Dr N Walji		11	
Queen Elizabeth, Birmingham (RT)	27/08/2014	Dr M S Anwar	*Dr A Stevens*	3	3
Royal Shrewsbury (RT)	29/08/2014	Dr L Pettit	*Dr S Khanduri*	6	6
Freeman's Hospital, Newcastle (RT)	06/02/2015	Dr H Turnbull	Dr D Lee	4	4
Leicester Royal Infirmary (RT)	06/03/2015	Dr K Sampson	Dr L Aznar-Garcia, *Dr I Bioangiu* , Dr K Kancherla	4	4
			TOTAL	**2621**	**2621**

Bold indicates radiotherapy centres
* Past PI(s) in italics

IMPORT Trial Management Group

Current membership

Abdulla Alhasso	Clare Griffin*	Elinor Sawyer
Wail Al Sarakbi	Susan Griffin	Mark Sculpher
Gillian Barnett	Emma Harris	Navita Somaiah
Judith Bliss*	Jo Haviland*	Mark Sydenham*
Murray Brunt	Penny Hopwood	Isabel Syndikus
Charlie Chan	Hayley James	Yatman Tsang
Hannah Chantler	Monica Jefford	Andrew Tutt
Charlotte Coles	Anna Kirby	Nicola Twyman
Ellen Donovan	Cliona Kirwan	Karen Venables
David Eaton	Sara Lightowlers	Duncan Wheatley
Ian Ellis	Andrew Poynter	Gordon Wishart
Philip Evans	Elena Provenzano	John Yarnold

Past members

Rajiv Agrawal	John Le Vay (deceased)	Judith Robinson
Sarah Barber	Anne McIntyre	Liba Stones*
Peter Bliss	Helen Mayles	Georges Sumo*
Laura Ciurlionis	Daniel Megias	Jenny Titley*
John Dewar	Wing Nip*	Alastair Thompson
Stephen Ebbs	Adeola Obamumoye*	Maggie Wilcox (deceased)
Marie Emson*	Judith Mills*	Anna Winship
Adrian Harnett	Jane Prince*	John Winstanley
Ronald Kaggwa* (deceased)	Christine Rawlings	Rada Zotova

* ICR-CTSU staff

Radiotherapy Quality Assurance team: Laura Ciurlionis, David Eaton, Daniel Megias, Elizabeth Miles, Yatman Tsang, Rada Zotova and Karen Venables.

Independent Trial Steering Committee members: Professor M Mason (Chair), Dr D Gilbert, Dr V Cosgrove, Professor P Poortmans, Professor D Sebag-Montefiore, (past members Dr J Barrett, Professor S Bentzen)
Independent Data Monitoring Committee members: Dr H Lucraft (Chair), Professor M Sydes, Professor J Staffurth, (past members Dr M Sharpe (deceased), Professor N Burnet)

Results of supplementary analyses of IBTR

Results for the per protocol sensitivity analysis of the primary endpoint (IBTR) were very similar to the ITT analysis. Excluding the 181 patients with major treatment deviations, the number of primary events were 18 for 40+16Gy, 19 for 48Gy and 32 for 53Gy, with estimated 5-year cumulative incidence of IBTR 1.8% (95%CI 1.1, 3.0), 2.0% (1.2, 3.3) and 3.1% (2.1, 4.6) respectively. HRs versus 40+16Gy were 1.05 (0,55, 2.00) for 48Gy and 1.79 (1.01, 3.20) for 53Gy, with 5-year absolute differences 0.1% (-0.8, 1.8) and 1.4% (0.01, 3.8) respectively. Results from a competing risks analysis of IBTR with death from any cause as a competing event were almost identical to those from the primary ITT analysis (HRs from competing risks model: 1.05 (95%CI 0.57, 1.93) for 48Gy versus 40+16Gy; 1.76 (1.01, 3.04) for 53Gy versus 40+16Gy).

Statistical considerations for original primary endpoint of reduction in palpable induration inside the boost volume

The original trial design evaluated reduction in palpable induration inside the boost volume for test group 1 (48Gy delivered to boost) versus test group 2 (53Gy) requiring a total of 840 patients to detect a 7% reduction at 3-years in 48Gy compared with 53Gy (assuming 20% in 53Gy, 80% power, 1-sided α=0·05, 5% loss to follow-up). The original trial design was not powered for AE comparisons between each test group and control, although the final sample size *does* have sufficient power for comparisons of the clinical assessments of late AE. The target sample size for PRO and photographic assessments remained 840 when the trial was expanded.

Figure A1: IMPORT HIGH trial schema

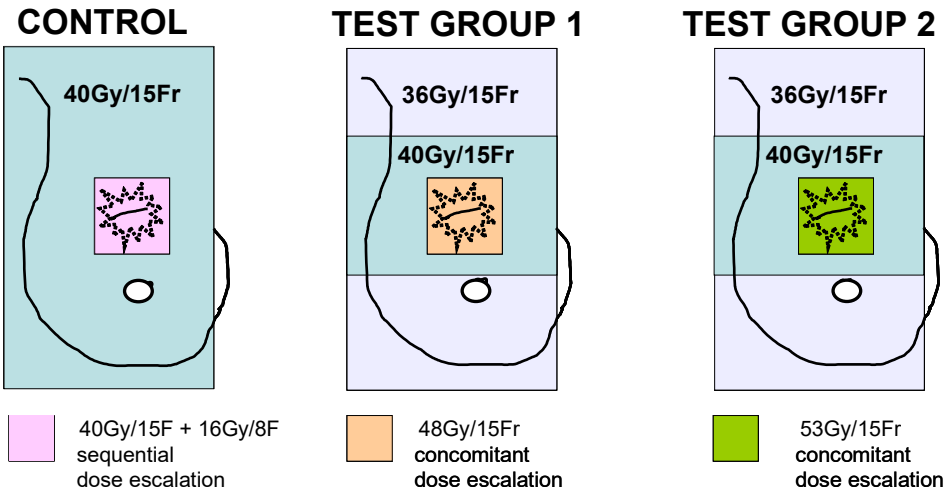
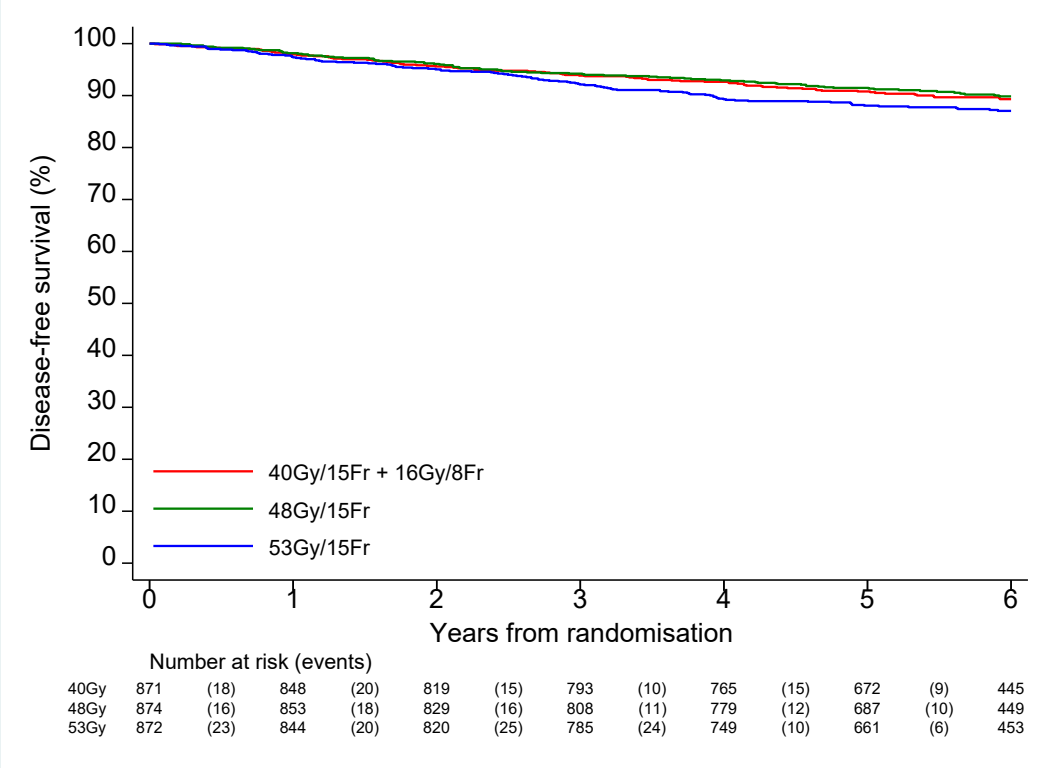
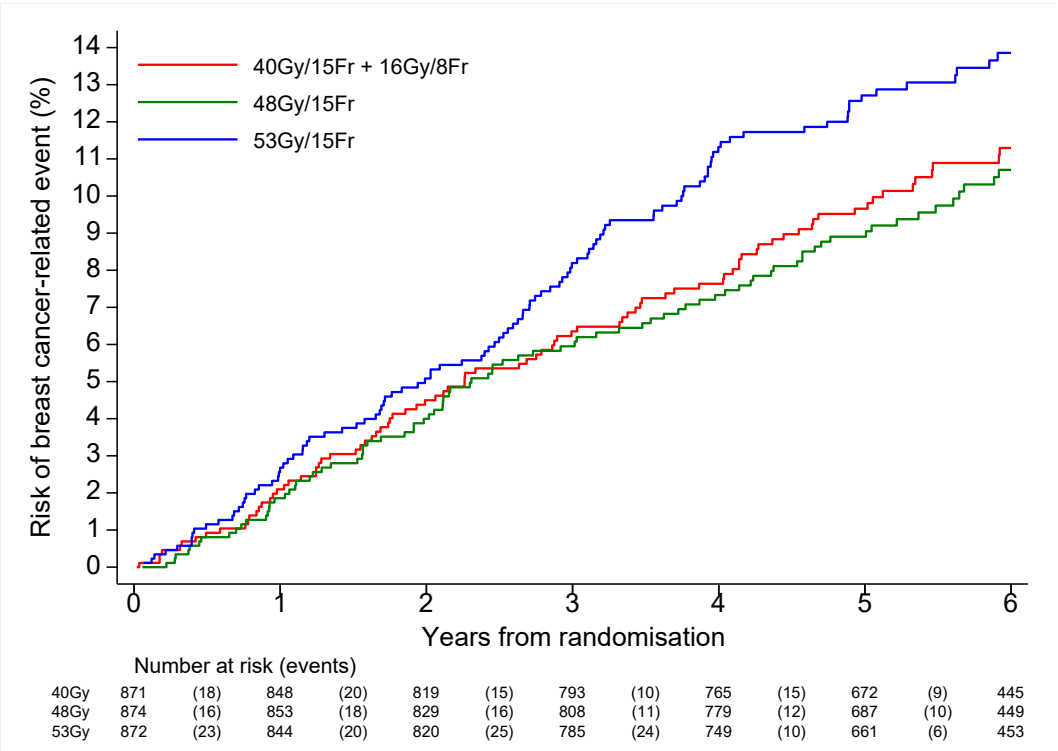


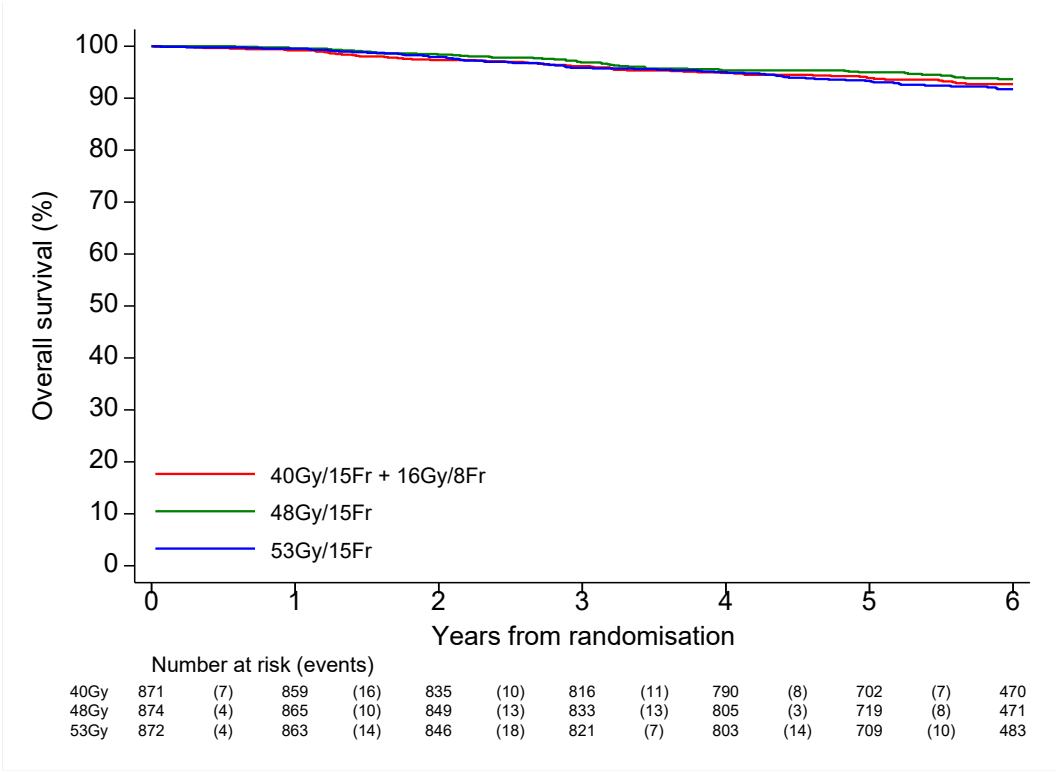
Figure A2a and A2b: Disease-free survival, by treatment group





* Any breast cancer-related event includes local, regional or distant relapse, breast cancer death, contralateral breast cancer

Figure A3a and A3b: Overall survival, by treatment group



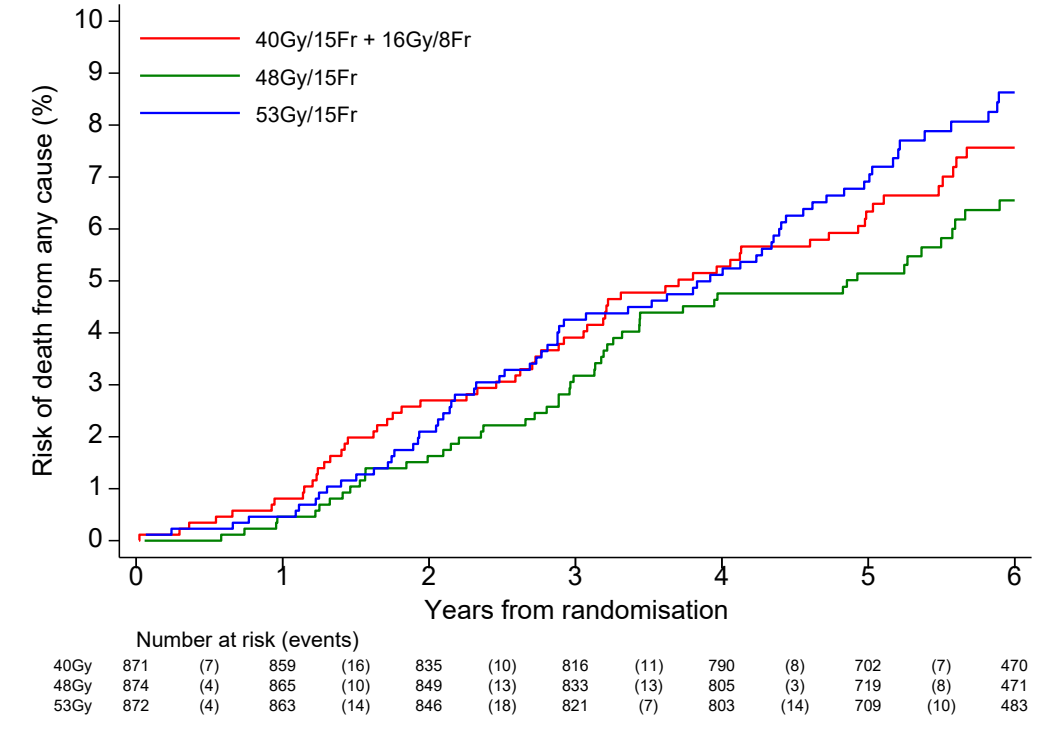
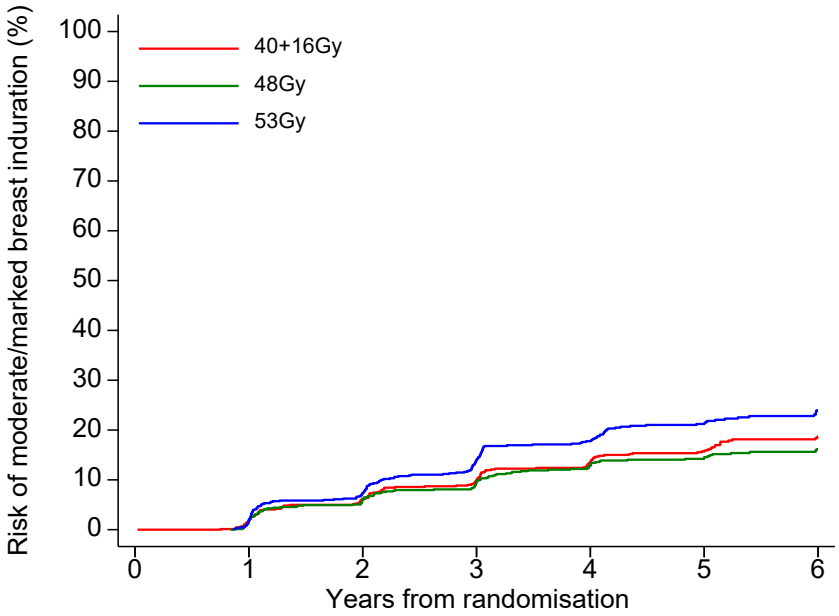


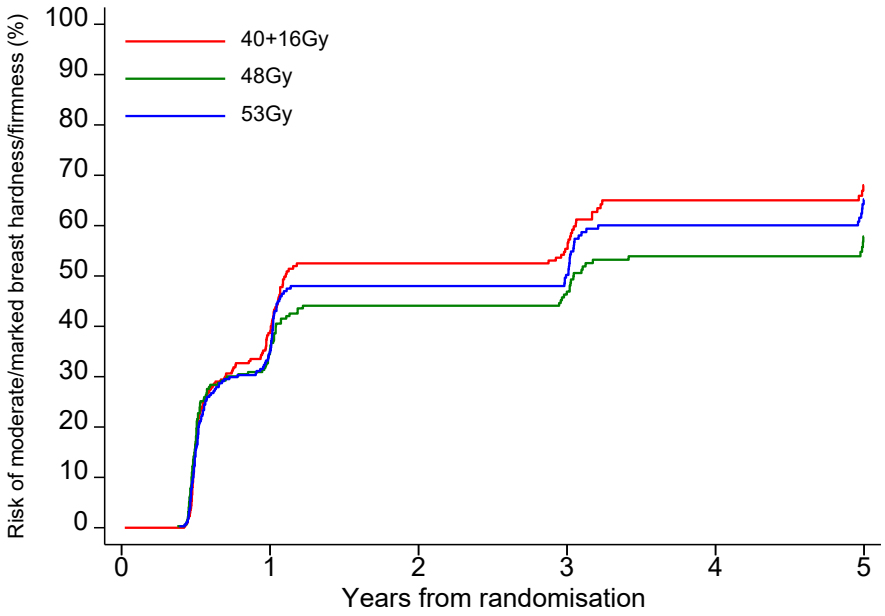
Figure A4a: Cumulative risk of clinician-assessed moderate / marked breast induration (in index quadrant) by treatment group



Number at risk (events)

40+16Gy	814	(15)	786	(33)	729	(26)	683	(25)	619	(12)	518	(13)	348
48Gy	834	(16)	816	(32)	765	(27)	717	(22)	654	(9)	549	(9)	358
53Gy	832	(15)	812	(43)	746	(47)	657	(24)	605	(20)	502	(11)	331

Figure A4b: Cumulative risk of patient-assessed moderate / marked breast hardness / firmness by treatment group

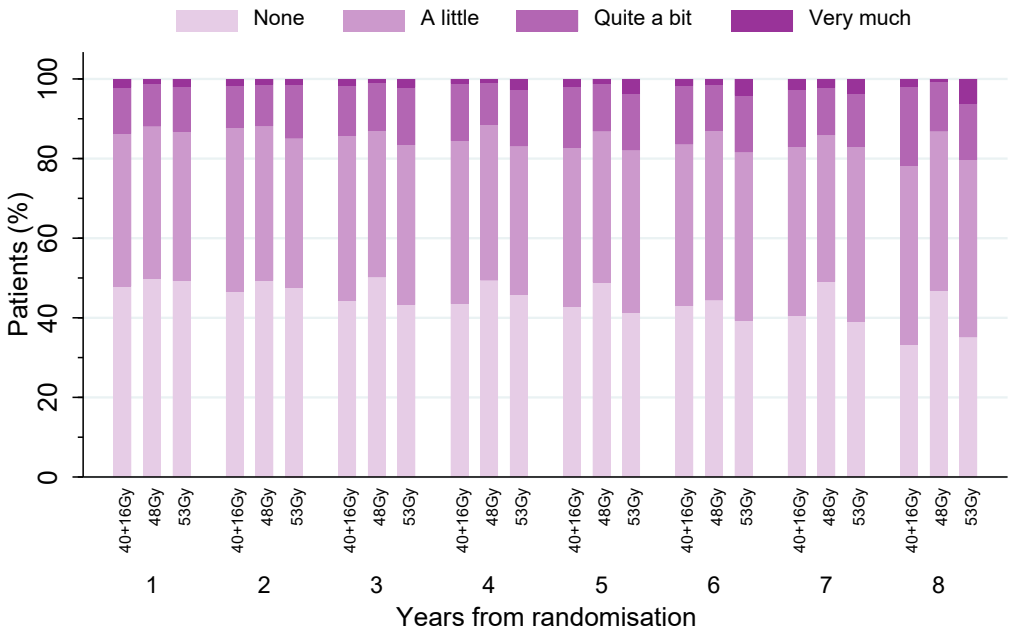


Number at risk (events)

40+16Gy	348	(110)	221	(28)	181	(5)	163	(14)	123	(3)	89
48Gy	324	(96)	218	(18)	189	(5)	167	(11)	144	(4)	85
53Gy	343	(100)	231	(28)	191	(4)	176	(16)	143	(6)	101

Figure A5: Clinician assessments of late normal tissue effects up to 8 years, by treatment group

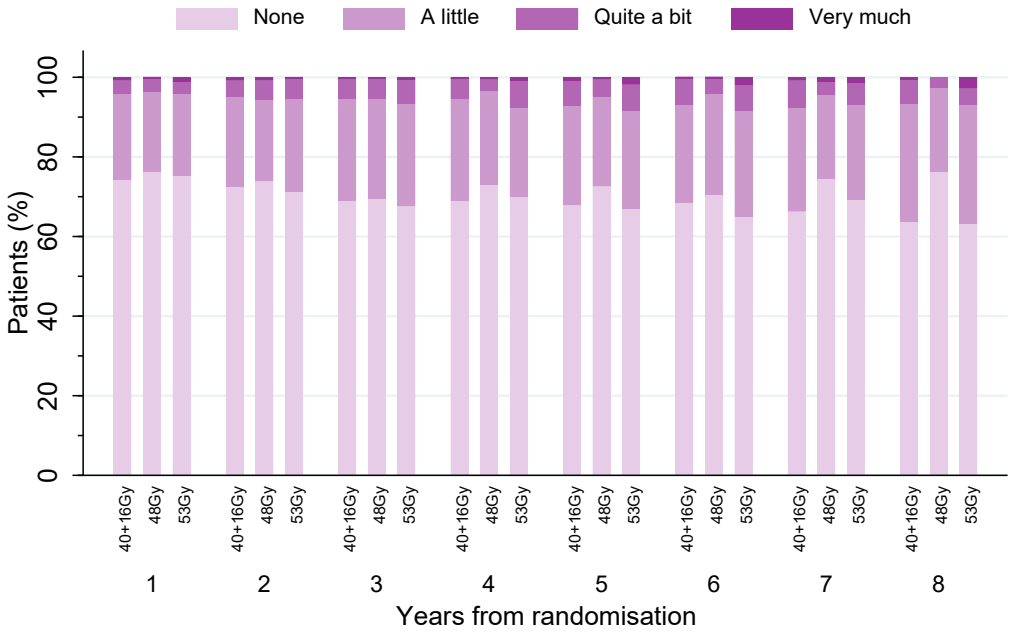
(a) Any breast AE*



Number of patients								
40+16Gy	720	699	689	657	606	421	276	165
48Gy	758	727	703	672	656	439	277	160
53Gy	750	718	688	658	632	430	281	148

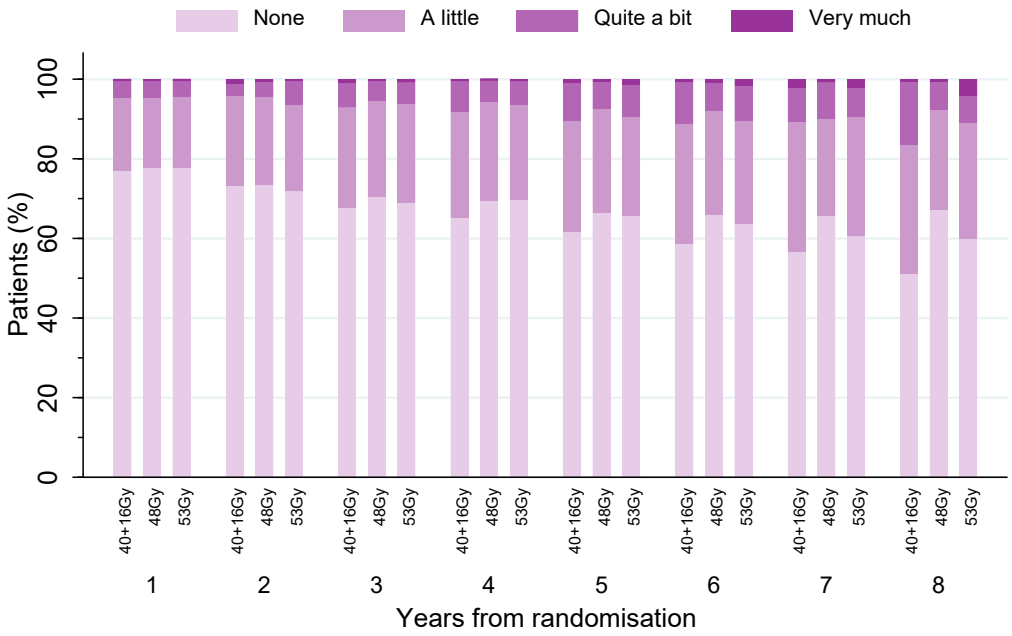
*Any AE in breast includes distortion, shrinkage, induration, telangiectasia, oedema

(b) Breast distortion



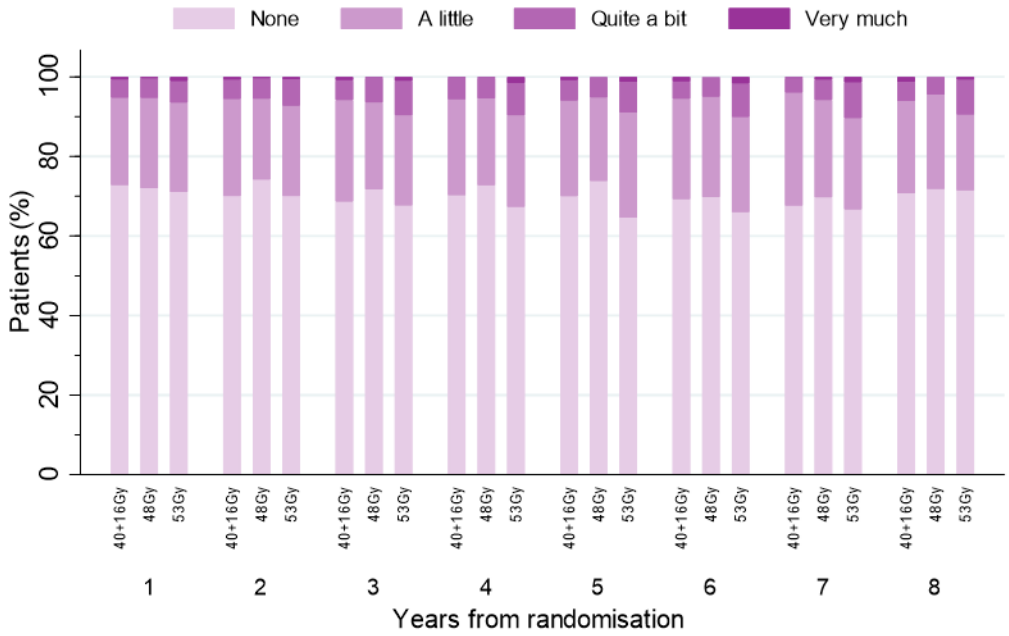
Number of patients								
40+16Gy	715	696	685	651	601	417	276	165
48Gy	750	725	700	664	651	435	272	156
53Gy	743	715	683	652	625	426	279	147

(c) Breast shrinkage



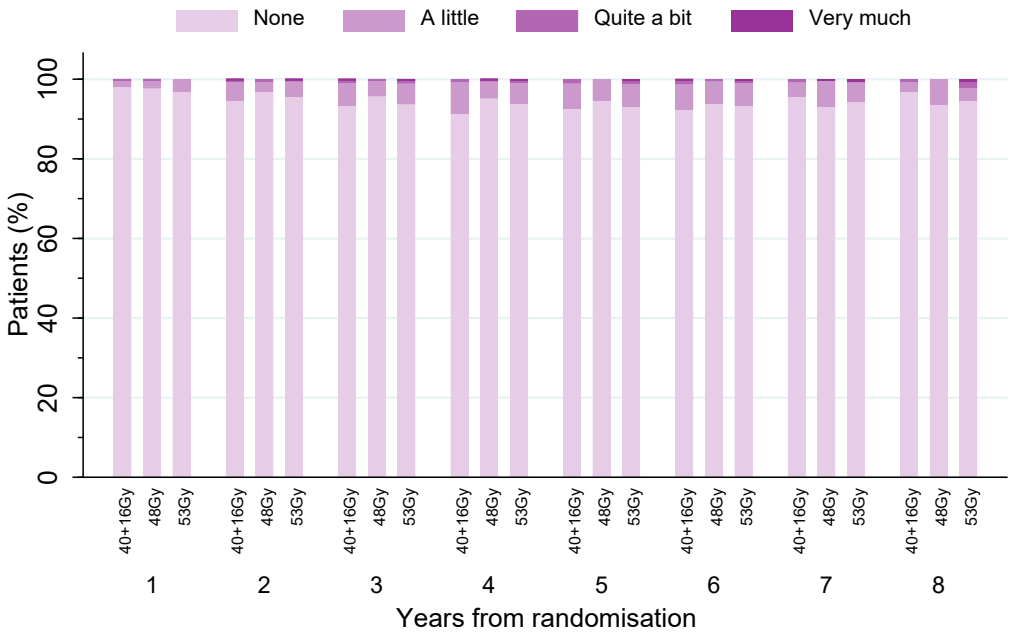
Number of patients								
40+16Gy	715	695	684	649	600	417	275	164
48Gy	750	725	700	665	652	436	272	156
53Gy	741	716	682	653	626	424	279	147

(d) Breast induration (index quadrant)



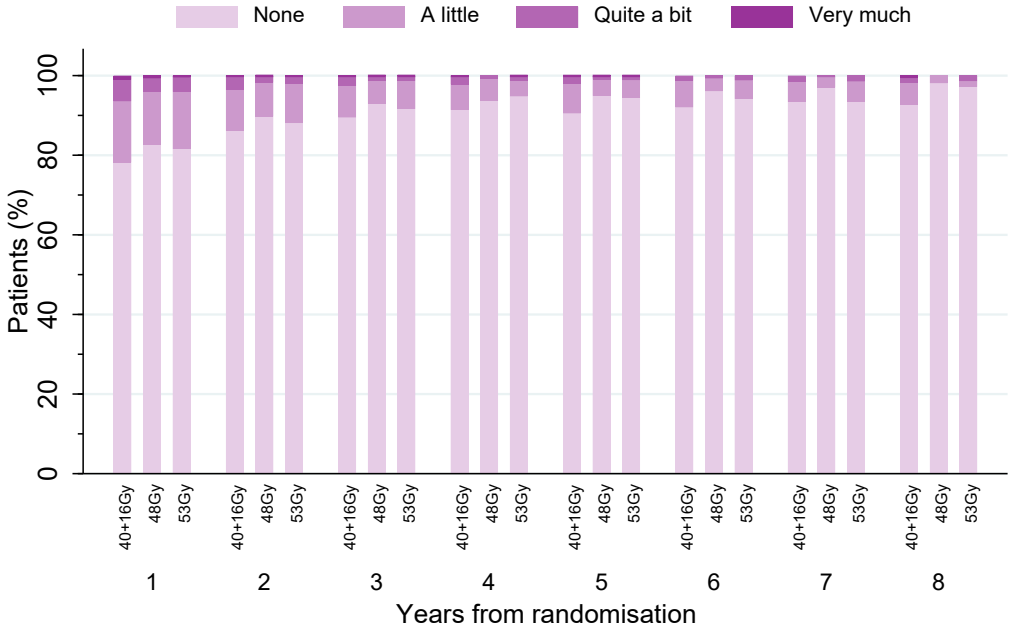
Number of patients								
40+16Gy	716	694	685	648	600	416	275	164
48Gy	750	721	699	664	653	437	274	156
53Gy	742	714	683	651	627	426	279	147

(e) Telangiectasia



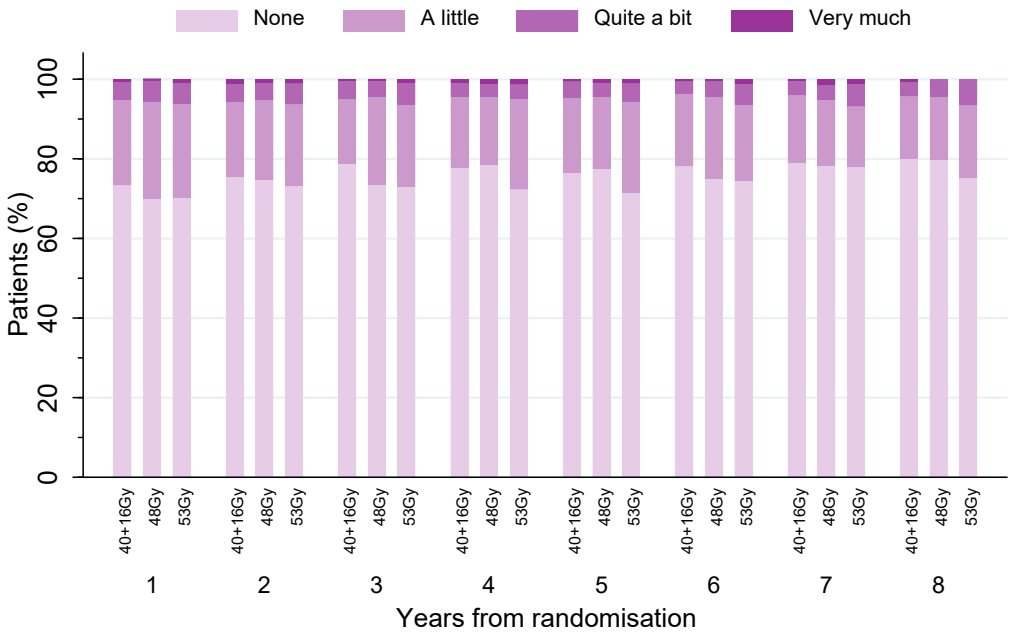
Number of patients								
40+16Gy	716	697	687	653	604	415	274	164
48Gy	750	723	702	666	655	438	273	159
53Gy	740	716	685	655	627	428	279	148

(f) Breast oedema



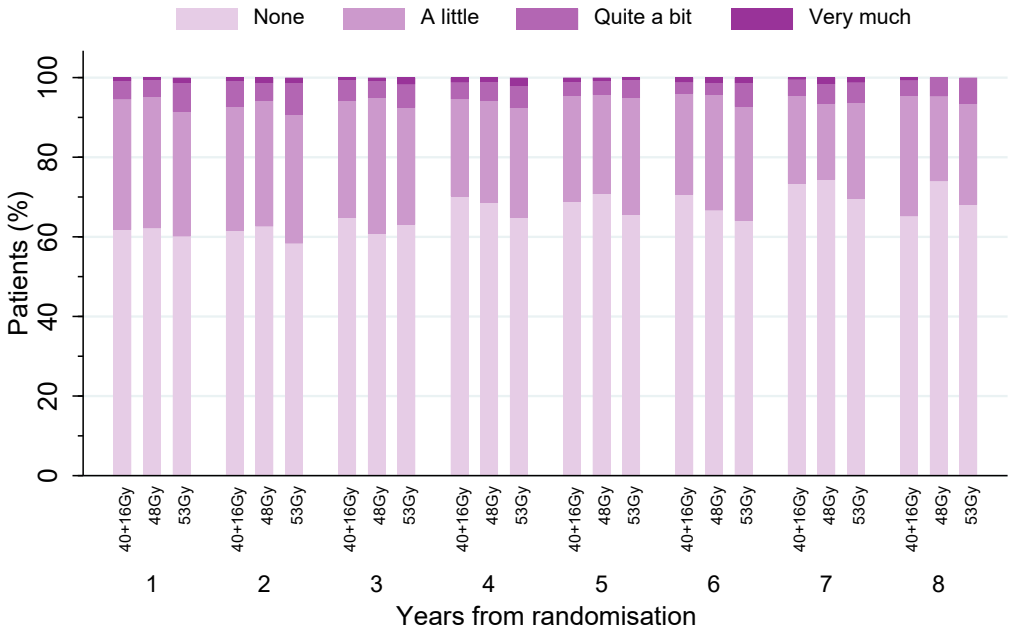
Number of patients								
40+16Gy	716	698	686	652	602	415	274	164
48Gy	756	722	700	663	652	437	274	159
53Gy	744	714	683	655	626	427	278	146

(g) Breast tenderness on palpation



Number of patients								
40+16Gy	504	596	645	653	610	417	277	165
48Gy	546	633	676	663	654	446	276	163
53Gy	520	609	651	655	625	428	281	154

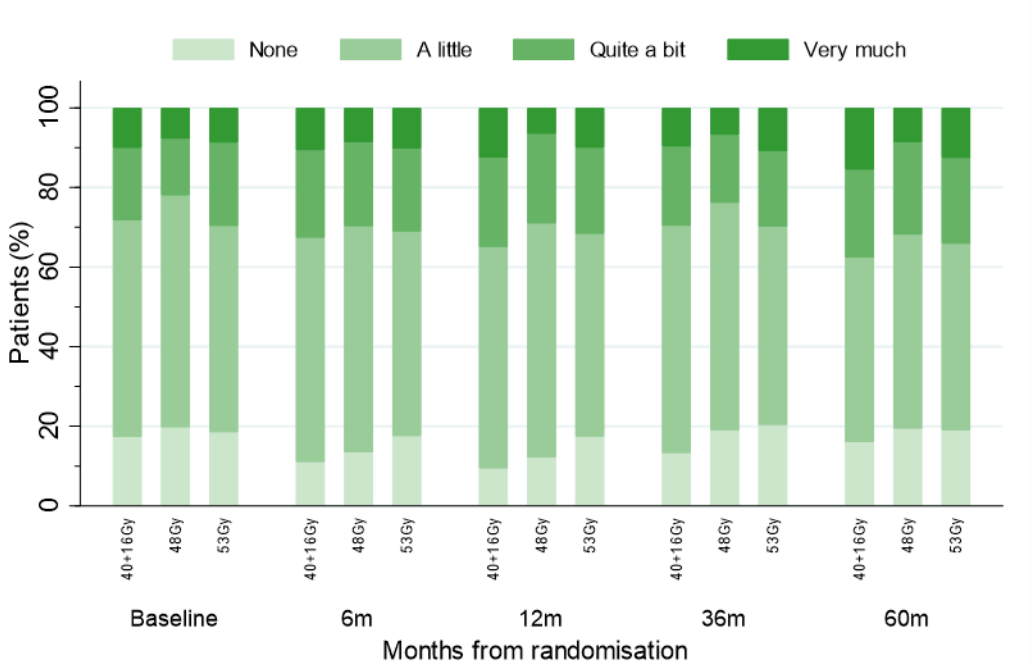
(h) Breast discomfort



Number of patients								
40+16Gy	500	476	531	521	522	354	241	158
48Gy	537	522	575	556	561	375	250	150
53Gy	504	497	545	551	530	370	256	138

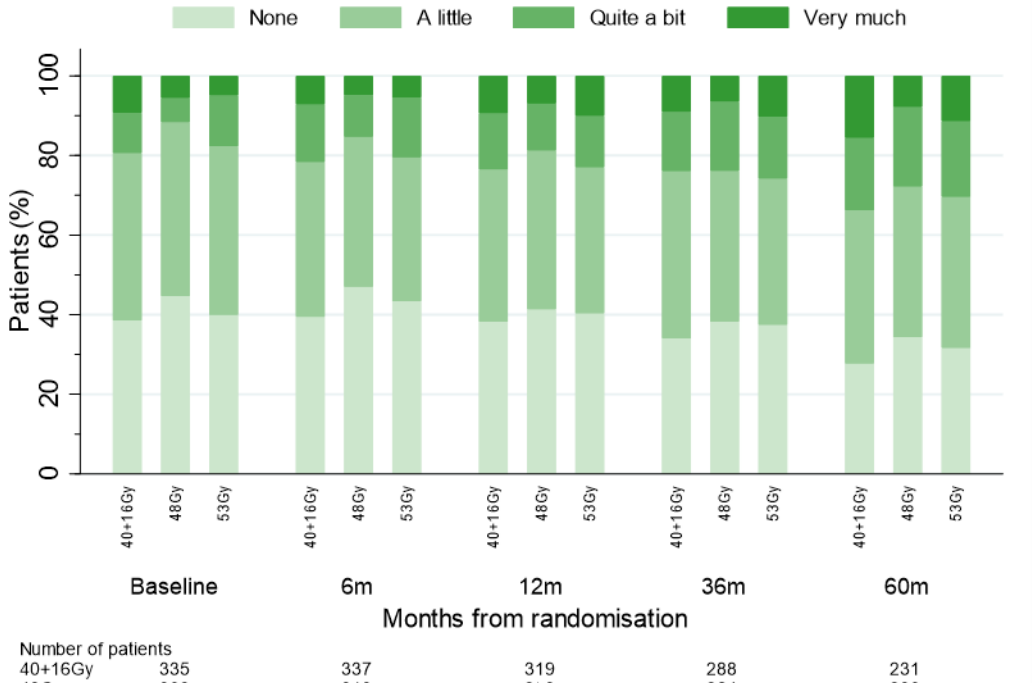
Figure A6: Patient assessments of late normal tissue effects up to 5 years, by treatment group

(a) Change in overall breast appearance



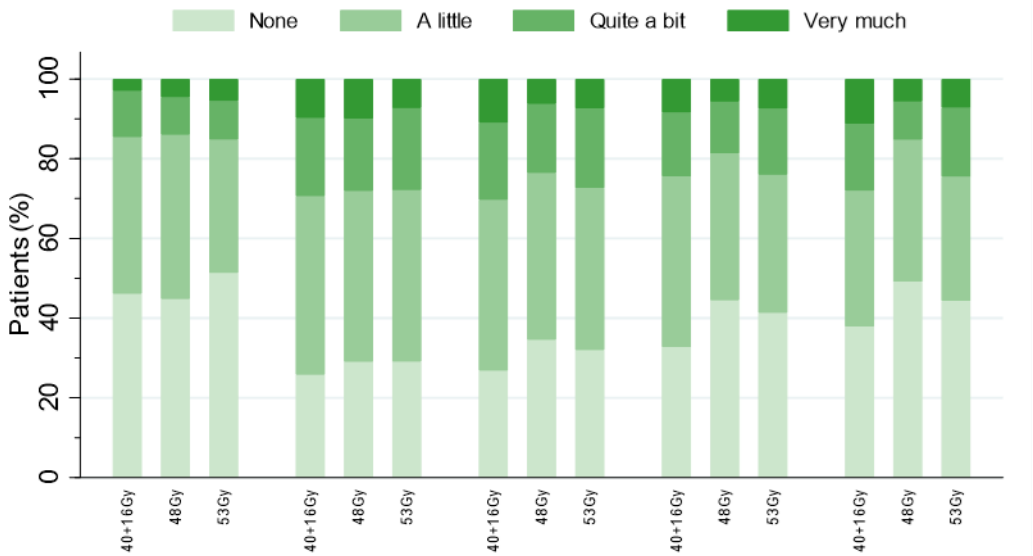
Number of patients					
40+16Gy	336	337	320	287	231
48Gy	309	312	289	264	232
53Gy	330	331	300	285	237

(b) Breast smaller



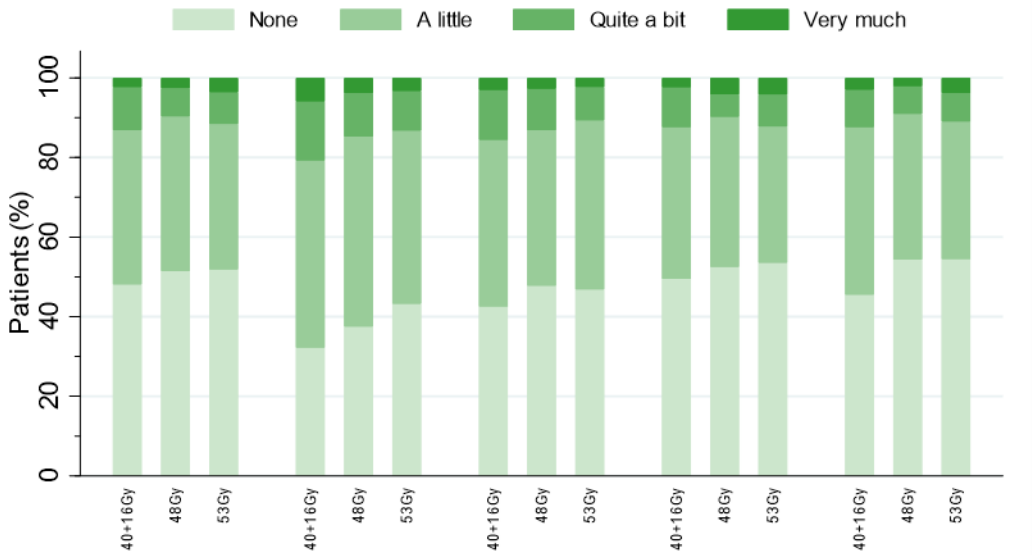
Number of patients					
40+16Gy	335	337	319	288	231
48Gy	309	313	288	264	230
53Gy	328	332	300	283	237

(c) Breast hardness / firmness



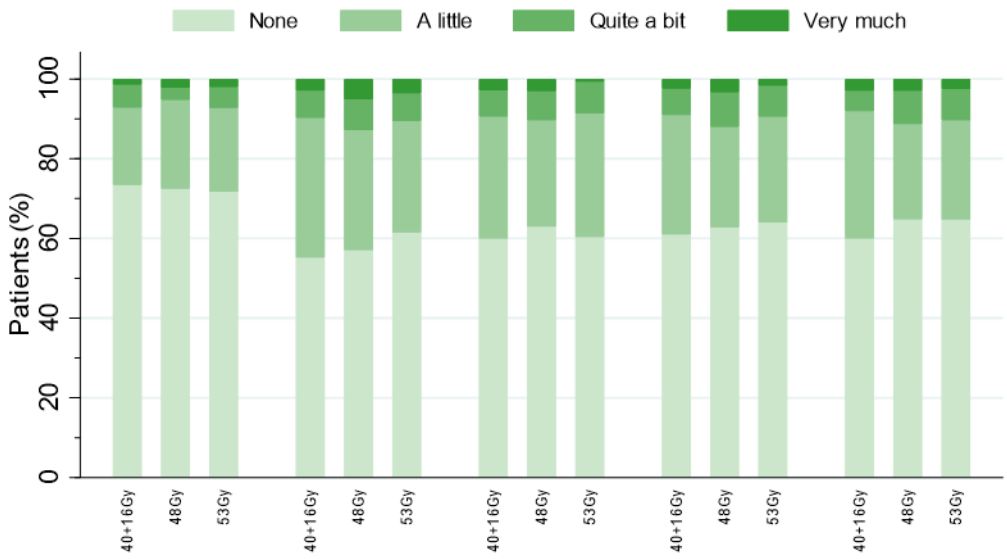
Number of patients					
40+16Gy	336	337	320	287	232
48Gy	308	313	289	263	230
53Gy	329	330	300	283	237

(d) Change in skin appearance on affected breast



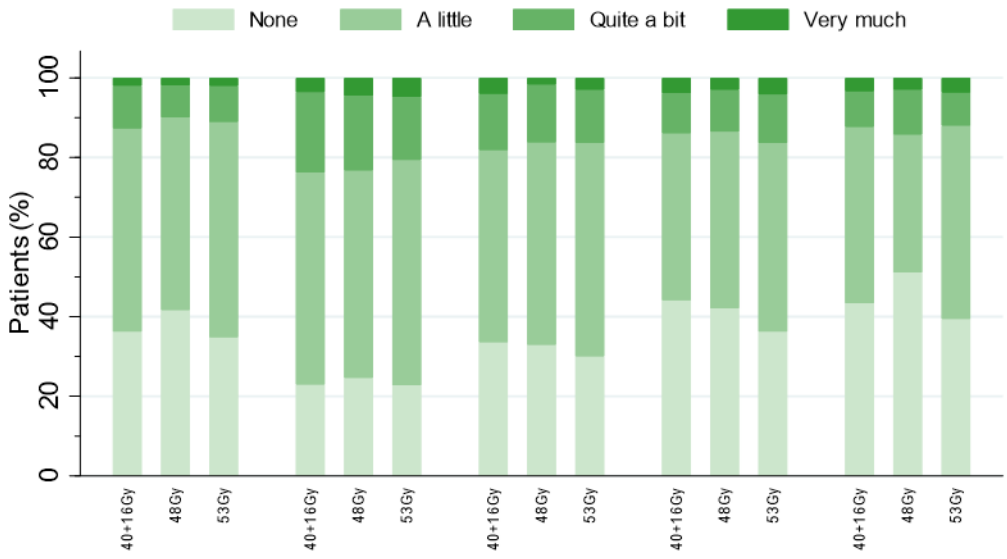
Number of patients					
40+16Gy	335	336	320	289	233
48Gy	309	312	289	265	232
53Gy	328	331	299	286	237

(e) Shoulder stiffness



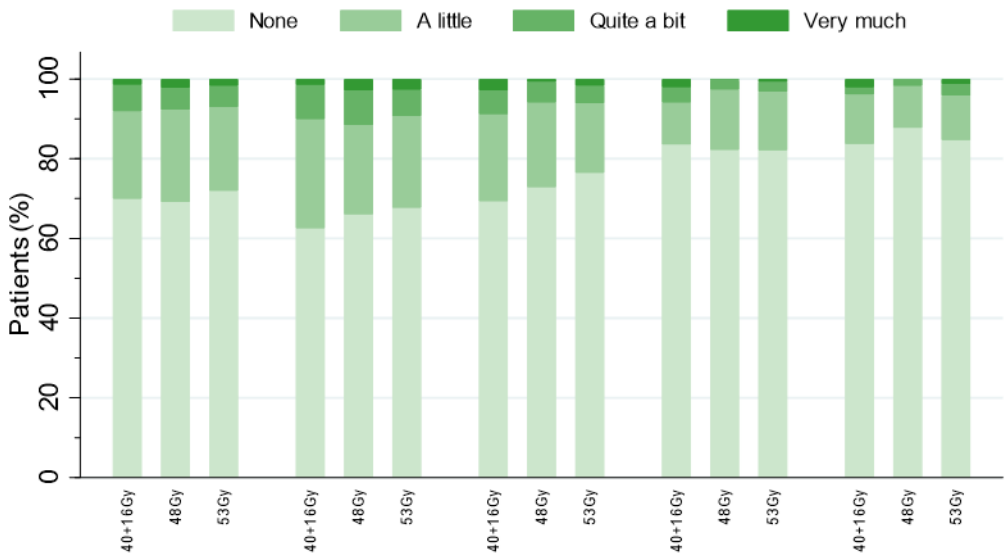
Number of patients					
40+16Gy	346	337	317	287	235
48Gy	323	312	289	266	230
53Gy	343	332	300	286	241

(f) Breast pain



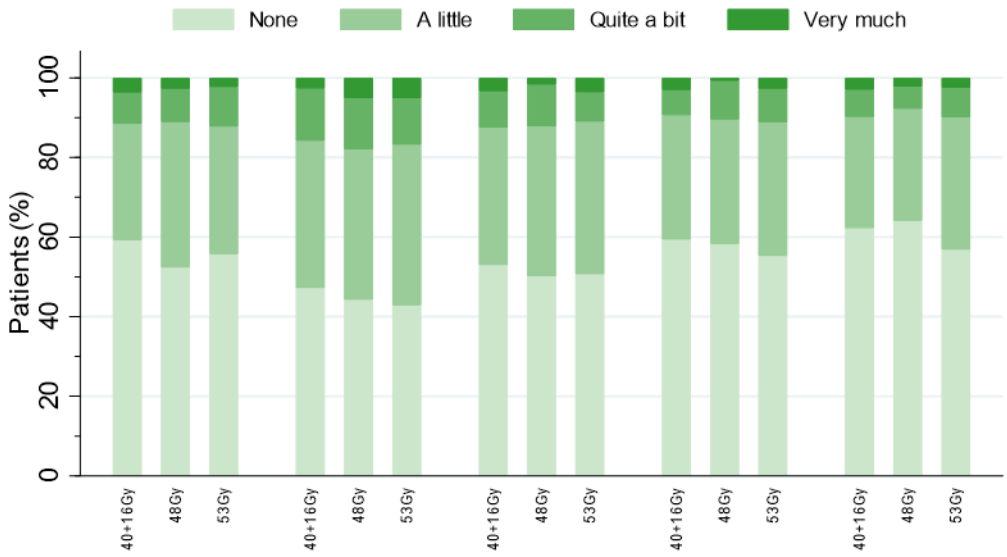
Number of patients					
40+16Gy	345	336	319	286	235
48Gy	322	313	289	266	231
53Gy	342	334	300	287	241

(g) Breast swollen



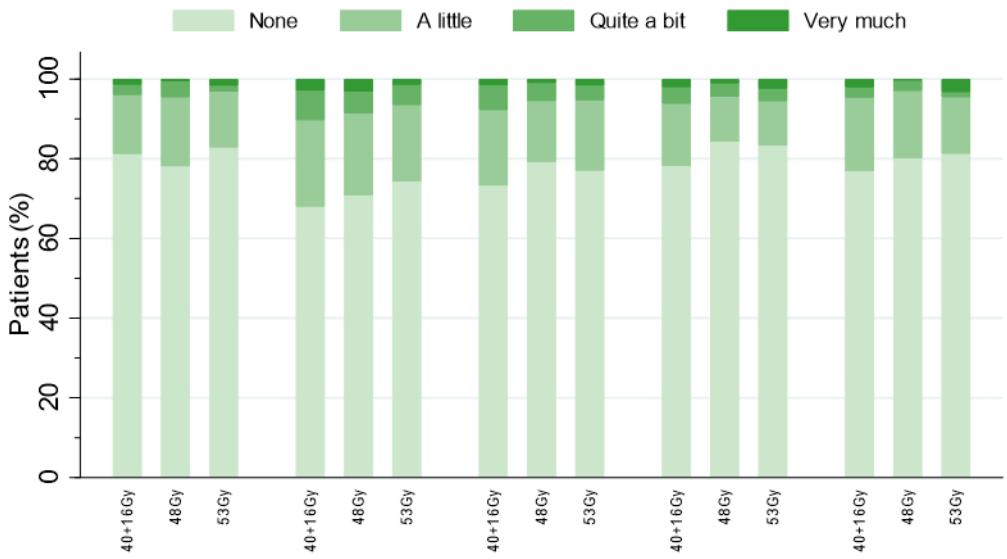
Number of patients					
40+16Gy	346	336	316	286	233
48Gy	324	312	287	264	229
53Gy	342	334	297	285	241

(h) Breast oversensitive



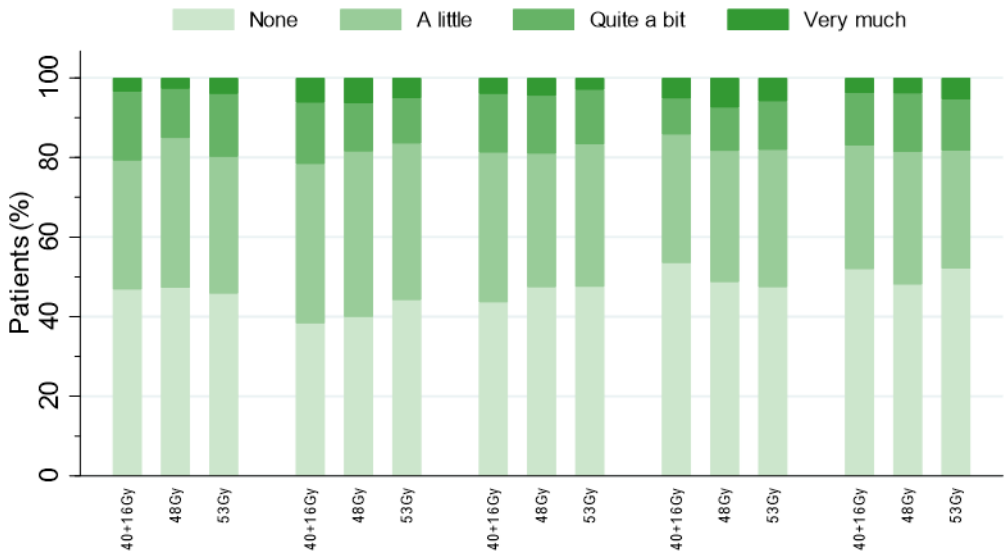
Number of patients					
40+16Gy	345	335	319	288	233
48Gy	323	312	287	266	231
53Gy	343	334	300	286	241

(i) Skin problems on breast



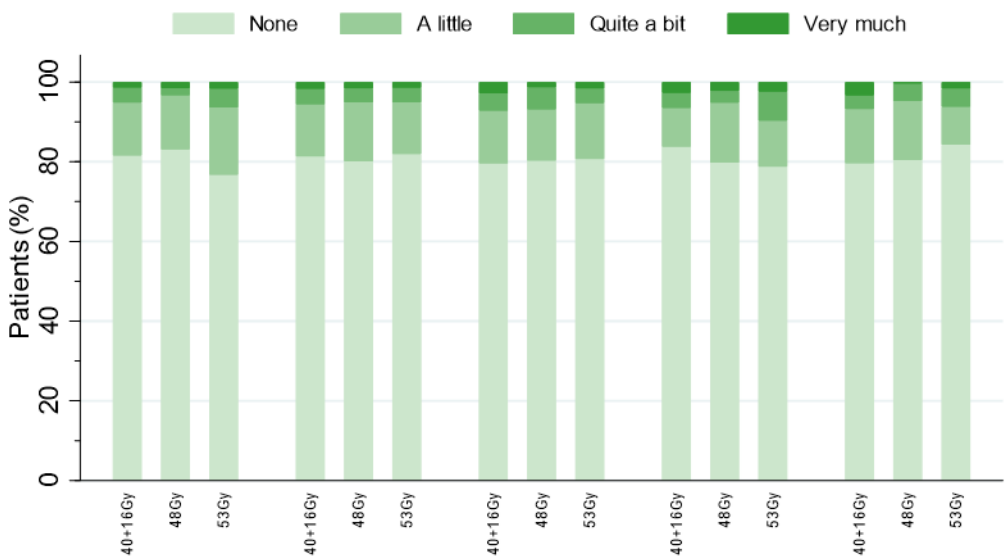
Number of patients					
40+16Gy	346	337	318	288	234
48Gy	324	312	288	267	231
53Gy	343	334	300	287	240

(j) Arm / shoulder pain



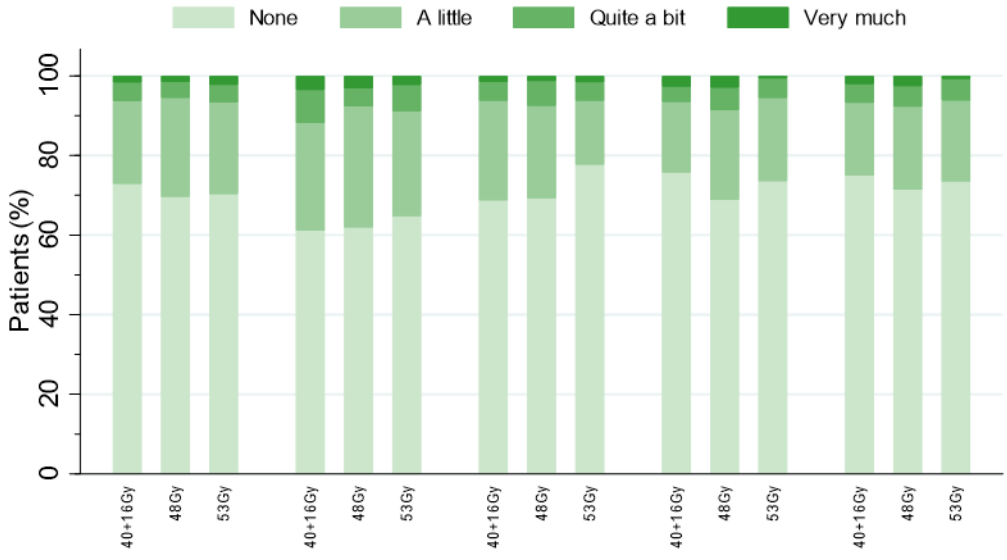
Number of patients					
40+16Gy	346	337	319	288	235
48Gy	324	313	289	267	231
53Gy	343	333	299	287	240

(k) Arm / hand swollen



Number of patients					
40+16Gy	346	337	318	289	235
48Gy	324	312	289	267	230
53Gy	343	332	300	287	241

(l) Difficulty raising arm or moving it sideways



Number of patients					
40+16Gy	346	337	316	288	235
48Gy	322	312	289	266	231
53Gy	343	334	300	287	241

Table A2: Summary of planning techniques in the IMPORT HIGH centres

	Planning Technique (total number)		
	Forward	**Inverse**	**Forward/Inverse**
Control	176	223	196
Test Group 1	161	307	159
Test Group 2	176	315	139
Total	**513**	**848**	**494**

Tomotherapy, a form of inverse IMRT, was used by one centre during the early stages of the trial as this was the available method of IMRT. Of note, this was a hybrid approach of linac-based whole breast radiotherapy and tomotherapy boost so that the low-dose irradiated volumes were limited. We do not have the data to identify numbers of these patients, but they would have been small

Table A3: Summary of dose targets for each treatment group and percentage of plans meeting each target

Treatment group	Volume	Target	Mandatory/ Optimal	Percentage of plans achieving target
40+16Gy	PTVwb - PTVtb	V36Gy > 90%	Mandatory	100
		Median dose 34-37Gy	Optimal	97.5
		V56Gy <5%	Mandatory	99.7
	PTVtb	V53.2Gy >95%	Mandatory	98.1
		Median dose 55.5-56.5Gy	Mandatory	97.0
		V60Gy <5%	Mandatory	99.8
		Global maximum dose <61.6Gy	Mandatory	100
48Gy	PTVwb - PTVpb	V32.4Gy >90%	Mandatory	99.8
		Median dose 34-37Gy	Optimal	97.5
		V40Gy <5%	Mandatory	97.4
	PTVpb - PTVtb	V36Gy >90%	Mandatory	99.1
		Median dose 40-44Gy	Optimal	98.8
	PTVtb	V45.6Gy > 95%	Mandatory	98.2
		Median dose 47.5-48.5Gy	Mandatory	98.5
		V51.4Gy <3%	Mandatory	99.8
		Global maximum dose <52.8Gy	Mandatory	99.5
53Gy	PTVwb - PTVpb	V32.4Gy >90%	Mandatory	99.7
		Median dose 34-37Gy	Optimal	97.8
		V40Gy <5%	Mandatory	92.1
	PTVpb - PTVtb	V36Gy >90%	Mandatory	99.8
		Median dose 40-44Gy	Optimal	94.3
	PTVtb	V50.4Gy >95%	Mandatory	96.0
		Median dose 52.5-53.5Gy	Mandatory	96.6
		V56.7 <3%	Mandatory	99.8

Treatment group	Volume	Target	Mandatory/ Optimal	Percentage of plans achieving target
		Global maximum dose <57Gy	Mandatory	100

Table A4: Summary of organ at risk (OAR) constraints and percentage of plans meeting each

Organ at risk	Constraint	Mandatory/ Optimal	Treatment group	Percentage of plans achieving constraint
Ipsilateral lung	V18Gy <15%	Mandatory	40+16Gy	97.7
			48Gy	98.5
			53Gy	97.4
	V18Gy <10%	Optimal	40+16Gy	70.0
			48Gy	66.7
			53Gy	66.0
	Mean dose <6Gy	Optimal	40+16Gy	77.0
			48Gy	74.2
			53Gy	64.0
Contralateral lung	V2.5Gy <15%	Mandatory	40+16Gy	100
			48Gy	98.8
			53Gy	99.7
	V2.5Gy <3%	Optimal	40+16Gy	92.0
			48Gy	88.5
			53Gy	67.1
	Mean dose <1Gy	Optimal	40+16Gy	99.1
			48Gy	95.8
			53Gy	92.5
Heart (left sided tumour)	V13Gy <10%	Mandatory	40+16Gy	100
			48Gy	99.1
			53Gy	99.4
	V13Gy <2%	Optimal	40+16Gy	70.2
			48Gy	69.8
			53Gy	68.7
	Mean dose <3Gy	Optimal	40+16Gy	76.9
			48Gy	69.5
			53Gy	56.3
Heart (right sided tumour)	V5Gy <6%	Optimal	40+16Gy	97.4
			48Gy	98.3
			53Gy	88.3
	Mean dose <1.7Gy	Optimal	40+16Gy	88.5
			48Gy	79.9
			53Gy	73.8
Contralateral breast	Mean dose <1.5Gy	Mandatory	40+16Gy	99.5
			48Gy	99.3
			53Gy	99.4
	Mean dose <0.5Gy	Optimal	40+16Gy	60.7
			48Gy	52.6
			53Gy	43.3

Table A5: Summary of means of mean heart doses for left and right sided tumours in each treatment group

Laterality of tumour	**Left**			**Right**		
Treatment group	**40+16Gy**	**48Gy**	**53Gy**	**40+16Gy**	**48Gy**	**53Gy**
Median mean heart dose	2.21	2.50	2.80	0.90	1.10	1.40

Mean of mean heart doses	2.39	2.68	2.93	0.99	1.25	1.38
IQR of mean heart doses	1.7 - 2.9	1.8 - 3.1	1.9 - 3.7	0.6 - 1.3	0.8 - 1.6	1.0 - 1.7

IQR = interquartile range

Table A6: Summary of means of mean ipsilateral and contralateral lung doses in each treatment group

Laterality of lung	**Ipsilateral**			**Contralateral**		
Treatment group	**40+16Gy**	**48Gy**	**53Gy**	**40+16Gy**	**48Gy**	**53Gy**
Median mean lung dose	5.20	5.30	5.60	0.34	0.46	0.52
Mean of mean lung doses	5.24	5.41	5.74	0.38	0.52	0.58
IQR of mean lung doses	4.2 - 6.2	4.4 - 6.1	4.7 - 6.6	0.2 - 0.5	0.3 - 0.6	0.4 - 0.7

IQR = interquartile range

Table A7: Summary of target volumes in each treatment group

Treatment group	**40+16Gy**	**48Gy**	**53Gy**
Median CTVtb volume (cm^3)	12.65	12.50	13.50
Mean CTVtb volume (cm^3)	19.86	17.58	18.45
IQR of CTVtb volumes	6.61 - 23.61	7.44 - 20.99	7.28 - 22.58
Median CTVtb/PTVwb ratio	0.015	0.015	0.015
Mean CTVtb/PTVwb ratio	0.022	0.019	0.020
IQR of CTVtb/PTVwb ratios	0.009 - 0.027	0.009 - 0.025	0.009 - 0.026
Percentage with CTVtb/PTVwb ratio > 0.05	5.8	3.3	4.2

IQR = interquartile range

Table A8: Relapses, second primary cancers and deaths by treatment group

Event	40+16Gy N=871	48Gy N=874	53Gy N=872	Total N=2617
Local relapse and ipsilateral new primary (primary endpoint)[1]	**20**	**21**	**35**	**76**
Local relapse only	16	16	25	57
Ipsilateral breast new primary	2	0	5	7
Cannot differentiate	0	2	1	3
Local and regional	2	3	4	9
Type of relapse / new primary				
Invasive	16	14	30	60
DCIS only	1	3	3	7
Unknown	3	4	2	9
Position of relapse / new primary				
Inside tumour bed PTV	10	14	10	34
Inside partial breast PTV but outside tumour bed PTV	0	4	8	12
Inside whole PTV but outside partial breast PTV	5	2	7	12
Outside whole breast PTV[2]	0	0	1	1
Unknown	5	1	9	15
Regional relapse[1,3]	**18**	**16**	**19**	**53**
Axilla	13	8	15	36
SCF	4	9	6	19
Other	6	2	5	13
Distant relapse	**66**	**67**	**74**	**207**
Site of distant relapse[3]				
Bone	31	40	33	104
Lung	24	27	28	79
Liver	26	20	35	71
Pleura	6	5	3	14
Brain	14	11	16	41
Distant nodes	7	9	12	28
Other	10	11	13	34
Contralateral breast new primary	**11**	**14**	**18**	**43**
Invasive	8	12	14	34
DCIS	1	2	4	7
Unknown	2	0	0	2
Non-breast new primary cancer	**19**	**21**	**23**	**63**
Gynaecological	3	2	7	12
Gastrointestinal	6	8	5	19
Lung	1	4	4	9
Urinary	2	2	1	5
Other[4]	7	5	6	18
Death	**71**	**59**	**76**	**206**
Breast cancer	53	49	61	163
Cardiac	0	0	2	2
Second cancer (non-breast cancer)	9	8	7	24
Other[5]	8	1	5	14
Unknown[6]	1	1	1	3
For breast cancer deaths:				

Event	40+16Gy N=871	48Gy N=874	53Gy N=872	Total N=2617
Uncontrolled local disease only at time of death	2	3	3	8
Uncontrolled distant disease only at time of death	42	34	41	117
Uncontrolled local and distant disease at time of death	9	11	16	36
Unknown	0	1	1	2

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

[1] Includes 9 patients with concurrent local and regional relapse (2 x 40+16Gy, 3 x 48Gy, 4 x 53Gy).

[2] For the one patient with IBTR reported as outside whole-breast PTV, this was reported as “lower, outer, lateral chest wall, some in breast tissue and tumour in chest wall muscle too. Out of quadrant, outside RT field”.

[3] More than one site of regional or distant relapse possible; patients with >1 site listed in each relevant row.

[4] Other non-breast second primary sites: 40Gy: myeloma; renal; hilar cholangiocarcinoma; peritoneal (x2); basal cell carcinoma; neuroendocrine. 48Gy: pancreas; renal; Hodgkin’s disease; myeloma; chronic myeloid leukemia. 53Gy: melanoma (x2); thyroid; squaumous cell carcinoma; basal cell carcinoma; peritoneal.

[5] Other causes of death: 40Gy: pneumonia (x2); urinary tract infection; renal stones and pneumonia; ruptured aortic aneurysm; COVID-19; lower respiratory tract infection; head injury after horse accident; advanced dementia, breast cancer and hip fracture. 48Gy: chronic obstructive pulmonary disease. 53Gy: chest infection, sepsis and liver failure; pneumonia (x3); chronic obstructive pulmonary disease.

[6] Unknown cause of death: 48Gy patient had second new primary (pancreatic cancer) 10 months before death.

[7] Unknown for one patient due to missing information on the case report forms and one patient died two days after completing radiotherapy

Table A9: Cross-sectional analysis of clinician-assessed late adverse effects at 5 years according to treatment group for 1947 patients with 5-year AE assessments

Adverse effect	40+16Gy N=627 (%)	48Gy N=674 (%)	53Gy N=646 (%)	Moderate/Marked vs. None/Mild								
				48Gy vs. 40+16Gy			53Gy vs. 40+16Gy			53Gy vs. 48Gy		
				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[1,2]
Any AE in breast[3]				0·76 (0·58, 0·98)	-4·2 (-8·2, -0·2)	0·041	1·03 (0·81, 1·31)	0·5 (-3·7, 4·8)	0·82	1·36 (1·05, 1·76)	4·8 (0·8, 8·7)	0·011
None	260 (43)	321 (49)	261 (41)									
Mild	241 (40)	249 (38)	258 (41)									
Moderate	93 (15)	78 (12)	90 (14)									
Marked	12 (2)	8 (1)	23 (4)									
Breast distortion				0·66 (0·42, 1·04)	-2·4 (-5·0, 0·2)	0·092	1·16 (0·79, 1·71)	1·2 (-1·8, 4·1)	0·46	1·75 (1·13, 2·69)	3·6 (0·8, 6·3)	0·007
None	409 (68)	473 (73)	419 (67)									
Mild	149 (25)	147 (23)	154 (25)									
Moderate	38 (6)	28 (4)	41 (6)									
Marked	5 (1)	3 (<1)	11 (2)									
Breast shrinkage				0·70 (0·49, 1·00)	-3·1 (-6·3, 0·03)	0·058	0·88 (0·63, 1·24)	-1·2 (-4·6, 2·1)	0·50	1·26 (0·87, 1·81)	1·9 (-1·1, 4·9)	0·13
None	371 (62)	433 (66)	411 (66)									
Mild	166 (28)	171 (26)	157 (25)									
Moderate	58 (10)	44 (7)	49 (8)									
Marked	5 (<1)	4 (1)	9 (1)									
Breast induration (index quadrant)				0·87 (0·55, 1·37)	-0·8 (-3·3, 1·8)	0·62	1·49 (0·99, 2·23)	2·9 (0, 5·9)	0·065	1·71 (1·14, 2·59)	3·7 (0·9, 6·5)	0·006
None	420 (70)	482 (74)	405 (65)									
Mild	144 (24)	137 (21)	166 (26)									
Moderate	31 (5)	33 (5)	48 (8)									
Marked	5 (1)	1 (<1)	8 (1)									
Telangiectasia				N/A	-1·0 (-1·8, -0·2)	0·012	1·12 (0·38, 3·32)	0·1 (-1·0, 1·3)	>0·99	N/A	1·1 (0·3, 1·9)	0·007
None	559 (93)	620 (95)	584 (93)									
Mild	39 (6)	35 (5)	36 (6)									
Moderate	6 (1)	0	4 (<1)									
Marked	0	0	3 (<1)									
Breast oedema				0·46 (0·17, 1·22)	-1·1 (-2·4, 0·3)	0·15	0·56 (0·22, 1·41)	-0·9 (-2·3, 0·5)	0·25	1·21 (0·41, 3·60)	0·2 (-0·9, 1·3)	0·47
None	545 (90)	619 (95)	591 (94)									
Mild	45 (7)	27 (4)	28 (4)									
Moderate	11 (2)	5 (1)	6 (1)									
Marked	1 (<1)	1 (<1)	1 (<1)									
Breast tenderness on palpation				0·97 (0·58, 1·60)	-0·1 (-2·4, 2·1)	0·89	1·22 (0·75, 1·98)	1·0 (-1·4, 3·5)	0·44	1·26 0·78, 2·04)	1·2 (-1·2, 3·6)	0·20
None												
Mild	467 (77)	507 (77)	447 (71)									
Moderate	115 (19)	118 (18)	143 (23)									
Marked	25 (4)	24 (4)	29 (5)									
	3 (<1)	5 (1)	6 (1)									
Breast discomfort				0·93 (0·53, 1·62)	-0·3 (-2·8, 2·1)	0·88	1·11 (0·65, 1·89)	0·5 (-2·1, 3·1)	0·78	1·19 (0·70, 2·04)	0·8 (-1·7, 3·3)	0·31
None	359 (69)	397 (71)	348 (66)									

Adverse effect	40+16Gy N=627 (%)	48Gy N=674 (%)	53Gy N=646 (%)	Moderate/Marked vs. None/Mild								
				48Gy vs. 40+16Gy			53Gy vs. 40+16Gy			53Gy vs. 48Gy		
				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[1,2]
Mild	139 (27)	140 (25)	155 (29)									
Moderate	19 (4)	20 (4)	24 (4)									
Marked	5 (<1)	4 (<1)	3 (1)									

Denominators vary due to missing grades for AE assessments; N/A = not available; [1] p-value for Fisher's exact test; [2] 1-sided p-value; [3] Any AE in breast includes distortion, shrinkage, induration (index quadrant), telangiectasia, oedema

Table A10: Longitudinal analysis of clinician-assessed late adverse effects including all annual follow-up assessments for 2496 patients with at least one annual clinical assessment

Adverse effect	No. moderate/marked events / total no. of assessments over follow-up (%)	Comparison with 40+16Gy Odds ratio[2] (95%CI); p-value[3]	Comparison between 53Gy & 48Gy Odds ratio[2] (95%CI); p-value[3,4]	Odds ratio for years of follow-up (95%CI); p-value[3]
Any AE in the breast[1]				1.06 (1.04, 1.08); <0.001
40+16Gy	666/4330 (15.4)	1	-	
48Gy	565/4467 (12.6)	0.81 (0.67, 0.99); 0.042	1	
53Gy	724/4393 (16.5)	1.10 (0.91, 1.33); 0.31	1.35 (1.11, 1.64); 0.001	
Breast distortion				1.06 (1.03, 1.10); <0.001
40+16Gy	246/4302 (5.7)	1	-	
48Gy	197/4427 (4.4)	0.74 (0.54, 1.01); 0.056	1	
53Gy	287/4355 (6.6)	1.11 (0.84, 1.47); 0.48	1.48 (1.09, 2.01); 0.005	
Breast shrinkage				1.16 (1.13, 1.19); <0.001
40+16Gy	345/4295 (8.0)	1	-	
48Gy	270/4430 (6.1)	0.80 (0.61, 1.05); 0.11	1	
53Gy	318/4354 (7.3)	0.90 (0.69, 1.17); 0.45	1.13 (0.87, 1.48); 0.18	
Breast induration (index quadrant)				1.03 (1.00, 1.06); 0.023
40+16Gy	245/4294 (5.7)	1	-	
48Gy	250/4428 (5.6)	0.94 (0.71, 1.24); 0.67	1	
53Gy	381/4355 (8.7)	1.52 (1.18, 1.96); 0.001	1.62 (1.24, 2.11); <0.001	
Telangiectasia				1.17 (1.07, 1.29);
40+16Gy	30/4307 (0.7)	1	-	<0.001
48Gy	16/4441 (0.4)	0.47 (0.18, 1.22); 0.129	1	
53Gy	33/4366 (0.8)	1.02 (0.47, 2.20); 0.95	2.20 (0.87, 5.55); 0.048	
Breast oedema				0.73 (0.68, 0.78);
40+16Gy	126/4304 (2.9)	1	-	<0.001
48Gy	67/4438 (1.5)	0.58 (0.38, 0.88); 0.010	1	
53Gy	79/4359 (1.8)	0.60 (0.39, 0.90); 0.015	1.08 (0.70, 1.68); 0.36	
Breast tenderness on palpation				0.97 (0.94, 1.01); 0.12
40+16Gy	185/3965 (4.7)	1	-	
48Gy	193/4133 (4.7)	0.95 (0.69, 1.29); 0.74	1	
53Gy	237/4011 (5.9)	1.22 (0.90, 1.64); 0.20	1.29 (0.95, 1.74); 0.050	
Breast discomfort				0.95 (0.92, 0.99); 0.008
40+16Gy	183/3399 (5.4)	1	-	
48Gy	183/3601 (5.1)	0.92 (0.68, 1.25); 0.60	1	
53Gy	255/3473 (7.3)	1.40 (1.06, 1.86); 0.018	1.52 (1.14, 2.02); 0.002	

[1] Any AE in breast includes distortion, shrinkage, induration, telangiectasia, oedema; [2] OR estimated from GEE model including all follow-up data, and represents relative odds of moderate/marked AE (versus none/mild) for each pairwise comparison of treatment groups across all follow-up assessments; [3] p-value from Wald test; [4] 1-sided p-value

Table A11: Cross-sectional analysis of patient-assessed adverse effects at 5 years according to treatment group for 708 patients with 5-year questionnaire data available

	40+16Gy N=235 (%)	48Gy N=231 (%)	53Gy N=242 (%)	Moderate/Marked vs. None/Mild								
				48Gy vs. 40+16Gy			53Gy vs. 40+16Gy			53Gy vs. 48Gy		
				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[1,2]
Protocol-specific items												
Breast appearance changed				0·85 (0·66, 1·09)	-5·8 (-14·4, 2·9)	0·21	0·91 (0·71, 1·16)	-3·5 (-12·2, 5·2)	0·44	1·07 (0·83, 1·.39)	2·3 (-6·2, 10·8)	0·34
None	37 (16)	45 (19)	45 (19)									
Mild	107 (46)	113 (49)	111 (47)									
Moderate	51 (22)	54 (23)	51 (21)									
Marked	36 (16)	20 (9)	30 (13)									
Breast smaller				0·82 (0·63, 1·08)	-5·9 (-14·3, 2·5)	0·19	0·90 (0·69, 1·17)	-3·4 (-11·8, 5·1)	0·49	1·09 (0·82, 1·45)	2·5 (-5·7, 10·8)	0·31
None	64 (28)	79 (34)	75 (32)									
Mild	89 (38)	87 (38)	90 (38)									
Moderate	42 (18)	46 (20)	45 (19)									
Marked	36 (16)	18 (8)	27 (11)									
Breast harder/firmer				0·54 (0·38, 0·78)	-12·8 (-20·2, -5·4)	0·001	0·87 (0·64, 1·18)	-3·5 (-11·5, 4·4)	0·40	1·61 (1·10, 2·35)	9·2 (2·1, 16·4)	0·008
None	88 (38)	113 (49)	105 (44)									
Mild	79 (34)	82 (36)	74 (31)									
Moderate	39 (17)	22 (10)	41 (17)									
Marked	26 (11)	13 (6)	17 (7)									
Skin appearance changed				0·73 (0·43, 1·24)	-3·4 (-9·0, 2·2)	0·30	0·88 (0·54, 1·45)	-1·5 (-7·3, 4·3)	0·67	1·21 (0·70, 2·09)	1·9 (-3·5, 7·3)	0·30
None	106 (45)	126 (54)	129 (54)									
Mild	98 (42)	85 (37)	82 (35)									
Moderate	22 (9)	16 (7)	17 (7)									
Marked	7 (3)	5 (2)	9 (4)									
Shoulder stiffness				1·40 (0·80, 2·45)	3·2 (-2·2, 8·6)	0·27	1·28 (0·73, 2·27)	2·3 (-2·9, 7·5)	0·43	0·92 (0·55, 1·54)	-0·9 (-6·5, 4·7)	0·43
None	141 (60)	149 (65)	156 (65)									
Mild	75 (32)	55 (24)	60 (25)									
Moderate	12 (5)	19 (8)	19 (8)									
Marked	7 (3)	7 (3)	6 (2)									
EORTC QLQ-BR23												
Breast pain				1·16 (0·73, 1·84)	1·9 (-4·2, 8·1)	0·59	0·97 (0·60, 1·58)	-0·3 (-6·2, 5·6)	0·52	0·84 (0·53, 1·34)	-2·2 (-8·3, 3·8)	0·28
None	102 (43)	118 (51)	95 (39)									
Mild	104 (44)	80 (35)	117 (48)									
Moderate	21 (9)	26 (11)	20 (8)									
Marked	8 (3)	7 (3)	9 (4)									
Breast swollen				0·45 (0·14, 1·45)	-2·1 (-5·1, 0·9)	0·26	1·07 (0·44, 2·60)	0·3 (-3·2, 3·8)	>0·99	2·38 (0·76, 7·47)	2·4 (-0·6, 5·4)	0·10
None	195 (84)	201 (88)	204 (85)									
Mild	29 (12)	24 (10)	27 (11)									

	40+16Gy N=235 (%)	48Gy N=231 (%)	53Gy N=242 (%)	Moderate/Marked vs. None/Mild								
				48Gy vs. 40+16Gy			53Gy vs. 40+16Gy			53Gy vs. 48Gy		
				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 [1,2]
Moderate	4 (2)	4 (2)	7 (3)									
Marked	5 (2)	0	3 (1)									
Breast oversensitive				0·79 (0·44, 1·42)	-2·1 (-7·2, 3·1)	0·51	1·01 (0·59, 1·74)	0·9 (-5·3, 5·5)	>0·99	1·28 (0·71, 2·29)	2·2 (-3·0, 7·3)	0·25
None	145 (62)	148 (64)	137 (57)									
Mild	65 (28)	65 (28)	80 (33)									
Moderate	16 (7)	13 (6)	18 (7)									
Marked	7 (3)	5 (2)	6 (2)									
Skin problems on breast				0·64 (0·25, 1·63)	-1·7 (-5·2, 1·8)	0·47	0·97 (0·43, 2·20)	-0·1 (-4·0, 3·7)	>0·99	1·51 (0·60, 3·83)	1·5 (-1·9, 5·0)	0·26
None	180 (77)	185 (80)	195 (81)									
Mild	43 (18)	39 (17)	34 (14)									
Moderate	6 (3)	6 (3)	3 (1)									
Marked	5 (2)	1 (<1)	8 (3)									
Arm/shoulder pain				1·09 (0·74, 1·62)	1·6 (-5·3, 8·5)	0·72	1·08 (0.73, 1.59)	1·3 (-5·5, 8·2)	0·72	0·.98 (0·67, 1·44)	0·3 (-7·3, 6·7)	0·52
None	122 (52)	111 (48)	125 (52)									
Mild	73 (31)	77 (33)	71 (30)									
Moderate	31 (13)	34 (15)	31 (13)									
Marked	9 (4)	9 (4)	13 (5)									
Arm/hand swollen				0·70 (0·33, 1·48)	-2·0 (-6·3, 2·2)	0·43	0·91 (0.46, 1.81)	-0.6 (-5·0, 3·8)	0·85	1·30 (0·61, 2·77)	1·4 (-2·7, 5·5)	0·32
None	187 (80)	185 (80)	203 (84)									
Mild	32 (14)	34 (15)	23 (9)									
Moderate	8 (3)	10 (4)	11 (5)									
Marked	8 (3)	1 (<1)	4 (2)									
Difficulty raising arm				1·14 (0·60, 2·19)	1·0 (-3·7, 5·7)	0·72	0·91 (0.46, 1.81)	-0·6 (-5·0, 3·8)	0·85	0·80 (0·41, 1·55)	-1·6 (-6·2, 3·0)	0·31
None	176 (75)	165 (71)	177 (73)									
Mild	43 (18)	48 (21)	49 (20)									
Moderate	11 (5)	12 (5)	13 (5)									
Marked	5 (2)	6 (3)	2 (<1)									

Denominators may vary due to missing items on the questionnaire; percentages are calculated out of totals with data available for each item; [1] p-value for Fisher's exact test; [2] 1-sided p-value

Table A12: Longitudinal analysis of moderate/marked patient-assessed adverse effects from baseline to 5 years for 1063 patients with at least one completed questionnaire*

Adverse effect	No. patients reporting moderate / marked event at baseline / total (%)	No. moderate/marked events / total no. of assessments over 6-60 months follow-up[1] (%)	Comparison with 40+16Gy Odds ratio[2] (95%CI); p-value[3]	Comparison between 53Gy & 48Gy Odds ratio (95%CI); p-value[3,4]	Odds ratio for years of follow-up (95%CI); p-value[3]
Protocol-specific items					
Breast appearance changed					1.04 (1.01, 1.07); 0.012
40+16Gy	95/336 (28.3)	394/1175 (33.5)	1	-	
48Gy	68/309 (22.0)	314/1097 (28.6)	0.78 (0.61, 0.99); 0.046	-	
53Gy	98/330 (29.7)	364/1153 (31.6)	0.95 (0.75, 1.19); 0.64	1.21 (0.95, 1.54); 0.063	
Breast smaller					1.16 (1.12, 1.19); <0.001
40+16Gy	65/335 (19.4)	295/1175 (25.1)	1	-	
48Gy	36/309 (11.6)	229/1095 (20.9)	0.77 (0.58, 1.01); 0.063	-	
53Gy	58/328 (17.7)	282/1152 (24.5)	0.94 (0.72, 1.23); 0.66	1.23 (0.93, 1.61); 0.073	
Breast harder/firmer					1.01 (0.98, 1.05); 0.430
40+16Gy	49/336 (14.6)	331/1176 (28.1)	1	-	
48Gy	43/308 (14.0)	240/1095 (21.9)	0.79 (0.62, 1.01); 0.063	-	
53Gy	50/329 (15.2)	300/1150 (26.1)	0.95 (0.75, 1.21); 0.69	1.20 (0.94, 1.54); 0.074	
Skin appearance changed					0.95 (0.91, 1.00); 0.035
40+16Gy	44/335 (13.1)	185/1178 (15.7)	1	-	
48Gy	30/309 (9.7)	131/1098 (11.9)	0.74 (0.55, 1.00); 0.047	-	
53Gy	38/328 (11.6)	137/1153 (11.9)	0.76 (0.57, 1.02); 0.064	1.03 (0.76, 1.40); 0.425	
Shoulder stiffness					1.05 (1.01, 1.11); 0.027
40+16Gy	25/346 (7.2)	108/1176 (9.2)	1	-	
48Gy	17/323 (5.3)	128/1097 (11.7)	1.18 (0.84, 1.65); 0.33	-	
53Gy	25/343 (7.3)	113/1159 (9.7)	1.07 (0.76, 1.50); 0.69	0.90 (0.65, 1.25); 0.728	
EORTC QLQ-BR23					
Breast pain					0.96 (0.92, 0.99); 0.026
40+16Gy	44/345 (12.7)	207/1176 (17.6)	1	-	

Adverse effect	No. patients reporting moderate / marked event at baseline / total (%)	No. moderate/marked events / total no. of assessments over 6-60 months follow-up[1] (%)	Comparison with 40+16Gy Odds ratio[2] (95%CI); p-value[3]	Comparison between 53Gy & 48Gy Odds ratio (95%CI); p-value[3,4]	Odds ratio for years of follow-up (95%CI); p-value[3]
48Gy	32/322 (9.9)	189/1099 (17.2)	0.91 (0.69, 1.22); 0.54	-	
53Gy	38/342 (11.1)	194/1162 (16.7)	0.94 (0.71, 1.25); 0.68	1.03 (0.77, 1.38); 0.41	
Breast swollen					0.79 (0.74, 0.85); <0.001
40+16Gy	28/346 (8.1)	88/1171 (7.5)	1	-	
48Gy	25/324 (7.7)	64/1092 (5.9)	0.85 (0.59, 1.23); 0.39	-	
53Gy	24/342 (7.0)	68/1157 (5.9)	0.79 (0.55, 1.13); 0.20	0.91 (0.62, 1.34); 0.68	
Breast oversensitive					0.92 (0.88, 0.97); <0.001
40+16Gy	40/345 (11.6)	143/1175 (12.2)	1	-	
48Gy	36/323 (11.1)	137/1096 (12.5)	1.03 (0.76, 1.39); 0.84	-	
53Gy	42/343 (12.2)	145/1161 (12.5)	1.05 (0.78, 1.41); 0.73	1.02 (0.76, 1.37); 0.44	
Skin problems on breast					0.94 (0.88, 1.00); 0.067
40+16Gy	14/346 (4.0)	89/1177 (7.6)	1	-	
48Gy	15/324 (4.6)	62/1098 (5.6)	0.82 (0.54, 1.24); 0.35	-	
53Gy	11/343 (3.2)	65/1161 (5.6)	0.73 (0.48, 1.11); 0.15	0.89 (0.57, 1.40); 0.69	
Arm / shoulder pain					1.00 (0.96, 1.03); 0.93
40+16Gy	72/346 (20.8)	214/1179 (18.1)	1	-	
48Gy	49/324 (15.1)	205/1100 (18.6)	0.95 (0.73, 1.23); 0.70	-	
53Gy	68/343 (19.8)	201/1159 (17.3)	0.95 (0.74, 1.23); 0.70	1.00 (0.77, 1.30); 0.50	
Arm / hand swollen					1.05 (0.99, 1.11); 0.11
40+16Gy	18/346 (5.2)	77/1179 (6.5)	1	-	
48Gy	11/324 (3.4)	61/1098 (5.6)	0.76 (0.49, 1.18); 0.22	-	
53Gy	22/343 (6.4)	76/1160 (6.5)	1.03 (0.69, 1.54); 0.88	1.36 (0.88, 2.10); 0.084	
Difficulty raising arm					0.99 (0.94, 1.05); 0.85
40+16Gy	22/346 (6.4)	95/1176 (8.1)	1	-	
48Gy	18/322 (5.6)	87/1098 (7.9)	0.96 (0.67, 1.37); 0.83	-	

Adverse effect	No. patients reporting moderate / marked event at baseline / total (%)	No. moderate/marked events / total no. of assessments over 6-60 months follow-up[1] (%)	Comparison with 40+16Gy Odds ratio[2] (95%CI); p-value[3]	Comparison between 53Gy & 48Gy Odds ratio (95%CI); p-value[3,4]	Odds ratio for years of follow-up (95%CI); p-value[3]
53Gy	23/343 (6.7)	80/1162 (6.9)	0.88 (0.61, 1.26); 0.48	0.91 (0.63, 1.32); 0.69	

* Number of patients with ≥1 completed questionnaire by treatment group: 362 (40+16Gy), 343 (48Gy), 358 (53Gy)

[1] % represents number of events out of number of assessments (& not out of number of patients), with >1 event possible per patient over follow-up; [2] OR estimated from logistic GEE model including all questionnaires (baseline to 5 years), and represents relative odds of moderate/marked AE (versus none/mild) for each pairwise comparison of treatment groups across all questionnaires; [3] p-value from Wald test; [4] 1-sided p-value

Table A13: Change in photographic breast appearance at 3 and 5 years by treatment group: results of longitudinal analysis for 698 patients with photographic assessments

Treatment group	3 years				5 years				Odds ratio for mild / marked change vs 40+16Gy (95%CI); p-value[1]	Comparison between 53Gy & 48Gy; Odds ratio (95%CI); p-value[1,2]
	N	None (%)	Mild (%)	Marked (%)	N	None (%)	Mild (%)	Marked (%)		
40+16Gy	218	183 (83·9)	25 (11·5)	10 (4·6)	163	103 (63·2)	51 (31·3)	9 (5·5)	1	-
48Gy	210	185 (88·1)	23 (10·9)	2 (1·0)	172	130 (75·6)	35 (20·3)	7 (4·1)	0·61 (0·41-0·93); 0·021	1
53Gy	213	177 (83·1)	32 (15·0)	4 (1·9)	178	129 (72·5)	41 (23·0)	8 (4·5)	0·80 (0·54-1·18); 0·26	1·29 (0·85-1·96); 0·12

[1] p-value from Wald test; [2] 1-sided p-value for comparison of 53Gy vs 48Gy; OR = odds ratio (estimated from GEE model including 3 and 5-year data); 95%CI=95% confidence interval

Table A14: Incidence of severe late adverse effects, by treatment group

	40+16Gy N	48Gy N	53Gy N
Symptomatic rib fracture			
Reported[1]	11	10	15
Confirmed[2] (Ipsilateral side)	*2 (1)*	*2 (2)*	*7 (6)*
Symptomatic lung fibrosis			
Reported[3]	2	3	12
Confirmed[2] (Ipsilateral side)	*1 (0)*	*2 (1)*	*4 (3)*
Ischaemic heart disease			
Reported[4]	5	3	4
Confirmed[2] (Left-sided)	*4 (4)*	*1 (0)*	*1 (1)*
Pneumonitis			
Reported[5]	19	18	19
Confirmed[2]	*1*	*4*	*1*

[1] Reported cases of symptomatic rib fracture include 14 not radiotherapy-related (8 trauma, 3 osteopenia, 3 reason not given but rib fracture clinically-diagnosed only and stated to be not due to radiotherapy)

[2] After imaging and further investigations; excluding cases not radiotherapy-related

[3] Reported cases of symptomatic lung fibrosis include 5 not radiotherapy-related (1 chronic changes, 1 interstitial lung disease, 3 reason not given but lung fibrosis clinically-diagnosed only and stated to be not due to radiotherapy)

[4] Reported cases of ischaemic heart disease include 3 patients with pre-existing heart disease at randomisation and 2 other cases not due to radiotherapy

[5] Reported cases of pneumonitis (persistent cough) include 38 stated to be not radiotherapy-related

Table A15 - risk stratification of ipsilateral breast tumour relapse according to the pathological characteristics at diagnosis – overall & by trial group

Risk stratification	Clinical characteristics	Pts with IBTR N (%)	Total pts within trial population
Very low risk	G1/2, ER+, HER2-, node-	10 (<1)	695
Higher risk (including one or more of the following: G3, ER-, HER+, node+)	G1/2, ER+, HER2+, node-	3 (4)	75
	G1/2, ER-, HER2-, node+	0	10
	G1/2, ER+, HER2-, node-	1 (4)	27
	G1/2, ER+, HER2-, node+	6 (2)	330
	G1/2, ER+, HER2+, node+	1 (3)	36
	G1/2, ER-, HER2+, node+	0	8
	G1/2, ER-, HER2+, node-	1 (5)	19
	G3, ER+, HER2-, node-	8 (2)	423
	G3, ER+, HER2+, node-	3 (2)	156
	G3, ER-, HER2-, node-	19 (5)	357
	G3, ER+, HER2-, node+	9 (5)	197
	G3, ER+, HER2+, node+	0	68
	G3, ER-, HER2-, node+	8 (8)	103
	G3, ER-, HER2+, node-	3 (4)	72
	G3, ER-, HER2+, node+	4 (15)	26

Risk stratification	Clinical characteristics	Pts with IBTR / total within treatment group population N (%)		
		40Gy	**48Gy**	**53Gy**
Very low risk	G1/2, ER+, HER2-, node-	2/243 (1)	3/233 (1)	5/219 (2)
Higher risk (including one or more of the following: G3, ER-, HER+, node+)	G1/2, ER+, HER2+, node-	0/23	1/20 (5)	2/32 (6)
	G1/2, ER-, HER2-, node+	0/3	0/4	0/3
	G1/2, ER+, HER2-, node-	0/10	1/5 (20)	0/12
	G1/2, ER+, HER2-, node+	2/117 (3)	2/105 (2)	1/108 (1)
	G1/2, ER+, HER2+, node+	0/14	0/7	1/15 (7)
	G1/2, ER-, HER2+, node+	0/4	0/3	0/1
	G1/2, ER-, HER2+, node-	0/6	0/4	1/9 (11)
	G3, ER+, HER2-, node-	3/130 (2)	3/148 (2)	2/145 (1)
	G3, ER+, HER2+, node-	2/63 (3)	0/46	1/47 (2)
	G3, ER-, HER2-, node-	5/109 (5)	3/127 (2)	11/121 (9)
	G3, ER+, HER2-, node+	1/66 (2)	3/64 (5)	5/67 (8)
	G3, ER+, HER2+, node+	0/20	0/31	0/17
	G3, ER-, HER2-, node+	2/29 (7)	4/45 (9)	2/29 (7)
	G3, ER-, HER2+, node-	1/19 (5)	1/20 (5)	1/33 (3)
	G3, ER-, HER2+, node+	1/7 (14)	0/8	3/11 (27)

IMPORT HIGH Protocol and radiotherapy planning pack

The protocol and radiotherapy planning pack are available online (https://www.icr.ac.uk/our-research/centres-and-collaborations/centres-at-the-icr/clinical-trials-and-statistics-unit/clinical-trials/import_high).