Dose-escalated simultaneous integrated boost radiotherapy in early breast cancer (IMPORT HIGH): a multicentre, phase 3, non-inferiority, open-label, randomised controlled trial

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Summary

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 tested simultaneous integrated boost against sequential boost with the aim of reducing treatment duration while maintaining excellent local control and similar or reduced toxicity.

Methods IMPORT HIGH is a phase 3, non-inferiority, open-label, randomised controlled trial that recruited women after breast-conserving surgery for pT1–3pN0–3aM0 invasive carcinoma from radiotherapy and referral centres in the UK. Patients were randomly allocated to receive one of three treatments in a 1:1:1 ratio, with computer-generated random permuted blocks used to stratify patients by centre. The control group received 40 Gy in 15 fractions to the whole breast and 16 Gy in 8 fractions sequential photon tumour-bed boost. Test group 1 received 36 Gy in 15 fractions to the whole breast, 40 Gy in 15 fractions to the partial breast, and 48 Gy in 15 fractions concomitant photon boost to the tumour-bed volume. Test group 2 received 36 Gy in 15 fractions to the whole breast, 40 Gy in 15 fractions to the partial breast, and 53 Gy in 15 fractions concomitant photon boost to the tumour-bed volume. The boost clinical target volume was the clip-defined tumour bed. Patients and clinicians were not masked to treatment allocation. The primary endpoint was ipsilateral breast tumour relapse (IBTR) analysed by intention to treat; assuming 5% 5-year incidence with the control group, non-inferiority was predefined as 3% or less absolute excess in the test groups (upper limit of two-sided 95% CI). Adverse events were assessed by clinicians, patients, and photographs. This trial is registered with the ISRCTN registry, ISRCTN47437448, and is closed to new participants.

Findings Between March 4, 2009, and Sept 16, 2015, 2617 patients were recruited. 871 individuals were assigned to the control group, 874 to test group 1, and 872 to test group 2. Median boost clinical target volume was 13 cm³ (IQR 7 to 22). At a median follow-up of 74 months there were 76 IBTR events (20 for the control group, 21 for test group 1, and 35 for test group 2). 5-year IBTR incidence was 1·9% (95% CI 1·2 to 3·1) for the control group, 2·0% (1·2 to 3·2) for test group 1, and 3·2% (2·2 to 4·7) for test group 2. The estimated absolute differences versus the control group were 0·1% (–0·8 to 1·7) for test group 1 and 1·4% (0·03 to 3·8) for test group 2. The upper confidence limit for test group 1 versus the control group indicated non-inferiority for 48 Gy. Cumulative 5-year incidence of clinician-reported moderate or marked breast induration was 11·5% for the control group, 10·6% for test group 1 (p=0·40 *vs* control group), and 15·5% for test group 2 (p=0·015 *vs* control group).

Interpretation In all groups 5-year IBTR incidence was lower than the 5% originally expected regardless of boost sequencing. Dose-escalation is not advantageous. 5-year moderate or marked adverse event rates were low using small boost volumes. Simultaneous integrated boost in IMPORT HIGH was safe and reduced patient visits.

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Introduction

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.[1–3] Randomised trials of breast-conserving surgery followed by whole-breast radiotherapy with or without a tumour-bed boost have showed 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 European Organisation for Research and Treatment of Cancer (EORTC) boost versus

Research in context

Evidence before this study

A comprehensive literature search was done before the trial opened using PubMed and MEDLINE to review all publications addressing (1) pathological and clinical studies investigating patterns of ipsilateral breast tumour relapse following radiotherapy, (2) breast tumour-bed boost studies, and (3) methods of tumour-bed definition and localisation for breast boost. We concluded that most ipsilateral breast tumour relapses occur in and around the tumour bed; all published breast boost trials used sequential boost radiotherapy, 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. Dose-intensity modulation using simultaneous integrated boost (SIB) was hypothesised to offer 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 3 randomised trial to publish 5-year outcome data using hypofractionated SIB and is substantially larger than any other reported SIB studies. In addition, to our knowledge, this trial 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. These measures ensured consistent boost volumes across the treatment groups, leaving timing of boost (synchronous *vs* sequential) as the main variable in the trial. At 5 years, hypofractionated SIB (48 Gy) 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 53 Gy SIB, which was associated with increased breast induration. By contrast, 48 Gy SIB showed similar or reduced normal tissue toxicity compared with control. Follow-up is ongoing 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 of SIB would be beneficial for both patients and health-care systems. For those centres that have adopted 1-week whole breast radiotherapy followed by 1-week boost, 3-week SIB is still an important treatment for patients requiring 3-week nodal radiotherapy, 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.

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See Online for appendix

no boost trial, risk of local failure at 10 years with boost was 13·5% in those 40 years and younger and 8·7% in patients aged 41–50 years.

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 (ie, fractions) thereby increasing treatment burden for patients and health-care systems.

IMPORT HIGH builds on the results of previous UK breast radiotherapy trials[9,10] and uses newer radiation techniques (ie, 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, which is known as a simultaneous integrated boost (SIB). The boost volume is minimised by targeting titanium clips (or gold seeds) placed in the tumour bed during surgery.[11,12] This method enables escalation of radiation dose to the tumour bed while delivering a standard dose to nearby breast tissue and a slightly lower dose to peripheries of breast tissue where the risk of relapse is lowest. IMPORT HIGH is the largest randomised trial to date testing dose-escalated SIB against standard sequential boost.

Methods

Study design

IMPORT HIGH is a multicentre, phase 3, non-inferiority, open-label, randomised controlled trial that tested the safety and efficacy of dose-escalated IMRT after breast-conserving surgery for early breast cancer in women with higher than average local relapse risk. Recruitment was done in 39 radiotherapy centres and 37 referral centres in the UK.

IMPORT HIGH was originally designed as a phase 2 trial with the primary endpoint of palpable induration inside the boost volume. These results were anticipated to inform the design of a subsequent practice-changing phase 3 trial evaluating ipsilateral breast tumour relapse (IBTR). However, additional funding was obtained to increase the sample size and allow robust statistical evaluation of IBTR. This amendment endorsed by the independent data monitoring committee and the trial steering committee enabled an efficient and streamlined evaluation of toxicity and cancer outcomes within one trial. The study was approved by the Cambridgeshire Research Ethics Committee 4 (reference number 08/H0305/13) and done in accordance with the principles of Good Clinical Practice.

Participants

Women aged 18 years or older receiving breast-conserving surgery 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 chemoradiotherapy. 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. All patients provided written informed consent.

For the **protocol and radiotherapy planning pack** see https://www.icr.ac.uk/our-research/centres-and-collaborations/centres-at-the-icr/clinical-trials-and-statistics-unit/clinical-trials/import_high

Randomisation and masking

Women were randomly assigned (1:1:1) to three groups. The control group received radiotherapy at 40 Gy in 15 fractions to the whole breast plus 16 Gy in 8 fractions sequential photon boost to the tumour bed. The second group (test group 1) received radiotherapy at 36 Gy in 15 fractions to the whole breast, 40 Gy in 15 fractions to the partial breast, and concomitant photon boost to the tumour bed at 48 Gy in 15 fractions. The third group (test group 2) received the same as test group 1, but had concomitant photon boost to the tumour bed at 53 Gy in 15 fractions instead (appendix p 5). In all groups, the dose to the lymph node regions in patients requiring nodal radiotherapy was 40 Gy in 15 fractions. To randomly assign a patient, centres telephoned The Institute of Cancer Research Clinical Trials and Statistics Unit (London, UK). Computer-generated random permuted blocks (mixed size of six and nine) were used to stratify patients by radiotherapy treatment centre. Treatment allocation was not masked for patients and clinicians.

Procedures

The tumour bed was localised with titanium surgical clips or gold seeds to enable radiotherapy planning and aid IGRT verification. IMPORT HIGH was recruiting when tumour-bed clip insertion was still being implemented into routine practice. Participants were CT-imaged in the supine position 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 tumour-bed clinical target volume (boosted clinical target volume) was defined as clips plus surrounding architectural distortion. The boosted clinical target volume was recommended to be 5% or less of the whole-breast planning target volume and was increased by 5 mm to create the boosted planning target volume. For patients randomly assigned to the test groups, the boosted clinical target volume was expanded by 15 mm to create the partial-breast clinical target volume, which was edited to be within whole-breast clinical target volume including cropping 5 mm from the skin. A 10 mm margin was added to the partial-breast clinical target volume and whole-breast clinical target volume to create the partial-breast planning target volume and whole-breast planning target volume. 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 and 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. The trial quality assurance included facility questionnaires, contouring and planning benchmark cases, process documents, dosimetry audits, and 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 for 10 years. Late adverse effects were assessed independently by clinicians, patients, and using photographs. Clinicians assessed adverse events annually for all patients. Centres could opt into patient-reported outcomes and photographic substudies; all patients at these centres were offered participation in both of the substudies. Photographs were taken at baseline (after surgery and before radiotherapy), 3 years, and 5 years. Patient-reported outcome questionnaires were administered at baseline (before randomisation), 6 months, 1 year, 3 years, and 5 years. Patient-reported outcomes included the EORTC QLQ-BR23 breast cancer module, Body Image Scale, and protocol-specific questions relating to ipsilateral breast changes following treatment.

At follow-up, 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, respectively), comparing the ipsilateral versus contralateral breast where relevant. Results for patient-reported outcomes relating to breast and arm or shoulder symptoms (scored on a 4-point ordinal scale as for the clinical assessments) are reported in this manuscript; further analysis of patient-reported outcomes 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 years and 5 years compared with baseline by three observers (3 years: CEC, JRY, and a non-author observer [a researcher]; 5 years: CEC, AMK, and the same non-author observer).[17] Observers were masked to treatment allocation but not to year of follow-up.

Outcomes

The primary outcome was IBTR, which was defined as invasive carcinoma or ductal carcinoma in situ presenting anywhere in the ipsilateral breast parenchyma or overlying skin whether considered local relapse or new primary

tumour. IBTR was localised as: (1) breast parenchyma or skin within boost volume (all groups), (2) breast parenchyma or skin within volume receiving 40 Gy in 15 fractions (all groups), (3) breast parenchyma or skin within volume receiving 36 Gy in 15 fractions (test groups only), and (4) marginal relapse in breast parenchyma, or skin or subcutaneous tissue on border or just outside (within 2 cm) of whole-breast volume (all groups).

Secondary efficacy outcomes included the location of local tumour relapse, time to first regional relapse (ie, in the axilla, supraclavicular fossa, and internal mammary chain), distant relapse, disease-free survival, and overall survival. Secondary outcomes relating to late adverse events were assessed by patients, photographs, and clinicians. These events included breast shrinkage, distortion, induration, breast oedema, breast tenderness on palpation, breast discomfort, and telangiectasia. Symptomatic rib fracture, symptomatic lung fibrosis, ischaemic heart disease, and pneumonitis were also recorded.

Acute toxicity was not recorded in the trial as 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 analysis

Assuming a 5% IBTR cumulative incidence rate by 5 years for the control group of this non-inferiority design, 856 patients per group (2568 total) were required in the sample to exclude an IBTR rate of 8% or greater in either test group (≥3% increase) with 80% power and one-sided $\alpha=0\cdot025$ (allowing for comparison of each test group *vs* control), assuming 7% of participants would be unevaluable at 5 years. Sample size justification for the original primary endpoint of palpable induration inside the boost volume is in the appendix (p 4).

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% CIs were obtained. Treatment effects for each test group versus control were summarised using hazard ratios (HRs; with 95% CIs) from Cox proportional hazards regression models and pairwise log-rank tests. Absolute differences (95% CIs) in 5-year IBTR were estimated by applying the HRs to the control group 5-year event-free estimate.

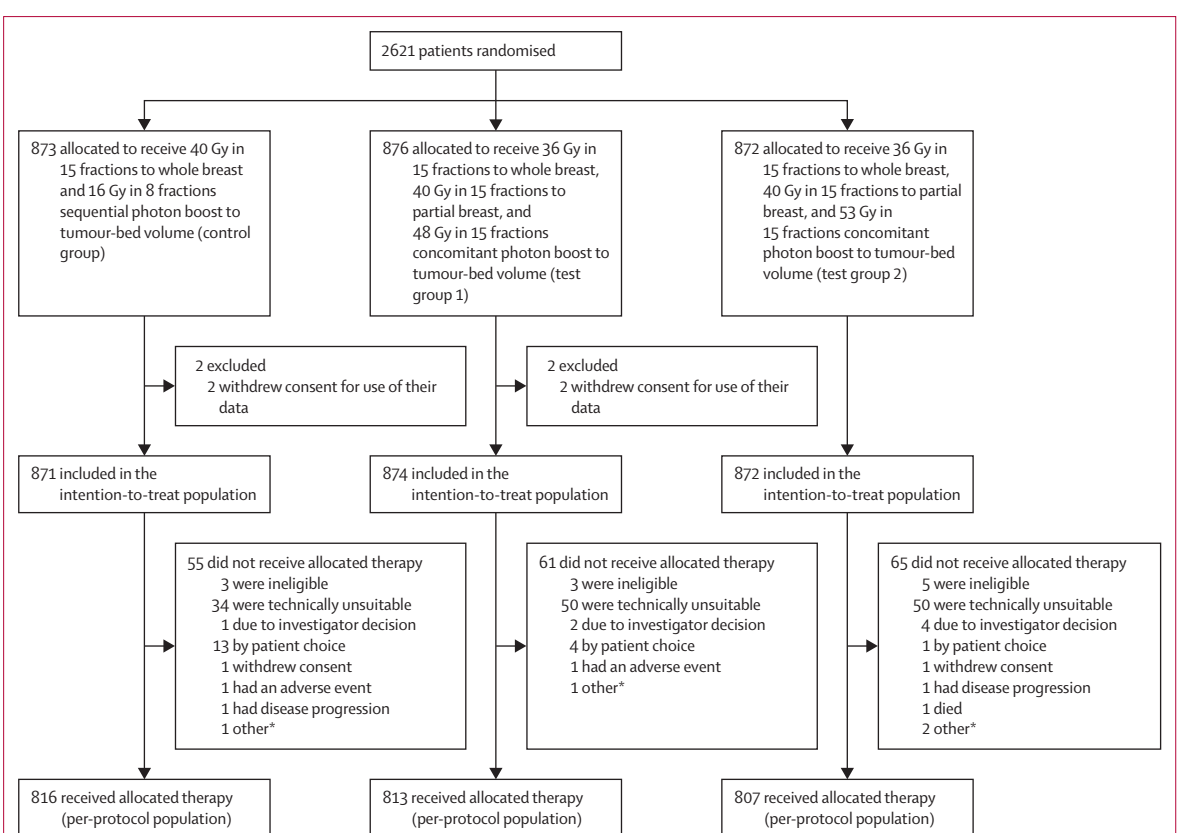

Figure 1: **Trial profile**

*Control group: no CT information for the third field as patient was simulated; the department standard treatment given instead. Test group 1: breakdown of kilo voltage imaging devices on two machines so there was therefore no appropriate verification and standard treatment was given instead. Test group 2: one due to a departmental planning problem that meant the patient was unable to fulfil trial criteria and standard treatment was given instead; one patient required a bolus.

The principal assessment of non-inferiority for IBTR for each test group versus control was whether the upper limit of the two-sided 95% CI (corresponding to one-sided 97·5% CI) for the absolute difference in 5-year IBTR was less than 3%. Following confidential review of the trial results, the independent data monitoring committee proposed that a range of hypothetical scenarios be presented to the trial management group without disclosing observed event rates. The trial management group discussions, which included 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 adverse events in the breast was derived using the worst score for distortion, shrinkage, induration, telangiectasia, and oedema separately for each timepoint. Clinician and patient assessments of late adverse events were dichotomised as none or mild versus moderate or marked and analysed in three ways. First, we did 5-year cross-sectional analyses that compared prevalence between groups using risk ratios (RRs) and risk differences, and Fisher's exact tests. Second, we did a survival analysis of time to first moderate or marked event, including Kaplan-Meier estimates of cumulative incidence, and compared groups using the HR from the Cox proportional hazards regression and the pairwise log-rank test. Participants not having an event were censored at last adverse event assessment (by clinician or patient as appropriate) or death. For patient-reported outcomes the Cox model was adjusted for baseline scores. Third, we did longitudinal analyses accounting for within-patient correlations between repeated measurements using generalised estimating equations including all assessments and compared treatment groups across the whole follow-up period using odds ratios (ORs) and the Wald test; generalised estimating equations models included a term representing years of follow-up. Generalised estimating equation models compared mild or marked change in photographic breast appearance between treatment groups. Due to multiple testing an α level of 0·01 was used for the clinician and patient adverse event assessments, except for clinician-assessed breast induration, which 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% CIs were calculated for all estimates. Analyses were by intention to treat. A sensitivity analysis of the primary outcome excluded

	Control group	Test group 1	Test group 2
Age (years; median [IQR])	49·4 (45·2–56·4)	48·9 (44·6–55·2)	49·2 (43·5–57·1)
Side of primary			
Left	429/871 (49·3%)	423/874 (48·4%)	445/872 (51·0%)
Right	439/871 (50·4%)	450/874 (51·5%)	426/872 (48·9%)
Unknown	3/871 (0·3%)	1/874 (0·1%)	1/872 (0·1%)
Location of primary tumour bed			
Central	174/871 (20·0%)	177/874 (20·3%)	163/872 (18·7%)
Upper outer	395/871 (45·4%)	425/874 (48·6%)	406/872 (46·6%)
Upper inner	147/871 (16·9%)	124/874 (14·2%)	149/872 (17·1%)
Lower outer	88/871 (10·1%)	97/874 (11·1%)	103/872 (11·8%)
Lower inner	62/871 (7·1%)	48/874 (5·5%)	45/872 (5·2%)
Unknown	5/871 (0·6%)	3/874 (0·3%)	6/872 (0·7%)
Pathological tumour size (cm)			
Median (IQR)	2·0 (1·5–2·8)	2·0 (1·5–2·7)	2·0 (1·5–2·7)
Unknown	2/871 (0·2%)	1/874 (0·1%)	1/872 (0·1%)
Tumour grade			
1	83/871 (9·5%)	71/874 (8·1%)	71/872 (8·1%)
2	340/871 (39·0%)	310/874 (35·5%)	329/872 (37·7%)
3	445/871 (51·1%)	492/874 (56·3%)	470/872 (53·9%)
Unknown	3/871 (0·3%)	1/874 (0·1%)	2/872 (0·2%)
Re-excision			
Yes	185/871 (21·2%)	185/874 (21·2%)	179/872 (20·5%)
No	683/871 (78·4%)	688/874 (78·7%)	692/872 (79·4%)
Unknown	3/871 (0·3%)	1/874 (0·1%)	1/872 (0·1%)
Axillary surgery			
Yes	852/871 (97·8%)	858/874 (98·2%)	854/872 (97·9%)
No	15/871 (1·7%)	15/874 (1·7%)	17/872 (1·9%)
Unknown	4/871 (0·5%)	1/874 (0·1%)	1/872 (0·1%)
Pathological node status			
Positive	260/871 (29·9%)	268/874 (30·7%)	251/872 (28·8%)
Negative	608/871 (69·8%)	605/874 (69·2%)	620/872 (71·1%)
Unknown	3/871 (0·3%)	1/874 (0·1%)	1/872 (0·1%)
Histological type			
Infiltrating ductal	774/871 (88·9%)	772/874 (88·3%)	772/872 (88·5%)
Mixed	30/871 (3·4%)	28/874 (3·2%)	29/872 (3·3%)
Other	66/871 (7·6%)	71/874 (8·1%)	70/872 (8·0%)
Unknown	1/871 (0·1%)	3/874 (0·3%)	1/872 (0·1%)
Lymphovascular invasion			
Yes	126/871 (14·5%)	116/874 (13·3%)	124/872 (14·2%)
No	307/871 (35·2%)	307/874 (35·1%)	306/872 (35·1%)
Uncertain	19/871 (2·2%)	25/874 (2·9%)	10/872 (1·1%)
Not reported*	419/871 (48·1%)	426/874 (48·7%)	432/872 (49·5%)
ER status			
Positive	683/871 (78·4%)	657/874 (75·2%)	652/872 (74·8%)
Poor	188/871 (21·6%)	216/874 (24·7%)	219/872 (25·1%)
Unknown	0/871	1/874 (0·1%)	1/872 (0·1%)

(Table 1 continues on next page)

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 Jan 11, 2021, and used Stata version 16.1.

This trial is registered with the ISRCTN registry, ISRCTN47437448.

Role of the funding source

Cancer Research UK provided peer-reviewed approval but had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From March 4, 2009, to Sept 16, 2015, 2621 patients were enrolled and randomly assigned (appendix pp 1–2); four patients withdrew consent for use of their data and were excluded from analyses, leaving 2617 participants (figure 1). 181 patients (6·9%) of 2617 did not receive their allocated treatment, predominantly due to difficulties outlining the tumour bed as they did not have surgical clips. The patient-reported outcomes sub-study recruited 1070 participants; 1052 of whom consented to photographic assessments. Demographic and clinical characteristics were well balanced across treatment groups (table 1). 5-year follow-up forms were available for 2335 (96·8%) of 2411 continuing participants (ie, not died or withdrawn). Median follow-up was 74·0 months (IQR 73·4–75·6). Patient ethnicity was 1884 (72·0%) White; 38 (1·5%) Asian or Asian British; 36 (1·4%) Black, Black British, Caribbean, or African; 15 (0·6%) mixed or multiple ethnic groups; and eight (0·3%) other ethnic group; 636 (24·3%) were not reported.

Radiotherapy plan assessment forms were available for 2030 (77·6%) of 2617 cases; all mandatory dosimetric constraints were met for 606 (95·9%) of 632 for the control group, 635 (96·4%) of 659 for test group 1, and 635 (95·2%) of 667 for test group 2. Median tumour-bed clinical target volume was 12·8 cm³ and the ratio of it to whole-breast planning target volume was 0·015. Whole-breast clinical target volume was 5% or less of the whole-breast planning target volume in 1877 (95·6%) of 1964 patients. The number of patients treated with deep-inspiratory breath-hold techniques is not known, but this would have been a very small number as it was only introduced towards the end of trial recruitment. Further details on radiotherapy planning techniques and dosimetry are in the appendix (pp 19–23).

IBTR was recorded in 76 patients (table 2). Estimated 5-year cumulative incidence of IBTR was 1·9% (95% CI 1·2 to 3·1) for the control group, 2·0% (1·2 to 3·2) for test group 1, and 3·2% (2·2 to 4·7) for test group 2 (table 2, figure 2). IBTR 5-year event rates were lower than anticipated; upper confidence limits for 5-year IBTR rate in all treatment groups were less than 5% (anticipated rate in control group). Estimated absolute differences in IBTR versus the control group were 0·1% (–0·8 to 1·7) for test group 1 and 1·4% (0·03 to 3·8) for test group 2, indicating non-inferiority in absolute terms according to the prespecified difference of 3% for test group 1 versus control, but not for test group 2. Non-inferiority was tested in terms of relative treatment effects: HRs were

	Control group	Test group 1	Test group 2
(Continued from previous page)			
PR status			
Positive	304/871 (34·9%)	289/874 (33·1%)	289/872 (33·1%)
Poor	195/871 (22·4%)	214/874 (24·5%)	207/872 (23·7%)
Unknown	4/871 (0·5%)	12/874 (1·4%)	5/872 (0·6%)
Not done	368/871 (42·3%)	359/874 (41·1%)	371/872 (42·5%)
HER2 status			
Positive	157/871 (18·0%)	139/874 (15·9%)	165/872 (18·9%)
Negative	710/871 (81·5%)	731/874 (83·6%)	705/872 (80·8%)
Unknown	4/871 (0·5%)	4/874 (0·5%)	2/872 (0·2%)
ER and HER2 status			
ER and HER2 positive	121/871 (13·9%)	104/874 (11·9%)	111/872 (12·7%)
ER positive and HER2 negative	558/871 (64·1%)	550/874 (62·9%)	540/872 (61·9%)
ER negative and HER2 positive	36/871 (4·1%)	35/874 (4·0%)	54/872 (6·2%)
ER and HER2 negative	152/871 (17·5%)	181/874 (20·7%)	165/872 (18·9%)
Unknown	4/871 (0·5%)	4/874 (0·5%)	2/872 (0·2%)
Adjuvant therapy received			
All patients			
Chemotherapy	564/869 (64·9%)	574/873 (65·8%)	578/872 (66·3%)
Unknown	2/869 (0·2%)	1/873 (0·1%)	0/872
HER2-positive patients			
Chemotherapy and trastuzumab	88/157 (56·1%)	74/139 (53·2%)	102/165 (61·8%)
Trastuzumab without chemotherapy	6/157 (3·8%)	1/139 (0·7%)	5/165 (3·0%)
Chemotherapy without trastuzumab	42/157 (26·8%)	48/139 (34·5%)	40/165 (24·2%)
No chemotherapy or trastuzumab	15/157 (9·6%)	15/139 (10·8%)	15/165 (9·1%)
Unknown	6/157 (3·8%)	1/139 (0·7%)	3/165 (1·8%)
ER-positive patients			
Endocrine therapy	665/683 (97·4%)	640/657 (97·4%)	636/652 (97·5%)
Unknown	2/683 (0·3%)	0	0
Radiotherapy to lymph nodes†			
Yes	93/869 (10·7%)	90/871 (10·3%)	87/871 (10·0%)
Supraclavicular fossa	85/93 (91·4%)	87/90 (96·7%)	77/87 (88·5%)
Axilla	7/93 (7·5%)	3/90 (3·3%)	10/87 (11·5%)
Unknown	1/93 (1·1%)	0/90	0/87
No	775/869 (89·2%)	778/871 (89·3%)	781/871 (89·7%)
Unknown	0/869	3/871 (0·3%)	2/871 (0·2%)

Data are n/N (%) unless otherwise specified. The control group received 40 Gy in 15 fractions to the whole breast, 16 Gy in 8 fractions sequential photon tumour-bed boost. Test group 1 received 36 Gy in 15 fractions to the whole breast, 40 Gy in 15 fractions to the partial breast, and 48 Gy in 15 fractions concomitant photon boost to the tumour-bed volume. Test group 2 received 36 Gy in 15 fractions to the whole breast, 40 Gy in 15 fractions to the partial breast, and 53 Gy in 15 fractions concomitant photon boost to the tumour-bed volume. ER=oestrogen receptor. PR=progestrone receptor. *These data were added to data collection forms around halfway through recruitment, so are not reported for around 50% of participants. †Six patients did not receive radiotherapy.

Table 1: **Baseline characteristics**

	Cumulative number of events	Kaplan-Meier estimate of cumulative incidence by 5 years (%, 95% CI)	HR *vs* control group (95% CI), p value*†	Estimated absolute difference *vs* control group at 5 years (%, 95% CI)‡
Ipsilateral breast tumour (local) relapse§				
Control group	20/871 (2·3%)	1·9% (1·2 to 3·1)	1 (ref)	..
Test group 1	21/874 (2·4%)	2·0% (1·2 to 3·2)	1·04 (0·56 to 1·92), p=0·91	0·1% (–0·8 to 1·7)
Test group 2	35/872 (4·0%)	3·2% (2·2 to 4·7)	1·76 (1·01 to 3·04), p=0·041	1·4% (0·03 to 3·8)
Local-regional relapse¶				
Control group	32/871 (3·7%)	3·0% (2·0 to 4·4)	1 (ref)	..
Test group 1	32/874 (3·7%)	3·1% (2·1 to 4·5)	0·99 (0·60 to 1·61), p=0·96	–0·04% (–1·2 to 1·8)
Test group 2	48/872 (5·5%)	4·7% (3·4 to 6·3)	1·50 (0·96 to 2·35), p=0·072	1·5% (–0·1 to 3·9)
Distant relapse				
Control group	66/871 (7·6%)	6·6% (5·1 to 8·5)	1 (ref)	..
Test group 1	67/874 (7·7%)	6·5% (5·1 to 8·4)	1·00 (0·71 to 1·41), p=0·99	0·02% (–1·8 to 2·6)
Test group 2	74/872 (8·5%)	7·8% (6·2 to 9·8)	1·12 (0·80 to 1·55), p=0·52	0·7% (–1·3 to 3·5)
Any relapse (local, regional, distant)				
Control group	84/871 (9·6%)	8·5% (6·8 to 10·6)	1 (ref)	..
Test group 1	81/874 (9·3%)	7·6% (6·0 to 9·6)	0·95 (0·70 to 1·29), p=0·74	–0·4% (–2·5 to 2·3)
Test group 2	103/872 (11·8%)	10·4% (8·6 to 12·7)	1·23 (0·92 to 1·64), p=0·16	1·8% (–0·6 to 5·0)
Any breast cancer-related event‖				
Control group	94/871 (10·8%)	9·2% (7·4 to 11·4)	1 (ref)	..
Test group 1	94/874 (10·8%)	8·5% (6·8 to 10·6)	0·99 (0·74 to 1·31), p=0·92	–0·1% (–2·3 to 2·7)
Test group 2	117/872 (13·4%)	11·9% (9·9 to 14·3)	1·25 (0·95 to 1·64), p=0·10	2·2% (–0·4 to 5·5)
All-cause mortality				
Control group	71/871 (8·1%)	6·1% (4·7 to 8·0)	1 (ref)	..
Test group 1	59/874 (6·7%)	5·0% (3·7 to 6·7)	0·82 (0·58 to 1·16), p=0·27	–1·1% (–2·5 to 0·9)
Test group 2	76/872 (8·7%)	6·7% (5·2 to 8·6)	1·06 (0·77 to 1·47), p=0·71	0·4% (–1·4 to 2·8)

Data are n/N (%); Kaplan-Meier estimated cumulative incidence (95% CI); HR (95% CI), p value; and absolute difference (95% CI). The control group received 40 Gy in 15 fractions to the whole breast and 16 Gy in 8 fractions sequential photon tumour-bed boost. Test group 1 received 36 Gy in 15 fractions to the whole breast, 40 Gy in 15 fractions to the partial breast, and 48 Gy in 15 fractions concomitant photon boost to the tumour-bed volume. Test group 2 received 36 Gy in 15 fractions to the whole breast, 40 Gy in 15 fractions to the partial breast, and 53 Gy in 15 fractions concomitant photon boost to the tumour-bed volume. HR=hazard ratio. *HR>1 favours control group. †Log-rank test (two-sided) for each test group compared with the control group. ‡Estimated absolute difference at 5 years for each test group versus the control group obtained from HR and Kaplan-Meier event-free estimate in the control group. §Ipsilateral breast tumour relapse includes local relapse and ipsilateral new primary. ¶Locoregional relapse defined as ipsilateral breast tumour relapse or regional relapse (axilla, supraclavicular fossa, other). ‖Breast cancer-related events: local, regional, or distant relapse, breast cancer death, and contralateral breast cancer (disease-free survival).

Table 2: **Relapse and mortality by treatment group (results of time-to-event analyses)**

1·04 (0·56 to 1·92) for test group 1 and 1·76 (1·02 to 3·04) for test group 2 versus the control group (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 test group 1 and p=0·61 for test group 2 versus the control group). Since the IBTR rate was lower than expected, non-inferiority tests were done against the post-hoc critical HR of 2·59 (obtained using the observed 1·9% control rate and assuming 3% absolute non-inferiority above this), with p=0·002 for test group 1 and p=0·082 for test group 2, confirming non-inferiority for test group 1.

Most IBTR events (66 of 76, 86·8%) were considered to be a relapse by treating clinicians rather than a new primary cancer (seven of 76, 9·2%); three events could not be differentiated (appendix pp 24–25). Location of the local relapse or new primary cancer reported showed that 34 (44·7%) of 76 were inside the tumour-bed planning target volume, 12 (15·8%) were inside the partial-breast planning target volume but outside the tumour-bed planning target volume, and 12 (15·8%) were inside the whole-breast planning target volume but outside the partial-breast planning target volume (appendix pp 24–25). Results of the per-protocol and competing risks analyses are in the appendix (p 4).

Regional relapses occurred in 53 (2·0%) of 2617 patients, nine of which were concurrent with IBTR (appendix pp 24–25). No significant differences were seen in locoregional relapse, distant relapse, any relapse, disease-free survival, and overall survival (table 2, appendix pp 6–7). Invasive contralateral breast cancer was reported for 34 (1·3%) of 2617 patients, and non-breast second primary cancers for 63 (2·4%; appendix pp 24–25) patients. A total of 206 (7·9%) patients died: 163 (79·1%) from breast cancer, 40 (19·4%) from other causes, and three (1·5%) from unknown causes with no evidence of disease relapse (appendix pp 24–25).

Clinical adverse event assessments were available at 1 or more years of follow-up for 2496 (95·4%) of 2617 patients. Prevalence of clinician-assessed moderate or marked effects were low across all groups (appendix pp 8–12). 5-year prevalence of moderate or marked breast induration was 6·0% (36 of 600) for the control group, 5·2% (34 of 653) for test group 1, and 8·9% (56 of 627) for test group 2 (appendix pp 26–27). Comparisons between groups were broadly similar from the 5-year cross-sectional, time to event, and longitudinal analyses, with similar levels of moderate or marked adverse events for test group 1 versus the control group and increased risk of adverse events for test group 2 versus test group 1 (table 3, appendix pp 26–28). Cumulative incidence of moderate or marked breast induration was similar for test group 1 and the control group (HR 0·90, 95% CI 0·71–1·14, p=0·40), and higher for test group 2 versus the control group (1·31, 1·05–1·63, p=0·015; table 3, appendix p 8). Except for breast oedema and discomfort that declined over time, there were significant increases in risk of adverse events with longer follow-up (appendix p 28).

At least one questionnaire was completed by 1063 (99·4%) of 1070 patients. Change in overall breast appearance was the item patients most frequently

reported as moderate or marked (table 4, appendix pp 13–18, 29–30). 5-year patient-reported moderate or marked breast hardness or firmness was significantly lower for test group 1 versus the control group (RR 0·54, 95% CI 0·38–0·78, p=0·001) and higher for test group 2 versus test group 1 (1·61, 1·10–2·35, p=0·008; appendix pp 29–30). There were no statistically significant differences between treatment groups in time to event and longitudinal analyses of patient-reported moderate or marked breast hardness or firmness and other patient-reported adverse events relating to breast, arm, and shoulder up to 5 years (table 4, appendix pp 8, 31–33).

Photographic assessments were available at 3 years or 5 years for 698 (76·0%) of 918 patients with a baseline photograph. At 3-years, mild or marked change in photographic breast appearance was observed in 35 (16·1%) of 218 patients in the control group, 25 (11·9%) of 210 patients in test group 1, and 36 (16·9%) of 213 patients in test group 2. 5-year prevalence of mild or marked changes increased in all treatment groups (control group 36·8%, 60 of 163; test group 1 24·4%, 42 of 172; and test group 2 27·5%, 49 of 178). There were no statistically significant differences in mild or marked change in photographic breast appearance between groups, but some indication of reduced risk for test group 1 versus the control group (OR for mild or marked change at 3 or 5 years 0·61, 95% CI 0·41–0·93; p=0·021; appendix p 34).

Severe late adverse events were rare, with 11 confirmed reports of symptomatic rib fracture, seven of symptomatic lung fibrosis, six of ischaemic heart disease, and six of pneumonitis (appendix p 35). A total of 103 (3·9%) of 2617 patients were referred to lymphoedema clinics (control group: 39 of 871, 4·3%; test group 1: 36 of 874, 4·1%; test group 2: 28 of 872, 3·2%).

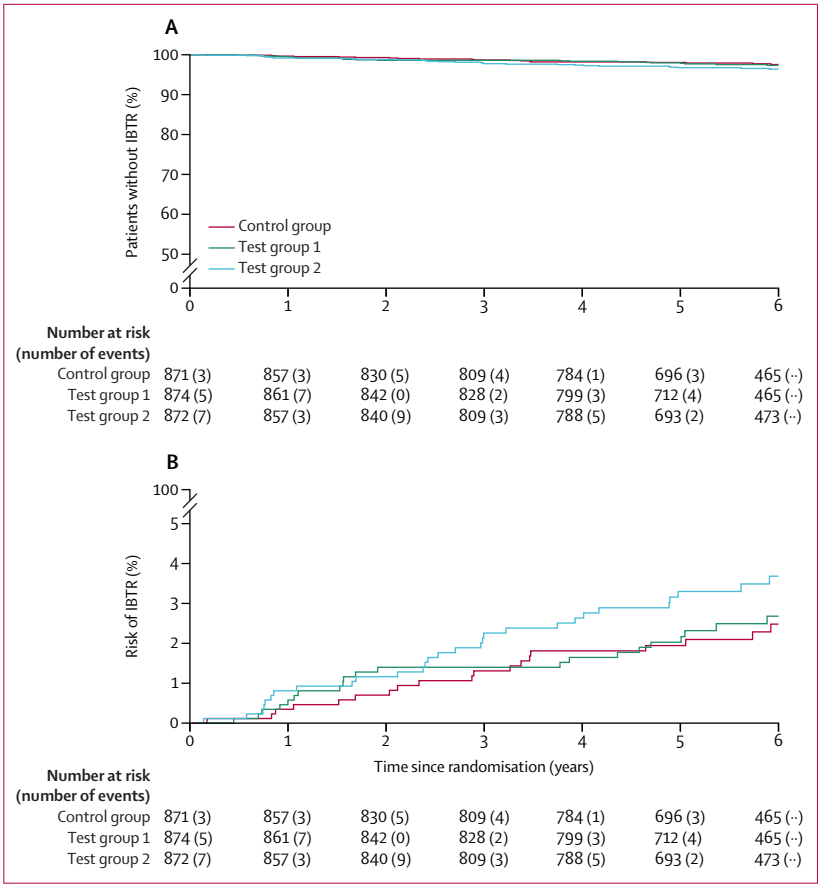

Figure 2: **IBTR by treatment group**
(A) Kaplan-Meier plot. (B) Cumulative risk plot. IBTR=ipsilateral breast tumour relapse. The control group received 40 Gy in 15 fractions to the whole breast and 16 Gy in 8 fractions sequential photon tumour-bed boost. Test group 1 received 36 Gy in 15 fractions to the whole breast, 40 Gy in 15 fractions to the partial breast, and 48 Gy in 15 fractions concomitant photon boost to the tumour-bed volume. Test group 2 received 36 Gy in 15 fractions to the whole breast, 40 Gy in 15 fractions to the partial breast, and 53 Gy in 15 fractions concomitant photon boost to the tumour-bed volume. Patients were censored at death or last follow-up. IBTR=ipsilateral breast tumour relapse.

Discussion

This trial showed 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 predefined critical HR translates to a smaller absolute difference, leading to dialogue around the importance of absolute versus relative treatment differences. In IMPORT HIGH, the trial management group, including patient advocates, discussed this specific dilemma while still masked to the observed results. It was agreed that the absolute 3% difference between groups and confirmation that event rates were low (compared with the 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 or 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. When compared with the control group, test group 1 was milder for clinician-reported oedema on time-to-event analysis, and for breast hardness or firmness on the patient-reported cross-sectional analysis. There was also a suggestion of decreased mild or marked adverse events on photographic assessment for test group 1 compared with the control group. By contrast, test group 2 showed increased clinician-reported breast induration compared with the control group for both time to event and longitudinal analyses. 48 Gy SIB delivered in 3 weeks in test group 1 had similar efficacy to sequential boost delivered over 4·5 weeks, with similar or milder rates of adverse events. 53 Gy SIB in test group 2 had no additional benefit in local cancer control but a higher risk of moderate or marked breast induration.

	Moderate or marked events*	Kaplan-Meier estimate of cumulative incidence of moderate or marked events (%, 95% CI)†		HR (95% CI), p value	
		By 3 years	By 5 years	Test groups *vs* control‡§	Test group 2 *vs* 1¶‖
Any adverse event in the breast**					
Control group	283/817 (34·6%)	23·5% (20·7–26·7)	33·1% (29·8–36·7)	1 (ref)	..
Test group 1	271/836 (32·4%)	20·8% (18·2–23·8)	29·9% (26·8–33·3)	0·90 (0·76–1·06), p=0·21	1 (ref)
Test group 2	302/834 (36·2%)	25·8% (23·0–29·0)	34·5% (31·2–38·0)	1·06 (0·90–1·24), p=0·50	1·18 (1·00–1·39), p=0·026
Breast distortion					
Control group	126/814 (15·5%)	8·6% (6·8–10·8)	13·8% (11·5–16·6)	1 (ref)	..
Test group 1	108/834 (12·9%)	8·4% (6·7–10·5)	12·2% (10·1–14·8)	0·82 (0·63–1·06), p=0·13	1 (ref)
Test group 2	140/833 (16·8%)	10·3% (8·3–12·6)	15·7% (13·3–18·5)	1·11 (0·87–1·41), p=0·39	1·36 (1·05–1·74), p=0·0085
Breast shrinkage					
Control group	145/813 (17·8%)	9·4% (7·5–11·6)	15·7% (13·2–18·6)	1 (ref)	..
Test group 1	143/834 (17·1%)	8·9% (7·1–11·0)	15·2% (12·8–18·0)	0·93 (0·74–1·17), p=0·56	1 (ref)
Test group 2	142/832 (17·1%)	9·5% (7·7–11·7)	15·7% (13·3–18·6)	0·95 (0·76–1·20), p=0·70	1·02 (0·81–1·29), p=0·42
Breast induration (index quadrant)					
Control group	143/814 (17·6%)	11·5% (9·5–14·0)	16·6% (14·1–19·5)	1 (ref)	..
Test group 1	134/834 (16·1%)	10·6% (8·6–12·9)	14·3% (12·0–16·9)	0·90 (0·71–1·14), p=0·40	1 (ref)
Test group 2	183/832 (22·0%)	15·5% (13·1–18·2)	20·0% (17·3–23·0)	1·31 (1·05–1·63), p=0·015	1·45 (1·16–1·81), p=0·0005
Telangiectasia					
Control group	17/815 (2·1%)	1·2% (0·6–2·2)	1·9% (1·1–3·2)	1 (ref)	..
Test group 1	14/835 (1·7%)	0·6% (0·3–1·5)	1·0% (0·5–2·0)	0·80 (0·40–1·63), p=0·56	1 (ref)
Test group 2	14/834 (1·7%)	0·8% (0·3–1·7)	1·6% (0·9–2·9)	0·82 (0·41–1·67), p=0·56	1·02 (0·49–2·14), p=0·48
Breast oedema					
Control group	70/814 (8·6%)	7·8% (6·1–9·9)	8·6% (6·8–10·8)	1 (ref)	..
Test group 1	44/836 (5·3%)	4·6% (3·4–6·3)	5·2% (3·9–7·0)	0·59 (0·41–0·87), p=0·0062	1 (ref)
Test group 2	54/834 (6·5%)	5·3% (3·9–7·1)	5·7% (4·3–7·6)	0·74 (0·52–1·05), p=0·091	1·24 (0·83–1·85), p=0·14
Breast tenderness on palpation					
Control group	112/804 (13·9%)	9·4% (7·5–11·7)	13·6% (11·3–16·3)	1 (ref)	..
Test group 1	111/821 (13·5%)	8·3% (6·6–10·4)	11·9% (9·8–14·5)	0·96 (0·73–1·24), p=0·74	1 (ref)
Test group 2	142/813 (17·5%)	10·5% (8·6–12·9)	15·0% (12·6–17·8)	1·26 (0·98–1·62), p=0·066	1·32 (1·03–1·69), p=0·014
Breast discomfort					
Control group	112/796 (14·1%)	9·7% (7·8–12·0)	13·6% (11·3–16·3)	1 (ref)	..
Test group 1	114/811 (14·1%)	8·6% (6·8–10·8)	13·1% (10·9–15·8)	0·98 (0·76–1·28), p=0·91	1 (ref)
Test group 2	153/804 (19·0%)	12·4% (10·3–15·0)	17·0% (14·5–19·9)	1·39 (1·09–1·77), p=0·0081	1·41 (1·10–1·79), p=0·0025

Data are n/N (%); Kaplan-Meier estimated incidence (95% CI); and HR (95% CI), p value. The control group received 40 Gy in 15 fractions to the whole breast and 16 Gy in 8 fractions sequential photon tumour-bed boost. Test group 1 received 36 Gy in 15 fractions to the whole breast, 40 Gy in 15 fractions to the partial breast, and 48 Gy in 15 fractions concomitant photon boost to the tumour-bed volume. Test group 2 received 36 Gy in 15 fractions to the whole breast, 40 Gy in 15 fractions to the partial breast, and 53 Gy in 15 fractions concomitant photon boost to the tumour-bed volume. HR=hazard ratio. *Adverse event data available for 2496 patients (control group: 820, test group 1: 837, test group 2: 839); denominators might vary due to missing clinician assessments for some events. †Rate estimated at 3 or 5 years and 3 months to allow for visits occurring up to 3 months after the due date. ‡p value for pairwise log-rank test. §HR>1 favours control group. ¶One-sided p value. ‖HR>1 favours test group 1. **Any adverse event in the breast—ie, distortion, shrinkage, induration, telangiectasia, or oedema.

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)**

The slightly higher IBTR rate in test group 2 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), the higher rate is most likely to be a chance finding and 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 (appendix p 36). Test group 1 also had a reduced dose region and showed similar IBTR rates to the control group. The EORTC boost versus no boost trial had a substudy randomly assigning patients with microscopically incomplete surgical margins to low boost dose (10 Gy) or high boost dose (26 Gy), both carried out in 2 Gy daily fractions.[19] The study did not recruit its planned sample size of 660 patients and only had 251 participants. A significant difference in local control could not be identified at 10 years, but the high boost dose significantly increased the risk of fibrosis. Taken with the results of IMPORT HIGH, these results

could suggest that there is a dose–response boost threshold for improvement in local control and increasing the boost dose beyond a higher equivalent dose in 2Gy fractions of around 60 Gy causes increased fibrosis with no benefit. Other strategies might be required to overcome tumour radioresistance. We await the local control results of the Young Boost Trial[20] that randomly assigned patients aged 50 years or younger to 16 Gy or 26 Gy following breast-conserving surgery. The IMPORT HIGH authors are evaluating the molecular clonality and spatial mapping of index tumours and local relapses to help understand relapse patterns.

Although direct comparisons of adverse events within other breast radiotherapy trials cannot be made due to differences in trial populations, protocols, and assessments, there is a suggestion that adverse events in IMPORT HIGH might be lower than observed in the Young Boost Trial (adverse events have been reported and the primary local control endpoint is awaited).[20] Boost techniques in the Young Boost Trial included photons, electrons, and interstitial brachytherapy and, although most patients received sequential boosts, some had SIB. Moderate or marked breast fibrosis as scored by clinicians at 4 years was 19% in the standard-boost group and 39% in the high-boost group, with 27% and 45% cumulative incidence, respectively. 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 that showed that tumour-bed coverage was often worse with electrons compared with photons. The trial management group were concerned that photon planning with more generous tumour-bed coverage could produce larger irradiated boost volumes and increased toxicity. Therefore, the clinical target volume was limited to tumour-bed clips and seroma with no additional margin. The clinical target volume–planning target volume margin was 5 mm with the IGRT determined by the GOLDSEED study.[11] This margin might account for the differences in fibrosis and induration rates seen between the two trials.

The Young Boost Trial publication also suggested that SIB increased the risk of adverse normal tissue events. However, the authors state that a possible explanation was that the Young Boost Trial SIB had a higher equivalent dose in 2 Gy fractions (EQD2) compared with the sequential boosts: EQD2 68·2 Gy versus 66 Gy and 79·5 Gy versus 76 Gy, assuming an α/β of 3Gy. The slightly milder induration seen with 48 Gy in IMPORT HIGH could be a result of an EQD2 of 60 Gy to tumour bed using an α/β of 3 Gy for normal tissue late effects compared with 62 Gy in the control.

A strength of IMPORT HIGH is the use of photon boosts only to standardise boost volume across all trial

	Moderate or marked events over follow-up*	Kaplan-Meier estimate of cumulative incidence of moderate or marked events (%, 95% CI)		HR (95% CI)†, p value	
		By 3 years	By 5 years	Test groups *vs* control‡§	Test group 2 *vs* 1¶‖
Protocol-specific items					
Breast appearance changed					
Control group	187/348 (53·7%)	46·8% (41·6–52·4)	52·8% (47·4–58·4)	1 (ref)	..
Test group 1	161/324 (49·7%)	42·6% (37·3–48·3)	48·0% (42·4–53·9)	0·98 (0·78–1·22), p=0·26	1 (ref)
Test group 2	174/343 (50·7%)	44·3% (39·1–49·9)	49·9% (44·5–55·7)	0·91 (0·73–1·12), p=0·42	0·92 (0·73–1·15), p=0·624
Breast smaller					
Control group	136/348 (39·1%)	31·7% (26·9–37·0)	38·4% (33·1–44·1)	1 (ref)	..
Test group 1	126/324 (38·9%)	28·8% (24·0–34·2)	39·6% (34·0–45·8)	1·11 (0·86–1·43), p=0·72	1 (ref)
Test group 2	137/343 (39·9%)	30·9% (26·2–36·2)	38·1% (32·9–43·8)	1·03 (0·80–1·32), p=0·83	0·92 (0·72–1·19), p=0·674
Breast harder or firmer					
Control group	165/348 (47·4%)	42·7% (37·5–48·2)	49·5% (44·0–55·3)	1 (ref)	..
Test group 1	139/324 (42·9%)	37·6% (32·5–43·2)	44·1% (38·5–50·0)	0·85 (0·67–1·07), p=0·26	1 (ref)
Test group 2	162/343 (47·2%)	39·6% (34·6–45·1)	48·1% (42·6–53·8)	0·97 (0·77–1·22), p=0·77	1·15 (0·91–1·47), p=0·197
Skin appearance changed					
Control group	104/348 (29·9%)	27·9% (23·4–33·0)	29·1% (24·5–34·4)	1 (ref)	..
Test group 1	84/323 (26·0%)	22·4% (18·2–27·5)	24·0% (19·5–29·1)	0·85 (0·62–1·15), p=0·27	1 (ref)
Test group 2	92/343 (26·8%)	21·1% (17·1–26·0)	26·7% (22·1–32·0)	0·89 (0·66–1·19), p=0·27	1·02 (0·74–1·41), p=0·491
Shoulder stiffness					
Control group	72/348 (20·7%)	16·5% (12·9–21·0)	21·3% (17·1–26·4)	1 (ref)	..
Test group 1	84/324 (25·9%)	19·9% (15·9–24·8)	25·5% (20·9–31·0)	1·40 (1·01–1·95), p=0·079	1 (ref)
Test group 2	76/343 (22·2%)	16·3% (12·7–20·8)	20·9% (16·7–25·9)	1·10 (0·79–1·53), p=0·66	0·78 (0·57–1·08), p=0·915

(Table 4 continues on next page)

	Moderate or marked events over follow-up*	Kaplan-Meier estimate of cumulative incidence of moderate or marked events (%, 95% CI)		HR (95% CI)†, p value	
		By 3 years	By 5 years	Test groups *vs* control‡§	Test group 2 *vs* 1¶‖
(Continued from previous page)					
EORTC QLQ-BR23 items					
Breast pain					
Control group	113/348 (32·5%)	30·8% (26·2–36·1)	33·4% (28·5–38·9)	1 (ref)	..
Test group 1	100/324 (30·9%)	29·1% (24·4–34·5)	31·7% (26·8–37·3)	1·02 (0·76–1·35), p=0·74	1 (ref)
Test group 2	113/343 (32·9%)	28·1% (23·6–33·2)	32·4% (27·6–37·8)	1·05 (0·80–1·38), p=0·98	1·03 (0·78–1·37), p=0·36
Breast swollen					
Control group	59/348 (16·9%)	15·5% (12·0–19·9)	16·7% (13·1–21·2)	1 (ref)	..
Test group 1	50/324 (15·4%)	15·6% (12·0–20·2)	16·0% (12·4–20·6)	0·88 (0·59–1·31), p=0·64	1 (ref)
Test group 2	42/343 (12·2%)	10·7% (7·8–14·6)	12·0% (8·9–16·2)	0·74 (0·49–1·12), p=0·093	0·83 (0·54–1·28), p=0·89
Breast oversensitive					
Control group	87/348 (25·0%)	23·0% (18·9–27·9)	25·8% (21·4–31·0)	1 (ref)	..
Test group 1	90/324 (27·8%)	24·1% (19·7–29·2)	29·1% (24·2–34·7)	1·11 (0·82–1·50), p=0·40	1 (ref)
Test group 2	97/343 (28·3%)	23·4% (19·2–28·3)	28·3% (23·6–33·6)	1·16 (0·86–1·57), p=0·38	1·02 (0·76–1·38), p=0·50
Skin problems on breast					
Control group	58/348 (16·7%)	14·2% (10·9–18·4)	16·8% (13·1–21·3)	1 (ref)	..
Test group 1	46/324 (14·2%)	12·8% (9·6–17·1)	14·4% (10·9–18·9)	0·85 (0·57–1·29), p=0·42	1 (ref)
Test group 2	40/343 (11·7%)	10·6% (7·7–14·4)	12·4% (9·3–16·6)	0·78 (0·51–1·18), p=0·063	0·89 (0·57–1·40), p=0·85
Arm or shoulder pain					
Control group	133/348 (38·2%)	31·1% (26·5–36·3)	37·3% (32·2–43·0)	1 (ref)	..
Test group 1	118/324 (36·4%)	28·9% (24·2–34·3)	34·6% (29·5–40·4)	0·97 (0·75–1·26), p=0·65	1 (ref)
Test group 2	113/343 (32·9%)	26·5% (22·1–31·7)	32·3% (27·4–37·9)	0·87 (0·67–1·13), p=0·17	0·90 (0·69–1·18), p=0·81
Arm or hand swollen					
Control group	48/348 (13·8%)	11·1% (8·2–15·0)	13·9% (10·5–18·3)	1 (ref)	..
Test group 1	41/323 (12·7%)	10·0% (7·1–13·9)	13·2% (9·7–17·8)	0·89 (0·57–1·38), p=0·75	1 (ref)
Test group 2	48/343 (14·0%)	10·2% (7·3–14·0)	14·6% (11·1–19·1)	1·00 (0·66–1·50), p=0·95	1·12 (0·72–1·73), p=0·35
Difficulty raising arm					
Control group	68/348 (19·5%)	16·0% (12·5–20·4)	18·9% (15·0–23·7)	1 (ref)	..
Test group 1	61/324 (18·8%)	13·5% (10·1–17·8)	17·7% (13·7–22·6)	1·05 (0·73–1·50), p=0·95	1 (ref)
Test group 2	56/343 (16·3%)	12·1% (9·0–16·1)	14·9% (11·3–19·4)	0·84 (0·58–1·21), p=0·31	0·80 (0·55–1·17), p=0·82

Data are n/N (%); Kaplan-Meier estimated incidence (95% CI); and HR (95% CI), p value. The control group received 40 Gy in 15 fractions to the whole breast, 16 Gy in 8 fractions sequential photon tumour-bed boost. Test group 1 received 36 Gy in 15 fractions to the whole breast, 40 Gy in 15 fractions to the partial breast, and 48 Gy in 15 fractions concomitant photon boost to the tumour bed volume. Test group 2 received 36 Gy in 15 fractions to whole breast, 40 Gy in 15 fractions to the partial breast, and 53 Gy in 15 fractions concomitant photon boost to the tumour-bed volume. HR=hazard ratio. *Follow-up questionnaires available for 1015 patients (control group: 348, test group 1: 324, test group 2: 343), denominators might vary due to missing assessments for some endpoints. †Adjusted for baseline assessment of adverse effect. ‡HR>1 favours control group. §Two-sided p value for log-rank test. ¶HR>1 favours test group 1. ‖One-sided p value for log-rank test.

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)**

groups. Therefore, the only variables were SIB, dose escalation in the 53 Gy 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 established the utility of clip-based image-guided boost IMRT.[12] In addition, participation of 39 UK radiotherapy centres showed 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,[21] which randomly assigned 502 patients to 50·4 Gy in 1·8 Gy daily fractions with a SIB to a total dose of 64·4 Gy over 5·5 weeks compared with a control group with sequential boost over 7 weeks. Non-inferiority for local control was reported at the 2-year median follow-up with no significant difference in cosmesis. The NRG RTOG 1005[22] randomised trial was similar to IMPORT HIGH's test group 1, but had two dose levels (40 Gy whole breast and 48 Gy SIB). The study population had a higher median age of 55 years versus 49 years and included some patients with high-grade ductal carcinoma in situ. 48 Gy 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 50 Gy in 25 fractions and 40 Gy in 15 fractions, 5 fractions weekly and SIBs were used. At 3-years median follow-up, there was no difference in arm lymphoedema, loco-regional recurrence, distant recurrence, or overall survival.

SIB is less burdensome for patients and their families, reducing travel costs and enabling return to work sooner. The method is an efficient use of resource for health-care providers whereby radiotherapy timeslots can be used for other patients. The same complexity of technology is required for SIB as for 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 adverse event reporting by clinicians and patients that could lead to bias. Masking treatment groups was not possible as patients can identify which group they belonged to on the basis of how many treatments they received. However, previous UK breast radiotherapy trials with similar designs have all shown that clinician-reported 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 the changing regional node irradiation during 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 40 Gy would be challenging to integrate with the reduced dose to the peripheries of breast tissue and the effect of 36 Gy on regional nodes is unknown. IMPORT HIGH results might not be completely generalisable to sequential boosts using different dose fractionations, which might have different cosmetic outcomes and relapse rates when compared to 16 Gy in 8 fractions. Trial sample diversity was a limitation as patient ethnicity was 72·0% White; 1·5% Asian or Asian British; 1·4% Black, Black British, Caribbean, or African; 0·6% mixed or multiple ethnic groups; and 0·3% other ethnic group; 24·3% were not reported.

The UK standard of care for boost radiotherapy is now either a 3-week 48 Gy SIB (two dose levels of 48 Gy SIB and 40 Gy in the rest of the breast) or 1 week of 26 Gy 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. Based on the results of FAST-Forward and IMPORT HIGH, the ultimate goal is 1-week SIB. 1-week SIB is a UK trial proposal under development that will also test 1-week internal mammary chain irradiation. A randomised trial with 200 patients in Belgium is testing a 31 Gy SIB in 5 fractions over 10–12 days with 28·5 Gy to the whole breast.[30] The group have reported favourable acute toxicity,[30] as expected given that acute side-effects are related to total dose.[31] A multicentre randomised trial in India, HYPORT-Adjuvant,[32] is currently recruiting and tests 32 Gy SIB in 5 fractions over 1 week with 26 Gy to the whole breast and aims to recruit 2100 patients. 1-week SIB is especially attractive for low-income and middle-income countries, as many people would otherwise forego treatment due to travelling and accommodation costs for longer radiotherapy courses.

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 prespecified difference of 3% for test group 1 versus control, but not for test group 2. This study highlights the challenges of assessing non-inferiority when primary outcome event rates become very low. Rates of 5-year moderate or marked adverse events are low and 48 Gy SIB showed similar or reduced toxicity compared with the control group. SIB is a safe treatment that requires fewer patient visits and further escalation of boost dose does not appear advantageous.

Contributors

CEC is the current chief investigator, JRY is the previous chief investigator, and AMK is the chief clinical coordinator for the trial. JMB is the trial's 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 were responsible for the statistical analyses and contributed to data interpretation. SVL, IB, AMB, CEC, EMD, EJS, IS, NIT, and HYCC are members of the IMPORT HIGH trial management group, 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 trial management group and provided guidance for study documentation and reports. PH was the lead for the patient-reported outcomes substudy. YMT and DJE were responsible for radiotherapy quality assurance. All authors reviewed and approved the manuscript. JSH and JMB had full access to study data. JSH and CLG accessed and verified the study data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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independent monitoring committees and is Chair of the *Lancet* Breast Cancer Commission. AMK is President of the European Society of Radiation Oncology. All other authors declare no competing interests.

Data sharing

De-identified 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 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.

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