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Published in:
The Lancet

DOI:
10.1016/S0140-6736(22)01246-6

Publication date:
2022

Radiation doses and fractionation schedules in non-low-risk ductal carcinoma in situ in the breast (BIG 3–07/TROG 07.01): a randomised, factorial, multicentre, open-label, phase 3 study

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Summary

Background Whole breast irradiation (WBI) after conservative surgery for ductal carcinoma in situ (DCIS) reduces local recurrence. We investigated whether a tumour bed boost after WBI improved outcomes, and examined radiation dose fractionation sensitivity for non-low-risk DCIS.

Methods The study was an international, randomised, unmasked, phase 3 trial involving 136 participating centres of six clinical trials organisations in 11 countries (Australia, New Zealand, Singapore, Canada, the Netherlands, Belgium, France, Switzerland, Italy, Ireland, and the UK). Eligible patients were women aged 18 years or older with unilateral, histologically proven, non-low-risk DCIS treated by breast-conserving surgery with at least 1 mm of clear radial resection margins. They were assigned to one of four groups (1:1:1:1) of no tumour bed boost versus boost after conventional versus hypofractionated WBI, or randomly assigned to one of two groups (1:1) of no boost versus boost after each centre prespecified conventional or hypofractionated WBI. The conventional WBI used was 50 Gy in 25 fractions, and hypofractionated WBI was 42·5 Gy in 16 fractions. A boost dose of 16 Gy in eight fractions, if allocated, was delivered after WBI. Patients and clinicians were not masked to treatment allocation. The primary endpoint was time to local recurrence. This trial is registered with ClinicalTrials.gov (NCT00470236).

Findings Between June 25, 2007, and June 30, 2014, 1608 patients were randomly assigned to have no boost (805 patients) or boost (803 patients). Conventional WBI was given to 831 patients, and hypofractionated WBI was given to 777 patients. Median follow-up was 6·6 years. The 5-year free-from-local-recurrence rates were 92·7% (95% CI 90·6–94·4%) in the no-boost group and 97·1% (95·6–98·1%) in the boost group (hazard ratio 0·47; 0·31–0·72; p<0·001). The boost group had higher rates of grade 2 or higher breast pain (10% [8–12%] *vs* 14% [12–17%], p=0·003) and induration (6% [5–8%] *vs* 14% [11–16%], p<0·001).

Interpretation In patients with resected non-low-risk DCIS, a tumour bed boost after WBI reduced local recurrence with an increase in grade 2 or greater toxicity. The results provide the first randomised trial data to support the use of boost radiation after postoperative WBI in these patients to improve local control. The international scale of the study supports the generalisability of the results.

Funding National Health and Medical Research Council of Australia, Susan G Komen for the Cure, Breast Cancer Now, OncoSuisse, Dutch Cancer Society, Canadian Cancer Trials Group.

Introduction

After breast-conserving surgery for ductal carcinoma in situ (DCIS) of the breast, patients are at risk of a local recurrence, of which 50% of cases are invasive with the potential for metastatic spread and an increased risk of mortality.[1] Randomised trials have provided strong evidence that whole-breast irradiation (WBI) after conservative surgery halves the local recurrence rates.[1–4] Thus, postoperative radiation therapy is integral to breast-conserving therapy for patients with DCIS.

A conventional WBI dose fractionation of 50 Gy in 2-Gy daily fractions has been used in randomised trials examining DCIS.[1] However, 10-year local recurrence rates were found to be high (17·3–20·7%) in some patient subgroups, including in those aged younger than 50 years or with multifocal or high-grade DCIS.[1] A boost to the tumour bed after WBI was found to significantly decrease local recurrence in most women with invasive breast cancer, but there were no similar randomised trial data for DCIS, and retrospective studies showed variable effects.[5–9]

A 5–6-week course of conventionally fractionated WBI decreases the quality of life of patients with breast cancer.[10] Hypofractionated WBI involves fewer but larger radiation

Lancet 2022; 400: 431–40

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*BIG 3–07/TROG 07.01 trial investigators are listed in the appendix (pp 2–5)

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See Online for appendix

Research in context

Evidence before this study

There is strong and consistent evidence from randomised trials that whole breast irradiation (WBI) after breast-conserving surgery for ductal carcinoma in situ (DCIS) of the breast significantly decreases ipsilateral breast events, in situ or invasive. The radiation dose fractionation used in the randomised trials was primarily the conventional schedule of 50 Gy in 2-Gy daily fractions over 35 days without a tumour bed boost. We searched PubMed from database inception to June 12, 2022, for articles published in any language using the search terms: "ductal carcinoma in situ", "DCIS", "boost radiotherapy", and "radiation dose fractionation". We identified 15 retrospective studies with conflicting results on the effect of boost radiation on local tumour control, and six retrospective studies that showed no differences between conventional WBI and hypofractionated WBI in patients administered breast-conserving therapy for DCIS. These search findings highlighted the need to prospectively examine the effects of tumour bed boost and radiation dose fractionation in the context of WBI after breast-conserving surgery in DCIS.

Added value of this study

The number of diagnosed DCIS cases had increased substantially since the implementation of mammographic screening. However, in contrast with invasive breast cancer, there has been little knowledge on the treatment and effects of treatment for DCIS to inform best practice. Randomised trials showed that local recurrence rates in subgroups of patients with DCIS were high after conventionally fractionated postoperative WBI without a tumour bed boost. Further, the inconvenience of a 5–6-week course of conventionally fractionated WBI decreased the quality of life of patients. Thus, tailoring radiation dose fractionation according to recurrence risk is a prominent controversy in the radiation treatment of DCIS.

To our knowledge, our study is the only randomised phase 3 trial that examines the effects of both a tumour bed boost and WBI dose fractionation in patients with non-low-risk DCIS. The study showed that a tumour bed boost after postoperative WBI significantly reduces local recurrence with an increase in grade 2 or higher toxicity. In addition, moderately hypofractionated WBI involving fewer, larger radiation doses administered over a shorter overall treatment time than conventional fractionation was as safe and effective as conventional fractionation in DCIS.

Implications of all the available evidence

Our results provide the first randomised trial data to support the use of boost radiation after postoperative WBI, and moderately hypofractionated WBI in patients with non-low-risk DCIS to improve the balance of local control, toxicity, and socioeconomic burdens of treatment. The international scale of our study supports the generalisability of the findings. Because the moderately hypofractionated WBI schedule used in our study might not be the clinical limit of hypofractionation in DCIS, future research on shorter WBI dose fractionation in DCIS might further improve patient convenience and streamline the use of radiotherapy resources to improve access to care for these patients.

doses administered over a shorter overall treatment time than conventional fractionation. Moderately hypofractionated WBI has been found to be as safe and effective as conventional fractionation in women with invasive breast cancer.[11–13] However, there were no randomised trial data to support the use of hypofractionated radiation therapy in DCIS.

The aims of the Breast International Group (BIG) 3–07 and Trans-Tasman Radiation Oncology Group (TROG) 07.01 study were to investigate whether a tumour bed boost after WBI decreased local recurrence, and to examine WBI fractionation sensitivity in patients with non-low-risk DCIS who were administered breast-conserving therapy.

Methods

Study design and participants

The study was an international, randomised, unmasked, phase 3 trial involving 136 participating centres of six clinical trials organisations in 11 countries (Australia, New Zealand, Singapore, Canada, the Netherlands, Belgium, France, Switzerland, Italy, Ireland, and the UK; appendix pp 2–5). Institutional research ethics review boards or ethics committees at each centre approved the study, and the patients provided written informed consent before study enrolment. Protocol amendments introduced three WBI categories for patients to be assigned to as well as allowing international participation (on Aug 27, 2007), and increased the sample size from 610 to 1600 patients (on Dec 21, 2011; appendix p 11). All amendments were approved by the relevant institutional research ethics review boards or ethics committees.

Eligible patients were women aged 18 years or older with unilateral, histologically proven, non-low-risk DCIS treated by breast-conserving surgery with at least 1 mm of clear radial resection margins (appendix p 6). Specimen radiography was performed to confirm the complete removal of radiological abnormalities. Axillary staging was not required.

Patients had at least one clinical or pathological marker for an increased local recurrence risk, including a younger age (<50 years), symptomatic presentation, palpable tumour, microscopic tumour size measuring 15 mm or more, multifocal disease, intermediate or high nuclear grade, central necrosis, comedo-histology, or a radial surgical margin of less than 10 mm, or a

combination. Patients were suitable for postoperative WBI and available for long-term follow-up of 10 years.

Patients were excluded if they had multicentric disease or extensive microcalcifications that could not be resected with radial margins of 1 mm or more, axillary nodal metastasis, or serious non-malignant disease that precluded definitive radiation therapy.

Randomisation and masking

Before local study activation, each centre chose to participate in one of three WBI categories (appendix p 10). Category A was a random assignment of patients to one of four groups: boost to the tumour bed versus no boost and conventional versus hypofractionated WBI (allocation ratio, 1:1:1:1). Category B was a two-group random assignment of boost versus no boost after conventional WBI, and category C was a two-group random assignment between boost versus no boost after hypofractionated WBI (allocation ratio for both, 1:1).

Before random assignment, patients were stratified by age (<50 years *vs* ≥50 years), planned endocrine therapy (yes or no), and by treating centre. Centralised electronic randomisation was performed through an in-house web-based system, hosted by the University of Adelaide's Data Management and Analysis Centre (Adelaide, SA, Australia). Random assignment was done at the trial centre by dynamic allocation, by the use of a minimisation algorithm generated by the Centre for Biostatistics and Clinical Trials (Melbourne, VIC, Australia) after the completed eligibility checklist was provided by the participating centre. Patients and clinicians were not masked to treatment allocation. The study research nurse, coordinator, or investigator entered the stratification information into the centralised electronic randomisation system. The allocated group was provided to each person by email. All these individuals were further involved in the trial.

Procedures

Patients received WBI within 12 weeks of the last breast surgical procedure using tangential, 4–18 megavoltage photon beams with wedges or subfields to optimise dose homogeneity. For left-sided treatment, the heart was excluded from the high-dose region. Bolus use and regional nodal irradiation were not permitted. The conventional WBI used was 50 Gy in 25 once-per-day fractions over 5 weeks. Hypofractionated treatment was 42·5 Gy in 16 once per day fractions over 3·5 weeks (appendix pp 7–8).

The boost to the tumour bed, if allocated, was delivered after WBI to the primary site with a 10 mm margin in all directions based on contouring the seroma cavity or surgical clips on CT scans, or both. This target volume was expanded by 5–10 mm in all directions to establish the treatment fields. CT-based treatment planning was mandatory. Boost radiation was administered using an incident electron beam or megavoltage photons via tangential or other field arrangements that conformed to the protocol-specified dose homogeneity criteria and normal tissue constraints. A boost dose of 16 Gy in eight fractions across 1·5 weeks was prescribed, irrespective of WBI dose fractionation.

Quality assurance audits for the central radiation therapy were conducted for the first five patients from each centre using the TROG Central Quality Management System. If no major protocol deviation was identified, the centre was audited on the basis of a 1-in-10 random sampling of subsequent patients. Adjuvant endocrine therapy use was prespecified at the time of random assignment at the discretion of treating physicians.

Patients had clinical follow-up at 3, 6, and 12 months, and then annually, as well as mammographic follow-up at 12 months from the date of the last bilateral mammogram, and then annually for 10 years after radiation therapy per protocol (appendix p 9). Local recurrence events were centrally audited using source documents. Adverse events and the overall study conduct were reviewed without allocation group data by the Study Steering Committee at least once every 6 months during accrual and subsequently once per year, and monitored by the Data, Safety, and Monitoring Committee at least annually.

Outcomes

The status of patients who were not lost to follow-up was known on Aug 29, 2019, the close-out date (when the status of all patients who had not ceased follow-up was known). The primary endpoint was the time to local recurrence, defined as the time from random assignment to the first evidence of recurrent disease in the ipsilateral breast, censored by distant recurrence, regional recurrence, and ipsilateral mastectomy if no other events were observed, the close-out date, or the date of the last mammogram, whichever came first. Of the two treatments (tumour bed boost and WBI dose fractionation), the effect of the boost on the primary endpoint was the primary analysis, and the secondary analysis was the effect of the WBI dose fractionation on this endpoint. The prespecified secondary endpoints were the time to disease recurrence, overall survival, treatment toxicity, cosmetic outcome (physical appearance of the breast after surgery and radiation therapy), and health-related quality of life. Time to disease recurrence was the time from random assignment to the first evidence of local, regional, or distant recurrence or contralateral breast cancer, censored by ipsilateral mastectomy, or the close-out date, or the date of the last mammogram if no other events were observed, whichever came first. Overall survival was the time from random assignment to death from any cause, censored at the date that the patient was last known to be alive. Cumulative incidence curves were calculated as part of a competing risks analysis (local recurrence *vs* distant recurrence *vs* death without recurrence). The source documents of all recurrence and

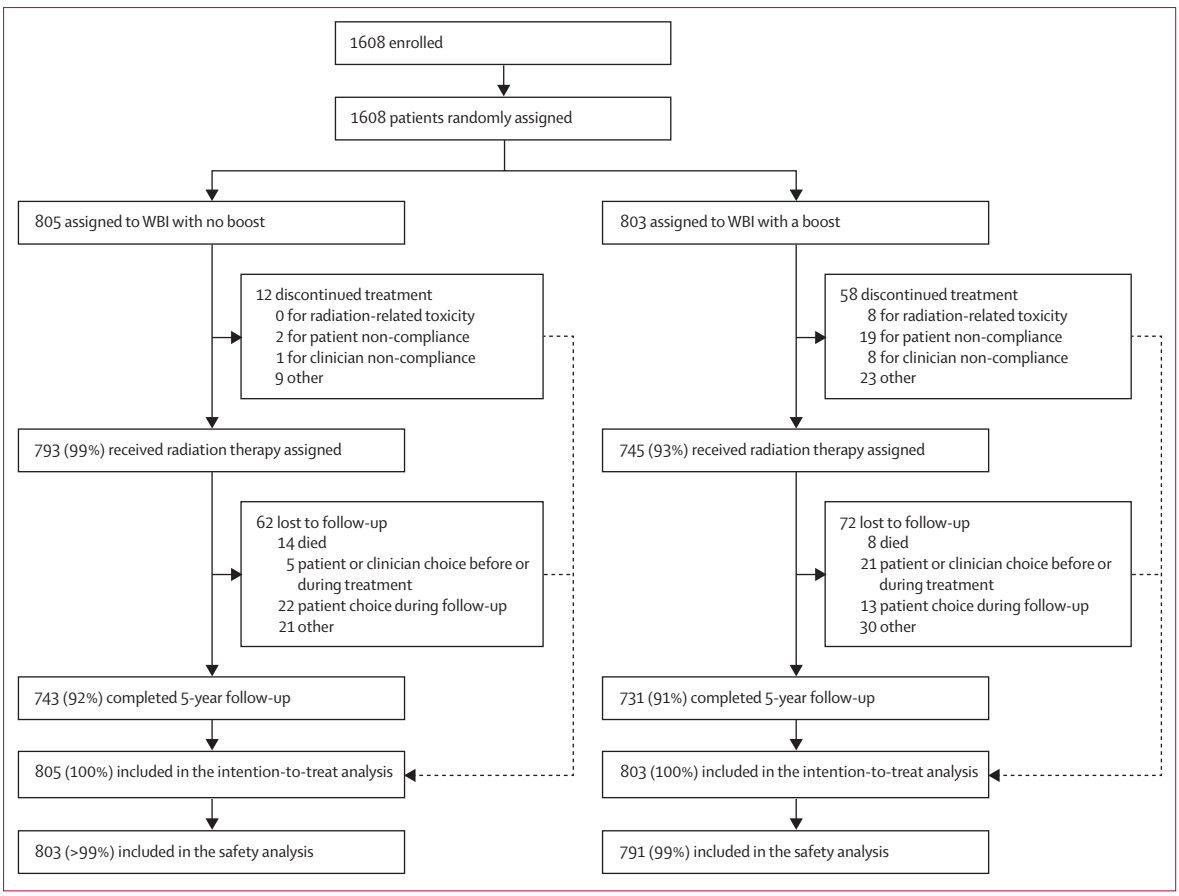

Figure 1: **CONSORT diagram for boost versus no-boost treatment groups**
WBI=whole breast irradiation.

contralateral breast cancer events were centrally reviewed by an author (BHC, AHW, GG, or IAO) to verify the diagnosis, and in the case of a local recurrence, its location in the breast. Treatment toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). The Data, Safety, and Monitoring Committee preapproved the allocated treatment analyses of 3-year cosmetic outcomes, and the effects of diagnosis and treatment on health-related quality of life at 2 years after radiation therapy.[14,15] The 5-year cosmetic and quality-of-life outcomes will be reported elsewhere.

Statistical analysis

The study was designed to detect a clinically relevant 3% difference in 5-year free-from-local-recurrence rates between the no-boost and boost groups (93% *vs* 96%; hazard ratio, 0·56) with 90% power, a 5% two-sided α level, and 1:1 allocation between the groups. To detect the difference, 127 local recurrences among 1514 evaluable patients were required, assuming an exponential time to local recurrence, a 5-year competing event rate of 5%, a 9-year accrual period with non-uniform accrual, and 5 years of follow-up. To allow for a 5% lost-to-follow-up rate, 1600 patients were to be accrued. Because accrual was completed in 7 years (2 years ahead of schedule), we estimated that 116 events would be observed at 5 years after recruitment with 87% power with a 5% two-sided α level.

The Data, Safety, and Monitoring Committee reviewed the data at a planned interim analysis, conducted by the study statistician, when 50% of the expected local recurrences (n=64) were reported, and recommended the release of results if $p<0·001$. After the completion of recruitment, the Data, Safety, and Monitoring Committee again reviewed the data in July, 2017 (appendix p 19), and the release of results was recommended when all patients in the study who had not been lost to follow-up had completed 5 years of follow-up. No changes to the study were recommended.

Analyses of the primary and secondary endpoints were performed on an intention-to-treat basis. The primary effect of the tumour bed boost was assessed on all randomly assigned patients. The secondary effect of WBI dose fractionation and the interaction between the boost and WBI fractionation was assessed on patients in category A; and, as a sensitivity analysis, on all patients.

Statistical tests were two-sided using a significance level of 5%. No change in significance level from 5% for

	No boost (n=805)	Boost (n=803)
Age (years)		
<50	133 (17%)	131 (16%)
50–59	306 (38%)	334 (42%)
60–69	292 (36%)	267 (33%)
≥70	74 (9%)	71 (9%)
Median	58 (52–64)	57 (51–65)
Tumour size (mm)		
≤10	211 (26%)	253 (32%)
>10 to ≤15	150 (19%)	132 (16%)
>15 to ≤20	145 (18%)	123 (15%)
>20 to ≤25	88 (11%)	64 (8%)
>25 to ≤50	151 (19%)	165 (21%)
>50	32 (4%)	32 (4%)
Unknown	28 (3%)	34 (4%)
Closest radial margin (mm)		
≤1	73 (9%)	66 (8%)
>1 to 2	61 (8%)	83 (10%)
>2 to 5	158 (20%)	161 (20%)
>5	205 (25%)	193 (24%)
Unknown	308 (38%)	300 (37%)
Median	5 (2–9)	5 (2–8)
High grade or comedo necrosis		
Yes	607 (75%)	569 (71%)
No	198 (25%)	234 (29%)
Endocrine therapy		
Yes	106 (13%)	105 (13%)
No	699 (87%)	698 (87%)
Sentinel node biopsy		
Yes	178 (22%)	166 (21%)
No	626 (78%)	626 (78%)
Unknown	1 (0%)	11 (1%)

Data are presented as n (%) or median (first quintile, third quintile). Additional details regarding the baseline patient characteristics are provided in the appendix (pp 13–15).

Table 1: **Patient characteristics at baseline in the intention-to-treat population**

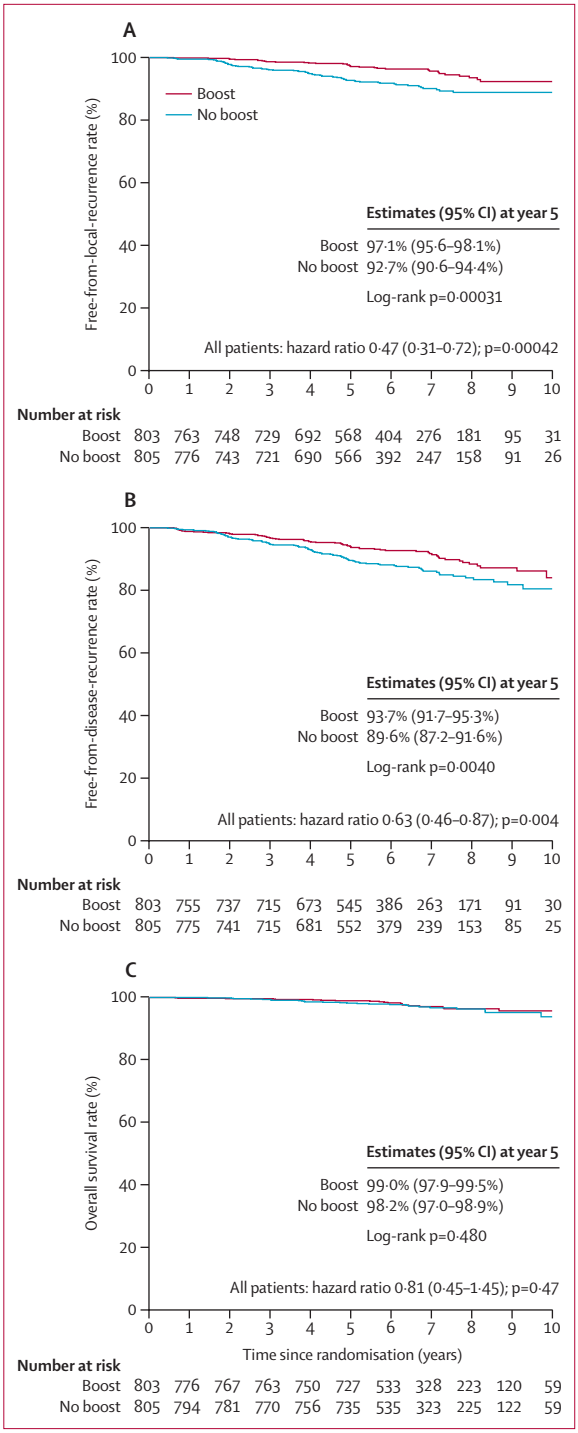

Figure 2: **5-year Kaplan–Meier estimates of time-to-event outcomes**
Kaplan-Meier estimates of free-from-local-recurrence rates (A), free-from-disease-recurrence rates (B), and overall survival rates (C) among all patients who were randomly assigned to receive no tumour bed boost versus those who were assigned to receive a boost after whole breast irradiation.

the primary effect of the tumour bed boost was made, even though there was an interim analysis. The stopping rule at the interim analysis was to release results if $p<0·001$, a strict p value. Any bias for the primary effect assessed at $p<0·05$ because of the interim analysis would be minimal and the results were unmasked only to the Data, Safety, and Monitoring Committee. CIs were calculated with a two-sided confidence coefficient of 95%.

The Kaplan-Meier method was used to estimate the time to local recurrence and time to disease recurrence. The Mantel-Cox log-rank test was used for the primary comparison of boost versus no boost adjusted for age, endocrine therapy use, and WBI dose fractionation; and the secondary comparison of conventional versus hypofractionated WBI adjusted for age, endocrine therapy use, and boost use. Cox proportional hazards regression was used to assess the significance of the boost and WBI dose fractionation, and their interaction with regard to time to local recurrence and disease recurrence, adjusted for age, endocrine therapy use, and

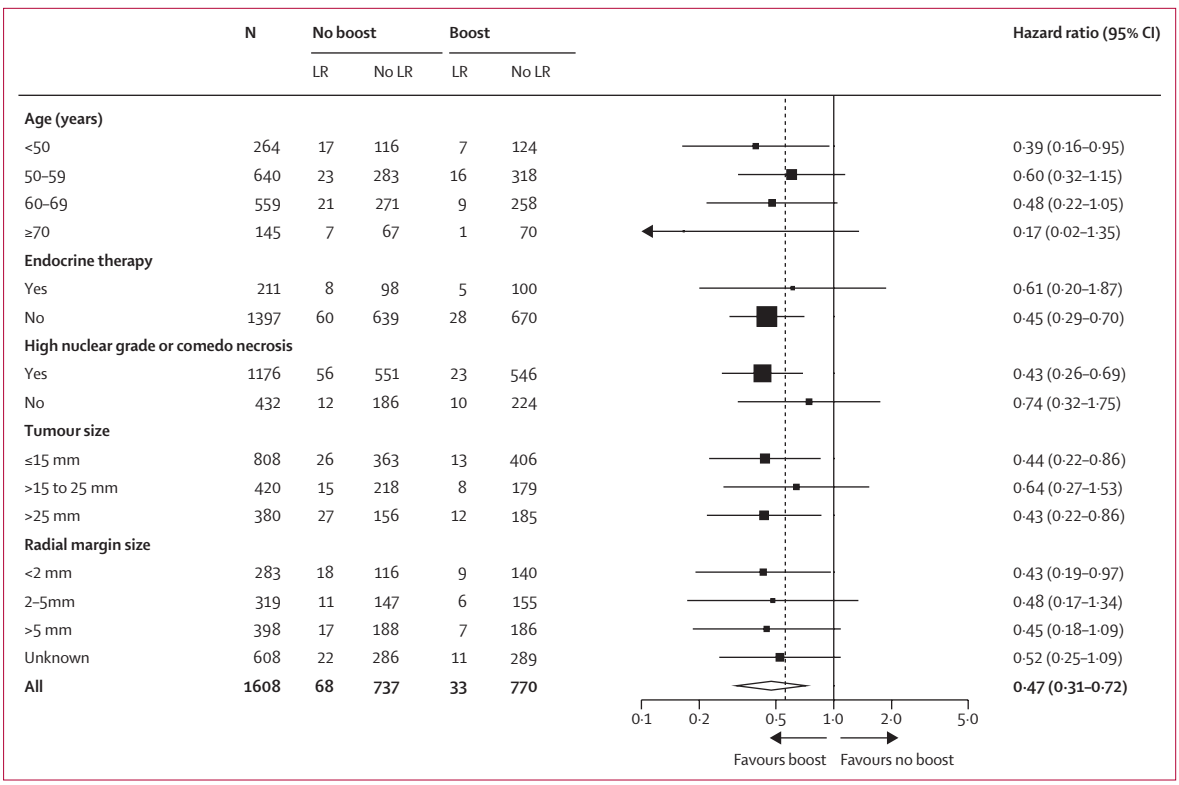

Figure 3: **Time to local recurrence by subgroup**
Hazard ratios for local recurrence among all patients randomly assigned by allocation to either the tumour bed boost group or the no-boost group. The dashed vertical line at 0·56 indicates the overall hazard ratio estimate deemed clinically relevant at study design. The hazard ratios are shown on a logarithmic scale. LR=local recurrence.

WBI dose fractionation. The centre the patient was at was included as a random effect, and analyses were stratified by WBI category. Exploratory subgroup analyses based on study stratification and other possible risk factors for local recurrence were undertaken, with hazard ratios presented in a forest plot. Logistic regression models across the three WBI categories were fitted to assess the effects of each treatment group, and the interaction between treatment groups, on the proportion of patients with grade 3 or higher acute toxicity within 3 months of completion of radiation therapy, and grade 2 or higher late toxicity after 3 months of completion of radiation therapy, with the incidence of late toxicities estimated using the Kaplan-Meier method. There was no imputation of missing data for an endpoint, and no adjustment of p values for multiple testing among secondary outcomes. All analyses were conducted using the SAS software (version 9.4). This study was registered with ClinicalTrials.gov (NCT00470236).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between June 25, 2007, and June 30, 2014, 1608 patients were randomly assigned (category A, 503 patients; category B, 581 patients; category C, 524 patients) to the no-boost group (805 patients) or the boost group (803 patients; figure 1). WBI was conventional in 831 patients, and hypofractionated in 777 patients.

Among patients randomly assigned to receive WBI only, one patient received a boost to the tumour bed. Among patients randomly assigned to receive a boost, 27 patients received WBI only. Adjuvant endocrine therapy was planned in 106 patients (13%) in the no-boost group and 105 patients (13%) in the boost group. Four patients (<1%) withdrew their consent, and 112 patients (7%) were lost to follow-up (appendix p 12). The median follow-up was 6·6 years.

The distribution of baseline characteristics separated by the boost and no-boost groups, and by WBI fractionation in category A or among all patients, showed that most patients were aged 50 years or older, and had a tumour measuring 20 mm or less in microscopic size that was resected with a median margin width of 5 mm (table 1; appendix pp 13–15). The closest radial margin width was not known in 38% of all patients, of whom 40% had one or more re-excision (table 1; appendix p 15).

Figure 2 shows that the 5-year free-from-local-recurrence rates were 92·7% in the no-boost group and 97·1% in the boost group (hazard ratio, 0·47; 95% CI 0·31–0·72; p<0·001). In the no-boost group, 44% of the local recurrences were invasive, and in the boost group, 45% of the local recurrences were invasive. Local recurrences were in the same quadrant in 81% of participants in the no-boost group and 73% in the boost group (appendix p 16). In an exploratory analysis, there were no significant differences found in the effect of the tumour bed boost on local recurrence according to age, tumour size, nuclear grade, comedo necrosis, surgical margin width, or endocrine therapy use (figure 3).

There were no statistically significant differences in 5-year free-from-local-recurrence rates between conventional (94·4%) and hypofractionated (93·7%) WBI groups in category A (hazard ratio, 0·94; 95% CI 0·51–1·73; p=0·84) or in all randomly assigned patients (94·9% conventional *vs* 94·9% hypofractionated; 0·94; 0·51–1·74; p=0·85; appendix p 20). The interaction between a tumour bed boost and WBI dose fractionation was not statistically significant in category A (1·09; 0·32–3·76; p=0·89) or in all randomly assigned patients (0·94; 0·41–2·18; p=0·89).

Table 2 shows that tumour bed boost and tumour size were independent risk factors for local recurrence in a multivariate model derived from protocol-defined non-low-risk criteria and treatment characteristics. The 5-year free-from-disease-recurrence rates were lower in the no-boost group (89·6%) than in the boost group (93·7%; hazard ratio, 0·63; 95% CI 0·46–0·87; p=0·0042; figure 2). Regional nodal recurrence, all axillary, was found in five patients (<1%) in the no-boost group, and no patient in the boost group (appendix p 16). The corresponding numbers for distant relapse were one patient (<1%) in the no-boost group and five patients (<1%) in the boost group.

There were no statistically significant differences in 5-year free-from-disease-recurrence rates between conventional (90·0%) versus hypofractionated (92·4%) WBI groups in category A (hazard ratio, 0·79; 95% CI 0·47–1·31; p=0·36) or in all randomly assigned patients (91·0% conventional *vs* 92·4% hypofractionated; 0·83; 0·50–1·38; p=0·46; appendix p 21). There was no statistically significant difference in 5-year overall survival rates between the no-boost (98·2%) and boost (99·0%) groups (0·81; 0·45–1·45; p=0·47; figure 2).

Table 3 summarises specific adverse events that were grade 2 or higher. Grade 4 adverse events were rare, and no grade 5 events were reported. The boost group had higher rates of grade 2 or greater breast pain (77 [10%] no boost *vs* 116 [14%] boost; p=0·003) and induration (49 [6%] no boost *vs* 110 [14%] boost; p<0·001) than the no-boost group (table 3), with no suggestion of interaction with WBI dose fractionation. The cumulative incidence over time for breast pain and induration is shown in the appendix (pp 24–25). There was no significant increase in radiation pneumonitis, cardiac disease, or radiation-related second malignancy in the boost group.

	Hazard ratio	95% lower confidence limit for hazard ratio	95% upper confidence limit for hazard ratio	χ^2	Probability >χ^2
Tumour bed boost	0·46	0·30	0·71	12·83	<0·001
Whole breast dose fractionation	1·03	0·55	1·91	0·01	0·94
Age ≥50 years	0·67	0·34	1·32	1·33	0·25
Premenopausal status	0·99	0·53	1·85	0·00	0·98
Symptomatic presentation	0·34	0·05	2·59	1·07	0·30
Palpable presentation	1·50	0·63	3·58	0·84	0·36
Tumour size <15 mm	0·52	0·33	0·83	7·54	0·006
Tumour size 15–25 mm	0·57	0·34	0·96	4·42	0·035
Tumour size >25 mm	1·00	NA	NA	NA	NA
High nuclear grade or central or comedo necrosis	0·72	0·44	1·18	1·69	0·19
Closest clear radial margin width ≤1 mm	1·00	NA	NA	NA	NA
Closest clear radial margin width >1–2 mm	1·17	0·54	2·53	0·16	0·69
Closest clear radial margin width >2–5 mm	0·59	0·28	1·24	1·92	0·17
Closest clear radial margin width >5 mm	0·65	0·32	1·30	1·51	0·22
Closest clear radial margin width unknown	0·62	0·32	1·19	2·08	0·15
Planned or receipt of endocrine therapy	1·07	0·58	1·98	0·05	0·83

Cox proportional hazards model with randomisation category strata, and the centre that the patient was at included as a random effect. There were 1608 patients used in the model, and the model χ^2 statistic was 56·1 (p<0·001).

Table 2: **Multivariable model to predict the time free from local recurrence in the intention-to-treat population**

Discussion

Tailoring radiation dose fractionation according to the risk of local recurrence is one of the most prominent controversies in the radiation treatment of DCIS. We have shown that a tumour bed boost after WBI decreased local recurrence, and that moderately hypofractionated WBI was as safe and effective as conventional WBI for women with resected, non-low-risk DCIS.

The absolute gain in local control with boost radiation was 4·4% at 5 years (5-year free-from-local-recurrence rates were 92·7% in the no-boost group, and 97·1% in the boost group), and 44% of local recurrences were invasive. The magnitude of these effects at 5 years was similar to the effects at 20 years observed in a randomised trial evaluating boost radiation for invasive breast cancer, and the estimated effects at 15 years in a large retrospective analysis of pooled patients with DCIS.[5,8] With a median follow-up of 6·6 years, it is expected that the local recurrence rates and the absolute benefit of boost radiation in our study will increase over time.[5,7] Although breast cancer mortality after a DCIS diagnosis is low, invasive recurrences have been associated with a

	No tumour bed boost (n=805)				Tumour bed boost (n=803)				Odds ratio for boost (95% CI)
	Grade			Total	Grade			Total	
	2	3	4		2	3	4		
Acute adverse events									
Any acute event	323	23	0	346 (43%)	418	45	2	465 (58%)	2·1 (1·3–3·5)
Radiation dermatitis	227	8	0	235 (29%)	338	23	1	362 (45%)	3·1 (1·4–6·9)
Fatigue	112	7	0	119 (15%)	131	11	1	143 (18%)	1·7 (0·7–4·4)
Breast pain	90	8	0	98 (12%)	116	10	1	127 (16%)	1·4 (0·6–3·5)
Gynaecomastia	35	3	0	38 (5%)	32	4	0	36 (4%)	1·4 (0·3–6·1)
Pneumonitis or pulmonary infiltrates	0	1	0	1 (<1%)	1	1	0	2 (<1%)	1·0 (0·1–15·4)
Late adverse events									
Any late event	159	32	2	193 (24%)	242	36	5	283 (35%)	1·8 (1·4–2·2)
Breast pain	67	10	0	77 (10%)	102	12	2	116 (14%)	1·6 (1·2–2·2)
Breast induration	44	5	0	49 (6%)	99	11	0	110 (14%)	2·5 (1·7–3·5)
Fatigue	33	5	0	38 (5%)	36	8	0	44 (5%)	1·2 (0·7–1·8)
Telangiectasia	4	3	0	7 (1%)	16	4	0	20 (2%)	2·9 (1·2–7·0)
Pulmonary events	2	0	0	2 (<1%)	6	1	0	7 (1%)	3·5 (0·7–17·1)
Cardiac events	0	1	0	1 (<1%)	1	0	3	4 (<1%)	4·0 (0·4–36·1)
Second malignancy	0	2	2	4 (<1%)	0	0	0	0	NE

Data presented as n (%). Listed are adverse events that were clinically significant or reported in more than 5% of patients in each treatment group. Events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Acute adverse events were reported at 3 months or earlier after the completion of radiation therapy. Late adverse events were reported after 3 months after the completion of radiation therapy. Odds ratios with 95% CIs and p values for the differences in rates of grade 3 or higher acute events and grade 2 or higher late events were estimated from logistic regression models, adjusted for randomly assigned treatment, age category, and endocrine therapy, and stratified by randomisation schedule. There was no adjustment for multiple testing. Pulmonary events included pneumonitis or pulmonary infiltrates or pulmonary fibrosis (radiographic changes). Cardiac events included cardiac ischaemia or infarction, cardiac general or supraventricular and nodal arrhythmia, and atrial fibrillation. NE=not estimable.

Table 3: **Adverse events (grade 2 or higher) related to radiation therapy among the safety population**

75% increase in mortality risk.[2] In addition, patients with a local recurrence often undergo a mastectomy with potentially significant psychosocial consequences. Thus, minimising recurrences and improving quality of life are the primary objectives of breast-conserving therapy. We have shown that local control was improved with the use of boost radiation in patients with non-low-risk DCIS. The observed effect size of hazard ratio 0·47 (0·31–0·72) for 5-year free-from-local-recurrence rates between the boost and no-boost groups encompassed the clinically significant effect of 0·56 that the study was designed to detect. This effect was consistent across all patient subgroups, suggesting that our findings are applicable to all patients eligible for the study.

Boost radiation is commonly used in patients with invasive breast cancer with an increased risk of local recurrence. However, the recurrence risk profiles in DCIS are not well defined using conventional clinical-pathological criteria.[1] Molecular profiling, complemented by clinical-pathological markers, has the potential to improve the precision of local recurrence risk prediction, and refine patient selection for boost radiation.[16–18]

Boost radiation of 16 Gy in eight fractions was associated with an increase in grade 2 or higher late breast pain and induration compared with no boost. However, grade 4 toxicity was rare, and no grade 5 toxicity was reported. Because late toxicity might increase over time, the protocol-specified report of local recurrence and toxicity at 10 years will be needed in weighing up the benefits and risks of the boost. We have previously shown that boost irradiation increased clinician-assessed cosmetic deterioration from an excellent or good cosmetic score at baseline to a fair or poor score at 3 years, from 9% to 16%.[14] We also previously reported that patient-reported cosmetic outcomes were slightly worse with a boost than with no boost, and these worse outcomes persisted at 2 years.[15] These findings were similar to the adverse effects reported in a study examining a boost radiation of 16 Gy in eight fractions in women with invasive breast cancer, but not when this boost schedule was used after a whole breast dose of 45 Gy in 25 fractions.[19–21] Our results on local control and toxicity associated with a tumour bed boost provide the evidence for shared treatment decision making by the patients and treating physicians, guided by the values and preferences of patients.

The boost schedule of 16 Gy in eight fractions reduced local recurrence in a randomised trial of 5318 patients with invasive breast cancer.[5] Another study in invasive breast cancer showed that boost radiation of 10 Gy in four fractions after WBI resulted in a similar relative risk reduction for local recurrence.[6] A shorter boost schedule might reduce the inconvenience of care, but whether it results in a similar efficacy as 16 Gy in eight fractions in DCIS requires further investigation. However, there would be considerable challenges in conducting a trial to address this question, particularly with the low event rates because of advances in multidisciplinary care for women with DCIS. Because moderately hypofractionated WBI has been shown to be as safe and effective as conventional WBI for non-low-risk DCIS, a similarly hypofractionated boost schedule might provide the opportunity to further improve the convenience of care.

The 10-year results of randomised trials involving more than 7000 patients with invasive breast cancer showed that moderately hypofractionated WBI of 40·0–42·5 Gy in 15–16 fractions over 3 weeks was at least as safe and effective as a conventionally fractionated schedule delivered over 5 weeks.[11–13] These results were consistent with those of another randomised trial of 1854 patients, including 246 patients with DCIS.[22] Hypofractionated WBI was shown to provide clear socioeconomic benefits for both patients and health systems.[23,24] Although randomised trial data supporting the use of moderately hypofractionated WBI in DCIS have been absent, the socioeconomic benefits, together with long-term outcomes of randomised trials predominantly in invasive breast cancer, have resulted in its adoption for DCIS in routine practice in some countries.[25] However, our study is the first randomised trial in patients with DCIS only to show that moderately hypofractionated WBI was as

effective as a conventional schedule. We have also previously reported that the two schedules produced equivalent cosmetic outcomes.[14] The 16-fraction schedule used in our study might not be the clinical limit of whole breast hypofractionation in DCIS. A randomised trial for invasive breast cancer showed that the WBI schedule of 26 Gy in five fractions over 1 week was non-inferior to 40 Gy in 15 fractions over 3 weeks for tumour control and normal tissue effects up to 5 years.[26]

There are potential limitations of our study. Data on compliance with adjuvant endocrine therapy were not captured. Thus, the effect of compliance with adjuvant endocrine therapy on study outcomes could not be examined. However, because only 13% of patients were prespecified to receive endocrine therapy, the reported outcomes were primarily a measure of the effect of local therapy without a substantial confounding effect of endocrine therapy. The closest radial margin width was not reported in 38% of all patients, of whom 40% had one or more re-excision, precluding the measurement of the closest margin width. The absence of these data might restrict the examination of the effect of surgical margins on local recurrence. However, the tumour bed boost was shown to consistently decrease local recurrence across all margin categories. Another potential limitation is the generalisability of our results, because information on ethnicity was not collected. However, the broad international participation from 136 centres in 11 countries in Australia, New Zealand, Canada, Europe, the UK, and Asia provides reasonable support for the generalisability of our findings.

Our results support the use of tumour bed boost radiation after postoperative WBI in patients with non-low-risk DCIS to optimise local control, and the adoption of moderately hypofractionated WBI in practice to improve the balance of local control, toxicity, and socioeconomic burdens of treatment.[25]

Contributors

BHC, IHK, TJW, AHW, GG, and IAO were responsible for the study design. GPD, IDC, PHG, and VA contributed to the study concept. BHC, EKL, IHK, TJW, AHW, GG, and IAO were members of the BIG 3–07/TROG 07·01 Trial Steering Committee, and oversaw the study conduct. All authors except EKL were involved in data collection. EKL prepared the statistical analysis plan, and BHC reviewed the drafts. BHC and EKL had full access and verified the study data. EKL performed the data analysis and wrote the statistical report. BHC, EKL, IHK, TJW, AHW, GG, and IAO interpreted the data. BHC, EKL, and IAO wrote the manuscript. All authors reviewed the drafts and gave final approval of the manuscript. BHC had final responsibility for the decision to submit for publication.

Declaration of interests

BHC reports research grants from National Health and Medical Research Council, Susan G Komen for the Cure, Breast Cancer Now, and OncoSuisse Swiss Federation Against Cancer to support the submitted work at Trans-Tasman Oncology Group (Newcastle, NSW, Australia), Centre for Biostatistics and Clinical Trials of Peter MacCallum Cancer Centre (Melbourne, VIC, Australia), and participating cooperative trials groups and sites; and in kind support from Veracyte and NanoString for biomarker testing, outside the submitted work. IHK and AHW report research grants to support the submitted work at the UK Trial Centre, University of Edinburgh (Breast Cancer Now); and research funding from the Dutch Cancer Society to support the submitted work in the Netherlands. TJW reports research funding and non-direct financial support for biomarker testing from Exact Sciences and Genomic Health for ongoing studies. All other authors declare no competing interests.

Data sharing

This manuscript focuses on a 5-year analysis of the primary endpoint, and final analysis will be based on 10 years of follow-up. Deidentified patient-level data can be made available to researchers for meta-analyses or developing new studies upon publication of the final analysis, subject to approval of the proposal by the trial steering committee, and a signed data access agreement.

Acknowledgments

We thank the patients, investigators, and support staff of all participating centres. The list of contributors from participating centres is provided in the appendix (pp 2–5). We acknowledge the support of the trial management staff of the Trans-Tasman Oncology Group, and participating cooperative trials groups including the Canadian Cancer Trials Group, the European Organisation for Research and Treatment of Cancer, the International Breast Cancer Trials Group, Cancer Trials Ireland, and the Scottish Cancer Trials Breast Group. We thank the Breast International Group in enabling international collaboration. We acknowledge the support of the Centre for Biostatistics and Clinical Trials of the Peter MacCallum Cancer Centre (Melbourne, VIC, Australia), and the Data and Safety Monitoring Committee (Richard Gelber, Boston, MA, USA; Lori Pierce, Ann Arbor, MI, USA; and Mary Gospodarowicz, Toronto, ON, Canada). We thank the National Health and Medical Research Council (grant numbers 454390 and 1099860), Susan G Komen for the Cure (grant number OG12-BIG), Breast Cancer Now (grant number PR55), OncoSuisse Swiss Federation Against Cancer (grant number KLS/KFS 02527–02–2010), and the Dutch Cancer Society (grant number 2009–4467) for directly funding the study, and the Canadian Cancer Society for indirectly funding the study through the Canadian Cancer Trials Group.

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