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[Intervention Review]

Tumour bed boost radiotherapy for women after breast-conserving surgery

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ABSTRACT

Background

Breast-conserving therapy, involving breast-conserving surgery followed by whole-breast irradiation and optionally a boost to the tumour bed, is a standard therapeutic option for women with early-stage breast cancer. A boost to the tumour bed means that an extra dose of radiation is applied that covers the initial tumour site. The rationale for a boost of radiotherapy to the tumour bed is that (i) local recurrence occurs mostly at the site of the primary tumour because remaining microscopic tumour cells are most likely situated there; and (ii) radiation can eliminate these causative microscopic tumour cells. The boost continues to be used in women at high risk of local recurrence, but is less widely accepted for women at lower risk. Reasons for questioning the boost are twofold. Firstly, the boost brings higher treatment costs. Secondly, the potential adverse events are not negligible. In this Cochrane Review, we investigated the effect of the tumour bed boost on local control and side effects.

Objectives

To assess the effects of tumour bed boost radiotherapy after breast-conserving surgery and whole-breast irradiation for the treatment of breast cancer.

Search methods

We searched the Cochrane Breast Cancer Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (January 1966 to 1 March 2017), Embase (1980 to 1 March 2017), the World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov on 1 March 2017. We also searched the European Society of Radiotherapy and Oncology Annual Meeting, the St Gallen Oncology Conferences, and the American Society for Radiation Oncology Annual Meeting for abstracts.

Selection criteria

Randomised controlled trials comparing the addition and the omission of breast cancer tumour bed boost radiotherapy.

Data collection and analysis

Two review authors (IK and CW) performed data extraction and assessed risk of bias using Cochrane's 'Risk of bias' tool, resolving any disagreements through discussion. We entered data into Review Manager 5 for analysis and applied GRADE to assess the quality of the evidence.

Main results

We included 5 randomised controlled trials analysing a total of 8325 women.

Tumour bed boost radiotherapy for women after breast-conserving surgery (Review)

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Local control appeared to be better for women receiving a tumour bed boost compared to no tumour bed boost (hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.55 to 0.75; 5 studies, 8315 women, low-quality evidence). Overall survival did not differ with or without a tumour bed boost (HR 1.04, 95% CI 0.94 to 1.14; 2 studies, 6342 women, moderate-quality evidence). Disease-free survival did not differ with or without a tumour bed boost (HR 0.94, 95% CI 0.87 to 1.02; 3 studies, 6549 women, low-quality evidence). Late toxicity scored by means of percentage of breast retraction assessment did not differ with or without a tumour bed boost (mean difference 0.38, 95% CI -0.18 to 0.93; 2 studies, 1526 women, very low-quality evidence). Cosmesis scored by a panel was better (i.e. excellent or good compared to fair or poor) in the no-boost group (odds ratio (OR) 1.41, 95% CI 1.07 to 1.85; 2 studies, 1116 women, low-quality evidence). Cosmesis scored by a physician did not differ with or without a tumour bed boost (OR 1.58, 95% CI 0.93 to 2.69; 2 studies, 592 women, very low-quality evidence).

We excluded two studies in a sensitivity analysis of local recurrence (because the biological equivalent dose (BED) to the tumour bed was lower, in situ tumours were included, or there was a high risk of selective reporting bias or blinding of outcome assessment bias), which resulted in a HR of 0.62 (95% CI 0.52 to 0.73; 3 studies, 6963 women, high-quality evidence). Subgroup analysis including women older than 40 years of age yielded a HR of 0.65 (95% CI 0.53 to 0.81; 2 studies, 5058 women, high-quality evidence).

We found no data for the outcomes of acute toxicity, quality of life, or costs.

Authors' conclusions

It appears that local control rates are increased with the boost to the tumour bed, but we found no evidence of a benefit for other oncological outcomes. Subgroup analysis including women older than 40 years of age yielded similarly significant results. Objective percentage of breast retraction assessment appears similar between groups. It appears that the cosmetic outcome is worse with the boost to the tumour bed, but only when measured by a panel, not when assessed by a physician.

PLAIN LANGUAGE SUMMARY

Tumour bed boost radiotherapy for women after breast-conserving surgery

What is the issue?

Breast cancer is the most common cancer in women worldwide. The two main treatment strategies are either breast-conserving therapy or mastectomy. To decrease the risk of recurrence and improve survival rates, standard care involves adjuvant radiotherapy (treatment with ionising radiation) after breast-conserving surgery. Adjuvant radiotherapy consists mainly of four to five weeks of whole-breast irradiation followed by an extra dose 'boost' to the tumour bed because breast cancer tends to come back in the same area where it was removed. Apart from maintaining the breast and achieving breast cancer control, a satisfying physical appearance (cosmesis) is important in breast-conserving therapy.

Why does it matter?

Guidelines for use of the tumour bed boost are often not clear-cut. Even though it is technically feasible to treat all women with a boost to the tumour bed after whole-breast irradiation, it remains unclear whether this is necessary or whether it may do more harm than good. Possible consequences of adding a boost dose to the tumour bed are poor cosmesis, as well as higher treatment costs and increased treatment times.

We asked whether not giving a tumour bed boost dose after whole-breast irradiation and breast-conserving surgery is as good as giving the boost dose. Omission of a boost to the tumour bed would need to have equivalent cancer control compared with giving a boost to the tumour bed. It would also be important that omission of a boost to the tumour bed results in fewer side effects compared with giving the tumour bed boost dose.

We found 5 studies involving a total of 8325 women. Our evidence is current to 1 March 2017. Local recurrence was less common with a tumour bed boost (low-quality evidence). There was no evidence of a difference in disease-free or overall survival with or without the administration of the tumour bed boost (low- and moderate-quality evidence, respectively). Cosmesis scored by a panel appeared to be worse for the tumour bed boost group (low-quality evidence). There was no difference in physician-scored cosmesis or percentage of breast retraction.

This means that adding a boost to the tumour bed increases the local control rate at a possible cost of worse cosmesis.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Boost compared to no boost in breast cancer radiotherapy

Boost compared to no boost in breast cancer radiotherapy

Patient or population: breast-conserving radiotherapy for breast cancer

Setting: radiotherapy centres

Intervention: boost

Comparison: no boost

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk without boost	Risk with boost				
Local control: recurrence at 5 years	Study population		HR 0.64 (0.55 to 0.75)	8315 (5 RCTs)	⊕⊕⊕⊖ LOW 1 2	Nice did not report 5-year local control.
	70 per 1000	45 per 1000 (39 to 53)				
Overall survival: mortality at 5 years	Study population		HR 1.04 (0.94 to 1.14)	6342 (2 RCTs)	⊕⊕⊕⊖ MODERATE 3	
	91 per 1000	94 per 1000 (86 to 103)				
Disease-free survival: disease progression/mortality at 5 years	Study population		HR 0.94 (0.87 to 1.02)	6549 (3 RCTs)	⊕⊕⊕⊖ LOW 4 5	EORTC did not report 5-year disease-free survival.
	221 per 1000	209 per 1000 (195 to 224)				
Late toxicity, pBRA	Mean pBRA 8.17, range 7.55 to 10	Mean pBRA 8.55, range 8.26 to 9.4	MD 0.38 higher (0.18 lower to 0.93 higher)	1526 (2 RCTs)	⊕⊕⊕⊖ VERY LOW 2 5	
Cosmesis, panel scored: fair or poor	Study population		OR 1.41 (1.07 to 1.85)	1116 (2 RCTs)	⊕⊕⊕⊖ LOW 1 2	
	202 per 1000	263 per 1000 (213 to 319)				
Cosmesis, physician-scored: fair or poor	Study population		OR 1.58 (0.93 to 2.69)	592 (2 RCTs)	⊕⊕⊕⊖ VERY LOW 1 5 6	
	85 per 1000	128 per 1000				

	(80 to 200)				
Sensitivity analysis: local control - recurrence at 5 years	Study population		HR 0.62 (0.52 to 0.73)	6963 (3 RCTs)	⊕⊕⊕⊕ HIGH
	74 per 1000	47 per 1000 (39 to 55)			
Subgroup analysis: local control - > 40 years old, recurrence at 5 years	Study population		HR 0.65 (0.53 to 0.81)	5058 (2 RCTs)	⊕⊕⊕⊕ HIGH
	59 per 1000	39 per 1000 (32 to 48)			

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **OR:** odds ratio; **pBRA:** percentage breast retraction assessment; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

¹High risk of selective reporting in one study.

²There was considerable clinical heterogeneity with respect to radiotherapy dose and the use of quality assurance procedures.

³One of the two studies has a very wide confidence interval.

⁴There was considerable clinical heterogeneity on statistical testing, but not on visual inspection.

⁵Both studies have wide confidence intervals.

⁶High risk of bias for blinding of outcome assessment in one study.

BACKGROUND

Description of the condition

Breast cancer is the most common cancer in women worldwide, with nearly 1.7 million new cases diagnosed in 2012 ([Globocan](#)). It represents about 12% of all new cancer cases in both sexes and 25% of all cancer cases in women ([Globocan](#)). Data from the World Health Organization (WHO) mortality and population database indicate that breast cancer accounted for the largest number of predicted cancer deaths in women in Europe; the estimated age-standardised (world) breast cancer mortality rate was 14.6 per 100,000 women in 2013 ([Malvezzi 2013](#)). As with any cancer, breast cancer can recur locally or at a distant site. Without (neo-)adjuvant therapy, up to 30% of node-negative and up to 70% of node-positive breast cancers in women will recur locally or spread to another organ after surgery ([Darby 2011](#); [EBCTCG 2005](#)).

Several unfavourable risk factors have been reported for local breast cancer recurrence after primary therapy, and predictive tools that can estimate breast cancer risk have been established. Besides nodal status, the reported risk factors are: the omission of radiotherapy/hormonal therapy/chemotherapy, young age, presence of lymphovascular invasion, presence of ductal carcinoma in situ (DCIS) besides invasive tumour, high histologic grade, large tumour diameter, and positive or dubious surgical margins ([Darby 2011](#); [Sanghani 2010](#); [van Werkhoven 2011](#)).

Description of the intervention

Breast-conserving therapy (BCT), involving breast-conserving surgery (BCS) followed by whole-breast irradiation (WBI) and optionally a boost to the tumour bed, is a standard therapeutic option for women with early-stage breast cancer. Randomised controlled trials have shown that local control rates and survival in women with early-stage disease treated with BCT are comparable to treatment with mastectomy ([Fisher 2002](#); [Litière 2012](#)). A boost to the tumour bed means that an extra dose of radiation is applied that covers the initial tumour site where the cancer is most likely to return. The rationale for a boost of radiotherapy to the tumour bed is (i) local recurrence occurs mostly at the site of the primary tumour because remaining microscopic tumour cells are most likely situated there; and (ii) radiation can eliminate these causative microscopic tumour cells.

The main goal of adjuvant radiotherapy (i.e. WBI and an optional boost to the tumour bed) after BCS is to decrease local recurrence and to permit breast conservation with minimal treatment-induced side effects. The necessity of adjuvant radiotherapy has been demonstrated by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). The meta-analysis conducted by the EBCTCG showed a reduction in the 10-year first recurrence rate from 35% to 19.3%, and a breast cancer survival gain of 3.8% at 15 years when adding adjuvant radiotherapy ([Darby 2011](#)).

The standard radiotherapy regimen is to treat the whole breast with a total radiation dose of 40 to 50 Gy with an optional tumour bed boost. The boost continues to be used in women at high risk of local recurrence, but is less widely accepted for women at lower risk. Reasons for questioning the boost are twofold. Firstly, the boost brings higher treatment costs. Secondly, the potential adverse events are not negligible. Short-term side effects of the tumour bed boost include fatigue, breast

oedema, skin erythema and hyperpigmentation, while the long-term risks include fibrosis, scarring of connective tissue, radiation pneumonitis, rib fractures, cardiac toxicity, and radiation-induced second cancers. The National Comprehensive Cancer Network recommends a boost in women at higher risk for recurrence ([NCCN](#)). This can be achieved by external beam radiotherapy with doses of 10 to 16 Gy, or by interstitial brachytherapy. European guidelines advise a boost to the tumour bed in women with at least one of the following risk factors: age up to 50 years, grade 3 tumours, extensive DCIS, vascular invasion, and possibly in cases of non-radical tumour excision ([Senkus 2015](#)).

How the intervention might work

After the initial treatment, a local recurrence can occur where residual microscopic cancerous cells grow back at the original site of the breast cancer. Data state that between 44% and 90% of local recurrences are located in or near the primary tumour bed ([Bartelink 2007](#); [Kuerer 2004](#); [Vaidya 2010](#)), and these numbers correlate well with pathological findings from Holland and colleagues ([Holland 1985](#)). To eliminate residual microscopic cancerous cells, an additional tumour bed boost is advocated ([Bartelink 2015](#); [van Werkhoven 2011](#)).

Ionising radiation is radiation with a high energy whose ionising tracks deposit energy in cells. The total ionising radiation dose, D , is measured in energy per unit mass. Radiation mainly damages chromatin, for example causing DNA double strand breaks (DSBs). An acute dose of 1 Gy makes many thousands of ionisations in the cell's nucleus, of which a small minority quickly induce DSBs. Most DSBs are repaired within the next half hour, and a few are misrepaired. At a typical dose of several Gy, at least one misrepair usually occurs, and this misrepair can be enough to kill the cell at the next cycle of cell division. Irradiation can also form other kinds of lethal lesions, such as lethal point mutations, meaning that the effect is unreparably lethal and not prone to repair or misrepair.

The effect of radiation on tumours is presented in the linear quadratic (LQ) model, which quantifies the effects of both unreparable damage and repairable damage susceptible to misrepair ([Kellerer 1972](#)). The model is based on the concept of a biologically effective dose (BED) that represents the physical dose required for a given effect. $BED = D [1 + d/(\alpha/\beta)] - \gamma T_t/\alpha$ where d is the dose per fraction, α and β are the LQ parameters, $\gamma = \ln(2)/T_{pot}$ and T_{pot} is the potential doubling time, and T_t is the treatment time ([Fowler 1989](#)).

Improved tumour control requires an increased radiation dose within the dose-response range of any residual tumour burden. The effect of radiation on the tumour (based on α/β) in breast tissue is no longer 10 Gy as historically assumed, but around 4.6 Gy ([Hennequin 2013](#); [START 2008](#)). With this in mind, existing dose schedules for local tumour control should be reconsidered by calculating all BEDs of the regimens used in studies in breast cancer.

Why it is important to do this review

With the introduction of the computed tomography (CT) scan and 3D-therapy planning in radiotherapy more than a decade ago, research has focused on optimising treatment techniques. Today, the tumour bed in breast tissue can be irradiated using a whole set of treatment techniques that include conventional radiation, 3D-conformal radiation, intensity-modulated radiation,

intraoperative radiation, or proton irradiation. The radiation oncologist also has a broad choice of fractionation schemes (i.e. delivering the total dose in different numbers or sizes of doses per fraction) - normofractionation (the standard regimen for breast irradiation equals 50 Gy in 25 fractions of 2 Gy, five days a week), hypofractionation (the total dose of radiation is divided into larger doses per fraction), or even single fraction radiotherapy - and a wide range of treatment times.

Even though research has provided a wide variety of treatment options, no consensus has been reached on the necessity of and consequently the indications for the boost to the tumour bed. The absolute size of the benefit of the tumour bed boost is linked to the baseline risk of local recurrence; the highest benefit is recorded in the highest-risk groups (Bartelink 2015). The effect of the boost dose seems to be independent of tumour characteristics such as grade or stage and adjuvant systemic treatment (Bartelink 2015). However, it may be dependent on age and surgical margin status (van Werkhoven 2011).

It is important to clearly determine those women who will benefit from having a boost to the tumour bed. In this review, we attempted to help practitioners weigh the benefit of better local control and survival against an increase in side effects (e.g. fibrosis, scarring of connective tissue), the inconvenience of a longer treatment time, and higher cost.

OBJECTIVES

To assess the effects of tumour bed boost radiotherapy after breast-conserving surgery and whole-breast irradiation for the treatment of breast cancer.

METHODS

Criteria for considering studies for this review

Types of studies

All parallel-group randomised controlled trials comparing the addition and the omission of breast cancer tumour bed boost radiotherapy.

Types of participants

Women with a histological diagnosis of breast cancer for the first time (not recurrent or metastatic disease) with no prior history of malignant disease (other than basal cell carcinoma of the skin).

We only included studies in which women had been treated with BCS. Breast-conserving surgery could include lumpectomy, wide local excision, quadrantectomy or segmental mastectomy with or without axillary dissection, axillary sampling or sentinel node biopsy. Women were not excluded based on age, race, tumour size or histological type.

Types of interventions

All women with BCS (lumpectomy, wide local excision, quadrantectomy or segmental mastectomy) followed by WBI (any standard schedule). We compared women who had received an additional boost to the tumour bed with women who had not received a boost to the tumour bed. The boost could be delivered with external beam radiation (electrons or photons) or with interstitial brachytherapy.

We excluded women who had received intraoperative radiotherapy.

We allowed systemic treatments such as hormones, chemotherapy, or monoclonal antibodies as long as they were applied equally to women in each arm of the trial.

Types of outcome measures

Primary outcomes

1. Local control, defined as the time (from randomisation) until the development of any local recurrence during follow-up (time-to-event outcome). We defined local recurrence as recurrence in the ipsilateral breast (i.e. the breast in which cancer had been diagnosed), the skin and parenchyma.
2. Acute toxicity related to radiotherapy, i.e. any toxic event occurring in the breast, skin, lung, and heart within six months of completion of radiotherapy. We intended for acute toxicity to be classified according to the scales the authors used and, if possible, converted to the score from the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE v4.0).

Secondary outcomes

1. Overall survival, defined as the time from randomisation to death from any cause during follow-up.
2. Disease-free survival, defined as the time from randomisation to relapse (local or distant) during follow-up.
3. Late toxicity related to radiotherapy, i.e. any toxic event occurring more than six months after radiotherapy. We classified these according to the scales the authors used, otherwise considering grade 3 or 4 toxic events according to the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE v4.0). In this review, we extracted data at 5, 10, 15, and 20 years.
4. Cosmesis, scored according to the Harvard scale in four classes: excellent, good, fair, and poor (Harris 1979).
5. Quality of life, to be classified according to validated scales the trial authors used or current scores on the EORTC Quality of Life scale (EORTC QoL).
6. Treatment costs, to be classified according to the scales the trial authors used.

Search methods for identification of studies

Electronic searches

We searched the following databases on 1 March 2017.

- Cochrane Breast Cancer Group's Specialised Register. Details of the search strategies used by the Group for the identification of studies and the procedure used to code references are outlined in the Group's module (www.mrw.interscience.wiley.com/cochrane/clabout/articles/BREASTCA/frame.html). Trials with the keywords 'randomized controlled trial, breast cancer, breast-conserving therapy, radiotherapy and boost' were extracted from the Register and considered for inclusion in the review.
- Cochrane Central Register of Controlled Trials (CENTRAL, Issue 2). See [Appendix 1](#).
- MEDLINE (via OvidSP) (January 1966 to 1 March 2017). See [Appendix 2](#).

- Embase (via Embase.com) (1980 to 1 March 2017). See [Appendix 3](#).
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/Default.aspx) for all prospectively registered and ongoing trials. See [Appendix 4](#).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov/). See [Appendix 5](#).

Searching other resources

Bibliographic searching

We searched reference lists of all included trials and relevant (systematic) reviews to identify other studies.

Conference proceedings

We searched the European Society of Radiotherapy and Oncology Annual Meeting, the St Gallen Oncology Conferences, and the American Society for Radiation Oncology Annual Meeting.

Data collection and analysis

Selection of studies

Two review authors (IK and CW) scanned the title, abstract, and keywords of every record identified by the search. We retrieved the full articles of all studies that potentially met our inclusion criteria according to types of studies, participants, and interventions. Two review authors (IK and CW) assessed these full articles for inclusion, resolving any disagreements by discussion. We recorded excluded trials in the '[Characteristics of excluded studies](#)' table with reasons for their exclusion. We included studies in English, French, German, and Dutch.

Data extraction and management

Two review authors (IK and CW) independently conducted data extraction, resolving any disagreements by discussion. We recorded data on data extraction forms that the same two review authors developed and piloted independently. For those studies with more than one publication, we extracted data from all publications, but considered the final or updated version of each study as the primary reference. We entered data into Review Manager 5 software ([RevMan](#)).

Where possible, we extracted the following information from the included primary studies to data extraction forms.

- Publication details: year of publication, authors.
- Methods: accrual, length of follow-up, trial setting and design, country.
- Participants: inclusion and exclusion criteria, population data (i.e. number of women, age of analysed women, time of diagnosis, tumour stage, receptor status, menstrual status, other adjuvant treatments, surgical margins), withdrawals.
- Interventions: doses, regimen, scheme, length, type of radiotherapy.
- Outcome measures.

We extracted outcome data on local control, overall survival, disease-free survival, late toxicity related to radiotherapy, and cosmesis. No data were available for acute toxicity and costs. [SGW](#) reported results on quality of life for the whole group without specifying whether or not participants had received a tumour bed boost.

For time-to-event outcomes we used the spreadsheet developed by Matthew Sydes ([Tierney 2007](#)). We used calculation methods 3 or 7 to derive $\ln(HR)$ and standard error using hazard ratios (HRs) and confidence intervals or P values and number of events on each arm.

The [Budapest](#) trial reported late toxicity related to radiotherapy according to the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (RTOG/EORTC) late radiation morbidity scheme for skin and subcutaneous tissue: grade 0, 1, 2, 3 ([Table 1](#)) ([Cox 1995](#)). The physician scored fibrosis as none, minimal, moderate, or severe in the [EORTC](#) trial. These were both 4-point scales; the results were dichotomised into 0/1 = none/minimal versus 2/3 = moderate/severe, with occurrence of 2/3 = moderate/severe being counted as 'events'. Breast retraction assessment (BRA) was measured in the [SGW](#) trials and percentage of BRA (pBRA) was measured in [EORTC](#) and [SGW](#) ([Figure 1](#)). The [Lyon](#) trial scored telangiectasia (spider veins) in the tumour bed as (0) absent, (1) a few visible, (2) covered one quadrant of the breast, and (3) obvious telangiectasia over more than one quadrant; we extracted data on 0 versus 1 and 2, counting 1 and 2 as 'events'. [SGW](#) reported on hypopigmentation (loss of skin colour) of the nipple-areolar complex.

Figure 1. Illustration of the breast retraction assessment (BRA) measurements as reported by EORTC. $BRA = \sqrt{(a_1 - b_1)^2 + (a_2 - b_2)^2}$; reference length = $\sqrt{(b_1^2 + b_2^2)}$; percentage breast retraction assessment = $(BRA/\text{reference length}) \times 100$.

Cosmetic results were scored by a 4-grade scale (excellent/good/fair/poor) according to Harris and colleagues (Table 2) (Harris 1979). We extracted data comparing excellent and good versus fair and poor, considering fair and poor as an 'event'. Scores were reported by a panel and by the BCCT.core software in the EORTC and SGW trials. Cosmesis was rated by a physician and by the participant in the Lyon and the SGW trials. Cosmesis was rated by the physician in Budapest.

To facilitate comparison of radiation doses given at different doses per fraction, we converted the radiation doses to the BED according to the following formula $BED = D [1 + d/(\alpha/\beta)] - \gamma T_t/\alpha$ where d is the dose per fraction, α and β are the LQ parameters, $\gamma = \ln(2)/T_{pot}$ and T_{pot} is the potential doubling time, and T_t is the treatment time (Fowler 1989). Values of $\alpha/\beta = 4.6$ Gy, $T_{pot} = 15$ days, and $\alpha = 0.3$ were used.

Assessment of risk of bias in included studies

Two authors (IK and CW) independently assessed the risk of bias of the included studies. Objective outcomes were local control, overall survival, disease-free survival, cosmesis score by the BCCT.core software, pBRA, and treatment costs. Subjective outcomes were acute toxicity, late toxicity, cosmesis scored by the participant, a panel, or the physician, and quality of life. We used Cochrane's 'Risk

of bias' tool, which contains domain-based judgements (Higgins 2011). A judgement of 'low risk' indicated a low risk of bias, 'high risk' indicated a high risk of bias, and 'unclear' indicated an uncertain risk of bias, according to the specific criteria for each domain. These domains were as follows.

- Sequence generation: was the allocation sequence adequately generated? We rated this domain as 'low risk' if the investigators described a random component in the sequence generation process such as: referring to a random-number table, using a computer random-number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots, or minimisation.
- Allocation concealment: was allocation adequately concealed? We rated this domain as 'low risk' if participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal the allocation: central allocation or sequentially numbered, opaque, sealed envelopes.
- Blinding of participants and personnel, and outcome assessors: was knowledge of the allocated interventions adequately prevented during the study? We rated this domain as 'low risk' if there was no blinding or incomplete blinding, but the review authors judged that the outcome was not likely to be influenced by the lack of blinding; or if blinding of participants, key study

personnel, and outcome assessment was ensured, and it was unlikely that the blinding could have been broken.

- Incomplete outcome data: were outcome data adequately assessed and accounted for? We rated this domain as 'low risk' if there were no missing outcome data; if the reasons for missing outcome data were unlikely to be related to the true outcome; if missing outcome data were balanced in numbers across intervention groups with similar reasons for missing data across groups; if for dichotomous data, the proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; if for continuous outcome data, the plausible effect size among missing outcomes was not enough to have a clinically relevant impact on the observed effect size; or if missing data were imputed using appropriate methods.
- Selective outcome reporting: were reports of the study free of the suggestion of selective outcome reporting? We rated this domain as 'low risk' if the study protocol was available and all of the study's prespecified outcomes that were of interest in the review were reported in the prespecified way; or when the study protocol was not available, if it was clear that the published reports included all expected outcomes, including those that were prespecified.
- Other potential threats to validity: was the study apparently free of other problems that could put it at risk of bias? We rated this domain as 'low risk' if the study appeared to be free of other sources of bias.

Measures of treatment effect

We presented dichotomous outcomes (two distinct possible outcomes, i.e. acute and late toxicity, cosmetic assessments) as odds ratios (ORs) with 95% confidence intervals (CIs). An OR equal to 1 indicated no difference in the incidence between the experimental group and the control group; an OR greater than 1 indicated that the incidence in the experimental group was higher than in the control group; and an OR less than 1 indicated that the incidence in the experimental group was lower than in the control group.

We summarised continuous outcomes (i.e. pBRA) using the mean difference (MD) with 95% CI. An MD greater than 0 indicated that the level in the experimental group was higher than in the control group; an MD less than 0 indicated that the level in the experimental group was lower than in the control group.

We expressed time-to-event outcomes (i.e. local recurrence, overall survival, disease-free survival) as hazard ratios (HRs) with 95% CIs. If we could not obtain the HR and associated variances directly from the trial publication or from the authors, we obtained these data indirectly using the methods described by Parmar and colleagues by employing the other available summary statistics or data extracted from published Kaplan-Meier curves (Parmar 1998).

Unit of analysis issues

The unit of analysis was the individual participant.

Dealing with missing data

Missing trial-level information

In the case of missing or unavailable trial-level information, as specified under [Data extraction and management](#) we contacted trial authors by email with a request for this information.

Missing participant-level data in published studies

No study reported results based on an inappropriate analysis set (e.g. per protocol where there is a difference in protocol violations between both treatment groups).

Assessment of heterogeneity

We used the I^2 statistic to assess the percentage of total variation across studies due to heterogeneity rather than chance, considering a value greater than 50% to indicate substantial heterogeneity (Higgins 2011). We also performed visual inspection of the forest plots. Where we identified significant heterogeneity, we explored the reasons for it and made a cautious attempt to explain heterogeneity.

Assessment of reporting biases

The reporting biases included publication, time-lag, multiple publication, location, citation, and language biases. We contacted trial authors regarding the reasons for the non-reporting of data for some outcomes.

Data synthesis

We performed meta-analyses based on summary information from published papers for all outcome variables for which at least two studies provided comparable data. We used the fixed-effect model for all outcome types because the number of trials was always fewer than 10.

We used the Mantel-Haenszel method to calculate pooled results for binary outcomes, and the inverse variance method for continuous outcomes. We used the generic inverse-variance method for time-to-event data (DerSimonian 1986).

We conducted meta-analyses using Review Manager 5 software (RevMan). We summarised the quality of the evidence for local control, overall survival, and disease-free survival at five years as well as late toxicity and cosmesis using the GRADE approach and developing a 'Summary of findings' table.

To calculate the absolute risk for the control group for time-to-event outcomes, we obtained the event rate at five years from reported event rates. We entered these estimated values in GRADEpro (GRADEpro), which automatically calculated the corresponding absolute risks for the intervention group at five years.

Subgroup analysis and investigation of heterogeneity

To correct for differences in dosage per fraction and overall treatment time, we used the BED to compare different radiation fractionation schemes.

EORTC, Nice, and SGW only included women with negative surgical margins. Data were insufficient to perform subgroup analysis according to the margin status. We performed a subgroup analysis for women older than 40 years of age.

Sensitivity analysis

We performed sensitivity analyses on the different levels of risk of bias. We performed the analysis both with and without trials at high risk of bias in order to assess the effect of risk of bias on the results.

RESULTS

Description of studies

See: [Characteristics of included studies](#) table.

Results of the search

We identified and screened 5276 references from the major medical databases and 7 additional references from other sources. After exclusion of duplicates and screening of references (by title or abstract), we evaluated 37 full-text references and excluded two references (relating to the one study) because the study design was not randomised controlled trial (see [Characteristics of excluded studies](#) table). We considered one study as ongoing ([ChiCTR-17010342](#)). The remaining 34 references related to five studies ([Budapest](#): 2 records; [EORTC](#): 22 records; [Lyon](#): 1 record; [Nice](#): 1 record; [SGW](#): 8 records) (see [Figure 2](#)). No studies were awaiting classification.

Figure 2. Study flow diagram.

Included studies

Design

Five studies randomised 8325 women ([Budapest](#); [EORTC](#); [Lyon](#); [Nice](#); [SGW](#)). These studies enrolled women from August 1995 to October 1998 ([Budapest](#)), May 1989 to June 1996 ([EORTC](#)), January 1986 to June 1992 ([Lyon](#)), 1987 to 1994 ([Nice](#)), and accrual was started in September 1996 without reporting an end date ([SGW](#)).

Sample size

[Budapest](#) enrolled 627 women; [EORTC](#) enrolled 5569 participants, of whom 5318 were randomised between a boost and no boost; [Lyon](#) enrolled 1028 participants; [Nice](#) enrolled 664 participants; and [SGW](#) enrolled 688 participants.

Setting

The [Budapest](#) and [Nice](#) trials were single-centre trials. The [Lyon](#) and [SGW](#) were conducted in centres in France and Australia, respectively. The [EORTC](#) trial was a multicentre trial in nine countries.

Participants

[Budapest](#) included women with stage I-II breast cancer excluding bilateral cases. [EORTC](#) enrolled 5569 patients with stage I or II (T1-2, N0-1, M0) invasive breast cancer who were younger than 70 years old. All patients in whom the tumour excision was microscopically complete according to the local pathologist (n = 5318) were randomised to either a boost and no boost to the tumour bed. Patients were excluded if they had pure carcinoma in situ. [Lyon](#) included women with invasive ductal carcinoma ≤ 3 cm and "free" pathological margins (absence of detectable cancer cells at the inked margin) and who were younger than 70 years old. [SGW](#) included women with T in situ, T1, T2 N0-3 breast cancer. [Nice](#) included patients with invasive breast cancer treated with axillary dissection.

Interventions

Experimental arm

Whole-breast irradiation:

- 50 Gy in 25 fractions in 5 weeks ([Budapest](#); [EORTC](#); [Nice](#))
- 50 Gy in 20 fractions in 5 weeks ([Lyon](#))
- 45 Gy in 25 fractions in 5 weeks ([SGW](#))

plus boost irradiation:

- 16 Gy external beam ([Budapest](#); [EORTC](#); [SGW](#))
- high-dose-rate brachytherapy 12 to 14.25 ([Budapest](#))
- 15 Gy by means of an iridium-192 implant at a dose rate of 0.5 Gy per hour ([EORTC](#))
- 10 Gy in 4 fractions in 1 week ([Lyon](#))
- 10 Gy in 5 fractions in 1 week ([Nice](#))

The BEDs for the experimental arm were 87.8 Gy in [Budapest](#) and [EORTC](#), 86.4 Gy in [Lyon](#), 79.9 Gy in [Nice](#), and 78.6 Gy in [SGW](#).

Control arm

Whole-breast irradiation:

- 50 Gy in 25 fractions in 5 weeks ([Budapest](#); [EORTC](#); [Nice](#); [SGW](#))
- 50 Gy in 20 fractions in 5 weeks ([Lyon](#))

The BEDs for the control arm were 66.7 Gy in [Budapest](#), [EORTC](#), [Nice](#), and [SGW](#), and 72.1 Gy in [Lyon](#).

Co-interventions

[Budapest](#) only provided detailed population information on the first 207 patients with at least 3 years of follow-up: 18% received hormonal therapy alone, 18% chemotherapy alone, and 6% hormonal therapy and chemotherapy. There were no significant differences between the boost and no boost group. In [EORTC](#), participants with axillary lymph node involvement received adjuvant systemic therapy (7%): premenopausal women received chemotherapy (38%) and postmenopausal women received tamoxifen (62%). In [Lyon](#), chemotherapy was administered in 22% of women and endocrine therapy in 30%. Premenopausal women with positive lymph nodes received adjuvant chemotherapy. For postmenopausal women, tamoxifen was always started in node-positive women and sometimes in node-negative women. In [SGW](#), 20% of women received chemotherapy and 39% received endocrine therapy. [Nice](#) did not report numbers on systemic therapy.

Outcomes

Primary outcomes

1. All five studies reported local control.
2. No study reported on acute toxicity related to radiotherapy.

Secondary outcomes

1. Two studies reported overall survival ([EORTC](#); [Lyon](#)).
2. Three studies reported disease-free survival ([Budapest](#); [EORTC](#); [Lyon](#)).
3. Four studies reported on late toxicity related to radiotherapy. [Budapest](#) described grade 2 to 3 side effects of skin and subcutaneous tissues. [EORTC](#) reported the grade of fibrosis as scored by the physician (none, minimal, moderate, severe) and the pBRA. [Lyon](#) scored telangiectasias as 0, 1, 2, or 3 and reported the scores for 0 versus 1 or 2. [SGW](#) reported the BRA, pBRA, and nipple-areolar complex hypopigmentation.
4. Cosmesis was rated by a physician in three studies ([Budapest](#); [Lyon](#); [SGW](#)). Participant scoring was reported in [Lyon](#) and [SGW](#). A panel of physicians scored cosmesis in [EORTC](#) and [SGW](#). [EORTC](#) and [SGW](#) evaluated cosmesis with the BCCT.core software.
5. [SGW](#) reported on quality of life, without analysis for boost versus no boost.
6. None of the studies reported treatment costs.

Excluded studies

We excluded two reports based on full-text analysis (see [Characteristics of excluded studies](#)).

Risk of bias in included studies

Refer to [Figure 3](#).

Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): Objective outcomes	Blinding of participants and personnel (performance bias): Subjective outcomes	Blinding of outcome assessment (detection bias): Objective outcomes	Blinding of outcome assessment (detection bias): Subjective outcomes	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Budapest	+	?	+	+	+	-	+	?	?
EORTC	+	+	+	+	+	?	+	+	+
Lyon	?	?	+	+	+	-	+	?	+
Nice	?	?	+	+	-	-	?	-	?
SGW	?	?	+	+	+	?	+	-	+

Allocation

We judged [Budapest](#) and [EORTC](#) to be at low risk of bias for sequence generation. [Lyon](#), [Nice](#), and [SGW](#) did not clearly report random sequence generation or allocation concealment and so were assessed as at unclear risk of bias. We considered allocation concealment as low risk for [EORTC](#). Allocation concealment appears to have been done in [Budapest](#), although the description was incomplete, which contributed to the judgement of unclear risk of bias.

Blinding

Objective outcomes

We judged blinding of participants and personnel and blinding of outcome assessment for objective outcomes as at low risk of bias in [Budapest](#), [EORTC](#), [Lyon](#), and [SGW](#). No study mentioned blinding of participants, which would have been difficult to do with this intervention, but the lack of blinding was unlikely to have introduced bias. The trials also did not mention blinding of physicians. This would have been difficult to do with the intervention, but we considered failure to do so less likely to have introduced bias because the follow-up (including mammographic screening) interval was prespecified in all four studies. No information on follow-up was provided in [Nice](#), so we judged assessed this domain as at high risk of bias.

Subjective outcomes

We judged blinding of participants and personnel for subjective outcomes as at low risk of bias in [Budapest](#), [EORTC](#), [Lyon](#), [Nice](#), and [SGW](#).

Colour-printed photographs were taken at predefined time points in [EORTC](#), and an external review panel scored the cosmetic result. Based on the use of a grading scale and the blinding of assessors, we judged this domain as at low risk of bias. However, since the physician was not blinded to the treatment arm to score fibrosis, we judged this domain as at unclear risk of bias. The clinical oncologist assessed subjective outcomes at follow-up in [Lyon](#) and [Budapest](#); because there was no blinding we judged these studies as at high risk of bias. No information on the blinding of assessors was provided for [SGW](#), therefore we judged this domain as at unclear risk of bias. No information on subjective outcomes was provided in the abstract of the [Nice](#) study, so we judged this domain as at high risk of bias.

Incomplete outcome data

In [Budapest](#), two participants were excluded with reasons and no attrition was reported. In [Lyon](#), two participants with bilateral breast cancer were excluded; there was no postrandomisation attrition. Because postrandomisation exclusions were detailed

with reasons, we deemed these studies to be at low risk of bias. In [EORTC](#) and [SGW](#), no exclusion or attrition was reported, so we judged this domain as at low risk of bias. No information was provided in the abstract of the [Nice](#) study, so we judged this domain as at unclear risk of bias.

Selective reporting

We did not have access to the study protocols for [Budapest](#) and [Lyon](#), therefore we judged this domain as at unclear risk of bias. All prespecified endpoints in the protocol were reported in the results of [EORTC](#), so we judged this domain as at low risk of bias. The results on local control in [Nice](#) were only available in an abstract, and results for [SGW](#) were briefly described in [Millar 2009](#) and [Graham 2007](#). Since no protocol was available and no further results on local recurrence have been reported, we judged this domain as at high risk of bias.

Other potential sources of bias

[EORTC](#), [Lyon](#), [Nice](#), and [SGW](#) were at low risk of bias for other potential sources of bias. Because [Budapest](#) and [Nice](#) were interim reports, we judged them as at unclear risk of bias for this domain.

Effects of interventions

See: [Summary of findings for the main comparison Boost compared to no boost in breast cancer radiotherapy](#)

See: [Summary of findings for the main comparison.](#)

Primary outcomes

Local control

There were 737 local recurrences in the 8315 women studied in five studies.

Local control appeared to be better with the administration of a tumour bed boost (HR 0.64, 95% CI 0.55 to 0.75; $P < 0.00001$; 5 studies, 8315 women, low-quality evidence, [Analysis 1.1](#); [Figure 4](#)). There was evidence of heterogeneity on visual inspection and statistical testing ($I^2 = 60\%$). We performed a sensitivity analysis based on excluding [Nice](#) and [SGW](#) because BED to the tumour bed was lower compared to the other three studies (79.9 Gy and 78.6 Gy, respectively compared to 86.4 Gy to 87.8 Gy); there was a high risk of selective reporting bias and blinding of outcome assessment bias for [Nice](#); and in situ tumours were included in [SGW](#). We found that a tumour bed boost versus no tumour bed boost was associated with significantly better local control (HR 0.62, 95% CI 0.52 to 0.73; $P < 0.00001$; 3 studies, 6963 women, high-quality evidence; [Analysis 1.2](#)). There was no evidence of heterogeneity on visual inspection and statistical testing ($I^2 = 24\%$).

Figure 4. Forest plot of comparison: 1 Tumour bed boost radiotherapy versus no boost, outcome: 1.1 Local control.

We performed subgroup analysis including only women older than 40 years of age. Local control appeared to be better with the administration of a tumour bed boost in the subgroup analysis (HR 0.65, 95% CI 0.53 to 0.81; $P < 0.0001$; 2 studies, 5058 women, high-quality evidence; [Analysis 1.3](#)). There was no heterogeneity on either visual inspection or statistical testing ($I^2 = 10\%$).

Acute toxicity

There were no data on acute toxicity.

Secondary outcomes

Overall survival

We found no difference in overall survival with or without a boost to the tumour bed with data from 1683 deaths in two studies with 6342 women (HR 1.04, 95% CI 0.94 to 1.14; $P = 0.44$; moderate-quality evidence; [Analysis 1.5](#); [Figure 5](#)). There was no heterogeneity on either visual inspection or statistical testing ($I^2 = 44\%$).

Figure 5. Forest plot of comparison: 1 Tumour bed boost radiotherapy versus no boost, outcome: 1.5 Overall survival.

Disease-free survival

We found no difference in disease-free survival with or without a boost to the tumour bed with data from 2810 events in three studies with 6549 women (HR 0.94, 95% CI 0.87 to 1.02; $P = 0.12$; low-quality evidence; [Analysis 1.6](#)). There was no evidence of heterogeneity on visual inspection, but there was on statistical testing ($I^2 = 77\%$). For sensitivity analysis, no studies were at high risk of bias for the domains of objective outcomes and other bias.

Late toxicity

We found no difference in pBRA with or without a boost to the tumour bed with data from 1526 women in two studies (MD 0.38,

95% CI -0.18 to 0.93; $P = 0.18$; very low-quality evidence; [Analysis 1.7](#)). There was evidence of heterogeneity on visual inspection and statistical testing ($I^2 = 75\%$).

Cosmesis

Panel-scored cosmesis appeared to be better without the administration of a boost to the tumour bed with data from 229 women with fair or poor scoring in two studies involving 1116 women (OR 1.41, 95% CI 1.07 to 1.86; $P = 0.01$; low-quality evidence; [Analysis 1.8](#); [Figure 6](#)). There was evidence of heterogeneity on visual inspection and statistical testing ($I^2 = 96\%$).

Figure 6. Forest plot of comparison: 1 Tumour bed boost radiotherapy versus no boost, outcome: 1.8 Cosmesis, Panel.

Treating physician-scored cosmesis did not differ significantly between boost and no-boost groups, however the confidence interval was very wide (OR 1.58, 95% CI 0.93 to 2.69; $P = 0.09$; 2 studies, 592 women; very low-quality evidence; [Analysis 1.9](#)). There was no evidence of heterogeneity on visual inspection and statistical testing ($I^2 = 0\%$).

There were no data per subgroup in the [Lyon](#) study, so a meta-analysis was not possible.

Quality of life

There were no data on quality of life.

Treatment costs

There were no data on treatment costs.

DISCUSSION

Summary of main results

Local control appeared to be better with a tumour bed boost than without. We found no evidence of a difference in overall survival or disease-free survival with or without a tumour bed boost. Percentage of breast retraction assessment did not appear affected with a boost to the tumour bed. Panel-scored cosmesis was significantly better (i.e. good or excellent) if no boost was administered. Physician-scored cosmesis did not differ significantly between groups.

We found no data for the effects of the boost to the tumour bed on acute toxicity, quality of life, and treatment costs.

Based on these findings, the tumour bed boost appears to be associated with a better local control. Local recurrence was decreased by 25 per 1000 women (range 17 to 41 per 1000) at 5 years.

Overall completeness and applicability of evidence

Overall, the validity of our results was high due to the high number of analysed women and the comprehensive search strategy. However, there were some limitations in completeness and applicability of evidence due to clinical heterogeneity between the studies, duration of follow-up, and little or no useful information available for some outcome measures.

Clinical heterogeneity between the trials

There was evident clinical heterogeneity in both the study participants and the interventions as follows.

- The radiotherapy dose varied between trials. The tumour bed boost dose was lower in [SGW](#) (78.6 Gy) and [Nice](#) (79.9 Gy) compared to the other three studies (86.4 Gy to 87.8 Gy). We conducted the sensitivity analysis for local control excluding these two studies.
- The radiotherapy boost technique differed, but there was no evidence of a difference in local control related to the boost technique ([Verhoeven 2015](#)).
- The techniques used to define the target volume differed. In [EORTC](#), the placement of a clip in the booster area was advised and a margin of 1.5 cm to 3 cm was taken as clinical target volume. In [Budapest](#), the walls of the excision cavity were marked with four to six titanium clips and a 1- to 1.5-centimetre margin was used to define the clinical target volume. No information was provided on target volume delineation in [Lyon](#), [Nice](#), and [SGW](#). The lack of a definition for target delineation and the omission of robust quality assurance meant that the radiotherapy in some of the studies was not reproducible. We thus cannot be certain of the dose delivered and the irradiated volume.
- In [SGW](#), 59 out of 688 women had an in situ carcinoma. The other four studies included only women with an invasive breast carcinoma.
- [EORTC](#) included the largest patient population and contributed over 79% of the weight in the meta-analysis for local control, overall survival, and disease-free survival.

Duration of follow-up

The median length of follow-up differed among all five studies: 60 months in [Budapest](#), 17.2 years in [EORTC](#), 73 months in [Nice](#), 3.3 years in [Lyon](#), and 6 years in [SGW](#). A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group confirmed the relationship between tumour control and overall survival. By adding radiotherapy to breast-conserving surgery, the 10-year any first-recurrence rate decreased from 35.0% to 19.3%, and breast cancer survival gains were 3.8% at 15 years. In other words, the prevention of four recurrences at 10 years avoids one breast cancer death at 15 years ([Darby 2011](#)). Since four out of the five studies included in this review reported a median follow-up of less than seven years, the effect on survival might still become apparent with longer follow-up in the future.

Little or no useful information available for some outcome measures

The [Budapest](#) study states that recurrence rates were compared for women younger than 40 years of age, but no P value is provided. In the [EORTC](#) study, cosmesis is measured using the BCCT.core

software, however no general cosmetic score was provided, so a comparison or meta-analysis with other studies was impossible. [SGW](#) reported quality of life data for the whole group of analysed women and did not provide a subgroup analysis for the boost versus no-boost group.

There was heterogeneity for the outcome of local control. We performed a sensitivity analysis excluding [Nice](#) and [SGW](#) because we judged selective reporting or blinding of outcome assessment, or both, as at high risk of bias. We made this assessment because the dose to the tumour bed was significantly lower compared to the other trials and because in situ carcinomas were included in the data set ([SGW](#)). In the meta-analysis for pBRA and for the panel-scored cosmesis, there was heterogeneity attributed to the lower dose to the tumour bed in [SGW](#), however there were no signs of heterogeneity in physician-scored cosmesis. As only two studies were included in the meta-analyses, we could not conduct a sensitivity analysis.

Treatment era

The five studies recruited women two decades ago, and treatment approaches have changed over time. The use of systemic therapy, especially hormonal therapy, in the included studies was low. Also, overall recurrence rates have decreased over time. This treatment era effect is not only based on the increased use of systemic therapy, but also on improvements in preoperative breast imaging and postoperative delineation of the lumpectomy cavity and greater attention to the obtainment of negative surgical margins ([Canavan 2014](#); [van Laar 2013](#)). Absolute numbers and effects of the tumour bed boost might thus be lower in the current population.

Quality of the evidence

The available evidence does allow for the drawing of conclusions with respect to the objective of the review: to assess the effects of tumour bed boost radiotherapy after breast-conserving surgery and whole-breast irradiation for the treatment of breast cancer. We found five studies with 8325 women.

Local recurrence

We downgraded for risk of bias because there was a high risk of bias for selective reporting in two studies. Regarding inconsistency ($I^2 = 60\%$), there was considerable clinical heterogeneity with respect to radiotherapy dose and the use of quality assurance procedures, so we downgraded the quality of the evidence. We did not downgrade for indirectness or imprecision. Given our systematic literature search, we did not downgrade for publication bias. The overall GRADE quality of evidence for this outcome was low.

The sensitivity analysis for local recurrence excluded two studies. We did not downgrade for risk of bias, indirectness, inconsistency, imprecision, or publication bias. The overall GRADE quality of evidence for this outcome was high.

We did not downgrade the quality of the evidence for the subgroup analysis for local recurrence in women at least 40 years old based on risk of bias, indirectness, inconsistency, imprecision, or publication bias. The overall GRADE quality of evidence for this outcome was high.

Overall survival

We did not downgrade for risk of bias, inconsistency, indirectness, or publication bias. We downgraded for imprecision because one of the two included studies had a very wide confidence interval. The overall GRADE quality of evidence for this outcome was moderate.

Disease-free survival

Only two out of the five studies reported five-year disease-free survival. We did not downgrade for risk of bias, indirectness, or publication bias. We downgraded for inconsistency due to statistical heterogeneity. We downgraded for imprecision because both included studies had a very wide confidence interval. The overall GRADE quality of evidence for this outcome was low.

pBRA

We downgraded for risk of bias because here was a high risk of bias for selective reporting in one study. Regarding inconsistency ($I^2 = 75\%$), there was considerable clinical heterogeneity with respect to radiotherapy dose and the use of quality assurance procedures, so we downgraded the quality of the evidence. We downgraded for imprecision because both included studies had a very wide confidence interval. The overall GRADE quality of evidence for this outcome was very low.

Panel-scored cosmesis

We downgraded for risk of bias because there was a high risk of bias for selective reporting in one study. Regarding inconsistency ($I^2 = 96\%$), there was considerable clinical heterogeneity with respect to radiotherapy dose and the use of quality assurance procedures, so we downgraded the quality of the evidence. We did not downgrade for indirectness, imprecision, or publication bias. The overall GRADE quality of evidence for this outcome was low.

Physician-scored cosmesis

We downgraded by two points for risk of bias because there was a high risk of bias for selective reporting in one study and a high risk of bias for blinding of outcome assessment in the other study. We downgraded for imprecision because both included studies had a very wide confidence interval. We did not downgrade for indirectness, inconsistency, or publication bias. The overall GRADE quality of evidence for this outcome was very low.

Potential biases in the review process

We believe we have identified all relevant, completed randomised controlled trials. Follow-up was relatively short for survival analysis in all but one study. This may improve in future updates, as more information with respect to these outcomes is reported.

Agreements and disagreements with other studies or reviews

We found one systematic review with a meta-analysis examining the role of boost irradiation in the conservative treatment of stage I-II breast cancer ([Polgár 2001](#)). The authors reported crude local recurrence rates of 6.7% versus 3.9% when adding a boost to the tumour bed ($P < 0.0001$). Five studies were analysed. Besides the [Budapest](#), [EORTC](#), [Lyon](#), and [Nice](#) trials, [Polgár 2001](#) reported data from an abstract presentation by Nagykalnai on the 2nd European Congress on Senology in 1994, but to the best of our knowledge these data are no longer available, and apparently the number of

participants was low and no statistical analysis was performed. Polgár 2001 did not include the SGW trial in their review. As in our meta-analysis, the review by Polgár justifies the use of the tumour bed boost after whole-breast irradiation. They also conclude that young age (< 50 years), positive or close surgical margins, and extensive intraductal component should be viewed as absolute indications for boost irradiation. A review by Bahadur reports that the significant effect on local control applies to all age groups, but that cosmetic results proved to be worse with the tumour bed boost and should be taken into consideration (Bahadur 2012). European Society for Medical Oncology guidelines report a 50% any-recurrence risk reduction with boost irradiation, which they indicate for patients who have unfavourable risk factors for local control such as age less than 50 years, grade 3 tumours, extensive ductal carcinoma in situ, vascular invasion, or non-radical tumour excision (focally, otherwise further surgery should be advocated) (Senkus 2015). NCCN guidelines advise the consideration of a tumour bed boost in the case of high risk of recurrence (such as age less than 50 years, high-grade disease, or focally positive margins) (NCCN).

AUTHORS' CONCLUSIONS

Implications for practice

It appears that local recurrence rates are decreased with the addition of a boost to the tumour bed in all women and in those at least 40 years old. We found no effect on overall survival or disease-free survival. Cosmetic outcomes might be worse with the boost, at least when scored by a panel. However, we found no difference in percentage of breast retraction assessment or in physician-scored cosmesis.

For treatment elaboration, a patient-tailored approach is suggested in which the benefit on local recurrence is balanced against the risk of inferior cosmetic outcome and higher treatment costs. We were unable to define with the currently available data any subgroups

to guide an individualised approach. To help the decision-making for each individual patient, nomograms can be used. A nomogram was developed based on the EORTC study to predict the 10-year risk of local recurrence and fibrosis (Collette 2008; van Werkhoven 2011). However, clinicians should use care in the implementation and interpretation of nomogram results when the nomogram is not externally validated, especially for patients not comparable to those on which the nomogram was based. Validation of the EORTC nomogram for local recurrence, such as in the University Hospitals of Leuven, demonstrated suboptimal discrimination (concordance probability estimate 0.54) and calibration, with an overestimation of the local recurrence risk in general (Kindts 2016).

Implications for research

Given that the Early Breast Cancer Trialists' Collaborative Group confirmed the relationship between tumour control and overall survival, the effect on overall survival in the included studies might still become apparent with longer follow-up in the future. Effects on breast cancer survival related to local control require long follow-up (Darby 2011), so survival data from all of the included studies but EORTC should be interpreted with care. Long-term follow-up of the included studies is needed to permit identification of any long-term oncologic outcomes as well as toxicity. Besides reporting longer follow-up, future research should also focus on developing and testing nomograms to predict the local recurrence rate and risk of side effects. Only when accurate rates are available can the absolute benefit or harm of the tumour bed boost be calculated and a solid assessment made on the indication of the tumour bed boost.

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EORTC {published data only}

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The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Budapest

Methods

Accrual: 1995 to 1998

Sanghani 2010

Sanghani M, Truong PT, Raad RA, Niemierko A, Lesperance M, Olivotto IA, et al. Validation of a web-based predictive nomogram for ipsilateral breast tumor recurrence after breast conserving therapy. *Journal of Clinical Oncology* 2010;**28**(5):718-22.

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Verhoeven K, Kindts I, Laenen A, Peeters S, Janssen H, Van Limbergen E, et al. A comparison of three different radiotherapy boost techniques after breast conserving therapy for breast cancer. *Breast* 2015;**24**(4):391-6.

Budapest (Continued)

Single-centre
Phase III RCT
Budapest, Hungary
Median follow-up: 60 months

Participants	<ul style="list-style-type: none"> 627 women with stage I-II breast cancer. Age from first 207 patients with at least 3 years' follow-up: 54 (range 34 to 79). Stage for first 207 patients with at least 3 years' follow-up: T1 61%, T2 39%, N0 76%, N1 24%. Surgical margins of first 207 patients with at least 3 years' follow-up: positive 8%. Notable exclusion criteria: bilateral breast cancer. Receptor status from the first 207 patients with at least 3 years' follow-up: ER+ 54%, ER- 38%, ER unknown 8%. Menstrual status: not reported. Other adjuvant treatments: from the first 207 patients with at least 3 years' follow-up: 18% received hormonal therapy alone, 18% chemotherapy alone, and 6% hormonal therapy and chemotherapy. No significant differences between boost and no-boost groups.
Interventions	<p>ARM 1: Intervention details (n = 307): WBI 50 Gy in 25 fractions in 5 weeks + 16-gray boost (n = 238) or 12- to 14.25-gray HDR-BT boost (n = 65). BED = 87.8 Gy.</p> <p>ARM 2: Comparator details (n = 320): WBI 50 Gy in 25 fractions in 5 weeks. BED = 66.7 Gy.</p>
Outcomes	<p>Primary outcomes</p> <ol style="list-style-type: none"> Local control. Relapse-free survival. <p>Secondary outcomes</p> <ol style="list-style-type: none"> Cancer-specific survival. Late side effects of skin and subcutaneous tissues scored by the RTOG/EORTC late radiation morbidity scheme. Cosmetic results, scored on a 4-grade scale (excellent, good, fair, poor), as suggested by Perez and colleagues (Perez 1996).
Notes	<ul style="list-style-type: none"> Boost technique was based on the treating radiation oncologist's preference. Brachytherapy implants were performed 3 weeks after WBI. For the first 207 patients with at least 3 years' follow-up: the HDR fractionation schedules were calculated using the Linear Quadratic model with an alpha/beta ratio of 4 Gy for late and 10 Gy for early effects. For the first 19 patients, the total boost dose was calculated to be equivalent to late effects of 20 Gy Low-dose-rate. Since serious side effects were not observed, the total boost dose was increased for the next 33 patients to be equivalent to the early side effects of 20 Gy LDR. So the prescribed HDR doses (calculated to 100% isodose surface) consisted of 3 fractions of 4 Gy (n = 19) and 4.75 Gy (n = 33) over 3 days for a total boost dose of 12 Gy and 14.25 Gy, respectively. For women with pN0 or pN1a, regional nodal irradiation was omitted. All others received RNI by an anterior supraclavicular/axillary field.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "Randomization was done by the study coordinator (S.P.)" and "patients were randomly allocated to treatment options by a sealed-envelope system in blocks of 20". Budapest 2002, page 616, paragraph 2.

Budapest (Continued)

Allocation concealment (selection bias)	Unclear risk	<p>Quote "patients were randomly allocated to treatment options by a sealed-envelope system in blocks of 20". Budapest 2002, page 616, paragraph 2.</p> <p>Allocation concealment appears to have been done, although the description was incomplete, which contributed to the judgement of unclear risk of bias.</p>
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	<p>Participants and personnel: not mentioned, unlikely to have been done.</p> <p>We judged this domain as at low risk of bias.</p>
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	<p>Participants and personnel: not mentioned, unlikely to have been done.</p> <p>We judged this domain as at low risk of bias.</p>
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	<p>Participants: not mentioned, unlikely to have been done.</p> <p>Personnel: not done, but in view of prespecified protocol of follow-up with regular mammography, unlikely to have introduced bias.</p> <p>Quote "Patients were seen every 3 months in the first 2 years after RT, and every 6 months thereafter. Mammography, chest X-ray, breast and abdominal ultrasound examinations, bone scan, and blood tests were performed at least annually. Local recurrence was defined ... proven by histological examination." Budapest 2002, page 618, paragraph 4.</p> <p>Unlikely to be a source of bias in view of the prespecified schedule for follow-up visits and investigations. Local recurrence required biopsy information, which would reduce the risk of bias in evaluation of this outcome.</p>
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	<p>Quote "Secondary endpoints were ... late side effects of skin and subcutaneous tissues scored by the RTOG/EORTC late radiation morbidity scheme, and cosmetic results scored by a 4-grade scale (excellent/good/fair/poor), as suggested by Perez et al." Budapest 2002, page 616, paragraph 4. Outcomes were measured by the treating physician.</p> <p>Because the assessment of subjective outcomes was not blinded, we judged this domain as at high risk of bias.</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Exclusions: 2 (ineligibility: early distant metastasis).</p> <p>Quote "One patient refused boost irradiation, but was analysed according to the assigned treatment group." Budapest 2002, page 616, paragraph 4.</p> <p>Postrandomisation exclusions are detailed without information on treatment arm, but with reasons. We deemed this outcome as at low risk of bias.</p>
Selective reporting (reporting bias)	Unclear risk	<p>Outcomes in methods section:</p> <p>Primary: ipsilateral breast tumour recurrence; occurrence of local, regional, or distant relapse (whichever came first) for relapse-free survival.</p> <p>Secondary: death from breast cancer, late side effects of skin and subcutaneous tissues scored by the RTOG/EORTC late radiation morbidity scheme, and cosmetic results scored on a 4-grade scale (excellent/good/fair/poor), as suggested by Perez and colleagues (Perez 1996).</p> <p>Outcomes reported in paper:</p> <ol style="list-style-type: none"> 1. Ipsilateral breast tumour recurrence, location of recurrence, local recurrence as first event, (mean time to) isolated local recurrence followed by subse-

Budapest (Continued)

quent metastases, mean time between isolated local relapse and distant relapse.

2. 5-year probability of local tumour control.
3. 5-year probability of relapse-free survival.
4. 5-year probability of cancer-specific survival.
5. Actuarial 5-year local recurrence rate for women younger and older than 40 years and for women with negative versus positive or close surgical margins.
6. RTOG/EORTC late radiation side effects.
7. Cosmetic results scored on a 4-grade scale.

We did not have access to the study protocol, so judged this domain as at unclear risk of bias.

Other bias	Unclear risk	Because this was an interim report (prospectively planned however), we judged it as at unclear risk of bias.
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EORTC

Methods	<p>Accrual: 1989 to 1996</p> <p>Multicentre: 31 centres in 9 countries</p> <p>Phase III RCT</p> <p>9 countries: the Netherlands, Belgium, France, Germany, Switzerland, the United Kingdom, Israel, Austria, Spain</p> <p>Median follow-up: 17.2 years</p>
Participants	<p>5569 participants randomised in the trial. 5318 participants with stage I or II (T1-2, N0-1, M0) breast cancer who had undergone macroscopically complete surgical removal of the tumour load and axillary dissection, with microscopically completely excised tumour.</p> <ul style="list-style-type: none"> • Less than 70 years old, median 56. • Stage: T1 52%, T2 48%, T3 < 1%. N0 90%, N1-2 7%, Nx 3%. • Indication of percentage of participants with positive surgical margins: only patients with negative section margins were included. • Notable exclusion criteria: pure carcinoma in situ, multiple tumour foci in more than 1 quadrant, tumourectomy more than 9 weeks before the start of radiotherapy or more than 6 months before the start of radiotherapy in case of chemotherapy. • Receptor status: ER+PR+ 39%, ER+PR- 10%, ER-PR+ 5%, ER-PR- 13%, unknown 33%. • Menstrual status: premenopausal 38%, postmenopausal 62%, unknown < 1%. • Other adjuvant treatments: participants with axillary lymph node involvement received adjuvant systemic therapy; premenopausal women received chemotherapy and postmenopausal women received tamoxifen.
Interventions	<p>ARM 1: Intervention details (n = 2661): WBI 50 Gy in 25 fractions in 5 weeks + boost dose of 16 Gy aimed at the tumour bed (in 8 fractions with fast electrons or tangential photon fields; or 15 Gy by means of an iridium-192 implant at a dose rate of 0.5 Gy per hour). BED 87.8 Gy.</p> <p>ARM 2: Comparator details (n = 2657): WBI 50 Gy in 25 fractions in 5 weeks. BED 66.7 Gy.</p>
Outcomes	<p>Primary outcomes:</p> <ol style="list-style-type: none"> 1. Overall survival defined as the time from randomisation to death from any cause during follow-up or to last visit. <p>Secondary outcomes:</p>

EORTC (Continued)

1. Local control defined as the time from randomisation until the development of any local recurrence during follow-up (time-to-event outcome). We define local recurrence as recurrence in the ipsilateral breast (i.e. the breast in which cancer had been diagnosed), the skin and parenchyma. Ipsilateral breast tumour recurrence as the first treatment failure was the event of interest and any other treatment failure as first event (including death) was considered a competing risk.
2. Cosmesis: panel score and BCCT.core score.
3. Fibrosis. Cumulative incidence of severe fibrosis was counted from the entry to the date of first report of severe fibrosis or until the last visit before a mastectomy. Mastectomy and death without severe fibrosis were competing risks for this analysis. pBRA was measured.

Exploratory endpoints:

1. Breast cancer mortality.
2. Time to distant metastasis defined as the time from randomisation to the first report of distant metastases (event), death without metastases (competing risk), or last visit (censored observation).
3. Disease-free survival was the time from day of first report of local ipsilateral breast tumour recurrence, to the day of first report of either a subsequent local failure or a failure at another site or to death of any cause.
4. Disease-free survival and overall survival after local failure: time to event was counted from the first ipsilateral breast tumour recurrence for all patients with local ipsilateral breast tumour recurrence as first failure.

Notes	<ul style="list-style-type: none"> • Target area for the additional dose of radiation was the site of the primary tumour, with a margin of 1.5 cm around the primary tumour after microscopically complete excision and of 3 cm in case of invasive cancer with extensive ductal carcinoma in situ. • Section margins were assessed for the presence of invasive carcinoma, but not for ductal carcinoma in situ.
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote "Patients were centrally randomised at the EORTC Headquarters according to a minimisation algorithm (variance method) in a 1:1 ratio." "Factors used in the minimization were age, menopausal status, presence of extensive ductal carcinoma in situ (ten or more ducts involved), clinical tumour size, nodal status and institute where the patient received treatment." Bartelink 2015, page 48, paragraph 3-4.</p> <p>We judged this domain as at low risk of bias.</p>
Allocation concealment (selection bias)	Low risk	<p>Quote "Patients were centrally randomised at the EORTC Headquarters according to a minimisation algorithm (variance method) in a 1:1 ratio." "Neither patients nor investigators were masked to treatment allocation" Bartelink 2015, page 48, paragraph 3-4.</p> <p>We judged this domain as at low risk of bias.</p>
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	<p>Participants and personnel: not mentioned, unlikely to have been done.</p> <p>We judged this domain as at low risk of bias.</p>
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	<p>Participants and personnel: not mentioned, unlikely to have been done.</p> <p>We judged this domain as at low risk of bias.</p>

EORTC (Continued)

Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	<p>Participants: not mentioned, unlikely to have introduced bias.</p> <p>Personnel: not done, but in view of prespecified protocol of follow-up with regular mammography, unlikely to have introduced bias.</p> <p>Quote "patients were followed up two or three times per year for 5 years, then once per year by mammography and clinical examination." Bartelink 2015, page 48, paragraph 8.</p> <p>Local recurrence is defined as any recurrence within the treated breast, confirmed by histology or cytology (protocol).</p> <p>Unlikely to be a source of bias in view of the prespecified schedule for follow-up visits and investigations.</p>
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	<p>Quote "The cosmetic outcome and assessment of therapy sequelae will be scored regularly. Therefore colour print photographs or slides have to be taken immediately after surgery (before radiotherapy), and thereafter every 3 years. ... An external review panel will score qualitatively the cosmetic result, based on the pictures, using a 4 point grading scale." Protocol, page 26, paragraph 2.</p> <p>Quote "At each visit except baseline, the physician (not blinded for the treatment arm) scored the grade of fibrosis (none/minimal/moderate/severe) for the whole breast and for the boost area" Collette 2008, page 2588, paragraph 8.</p> <p>We would have judged this domain as at low risk of bias based on the use of a grading scale and the blinding of assessors; however, since the physician was not blinded to the treatment arm to score fibrosis, we assessed it as at unclear risk of bias.</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Exclusions: 0</p> <p>Attritions: 0</p> <p>Intention-to-treat analysis</p>
Selective reporting (reporting bias)	Low risk	<p>Outcomes in the protocol</p> <ol style="list-style-type: none"> 1. Local recurrence rate. 2. Cosmetic results. 3. Survival. <p>Outcomes in the results</p> <ol style="list-style-type: none"> 1. Overall survival. 2. Breast cancer mortality. 3. Distant metastases. 4. Second primary tumour in the contralateral breast. 5. Overall incidence of breast cancer-related events. 6. Disease-free survival. 7. Time to any recurrence. 8. Local recurrence. 9. Locoregional recurrence. 10. Second primary ipsilateral breast cancers. 11. Fibrosis. 12. Cosmesis.

EORTC (Continued)

We had access to the study protocol and all prespecified endpoints were reported, so we judged this domain as at low risk of bias.

Other bias	Low risk	No other sources of bias identified.
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Lyon

Methods	<p>Accrual: 1986 to 1992</p> <p>2 centres: Hospices civils de Lyon and Centre Léon Bérard</p> <p>Phase III RCT</p> <p>France</p> <p>Median follow-up: 3.3 years</p>
Participants	<ul style="list-style-type: none"> • 1028 women with invasive ductal adenocarcinoma ≤ 3 cm and "free" pathological margins (absence of detectable cancer cells at the inked margin M0). • Less than 70 years old, mean 53. • T ≤ 2 cm 81%, > 2 cm 19%; N0 73%, N1 27%. • Free margins 98%. • Notable exclusion criteria: > 70 years old. • ER+: not reported. • Menopausal state: not reported. • Other adjuvant treatments: chemotherapy in 22%, endocrine therapy in 30%. N+ in premenopausal women: adjuvant chemotherapy. N+ in postmenopausal women: tamoxifen, sometimes even if N0.
Interventions	<p>ARM 1: Intervention details (n = 521): WBI 50 Gy cobalt 60/20 fractions of 2.5 Gy 4 per week + boost 10 Gy 9 or 12 MeV 4 fractions 1 week. BED 86.4 Gy.</p> <p>ARM 2: Comparator details (n = 503): WBI 50 Gy cobalt 60/20 fractions of 2.5 Gy 4 per week. BED 72.1 Gy.</p>
Outcomes	<p>Primary outcomes</p> <ol style="list-style-type: none"> 1. Ipsilateral breast tumour recurrence, defined as any recurrence within the irradiated breast. Time to local recurrence, with death from any cause apart from metastases considered censored events. <p>Secondary outcomes</p> <ol style="list-style-type: none"> 1. Overall survival. 2. Disease-free survival. 3. Local, regional, or metastatic relapse. 4. Toxicity: telangiectasia, assessed by clinician. 5. General cosmetic score, assessed by clinician and participant.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote "Stratification factors were the pathologic stages of the tumour (T1 v T2) and node (N0 v N1-2)." Lyon, page 964, paragraph 2.</p> <p>We did not have access to the study protocol, so judged this domain as at unclear risk.</p>

Lyon (Continued)

Allocation concealment (selection bias)	Unclear risk	<p>Quote "Patients were entered onto the study by the radiation oncologist when first evaluated after surgery, and were randomised at the start of irradiation." Lyon, page 964, paragraph 2.</p> <p>We did not have access to the study protocol, so judged this domain as at unclear risk.</p>
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	<p>Participants and personnel: not mentioned, unlikely to have been done.</p> <p>We judged this domain as at low risk of bias.</p>
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	<p>Participants and personnel: not mentioned, unlikely to have been done.</p> <p>We judged this domain as at low risk of bias.</p>
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	<p>Participants: not mentioned, unlikely to have been done.</p> <p>Personnel: not done, but in view of prespecified protocol of follow-up with regular mammography, unlikely to have introduced bias.</p> <p>Quote "Clinical follow-up evaluation was performed every 4 months during the first 2 years, every 6 months up to the fifth year, and then annually. Bilateral mammography was performed every year." Lyon, page 964, paragraph 2.</p> <p>Local recurrence is defined as any recurrence within the treated breast, without further specifying if this required biopsy information.</p> <p>Unlikely to be a source of bias in view of the prespecified schedule for follow-up visits and investigations.</p>
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	<p>Quote "Toxicity was evaluated only as teleangiectasias, assessed regularly by the clinical oncologist during follow-up evaluation as follows: 0, absent; 1, a few visible areas of teleangiectasia in the tumour bed; 2, teleangiectasia that covered one quadrant of the breast; and 3, obvious teleangiectasia over more than one quadrant. The general cosmetic score, assessed by both the clinical oncologist and the patients themselves, was as follows: 1, excellent; 2, good; 3, fair; 4, poor." Lyon, page 965, paragraph 2.</p> <p>Because the assessment of subjective outcomes was not blinded, we judged this domain as at high risk of bias.</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Quote "Two patients presented with bilateral synchronous breast cancer, which corresponded to four cases. Since this situation had not been planned for in the initial protocol, these two patients were excluded after randomization. ... Forty patients had not received the assigned treatment: 31 in the control group who had erroneously received a boost, and nine in the experimental group who had not received the assigned boost. The analysis was performed on an intent-to-treat basis." Lyon, page 965, paragraph 4.</p> <p>Quote "Thirty-two patients (17 in the control group and 15 in the experimental group) were lost to follow-up after treatment. In 4 years, 194 patients were lost to follow-up for local recurrence in the control group and 171 in the experimental group." Lyon, page 965, paragraph 6.</p> <p>Postrandomisation exclusions are detailed without information on treatment arm, but with reasons. There was no postrandomisation attrition. We judged this domain as at low risk of bias.</p>

Lyon (Continued)

Selective reporting (reporting bias)	Unclear risk	<p>Outcomes in methods section</p> <p>Primary outcome: time to local recurrence (any recurrence within the irradiated breast).</p> <p>Secondary outcomes: overall survival; disease-free survival; local, regional, or metastatic relapse; telangiectasia; general cosmetic score.</p> <p>Outcomes reported in paper</p> <ol style="list-style-type: none"> 1. Time to local recurrence. 2. Distant treatment failure as first relapse. 3. Disease-free survival. 4. Overall survival. 5. Telangiectasia. 6. Cosmetic score. <p>We did not have access to the study protocol, so judged this domain as at unclear risk of bias.</p>
Other bias	Low risk	No other sources of bias identified.

Nice

Methods	<p>Accrual: 1987 to 1994</p> <p>RCT</p> <p>Nice, France</p> <p>Median follow-up: 73 months</p>
Participants	<ul style="list-style-type: none"> • 664 women with invasive breast cancer, treated by conservative surgery. • Tumour-free margins. • Axillary dissection. • Systemic therapy by hormonotherapy or chemotherapy, or both, was possible.
Interventions	<p>ARM 1: Intervention details: WBI 50 Gy/25 fractions + boost 10 Gy/5 fractions. BED 79.9 Gy.</p> <p>ARM 2: Comparator details: WBI 50 Gy/25 fractions. BED 66.7 Gy.</p>
Outcomes	Primary outcome: local control.
Notes	Abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	We did not have access to the study protocol, so judged this domain as at unclear risk.
Allocation concealment (selection bias)	Unclear risk	We did not have access to the study protocol, so judged this domain as at unclear risk.
Blinding of participants and personnel (performance bias)	Low risk	<p>Participants and personnel: not mentioned, unlikely to have been done.</p> <p>We judged this domain as at low risk of bias.</p>

Tumour bed boost radiotherapy for women after breast-conserving surgery (Review)

Nice (Continued)

Objective outcomes

Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	Participants and personnel: not mentioned, unlikely to have been done. We judged this domain as at low risk of bias.
Blinding of outcome assessment (detection bias) Objective outcomes	High risk	We did not have access to this information in the abstract, so judged this domain as at high risk of bias.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	We did not have access to this information in the abstract, so judged this domain as at high risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No exclusions or attrition of participants reported. We would have judged this domain as at low risk of bias, however since only the abstract was available, we assessed it as at unclear risk of bias.
Selective reporting (reporting bias)	High risk	Only the results on local control are described in the abstract. Since no protocol was available and no further results on local recurrence were reported, we judged this domain as at high risk of bias.
Other bias	Unclear risk	Because this was an interim report and only the abstract was available, we judged this domain as at unclear risk of bias.

SGW

Methods	<p>Accrual: 1996 to not reported</p> <p>Multicentre: St George and Wollongong hospitals, NSW and Liverpool Hospital, Sydney RCT Australia Median follow-up: 8.5 years</p>
Participants	<ul style="list-style-type: none"> 688 women with in situ tumours, T1, T2 N0-3 breast cancer after lumpectomy. Mean 59 years old, range 24 to 85. Mean tumour size 18 mm, extensive intraductal carcinoma in 10%, N+: 24%. Indication of percentage of women with positive surgical margins: only women with negative section margins were included. Notable exclusion criteria: gross multifocal disease, involvement of margins, bilateral breast cancer. ER+: 76%. 20% premenopausal, 74% postmenopausal, 6% perimenopausal. Other adjuvant treatments: chemotherapy in 20%, endocrine therapy in 39%.
Interventions	<p>ARM 1: Intervention details: WBI 45 Gy/25 fractions + boost 16 Gy/8 fractions. BED 78.6 Gy.</p> <p>ARM 2: Comparator details: WBI 50 Gy/25 fractions. BED 66.7 Gy.</p>
Outcomes	<p>Primary outcomes</p> <p>1. Local control.</p> <p>Secondary outcomes</p>

SGW (Continued)

1. Cosmesis:
 - Women were asked to compare the treated with the untreated breast and score the overall result. Results were dichotomised into "normal/excellent/good" and "marked/severe".
 - 5-person panel evaluated digital photographs. The treated breast was compared with the untreated breast and scored using a 4-point scale developed by Harris and colleagues. Nipple-areolar complex hypopigmentation was scored.
 - At each follow-up the clinician was asked to assess the cosmetic scores. Fibrosis and oedema were scored as "nil", "mild", "marked", and "severe". Overall cosmesis was scored as "excellent", "good", "fair", "poor".
 - Objective BRA, pBRA.
 - BCCT.core software cosmesis score.
2. Quality of life: EORTC QLQ-C30 (version 2.0) + functional assessment by asking the participant to score the degree of arm swelling, arm pain, limitation of arm movement, loss of feeling in fingers.

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	We did not have access to the study protocol, so judged this domain as at unclear risk.
Allocation concealment (selection bias)	Unclear risk	We did not have access to the study protocol, so judged this domain as at unclear risk.
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Participants and personnel: not mentioned, unlikely to have been done. We judged this domain as at low risk of bias.
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	Participants and personnel: not mentioned, unlikely to have been done. We judged this domain as at low risk of bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Quote "Digital photographs were taken at 1, 2 and 3 years as well as at 5 and 10 years post-surgery by investigator P.G." SGW 2014, page 230, paragraph 3. Quote "the relative breast retraction assessment was performed by a single observer using another custom written computer software." SGW 2012, page 685, paragraph 2. Also, the BCCT.core software was used. Tumour recurrences were classified as ipsilateral in-breast recurrence. Quote "Patients were assessed 6 weeks after radiotherapy, every 6 months for 2 years, then annually thereafter with annual breast imaging. We judged this domain as at low risk of bias.
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	Concerning digital photographs: quote "A five-person panel (two radiation oncologists, one breast surgeon, one breast clinical nurse consultant, one radiotherapy clinical nurse specialist; four women, one man) all with experience in the treatment of breast cancers were asked to evaluate the images" "The treated breast was compared with the untreated breast and scored using a 4-point scale developed by Harris et al." Evaluation was done independently. SGW 2012, page 683, paragraph 5. Quote "Functional assessments were performed by asking the patient to score the degree of arm swelling, arm pain, limitation of arm movement, loss of feel-

SGW (Continued)

		<p>ing in fingers, breast sensitivity and breast tenderness. For the cosmetic assessment, the patient was asked to compare the treated with the untreated breast and score the overall result. SGW 2013, page 116, paragraph 5. EORTC QLQ-C30 was used for quality of life.</p> <p>Quote "At each follow-up visit the clinician was asked to assess the cosmetic outcomes. Fibrosis and edema were scored as nil, mild, marked and severe and overall cosmesis was scored as excellent, good, fair and poor. The patient-self-assessment normal, excellent, good, fair, poor." SGW 2012, page 684, paragraph 2; page 685, paragraph 1.</p> <p>As we had no information on the blinding of assessors, we judged this domain as at unclear risk of bias.</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>346 women allocated to the experimental group, 342 to the control group. At 5 years 253 and 260 were alive, respectively, at the St George Hospital and for 183 and 202, respectively, digital photographs were available. (Figure 1) SGW 2012, page 683.</p> <p>Quote: "... randomized 688 patients into the boost and no boost arms. 609, 580, and 428 patients had baseline, 5 and 10 years cosmetic data available, respectively."</p> <p>No exclusions or attrition of participants reported. We judged this domain as at low risk of bias.</p>
Selective reporting (reporting bias)	High risk	<p>Outcomes in methods section</p> <ol style="list-style-type: none"> 1. Photographs: panel assessment, BCCT.core score, pBRA measurements, nipple-areolar complex alterations. 2. Participant and clinician live assessment. 3. Quality of life. <p>Outcomes in results</p> <ol style="list-style-type: none"> 1. Photographs: panel assessment, BCCT.core score, pBRA measurements, nipple-areolar complex alterations. 2. Participants and clinician live assessment. 3. Quality of life. <p>The results on local control are only briefly described in Millar 2009 and Graham 2007. Since no protocol was available and no further results on local recurrence were reported, we judged this domain as at high risk of bias.</p>
Other bias	Low risk	No other sources of bias identified.

BED: biologically equivalent dose

BRA: breast retraction assessment

ER: oestrogen receptor

HDR-BT: high-dose-rate brachytherapy

MeV: megaelectron volt

N: lymph node

pBRA: percentage breast retraction assessment

PR: progesterone receptor

RCT: randomised controlled trial

RT: radiation therapy

RTOG/EORTC: Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer

RNI: regional nodal irradiation

WBI: whole-breast irradiation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Cost-effectiveness	Not a randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR-IOR-17010342

Trial name or title	Prospective randomized controlled clinical trial of external beam radiotherapy + interstitial brachytherapy for breast cancer after breast-conserving surgery
Methods	Accrual: 2017 to 2022 Single-centre Phase III randomised controlled trial Changchun, Jilin, China
Participants	<ul style="list-style-type: none"> 100 women with stage DCIS-I-II breast cancer with tumour < 3 cm. Age 30 to 75.
Interventions	ARM 1: Intervention details (n = 50): WBI + interstitial brachytherapy boost. ARM 2: Comparator details (n = 50): WBI.
Outcomes	Primary outcomes 1. Local control. 2. Overall survival. 3. Recurrence-free survival. 4. Distant metastasis-free survival. 5. Quality of life. Secondary outcomes 1. Safety. 2. Cosmetic effect.
Starting date	1 February 2017
Contact information	chengghcjuh@sina.com
Notes	

DCIS: ductal carcinoma in situ

WBI: whole-breast irradiation

DATA AND ANALYSES

Comparison 1. Tumour bed boost radiotherapy versus no boost

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Local control	5	8315	Hazard Ratio (Fixed, 95% CI)	0.64 [0.55, 0.75]
2 Local control - sensitivity analysis	3	6963	Hazard Ratio (Fixed, 95% CI)	0.62 [0.52, 0.73]
3 Local control - subgroup +40 years	2	5058	Hazard Ratio (Fixed, 95% CI)	0.65 [0.53, 0.81]
4 Local control - subgroup low boost dose	2	1352	Hazard Ratio (Fixed, 95% CI)	0.95 [0.55, 1.62]
5 Overall survival	2	6342	Hazard Ratio (Fixed, 95% CI)	1.04 [0.94, 1.14]
6 Disease-free survival	3	6549	Hazard Ratio (Fixed, 95% CI)	0.94 [0.87, 1.02]
7 Late toxicity, pBRA	2	1526	Mean Difference (IV, Fixed, 95% CI)	0.38 [-0.18, 0.93]
8 Cosmesis, Panel	2	1116	Odds Ratio (M-H, Fixed, 95% CI)	1.41 [1.07, 1.86]
9 Cosmesis, Physician	2	592	Odds Ratio (M-H, Fixed, 95% CI)	1.58 [0.93, 2.69]

Analysis 1.1. Comparison 1 Tumour bed boost radiotherapy versus no boost, Outcome 1 Local control.

Analysis 1.2. Comparison 1 Tumour bed boost radiotherapy versus no boost, Outcome 2 Local control - sensitivity analysis.

Analysis 1.3. Comparison 1 Tumour bed boost radiotherapy versus no boost, Outcome 3 Local control - subgroup +40 years.

Analysis 1.4. Comparison 1 Tumour bed boost radiotherapy versus no boost, Outcome 4 Local control - subgroup low boost dose.

Analysis 1.5. Comparison 1 Tumour bed boost radiotherapy versus no boost, Outcome 5 Overall survival.

Analysis 1.6. Comparison 1 Tumour bed boost radiotherapy versus no boost, Outcome 6 Disease-free survival.

Analysis 1.7. Comparison 1 Tumour bed boost radiotherapy versus no boost, Outcome 7 Late toxicity, pBRA.

Analysis 1.8. Comparison 1 Tumour bed boost radiotherapy versus no boost, Outcome 8 Cosmesis, Panel.

Analysis 1.9. Comparison 1 Tumour bed boost radiotherapy versus no boost, Outcome 9 Cosmesis, Physician.

ADDITIONAL TABLES

Table 1. RTOG/EORTC late radiation morbidity scoring scheme

Organ tissue	0	Grade 1	Grade 2	Grade 3	Grade 4
Skin	None	Slight atrophy; pigmentation change; some hair loss	Patchy atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration
Subcutaneous tissue	None	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; < 10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture > 10% linear measurement	Necrosis

RTOG/EORTC: Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer

Table 2. Harvard cosmetic score

Cosmetic score
Excellent
Good
Fair
Poor

APPENDICES

Appendix 1. CENTRAL

1. MeSH descriptor: [Breast Neoplasms] explode all trees
2. breast near cancer*
3. breast near neoplasm*
4. breast near carcinoma*

5. breast near tumour*
6. breast near tumor*
7. #1 or #2 or #3 or #4 or #5 or #6
8. MeSH descriptor: [Radiotherapy, Adjuvant] explode all trees
9. MeSH descriptor: [Radiotherapy, Conformal] explode all trees
10. MeSH descriptor: [Radiotherapy, Intensity-Modulated] explode all trees
11. MeSH descriptor: [Brachytherapy] explode all trees
12. radiation therapy
13. external beam and (radiation or irradiation or radiotherapy)
14. three dimension* and (radiation or irradiation or radiotherapy)
15. 3 d and (radiation or irradiation or radiotherapy)
16. 3-d and (radiation or irradiation or radiotherapy)
17. 3 d conformal and (radiation or irradiation or radiotherapy)
18. 3-d conformal and (radiation or irradiation or radiotherapy)
19. cobalt-60 and (radiation or irradiation or radiotherapy)
20. bed boost and (radiation or irradiation or radiotherapy)
21. whole breast and (radiation or irradiation or radiotherapy)
22. interstitial and (radiation or irradiation or radiotherapy)
23. electron and (radiation or irradiation or radiotherapy)
24. photon and (radiation or irradiation or radiotherapy)
25. #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
26. MeSH descriptor: [Mastectomy, Segmental] explode all trees
27. lumpectomy
28. quadrantectomy
29. breast conserving surgery
30. breast conserving therapy
31. surgery near breast*
32. wide excision
33. wide local excision
34. WLE
35. #26 or #27 or #28 or #29 or #31 or #32 or #33 or #34
36. #7 and #25 and #35

Appendix 2. MEDLINE

1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomized.ab.
4	placebo.ab.
5	Clinical Trials as Topic/
6	randomly.ab.
7	trial.ti.
8	(crossover or cross-over).tw.
9	Pragmatic Clinical Trials as Topic/

(Continued)

10	pragmatic clinical trial.pt.
11	or/1-10
12	exp Breast Neoplasms/
13	(breast adj6 cancer\$).tw.
14	(breast adj6 neoplasm\$).tw.
15	(breast adj6 carcinoma\$).tw.
16	(breast adj6 tumo?r\$).tw.
17	or/12-16
18	exp Radiotherapy, Adjuvant/
19	(external beam and (radiation or radiotherapy or irradiation)).tw.
20	(three dimensional and (radiation or radiotherapy or irradiation)).tw.
21	(3D and (radiation or radiotherapy or irradiation)).tw.
22	(3-D and (radiation or radiotherapy or irradiation)).tw.
23	(3D conformal and (radiation or radiotherapy or irradiation)).tw.
24	(3-D conformal and (radiation or radiotherapy or irradiation)).tw.
25	(three dimensional conformal and (radiation or radiotherapy or irradiation)).tw.
26	(cobalt-60 and (radiation or radiotherapy or irradiation)).tw.
27	(whole breast and (radiation or radiotherapy or irradiation)).tw.
28	exp Radiotherapy, Conformal/
29	Radiotherapy, Intensity-Modulated/
30	exp brachytherapy/
31	exp radiotherapy, computer-assisted/
32	exp radiotherapy, high-energy/
33	exp radiotherapy, image-guided/
34	bed boost.tw.
35	(interstitial and (radiation or radiotherapy or irradiation)).tw.
36	(electron and (radiation or radiotherapy or irradiation)).tw.
37	(photon and (radiation or radiotherapy or irradiation)).tw.

(Continued)

38	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39	exp Mastectomy, Segmental/
40	lumpectomy.tw.
41	quadrantectomy.tw.
42	breast conserving surgery.tw.
43	breast conserving therapy.tw.
44	(surgery adj5 breast\$.tw.
45	wide excision.tw.
46	wide local excision.tw.
47	WLE.tw.
48	39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
49	11 and 17 and 38 and 48
50	Animals/ not Humans/
51	49 not 50

Appendix 3. Embase

1. random* OR factorial* OR crossover* OR cross NEXT/1 over* OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer* OR 'crossover procedure'/exp OR 'crossover procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'single blind procedure'/exp OR 'single blind procedure'
2. 'breast'/exp OR 'breast disease'/exp AND 'neoplasm'/exp OR 'breast tumor'/exp OR (breast* NEAR/5 neoplas*):ab,ti OR (breast* NEAR/5 cancer*):ab,ti OR (breast* NEAR/5 carcin*):ab,ti OR (breast* NEAR/5 tumo*):ab,ti OR (breast* NEAR/5 metasta*):ab,ti OR (breast* NEAR/5 malig*):ab,ti
3. 'breast cancer'/exp OR 'breast cancer' OR 'breast neoplasm' OR 'breast carcinoma'/exp OR 'breast carcinoma' OR 'breast tumour' OR 'breast tumor'/exp OR 'breast tumor'
4. #2 OR #3
5. 'radiotherapy adjuvant'/exp
6. 'external beam' AND (radiation OR radiotherapy OR irradiation)
7. 'three dimensional' AND (radiation OR radiotherapy OR irradiation)
8. 3d AND (radiation OR radiotherapy OR irradiation)
9. '3 d' AND (radiation OR radiotherapy OR irradiation)
10. '3 d' AND conformal AND (radiation OR radiotherapy OR irradiation)
11. 'three dimensional conformal radiation therapy'
12. 'cobalt 60' AND (radiation OR radiotherapy OR irradiation)
13. 'cobalt therapy'/exp
14. 'external beam radiotherapy'/exp
15. 'intensity modulated radiation therapy'/exp
16. 'whole breast' AND (radiation OR radiotherapy OR irradiation)
17. 'interstitial radiation'/exp

18.'brachytherapy'/exp OR brachytherapy
19.'computer assisted radiotherapy'/exp
20.'megavoltage radiotherapy'/exp
21.'image guided radiotherapy'/exp
22.'bed boost' AND (radiation OR radiotherapy OR irradiation)
23.'electron' AND (radiation OR radiotherapy OR irradiation)
24.'photon' AND (radiation OR radiotherapy OR irradiation)
25.#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
26.'segmental mastectomy'/exp
27.'partial mastectomy'/exp OR lumpectomy
28.quadrantectomy
29.'breast conserving surgery'
30.'breast conserving therapy'
31.surgery NEAR/5 breast*
32.'wide local excision' OR 'wide excision' OR WLE
33.#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32
34.#1 AND #4 AND #25 AND #33
35.#34 AND [humans]/lim AND [embase]/lim

Embase search 01/03/2017 via OvidSP

1	Randomized controlled trial/
2	Controlled clinical study/
3	Random\$.ti,ab.
4	randomization/
5	intermethod comparison/
6	placebo.ti,ab.
7	(compare or compared or comparison).ti.
8	(open adj label).ti,ab.
9	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
10	double blind procedure/
11	parallel group\$1.ti,ab.
12	(crossover or cross over).ti,ab.
13	((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or intervention\$1 or patient\$1 or subject\$1 or participant\$1)).ti,ab.
14	(assigned or allocated).ti,ab.
15	(controlled adj7 (study or design or trial)).ti,ab.
16	(volunteer or volunteers).ti,ab.

(Continued)

17	trial.ti.
18	or/1-17
19	exp breast/
20	exp breast disease/
21	(19 or 20) and exp neoplasm/
22	exp breast tumor/
23	exp breast cancer/
24	exp breast carcinoma/
25	(breast\$ adj5 (neoplas\$ or cancer\$ or carcin\$ or tumo\$ or metasta\$ or malig\$)).ti,ab.
26	or/21-25
27	exp adjuvant radiotherapy/
28	(external beam and (radiation or radiotherapy or irradiation)).tw.
29	(three dimensional and (radiation or radiotherapy or irradiation)).tw.
30	(3D and (radiation or radiotherapy or irradiation)).tw.
31	(3D conformal and (radiation or radiotherapy or irradiation)).tw.
32	(3-D conformal and (radiation or radiotherapy or irradiation)).tw.
33	(three dimensional conformal and (radiation or radiotherapy or irradiation)).tw.
34	(cobalt-60 and (radiation or radiotherapy or irradiation)).tw.
35	exp cobalt therapy/
36	exp external beam radiotherapy/
37	exp intensity modulated radiation therapy/
38	(whole breast and (radiation or radiotherapy or irradiation)).tw.
39	exp radioisotope therapy/
40	exp brachytherapy/
41	brachytherapy.tw.
42	exp computer assisted radiotherapy/
43	exp megavoltage radiotherapy/
44	exp image guided radiotherapy/

(Continued)

45	(bed boost and (radiation or radiotherapy or irradiation)).tw.
46	(electron and (radiation or radiotherapy or irradiation)).tw.
47	(photon and (radiation or radiotherapy or irradiation)).tw.
48	or/27-47
49	exp segmental mastectomy/
50	exp partial mastectomy/
51	lumpectomy.tw.
52	quadrantectomy.tw.
53	breast conserving surgery.tw.
54	breast conserving therapy.tw.
55	(surgery adj5 breast\$).tw.
56	wide excision.tw.
57	wide local excision.tw.
58	WLE.tw.
59	or/49-58
60	18 and 26 and 48 and 59
61	limit 60 to (human and embase)
62	limit 61 to yr="2015 -Current"

Appendix 4. WHO ICTRP

Basic Searches:

1. breast cancer AND tumour bed boost
2. breast cancer AND radiotherapy AND breast conserving surgery
3. breast cancer AND radiotherapy AND partial mastectomy

Advanced Searches:

1.

Title: Tumour bed boost radiotherapy for women with breast cancer

Recruitment Status: ALL

2.

Condition: breast cancer OR breast neoplasm

Intervention: (radiation OR irradiation OR radiotherapy) AND (breast conserving surgery OR breast conserving therapy OR partial mastectomy OR lumpectomy)

Recruitment Status: ALL

3.

Condition: breast cancer OR breast neoplasm

Intervention: bed boost AND (breast conserving surgery OR breast conserving therapy OR partial mastectomy OR lumpectomy)

Recruitment Status: ALL

4.

Condition: breast cancer OR breast neoplasm

Intervention: (cobalt-60 OR brachytherapy OR interstitial therapy) AND (breast conserving surgery OR breast conserving therapy OR partial mastectomy OR lumpectomy)

Recruitment Status: ALL

Appendix 5. ClinicalTrials.gov

Basic Searches:

1. breast cancer AND tumour bed boost
2. breast cancer AND radiotherapy AND breast conserving surgery
3. breast cancer AND radiotherapy AND partial mastectomy

Advanced Searches:

1.

Title: Tumour bed boost radiotherapy for women with breast cancer

Recruitment: All Studies

Study Results: All Studies

Study Type: All Studies

Gender: All Studies

2.

Condition: breast cancer OR breast neoplasm

Intervention: (breast irradiation OR tumour bed boost OR tumour bed boost) AND (breast conserving surgery OR breast conserving therapy OR segmental mastectomy OR partial mastectomy OR lumpectomy)

Recruitment: All Studies

Study Results: All Studies

Study Type: All Studies

Gender: All Studies

3.

Condition: breast cancer OR breast neoplasm

Intervention: (external beam irradiation OR conformal irradiation OR cobalt-60 OR intensity-modulated irradiation) AND (breast conserving surgery OR breast conserving therapy OR segmental mastectomy OR partial mastectomy OR lumpectomy)

Recruitment: All Studies

Tumour bed boost radiotherapy for women after breast-conserving surgery (Review)

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Study Results: All Studies

Study Type: All Studies

Gender: All Studies

4.

Condition: breast cancer OR breast neoplasm

Intervention: (brachytherapy OR interstitial therapy OR electron radiotherapy OR photon radiotherapy OR adjuvant radiotherapy) AND (breast conserving surgery OR breast conserving therapy OR segmental mastectomy OR partial mastectomy OR lumpectomy)

Recruitment: All Studies

Study Results: All Studies

Study Type: All Studies

Gender: All Studies

CONTRIBUTIONS OF AUTHORS

Isabelle Kindts (IK): drafted the protocol, selected which trials to include, extracted data from trials, entered data into Review Manager 5, carried out the analysis, interpreted the analysis, drafted the final review.

Annouschka Laenen (AL): drafted the protocol, carried out the analysis, interpreted the analysis and drafted the final review.

Tom Depuydt (TD): was to be consulted by IK and CW in case of disagreement on selected or extracted data.

Caroline Weltens (CW): drafted the protocol, selected which trials to include, extracted data from trials, entered data into Review Manager 5, interpreted the analysis, drafted the final review.

DECLARATIONS OF INTEREST

IK: None known.

AL: None known.

TD: None known.

CW: None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol stated that only women with invasive breast cancer would be included in the analysis. However, we reconsidered this based on the [SGW](#) study in which women with carcinoma in situ were also included (59 out of 688 participants). We excluded [SGW](#) in the sensitivity analysis for local control. However, we included [SGW](#) in the meta-analysis for toxicity and cosmesis.

INDEX TERMS

Medical Subject Headings (MeSH)

*Postoperative Care; *Re-Irradiation [adverse effects]; Breast Neoplasms [mortality] [*radiotherapy] [*surgery]; Disease-Free Survival; Mastectomy, Segmental; Neoplasm Recurrence, Local [mortality] [prevention & control] [radiotherapy]; Neoplasm, Residual; Randomized Controlled Trials as Topic

MeSH check words

Adult; Female; Humans; Middle Aged