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Partial breast irradiation for early breast cancer (Review)

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[Intervention Review]

Partial breast irradiation for early breast cancer

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ABSTRACT

Background

Breast-conserving therapy for women with breast cancer consists of local excision of the tumour (achieving clear margins) followed by radiotherapy (RT). RT is given to sterilize tumour cells that may remain after surgery to decrease the risk of local tumour recurrence. Most true recurrences occur in the same quadrant as the original tumour. Whole breast radiotherapy (WBRT) may not protect against the development of a new primary cancer developing in other quadrants of the breast. In this Cochrane review, we investigated the delivery of radiation to a limited volume of the breast around the tumour bed (partial breast irradiation (PBI)) sometimes with a shortened treatment duration (accelerated partial breast irradiation (APBI)).

Objectives

To determine whether PBI/APBI is equivalent to or better than conventional or hypo-fractionated WBRT after breast-conserving therapy for early-stage breast cancer.

Search methods

We searched the Cochrane Breast Cancer Group Specialized Register (4 May 2015), the Cochrane Central Register of Controlled Trials (CENTRAL) (2015, Issue 5), MEDLINE (January 1966 to 4 May 2015), EMBASE (1980 to 4 May 2015), CINAHL (4 May 2015) and Current Contents (4 May 2015). We searched the International Standard Randomised Controlled Trial Number Register (5 May 2015), the World Health Organization's International Clinical Trials Registry Platform (4 May 2015) and ClinicalTrials.gov (17 June 2015). We searched for grey literature: OpenGrey (17 June 2015), reference lists of articles, several conference proceedings and published abstracts, and applied no language restrictions.

Selection criteria

Randomized controlled trials (RCTs) without confounding, that evaluated conservative surgery plus PBI/APBI versus conservative surgery plus WBRT. Published and unpublished trials were eligible.

Data collection and analysis

Two review authors (BH and ML) performed data extraction and used Cochrane's 'Risk of bias' tool, and resolved any disagreements through discussion. We entered data into Review Manager 5 for analysis.

Main results

We included seven RCTs and studied 7586 women of the 8955 enrolled.

Local recurrence-free survival appeared worse for women receiving PBI/APBI compared to WBRT (hazard ratio (HR) 1.62, 95% confidence interval (CI) 1.11 to 2.35; six studies, 6820 participants, low-quality evidence). Cosmesis (physician-reported) appeared worse with PBI/APBI (odds ratio (OR) 1.51, 95% CI 1.17 to 1.95, five studies, 1720 participants, low-quality evidence). Overall survival did not differ with PBI/APBI (HR 0.90, 95% CI 0.74 to 1.09, five studies, 6718 participants, high-quality evidence).

Late radiation toxicity (subcutaneous fibrosis) appeared worse with PBI/APBI (OR 6.58, 95% CI 3.08 to 14.06, one study, 766 participants, moderate-quality evidence). Acute skin toxicity appeared reduced with PBI/APBI (OR 0.04, 95% CI 0.02 to 0.09, two studies, 608 participants). Telangiectasia (OR 26.56, 95% CI 3.59 to 196.51, 1 study, 766 participants) and radiological fat necrosis (OR 1.58, 95% CI 1.02 to 2.43, three studies, 1319 participants) appeared worse with PBI/APBI. Late skin toxicity (OR 0.21, 95% CI 0.01 to 4.39, two studies, 608 participants) and breast pain (OR 2.17, 95% CI 0.56 to 8.44, one study, 766 participants) appeared not to differ with PBI/APBI.

'Elsewhere primaries' (new primaries in the ipsilateral breast) appeared more frequent with PBI/APBI (OR 3.97, 95% CI 1.51 to 10.41, three studies, 3009 participants).

We found no clear evidence of a difference for the comparison of PBI/APBI with WBRT for the outcomes of: cause-specific survival (HR 1.08, 95% CI 0.73 to 1.58, five studies, 6718 participants, moderate-quality evidence), distant metastasis-free survival (HR 0.94, 95% CI 0.65 to 1.37, four studies, 3267 participants, moderate-quality evidence), relapse-free survival (HR 1.36, 95% CI 0.88 to 2.09, three studies, 3811 participants), loco-regional recurrence-free survival (HR 1.80, 95% CI 1.00 to 3.25, two studies, 3553 participants) or mastectomy rates (OR 1.20, 95% CI 0.77 to 1.87, three studies, 4817 participants, low-quality evidence). Compliance was met: more than 90% of the women in all studies received the RT they were assigned to receive. We found no data for the outcomes of costs, quality of life or consumer preference.

Authors' conclusions

It appeared that local recurrence and 'elsewhere primaries' (new primaries in the ipsilateral breast) are increased with PBI/APBI (the difference was small), but we found no evidence of detriment to other oncological outcomes. It appeared that cosmetic outcomes and some late effects were worse with PBI/APBI but its use was associated with less acute skin toxicity. The limitations of the data currently available mean that we cannot make definitive conclusions about the efficacy and safety or ways to deliver of PBI/APBI. We await completion of ongoing trials.

PLAIN LANGUAGE SUMMARY

Partial breast irradiation for early breast cancer

What is the issue?

Women with early breast cancer who choose to keep their breast need to have radiotherapy (RT) as well as surgery to remove the cancer to make sure it does not regrow in the breast. RT is treatment with high energy x-rays. Having RT for breast cancer usually means 25 to 30 visits to the RT department, five times per week.

If breast cancer does regrow in the same breast (called local recurrence), it tends to come back in the area it was removed from. Women can also grow a new cancer (new 'elsewhere primary') in another part of the same breast. We are not sure if the RT given to stop cancer regrowth where the first cancer was does stop the growth of 'elsewhere primaries'.

Breast cancer is the most common cancer that women get. When women choose to keep their breast, it is important that they are happy with how it looks after treatment (cosmesis).

Why does it matter?

We always want to treat the smallest area we can with RT because this means fewer side effects. Treating only part of the breast could mean that RT might be able to be used again in another part of the same breast if needed. New ways of giving RT mean that treating part of the breast can be done with fewer treatments. This is likely to be easier for women and cost less money.

We asked if giving RT to part of the breast (called partial breast irradiation (PBI)) is as good as giving RT to the whole breast. It would need to control the cancer as well as giving RT to the whole breast does. It would also be important that the PBI gives about the same side effects and breast appearance as treating the whole breast.

We found seven studies, which involved 7586 women. Our evidence is current to May 2015. Local recurrence was rare, but more common with PBI (low-quality evidence) and the breast appearance (scored by doctors) was worse with PBI (low-quality evidence). Survival did not differ (high-quality evidence). Scarring in the breast was worse with PBI (moderate-quality evidence). The same number of women died of breast cancer with either treatment (moderate-quality evidence). The same number of women developed spread of breast cancer around their body with either treatment (moderate-quality evidence). There appeared to be the same number of women who eventually needed the breast removed (mastectomy) after both treatments. Mastectomy could happen because of cancer regrowth in the breast or bad side effects (low-quality evidence).

This means that at the moment, PBI does not give the same cancer control in the breast as treating the whole breast, but the difference was small. It may cause worse side effects. There are five big ongoing studies that will be important to answer this question. We hope to have a clearer answer in the next update of this review.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Partial breast irradiation (PBI)/accelerated partial breast irradiation (APBI) for early breast cancer

PBI/APBI for women with early breast cancer

Patient or population: women with early breast cancer

Setting: radiotherapy centres

Intervention: PBI/APBI

Comparison: whole breast radiotherapy (WBRT)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with WBRT	Risk with PBI/APBI				
Local recurrence-free survival at 5 years	Study population		HR 1.62 (1.11 to 2.35)	6820 (6 RCTs)	⊕⊕⊕⊖ Low 3,4,5,6	-
	10 per 1000 ¹	16 per 1000 (11 to 23)				
Cosmesis assessed with 4-point scale Follow-up: range 29-122 months	Study population		OR 1.51 (1.17 to 1.95)	1720 (5 RCTs)	⊕⊕⊕⊖ Low 6,7,8,9	Cosmesis was assessed using a 4-point scale. We reported those women with poor/fair cosmesis at final review
	150 per 1000	218 per 1000 (174 to 272)				
Late radiotherapy toxicity (subcutaneous fibrosis) Follow-up: median 36 months	Study population		OR 6.58 (3.08 to 14.06)	766 (1 RCT)	⊕⊕⊕⊖ Moderate 5,7,10	Assessed using National Cancer Institute 3-point scale, events were defined as: Grade II or higher toxicity Physician assessors, at 3 years' follow-up
	22 per 1000	128 per 1000 (64 to 239)				
Cause-specific survival at 5 years	Study population		HR 1.08 (0.73 to 1.58)	6718 (5 RCTs)	⊕⊕⊕⊖ Moderate 5,11	-
	20 per 1000 ²	22 per 1000 (15 to 32)				
Distant metastasis-free survival at 5 years	Study population		HR 0.94 (0.65 to 1.37)	3267 (4 RCTs)	⊕⊕⊕⊖ Moderate 5,12	-
	33 per 1000 ²	31 per 1000				

	(21 to 44)				
Mastectomy rate	Study population	OR 1.20 (0.77 to 1.87)	4817 (3 RCTs)	⊕⊕⊕⊖ Low 5,11,13	Mastectomy rate reflected both local recurrence and adverse cosmetic outcome
Follow-up: range 29-122 months	15 per 1000 18 per 1000 (12 to 28)				
Mortality (follow-up: 5 years survival)	Study population	HR 0.90 (0.74 to 1.09)	6718 (5 RCTs)	⊕⊕⊕⊕ High	Survival advantage from radiotherapy for breast cancer is not apparent before 15 years' follow-up (EBCTCG 2011)
	51 per 1000 ² 46 per 1000 (38 to 55)				

***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; **OR:** odds ratio; **RCT:** randomized 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 effect

¹ The baseline risk for the control group was calculated at the 5-year time point from 5 studies.

² The baseline risks for the control groups were calculated at the 5-year time point from 4 studies.

³ There was considerable clinical heterogeneity with respect to radiotherapy dose, technique and use of quality assurance procedures. However, the techniques employed delivered a dose that was the same or higher in the accelerated partial breast irradiation arm than the whole breast radiotherapy arm, which should mean the local recurrence-free survival is better or at least the same.

⁴ 38% of the women contributing to this outcome came from a study deemed at high risk of bias for short follow-up.

⁵ There were fewer than 300 events.

⁶ Confidence intervals did not exclude both clinically important and clinically unimportant harms.

⁷ Optimum sample size was not met, therefore downgraded.

⁸ There was evidence of considerable heterogeneity on statistical testing ($I^2 = 71\%$; P value < 0.00001).

⁹ Less than 30% of events came from studies deemed at high risk of bias for subjective outcomes.

¹⁰ Testing for heterogeneity was not appropriate, given that there was only one study contributing to this outcome.

¹¹ Confidence intervals did not exclude either clinically significant benefits or harms.

¹² Confidence intervals did not exclude the possibility of clinically significant harms.

¹³ One of the two included studies had median follow-up of 29 months, which was too short to report this outcome.

BACKGROUND

Description of the condition

Breast cancer is the most common cancer occurring in women. One in eight women living in the US and the UK has a lifetime risk of being diagnosed with breast cancer; while one in nine women living in Australia are at risk (AIHW 2012; Howlader 2009; ONS 2010). Breast cancer is the second most common cause of cancer death in women.

Historically, mastectomy was the recommended therapeutic option for all stages of breast cancer. However, large randomised controlled trials (RCTs) demonstrated equivalent survival for women with early-stage disease (Stages I, II) whether they were treated with breast-conserving therapy or mastectomy (EBCTCG 1995; Fisher 1995; Fisher 2002; Jacobson 1995; Poggi 2003; van Dongen 2000; Veronesi 1995; Veronesi 2002). Consequently, breast conservation has become the preferred management option for these women.

Breast-conserving therapy consists of local excision of the tumour (achieving clear margins) followed by radiotherapy (RT). RT is given to sterilize tumour cells that may remain after surgery. This practice is supported by data from detailed pathological examination of mastectomy specimens where residual tumour was found more than 2 cm from the original tumour in 41% of participants (Holland 1985). Conventional RT delivers 45 to 50 Gray (Gy) to the whole breast over five weeks frequently followed by a boost to the tumour bed (the most likely site of residual tumour cells) of 10 to 16 Gy over one to two weeks. This prolonged duration of treatment negatively impacts on quality of life (Whelan 2000), and contributes to the higher mastectomy rates observed in women residing in rural and remote areas who wish to avoid being away from home and family for extended periods (Schroen 2005).

Hypofractionated whole breast radiotherapy (WBRT) regimens, in which 40 to 42.5 Gy is delivered to the whole breast over three to four weeks using a larger radiation dose with each treatment have been investigated. Compared to conventional WBRT, hypofractionated WBRT results in no difference in breast recurrence rates at five and 10 years, no difference in overall survival (OS) and an improvement in cosmetic outcomes (START 2008; START B 2008; Whelan 2002).

RCTs have shown that the addition of conventional or hypofractionated WBRT to local excision decreases ipsilateral breast (same breast) recurrence rates from 30% to 40% (Fisher 1995; Fisher 2002; Freeman 1981; Lagios 1983; Montgomery 1978) to 10% to 20% with 10 to 15 years of follow-up (Fisher 1995; Fisher 2002). Modern breast-conserving therapy with postoperative WBRT achieves local control rates of 3.3% to 3.4% at five years and 5.2% to 6.7% at 10 years (Haviland 2013). With careful patient selection (aged 65 years or greater, T1-2 tumours, tumour not greater than 3 cm, margin negative, oestrogen receptor positive and all receiving tamoxifen), surgery alone can achieve local recurrence rates of 4.1% at five years (Kunkler 2015). An ipsilateral recurrence can either be a true recurrence of the original cancer (typically arising in the same quadrant as the original tumour and known as local recurrence) or a second primary tumour developing elsewhere in that same breast. Studies evaluating ipsilateral breast tumour recurrence patterns showed that new primaries increasingly contribute to the rate of recurrence after five

to eight years while true recurrence rates stabilize (Krauss 2004; Smith 2000). If WBRT was successful in preventing the recurrence of new primary cancers, the rate of such cancers in the treated breast should be lower than the rate of development of cancers in the other breast (contralateral breast cancer). Studies of ipsilateral breast tumour recurrence patterns have not found this (Krauss 2004; Smith 2000). Furthermore, studies examining primary and re-excision pathological specimens removed at the time of breast-conserving surgery revealed residual tumour 15 mm or less from the primary tumour in 91% of the specimens (Wallner 2004).

Thus, as most true recurrences occur in the same quadrant as the original tumour and as WBRT does not appear to protect against the development of new primary cancer, investigators are examining the role of partial breast irradiation (PBI).

Description of the intervention

PBI (also known as less than WBRT) refers to irradiation of a limited volume of breast tissue around the tumour bed. It may be achieved by any of the following techniques.

1. Intracavitary brachytherapy or MammoSite® (applying radioactive sources directly into the cavity left after surgical removal of the tumour either at the time of surgery or at a later date, the latter requiring a second procedure).
2. Interstitial brachytherapy (inserting catheters into the surgical cavity and surrounding tissue to temporarily deliver radioactive sources).
3. Intra-operative techniques using electrons or x-rays at 50 kVp (using a dedicated machine to deliver a very localized radiation dose to the surgical cavity in the operating room or by moving the person with an open wound to the radiation machine, which may be in a different part of the hospital).
4. External beam radiotherapy (EBRT) using either three-dimensional conformal radiotherapy (3D-CRT) (EBRT delivered in the postoperative setting to a volume of breast tissue around the tumour cavity using a standard linear accelerator in a radiation oncology department) or other methods.

Conventional RT typically delivers a radiation dose of 2 Gy with each treatment. Some PBI techniques deliver a larger than standard dose of radiation with each treatment, allowing the overall duration of treatment to be shortened. This is termed accelerated partial breast irradiation (APBI).

How the intervention might work

PBI/APBI will only be of benefit if it confers the same local control benefit as standard WBRT with acceptable toxicity and cosmesis. Currently, some authorities consider PBI/APBI to be an experimental therapy (Clinical Evidence). The National Comprehensive Cancer Network (NCCN) state, "Preliminary studies of APBI suggest rates of local control in patients with early-stage breast cancer may be comparable to those treated with WBRT. Follow-up, however is limited and studies are ongoing" (NCCN). Because this technique has been widely adopted outside the context of clinical trials, published guidelines exist that identify women with early breast cancer for whom this technique may be safe. For those women ineligible for a trial, carefully selected women with early breast cancer may be offered PBI/APBI (Bellon 2011; Polgár 2010; Smith 2009).

PBI/APBI has a number of potential advantages including:

1. a reduction in treatment-related toxicities, as a smaller volume of breast tissue is irradiated;
2. increased utilization of breast conservation;
3. a reduction in RT waiting times; a reduction in the overall treatment duration of a common malignancy has the potential to substantially impact on RT waiting times in countries with strained resources (including the UK, Canada, Australia and New Zealand);
4. a greater chance of preserving the breast should a recurrence occur elsewhere in the breast;
5. easier integration with chemotherapy schedules because RT time will be shorter, thus avoiding delays.

PBI/APBI has a number of potential disadvantages including:

1. an increased risk of local recurrence due to geographic miss. This is either because treatment was delivered before full pathological examination was obtained or because of difficulty in reproducing the target volume (the tissue that needed to be treated with RT) daily;
2. increased late toxicity. The late effects of radiation are dependent on the dose of radiation given at each treatment and, as PBI/APBI delivers a large radiation dose per fraction, late toxicity may be increased with resultant poor cosmetic outcome or breast appearance (cosmesis);
3. more patient inconvenience as some techniques may require a second anaesthetic or a further invasive procedure;
4. a number of techniques (e.g. interstitial and intracavitary brachytherapy) require operator expertise and specialized equipment that may not be available in all centres;
5. invasive techniques of delivering PBI/APBI (e.g. interstitial and intracavitary brachytherapy) may be associated with toxicity such as infection and delays in wound healing. Scarring post-insertion of interstitial brachytherapy catheters can negatively impact on cosmetic appearance.

Why it is important to do this review

PBI/APBI has the potential to change the pattern of practice for a common malignancy and thereby impact on resource utilization, patient satisfaction and quality of life. However, as PBI/APBI is currently an experimental therapy, it must be thoroughly evaluated before being adopted as the new standard of care for early-stage breast cancer. PBI/APBI can be recommended if it is as effective or better than conventional or hypofractionated WBRT for cancer-related outcomes (local relapse-free survival (LR-FS), survival, breast cancer-specific survival and metastasis-free survival) as well as patient-orientated outcomes (cosmesis, quality of life and consumer preference). We found one systematic review that concluded, "The data on PBI/APBI compared to whole-breast irradiation are insufficient to draw any conclusions about the relative effectiveness of these modalities" ([BlueCross BlueShield](#)). The fact that the benefit versus risk profile of PBI/APBI is currently unknown makes it an ideal topic for a systematic review.

OBJECTIVES

To determine whether PBI/APBI is equivalent to or better than conventional or hypofractionated WBRT after breast-conserving therapy for early-stage breast cancer.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) evaluating conservative surgery plus PBI/APBI versus conservative surgery plus WBRT. The comparisons had to be unconfounded (i.e. treatments given to the randomized groups had to differ only in relation to the volume of the breast irradiated). Trials incorporating adjuvant treatments, such as chemotherapy, monoclonal antibodies or hormonal therapy, were eligible if the RCT applied these other treatments in exactly the same way to both groups. Published and unpublished studies were eligible.

We did not consider studies in which PBI was used as a boost following conventional EBRT for inclusion.

Types of participants

Women with histologically confirmed early-stage breast cancer who had conservative surgery. Early breast cancer included tumours classified as American Joint Committee on Cancer (AJCC) stage T1-2N0-1M0 ([Fleming 1997](#)). Surgery could include lumpectomy and wide local excision or quadrantectomy, with or without axillary dissection, axillary sampling or sentinel node biopsy. Women with a previous diagnosis of breast cancer were not eligible for inclusion.

Types of interventions

Radiation delivered to the partial breast (PBI) and PBI using larger than standard radiation dose per fraction such that the overall treatment time was reduced (APBI). We considered any method of PBI/APBI delivery including, but not limited to, intracavitary brachytherapy or MammoSite®, interstitial brachytherapy, intra-operative techniques such as electrons or x-rays at 50 kVp or EBRT using either 3D-CRT or other methods. Conventional breast RT is delivered to the whole breast with or without the supra-clavicular fossa and axilla, using standard fractionation (1.8 to 3.0 Gy per fraction) to deliver a total of 40 to 61 Gy at the reference point. Treatment could include a boost (using electrons, interstitial therapy, EBRT or new techniques).

Types of outcome measures

Primary outcomes

1. Local recurrence-free survival (LR-FS) in the ipsilateral breast. We defined local recurrence as a recurrence of the same histological type of cancer within the same quadrant of the breast as the primary cancer.
2. Cosmesis (cosmetic outcome or breast appearance).

Secondary outcomes

1. Overall survival (OS, time from date of randomization to death from any cause, or number of deaths from any cause).
2. Toxicity (including acute and late effects of RT, chemotherapy-related toxicity and surgical toxicity; individual protocol-based definitions).
3. New primary tumours in ipsilateral breast, 'elsewhere primary'. We defined a new primary as a lesion arising in a quadrant of the breast that was different from the original cancer or a tumour of

a different histological subtype occurring anywhere within the breast.

4. Cause-specific survival (C-SS, deaths due to breast cancer at five years).
5. Distant metastasis-free survival (DM-FS, in isolation or at the same time as local recurrence (the occurrence of metastases at five years)).
6. Relapse-free survival (R-FS, length of time after treatment during which no recurrence was found). Recurrence referred to breast cancer in the ipsilateral breast or elsewhere in the body, excluding a new breast cancer in the contralateral breast.
7. Loco-regional recurrence-free survival (L-RR-FS, comprised local recurrence, "elsewhere" ipsilateral breast primaries (a new primary cancer in the same breast) and regional nodal relapse).
8. Subsequent mastectomy (ipsilateral partial mastectomy, modified radical mastectomy or radical mastectomy).
9. Compliance, defined as the number of women who commenced treatment with PBI/APBI or conventional external beam radiotherapy (EBRT) and completed the treatment course.
10. Costs (monetary costs of PBI versus EBRT) to women, government and insurance companies.
11. Quality of life (using trial-specific instruments). The effects of PBI/APBI and EBRT on global quality of life and the physical, emotional and psychological domains.
12. Consumer preference, that is, did women prefer PBI/APBI or WBRT given the advantages and disadvantages of each approach.

Search methods for identification of studies

Electronic searches

Electronic databases

We searched the following databases:

1. the Cochrane Breast Cancer Group Specialized Register (4 May 2015). Details of search strategies used to identify studies and the procedure used to code references are outlined in the group's module ([Cochrane Breast Cancer Group](#)). We extracted studies on the specialized register with keywords 'early breast cancer', 'radiotherapy', 'partial breast irradiation', 'whole breast irradiation', 'whole breast radiotherapy', 'brachytherapy', 'high-dose-rate brachytherapy', 'accelerated partial breast irradiation', 'tumour bed boost', 'sole tumour bed irradiation', 'MammoSite', 'radiotherapy', 'PBI', 'APBI' and 'interstitial brachytherapy' for consideration;
2. the Cochrane Central Register of Controlled Trials (CENTRAL) (2015, Issue 3; [Appendix 1](#));
3. MEDLINE (January 1966 to 4 May 2015; [Appendix 2](#));
4. EMBASE (1980 to 4 May 2015; [Appendix 3](#));
5. CINAHL (1981 to 4 May 2015; [Appendix 4](#));
6. Current Contents (1998 to 4 May 2015; [Appendix 5](#)).

We modified the MEDLINE search strategy ([Appendix 2](#)) to search the other databases, without language restrictions.

Unpublished literature

We searched following registers for ongoing clinical trials:

1. the International Standard Randomised Controlled Trial Number Register (www.controlled-trials.com/iscrtcn) (5 May 2015);
2. the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) search portal (apps.who.int/trialsearch/Default.aspx) (4 May, 2015; [Appendix 6](#));
3. US clinical trials registry (www.clinicaltrials.gov) (17 June 2015; [Appendix 7](#)).

Grey literature

We checked OpenGrey (www.opengrey.eu/) (17 June 2015; [Appendix 8](#)).

Searching other resources

We contacted researchers located from the grey literature and unpublished literature to ask if they were aware of any other trials on this topic. We contacted the Barcelona authors on 15 October 2012 for more information. We contacted the IRMA authors on 2 October 2012 and they supplied us with the trial protocol. We contacted the authors of [Polgár 2007](#) on 24 August 2013; we gratefully received and incorporated data from the authors of [Polgár 2007](#) in November 2013.

Handsearching

We handsearched a number of conference proceedings and published abstracts including:

1. Adjuvant Therapy for Primary Breast Cancer International Conference (2001);
2. Primary Therapy of Early Breast Cancer (2001 and 2003);
3. 6th and 7th Nottingham International Breast Cancer Meeting Conference Reports;
4. 23rd and 24th Congress of the International Association for Breast Cancer Research;
5. 3rd and 4th Perspectives in Breast Cancer Conference Reports;
6. 26th and 27th Annual San Antonio Breast Cancer Symposium;
7. 4th European Breast Cancer Conference;
8. 94th and 95th American Association of Cancer Research;
9. American Society for Clinical Oncology (1995 to 2005);
10. European Society for Therapeutic and Radiation Oncology (1990, 1993, 2000 to 2010, 2012);
11. 5th and 6th Milan Breast Cancer Conference;
12. Australian Breast Cancer Conference (2004);
13. 27th and 28th Annual Symposium of the American Society of Breast Disease;
14. Centers for Disease Control and Prevention (CDC) Cancer Conference (2003);
15. International Journal of Radiation Oncology Biology Physics: proceedings of American Society for Radiation Oncology (ASTRO) 2011 to 2015;
16. Radiotherapy and Oncology: Proceedings of World Congress of Brachytherapy 2012;
17. American Society of Clinical Oncology (ASCO) from 1995 to 2010.

Data collection and analysis

Selection of studies

Three review authors (ML, BH and DF) checked the titles and abstracts retrieved by the searches. Each review author independently assessed the full text of the studies thought relevant to the review and we resolved any differences in assessment by discussion. We performed trial assessments with the results masked. In cases where data were limited or information on trial methods was limited, we requested further information from the trial authors.

Data extraction and management

Two review authors (ML and BH) performed data extraction and resolved disagreements through discussion. We entered data into Review Manager 5 for analysis (RevMan 2012). Where possible, we extracted data on tumour stage, nodal status, margin status, receptor status, hormonal manipulation, treatment allocation and surgery performed. The information extracted on RT included overall treatment time, radiation dose, dose per fraction and method of PBI. We extracted outcome data on local recurrence, deaths (all-cause and breast cancer deaths), new ipsilateral primaries, mastectomy rate, distant metastases, treatment-related toxicity (including that related to acute and late effects of RT and to surgery), cosmesis, costs of treatment, consumer preference and quality of life.

We derived data for OS, LR-FS, DM-FS, disease-free survival and C-SS from information in the text (ELIOT; Livi 2015; RAPID; Rodriguez; TARGIT) and data received from trial authors (Polgár 2007). Trial authors of Polgár 2007 provided the HR, 95% CI and P values, together with the number of events with further follow-up. We used the spreadsheet developed by Matthew Sydes (Tierney 2007) to derive O-E (observed minus expected events) and variance using the number of events, HRs, P values where available or calculated using the Review Manager 5 calculator (RevMan 2012). Although there were data for loco-regional recurrence for ELIOT, we did not include them in the analysis, because some women were treated with regional nodal RT.

We converted the radiation doses to the equivalent dose in 2 Gy fractions (EQD₂) (Maciejewski 1986; Withers 1983), using the formula: $EQD_2 = D [d + (\alpha/\beta)/2 + \alpha/\beta]$, where D = total dose, d = dose per fraction and $\alpha/\beta = 4$ Gy (Owen 2006). This was to facilitate comparison of radiation doses given at differing dose per fraction.

We plan to convert brachytherapy (radiation sources applied directly to the body) to the biological equivalent dose (BED) using the method of Stitt 1992 should it be necessary to pool brachytherapy data in future updates of this review.

Studies reported global cosmetic outcome using the Harvard Cosmetic Score (Polgár 2007; Livi 2015; Rodriguez), the European Organization for Research and Treatment of Cancer (EORTC) Cosmetic rating System for Breast Cancer (Aaronson 1998; RAPID), and a software program (TARGIT). These were all four-point scales; the results were dichotomized into good/excellent and fair/poor, with occurrence of fair/poor being counted as 'events'. See Table 1.

One study reported telangiectasia (RAPID; using NCI CTCAE Version 3.0; also a three-point scale): we recorded any women with Grade 2 or higher toxicity as having events.

Three studies reported radiological or asymptomatic fat necrosis (ELIOT; Polgár 2007; RAPID); we were able to report Grade 1 fat necrosis, as this had the same definition in all three scales.

Assessment of risk of bias in included studies

BH and ML assessed trials to check that they met the inclusion criteria and independently assessed methodological quality. BH undertook 'Risk of bias' tables assessments, which were checked by ML, and reported them in the text and as a figure.

We described the risk of bias for each included trial. BH and ML judged risk of bias in eight specific domains, and resolved any differences through discussion. The eight domains were:

1. random sequence generation;
2. allocation concealment;
3. blinding of participants and personnel;
4. blinding of outcome assessors for objective outcomes;
5. blinding of outcome assessors for subjective outcomes;
6. incomplete outcome data;
7. selective outcome reporting;
8. other sources of bias (i.e. early stopping and differences in follow-up examinations).

We will perform sensitivity analyses on the basis of trial quality when additional trials are available. We plan to perform the analysis both with and without trials at low risk of bias to assess the effect of bias on the results when more trials are available to examine.

Measures of treatment effect

We presented results as hazard ratios (HR) for time-to-event data and odds ratios (OR) with 95% confidence intervals (CI) where this was not possible (Deeks 2004).

For future updates, if we find results for continuous variables (such as quality of life), we will summarize them using the mean difference or the standardized mean difference when different measurement scales are used (Deeks 2004).

Unit of analysis issues

Because the unit of analysis was the individual participant, we did not anticipate any unit of analysis issues.

Dealing with missing data

If data are missing in future updates, we will contact the original investigators (by written correspondence).

We will specify what assumptions we make, for example, if we presume the missing data were missing at random, or that missing data were assumed to have a particular value such as a poor outcome. We will, if necessary, perform a sensitivity analysis to see how sensitive results are to the assumptions we have made. We will address the potential implications of this in the 'Discussion' section.

Assessment of heterogeneity

We assessed heterogeneity both visually and statistically using the χ^2 test of heterogeneity (Altman 1992; Walker 1988), and I^2 statistic (Higgins 2002; Higgins 2003). The criterion for identification of heterogeneity is a P value less than 0.10 for the χ^2 test (acknowledging the limitations of this process) and an I^2 statistic greater than 50%. Where we identified significant heterogeneity, we explored the reasons for it and made a cautious attempt to explain the heterogeneity.

Assessment of reporting biases

We acknowledge that there are multiple potential sources of reporting biases, including, but not limited to, publication bias, time-lag bias, duplicate publication bias and selective outcome reporting. By searching multiple sources including trial registries, we hope to minimize publication bias. We noted the early reporting for the TARGIT was an example of time-lag bias. We planned to use funnel plots to evaluate funnel plot asymmetry, but took into account that visual interpretation is subjective and that statistical methods to evaluate funnel plot asymmetry are unlikely to be valid if there are fewer than 10 included trials.

Data synthesis

We applied the intention-to-treat principle in analyzing data from the trials and determined a weighted mean treatment effect using the fixed-effect model to combine results (Mantel 1959) with Review Manager 5 software (RevMan 2012).

We used the Mantel-Haenszel methods to calculate pooled results when there was no significant heterogeneity (Greenland 1985; Mantel 1959), or if otherwise, the random-effects model of Der Simonian and Laird (DerSimonian 1986).

We excluded two studies from the analysis (Dodwell 2005; Ribeiro 1993), because they used staging, surgery and RT techniques that do not reflect current practice (see [Characteristics of excluded studies](#) table).

We graded the quality of the evidence and created a 'Summary of findings' table using the following outcomes.

1. LR-FS.
2. Cosmesis.
3. Mortality (follow-up: 5-year survival).
4. Late toxicity: late subcutaneous breast fibrosis.
5. C-SS.
6. DM-FS.
7. Subsequent mastectomy.

The population included women with early breast cancer and the intervention was PBI/APBI versus WBRT. We used GRADEpro and the GRADE approach to evaluate the strength of the evidence (GRADE Working Group 2004). To calculate the absolute risk for the control group for time-to-event outcomes, we estimated the event

rate at a specific time point (five years for LR-FS, BC-SS, DM-FS and OS) from the Kaplan-Meier curves or reported event rates. We entered these estimated values in GRADEpro, which automatically calculated the corresponding absolute risks for the intervention group at five years.

Subgroup analysis and investigation of heterogeneity

In future updates if data are available, we may perform subgroup analyses to investigate whether the effects of using PBI/APBI or conventional breast RT differ depending on nodal status, margin status, receptor status, hormonal manipulation or tumour stage.

If heterogeneity is identified in future updates, we will assess it both statistically and visually using the χ^2 test of heterogeneity (Altman 1992; Walker 1988), and I^2 statistic (Higgins 2002; Higgins 2003). If we do identify significant heterogeneity, we will explore the reasons for it and attempt to explain it.

Sensitivity analysis

We performed a sensitivity analysis by excluding the trials at high risk of bias for subjective outcomes (ELIOT; Livi 2015; Polgár 2007; Rodriguez). In future updates, if adequate data are available, we will perform a sensitivity analysis to assess the robustness of the results by excluding studies at high risk of bias for subjective outcomes and unpublished trials.

RESULTS

Description of studies

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

Results of the search

For this review update, based on our search strategy, we identified and screened 3630 references from the major medical databases and identified 46 additional references from other sources. After exclusion of duplicates and screening of references (by title or abstract), we evaluated 46 full-text references and excluded eight references (see [Characteristics of excluded studies](#) table). Of the remaining 38 references, 17 records related to five new included studies (ELIOT; GEC-ESTRO; Livi 2015; RAPID; Rodriguez), six records provided data for two previously included studies (Polgár 2007; TARGIT), 14 records for four ongoing studies (IMPORT; IRMA; NSABP-B39/RTG; SHARE), and one record for one study awaiting classification (NCT02375048).

Overall, when combining the original and review update, there were 44 records relating to seven included studies, 14 records relating to four ongoing studies and one record awaiting classification (see [Figure 1](#)). Two studies that were included in the original review have now been excluded (Dodwell 2005; Ribeiro 1993). This is because the surgery and techniques used to define volume of breast treated and the technology used in these two studies do not reflect current RT practice. In sum, this review update included seven studies and the qualitative analysis included six studies.

Figure 1. Study flow diagram.

Included studies

Design

Seven RCTs enrolled 8955 women ([ELIOT](#); [GEC-ESTRO](#); [Livi 2015](#); [Polgár 2007](#); [RAPID](#); [Rodriguez](#); [TARGIT](#)); we studied 7586 women included in these studies. These studies enrolled women from July 1998 to May 2004 ([Polgár 2007](#)), February 2006 to July 2011 ([RAPID](#)), November 2000 to December 2007 ([ELIOT](#)), March 2000 to June 2011 ([TARGIT](#)), March 2005 to June 2013 ([Livi 2015](#)), and April 2004 to July 2009 ([GEC-ESTRO](#)); [Rodriguez](#) did not state accrual dates.

Sample size

[Polgár 2007](#) enrolled 258 women of a planned sample size of 570 participants, [RAPID](#) enrolled 2135 women, [Rodriguez](#) enrolled 102 women, [ELIOT](#) enrolled 1305 women, [TARGIT](#) enrolled 3451 women, [Livi 2015](#) enrolled 520 women and [GEC-ESTRO](#) enrolled 1184 women.

Setting

Four studies were single institution trials from tertiary institutions: one in Hungary ([Polgár 2007](#)), two in Italy ([ELIOT](#); [Livi 2015](#)), and one in Spain ([Rodriguez](#)). [GEC-ESTRO](#), [TARGIT](#), and [RAPID](#) were multicentred, international studies.

Participants

[Polgár 2007](#) included women with invasive breast cancer after wide local excision of tumour and negative pathological margins (unifocal tumours, tumour size less than 20 mm, clinically or pathologically N0, or single microscopic nodal metastasis (greater than 0.2 mm and less than 2.0 mm), that is, pT1N0-1miM0, Grade I or II; T1N0-N1miM0, Grade I or II. [RAPID](#) enrolled women with either invasive ductal carcinoma or ductal carcinoma in situ with tumours 3.3 cm or greater, with negative margins and no involved axillary nodes. [Rodriguez](#) included women with pT1-2pN0M0 invasive ductal carcinoma, with tumour size 3 cm or less, with negative margins and Grade I or II histology. [ELIOT](#) enrolled women aged 48 to 75 years with early breast cancer, maximum tumour diameter 2.5 cm, "suitable for breast conservation". [TARGIT](#) enrolled women aged 45 years or over, with T1 and small T2N0-1M0 invasive breast cancer, suitable for breast-conserving surgery, available for 10 years' follow-up. [Livi 2015](#) included women aged over 40 years who had wide local excision or quadrantectomy for invasive breast cancer, negative margins and tumour size 2.5 cm or less. [GEC-ESTRO](#) included women aged 40 years or more, small T1-2N0-miM0 (less than 3 cm) with negative margins and no lympho-vascular invasion (LVI) and excluded women with multifocal tumours. [GEC-ESTRO](#) included Tis. See [Characteristics of included studies](#) table.

Interventions

Experimental arm

PBI using either:

1. brachytherapy:
 - a. high-dose-rate (HDR) brachytherapy: seven $\times$ 5.2 Gy HDR multi-catheter brachytherapy for 88/128 women ([Polgár 2007](#)); 30.3 to 32.0 Gy/seven or eight fractions ([GEC-ESTRO](#));
 - b. pulsed-dose-rate (PDR) brachytherapy: 50 Gy at 0.6 to 0.8 Gy/hour in [GEC-ESTRO](#) or

2. EBRT to partial breast. PBI delivered via EBRT was delivered:
 - a. via conventionally fractionated (2 Gy per fraction) in 50 Gy/25 fraction electron beam RT delivered using a linear accelerator to the partial breast for 40/128 women ([Polgár 2007](#));
 - b. at greater than 2 Gy per fraction delivered using a linear accelerator. [RAPID](#) used 3D-CRT in 38.5 Gy/10 fractions over five to eight days (with a minimum six hour gap between fractions given on the same day) and [Rodriguez](#) used 37.5 Gy/10 fractions twice daily over five days. [Livi 2015](#) delivered 30 Gy in five fractions using intensity-modulated radiotherapy (IMRT);
 - c. using electrons: intraoperative electron therapy to deliver 21 Gy in one fraction at the 90% isodose delivered at the time of surgery after tumour excision using 6 to 9 MeV ([ELIOT](#));
 - d. using kilovoltage EBRT: [TARGIT](#) used a single fraction of RT given intraoperatively (using Intrabeam); 50 kV 20 Gy/one fraction at 2 mm beyond surface of 1.5 to 5.0 cm spherical applicator placed in excision cavity.

Control arm

WBRT using conventional fractionation:

1. [ELIOT](#) and [Polgár 2007](#) used 50 Gy/25 fractions WBRT;
2. [RAPID](#) permitted two doses for WBRT: 50 Gy/25 fractions or 42.5 Gy/16 fractions;
3. [Rodriguez](#) gave 48 Gy in 24 fractions;
4. [TARGIT](#) gave "Standard post-operative RT (40 to 56 Gy $\pm$ 10 to 16 Gy boost)";
5. [Livi 2015](#) used 50 Gy/25 fractions plus 10 Gy boost;
6. [GEC-ESTRO](#) used 50 to 50.4 Gy in 1.8 to 2.0 Gy/fraction using 4 to 10 MV beams plus 10 Gy/5 fraction boost.

Co-interventions

Chemotherapy and hormonal manipulation: in [Livi 2015](#), [Polgár 2007](#), [GEC-ESTRO](#), [RAPID](#), and [TARGIT](#), women received adjuvant systemic therapy according to institutional protocol, and [Rodriguez](#) treated oestrogen receptor positive women with hormonal manipulation. Systemic therapy in [ELIOT](#) was "administered according to the European Institute of Oncology policy" at the time (see [Characteristics of included studies](#) table for further details). In total, 6372/6820 (93%) women received hormonal manipulation and 977/6820 (14.3%) of the women received chemotherapy.

[ELIOT](#) treated any women with four or more involved nodes with regional nodal RT. No women in any of the other included studies received regional nodal RT.

Outcomes

Primary outcomes

Local recurrence-free survival

Six trials reported local recurrence in the ipsilateral breast as a discrete outcome ([GEC-ESTRO](#); [Rodriguez](#); [ELIOT](#); [Livi 2015](#); [Polgár 2007](#); [TARGIT](#)).

Cosmesis

Six trials reported cosmesis (cosmetic outcome). [Polgár 2007](#), [Livi 2015](#), and [Rodriguez](#) reported a global cosmetic result (used the Harvard Cosmetic score (see [Table 1](#))) and [RAPID](#) used the EORTC Cosmetic rating System for Breast Cancer ([Aronson](#)

1998); both were four-point scales. [GEC-ESTRO](#) evaluated cosmesis using digital photos, with both participant-reported outcomes and physician-reported outcomes using a four-point scale ([Wazer 1992](#); see [Table 2](#)). [Rodríguez](#) and [RAPID](#) reported participant-reported cosmetic outcomes. [RAPID](#) blinded assessment of cosmetic outcome. [TARGIT](#) assessed cosmetic outcome at a single centre in a sub-study that included 105 women. A software program, blinded to treatment arm, assessed digital photos at a median 23 months using a four-point scale.

Secondary outcomes

Overall survival

Six trials reported OS ([GEC-ESTRO](#); [Rodríguez](#); [ELIOT](#); [Livi 2015](#); [TARGIT](#); [Polgár 2007](#)).

Toxicity

Four trials reported acute skin toxicity. [Rodríguez](#), [Livi 2015](#), and [TARGIT](#) used the Radiation Therapy Oncology Group Common Toxicity Criteria (RTOG CTC) ([Cox 1995](#); [Table 3](#)) and [ELIOT](#) used a five-point scale (which was not referenced).

Five trials reported late toxicity (telangiectasia (small blood vessels visible on the treated skin), breast pain, fat necrosis and subcutaneous fibrosis). [Polgár 2007](#) reported fat necrosis at four years according to a five-point institutional scale ([Table 4](#)); [RAPID](#) reported late RT toxicity (telangiectasia, induration (subcutaneous fibrosis), breast pain and fat necrosis) using the National Cancer Institute Common Toxicity Criteria (NCI CTC 3.0; [NCI](#); three-point scales; [Table 5](#)). [GEC-ESTRO](#) reported late toxicity (breast pain, late subcutaneous toxicity and late RT skin toxicity) using the RTOG CTC ([Cox 1995](#)). [ELIOT](#) reported fat necrosis and radiological radiation pneumonitis using late effects of normal tissue - subjective objective management analytic criteria (LENT-SOMA; [Pavy 1995](#)). [Livi 2015](#) scored late RT toxicity using RTOG CTC ([Cox 1995](#)). [TARGIT](#) reported "complications arising six months after randomisation" and reported RTOG CTC ([Cox 1995](#)) Grade III or IV RT-related skin complications, haematomas/seromas requiring greater than three aspirations or surgery, wound infections requiring intravenous antibiotics or surgery and skin breakdown/delayed wound healing.

New primary tumours in ipsilateral breast ('elsewhere primaries')

Three trials reported new primary tumours in ipsilateral breast ([ELIOT](#); [GEC-ESTRO](#); [Livi 2015](#)).

Cause-specific survival

Five trials reported C-SS (where an independent clinician, blinded to treatment arm, determined cause of death) ([ELIOT](#); [GEC-ESTRO](#); [Livi 2015](#); [Polgár 2007](#); [TARGIT](#)).

Distant metastasis-free survival

Five trials reported DM-FS ([ELIOT](#); [GEC-ESTRO](#); [Livi 2015](#); [Polgár 2007](#); [Rodríguez](#)).

Relapse-free survival

One trial reported R-FS ([Polgár 2007](#)).

Loco-regional recurrence-free survival

Three trials reported L-RR-FS ([ELIOT](#); [GEC-ESTRO](#); [TARGIT](#)).

Subsequent mastectomy

Three trials reported subsequent mastectomy ([GEC-ESTRO](#); [Polgár 2007](#); [TARGIT](#)).

Compliance

Three trials reported compliance ([GEC-ESTRO](#); [Polgár 2007](#); [TARGIT](#)).

Costs

We found no trials reporting cost.

Quality of life

Two trials reported quality of life. [RAPID](#) used the Breast Cancer Questionnaire (a validated modification of the Breast Cancer Chemotherapy Quality of Life Questionnaire; [Levine 1998](#)) and [GEC-ESTRO](#) used the EORTC QLQ-C30 and QLQ-BR23 ([Levine 1998](#)).

Consumer preference

We found no trials reporting consumer preference.

The included RCTs differed in several ways.

1. Population included: see above.
2. Surgery performed: margins were negative for women in [GEC-ESTRO](#) (2 mm or greater); [Rodríguez](#) (greater than 3 mm); [Polgár 2007](#) (less than 2 mm: 1/258, 2 mm or greater: 246/258 or had no tumour at ink: 11/258); [RAPID](#) ("microscopically clear") and [TARGIT](#) (1 mm or greater). [ELIOT](#) did not describe margin status. Surgery in [Livi 2015](#) could be either wide local excision or quadrantectomy (margins 5 mm or greater); in [TARGIT](#) if margins were close/involved (invasive disease or in situ disease 1 mm or greater from margin) re-excision was strongly advised.
3. Target volume definition for the treated PBI/APBI volume varied between the trials. [Polgár 2007](#) clipped the cavity and the planning target volume (PTV) comprised the cavity plus a 1 to 2 cm margin isotropically (in all directions three dimensionally) for those women treated with interstitial therapy. If electrons were used, 6 to 15 MeV were used to treat the cavity with a 2 cm margin. In [RAPID](#), the clinical target volume (CTV) was defined as the tumour bed seen on computer tomography (CT), including the surgical clips plus a 1 cm margin, with a 1 cm margin on CTV to derive PTV. In [Rodríguez](#), the involved breast quadrant was contoured. In [ELIOT](#), the "clinical target volume was decided according to the site and size of the tumour". In [Livi 2015](#), a CTV was drawn on a planning CT with a uniform 1 cm margin around the surgical clips, then a 1 cm margin added to construct the PTV. The target volume was the tumour cavity for [TARGIT](#). In [GEC-ESTRO](#), the target volume was defined individually for each woman, the CTV was the tumour bed plus a "safety margin" 2 cm or greater, this was planned using CT.
4. Radiation dose prescribed differed greatly between the trials. The PBI/APBI arm dose was higher than the WBRT dose for all studies except [ELIOT](#) (see [Table 6](#) for dose, fraction size and dose prescription point, where it was specified).
5. The trials differed in fractionation used for APBI. In [Polgár 2007](#), most women (88/128) received accelerated RT, [RAPID](#) used 3.85 Gy fractions, [Rodríguez](#) delivered 3.75 Gy fractions using daily RT and [Livi 2015](#) used 6 Gy per fraction. [GEC-ESTRO](#) used seven or eight fractions for HDR and 0.6 to 0.8 Gy pulses for PDR. [ELIOT](#) used 21 Gy at the 90% isodose delivered in a single fraction.

TARGIT used 20 Gy to the cavity surface delivered in a single fraction (Table 6).

6. RT technique for PBI/APBI delivery differed. In Polgár 2007, most women (88/128) in the PBI/APBI arm received interstitial brachytherapy, but 40/128 women received EBRT, as they were not suitable for brachytherapy (Table 7). RAPID and Rodriguez used 3D-CRT (using EBRT); Livi 2015 used IMRT to deliver EBRT; ELIOT delivered intraoperative electron therapy at the time of surgery after tumour excision using 6 to 9 MeV and TARGIT inserted a spherical applicator into the operative bed and sutured it in place to treat the tumour cavity (see Table 7).
7. Quality assurance differed. RAPID included an extensive quality assurance programme with credentialing, real-time and post-hoc review of radiation quality. GEC-ESTRO involved both pre- and post-implant assessment of geometry using CT, dose prescription and calculations were in accordance with International Commission of Radiation Units and Measurements (ICRU) 58 and strict dose volume histogram and dose maximums were mandated, the post-hoc quality assurance requirements were clearly detailed in the study protocol. For the WBRT component of TARGIT, as long as treating centres conformed to a formal quality management system issued by the International Standards Organization, no additional quality assurance was required. For the APBI, quality assurance performed according to the manufacturer's instructions was to be performed and the resulting data to be made available to the trials centre. Data were submitted either annually or after every 50th participant treated with Intrabeam. Rodriguez, ELIOT, and Livi 2015 did not mention trial-specific quality assurance to assess quality of the delivered RT. Polgár 2007 did not mention quality assurance for APBI using electrons or WBRT.
8. One study did not accrue the full sample size: Polgár 2007 stopped early because a competing multicentred RCT was started.

Excluded studies

In the 2015 review update, we excluded eight studies (see Characteristics of excluded studies table).

Risk of bias in included studies

Allocation

We judged the risk of bias for random sequence generation and allocation concealment as follows: ELIOT, GEC-ESTRO, Livi 2015, Livi 2015, RAPID, Rodriguez, and TARGIT were at low risk of bias for sequence generation. Polgár 2007 was randomized, the method (sealed envelopes) described and allocation was done by the chief investigator. TARGIT, Livi 2015, and GEC-ESTRO were at low risk of bias for allocation concealment. ELIOT, RAPID, Rodriguez, and Polgár 2007 did not clearly report allocation concealment, so were at unclear risk of bias.

Blinding

Objective outcomes

RAPID and Rodriguez did not mention blinding of participants. It would have been difficult to do so with this intervention, but the lack of blinding was unlikely to have introduced bias (Polgár 2007). Participants in GEC-ESTRO, Livi 2015, and TARGIT were not blinded to treatment arm, but we considered this unlikely to introduce bias.

ELIOT did not blind participants; for objective outcomes, the clearly pre-specified criteria for endpoints and the pre-specified follow-up protocol meant we deemed this domain at low risk of bias.

The trials did not mention blinding of physicians. It would have been difficult to do so with this intervention, but failure to do so is less likely to have introduced bias when the mammographic screening interval was pre-specified as in GEC-ESTRO, Livi 2015, RAPID, and Rodriguez. Polgár 2007 had a pre-specified follow-up protocol with pre-determined interval for mammographic evaluation and Polgár 2007 and Rodriguez required biopsy confirmation for any local recurrence; therefore, this domain was at low risk of bias. This served to make the objective outcomes at low risk of bias. In TARGIT, physicians were not blinded to treatment allocation, which is unlikely to have been a source of bias.

ELIOT did not blind personnel; for objective outcomes, the clearly pre-specified criteria for endpoints and the pre-specified follow-up protocol meant we deemed this domain at low risk of bias.

Polgár 2007 did not mention blinding of outcome assessors, but the pre-determined mammographic follow-up protocol and requirement for biopsy confirmation of local recurrence would have reduced the risk of bias. TARGIT did not blind outcome assessors, but the pre-specified follow-up protocol minimized the risk of bias. TARGIT reported that the analyses were done blinded, which reduced the risk of bias. ELIOT, GEC-ESTRO, Livi 2015, RAPID, and Rodriguez were at low risk of bias for this outcome.

Subjective outcomes

Blinding of participants for subjective outcomes was not reported, but it is unlikely to have introduced bias because only two trials reported participant-reported outcomes (RAPID; Rodriguez).

Polgár 2007 and Livi 2015 did not mention blinding of physicians and this may have introduced bias. In RAPID, the physician reviewers were blinded to treatment arm; this was not stated for the trained nurse observers, but we deemed the outcome at low risk of bias despite this.

As Polgár 2007 did not mention blinding of outcome assessors, it is unlikely to have been done and is potentially a source of bias and, therefore, at high risk of bias. The authors of TARGIT did not report blinding of outcome assessors, so it seems unlikely that they were. However, the use of a pre-determined data collection form for toxicity would have reduced the risk of bias, because data were collected for all women studied. TARGIT performed a blinded assessment of cosmesis in a sub-set of 105 women. The outcome assessors in ELIOT and GEC-ESTRO were not blinded for assessment of subjective outcomes, so we deemed this domain at high risk of bias. In Rodriguez, although they noted a participant-reported outcome, more data came from the physicians (not blinded to treatment arm), so this outcome of cosmesis was at high risk of bias.

Incomplete outcome data

ELIOT excluded no women, none were lost to follow-up and there was no attrition reported, thus this study was at low risk of bias. Polgár 2007 excluded no women and they reported attrition by arm (without providing reasons), and the risk of bias was low. GEC-ESTRO reported on all women randomized, and they reported post-randomization exclusions by arm, with reasons, so we deemed this at low risk of bias. RAPID and Rodriguez were both interim reports of

ongoing studies, so they were at unclear risk of bias for this domain. [Livi 2015](#) reported no exclusion or attrition, so we deemed this at low risk of bias. [TARGIT](#) was at low risk of bias for this domain.

Selective reporting

For [ELIOT](#), [Livi 2015](#), and [Polgár 2007](#), the trial protocols were not available for review and we judged them at unclear risk of bias. [TARGIT](#) did not report on all the outcomes pre-specified in the protocol, but it is likely that these outcomes will form the basis of future publications so we judged this at low risk of bias. [RAPID](#) and [Rodriguez](#) were interim reports; therefore, we deemed them at unclear risk of bias. [GEC-ESTRO](#) did not report on all their planned

outcomes, but stated they will be the subject of a future paper, so we deemed this domain at low risk of bias.

Other potential sources of bias

Regarding other potential sources of bias: [Polgár 2007](#) had low risk of bias. [Polgár 2007](#) stopped the trial early because a competing trial started recruiting ([GEC-ESTRO](#)). [TARGIT](#) had short median follow-up, which put it at high risk of bias (see [Figure 2](#)). [RAPID](#) and [Rodriguez](#) were interim reports; therefore, we deemed them at unclear risk of bias. We identified no other sources of bias [GEC-ESTRO](#), [Livi 2015](#), or [ELIOT](#), so deemed them at low risk of bias (see [Figure 2](#)).

Figure 2. 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
ELIOT	+	?	+	+	+	-	+	?	+
GEC-ESTRO	+	+	+	+	+	-	+	+	+
Livi 2015	+	+	+	+	+	-	+	?	+
Polgár 2007	+	?	+	+	+	-	+	?	+
RAPID	+	?	+	+	+	+	?	?	?
Rodriguez	+	?	+	+	+	-	?	?	?
TARGIT	+	+	+	+	+	+	+	+	-

Effects of interventions

See: [Summary of findings for the main comparison Partial breast irradiation \(PBI\)/accelerated partial breast irradiation \(APBI\) for early breast cancer](#)

Partial breast irradiation for early breast cancer (Review)

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Primary outcomes

Local recurrence-free survival in the ipsilateral breast

There were 89 local recurrences in the 6820 women studied in six studies.

LR-FS appeared worse with PBI/APBI (HR 1.62, 95% CI 1.11 to 2.35; six studies, 6820 participants; [Analysis 1.1](#); [Figure 3](#)). There was evidence of heterogeneity on visual inspection and statistical testing (P value = 0.008, I^2 = 71%).

Figure 3. Forest plot of comparison: 1 Partial breast irradiation (PBI)/accelerated partial breast irradiation (APBI) versus whole breast radiotherapy (WBRT), outcome: 1.1 Local recurrence-free survival.

We performed sensitivity analysis based on excluding studies deemed at high risk of bias (for the domains of objective outcomes and other bias; [TARGIT](#)). We found PBI/APBI versus WBRT was associated with worse LR-FS (HR 1.48, 95% CI 0.95 to 2.29). There appeared to be some evidence of heterogeneity both on visual inspection and statistical testing (P value = 0.07, I^2 = 68.6%).

Cosmesis

Cosmetic outcome appears worse with PBI/APBI when:

1. participant-reported (OR 1.74, 95% CI 1.06 to 2.87; P value = 0.03, not tested for heterogeneity). We identified 89 events in 328 participants from one study ([RAPID](#));
2. assessed by trained nurse observers (OR 3.14, 95% CI 1.81 to 5.45; P value < 0.0001). We did not test for heterogeneity, as we studied 78 events in 335 participants deriving from one study ([RAPID](#));
3. physician-reported (OR 1.51, 95% CI 1.17 to 1.95; P value = 0.002). There was considerable heterogeneity (I^2 = 88%; P

value = 0.00004; [Analysis 1.2](#)). We studied 315 events in 1720 participants in five studies.

We performed sensitivity analysis by excluding studies at high risk of bias for blinding of outcome assessors for subjective outcomes ([ELIOT](#); [Livi 2015](#); [Polgár 2007](#); [Rodriguez](#)) for physician reported cosmesis. We found cosmesis was worse with PBI/APBI versus WBRT (OR 2.32, 95% CI 1.69 to 3.18; P value = 0.00001). Testing for heterogeneity revealed the presence of considerable heterogeneity (I^2 = 84%; P value = 0.01).

Secondary outcomes

Overall survival

We found no difference in OS with PBI/APBI versus WBRT with data from 268 deaths in five studies with 6718 participants (HR 0.90, 95% CI 0.74 to 1.09; P value = 0.27; [Analysis 1.3](#); [Figure 4](#)). There was no heterogeneity on either visual inspection or statistical testing (I^2 = 40%; P value = 0.15).

Figure 4. Forest plot of comparison: 1 Partial breast irradiation (PBI)/accelerated partial breast irradiation (APBI) versus whole breast radiotherapy (WBRT), outcome: 1.3 Overall survival.

Toxicity

PBI/APBI reduced acute skin toxicity compared with WBRT (OR 0.04, 95% CI 0.02 to 0.09; P value < 0.00001; [Analysis 1.4](#)). We studied 150 events in 608 participants in two studies. We found little evidence of heterogeneity (I² = 27%; P value = 0.24).

There was no difference in haematomas needing surgical aspiration between APBI and WBRT (P value = 0.338; figure from text; [TARGIT](#)).

Seromas needing greater than three aspirations were more frequent with APBI compared with WBRT (P value = 0.012; figure from text; [TARGIT](#)).

There was no difference in infection requiring intravenous antibiotics or surgical intervention between APBI and WBRT (P value = 0.292; figure from text; [TARGIT](#)).

There was no difference in skin breakdown or delayed healing between APBI and WBRT (P value = 0.155; figure from text; [TARGIT](#)).

Regarding late toxicity:

1. there was no difference in late skin toxicity with PBI/APBI versus WBRT (OR 0.21, 95% CI 0.01 to 4.39; P value = 0.31; data from two events in 608 participants in two studies; [Analysis 1.5](#)). There was no difference in late RT skin toxicity between PBI and WBRT in [GEC-ESTRO](#) (P value = 0.08; figure from text);
2. telangiectasia appeared worse with PBI/APBI compared with PBI (OR 26.56, 95% CI 3.59 to 196.51; P value = 0.001; data from one study with 28 events in 766 evaluable women; [RAPID](#));

3. PBI/APBI increased radiological fat necrosis compared with WBRT (OR 1.58, 95% CI 1.02 to 2.43; P value = 0.04; three studies with 100 events in 1319 participants). We found little evidence of heterogeneity (I² = 49%; P value = 0.14; [Analysis 1.6](#));

4. PBI/APBI increased subcutaneous fibrosis compared with WBRT (OR 6.58, 95% CI 3.08 to 14.06; P value < 0.00001; data from one study with 59 events in 766 women). There was no difference in late subcutaneous toxicity between PBI and WBRT in [GEC-ESTRO](#) (P value = 0.53; figures from text);

5. there was no difference in breast pain with PBI/APBI versus WBRT (OR 2.17, 95% CI 0.56 to 8.44; P value = 0.27; 10 events in one study with 766 evaluable women); [ELIOT](#) reported no difference in breast pain (data not shown). Breast pain was reduced with PBI compared with WBRT in [GEC-ESTRO](#) (P value = 0.04; figures from text).

New primary tumours in ipsilateral breast 'elsewhere primaries'

New primaries in the treated breast appeared more frequent with PBI/APBI compared with WBRT (OR 3.97, 95% CI 1.51 to 10.41; [Analysis 1.7](#)). There were 24 events in 3009 participants in three studies. There was evidence of heterogeneity (I² = 74%; P value = 0.02).

Cause-specific survival

We found no clear evidence that C-SS differed with PBI/APBI versus WBRT (HR 1.08, 95% CI 0.73 to 1.58, 107 breast cancer deaths in 6718 participants in five studies; [Analysis 1.8](#); [Figure 5](#)). We found no evidence of heterogeneity on either visual inspection or statistical testing (I² = 0%; P value = 0.81; [Analysis 1.8](#)).

Figure 5. Forest plot of comparison: 1 Partial breast irradiation (PBI)/accelerated partial breast irradiation (APBI) versus whole breast radiotherapy (WBRT), outcome: 1.8 Cause-specific survival.

Distant metastasis-free survival

We found no clear evidence that DM-FS differed with PBI/APBI versus WBRT (HR 0.94, 95% CI 0.65 to 1.37, 110 events in 3267

participants in four studies; [Analysis 1.9](#); [Figure 6](#)). We found no heterogeneity with either visual inspection or statistical testing ($I^2 = 0\%$; P value = 1.0).

Figure 6. Forest plot of comparison: 1 Partial breast irradiation (PBI)/accelerated partial breast irradiation (APBI) versus whole breast radiotherapy (WBRT), outcome: 1.9 Distant metastasis-free survival.

Relapse-free survival

We found no clear evidence that R-FS differed with PBI/APBI versus WBRT (HR 1.36, 95% CI 0.88 to 2.09; P value = 0.16; 87 relapses in 3811 participants in three studies; [Analysis 1.10](#)). We found little evidence of heterogeneity ($I^2 = 46\%$; P value = 0.17). R-FS did not differ in [GEC-ESTRO](#) (P value = 0.79; figure from text).

Loco-regional recurrence-free survival

We found that L-RR-FS was worse with PBI/APBI versus WBRT (HR 1.80, 95% CI 1.00 to 3.25; [Analysis 1.11](#)). We studied 48 events in 3553 participants in two studies.

Subsequent mastectomy

Subsequent mastectomy rate did not appear to differ between PBI/APBI and WBRT (OR 1.20, 95% CI 0.77 to 1.87; [Analysis 1.12](#)). There were 79 events in 4817 participants in three studies. There was no evidence of heterogeneity ($I^2 = 0\%$; P value = 0.45).

Compliance

Greater than 90% of the women randomized to PBI/APBI received treatment in all of the included studies. For those women randomized to receive WBRT, greater than 90% of the women received the planned RT in all of the included studies.

Costs

There were no data on costs.

Quality of life

There were no data on quality of life, although it was assessed in [RAPID](#).

Consumer preference

There were no data on consumer preference.

DISCUSSION**Summary of main results**

LR-FS appeared worse with PBI/APBI compared with WBRT ([Analysis 1.1](#)). Cosmetic outcome appeared worse with PBI/APBI compared with WBRT when participant-reported (OR 1.74, 95% CI 1.06 to 2.87; P value = 0.03), assessed by trained nurse observers (OR

3.14, 95% CI 1.81 to 5.45; P value = 0.00001) or physician-reported (OR 1.51, 95% CI 1.17 to 1.95; P value = 0.002) ([Analysis 1.2](#)).

We found no evidence of a difference in OS when PBI/APBI was used compared with WBRT (HR 0.90, 95% CI 0.74 to 1.09; P value = 0.27; [Analysis 1.3](#)).

We found PBI/APBI versus WBRT was associated with decreased acute skin toxicity (OR 0.04, 95% CI 0.02 to 0.09; P value < 0.00001; [Analysis 1.4](#)). Late skin toxicity did not differ with PBI/APBI versus WBRT, neither did breast pain, but we found it was associated with more telangiectasia, radiologically evident fat necrosis and more subcutaneous fibrosis. We found PBI/APBI versus WBRT was associated with more 'elsewhere primaries' (OR 3.97, 95% CI 1.51 to 10.41; [Analysis 1.7](#)).

We found no clear evidence of a difference in C-SS ([Analysis 1.8](#)), DM-FS ([Analysis 1.9](#)) or R-FS ([Analysis 1.10](#)) with PBI/APBI compared with WBRT but we could not exclude potentially important differences between the treatment groups. We found no difference with PBI/APBI versus WBRT for L-RR-FS (HR 1.80, 95% CI 1.00 to 3.25; P value = 0.05; [Analysis 1.11](#)). The mastectomy rate did not appear affected with PBI/APBI compared with WBRT ([Analysis 1.12](#)). Compliance with allocated treatment was high at greater than 90% for all women studied. We found no data for the effects of PBI/APBI and WBRT on costs, quality of life and consumer preference.

Based on these findings, PBI/APBI appeared to be associated with worse LR-FS in comparison to WBRT. Local relapse was rare in the carefully selected participant population in this review. Local relapse was increased by 5 per 1000 women (range 1/1000 to 11/1000) with PBI/APBI. The use of PBI/APBI was associated with decreased acute toxicity. There was no strong evidence that PBI/APBI was associated with increased breast pain or late skin toxicity. We found that PBI/APBI caused increased telangiectasia, radiologically evident fat necrosis ([Table 4](#)) and subcutaneous fibrosis (see Results, Description of studies, included studies for definitions).

Overall completeness and applicability of evidence

There were limitations in completeness and applicability of evidence due to clinical heterogeneity between the trials, 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.

The PBI/APBI delivered was heterogeneous in dose, technique, fractionation and target delineation.

1. The RT doses varied between the trials. In all studies, the EQD2 delivered in the APBI arm was higher than the WBRT dose (with the exception of [ELIOT](#); see [Table 6](#)). Despite the dose escalation in the APBI arm, we found that LR-FS was worse with APBI, which suggests there may be technical issues with RT delivery (e.g. target volume definition or target coverage).
2. The RT techniques used to deliver PBI/APBI varied (see [Table 7](#)).
3. The trials differed in fractionation used; all the studies used greater than 2 Gy per fraction in the experimental arm, with the exception of [Polgár 2007](#), where some of the women in the PBI/APBI arm received 2 Gy per fraction (see [Table 6](#)).
4. The techniques used to define the target volume in [GEC-ESTRO](#), [Livi 2015](#), [Polgár 2007](#), [RAPID](#), and [TARGIT](#) were consistent with current practice, but [ELIOT](#) provided inadequate details for the technique used in to be certain of this.

Avoiding geographic miss is imperative in RT. Delivery of RT is a technical exercise. [Peters 2010](#) demonstrated the extremely important role that quality assurance plays in the delivery of high-quality RT. Poor-quality RT (a non-compliant plan) for locally advanced head and neck cancer was associated with a 20% detriment in survival and a 29% detriment to loco-regional control ([Peters 2010](#)). Three studies did not mention quality assurance ([ELIOT](#); [Livi 2015](#); [Rodriguez](#)). Although [Polgár 2007](#) assessed implant quality, less than 20% of the implants had post-implant CT to document PTV coverage and quality assurance for APBI using electrons or WBRT was not mentioned (see [Characteristics of included studies](#) table). [RAPID](#) included an extensive quality assurance programme with credentialling, real-time and post-hoc review of radiation quality. [GEC-ESTRO](#) had rigorous pre- and post-implant quality assurance procedures.

The lack of precision in target definition, the variety of methods used to deliver PBI/APBI (even within the experimental arm of the trials; see [Table 7](#)) and the omission of robust quality assurance mean that the RT delivered in some of the trials was not reproducible. We cannot be certain of the dose delivered and the volume of breast treated.

We found there was heterogeneity for the outcome of cosmesis (physician-reported). There were some possible sources of clinical heterogeneity that may have contributed to this: in [Polgár 2007](#), 40/128 (30%) women in the PBI/APBI arm received 50 Gy in 25 fractions to the tumour bed using EBRT; these women who had conventionally fractionated RT at the same dose as the WBRT arm were likely to have very similar cosmetic outcome. [Livi 2015](#) delivered PBI/APBI using IMRT, with careful dose constraints applied: we know that IMRT is associated with improvement in cosmetic outcome in the setting of WBRT ([Donovan 2007](#); [Pignol 2008](#)).

Modern breast-conserving therapy with postoperative WBRT achieves local control rates of 3.3% to 3.4% at five years and 5.2% to 6.7% at 10 years ([Haviland 2013](#)). With careful participant selection (aged 65 years or greater, T1-2 tumours, not greater than 3

cm, margin negative, oestrogen receptor positive and all receiving tamoxifen), surgery alone can achieve local recurrence rates of 4.1% at five years ([Kunkler 2015](#)). The risk of local recurrence continues with longer follow-up, in modern series where women with good prognosis were treated with surgery alone, the 10-year risk of loco-regional or distant recurrence was 19.9% (reduced to 6.3% with RT; [Blamey 2013](#); [Fisher 2002](#); [Fyles 2004](#); [Hughes 2004](#); [Potter 2007](#); [Prescott 2007](#); [Winzer 2010](#)). Even if PBI/APBI is poorly targeted, in a low-risk population being treated with systemic therapy, low local recurrence rates can be expected.

The paradigm for PBI/APBI relies on the basis that WBRT does not reduce the number of 'elsewhere primaries' within the treated breast, but we found that PBI/APBI appeared to be associated with an increase in 'elsewhere primaries' (OR 3.97, 95% CI 1.51 to 10.41; [Analysis 1.7](#)).

Duration of follow-up

The length of follow-up in five of the included trials was adequate to detect local recurrences (10 years ([Polgár 2007](#)), 69 months ([ELIOT](#)), 65 months ([Livi 2015](#)), 60 months ([Rodriguez](#)), 79.2 months ([GEC-ESTRO](#))). The median follow-up for [TARGIT](#), of 29 months, made it inadequate for the outcome of local control. Local recurrences do continue to increase over time (at about 1% per year), as can be seen in the START data: 3.3% to 3.4% at five years and 5.2% to 6.7% at 10 years ([Haviland 2013](#)). Any effect on breast C-SS related to local control requires much longer follow-up ([EBCTCG 2011](#)). None of the included trials had long enough follow-up to report OS results.

We know that RT reduces the risk of any first recurrence, and although the proportional reduction is most evident in the first year post-treatment, it is still present in years five to nine (RR 0.59, 95% CI 0.5 to 0.7; [EBCTCG 2011](#)). Even in modern studies that included low-risk women treated with lumpectomy (enrolled after 1989), the 10-year risk of loco-regional and distant recurrence was 19.9% (reduced to 6.3% with RT; [Blamey 2013](#); [Fisher 2002](#); [Fyles 2004](#); [Hughes 2004](#); [Potter 2007](#); [Prescott 2007](#); [Winzer 2010](#)). Even women at low risk of recurrence (if they are at risk for another 30 years) are likely to have increases in recurrence with longer follow-up. The use of PBI/APBI may mean they are at risk of 'elsewhere primaries' for this time period.

Little or no useful information available for some outcome measures

The authors of [TARGIT](#) (completed, but with short follow-up) indicated that cosmesis, participant satisfaction, health economics and participant preference will be the subject of a sub-protocol and information with respect to these outcomes will be available in the future. The five ongoing trials that we found are likely to address these outcomes ([IMPORT](#); [IRMA](#); [NSABP-B39/RTOG](#); [SHARE](#); see [Characteristics of ongoing studies](#) table).

Quality of the evidence

The available evidence does allow for the drawing of robust conclusions in respect of the objective of the review: to determine whether PBI/APBI is equivalent to or better than conventional or hypo-fractionated WBRT after breast-conserving therapy for early-stage breast cancer. We found seven studies with 8895 participants.

LR-FS: we downgraded for risk of bias because 3451/6820 (38%) women contributing to this outcome came from a study deemed at high risk of bias because of short follow-up. We did not downgrade for indirectness because the included studies used contemporary RT techniques. With respect to inconsistency ($I^2 = 71\%$; P value = 0.008), there was considerable clinical heterogeneity with respect to RT dose, technique and use of quality assurance procedures. However, the RT techniques employed all delivered a dose that was the same or higher in the PBI/APBI arm than the WBRT arm, which should mean the LR-FS is better or the same (see [Table 6](#)). We downgraded for imprecision; there were fewer than 300 events, and although the optimum information size (OIS) had been met, the CIs did not exclude either clinically unimportant harms or clinically important harms. We did not downgrade for publication bias, given the systematic literature search we had performed. The overall GRADE ([GRADE Working Group 2004](#)) quality of evidence for this outcomes was low.

Cosmesis: we did not downgrade for risk of bias because less than 30% of events came from studies at high risk of bias for lack of blinding of outcome assessors, which is particularly important for a subjective outcome such as cosmesis. We did not downgrade for indirectness, but did so for inconsistency ($I^2 = 88\%$; P value < 0.00001) even though all assessments used the same four-point scale. We did downgrade for imprecision (there were greater than 300 events (315 events)) and the CIs did not exclude the possibility of clinically unimportant harms. We did not downgrade for publication bias given the systematic literature search we had performed. The overall GRADE ([GRADE Working Group 2004](#)) quality of evidence for this outcomes was low.

OS: we did not downgrade for risk of bias, indirectness, inconsistency ($I^2 = 40\%$; P value = 0.15) or imprecision (the CIs crossed one, but excluded clinically significant harms or benefits). We did not downgrade for publication bias (based on examination of a Funnel plot). The overall GRADE ([GRADE Working Group 2004](#)) quality of evidence for this outcome was high.

Late RT toxicity (subcutaneous fibrosis): we did not downgrade for risk of bias, indirectness or inconsistency (heterogeneity testing was not appropriate as only one study contributed data for this outcome). We downgraded for imprecision, as there were fewer than 300 events and the OIS was not met (the studies in PBI/APBI were powered for other endpoints than this one) and CIs did not exclude clinically important harms. We did not downgrade for publication bias. The overall GRADE ([GRADE Working Group 2004](#)) quality of evidence for this outcomes was moderate.

C-SS: we did not downgrade for risk of bias, indirectness or inconsistency ($I^2 = 0\%$; P value = 0.81). We did downgrade for imprecision, given there were fewer than 300 events (99 events) and the CIs did not include the possibility of clinically significant benefits or harms from PBI/APBI. We did not downgrade for publication bias for this outcome. The overall GRADE ([GRADE Working Group 2004](#)) quality of evidence for this outcomes was moderate.

DM-FS: we did not downgrade for risk of bias, indirectness or inconsistency ($I^2 = 0\%$; P value = 1.0). We did downgrade for imprecision as there were fewer than 300 events (100 events) and the CIs did not exclude clinical meaningful benefits or harms. We did not downgrade for publication bias. The overall GRADE ([GRADE](#)

[Working Group 2004](#)) quality of evidence for this outcomes was moderate.

Subsequent mastectomy: we downgraded for risk of bias, because one of the studies contributing data had follow-up too short for assessment of this outcome. We did not downgrade for indirectness or inconsistency ($I^2 = 0\%$; P value = 0.45). We did downgrade for imprecision as there were fewer than 300 events (78 events) and the CIs did not exclude clinically meaningful benefits or harms. The overall GRADE ([GRADE Working Group 2004](#)) quality of evidence for this outcomes was low.

Refer to the [Summary of findings for the main comparison](#).

Potential biases in the review process

We consider that we have identified all the relevant completed RCTs. For reporting of adverse effects, the precision was low because the OIS was not met. 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 five systematic reviews examining PBI/APBI compared with WBRT.

We found one meta-analysis ([Valachis 2010](#)), which included one study ([Polgár 2007](#)) in common with our systematic review and recruited 1140 women ([Dodwell 2005](#); [Polgár 2007](#); [Ribeiro 1993](#)). They found no difference for mortality (OR 0.91, 95% CI 0.67 to 1.23; P value = 0.55) and distant metastasis (OR 0.74, 95% CI 0.51 to 1.08; P value = 0.12) for the comparison of PBI/APBI versus WBRT. PBI/APBI was associated with increased local recurrence (OR 2.15, 95% CI 1.40 to 3.31; P value = 0.001) and axillary recurrence (OR 3.43, 95% CI 2.06 to 5.71; P value < 0.0001) when compared with WBRT. They concluded that PBI does not seem to jeopardize survival and may be used as an alternative to WBRT ([Valachis 2010](#)). The authors pooled the data from the trials (see [Data synthesis](#) section).

We found one systematic review with a search date in 2010 ([BlueCross BlueShield](#)). They included two RCTs ([Polgár 2007](#); [Ribeiro 1993](#) (which we excluded)) and seven non-RCTs. They concluded that "the body of evidence on interstitial PBI/APBI compared to conventional whole-breast irradiation is weak, and it is extremely weak (i.e. no comparative studies) for balloon brachytherapy, intraoperative PBI/APBI, and external-beam PBI/APBI. The data on PBI/APBI compared to whole-breast irradiation are insufficient to draw any conclusions about the relative effectiveness of these modalities. Furthermore, it is becoming increasingly clear that each type of PBI/APBI should be judged on its own merits, and studies comparing different PBI/APBI techniques to each other as well as to whole-breast irradiation are needed" ([BlueCross BlueShield](#)).

We found one review that used a systematic search (search date February 2014) ([Marta 2015](#)). Our review differed in that we included updated data for [TARGIT](#) and they included [Dodwell 2005](#) and [Ribeiro 1993](#) (which we excluded). They reported decreased local control with APBI versus WBRT (HR 4.54, 95% CI 1.78 to 11.61; P value = 0.002). They concluded that APBI was associated with an increase in local recurrence, but found no difference in other outcomes.

Kong 2014 did a systematic search (search date June 2012). They included 10 studies, and included two retrospective cohorts, two matched pair analyses and three prospective cohort studies. They found that PBI/APBI was associated with increased local recurrence (OR 1.54, 95% CI 1.15 to 2.06; P value = 0.004). They found no difference for the comparison of PBI/APBI for the outcomes of distant metastases, OS and disease-free survival.

One review by Ye 2013 studied 919 women in four studies; their search was not systematic (search date June 2013). They included a matched pair analysis, and the fourth study was not referenced. They reported no difference in local control, but appeared to have double counted the data for Polgár 2007 at two time points. They concluded that other outcomes did not differ, although they reported more women who were treated with APBI had good/excellent cosmesis.

The review in Clinical Evidence (search date April 2009) compared intraoperative RT versus standard postoperative RT in women receiving breast-conserving surgery, and found no fully published RCTs (see comment, ASERNIP-S 2002). The review concluded, "Studies are currently attempting to address the question as to whether partial breast irradiation may be sufficient treatment for some sub-groups of breast cancer. Until those studies are complete and the follow-up data mature, it is not possible to recommend partial breast irradiation as an appropriate treatment for breast cancer outside of a properly conducted trial" (Clinical Evidence).

Several guidelines have been published on PBI/APBI. The American Society of Therapeutic Radiology and Oncology (ASTRO) consensus evolved because it was clear that many women are treated in the US with PBI/APBI outside clinical trials (over 32,000 women have had treatment using MammoSite®; Cytec). They indicated a patient population "suitable" for PBI/APBI outside the context of a clinical trial: women aged 60 years and over, with pT1N0(i-, i+)M0, margins greater than 2 mm, unifocal disease, oestrogen receptor positive, who have had no neoadjuvant therapy. They also described women deemed unsuitable for PBI/APBI. They state that, "patients who choose treatment with PBI/APBI should be informed that whole-breast irradiation (WBI) is an established treatment with a much longer track record that has documented long-term effectiveness and safety" (Smith 2009). This statement provides guidance in selecting participants who may be appropriate for PBI/APBI outside the context of a clinical trial, but the Task Force strongly endorsed enrolment of all eligible participants considering PBI/APBI onto NSABP-B39/RTOG and encouraged enrolment of other participants considering PBI/APBI, particularly those not in the "suitable" group, into prospective clinical studies to address many of the unanswered questions in PBI/APBI (Smith 2009). NCCN states, "patients are encouraged to enter clinical trials, and endorses the ASTRO guidelines".

In the absence of an available trial, the American College of Radiology (ACR) Appropriateness Criteria® panel recommends following the consensus guidelines of the ASTRO (Bellon 2011).

The GEC-ESTRO Breast Cancer Working Group recommends three categories guiding patient selection for PBI/APBI:

1. a low-risk group for whom PBI/APBI outside the context of a clinical trial is an acceptable treatment option; including participants aged at least 50 years with unicentric, unifocal, pT1-2 (less than 30 mm) pN0, non-lobular invasive breast cancer without the presence of an extensive intraductal component (EIC) and LVI and with negative surgical margins of at least 2 mm;
2. a high-risk group, for whom PBI/APBI is considered contraindicated; including participants aged 40 years or less; having positive margins, with or without any of the following pathological features (multicentric or large (greater than 30 mm) tumours, EIC positive or LVI positive tumours, four or more positive lymph nodes, unknown axillary status (pNx)); and
3. an intermediate-risk group, for whom PBI/APBI is considered acceptable only in the context of prospective clinical trials (Polgár 2010).

AUTHORS' CONCLUSIONS

Implications for practice

It appears that local recurrence and 'elsewhere primaries' (new primaries in the ipsilateral breast) are increased with accelerated partial breast irradiation (APBI) or partial breast irradiation (PBI), that is, APBI does not offer the same cancer control as whole breast radiotherapy (WBRT) (but the difference is small). We found no evidence of detriment to other oncological outcomes. It appears that cosmetic outcomes and some late effects are worse with PBI/APBI but its use is associated with less acute skin toxicity. The limitations of the data currently available mean that we cannot make definitive conclusions about the efficacy and safety or ways to deliver of PBI/APBI. We await completion of ongoing trials.

Implications for research

The ongoing trials will address relevant clinical outcomes. PBI/APBI is a highly technical intervention that is operator dependent and requires careful quality assurance. Interpretation of these trials will require consideration of the quality of the RT delivered, with respect to target definition and treatment verification.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

ELIOT

Methods

Phase III RCT

ELIOT (Continued)

Single-centred, tertiary institution

Country: Italy

Median follow-up: 68 months

Participants	Women aged 48-75 years with early breast cancer, maximum tumour diameter 2.5 cm, "suitable for breast conservation". All women with positive sentinel node biopsy had axillary dissection
Interventions	<p>Experimental arm: intraoperative electron therapy to deliver 21 Gy at the 90% isodose delivered at the time of surgery after tumour excision using 6-9 MeV</p> <p>Control arm: postoperative EBRT (50 Gy/25 fractions + 10 Gy/5 fraction boost using electrons)</p>
Outcomes	<ol style="list-style-type: none"> 1. Ipsilateral breast tumour recurrence that included both local recurrence and new ipsilateral breast primaries 2. Overall survival 3. Regional nodal failure 4. Distant metastases 5. Late toxicity (measured using LENT-SOMA)
Notes	<p>Target volume: 4-12 MeV to 90% isodose 10-30 mm around sutured surgical breach</p> <p>NB: women with ≥ 4 involved nodes were treated with RNI (50 Gy/25 fractions). Adjuvant therapies were administered according to the European Institute of Oncology policy at the time</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "At the data centre, allocation was done by telephone with a computer-generated list using a randomly permuted block design, stratified by tumour size (<1.0 cm vs 1.0-1.4 cm vs ≥ 1.5 cm)", page 1270, paragraph 3</p> <p>This method represented an adequate randomization method, therefore, we judged this domain at low risk of bias</p>
Allocation concealment (selection bias)	Unclear risk	<p>Quote: "Immediately before the intervention, the surgeon contacted the data centre by telephone to receive the allocation group. At the data centre, allocation was done by telephone", page 1270, paragraph 3</p> <p>Because the details of how this was done were not reported, we judged this domain at unclear risk of bias</p>
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	<p>Quote: "Study coordinators, clinicians who verified eligibility criteria after pathological assessment of the surgical specimen, clinicians who followed up patients, investigators who did the statistical analyses, and the patients themselves were aware of the assignment", page 1270, paragraph 3</p> <p>We judged this domain at low risk of bias</p>
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	<p>Quote: "Study coordinators... clinicians who followed up patients... and the patients themselves were aware of the assignment", page 1270, paragraph 3</p> <p>We judged this domain at low risk of bias</p>
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	<p>Quote: "We defined local recurrence as the reappearance of the carcinoma at the site of the surgical intervention. We defined second ipsilateral breast tumours as any new carcinoma appearing in other quadrants of the same breast. IBTR was defined as the sum of local recurrence plus second ipsilateral tu-</p>

ELIOT (Continued)

		<p>mours. A regional nodal failure included any recurrence in the ipsilateral axillary, supraclavicular, or internal mammary nodal regions. Distant metastases were defined as any recurrence to distant organs. Overall survival was defined as the time from diagnosis to last follow-up or time of death"</p> <p>Quote: "Patients were followed up with a clinical examination every 3 months, an ultrasound mammary scan every 6 months, and a mammogram every year; examinations of the lung, liver, and bone were modulated according to a personalised assessment of risk"</p> <p>Quote: "investigators who did the statistical analyses", page 1270, paragraph 3</p> <p>Although the outcome assessors for objective outcomes were not blinded, the clear pre-specified definitions of what constituted outcomes and the pre-specified follow-up protocol reduced the risk of bias for this domain</p>
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	<p>Quote: "Study coordinators, clinicians who verified eligibility criteria after pathological assessment of the surgical specimen, clinicians who followed up patients, investigators who did the statistical analyses, and the patients themselves were aware of the assignment", page 1270, paragraph 3</p> <p>Quote: "Side-effects were scored using the Late Effect of Normal Tissue- Subjective Objective Management Analytic criteria"</p> <p>Because the assessment of subjective outcomes was not blinded, we judged this domain at high risk of bias</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions were reported and there was no post-randomization attrition (see Figure 1) so we judged this domain at low risk of bias
Selective reporting (reporting bias)	Unclear risk	<p>Outcomes specified in paper:</p> <ol style="list-style-type: none"> 1. Primary outcome: IBTR (in breast true recurrences) 2. Secondary outcome: overall survival <p>Outcomes reported:</p> <ol style="list-style-type: none"> 1. IBTR 2. True local recurrences 3. New ipsilateral breast cancer 4. Loco-regional recurrence 5. Contralateral breast cancer 6. Distant metastases 7. Non-breast cancer in other sites 8. Overall survival 9. Breast cancer deaths 10. Skin radiation toxicity 11. Pulmonary fibrosis <p>We did not have access to the study protocol, so judged this domain at unclear risk of bias</p>
Other bias	Low risk	No other sources of bias identified

GEC-ESTRO

Methods	Phase III RCT
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Partial breast irradiation for early breast cancer (Review)

GEC-ESTRO (Continued)

Open-label trial

Country: Germany

Median follow-up: 79.2 months

Participants	Women aged > 40 years with Stage 0, I or II breast cancer (including DCIS), no lymph or vascular invasion, lesions < 3 cm in diameter, pN0/pNmi, DCIS alone, sentinel node biopsy optional. Clear margin ($\geq$ 2 mm in invasive disease, 5 mm in DCIS), unifocal or unicentric disease only
Interventions	Experimental arm: APBI Interstitial brachytherapy HDR 32 Gy/8 fractions or 30.3 Gy/7 fractions PDR 50 Gy at 0.6-0.8 Gy/fractions given hourly Control arm: external beam WBRT 50.0-50.4 Gy/1.8-2.0 Gy fractions (5-28) plus 10 Gy/5 fraction boost
Outcomes	Primary: 1. Local control Secondary: 1. Incidence and severity of acute and late adverse effects 2. Differences in cosmetic results 3. Distant metastases disease-free survival 4. Survival rates (overall survival, disease-free survival) 5. Contralateral breast cancer rate 6. Quality of life
Notes	Target volume: tumour bed plus 20- to 30-mm radial margin

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation was stratified by study centre, menopausal status, and tumour type (e.g., invasive carcinoma vs DCIS), with a block size of ten, according to an automated dynamic algorithm", page 3, randomization and masking, paragraph 1 We judged this at low risk of bias
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomised centrally at the Department of Medical Informatics, Biometry and Epidemiology, University Erlangen-Nuremberg, Germany, via an online interface", page 3, randomization and masking, paragraph 1 This process was described as concealed and remote, so we judged this at low risk of bias
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Quote: "Neither patients nor investigators were masked to treatment allocation", page 3, randomization and masking, paragraph 1 Although participants and personnel were not blinded, it is unlikely to have introduced bias, so we judged this domain at low risk of bias

GEC-ESTRO (Continued)

Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	Quote: "Neither patients nor investigators were masked to treatment allocation", page 3, randomization and masking, paragraph 1 Although participants and personnel were not blinded, it is unlikely to have introduced bias, so we judged this domain at low risk of bias
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Quote: "Follow up mammography was scheduled at 6, 12, 18 and 24 months after radiation therapy", page 3, paragraph 8 Although outcome assessors were not blinded, we considered the pre-specified follow-up protocol meant this domain was at low risk of bias
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Quote: "Clinical examination included documentation of late side-effects with Common Terminology Criteria for Adverse Events and with the Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) Late Radiation Morbidity Scoring Schema 14", page 3 Blinding of outcome assessors was not mentioned, we thought despite the pre-specified follow-up schema and the use of a Grading system for documenting late effects, meant this domain was at high risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "after randomisation, 98 patients...administrative error", page 4, paragraph 1 Post-randomization exclusions are detailed by arm, with reasons, so we deemed this outcome at low risk of bias
Selective reporting (reporting bias)	Low risk	Quote: "Detailed analyses of early and late side-effects, quality of life, and cosmetic results are not presented here", page 4, paragraph 1 Although detailed reporting of acute and late adverse effects and quality of life were not in this publication, the authors made it clear there will be further publications, so we judged this at low risk of bias. We had access to the study protocol
Other bias	Low risk	We did not consider there was other bias, so judged this domain at low risk of bias.

Livi 2015

Methods	RCT Single centre Setting: cancer centre Country: Italy Median follow-up: 60 months
Participants	Women aged > 40 years, wide local excision or quadrantectomy for invasive breast cancer, negative margins, tumour size ≤ 25 mm
Interventions	PBI/APBI (using IMRT) vs. WBRT (conventional RT)
Outcomes	Not specified in report
Notes	Study has not completed accrual (target 520 women)

Partial breast irradiation for early breast cancer (Review)

Livi 2015 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to receive either WBI or APBI using IMRT in a 1:1 ratio. Allocation was performed with a computer-generated sequence using a randomly permuted block design, without any stratification of main prognostic factors", page 453, paragraph 1 We judged this at low risk of bias
Allocation concealment (selection bias)	Low risk	Quote: "The random sequence was kept by an external centre (local Oncological Centre for Departmental Reference, CORD). The clinicians were required to query it every time an eligible patient had provided written informed consent to determine the allocation arm", page 453, paragraph 1 We judged this at low risk of bias
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Quote: "Clinicians, investigators and the patients themselves were aware of the arm assignment", page 453, paragraph 1 Blinding would have been difficult in view of the 2 very obviously different treatments, we judged this domain at low risk of bias
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	Quote: "Clinicians, investigators and the patients themselves were aware of the arm assignment", page 453, paragraph 1 Blinding would have been difficult in view of the 2 very obviously different treatments, we judged this domain at low risk of bias
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Clinicians and investigators were not blinded to treatment arm, but the pre-specified mammographic follow-up would have reduced the risk of bias related to the primary outcome
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Quote: "mammography was annually programmed", page 454, paragraph 13 The clinicians and investigators were not blinded to treatment arm, which makes assessment of subjective outcomes at high risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions or attrition reported, so we judged this domain at low risk of bias
Selective reporting (reporting bias)	Unclear risk	We did not review the protocol, so judged this domain at unclear risk of bias
Other bias	Low risk	We did not identify any other sources of bias

Polgár 2007

Methods	RCT
	Single-centre trial
	Country: Hungary
	Accrual dates July 1998 to May 2004

Polgár 2007 (Continued)

Median follow-up: 10.2 years

Participants	<p>258 women with invasive breast cancer</p> <p>Inclusion criteria: wide excision with negative margins, unifocal tumour, tumour size < 20 mm, clinically or pathologically N0, or single microscopic nodal metastasis (> 0.2 mm and < 2.0 mm), i.e. pT1N0-1miM0, Grade I or II</p> <p>Exclusion criteria: bilateral breast cancer, prior unilateral or contralateral breast cancer, concomitant or previous other malignancies, invasive lobular cancer, pure ductal or lobular cancer in situ (pTis). After 2001, women aged < 40 years excluded</p> <p>Mean age 58-59 years (given for each arm)</p>
Interventions	<p>Experimental arm: PBI; 88/128 women had 7 × 5.2 Gy HDR multi-catheter brachytherapy and 40/128 women unsuitable for HDR had 50 Gy/25 fractions electron beam RT to partial breast</p> <p>Control arm: 50 Gy/25 fractions WBRT (130 women)</p> <p>Surgery: wide excision (resection of tumour with ≥ 1 cm macroscopic free margin). Cavity marked with titanium clips</p> <p>Central pathology review performed</p> <p>Systemic therapy given according to institutional protocol</p> <p>Baseline mammography was performed at 6 months after RT then annually. Women were seen every 3 months in the first year, then once every 6 months</p>
Outcomes	<p>Primary:</p> <ol style="list-style-type: none"> 1. Local recurrence in the ipsilateral breast at 5 years 2. Cosmetic outcome (using the Harvard cosmetic score; Table 1) <p>Secondary:</p> <ol style="list-style-type: none"> 1. Overall survival 2. Toxicity - late toxicity will be reported elsewhere 3. Cause-specific mortality (deaths due to breast cancer at 5 years) 4. Distant metastasis-free survival at 5 years 5. Relapse-free survival at 5 years 6. Subsequent mastectomy (ipsilateral partial mastectomy, modified radical mastectomy or radical mastectomy) 7. Compliance, defined as the number of women who commence treatment with PBI/APBI or conventional EBRT and complete the treatment course
Notes	<p>Early stopping at 258 women enrolled because another multicentred trial commenced</p> <p>LR defined as any detection of cancer in the treated breast, confirmed histologically. An "elsewhere breast failure" defined as ipsilateral (LR) ≥ 2 cm from the clips. All other LR classified as true recurrence or marginal miss</p> <p>Cosmetic score Harvard criteria, scored by treating radiation oncologist and chief investigator at analysis date (June to August 2006). In case of discrepancy, worst score used for analysis</p> <p>Event-free intervals defined as time between date of surgery and date of event or last follow-up</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
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Polgár 2007 (Continued)

Random sequence generation (selection bias)	Low risk	<p>Quote: "were randomised". Polgár 2007, page 694, paragraph 3</p> <p>Quote: "randomly allocated to treatment options by a sealed envelope system in blocks of 10"</p> <p>Randomization was done by the main investigator (C.P.) Polgár 2007, page 695, paragraph 2</p> <p>The trial was likely to have been randomized</p>
Allocation concealment (selection bias)	Unclear risk	<p>Quote: "randomly allocated to treatment options by a sealed envelope system in blocks of 10". Polgár 2007, page 695, paragraph 2</p> <p>Allocation concealment appears to have been done, although the description was incomplete, which contributed to the judgement of unclear bias risk</p>
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	<p>Participants: not mentioned, unlikely to have been done</p> <p>Quote: "Blinding of physicians performing treatments and follow-up of patients was not possible for technical reasons". Polgár 2007, page 695, paragraph 2</p> <p>Physicians: not done</p> <p>Quote: "Blinding of physicians performing treatments and follow-up of patients was not possible for technical reasons". Polgár 2007, page 695, paragraph 2</p> <p>We judged this domain at low risk of bias</p>
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	<p>Participants: not mentioned, unlikely to have been done</p> <p>Quote: "Blinding of physicians performing treatments and follow-up of patients was not possible for technical reasons". Polgár 2007, page 695, paragraph 2</p> <p>Physicians: not done</p> <p>Quote: "Blinding of physicians performing treatments and follow-up of patients was not possible for technical reasons". Polgár 2007, page 695, paragraph 2</p> <p>We judged this domain 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>Quote: "Blinding of physicians performing treatments and follow-up of patients was not possible for technical reasons". Polgár 2007, page 695, paragraph 2</p> <p>Physicians: not done, but in view of pre-specified follow-up protocol, with regular mammography, unlikely to have introduced bias</p> <p>Quote: "Patients were seen every three months in the first two years after RT and every six months thereafter. Baseline mammography was performed six months after completion of RT and yearly thereafter". Polgár 2007, page 697, paragraph 6</p> <p>Quote: "Blinding of physicians performing treatments and follow-up of patients was not possible for technical reasons". Polgár 2007, page 695, paragraph 2</p>

Polgár 2007 (Continued)

Quote: "Local recurrence...proved by histological confirmation in every case". [Polgár 2007](#), page 697, paragraph 6

Assessors: not done

Unlikely to be a source of bias in view of the pre-specified schedule for follow-up visits and investigations. Local recurrence required biopsy confirmation, which would reduce the risk of bias in evaluation of this outcome

Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	<p>Participants: not mentioned, unlikely to have introduced bias</p> <p>Physicians: not mentioned, may be a source of bias</p> <p>Assessors: not mentioned, unlikely to have been done, this is potentially a source of bias</p> <p>Quote: "Cosmetic outcome scored independently by treating radiation oncologist and the main investigator...in the case of discrepancy, the worse cosmetic score was used for analysis". Polgár 2007, page 697, paragraph 5</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Exclusions: none</p> <p>Attrition: 0 in experimental group, 2 in control group (declined follow-up at 18 and 22 months postoperatively)</p>
Selective reporting (reporting bias)	Unclear risk	<p>Outcomes in methods section:</p> <ol style="list-style-type: none"> 1. Primary: local recurrence at 5 years 2. Differences in cosmetic outcome <p>Outcomes reported in paper:</p> <ol style="list-style-type: none"> 1. LR 2. LR-FR at 5 years 3. 5-year actuarial LR rate, true recurrence and marginal miss 4. Overall survival at 5 years 5. Cancer-specific survival at 5 years 6. Distant metastasis-free survival at 5 years 7. Disease-free survival at 5 years 8. Probability of developing contralateral cancer at 5 years 9. Salvage therapy 10. Modified radical mastectomy rate 11. Cosmetic outcome <p>Outcomes in methods and protocol: protocol not reviewed</p>
Other bias	Low risk	<p>Trial stopped early (the trial enrolled 258 women of a planned sample size of 570 participants) because of a competing trial, GEC-ESTRO, started recruiting</p>

RAPID

Methods	<p>Phase III RCT; stratified for age, tumour histology, tumour size, adjuvant hormonal therapy and clinical centre</p> <p>Country: Canada, Australia, New Zealand</p> <p>Median follow-up: 36 months</p>
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RAPID (Continued)

Participants	Women aged ≥ 40 years with new diagnosis of DCIS or with microscopically clear margins after BCS of non-invasive or invasive disease (or no residual disease on re-excision). Negative axillary nodal involvement including micrometastasis (> 0.2 mm or positive cells only identified on IHC as determined by sentinel node biopsy; axillary node dissection; or clinical examination for DCIS only. Tumour size ≤ 3 cm
Interventions	Experimental arm: APBI (3D-CRT: 38.5 Gy in 10 fractions, bd over 5-8 days. 6-8 hour gap between doses required) Control arm: WBRT (42.5 Gy in 16 fractions daily over 22 days). Women with large breast size: 50 Gy in 25 fractions over 25 days. Boost 10 Gy in 4 or 5 fractions over 4-7 days is permitted for those women deemed at moderate to high risk of LR as per local cancer centre guidelines
Outcomes	Primary: 1. Ipsilateral breast tumour recurrence (defined as recurrent invasive or in situ cancer in the ipsilateral breast including the axillary tail) Secondary: 1. Adverse cosmetic outcome 2. Disease-free survival 3. Event-free survival 4. Overall survival 5. Radiation toxicity 6. Quality of life 7. Cost effectiveness
Notes	QA: extensive QA processes (credentialling, real-time and post-hoc plan review) NCT00282035

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "were randomly assigned using a telephone-based central minimization procedure" This was deemed an adequate method of sequence generation and the domain judged at low risk of bias
Allocation concealment (selection bias)	Unclear risk	The sequence generation was described as "telephone-based central minimization procedure", inadequate details were provided, so we deemed this at unclear risk of bias
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	For technical reasons, blinding of participants and personnel was not possible, but is unlikely to have introduced bias
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	For technical reasons, blinding of participants and personnel was not possible, but is unlikely to have introduced bias
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Quote: "Bilateral mammograms were performed annually"

RAPID (Continued)

		We judged this domain at low risk of bias, because the mammography interval was pre-specified and this ensures the primary objective outcome (IBTR) was at low risk of bias
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Quote: "...addition to nurse and patient assessments, cosmesis was assessed by two panels of three radiation oncologists using the digital photographs. The physicians had breast cancer expertise and were trained to use the EORTC Cosmetic Rating System. After demonstrating good agreement in the ability to identify adverse cosmesis (0.71; Appendix, online only), each panel reviewed half of the available 3-year post-RT photographs. The panels, blinded to treatment allocation, provided one consensus global cosmetic score for each patient (Appendix, online only)" It was not stated whether the trained nurses evaluating the cosmetic outcome were blinded to treatment arm; however, the physician reviewers were blinded to treatment arm, so we judged this at low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Because this was an interim report, we were unable to assess the number of exclusions or attrition, so judged the domain at unclear risk of bias
Selective reporting (reporting bias)	Unclear risk	Because this was an interim report, we judged this domain at unclear risk of bias
Other bias	Unclear risk	No other sources of bias noted

Rodriguez

Methods	Phase III RCT (relative non-inferiority) Country: Spain Accrual dates: not stated, started accrual 2004 Median follow-up: 60 months
Participants	102 women with invasive ductal carcinoma (pT1-2cNO MO), aged ≥ 60 years old, unifocal tumour, ≤ 3 cm, Grade I or II
Interventions	Experimental arm: PBI/APBI delivered by 3D-CRT at 48 Gy/24 fractions ± 10 Gy boost (depending on risk factors for local recurrence). 51 women Control arm: conventional WBRT at 48 Gy/24 fractions ± 10 Gy boost (51 women)
Outcomes	1. Local control 2. Dosimetry and toxicity (using RTOG CTC) 3. Skin elasticity measured using a dedicated device
Notes	QA: not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by a computer-generated, randomized list", page 1052, paragraph 5

Rodriguez (Continued)

		This was an adequate method of sequence generation, so we judge this domain at low risk of bias
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not clearly described, so we judged this domain at unclear risk of bias
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding of participants and personnel was not mentioned, and probably not done, as it would have been difficult in view of the technical aspects of the 2 intervention arms. We judged this domain at low risk of bias
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	Blinding of participants and personnel was not mentioned, and probably not done, as it would have been difficult in view of the technical aspects of the 2 intervention arms. We judged this domain at low risk of bias
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Quote: "Baseline mammography was performed 6 months after the completion of radiation therapy and yearly thereafter. Abdominal ultrasonography, chest radiography, and blood tests were performed at least annually. Local recurrence was defined as any histologically confirmed cancer tissue in the treated breast", page 1053, paragraph 2 Because the mammography intervals were pre-specified and local recurrence required histological confirmation, the lack of blinding on the part of the outcome assessors was not judged at high risk of bias
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Quote: "Cosmetic results were evaluated according to the Harvard criteria at baseline and at each follow-up visit by the treating radiation oncologist", page 1053, paragraph 5 All participants who had a minimum of 1 year follow-up were asked to rate cosmetic results on a 10-point scale, as follows: excellent (10-9), good (8-6), fair (5-4), or poor (3-1) Acute, late RT toxicity and cosmesis were evaluated by the treating physician (not blinded, so at risk of bias). However, participants also rated the cosmetic outcome as well. Despite this participant-reported outcome, we judged this outcome at high risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Because this was an interim report, we judged it at unclear risk of bias
Selective reporting (reporting bias)	Unclear risk	Because this was an interim report, we judged it at unclear risk of bias
Other bias	Unclear risk	Because this was an interim report, we judged it at unclear risk of bias

TARGET

Methods	Multicentre international randomized non-inferiority Phase III trial Accrual: March 2000 - data lock 2 May 2010 Country: 11 countries (across Europe, UK, US and Australia) Median follow-up: 29 months (1222/3451 (35%)) had 60 months' follow-up	
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TARGIT (Continued)

Participants	1113 women aged ≥ 45 years, with T1 and small T2N0-1M0 invasive breast cancer, suitable for BCS, available for 10 years' follow-up
Interventions	<p>Experimental arm: 1 fraction of RT given intraoperatively (using Intrabeam); 50 kV 20 Gy/fraction at 2 mm beyond surface of 1.5-5.0 cm spherical applicator placed in excision cavity</p> <p>Control arm: standard postoperative RT (40-56 Gy $\pm$ 10-16 Gy boost)</p>
Outcomes	<p>Primary:</p> <ol style="list-style-type: none"> 1. Pathologically confirmed local relapse within the treated breast <p>Secondary:</p> <ol style="list-style-type: none"> 1. Site of relapse within the breast 2. Relapse-free survival and overall survival 3. Local toxicity 4. Local morbidity
Notes	<p>Intrabeam uses low kilovolt x-rays to deliver 20 Gy at the surface of the tumour bed, attenuating to 5-7 Gy at 1 cm. QA: training and auditing by member of International Standards Organisation (ISO) required before centre could join</p> <p>NCT00983684, ISCTN 34086741, ISRCTN 34086741, REC No. 99/0307, UKCRN</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation schedules were generated centrally by computer (securely kept in trial centres in Perth for Australian centres and London, UK, for all other centres)", page 94, paragraph 1
Allocation concealment (selection bias)	Low risk	<p>Quote: "Patients were randomly assigned in a 1:1 ratio...with blocks stratified by centre". Abstract, page 1, paragraph 2</p> <p>Quote: "The randomisation schedules were generated centrally by computer (securely kept in trial centres in Perth for Australian centres, and London, UK for all other centres). Requests for randomisation were via telephone or fax to the trials office (Perth or London), where a trained member of staff checked patient eligibility. Treatment was allocated from a pre-printed randomisation schedule available to authorised staff only. Written confirmation of randomisation was sent by fax to the site". Methods, page, 94, paragraph 1</p> <p>This trial was likely to have had adequate allocation concealment</p>
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	<p>Participants: "Neither patients nor investigators or their teams were masked to treatment assignment". Abstract, page 1, paragraph 2</p> <p>Physicians: "Neither patients nor investigators or their teams were masked to treatment assignment". Abstract, page 1, paragraph 2</p> <p>Quote: "Individual centres were unblinded to treatment given in their own centres, but they were not given access to these data for other sites". Methods, page 1, paragraph 3</p> <p>Quote: "Patient assessments were scheduled at entry"</p> <p>Because of the nature of the intervention, it was not possible to blind the women participating or the personnel involved in their care, this is not likely to have resulted in bias. Because the patient assessments were scheduled at trial</p>

TARGET (Continued)

		entry with pre-specified times for follow-up visits this is likely to have reduced the risk of bias from the lack of blinding of personnel
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	<p>Participants: "Neither patients nor investigators or their teams were masked to treatment assignment". Abstract, page 1, paragraph 2</p> <p>Physicians: "Neither patients nor investigators or their teams were masked to treatment assignment". Abstract, page 1, paragraph 2</p> <p>Quote: "Individual centres were unblinded to treatment given in their own centres, but they were not given access to these data for other sites". Methods, page 4, paragraph 3</p> <p>Quote: "Patient assessments were scheduled at entry"</p> <p>Because of the nature of the intervention, it was not possible to blind the women participating or the personnel involved in their care, this is not likely to have resulted in bias. Because the participant assessments were scheduled at trial entry with pre-specified times for follow-up visits this is likely to have reduced the risk of bias from the lack of blinding of personnel</p>
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	<p>Participants: not relevant</p> <p>Physicians: not relevant</p> <p>Assessors: "Patient's assessments were scheduled at entry, 3 months and 6 months", page 94, paragraph 4</p> <p>This means the risk of lead time bias was reduced</p> <p>Quote: "We recommend that mammography of the ipsilateral breast occurs annually and of the contralateral breast at least every three years". TARGET protocol, 7.1 page 25</p> <p>Quote: "Confidential unblinded reports for the DMC, and blinded reports for the ISO were produced by the trial statistician. Unblinded analyses were done according to a prespecified statistical analysis plan". Methods, page 4, paragraph 3</p> <p>If there were pre-specified time intervals for mammography, this would have reduced the risk of bias for detection of the primary endpoint: local relapse</p>
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	<p>Quote: "The secondary outcome measure of local toxicity, or morbidity was assessed from data recorded on the complications form which contained a prespecified checklist", page 94, paragraph 3</p> <p>It was not stated who assessed the subjective outcomes, however, we know: "Neither patients nor investigators or their teams were masked to treatment assignment". Abstract, page 1, paragraph 2</p> <p>The blinding of outcome assessors was not reported, this does mean that there was risk of bias with assessment of toxicity; however, the use of a pre-specified form would help to reduce bias because the data would be collected for all women</p> <p>Quote: "digital photographs...were assessed, blinded to treatment arm" (Keshtgar et al. Journal of Clinical Oncology Vol. 28. 2010:7S, abstract 570)</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All randomised patients were included in the intention-to-treat analysis". Abstract, page 1, paragraph 2

TARGET (Continued)

Quote: "When displaying the results, we restricted the duration of follow up to four years...since fewer than 420 (< 20%) patients had follow up beyond this point", page 95, paragraph 4

Because the outcomes were reported with a follow-up duration of 4 years, this does mean there is a high risk of bias because they reported on < 20% of the participants

Selective reporting (reporting bias)	Low risk	<p>Outcomes specified in the protocol:</p> <ol style="list-style-type: none"> 1. Local tumour control 2. Site of relapse within the breast 3. Relapse-free survival 4. Overall survival 5. Local toxicity and morbidity 6. Cosmesis, participant satisfaction, health economics, participant preference will be the subject of a sub-protocol <p>Outcomes specified in methods:</p> <ol style="list-style-type: none"> 1. Primary: <ol style="list-style-type: none"> a. "Pathologically confirmed local relapse within the treated breast", page 94, paragraph 5 2. Secondary: <ol style="list-style-type: none"> a. Prospectively collected local toxicity or morbidity (checklist included haematoma, seroma, wound infection, skin breakdown, delayed wound healing) b. RTOG Grade III/IV dermatitis c. Telangiectasia d. Pain in irradiated field or other e. "To assess extent of local surgery we analysed specimen weight, margin status and re-operation for margins", page 95, paragraph 1 <p>Outcomes reported in paper:</p> <ol style="list-style-type: none"> 1. Median amount of tissue resected 2. Re-excision rates 3. Any complication 4. Clinically significant complications 5. RTOG toxicity score of III/IV 6. Major toxicity rate 7. Axillary recurrences 8. Uncontrolled local recurrences 9. Local recurrences at 4 years <p>The authors stated that, "no changes were made to trial outcomes after commencement of the trial"</p> <p>The outcomes pre-specified in the protocol were not all reported, this probably reflects the short follow-up duration, but we consider these outcomes are likely to be reported in future publications</p>
Other bias	High risk	Short duration of follow-up puts the outcomes reported at high risk of bias

3D-CRT: 3-dimensional conformal radiotherapy; APBI: accelerated partial breast irradiation; BCS: breast-conserving surgery; bd: twice a day; DCIS: ductal carcinoma in situ; DMC: data monitoring committee; EBRT: external beam radiotherapy; Gy: Gray; HDR: high-dose-rate; IBRT: ipsilateral breast tumour recurrence; IHC: immunohistochemistry; IMRT: intensity-modulated radiotherapy; LENT-SOMA: late effects in normal tissues - subjective, objective, management and analytic; LR: local recurrence; M: metastases; MeV: mega electron volts; N: lymph

node; PBI: partial breast irradiation; PDR: pulsed-dose-rate; QA: quality assurance; RCT: randomized controlled trial; RNI: regional nodal irradiation; RT: radiotherapy; RTOG CTC: Radiation Therapy Oncology Group Common Toxicity Criteria; WBRT: whole breast radiotherapy.

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

Study	Reason for exclusion
Dodwell 2005	RCT, but used surgical, systemic management and RT techniques that were not consistent with contemporary practice
NCT00892814	Phase II RCT
NCT01185132	PBI used in both study arms
NCT01928589	PBI used in both study arms
NCT02003560	PBI used in both study arms
Ribeiro 1993	RCT, but used surgical, systemic management and RT techniques that were not consistent with contemporary practice
TARGIT-B	WBRT used in both study arms
TROG	Feasibility study and not an RCT

PBI: partial breast irradiation; RCT: randomized controlled trial; RT: radiation treatment; WBRT: whole breast radiotherapy.

Characteristics of studies awaiting assessment *[ordered by study ID]*

[NCT02375048](#)

Methods	Randomized Phase II trial
Participants	<p>Women aged 55-70 years</p> <p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. aged 55-70 years 2. Tumour size $\leq$ 2 cm 3. pN0 (SN biopsy or ALND) 4. ER/PgR positive 5. Margins $>$ 5 mm (either at initial surgery or at re-excision) 6. Clips placed in the surgical bed (minimum of 4 clips) 7. Unicentric only 8. No lympho-vascular invasion 9. Any grade 10.No extensive intraductal component ($>$ 25%) 11.Written informed consent <p>Exclusion criteria:</p> <ol style="list-style-type: none"> 1. Prior thoracic radiotherapy 2. Oncoplastic surgery/no clips in the surgical bed 3. Multicentric cancer 4. Autoimmune disease, vasculitis, collagenopathy or scleroderma that may predispose to late sequelae

NCT02375048 (Continued)

Interventions	<p>Experimental arm: APBI</p> <p>APBI was delivered at a dose of 30 Gy in 5-6 Gy/day fractions over 10 days (every other day) with IGRT at each treatment</p> <p>Control arm: hypofractionated WBRT</p> <p>Dose prescription was 40.5 Gy to planning target volume whole breast (PTV WB) and 48.0 Gy to PTV boost in 15 fractions over 3 weeks, with simultaneous integrated boost delivering 2.7 and 3.2 Gy/fraction for each PTV, respectively. Daily IGRT were generated before each treatment session in each participant to verify the set-up</p>
Outcomes	<p>Primary:</p> <ol style="list-style-type: none"> 1. Toxicity will be measured with CTCAE v.4.0 2. Cosmesis will be measured with Harvard scale <p>Secondary:</p> <ol style="list-style-type: none"> 1. Rate of local control 2. Disease-free survival 3. Overall survival 4. Quality of life questionnaire
Notes	<p>Randomized study on postmenopausal women with early-stage breast cancer: adjuvant hypofractionated WBI vs. APBI. Starts 2015, 700 women</p> <p>Email: marta.scorsetti%40humanitas.it</p>

ALND: axillary lymph node dissection; APBI: accelerated partial breast irradiation; ER: oestrogen receptor; GTV: gross tumour volume; Gy: Gray; IGRT: image-guided radiotherapy; N: lymph node; PgR: progesterone receptor; PTV: planning target volume; SN: sentinel node biopsy; WBI: whole breast irradiation.

Characteristics of ongoing studies [ordered by study ID]

IMPORT

Trial name or title	Randomized Trial Testing Intensity Modulated and Partial Organ Radiotherapy After Breast Conservation Surgery for Early Breast Cancer
Methods	Randomized, Phase III multicentre trial
Participants	Women aged > 50 years, with invasive breast cancer pT1-2pN0, who have had BCS with negative margins (≥ 2 mm) who have < 1% annual risk of local recurrence
Interventions	<p>Experimental arm 1: reduced WBRT and standard PBI once daily on days 1-5 for 3 weeks</p> <p>IMRT</p> <p>Arm 1: 40 Gy/15 fractions</p> <p>Arm 2: 40 Gy/15 fractions + integrated boost to WB 36 Gy/15 fractions</p> <p>Experimental arm 2: PBI daily on days 1-5 for 3 weeks</p> <p>Control: standard WBRT day 1-5 for 3 weeks</p>
Outcomes	Primary: local tumour control in the ipsilateral breast

IMPORT (Continued)

	Secondary: location of tumour relapse, contralateral primary breast cancer, regional or distant metastases, late adverse effects in normal tissues (photographic, physician and participant assessments), quality of life, cost-effectiveness
Starting date	October 2006
Contact information	J Yarnold, Royal Marsden, London
Notes	NCT00814567 CSDR0000629765, ICR-IMPORT-LOW, ICR-CTSU/2006/10001, ISCTN12852634, EU-20896 Target volume: 6 pairs of clips in cavity = CTV + 10 mm = PTV

IRMA

Trial name or title	Breast Cancer with Low Risk of Local Recurrence: Partial and Accelerated Radiation with Three-Dimensional Conformal Radiotherapy (3DCRT) Vs. Standard Radiotherapy After Conserving Surgery (Phase III Study)
Methods	Multicentre Phase III controlled randomized, unblinded study of non-inferiority
Participants	Women aged ≥ 49 years, ECOG 0-2, undergoing conservative breast surgery for invasive breast cancer, pT1-2 (< 3 cm in diameter) pN0-N1 M0, unifocal, resection margins histologically negative (2 mm) at first intervention or after subsequent widening
Interventions	Experimental arm: 38.5 Gy total in 10 fractions (3.85 Gy per fraction), twice a day with an interval of at least 6 hours between the 2 fractions, for 5 consecutive working days of the sole cavity Control arm: 50.0 Gy in 25 fractions (2 Gy per fraction), once a day for 5 days in the week RT of the entire breast
Outcomes	Primary: survival free of local ipsilateral recurrence as prime event Secondary: global survival, loco-regional recurrence-free, distant recurrence-free, acute and late toxicity (RTOG) and cosmetic result
Starting date	-
Contact information	Data Center Office Clinical Trials Office, Integrated Department of Oncology and Hematology Polyclinic Hospital, University of Modena and Reggio Emilia R. D'Amico, G. Jovic, R. Vicini Tel. 059 4223865 Email: Roberto.damico@unimore.it
Notes	Study currently accruing participants. Target volume: GTV + 15 mm = CTV + 5 mm = PTV

NSABP-B39/RTOG

Trial name or title	A Randomised Phase II Study of Conventional Whole Breast Irradiation (WBI) Versus Partial Breast Irradiation (PBI) for Women with Stage 0, I, or II Breast Cancer
Methods	Randomized, multicentre Phase III trial
Participants	Women aged > 18 years with histologically confirmed DCIS or invasive adenocarcinoma of the breast, negative histological margins, no more than 3 axillary nodes involved, must have had BCS
Interventions	Experimental arm: PBI 5 days per week for 5-7 weeks Control arm: WBRT bd on 5 days over 5-10 days (50 Gy in 25 fractions at 1.8-2 Gy per fraction, optional boost to 60-66 Gy) Brachytherapy 34 Gy/10 fractions MammoSite 34 Gy/10 fractions 3DCRT 38.5 Gy/10 fractions
Outcomes	Primary: in-breast tumour recurrence Secondary: survival, event-free survival, distant disease-free survival, quality of life and participant-reported cosmesis, physician-reported cosmesis and toxicity
Starting date	March 2005
Contact information	Study chair: F Vicini, William Beaumont Hospital- Royal Oak Campus J White, Medical College of Wisconsin
Notes	NCT00103181 NSABP B-39/RTOG 0413, SWOG-NSABP-B-39 Collaborators: Southwest Oncology Group, National Cancer Institute, RTOG, National Surgical Adjuvant Breast and Bowel Project For brachytherapy and 3DCRT: cavity plus 15 mm = CTV + 10 mm = PTV MammoSite: PTV = 10 mm expansion on balloon minus balloon volume

SHARE

Trial name or title	Standard or Hypofractionated Radiotherapy Versus Accelerated Partial Breast Irradiation (PBI/APBI) for Breast Cancer (SHARE) Phase III Multicentric Trial Comparing Accelerated Partial Breast Irradiation (PBI/APBI) Versus Standard or Hypofractionated Whole Breast Irradiation in Low Risk of Local Recurrence of Breast Cancer
Methods	Multicentre RCT
Participants	Inclusion criteria: 1. Women aged ≥ 50 years 2. Menopausal status confirmed 3. Pathology confirmation of invasive carcinoma (all types) 4. Complete tumour removal and conservative surgery 5. Pathologic tumour size of invasive carcinoma ≤ 2 cm (including the in situ component) pT1 6. All histopathological grades

SHARE (Continued)

7. Clear lateral margins for the invasive and in situ disease (> 2 mm)
8. pN0 or pN(i+)
9. No metastasis
10. RT should be started > 4 weeks and < 12 weeks after last surgery
11. Surgical clips (4 or 5 clips in the tumour bed)
12. No prior breast or mediastinal RT
13. ECOG 0-1
14. Information to the participant and signed informed consent

Exclusion criteria:

1. Multifocal invasive ductal carcinoma defined as the presence of ≥ 2 distinct tumours that are separated by normal tissue or when the distance between the 2 lesions does not permit conservative surgery
2. Bilateral breast cancer
3. No or < 4 surgical clips in the tumour bed
4. Nodal involvement: pN1 (including micrometastasis, mi+), pN2, pN3
5. Metastatic disease
6. Internal mammary node involvement or supraclavicular lymph node involvement
7. Indication of chemotherapy or trastuzumab
8. Involved or close lateral margins for the invasive with or without in situ components (< 2 mm) AND impossibility to re-operate or impossible to perform another conservative surgery
9. Women with known BRCA1 or BRCA2 mutations
10. Previous mastoplasmy
11. Previous homolateral breast or mediastinal irradiation, or both
12. Previous invasive cancer (except basocellular epithelioma or in situ carcinoma of the cervix)
13. No geographical, social or psychological reasons that would prevent study follow-up

Interventions	<p>Experimental arm: APBI</p> <p>3D-CRT</p> <p>40 Gy/10 fractions Tumour bed 40 Gy in 10 fractions, 2 fractions of 4 Gy per day in 5-7 days. PBI/APBI using 3D-CRT technique, in 5 days, 40 Gy to the tumour bed</p> <p>Control arm: standard or hypofractionated radiotherapy</p>
Outcomes	<p>Primary:</p> <ol style="list-style-type: none"> 1. Rate of local recurrence <p>Secondary:</p> <ol style="list-style-type: none"> 1. Ipsilateral breast recurrence-free survival 2. Nodal regional recurrence-free survival 3. Distant recurrence-free survival 4. Disease-specific survival 5. Overall survival 6. Toxicities: measurement of the rate and type of toxicity (acute and late toxic effects) 7. Cosmetic: comparison of the cosmetic result (according to both the physician and the participant) 8. Quality of life and satisfaction 9. Medico-economic study
Starting date	October 2010

SHARE (Continued)

Contact information

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Notes

3D-CRT: 3-dimensional conformal radiotherapy; APBI: accelerated partial breast irradiation; BCS: breast-conserving surgery; bd: twice a day; CTV: clinical target volume; DCIS: ductal carcinoma in situ; ECOG: Eastern Cooperative Oncology Group; ER: oestrogen receptor; GTV: gross tumour volume; Gy: Gray; IGRT: image-guided radiotherapy; IMRT: intensity-modulated radiotherapy; M: metastases; N: lymph node; PBI: partial breast irradiation; PgR: progesterone receptor; PTV: planning target volume; RCT: randomized controlled trial; RT: radiotherapy; RTOG: Radiation Therapy Oncology Group; SN: sentinel node biopsy; WB: whole breast; T: tumour; WBRT: whole breast radiotherapy.

DATA AND ANALYSES

Comparison 1. Partial breast irradiation (PBI)/accelerated partial breast irradiation (APBI) versus whole breast radiotherapy (WBRT)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Local recurrence-free survival	6	6820	Hazard Ratio (95% CI)	1.62 [1.11, 2.35]
1.1 2.4 years' median follow-up	1	3451	Hazard Ratio (95% CI)	2.05 [1.00, 4.21]
1.2 5 years' follow-up	4	3111	Hazard Ratio (95% CI)	2.50 [1.21, 5.15]
1.3 10 years' follow-up	1	258	Hazard Ratio (95% CI)	1.09 [0.63, 1.89]
2 Cosmesis, physician-reported	5	1720	Odds Ratio (M-H, Fixed, 95% CI)	1.51 [1.17, 1.95]
3 Overall survival	5	6718	Hazard Ratio (95% CI)	0.90 [0.74, 1.09]
4 Acute radiotherapy (RT) skin toxicity	2	608	Odds Ratio (M-H, Fixed, 95% CI)	0.04 [0.02, 0.09]
5 Late RT skin toxicity	2	608	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.39]
6 Fat necrosis	3	1319	Odds Ratio (M-H, Fixed, 95% CI)	1.58 [1.02, 2.43]
7 'Elsewhere primary'	3	3009	Odds Ratio (M-H, Fixed, 95% CI)	3.97 [1.51, 10.41]
8 Cause-specific survival	5	6718	Hazard Ratio (95% CI)	1.08 [0.73, 1.58]
9 Distant metastasis-free survival	4	3267	Hazard Ratio (95% CI)	0.94 [0.65, 1.37]
10 Relapse-free survival	3	3811	Hazard Ratio (95% CI)	1.36 [0.88, 2.09]
11 Loco-regional recurrence-free survival	2	3553	Hazard Ratio (95% CI)	1.80 [1.00, 3.25]
12 Mastectomy	3	4817	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.77, 1.87]

Partial breast irradiation for early breast cancer (Review)

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Analysis 1.1. Comparison 1 Partial breast irradiation (PBI)/accelerated partial breast irradiation (APBI) versus whole breast radiotherapy (WBRT), Outcome 1 Local recurrence-free survival.

Analysis 1.2. Comparison 1 Partial breast irradiation (PBI)/accelerated partial breast irradiation (APBI) versus whole breast radiotherapy (WBRT), Outcome 2 Cosmesis, physician-reported.

Study or subgroup	PBI/APBI n/N	WBRT n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Test for overall effect: $Z=3.14(P=0)$					
Favours PBI/APBI 0.01 0.1 1 10 100 Favours WBRT					

Analysis 1.3. Comparison 1 Partial breast irradiation (PBI)/accelerated partial breast irradiation (APBI) versus whole breast radiotherapy (WBRT), Outcome 3 Overall survival.

Study or subgroup	PBI/APBI n/N	WBRT n/N	Hazard Ratio 95% CI	Weight	Hazard Ratio 95% CI
ELIOT	34/651	31/654		15.58%	1.1[0.67,1.81]
GEC-ESTRO	27/633	32/551		14.8%	0.66[0.39,1.1]
Livi 2015	1/260	7/260		0.89%	0.17[0.02,1.39]
Polgár 2007	25/128	23/130		47.45%	1.05[0.79,1.4]
TARGIT	37/1721	51/1730		21.28%	0.72[0.47,1.1]
Total (95% CI)	3393	3325		100%	0.9[0.74,1.09]
Total events: 124 (PBI/APBI), 144 (WBRT)					
Heterogeneity: $\tau^2=0$; $\chi^2=6.68$, $df=4(P=0.15)$; $I^2=40.15\%$					
Test for overall effect: $Z=1.1(P=0.27)$					
Favours PBI/APBI 0.01 0.1 1 10 100 Favours WBRT					

Analysis 1.4. Comparison 1 Partial breast irradiation (PBI)/accelerated partial breast irradiation (APBI) versus whole breast radiotherapy (WBRT), Outcome 4 Acute radiotherapy (RT) skin toxicity.

Study or subgroup	PBI/APBI n/N	WBRT n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Livi 2015	5/246	98/260		74.89%	0.03[0.01,0.09]
Rodriguez	9/51	38/51		25.11%	0.07[0.03,0.19]
Total (95% CI)	297	311		100%	0.04[0.02,0.09]
Total events: 14 (PBI/APBI), 136 (WBRT)					
Heterogeneity: $\tau^2=0$; $\chi^2=1.37$, $df=1(P=0.24)$; $I^2=27.09\%$					
Test for overall effect: $Z=9.1(P<0.0001)$					
Favours PBI/APBI 0.01 0.1 1 10 100 Favours WBRT					

Analysis 1.5. Comparison 1 Partial breast irradiation (PBI)/accelerated partial breast irradiation (APBI) versus whole breast radiotherapy (WBRT), Outcome 5 Late RT skin toxicity.

Study or subgroup	PBI/APBI n/N	WBRT n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Livi 2015	0/246	2/260		100%	0.21[0.01,4.39]
Rodriguez	0/51	0/51			Not estimable
Total (95% CI)	297	311		100%	0.21[0.01,4.39]
Total events: 0 (PBI/APBI), 2 (WBRT)					
Favours PBI/APBI 0.01 0.1 1 10 100 Favours WBRT					

Study or subgroup	PBI/APBI n/N	WBRT n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Heterogeneity: Not applicable Test for overall effect: Z=1.01(P=0.31)					
Favours PBI/APBI 0.01 0.1 1 10 100 Favours WBRT					

Analysis 1.6. Comparison 1 Partial breast irradiation (PBI)/accelerated partial breast irradiation (APBI) versus whole breast radiotherapy (WBRT), Outcome 6 Fat necrosis.

Study or subgroup	PBI/APBI n/N	WBRT n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
ELIOT	22/151	10/146		26.13%	2.32[1.06,5.09]
Polgár 2007	26/127	26/129		61.71%	1.02[0.55,1.87]
RAPID	12/399	4/367		12.16%	2.81[0.9,8.8]
Total (95% CI)	677	642		100%	1.58[1.02,2.43]
Total events: 60 (PBI/APBI), 40 (WBRT) Heterogeneity: Tau ² =0; Chi ² =3.89, df=2(P=0.14); I ² =48.53% Test for overall effect: Z=2.06(P=0.04)					
Favours PBI/APBI 0.01 0.1 1 10 100 Favours WBRT					

Analysis 1.7. Comparison 1 Partial breast irradiation (PBI)/accelerated partial breast irradiation (APBI) versus whole breast radiotherapy (WBRT), Outcome 7 'Elsewhere primary'.

Study or subgroup	PBI/APBI n/N	WBRT n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
ELIOT	14/651	0/654		9.31%	29.77[1.77,500.15]
GEC-ESTRO	3/633	4/551		81.27%	0.65[0.15,2.92]
Livi 2015	3/260	0/260		9.42%	7.08[0.36,137.78]
Total (95% CI)	1544	1465		100%	3.97[1.51,10.41]
Total events: 20 (PBI/APBI), 4 (WBRT) Heterogeneity: Tau ² =0; Chi ² =7.67, df=2(P=0.02); I ² =73.94% Test for overall effect: Z=2.8(P=0.01)					
Favours PBI/APBI 0.01 0.1 1 10 100 Favours WBRT					

Analysis 1.8. Comparison 1 Partial breast irradiation (PBI)/accelerated partial breast irradiation (APBI) versus whole breast radiotherapy (WBRT), Outcome 8 Cause-specific survival.

Study or subgroup	PBI/APB n/N	WBRT n/N	Hazard Ratio 95% CI	Weight	Hazard Ratio 95% CI
ELIOT	23/651	20/654		41.01%	1.2[0.66,2.18]
GEC-ESTRO	4/633	4/551		7.67%	0.87[0.22,3.46]
Livi 2015	1/260	3/260		2.87%	0.38[0.04,3.63]
Polgár 2007	6/128	10/130		14.37%	0.78[0.28,2.15]
TARGIT	20/1721	16/1730		34.07%	1.25[0.65,2.41]
Favours PBI/APBI 0.01 0.1 1 10 100 Favours WBRT

Analysis 1.9. Comparison 1 Partial breast irradiation (PBI)/accelerated partial breast irradiation (APBI) versus whole breast radiotherapy (WBRT), Outcome 9 Distant metastasis-free survival.

Analysis 1.10. Comparison 1 Partial breast irradiation (PBI)/accelerated partial breast irradiation (APBI) versus whole breast radiotherapy (WBRT), Outcome 10 Relapse-free survival.

Analysis 1.11. Comparison 1 Partial breast irradiation (PBI)/accelerated partial breast irradiation (APBI) versus whole breast radiotherapy (WBRT), Outcome 11 Loco-regional recurrence-free survival.

Analysis 1.12. Comparison 1 Partial breast irradiation (PBI)/accelerated partial breast irradiation (APBI) versus whole breast radiotherapy (WBRT), Outcome 12 Mastectomy.

ADDITIONAL TABLES

Table 1. Harvard cosmetic score

Cosmetic score
Excellent
Good
Fair
Poor

Table 2. Brachytherapy cosmetic score

Score	Definition
Excellent	Perfect symmetry, no visible distortion or skin changes and no visible catheter entry/exit sequelae
Good	Slight skin distortion, retraction or oedema, any visible telangiectasia, any visible catheter entry/exit scar or mild hyperpigmentation

Table 2. Brachytherapy cosmetic score (Continued)

Fair	Moderate distortion of the nipple or breast symmetry, moderate hyperpigmentation, or prominent skin retraction, oedema or telangiectasia
Poor	Marked distortion, oedema, fibrosis or severe hyperpigmentation

Table 3. RTOG CTC acute skin toxicity

RTOG CTC	Grade I	Grade II	Grade III	Grade IV
Description	Follicular, faint or dull erythema / epilation / dry desquamation / decreased sweating	Tender or bright erythema, patchy moist desquamation / moderate oedema	Confluent, moist desquamation other than skin folds, pitting oedema	Ulceration, haemorrhage, necrosis

RTOG CTC: Radiation Therapy Oncology Group Common Toxicity Criteria.

Table 4. Fat necrosis

Grade	Findings
0	No fat necrosis
1	Asymptomatic fat necrosis (only radiological or cytological findings, or both)
2	Symptomatic fat necrosis not requiring medication (palpable mass with or without mild pain)
3	Symptomatic fat necrosis requiring medication (palpable mass with significant pain)
4	Symptomatic fat necrosis requiring surgical intervention

Table 5. NCI CTC 3.0

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Induration (subcutaneous fibrosis)	Increased density on palpation	Moderate increase in density, not interfering with ADL; marked increase in density and firmness on palpation with or without minimal retraction	Dysfunction interfering with ADL; very marked density, retraction or fixation	-
Telangiectasia	Few	Moderate	Many and confluent	-
Pain	Pain mild, not interfering with function	Moderate pain; pain or analgesics interfering with function, but not with ADL	Severe pain; pain or analgesics interfering with ADL	Disability

ADL: activities of daily living; NCI CTC: National Cancer Institute Common Toxicity Criteria.

Table 6. Radiotherapy doses prescribed

Trial	PBI/APBI dose	Fraction size (Gy)	EQD ² PBI/APBI	Control dose	Fraction size (Gy)	EQD ² Control
TARGET	20 Gy at surface of the applicator (attenuated to 5-7 Gy at 1 cm) (APBI)	80 at cavity surface 12.8 at 1 cm	80 Gy at cavity surface 12.8 Gy at 1 cm	40-56 Gy/20-28 fractions ± 10-16 Gy boost	2	40-56 Gy ± 10-16 Gy
Livi 2015	30 Gy/5 daily fractions EBRT IMRT. 100% of the PTV was covered by 95% of the prescribed dose	6	75 Gy	50 Gy/25 fractions + 10 Gy/5 fractions boost	2	50 + 10 = 60 Gy
RAPID	38.5 Gy/10 fractions bd (with 6 hour gap) Dose-evaluation volume (that part of PTV within the breast) received 95-107% of prescription dose	3.85	74.1 Gy	50 Gy/25 fractions or 42.5 Gy/16 fractions ± boost (10 Gy/4-5 fractions) based on criteria such as young age or close margins, pre-specified by centre	2 or 2.65	50 or 47.1 Gy
Rodriguez	37.5 Gy/10 fractions bd (with 6 hour gap) (APBI). PTV covered by ≥ 95% of prescribed dose, with < 105% hot spot	3.75	71.22 Gy	48 Gy/24 fractions ± 10 Gy/5 fractions boost	2	48 ± 10 = 48-58 Gy
Polgár 2007	7 × 5.2 Gy HDR (APBI) or 50 Gy/25 fractions (PBI). Women not suitable for HDR had 6-15 MeV beam to tumour bed plus 2 cm margin (field size defined using CT-planning or simulation films)	5.2 or 2	53.6 Gy or 50 Gy	50 Gy/25 fractions (3D-CRT was not used)	2	50 Gy
GEC-ESTRO	30.3 Gy/7 fractions or 32 Gy/8 fractions HDR twice daily or 50 Gy at 0.6-0.8 Gy/hour pulses (1 pulse per hour, 24 hours per day) PDR	7-8	41.64-42.67 Gy	50.0-50.4 Gy to a reference point + 10 Gy/5 fractions boost. Electron dose was prescribed to the point of maximum dose on the beam axis (D _{max}), ensuring the 85% isodose encompassed the tumour bed	1.8-2.0	48.72-50 + 10 = 58.72-60 Gy

Table 6. Radiotherapy doses prescribed (Continued)

ELIOT	21 Gy/1 fraction at 90% using 6-9 MeV	21	131.2 Gy	50 Gy/25 fractions + 10 Gy/5 fractions boost (using electrons)	2.0	50 + 10 Gy
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3D-CRT: 3-dimensional conformal radiotherapy; APBI: accelerated partial breast irradiation; bd: twice daily; CT: computer tomography; EBRT: external beam radiotherapy; EQD2: equivalent dose in 2 Gy fractions; Gy: Gray; HDR: high-dose-rate; IMRT: intensity-modulated radiotherapy; MeV: mega electron volt; PBI: partial breast irradiation; PDR: pulsed-dose-rate; PTV: planning target volume.

Table 7. Radiotherapy techniques

Trial	RT technique
Polgár 2007	Interstitial brachytherapy (88/128) EBRT using photons (40/128)
ELIOT	intra-operative electrons
Livi 2015	EBRT (IMRT)
TARGIT	intra-operative kV RT
RAPID	EBRT
Rodriguez	EBRT (3D-CRT)

3D-CRT: 3-dimensional conformal radiotherapy; EBRT: external beam radiotherapy; IMRT: intensity-modulated radiotherapy; RT: radiotherapy.

APPENDICES

Appendix 1. The Cochrane Central Register of Controlled Trials (CENTRAL)

- MESH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES
- breast AND (cancer* OR tumour* OR tumor* OR neoplas*)
- #1 OR #2
- brachytherapy:MH
- brachytherapy
- partial breast
- partial breast irradiation
- whole breast irradiation
- whole breast radiotherapy
- less than whole breast rad\$
- high-dose-rate brachytherapy
- acceleration partial breast irradiation
- acceleration irradiation

14. tumour bed boost
15. sole tumour boost
16. tumour bed boost
17. tumor bed boost
18. sole tumour bed irradiation
19. mammosite
20. MESH DESCRIPTOR Radiotherapy, Conformal EXPLODE ALL TREES WITH QUALIFIERS AE
21. MESH DESCRIPTOR Radiotherapy, Conformal EXPLODE ALL TREES WITH QUALIFIERS MT
22. (balloon dilation):MH
23. MESH DESCRIPTOR Radiotherapy
24. OR/4-23
25. #3 AND #24

Appendix 2. MEDLINE (Ovid) (1966 to present)

- 1.RANDOMIZED CONTROLLED TRIAL.pt
2. CONTROLLED CLINICAL TRIAL.pt
3. RANDOMIZED CONTROLLED TRIALS.sh
4. RANDOM ALLOCATION.sh
5. DOUBLE BLIND METHOD.sh
6. SINGLE BLIND METHOD.sh
7. or/1-6
8. (ANIMALS not HUMANS).sh
9. 7 not 8
10. CLINICAL TRIAL.pt
11. exp CLINICAL TRIALS/
12. (clin\$ adj25 trial\$).ti,ab
13. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab
14. PLACEBOS.sh
15. placebo\$.ti,ab
16. random\$.ti,ab
17. RESEARCH DESIGN.sh
18. or/10-16
19. 18 not 8
20. 19 not 9
21. 9 or 20
22. exp breast neoplasms/
23. exp "neoplasms, ductal, lobular, and medullary"/
24. exp breast/
25. exp neoplasms/
26. 24 AND 25
- 27 (breast\$ adj5 (neoplasm\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or dcis or ductal or infiltrat\$ or intraductal\$ or lobular or medullary)).mp.
- 28 exp mammary neoplasms/
- 29 (mammar\$ adj5 (neoplasm\$ or cancer\$ or tumo?r\$ or carcinoma\$ or adenocarcinoma\$ or sarcoma\$ or dcis or ductal or infiltrat\$ or intraductal\$ or lobular or medullary)).mp
30. or/22, 23,26-29
31. partial breast irradiation.sh,kw,ti,ab
32. partial breast.sh,kw,ti,ab
33. whole breast irradiation.sh,kw,ti,ab
34. whole breast radiotherapy.mp
35. less than whole breast rad\$.mp
36. brachytherapy.sh,kw,ti,ab
37. high-dose-rate brachytherapy.sh,kw,ti,ab

Partial breast irradiation for early breast cancer (Review)

38. accelerated partial breast irradiation.sh,kw,ti,ab
39. tumour bed boost.sh.kw.ti.ab
40. sole tumour bed irradiation.sh,kw,ti,ab
41. MammoSite.sh.kw.ti.ab
42. Breast Neoplasms/ rt.sh
43. Radiotherapy, Conformal/adverse events.sh
44. Radiotherapy, Conformal/methods.sh
45. Brachytherapy.sh
46. Balloon dilation.sh
47. Radiotherapy/.sh
48. or/31-47
49. 48 AND 30
50. 49 AND 21

Appendix 3. EMBASE

1. randomised AND controlled AND trial
2. controlled AND clinical AND trial
3. randomi*ed:ab
4. placebo:ab
5. randomly:ab
6. trial:ab
7. groups:ab
8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9. 'breast'/exp AND 'neoplasm'/exp
10. locally AND advance* NEAR/6 breast AND cancer*
11. locally AND advance* NEAR/6 breast AND neoplas*
12. locally AND advance* NEAR/6 breast AND carcinoma*
13. locally AND advance* NEAR/6 breast AND tumour*
14. locally AND advance* NEAR/6 breast AND tumor*
15. early NEAR/6 breast AND cancer*
16. early NEAR/6 breast AND neoplas*
17. early NEAR/6 breast AND carcinoma*
18. early NEAR/6 breast AND tumour*
19. early NEAR/6 breast AND tumor*
20. #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
21. 'radiotherapy'/exp OR radiotherapy
22. 'adjuvant'/exp OR adjuvant AND ('radiotherapy'/exp OR radiotherapy)
23. 'radiation'/exp OR radiation AND ('therapy'/exp OR therapy)
24. #21 OR #22 OR #23
25. #8 AND #20 AND #24

Appendix 4. CINAHL

1. MH Clinical Trials
2. PT Clinical Trial
3. TX clini* n1 trial*
4. TX ((singl* n1 blind*) or (singl* n1 mask**))
5. TX randomi* control* trial*
6. MH random assignment
7. TX random* allocat*
8. TX placebo*
9. MH "Placebos"
10. MH Quantitative Studies
11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12. MH breast neoplasms
13. TI breast cancer OR SU breast cancer OR AB breast cancer
14. TI breast tumour OR SU breast tumour OR AB breast tumour
15. MM "Carcinoma, Ductal, Breast"
16. #12 OR #13 OR #14 OR #15
17. MM "radiotherapy, Conformal/AE"
18. MM "radiotherapy, Conformal/methods"
19. SU partial breast OR TI partial breast OR AB partial breast
20. SU whole breast irradiation OR TI whole breast irradiation OR AU whole breast irradiation
21. SU whole breast radiotherapy
22. SU whole breast rad\$ OR TI whole breast rad\$ OR AB whole breast rad\$
23. SU brachytherapy OR TI brachytherapy OR AB brachytherapy
24. MH brachytherapy
25. MH radiotherapy
26. SU whole breast radiotherapy OR TI whole breast radiotherapy OR AB whole breast radiotherapy
27. SU high-dose-rate brachytherapy OR AB high-dose-rate brachytherapy OR TI high-dose-rate brachytherapy
28. SU accelerated partial breast irradiation OR TI accelerated partial breast irradiation OR AB accelerated partial breast irradiation
29. SU tumour bed boost OR TI tumour bed boost OR AB tumour bed boost
30. SU MammoSite OR TI MammoSite OR AB MammoSite
31. MH "Breast Neoplasms+/RT"
32. #17 OR #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
33. #11 AND #16 AND #32

Appendix 5. Current Contents

1. TS = clinical trial*
2. TS = research design
3. TS = comparative stud*
4. TS = evaluation stud*
5. TS = controlled trial*
6. TS = follow-up study
7. TS = prospective stud*
8. TS = random*
9. TS = placebo
10. TS = single blind*
11. TS = double blind*
12. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13. TS = breast cancer
14. TS = breast neoplasms
15. #12 OR #13
16. TS = partial breast irradiation
17. TS = whole breast irradiation
18. TS = less than whole breast
19. TS = brachytherapy
20. TS = tumour bed boost
21. TS = Mammosite
22. #15 OR #16 OR #17 OR #18 OR #19 OR #20
23. TS = radiotherapy
24. TS = radiation therapy
25. #22 OR #23
26. #12 AND #21 AND #24

Appendix 6. WHO ICTRP search portal

Basic search:

1. Partial irradiation for early breast cancer
2. Early breast cancer AND partial irradiation
3. Early breast cancer AND partial breast irradiation
4. Early breast cancer AND Mammosite
5. Early breast cancer AND Intracavitary brachytherapy
6. Early breast cancer AND Interstitial brachytherapy
7. Early breast cancer AND accelerated partial breast irradiation
8. Early breast cancer and less than whole breast radiotherapy

Advanced search:

1. Title: Partial irradiation for early breast cancer

Recruitment status: all

2. Condition: early breast cancer

Intervention: partial breast irradiation OR Mammosite OR intracavitary brachytherapy OR interstitial brachytherapy OR accelerated partial breast irradiation OR less than whole breast radiotherapy

Recruitment status: all

Appendix 7. ClinicalTrials.gov

Basic searches:

1. Partial irradiation for early breast cancer
2. Early breast cancer AND partial irradiation
3. Early breast cancer AND partial breast irradiation
4. Early breast cancer AND Mammosite
5. Early breast cancer AND Intracavitary brachytherapy
6. Early breast cancer AND Interstitial brachytherapy
7. Early breast cancer AND accelerated partial breast irradiation
8. Early breast cancer and less than whole breast radiotherapy

Advanced searches:

1. Search terms: Partial irradiation for early breast cancer

Recruitment: All studies

Study type: All studies

Gender: All studies

2. Condition: Early breast cancer

Intervention: Partial breast irradiation OR Mammosite OR intracavitary brachytherapy OR interstitial brachytherapy OR accelerated partial breast irradiation OR less than whole breast radiotherapy

Recruitment: All studies

Study type: All studies

Gender: All studies

Appendix 8. OpenGrey

1. (breast cancer OR breast neoplasm* OR breast adenocarcinoma) AND (radiation OR irradiation OR radiotherapy OR radio-therapy))

WHAT'S NEW

Date	Event	Description
5 May 2015	New search has been performed	Performed search for new studies on 4 May 2015
4 May 2015	New citation required but conclusions have not changed	Five new studies were included, adding 5333 participants. An additional 2 'ongoing studies' have been identified

HISTORY

Protocol first published: Issue 2, 2008

Review first published: Issue 6, 2014

Date	Event	Description
15 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

ML, BH and DF wrote the protocol.

BH extracted data, created 'Risk of bias' tables and 'Characteristics of included studies' tables, analyzed the data, wrote the results section and discussion, and responded to editorial and peer review (in consultation with ML).

ML checked the analyses, 'Risk of bias' tables, collaborated with writing the results, discussion and conclusion sections.

AS checked the extracted data and ran the search strategy.

DECLARATIONS OF INTEREST

MH: none known.

BH: none known.

DF: none known.

AS: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Princess Alexandra Cancer Collaborative Group, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We reported time-to-event data where possible for cancer-related outcomes. We reported local relapse-free survival (LR-FS) rather than local relapse (LR), distant metastasis-free survival (DM-FS) rather than distant metastases (DM), we reported loco-regional relapse-free survival (L-R R-FS) rather than loco-regional control (LRC) as a secondary endpoint. We added the words "elsewhere primary" to the name of the endpoint "new primary in ipsilateral breast" because this term is used in the relevant literature, in order to add clarity for the reader.

We initially indicated that we would convert doses to their biological equivalent (BED), but have in fact used equivalent dose in 2 Gy fractions (EQD₂). This allows numerical addition of separate components of a treatment and is more readily understood by clinical radiation oncologists because it results in numbers which can be directly related to clinical experience.

We added APBI as well as PBI: modern RT techniques that reduce the treated volume allow the use of high dose per fraction to the smaller treated volume. The ongoing studies tend to use APBI, which reflects modern RT practice, making the review results more applicable.

We added blinding to assessment of risk of bias, because the lack of blinding for the primary outcome of cosmesis would be a significant cause of bias. We searched an additional database (i.e. EMBASE.com) and trial registry (WHO ICTRP) to our search strategy, and also handsearched other resources. This ensured that our searches were as comprehensive as possible, and complied with Cochrane search requirements.

We included studies which included women with ductal carcinoma in situ ([RAPID](#)) for reporting of toxicity endpoints. [ELIOT](#) used regional nodal irradiation for those women with more or more involved nodes (5% of the cohort), we excluded [ELIOT](#) from the analysis of L-RR-FS.

We pooled the studies in a quantitative meta-analysis, but excluded the older studies, which used surgical, RT and systemic management practices which do not reflect current practice. We had planned sensitivity analysis based on excluding studies which used outmoded RT and surgical techniques, but as we decided to exclude them from our analysis, we did not do so. These studies were included in the previous iteration of this review, but were removed for the 2015 update.

We corrected the list and table of excluded studies so we are now compliant with MECIR guidelines, so that this list only includes studies that might reasonably be expected to be included, but which we deemed ineligible.

INDEX TERMS

Medical Subject Headings (MeSH)

Breast [radiation effects]; Breast Neoplasms [pathology] [*radiotherapy] [surgery]; Combined Modality Therapy [methods]; Disease-Free Survival; Mastectomy, Segmental; Neoplasm Recurrence, Local [prevention & control]; Organ Sparing Treatments [*methods]; Radiation Dose Hypofractionation; Radiotherapy [adverse effects] [methods]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans