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Post-mastectomy radiotherapy for women with early breast cancer and one to three positive lymph nodes

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Abstract

Background

Continual improvement in adjuvant therapies has resulted in a better prognosis for women diagnosed with breast cancer. A surrogate marker used to detect the spread of disease after treatment of breast cancer is local and regional recurrence (LRR). The risk of LRR after mastectomy increases with the number of axillary lymph nodes affected by cancer. There is a consensus to use radiotherapy as an adjuvant treatment after mastectomy (post-mastectomy radiotherapy - PMRT) in women diagnosed with breast cancer and found to have disease in four or more positive axillary lymph nodes. Despite data showing almost double the risk of LRR in women treated with mastectomy and found to have one to three positive lymph nodes, there is a lack of international consensus on the use of PMRT in this group.

Objectives

To assess the effects of post-mastectomy radiotherapy (PMRT) in women diagnosed with early breast cancer and found to have one to three positive axillary lymph nodes.

Search methods

We searched the Cochrane Breast Cancer Group's Specialised Register, CENTRAL, MEDLINE, Embase, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), and ClinicalTrials.gov up to 24 September 2021.

Selection criteria

We included randomised controlled trials (RCTs). The inclusion criteria included women diagnosed with breast cancer treated with simple or modified radical mastectomy and axillary surgery (sentinel lymph node biopsy (SLNB) alone or those undergoing axillary lymph node clearance with or without prior SLNB). We included only women receiving PMRT using X-rays (electron and photon radiation) and we defined the radiotherapy dose to reflect what is currently being recommended i.e., 40 Gray (Gy) to 50 Gy in 15 to 25/28 fractions in 3 to 5 weeks. The included studies did not administer any boost to the tumour bed. In this review, we excluded studies using neoadjuvant chemotherapy as a supportive treatment before surgery.

Data collection and analysis

We used Covidence™ to screen records. We collected data on tumour characteristics, adjuvant treatments and the outcomes of LRR, overall survival, disease-free survival, time to progression, short-term and long-term adverse events, and quality of life. We reported on time-to-event outcome measures using the hazard ratio (HR) and sub-distribution HR. We used Cochrane's risk of bias assessment tool recommended by Cochrane and overall certainty of the evidence was presented using the GRADE approach.

Main results

The RCTs included in this review were sub-group analyses of original RCTs conducted in the 1980s to assess the effectiveness of PMRT. Hence the type and duration of adjuvant systemic treatments used in the studies included in this review were suboptimal compared to the current standard of care.

The review involved three RCTs with a total of 829 women diagnosed with breast cancer and low-volume axillary disease. Amongst the included studies, only a single study pertained to the modern-day radiotherapy practice. The results from this one study showed a reduction of LRR (HR 0.20; 95% CI 0.13 to 0.33; 1 study; 522 participants; low certainty of evidence) and improvement in overall survival with PMRT (HR 0.76; 95% CI 0.60 to 0.97; 1 study; 522 participants; moderate certainty of evidence). One of the other studies using radiotherapy techniques that do not reflect modern day practice reported on disease-free survival in women with low-volume axillary disease (subdistribution HR =

0.63; 95% CI, 0.41 to 0.96; 1 study; 173 participants). None of the included trials reported on PMRT side effects or quality of life outcome measures.

Authors' conclusions

Based on one study, the use of PMRT in women diagnosed with breast cancer and low-volume axillary disease indicated a reduction in locoregional recurrence and an improvement in survival. There is a need for more research to be conducted using modern-day radiotherapy equipment and methods to support and supplement the review findings.

Plain language summary

Is X-ray treatment (radiotherapy) after removal of breast tissue (mastectomy) better than no X-ray treatment in women diagnosed with breast cancer that has spread to one to three armpit lymph nodes?

Key message:

The review showed that radiotherapy after a mastectomy may reduce cancer returning to the chest wall and in the nearby lymph nodes (local and regional recurrence) and probably improves survival in women diagnosed with breast cancer and found to have one to three involved lymph nodes. The studies did not report on the short- or long-term side effects and quality of life (QoL) of postmastectomy radiotherapy in breast cancer survivors.

There is currently one ongoing international multi-centre study, which has completed recruitment and is in the active follow-up phase, which could further add valuable insight into the role of PMRT.

What is the condition of interest in this review?

Breast cancer is the commonest malignancy affecting women. The improvements in systemic treatments (anti-cancer drugs) over the last two decades have resulted in fewer cancer-related deaths. The development of local and regional recurrence after the initial treatment of breast cancer can increase the risk of cancer spreading. It has been shown that the risk of local and regional recurrence was more than doubled in women diagnosed with one to three positive axillary lymph nodes compared to node-negative disease.

What is the role of additional supportive treatment in the management of breast cancer?

Radiotherapy is a well-established supportive local treatment that reduces local and regional recurrence after surgery in women diagnosed with breast cancer. However, researchers over the last 2 to 3 decades were not able to show without doubt that, the reduction in local and regional recurrence with radiotherapy led to fewer breast cancer-related deaths. There is overall consensus about the use of PMRT in women with high-risk breast cancer characteristics, like large tumour size (> 5cm) and ≥ 4 axillary lymph nodes affected with breast cancer. However, there is still uncertainty about the role of PMRT in women found to have one to three axillary lymph nodes affected by breast cancer.

What did the reviewers want to find out?

For women diagnosed with breast cancer and found to have one to three lymph nodes affected by cancer, we asked:

1) Does post-mastectomy radiotherapy reduce the occurrence of local and regional recurrence compared to no radiotherapy?

2) Is there any survival advantage in women undergoing post-mastectomy radiotherapy compared to those not having radiotherapy?

3) What are the short- and long-term side effects of post-mastectomy radiotherapy?

4) Is there any difference in the quality of life for women undergoing radiotherapy compared to those with no radiotherapy?

Methods

We searched for studies that compared post-mastectomy radiotherapy against no radiotherapy in women diagnosed with breast cancer and found to have one to three involved axillary lymph nodes. Once we identified the relevant studies, we compared and summarised the results. We have also assessed and rated our confidence in the presented evidence based on the study methods and the number of women who participated in the studies.

What did we find?

We identified three studies, involving 725 women, with 355 women receiving PMRT and no PMRT in 370. The largest study was conducted in Denmark and involved 552 women. The remaining two studies were conducted in Sweden, and involved 104 pre-menopausal and 173 post-menopausal women. Only the Danish study administered radiotherapy using methods that are comparable to modern-day practice. All included studies had long-term follow-up (15 years or more). The studies were funded by independent charitable organisations with no funding obtained through private or pharmaceutical companies.

Main results of the review

The use of post-mastectomy radiotherapy compared to no radiotherapy in women diagnosed with breast cancer and found to have one to three involved axillary lymph nodes:

- May lead to a reduction in the local and regional recurrence, and
- Probably improves survival by 24% in women

We did not identify any study to reliably answer the effect of PMRT on disease-free survival, short or long-term side effects and quality of life in breast cancer survivors.

What are the limitations of the evidence?

Our confidence in the evidence is low to moderate, and the results of future research could differ from the results of this review. There are three main reasons for the low confidence in the presented evidence. The included studies were all conducted prior to the introduction of modern and more effective supportive systemic (anti-cancer drugs) treatment for breast cancer. Although we identified three studies, the results could only be interpreted from a single study that reflected modern day radiotherapy techniques. Finally, the included studies did not provide data on all the outcome measures of interest and/or we were unable to extract relevant data.

The evidence presented here is up-to-date to September 2021.

Summary of findings

Summary of findings 1

Summary of findings table - Post-mastectomy radiotherapy (PMRT) compared to no PMRT in women with breast cancer and one to three positive lymph nodes

Post-mastectomy radiotherapy (PMRT) compared to no PMRT in women with breast cancer and one to three positive lymph nodes

Patient or population: women with breast cancer and one to three positive lymph nodes
Setting:
Intervention: Post-mastectomy radiotherapy (PMRT)
Comparison: no PMRT

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no PMRT	Risk with Post-mastectomy radiotherapy (PMRT)				
Locoregional recurrence (LRR) follow-up: 15 years	10-year risk of LRR 255 per 1000[a]	**57 per 1000** (38 to 93)	**HR 0.20** (0.13 to 0.33) [Locoregional recurrence]	552 (1 RCT)	⊕⊕⊖⊖ Low[b,c]	
Overall survival (OS) follow-up: 25 years	10-year risk of death 403 per 1000[a]	**324 per 1000** (266 to 394)	**HR 0.76** (0.60 to 0.97) [Overall survival]	552 (1 RCT)	⊕⊕⊕⊖ Moderate[b]	
Disease-free survival (DFS)			(0 studies)	-	No randomised controlled trials reported on disease-free survival in PMRT women with low-volume axillary disease	
Time to progression			(0 studies)	-	No randomised controlled trials reported time to progression outcome in PMRT women with low-volume axillary disease.	
Short term adverse events			(0 studies)	-	No randomised controlled trials evaluated PMRT short-term adverse events like erythema, hyperpigmentation, and breast oedema.	
Long term adverse events			(0 studies)	-	No randomised controlled trials evaluated the long-term adverse events of PMRT like lymphoedema, cardiac toxicity, pulmonary toxicity, bone necrosis, and development of secondary radiation-induced cancers.	
Quality of life (QoL)			(0 studies)	-	No randomised controlled trials measured or reported on the quality of life indicators after PMRT.	

*__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

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table:
https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_433754310228759346.

[a] Estimated from the no PMRT group published Kaplan-Meier curve in one study (Overgaard 2007).
[b] Downgraded quality of evidence by one level due to "serious concern about the risk of bias" originating from inadequate random sequence generation, lack of allocation concealment and not attempting to blind

the assessors.

[c] Downgraded quality of evidence by one level due to the "serious imprecision" because of uncertainty in confidentially determining the spread of the observed effect in the PMRT group.

Background

Description of the condition

Breast cancer is the most common malignancy to affect women; in 2018, more than 2 million breast cancer cases were diagnosed globally, which accounted for 24.5% of all cancers in women (Bray 2018). The American Cancer Society has estimated that in 2020 around 276,480 new cases of invasive breast cancer will be diagnosed in the USA, with an estimated 42,690 deaths (Siegel 2020). Early diagnosis through screening, and advancements in supportive (adjuvant) treatments over the years, have resulted in improved outcomes for breast cancer survivors. This is reflected in the 1.5% average reduction in the age-adjusted death rate per year between 2008 and 2017 in the USA compared to a 0.3% average rise of age-adjusted new cases in the same period (SEER 2020).

The development of local and regional recurrence (LRR) of breast cancer is a dreaded outcome that affects 5% to 15% of women diagnosed with breast cancer after mastectomy (removal of all breast tissue) and radiotherapy (EBCTCG 2014). LRR after primary breast cancer treatment is typically associated with an increased risk of concurrent and future spread of cancer elsewhere in the body (Van Tienhoven 1999). The 10-year relative survival (cancer survival in the absence of other causes of death) after LRR has been shown to be in the region of 25% to 50% even after attempts to remove the cancer recurrence (Van Tienhoven 1999; Chagpar 2003). The commonest area of LRR after mastectomy is the chest wall (53%) followed by lymph nodes above and below the collar bone (26%) and in the armpit (13%) (Katz 2000; Wallgren 2003; Nielsen 2006). A palpable lump in these sites, painful enlarged lymph nodes and in some cases elevated red patches on the chest wall are common symptoms. The risk of LRR after mastectomy substantially increases with the number of axillary lymph nodes containing breast cancer. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) individual participant data meta-analysis demonstrated that the risk of LRR is more than doubled in women who had a mastectomy with one to three lymph nodes affected with cancer compared to node-negative women with breast cancer (EBCTCG 2005).

Description of the intervention

Breast cancer is a systemic disease and radiotherapy is a well-established additional treatment (adjuvant) that aims to reduce LRR (Fisher 1998; Fisher 2002). Radiotherapy involves radiation treatment using X-rays or other forms of ionising radiation and the dose are measured in Gray (Gy). Radiotherapy is administered in fractions to achieve maximum cancer control while attempting to reduce local complications. Up until April 2020, the standard practice in the UK for post-mastectomy chest wall radiotherapy was 40 Gy in 15 fractions over a period of three weeks based on the evidence from the UK START A & B trials (START TRIAL A; START TRIAL B). Amongst women with node-positive or high-risk node-negative breast cancer, the addition of regional nodal radiotherapy is dependent on risk stratification based on the characteristics of their cancer. The role of regional nodal irradiation has been evaluated in two large randomised controlled trials (RCTs) and both failed to identify any overall survival benefit but did show a significant reduction in breast cancer recurrence (Poortmans 2015; Whelan 2015). In contrast, a Danish population-based cohort study showed an overall survival benefit of 4% for those women who received radiotherapy to lymph nodes near their breast bone (internal mammary) (Thorsen 2016). However, due to the lack of conclusive evidence of overall survival benefits in RCTs (Hennequin 2013; Poortmans 2015), regional nodal irradiation is recommended only in people with a high index of suspicion of nodal involvement or confirmed significant axillary nodal metastatic cancer (NICE 2018).

How the intervention might work

Radiotherapy has been shown to reduce the 10-year risk of LRR by two-thirds in women affected with breast cancer (EBCTCG 1995). However, the improvement in LRR has not been shown to translate into a consistent survival advantage. The EBCTCG overview showed that for every 1.5 LRR prevented in the first 10 years after radiotherapy, one breast cancer-specific death could be prevented in 20 years (EBCTCG 2014). The absolute benefit in survival advantage might be much higher if we consider the advances in radiotherapy techniques over the last 20 years (EBCTCG 1995; Truong 2005). These include methods used to protect the heart, lungs and major blood vessels inside the chest wall from radiotherapy-induced morbidity and mortality in women with breast cancer. The findings of the EBCTCG overview (EBCTCG 2000), and long-term outcomes of some seminal RCTs (Ragaz 2005; Overgaard 2007), were considered by the St Gallen Consensus Guidelines (2009) which recommended post-mastectomy radiotherapy for women affected with breast cancer who had a 20% or greater 10-year risk of LRR (Goldhirsch 2009).

Why it is important to do this review

Post-mastectomy radiotherapy (PMRT) is currently recommended for women with breast cancer who have four or more lymph nodes involved with metastatic cancer. There is still no international consensus on whether to offer PMRT in women with breast cancer and one to three axillary lymph nodes affected with cancer (low volume axillary metastatic disease). The National Comprehensive Cancer Network (NCCN) guideline recommends giving strong consideration to providing PMRT to women with one to three metastatic axillary lymph nodes (Salerno 2017). However, there is currently no risk stratification model based on demographic or cancer characteristics to enable clinicians to make these difficult choices and decisions. Age, location of the tumour in the inner aspect of the breast, nodal ratio (i.e. the number of lymph nodes with cancer versus the total number of lymph nodes removed during axillary surgery), lymphovascular invasion (cancer invading the small blood vessels and lymphatics in the breast tissue) and oestrogen receptor (ER) negativity (i.e. an absence of female hormone molecule binding sites on the surface of cancer cells) tumour size, and positive resection margins(Truong 2005; Garg 2007), are some of the variables that have been shown to be predictors of LRR in PMRT-women with low volume axillary nodal disease. Predictive tools such as the Cambridge PMRT index have been developed to try and select patients who benefit from radiotherapy in this setting (Mukesh 2014). The predictive role of age was considered by both the NCCN and the European Society of Breast Cancer Specialists and they recommend PMRT in young women affected with breast cancer and metastasis in one to three axillary lymph nodes (Cardoso 2012; Recht 2016; Salerno 2017). Similarly, the St Gallen breast cancer meeting in 2019 recommended PMRT in triple-negative breast cancer (i.e. where there is a lack of expression of oestrogen, progesterone and human epidermal growth factor receptor-2 protein molecule binding sites on the surface of cancer cells) with one to three positive axillary lymph nodes (Burstein 2019).

The SUPREMO trial is the only ongoing RCT that might shed light on the role of modern adjuvant systemic treatment (anti-hormonal tablets or chemotherapy) in PMRT for women diagnosed with breast cancer and found to have metastasis in one to three lymph nodes. Since the result of this trial is not expected to be published before 2024, this review will try to bridge the gap in the literature by evaluating the long-term outcomes of published RCTs to address the uncertainty surrounding the use of PMRT in women with breast cancer who have a low volume of axillary lymph node disease.

Objectives

To assess the effects of post-mastectomy radiotherapy (PMRT) in women diagnosed with early breast cancer and found to have one to three positive axillary lymph nodes.

Methods

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) evaluating post-mastectomy radiotherapy (PMRT) in women diagnosed with early breast cancer and low-volume axillary metastatic disease - defined as the involvement of cancer cells in one to three axillary lymph nodes after sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND).

Types of participants

We included women diagnosed with early breast cancer and found to have one to three positive axillary lymph nodes. This included women who have a macroscopic (≧ 2 mm in size) deposit of cancer in the axillary lymph nodes (macrometastases). We contacted the corresponding authors to obtain data on macrometastasis if data were missing, or described only as part of a subgroup analysis within the published manuscripts.

We included women diagnosed with breast cancer treated with mastectomy and SLNB without any further axillary surgery as well as those undergoing ALND with or without initial SLNB. We included women undergoing either simple or modified radical mastectomy, while excluded those undergoing radical mastectomy. To improve the generalisability of the results, we included women of all ages and ethnicities, who have been diagnosed with breast cancer, with any tumour size(s) and histological types.

Types of interventions

We included only studies in which radiotherapy was given using X-rays (photon radiation) and electrons. The total radiation dose administered for treatment should be consistent with the current recommendations, i.e. 40 Gy to 50 Gy in 15 to 25/28 fractions over three to five weeks. We included studies in which post-mastectomy radiotherapy was given to the ipsilateral chest wall, axilla, supraclavicular fossa, and internal mammary nodes. We excluded studies in which women diagnosed with breast cancer received only intra-operative radiation, brachytherapy or radiotherapy given using gamma rays.

We included studies where adjuvant treatments (endocrine, chemotherapy and/or biological agents) were given to both the intervention and comparison groups. While we included women who were given chemotherapy after mastectomy (adjuvant chemotherapy), we excluded studies that used neoadjuvant chemotherapy (NACT), where chemotherapy was given before surgery. NACT was usually offered to women diagnosed with large breast cancers and/or those with multiple positive axillary lymph nodes. It was given with the intention of reducing the size of cancer to facilitate breast-conserving surgery and aid in the decision-making of post-surgical adjuvant treatment. In most cases, progression of the disease or poor response to NACT was the commonest reason for offering mastectomy before or after completion of NACT. Finally, the pre-NACT cancer characteristics mainly guide the decision to give adjuvant radiotherapy to these women with breast cancer. All these factors detract from the main focus of this review, hence we have excluded studies where NACT was administered.

We have compared PMRT in women with early breast cancer with the low-volume axillary disease to those who did not receive any radiotherapy.

Types of outcome measures

Primary outcomes

- Local and regional recurrence (LRR). LRR was defined as the duration in years between the treatment of breast cancer and recurrence of breast cancer in the ipsilateral chest wall, axilla, supraclavicular fossa, infraclavicular fossa or internal mammary nodes. We considered LRR as the first event after treatment of breast cancer, i.e. prior to the development of any systemic recurrence (i.e. recurrence of

breast cancer anywhere else in the body other than those sites involved by LRR). In this review, when it was not possible to extract results for the time to LRR, we attempted to extract the percentage of patients who have had a LRR at 5, 10 and 15 years.

Secondary outcomes

- Overall survival (OS): defined as the duration between the diagnosis of breast cancer or the date of surgery to the date of death from any cause.
- Disease-free survival (DFS): defined as the duration between the diagnosis of breast cancer or time of surgery to the date of loco-regional or systemic recurrence or death, whichever occurs first.
- Time to progression (TTP): defined as the duration between the diagnosis of breast cancer or time of surgery to the date of loco-regional or systemic recurrence, whichever occurs first.
- Adverse events, including short- and long-term events. Short-term adverse events will include erythema, hyperpigmentation, and breast oedema. Long-term adverse events will include lymphoedema, cardiac toxicity, pulmonary toxicity, bone necrosis, and the development of secondary radiation-induced cancers.
- Quality of life (QOL): measured using any validated tool(s).

Search methods for identification of studies

Electronic searches

We searched the following databases and registries on the 24 September 2021:

- The Cochrane Breast Cancer Group's (CBCG's) Specialised Register. Details of the search strategies used by the Group for the identification of studies, and the procedure used to code references, are outlined in the Group's module (https://breastcancer.cochrane.org/specialised-register). Trials with the keywords "breast cancer", “mastectomy”, “radiotherapy”, “radiation therapy”, “post-operative radiotherapy” and “post-mastectomy radiotherapy” were extracted and considered for inclusion in the review.
- CENTRAL (The Cochrane Library, 24 September 2021). See Appendix 1.
- MEDLINE (via OvidSP) from inception to 24 September 2021. See Appendix 2.
- EMBASE (via OvidSP) from inception to 24 September 2021. See Appendix 3.
- The WHO International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/Default.aspx) for all prospectively registered and ongoing trials. See Appendix 4.
- Clinicaltrials.gov (http://clinicaltrials.gov/). See Appendix 5.

Searching other resources

Bibliographic searching

We reviewed the reference lists of the included trials or reviews identified through the search.

Data collection and analysis

Selection of studies

Two authors (RV and MC) reviewed the studies identified from the search strategy independently. Each author applied the selection criteria to identify relevant studies for inclusion. If there was disagreement, a consensus was reached through deliberation with the help of a third reviewer (SSR). We used the PRISMA flow diagram to describe the

selection process and recorded all excluded studies in the characteristics of the excluded studies table. We did not apply any restrictions regarding the language or publication date of the studies.

Data extraction and management

Two review authors (RV and MC) extracted the data and any disagreements were resolved through discussion with JB and SSR. We collected available data on demographics (age), tumour characteristics (tumour size, grade and receptor status), adjuvant treatments, and outcome measures. We performed pooled statistical analysis on outcome measures when there was sufficient data available from the included studies.

We entered data into RevMan Web for analysis. We requested further information from the corresponding authors of the studies as required about the statistical methods, analysis, and results. In circumstances where corresponding authors did not provide the data that we requested, we have attempted to extract the necessary information from the published results using well-established statistical methods (Tierney 2007).

Assessment of risk of bias in included studies

Two review authors (RV and MC) assessed the risk of bias independently for each of the included studies and any disagreement was resolved by discussion with the corresponding author (SSR). We used the risk of bias assessment tool recommended by Cochrane (Higgins 2011). This tool involves seven domains to address the quality of randomisation and the degree of bias arising in a RCT. Each domain was divided into three categories - 'low', 'unclear' or 'high' risk - on the basis of specific criteria described in the tool. These judgements enabled us to categorise studies on the basis of their risk of bias and to perform sensitivity analysis when required to assess the effect of the quality of the included studies on the results.

Measures of treatment effect

We reported on time-to-event outcome measures (i.e. LRR, OS and DFS) as hazard ratios (HR) with 95% confidence intervals (CIs). We extracted the data indirectly from reported results (e.g. log-rank P-values) or Kaplan-Meier survival curves (Parmar 1998; Tierney 2007) when the HR and associated variance were not reported in the published literature.

We reported dichotomous outcomes as risk ratios (RR) with 95% CIs. RR values less than one will indicate that post-mastectomy radiotherapy is the better treatment option, while RR values greater than one will indicate that no radiotherapy after mastectomy is better for women with breast cancer and low-volume axillary disease.

For future review versions, if continuous outcome measures (i.e. QoL) are reported, we will use the standardised mean difference and 95 % CI where different scales are used to measure QoL across studies. If similar scales are used to measure QoL, we will report the mean difference.

Unit of analysis issues

The unit of analysis was each individual woman diagnosed with breast cancer. Since we were comparing the effect of PMRT against no radiotherapy in low-volume axillary disease, we did not consider cross-over trials and multiple intervention groups. Multiple events per participant were considered only when the second event was a different outcome measure, i.e. if a person develops LRR as the first event and then dies due to breast cancer or any other cause (DFS or OS).

Dealing with missing data

There was minimal attrition bias among the included studies in this review. All the studies identified as being eligible for inclusion were sub-group analyses of original RCT performed to address the effectiveness of PMRT in women diagnosed with breast cancer.

Assessment of heterogeneity

We used Cochran's Q test and the I^2 statistic for assessing statistical heterogeneity (Cochran 1954; Higgins 2003). For the I^2 statistic, a value of 25% to 50% may represent mild statistical heterogeneity, 50% to 75% moderate statistical heterogeneity, and > 75% considerable statistical heterogeneity (Higgins 2011). We used a random-effects model for analysis when there was clinical heterogeneity (i.e. variation in participants, interventions or outcomes) or methodological heterogeneity (i.e. variation in study design, outcome measurement or risk of bias) in the included studies.

Assessment of reporting biases

We could not assess for publication bias using a funnel plot due to less than 10 eligible studies included in the review as recommended by the Cochrane Handbook of Systematic Reviews (Higgins 2011).

Data synthesis

We performed data synthesis and statistical analysis in RevMan Web software. We used random-effects models that employ the DerSimonian and Laird method (DerSimonian 1986) as the I^2 statistic showed moderate to substantial statistical heterogeneity. Some of the outcome measures were represented narratively due to the lack of sufficient studies to pool the results or when it was not reported in any of the included studies.

Subgroup analysis and investigation of heterogeneity

We failed to identify any studies investigating the role of age, type of axillary surgery (SLNB alone versus ALND), oestrogen receptor (ER) and human epidermal growth factor-2 receptor (Her2) status on LRR in women with early breast cancer and low volume axillary nodal disease treated with or without PMRT. Hence, we did not perform any subgroup analysis within an individual study or across included studies.

Sensitivity analysis

A sensitivity analysis was not performed as only three studies were identified and the outcome from a single study pertaining to modern-day radiotherapy practice is described in this review.

Summary of findings and assessment of the certainty of the evidence

Two authors (RV and MC) assessed the overall certainty of the evidence by using the GRADE approach (Schünemann 2020). This involved assessing the evidence for each outcome measure using five domains. These domains relate to the risk of bias in the included studies, inconsistency, indirectness, imprecision and publication bias. A summary of findings table was created addressing each of these domains for the included studies using GRADEpro GDT software for primary and secondary outcome measures.

All the included studies in this review were sub-group analyses of the original randomised cohort of women diagnosed with breast cancer and treated with PMRT. Hence none of the included studies was statistically powered to determine the desired or reported outcome measures. Moreover, the type and duration of adjuvant systemic treatments used in the studies included in this review were suboptimal compared to the current standard of care.

The authors of the SSBCG trials have acknowledged that a lack of a primary hypothesis with no distinction between primary and secondary outcome measures could have resulted in a sample size calculation which was inadequate (Killander 2009). This was compounded by the fact that they failed to accrue enough participants (150 women in each of the three arms of the trial) as per the proposed sample size calculation (Killander 2009). In both studies, there was a gap of 3 weeks between the first 12 doses of radiotherapy and the last 8 doses. This is not a standard practice in the modern-day administration of radiotherapy following mastectomy.

Results

Description of studies

Results of the search

We retrieved 5328 records from medical databases (CENTRAL, Medline, Embase and Cochrane Breast Cancer Group's Specialised Register) and 354 records from clinical trial registries (ClinicalTrials.gov & WHO ICTRP). After the removal of duplicate records, we screened 5461 records. Since the review was specifically looking at RCTs, we used the RCT classifier to help distinguish between RCTs (3400 records; high probability group) and non-RCTs (1928 records; low probability group). Two authors (RV and MC) screened the high-probability group for eligible studies and achieved consensus through discussion with the third reviewer (SSR). One author (SSR) screened the low probability group and discussed any uncertainties with a second reviewer (RV). We identified 25 records for full-text or further review from the high-probability group and none from the low-probability group. We selected three studies to be included and one ongoing study for the review, and excluded 21 studies with the reasons described in the PRISMA flow chart and Characteristics of excluded studies. See Figure 1.

Included studies

Three studies that fulfilled the eligibility criteria for this review originated from two of the largest randomised trials undertaken in the early 1980s to address the role of PMRT in adjuvant settings (Killander 2007; Killander 2009; Overgaard 2007). Of these three studies, one study used radiotherapy techniques that are directly comparable to modern-day practice (Overgaard 2007).

Overgaard 2007 was a subgroup analysis undertaken from the original Danish Breast Cancer Co-operative Group (DBCG) trials investigating the role of PMRT in addition to adjuvant systemic therapy in pre-menopausal (DBCG 82b; Overgaard 1997) and post-menopausal (DBCG 82c; Overgaard 1999) women diagnosed with breast cancer. The subgroup analysis involved only those randomised women with 8 or more lymph nodes removed during axillary node clearance and then found to have one to three lymph nodes involved with breast cancer (Overgaard 2007). Patients were randomised to PMRT (n = 256) or no PMRT (n = 256) after total mastectomy and removal of level 1 and partly level 2 axillary lymph nodes. The radiotherapy was administered using a linear accelerator with a target volume of 50 Gy in 25 fractions over 35 days or 48 Gy in 22 fractions over 38 days. Systemic adjuvant therapy was offered based on the menopausal status. All the pre-menopausal and menopausal women received 8 to 9 cycles of cyclophosphamide, methotrexate and 5-fluorouracil (CMF regimen) intravenously every 4 weeks for 9 months. Whereas, postmenopausal women received oral tamoxifen 30 mg daily for 48 weeks. The outcome measures reported in this study included both the loco-regional recurrence and overall survival.

The South Sweden Breast Cancer Group randomised trial (SSBCG), published their outcome separately for premenopausal women (Killander 2009) and postmenopausal women (Killander 2007). The data specific to women diagnosed with breast cancer and found to have one to three involved lymph nodes were available in both the above trials published by the SSBCG. In Killander 2009 and Killander 2007, either premenopausal or postmenopausal women diagnosed with breast cancer and treated with modified radical mastectomy and axillary node clearance were randomised. The randomisation was stratified to the department, tumour size and the number of positive axillary lymph nodes. The trial participants were randomised in a 1:1:1 fashion to receive radiotherapy alone, radiotherapy with adjuvant systemic treatment (PMRT group) and only adjuvant systemic treatment (no PMRT group). We did not include the radiotherapy alone group in this review as the group did not receive any adjuvant systemic treatment and hence were not comparable to the other two groups (i.e PMRT and no PMRT). The radiotherapy was administered using an orthovoltage ventral beam or an electron ventral field technique to the chest wall with megavoltage photons to the lymph node regions. There was a 3-week

gap between the first 12 doses of radiotherapy and the last 8 doses. The maximum targeted skin dose of 45 Gy was administered in 20 fractions over a period of 5 weeks. The treatment protocol with a 3-week gap to diminish skin reactions on the chest wall resulted in a large reduction in the total effective treatment dose. Haviland 2016 estimated that in breast cancer 0.6 Gy per day may be lost in the gap when using regimens of 2 Gy per fraction. The 1.9 Gy per fraction used in this protocol is very close to 2 Gy and therefore it is estimated that as much as 12.6 Gy of dose could be lost in a 3-week gap during treatment.

Killander 2007 (postmenopausal group) involved women randomised to receive PMRT (n = 79) and no PMRT (n = 94). Both groups were given tamoxifen (30 mg/day) for one year as adjuvant treatment. They reported on LRR, time to systemic disease (a surrogate marker for disease-free survival) and overall mortality without any distinction between primary and secondary outcome measures.

Killander 2009 (premenopausal group) involved women randomised to receive PMRT (n = 54) or no PMRT (n = 50). Both groups were given 12 cycles of oral cyclophosphamide as adjuvant chemotherapy every 4 weeks. The outcome measures considered were LRR with the occurrence of systemic disease and death being competing events, time to systemic disease (a surrogate marker for DFS) with the occurrence of non-breast cancer death as a competing event and overall mortality. The results were described using cumulative incidence and mortality curves. There was insufficient information provided to extract the hazard ratio for the outcome measures using the methods described by Tierney et al (Tierney 2007) in this study. As per Killander 2007, there was no distinction between primary and secondary outcome measures in this trial.

Ongoing studies

We identified one ongoing study in follow-up phase and the results are expected in early 2024 (SUPREMO Trial - Velikova 2018). The SUPREMO trial is an open-label, parallel-group, RCT which has finished recruiting but is in the active phase of follow-up. Eligible patients were women aged 18 years or older undergoing mastectomy for unilateral intermediate-risk breast cancer. The intermediate-risk was defined as those women with a tumour size less than 5 cm and one to three involved lymph nodes as well as those that are node-negative with tumour size more than 2 cm but does not involve the skin or underlying muscle. There was only a single study that specifically addressed the QoL outcome after PMRT (Velikova 2018).

The SUPREMO QoL substudy was pre-planned and aimed to examine the effect of PMRT on several QoL outcome measures at 1, 2, 5 and 10 years only from women recruited in the United Kingdom. They published their preliminary results of the QoL outcome after 2-years of follow-up (Velikova 2018). However, the published results included all patients randomised including patients with no involved lymph nodes after axillary staging surgery (N0 disease). Since the study is still ongoing, the authors were unable to release the data specific to women with one to three involved lymph nodes (N1 disease).

Excluded studies

We excluded 21 studies after full-text review (Arriagada 1995; Baum 1980; Cahlon 2015; Nielsen 2006; Friedl 1983; Gustavsson 1999; Houghton 1994; Højris 1999; Højris 2000; Killander 2014; Morgan 2002; Osman 2014; Overgaard 2020; Ragaz 2005; Rutqvist 1990; Rutqvist 1992; Rutqvist 2006; Schmoor 2000; Seegenschmiedt 2000; Shi 2011; Smith 2001). The reasons for exclusions are detailed in the Characteristics of excluded studies tables.

Risk of bias in included studies

See Figure 2.

Allocation

Two studies used adequate methods to generate a random sequence and centralised stratified randomisation process (Killander 2007; Killander 2009) and judged as low risk of bias.

One study (Overgaard 2007), which was a subgroup analysis of randomised women with one to three lymph nodes, selected only those women with eight or more lymph nodes removed during the axillary node clearance. This was done to increase the internal and external validity of the subgroup study as the original randomised cohort of the DBCG 82b (Overgaard 1997) and 82c (Overgaard 1999) trials had only a median of seven lymph nodes removed during the axillary nodal clearance. The authors of the study have not clearly stated how many randomised women with one to three lymph nodes were excluded in this sub-group analysis introducing selection bias. Thus the study was assessed as having an inadequate randomisation method and judged as high risk of bias in this domain. The same study did use closed envelope randomisation at each of the recruiting departments (Overgaard 2007) and was assessed as having adequate allocation concealment.

Blinding

Blinding of neither the participants nor those administering the treatment was possible due to the use of radiotherapy as the primary intervention. We were not able to identify any description of blinding being considered or attempted in the published manuscript of the included studies.

A lack of blinding of participants and personnel and when assessing outcomes was not considered to be a serious concern of bias given the objective nature of the outcomes reported. All three studies were deemed at unclear risk of bias for performance and detection bias.

Incomplete outcome data

The studies included in this review reported on a subgroup of women identified to have one to three involved lymph nodes amongst the entire randomised cohort. The use of ongoing follow-up data, revisiting individual hospital records and the national population registry maintained in Denmark and South Sweden ensured near-complete follow-up data of the included women. Hence in this review, none of the included studies reported a dropout rate of more than 10% and thus minimised the attrition bias (Killander 2007; Killander 2009; Overgaard 2007).

Selective reporting

The included studies were all registered with the clinical trial registries and all the relevant outcome measures were reported as described in the trial protocol. Thus all three studies were deemed at low risk of bias for selective reporting of outcomes.

However, it should be emphasised that all the studies were originally recruited to evaluate the role of PMRT in women diagnosed with breast cancer. Hence evaluating the role of PMRT in a subgroup of women with low volume axillary disease was unplanned.

Other potential sources of bias

In a very small proportion of patients (n = 133; 4.3%) in the entire randomised cohort (n = 3078) of the DBCG 82b (Overgaard 1997) and 82c trials (Overgaard 1999), orthovoltage radiotherapy was used instead of using a linear accelerator to deliver electrons/photons. The lowest intended dose was 36 Gy in 20 fractions given over 4 weeks using the McWhirter technique (Overgaard 1999). However, it was not possible to ascertain how many of these women were part of the subgroup analysis of 552 women with one to three positive lymph nodes (Overgaard 2007) relevant to this review. Given the small number of randomised women to whom orthovoltage radiotherapy was given, we did not consider that it would influence influence the outcome measures considered in this review.

In Killander 2007 and Killander 2009, radiotherapy was administered using two different techniques to the chest wall and lymph nodal regions. Moreover, there was a 3-week gap

between the 12th dose and the final 8 doses of radiotherapy. This resulted in a reduction of 12.6 Gy biological equivalent dose (BED) delivered to the chest wall and nodal regions. Hence the outcome from both these trials was not pooled for performing a meta-analysis and has been explained in a descriptive manner.

The adjuvant treatment in all the included studies was sub-optimal compared to current standard practice. In postmenopausal women, tamoxifen was given (30 mg/day) for one year only (Killander 2007; Killander 2009; Overgaard 2007) compared to the current standard practice of a minimum of 5 years of adjuvant endocrine treatment. Moreover, in post-menopausal women, tamoxifen was given as adjuvant systemic treatment irrespective of the oestrogen receptor status (Killander 2007).

The use of adjuvant systemic chemotherapy has evolved and is significantly different from the agents used in the included studies. Killander 2009 used 12 courses of oral cyclophosphamide 130mg/m^2 for 14 days every 4 weeks while Overgaard 2007 used 8 to 9 cycles of CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, and 5-fluorouracil 600 mg/m^2) intravenously every 4 weeks for 9 months. These differences in practice should be considered while interpreting the results of this review.

Effects of interventions

Local and regional recurrence (LRR)

The primary outcome measure was described in one study, which used radiotherapy techniques comparable to modern-day radiotherapy methods (Overgaard 2007). There was a substantial reduction in LRR in the PMRT group (HR 0.20; 95% CI 0.13 to 0.33; 522 participants; low certainty of evidence; Analysis 1.1).

In the remaining two studies (Killander 2007; Killander 2009), there was insufficient information provided to extract HRs for LRR and we were unable to obtain the individual data from the authors. However, cumulative incidence at 20 years, accounting for the competing risks of distant recurrence and death, was reported in both studies. Both studies (Killander 2007; Killander 2009) reported decreased cumulative incidence of LRR at 20 years in the PMRT group compared to the no PMRT group. In post-menopausal women, the cumulative incidence of LRR was 2.6% (95% CI, 0.5 to 8.3, 79 participants) in the PMRT group and 25.9% (95% CI, 17.5 to 35.1; 94 participants) in the no PMRT group (Killander 2007). In pre-menopausal women, the cumulative incidence of LRR was 3.9% (95% CI, 0.7 to 11.9; 54 participants) and 14.8% (95% CI, 6.5 to 26.3; 50 participants) respectively (Killander 2009). Even though we were unable to extract the HR from these two studies, there was concordance in the findings suggesting a reduction in LRR amongst the PMRT group compared to the no PMRT group.

Overall survival (OS)

The OS was reported in two studies at 15 years (Overgaard 2007) and 25 years (Killander 2007) follow-up. The one study that used radiotherapy techniques comparable to modern-day radiotherapy methods reported an improvement in OS amongst the PMRT group compared to the no PMRT group (HR 0.76; 95% CI 0.60 to 0.97; 552 participants; moderate certainty of evidence; Analysis 1.2; Overgaard 2007).

In the other study involving postmenopausal women (Killander 2007), there was little difference in OS amongst the PMRT group compared to the no PMRT group (HR 0.90; 95% CI 0.66 to 1.20; 173 participants).

It was not possible to extract hazard ratios for the study involving premenopausal women (Killander 2009) but overall mortality at 20 years was reported in the PMRT group as 33% (95% CI 25 to 48) compared to the no PMRT group at 50% (95% CI 38 to 64) and did not reach statistical significance (P = 0.086).

Disease-free survival (DFS)

Data for DFS were not reported by the one study using radiotherapy techniques comparable to modern radiotherapy methods (Overgaard 2007).

The remaining studies reported some DFS data. Killander 2007 reported the outcome in a cumulative incidence curve, accounting for the competing risk of non-breast cancer deaths. Applying the methods described by Tierney 2007, a subdistribution HR was extracted comparing the cumulative incidence of DFS in the PMRT group compared to the no PMRT group (Fine 1999). The subdistribution HR should be interpreted in the context of a competing risks analysis, where the impact of factors affecting the competing risk on the cumulative incidence of DFS was taken into account (McCaw 2022). The subdistribution HR extracted from the cumulative incidence curves reported by Killander 2007 showed a statistically significant improvement in DFS amongst the PMRT group (subdistribution HR = 0.63; 95% CI 0.41 to 0.96; 173 participants; Analysis 1.3).

Killander 2009 provided the cumulative incidence of DFS at 20 years in the premenopausal group and reported no difference in the cumulative incidence of systemic disease between the PMRT group (35%; 95% CI 22 to 48) and no PMRT group (38%; 95% CI 24 to 51).

Time to progression (TTP)

The studies did not report this outcome for women diagnosed with breast cancer and one to three positive lymph nodes and randomised to have PMRT.

Short-term adverse events

The studies did not report this outcome for women diagnosed with breast cancer and one to three positive lymph nodes and randomised to have PMRT.

Long-term adverse events

The studies did not report this outcome for women diagnosed with breast cancer and one to three positive lymph nodes and randomised to have PMRT.

Quality of life (QoL)

We identified one ongoing study (SUPREMO) which reported on the 2-year QoL outcome after PMRT (Velikova 2018). However since the study is in the active follow-up stage, the trial authors could not release the data specific to women diagnosed with one to three involved lymph nodes. Hence, we were unable to report on this important outcome measure in the current review.

Discussion

Summary of main results

Three RCTs met the inclusion criteria (Killander 2007; Killander 2009; Overgaard 2007), with only one study using radiotherapy techniques that are comparable to modern-day practice (Overgaard 2007). All studies were all sub-group analyses of original RCTs conducted in the 1980s to assess the effectiveness of PMRT in women diagnosed with breast cancer. Hence the type and duration of adjuvant systemic treatments used in the included studies were suboptimal compared to the current standard of care.

The one study that most reflected current radiotherapy practice (Overgaard 2007) reported local and regional recurrence and overall survival. Low certainty of evidence indicated an improvement in local and regional recurrence. Moderate certainty of evidence showed an improvement in OS amongst the PMRT group compared to the no PMRT group.

One of the other studies that did not use modern-day radiotherapy techniques reported DFS and showed a significantly better 20-year DFS in the PMRT group than the no-PMRT group (Killander 2007.

The lack of published evidence meant that we were not able to report on the TTP, adverse events and QoL secondary outcomes in this review. A recent study has reported on QoL outcomes after PMRT (Velikova 2018) as a sub-study of the ongoing SUPREMO trial. However, the trial investigators were unable to provide QoL data specifically for women diagnosed with one to three positive lymph nodes due to the ongoing nature of the SUPREMO trial.

Overall completeness and applicability of evidence

There is a paucity of data on this topic. The results presented in this review were drawn from 3 RCTs. We were not able to pool the results to perform a meta-analysis as only one study pertained to the modern-day radiotherapy technique. The result for the primary endpoint of LRR was extracted from a single RCT. We were not able to identify any studies to address the secondary outcome measures related to TTP, short and long-term side effects and QoL after PMRT.

The included studies were all subgroup analyses of previously conducted RCTs performed to evaluate the role of PMRT in women diagnosed with breast cancer. Hence, they were not designed specifically to answer the effectiveness of PMRT in women with breast cancer and one to three positive lymph nodes.

There is a lack of evidence within the literature on the effectiveness of the current standard-of-care radiotherapy techniques in women with breast cancer and low-volume axillary disease. The radiotherapy in all included studies was sup-optimal compared to the current standard practice with modern photon radiotherapy. None of the trials reviewed used megavoltage photons as the primary treatment for the chest wall target area. The use of intensity-modulated photon radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) and deep inspiratory breath hold radiotherapy (DIBH) was not standard practice at the time of the included trials in this review. These modern radiotherapy techniques can improve the therapeutic ratio between cancer outcomes and late toxicity. Due to the lack of data on modern radiotherapy techniques in the low-volume axillary disease group, we limited our inclusion of radiotherapy intervention to those techniques considered acceptable to the current ongoing SUPREMO trial so that future comparisons could be made and excluded older interventions such as cobalt-60 radiotherapy.

Further consideration should be given while interpreting the results of this review in light of the type of systemic endocrine and chemotherapy medications used in the included trials. The advancement in modern endocrine, chemotherapy and targeted immunotherapy treatments may mitigate or reduce the magnitude of the improvement in overall survival observed with PMRT in this review.

There was a lack of published and available data to evaluate the role of dose escalation, uses of chest wall bolus and chest wall boost as part of the PMRT technique in this review.

Quality of the evidence

We identified three RCTs that fulfilled the inclusion criteria involving a total of 829 women (PMRT = 409; no PMRT = 420). We were unable to extract data from one of the included studies Killander 2009 to pool the outcome measures and hence described the findings in a descriptive manner (PMRT = 54; no PMRT = 50).

The internal validity of one of the largest studies (Overgaard 2007) was compromised due to the method used for randomisation and allocation concealment. The studies included in this review were all subgroup analyses of original RCTs conducted in the early 1980s to evaluate the role of PMRT in breast cancer. This allowed the included studies to be comparable and hence reduced statistical heterogeneity. However, the type and duration of various systemic adjuvant treatments being offered to the women randomised in these trials were substantially different in efficacy compared to the modern chemo-endocrine treatments. There was a very low attrition bias at the expense of compromised power due to the subgroup analysis performed in the included studies.

The overall confidence in the primary outcome measure (LRR) is low due to the inability to pool the data and the concerns about the quality of the evidence of the only study from which the data were extracted. The estimated effect seen for overall survival was more likely to be closer to the expected true effect.

Potential biases in the review process

Since this was an interventional review, it was essential to include only randomised controlled trials to ensure that both PMRT and no PMRT groups remain comparable. Even though this minimised selection bias, it resulted in the identification of only three RCTs eligible for inclusion in this review. We wanted to ensure that the type of radiotherapy used in the included trials was comparable to what would be acceptable as close to the current standard practice as possible and therefore accepted techniques that would be included in the ongoing SUPREMO trial (Velikova 2018). Hence, amongst three eligible RCTs, only a single trial pertaining to the modern-day radiotherapy technique was represented in the main outcome measures to allow us to combine the data once the results of the SUPREMO trial are published. This also limited the number of trials that could be included in this review compared to some other larger reviews and meta-analyses that have been published (EBCTCG 2014; Li 2013; Whelan 2000). There are very few trials that have reported short-term side effects after PMRT and we were unable to identify any trials reporting long-term side effects. This was potentially due to two factors, lack of side effects reported specifically in the one to three positive lymph node groups and lack of pre-defined follow-up of RCTs to ascertain the long-term side effects.

We identified two additional studies that could have been included in this review. However, the lack of information in the published report and the inability to gather information from the authors meant that it was not possible to ascertain whether these studies were randomised, quasi-randomised or prospective cohort studies (Osman 2014; Shi 2011). We were unable to combine the data for performing a pooled analysis for our primary and secondary outcome measures. This was due to only one out of the three eligible trials using radiotherapy techniques which are comparable to modern-day methods. There were also different statistical methods used for reporting the secondary outcome measures in the eligible trials for inclusion with some studies reporting insufficient information to extract HRs. Finally, we were unable to obtain any data on the side effects and QoL outcomes after PMRT. Both of these outcome measures are important in helping to understand the overall effect of PMRT in women with one to three positive lymph nodes.

Agreements and disagreements with other studies or reviews

There are four published meta-analyses evaluating the role of PMRT in women with one to three positive lymph nodes (Li 2013; EBCTCG 2014; Headon 2016; Whelan 2000).

Whelan 2000 presented one of the earliest meta-analyses evaluating the role of PMRT and included 18 randomised trials between 1967 and 1999, involving 6367 women diagnosed with breast cancer. They included all trials in which PMRT was administered irrespective of the axillary lymph nodal status. In spite of this, they were able to demonstrate an OS benefit for women undergoing PMRT. Li 2013 performed a meta-analysis of non-randomised cohort studies reporting on the role of PMRT in one to three positive nodes. They were able to show that there was a substantial improvement in LRR with PMRT (df = 9; RR = 0.348; 95% CI, 0.254 to 0.477) from the 10 studies eligible for inclusion. However, the pooled analysis from 6 eligible studies showed no improvement in OS amongst women receiving PMRT. However, it should be noted that most of the participants in these studies were treated between 1983 and 2006 resulting in substantial variability in the adjuvant treatments being offered, which would have an effect on the reported outcome measures.

The EBCTCG 2014 published an exhaustive meta-analysis of 22 RCTs from 1964 to 1986 evaluating the role of PMRT in women with one to three lymph node-positive diseases. The meta-analysis included all the studies included in this review. We excluded

the remaining 19 studies due to the use of Cobalt-60 radiotherapy, having a target dose of more than 50Gy and not performing an axillary surgery to adequately stage the breast cancer. We based the permissible radiotherapy techniques in this review on those acceptable to the SUPREMO trial to enable future comparisons to be made. We also excluded dose-escalation e.g. in the form of chest wall boost dose as there is no standard consensus for this approach. The EBCTCG 2014 of 1133 women who received some form of adjuvant systemic treatment (chemotherapy and/or endocrine) demonstrated that PMRT substantially reduces 10-year LRR (4.3% vs 21%; 2p < 0.00001) and improves 20-year breast cancer-specific mortality (41.5% vs 49.4%; RR = 0.78; 95% CI 0.64 to 0.94; 2p = 0.01). Most of the patients had systemic chemotherapy using the CMF regimen, systemic treatments involving ovarian irradiation were administered in two trials and systemic endocrine (tamoxifen) treatment was administered only in three trials. Hence, similar to our results, care should be taken while interpreting the magnitude of these results due to the difference in the effectiveness of the systemic treatment used in the included trials compared to that of the modern chemo-endocrine agents.

Headon 2016 presented a meta-analysis combining retrospective cohort studies and RCTs evaluating the effect of PMRT in women with 1 to 3 positive axillary lymph nodes. The LRR analysis included 11 studies, and only 2 of these were RCTs. The remaining 9 were retrospective studies. The 2 RCTs included in the LRR analysis were Overgaard et al. (Overgaard 2007) and Ragaz et al. (Ragaz 2005) with a total weightage of RCTs in the analysis being 59%. There was a statistically significant lower LRR amongst PMRT women compared to no PMRT (RR = 0.30; 95% CI 0.23 to 0.38). We excluded Ragaz et al. (Ragaz 2005) from our review as they have used Cobalt-60 radiotherapy, which is not considered an international standard of care moving forward. The OS analysis involved only a single RCT (Ragaz 2005) with a weightage of 3.5% and showed a 3% improvement in overall survival amongst the PMRT group but did not reach statistical significance.

Authors' conclusions

Implications for practice

Based on one study, this review showed a reduction in locoregional recurrence and improvement in overall survival with the use of post-mastectomy radiotherapy amongst women diagnosed with breast cancer and found to have one to three positive axillary lymph nodes. There is a lack of published evidence to draw conclusions on the side effects and QoL outcome measures after post-mastectomy radiotherapy.

Implications for research

There is currently a paucity of evidence within the literature to evaluate the effectiveness of post-mastectomy radiotherapy in women diagnosed with breast cancer and low-volume axillary disease. Currently, there is a single ongoing multi-centre international randomised trial trying to address this question and could add further insight into the role of PMRT in women with low volume axillary disease. Despite this, it is likely that further trials in the future will still be needed to address the same question with updated current radiotherapy techniques to truly evaluate the benefit of treatment in view of the reduction in late adverse effects these newer techniques have to offer.

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Data and analyses

Comparison 1

PMRT versus no PMRT in women with one to three positive lymph nodes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size	
1.1 Locoregional recurrence (LRR)	1	552	Hazard Ratio (IV, Random, 95% CI)	0.20 [0.13, 0.33]	
1.2 Overall survival (OS)	1	552	Hazard Ratio (IV, Random, 95% CI)	0.76 [0.60, 0.97]	
1.3 Disease-free survival (DFS)	1	173	Sub-distribution Hazard Ratio (IV, Random, 95% CI)	0.63 [0.41, 0.96]	

What's new

Date	Event	Description
2 October 2021	Amended	Updated work affiliation.

History

Protocol first published: Issue 9, 2021

Contributions of authors

1. Drafted the protocol: SSR, CA and JB.
2. Proofread the protocol: SSR, RV and MC.

Declarations of interest

RV: none known. currently working as an Oncoplastic Breast Surgeon in the UK National Health Service.
MC: none known; currently working as a speciality registrar in Breast Surgery in the UK National Health Service.
JB: none related to this topic. Received grant and salary support from the Medical Research Council UK and honorarium from the Royal Statistical Society of Belgium.
CA: none known; currently working as a Clinical Oncologist in the UK National Health Service. CA is involved as a Principal Investigator in the SUPREMO trial, a relevant study on this topic, however, does not receive any direct payments for this work.
SSR: none known; currently working as an Oncoplastic Breast Surgeon in the UK National Health Service.

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Internal sources

- Not applicable , Other
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Differences between protocol and review

Not applicable.

Characteristics of studies

Characteristics of included studies [ordered by study ID]

Killander 2007

Study characteristics	
Methods	The South Sweden Breast Cancer Group (SSBCG II:1) randomly assigned postmenopausal women to radiotherapy (PMRT) or no radiotherapy (no PMRT) after surgery. The randomisation was stratified on department, tumour size and the number of positive axillary nodes (N0, N1-3 and N≥4).
Participants	Postmenopausal women (defined as at least 5 years of amenorrhoea), aged 71 years or below with stage 2 invasive breast cancer were recruited from all the 15 surgical departments in South Sweden. They underwent modified radical mastectomy with en-bloc dissection of level 1 and 2 lymph nodes in the axilla prior to randomisation. Exclusion criteria a) Non-radical surgery b) Other malignant diseases except for squamous cell cancer of the skin or cervical cancer in situ c) Bilateral breast cancer.
Interventions	Women were randomised into, a) Post-operative radiotherapy only (n=239), b) Radiotherapy with tamoxifen (**PMRT**) (n=234) c) Tamoxifen-only arms (**no PMRT)** (n=251) The radiotherapy was administered using a ventral photon beam with the maximum targeted skin dose of 45 Gy administered in 20 fractions over a period of 5 weeks. The target volume consists of four sub-volumes, i.e., the lymph nodes in the supra and infraclavicular fossae, axilla, chest wall and the ipsilateral parasternal mammary lymph nodes. PMRT and no PMRT groups were offered Tamoxifen as adjuvant treatment (30mg/day for one year). The number of women with 1 to 3 positive lymph nodes that were randomised and included in this analysis, a) Radiotherapy with tamoxifen (**PMRT**) = 79 b) Tamoxifen only (**no PMRT**) = 94
Outcomes	1) Loco-regional recurrence (The occurrence of systemic disease and death were competing events)

	2) Time to systemic disease (the equivalent of Disease-Free Survival - DFS) -Time to the first event of the distant disease or death from breast cancer (The occurrence of non-breast cancer death was a competing event) 3) Overall mortality was reported (Instead of overall survival). No distinction was made between primary and secondary endpoints.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomization was stratified on department, tumour size and number of positive axillary lymph nodes with block size of six within strata.
Allocation concealment (selection bias)	Low risk	It was performed by calling the South Sweden Breast Cancer group's central secretariat at which a closed envelope with a prerandomized allocation was selected. The identity of the patient, date, department and allocated treat- ment was documented by the secretariat.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	A lack of blinding of participants and personnel was not considered to be a serious concern given given the objective nature of the outcomes reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	A lack of blinding of for outcome assessment was not considered to be a serious concern of bias given the objective nature of the outcomes reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	56 out of 724 patients randomized (7.7%) were lost to follow-up. A clear definition of missing data and loss of follow-up was depicted in the CONSORT diagram (Figure.1).
Selective reporting (reporting bias)	Low risk	All relevant primary outcome measures (LRR, DFS and OS) were considered and adequately defined. The long-term outcome measures including side effects described in the paper have been collected retrospectively and was not been powered. Also, there is no representation of data specific to the N1-N3 category of patients for the long-term outcome measures or side effects.
Other bias	Low risk	By mistake the secretariat did not record the allocated treatment for the first 47 patients, but only date, their identity and institution. The adjuvant treatment with Tamoixfen was given irrespective of the Oestrogen receptor status.

Killander 2009

Study characteristics	
Methods	The South Sweden Breast Cancer Group (SSBCG) randomly assigned pre-menopausal women to radiotherapy (PMRT) or no radiotherapy (no PMRT) after surgery. The randomisation was stratified on department, tumour size and the number of positive axillary nodes (N0, N1-3 and N≥4).
Participants	Premenopausal women with stage 2 invasive breast cancer were recruited from all the 15 surgical departments in South Sweden. They underwent modified radical mastectomy with en-bloc dissection of level 1 and 2 lymph nodes in the axilla prior to randomisation. Exclusion criteria a) Non-radical surgery b) Other malignant diseases except for squamous cell cancer of the skin or cervical cancer in situ c) Bilateral breast cancer.
Interventions	Women were randomised into, a) Post-operative radiotherapy only (n=134), b) Radiotherapy and Cyclophosphamide (**PMRT**) (n=125) c) Cyclophosphamide-only arms (**no PMRT)** (n=136)

	The radiotherapy was administered using a ventral photon beam with the maximum targeted skin dose of 45 Gy administered in 20 fractions over a period of 5 weeks. The target volume consists of four sub-volumes, i.e. the lymph nodes in the supra and infraclavicular fossae, axilla, chest wall and the ipsilateral parasternal mammary lymph nodes. PMRT and no PMRT groups were offered 12 cycles of 130mg/m^2 oral cyclophosphamide (chemotherapy) 1 to 14 days in 28 days cycles. The number of women with 1 to 3 positive lymph nodes that were randomised, a) Radiotherapy with tamoxifen (**PMRT**) = 54 b) Tamoxifen only (**no PMRT**) = 50
Outcomes	1) Loco-regional recurrence (The occurrence of systemic disease and death were competing events) illustrated using a cumulative incidence curve 2) Time to systemic disease (the equivalent of Disease-Free Survival - DFS) -Time to the first event of the distant disease or death from breast cancer (The occurrence of non-breast cancer death was a competing event) illustrated using a cumulative incidence curve 3) Overall mortality was reported (Instead of overall survival) using cumulative mortality curves. No distinction was made between primary and secondary endpoints.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified randomisation based on department, tumour size and number of lymph nodes with block size of 6 with the strata
Allocation concealment (selection bias)	Low risk	was performed by calling the South Sweden Breast Cancer group's central secretariat at which a closed envelope with a pre-randomized allocation was selected. The identity of the patient, date, department and allocated treatment was documented by the secretariat.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	A lack of blinding of participants and personnel was not considered to be a serious concern given given the objective nature of the outcomes reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	A lack of blinding of for outcome assessment was not considered to be a serious concern of bias given the objective nature of the outcomes reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was low (<5%) in the randomised patients. In one institution more than 80% of the randomized patients' records were destroyed. Since the missing records very well might differ systematically from those retained, all patients from this institution were excluded (5% of all randomised patients), except in analyses of overall survival. Follow-up of all the selected group of patients from the initial randomised group was complete (N1-N3)
Selective reporting (reporting bias)	Low risk	All endpoints were analyzed according to the intention to treat prin-ciple. Survival and other time to event endpoints were determined from date of randomization and analyzed by survival analysis techniques. Times to loco-regional recurrence and systemic disease are illustrated by means of cumulative incidence curves, considering the competing risks of other events.
Other bias	Low risk	One arm of the 1:1:1 randomisation involved giving oral cyclophospamide alone as adjuvant treatment. During interim review due to the high incidence of event, this arm of the study was terminated in June 1983.

Overgaard 2007

Study characteristics	
Methods	The Danish Breast Cancer Cooperative Group (DBCG) enrolled a total number of 3083 women into their 82b (Pre-menopausal and menopausal, n=1708) and 82c (postmenopausal and below 70 years, n=1375) randomised controlled trials. All

	patients underwent a total mastectomy, and removal of level 1 and partly level 2 axillary lymph nodes. Patients were then randomised to postoperative radiotherapy (PMRT) or no radiotherapy (no PMRT).
Participants	A subgroup of 552 women who were randomised and met the criteria of 8 or more axillary lymph nodes removed at the time of surgery and found to have 1 to 3 positive nodes was selected for this study. Inclusion criteria: a) High-risk breast cancer is defined as women with breast cancer who were node-positive and/or T3 or T4 tumour and/or skin or deep fascia invasion. b) No evidence of metastatic distant disease from physical examination, biochemical tests, chest radiography and bone scintigraphy, or bone radiography c) No previous or concomitant other malignant diseases Exclusion criteria: a) Patients with macroscopic residual tumour
Interventions	After surgery randomised to, a) Post mastectomy radiotherapy (**PMRT**) = 276 b) No post-mastectomy radiotherapy (**no PMRT**) = 276 Radiotherapy was administered to most women using a linear accelerator with a target volume of 50Gy in 25 fractions over 35 days or 48Gy in 22 fractions over 38 days. The radiotherapy was administered to the chest wall and regional nodes (axilla, internal mammary, supra and infra-clavicular nodes). The systemic adjuvant therapy was offered based on the menopausal status. All the pre-menopausal and menopausal women received 8–9 cycles of CMF (600, 40, and 600 mg/m2 respectively) intravenously every 4 weeks for 9 months. Whereas oral Tamoxifen 30 mg daily for 48 weeks was given for the postmenopausal women.
Outcomes	a) Overall survival b) Loco-regional recurrence (without simultaneous distant recurrence)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Described in the Overgaard et al 1997 paper. Only a closed envelope in the recruiting department was used for randomisation and no stratification was performed for randomisation.
Allocation concealment (selection bias)	Low risk	Described in the Overgaard et al 1997 paper. A closed envelope in the recruiting department was used for randomisation and no stratification was performed for randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	A lack of blinding of participants and personnel was not considered to be a serious concern given given the objective nature of the outcomes reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	A lack of blinding of for outcome assessment was not considered to be a serious concern of bias given the objective nature of the outcomes reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis was performed. A clear definition of the excluded patients was described. There was no issue with attrition as this was a highly selected group with more than 8 lymph nodes removed from the initial randomised cohort.
Selective reporting (reporting bias)	Low risk	A subgroup of 1152 patients who met the criteria of having 8 or more nodes removed (above the median value) and who were node positive.
Other bias	High risk	A potential source of selction bias due to the inclusion of patients considered to be advanced disease rather than early breast cancer. Only a small number of patients were T3 disease and no one was T4. 4% and 5% in the RT and no RT group.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Arriagada 1995	Wrong radiotherapy intervention - Gamma rays were used for administering radiotherapy to the axilla and SCF. X-ray (electrons) was used only in the chest wall and internal mammary nodes.
Baum 1980	Wrong surgical intervention - No axillary surgery was performed
Cahlon 2015	Wrong study population - There was no data specific to randomised women with 1 to 3 involved nodes. The authors were unable to provide the individual data for the randomised participants with 1 to 3 involved lymph nodes.
Friedl 1983	Wrong radiotherapy intervention - Doesn't comply with the radiotherapy inclusion criteria. Randomised women were given a total dose of 60Gy or 6000 rad.
Gustavsson 1999	Wrong study design - A highly selected sample from the randomised cohort was selected for performing this analysis.
Houghton 1994	Wrong surgical intervention - No axillary surgery was performed as part of the breast cancer treatment and hence doesn't meet the inclusion criteria.
Højris 1999	Wrong study population - The entire radiotherapy vs no radiotherapy cohort has been analysed without data specific to women with 1 to 3 involved nodes.
Højris 2000	Wrong study design - The study include only a selective group of patients who were initially randomised from a single centre.
Killander 2014	Wrong study population - The study reported on the cardiac and cerebrovascular adverse events for the entire cohort of patients (i.e. N0, N1 and N2). There is no data on randomised participants with 1 to 3 involved lymph nodes for any of the outcomes (overall mortality, breast cancer-specific mortality and morbidity, mortality and morbidity from heart disease & cerebrovascular disease).
Morgan 2002	Wrong surgical intervention - Patients included in this study didn't undergo adequate axillary staging procedure. One node from the lower axilla, one node from the apex and one node from the 2nd intercostal space as IM node were removed at the time of mastectomy. If no nodes were positive they were classified as Stage A, low axillary node positive as Stage B and if either apical or IM node-positive as Stage C.
Nielsen 2006	Wrong study population - There is no data available on women with 1 to 3 involved lymph nodes.
Osman 2014	Wrong study design - Detailed methodology of randomisation process not available. Not certain whether the study was randomised or just a controlled study with the comparison group. Multiple attempts were made to contact the authors without any success.
Overgaard 2020	Wrong study population - No separate data on N1 disease was published. The data for the entire randomised cohort was published. An attempt was made to contact the authors to request data for patients with N1 disease without any success.
Ragaz 2005	Wrong radiotherapy intervention - Radiotherapy was given using gamma rays
Rutqvist 1990	Duplicate publication - earlier results before the full follow-up was completed. Wrong intervention - Gamma rays were used for administering radiotherapy to the axilla and SCF. X-ray (electrons) was used only in the chest wall and internal mammary nodes.
Rutqvist 1992	Wrong radiotherapy intervention - Gamma rays were used for administering radiotherapy to the axilla and SCF. X-ray (electrons) was used only in the chest wall and internal mammary nodes.
Rutqvist 2006	Wrong radiotherapy intervention - Gamma rays were used for administering radiotherapy to the axilla and SCF. X-ray (electrons) was used only in the chest wall and internal mammary nodes.
Schmoor 2000	Wrong radiotherapy intervention - Most of the patients received PMRT using gamma rays with telecobalt. The corresponding author was contacted to confirm the type of radiotherapy being used in the study population.
Seegenschmiedt 2000	Duplicate publication - There was no separate outcome data for randomised women with N1-3 disease. Duplicate publication in German.
Shi 2011	Wrong study design - Unable to verify randomisation and study methodology Multiple attempts were made to contact the authors without any success.
Smith 2001	Trial terminated due to failure to accure

Characteristics of ongoing studies [ordered by study ID]

Velikova 2018

Study name	SUPREMO Trial
Methods	Open-label, parallel-group, randomised, controlled trial.
Participants	Patients aged 18 years or older who had undergone mastectomy for unilateral breast cancer. Patients were eligible if they had intermediate-risk breast cancer (defined as pT1–2N1; pT3N0; or pT2N0 if also grade III or with lymphovascular invasion on histology). Patients needed to be fit for surgery, radiotherapy, or adjuvant systemic therapy. Exclusion criteria included previous or concurrent malignancy (apart from non-melanomatous skin cancer and carcinoma in situ of the cervix), ductal carcinoma in situ, bilateral breast cancer, pregnancy at the time of radiotherapy treatment, and male sex
Interventions	Chest wall radiotherapy or no chest wall radiotherapy
Outcomes	In this publication, only the QOL secondary outcome measures were considered for the entire cohort of randomised patients. The primary outcome measure was 10-year overall survival. QOL is a secondary endpoint alongside chest wall recurrence, regional recurrence, disease-free survival, acute and late morbidity, cost-effectiveness, metastasis-free survival, and cause of death.
Starting date	04/08/2006 to 29/04/2013 - Currently undergoing data collection and follow-up
Contact information	Prof Galina Velikova, Leeds Institute of Cancer andPathology, University of Leeds, Leeds Cancer Centre, St James's University Hospital, Leeds LS9 7TF, UK g.velikova@leeds.ac.uk Author was contacted to gather data specific to N1-3 disease patients as the data published in this paper included both N1 and N0 patients.
Notes	In 2011, the eligibility criteria for the SUPREMO Trial was widened, following a protocol amendment (version 29; Aug 30, 2010) approved by the ethics committee, to include the use of neoadjuvant chemotherapy, according to contemporary guidelines. As per meta-analysis exclusion criteria, patients having NACT should have to be excluded from the analysis

Appendices

Appendix 1. CENTRAL

#1 MeSH descriptor: [Breast Neoplasms] explode all trees
#2 breast near neoplasm*
#3 breast near carcinoma*
#4 breast near cancer*
#5 breast near tumour*
#6 breast near tumor*
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 MeSH descriptor: [Mastectomy] explode all trees
#9 mastectom*
#10 #8 or #9
#11 MeSH descriptor: [Radiotherapy] explode all trees
#12 MeSH descriptor: [Radiotherapy, Adjuvant] explode all trees
#13 radiotherap*
#14 irradiat*
#15 post-mastectomy NEAR radiotherap*
#16 postmastectomy NEAR radiotherap*
#17 PMRT
#18 post-mastectomy NEAR radiat*
#19 postmastectomy NEAR radiat*
#20 radiation NEAR therap*
#21 post-operative NEAR radiotherap*
#22 postoperative NEAR radiotherap*
#23 post-operative NEAR radiat*
#24 postoperative NEAR radiat*
#25 {OR #11-#24}
#26 #7 AND #10 AND #25 in Trials

Appendix 2. Medline (via OvidSP)

#	Searches
1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomized.ab.
4	placebo.ab.
5	Clinical Trials as Topic/
6	randomly.ab.
7	trial.ti.
8	(crossover or cross-over).tw.
9	Pragmatic Clinical Trials as Topic/
10	pragmatic clinical trial.pt.
11	or/1-10
12	exp Breast Neoplasms/
13	(breast adj6 cancer$).tw.
14	(breast adj6 neoplasm$).tw.
15	(breast adj6 carcinoma$).tw.
16	(breast adj6 tumo?r$).tw.
17	or/12-16
18	exp Mastectomy/
19	mastectom*.tw.
20	or/18-19
21	exp Radiotherapy/
22	exp Radiotherapy, Adjuvant/
23	radiotherap*.tw.
24	post-mastectomy radiotherap*.tw.
25	post mastectomy radiotherap*.tw.
26	postmastectomy radiotherap*.tw.
27	PMRT.tw.
28	post-mastectomy radiat*.tw.
29	post mastectomy radiat*.tw.
30	postmastectomy radiat*.tw.
31	radiation therap*.tw.
32	post-operative radiotherap*.tw.
33	post operative radiotherap*.tw.
34	postoperative radiotherap*.tw.
35	post-operative radiat*.tw.
36	post operative radiat*.tw.
37	postoperative radiat*.tw.
38	irradiat*.tw.
39	or/21-38
40	11 and 17 and 20 and 39
41	animals/ not humans/
42	40 not 41
43	remove duplicates from 42

Appendix 3. EMBASE (via OvidSP)

#	Searches
1	Randomized controlled trial/
2	Controlled clinical study/
3	Random$.ti,ab.
4	randomization/
5	intermethod comparison/
6	placebo.ti,ab.
7	(compare or compared or comparison).ti.
8	(open adj label).ti,ab.

9	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
10	double blind procedure/
11	parallel group$1.ti,ab.
12	(crossover or cross over).ti,ab.
13	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.
14	(assigned or allocated).ti,ab.
15	(controlled adj7 (study or design or trial)).ti,ab.
16	(volunteer or volunteers).ti,ab.
17	trial.ti.
18	or/1-17
19	exp breast/
20	exp breast disease/
21	(19 or 20) and exp neoplasm/
22	exp breast tumor/
23	exp breast cancer/
24	exp breast carcinoma/
25	(breast$ adj5 (neoplas$ or cancer$ or carcin$ or tumo$ or metasta$ or malig$)).ti,ab.
26	or/21-25
27	exp mastectomy/
28	mastectom*.tw.
29	or/27-28
30	exp radiotherapy/
31	exp adjuvant radiotherapy/
32	radiotherap*.tw.
33	post-mastectomy radiotherap*.tw.
34	post mastectomy radiotherap*.tw.
35	postmastectomy radiotherap*.tw.
36	PMRT.tw.
37	post-mastectomy radiat*.tw.
38	post mastectomy radiat*.tw.
39	postmastectomy radiat*.tw.
40	radiation therap*.tw.
41	post-operative radiotherap*.tw.
42	post operative radiotherap*.tw.
43	postoperative radiotherap*.tw.
44	post-operative radiat*.tw.
45	post operative radiat*.tw.
46	postoperative radiat*.tw.
47	irradiat*.tw.
48	exp irradiation/
49	or/30-48
50	18 and 26 and 29 and 49
51	limit 50 to (human and (conference abstracts or embase))
52	remove duplicates from 51

Appendix 4. WHO ICTRP

Basic search

1. breast cancer AND post-mastectomy AND radiotherapy OR breast cancer AND postmastectomy AND radiotherapy

2. breast cancer AND post-mastectomy AND radiation OR breast cancer AND postmastectomy AND radiation

3. breast cancer AND post-operative AND radiotherapy OR breast cancer AND postoperative AND radiotherapy

4. breast cancer AND post-operative AND radiation OR breast cancer AND postoperative AND radiation

Advanced search

1. Condition: Breast cancer
Intervention: post-mastectomy AND radiotherapy OR postmastectomy AND radiotherapy
Recruitment status: All

2. Condition: Breast cancer
Intervention: post-mastectomy AND radiation OR postmastectomy AND radiation
Recruitment status: All

3. Condition: Breast cancer
Intervention: post-operative AND radiotherapy OR postoperative AND radiotherapy
Recruitment status: All

4. Condition: Breast cancer
Intervention: post-operative AND radiation OR postoperative AND radiation
Recruitment status: All

Appendix 5. ClinicalTrials.gov

Basic search

1. Condition or disease: breast cancer
Other terms: post-mastectomy radiotherapy

2. Other terms: PMRT

Advanced search

1. Condition or disease: Breast cancer
Intervention/treatment: post-mastectomy radiotherapy OR postmastectomy radiotherapy

2. Condition or disease: Breast cancer
Intervention/treatment: post-mastectomy radiation OR postmastectomy radiation

3. Condition or disease: Breast cancer
Intervention/treatment: post-operative radiotherapy OR postoperative radiotherapy

4. Condition or disease: Breast cancer
Intervention/treatment: post-operative radiation OR postoperative radiation

References

References to studies included in this review

Killander 2007 {published data only (unpublished sought but not used)}

20968364

* Killander F, Anderson H, Ryden S, Moller T, Aspegren K, Ceberg J, et al. Radiotherapy and tamoxifen after mastectomy in postmenopausal women – 20 year follow-up of the South Sweden Breast Cancer group randomised trial SSBCG II:I. European Journal of Cancer 2007;43:2100-8. 20968365

Killander 2009 {published data only}

20968366[DOI: 10.1016/j.breast.2009.09.006]

* Killander F, Anderson H, Ryde S, Moller T, Hafstrom LO, Malmstrom P. Efficient reduction of loco-regional recurrences but no effect on mortality twenty years after postmastectomy radiation in premenopausal women with stage II breast cancer – A randomized trial from the South Sweden Breast Cancer Group. The Breast 2009;18:309-15. 20968367

Overgaard 2007 {published data only}

20968368[DOI: 10.1016/j.radonc.2007.02.001]

* Overgaard M, Nielsena HM, Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. Radiotherapy and Oncology 2007;82:247-53. 20968369

References to studies excluded from this review

Arriagada 1995 {published data only}

20968370

Arriagada R, Rutqvist L E, Mattsson A, Kramar A, Rotstein S. Adequate locoregional treatment for early breast cancer may prevent secondary dissemination. Journal of Clinical Oncology 1995;13(12):2869-78. 20968371

Baum 1980 {published data only}

20968372

Baum M, Haybittle JL, Berstock DA. Cancer research campaign (King's/Cambridge) trial for early breast cancer. A detailed update at the 10th year. Lancet 1980;2(8185):55-60. 20968373

Cahlon 2015 {published data only}

20968374

Cahlon O, MacDonald S. Increased cardio and cerebrovascular mortality in breast cancer patients treated with postmastectomy radiotherapy - 25 year follow-up of a randomised trial from the South Sweden Breast Cancer Group: Killander F, Anderson H, Kjellen E, et al (Skane Univ Hosp, Lund, Sweden; Lund Univ, Sweden) Eur J Cancer 50:2201-2210, 2014. Breast Diseases 2015;26(1):74-6. 20968375

Friedl 1983 {published data only}

20968376

Friedl W, Scheurlen HR, Henningsen B. The value of radiotherapy after modified radical mastectomy. 10 year results of the Heidelberg Study. Deutsche Medizinische Wochenschrift 1983;108(9):325-30. 20968377

Gustavsson 1999 {published data only}

20968378

Gustavsson A, Bendahl PO, Cwikiel M, Eskilsson J, Thapper KL, Pahlm O. No serious late cardiac effects after adjuvant radiotherapy following mastectomy in premenopausal women with early breast cancer. International Journal of Radiation Oncology, Biology, Physics 1999;43(4):745-54. 20968379

Houghton 1994 {published data only}

20968380

Houghton J, Baum M, Haybittle JL. Role of radiotherapy following total mastectomy in patients with early breast cancer. The Closed Trials Working Party of the CRC Breast Cancer Trials Group. World Journal of Surgery 1994;18(1):117-22. 20968381

Højris 1999 {published data only}

20968382

Højris I, Overgaard M, Christensen JJ, Overgaard J. Morbidity and mortality of ischaemic heart disease in high-risk breast-cancer patients after adjuvant postmastectomy systemic treatment with or without radiotherapy: analysis of DBCG 82b and 82c randomised trials. Radiotherapy Committee of the Danish Breast Cancer Cooperative Group. Lancet (London, England) 1999;354(9188):1425-30. 20968383

Højris 2000 {published data only}

20968384

Højris I, Andersen J, Overgaard M, Overgaard J. Late treatment-related morbidity in breast cancer patients randomized to postmastectomy radiotherapy and systemic treatment versus systemic treatment alone. Acta Oncologica 2000;39(3):355-72. 20968385

Killander 2014 {published data only}

20968386

Killander F, Anderson H, Kjellen E, Malmstrom P. Increased cardio and cerebrovascular mortality in breast cancer patients treated with postmastectomy radiotherapy--25 year follow-up of a randomised trial from the South Sweden Breast Cancer Group. European Journal of Cancer 2014;50(13):2201-10. 20968387

Morgan 2002 {published data only}

20968388

Morgan DA, Berridge J, Blamey RW. Postoperative radiotherapy following mastectomy for high-risk breast cancer. A randomised trial. European Journal of Cancer 2002;38(8):1107-10. 20968389

Nielsen 2006 {published data only}

20968390

Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. Journal of Clinical Oncology 2006;24(15):2268-75. 20968391

Osman 2014 {published data only}

20968392

Osman MAM, Elkady MS, Nasr KE. For stage II node-positive breast cancer, is it worthwhile to consider adjuvant radiotherapy following mastectomy? Frontiers in Oncology 2014;4:1-8. 20968393

Overgaard 2020 {published data only}

20968394

Overgaard M, Melgaard Nielsen H, Tramm T, Hojris I, Grantzau T, et al. Postmastectomy RT in high-risk breast cancer. A 30-year update of the DBCG 82bc randomized trial. Radiotherapy and Oncology 2020;152:S171. 20968395

Ragaz 2005 {published data only}

20968396

Ragaz J, Olivotto IA, Spinelli JJ, Phillips N, Jackson SM, Wilson KS, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. Journal of the National Cancer Institute 2005;97(2):116-26. 20968397

Rutqvist 1990 {published data only}

20968398

Rutqvist LE, Cedermark B, Glas U, Johansson H, Rotstein S, Skoog L, et al. Randomized trial of adjuvant tamoxifen combined with postoperative radiation therapy or adjuvant chemotherapy in postmenopausal breast cancer. Cancer 1990;66(1):89-96. 20968399

Rutqvist 1992 {published data only}

20968400

Rutqvist LE, Lax I, Fornander T, Johansson H. Cardiovascular mortality in a randomized trial of adjuvant radiation therapy versus surgery alone in primary breast cancer. International Journal of Radiation Oncology, Biology, Physics 1992;22(5):887-96. 20968401

Rutqvist 2006 {published data only}

20968402

Rutqvist LE, Johansson H. Long-term follow-up of the Stockholm randomized trials of postoperative radiation therapy versus adjuvant chemotherapy among 'high risk' pre- and postmenopausal breast cancer patients. Acta Oncologica 2006;45(5):517-27. 20968403

Schmoor 2000 {published and unpublished data}

20968404

Schmoor C, Bastert G, Dunst J, Bojar H, Christmann D, Unbehaun V, et al. Randomized trial on the effect of radiotherapy in addition to 6 cycles CMF in node-positive breast-cancer patients. The German Breast-Cancer Study Group. International Journal of Cancer 2000;86(3):408-15. 20968405

Seegenschmiedt 2000 {published data only}

20968406

Seegenschmiedt MH. Long-term cardiac sequelae of adjuvant radiotherapy after mastectomy? Analysis of Danish DBCG-82b/82c trials. Strahlentherapie und Onkologie 2000;176(4):197-8. 20968407

Shi 2011 {published data only}

20968408

Shi M, Ling R, Xia Y, Luo S, Fu X, Xiao F, et al. Adjuvant chemotherapy and radiotherapy in triple-negative breast carcinoma: A prospective randomized controlled multi-center trial. Radiotherapy and Oncology 2011;100(2):200-4. 20968409

Smith 2001 {unpublished data only}

20968410

Smith L, Mortimer JE. Randomized trial of post-mastectomy radiotherapy in stage II breast cancer in women with one to three positive axillary nodes, phase III. ClinicalTrials.gov 2001. 20968411

References to ongoing studies

Velikova 2018 {published and unpublished data}

20968412

Velikova G, Williams LJ, Willis S, Dixon JM, Kunkler IH, Russell NS, et al. Quality of life after postmastectomy radiotherapy in patients with intermediate-risk breast cancer (SUPREMO): 2-year follow-up results of a randomised controlled trial. Lancet Oncology 2018;19(11):1516-29. 20968413

Additional references

Bray 2018

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians 2018;68(6):394-424.

Burstein 2019

Burstein HJ, Curigliano G, Loibl S, Dubsky P, Gnant M, Poortmans P, et al. Estimating the benefits of therapy for early-stage breast cancer: The St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. Annals of Oncology 2019;30(10):1541-57.

Cardoso 2012

Cardoso F, Loibl S, Pagani O, Graziottin A, Panizza P, Martincich L, et al. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. European Journal of Cancer 2012;48(18):3355-77.

Chagpar 2003

Chagpar A, Kuerer HM, Hunt KK, Strom EA, Buchholz TA. Outcome of treatment for breast cancer patients with chest wall recurrence according to initial stage: implications for post-mastectomy radiation therapy. International Journal of Radiation Oncology, Biology, Physics 2003;57(1):128-35.

Cochran 1954

Cochran WG. The combination of estimates from different experiments. Biometrics 1954;10(1):101-29.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986;7(3):177-88.

EBCTCG 1995

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. Early Breast Cancer Trialists' Collaborative Group. New England Journal of Medicine 1995;333(22):1444-55.

EBCTCG 2000

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Lancet 2000;355(9217):1757-70.

EBCTCG 2005

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;366(9503):2087-106.

EBCTCG 2014

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 2014;383(9935):2127-35.

Fine 1999

Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association 1999;94:496-509.

Fisher 1998

Fisher B, Dignam J, Wolmark N, Mamounas E, Costantino J, Poller W, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-17. Journal of Clinical Oncology 1998;16(2):441-52.

Fisher 2002

Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. New England Journal of Medicine 2002;347(16):1233-41.

Garg 2007

Garg AK, Oh JL, Oswald MJ, Huang E, Storm EA, Perkins GH, et al. Effect of postmastectomy radiotherapy in patients <35 years old with stage II-III breast cancer treated with doxorubicin-based neoadjuvant chemotherapy and mastectomy. International Journal of Radiation Oncology, Biology, Physics 2007;69(5):1478-83.

Goldhirsch 2009

Goldhirsch A, Ingle JN, Gelber RD, Coates AS, Thürlimann B, Senn HJ. Thresholds for therapies: highlights of the St Gallen international expert consensus on the primary therapy of early breast cancer 2009. Annals of Oncology 2009;20(8):1319-29.

GRADEpro GDT [Computer program]

GRADEpro GDT. Version accessed 3 March 2020. Hamilton (ON): McMaster University (developed by Evidence Prime), 2020. Available at gradepro.org.

Haviland 2016

Havilnad JS, Bentzen SM, Bliss JM, Yarnold JR. Prolongation of overall treatment time as a cause of treatment failure in early breast cancer: An analysis of the UK START (Standardisation of Breast Radiotherapy) trials of radiotheray fractionation. Radiotherapy and Oncology 2016;121:420-3.

Headon 2016

Headon H, Kasem A, Almukbel R, Mokbel K. Improvement of survival with postmastectomy radiotherapy in patients with 1-3 positive axillary nodes: A systematic review and meta analysis of the current literature. Molecular and Clinical Oncology 2016;5:429-36.

Hennequin 2013

Hennequin C, Bossard N, Servagi-Vernat S, Maingon P, Dubois JB, Datchary J, et al. Ten-year survival results of a randomized trial of irradiation of internal mammary nodes after mastectomy. International Journal of Radiation Oncology, Biology, Physics 2013;86(5):860-6.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

Katz 2000

Katz A, Strom EA, Buchholz TA, Thames HD, Smith CD, Jhingran A, et al. Locoregional recurrence patterns after mastectomy and doxorubicin-based chemotherapy: implications for postoperative irradiation. Journal of Clinical Oncology 2016;18(15):2817-27.

Li 2013

Li Y, Moran MS, Huo Q, Haffty BG. Post-mastectomy radiotherapy for breast cancer patients with T1-T2 and 1-3 positive lymph nodes: a meta-analysis. PloS ONE 2013;8 (12):e81765.

McCaw 2022

McCaw ZR, Claggett BL, Tian L, Solomon SD, Berwanger O, Pfeffer MA, et al. Practical recommendations on quantifying and interpreting treatment effects in the presence of terminal competing risks: a review. JAMA Cardiology 2022;7(4):450-6.

Mukesh 2014

Mukesh MB, Duke S, Parashar D, Wishart G, Coles CE, Wilson C. The Cambridge post-mastectomy radiotherapy (C-PMRT) index: a practical tool for patient selection. Radiotherapy and Oncology 2014;110(3):461-6.

NICE 2018

National Collaborating Centre for Cancer. Early and locally advanced breast cancer: diagnosis and management. NICE Clinical Guidelines, NG101 2018.

Nielsen 2006

Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: Long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. Journal of Clinical Oncology 2016;24(15):2268-75.

Osman 2014

Osman MAM, Elkady MS, Nasr KE. For stage II node positive breast cancer, is it worthwhile to consider adjuvant radiotherapy following mastectomy? Frontiers in Oncology 2014;4:1-8. [DOI: https://doi.org/10.3389/fonc.2014.00326]

Overgaard 1997

Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. New England Journal of Medicine 1997;337(14):949-55.

Overgaard 1999

Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, et al. Postoperative radiotherapy in high-risk postmenopausal breast cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 199;353(9165):1641-8. [DOI: 10.1016/S0140-6736(98)09201-0.]

Overgaard 2007

Overgaard M, Nielsen HM, Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. Radiotherapy and Oncology 2007;82(3):247-53.

Parmar 1998

Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Statistics in Medicine 1998;17(24):2815-34.

Poortmans 2015

Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. New England Journal of Medicine 2015;373(4):317-27.

Ragaz 2005

Ragaz J, Olivotto IA, Spinelli JJ, Phillips N, Jackson SM, Wilson KS, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. Journal of the National Cancer Institute 2005;97(2):116-26.

Recht 2016

Recht A, Comen EA, Fine RE, Fleming GF, Hardenbergh PH, Ho AY, et al. Postmastectomy radiotherapy: an American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology focused guideline update. Journal of Clinical Oncology 2016;34(36):4431-42.

RevMan Web [Computer program]

Review Manager Web (RevMan Web). Version 1.22. The Cochrane Collaboration, 2020. Available from revman.cochrane.org.

Salerno 2017

Salerno KE. NCCN guidelines update: evolving radiation therapy recommendations for breast cancer. Journal of the National Comprehensive Cancer Network 2017;15(s5):682-4.

Schünemann 2020

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, et al, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.

SEER 2020

Surveillance, Epidemiology, and End Results Program - National Cancer Institute, 2020. Female Breast Cancer - Cancer stat facts. Available from seer.cancer.gov/statfacts/html/breast.html (accessed July 2021).

Shi 2011

Shi M, Ling R, Xia Y, Luo S, Fu X, Xiao F, et al. Adjuvant chemotherapy and radiotherapy in triple-negative breast carcinoma: A prospective randomized controlled multi-center trial. Radiotherapy and Oncology 2011;100(2):200-4.

Siegel 2020

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA: A Cancer Journal for Clinicians 2020;70(1):7-30.

START TRIAL A

The START Trialist Group. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncology 2008;9(4):331-41.

START TRIAL B

The START Trialist Group. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet 2008;371(9618):1098-107.

Thorsen 2016

Thorsen LB, Offersen BV, Danø H, Berg M, Jensen I, Pedersen AN, et al. DBCG-IMN: a population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. Journal of Clinical Oncology 2016;34(4):314-20.

Tierney 2007

Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.

Truong 2005

Truong PT, Olivotto IA, Kader HA, Panades M, Speers CH, Berthelet E. Selecting breast cancer patients with T1-T2 tumors and one to three positive axillary nodes at high postmastectomy locoregional recurrence risk for adjuvant radiotherapy. International Journal of Radiation Oncology, Biology, Physics 2005;61(5):1337-47.

Van Tienhoven 1999

Van Tienhoven G, Voogd AC, Peterse JL, Nielsen M, Andersen KW, Mignolet F, et al. Prognosis after treatment for loco-regional recurrence after mastectomy or breast conserving therapy in two randomised trials (EORTC 10801 and DBCG- 82TM). European Journal of Cancer 1999;35(1):32-8.

Wallgren 2003

Wallgren A, Bonetti M, Gelber RD, Goldhirsch A, Castiglione-Gertsch M, Holmberg SB, et al. Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. Journal of Clinical Oncology 2003;21(7):1205-13.

Whelan 2000

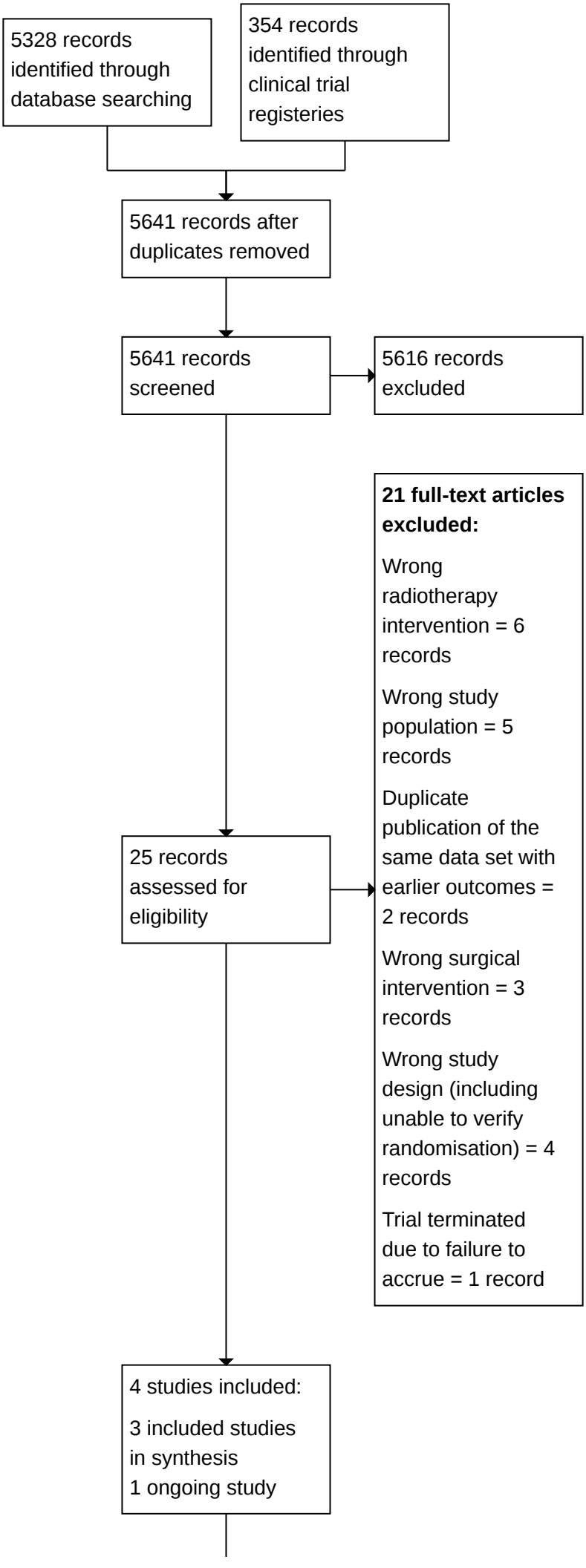
Whelan TJ, Julian J, Wright J, Jadad AR, Levine ML. Does locoregional radiation therapy improve survival in breast cancer? A meta- analysis. Journal of Clinical Oncology March 2000;18(6):1220-9.

Whelan 2015

Whelan TJ, Olivotto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, et al for the MA20 Study Investigators. Regional nodal irradiation in early-stage breast cancer. New England Journal of Medicine 2015;373(4):307-16.

Figures and tables

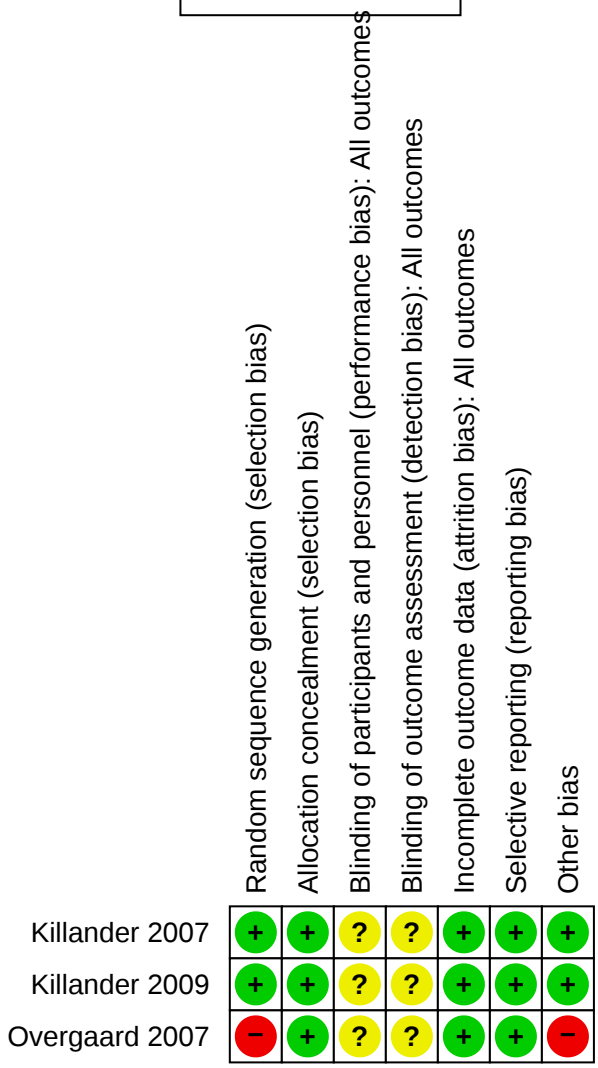
Figure 1


5328 records identified through database searching
354 records identified through clinical trial registeries
5641 records after duplicates removed
5641 records screened
5616 records excluded
21 full-text articles excluded:
Wrong radiotherapy intervention = 6 records
Wrong study population = 5 records
Duplicate publication of the same data set with earlier outcomes = 2 records
Wrong surgical intervention = 3 records
Wrong study design (including unable to verify randomisation) = 4 records
Trial terminated due to failure to accrue = 1 record
25 records assessed for eligibility
4 studies included:
3 included studies in synthesis
1 ongoing study

PRISMA flow diagram

3 studies included in quantitative synthesis (meta-analysis)

Figure 2

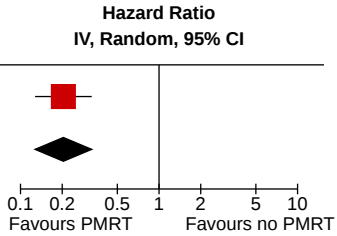


Risk of bias summary for the included studies

Analysis 1.1

Study or Subgroup	log[Hazard Ratio]	SE	PMRT Total	No PMRT Total	Weight	Hazard Ratio IV, Random, 95% CI
Overgaard 2007	-1.59	0.24	276	276	100.0%	0.20 [0.13 , 0.33]
Total (95% CI)			**276**	**276**	**100.0%**	**0.20 [0.13 , 0.33]**

Heterogeneity: Not applicable
Test for overall effect: Z = 6.63 (P < 0.00001)
Test for subgroup differences: Not applicable

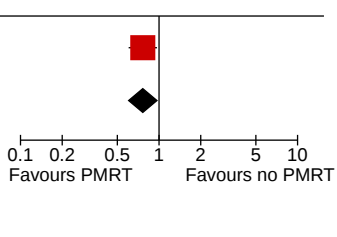


Comparison 1: PMRT versus no PMRT in women with one to three positive lymph nodes , Outcome 1: Locoregional recurrence (LRR)

Analysis 1.2

Study or Subgroup	log[Hazard Ratio]	SE	PMRT Total	No PMRT Total	Weight	Hazard Ratio IV, Random, 95% CI
Overgaard 2007	-0.27	0.12	276	276	100.0%	0.76 [0.60 , 0.97]
Total (95% CI)			**276**	**276**	**100.0%**	**0.76 [0.60 , 0.97]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.25 (P = 0.02)
Test for subgroup differences: Not applicable

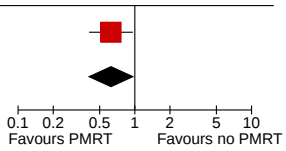


Comparison 1: PMRT versus no PMRT in women with one to three positive lymph nodes , Outcome 2: Overall survival (OS)

Analysis 1.3

Study or Subgroup	log[Sub-distribution Hazard Ratio]	SE	PMRT Total	No PMRT Total	Weight	Sub-distribution Hazard Ratio IV, Random, 95% CI
Killander 2007	-0.47	0.22	79	94	100.0%	0.63 [0.41 , 0.96]
Total (95% CI)			**79**	**94**	**100.0%**	**0.63 [0.41 , 0.96]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.14 (P = 0.03)
Test for subgroup differences: Not applicable



Comparison 1: PMRT versus no PMRT in women with one to three positive lymph nodes , Outcome 3: Disease-free survival (DFS)