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Sequencing of chemotherapy and radiotherapy for early breast cancer (Review)

Hickey BE, Francis DP, Lehman M

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[Intervention Review]

Sequencing of chemotherapy and radiotherapy for early breast cancer

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ABSTRACT

Background

After surgery for localised breast cancer, radiotherapy (RT) improves both local control and breast cancer-specific survival. In patients at risk of harbouring micro-metastatic disease, adjuvant chemotherapy (CT) improves 15-year survival. However, the best sequence of administering these two types of adjuvant therapy for early-stage breast cancer is unclear.

Objectives

To determine the effects of different sequencing of adjuvant CT and RT for women with early breast cancer.

Search methods

An updated search was carried out in the Cochrane Breast Cancer Group's Specialised Register (20 May 2011), MEDLINE (14 December 2011), EMBASE (20 May 2011) and World Health Organization (WHO) International Clinical Trials Registry Platform (20 May 2011). Details of the search strategy and methods of coding for the Specialised Register are described in the Group's module in *The Cochrane Library*. We extracted studies that had been coded as 'early', 'chemotherapy' and 'radiotherapy'.

Selection criteria

We included randomised controlled trials evaluating different sequencing of CT and RT.

Data collection and analysis

We assessed the eligibility and quality of the identified studies and extracted data from the published reports of the included trials. We derived odds ratios (OR) and hazard ratios (HR) from the available numerical data. Toxicity data were extracted, where reported. We used a fixed-effect model for meta-analysis and conducted analyses on the basis of the method of sequencing of the two treatments.

Main results

Three trials reporting two different sequencing comparisons were identified. There were no significant differences between the various methods of sequencing adjuvant therapy for local recurrence-free survival, overall survival, relapse-free survival and metastasis-free survival based on 1166 randomised women in three trials. Concurrent chemoradiation increased anaemia (OR 1.54; 95% confidence interval (CI) 1.10 to 2.15), telangiectasia (OR 3.85; 95% CI 1.37 to 10.87) and pigmentation (OR 15.96; 95% CI 2.06 to 123.68).

Treated women did not report worse cosmesis with concurrent chemoradiation but physician-reported assessments did (OR 1.14; 95% CI 0.42 to 3.07). Other measures of toxicity did not differ between the two types of sequencing. On the basis of one trial (244 women), RT before CT was associated with an increased risk of neutropenic sepsis (OR 2.96; 95% CI 1.26 to 6.98) compared with CT before RT, but other measures of toxicity did not differ.

Authors' conclusions

The data included in this review, from three well-conducted randomised trials, suggest that different methods of sequencing CT and RT do not appear to have a major effect on recurrence or survival for women with breast cancer if RT is commenced within seven months after surgery.

PLAIN LANGUAGE SUMMARY

Sequencing of chemotherapy and radiotherapy for women following surgery for early breast cancer

Both chemotherapy and radiotherapy reduce the risk of breast cancer recurring and the risk of dying from breast cancer. Generally, these therapies are given after surgery but there is uncertainty about whether they should be given at the same time (concurrently) or one after the other (sequentially). If they are used sequentially, the radiotherapy or the chemotherapy could be used first and concerns have been expressed that the effectiveness of the therapy that is delayed might be reduced. However, it has also been suggested that using chemotherapy and radiotherapy at the same time may be more toxic than keeping them separate. This review examined the current evidence on the best way to administer chemotherapy and radiotherapy following breast-conserving surgery. We were able to include three randomised trials. Two of these, with 853 women, assessed radiotherapy and chemotherapy given at the same time versus chemotherapy given first followed by radiotherapy. The third trial randomised 244 women to radiotherapy followed by chemotherapy versus chemotherapy followed by radiotherapy. The evidence produced by these three well-conducted trials suggests that recurrence of a woman's cancer and her chances of dying from breast cancer are similar regardless of the order of the treatments, provided that both radiotherapy and chemotherapy are commenced within seven months of the surgery. The trials provided limited information regarding adverse events, side effects or quality of life associated with the different sequences of treatment. The limited evidence available does suggest that the frequency and severity of side effects of chemotherapy and radiotherapy are similar regardless of which sequence is used. However, it should be noted that the women in these trials were treated, on average, in the early 2000s. As a result, the trials do not assess the modern types of radiotherapy, and new types of chemotherapy (such as taxanes) or other drugs (such as Herceptin). We will add relevant trials that include these more recent treatments to future updates of this review.

BACKGROUND

Description of the condition

For women with localised breast cancer who undergo conservative surgery or mastectomy, adjuvant radiotherapy (RT) reduces the risk of local recurrence and improves breast cancer-specific survival (EBCTCG 2011; Ragaz 2005). Adjuvant chemotherapy (CT) has also been shown to improve 15-year survival (EBCTCG 2005b).

Description of the intervention

Current practices for the sequencing of RT and CT include administering CT before RT, administering CT and RT concurrently, or 'sandwiching' RT in the middle of the CT course. It is not clear which of these different sequences is the most effective for women with early-stage breast cancer. It has been suggested that the sequence of these two treatments may affect patient outcome (Recht 1996). For example, a delay in initiating RT was found to increase the risk of local recurrence (odds ratio (OR) 2.28, 95% confidence interval (CI) 1.45 to 3.57) (Huang 2003). However, a delay in commencing CT may also have a detrimental effect on survival.

How the intervention might work

One published randomised trial initially found a non-significant improvement in overall survival if CT was given first (Recht 1996)

but longer follow-up did not reveal any difference in the rates of local or distant recurrence or death between the two treatment groups (Bellon 2001). Additionally, some non-randomised studies have suggested that delaying RT while CT is administered first could increase local recurrence rates (Buchholz 1993; Buchholz 1999; Buzdar 1993; Donato 2004; Hartsell 1995; Leonard 1995; McCormick 1996; Meek 1996; Recht 1991; Slotman 1994). Conversely, a delay in the administration of systemic CT while RT is delivered could allow the proliferation of micro-metastatic disease to an extent that it can no longer be dealt with adequately by the CT.

Why it is important to do this review

In many parts of the world there are waiting lists for RT (Ash 2000; Kenny 2004; MacKillop 1994; MacKillop 1995). The delivery of CT first allows patients to start treatment and overcomes the problem of RT waiting lists (Kenny 2004).

If a systematic review helps to resolve this uncertainty about the relative effects of different sequences of CT and RT, it will assist in making these choices. For example, if it shows that sequencing of the two treatments makes little or no difference for cancer-related outcomes such as survival and local recurrence, then choosing to give CT first may be preferable for both logistic reasons and patient preference.

This 2011 review is an update of the Cochrane systematic review first published in 2006.

OBJECTIVES

To determine the effects of different sequencing of RT and CT for women with early-stage breast cancer who have been treated surgically.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) evaluating different ways of sequencing RT and CT were eligible. The comparison between different sequences had to be unconfounded (i.e. the randomised groups differed only in relation to the sequencing of the two treatments). Trials incorporating the use of other adjuvant treatments, such as monoclonal antibodies or hormonal therapy, were eligible if these other treatments were applied in both groups in the RCT. Published and unpublished studies were eligible.

Types of participants

Women with surgically treated, histologically confirmed early-stage breast cancer who required both adjuvant CT and RT were included. Early breast cancer included tumours classified as Union for International Cancer Control (UICC) stage T1-3N0-1M0. Surgery could comprise mastectomy, lumpectomy, wide local excision or quadrantectomy, with or without axillary dissection, axillary sampling or sentinel node biopsy. Women who had previously received adjuvant therapy for breast cancer were not eligible.

Types of interventions

The following comparisons were eligible:

1. adjuvant RT followed by adjuvant CT versus adjuvant CT followed by adjuvant RT;
2. adjuvant CT followed by adjuvant RT versus a 'sandwich technique' (when one or more courses of CT were followed by RT, which was followed by further CT);
3. adjuvant CT followed by adjuvant RT versus concurrent adjuvant CT and RT.

CT regimens included those delivered at standard doses (i.e. not high dose), and could include drugs such as cyclophosphamide, 5-fluorouracil, anthracyclines, taxanes and other agents.

RT had to be delivered to the breast or chest wall, including or excluding the supraclavicular fossa and axilla. Standard fractionation (1.8 to 3.0 Gray (Gy) per fraction) had to be used, delivering 40 to 61 Gy at the reference point. It could include a boost (using electrons, interstitial therapy or external beam) or new techniques.

Types of outcome measures

Primary outcomes

- Local recurrence in the ipsilateral (i.e. same) breast and cause-specific mortality. We defined local recurrence as including recurrence in the ipsilateral breast (i.e. the breast in which cancer had been diagnosed), the skin and parenchyma.

Secondary outcomes

- Overall survival.
- Distant metastases (in isolation or at the same time as local recurrence).
- Relapse-free survival.
- Subsequent mastectomy.
- Harms, including acute and late effects of RT- and CT-related toxicity.
- Ability to deliver the prescribed dose of CT and ability to deliver the prescribed dose of RT. We set an arbitrary threshold of 80% when assessing the ability to deliver the prescribed dose of CT or RT.

- Costs.
- Quality of life (QoL).
- Consumer preference.

Search methods for identification of studies

Electronic searches

For the original review published in 2006, we searched the Cochrane Breast Cancer Group's Specialised Register. Details of the search strategy used by the Group to create this register and the procedure used to code the references are described in the Group's module in *The Cochrane Library*. We extracted studies coded with each of the three terms 'early', 'chemotherapy' and 'radiotherapy' for consideration. We also conducted electronic searches of CENTRAL (Issue 4, 2005), MEDLINE, CINAHL Current Contents and the Science Citation Index.

For the 2011 review update, a further search on the Cochrane Breast Cancer Group's Specialised Register on 20 May 2011, MEDLINE (14 December 2011; see Appendix 1 for the search strategy), EMBASE (20 May 2011; see Appendix 2 for the search strategy), Current Contents (December 2011), CINAHL (20 January 2012; see Appendix 3) and Science Citation Index (12 March 2012; see Appendix 4).

We also searched registers of ongoing clinical trials for the 2011 update. These included the US clinical trials registry (www.clinicaltrials.gov), the International Standard Randomised Controlled Trial Number Register (www.controlled-trials.com/isrctn) and the UKCCR National Register of Cancer Trials and the WHO International Clinical Trials Registry Platform (20 May 2011; see Appendix 5 for the search strategy).

We also searched other sources of unpublished trials (Greynet, National Research Register) on 25 January 2012 and we contacted researchers to ask if they were aware of any other trials on this topic.

We checked for additional citations in eligible articles.

No language restrictions were employed.

Searching other resources

We handsearched a number of conference proceedings and published abstracts. These included: 2001 Adjuvant Therapy for Primary Breast Cancer International Conference; Era of Hope, Department of Defence Breast Cancer Research Program Meeting; 2001 and 2003: Primary Therapy of Early Breast Cancer; 6th and 7th Nottingham International Breast Cancer Meeting Conference Report; 23rd and 24th Congress of the International Association for Breast Cancer Research; 3rd and 4th Perspectives in Breast Cancer Conference Report; 26th and 27th Annual San Antonio Breast Cancer Symposium; 4th European Breast Cancer Conference; 94th and 95th American Association of Cancer Research; American Society for Clinical Oncology (1995 to 2005); European Society for Therapeutic and Radiation Oncology (2000 to 2004); 5th and 6th Milan Breast Cancer Conference; Australian Breast Cancer Conference (2004); 27th and 28th Annual Symposium of the American Society of Breast Disease; CDC Cancer Conference (2003); British Cancer Meeting Report; Canadian Breast Cancer Research Conference: Reasons for Hope.

Data collection and analysis

Selection of studies

All three review authors (BH, ML and DF) checked the titles and abstracts retrieved by all searches. Each author assessed independently the full text of the studies we thought might be relevant to the review, resolving differences through discussion. We assessed trials with the results masked. In cases where only limited data, information on study methods or both was reported, we requested further information from the authors of the original articles.

Data extraction and management

Two review authors (BH and ML) performed data extraction, with disagreements resolved by discussion. We contacted the original authors for data from unpublished trials or published trials that did not report data needed for this review. Data were entered into Reference Manager software (RevMan 2011) for analyses. Where possible, we extracted data on tumour stage, nodal status (pathological), margin status, receptor status, hormonal manipulation, treatment allocation and surgery performed. The information we extracted on RT and CT included time from randomisation to the start of RT and CT, duration of CT, duration of RT, radiation dose and dose per fraction. We extracted outcome data for local recurrence, distant metastases, deaths (cause-specific and all-cause), treatment-related toxicity (including that related to acute and late effects of RT and CT), costs of treatment, consumer preference and quality of life.

Assessment of risk of bias in included studies

Two review authors (BH and ML) judged and graded each RCT by using the Cochrane's 'Risk of bias' assessment tool as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Grades given by each author were compared and disagreements were resolved by discussion. The tool contains six domains and each domain was assigned a judgement related to the risk of bias. A judgement of 'low' indicated a low risk of bias, 'high' indicated a high risk of bias and 'unclear' indicated an unknown risk of bias. The six domains were:

1. sequence generation;
2. allocation concealment;

3. blinding of participants, personnel and outcome assessors;
4. incomplete outcome data;
5. selective outcome reporting; and
6. other sources of bias.

The judgements of these domains for each RCT were reported in the 'Risk of bias' tables.

Measures of treatment effect

Dichotomous results (e.g. acute and late toxicity, cosmesis) were presented as ORs with 95% CI (Deeks 2003). We used Mantel-Haenszel methods to calculate pooled results (Greenland 1985; Mantel 1959).

Time-to-event outcomes (e.g. local recurrence-free survival) were presented as hazard ratios (HR).

Dealing with missing data

We contacted the original authors for data from unpublished trials or published trials that did not report data needed for this review.

Assessment of heterogeneity

We assessed heterogeneity both visually and statistically using the Chi^2 test of heterogeneity (Altman 1992; Walker 1988). We did not identify significant heterogeneity among the results of the trials in the current analysis, but if heterogeneity is identified in updates of this review, the reasons for it will be explored and we will make a cautious attempt to explain it.

Data synthesis

We used the intention-to-treat principle in analysing data from the trials and determined a weighted average treatment effect by using the fixed-effect model to combine results (Mantel 1959) in Review Manager software (RevMan 2011).

For the comparisons of concurrent versus sequential CT and RT, raw data were not reported and therefore the HR and associated statistics were calculated, where necessary, using an Excel spreadsheet developed by the Matthew Sydes (Cancer Division) in collaboration with the Meta-analysis Group of the MRC Clinical Trials Unit, London (Sydes). This spreadsheet was used for the end points of overall survival and relapse-free survival (Arcangeli 2006; ARCOSEIN).

Similarly, for the comparison of RT then CT versus CT then RT, raw data were not reported and therefore the HR and associated statistics were calculated, where necessary, using an Excel spreadsheet developed by the Matthew Sydes (Cancer Division) in collaboration with the Meta-analysis Group of the MRC Clinical Trials Unit, London (Sydes). In this case, the spreadsheet was used for the end points of overall survival, distant metastases and relapse-free survival (Bellon 2005).

Acute toxicity was dichotomised and we reported the OR with 95% CI. The authors used a four-point scale to report cosmesis (see Table 1) and reported the proportion of women with excellent cosmetic results (Bellon 2005).

For late toxicity (breast atrophy, breast fibrosis, telangiectasia, lymphoedema and cosmesis), the data were dichotomised and we reported the Grade III/IV toxicity on the LENT-SOMA scale (see Table 2). For pigmentation (not included in LENT-SOMA) we reported those who had poor or very poor pigmentation (see Table 3). Late cosmetic toxicity was dichotomised and we reported the proportion who had poor or very poor cosmesis on a five-point scale (see Table 4).

If quality of life scores are available for future updates, we will obtain the standard deviation and the mean to analyse the data. If different scales are reported in the trials, we will use the standardised mean difference to summarise data (Deeks 2003).

Subgroup analysis and investigation of heterogeneity

The current version of this review does not include any subgroup analyses because of the lack of data. However, if sufficient data become available in future updates, we may perform subgroup analyses to investigate whether the effects of different sequences of RT and CT differ depending upon nodal status, margin status, receptor status, hormonal manipulation and tumour stage.

Sensitivity analysis

Sufficient data were not available to perform a sensitivity analysis. In future updates, if adequate data are available, we would perform sensitivity analyses to assess the robustness of our results by repeating the analysis with the following adjustments:

1. repeating the analysis excluding studies with high risk of bias;
2. repeating the analysis each time excluding unpublished trials.

RESULTS

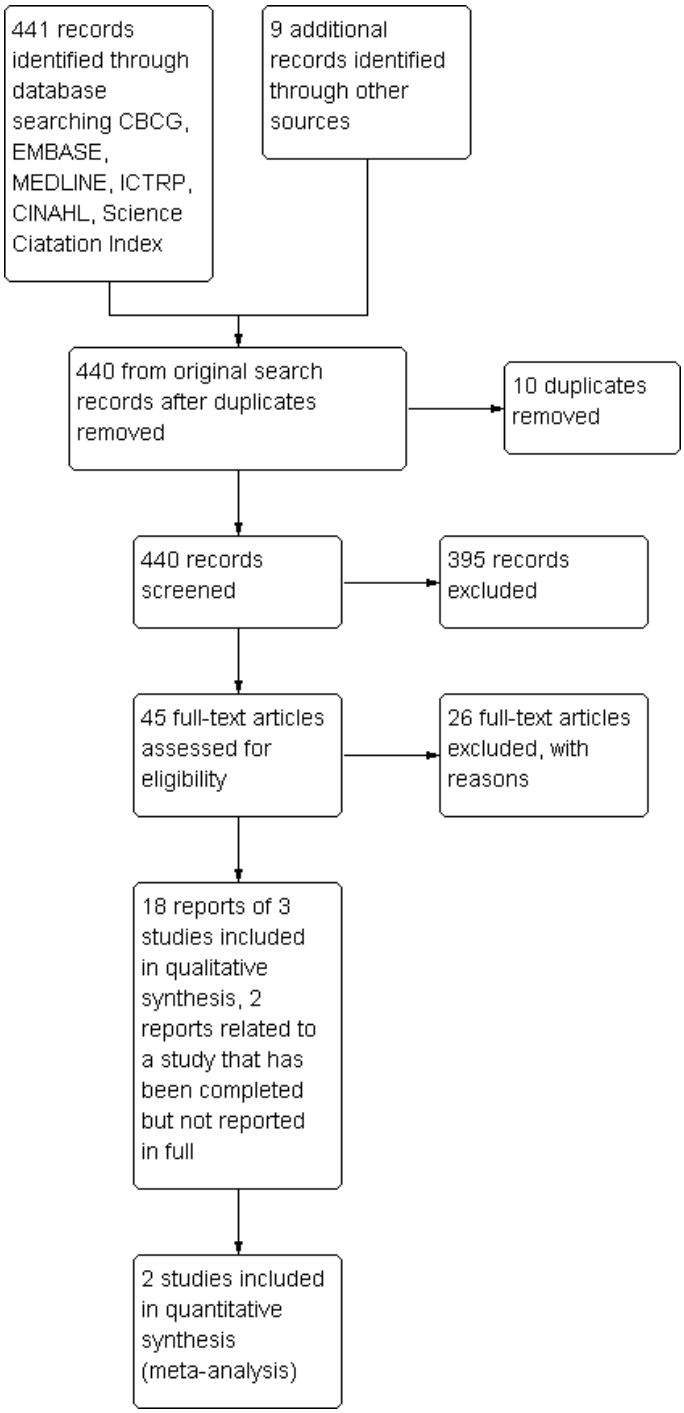
Description of studies

Results of the search

After screening the titles and abstracts retrieved electronically and by handsearching, we identified 441 reports for possible inclusion in this review. Further screening of these reduced the number to 45 reports and, where possible, we obtained the full articles for these. The results presented in these articles were masked and the remaining text was assessed by two review authors (BH and ML).

This revealed that 19 of the reports did not relate to RCTs (Bellon 2004; Buzdar 1993; Cakir 2003; Denham 1995; Dubey 1999; Faul 1998; Faul 2003; Fiets 2003; Garcia 1996; Hartsell 1995; Hasbini 2000; Isaac 2002; Lamb 1999; Leonard 1995; Recht 1991; Rubens 1980; Sauer 1996; Stemmer 2003; Zambetti 1999) and the treatments investigated in six were not eligible for this review (Assersohn 1999; Bellantone 1998; Blomqvist 1992; Donato 2004; Wallgren 1996; Warner 1998). One study investigated different sequences of therapy but was confounded (and, therefore, ineligible) because the CT regimens were different in the two randomised groups (Rouesse 2002). Eighteen reports did relate to four studies that appeared to meet our inclusion criteria (Arcangeli 2006; Arcangeli 2004 (see Arcangeli 2006); Bellon 2002 (see Bellon 2005); Bellon 2005; Bellon 2001; Calais 1998a; Calais 1998b; Calais 2002; Calais 2004; Fernando 2011 (see SECRAB); ISRCTN84214355 (see SECRAB); Hardenbergh 1999; Pinnaro 2011; Recht 1996; Toledano 2006a (see ARCOSEIN); Toledano 2006b (see ARCOSEIN); Toledano 2007a (see ARCOSEIN); Toledano 2007b (see ARCOSEIN)). One study (SECRAB) has completed accrual, but has only been reported in abstract form (Figure 1).

Figure 1. Study flow diagram (updated search results to 14 December 2011).



The eighteen reports that met the inclusion criteria related to three separate studies because some of the trials had published their results at different times, with different periods of follow-up. In these cases we used the most recent publication as the main source for this review, supplementing this with information from earlier reports if necessary. Thus, for Bellon 2005, the main source was the Bellon 2005 article, with four other publications found for this trial (Bellon 2001; Bellon 2002; Hardenbergh 1999; Recht 1996). Similarly, for ARCOSEIN, our primary source for data extraction was Calais 2004, with some information also available in seven other publications (Calais 1998a; Calais 1998b; Calais 2002; Toledano 2006a, Toledano 2006b; Toledano 2007a; Toledano 2007b). For Arcangeli 2006, our primary source was Pinnaro 2011, with some information available from Arcangeli 2006.

One report (Calais 1998b) required translation from French to English, while another (Garcia 1996) required translation from Spanish to English.

Of the three authors we contacted, two provided us with additional data on their studies (Arcangeli 2006; Rouesse 2002). We are awaiting further information from one (Bellon 2005), as of 18/03/13, this had not been provided.

Included studies

Participants, follow-up and treatment regimens

The three RCTs, included in the updated version of this review, randomised 1166 patients. Two studies (Arcangeli 2006; ARCOSEIN), with 922 patients, compared concurrent CT and RT with sequential administration of CT before RT. Arcangeli 2006 initially reported results at 65 months' follow-up then again after median follow-up of 111 months. ARCOSEIN reported at 60 months' median follow-up, but late effects were reported at a median of 6.7 years' follow-up. First-generation chemotherapeutic agents were used (i.e. no anthracyclines or taxanes).

Delay to start of radiotherapy

In the two studies (Arcangeli 2006; ARCOSEIN) that compared concurrent CT and RT with sequential administration of CT before RT, RT was started by a maximum of 161 days (about 5.3 months) in ARCOSEIN and by 210 days (seven months) in Arcangeli 2006. In Bellon 2005, which compared RT followed by CT to CT followed by RT, RT started by 84 days (about 2.8 months) after surgery.

The third RCT (Bellon 2005) compared RT followed by CT to CT followed by RT in 244 patients. Bellon 2005 reported at a median follow-up of 135 months. More information on the three included studies can be found in the 'Characteristics of included studies' table. Anthracyclines were used but not taxanes.

Local recurrence

For the comparison of concurrent versus sequential CT and RT, local recurrence was reported in Arcangeli 2006, but loco-regional recurrence was reported in ARCOSEIN, so we were not able to combine the results for this outcome. For the comparison of RT then CT versus CT then RT, local recurrence was reported as first-event data and we have contacted the authors (Bellon 2005) in order to clarify this but await their reply.

Toxicity

Acute toxicity was assessed at one month after completion of RT (ARCOSEIN) and was reported for 30% (214/716) of women randomised. Grade III/IV acute toxicity was reported (however, the scoring system was not given; ARCOSEIN). Acute haematological and skin toxicity was reported using the common toxicity criteria (CTC) acute scoring system (Bellon 2005).

Late toxicity was assessed in ARCOSEIN and scored prospectively at a median follow-up of 6.7 years in 29% (214/716) of those women randomised. Two hundred and ninety-seven women from the five larger participating institutions were asked to report for a follow-up examination and 72% (214/297) of these women were evaluated for late toxicity. Late toxicity was scored using the Late Effects Normal Tissue Task Force (LENT)/Subjective, Objective, Management, Analytic (SOMA) scale (validated scale) by an observer blinded to the treatment arm (see Table 2). A personal five-point scoring system was used to score pigmentation (not included in the LENT/SOMA scale; see Table 3). Late toxicity was scored as a single event at last follow-up. Breast oedema was defined as "permanent swelling with an increased volume of the breast" and fibrosis was detected by palpation, in comparison to the untreated breast. Oedema was reported when the measurements differed. Cardiac events were defined as myocardial infarction or clinical evidence of congestive cardiac failure. Symptomatic radiation pneumonitis was characterised by a cough, fever and shortness of breath that occurred two to nine months after completing RT.

In Bellon 2005, cardiac toxicity was assessed in 231/244 (95%) women at a median follow-up of 53 months. Cardiac events were defined as myocardial infarction or congestive cardiac failure. Late toxicity data were extracted from medical records and not prospectively collected. Cellulitis was defined as the "inflammation of the breast unresponsive to antibiotics" and lymphoedema was recorded if there was a description of a "swollen or oedematous arm in the treatment record" (no measurements were made at baseline or of the contralateral arm). Brachial plexopathy was evaluated only in those women who had regional nodal RT.

Cosmesis

For the comparison of concurrent versus sequential CT and RT, cosmetic outcome was reported for 29% (214/716) of women after a median of 6.7 years' follow-up. Seventy-two per cent (214/297) of women from the five larger participating institutions who were asked to report for a follow-up examination were evaluated for cosmesis. The primary reason for refusal was a reluctance to attend the hospital for clinical assessments. In ARCOSEIN, cosmesis was evaluated both by the patient (using a five-point scale; Hoeller 2003) and physician blinded to treatment allocation. Physician-assessed cosmesis was scored thus by an overall cosmetic satisfaction score based on the comparison between the treated and untreated breast (see Table 5) using "Harris's classification modified by Beadle" (Beadle 1984; Harris 1979; see Table 4). The second score was derived using a detailed definition of how to score cosmesis satisfaction (Fehlauer 2003). To lessen inter-observer variability, two observers examined 40 patients and the ratings were reproducible. There was "fair correlation" reported between the patient's and physician's assessment of cosmesis. The two methods of scoring cosmetic outcome by physicians were reported to be concordant (ARCOSEIN).

For the comparison of RT then CT versus CT then RT, cosmetic outcome was assessed in women without recurrence by a single radiation oncologist at 18 to 30 months after treatment (31% (76/244) of those women randomised; Bellon 2005). The authors reported those in each group who had "excellent" cosmetic results (i.e. a virtual absence of changes due to treatment) on a four-point scale (see Table 1; Harris 1979). Figures were derived from the percentages given in the text (Bellon 2005).

Excluded studies

See Excluded studies table.

Risk of bias in included studies

Allocation

All three included studies were randomised (Arcangeli 2006; ARCOSEIN; Bellon 2005). Details about the methods of randomisation were given in Arcangeli 2006 where the authors stated a "balanced randomisation method" was used. It appears that the studies were truly randomised and had a low risk of selection bias.

Blinding

In Arcangeli 2006, blinding was not reported for the assessors of objective outcomes, if investigations such as mammograms or bone scans were performed at different times in the two groups, it may have introduced lead time bias. In ARCOSEIN, for the subjective outcome of cosmesis, the assessor was blinded, which minimises the risk of bias for this outcome. Detection bias was less likely because there were pre-specified intervals for clinical examination and investigations. Assessment of both late toxicity and cosmetic outcome were blinded, which minimises the risk of bias (ARCOSEIN). No mention was made of any blinding for either objective or subjective outcomes in Bellon 2005, this means the findings are at risk of bias.

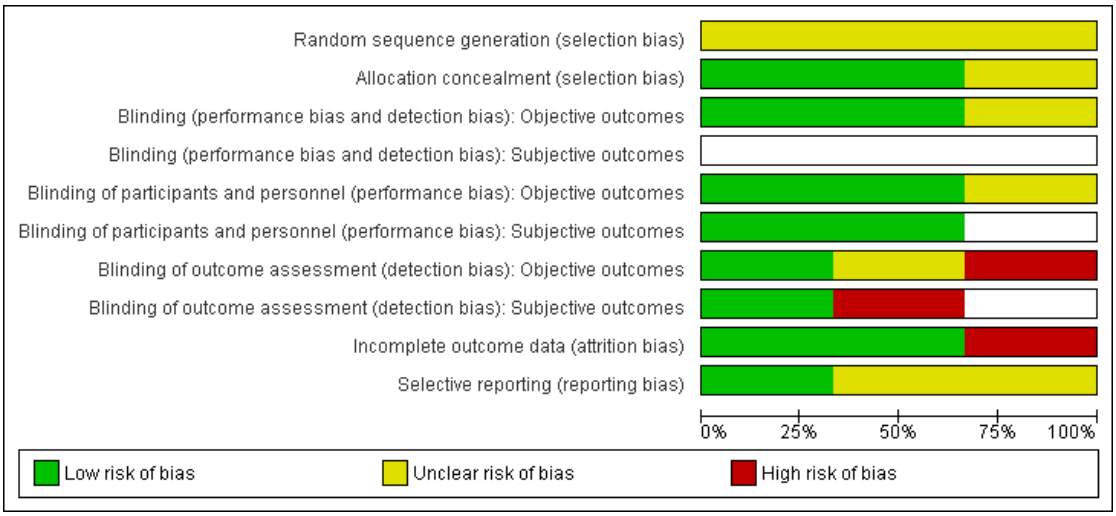
Incomplete outcome data

All women randomised in the Arcangeli trial (Arcangeli 2006) were included in the analysis. All women were analysed for the primary end point. A total of 214 of 647 (33%) women were included in the acute toxicity analysis in the ARCOSEIN trial (ARCOSEIN). The remainder of the analyses were performed on 96% and 98% of the included women. Both Arcangeli 2006 and ARCOSEIN were thought to be at low risk of attrition bias. In Bellon 2005, those women lost to follow-up were described, and the trial authors comment that an intention-to-treat analysis was performed, but it can be seen from a table in the text that smaller numbers were available for evaluation at five years, which suggests there was a large amount of attrition in addition to the numbers lost to follow-up reported in each arm. This makes the Bellon trial at high risk of attrition bias (Bellon 2005).

Selective reporting

We did not review the protocols for any of the included trials. Cosmetic outcome has not been reported (although the trial authors indicated that they would in the methods) for Arcangeli 2006. For ARCOSEIN and Bellon 2005, the end points indicated in the text were all reported. The included studies are therefore at unclear risk of reporting bias (Figure 2).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Effects of interventions

Concurrent treatment versus chemotherapy followed by radiotherapy

For this comparison, first-generation chemotherapeutic agents were used (i.e. no anthracyclines or taxanes).

There were two studies, enrolling 853 women, in this comparison (Arcangeli 2006; ARCOSEIN). In the results presented, ratios of treatment effects are given such that an OR or HR of less than 1.0 would indicate a beneficial effect of concurrent treatment compared with sequential treatment. The results for each outcome are as follows.

- Local recurrence-free survival (ipsilateral): both studies reported results for local recurrence. There were 14 such recurrences in 602 randomised women. There was no evidence to suggest that local recurrence -free survival differed when concurrent CT/RT was compared with sequential at:

  i) five-year follow-up: HR 0.96 (95% CI 0.14 to 6.82) (Arcangeli 2006)(Analysis 1.1) or

  ii) 10-year follow-up: HR 1.05 (95% CI 0.30 to 3.62) (Arcangeli 2006). As data were available from one trial, testing for heterogeneity was not appropriate (Analysis 1.1).

- Cause-specific survival: neither trial reported on this outcome.

- Overall survival: did not differ when concurrent CT/RT was compared with sequential at:

  i) five year follow-up: HR 0.97; 95% CI 0.83 to 1.13 (Arcangeli 2006; ARCOSEIN; Analysis 1.4). No heterogeneity was detected (I^2 = 0%, P = 0.92);

  ii) median follow-up of 111 months: HR 0.92; 95% CI 0.33 to 2.55 (Arcangeli 2006). As data were available from one trial, testing for heterogeneity was not appropriate.

- Metastasis-free survival: 68/853 (8%) of the women in the two trials combined had distant metastases diagnosed. Metastasis-free survival did not differ when concurrent CT/RT was compared with sequential at:

  i) median follow-up of 60 to 65 months: HR 0.86; 95% CI 0.60 to 1.24) (Arcangeli 2006; ARCOSEIN). No heterogeneity was detected (I^2 = 0%, P = 0.63);

  ii) median follow-up of 111 months: HR 0.57; 95% CI 0.20 to 1.62) (Arcangeli 2006). As data were available from one trial, testing for heterogeneity was not appropriate.

- Relapse-free survival did not differ when concurrent CT/RT was compared with sequential at:

  i) median follow-up of 50 to 65 months: HR 0.98; 95% CI 0.84 to 1.15 (Arcangeli 2006; ARCOSEIN). No heterogeneity was detected (I^2 = 0%, P = 0.75) (Analysis 1.2);

  ii) median follow-up of 111 months: HR 1.10; 95% CI 0.57 to 2.13 (Arcangeli 2006) (Analysis 1.2). As data were available from one trial, testing for heterogeneity was not appropriate.

- Mastectomy rate: no data.

- Harms and toxicity:

i) acute toxicity: the Arcangeli 2006 report included the comment that acute toxicity was "mild in both groups, with infrequent moist desquamation in limited areas". The other study (ARCOSEIN), with 647 women, reported acute toxicity for 214/647(33%) women studied. Anaemia increased with concurrent CT/RT while nausea/vomiting and grade III/IV skin, infection or oesophagitis did not (ARCOSEIN; see Table 6);

ii) late toxicity: in Arcangeli 2006, the authors indicated that late toxicity is currently being evaluated and will be reported separately. Late toxicity (including cosmesis) was reported in detail for a subgroup of 214/647 (33%) of women studied (ARCOSEIN). Telangiectasia and pigmentation were worse with concurrent CT/RT but atrophy, fibrosis and lymphoedema did not differ (ARCOSEIN; see Table 7). The women studied did not report worse cosmetic outcome for overall cosmesis, skin colour and scarring with concurrent CT/RT but the physician-reported assessments indicated that cosmetic outcome was worse with concurrent CT/RT (ARCOSEIN; see Table 8);

iii) no cardiac events occurred in the ARCOSEIN trial;

iv) no woman had symptomatic pneumonitis in the ARCOSEIN trial;

v) one woman in each treatment arm developed acute myelogenous leukaemia in the first 18 months after treatment in the ARCOSEIN trial.

- Compliance:

i) ability to deliver the prescribed CT dose (compliance): our arbitrary threshold of the delivery of at least 80% of the prescribed CT was achieved for all women in both trials (OR 0.57; 95% CI 0.35 to 0.92) (Arcangeli 2006; ARCOSEIN) (Analysis 1.3);

ii) ability to deliver the prescribed RT dose (compliance): all patients in both randomised groups in the Arcangeli 2006 trial received 100% of their planned RT, and there was no significant difference in the total dose delivered in both groups in the ARCOSEIN trial.

- Costs: no data.
- QoL: no data.
- Consumer preference: no data.

Radiotherapy followed by chemotherapy versus chemotherapy followed by radiotherapy

For this comparison, anthracyclines but not taxanes were used. One study, including 244 women, was available for this comparison (Bellon 2005). The following results are presented such that an OR or HR of less than 1.0 favoured the group allocated to receive RT first.

- Local recurrence-free survival (ipsilateral): local control was reported but only as first-event data. We are awaiting a reply from the author and will modify future updates of this review when these data have been obtained (as of 18/03/13 this had not been provided).
- Cause-specific survival at five years: no data.
- Overall survival did not differ between the two groups at:

i) five-year follow-up: HR 1.52; 95% CI 0.90 to 2.55 (Bellon 2005);

ii) 10-year follow-up: HR 1.20; 95% CI 0.76 to 1.89 (figures from the text; Bellon 2005).

- Metastasis-free survival did not differ between the two groups when RT then CT versus CT then RT was compared at:

i) 5-follow-up: HR 1.62; 95% CI 1.00 to 2.61 (Bellon 2005);

ii) 11.2-year follow-up: HR 1.08; 95% CI 0.71 to 1.64 (Bellon 2005).

- Relapse-free survival did not differ between the two groups when RT then CT versus CT then RT was compared at:

i) five-year follow-up: HR 1.37; 95% CI 0.88 to 2.14 (Bellon 2005);

ii) 11.2-year follow-up: HR 1.03; 95% CI 0.73 to 1.46 (Bellon 2005).

- Mastectomy rate: no data.
- Harms and toxicity:

i) acute toxicity: neutropenic sepsis was worse with RT then CT, but other measures of acute toxicity (i.e. pneumonia, skin and haematological toxicity) did not differ (see Table 9);

ii) late toxicity: pneumonitis, cosmesis and cellulitis lymphoedema did not differ with RT then CT versus CT then RT (see Table 10).

- Compliance:

i) ability to deliver the prescribed CT dose (compliance): the RT first group received 81% of the planned CT dose, the CT first group received 88% of the planned CT dose (P = 0.01; Bellon 2005);

ii) ability to deliver the prescribed RT dose (compliance): the median RT dose and duration of RT did not differ between the two groups (no P value was reported; Bellon 2005).

- Costs: no data.
- QoL: no data.
- Consumer preference: no data.

DISCUSSION

For women who elect to have breast-conservation surgery for early breast cancer, achieving and maintaining local control and improving survival are of paramount importance. The Early Breast Cancer Trialists' Collaborative Group overview has shown the benefits

of CT and RT as adjuvant treatments (EBCTCG 2011; EBCTCG 2005b) and this review set out to explore whether there is an optimal sequencing of adjuvant CT and RT as part of the conservative management of women with early breast cancer.

Summary of main results

We have been able to include data from three RCTs of two different comparisons of sequencing. The comparisons are concurrent versus sequential treatment (with CT before RT using first-generation chemotherapeutic agents, i.e. no anthracyclines or taxanes) and RT followed by CT versus CT followed by RT (using anthracyclines but no taxanes). In both comparisons the evidence suggests that there are no major differences between the sequencing techniques in regards to mortality and local or distant recurrence. There is some evidence for differences in toxicity between sequencing techniques but most of the harms reported in the trials were not significantly different between the randomised groups and CIs were wide (see Table 6; Table 7; Table 8; Table 9; Table 10). We found that there was disparity between the patient and physician assessment of cosmesis with physicians reporting worse cosmetic outcomes than the women themselves (ARCOSEIN; see Table 8). Others have also reported this difference in the perception of cosmetic outcome (Thomson 2008). No data were available for costs, quality of life or consumer preference. However, caution in interpreting these results is advised as, given the low event rate for some end points such as local recurrence, the statistical power for detecting a clinically important risk difference in such outcomes is very small.

Overall completeness and applicability of evidence

The findings of this review provide reassurance that the general practice of giving CT before RT is not detrimental in terms of overall survival and toxicity in comparison with either the opposite sequence or the concurrent administration of CT and RT. However, some caveats are important in applying these results to current practice. First, the treatments in the included trials were given in the early 2000s on average and the CT regimens may not be considered optimal today. In this case, first-generation chemotherapeutic agents were used (i.e. no anthracyclines or taxanes) in Arcangeli 2006 and ARCOSEIN trials while anthracyclines were used in the Bellon 2005 trial. Second, the surgical outcomes in the trials might be considered unacceptable today. Positive surgical margins are an independent predictor of local recurrence (Leong 2004) but women who had positive surgical margins were eligible for the study of RT followed by CT versus CT followed by RT (Bellon 2005). The standard of practice today would be to try to ensure negative surgical margins were achieved before RT. Finally, although the length of follow-up in the included trials is adequate to detect differences in local recurrences, it is not yet long enough to assess the effects on breast cancer mortality even with 10-year data for two studies (Arcangeli 2006; Bellon 2005). Local recurrence after breast-conserving therapy reaches a peak at about two years (Churn 2001) and continues at one per cent per year for at least the next two decades (Kurtz 1987; Lippman 1995). Distant recurrences and deaths from breast cancer take longer (EBCTCG 2011) and would not have been captured with the relatively short follow-up of these trials. The length of follow-up is also short for evaluation of some late toxicity namely, cardiac and second malignancy.

It has not been possible to answer some questions with this initial version of the review. These include:

1. Harms, costs, patient preferences and impact on the QoL

The treatment-related toxicity differed little between the sequencing techniques. The women treated did not report worse cosmetic outcome with concurrent CT/RT, but the physician-reported outcomes for cosmesis were worse with concurrent CT/RT (Table 8). There was no information regarding the QoL, women's preferences or costs in the included trials. It has been shown that concurrent CT/RT can decrease a woman's QoL but this seems similar to that found with sequential therapy, and there may be an advantage for concurrent therapy arising from its shorter duration (Macquart-Moulin 1999).

2. The impact of new CT regimens and biological agents

The original standard CT regimen of CMF (cyclophosphamide, methotrexate and 5-fluorouracil) has been superseded by anthracycline-based regimens, particularly in high-risk younger women (EBCTCG 2005b). In theory, these regimens should be less toxic than the older regimens if delivered over the same or shorter time period. Taxanes (paclitaxel and docetaxel) are new CT agents that reduce the risk of death when used in the adjuvant setting for women with early breast cancer (Henderson 2003; Martin 2005). There is currently no information regarding the optimum sequencing of RT with taxanes. If taxanes were used sequentially with standard CT agents (Henderson 2003), this would lead to an extended delay in starting RT, which has the potential to increase the local recurrence rate. Reassuringly, in one trial in which RT was delayed by the delivery of paclitaxel, there was a reduction in local recurrence for those women who had undergone breast-conserving therapy and received paclitaxel (Henderson 2003). Furthermore, new agents are continually being developed for treating women with breast cancer (e.g. trastuzumab (Herceptin®) and lapatinib), but the evidence to guide decisions about how these should be sequenced with RT is limited. The delay to start of RT in the included studies was less than seven months (see discussion of Included Studies), more modern chemotherapeutic regimens including taxanes can be delivered within this time frame, assuming no delays in CT delivery.

3. The impact of new modes of RT

New techniques for breast irradiation after breast-conserving surgery are emerging, such as partial breast irradiation using a va-

riety of methods. These techniques generally seek to reduce the amount of normal tissue radiated in order to reduce the incidence of acute and late side effects. However, there is also one completed trial (MA20) examining the role of nodal irradiation after conservative surgery. Early release of data suggest improved disease-free survival with the addition of nodal radiation. The potential impact of this on clinical practice would be to increase the volume of tissue radiated (Whelan 2011). Changes to the fractionation used for RT after conservative surgery should also lead to less time being needed for RT (Whelan 2002). If these techniques are effective, this may allow RT to be delivered quickly and easily, before prolonged courses of CT. There is currently no reliable information regarding the best sequencing of CT with these RT techniques.

4. Concurrent administration of modern CT and RT

The concurrent use of CT and RT minimises any delay in starting RT and the concurrent use of CMF and RT does not appear to affect objectively measured acute or late cosmetic outcomes or complications (Arcangeli 2006; Faul 2003; Lamb 1999). There is some non-randomised evidence that the concurrent use of more modern anthracycline CT and RT is associated with more high-grade skin toxicity and higher hospitalisation rates, which have been deemed by some to be unacceptable (Fiets 2003). We identified one ongoing study, which has completed accrual and has reported in abstract form, which will provide information about the feasibility and effectiveness of concurrent RT and anthracyclines (SECRAB). Finally, some researchers maintain that the concurrent use of RT and paclitaxel is feasible and have reported its use without dose reductions, pneumonitis or brachial plexopathy (Formenti 2003). However, others have reported pneumonitis rates as high as 14% and have concluded that caution is required (Taghian 2001).

Quality of the evidence

We studied 1166 women randomised in three studies with follow-up to 10 years. There is high-quality objective evidence related to the toxicity and cosmetic outcomes when concurrent RT is compared to sequential RT for early breast cancer. There is high-quality evidence that local control and overall survival are similar for concurrent CT and RT, RT followed by CT and CT followed by RT for women with early breast cancer.

Potential biases in the review process

All three studies were at low risk of selection bias. In Arcangeli 2006, lack of blinding for objective outcomes may have introduced lead-time bias. In ARCOSEIN, blinding reduced the risk of bias for the subjective outcomes of cosmesis and toxicity. Blinding was not mentioned in Bellon 2005, which makes the evaluation of objective outcomes (cosmesis and toxicity) at risk of bias. While Arcangeli 2006 and ARCOSEIN were at low risk of bias for attrition, Bellon 2005 was at high risk of bias. As we were not able to review protocols, the risk of selective reporting bias for all three studies was unclear (Figure 2).

Agreements and disagreements with other studies or reviews

We found no other systematic reviews or meta-analyses on this topic.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence from three well-conducted RCTs indicated that local control and overall survival is similar for concurrent CT and RT, RT followed by CT, and CT followed by RT for women with early breast cancer when the RT was commenced within seven months after surgery (as this was the maximum delay in the included studies). These data were based on the use of first-generation chemotherapeutic agents (thus excluding anthracyclines and taxanes) for the comparison of concurrent versus sequential CT.

Implications for research

RCTs are needed to assess the relative effects of sequencing traditional and new RT techniques with new CT regimens and biological therapies, including taxanes and Herceptin. Future trials should collect data on costs, QoL, and patient preference; as well as on local and distant recurrence, cause specific mortality and harms.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Arcangeli 2006

Methods	Accrual: January 1997 to November 2002 Single centre, Italy Randomisation balanced to strata: method not specified Stratified according to tumour diameter, age and lymph node status Baseline: no differences Power calculation
Participants	206 women with breast cancer (pT1-2N0-1M0), who had quadrantectomy and axillary dissection, negative margins, no previous radiotherapy (RT) Aged 18 to 76 years
Interventions	Experimental: concurrent (cyclophosphamide, methotrexate and 5-fluorouracil (CMF) synchronous with RT) Control: sequential (CMF then RT at 7 months) CMF: included cyclophosphamide 600 mg/m^2 intravenously, days 1, 8, every 28 days, 6 cycles RT: 50 Gy/20 fractions + boost 10 Gy/6 fractions Tamoxifen: oestrogen-receptor positive women received tamoxifen for 5 years after completion of CT and RT. 65/106 in the CT/RT arm and 53/100 in the CT then RT arm were oestrogen-receptor positive, but the numbers of women who received tamoxifen were not reported
Outcomes	Primary: breast recurrence-free interval Other: overall survival, locoregional recurrence, distant metastases, toxicity
Notes	Median follow-up: 111 months All randomised patients used in time-to-event analyses First-generation chemotherapeutic agents used (i.e. no anthracyclines or taxanes)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "were randomised" (abstract, paragraph 2) Quote: "were randomised" (methods and materials, paragraph 3, page 162) Quote: "after stratification, patients were assigned to the study group with a balanced randomisation method, to ensure closely balanced patient numbers in each group according to the planned strata" (statistical methods, paragraph 5, page 163)

Allocation concealment (selection bias)	Unclear risk	Not mentioned, uncertain whether done, therefore uncertain risk of bias
Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	Not mentioned, probably not done. There is no information given about follow up in each of the 2 arms, or prescribed intervals for investigations Quote: "Baseline mammogram was obtained in the first year after RT" (paragraph 15, page 67) This may cause a high risk of bias, e.g. if unblinded investigators performed investigations (mammograms or bone scans) at different time intervals for women in different arms, it could introduce lead time bias
Blinding of participants and personnel (performance bias) Objective outcomes	Unclear risk	Not mentioned, but not possible to do, as the 2 treatment arms differed greatly, probably of little consequence for objective outcomes, and as there were no patient-related outcomes, it is unlikely to be a high risk of bias
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	Cosmetic outcome was patient-assessed (not possible to blind). This is unlikely to have introduced bias
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	Not mentioned, probably not done, it would be difficult to do given the differences in the treatment arms. Unlikely to be a high risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	N = 206 Arm 1 = 106 Arm 2 = 100 All patients included in the analysis None lost to follow-up
Selective reporting (reporting bias)	Unclear risk	**Outcomes specified in the methods/protocol:** 1. breast recurrence-free survival 2. overall survival 3. loco-regional recurrence 4. distant metastases 5. toxicity (using European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group (EORTC/RTOG) scoring system) 6. whether or how concurrent

		chemotherapy (CT) administration was influenced by RT 7. whether or how RT administration influenced by concurrent CT 8. cosmetic result **Outcomes actually reported in the paper:** 1. breast recurrence-free survival 2. metastasis-free survival 3. distant failure 4. overall survival 5. site of first recurrence 6. numbers of events in each group 7. breast recurrences 8. nodal recurrences 9. distant metastases 10. contralateral breast cancer or second primary other site 11. toxicity - acute local toxicity (not quantified) 12. RT compliance, dose delivered, any breaks in RT 13. CT compliance, number of cycles received, mean dose intensity We were unable to review the protocol, therefore it has been designated as unclear risk of bias

ARCOSEIN

Methods	Accrual: March 1996 to May 2000 Multicentre, France Patients were stratified according to axillary status Randomisation method not specified Baseline imbalances: the 2 groups were balanced regarding age, stage, performance status, histology, hormonal receptors, tumour margins, in situ components and axillary status
Participants	647 women who had breast-conserving surgery for breast cancer Median age: experimental group 58.6 years, control group 49.5 years
Interventions	Experimental: chemotherapy (CT) plus radiotherapy (RT) concurrently Control: CT followed by RT sequentially CT: 5-fluorouracil 500 mg/m^2, mitoxantrone 12 mg/m^2, cyclophosphamide 500 mg/m^2: 6 cycles given at 21 days Post- or peri-menopausal women with oestrogen-receptor-positive tumours or progesterone-receptor-positive tumours (or both) received tamoxifen; this was started during or after RT at the discretion of the treating physician. 171/352 women in the CT/RT arm and 160/343 women in the CT followed by RT arm received tamoxifen RT: 50 Gy with or without 10 to 20 Gy boost to tumour bed. Boost given if there were

ARCOSEIN (*Continued*)

	factors for local recurrence (not specified): given during cycles 1 to 3 of CT (experimental) or after CT (control)
Outcomes	Local and regional recurrences, distant metastases, secondary cancers, overall survival, acute toxicity, protocol adherence, antitumour effects
Notes	Median follow-up: 60 months First-generation chemotherapeutic agents used (i.e. no anthracyclines or taxanes)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of generating randomisation sequence was not specified Quote: "phase III randomised" (abstract, paragraph 1, page 405) Quote: "were randomly assigned"
Allocation concealment (selection bias)	Low risk	Concealment of randomisation was not specified, but appears to have been central, so probably was concealed Quote: "random assignment was performed at the Biostatistics Unit at .." (patients and methods, paragraph 11, page 406)
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Not mentioned, probably not done, unlikely to have introduced bias as no patient-reported outcomes included
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Not mentioned, probably not done, unlikely to have introduced bias, it would be difficult to blind personnel, given the nature of the interventions. Unlikely to be a source of bias
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	Quote: "..the Physician in charge of the evaluation did not have knowledge of the patient's (self) assessment was kept blinded to treatment arm" (methods and materials, paragraph 17, page 67). This makes the assessment of subjective outcomes such as cosmesis at low risk of bias
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Blinding not mentioned, but risk of bias reduced by having pre-specified time points for clinical examination and mammography

		Quote: "all patients were monitored routinely for at least five years after RT. Our follow-up consisted of a twice-yearly clinical examination, and an annual mammogram" (paragraph 14, page 67)
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	i) Cosmetic outcome assessment blinded to treatment arm Quote: "toxicity assessment, blinded to treatment allocation…" (paragraph 16, page 67) Quote: "To avoid bias, the physician in charge of the evaluation (A.H.T.) did not have knowledge of the patient's assessment and was kept blinded to the treatment arm" (paragraph 19, page 67) Cosmetic outcome assessed by a blinded doctor, therefore there was low risk of bias with this objective outcome ii) Late toxicity: assessment was blinded to treatment allocation iii) Quote: "this toxicity assessment, blinded to treatment allocation" (paragraph 15, page 67)
Incomplete outcome data (attrition bias) All outcomes	Low risk	CT plus RT arm: 15 women found to be ineligible and excluded CT followed by RT arm: 6 found ineligible CT plus RT arm: 10 women lost to follow-up CT followed by RT arm: 3 lost to follow-up 716 women were randomised, 352 in the CT plus RT arm and 343 in the CT followed by RT arm were included in the analysis. The primary end point (disease-free survival) was an intention-to-treat analysis so 358 women were analysed for this end point in each arm. The authors described the reasons the women were found to be ineligible, it was felt to be at low risk of bias
Selective reporting (reporting bias)	Unclear risk	**Outcomes specified in the methods/protocol** Primary end point: 1. disease-free survival Secondary end point: 1. incidence of adverse effects 2. cosmesis

		3. overall survival **Outcomes actually reported in the paper:** 1. compliance 2. median CT dose 3. median time to complete CT 4. dose-intensity of CT 5. RT dose 6. RT interruptions 7. acute toxicity (oesophagitis, acute systemic symptoms, nausea/vomiting, anaemia) 8. late toxicity (subcutaneous fibrosis, telangiectasia, skin pigmentation, breast atrophy, pain, breast oedema, lymphoedema, acute myeloid leukaemia) 9. disease-free survival at 5 years 10. local recurrence-free survival 11. metastasis-free survival 12. overall survival 13. rates of death 14. local recurrence 15. regional or distant metastases as first site of recurrence 16. breast cancer deaths 17. alive, no evidence of disease We were not able to review the protocol

Bellon 2005

Methods	Accrual: June 1984 to October 1992 Multicentre, USA Randomisation method not specified Stratified by: number of nodes involved, menopausal status Baseline imbalances: radiotherapy (RT) first group had more patients with tumour size 1 to 2 cm and intraductal component. Had fewer patients with boost dose of 16 Gy or higher Power calculation
Participants	244 women with stage I or II breast cancer who had undergone conservative therapy (excision of all gross disease and level I/II axillary dissection) Aged 20 to 68 years
Interventions	Experimental: RT then chemotherapy (CT) Control: CT then RT CT: CAMFP 4 cycles, given every 21 days (cyclophosphamide 500 mg/m^2, doxorubicin 45 mg/m^2, methotrexate 40 mg/m^2, 5-fluorouracil 500 mg/m^2, prednisone 40 mg/m^2, leucovorin 10 mg/m^2, orally, 4 times per day, days 2 to 4) Initially, no women was to receive tamoxifen, but in September 1988, a protocol amend-

	ment was made, so that all women with oestrogen-receptor-positive tumours were to receive tamoxifen for 5 years (after completion of all CT and RT). 7/122 women in the RT then CT arm and 11/122 women in the CT then RT arm received tamoxifen RT: 45 Gy/25 fractions + 16- to 18-Gy boost
Outcomes	Overall survival (10 years), event-free survival, local recurrence, distant/regional recurrence. Toxicity outcomes (cardiac events, lymphoedema and brachial plexopathy) reported as retrospective data from chart review
Notes	Median follow-up: 135 months (range 17 to 196) No taxanes were used

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details about method of random sequence generation given. Quote: "prospective randomised trial" (abstract, page 1934) Quote: "were randomly assigned" (abstract, paragraph 2, page 1934) Quote: "were randomly assigned" (patients and methods, paragraph 3, page 1935)
Allocation concealment (selection bias)	Low risk	It was not specified that allocation was concealed, but it probably was, therefore at low risk of bias. Quote: "patients were registered centrally" (statistical analysis, paragraph 5, page 1357)
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Not mentioned, probably not done. It would be quite difficult to do, given the differences in the treatment arms. Probably not important, as no patient-reported outcomes
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Not mentioned, probably not done. It would be quite difficult to do, given the differences in the treatment arms. Probably not important
Blinding of outcome assessment (detection bias) Objective outcomes	High risk	Not mentioned, probably not done. This may introduce bias, especially in assessment of toxicity. No pre-specified follow-up schedule or investigations schedule, which may introduce bias in detection of local recurrence and distant metastases

Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Quote: "cosmetic outcome assessed in patients without recurrence who were seen in follow up by a radiation oncologist..." There is no mention of blinding of the radiation oncologist who evaluated cosmesis, which make these findings at high risk of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	RT then CT arm: 4 lost to follow-up CT then RT arm: 5 lost to follow-up Comment that intention-to-treat analysis performed, but see from Table 2, that smaller numbers were available for evaluation at 5 years, which suggests there was a large amount of attrition in addition to the numbers
Selective reporting (reporting bias)	Low risk	**Outcomes specified in the methods/protocol** 1. time to first recurrence 2. time to distant metastases 3. overall survival 4. contralateral breast cancer 5. second non-breast cancer primary 6. local recurrence 7. distant metastases 8. local recurrence 9. regional recurrence 10. other failures (contralateral breast cancer, other primaries (non-breast cancer), death from other causes **Outcomes actually reported in the paper:** 1. distant metastases and freedom from distant metastases 2. deaths 3. any recurrence 4. overall survival 5. time to first recurrence 6. time to distant recurrence 7. site of first recurrence 8. local recurrence 9. breast cancer recurrence 10. contralateral breast cancer 11. second (non-breast cancer) malignancy 12. median dose CT delivered 13. median time required to complete

Bellon 2005 (*Continued*)

		CT 14. median RT dose 15. median duration RT 16. acute toxicity 17. haematological 18. fever or neutropenia requiring hospitalisation 19. pneumonia pneumonitis 20. moist/extensive desquamation 21. cosmesis assessed in cohort of 39 women seen at the joint centre The protocol was not reviewed

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

Study	Reason for exclusion
Assersohn 1999	Did not compare sequences of adjuvant radiotherapy and adjuvant chemotherapy, as required by our inclusion criteria
Bellantone 1998	Did not compare sequences of adjuvant radiotherapy and adjuvant chemotherapy, as required by our inclusion criteria. Treatments were given before surgery rather than after surgery, as required by our inclusion criteria
Bellon 2004	Not a randomised trial
Blomqvist 1992	Did not compare sequences of adjuvant radiotherapy and adjuvant chemotherapy, as required by our inclusion criteria
Buzdar 1993	Not a randomised trial
Cakir 2003	Not a randomised trial
Denham 1995	Not a randomised trial
Donato 2004	Did not compare sequences of adjuvant radiotherapy and adjuvant chemotherapy in post-surgery patients with early stage breast cancer, as required by our inclusion criteria
Dubey 1999	Not a randomised trial
Faul 1998	Not a randomised trial
Faul 2003	Not a randomised trial
Fiets 2003	Not a randomised trial
Garcia 1996	Not a randomised trial

(*Continued*)

Hartsell 1995	Not a randomised trial
Hasbini 2000	Not a randomised trial
Isaac 2002	Not a randomised trial
Kim 2010	Surgery involved mastectomy
Lamb 1999	Not a randomised trial
Leonard 1995	Not a randomised trial
Recht 1991	Not a randomised trial
Rouesse 2002	Randomised trial, but confounded by different chemotherapy regimens in the 2 study groups
Rubens 1980	Not a randomised trial
Sauer 1996	Not a randomised trial
Stemmer 2003	Not a randomised trial
Wallgren 1996	Sequences of adjuvant chemotherapy and adjuvant radiotherapy were not consistent with our inclusion criteria
Warner 1998	Did not compare sequences of adjuvant radiotherapy and adjuvant chemotherapy, as required by our inclusion criteria
Zambetti 1999	Not a randomised trial

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

SECRAB

Methods	Multicentred randomised controlled trial
Participants	Women with histological diagnosis of invasive breast cancer who had undergone wide local excision or mastectomy
Interventions	Sequential chemotherapy/radiotherapy and 'sandwich' chemotherapy/radiotherapy/chemotherapy
Outcomes	Primary end point: local recurrence at 5 years Secondary end points: distant metastases; relapse rates; overall survival at 5, 10 and 15 years. A sample of 300 will be studied for toxicity, cosmesis and quality of life
Notes	ISRCTN 84214355 Multicentred randomised controlled trial Setting: UK Accrual completed

DATA AND ANALYSES

Comparison 1. Concurrent versus sequential (chemotherapy first)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Local recurrence-free survival	1		Hazard Ratio (95% CI)	Subtotals only
1.1 Local recurrence-free survival at 5 years	1	0	Hazard Ratio (95% CI)	0.96 [0.14, 6.82]
1.2 Local recurrence-free survival at 10 years	1	0	Hazard Ratio (95% CI)	1.05 [0.30, 3.62]
2 Relapse-free survival	2		Hazard Ratio (95% CI)	Subtotals only
2.1 Relapse-free survival HR at 5 years	2	0	Hazard Ratio (95% CI)	0.98 [0.84, 1.15]
3 Compliance with chemotherapy	2	901	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.35, 0.92]
4 Overall survival	2		Hazard Ratio (95% CI)	Subtotals only
4.1 Overall survival at five years	2	901	Hazard Ratio (95% CI)	0.97 [0.83, 1.13]
5 Metastasis-free survival	2		Hazard Ratio (95% CI)	Subtotals only
5.1 Metastasis-free survival at 5 years	2	0	Hazard Ratio (95% CI)	0.86 [0.60, 1.24]
5.2 Metastasis-free survival at 10 years	1	0	Hazard Ratio (95% CI)	0.57 [0.20, 1.62]

Comparison 2. Radiotherapy then chemotherapy versus chemotherapy then radiotherapy

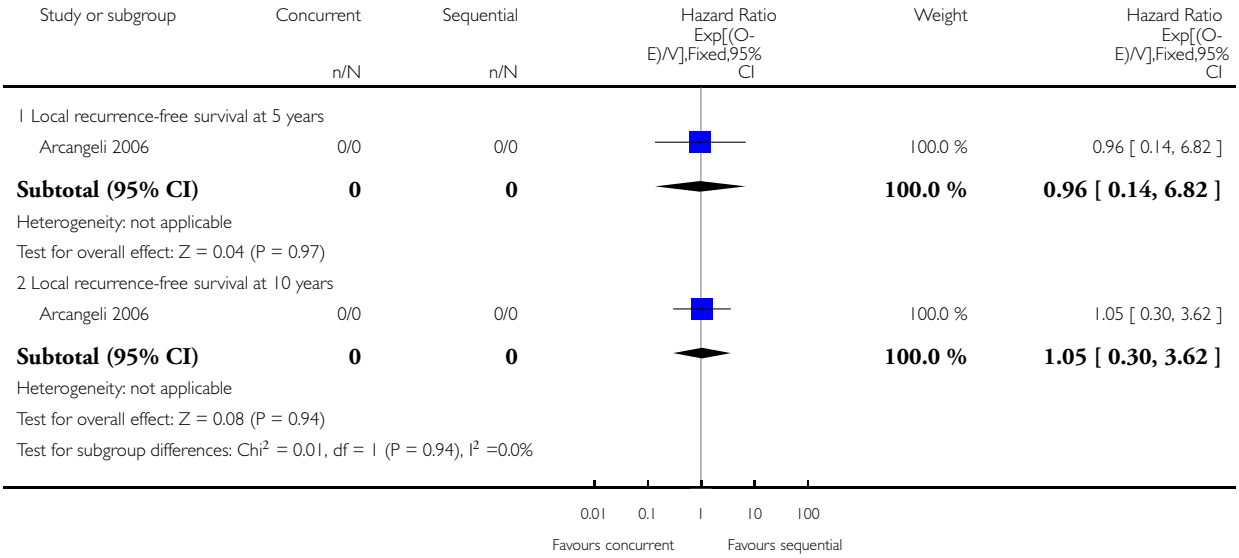
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	1		Hazard Ratio (95% CI)	Subtotals only
1.1 Overall survival at 5 years	1	0	Hazard Ratio (95% CI)	1.52 [0.90, 2.55]
1.2 Overall survival at 10 years	1	0	Hazard Ratio (95% CI)	1.20 [0.76, 1.89]
2 Metastasis-free survival	1		Hazard Ratio (95% CI)	Subtotals only
2.1 Distant metastases at 5 years	1	0	Hazard Ratio (95% CI)	1.62 [1.00, 2.61]
2.2 Distant metastases at 10 years	1	0	Hazard Ratio (95% CI)	1.08 [0.71, 1.64]
3 Relapse-free survival	1		Hazard Ratio (95% CI)	Subtotals only
3.1 Relapse-free survival at 5 years	1	0	Hazard Ratio (95% CI)	1.37 [0.88, 2.14]
3.2 Relapse-free survival at 10 years	1	0	Hazard Ratio (95% CI)	1.03 [0.73, 1.46]
4 Cosmesis	1	77	Odds Ratio (M-H, Fixed, 95% CI)	1.30 [0.51, 3.31]

Analysis 1.1. Comparison 1 Concurrent versus sequential (chemotherapy first), Outcome 1 Local recurrence-free survival.

Review: Sequencing of chemotherapy and radiotherapy for early breast cancer

Comparison: 1 Concurrent versus sequential (chemotherapy first)

Outcome: 1 Local recurrence-free survival



Analysis 1.2. Comparison 1 Concurrent versus sequential (chemotherapy first), Outcome 2 Relapse-free survival.

Review: Sequencing of chemotherapy and radiotherapy for early breast cancer

Comparison: 1 Concurrent versus sequential (chemotherapy first)

Outcome: 2 Relapse-free survival

Study or subgroup	Concurrent n/N	Sequential n/N	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI
1 Relapse-free survival HR at 5 years					
Arcangeli 2006	0/0	0/0		5.0 %	1.00 [0.49, 2.04]
ARCOSEIN	0/0	0/0		95.0 %	0.98 [0.83, 1.16]
Subtotal (95% CI)	**0**	**0**		**100.0 %**	**0.98 [0.84, 1.15]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.96); I^2 =0.0%					
Test for overall effect: Z = 0.21 (P = 0.83)					
Test for subgroup differences: Not applicable					

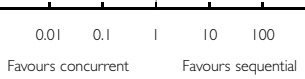
Analysis 1.3. Comparison 1 Concurrent versus sequential (chemotherapy first), Outcome 3 Compliance with chemotherapy.

Review: Sequencing of chemotherapy and radiotherapy for early breast cancer

Comparison: 1 Concurrent versus sequential (chemotherapy first)

Outcome: 3 Compliance with chemotherapy

Study or subgroup	Concurrent n/N	Sequential n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Arcangeli 2006	99/106	95/100		14.1 %	0.74 [0.23, 2.43]
ARCOSEIN	309/352	319/343		85.9 %	0.54 [0.32, 0.91]
Total (95% CI)	**458**	**443**		**100.0 %**	**0.57 [0.35, 0.92]**
Total events: 408 (Concurrent), 414 (Sequential)					
Heterogeneity: Chi^2 = 0.24, df = 1 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 2.31 (P = 0.021)					
Test for subgroup differences: Not applicable					



Analysis 1.4. Comparison 1 Concurrent versus sequential (chemotherapy first), Outcome 4 Overall survival.

Review: Sequencing of chemotherapy and radiotherapy for early breast cancer

Comparison: 1 Concurrent versus sequential (chemotherapy first)

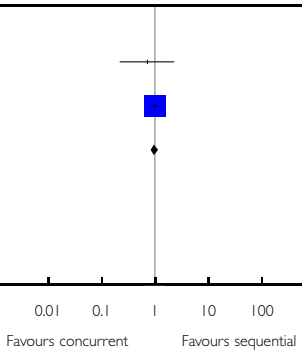
Outcome: 4 Overall survival

Study or subgroup	Concurrent n/N	Sequential n/N	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI
1 Overall survival at five years					
Arcangeli 2006	0/106	0/100		1.8 %	0.71 [0.22, 2.25]
ARCOSEIN	0/352	0/343		98.2 %	0.98 [0.83, 1.14]
Subtotal (95% CI)	**458**	**443**		**100.0 %**	**0.97 [0.83, 1.13]**

Heterogeneity: $Chi^2 = 0.29$, df = 1 (P = 0.59); $I^2 = 0.0\%$

Test for overall effect: Z = 0.38 (P = 0.70)

Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1 Concurrent versus sequential (chemotherapy first), Outcome 5 Metastasis-free survival.

Review: Sequencing of chemotherapy and radiotherapy for early breast cancer

Comparison: 1 Concurrent versus sequential (chemotherapy first)

Outcome: 5 Metastasis-free survival

Study or subgroup	Concurrent n/N	Sequential n/N	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI
1 Metastasis-free survival at 5 years					
Arcangeli 2006	0/0	0/0		10.5 %	0.66 [0.21, 2.04]
ARCOSEIN	0/0	0/0		89.5 %	0.89 [0.60, 1.31]
Subtotal (95% CI)	**0**	**0**		**100.0 %**	**0.86 [0.60, 1.24]**
Heterogeneity: Chi^2 = 0.24, df = 1 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 0.80 (P = 0.42)					
2 Metastasis-free survival at 10 years					
Arcangeli 2006	0/0	0/0		100.0 %	0.57 [0.20, 1.62]
Subtotal (95% CI)	**0**	**0**		**100.0 %**	**0.57 [0.20, 1.62]**
Heterogeneity: not applicable					
Test for overall effect: Z = 1.06 (P = 0.29)					
Test for subgroup differences: Chi^2 = 0.54, df = 1 (P = 0.46), I^2 =0.0%					

Analysis 2.1. Comparison 2 Radiotherapy then chemotherapy versus chemotherapy then radiotherapy, Outcome 1 Overall survival.

Review: Sequencing of chemotherapy and radiotherapy for early breast cancer

Comparison: 2 Radiotherapy then chemotherapy versus chemotherapy then radiotherapy

Outcome: 1 Overall survival

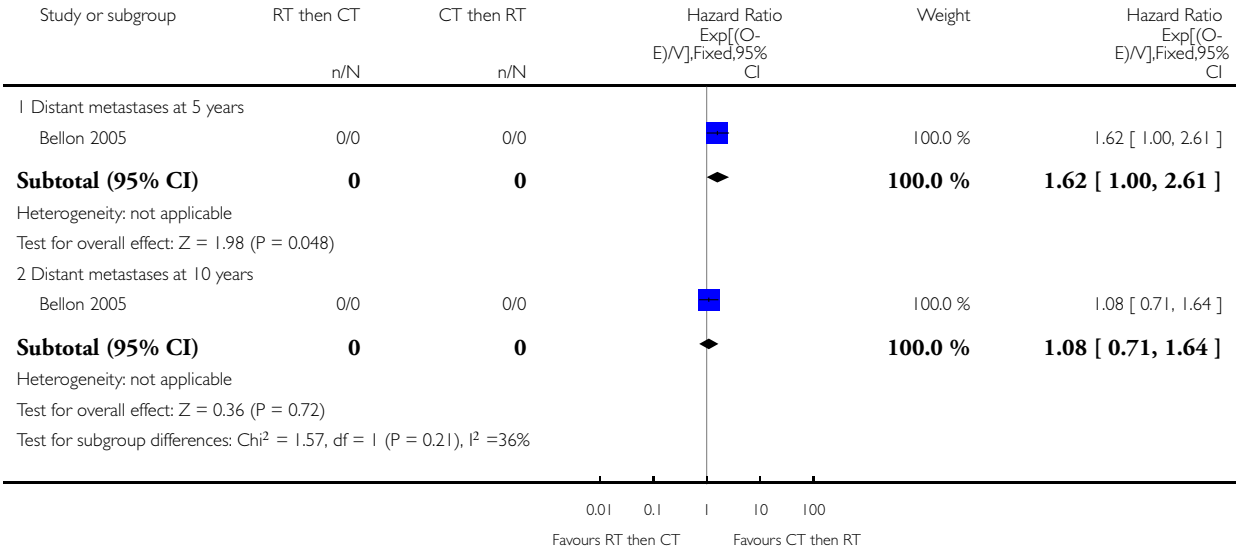
Study or subgroup	RT then CT n/N	CT then RT n/N	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Hazard Ratio Exp[(O-E)/V],Fixed,95% CI
1 Overall survival at 5 years					
Bellon 2005	0/0	0/0		100.0 %	1.52 [0.90, 2.55]
Subtotal (95% CI)	**0**	**0**		**100.0 %**	**1.52 [0.90, 2.55]**
Heterogeneity: not applicable					
Test for overall effect: Z = 1.58 (P = 0.11)					
2 Overall survival at 10 years					
Bellon 2005	0/0	0/0		100.0 %	1.20 [0.76, 1.89]
Subtotal (95% CI)	**0**	**0**		**100.0 %**	**1.20 [0.76, 1.89]**
Heterogeneity: not applicable					
Test for overall effect: Z = 0.79 (P = 0.43)					
Test for subgroup differences: Chi^2 = 0.45, df = 1 (P = 0.50), I^2 =0.0%					

Analysis 2.2. Comparison 2 Radiotherapy then chemotherapy versus chemotherapy then radiotherapy, Outcome 2 Metastasis-free survival.

Review: Sequencing of chemotherapy and radiotherapy for early breast cancer

Comparison: 2 Radiotherapy then chemotherapy versus chemotherapy then radiotherapy

Outcome: 2 Metastasis-free survival

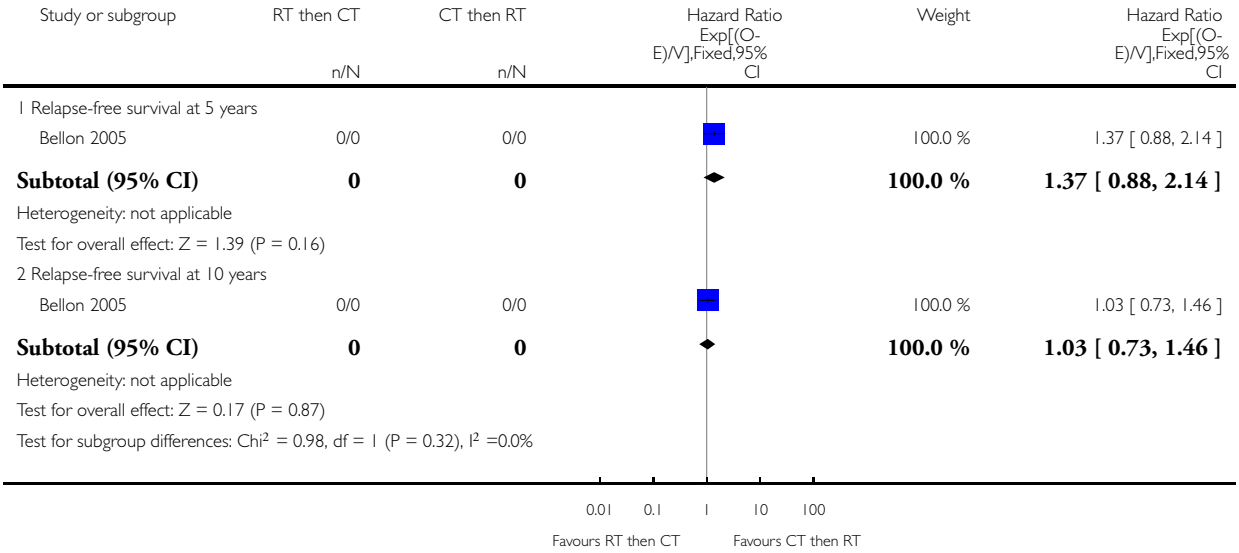


Analysis 2.3. Comparison 2 Radiotherapy then chemotherapy versus chemotherapy then radiotherapy, Outcome 3 Relapse-free survival.

Review: Sequencing of chemotherapy and radiotherapy for early breast cancer

Comparison: 2 Radiotherapy then chemotherapy versus chemotherapy then radiotherapy

Outcome: 3 Relapse-free survival

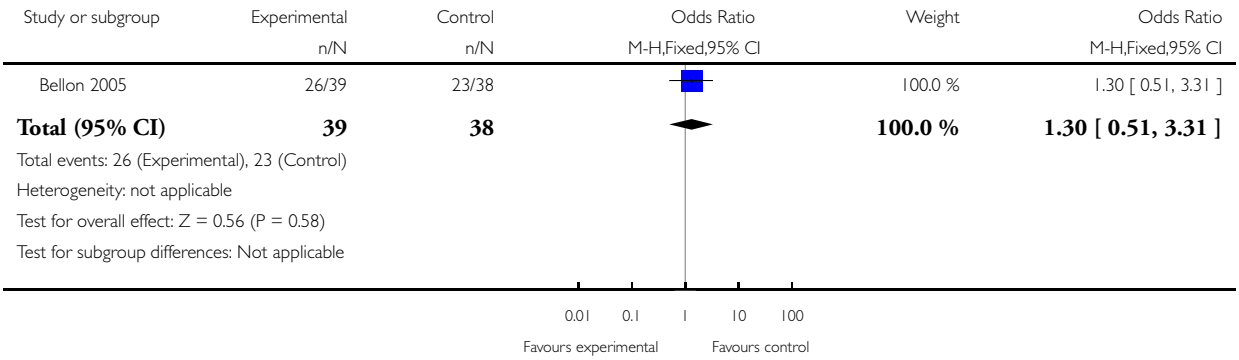


Analysis 2.4. Comparison 2 Radiotherapy then chemotherapy versus chemotherapy then radiotherapy, Outcome 4 Cosmesis.

Review: Sequencing of chemotherapy and radiotherapy for early breast cancer

Comparison: 2 Radiotherapy then chemotherapy versus chemotherapy then radiotherapy

Outcome: 4 Cosmesis



ADDITIONAL TABLES

Table 1. Harris's classification

Cosmetic score
Excellent
Good
Fair
Poor

Table 2. LENT/SOMA scoring scale

Type of outcome	Category	Grade 1	Grade 2	Grade 3	Grade 4
Subjective	Pain	Occasional and minimal, hypersensation, pruritus	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Objective	Oedema	Asymptomatic	Symptomatic	Secondary dysfunction	-

Table 2. LENT/SOMA scoring scale (*Continued*)

	Fibrosis	Barely palpable, increased density	Definite increased density and firmness	Very marked increased density, retraction and fixation	-
	Telangiectasia	< 1 cm^2	1 to 4 cm^2	> 4 cm^2	-
	Lymphoedema	2 to 4 cm	> 4 to 6 cm	> 6 cm	Useless arm
	Atrophy/retraction	10% to 25%	> 25% to 40%	> 40% to 75%	Whole breast
	Ulcer	Epidermal only $\leq$ 1 cm^2	Dermal > 1 cm	Subcutaneous	Bone exposed/ necrosis
Management	Pain	Occasional, non-narcotic	Regular narcotic	Regular narcotic medical intervention	Surgical intervention
	Oedema	-	-	Medical intervention	Surgical intervention/mastectomy
	Lymphoedema arm	-	Elevate arm, elastic stocking	Compression wrapping, intensive physiotherapy	Surgical intervention/amputation
	Atrophy	-			Surgical intervention/mastectomy
	Ulcer	-	Medical intervention	Surgical intervention/debridement	Surgical intervention/mastectomy
Analytic	Photographic assessment of skin change	Yes/no	Date:	-	-
	Tape measurement of breast size and arm diameter	Yes/no	Date:	-	-
	Mammogram assessment of skin thickness and density	Yes/no	Date:	-	-
Yes/no	Date: computer tomography/magnetic resonance imaging assessment of size, fat atrophy, fibrosis	Yes/no	Date:	-	-

Table 3. Pigmentation scoring scale

Pigmentation scoring scale
Excellent
Good
Moderate
Poor
Very poor

Table 4. Harris's classification modified by Beadle cosmetic scale

Cosmetic score
Excellent
Good
Acceptable
Poor
Very poor

Table 5. LENT-SOMA cosmetic outcome assessment

Category	Description
Very poor	Very marked density, retraction, fixation and breast asymmetry 40% to 75%
Poor	Marked distortion of nipple, breast asymmetry 25% to 40%, marked contour difference, severe hyperpigmentation, severe oedema, marked mammillary deviation
Acceptable	Moderate distortion of nipple, absent nipple-areola complex, breast asymmetry 10% to 25%, telangiectasia, moderate hyperpigmentation, increased density and firmness, slight oedema, prominent scar with surrounding retraction/volume loss, moderate contour difference, moderate mammillary deviation
Good	Minimal differences between treated and untreated breast, slight distortion of nipple, mild hyperpigmentation, breast asymmetry < 10%, mild telangiectasia
Very good	Treated breast looks almost identical to untreated breast, perfect symmetry, no visible distortion

Table 6. Acute toxicity: concurrent versus sequential

Type of toxicity	Trials	Concurrent	Sequential	OR (95% CI)
Anaemia	ARCOSEIN	111/352	81/358	1.54 (1.10 to 2.15)
Grade II/IV skin	ARCOSEIN	13/107	11/107	1.21 (0.51 to 2.83)
Grade III/IV infection	ARCOSEIN	1/107	3/107	0.33 (0.03 to 3.20)
Grade III/IV neutropenia	ARCOSEIN	19/107	25/107	0.71 (0.36 to 1.38)
Nausea or vomiting	ARCOSEIN	235/352	248/343	0.77 (0.56 to 1.06)
Grade III/IV oesophagitis	ARCOSEIN	3/107	0/107	7.20 (0.37 to 141.12)

CI: confidence interval; OR: odds ratio.

Table 7. Late Grade III/IV toxicity: concurrent versus sequential

Toxicity type	Study	Concurrent	Sequential	OR (95% CI)
Atrophy	ARCOSEIN	19/107	10/107	2.09 (0.92 to 4.75)
Telangiectasia	ARCOSEIN	17/107	5/107	3.85 (1.37 to 10.87)
Fibrosis	ARCOSEIN	6/107	0/107	13.77 (0.77 to 247.54)
Lymphoedema	ARCOSEIN	2/107	1/107	2.02 (0.18 to 22.61)
Pigmentation	ARCOSEIN	12/105	1/106	13.55 (1.73 to 106.19)

CI: confidence interval; OR: odds ratio.

Table 8. Late toxicity (cosmesis): concurrent versus sequential

Cosmetic outcome	Study	Concurrent	Sequential	Physician-reported OR (95% CI)	Participant-reported OR (95% CI)
Bad or very bad overall cosmesis	ARCOSEIN	Physician 43/107 Participant 9/107	Physician 16/107 Participant 8/107	3.82 (1.98 to 7.37)	1.14 (0.42 to 3.07)
Poor/very poor skin colour	ARCOSEIN	Physician 14/107 Participant 3/107	Physician 1/107 Participant 1/107	15.96 (2.06 to 123.68)	3.06 (0.31 to 29.87)

Table 8. Late toxicity (cosmesis): concurrent versus sequential (*Continued*)

Poor/very poor scar	ARCOSEIN	Physician 24/107 Participant 17/107	Physician 15/107 Participant 12/107	1.77 (0.87 to 3.61)	1.50 (0.68 to 3.31)

CI: confidence interval; OR: odds ratio.

Table 9. Acute toxicity: RT then CT versus CT then RT

Toxicity type	Study	RT then CT	CT then RT	OR (95% CI)
Neutropenic sepsis	Bellon 2005	21/122	8/122	2.96 (1.26 to 6.98)
Pneumonia		6/122	1/122	6.26 (0.74 to 52.79)
Haemoglobin (CTC Grade III/IV)		3/114	4/120	0.78 (0.17 to 3.58)
Platelet (CTC Grade III/IV)		0/114	3/120	0.15 (0.01 to 2.87)
Skin (CTC Grade III/IV)		17/115	12/112	1.45 (0.66 to 3.18)

CI: confidence interval; CT: chemotherapy; CTC: common toxicity criteria; OR: odds ratio; RT: radiotherapy.

Table 10. Late toxicity: RT then CT versus CT then RT

Toxicity type	Study	RT then CT	CT then RT	OR (95% CI)
Pneumonitis	Bellon 2005	5/122	0/122	11.47 (0.63 to 209.70)
Cosmesis		26/39	23/38	1.30 (0.51 to 3.31)
Cardiac		0/113	0/118	
Cellulitis		6/117	3/119	2.09 (0.051 to 8.56)
Lymphoedema		8/117	4/119	2.11 (0.67 to 7.21)
Brachial plexopathy		1/42	0/43	3.14 (0.12 to 79.39)

CI: confidence interval; CT: chemotherapy; OR: odds ratio; RT: radiotherapy.

APPENDICES

Appendix 1. MEDLINE search strategy

1. RANDOMIZED CONTROLLED TRIAL.pt
2. CONTROLLED CLINICAL TRIAL.pt
3. RANDOMIZED CONTROLLED TRIALS.sh
4. RANDOM ALLOCATION.sh
5. DOUBLE BLIND METHOD.sh
6. SINGLE BLIND METHOD.sh
7. 1 or 2 or 3 or 4 or 5 or 6
8. (ANIMALS not HUMAN).sh
9. 7 not 8
10. CLINICAL TRIAL.pt
11. exp CLINICAL TRIALS/
12. (clin$ adj25 trial$).ti,ab
13. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab
14. PLACEBOS.sh
15. placebo$.ti,ab
16. random$.ti,ab
17. RESEARCH DESIGN.sh
18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 18 not 8
20. 19 not 9
21. 9 or 20
22. Breast Neoplasms.me
23. breast cancer.ti,ab,sh,kw
24. breast tumour.ti,ab,sh,kw
25. Mamm$ near Carcinoma.kw,sh,sb
26. Carcinoma, Ductal, Breast.mp
27. 22 or 23 or 24 or 25 or 26
28. Chemotherapy, adjuvant.me
29. adjuvant chemotherapy.kw,sh,ti,ab
30. Antineoplastic Combined Chemotherapy Protocols
31. Breast Neoplasms/dt
32. cyclophosphamide/tu
33. Doxorubicin/tu
34. Methotrexate/tu
35. fluorouracil/tu
36. Carcinoma, Ductal, Breast/dt
37. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. radiotherapy, adjuvant.me
39. radiotherapy.sh,kw,ti,ab
40. radiation therapy.sh,kw,ti,ab
41. Breast Neoplasms/rt
42. Carcinoma, Ductal, Breast/rt
43. 38 or 39 or 40 or 41 or 42
44. exp MASTECTOMY, SUBCUTANEOUS/
45. exp MASTECTOMY, MODIFIED RADICAL/
46. mastectomy.mp
47. exp MASTECTOMY, EXTENDED RADICAL/
48. exp MASTECTOMY, SEGMENTAL/
49. MASTECTOMY, RADICAL/

50. exp MASTECTOMY/
51. exp MASTECTOMY, SIMPLE
52. Breast neoplasms/su
53. mastectomy.kw,ab,ti,sh.
54. lumpectomy.kw,ab,ti,sh
55. wide local excision.kw,ab,ti,sh
56. quadrantectomy.kw,ab,ti,sh.
57. Neoplasm Recurrence, Local/su
58. 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56
59. 21 and 27 and 37 and 43 and 58

Appendix 2. EMBASE search strategy

#45 #44 AND [humans]/lim AND [embase]/lim AND [2008-2011]/py
#44 #8 AND #20 AND #28 AND #32 AND #43
#43 #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42
#42 'quadrantectomy'/exp OR quadrantectomy
#41 wide AND local AND ('excision'/exp OR excision)
#40 'lumpectomy'/exp OR lumpectomy
#39 simple AND ('mastectomy'/exp OR mastectomy)
#38 modified AND ('radical'/exp OR radical) AND ('mastectomy'/exp OR mastectomy)
#37 'radical'/exp OR radical AND ('mastectomy'/exp OR mastectomy)
#36 segmental AND ('mastectomy'/exp OR mastectomy)
#35 extended AND ('radical'/exp OR radical) AND ('mastectomy'/exp OR mastectomy)
#34 'subcutaneous'/exp OR subcutaneous AND ('mastectomy'/exp OR mastectomy)

(*Continued*)

#33 'mastectomy'/exp OR mastectomy
#32 #29 OR #30 OR #31
#31 'radiation'/exp OR radiation AND ('therapy'/exp OR therapy)
#30 'adjuvant'/exp OR adjuvant AND ('radiotherapy'/exp OR radiotherapy)
#29 'radiotherapy'/exp OR radiotherapy
#28 #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
#27 'fluorouracil'/exp OR fluorouracil
#26 'methotrexate'/exp OR methotrexate
#25 'doxorubicin'/exp OR doxorubicin
#24 'cyclophosphamide'/exp OR cyclophosphamide
#23 antineoplastic AND combined AND ('chemotherapy'/de OR chemotherapy) AND protocols
#22 'adjuvant'/exp OR adjuvant AND ('chemotherapy'/exp OR chemotherapy)
#21 'chemotherapy'/exp OR chemotherapy
#20 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#19 early NEAR/6 breast AND tumor*
#18 early NEAR/6 breast AND tumour*

(*Continued*)

#17 early NEAR/6 breast AND carcinoma*
#16 early NEAR/6 breast AND neoplas*
#15 early NEAR/6 breast AND cancer*
#14 locally AND advance* NEAR/6 breast AND tumor*
#13 locally AND advance* NEAR/6 breast AND tumour*
#12 locally AND advance* NEAR/6 breast AND carcinoma*
#11 locally AND advance* NEAR/6 breast AND neoplas*
#10 locally AND advance* NEAR/6 breast AND cancer*
#9 'breast'/exp AND 'neoplasm'/exp
#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#7 groups:ab
#6 trial:ab
#5 randomly:ab
#4 placebo:ab
#3 randomi*ed:ab
#2 controlled AND clinical AND trial

(*Continued*)

#1 randomised AND controlled AND trial

Appendix 3. CINAHL search strategy

S1. (MH ”Clinical Trials+)
S2. PT Clinical trial
S3. TX clini* n1 trial*
S4. TX ((singl* n1 blind*) or (singl* n1 mask**))
S5. TX randomi* control* trial*
S6. (MH “Random Assignment”)
S7. TX random* allocat*
S8. TX placebo*
S9. (MH “Placebps”)
S10. (MH “Quantitative Studies”)
S11. TX allocat* random*
S12. S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11
S13. (MH “Breast Neoplasms+”)
S14. (TI breast cancer) or (SU breast cancer) or (AB breast cancer)
S15. (TI breast tumour) or (SU breast tumour) or (AB breast tumour)
S16. (SU Mamm* n1 Carcinoma) or (TI Mamm* n1 Carcinoma) or (AB Mamm* n1 Carcinoma)
S17. (MM “CArcinoma, Ducatal, Breast”)
S18. S13 or S14 or S15 or S16 or S 17
S19. (MM “Chemotherapy, Adjuvant)
S20. (Su adjuvant chemotherapy) or (TI adjuvant chemotherapy) or (AB adjuvant chemotherapy)

(*Continued*)

S21. Antineoplastic Combined Chemotherapy Protocls
S22. (MH ”BReast Neoplasms +/DH“)
S23. (MH ”Cyclophosphamide+/TU“)
S24. (MH ”Doxorubicin+/TU“)
S25 (MM ”Methotrexate/TU“)
S26. (MM ”Fluorouracil/TU“)
S27. (MM ”Carcinoma, Ductal, Breast/DT“)
S28. S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27
S29. (MM ”Radiotherapy Adjuvant“)
S30. (SU radiotherapy) or (TI radiotherapy) or (AB radiotherapy)
S31. (SU radiation therapy) or (TI radiation therapy) or (AB radiation therapy)
S32. (MH ”Breast Neoplasms+/RT)
S33. (MM “Carcinoma, Ductal, Breast/RT”)
S34. S29 or S30 or S31 or S32 or S33
S35. (MH “Mastectomy+)
S36. ”Mastectomy“
S37. (MM ”Breast Neoplasms/SU“)
S38. (SU mastectomy) or (AB mastectomy) or TI mastectomy)
S39. (SU Lumpectomy) or (AB mastectomy) or (TI mastectomy)
S40. (SU quadrenectomy) or (AB quadrentectomy) or (TI quadrantectomy)
S41. (SU ”wide local excision“) or (AB ”wide local excision“) or (TI ”wide local excision)
S42. (MM “Neoplasm Recurrence, Local”)
S43. S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42
S44. S12 and S18 and S28 and S34 and S42

Appendix 4. Science Citation Index search strategy

1. (breast near/5 cancer OR breast neoplasms OR breast near/5 tumour OR Mamm near/5 carcinoma) in Topic, AND
2. (chemotherapy OR cyclophosphamide OR duxorubicin OR methotrexate OR fluorouracil OR radiotherapy OR radi* therapy) in Topic, AND
3. (Mastectomy OR radical mastectomy OR lumpectomy OR quadrenectomy OR wide local excision) in Topic

Appendix 5. WHO ICTRP search strategy

Advanced search:

1. Title: Sequencing of chemotherapy and radiation therapy for early breast cancer
Recruitment Status: ALL
2. Condition: breast cancer%
Intervention: (chemotherapy OR adjuvant chemotherapy OR Antineoplastic Combined Chemotherapy Protocols OR Cyclophosphamide OR Doxorubicin OR Methotrexate OR Fluorouracil) AND (radiotherapy OR adjuvant radiotherapy OR radiation therapy) AND (mastectomy OR lumpectomy OR quadrantectomy)
Recruitment Status: ALL
3. Condition: locally advanced breast cancer%
Intervention: (chemotherapy OR adjuvant chemotherapy OR Antineoplastic Combined Chemotherapy Protocols OR Cyclophosphamide OR Doxorubicin OR Methotrexate OR Fluorouracil) AND (radiotherapy OR adjuvant radiotherapy OR radiation therapy) AND (mastectomy OR lumpectomy OR quadrantectomy)
Recruitment Status: ALL
4. Condition: early breast cancer%
Intervention: (chemotherapy OR adjuvant chemotherapy OR Antineoplastic Combined Chemotherapy Protocols OR Cyclophosphamide OR Doxorubicin OR Methotrexate OR Fluorouracil) AND (radiotherapy OR adjuvant radiotherapy OR radiation therapy) AND (mastectomy OR lumpectomy OR quadrantectomy)
Recruitment Status: ALL

WHAT'S NEW

Last assessed as up-to-date: 20 May 2011.

Date	Event	Description
17 January 2012	New citation required but conclusions have not changed	Further data for included studies added, involving 313 patients. Full risk of bias tables added. Conclusions remain unchanged
20 May 2011	New search has been performed	Performed search for new studies on 20 May 2011.

HISTORY

Protocol first published: Issue 2, 2005

Review first published: Issue 4, 2006

Date	Event	Description
14 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

BH and ML both contributed to writing the protocol, data extraction, analysis and writing of the discussion.

DF wrote the search strategy for the initial version, as well as in the update, and contributed to data extraction, analysis and writing of the paper.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Princess Alexandra Hospital Cancer Collaborative Group, Australia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have reported the late effect cosmesis (where available) although we did not specify that we would do so in our protocol. Where information has allowed us to present HRs, we have done so.

INDEX TERMS

Medical Subject Headings (MeSH)

Anemia [etiology]; Breast Neoplasms [*drug therapy; mortality; *radiotherapy; surgery]; Chemotherapy, Adjuvant [adverse effects; *methods]; Pigmentation Disorders [etiology]; Radiotherapy, Adjuvant [adverse effects; *methods]; Randomized Controlled Trials as Topic; Telangiectasis [etiology]; Time Factors

MeSH check words

Female; Humans