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[Intervention Review]

Hypofractionated radiation therapy for early breast cancer

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ABSTRACT

Background

Shortening the duration of radiation therapy would benefit women with early breast cancer treated with breast conserving surgery. It may also improve access to radiation therapy by improving efficiency in radiation oncology departments globally. This can only happen if the shorter treatment is as effective and safe as conventional radiation therapy. This is an update of a Cochrane Review first published in 2008 and updated in 2009.

Objectives

To assess the effect of altered radiation fraction size for women with early breast cancer who have had breast conserving surgery.

Search methods

We searched the Cochrane Breast Cancer Specialised Register (23 May 2015), CENTRAL (*The Cochrane Library* 2015, Issue 4), MEDLINE (Jan 1996 to May 2015), EMBASE (Jan 1980 to May 2015), the WHO International Clinical Trials Registry Platform (ICTRP) search portal (June 2010 to May 2015) and ClinicalTrials.gov (16 April 2015), reference lists of articles and relevant conference proceedings. No language or publication constraints were applied.

Selection criteria

Randomised controlled trials of altered fraction size versus conventional fractionation for radiation therapy in women with early breast cancer who had undergone breast conserving surgery.

Data collection and analysis

Two authors performed data extraction independently, with disagreements resolved by discussion. We sought missing data from trial authors.

Main results

We studied 8228 women in nine studies. Eight out of nine studies were at low or unclear risk of bias. Altered fraction size (delivering radiation therapy in larger amounts each day but over fewer days than with conventional fractionation) did not have a clinically meaningful effect on: local recurrence-free survival (Hazard Ratio (HR) 0.94, 95% CI 0.77 to 1.15, 7095 women, four studies, high-quality evidence), cosmetic outcome (Risk ratio (RR) 0.90, 95% CI 0.81 to 1.01, 2103 women, four studies, high-quality evidence) or overall survival (HR 0.91, 95% CI

0.80 to 1.03, 5685 women, three studies, high-quality evidence). Acute radiation skin toxicity (RR 0.32, 95% CI 0.22 to 0.45, 357 women, two studies) was reduced with altered fraction size. Late radiation subcutaneous toxicity did not differ with altered fraction size (RR 0.93, 95% CI 0.83 to 1.05, 5130 women, four studies, high-quality evidence). Breast cancer-specific survival (HR 0.91, 95% CI 0.78 to 1.06, 5685 women, three studies, high quality evidence) and relapse-free survival (HR 0.93, 95% CI 0.82 to 1.05, 5685 women, three studies, moderate-quality evidence) did not differ with altered fraction size. We found no data for mastectomy rate. Altered fraction size was associated with less patient-reported ($P < 0.001$) and physician-reported ($P = 0.009$) fatigue at six months (287 women, one study). We found no difference in the issue of altered fractionation for patient-reported outcomes of: physical well-being ($P = 0.46$), functional well-being ($P = 0.38$), emotional well-being ($P = 0.58$), social well-being ($P = 0.32$), breast cancer concerns ($P = 0.94$; 287 women, one study). We found no data with respect to costs.

Authors' conclusions

We found that using altered fraction size regimens (greater than 2 Gy per fraction) does not have a clinically meaningful effect on local recurrence, is associated with decreased acute toxicity and does not seem to affect breast appearance, late toxicity or patient-reported quality-of-life measures for selected women treated with breast conserving therapy. These are mostly women with node negative tumours smaller than 3 cm and negative pathological margins.

PLAIN LANGUAGE SUMMARY

Fraction size in radiation therapy for breast conservation in early breast cancer

Review question

We asked if giving fewer radiation treatments (using a higher radiation dose at each visit) was as effective as the conventional 25 to 30 radiation treatments for women with early breast cancer who have breast conserving therapy (keep their breast).

Background

Breast cancer is the most common cancer diagnosed in women, with one in eight women in the United States and Australia, and one in nine women in the United Kingdom being diagnosed with the condition by age 85 years. Breast conserving therapy (removing the tumour but keeping an intact breast) has proven to be as effective as mastectomy (removing the breast tissue) in terms of survival for women with cancer confined to the breast (or the local lymph nodes, or both), as long as a five to six-week course of radiation therapy is delivered. This involves 25 to 30 visits to a radiation oncology department. Without radiation therapy after breast conserving surgery there is a significant risk of breast cancer returning in the breast (local recurrence). Furthermore, for every local recurrence avoided with radiation, one death is avoided at 15 years. Many women prefer breast conservation which has resulted in an increased demand for radiation services. Giving fewer daily radiation treatments (fractions) would be beneficial to women if this has the same effect on tumour control and survival, and cosmetic outcome. In order to reduce the number of treatments, the radiation dose delivered per fraction is increased. This may also reduce demand on radiation resources and be more convenient for women.

Study characteristics

Nine studies, involving 8228 women, were included in this review. Most of the women in the studies (91%) had tumours 3 cm or less in size, all had complete removal of the tumour on pathology and 68% had no evidence of cancer in their lymph nodes. Where the breast size was known, 83% had small or medium breasts.

Key results

The evidence is current up to May 2015. Local recurrence was not different for women having fewer treatments (four fewer local relapses per 1000 (where the true value may be anywhere between 16 fewer to 10 more local relapses per 1000)). Breast appearance was not different for women undergoing fewer treatments (31 fewer fair/poor breast appearance per 1000 (where the true value may be anywhere between 59 fewer to 3 more per 1000 with fair/poor breast appearance)). Survival was not altered by having fewer treatments (13 fewer deaths per 1000 (where the true value could be between 31 fewer to 5 more deaths per 1000)) and there was no significant difference in late skin toxicity (4 more episodes of toxicity per 1000; where the true value may be anywhere between 14 fewer to 36 more episodes of toxicity per 1000) or radiation toxicity. Acute skin toxicity is decreased with fewer treatments (326 fewer events per 1000 (where the true value may be anywhere between 264 fewer to 374 fewer acute skin toxicity events per 1000)). This review indicates that for women who fit these criteria, using fewer radiation treatments after tumour removal gives the same cancer control, with less skin reaction at the time and the likely the same side-effects in the long term.

Quality of the evidence

We found high quality evidence for the following outcomes: local recurrence-free survival, breast appearance, toxicity, overall survival and breast cancer-specific survival. We found moderate quality evidence for relapse-free survival, and no data for mastectomy rate (mastectomy may be required because of local recurrence or unacceptable treatment-related toxicity) or costs.

Summary of findings for the main comparison. Hypofractionated radiation therapy compared to conventionally fractionated radiation therapy for women treated with breast conserving therapy for early breast cancer

Hypofractionated radiation therapy compared to conventionally fractionated radiation therapy for women treated with breast conserving therapy for early breast cancer

Patient or population: women treated with breast conserving therapy for early breast cancer
Setting: cancer centres
Intervention: hypofractionated radiation therapy
Comparison: conventionally fractionated radiation therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with conventionally fractionated radiation therapy	Risk with hypofractionated radiation therapy				
Local recurrence-free survival (LR-FS) at 10 years	Study population		HR 0.94 (0.77 to 1.15)	7095 (4 RCTs)	⊕⊕⊕⊕ HIGH	
	70 per 1,000[1]	66 per 1,000 (54 to 80)				
Cosmesis assessed with fair/poor on 4-point scale, follow-up: range 42 months-12 years	Study population		RR 0.90 (0.81 to 1.01)	2103 (4 RCTs)	⊕⊕⊕⊕ HIGH	
	311 per 1,000	280 per 1,000 (252 to 314)				
Mortality at 10 years	Study population		HR 0.91 (0.80 to 1.03)	5685 (3 RCTs)	⊕⊕⊕⊕ HIGH	
	166 per 1,000[1]	153 per 1,000 (135 to 171)				
Late subcutaneous toxicity assessed with ≥ Grade 2 on 4-point scale, follow-up: median 6 years	Study population		RR 0.93 (0.83 to 1.05)	5130 (4 RCTs)	⊕⊕⊕⊕ HIGH [2]	
	4 per 1,000	4 per 1,000 (3 to 4)				
Breast cancer-specific survival (BC-SS) at 10 years	Study population		HR 0.91 (0.78 to 1.06)	5685 (3 RCTs)	⊕⊕⊕⊕ HIGH	
	123 per 1,000[1]	113 per 1,000				

		(98 to 130)				
Relapse-free survival (RFS) at 10 years	Study population		HR 0.93 (0.82 to 1.05)	5685 (3 RCTs)	⊕⊕⊕⊖ MODERATE [3]	
	224 per 1,000[1]	210 per 1,000 (188 to 234)				
Mastectomy rate - not measured	see comment	see comment	not estimable	(studies)	-	We found no data with respect to subsequent mastectomy

*__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; **RR:** risk ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]The baseline risks for the control groups were calculated using 10-year event data from the included studies
[2] No blinding for assessment of subjective outcomes (for 5% of events only)
[3]Statistical testing as well as examination of the forest plots suggested there was some heterogeneity

BACKGROUND

Description of the condition

This review is an update of a review previously published in the *Cochrane Database of Systematic Reviews* 2009, Issue 11 on fraction size in radiation therapy for breast conservation in early breast cancer. Breast cancer is the most common cancer diagnosed in women and the second most common cause of cancer death in women. The lifetime risk to age 85 years of being diagnosed with breast cancer for women living in Australia and the United States is one in eight, and one in nine for women living in the United Kingdom (AIHW 2006; ONS 1999; Ries 2004).

A significant change has occurred in the management of women with early breast cancer (cancer confined to the breast and nearby lymph nodes) over the last three decades. Previously most women with early breast cancer underwent removal of the whole breast (mastectomy). Evidence from several randomised controlled trials (Fisher 1989; Veronesi 1990) and a meta-analysis of 36 trials (EBCTCG 1995) confirms that long-term overall survival is equivalent using breast conserving treatment compared with mastectomy. Breast conserving treatment comprises removal of the portion of the breast containing the tumour followed by radiation therapy to the remaining breast tissue. Other studies have shown that quality of life is enhanced in women who undergo breast conserving treatment (Al-Ghazal 2000). Consequently, breast conserving treatment has become the recommended option for women with early breast cancer in many Western countries (NBCC 2001; NIH 1991). Breast conserving surgery now accounts for 70% of breast cancer operations in some series (Chouillet 1994) and, as a result, demand for radiation therapy services has increased. Some health services have struggled to meet this increasing demand because of a shortage of trained personnel and expensive radiation treatment machines (Ash 2000; Mackillop 1994).

Description of the intervention

Radiation following breast conserving surgery involves treatment to the breast with ionising radiation. Typically the radiation is delivered over a period of five to six weeks using a standard 2 Gy (Gray) radiation dose per fraction, in 25 to 30 treatment episodes, to a total dose of 50 to 60 Gy.

How the intervention might work

Recently there has been interest from cancer service providers in shortening the overall treatment time. One method of achieving this is to increase the size of each fraction thereby decreasing the total number of fractions required. For example, case series using 40 Gy in 15 fractions or 36 Gy in 12 fractions have been reported (Ash 2000; Olivotto 1996). Shorter fractionation schedules have the advantages of using machine and staff time more efficiently and reducing patient inconvenience.

Concerns have been raised, however, as to whether shorter fractionation schedules have equivalent outcomes in terms of local tumour control, breast appearance (cosmesis), late toxicity, overall survival and patient satisfaction. The concern with larger fraction sizes is based on radiobiological principles which state that the fraction size is the dominant factor in determining late side effects. The aim of conventional fractionation at 2 Gy per fraction is to decrease the rate of late tissue damage whilst aiming to maximise tumour control with acceptable acute toxicity (Hall 1994). Higher fraction size could lead to increased scarring and retraction of breast tissue as well as skin atrophy (thinning) and telangiectasia (dilated blood vessels).

Why it is important to do this review

The optimal fractionation schedule is not well-established (Whelan 1993) but evidence from clinical trials suggests that the results of shorter schedules may be equivalent with respect to local control and cosmesis (Whelan 2002a; Yarnold 1994). Published trials to date have been too small to detect differences in cancer recurrence rates reliably.

If a shorter fractionation schedule was shown to provide equivalent outcomes for women this could lead to more efficient use of radiation services and more expedient treatment for women with early breast cancer.

OBJECTIVES

To assess the effect of altered radiation fraction size for women with early breast cancer who have had breast conserving surgery.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials were considered for inclusion. We required the comparisons to be unconfounded, that is the treatment given to the intervention and comparator groups could differ only in relation to the fractionation schedule used. Trials where the participants received adjuvant treatment in the form of chemotherapy, monoclonal antibody treatment, or hormonal therapy were eligible providing these treatments were applied equally to all study groups. Published and unpublished studies were eligible. Outcomes were not used as criteria for considering studies for inclusion in this review.

Types of participants

Women with histologically confirmed early breast cancer who had undergone breast conserving surgery. Early breast cancer is defined as invasive adenocarcinoma restricted to the breast, plus or minus the local lymph nodes, which can be removed surgically (EBCTCG 2011), that is T1-2, N0-1, M0 (Fleming 1997).

Surgery could include lumpectomy, wide local excision, quadrantectomy, or segmental resection; with or without axillary dissection, node sampling, or sentinel node biopsy. If a study included the relevant population as a subgroup and the outcomes relating to this group were reported separately, we included those participants eligible for this review (e.g. Saha 2009).

Types of interventions

Postoperative radiation to the breast alone and delivered using conventional fractionation (1.8 to 2 Gy per fraction) versus postoperative radiation to the breast alone at greater than 2 Gy per fraction. The dose prescribed and the prescription point had to be clearly identified. We specified the dose in accordance with the International Commission on Radiation Units and Measurements' (ICRU 50)(Jones 1994) recommendations with respect to dose, dose specification point and dose per fraction.

Where possible, we converted data found in studies into this form. Partial breast irradiation was excluded because it is the subject of another Cochrane systematic review (see: Lehman 2014).

Types of outcome measures

Primary outcomes

1. Local recurrence-free survival (LR-FS) in the ipsilateral breast (i.e. events defined as cancer detected in the same breast where the cancer had been diagnosed).
2. Appearance or cosmesis (objective and subjective) of the treated breast.

Secondary outcomes

1. Overall survival (OS; time from date of randomisation to death from any cause, or number of deaths from any cause).
2. Toxicity (including acute and late effects of radiation therapy and chemotherapy-related toxicity); we used individual protocol-based definitions.
3. Breast cancer-specific survival (BC-SS; events were: death due to breast cancer).
4. Relapse-free survival (RFS; events included local recurrence, loco-regional recurrence, distant metastasis and death).
5. Mastectomy rate (salvage following local recurrence or unacceptable toxicity).
6. Quality of life (trial-specific instruments).
7. Costs (to women and health services).

Search methods for identification of studies

Searches were not limited by language or date.

Electronic searches

We searched the following databases:

1. Cochrane Breast Cancer Specialised Register (23 May 2015). The details of search strategies used by the Group for the identification of studies and the procedure used to code references are outlined in their module (Breast Cancer Group 2016). We extracted studies coded as 'early' and 'radiotherapy' and 'dose intensity' in the Specialised Register for consideration;
2. CENTRAL (*The Cochrane Library* 2015, Issue 4). See Appendix 1 for search strings;
3. MEDLINE (OVID) (1966 to May 2015). See Appendix 2 for search strings;
4. EMBASE (OVID) (1980 to May 2015). See Appendix 3 for search strings;
5. WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/) for the period 10 June 2010 until May 2015. See Appendix 4;
6. ClinicalTrials.gov (clinicaltrials.gov) on 16 April 2015. See Appendix 5;
7. Grey literature (opengrey.org) on 06 May 2015. See Appendix 6.

Searching other resources

We handsearched the following conference proceedings:

1. American Society of Oncology: 1995-2010;
2. European Society for Therapeutic Radiation Oncology: 1990, 1993, 2000-2010, 2012;
3. American Society for Therapeutic Radiation: 2011, 2012, 2014;
4. We searched reference lists of published studies and review articles.

Data collection and analysis

Selection of studies

In the previous versions and 2015 review update, two or more authors checked the titles and abstracts retrieved by the searches (previous versions: four authors; 2015 review update: BH and MJ). Two authors (BH and MJ) independently assessed the full text of all studies we thought relevant to the review with differences being resolved by discussion.

Data extraction and management

Two authors (BH and ML) performed data extraction independently, with disagreements being resolved by discussion. We entered data into Review Manager 5.3 (RevMan 2014) for analysis. Where data were limited, we requested further information from the authors of the original studies. We received data from the authors of START A 2008; START B 2008 and Owen 2006a. Data for local recurrence events was derived from percentages (Whelan 2002b) where raw numbers were not available (we assumed the denominators used were the numbers in each arm of the trial). Where there were two experimental arms using altered fraction size (Owen 2006a; START A 2008), we combined the number of events and denominators to form a single experimental arm.

We calculated the log rank statistic (O-E) and its variance for time-to-event outcomes using an Excel spreadsheet developed by Matthew Sydes (Cancer Division) in collaboration with the Meta-analysis Group of the MRC Clinical Trials Unit, London (Sydes 2007). For START B 2008, to derive O-E and variance for: LR-FS, OS, BC-SS and RFS, we used Method four (where HR, number of events in each arm and the randomisation is 1:1). We used Method four to derive O-E and variance for OS (Whelan 2002b). We used Method six to derive O-E and variance for LR-FS (Owen 2006a; START A 2008) (where HR and total number of events are available and randomisation need not be 1:1), OS, RFS and BC-SS (START A 2008). We used Method eleven to derive LR-FS and R-FS (Whelan 2002b; data extracted from the curve where numbers at risk are available). Method seven was used to derive O-E and variance for BC-SS (Whelan 2002b; where P value, events in each arm available and randomisation ratio is 1:1).

We reported cosmetic outcome using a four-point scale (see additional Table 1: Owen 2006a; Taher 2004; Whelan 2002b). This was dichotomised and those who had fair/poor results were counted as having events. For Owen 2006a and Whelan 2002b, we derived figures from percentages given in the text.

Acute toxicity: two different five-point scales were used (Cox 1995; NCI); any woman who had Grade II toxicity or more was scored as having an event. Although they are both five-point scales, the NCI does not always use all five grades. After examining the descriptions for each grade in the two different scales, we chose to report any women with Grade 2 toxicity or more as having an event (see Table 2 and Table 3).

Late radiation therapy (RT) toxicity (telangiectasia, breast oedema, subcutaneous toxicity): any woman who had Grade 2 toxicity or more was scored as having an event.

Rib fractures: we reported radiologically confirmed rib fractures (excluding those related to metastases and trauma).

We reported ischaemic heart disease for those women with left-sided tumours, and those with pre-existing heart disease were excluded.

Pulmonary fibrosis was confirmed radiologically.

We converted the radiation doses to the equivalent dose in 2 Gy fractions (EQD^2) (Maciejewski 1986; Withers 1983), using the formula: $EQD^2 = D (d + alpha/beta/2 + alpha/beta)$, where D = total dose, d = dose per fraction and alpha/beta = 4 Gy (Owen 2006b; see Table 4). This was to facilitate comparison of radiation doses given at differing dose per fraction. We converted brachytherapy (radiation sources applied directly to the body) to the biological equivalent dose (BED) using the method of Stitt 1992.

We reported the P values for any difference in the mean score (measured at baseline and six months) for patient-reported quality of life measures scored using FACT-B (Brady 1997; Webster 2003).

Assessment of risk of bias in included studies

Two review authors (BH, ML) categorised the risk of bias of each eligible study using the system outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). DF resolved any discrepancies that arose. BH constructed and ML reviewed 'Risk of bias' tables for the included studies, with any discrepancies resolved by discussion. We constructed a 'Risk of bias' graph with review authors' judgements about each methodological quality item (presented as percentages across all included studies). We separated assessment of risk of bias into subjective (e.g. cosmesis) and objective outcomes (e.g. LR-FS).

We planned sensitivity analysis on the basis of study quality, which was to be performed with and without trials of low quality to assess the effect of quality on the results.

Measures of treatment effect

We presented results so that a result less than one favoured the experimental arm (hypofractionation). Summary statistics for dichotomous measures were presented as risk ratios (RR) with 95% confidence intervals (CI) (Deeks 2003). Summary statistics for continuous variables were presented as mean differences (MD), where possible. We used Mantel-Haenszel methods to calculate pooled risk ratios (Greenland 1985; Mantel 1959). Where possible, we used the HR to present time-to-event data for the endpoints of LR-FS, OS, RFS, with 95% CI.

We deemed that a HR equal to or less than 0.75 and equal to or greater than 1.25 was clinically meaningful. In the absence of clear direction in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b), we made a pragmatic decision based on our expert opinions as clinicians and used the Federal Drug Administration (FDA) method (AHRQ 2011) to choose (post-hoc) the minimal clinically important difference (MID), using a figure 50% of the difference tested for in a randomised study (START A 2008). START A 2008 was powered to detect a 5% difference in local relapse, so we chose 2.5% for our MID. We considered that for LR-FS, BC-SS and OS, a reasonable MID was 2.5%, as this is less than half the effect size sought in START A 2008 (5%), and was chosen to be deliberately conservative. Therefore if the upper limit of the confidence interval indicated the intervention was less then 2.5% worse than the control, we concluded non-inferiority.

Unit of analysis issues

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

Dealing with missing data

We contacted the study authors for any missing data.

Assessment of heterogeneity

We assessed heterogeneity both visually and statistically using the Chi^2 test (Altman 1992; Walker 1988) and the Higgins I^2 statistic (Higgins 2002; Higgins 2003). We acknowledge that with few studies the statistical power to detect heterogeneity is low.

Assessment of reporting biases

We used funnel plots to assess for publication bias where we had five or more studies.

Data synthesis

We extracted data from the trials according to the intention-to-treat (ITT) principle where possible and determined a weighted average treatment effect using the fixed-effect model to combine results (Mantel 1959) in RevMan 5.3 (RevMan 2014). Where it was possible to derive the log rank statistic (O-E) and its variance from the presented data, we used Peto's method to estimate the pooled hazard ratio (HR). Our comparison of interest was altered fraction size (hypofractionation) versus conventional fractionation, so when analysing the trials we combined the two different 'fractionation dose' altered arms of the Owen 2006a and START A 2008 trials as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). In the future, if more information becomes available, separate analysis may be possible to investigate a dose effect for different fractionation schedules.

Acute radiation toxicity

1. Acute skin toxicity was reported for FAST 2011; START A 2008; START B 2008 and Taher 2004.

Late radiation toxicity

1. Late skin toxicity (Whelan 2002b) was assessed at five and ten years using a five-point scale (Winchester 1992) (see additional Table 5) and analysed as a dichotomous outcome using RR. The results were dichotomised into: none or mild versus moderate, marked or severe. We reported the women who had ≥ Grade II toxicity for each arm (percentages given in text converted to numbers).
2. Ischaemic heart disease for women with left-sided tumours without pre-existing heart disease (at median follow-up 9.3 to 9.9 years) was reported in full (START A 2008; START B 2008).
3. Rib fractures, those confirmed and excluding those secondary to trauma or metastatic disease (at median follow-up 9.3 to 9.9 years) were reported in full (START A 2008; START B 2008).
4. Induration (fibrosis) and subcutaneous toxicity:

We assumed that induration and subcutaneous toxicity, reported by or at five years by Owen 2006a and Whelan 2002b respectively and at ten years (START A 2008; START B 2008) represented the same outcome and could, therefore, be combined for analysis. Whelan 2002b used the RTOG/EORTC five-point late radiation morbidity scale, with the women assessed by a trained nurse (Winchester 1992) (see Additional Table 5). Owen 2006a used a four-point trial-specific scale (see Additional Table 6) and the outcome was assessed by physicians. In START A 2008 and START B 2008, the women were assessed by physicians using a four-point scale (see Table 7) and the results dichotomised: those women with Grade II toxicity or above had an event recorded. The results were dichotomised in the Owen 2006a report but reported in full in Whelan 2002b. In order to combine the results, we dichotomised the Whelan 2002b results into two groups: those with nil or slight late radiation toxicity, and those who had any greater toxicity; that is the women who had scores of two or more were counted as having toxicity. No participant in Whelan 2002b had severe (Grade 4) toxicity.

Marked or any change in breast appearance: results were dichotomised in the report (Owen 2006a).

If sufficient data becomes available in future updates we will use recommended methods to collect and combine the data. We will use the mean difference method unless trials have reported results on different scales, in which case we will use a standardised mean difference to summarise data (Deeks 2011).

'Summary of findings' table

Using the GRADE approach, we created a 'Summary of findings' table based on the following outcomes.

1. Local recurrence-free survival
2. Cosmesis
3. Overall survival (called mortality in Summary of Findings Table)
4. Toxicity (late sub-cutaneous toxicity/fibrosis)
5. Breast cancer-specific survival
6. Relapse-free survival
7. Mastectomy rate

Refer to Summary of findings for the main comparison. To calculate the absolute risk for the control group for time-to-event outcomes in the 'Summary of Findings' table, we estimated the event rate at a specific time point (10 years for LR-FS, Mortality, BC-SS, and RFS) from the Kaplan-Meier curves or reported event rates in the included studies. These estimated values were entered in GRADEproGDT software and the corresponding absolute risks for the intervention group at 10 years were automatically populated by the software.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analysis based on length of follow-up (4.2 years versus approximately 10 years) and by dose (experimental arm < 50 Gy versus ≥ 50 Gy). In the two studies with two intervention arms where the doses were both less than 50 Gy and equal to or greater than 50 Gy (Owen 2006a; FAST 2011) and the results were not reported by dose stratum, we were not able to include them in the subgroup analysis.

If sufficient data become available in future updates we may perform subgroup analyses to investigate whether the effects of different radiation fraction schedules differ depending on nodal status, margin status, hormone receptor status, and tumour stage or other factors which may become relevant in the future. If heterogeneity is detected we will first check the data to ensure accuracy, in the knowledge that with small study numbers, the power of statistical testing for heterogeneity is low.

Sensitivity analysis

We did sensitivity analysis based on risk of bias, excluding studies deemed at high risk of bias (Whelan 2002b).

RESULTS

Description of studies

Results of the search

For this update of the review, we screened a total of 2627 abstracts, and considered 53 papers in full for eligibility. We excluded 25 full-text publications (see Characteristics of excluded studies) and identified 28 new reports. Twelve reports referred to five new included studies (FAST 2011; Patni 2012; Saha 2009; Shaitelman 2015; Taher 2004). Eight reports related to three previously included studies (Owen 2006a; START A 2008; Whelan 2002b). Eight reports referred to five ongoing studies (NCT00459628; NCT01266642; NCT00909818; NCT01349322; NCT01413269). See Figure 1.

Figure 1. Study flow diagram for updated review

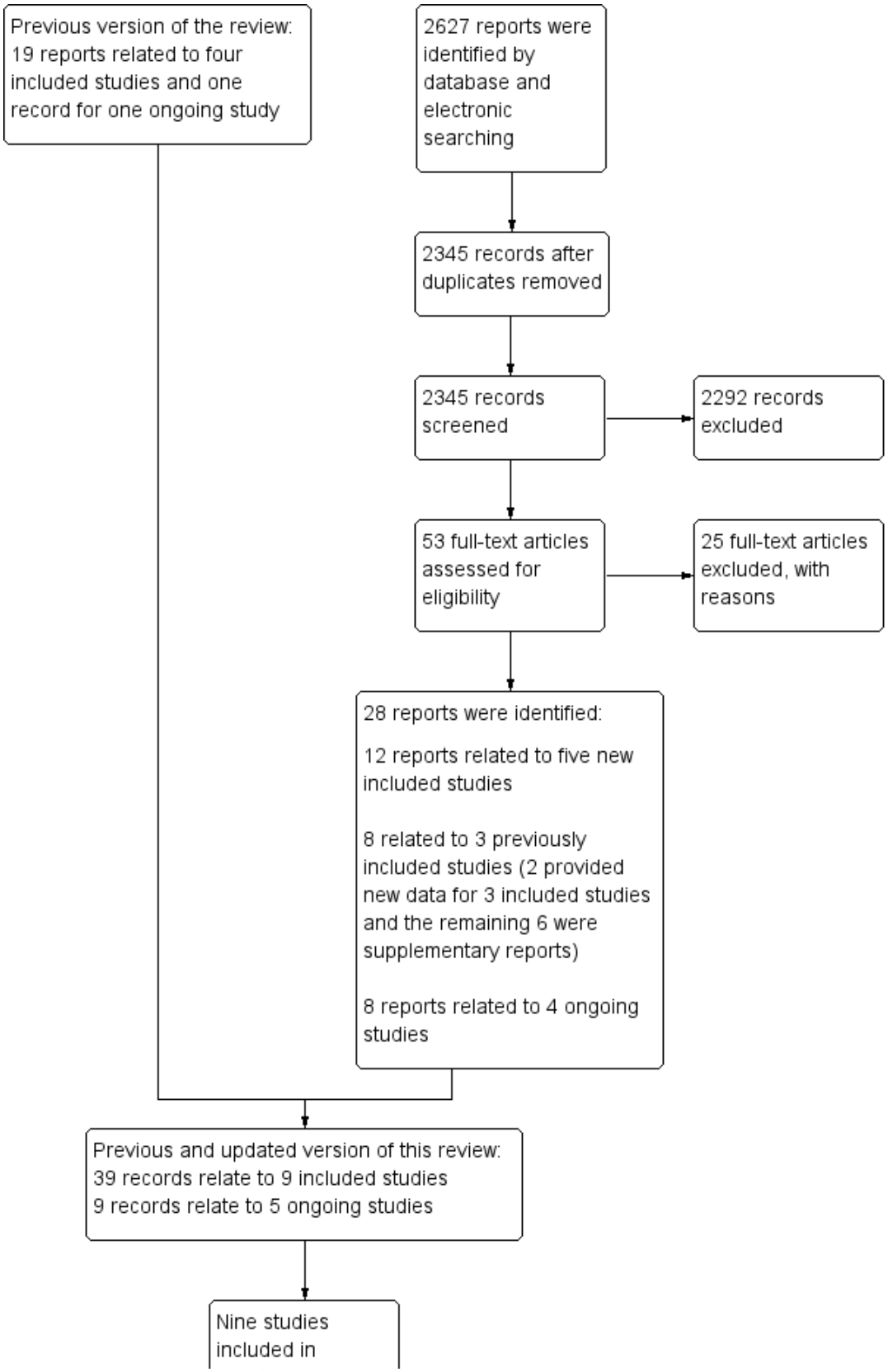
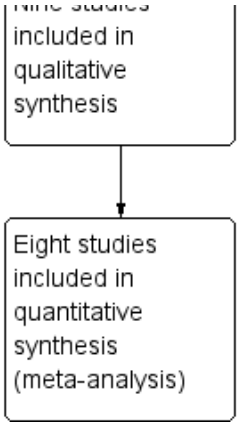


Figure 1. (Continued)



When combining studies from the previous review and this update, 39 reports that met the inclusion criteria related to nine separate studies (FAST 2011; Owen 2006a; Patni 2012; Saha 2009; Shaitelman 2015; START A 2008; START B 2008; Taher 2004; Whelan 2002b). All of the trials had published their results at different times with different periods of follow-up. We used the most recent publication as the source for the review, supplementing this with information from earlier reports if necessary. Thus, for the Owen 2006a trial the primary source is Owen 2006a, with 10 other records found for this trial. The primary source for the Whelan 2002b was Whelan 2002b, with six other reports found. For START A 2008, there were seven records with one publication (Sumo 2008) that was also relevant to START B 2008. START B 2008 had two reports, FAST 2011 contained seven records, Shaitelman 2015 had two records and Taher 2004 had one record while Patni 2012 and Saha 2009 were reported only in one report each in abstract form.

Included studies

The nine randomised trials included in this current version of the review involved a total of 8228 women.

Participants

The women studied in this review were mostly women with early breast cancer (6829/7553 (90.4%)) and 4580 out of 8010 (57%) women were aged 50 or more where reported (FAST 2011; Owen 2006a; START A 2008; START B 2008; Whelan 2002b). Seventy-two out of 287 (25%) of the women in Shaitelman 2015 and 59 women in Owen 2006a had Stage 0 early breast cancer or ductal carcinoma in situ (DCIS): in total, 131/8228 (0.15%) women had DCIS. Further, 6701/6701 (100%) of the women studied in this review had negative pathological margins, where reported (FAST 2011; Saha 2009; Shaitelman 2015; START A 2008; START B 2008; Taher 2004; Whelan 2002b). Most tumours (3916/6600 (59%)) were 2 cm or less in size, where size was reported (FAST 2011; START A 2008; START B 2008; Whelan 2002b) and 4457/4853 (91%) were 3 cm or less in size (FAST 2011; START A 2008; START B 2008). Women with T3 tumours (that is tumour size greater than 5 cm) were eligible for the START A 2008 and START B 2008 studies. They comprised 1.6% (22/1410) of the women studied in Owen 2006a. T stage was not reported in START A 2008 and START B 2008, but 15% (702/4451) of women had tumours larger than 3 cm. Most women 5040/6135 (82%) studied in this review, had small to medium breasts (where breast size was reported) (FAST 2011; Owen 2006a; START A 2008; START B 2008; Whelan 2002b), in Shaitelman 2015 (those with cup size D or less). Most women (5332/7824 (68%)) studied in this review were node negative where reported (FAST 2011; Owen 2006a; START A 2008; START B 2008; Whelan 2002b) and most women (7675/8188 (93.7%)) studied were treated with breast conserving surgery. Saha 2009 included 131 women with early breast cancer, we included the 47 women treated with breast conserving surgery, where the results were reported separately.

Interventions

Radiation therapy dose

Shaitelman 2015; Taher 2004 and Whelan 2002b compared two different fractionation regimens (42.5 Gy in 16 fractions and 50 Gy in 25 fractions). Owen 2006a compared three fractionation regimens (39 Gy in 13 fractions, 42.9 Gy in 13 fractions, and 50 Gy in 25 fractions). START A 2008 compared three regimens (41.6 Gy in 13 fractions, 39 Gy in 13 fractions and 50 Gy in 25 fractions). Patni 2012 and START B 2008 compared two fractionation regimens (40 Gy in 15 fractions and 50 Gy in 25 fractions). FAST 2011 compared three regimens: 30 Gy in five fractions, 28.5 Gy in five fractions and 50 Gy in 25 fractions. Saha 2009 compared 30 Gy in 5 fractions versus 50 Gy in 25 fractions. See Table 4 for comparison of BED and EQD_2.

The RT delivered in Shaitelman 2015 used techniques to:

1. improve dose heterogeneity (wedging, 3D compensation or intensity modulated RT (IMRT)); they specified that dose received did not exceed 108% of prescribed dose;
2. reduce lung dose (respiratory gating);
3. improve accuracy (CT planning).

Boost to tumour bed

Overall, 3454/7715 (44.7%) of the women studied received a boost (an extra dose delivered to the tumour bed) (Owen 2006a; Patni 2012; Saha 2009; Shaitelman 2015; START A 2008; START B 2008, Taher 2004). In the experimental arm, 1390/3581 (38.8%) of women received a boost and in the control arm 972/2772 (35%) received a boost (data excludes Owen 2006a and Saha 2009, where boost was not reported by study arm; see Table 8).

Owen 2006a: 1051/1410 (75%) were treated with a boost of 14 Gy at 90% in seven fractions. The authors did not report how many women in each arm received a boost. For women with negative margins, if the clinician felt it was appropriate, there

was a sub-randomisation to boost or no boost from January 1986 to May 1994. After this, all 687 participants were offered an elective boost (see additional Table 8). The boost dose delivered was not reported in Patni 2012. The planning target volume (PTV) for the boost was clearly defined in Shaitelman 2015. START A 2008: for women treated with breast conservation, 771/1269 (61%) of women in the experimental arm and 381/631 (60%) of women in the control arm received a boost of 10 Gy in five fractions using electrons. In total, 1152/1900 (61%) received a boost. Each participating department specified in advance whether participants enrolled from that site would receive radiotherapy boost (see additional Table 8). START B 2008: for women treated with breast conservation, 446/1018 (44%) and 422/1020 (41%) received a 10 Gy on five fraction boost using electrons. In total, 868/2038 (43%) received a boost. Each participating department specified in advance whether participants enrolled from that site would receive radiotherapy boost (see additional Table 8). 15/30 women in Taher 2004 (all the conventional arm) received a boost (see Table 8).

No women in FAST 2011 or Whelan 2002b were treated with boosts.

Regional nodal irradiation

318/2236 (1.3%) of women in START A 2008 and 161/2215 (7%) women in START B 2008 were treated with regional nodal RT.

Co-interventions

In total, 5566/7513 (74%) women received hormonal manipulation (mostly tamoxifen) and 1709/8188 (21%) received chemotherapy. No women in FAST 2011 received adjuvant chemotherapy, 704 received tamoxifen and 102 an aromatase inhibitor. In total, 196/1410 women received chemotherapy and 1074/1410 received tamoxifen (numbers not given by study arm; Owen 2006a). All (47/47) the women in Saha 2009 received chemotherapy. In START A 2008 1758/2236 women received tamoxifen and 793/2236 women received chemotherapy and in START B 2008 1928/2215 women received tamoxifen and 491/2215 women received chemotherapy. Taher 2004 treated 20/30 women with chemotherapy +/- hormonal therapy (not detailed by study arm) and 17/30 women received chemotherapy. One hundred and thirty-six out of 1234 women in Whelan 2002b received chemotherapy, 28 out of 287 women in Shaitelman 2015 received neoadjuvant chemotherapy and in total, 28/7800 (0.3%) of women received neoadjuvant chemotherapy.

No co-interventions were reported in Patni 2012.

Quality assurance for radiation therapy

Both START A 2008 and START B 2008 had a rigorous quality assurance programme to ensure the RT delivered was adherent to protocol. In Shaitelman 2015 there was no trial-specific quality assurance, other than institutional peer review process of radiation therapy plans.

Outcomes

Local recurrence-free survival

LR-FS was reported at three and a half years (Saha 2009) and ten years or more follow-up in Owen 2006a; START A 2008; START B 2008 and Whelan 2002b.

Cosmesis

Participant-reported cosmetic outcome was reported in Shaitelman 2015. Trained clinical trials nurses in Whelan 2002b and a blinded physician panel in Shaitelman 2015 assessed global cosmetic outcome using the four-point European Organisation for Research and Treatment of Cancer (EORTC) Cosmetic Rating System (Table 1). Of the women in the trial, 1220/1234 (98.8%) had baseline cosmetic assessment. Cosmetic outcome was assessed in the 735/1220 women with five years' follow-up at the time of assessment (Table 8). Cosmetic assessment was done for 1220 women at baseline and complete cosmetic data was reported for 735 women at five years (the time of interest for the outcome). We have no indication that these women were different to the remainder of those randomised. Triallists used a four-point scale (Aaronson 1988) and the results were dichotomised as good or excellent versus poor or fair (Table 1). The study reported these results as percentages at three and five years with the total number of women available for evaluation at each time period; as we did not know the numbers in each arm, we were unable to derive figures from these data. In Taher 2004 and Saha 2009, the same four-point scale was used to assess cosmesis, by an observer blinded to treatment arm (Taher 2004) and the results were dichotomised as in Whelan 2002b.

Owen 2006a reported breast cosmesis (median follow-up of 9.7 years, maximum 15 years) using a four-point scale (Table 9). A total of 806 women (see Description of studies) were assessed and the results were reported for a dichotomous outcome in the report. We have no evidence that these women were substantially different to the remainder of women in the trial: the reasons that women were not followed up were not related to which arm they were randomised to and were not related to whether they had local relapse or late normal tissue side-effects from treatment. Quote: "Reasons for non-availability were explored, and no evidence was observed that this was associated with either the fractionation schedule or to the probability of experiencing future normal tissue event or local relapse (Owen 2006a)." The clinical assessment results were dichotomised in the report into fair or poor versus good or excellent (Owen 2006a).

Late change in breast appearance (assessed by blinded observers) was reported in Owen 2006a; START A 2008 and START B 2008 and will be reported in FAST 2011 when the follow-up is longer. Late change in breast appearance (photographic) was assessed in the 1055 (START A 2008) and 923 (START B 2008) women who had both a photo at baseline and a follow-up photo (START A 2008; START B 2008). Not all participants had a photo at five years. Those with photos at two and five years were combined when reported, and the authors did not report how many had five-year follow-up. We have no evidence that these women were substantially different to the remainder of women in the trial. Quote: "There were no associations between score for change in breast appearance (photographic) at two years or patient demographic or treatment characteristics and whether or not the participant had a five-year assessment (data not shown)".

The primary outcome measure in Owen 2006a was late change in breast appearance, which was assessed in the 1202 women who had photographs available at baseline and at least a single follow-up. Pairs of photographs were available as follows: 1128 at year one, 1004 at year two, 525 at three years, 472 at four years, 765 at five

years and 141 at 10 years, i.e. photographic follow-up was reported for 63% of women at five years, and 11% at 10 years.

Overall survival

Overall survival was reported at ten years or more in START A 2008; START B 2008 and Whelan 2002b.

Acute skin radiation therapy toxicity

This was assessed using the RTOG CTCAE scoring system, a five-point scale (Cox 1995) in FAST 2011; Patni 2012 and Taher 2004 (see Table 2). Acute toxicity was assessed in Shaitelman 2015 using NCI CTC version 4.0 (NCI; see Table 3). Those women who experienced extensive moist desquamation were reported in START A 2008 and START B 2008 (not reported by study arm).

Late radiation therapy toxicity

Owen 2006a reported late RT toxicity (un-blinded physician assessment). Breast pain, oedema, subcutaneous fibrosis (induration), hyperpigmentation and telangiectasia were reported in Patni 2012 using RTOG CTCAE (Cox 1995). Late RT toxicity was assessed in Saha 2009 using LENT-SOMA. Physicians (Shaitelman 2015) and trained nurses (Whelan 2002b) assessed late radiation toxicity using the five-point Radiation Oncology Group/ EORTC late radiation morbidity scale (Winchester 1992) to report skin toxicity (Table 5). START A 2008 and START B 2008 reported late RT toxicity: breast shrinkage, telangiectasia and breast oedema was assessed annually (by physicians) in START A 2008 and START B 2008 using a four-point scale. Any women with Grade II toxicity or above were regarded as having an event.

Breast cancer-specific survival

BC-SS was reported at ten years or more in START A 2008; START B 2008 and Whelan 2002b.

Relapse-free survival

RFS was reported at five years (Whelan 2002b) and at ten years in START A 2008 and START B 2008.

Mastectomy rate

Mastectomy rates were not reported.

Quality of life

Quality of life was reported separately for 1129/2236 women in START A 2008 and 1079/2215 women in START B 2008. Centres either opted in or out of participating in the quality-of-life data collection, but the authors report that there was no difference in terms of RT planning or delivery between centres opting to participate in the quality-of-life data collection or not. START A 2008 and START B 2008 enrolled 2208 women in the quality-of-life assessments. The EORTC general cancer quality-of-life scale (EORTC QLQ-C30; Aaronson 1993), breast cancer module (BR23; Sprangers 1996), the Body Image Scale (BIS; Hopwood 2001) and the Hospital Anxiety and Depression Scale (HADS; Zigmond 1983) were used to evaluate quality of life. The initial publication describes the quality of life in the overall cohort of participants, and was performed prior to breaking the randomisation code. EORTC QLQ-C30 (Aaronson 1993) and BR23 (Sprangers 1996) were used, with a questionnaire at baseline, 6, 12, 24 and 60 months after RT. Shaitelman 2015 evaluated quality of life at six months, using FACT-B (Brady 1997; Webster 2003), FACT-G (Fairclough 1996), BIS (Hopwood 2001), Appearance Schemas Inventory-Revised (ASI-R), and included both participant- and physician-reported fatigue.

Costs

Costs were not reported.

Follow-up

FAST 2011 had a median follow-up of 37.3 months. Owen 2006a had a median follow-up of 9.7 years. Patni 2012 had a median follow-up of seven months. Saha 2009 reported at a median follow-up of 42 months. START A 2008 had a median follow-up of 9.3 years. START B 2008 had a median follow-up of 9.9 years. Taher 2004 reported cosmesis at a median follow-up of 22 months. Whelan 2002b had a median follow-up of 12 years. Shaitelman 2015 had "minimum follow up of six months."

Shaitelman 2015; START A 2008 and Whelan 2002b addressed non-inferiority: START A 2008 was an equivalence study. There was inadequate detail to assess FAST 2011; Owen 2006a; Saha 2009 and Taher 2004 in this respect.

Further detail is available in the Characteristics of included studies table.

Excluded studies

Fifty-three studies were reviewed in full, of these, 25 were excluded (see Characteristics of excluded studies).

Studies awaiting classification

No studies await classification.

Ongoing studies

We identified five ongoing studies (see Characteristics of ongoing studies).

Risk of bias in included studies

Summary assessment of risk of bias

For the outcome LR-FS, one study (Whelan 2002b) was deemed at high risk of bias, but this was for subjective outcomes, so was unlikely to have made this outcome at high risk of bias.

Cosmesis: one study (Whelan 2002b) was deemed at high risk of bias, so we felt that for the domain of subjective outcomes this outcome was at high risk of bias.

Overall survival: although two studies were deemed at high risk of bias for some subjective outcomes, for this objective outcome, we did not deem this outcome to be at high risk of bias.

Toxicity: no study reporting acute toxicity was deemed at high risk of bias. Whelan 2002b was deemed at high risk of bias for no blinding for subjective outcomes. We felt this would have had an impact on the subjective outcome of late RT toxicity.

Cancer-specific survival: although Whelan 2002b was at high risk of bias, we did not feel it would impact on this outcome.

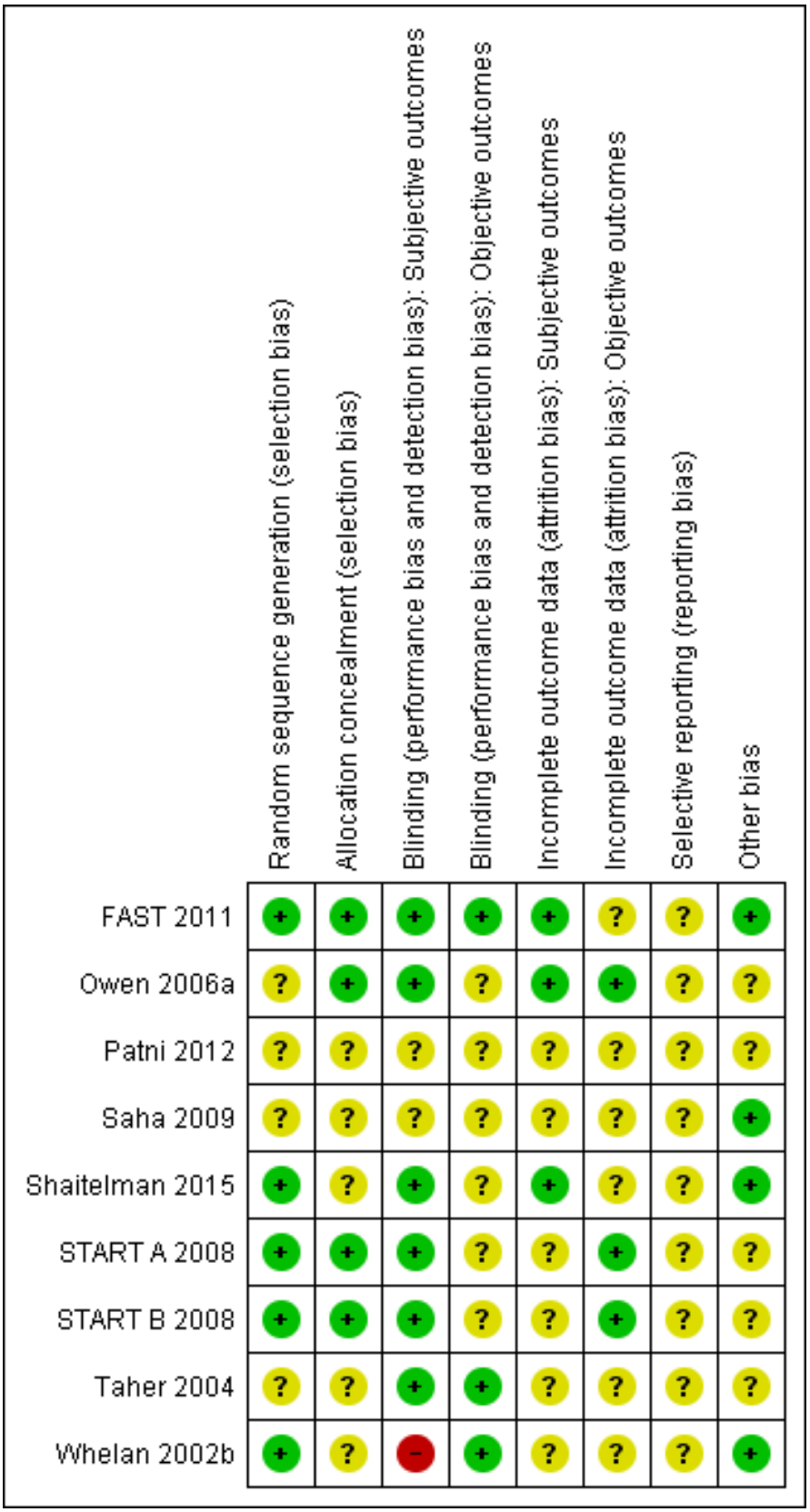
Relapse-free survival: although Whelan 2002b was at high risk of bias, we did not feel it would impact on this outcome.

Mastectomy rate: because this is an objective outcome, we did not feel it was a high risk of bias.

Quality of life: the most reliable information would come from patient-reported outcomes, so assessment of risk of bias for this outcome would require information about how the data were collected.

Costs: we did not feel this was at high risk of bias. RIsk of bias is summarised in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Sequence generation was adequate for the following studies: FAST 2011; Shaitelman 2015; START A 2008; START B 2008 and Whelan 2002b; for Owen 2006a this was unclear. We know for FAST 2011; START A 2008, START B 2008 and Whelan 2002b that this allocation was computer-generated. In Patni 2012; Saha 2009 and Taher 2004 there was inadequate detail with respect to the method used for sequence generation.

Concealment of allocation was adequate for FAST 2011; Owen 2006a; START A 2008 and START B 2008. Computer-generated permuted blocks were used in FAST 2011; START A 2008 and START B 2008, which may allow prediction of the next randomisation in the sequence. If those undertaking recruitment are not aware that permuted blocks are being used, or the block size, then this should not distort the recruitment. In Whelan 2002b the process was central, although not explicitly described as concealed. In Taher 2004 "closed envelopes" were used, but few details given about the process used. In Saha 2009 there were no details given about allocation concealment and inadequate details ("were randomly assigned") in Patni 2012 and Shaitelman 2015.

Blinding

Subjective outcomes

In Whelan 2002b, the participants and personnel were not mentioned as blinded (which was unlikely to have an impact on risk of bias), but we judged Whelan 2002b to be at high risk of bias because the likely lack of blinding (not mentioned) could have introduced bias, particularly for assessment of cosmesis.

No details about blinding participants, personnel or assessors were given in Patni 2012 and Saha 2009 for subjective outcomes so these were deemed at unclear risk of bias.

In Shaitelman 2015 the participants and personnel were not mentioned as blinded (unlikely to have impact on risk of bias) and although the assessors of acute toxicity were not blinded, the use of a pre-specified toxicity scale reduced the associated risk of bias and as quality of life used participant-reported outcomes, this domain was judged to be at low risk of bias.

In FAST 2011; START A 2008 and START B 2008 the participants and personnel were not mentioned as blinded (unlikely to have an impact on risk of bias). The assessors for photographic appearance (FAST 2011; START A 2008; START B 2008) were blinded which was most important for assessment of this subjective primary outcome, so we judged this at low risk of bias.

The assessors for photographic appearance (Owen 2006a) were blinded which was most important for assessment of this subjective primary outcome, so we judged this at low risk of bias. Clinical assessments were not blinded (Owen 2006a), although they were done by many people, which may potentially reduce the risk of bias, so we judged this outcome to be at low risk of bias.

Although assessment of acute RT toxicity was not described as blinded, the assessment of cosmetic outcome was blinded in Taher 2004 so we judged it to be at low risk of bias.

Objective outcomes

Blinding was not mentioned in Owen 2006a; START A 2008 or START B 2008 therefore it was probably not done. The time points for clinical examinations were pre-specified, but the timing for mammography was not reported in Owen 2006a; START A 2008 or START B 2008. There may have been lead time bias in diagnosis of local recurrence by un-blinded assessors, so we deemed this outcome to be at unclear risk of bias for these studies. Blinding of outcome assessors was not mentioned in Whelan 2002b, therefore probably not done, however, lead time bias in diagnosis of local recurrence by un-blinded clinical assessors would be reduced by the pre-specified mammography and clinical examination intervals in Whelan 2002b, so we judged this outcome to be at low risk of bias. In Taher 2004, the study was described as "open", which suggests it was not blinded, so judged to be at low risk of bias. Blinding of assessors for objective outcomes: no details were given in Saha 2009 (deemed at unclear risk of bias). No objective outcomes were reported in Patni 2012 and Shaitelman 2015 (as they were interim reports) and we deemed them to be at unclear risk of bias. FAST 2011 was not blinded, but deemed to be at low risk of bias.

Incomplete outcome data

Subjective outcomes

In Owen 2006a, 1202/1410 women had photos at both baseline and at a later time point for the subjective cosmetic and toxicity outcomes assessment. Reasons for attrition were not detailed, but the number of women without a photo comprised less than 15% of the cohort, so we judged it at low risk of bias. No details were given with respect to attrition in Patni 2012 and Taher 2004. In START A 2008, 1306/2236 enrolled in the photographic study: assessed in 1055 participants with both a baseline and a follow-up photograph. In START B 2008 1094/2215 enrolled in the photographic study. For both START A 2008 and START B 2008 it is not clear why not all participants were enrolled, a source of possible bias, so deemed at unclear risk of bias.

Cosmetic outcome was assessed in 735/1220 women; those who had follow-up to five years at the time of the initial trial report (Whelan 2002b). It may be that the reason others did not have five years follow-up is because they had not been in the trial long enough, but it could also potentially be due to other reasons, perhaps because of withdrawal or non-attendance, a possible source of bias.

Late radiation toxicity was assessed in 752/1220 women at five years. It may be that not all women had five years follow-up, but this is not made clear (Whelan 2002b). The authors make the point that most of the toxic effects of radiotherapy are evident by five years follow-up.

For quality of life, the first 806/1410 women were selected to enrol in the prospectively collected physician assessments (START A 2008). In START B 2008, 1079/2215 enrolled in the quality-of-life study. It is not clear how the participants enrolled in the quality-of-life study were selected in both studies (START A 2008; START B 2008) so we deemed it to be at unclear risk of bias. No details regarding attrition were given in Saha 2009, so this was deemed at unclear risk of bias. For Shaitelman 2015, attrition was clearly reported by study arm, so was deemed to be at low risk of bias.

Objective outcomes

For FAST 2011 and Owen 2006a there were explicit details given with respect to the numbers lost to follow-up and the reasons (per treatment arm) given. Attrition was clearly described in START A 2008 and START B 2008. In Whelan 2002b there was no detail given regarding attrition, which is a potential source of bias. No details regarding attrition were given in Saha 2009 or Taher 2004. There were no objective outcomes reported in the first study reports of Patni 2012 and Shaitelman 2015, but they are likely to be reported in the future, so we deemed them to be at unclear risk of bias.

Selective reporting

All nine studies reported most of the outcomes detailed in the methods, but we were not able to review the protocols. START A 2008 and START B 2008 have not yet reported the health economics consequences. Without comparing the reports with the trial protocols, we could not be sure all outcomes had been reported. Therefore we judged them all at unclear risk of bias.

Other potential sources of bias

Some studies were potentially biased by early reporting. Owen 2006a reported "minimum 5 year follow-up" for the subjective primary outcome, so we judged it to be at unclear risk of bias. The trial was stopped early because the START A 2008 and START B 2008 trials started. For the subjective outcome assessed photographically in both START A 2008 and START B 2008, not all women were assessed at five years, so it is possible that only a small number of women were assessed with five years' follow-up. We found no other sources of bias in FAST 2011; Saha 2009; Shaitelman 2015 (so we judged this domain at low risk of bias). There was inadequate detail given to judge Patni 2012 and Taher 2004 (deemed at unclear risk of bias). For Whelan 2002b, we did not identify any other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Hypofractionated radiation therapy compared to conventionally fractionated radiation therapy for women treated with breast conserving therapy for early breast cancer

In the results presented, ratios of treatment effects are given such that HRs and RRs greater than 1.0 would indicate a beneficial effect of altered fraction size over conventional fractionation (although, as noted below, most of these results were not statistically significant).

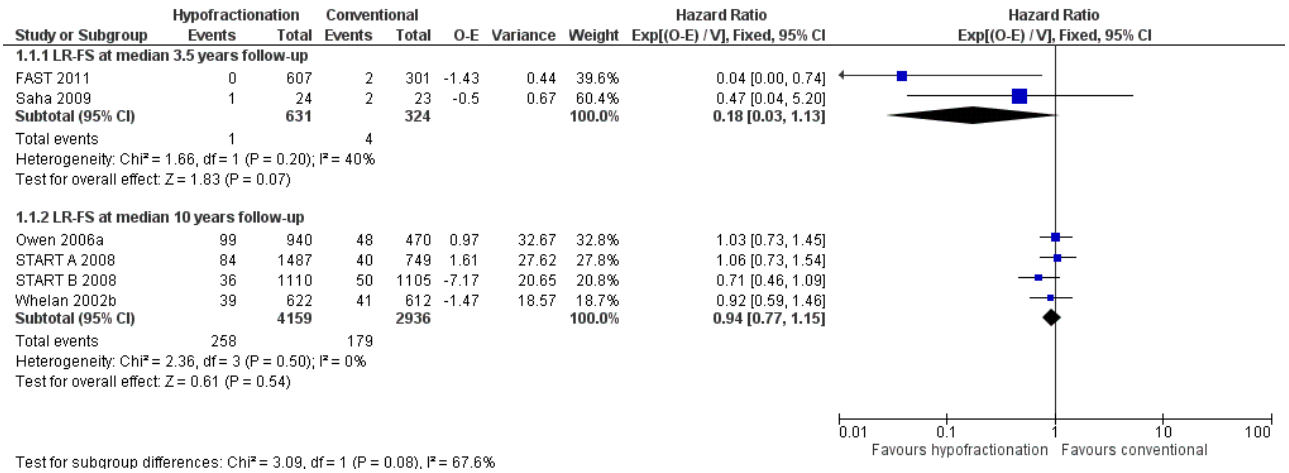
Primary outcomes

Local recurrence-free survival

We studied 442 local recurrences in 8050 women enrolled in six studies.

For the comparison of altered fraction size versus conventional fractionation we found that there was no clinically meaningful difference in local recurrence-free survival: HR 0.18 (95% CI 0.03 to 1.13) using observed events at 3.5 years and a HR 0.94 (95% CI 0.77 to 1.15) using observed events at ten years (Analysis 1.1; Figure 3). In absolute terms, this means 4 fewer local recurrences per 1000 women at median follow-up ten years (95% CI 14 fewer to 9 more). This represents 1.4% fewer local relapses (95% CI 1.6% fewer to 1.0% more) i.e. clinically meaningful harms or benefits have been excluded. Specifically, altered fractionation is non-inferior, not more than 2.5% worse than conventional fractionation. We found no evidence of heterogeneity: I^2 = 0%, P = 0.54 (FAST 2011; Owen 2006a; Saha 2009; START A 2008; START B 2008; Whelan 2002b).

Figure 3. Forest plot of comparison: 1 Hypofractionation versus conventional fractionation, outcome: 1.1 Local recurrence-free survival (LR-FS).



Sensitivity analysis

Our results were robust to sensitivity analysis, we excluded studies deemed at high risk of bias (Whelan 2002b). We found no difference in LR-FS: HR 0.94, 95% CI 0.76 to 1.17, P = 0.57. We found no evidence of heterogeneity: I^2 = 0%, P = 0.45.

Subgroup analysis

We did subgroup analysis by:

1. dose in the experimental arm < 50 Gy (START A 2008; START B 2008; Whelan 2002b) and ≥ 50 Gy (Saha 2009): HR 0.89 (95% CI 0.70 to 1.14, P = 0.36; Analysis 1.2). We found no heterogeneity:

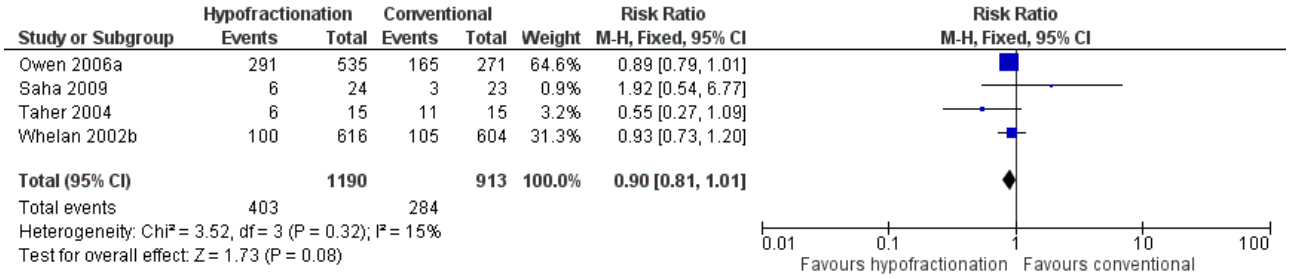
I^2 = 0%, P = 0.53. We tested for statistical difference between the subgroups (Chi^2 = 0.27, I^2 = 0%, P = 0.60) and found no difference between the subgroups;

2. length of follow-up 4.2 years versus 9.3 to 12 years. We tested for statistical difference between the subgroups (I^2 = 0%, P = 0.58) and found no difference between the subgroups.

Cosmesis: appearance (objective and subjective) of the post-treatment breast

We found no clinically meaningful difference in cosmesis for the comparison of altered fraction size versus conventional fractionation (687 events, 2103 women, four studies): RR 0.90, 95% CI 0.81 to 1.01, P = 0.08 (Analysis 1.3; Figure 4). In absolute terms, this represents 31 fewer women with poor or fair cosmetic outcome per 1000 women treated with altered fraction size (95% CI 59 fewer to 3 more), i.e. clinically meaningful harms have been excluded, but there may be meaningful benefit. We found little evidence of heterogeneity, I^2 = 15%, P = 0.32 (Owen 2006a; Saha 2009; Taher 2004; Whelan 2002b) (Analysis 1.3).

Figure 4. Forest plot of comparison: 1 Hypofractionation versus conventional fractionation, outcome: 1.3 Cosmesis (fair/poor).



Sensitivity analysis

We excluded studies deemed at high risk of bias (Whelan 2002b). We found that there may be an improvement in cosmesis for the comparison of altered fraction size versus conventional fractionation: RR 0.89, 95% CI 0.79 to 1.00, P = 0.06. There may be some heterogeneity; I^2 = 40%, P = 0.19.

START A 2008 reported photographic assessment of change in breast appearance for those women treated with breast conserving surgery (median follow-up of 6.0 years, maximum 6.2 years) using a three-point scale. A total of 1055 women (see Description of studies) were assessed at a mix of two and five years and were dichotomised into mild or marked change or no change (figures reported from text). For comparison of 41.6 Gy versus 50 Gy: HR 1.09 (95% CI 0.85 to 1.40, P = 0.62). For comparison of 39 Gy versus 50 Gy: HR 0.69 (95% CI 0.52 to 0.91, P = 0.01).

START B 2008 reported photographic assessment of change in breast appearance for those women treated with breast conserving surgery (median follow-up of 5.1 years, maximum six years) using a three-point scale. A total of 923 women (see Description of studies) were assessed at a mix of two and five years and were dichotomised into mild or marked change or no change (figures reported from text): HR 0.83 (95% CI 0.66 to 1.04, P = 0.06).

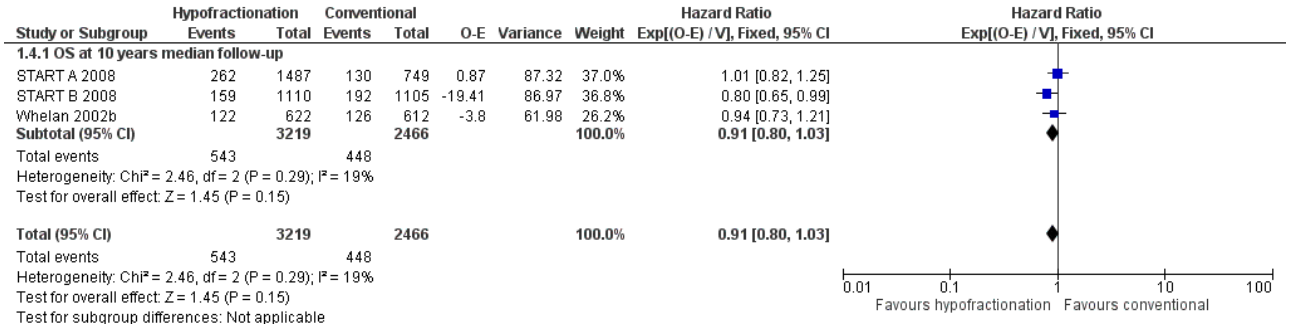
Owen 2006a reported minimum five-year follow-up for any or marked change in breast appearance and found no significant difference between the altered and conventional arms for any change: RR 1.01 (95% CI 0.88 to 1.17, P = 0.86) or for marked change: RR 1.24 (95% CI 0.77 to 2.00, P = 0.37). There was no difference in moderate or marked breast distortion between the two trial arms: RR 1.01 (95% CI 0.87 to 1.17, P = 0.90).

Secondary outcomes

Overall survival

We studied 991 deaths in 5685 women enrolled in three studies. For the comparison of altered fraction size versus conventional fractionation we found that there was no clinically meaningful effect on survival (median survival 9.3 to 9.9 years): HR 0.91 (95% CI 0.80 to 1.03, P = 0.15; Analysis 1.4; Figure 5). In absolute terms, there were 13 fewer deaths per 1000 women treated with altered fraction size (95% CI 31 fewer to 5 more). This represents 1.3% fewer deaths (95% CI 3.1% fewer to 0.5% more) i.e. clinically meaningful harms or benefits have been excluded. Specifically, altered fractionation is non-inferior, not more than 2.5% worse than conventional fractionation. We found little evidence of heterogeneity, I^2 = 19%, P = 0.29 (START A 2008; START B 2008; Whelan 2002b).

Figure 5. Forest plot of comparison: 1 Hypofractionation versus conventional fractionation, outcome: 1.4 Overall survival (OS).



Sensitivity analysis

Our results were robust to the exclusion of the study at high risk of bias (Whelan 2002b) with a HR 0.90 (95% CI 0.78 to 1.04). We found evidence of heterogeneity (I^2 = 58%, P = 0.12).

Toxicity

This outcome covers acute and late effects of radiation therapy, and chemotherapy-related toxicity.

Individual protocol-based definitions were used. Toxicity and late effects were reported on assessable numbers.

Acute radiation skin toxicity

We studied acute radiation skin toxicity: 93 events were reported in 357 women enrolled in two studies (FAST 2011; Taher 2004). Acute radiation toxicity was decreased by a clinically meaningful amount in the altered fractionation arm: RR 0.32, 95% CI 0.22 to 0.45, P < 0.00001. There may be some heterogeneity: (I^2 = 78%, P = 0.03; Analysis 1.5).

In Patni 2012 more acute skin toxicity was reported in the altered fractionation arm at seven to 10 days (90% versus 66.3%, P = 0.204; figures from text).

"Two patients (both 50 Gy in 25 fractions) experienced an unusually marked acute skin reaction during their radiation therapy, culminating in extensive moist desquamation" in START A 2008.

In START B 2008, "an unusually marked acute reaction during radiotherapy was recorded for 16 patients (13 after 50 Gy), three after 40 Gy. Of these, 14 cases were severe skin reactions (extensive moist desquamation)" (not reported by study arm).

Late radiation toxicity

Late skin toxicity

Skin toxicity was reported at 12 years: there were 39 events in 455 women from one study (Whelan 2002b). No woman had severe (Grade IV) skin toxicity. There was no clinically meaningful increase in late RT skin toxicity for women treated with altered fraction size RR 1.09 (95% CI 0.60 to 1.99, P = 0.77). In absolute terms, three more per 1000 women treated with altered fraction size (95% CI 15 fewer to 36 more), i.e. clinically meaningful harms or benefits have not been excluded. A test for heterogeneity was not applicable with only one trial.

Late radiation subcutaneous toxicity

This did not differ at:

1. five years: RR 1.07 (95% CI 0.85 to 1.35, P = 0.55, 806 participants, 1 study (Owen 2006a) (Analysis 1.7);
2. 10 years: RR 0.89 (95% CI 0.78 to 1.02, P = 0.10, 4324 participants, 2 studies (START A 2008; START B 2008) (Analysis 1.7).

We found no clinically meaningful difference in late radiation subcutaneous toxicity (975 events in 5130 women, four studies) for women treated with altered fraction size: RR 0.93, 95% CI 0.83 to 1.05, P = 0.24). In absolute terms, we found no fewer women with late RT toxicity per 1000 women treated with altered fraction size (95% CI 1 fewer to 0 more), i.e. clinically meaningful harms or benefits have been excluded. We found no heterogeneity: I^2 = 0%, P = 0.40. Test for subgroup difference, Chi^2 = 1.81, I^2 = 44.7%.

Late induration (sub-cutaneous fibrosis)

Measured at six months post RT this was "comparable" between the two arms (Patni 2012; no figures given).

Telangiectasia

Telangiectasia (190 events in 4632 women, three studies) was reduced by a clinically meaningful amount in women treated with altered fraction size compared with conventional fractionation: RR 0.68 (95% CI 0.52 to 0.91, P = 0.009; Analysis 1.8). In absolute terms, we found 16 fewer women developed telangiectasia with altered fraction size (95% CI 4 fewer to 23 fewer). We found no evidence of heterogeneity: I^2 = 0%, P = 0.85. Telangiectasia, measured at six months post RT was "comparable" between the two arms (Patni 2012; no figures given).

Breast oedema

Breast oedema (332 events in 4140 women, three studies) was reduced by a clinically meaningful amount in women treated with altered fraction size compared with conventional fractionation: RR 0.63 (95% CI 0.51 to 0.78, P < 0.0001; Analysis 1.9). In absolute terms, 36 fewer women developed breast oedema with altered fraction size (95% CI 21 fewer to 48 fewer) i.e. clinically meaningful benefit has not been excluded. We found no evidence of heterogeneity: I^2 = 0%, P = 0.43. Breast oedema, measured at six months post RT was "comparable" between the two arms (Patni 2012; no figures given).

Breast shrinkage

Breast shrinkage (950 events in 3869 women, two studies) did not differ by a clinically meaningful amount for the comparison of altered fraction size versus conventional fractionation: RR 0.89 (95% CI 0.79 to 1.00, P = 0.04; Analysis 1.10). In absolute terms, 26 fewer women developed breast shrinkage with the use of altered fraction size (95% CI 0 fewer to 49 fewer), i.e. clinically meaningful harms or benefits have been excluded. We found no evidence of heterogeneity: I^2 = 0%, P = 0.54.

Ischaemic heart disease

Ischaemic heart disease in women with left-sided tumours (18 events in 4451 women, two studies: START A 2008; START B 2008) appeared reduced by a clinically meaningful amount for the comparison of altered fraction size versus conventional fractionation: RR 0.71 (95% CI 0.28 to 1.79, P = 0.47). In absolute terms, one fewer woman developed ischaemic heart disease with altered fraction size (95% CI 3 fewer to 4 more), i.e. clinically meaningful harms or benefits have not been excluded. There was no heterogeneity: I^2 = 0%, P = 0.80 (Analysis 1.11).

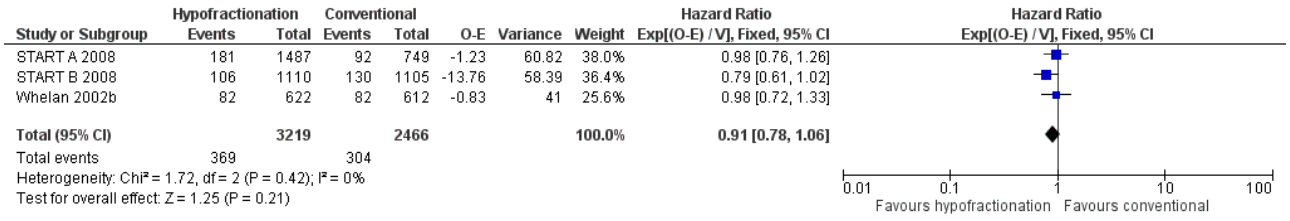
Rib fractures

Incidence of rib fractures (8 events in 5685 women, three studies: START A 2008; START B 2008; Whelan 2002b) was reduced by a clinically insignificant amount for the comparison of altered fraction size versus conventional fractionation: RR 0.87 (95% CI 0.25 to 3.10, P = 0.83). In absolute terms, no fewer women developed rib fractures with altered fraction size (95% CI 1 fewer to 3 more) i.e. clinically meaningful harms or benefits have not been excluded. There was no heterogeneity (I^2 = 0%, P = 0.78; Analysis 1.12).

Breast cancer-specific survival

We studied 673 breast cancer deaths in 5685 women enrolled in three studies (START A 2008; START B 2008; Whelan 2002b). For the comparison of altered fraction size versus conventional fractionation we found that there was no clinically meaningful difference for the outcome of breast cancer-specific survival: HR 0.91 (95% CI 0.78 to 1.06, P = 0.21; Analysis 1.13; Figure 6). In absolute terms, we found 10 fewer breast cancer deaths per 1000 women treated with altered fraction size (95% CI 25 fewer to 7 more). This represents 1.0% fewer breast cancer deaths (95% CI 2.5% fewer to 0.7% more) with altered fractionation i.e. clinically meaningful harms or benefits have been excluded. Specifically, altered fractionation is non-inferior, not more than 2.5% worse than conventional fractionation. We found no evidence of heterogeneity: I^2 = 0%, P = 0.42 (Analysis 1.13).

Figure 6. Forest plot of comparison: 1 Hypofractionation versus conventional fractionation, outcome: 1.13 Breast cancer-specific survival.



Relapse-free survival

We studied 870 relapses in 5685 women enrolled in three studies. We found no clinically meaningful evidence that the use of hypofractionation was detrimental to relapse-free survival (START A 2008; START B 2008; Whelan 2002b): HR 0.93, 95% CI 0.82 to 1.05, P = 0.24 (Analysis 1.14). In absolute terms, we found 14 fewer relapses per 1000 women treated with altered fraction size (95% CI 36 fewer to 10 more). This represents 1.4% fewer relapses (95% CI 3.6% fewer to 1.0% more) i.e. clinically meaningful harms or benefits have been excluded. Specifically, altered fractionation is non-inferior, not more than 2.5% worse than conventional fractionation. i.e. clinically meaningful benefits or harms have been excluded. We found some evidence of heterogeneity, I^2 = 62% , P = 0.07.

Sensitivity analysis

These results were robust to sensitivity analysis. We excluded a study deemed at high risk of bias (Whelan 2002b): HR 0.90, 95% CI 0.78 to 1.03. We found evidence of heterogeneity: I^2 = 74%, P = 0.05.

Mastectomy rate

No data.

Quality of life (trial-specific instruments)

Shaitelman 2015 reported less patient-reported fatigue (P < 0.001) and physician-reported fatigue (P = 0.009) for those women treated with altered fraction size (figures from text) compared to women treated with conventional fractionation at six months. Shaitelman 2015 reported no difference in mean FACT-B scores from baseline to six months for the following outcomes: physical well-being (P = 0.46), functional well-being (P = 0.38), emotional well-being (P = 0.58), social well-being (P = 0.32), FACT-G total score (P = 0.73), breast cancer concerns (P = 0.94) and FACT-B total score (P = 0.79).

Costs (to women and health services)

No data.

DISCUSSION

Summary of main results

We deemed that the Hazard Ratio of 0.75 or less and 1.25 or more was clinically meaningful and if the 95% confidence interval was greater than 0.75 or less and 1.25 or more, clinically meaningful benefits or harms had not been excluded. For the outcomes of local recurrence-free survival, overall survival, breast cancer-specific

survival and relapse-free survival, we determined (post-hoc) the MID was 2.5%.

Local recurrence-free survival

For these comparisons, there appears to be no clinically meaningful difference between the fractionation techniques for local recurrence-free survival, and clinically meaningful benefits or harms have been excluded.

Breast appearance (cosmesis)

For this comparison, there appears to be no clinically meaningful difference between the fractionation techniques for cosmetic outcome, and clinically meaningful benefits or harms have been excluded.

Overall survival

For this comparison, there was no clinically meaningful difference between the fractionation techniques, and clinically meaningful benefits or harms have been excluded.

Acute RT skin toxicity

For these comparisons, there appears to be a clinically meaningful reduction in acute RT toxicity when altered fraction size is used versus conventional fractionation.

Late RT toxicity

For the comparison of altered fraction size versus conventional fractionation for the following outcomes there was no difference: late skin toxicity, late subcutaneous toxicity, breast shrinkage, ischaemic heart disease and rib fractures. Both telangiectasia and breast oedema were reduced in women who had altered fraction size, compared with conventional fractionation.

Breast cancer-specific survival

For this comparison, we found no clinically meaningful difference between the fractionation techniques, and clinically meaningful benefits or harms have been excluded.

Relapse-free survival

For this comparison, we found no clinically meaningful difference between the fractionation techniques, and clinically meaningful benefits or harms have been excluded.

Mastectomy rate

For this comparison, we found no data with respect to subsequent mastectomy rates.

Quality of life

Shaitelman 2015 reported less patient- and physician-reported fatigue for those women treated with altered fraction size. Shaitelman 2015 reported no difference in mean FACT-B scores for: physical well-being (P = 0.46), functional well-being (P = 0.38), emotional well-being (P= 0.58), social well-being (P = 0.32), FACT-G total score (P = 0.73), breast cancer concerns (P = 0.94) and FACT-B total score (P = 0.79).

Costs

We found no data with respect to costs or women's preference for either altered or conventional fractionation.

For women with early breast cancer, achieving and maintaining local control in addition to maximising survival are the main goals of management. Whilst conservative surgery followed by radiation therapy allows preservation of the breast, the requirement for five to six weeks of radiation therapy, which may only be available at some distance from the woman's residence, can be a burden. The many costs involved (monetary and other) may mean that women choose mastectomy over breast-conserving therapy to avoid the necessity for radiation therapy (Nattinger 2001).

Shortening the duration of postoperative breast radiation would provide the advantage of shorter disruption of normal activities and less time away from home and family. Reducing the number of fractions required would also free up radiation therapy machine time. This may reduce waiting lists and improve timely access to radiation therapy for other people with cancer. The ability to reduce the number of fractions required to treat women with early breast cancer safely may, therefore, result in many benefits at a personal, national and international level provided acceptable local control, toxicity and survival can be maintained with this approach.

This review set out to explore whether shortened (altered fraction size) regimens used to treat women who have had conservative surgery for early breast cancer can offer the same tumour control and cosmetic results as longer fractionation regimens. We have been able to include data from nine randomised controlled trials that compared different fractionation schemes. The comparison studied is altered fraction size (fraction size greater than 2 Gy) versus conventional fractionation (2 Gy per fraction).

The findings of this review provide reassurance that the practice of offering shortened radiation fractionation regimens to carefully selected groups of women with early breast cancer is equivalent in terms of local control, breast appearance, survival and late radiation breast toxicity, with associated improvements in some cosmetic parameters (telangiectasia and breast oedema).

Overall completeness and applicability of evidence

Participants

These results are mostly applicable to women with small to medium breasts, aged greater than 50 years, with node negative tumours less than 3 cm in size, with negative pathological margins.

Sixty-eight percent (5332/7824) of the women enrolled in the nine studies were node negative (see Table 4) and 100% of the women studied in this review had negative pathological margins (not stated in Saha 2009 or Owen 2006a). T3 tumours (larger than 5 cm) account for 9% (724/7513) of the total number of women studied. Most women studied in this review had small to medium breasts (83%; 4859/5845, where breast size was reported).

Treatment and follow-up

The length of follow-up was not adequate to detect differences in breast cancer mortality (not apparent before 15 years' follow-up) (EBCTCG 2011). If, however, there are truly no differences in local recurrence or late toxicity (e.g. cardiac morbidity) one would not expect to see differences in mortality. We did not see an increase in either late RT skin toxicity (Analysis 1.6) or late subcutaneous toxicity (Analysis 1.7) at either five or 10 years' follow-up. We found no differences in breast shrinkage (Analysis 1.10), rib fractures (Analysis 1.12) or ischaemic heart disease

(Analysis 1.11) with longer follow-up. With respect to radiation therapy-induced ischaemic heart disease (IHD), there is an excess risk of IHD after radiation therapy which is proportional to the mean heart dose (MHD) received. This increased risk is apparent at four years and persists for many years (Darby 2013). It is axiomatic that the reduction in MHD dose received may be of clinical benefit, reducing the risk of IHD for women with left-sided breast cancer treated with radiation therapy. The use of specialised radiotherapy techniques, such as deep inspiration breath hold (DIBH) can dramatically reduce MHD (Eldrege-Hindy 2015; Sixtel 2001).

It is possible that the reduction in acute radiotherapy toxicity seen when altered fraction size is used (Analysis 1.5), resulted in a reduction in consequential late radiation-induced effects, such as telangiectasia (Analysis 1.8) and breast oedema (Analysis 1.9).

Radiation dose

In total, 442 local recurrences were reported in 8050 women. Using an alpha/beta ratio of four for breast tumour cells (Fowler 1989; Steel 1987; Williams 1985) allows conversion of radiation doses to EQD_2 (Maciejewski 1986; Withers 1983). When the altered fraction size regimen radiation doses are converted to EQD_2 (see Table 4), it is clear that some of the altered regimens (39 Gy in 13 fractions, 42.5 Gy in 13 fractions, 41.6 Gy in 13 fractions and 40 Gy in 15 fractions) (Owen 2006a; START A 2008; START B 2008; Whelan 2002b) have lower EQD_2 than the conventional 50 Gy in 25 fractions. Subgroup analysis by dose (less than 50 Gy versus 50 Gy) did not reveal any differences: $Chi^2 = 0.27$, $I^2 = 0\%$, P = 0.06. Bartelink 2008 showed that all women irrespective of age showed improved local control with addition of a 16 Gy boost to conventionally fractionated radiotherapy. The reason for the lack of a difference in local control with lower EQD_2 used in the altered fraction size trials is uncertain. Possible reasons include the impact of the boost used in 44% of women treated (see Table 8), but it may reflect the effect of the use of more and better systemic therapy which also improves local control. For Shaitelman 2015, START A 2008 and START B 2008, the use of a boost was roughly equally divided between the treatment arms. While boosts are associated with decreased local recurrence, they are also associated with poorer cosmesis (Bartelink 2007).

Cost, peoples' preference and quality of life

It has not been possible at this time to answer questions of cost and patient preferences within this review. There was significantly less acute radiation toxicity in the altered arm and one could reasonably expect that shorter regimens are more readily tolerated and, therefore, would enhance the treatment experience for women. The use of altered fraction size was associated with less fatigue (both participant- and physician-reported) and there was no effect on patient-reported quality-of-life measures at six months, suggesting there was no detrimental effect on quality of life.

A detailed assessment of quality of life is planned for a subset of women enrolled in START A 2008 and START B 2008, which may provide more information. These data have not yet been reported by study arm, so we could not include them in this version of the review. Little is known about patient preferences in this setting but as rural women have consistently been shown to have more mastectomies in comparison with women who live in bigger centres (Nattinger 2001; Schroen 2005) it may be that they choose mastectomy to reduce their time away from home (assuming they are offered conservative treatment as frequently as women in urban areas).

Adjuvant therapies

We do not have information about combining other therapies (for example, trastuzumab) with these fractionation regimens, although observational data suggest it to be a safe practice with conventionally fractionated radiation therapy (Romond 2005).

Optimum fraction size

The optimum 'dose' of altered fraction size remains unknown. In FAST 2011; Owen 2006a and START A 2008, two novel altered fraction size schedules were tested, however we were not able to analyse them separately to see if one was superior to the other. We did not find a difference in LR-FS when we analysed by dose less than 50 Gy versus 50 Gy or more in the experimental arm (test for subgroup difference $I^2 = 0\%$, P = 0.58). In addition, new techniques (such as accelerated partial breast irradiation) shorten treatment time even more by using larger fraction sizes to a smaller volume of breast tissue. These techniques are the subject of a number of ongoing trials.

Technological innovations

New technology, for example, intensity modulated radiation therapy (IMRT), which uses multiple radiation beams in order to make treatment highly conformal (thus reducing dose to normal structures) and improve dose distribution has been shown to decrease acute radiotherapy toxicity (Donovan 2007) and improve cosmesis (Pignol 2008).

Quality of the evidence

We studied 8228 women enrolled in nine trials. There is now a large body of high quality evidence allowing robust conclusions.

Local recurrence-free survival

For the outcome of LR-FS we did not downgrade for risk of bias, indirectness, inconsistency ($I^2 = 0\%$, P = 0.61), imprecision (more than 300 events (360), optimum information size (OIS) was met and 95% confidence intervals (CIs) excluded clinically meaningful benefits or harms) or publication bias. The GRADE quality of evidence was therefore judged to be 'high'.

Cosmesis

For the outcome of cosmesis we downgraded for risk of bias, because one study (Whelan 2002b) did not blind outcome assessors for subjective outcomes, this study contributed 1220/2103 (60%) of the data for cosmetic outcome. We did not downgrade for indirectness, inconsistency ($I^2 = 15\%$, P = 0.32), imprecision (more than 300 events (687), OIS met and 95% CIs included one, and excluded clinically meaningful benefits or harms) or publication bias. The GRADE quality of evidence was therefore judged to be 'high'.

Toxicity - late subcutaneous fibrosis

For late subcutaneous fibrosis we did not downgrade for risk of bias, as only 5% of events were contributed from a study at high risk of bias for lack of blinding. We did not downgrade for indirectness, or inconsistency ($I^2 = 0$, P = 0.4). We did not downgrade for imprecision

(because there were more than 300 events (975), OIS was met and CIs included one, but excluded clinically meaningful benefits or harms) or publication bias. The GRADE quality of evidence was therefore judged to be 'high'.

Overall survival

For overall survival we did not downgrade for risk of bias, indirectness or inconsistency (I^2 = 19, P = 0.29). We did not downgrade for imprecision (more than 300 events (991), OIS was met and the CIs included one, and excluded clinically meaningful benefits or harms) or publication bias. The GRADE quality of evidence was therefore judged to be 'high'.

Breast cancer-specific survival

For breast cancer-specific survival we did not downgrade for risk of bias (12% of events came from a study deemed at high risk of bias because of a lack of blinding), indirectness, or inconsistency (I^2 = 0%, P = 0.42). We did not downgrade for imprecision (because there were more than 300 events (673), OIS was met and CIs included one, but excluded clinically meaningful benefits or harms) or publication bias. The GRADE quality of evidence was therefore judged to be 'high'.

Relapse-free survival

For relapse-free survival, we did not downgrade for risk of bias or indirectness, but did downgrade for inconsistency (I^2 = 74%, P = 0.05). We did not downgrade for imprecision (because there were more than 300 events (673), OIS was met and CIs included one, but excluded clinically meaningful benefits or harms) or publication bias. The GRADE quality of evidence was therefore judged to be 'moderate'.

Mastectomy rate

We found no data with respect to this outcome.

Potential biases in the review process

We believe we have identified the relevant studies, and we have identified five ongoing studies (see NCT00459628; NCT00909818; NCT01266642; NCT01349322; NCT01413269). The ongoing studies will include women treated with more modern chemotherapy agents and hormonal manipulation.

There are limitations related to assessment of subjective outcomes, such as cosmesis and breast induration, but this was well-performed using standardised tools by trained observers in Owen 2006a and Whelan 2002b, with blinding of the outcome assessors to the treatment allocation in FAST 2011; Owen 2006a START A 2008; START B 2008; Shaitelman 2015 Taher 2004 and Whelan 2002b.

Agreements and disagreements with other studies or reviews

Published guidelines with respect to this question are as follows.

NICE guidelines state: "Use external beam radiotherapy giving 40 Gy in 15 fractions as standard practice for patients with early invasive breast cancer after breast conserving surgery or mastectomy".

NCCN guidelines state: "The breast should receive 45-50 Gy in 23 to 25 fractions or 40 to 42.5 Gy in 15 to 16 fractions (short course is preferred)".

American Society for Therapeutic Radiation Oncology (ASTRO) guidelines state: "Evidence from randomized clinical trials has demonstrated that hypo-fractionated- whole breast irradiation (HF-WBI) and conventionally fractionated (CF)-WBI are equally effective for in-breast tumour control and comparable in long term side effects for patients meeting all the criteria listed (see Table 10). The task force was unable to reach agreement as to the equivalence of HFWBI to CF-WBI for patients who do not satisfy all these criteria, and thus, we could not make a recommendation either for or against the use of HF-WBI in such patients." (Smith 2011).

We found one systematic review of hypofractionation for breast and prostate cancer (Ray 2015). The authors searched Web of Science, PubMed, Google Scholar and ICTRP (search date not reported) as well as trawling reference lists. They conclude: "Hypofractionation in breast cancer treatment is now the standard protocol in the UK. " (Ray 2015).

AUTHORS' CONCLUSIONS

Implications for practice

In selected women with early breast cancer (with negative margins and size 3 cm or less, with small to medium sized breasts), shortened fractionation regimens are not detrimental for cancer-related outcomes (no clinically meaningful difference with the use of altered fraction size. Clinically meaningful benefits or harms excluded for local recurrence-free survival, overall survival, relapse-free survival and breast cancer-specific survival) and altered fraction size may be associated with a reduction in late radiation therapy toxicity. There still remains uncertainty about the effect of altered fraction size on ischaemic heart disease, although new radiation techniques, which avoid treating the heart, mean this of less importance.

Implications for research

There are a number of questions still unanswered with respect to costs and quality of life that relate to the use of altered fraction size in the treatment of early breast cancer for women undergoing breast cancer surgery. These questions are likely to be answered by both ongoing studies and future publications of completed studies.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

FAST 2011

Methods	Randomised controlled trial, multi-centred, set in UK
Participants	N = 729/915 women ≥ 50 years, invasive BC, treated with BCS, tumour size < 3 cm, negative margins, negative axilla (surgically staged). Excluded: RNI, MRM, boost and neoadjuvant or adjuvant chemotherapy
Interventions	Altered fraction size: N = 613; 30 Gy/5 # or 28.5 Gy/5 # Conventional RT: N = 302; 50 Gy/25 #
Outcomes	Primary outcome: photographic change in beast appearance Secondary outcome: clinically assessed RT-induced changes in breast, local control
Notes	Median follow-up 37.3 months Funding: NHS, Cancer Research UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "treatment allocation used computer-generated random permuted blocks" page 94, paragraph 3
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed by telephone or facsimile" Page 94, paragraph 3
Blinding (performance bias and detection bias) Subjective outcomes	Low risk	Quote: "All photographs were scored by three observers blinded to patient identity and treatment allocation", page 94, paragraph 8
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Quote: "Treatment allocation could not be blinded due to the nature of the intervention" page 94, paragraph 3
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	Attrition was clearly detailed, by arm, with reasons given; page 96, Figure 1
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	Attrition was clearly detailed, by arm, with reasons given; page 96, Figure 1
Selective reporting (reporting bias)	Unclear risk	We did not have access to the study protocol, so judged this domain to be at unclear risk of bias
Other bias	Low risk	We found no other sources of bias

Owen 2006a

Methods	Randomised, multi-centre setting: tertiary cancer centres, set in UK
Participants	1410 British women with operable (T1-3N0-1MO) invasive breast cancer requiring radiotherapy. 1138 women had small or medium breasts (from photographs at baseline). Median follow-up 9.7 years (range 7.8 to 11.8) Mean age of women: 54.5 years.
Interventions	Experimental arm (n = 474): 39 Gy in 13 fractions, or 42.9 Gy in 13 fractions (N = 466) over 5 weeks Control arm (N = 470): 50 Gy in 25 fractions over 5 weeks
Outcomes	Primary outcome: late change in breast appearance (scored from photos) Secondary endpoints: palpable breast induration and ipsilateral breast recurrence. Women reviewed 3-monthly to 36 months, 6-monthly to 60 months, then annually. Annual physician toxicity review. Photographs annually to 60 months, then at 10 years in all evaluable participants
Notes	Photos: frontal photos taken after surgery before RT, then annually to 5 years and at 10 years under standard conditions. Photos scored by 3 observers In total, 196/1410 women received chemotherapy and 1074/1410 received tamoxifen (numbers not given by study arm) Funding: Marks and Spencer PLC and Cancer Research UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "were randomised" (Abstract). Not adequately described to be sure it was truly randomised
Allocation concealment (selection bias)	Low risk	Quote: "randomisation achieved by a telephone call to the Clinical trials and Statistics Unit at the Institute of Cancer Research, Sutton" (Para 3, page 10) Quote: "Randomisation was done by telephone at the Clinical trials and Statistics Unit (ICR-CTSU) at the Institute of Cancer Research, Sutton by the clinician (early in the trial), who recorded it in the patient's notes and did not have any further role in the randomisation process, and then by a research nurse. Although randomisation was not blinded" (Paragraph 2, page 3)
Blinding (performance bias and detection bias) Subjective outcomes	Low risk	Participant: not mentioned, unlikely to be a problem for nurse- or clinician-assessed outcomes Personnel: not mentioned, probably not done Assessors: photographic assessors blinded to treatment arm. Quote: "Assessments of the change in breast appearance were blinded" (Paragraph 3, page 2). Clinical assessments were not blinded (although done by many people, which may potentially reduce bias)
Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	Participant: not mentioned, probably not done, unlikely to be a source of bias Personnel: not mentioned, probably not done Assessors: not mentioned, probably not done Although time points for clinical examinations were pre-specified, there is no mention of the timing of mammograms
Incomplete outcome data (attrition bias)	Low risk	Cosmetic outcome, late radiation toxicity and quality of life: 1202/1410 women had photos at both baseline and at a later time point. Quote: "reasons for non-

Owen 2006a *(Continued)*

Subjective outcomes		availability explored, and no evidence was observed that this was associated with either the fractionation schedule or to the probability of experiencing future normal tissue event or local relapse." (These data not reported) Reasons for attrition not detailed, a potential source of bias, but the number of women without a photo comprised < 15% of the cohort, so judged at low risk of bias. The first 806/1410 women had prospectively collected physician assessments (including normal tissue effects) for ten years. It is not clear why these women were chosen and the others excluded from the sample
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	Attrition: 42.9 Gy in 13 fractions; 8 lost to follow-up, 4 moved, 4 unable to attend 39 Gy in 13 fractions; 2 lost to follow-up, 1 emigrated, 1 unable to be traced 50 Gy in 25 fractions; 8 lost to follow-up, 7 moved (2 emigrated), 1 did not attend appointments and was then discharged
Selective reporting (reporting bias)	Unclear risk	Outcomes specified in methods/protocol: late change in breast appearance (scored from photographs), palpable breast induration (fibrosis), ipsilateral tumour recurrence Outcomes reported in paper: late change in breast appearance (scored from photographs), clinical assessment of cosmesis, breast shrinkage, distortion, oedema, induration, telangiectasia, arm oedema, shoulder stiffness, local recurrence, distant relapse, contralateral breast cancer
Other bias	Unclear risk	Premature reporting for primary endpoint (subjective). Quote: "minimum 5 year follow-up". Study stopped early because START trials commenced

Patni 2012

Methods	RCT
Participants	N = 40 women with early breast cancer
Interventions	Experimental arm: 40 Gy/15 fractions + electron or brachytherapy boost Control arm: 50 Gy/25 fractions + electron or brachytherapy boost
Outcomes	Acute RT toxicity assessed at 7-10 days after RT (dermatitis, breast pain, breast oedema, heat sensations) Chronic toxicity assessed at 6 months Locoregional control and disease-free survival
Notes	CTCAE version 3.0 used

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote:"randomly assigned" no further details, so judged at unclear risk of bias
Allocation concealment (selection bias)	Unclear risk	No description, so judged at unclear risk of bias

Patni 2012 *(Continued)*

Blinding (performance bias and detection bias) Subjective outcomes	Unclear risk	No details described, probably not done
Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	No details described, probably not done
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	No details given
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	No details given
Selective reporting (reporting bias)	Unclear risk	No information, study reported in abstract form
Other bias	Unclear risk	Nil observed

Saha 2009

Methods	Randomised, single institution pilot study, country: India
Participants	N = 131 women with early breast cancer, treated with mastectomy (N = 84, BCS = 47)
Interventions	Experimental arm: N = 69 (24/69 had BCS) 30 Gy/5 # Control arm: N = 62 (23/62 had BCS) 50 Gy/25 #
Outcomes	Locoregional recurrences, late toxicity (scored using LENT-SOMA) and cosmetic outcome (evaluated by a panel using four-point scale)
Notes	All women received FAC (6 cycles) Median follow-up: 42 months Sequential boost, using HDR given in 41/47 BCS participants Funding: no details given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised". No details given, so graded as unclear
Allocation concealment (selection bias)	Unclear risk	No details given so graded as unclear
Blinding (performance bias and detection bias) Subjective outcomes	Unclear risk	No details given so graded as unclear

Saha 2009 *(Continued)*

Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	No details given so graded as unclear
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	No details given so graded as unclear
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	No details given so graded as unclear
Selective reporting (reporting bias)	Unclear risk	As we only had an abstract, this domain was graded as unclear
Other bias	Low risk	We found no other sources of bias

Shaitelman 2015

Methods	RCT
Participants	N = 287 women with Stage Tis, 1-2N0-1aM0 BC breast cancer treated with BCS, with negative margins
Interventions	Experimental arm: N = 138; 42.5 Gy in 16 fractions + 10-12.5 Gy boost in 4-5 fractions Control arm: N = 149; 50 Gy in 25 fractions + 10-14 Gy boost in 5-7 fractions
Outcomes	Primary: Participant-reported cosmesis at three years Secondary: Dr-reported cosmesis, acute toxicity, patient-reported quality of life, in breast tumour recurrence (IBTR)
Notes	Quality of life assessed using FACT-B Acute toxicity assessed by physicians RTOG CTCAE Fatigue assessed by both participants and clinicians Dose homogeneity required (cold use wedges, 3DCRT or IMRT) to achieve max < 108% of prescribed RT dose Respiratory gating allowed Funding: no details supplied

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote:"were randomly allocated", page E2, paragraph 7 Quote:"The Popcock-Simon randomisation methods was used", page E2, paragraph 7
Allocation concealment (selection bias)	Unclear risk	Quote:"were randomly assigned" Abstract, paragraph 1 No details given, so judged to be at unclear risk of bias

Shaitelman 2015 *(Continued)*

Blinding (performance bias and detection bias) Subjective outcomes	Low risk	Quote: "Acute toxicity...as assessed by physicians", no mention of blinding, therefore judged as unclear Cosmetic outcome was physician-reported, quote: "postoperative physician reported cosmetic assessment", E2, paragraph 7 and no mention is made of blinding, but the protocol makes it clear the physician panel is blinded to treatment arm, which makes this domain at low risk of bias. Quote: "patient-reported QOL" Page E2, paragraph 9, which makes this at low risk of bias. We deemed this to be at low risk of bias, these results were not presented in this report. The use of a pre-specified toxicity reporting scale may have reduced the risk of bias even though it was assessed in an unblinded fashion.
Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	No objective outcomes reported, so judged at unclear risk of bias
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	Attrition: Experimental 0 (acute RT toxicity), 7 (late RT toxicity), 20 (QOL at 6 months) Control: 0 (acute RT toxicity), 9 (late RT toxicity) 0 QOL at 6 months. SInce attrition was reported clearly by study arm, we deemed this to be at low risk of bias
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	No objective outcomes reported, but this is a first report, focusing on subjective outcomes, we judged this to be at unclear risk of bias
Selective reporting (reporting bias)	Unclear risk	This report of the study does not include physician reported cosmetic outcomes, but these will likely be reported in the future, we judged this to be at unclear risk of bias
Other bias	Low risk	We found no other sources of bias

START A 2008

Methods	Randomised, multi-centre setting: tertiary cancer centres
Participants	2236 British women with operable (T1-3N0-1M0) invasive breast cancer requiring radiotherapy. 1071/1250 women (with photographs available at baseline) had small or medium breasts. Median follow-up 9.3 years. Mean age 57.2 years.
Interventions	Experimental arm (N = 750): 41.6 Gy in 13 fractions or 39 Gy in 13 fractions (N = 737) over 5 weeks Control arm (N = 749): 50 Gy in 25 fractions over 5 weeks
Outcomes	Primary outcome: loco-regional relapse, normal tissue effects and quality of life Secondary outcomes: disease-free survival, overall survival, second primaries, health economics consequences (not specified) and toxicity. Women reviewed annually for loco-regional relapse and normal tissue effects.
Notes	Normal tissue effects assessed by photos, patient and doctor assessments Photos at baseline, 2 and 5 years (blinded assessment) Funding: Cancer Research UK, UK Medical Research Council, UK Department of Health
Risk of bias	

START A 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned" (Abstract). Quote: "computer generated and not blinded" (Abstract). Quote: "START A patients were randomised" (Para 3, page 3). Probably done
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was arranged via telephone at the Clinical Trials and Statistics Unit at the Institute of Cancer Research (ICR-CTSU), Sutton, UK, where the patient details were recorded and treatment allocated. Randomisation was not blinded. Computer-generated permuted blocks were used as a method of allocation" (Para 4, page 3) Provided those undertaking recruitment are not aware that permuted blocks are being used, or the block size, then this should not distort the recruitment
Blinding (performance bias and detection bias) Subjective outcomes	Low risk	Participant: not mentioned, probably not done; unlikely to have impact Personnel: not mentioned, probably not done; unlikely to have impact Assessors: Quote: "Changes in breast appearance (photographic) were scored by three observers blinded to patient identity, treatment allocation and year of follow up" (Para 3, page 4). Probably done and this is most important for assessment of this subjective primary outcome
Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	Participant: not mentioned, probably not done; unlikely to have impact Personnel: not mentioned, probably not done; unlikely to have impact Assessors: not mentioned, probably not done. Although time points for clinical examinations were pre-specified, there is no mention of the timing of mammograms, which may be a source of bias
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	Cosmetic outcome, late radiation toxicity and quality of life: Quote: "1129/2236 enrolled in quality of life study" It is not clear how the participants enrolled in the quality-of-life study were selected 1306/2236 enrolled in photographic study: assessed in 1055 participants with both a baseline and a follow-up photograph Quote: "There were no associations between score for change in breast appearance (photographic) at two years or patient demographic or treatment characteristics and whether or not the patient had a five-year assessment (data not shown)." It is not clear why not all participants were enrolled in the photographic study
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	Attrition described clearly: Quote: "41.6 Gy in 13 fractions; 2 with baseline data only, 1 moved, 1 unknown, 39 Gy in 13 fractions; 2 with baseline data only, 2 withdrew consent to follow up after randomisation, 50 Gy in 25 fractions; 5 with baseline data only, 3 withdrew consent to follow up after randomisation, 2 moved"
Selective reporting (reporting bias)	Unclear risk	Outcomes specified in methods/protocol: local-regional tumour relapse, late normal tissue effects (photographic change in breast appearance). Quality of life, disease-free survival, overall survival, second primary cancers, health economic consequences, ischaemic heart disease, symptomatic rib fracture, symptomatic lung fibrosis, brachial plexopathy.

START A 2008 *(Continued)*

		Outcomes reported in paper: local-regional tumour relapse, distant relapse, disease-free survival, overall survival, second primary cancers, ischaemic heart disease, symptomatic rib fracture, symptomatic lung fibrosis, brachial plexopathy, disease-free survival, overall survival, second primary cancers, ischaemic heart disease, symptomatic rib fracture, symptomatic lung fibrosis, brachial plexopathy "Quality of life outcomes will be the subject of another paper". Health economic consequences not reported
Other bias	Unclear risk	Quote: "Not all patients had photographs available at both 2 and 5 years, for reasons including the 5-year assessment not being yet due at the time of scoring and analysis..." This may represent early reporting

START B 2008

Methods	Randomised, multi-centre setting: tertiary cancer centres
Participants	2215 British women with operable (T1-3N0-1M0) invasive breast cancer requiring radiotherapy. 858/1036 women treated with breast conserving surgery (with photographs available at baseline) had small or medium-sized breasts. Median follow-up 9.7 years. Mean age 57.4 years
Interventions	Experimental arm (N = 1110): 40 Gy in 15 fractions over 3 weeks Control arm (N = 1105): 50 Gy in 25 fractions over 5 weeks
Outcomes	Primary outcome: loco-regional relapse, normal tissue effects and quality of life. Secondary outcomes: disease-free survival, overall survival, second primaries, health economics consequences (not specified) and toxicity. Women reviewed annually for loco-regional relapse and normal tissue effects
Notes	Normal tissue effects assessed by photos, patient and doctor assessments Photos at baseline, 2 and 5 years (blinded assessment) Funding: Cancer Research UK, UK Medical Research Council, UK Department of Health

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned" (Abstract). Quote: "computer generated and not blinded" (Abstract). Quote: "START B patients were randomised" (Para 2, page 2). Probably done
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was arranged via telephone at the Clinical Trials and Statistics Unit at the Institute of Cancer Research (ICR-CTSU), Sutton, UK, where the patient details were recorded and treatment allocated. Randomisation was not blinded. Computer-generated permuted blocks were used as a method of allocation" (Para 2, page 2) Provided those undertaking recruitment are not aware that permuted blocks are being used, or the block size, then this should not distort the recruitment
Blinding (performance bias and detection bias) Subjective outcomes	Low risk	Participant: not mentioned, probably not done; unlikely to have impact Personnel: not mentioned, probably not done; unlikely to have impact

START B 2008 *(Continued)*

		Assessors: Quote: "Changes in breast appearance (photographic) were scored by three observers blinded to patient identity, treatment allocation and year of follow up" (Para 2, page 3). Probably done and this is most important for assessment of this subjective primary outcome
Blinding (performance bias and detection bias) Objective outcomes	Unclear risk	Participant: not mentioned, probably not done; unlikely to have impact Personnel: not mentioned, probably not done; unlikely to have impact Assessors: not mentioned, probably not done. Although time points for clinical examinations were pre-specified, there is no mention of the timing of mammograms, which may be a source of bias
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	Cosmetic outcome, late radiation toxicity, quality of life 1094/2215 enrolled in photographic study Quote: "There were no associations between score for change in breast appearance (photographic) at two years or patient demographic or treatment characteristics and whether or not the patient had a five-year assessment (data not shown)." It is not clear why not all participants were enrolled in photographic study 1079/2215 enrolled in quality-of-life study It is not clear how the women enrolled in the quality-of-life study were selected
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	Attrition: 40 Gy in 15 fractions arm; 10 with baseline data only, 3 ineligible, 7 withdrew consent to follow-up after randomisation 50 Gy in 25 fractions; 9 with baseline data only, 5 withdrew consent to follow-up after randomisation, 2 moved, 2 unknown (Fig 1) Unlikely to introduce bias in objective outcomes
Selective reporting (reporting bias)	Unclear risk	Outcomes specified in methods/protocol: local-regional tumour relapse, late normal tissue effects (breast, arm and shoulder) assessed by photographic, self-reported and doctor assessed. Quality of life, disease-free survival, overall survival, second primary cancers, health economic consequences, ischaemic heart disease, symptomatic rib fracture, symptomatic lung fibrosis, brachial plexopathy. Outcomes reported in paper: local-regional tumour relapse, distant relapse, disease-free survival, overall survival, change in breast appearance (photographic), patient self-assessment of breast, ischaemic heart disease, symptomatic rib fracture, symptomatic lung fibrosis, brachial plexopathy, acute radiation therapy reactions, contralateral breast cancers, second primary cancers. Health economic consequences have not been reported
Other bias	Unclear risk	Version of "early stopping" or early reporting, (median follow-up 6.0 years). 1094 enrolled in photographic study, but the outcome assessed in 923 women (with both photograph at baseline and either 2 or 5 years follow-up) It is possible that the numbers of women with 5 years' follow-up is small, but detail is not given

Taher 2004

Methods	RCT, setting Egypt
Participants	N = 30 women > 65 years, with T1-2N0M0 treated with BCS, negative margins, ⩾ 10 nodes removed, with separation < 25 cm,
Interventions	Experimental arm: 42.5 Gy/16 fractions plus Control arm: 50 Gy/25 fractions plus 10 Gy/5 fraction boost
Outcomes	Acute skin toxicity Late cosmetic outcome
Notes	Chemotherapy (20/30) and hormonal therapy given (but not detailed by arm) Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "a controlled randomized, open (with allocation concealment using closed-envelope method)" Page 179, paragraph 3. Inadequate detail given, so deemed at unclear risk of bias.
Allocation concealment (selection bias)	Unclear risk	Quote: "a controlled randomized, open (with allocation concealment using closed-envelope method)" Page 179, paragraph 3. Inadequate detail given, so deemed at unclear risk of bias. The use of closed envelopes can lead to high risk of bias, so more details required to make a judgement.
Blinding (performance bias and detection bias) Subjective outcomes	Low risk	Quote: 'The RTOG scoring system for radiation reactions were used to score radiation toxicity. The cosmetic outcome was assessed at 6, 12 and 24 months. The second author was the one to score cosmesis blinded to the treatment arm', page 180, paragraph 2. Although it is not stated that the assessor for acute toxicity was blinded, the assessor for cosmesis was, so we deemed this category at low risk of bias.
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Quote: "a controlled randomized, open" Page 179, paragraph 3. Not blinded, which would have been difficult, given the nature of the intervention, deemed at low risk of bias.
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	Not mentioned therefore judged at unclear risk of bias
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	Not mentioned, therefore judged to be at unclear risk of bias
Selective reporting (reporting bias)	Unclear risk	We did not have access to the protocol, so judged this domain to be at unclear risk of bias
Other bias	Unclear risk	There was inadequate detail to allow judgement

Whelan 2002b

Methods	Randomised, multi-centred, setting: tertiary institutions
Participants	1234 Canadian women with invasive breast cancer (< 5 cm, i.e. no T3/T4 lesions, negative margins and node negative) treated with lumpectomy. Exclusions: those with multi-centric disease, large breasts (separation > 25 cm) and those with bilateral breast cancer. Median follow-up 12 years. Approximately 75% of the women were aged over 50 years
Interventions	Experimental arm (N = 622): radiation dose to breast alone; 42.5 Gy in 16 fractions (dose per fraction 2.65 Gy, BED = 70.65) Control arm (N = 612): radiation dose 50 Gy in 25 fractions (dose per fraction 2.0 Gy, BED = 75)
Outcomes	Primary outcome: local recurrence of invasive breast cancer in treated breast Secondary outcomes: distant recurrence of invasive breast cancer, death, breast cosmesis and late radiation toxicity. Cosmesis assessed using EORTC Cosmetic Rating System (by trained nurse). Global cosmetic outcome assessed using 4-point scale. Late radiation toxicity assessed by trained nurse using RTOG/EORTC late radiation morbidity scale
Notes	Concurrent interventions were evenly divided between the 2 arms: 254 women in the experimental arm received tamoxifen and 251 in the control arm, 70 women in the experimental arm received chemotherapy and 66 in the control arm. Moderate risk of bias Funding: National Cancer Institue Canada and Ontario Clinical Oncology Group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned" (Abstract) Quote: "computer-generated central randomisation schedule within strata defined by age (< 50 years or ≥ 50 years), tumour size (≤ 2 cm or > 2 cm), adjuvant systemic therapy (tamoxifen, any chemotherapy or on therapy) and centre" (Para 3, page 4) It sounds as if it was truly randomised
Allocation concealment (selection bias)	Unclear risk	Quote: "computer-generated central randomisation schedule within strata defined by age (< 50 years or ≥ 50 years), tumour size (≤ 2 cm or > 2 cm), adjuvant systemic therapy (tamoxifen, any chemotherapy or on therapy) and centre" (Para 3, page 4) It is not explicitly stated that the randomisation process was concealed, although it was central
Blinding (performance bias and detection bias) Subjective outcomes	High risk	Participant: not mentioned, but the participant cannot have been blinded, as they would know how many fractions of RT they received. This may affect how they report the subjective outcomes, although they were not participant-assessed Personnel: not mentioned, probably not done Assessors: not mentioned (unlikely, given the lack of blinding in other personnel) but likely to introduce bias, particularly for subjective outcomes e.g. cosmesis.
Blinding (performance bias and detection bias) Objective outcomes	Low risk	Participant: not mentioned, but the participant cannot have been blinded, as they would know how many fractions of RT they received. Not possible to blind participant, but unlikely to introduce bias in objective outcomes, espe-

Whelan 2002b *(Continued)*

		cially as interval for mammography pre-specified. Quote: "mammograms six monthly, then annually" Personnel: not mentioned, probably not done Assessors: no comment made, but as regular mammograms performed, a lack of blinding in outcome assessors could contribute to lead time bias in the diagnosis of local recurrence, but this would be unlikely to be significant over a prolonged follow-up period
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	Cosmetic outcome was assessed in 735/1220 women; those who had follow-up to 5 years at the time of the initial trial report. It may be that the reason others did not have five years' follow-up is because they had not been in the trial long enough, but it could also potentially be due to other reasons, perhaps because of withdrawal or non-attendance Late radiation toxicity was assessed in 752/1220 women at 5 years. It may be that not all women had 5 years' follow-up, but this is not made clear. The authors make the point that most of the toxic effects of RT are evident by 5 years' follow-up.
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	Exclusions: 0 Although the number analysed equals the number randomised, it seems unlikely that all the participants would be available for follow-up after a period of as long as 10 years. If there are missing data, there is no information given about how they were dealt with
Selective reporting (reporting bias)	Unclear risk	Outcomes specified in methods/protocol: any local recurrence in treated breast, distant recurrence, death, breast cosmesis, late RT toxicity. Cosmetic outcome: at 3 and 5 years. Late RT toxicity: at 3 and 5 years. Outcomes reported in paper: local recurrence-free survival, local recurrence rate, disease-free survival, death, breast cosmesis, late RT toxicity (both at 3 and 5 years), skin toxicity, subcutaneous toxicity, rib fractures and pneumonitis
Other bias	Low risk	No other sources of bias identified

BC: breast cancer
BCS: breast conserving surgery
BED: biological equivalent dose
Gy: Gray
M: metastases
MRM: modified radical mastectomy
N: lymph node
QoL: quality of life
RNI: regional nodal irradiation
RT: radiotherapy
T: tumour
#: fraction

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

Study	Reason for exclusion
Anon 1981	Surgery was wide local excision versus mastectomy

Study	Reason for exclusion
Baglan 2001	Did not examine external beam radiation
Baillet 1990	This is a preliminary report of an RCT, describing 230 of the 525 planned enrolment of women with breast cancer, 50% were treated with mastectomy, 21% managed without surgery and 26%-30% had clinically apparent nodes at baseline, 17% had inflammatory breast cancer. This population was ineligible for inclusion in our review
Bates 1975	Surgery was modified radical mastectomy
Bates 1988	Surgery was modified radical mastectomy
Brinkley 1984	Surgery was modified radical mastectomy
Bruce 1971	Surgery was modified radical mastectomy versus simple mastectomy
Dvivedi 1978	Surgery was modified radical mastectomy and regional radiation therapy was examined
FAST-forward 2014	Control arm is 40 Gy/15 fractions (> 2 Gy per fraction)
Formenti 2002	Partial breast radiation therapy was examined
Goel 2000	Surgery was modified radical mastectomy
Liljegren 1993	Intervention was radiation therapy in experimental arm only
NCT00793962	Not breast conservation
NCT01247233	Partial breast irradiation
Olivotto 1996	Intervention was +/- aspirin
Ptaszynski 1999	Examined boost versus no boost
Romestaing 1997	Examined boost versus no boost
Sanguineti 2001	Was a chemotherapy trial
Spooner 2012	Study of immediate versus delayed RT. RT randomised to 40 Gy/15 versus 50 Gy/25 fractions, but study ineligible because RT volume included breast, SCF and axilla
UK-FAST 2009	Control arm not conventional radiotherapy
Vermessen 2012	45/121 (37%) women had mastectomy, 37/121 (30%) with involved nodes were treated with regional nodal radiotherapy and 42/121 (34%) received concurrent chemotherapy
Vrieling 2000	Examined boost versus no boost
Wallace 1993	Women were treated with regional nodal irradiation
Wallgren 1978	Investigates preoperative radiation therapy
Wang 2013	Surgery was mastectomy

RCT: randomised controlled trial

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

NCT00459628

Trial name or title	Tomobreast
Methods	RCT
Participants	Ages eligible for study: 18 years and older Genders eligible for study: female Accepts healthy volunteers: no Inclusion Criteria: Informed consent Histologically proven breast carcinoma Stage I or II (T1-3N0 or T1-2N1 M0, AJCC/TNM 6th edition) Surgery with clear margins Pre-operative medical imaging (at least CT, MRI, and/or PET-scan) Exclusion Criteria: Prior breast or thoracic radiotherapy Pregnancy or lactation Fertile women without effective contraception Psychiatric or addictive disorders
Interventions	Experiental arm: CT image guided intensity modulated radiation therapy delivered by the Tomotherapy HiArt system (45 Gy/15 #) Conventional radiotherapy: Radiation therapy delivered by conventional linear accelerator using matching fields (50 Gy/25 #)
Outcomes	Primary outcome measures: Change from baseline in pulmonary function and heart function tests Assessment by pulmonary function tests and by heart echocardiography, compared with test values prior to treatment Secondary outcome measures: Local-regional recurrences Local-regional recurrences are assessed at time intervals as per the institution's standard practice for the clinical surveillance of women
Starting date	May 2007
Contact information	Vincent Vinh-Hung, MD, PhD, Clinical Professor, Vrije Universiteit Brussel
Notes	N = 118 Accrual May 2007-Dec 2016

NCT00909818

Trial name or title	Hypofractionated versus standard fractionated whole breast irradiation to node-negative breast cancer
Methods	Randomised controlled trial Parallel assignment
Participants	Participants: women ⩾ 41 years old Inclusion criteria: operated with breast concerning strategy for (i) invasive breast cancer, pT1-2, pN0-1 mi, M0 OR (ii) carcinoma in situ of the breast, tissue ⩾ 20 mm and/or van Nuys > 1 and/or margin < 10 mm

NCT00909818 *(Continued)*

Interventions	Arm 1: standard fractionated radiotherapy (active comparator) 50 Gy / 25 fractions, 2 Gy/fraction, 5 fractions per week Arm 2: hypofractionated radiotherapy (experimental) Hypofractionated radiotherapy 40 Gy/15 fractions
Outcomes	Grade 2 or 3 fibrosis 3 years after radiotherapy Any other late morbidity after adjuvant radiotherapy Genetic risk profile for late morbidity Recurrent/Survival
Starting date	May 2009
Contact information	Birgitte Offersen (bvo@oncology.dk)
Notes	Anticipated end date: May 2022

NCT01266642

Trial name or title	Randomized Trial of Hypofractionated Whole Breast Irradiation Versus Conventionally Fractionated Whole Breast Irradiation for Ductal Carcinoma in Situ and Early Invasive Breast Cancer
Methods	Randomised safety study
Participants	Inclusion Criteria: Pathologically confirmed ductal carcinoma in situ of the breast or early invasive breast cancer defined as pathologic stage Tis, T1, or T2, N0, N1mic, or N1a (pathologic staging of the axilla is required for all patients with invasive disease but is not required for patients with DCIS only). (Upfront pathologic stage cannot be assigned to patients treated with neoadjuvant chemotherapy. For such patients, the criteria for pathologic stage shall be applied to the initial clinical stage) Treatment with breast conserving surgery Final surgical margins must be negative, defined as no evidence for ductal carcinoma in situ or invasive breast cancer touching the inked surgical margin. If the invasive or in situ breast cancer approaches within less than 1 mm of the final surgical margin, then a re-excision is strongly encouraged. Lobular carcinoma in situ at the final surgical margin will be disregarded. Age 40 years or older. This age cutoff is justified because breast cancers in women under the age of 40 are known to have a significantly higher risk of IBTR presumably due to underlying biologic differences Female Attending radiation oncologist declares intention to treat the whole breast only and that a third radiation field to treat regional lymph nodes is not planned (radiation of the un-dissected level I/II axilla with high tangents is allowed) If the patient has a history of a prior non-breast cancer, all treatment for this cancer must have been completed prior to study registration and the patient must have no evidence of disease for this prior non-breast cancer Patients must be enrolled on the trial within 12 weeks of the later of two dates: the final breast conserving surgical procedure or administration of the last cycle of cytotoxic chemotherapy Exclusion Criteria: Pathologic or clinical evidence for a stage T3 or T4 breast cancer Pathologic evidence for involvement of 4 or more axillary lymph nodes, or imaging evidence of involvement of infraclavicular, supraclavicular, or internal mammary lymph nodes Clinical or pathologic evidence for distant metastases Any prior diagnosis of invasive or ductal carcinoma in situ breast cancer in either breast Current diagnosis of bilateral breast cancer History of therapeutic irradiation to the breast, lower neck, mediastinum or other area in which there could potentially be overlap with the affected breast

NCT01266642 *(Continued)*

	Patients not fluent in English or Spanish. (The Informed Consent will be available in these two languages) Patient is pregnant
Interventions	Radiation: hypofractionated whole breast irradiation 42.56 Gy in 16 fractions delivered to the whole breast on consecutive treatment days Boost of 10 Gy in 4 fractions or 12.5 Gy in 5 fractions delivered on consecutive days beginning on treatment day following completion of whole breast irradiation Radiation: conventionally fractionated whole breast irradiation 50 Gy in 25 fractions delivered to whole breast on consecutive treatment days Boost of 10 Gy in 5 fractions or 14 Gy in 7 fractions delivered on consecutive treatment days, beginning on treatment day following completion of whole breast irradiation
Outcomes	Primary Outcome Measures: Percentage of women with adverse cosmetic scores at 3 Years (time frame: 3 years) (designated as safety issue: Yes) Comparison of patient-reported cosmetic outcomes using Breast Cancer Treatment Outcomes Scale (BCTOS): 1) Hypofractionated whole breast irradiation (HF-WBI) versus 2) Conventionally fractionated whole breast irradiation (CF-WBI). Number of women with adverse cosmetic scores at 3 years after completion of breast conserving surgery, as determined by the patient-reported BCTOS where a score of 2.5 or more indicates an adverse cosmetic outcome
Starting date	February 2011
Contact information	Smith, B
Notes	N = 288 Study commenced Feb 2011

NCT01349322

Trial name or title	A phase III trial of accelerated whole breast irradiation with hypofractionation plus concurrent boost versus standard whole breast irradiation plus sequential boost for early-stage breast cancer
Methods	Phase II open label RCT
Participants	Women aged 18-70 Disease characteristics: 1. Pathologically proven diagnosis of breast cancer resected by lumpectomy and whole-breast irradiation (WBI) with boost without regional nodal irradiation planned 2. Must meet one of the following three criteria: pStage I or II breast cancer and at least one of the following: age < 50 years or positive axillary nodes or lymphovascular space invasion (LVI) or at least 2 close resection margins (> 0 mm to ≤ 2 mm) or one close resection margin and extensive in-situ component (EIC) or focally positive resection margins or non-hormone-sensitive breast cancer (oestrogen and progesterone receptor negative (ER- and PR-) or grade III histology or oncotype recurrence score > 25 or pStage 0 breast cancer with nuclear grade 3 ductal carcinoma in situ (DCIS) and patient age < 50 years or 3. If multifocal breast cancer, then it must have been resected through a single lumpectomy incision with negative margins 4. Breast-conserving surgery with margins defined as follows: negative margins defined as no tumour at the resected specimen edge. Close resection margins > 0 mm to ≤ 2 mm as follows: 1 close resection margin and EIC; 2 or more close resection margins; a focally positive resection margin 5. Allowable options for mandatory axillary staging include: sentinel node biopsy alone (if sentinel node is negative, pN0, pN0[IHC-,+]); sentinel node biopsy alone, or followed by axillary node dissection, for clinically node-negative patients as described below; microscopic sentinel node (SN)

NCT01349322 *(Continued)*

positive (pN1mic); 1 or 2 SNs positive (pN1) without extracapsular extension; negative SN biopsy after neoadjuvant chemotherapy. Axillary node dissection is required following SN biopsy with a minimum total of 6 axillary nodes if any of the following exist: for > 2 positive SN; any positive SN biopsy after neoadjuvant chemotherapy; for clinically (by either imaging or examination) T3 disease; for extracapsular extension. Axillary dissection alone (with a minimum of 6 axillary nodes)

6. CT-imaging of the ipsilateral breast within 28 days of study entry for the radiation therapy planning. Must be able to delineate on CT scan the extent of the target lumpectomy cavity for boost (placement of surgical clips to assist in treatment planning of the boost is strongly recommended)
7. No clinical evidence for distant metastases, based upon the following minimum diagnostic workup: history/physical examination, including breast exam (inspection and palpation of the breasts) and documentation of weight and Zubrod Performance Status of 0-2 within 28 days prior to study entry; a mammogram of both right and left breast within only 1 time point of 90 days of the diagnostic biopsy establishing the diagnosis
8. No prior invasive or in-situ carcinoma of the breast (prior LCIS is eligible)
9. No American Joint Committee on Cancer (AJCC) pathologic T4, N2 or N3, or M1 breast cancer
10. Must not have two or more breast cancers that are not resectable through a single lumpectomy incision
11. Must not be DCIS and ≥ 50 years old
12. Must not be DCIS only (without an invasive component), nuclear grade 1 or 2 and < 50 years old
13. No suspicious unresected microcalcification, densities, or palpable abnormalities (in the ipsilateral or contralateral breast) unless biopsied and found to be benign
14. No non-epithelial breast malignancies such as sarcoma or lymphoma
15. No Paget disease of the nipple
16. No male breast cancer
17. Breast implants allowed

Patient characteristics:

1. ANC ≥ 1,800/mm^3
2. Platelet count ≥ 75,000/mm^3
3. Haemoglobin ≥ 8.0 g/dL (transfusion or other intervention to achieve Hgb ≥ 8.0 g/dL is acceptable)
4. Negative urine or serum pregnancy test within 14 days of study entry
5. Women of childbearing potential must not be pregnant or nursing and willing to use medically acceptable form of contraception during radiotherapy
6. No prior invasive non-breast malignancy (except non-melanomatous skin cancer or carcinoma in situ of the cervix) unless disease free for a minimum of 5 years prior to study entry
7. No severely active co-morbidity, defined as follows: unstable angina and/or congestive heart failure requiring hospitalisation within the last 6 months; transmural myocardial infarction within the past 6 months; acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration; chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalisation or precluding study therapy within 30 days before registration; hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol; Acquired Immune-Deficiency Syndrome (AIDS) based upon current CDC definition (HIV testing is not required for entry into this protocol)
8. No active systemic lupus, erythematosus, or any history of scleroderma or dermatomyositis with active rash
9. Medical, psychiatric, or other condition that would prevent the patient from receiving the protocol therapy or providing informed consent

Prior concurrent therapy:

1. See disease characteristics
2. Study entry must be within 50 days of last breast/axillary surgery and/or last chemotherapy
3. No treatment plan that includes regional-node radiotherapy
4. No prior radiotherapy to the breast or prior radiation to the region of the ipsilateral breast that would result in overlap of radiation therapy fields

NCT01349322 *(Continued)*

	5. No intention to administer concurrent chemotherapy for current breast cancer
Interventions	Active Comparator: Arm I participants undergo standard whole-breast radiotherapy (WBI) comprising intensity-modulated radiation therapy (IMRT) or three-dimensional conformal radiotherapy (3D-CRT) 5 days a week for 3-5 weeks followed by a sequential radiotherapy boost to the lumpectomy area 5 days a week for 1-1½ weeks in the absence of disease progression or unacceptable toxicity Experimental: Arm II participants undergo accelerated hypofractionated WBI comprising IMRT or 3D-CRT with a concurrent boost to the lumpectomy area 5 days a week for 3 weeks in the absence of disease progression or unacceptable toxicity
Outcomes	Primary outcome measures: local control (time frame: from randomisation to the date of first local failure or last follow-up. Analysis occurs after 245 local failures have been reported.) (Designated as safety issue: no) Secondary outcome measures: overall survival (time frame: from randomisation to date of death due to any cause or last follow-up.) (Designated as safety issue: no) Disease-free survival (time frame: from randomisation to date of local-regional disease recurrence, distant metastases, second primary, death due to any cause or last follow-up.) (Designated as safety issue: no) Distant disease-free survival (time frame: from randomisation to date of distant metastases, second primary, death due to any cause or last follow-up.) (Designated as safety issue: no) Changes in breast-related symptoms and side effects and cosmesis (time frame: from randomisation to 3 years.) (Designated as safety issue: no) Correlation between dose-volume data and both adverse events and efficacy (time frame: from randomisation to end of follow-up.) (Designated as safety issue: no) Treatment cost of accelerated course of hypofractionated WBI versus standard WBI with a sequential boost (time frame: from randomisation to end of treatment.) (Designated as safety issue: no)
Starting date	May 2011- Aug 2020
Contact information	Principal investigator: Frank Vicini St Joseph Mercy Oakland
Notes	N = 2312

NCT01413269

Trial name or title	Phase 3 Open-labeled Randomized Clinical Study of Comparing Hypofractionated and Conventional Radiotherapy for Breast Cancer Patients After Breast Conservative Surgery
Methods	Phase III RCT
Participants	Women aged 18-70 years Inclusion Criteria: 1. KPS >= 60 2. histology confirmed invasive breast cancer 3. received breast conservative surgery (wide local excision and axilla dissection, or axillary sentinel node biopsy if sentinel node is negative) 4. surgical margins negative 5. primary tumour ≤ 5 cm in the largest diameter 6. no internal mammary node or supraclavicular node metastases or distant metastasis 7. can tolerate chemotherapy, hormone therapy (if needed) and radiotherapy 8. for participants not needing chemotherapy enrolment date is required no more than 8 weeks from surgery date

NCT01413269 *(Continued)*	9. for participants with chemotherapy first enrolment date is required no more than 8 weeks from the last date of chemotherapy 10. participants signed written inform consent form Exclusion Criteria: 1. ductal carcinoma in situ 2. prior neoadjuvant chemotherapy 3. prior breast cancer history 4. bilateral breast cancer 5. pregnant or lactating 6. prior or concomitant malignant tumour excluded skin cancer (not malignant melanoma) and cervix carcinoma in situ 7. active collagen vascular disease 8. prior neoadjuvant hormone therapy 9. immediate ipsilateral breast reconstruction
Interventions	Experimental: hypofractionation radiotherapy, irradiation to the whole breast to a total dose of 43.5 Gy,at 2.9 Gy per fraction, 5 fractions a week, followed by tumour bed boost of 8.7 Gy, at 2.9 Gy per fraction 5 fractions a week Active Comparator: conventional fractionation radiotherapy, irradiation to the whole breast to a total dose of 50 Gy,at 2.0 Gy per fraction, 5 fractions a week, followed by tumour bed boost of 10 Gy, at 2.0 Gy per fraction 5 fractions a week
Outcomes	Primary outcome measures: in-breast recurrence rate (time frame: 5 years) evidence of ipsilateral breast local recurrence confirmed by histology Secondary outcome measures: regional node recurrence rate (time frame: 5 years) ipsilateral axillary node, internal mammary node and supraclavicular node recurrence confirmed by physical examination, image evaluation or histology; disease-free survival (time frame: 5 years); overall survival (time Frame: 5 years); acute toxicity (time frame: 6 months) radiation dermatitis and radiation pneumonitis evaluated and graded by CTC3.0 criteria; late complication (time frame: 3-10 years) breast cosmetic effect, ischaemic heart disease, rib fracture, arm edema and shoulder joint dysfunction
Starting date	June 2010-June 2019
Contact information	Study Chair: Ye-xiong Li, Principal Investigator: Shu-lian Wang Chinese Academy of Medical Science
Notes	N = 630

DATA AND ANALYSES

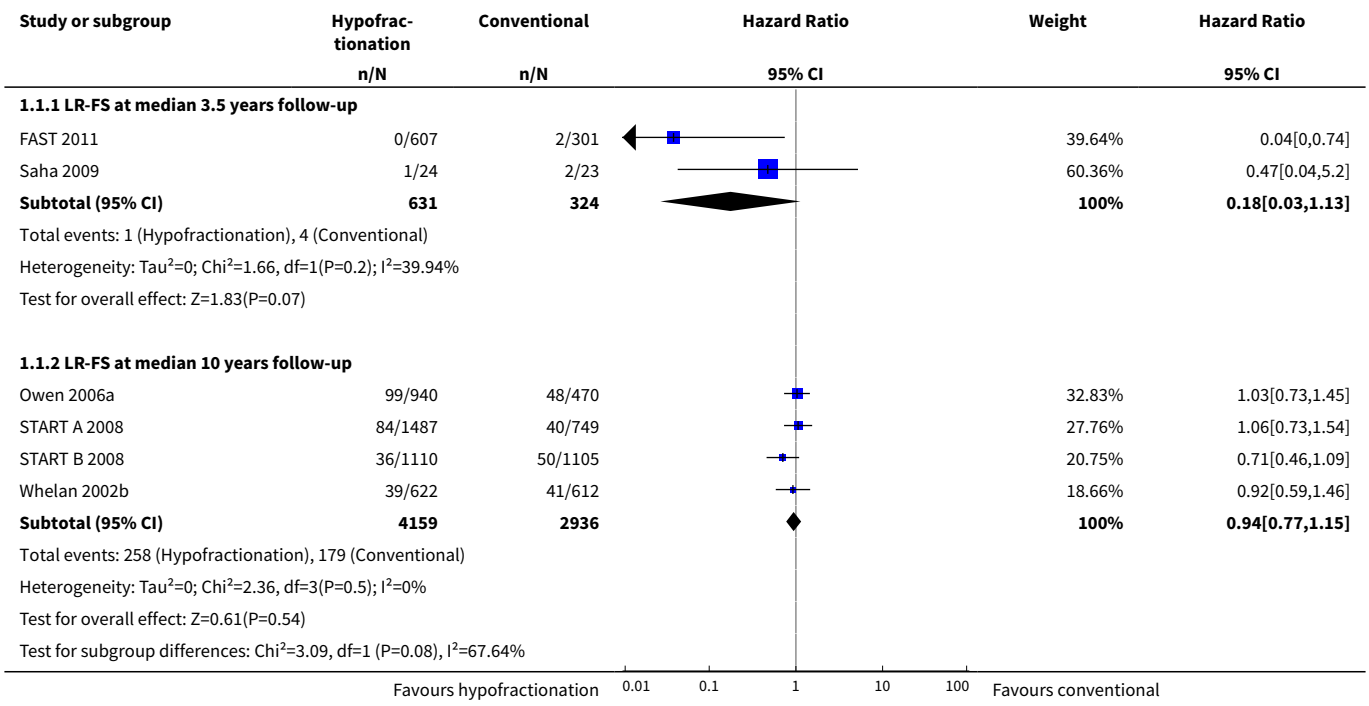
Comparison 1. Hypofractionation versus conventional fractionation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Local recurrence-free survival (LR-FS)	6		Hazard Ratio (95% CI)	Subtotals only
1.1 LR-FS at median 3.5 years follow-up	2	955	Hazard Ratio (95% CI)	0.18 [0.03, 1.13]

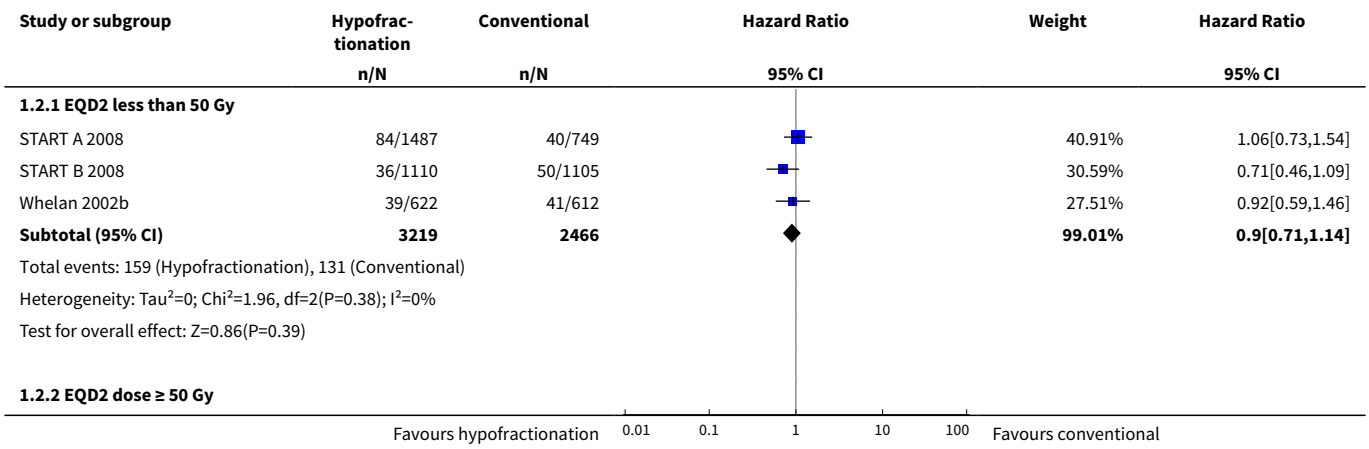
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 LR-FS at median 10 years follow-up	4	7095	Hazard Ratio (95% CI)	0.94 [0.77, 1.15]
2 LR-FS by dose	4	5732	Hazard Ratio (95% CI)	0.89 [0.70, 1.14]
2.1 EQD_2 less than 50 Gy	3	5685	Hazard Ratio (95% CI)	0.90 [0.71, 1.14]
2.2 EQD_2 dose ≥ 50 Gy	1	47	Hazard Ratio (95% CI)	0.47 [0.04, 5.20]
3 Cosmesis (fair/poor)	4	2103	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.81, 1.01]
4 Overall survival (OS)	3	5685	Hazard Ratio (95% CI)	0.91 [0.80, 1.03]
4.1 OS at 10 years median follow-up	3	5685	Hazard Ratio (95% CI)	0.91 [0.80, 1.03]
5 Acute skin radiation toxicity	2	357	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.22, 0.45]
6 Late skin toxicity	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Late skin RT toxicity at 10 years	1	455	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.60, 1.99]
7 Late subcutaneous toxicity (fibrosis))	4	5130	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.83, 1.05]
7.1 Subcutaneous skin toxicity at 5 years	1	806	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.85, 1.35]
7.2 Subcutaneous skin toxicity at 10 years	3	4324	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.78, 1.02]
8 Telangiectasia	3	4632	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.52, 0.91]
9 Breast oedema	3	4140	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.51, 0.78]
10 Breast shrinkage	2	3869	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.79, 1.00]
11 Ischaemic heart disease (left-sided tumours)	2	4451	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.28, 1.79]
12 Rib fractures	3	5685	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.25, 3.10]
13 Breast cancer-specific survival	3	5685	Hazard Ratio (95% CI)	0.91 [0.78, 1.06]
14 Relapse-free survival	3	5685	Hazard Ratio (95% CI)	0.93 [0.82, 1.05]

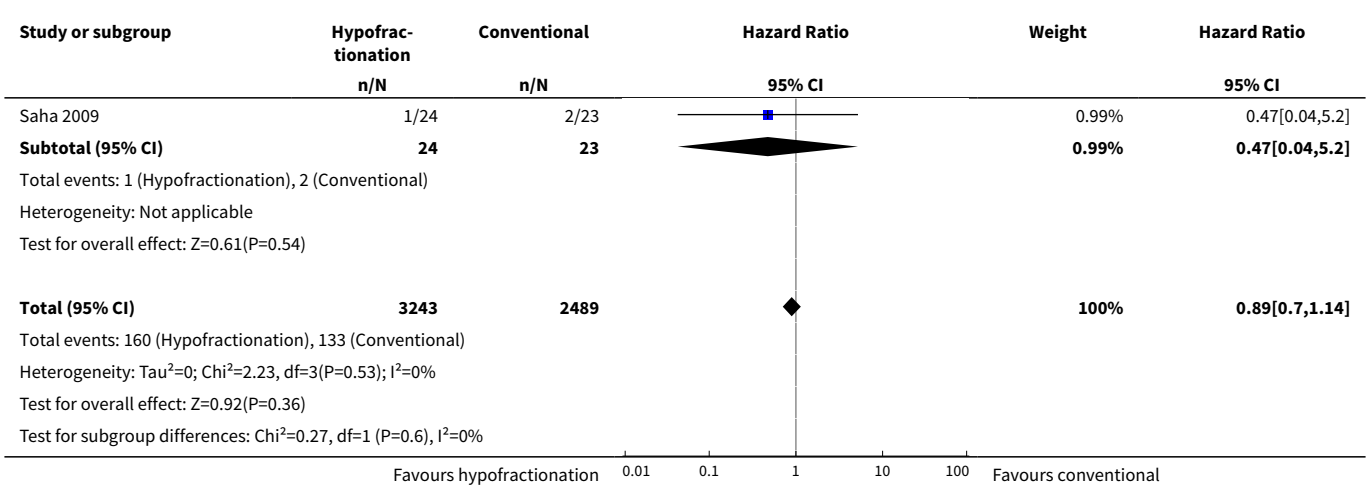
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Relapse-free survival at median 5 years follow-up	1	1234	Hazard Ratio (95% CI)	1.10 [0.81, 1.49]
14.2 Relapse-free survival at 10 years median follow-up	2	4451	Hazard Ratio (95% CI)	0.90 [0.78, 1.03]

Analysis 1.1. Comparison 1 Hypofractionation versus conventional fractionation, Outcome 1 Local recurrence-free survival (LR-FS).

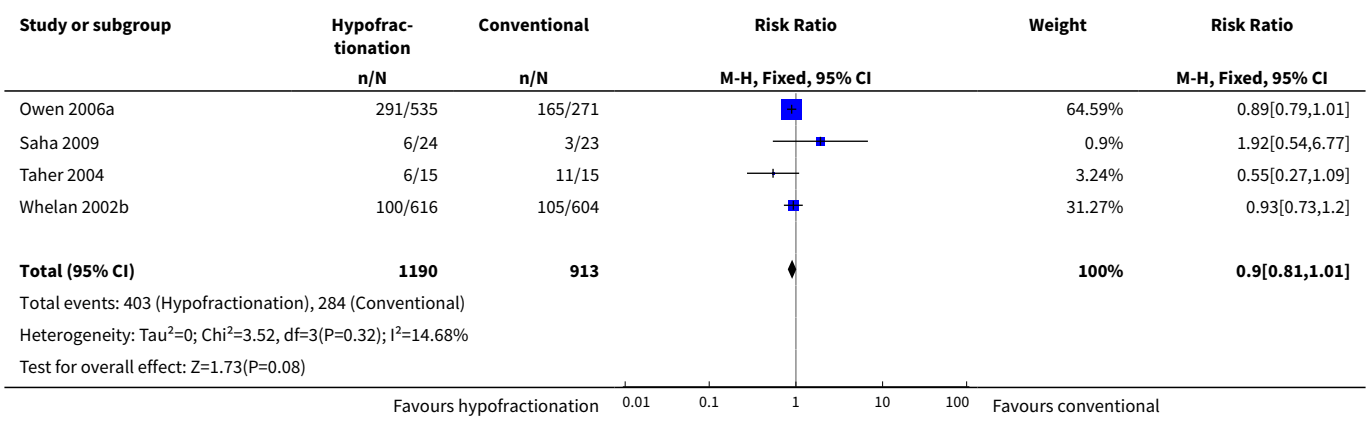


Analysis 1.2. Comparison 1 Hypofractionation versus conventional fractionation, Outcome 2 LR-FS by dose.

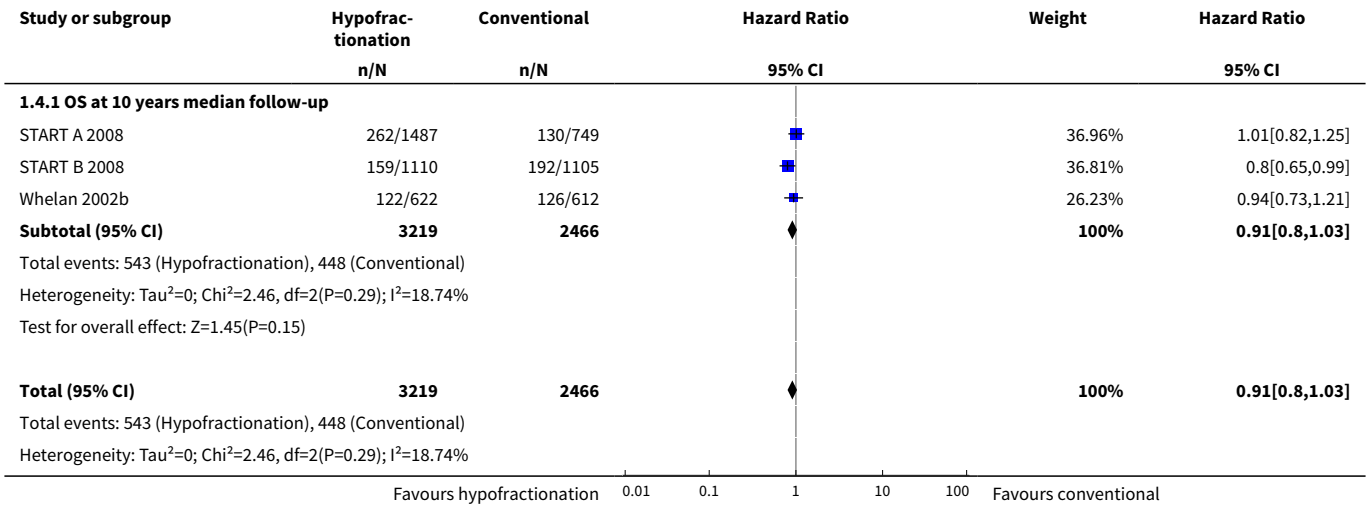


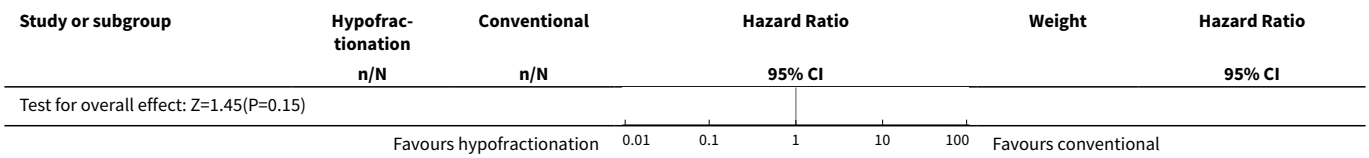


Analysis 1.3. Comparison 1 Hypofractionation versus conventional fractionation, Outcome 3 Cosmesis (fair/poor).

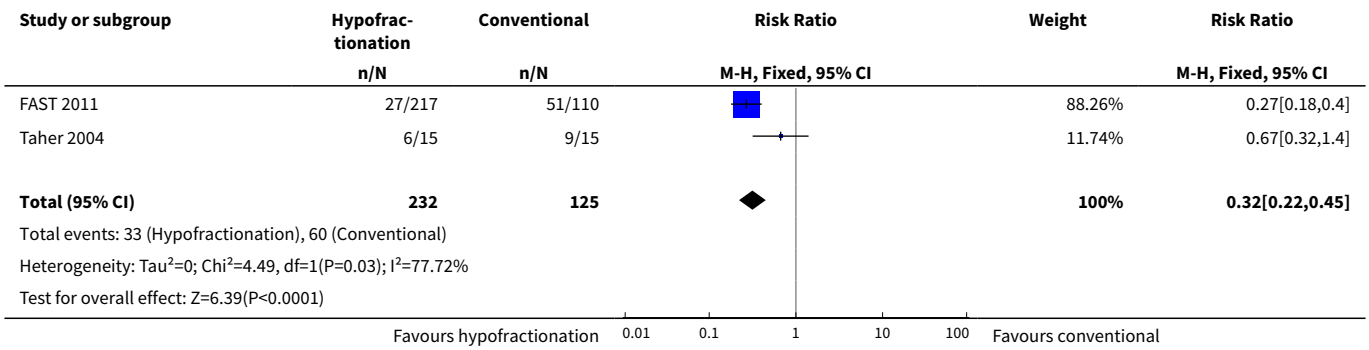


Analysis 1.4. Comparison 1 Hypofractionation versus conventional fractionation, Outcome 4 Overall survival (OS).

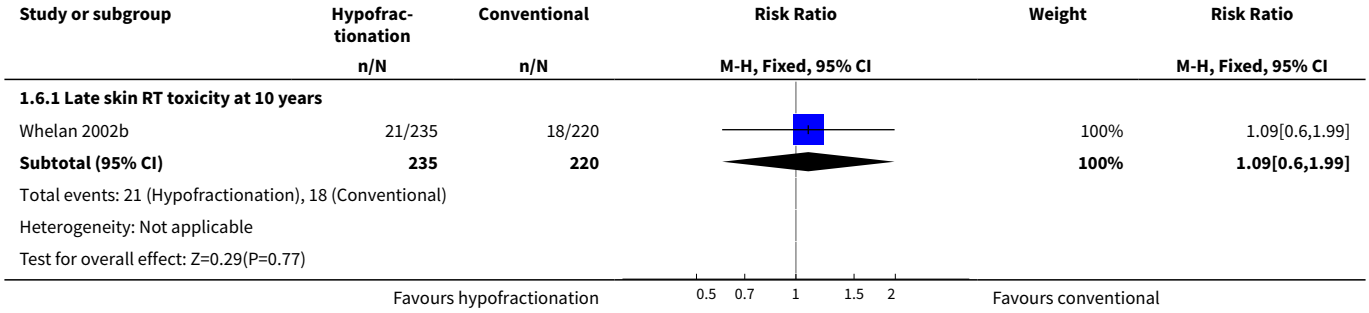




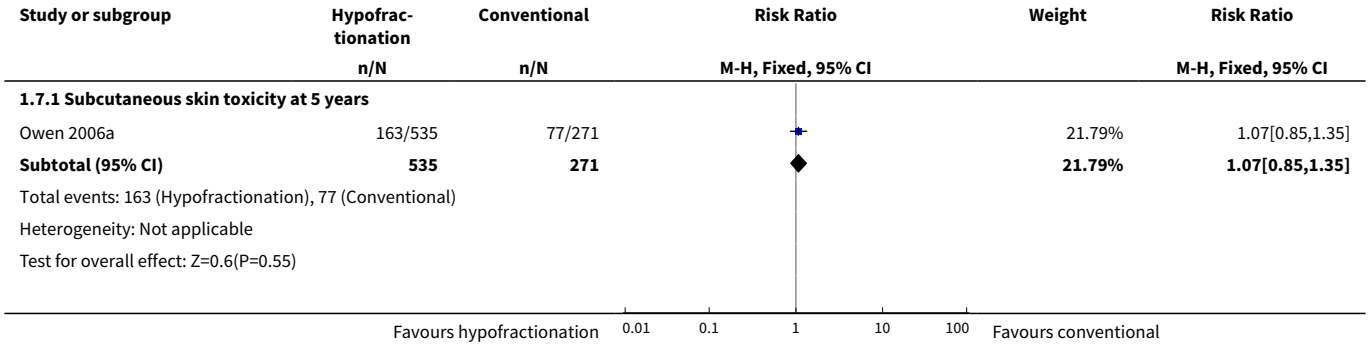
Analysis 1.5. Comparison 1 Hypofractionation versus conventional fractionation, Outcome 5 Acute skin radiation toxicity.



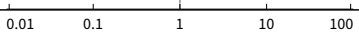
Analysis 1.6. Comparison 1 Hypofractionation versus conventional fractionation, Outcome 6 Late skin toxicity.



Analysis 1.7. Comparison 1 Hypofractionation versus conventional fractionation, Outcome 7 Late subcutaneous toxicity (fibrosis)).



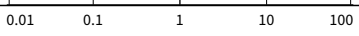
Study or subgroup	Hypofractionation n/N	Conventional n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.2 Subcutaneous skin toxicity at 10 years					
START A 2008	260/1244	142/616		40.49%	0.91[0.76,1.09]
START B 2008	129/1006	153/1003		32.66%	0.84[0.68,1.04]
Whelan 2002b	28/235	23/220		5.06%	1.14[0.68,1.92]
Subtotal (95% CI)	**2485**	**1839**		**78.21%**	**0.89[0.78,1.02]**
Total events: 417 (Hypofractionation), 318 (Conventional)					
Heterogeneity: Tau^2=0; Chi^2=1.17, df=2(P=0.56); I^2=0%					
Test for overall effect: Z=1.63(P=0.1)					
Total (95% CI)	**3020**	**2110**		**100%**	**0.93[0.83,1.05]**
Total events: 580 (Hypofractionation), 395 (Conventional)					
Heterogeneity: Tau^2=0; Chi^2=2.98, df=3(P=0.4); I^2=0%					
Test for overall effect: Z=1.17(P=0.24)					
Test for subgroup differences: Chi^2=1.81, df=1 (P=0.18), I^2=44.68%					



Favours hypofractionation — Favours conventional

Analysis 1.8. Comparison 1 Hypofractionation versus conventional fractionation, Outcome 8 Telangiectasia.

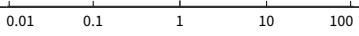
Study or subgroup	Hypofractionation n/N	Conventional n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Shaitelman 2015	0/129	1/142		1.3%	0.37[0.02,8.92]
START A 2008	61/1456	42/730		51.01%	0.73[0.5,1.07]
START B 2008	34/1094	52/1081		47.69%	0.65[0.42,0.99]
Total (95% CI)	**2679**	**1953**		**100%**	**0.68[0.52,0.91]**
Total events: 95 (Hypofractionation), 95 (Conventional)					
Heterogeneity: Tau^2=0; Chi^2=0.32, df=2(P=0.85); I^2=0%					
Test for overall effect: Z=2.63(P=0.01)					



Favours hypofractionation — Favours conventional

Analysis 1.9. Comparison 1 Hypofractionation versus conventional fractionation, Outcome 9 Breast oedema.

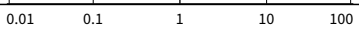
Study or subgroup	Hypofractionation n/N	Conventional n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Shaitelman 2015	2/129	7/142		3.38%	0.31[0.07,1.49]
START A 2008	110/1244	78/616		52.93%	0.7[0.53,0.92]
START B 2008	49/1006	86/1003		43.69%	0.57[0.4,0.8]
Total (95% CI)	**2379**	**1761**		**100%**	**0.63[0.51,0.78]**
Total events: 161 (Hypofractionation), 171 (Conventional)					
Heterogeneity: Tau^2=0; Chi^2=1.67, df=2(P=0.43); I^2=0%					
Test for overall effect: Z=4.31(P<0.0001)					



Favours hypofractionation — Favours conventional

Analysis 1.10. Comparison 1 Hypofractionation versus conventional fractionation, Outcome 10 Breast shrinkage.

Study or subgroup	Hypofractionation n/N	Conventional n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
START A 2008	308/1244	165/616		46.26%	0.92[0.79,1.09]
START B 2008	221/1006	256/1003		53.74%	0.86[0.74,1.01]
Total (95% CI)	**2250**	**1619**		**100%**	**0.89[0.79,1]**
Total events: 529 (Hypofractionation), 421 (Conventional)					
Heterogeneity: Tau^2=0; Chi^2=0.38, df=1(P=0.54); I^2=0%					
Test for overall effect: Z=2.02(P=0.04)					



Favours hypofractionation — Favours conventional

Analysis 1.11. Comparison 1 Hypofractionation versus conventional fractionation, Outcome 11 Ischaemic heart disease (left-sided tumours).

Study or subgroup	Hypofractionation n/N	Conventional n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
START A 2008	5/1487	4/749		51.5%	0.63[0.17,2.34]
START B 2008	4/1110	5/1105		48.5%	0.8[0.21,2.96]
Total (95% CI)	**2597**	**1854**		**100%**	**0.71[0.28,1.79]**
Total events: 9 (Hypofractionation), 9 (Conventional)					
Heterogeneity: Tau^2=0; Chi^2=0.06, df=1(P=0.8); I^2=0%					
Test for overall effect: Z=0.72(P=0.47)					

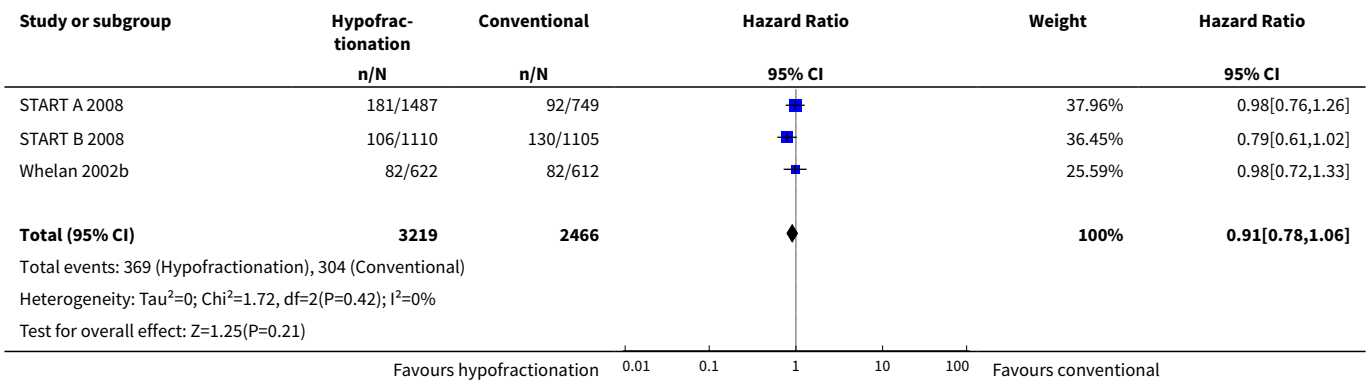
Favours hypofractionation — Favours conventional

Analysis 1.12. Comparison 1 Hypofractionation versus conventional fractionation, Outcome 12 Rib fractures.

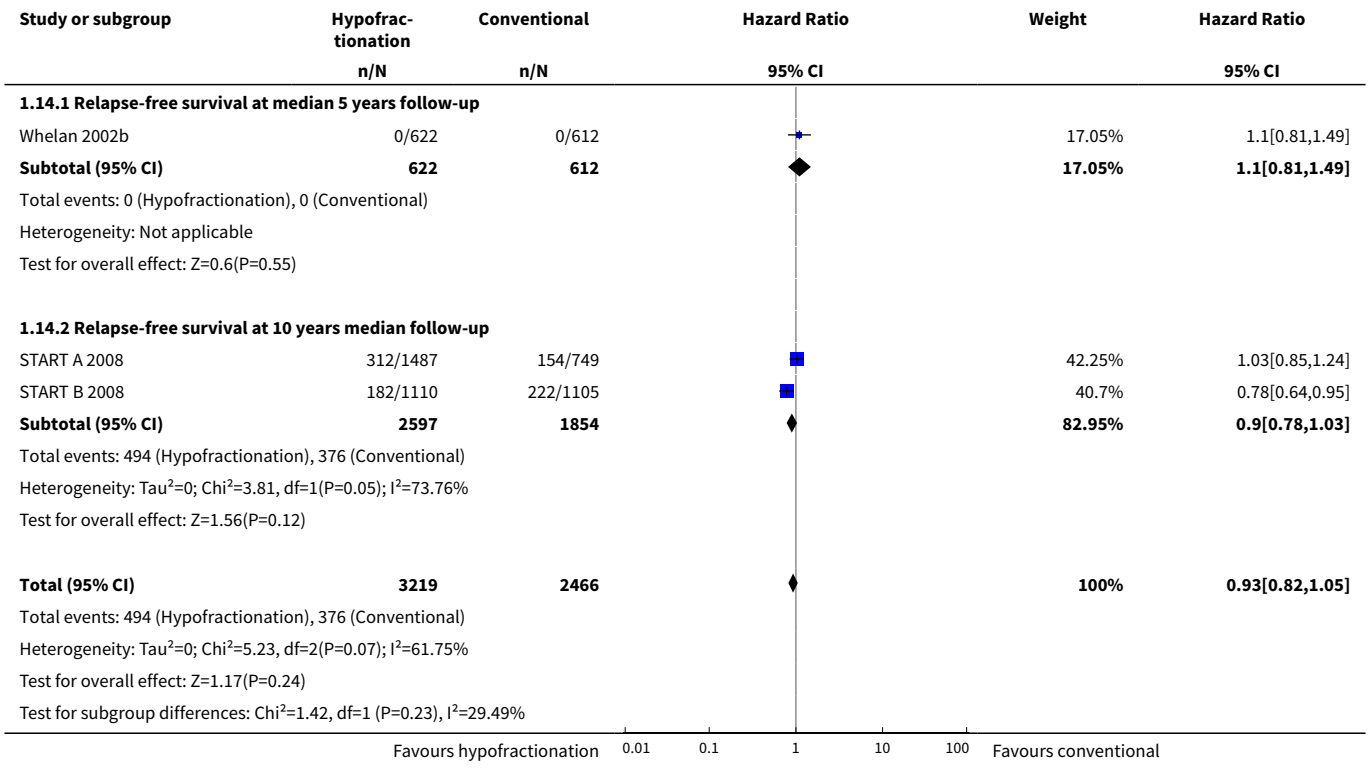
Study or subgroup	Hypofractionation n/N	Conventional n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
START A 2008	1/1487	0/749		12.86%	1.51[0.06,37.07]
START B 2008	3/1105	3/1110		57.89%	1[0.2,4.97]
Whelan 2002b	0/622	1/612		29.25%	0.33[0.01,8.04]
Total (95% CI)	**3214**	**2471**		**100%**	**0.87[0.25,3.1]**
Total events: 4 (Hypofractionation), 4 (Conventional)					
Heterogeneity: Tau^2=0; Chi^2=0.5, df=2(P=0.78); I^2=0%					
Test for overall effect: Z=0.21(P=0.83)					

Favours hypofractionation — Favours conventional

Analysis 1.13. Comparison 1 Hypofractionation versus conventional fractionation, Outcome 13 Breast cancer-specific survival.



Analysis 1.14. Comparison 1 Hypofractionation versus conventional fractionation, Outcome 14 Relapse-free survival.



ADDITIONAL TABLES

Table 1. EORTC Cosmetic Rating System

	Global cosmetic
0	No difference or excellent

Table 1. EORTC Cosmetic Rating System *(Continued)*

1	Small difference or good
2	Moderate difference or fair
3	Large difference or poor

Table 2. RTOG CTCAE acute skin toxicity

Grade	Description
0	No visible change
1	Faint/dull erythema
2	Tender/bright erythema +/- dry desquamation
3	Patchy moist desquamation, moderate erythema
4	Confluent moist desquamation, pitting oedema

Table 3. NCI CTCAE Version 4.0

Grade	Description
I	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL
3	Life-threatening consequences; urgent intervention indicated
3	Death related to adverse event

ADL: activities of daily living

Table 4. Conversion of altered fractionation regimen to EQD_2

Study	**Dose**	**Fractions**	EQD_2

Table 4. Conversion of altered fractionation regimen to EQD_2 *(Continued)*

Owen 2006a	42.9 Gy	13	52.19
Control arm dose	50.0 Gy	25	50.00
FAST 2011 Saha 2009	30.0 Gy	5	50.00
START A 2008	41.6 Gy	13	49.92
FAST 2011	28.5 Gy	5	46.07
Whelan 2002b Shaitelman 2015 Taher 2004	42.5 Gy	16	45.76
Owen 2006a START A 2008	39.0 Gy	13	45.50
START B 2008 Patni 2012	40.0 Gy	15	42.90

Table 5. RTOG/EORTC late radiation morbidity scale

Score	Definition
0	No toxicity
1	Slight toxicity
2	Moderate toxicity
3	Marked toxicity
4	Severe toxicity

Table 6. Induration scale (Owen 2006a)

Score	Definition
0	None
1	Mild
2	Moderate
3	Marked

Table 7. START A & B Late RT toxicity scale

Grade	Description
0	"none"
I	"a little"
II	"quite a bit"
III	"very much"

Table 8. Boost for women treated with breast conservation

STUDY	Breast conservation	Boost experimental arm	Boost control arm	Total
START A 2008	1900	41.6 Gy/13 fractions arm: 391/750 (61%) 39 Gy/13 fractions arm: 380/737 (60.5%) Total number with boost: 771/1269 (61%)	381/631 (60%)	1152/1900 (61%)
START B 2008	2038	446/1018 (44%)	422/1020 (41%)	868/2038 (43%)
Owen 2006a	1410	—	—	1051/1410 (75%)
FAST 2011	729	0/613	0/302	0/729 (0%)
Whelan 2002b	1234	0/622	0/612	0/1234 (0%)
Saha 2009	47	-	-	41/47 (0%)
Taher 2004	30	15/15	0/15	15/30 (50%)
Shaitelman 2015	287	138/138	149/149	287/287 (100%)
Patni 2012	40	20/20	20/20	40/40
Total number boosted				3454/7715 (44%)

Table 9. Cosmesis scale (Owen 2006a)

Breast Cosmesis
Excellent
Good
Fair

Table 9. Cosmesis scale (Owen 2006a) *(Continued)*

Poor

Table 10. ASTRO 'suitable' patients for hypofractionated whole breast radiotherapy

Patient is 50 years or older at diagnosis
Pathologic stage is T1–2 N0 and patient has been treated with breast conserving surgery
Patient has not been treated with systemic chemotherapy
Within the breast along the central axis, the minimum dose is no less than 93% and maximum dose is no greater than 107% of the prescription dose (7%;) (as calculated with 2-dimensional treatment planning without heterogeneity corrections)

T: tumour
N: lymph node

APPENDICES

Appendix 1. CENTRAL

1 MeSH descriptor: [Breast Neoplasms] explode all trees
2 breast and (tumour* or tumor*)
3 breast and (cancer* or neoplas* or adenocarcinoma)
4 1 or 2 or 3
5 MESH DESCRIPTOR: [Radiotherapy Dosage] explode all trees
6 MESH DESCRIPTOR: [Dose-Response Relationship, Radiation] explode all trees
7 MESH DESCRIPTOR: [Dose fractionation] explode all trees
8 5 or 6 or 7
9 radiotherap* or (radiation therap*)
10 dose or dosage or fraction$
11 4 and 9 and 10
12 8 or 11

Appendix 2. MEDLINE (Ovid)

1 breast neoplasms/
2 (breast cancer or breast adenocarcinoma).ti.
3 1 or 2
4 rt.fs.
5 radiotherapy dosage/
6 dose response relationship, radiation/
7 Dose Fractionation/
8 radiotherapy/
9 radiotherapy adjuvant/
10 exp radiotherapy, computer assisted/
11 or/4-10
12 (letter or news).pt.
13 (systematic$ adj3 (review$ or overview)).mp.
14 meta-analysis/ or meta-analysis.pt.
15 13 or 14
16 3 and 11 and 15
17 16 not 12
18 randomized controlled trials/ or randomized controlled trial.pt.
19 randomization/ or double blind method/ or single blind method/
20 18 or 19

21 3 and 11 and 20
22 21 not 12
23 22 not 17
24 (breast cancer or breast neoplasm$ or breast adenocarcinoma).ti,ab.
25 (radiotherapy or radiation therapy).ti,ab.
26 (dose or dosage or fraction$).mp.
27 24 and 25 and 26
28 20 and 27
29 28 not 23
30 23 or 29
31 17 or 30

Appendix 3. EMBASE (Ovid)

1 breast cancer/ or breast adenocarcinoma/ or breast carcinoma/
2 (breast cancer or breast adenocarcinoma).ti.
3 1 or 2
4 Randomized Controlled Trial/
5 RANDOMIZATION/
6 Double Blind Procedure/
7 Single Blind Procedure/
8 or/4-7
9 3 and 8
10 radiotherapy/
11 radiation response/
12 radiation dose fractionation/
13 radiation dose/
14 radiation depth dose/
15 computer assisted radiotherapy/
16 rt.fs.
17 or/10-16
18 17 and 9
19 (breast cancer or breast neoplasm$ or breast adenocarcinoma).tw.
20 (radiotherapy or radiation).tw.
21 (dose or doses or dosage or fraction$).tw.
22 and/19-21
23 9 and 22
24 18 or 23
25 letter/
26 24 not 25
27 meta-analysis/
28 (meta-analy$ or metaanaly$).mp.
29 (systematic$ adj3 (review$ or overview)).mp.
30 or/27-29
31 22 and 30
32 3 and 17 and 30
33 31 or 32

Appendix 4. WHO ICTRP Search Portal

Advanced search (with Recruitment set at ALL):

Search 1.
Condition field: breast cancer
Intervention field: fraction size AND radiation
Search 2.
Condition field: adenocarcinoma AND breast
Intervention field: radiation
Search 3.
Condition field: adenocarcinoma AND breast
Intervention field: irradiation
Search 4.
Condition: breast cancer

Intervention field: irradiation
Search 5.
Condition: breast cancer
Intervention: hypofractionated radiation

Appendix 5. ClinicalTrials.gov

Basic Searches:

1. breast cancer AND radiotherapy AND fraction

2. breast cancer AND radiotherapy AND breast conservation

Advanced Searches:

1.Title: fraction size in radiation treatment for breast conservation in early breast cancer

Recruitment:All studies

Study Results: All studies

Study Type: All studies

Gender: All studies

2.Conditions: breast cancer

Intervention: (radiotherapy OR radiation therapy) AND (dose OR fraction)

Recruitment:All studies

Study Results: All studies

Study Type: All studies

Gender: All studies

Appendix 6. opengrey.org

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

WHAT'S NEW

Date	Event	Description
11 September 2017	Amended	Title has been amended to reflect standard medical nomenclature.

HISTORY

Protocol first published: Issue 4, 2002
Review first published: Issue 3, 2008

Date	Event	Description
23 May 2015	New search has been performed	Performed search for new studies on 23 May 2015
23 May 2015	New citation required but conclusions have not changed	Five new studies added, adding 1133 participants

Date	Event	Description
18 September 2009	New citation required and conclusions have changed	Two new studies included, adding 4451 participants. Conclusions changed and new outcomes presented.
23 June 2009	New search has been performed	Performed search for new studies on the 23rd June 2009.
11 April 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

The protocol was co-authored by Melissa James, Margot Lehman, Brigid Hickey, Phil Hider and Mark Jeffery.

Brigid Hickey was involved in conceiving and designing the review, screening papers against the inclusion criteria, appraising the quality of papers, extracting data, analysing data, providing a clinical perspective, writing the review, providing general advice and securing funding for the initial review and the update. Brigid Hickey was involved in screening papers against inclusion criteria, appraising the quality of papers, extracting data, analysing data, providing a clinical perspective, writing the review, constructing the Summary of Findings Table responding to peer reviewers' comments and providing general advice for the 2016 update.

Melissa James was involved in conceiving and designing the review, writing the protocol, screening search results, organising paper retrieval, screening papers against inclusion criteria, appraising quality of papers, writing to authors, screening data on unpublished studies, providing a clinical perspective and writing the review. Melissa James provided clinical perspective, editing and checked the data for the 2016 update.

Margot Lehman was involved in screening papers against the inclusion criteria, appraising the quality of papers, securing funding, extracting data, providing a clinical perspective and providing advice regarding the review, and securing funding for the initial review and the update. Margot Lehman was involved in screening papers against inclusion criteria, appraising quality of papers, securing funding, extracting data, providing a clinical perspective and providing advice regarding the review for the 2016 update.

Phil Hider was involved in designing the review, doing the search, providing methodological perspective, writing the review, and providing general advice regarding the review.

Mark Jeffery was involved in designing the review, co-ordinating the review, screening search results, organising paper retrieval, screening papers against the inclusion criteria, appraising quality of papers, writing to authors, obtaining data on unpublished studies, providing clinical perspective and writing the review. Mark Jeffery provided clinical perspective and editing for the update.

Daniel Francis was involved in co-ordinating the review, doing the search, screening search results, organising paper retrieval, screening against the inclusion criteria, writing to authors, providing a methodological perspective, and providing general advice for all versions of this review.

Adrienne See performed the literature searches for this and previous versions of the review.

DECLARATIONS OF INTEREST

BH: None known.
MJ: None known.
ML: None known.
PH: None known.
MJ: None known.
DF: None known.

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Internal sources

- Princess Alexandra Hospital Cancer Collaborative Group, Australia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Women with T3 tumours (that is tumour size greater than 5 cm) were eligible for the START A 2008 and START B 2008 studies. They comprised 1.6% (22/1410) of the women studied in Owen 2006a. T stage was not reported in START A 2008 and START B 2008, but 0.15% (702/4451) women had tumours larger than 3 cm. T3 tumours (larger than 5 cm) accounted for 0.02% (22/7513) of the total number of women studied.

With this update, we have adapted the review to meet the MECIR guidelines for conduct and reporting of systematic reviews.

We now report local recurrence-free survival as our primary outcome measure (in distinct to local recurrence). We have reported time-to event data where possible for cancer-related outcomes. We also report breast cancer-specific survival rather than cancer-specific mortality (as time-to-event endpoints are preferred for cancer outcomes) in order to be consistent.

Radiation doses converted to EQD_2, whereas we used BED initially, this is because it is more meaningful for clinicians.

We performed subgroup analysis based on study arm dose (less than 50Gy versus 50Gy or more) and length of follow-up (4.2 years versus approximately 10 years).

We have rationalised the Table of Excluded Studies, so it only includes those studies one might reasonably think might be eligible for inclusion. Those excluded because they are not randomised have been removed from this table.

We included Shaitelman 2015, even though they included DCIS. The outcomes reported relate to acute toxicity, cosmetic outcome and quality of life, so we felt it was appropriate to include the study.

INDEX TERMS

Medical Subject Headings (MeSH)

*Radiation Dose Hypofractionation; Breast Neoplasms [*radiotherapy] [surgery]; Combined Modality Therapy [methods]; Dose Fractionation, Radiation; Mastectomy, Segmental; Radiation Injuries [complications] [mortality]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans