Fraction size in radiation treatment for breast conservation in early breast cancer (Review)

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TABLE OF CONTENTS

[Intervention Review]

Fraction size in radiation treatment for breast conservation in 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 conservation. 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.

Objectives

To assess the effects of altered fraction size on women with early breast cancer who have undergone breast conserving surgery.

Search strategy

We searched the Cochrane Breast Cancer Group Specialised Register (June 2006), MEDLINE (November 2006), EMBASE (November 2006), reference lists for articles, and relevant conference proceedings. No language constraints were applied.

Selection criteria

Randomised controlled trials of unconventional versus conventional fractionation in women with early breast cancer who had undergone breast conserving surgery.

Data collection and analysis

Data extraction was performed independently by the authors with disagreements resolved by discussion. Missing data was sought by contacting the authors concerned.

Main results

Two trials were included and reported on 2644 women. The women were highly selected with node negative tumours smaller than 5 cm and negative pathological margins; 46% of the women had a cup separation size of less than 25 cm. The studies were of high quality. Data for local recurrence and breast appearance were not available in a form which could be combined. Unconventional fractionation (delivering radiation therapy in larger amounts each day but over fewer days than with conventional fractionation) did not appear to affect: (1) local-recurrence free survival (absolute difference 0.4%, 95% CI -1.5% to 2.4%), (2) breast appearance (risk ratio (RR) 1.01, 95% CI 0.88 to 1.17; P = 0.86), (3) survival at five years (RR 0.97, 95% CI 0.78 to 1.19; P = 0.75), (4) late skin toxicity at five years (RR 0.99, 95% CI 0.44 to 2.22; P = 0.98, or (5) late radiation toxicity in sub-cutaneous tissue (RR 1.0, 95% CI 0.78 to 1.28; P = 0.99).

Authors' conclusions

We have evidence from two high quality randomised trials that the use of unconventional fractionation regimes (greater than 2 Gy per fraction) does not affect breast appearance or toxicity and does not seem to affect local recurrence for selected women treated with breast conserving therapy. These are women with node negative tumours smaller than 5 cm and negative pathological margins. Two new trials have been published in March 2008. Their results are consistent with our findings. The results of these trials will be incorporated in the next update of this review.

PLAIN LANGUAGE SUMMARY

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

Using fewer radiation treatments for women with early breast cancer who wish to preserve their breast achieves similar outcomes in breast appearance and survival. In addition, cancer control in the breast appears to be similar. Breast cancer is an important disease for women, with one in eight women in the United States and Australia and one in nine women in the United Kingdon being diagnosed with the condition. 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, with or without evidence of cancer in the local lymph nodes, as long as a five to six week course of radiation therapy is delivered. This involves 25 to 30 daily visits to a radiation oncology department. Without radiation therapy after breast conserving surgery there is a high risk of breast cancer returning in the breast (local recurrence), in as many as 30 to 40 women per 100. This means that for every local recurrence avoided with radiation, one death is avoided at 15 years. Many women prefer breast conservation so that the demand for radiation services has increased. Giving fewer radiation treatments (fractions) would be beneficial to women where this has the same effect on tumour control and survival without poorer cosmetic outcomes. 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.

Two trials were included in this review and involved 2644 women. Breast appearance was not significantly different for women undergoing fewer treatments. Survival was not altered by having fewer treatments and there was no significant difference in late skin toxicity or radiation toxicity. The available information for local control, that is when the tumour does not recur in the treated breast, could not be combined but was similar in each trial. Most of the women in the trials (98.4%) had tumours less than 5 cm and complete removal of the tumour on pathology; 91% had no evidence of cancer in their lymph nodes. This review indicates that for women who fit these criteria, using fewer radiation treatments after tumour removal could be considered.

BACKGROUND

Description of the condition

Breast cancer is the most common cancer occurring in women. The lifetime risk 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). Breast cancer is the second most common cause of cancer death in females.

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 treatment 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 treatment 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 cancer site with ionising radiation. Typically the radiation is delivered over a period of 5 to 6 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.

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), 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 2000; Yarnold 1994). Published trials to date have been too small to reliably detect differences in cancer recurrence rates.

If a shorter fractionation schedule can be established as providing equivalent outcomes for women this could lead to more efficient use of radiation services and more expedient treatment for patients.

OBJECTIVES

To determine the effect of altered radiation fraction size on outcomes for women with early breast cancer who have undergone breast conserving surgery.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials were considered for inclusion. The comparisons were required to be unconfounded, that is the treatment given to the intervention and comparator groups could differ only in relation to the fractionation scheme 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.

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 2002), 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.

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. In order to compare the differing dose schedules we converted fractionation schemes to biologically equivalent doses (BED). 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) recommendations with respect to dose, dose specification point, and dose per fraction. Where possible, we converted data found in studies into this form.

Types of outcome measures

Primary outcomes

1. Local recurrence in the ipsilateral breast (i.e. the same breast where the cancer had been diagnosed)
2. Appearance or cosmesis (objective and subjective) of the post-treatment breast

Secondary outcomes

1. Overall survival (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; individual protocol-based definitions were used
3. Cancer-specific mortality
4. Relapse-free survival
5. Mastectomy rate (following local recurrence)
6. Quality of life (trial-specific instruments)
7. Costs (to women and health services)

Search methods for identification of studies

The Cochrane Breast Cancer Group Specialised Register was searched (June 2006). 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 (http://www.mrw.interscience.wiley.com/cochrane/clabout/articles/BREASTCA/frame.html). Studies coded as 'early' and 'radiotherapy and dose intensity' on the Specialised Register were extracted for consideration.

In addition, a comprehensive search of MEDLINE (OVID) (1966 to June 2006) (see Appendix 1) and EMBASE (OVID) (1980 to October 2006) (see Appendix 2) was conducted.

Searches were not limited by language or date.

Data collection and analysis

Selection of studies

All four original authors checked the titles and abstracts retrieved by the searches. The newer authors did so for the repeated search. Each author independently assessed the full text of all studies we thought relevant to the review with differences being resolved by discussion.

Data extraction and management

Data extraction was performed independently by three authors (BH, ML, and DF) with disagreements being resolved by discussion. Data were entered into RevMan 4.2 for analysis. Where data was limited, we requested further information from the authors of the original studies.

Assessment of methodological quality of included studies

Two review authors (BH, ML) categorised the methodological quality of each eligible study using the system outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2006). DF resolved any discrepancies which arose.

The quality of trials was assessed according to the following.

Low risk of bias: plausible bias unlikely to seriously alter results, all of the quality criteria met.

Moderate risk of bias: plausible bias that raised some doubt about results. One or more of the quality criteria partly met.

High risk of bias: plausible bias that seriously weakened confidence in results. One or more of the quality criteria not met.

Specific quality measures included: adequacy of concealment of randomisation, whether the analysis was by intention to treat, presence of blinding, and adequacy of follow up. Because of the nature of the interventions involved in this review, blinding of participants and investigators was not possible although blinding of outcome assessment was possible (for cosmesis and late toxicity). As a result this was regarded as an important feature in our quality assessment. We did use adequacy of follow up as a quality criterion, setting an arbitrary threshold of 80% follow up as adequate. The studies were assessed in relation to whether the methods and procedures were adequate, inadequate, or unclear.

Sensitivity analysis was planned on the basis of study quality and was to be performed with and without trials of low quality to assess the effect of quality on the results. This was not possible with only two included trials.

Measures of treatment effect

Dichotomous measures were presented as risk ratios (RR) with 95% confidence intervals (CI) (Deeks 2003). Continuous variables were presented as weighted mean difference, where possible. We used Mantel-Haenszel methods to calculate pooled results (Greenland 1985; Mantel 1959).

Data synthesis (meta-analysis)

We applied the intention-to-treat principle in analysing data from the trials and determined a weighted average treatment effect using the fixed-effect model to combine results (Mantel 1959) on RevMan 4.2. Because our comparison of interest was unconventional fractionation versus conventional fractionation, when analysing the trials we combined the two different 'fractionation dose' unconventional arms of the Owen 2006 trial. In the future,

if more information becomes available then separate analysis may be possible to investigate a dose effect for different fractionation schedules.

Continuous variables, for example cosmesis, were dichotomised in the reports so we reported them as RRs. For late skin toxicity, percentages given in the text were converted to numbers and a RR reported (as there were data from one trial only a weighted mean difference could not be calculated).

Global cosmetic outcome (appearance) was reported for 735 women at five years (Whelan 2002) as a dichotomised outcome. The four-point scale European Organisation for Research and Treatment of Cancer (EORTC) Cosmetic Rating System (Aaronson 1988) was used and the results were dichotomised as: good or excellent versus poor or fair.

Skin toxicity (Whelan 2000) was assessed using a five-point scale (Winchester 1992) (see Additional Table 1) and analysed as a dichotomous outcome using RR.The results were dichotomised into: none or mild versus moderate, marked or severe.

We assumed that induration and subcutaneous toxicity (at five years), reported by Owen 2006 and Whelan 2002 respectively, represented the same outcome and could, therefore, be combined for analysis. Whelan 2002 used the TROG/EORTC five-point late radiation morbidity scale (Winchester 1992) (see Additional Table 1) and Owen 2006 used a four-point trial-specific scale (see Additional Table 2). No patient in Whelan 2002 had severe (Grade 4) toxicity. The results were dichotomised in the Owen 2006 report but reported in full in Whelan 2000. In order to combine the results, the Whelan 2000 results were dichotomised 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.

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

If sufficient data become 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 2003).

Subgroup analysis and investigation of heterogeneity

The current version of the review does not contain any subgroup analyses because of the lack of data. However, if sufficient data become available in future updates we may perform subgroup analyses to investigate whether the effects of different radiation fraction schemes differ depending on nodal status, margin status, hormone receptor status, and tumour stage or other factors which may become relevant in the future.

We assessed heterogeneity both visually and statistically using the chi-squared test (Altman 1992; Walker 1988).

Radiation doses were converted to the biological equivalent dose (BED), where BED = nd (1+d/alpha/beta) (Fowler 1989; Steel 1997). This was to facilitate comparison of radiation doses given at differing dose per fraction. The value of alpha/beta used for breast tumour cells was four (Steel 1997; Thames 1987; Williams 1985). Using these values, we aimed to compare those studies with a BED < 75 and a BED > 75. Brachytherapy (radiation sources applied directly to the body) would be converted to BED using the method of Stitt (Stitt 1992; Yamada 1999). For brachytherapy we will record data, where possible, in the form of dose, dose specification point, plane of interest (for example at 1 cm from the central plane), mean central dose, and peripheral dose.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

A total of 2119 abstracts were screened, 61 papers in full were considered for eligibility. Two were identified as ongoing studies and 47 were excluded (see table Characteristics of excluded studies).

The 12 reports that met the inclusion criteria (Anon 1997; OCOG 1992; Owen 1994; Owen 2006; Whelan 2000; Whelan 2002; Yarnold 1992; Yarnold 1994; Yarnold 1994a; Yarnold 2001; Yarnold 2001a; Yarnold 2005) related to two separate studies (Owen 2006; Whelan 2002) . Both 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 2006 trial the primary source is Owen 2006, with eight other publications found for this trial (Anon 1997; Owen 1994; Yarnold 1992; Yarnold 1994; Yarnold 1994a; Yarnold 2001; Yarnold 2001a; Yarnold 2005). The primary source for the second trial was Whelan 2002, with two other publications found (OCOG 1992; Whelan 2000).

The two randomised trials included in this current version of the review involved a total of 2644 women.

Whelan 2002 was a randomised controlled trial comparing two different fractionation regimes (42.5 Gy in 16 fractions and 50 Gy in 25 fractions). The trial was multicentred with patients recruited from tertiary institutions. This study included 1234 women with invasive breast cancer who were without nodal involvement, were treated with lumpectomy, and had negative pathological margins. Patients with large breasts (as defined by a cup size separation of greater than 25 cm, that is the breast measured greater than 25 cm left to right at its widest part) were excluded. The primary outcome measure was local recurrence of invasive breast cancer in the treated breast. The trial reported breast appearance and late radiation toxicity but did not assess costs or quality of life. For reporting skin toxicity, Whelan 2002 used the five-point Radiation Oncology Group/ EORTC late radiation morbidity scale (Winchester 1992) (Additional Table 1). Global cosmetic outcome was assessed

by trained clinical trials nurses using the four-point European Organisation for Research and Treatment of Cancer (EORTC) Cosmetic Rating System (Additional Table 3).

More detail is available in the table Characteristics of included trials.

The second study (Owen 2006) was a randomised controlled trial comparing three fractionation regimens (39 Gy in 13 fractions, 42.9 Gy in 13 fractions, and 50 Gy in 25 fractions). The trial was multicentred in a tertiary setting. The study included 1410 women with invasive breast cancer who were treated with breast conserving surgery and had negative pathological margins. The primary outcome measure was late change in breast appearance. The trial reported both cosmesis and late radiation toxicity but did not assess costs or quality of life. Cosmesis (appearance) was assessed in 806 women at annual follow-up visits; clinicians used a four-point scale (Additional Table 4). We have no evidence that these women were substantially different to the remainder of women in the trial. These results were dichotomised in the report into fair or poor versus good or excellent (Owen 2006).

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

Risk of bias in included studies

Owen 2006 and Whelan 2002 had adequate follow up. Analysis was by intention to treat in Whelan 2002 but this was not stated in Owen 2006. Randomisation was adequate and concealed (Owen 2006; Whelan 2002). It was not stated whether outcome assessors were blinded to treatment allocation in Whelan 2002 but those who assessed cosmesis in Owen 2006 were not aware which study group the women belonged to. The results of our categorisation are available in the Characteristics of included studies table.

Effects of interventions

Two trials enrolling 2644 women were included in the review. In the results presented here, ratios of treatment effects are given such that RRs < 1.0 would indicate a beneficial effect of unconventional fractionation over conventional fractionation (although, as noted below, most of these results were not statistically significant).

Primary outcomes

Ipsilateral local recurrence

Data were provided for this comparison but could not be readily analysed. Owen 2006 reported local recurrence but it was reported as number of events in each arm per person years. The data was reported as first event data in Whelan 2002, that is events included local recurrence, distant recurrence, and death. This meant that not all local recurrences were reported. We have contacted the authors for more information but unsuccessfully.

In Whelan 2002, 44 local recurrences in 1234 women were reported as first event data at five years: 21 in the unconventional arm and 23 in the conventional arm. The authors reported that local-recurrence free survival at five years was 97.2% in the unconventional arm and 96.8% in the conventional arm (absolute difference 0.4%, 95% CI -1.5 to 2.4). These figures were directly extracted from the text (Whelan 2002); that is local recurrence rates were 2.8% in the unconventional arm and 3.2% in the conventional arm.

Owen 2006 reported 158 events in 1410 randomised women. These were reported as number of events in each arm per person years with a median follow up of 9.7 years and a maximum follow up of 18.4 years (see Additional Table 5). The authors reported that the risk of ipsilateral tumour recurrence at 10 years was 14.8% (95% CI 11.2 to 18.3) for the 39 Gy in the 13 fractions arm; 9.6% (95% CI 6.7 to 12.6) for the 42.9 Gy in 13 fractions arm; and 12.1% (95% CI 8.8 to 15.5) for the 50 Gy in 25 fractions arm (figures from text) (Yarnold 2005). If this is converted to incidence ratios relative to the control group (that is 50 Gy in 25 fractions), the incidence ratio for 42.9 Gy in 13 fractions was 0.87 (95% CI 0.56 to 1.33; P = 0.50); and for 39 Gy in 13 fractions it was 1.35 (95% CI 0.92 to 1.98; P = 0.11).

Appearance (objective and subjective) of the post-treatment breast (cosmesis)

Data were available from both trials but not in a form which could be combined in analysis.

Global cosmetic outcome was reported for 735 women at five years (Whelan 2002). The triallists performed cosmetic assessment on 1220 women at baseline and had complete cosmetic data on 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. A four-point scale (Aaronson 1988) was used and the results were dichotomised as: good or excellent versus poor or fair. These results were reported 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. At five years, the percentage of patients with good or excellent global cosmetic outcome was 76.8% in the altered fractionation arm and 77.4% in the conventional fractionation arm (absolute difference -0.6%, 95% CI -6.5% to 5.5%); figures from the text (Whelan 2002).

Owen 2006 reported breast cosmesis (median follow up of 8.1 years, maximum 15 years) using a four-point scale (see Additional Table 4). A total of 806 women (see Description of studies) were assessed and the results were reported as a dichotomised outcome in the report. Of 535 women in the altered fractionation arm, 224 (41.8%) were scored as having a good or excellent result and 106 of 271 (39.1%) in the conventional fractionation arm had good or excellent result (figures derived from the text): RR 1.07 (95% CI 0.90 to 1.28; P = 0.46). Testing for heterogeneity was not applicable.

Secondary outcomes

1. Overall survival (time from date of randomisation to death from any cause, or number of deaths from any cause at five years)

The RR was 0.97 (95% CI 0.78 to 1.19; P = 0.75). There was no heterogeneity (P = 0.79) between the trials (Comparisons and data 01.01).

2. Toxicity (including 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.

Skin toxicity (Whelan 2002) was assessed using the Radiation Oncology Group/ EORTC late radiation morbidity scale (Winchester 1992), which has a five-point scale (Table 1). No woman had severe (Grade 4) skin toxicity: RR 0.99 (95% CI 0.44 to 2.22; P = 0.98). A test for heterogeneity was not applicable with only one trial.

Late radiation subcutaneous toxicity: the RR was 1.00 (95% CI 0.78 to 1.28; P = 0.99). There was no heterogeneity (P = 0.21) between the trials (Owen 2006; Whelan 2002) (Comparisons and data 01.02.)

Owen 2006 reported five year follow up for any or marked change in breast appearance and found no significant difference between the unconventional 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) (Owen 2006).

Late toxicity outcomes were reported in Whelan 2002. Two women in the unconventional arm and two in the conventional arm developed radiation pneumonitis. One woman in the conventional arm fractured a rib.

3. Cancer specific mortality

No data.

4. Relapse-free survival

No data.

5. Mastectomy rate

No data.

6. Quality of life (trial-specific instruments)

No data.

7. Costs (to women and health services)

No data.

DISCUSSION

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 patients with cancer. The ability to safely reduce the number of fractions required to treat women with early breast cancer may, therefore, result in many benefits at a personal, national, and international level provided acceptable local control can be maintained with this approach.

This review set out to explore whether shortened (altered fractionation) regimes 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 regimes. We have been able to include data from two randomised controlled trials that compared different fractionation schemes. The comparison studied is altered fractionation (fraction size greater than 2 Gy) versus conventional fractionation (2 Gy per fraction).

It was not possible to combine the data because of reporting issues, but local recurrence rates appear similar in each of the trial arms. The reported risk of ipsilateral tumour recurrence at 10 years was 14.8% (95% CI 11.2 to 18.3) for the 39 Gy in 13 fractions arm, 9.6% (95% CI 6.7 to 12.6) for the 42.9 Gy in 13 fractions arm, and 12.1% (95% CI 8.8 to 15.5) for the 50 Gy in 25 fractions arm (Yarnold 2005). In Whelan 2002, local recurrence rates were 2.8% in the unconventional arm and 3.2% in the conventional arm.

For these comparisons, there are no significant differences between the fractionation techniques in regard to cosmesis, late skin toxicity, and late radiation toxicity. For overall survival, there was no significant difference between the techniques. No data were available for costs, quality of life, or women's preference. 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 both trials (Owen 2006; Whelan 2002); with blinding of the outcome assessors to the treatment allocation in Owen 2006.

Although both trials independently showed no difference in local control with altered fractionation, the reporting did not allow combination of data. The findings of this review provide reassurance that the practice of offering shortened radiation fractionation regimes to carefully selected groups of patients is unlikely to be detrimental in terms of breast appearance, late radiation breast toxicity, or survival. However, there are some caveats.

(1) These results are mostly applicable to women with node negative T1-2 tumours with negative pathological margins.

A total of 92% of the women enrolled in the two trials were node negative (all of the 1234 women in Whelan 2002, and 1187 of 1410 women enrolled in Owen 2006) and they all had negative

pathological margins. The vast majority (2622/2644) of women had T1-2 tumours (that is tumour size less than 5 cm). Whelan limited the eligible women to those with a cup size separation of 25 cm or less because, for women with larger breasts, there is concern that altered fractionation may cause more toxicity (this represents 46% of the total number of women included in the analysis). Although women with T3 tumours (size greater than 5 cm) were eligible for the Owen study, they comprised 1.6% (22/1410) of the study population and only 0.83% of the women analysed in the review.

(2) The follow up (five years) is not adequate to detect differences in breast cancer mortality. If, however, there are truly no differences in local recurrence one would not expect to see differences in mortality.

In total, 222 local recurrences were reported in 2644 women, but the 44 recurrences in Whelan 2002 were those presenting as first events (a composite endpoint including local recurrence, distant metastases, and death); so this figure may underestimate the total number of local recurrences. The Owen trial was not powered to detect significant differences in local recurrence. Using an alpha/beta ratio of 4 for breast tumour cells (Fowler 1989; Steel 1987; Williams 1985) allows conversion of radiation doses to a common biological equivalent dose (BED) (Fowler 1989; Steel 1997). When the altered fractionation regime radiation doses are converted to BED (see Additional Table 6), it is clear that two regimens (39 Gy in 13 fractions and 42.5 Gy in 16 fractions) (Whelan 2002) have lower biological equivalent doses than the conventional 50 Gy in 25 fractions.

It has not been possible at this time to answer questions of cost, quality of life, and patient preferences within this review. There is no information about the acute toxicity related to the different fractionation regimens but one could reasonably expect that shorter regimens are more readily tolerated and, therefore, would enhance quality of life for women.

A detailed assessment of quality of life is planned for a subset of patients enrolled in the START trial (Yarnold 1999), which may provide more information. 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 the city). Another trial has been identified (Wallace 1993) and we have contacted the authors requesting further information.

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

(4) The optimum 'dose' of altered fractionation remains unknown. In Owen 2006, two novel altered fractionation schedules were tested; however, we were not able to analyse them separately to see if one was superior to the other. 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.

AUTHORS' CONCLUSIONS

Implications for practice

In selected women with early breast cancer (node negative tumours with negative margins and size 5 cm or less) shortened fractionation regimens may be considered.

Implications for research

There are a number of questions still unanswered that relate to the use of altered fraction size in the treatment of early breast cancer for women undergoing breast cancer surgery. The authors know of one pending trial (see Ongoing studies) which has been designed to test the effects of using fraction sizes greater than 2 Gy in terms of normal tissue responses, loco-regional tumour control, quality of life (cohort followed for QOL), and economic consequences. This study will be included in the next update of this review.

A trial which has completed accrual but is awaiting further follow up and analysis was identified. The START trial (A and B) was designed to test the effects of using fraction sizes greater than 2 Gy in terms of normal tissue responses, loco-regional tumour control, quality of life (cohort followed for QOL), and economic consequences. This study will be included in the next update of this review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Owen 2006

Methods	Centrally randomised, multicentre setting: tertiary cancer centres
Participants	1410 women with operable (T1-3N0-1MO) invasive breast cancer requiring radiotherapy
Interventions	Experimental arm (n=474): 39 Gy in 13 fractions, or 42.9 Gy in 13 fractions (n=466) over 5 weeks. Control arm: 50 Gy in 25 fractions (n=470) over 5 weeks
Outcomes	Primary outcome: late change in breast appearance (scored from photos). Secondary endpoints: palpable breast induration (fibrosis) 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 patients
Notes	Photos: frontal photos taken after surgery before RT, then annually to 5 years and at 10 years under standard conditions. Photos scored by three observers Low risk of bias

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - adequate

Whelan 2002

Methods	Centrally randomised, multicentred, setting: tertiary institutions, intention to treat analysis, no post-randomization exclusions
Participants	1234 women with invasive breast cancer (< 5cm, i.e. no T3/T4 lesions, negative margins and node negative) treated with lumpectomy. Exclusions: those with multicentric disease, large breasts (separation > 25cm) and those with bilateral breast cancer
Interventions	Experimental arm (n=622): radiation dose to breast alone, 42.5 Gy in 16 fractions (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 (trained nurse). Global cosmetic outcome assessed using 4-point scale. Late radiation toxicity assessed by trained nurse using RTOG/EORTC late radiation morbidity scale

Whelan 2002 (*Continued*)

Notes	Concurrent interventions were evenly divided between the 2 arms: 254 women in the experimental arm received tamoxifen and 251 in the control arm, 66 women in the experimental arm received chemotherapy and 66 in the control arm. Moderate risk of bias

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - adequate

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

Study	Reason for exclusion
Angelakis 1973	Not RCT
Anon 1981	Surgery was wide local excision versus mastectomy
Anon 1982	Not RCT
Anon 1999	Not RCT
Ash 1995	Not RCT
Asrari 1999	Not RCT
Baglan 2001	Did not examine external beam radiation
Baillet 1990	Did not examine 2 Gy versus > 2 Gy per fraction
Bartelink 1998	Not RCT
Bates 1975	Surgery was modified radical mastectomy
Bates 1988	Surgery was modified radical mastectomy
Bedwinik 1990	Not RCT
Brinkley 1984	Surgery was modified radical mastectomy
Bruce 1971	Surgery was modified radical mastectomy versus simple mastectomy
Di Biase 2002	Not RCT
Dvivedi 1978	Surgery was modified radical mastectomy and regional radiation therapy was examined

(*Continued*)

EBCTG 2000	Not RCT
Fentiman 1991	Not RCT
Formenti 2002	Partial breast radiation therapy was examined
Goel 2002	Surgery was modified radical mastectomy
Gorodetsky 1999	Not RCT
Kovarik 1995	Not RCT
Liljegren 1993	Intervention was radiation therapy in experimental arm only
Mladenovic 2001	Not RCT
Moody 1994	Refers to women randomised in Owen 2006, but only patients randomised from 1986 to 1991
Moonen 1994	Not RCT
Nyman 1994	Not RCT
Nyman 1995	Not RCT
Olivotto 1996	Intervention was +/- aspirin
Ortholan 2003	Not RCT
Poortmans 2001	Not RCT
Ptaszynski 1999	Examined boost versus no boost
Rodger 1998	Not RCT
Romestaing 1997	Examined boost versus no boost
Sanguineti 2001	Was a chemotherapy trial
Shelley 2000	Not RCT
Svoboda 1992	Not RCT
Turesson 1984	Not RCT
van Tienhoven 1991	Not RCT
Veronesi 2001	Not RCT

(*Continued)*

Vicini 1997	Not RCT
Vicini 2001	Not RCT
Vrieling 2000	Examined boost versus no boost
Wallgren 1978	Investigates preoperative radiation therapy
Wazer 2002	Not RCT
Yamada 1999	Not RCT
Yarnold 1991	Not RCT

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

Wallace 1993

Trial name or title	WMOA (West Midlands Oncolgy Association Trial)
Methods	
Participants	Women attending Queen Elizabeth Hospital Birmingham for postoperative radiation following lumpectomy for carcinoma of the breast
Interventions	Experimental (n=31): 40 Gy in 15 fractions plus boost 10-14 MeV of 15 Gy in 5 fractions. Conventional (n=32): 50 Gy in 25 fractions plus boost as above
Outcomes	
Starting date	
Contact information	
Notes	This represents a cohort of a larger trial - more details have been requested

Yarnold 1999

Trial name or title	Standardisation of breast radiotherapy (START) trial
Methods	
Participants	1. Patients must be 18 years and above, have operable unilateral breast cancer (T1-3, NO-1, MO at presentation) 2. There must be histological confirmation of invasive carcinoma and complete macroscopic excision of tumour by breast conserving surgery or mastectomy 3. The patient must consent to be part of the study and be available for follow up

Yarnold 1999 (*Continued*)

Interventions	Radiotherapy schedules using fraction sizes larger than 2.0 Gy
Outcomes	In this study several endpoints are being investigated (tumour recurrence, normal tissue effect, quality of life) . It is intended that each will be analysed separately. If there is discordance between the endpoints in terms of treatment outcome this will allow discussion of clinical trade-offs. In a subset of patients there will be a detailed assessment of quality of life. Health economic consequences will also be determined
Starting date	01/01/1999
Contact information	clinical.trial@headoffice.mrc.ac.uk
Notes	http://www.controlled-trials.com/ISRCTN59368779/

DATA AND ANALYSES

Comparison 1. Unconventional fractionation versus conventional fractionation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deaths at 5 years	2	2644	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.78, 1.19]
2 Late radiation toxicity at 5 years - sub-cutaneous tissue	2	1558	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.78, 1.28]

Analysis 1.1. Comparison 1 Unconventional fractionation versus conventional fractionation, Outcome 1 Deaths at 5 years.

Review: Fraction size in radiation treatment for breast conservation in early breast cancer

Comparison: 1 Unconventional fractionation versus conventional fractionation

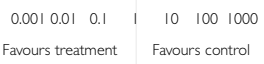
Outcome: 1 Deaths at 5 years

Study or subgroup	Unconventional n/N	Conventional n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Owen 2006	146/940	74/470		65.7 %	0.99 [0.76, 1.28]
Whelan 2002	48/622	51/612		34.3 %	0.93 [0.63, 1.35]
Total (95% CI)	**1562**	**1082**		**100.0 %**	**0.97 [0.78, 1.19]**

Total events: 194 (Unconventional), 125 (Conventional)

Heterogeneity: $Chi^2 = 0.07$, df = 1 (P = 0.79); $I^2 = 0.0\%$

Test for overall effect: Z = 0.32 (P = 0.75)

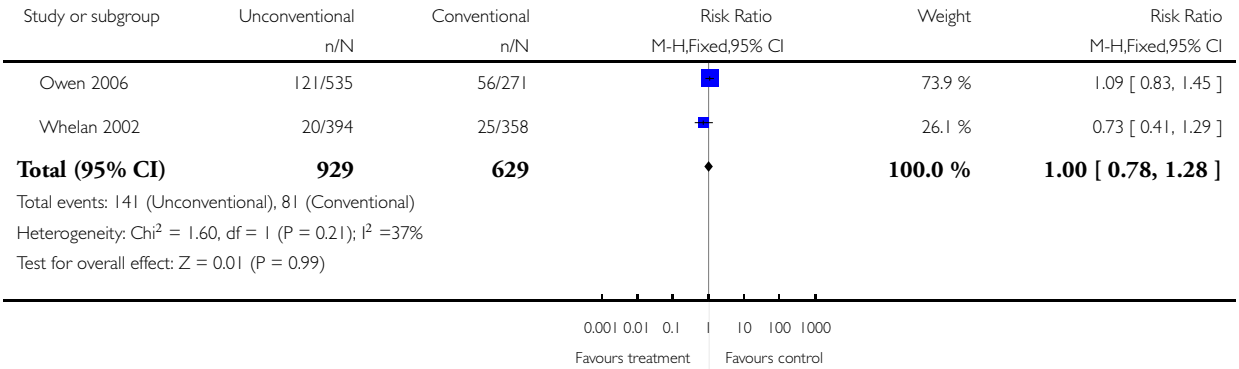


Analysis 1.2. Comparison 1 Unconventional fractionation versus conventional fractionation, Outcome 2 Late radiation toxicity at 5 years - sub-cutaneous tissue.

Review: Fraction size in radiation treatment for breast conservation in early breast cancer

Comparison: 1 Unconventional fractionation versus conventional fractionation

Outcome: 2 Late radiation toxicity at 5 years - sub-cutaneous tissue



ADDITIONAL TABLES

Table 1. RTOG/EORTC late radiation morbidity scale

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

Table 2. Induration of treated breast (four point scale used in Owen 2006)

Score	Definition
0	None
1	Mild

Table 2. Induration of treated breast (four point scale used in Owen 2006) (*Continued*)

2	Moderate
3	Marked

Table 3. EORTC Cosmetic Rating System

Global cosmetic
0 = no difference of excellent
1 = small difference or good
2 = moderate difference or fair
3 = large difference or poor

Table 4. Four-point scale used to report breast cosmesis in Owen 2006

Breast Cosmesis
Excellent
Good
Fair
Poor

Table 5. Local recurrences reported in Owen 2006

Trial arms	**Relapses/ person yrs**
Experimental: 42.9 Gy in 13 fractions	42/ 3840
Experimental: 39 Gy in 13 fractions	66/3890
Control: 50 Gy in 25 fractions	50/3965

Table 6. Conversion of altered fractionation regime to BED

Gray	BED (Alpha/beta=4)
42.9 Gy/1/6#	70.72
49 Gy/13#	95.17
42.9 Gy/13#	78.29
50 Gy/25#	75

APPENDICES

Appendix 1. Search strategy - MEDLINE (Ovid) 1966 to October 2006

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 2. Search strategy - EMBASE (Ovid) 1980 to June 2006

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

WHAT'S NEW

Last assessed as up-to-date: 22 April 2006.

Date	Event	Description
11 April 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 2002

Review first published: Issue 3, 2008

CONTRIBUTIONS OF AUTHORS

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

Melissa James was involved in conceiving and designing the review, 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.

Brigid Hickey was involved in conceiving and designing the review, screening papers against 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 review.

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, and securing funding for the review.

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, coordinating the review, screening search results, organising paper retrieval, screening papers against inclusion criteria, appraising quality of papers, writing to authors, obtaining data on unpublished studies, providing clinical perspective, and writing the review.

Daniel Francis was involved in coordinating the review, doing the search, screening search results, organising paper retrieval, screening against inclusion criteria, writing to authors, providing methodological perspective, writing the review, and providing general advice.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Princess Alexandra Hospital Cancer Collaborative Group, Australia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Women with T3 tumours (that is tumour size greater than 5 cm) were eligible for the Owen study (Owen 2006). They comprised 1.6% (22/1410) of the women studied and only 0.83% of the women studied in the review.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Female; Humans