Partial breast irradiation for early breast cancer (Protocol)

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Partial breast irradiation for early breast cancer (Protocol)

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Partial breast irradiation for early breast cancer

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

The objective of this review is to determine whether APBI has a role in breast conservation therapy for early-stage breast cancer.

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 1 in 8; it is 1 in 9 for women living in the United Kingdom (AIHW 2006; ONS 1999; Ries 2006). Breast cancer is the second most common cause of cancer death in females.

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

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

Randomised studies have shown that addition of radiation therapy decreases ipsilateral breast (same breast) recurrence rates from 30 to 40% (treated with lumpectomy alone) (Fisher 1995; Fisher 2002; Freeman 1981; Lagios 1983; Montgomery 1978) to 10 to 20% in 10 to 15 years of follow up (Fisher 1995; Fisher 2002). An ipsilateral recurrence can either be a true recurrence of the original cancer (typically arising in the same quadrant as the original...
tumour and known as local recurrence) or a second primary tumour developing elsewhere in that same breast. Studies evaluating ipsilateral breast tumour recurrence patterns show that new primaries increasingly contribute to the rate of recurrence after five to eight years while true recurrence rates stabilise (Krauss 2004; Smith 2000). If radiation given to the whole breast (whole breast radiation therapy) was successful in preventing the recurrence of new primary cancer, the rate of such cancers in the treated breast should be lower than the rate of development of cancers in the other breast (contralateral breast cancer). This has not been found in studies of ipsilateral breast tumour recurrence patterns (Krauss 2004, Smith 2000). Furthermore, more recent studies examining primary and re-excision pathological specimens removed at the time of breast conserving surgery revealed residual tumour less than 10 and 15 mm from the primary tumour in 81% and 91% of the specimens, respectively (Wallner 2004).

Thus, as most true recurrences occur in the same quadrant as the original tumour and as whole breast radiation therapy (RT) does not appear to protect against the development of new primary cancer, investigators have begun to examine the role of partial breast irradiation (PBI).

**Description of the intervention**

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

(1) Intracavitary brachytherapy or MammoSite® (applying radioactive sources directly into the cavity left after surgical removal of the tumour either at the time of surgery or at a later date, the latter requiring a second procedure).

(2) Interstitial brachytherapy (inserting catheters into the surgical cavity and surrounding tissue to temporarily deliver radioactive sources).

(3) Intra-operative techniques using electrons or X-rays at 50 kVp (using a dedicated machine to deliver a very localised radiation dose to the surgical cavity in the operating room or by moving the patient with an open wound to the radiation machine, which may be in a different part of the hospital).

(4) External beam radiotherapy using either three-dimensional conformal RT (external beam radiation therapy delivered in the post-operative setting to a volume of breast tissue around the tumour cavity using a standard linear accelerator in a radiation oncology department) or other methods.

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

**How the intervention might work**

APBI will only be of benefit if it confers the same local control benefit as standard whole breast radiotherapy with acceptable toxicity and cosmesis. APBI is currently an experimental therapy.

The use of APBI has a number of potential advantages including:

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

The use of APBI has a number of potential disadvantages including:

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

**Why it is important to perform this review**

APBI has the potential to change the pattern of practice for a common malignancy and thereby impact on resource utilisation, patient satisfaction and quality of life. However, as APBI is currently an experimental therapy it must be thoroughly evaluated before being adopted as the new standard of care for early-stage breast cancer. The fact that the benefit versus risk profile of APBI is currently unknown makes it an ideal topic for a systematic review.
OBJECTIVES

The objective of this review is to determine whether APBI has a role in breast conservation therapy for early-stage breast cancer.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised trials evaluating conservative surgery plus APBI versus conservative surgery plus whole breast radiotherapy. The comparisons must be un-confounded (that is treatments given to the randomised groups must differ only in relation to the volume of the breast radiated). Trials incorporating the use of adjuvant treatments, such as chemotherapy, monoclonal antibodies or hormonal therapy, are eligible if these other treatments were applied in exactly the same way to both groups in the randomised trial. Published and unpublished studies are eligible.

Studies in which partial breast irradiation is used as a boost following conventional external beam radiation therapy will not be considered for inclusion.

Types of participants

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

Types of interventions

Radiation delivered to the partial breast (PBI) using larger than standard radiation dose per fraction such that the overall treatment time is reduced (APBI). Any method of delivery of APBI will be considered including but not limited to intracavitary brachytherapy or MammoSite®, interstitial brachytherapy, intra-operative techniques such as electrons or X-rays at 50 kVp or external beam radiation therapy using either three-dimensional conformal therapy or other methods. Conventional breast radiation therapy is delivered to the whole breast, including or not including the supraclavicular fossa and axilla, using standard fractionation (1.8 to 3.0 Gy per fraction) to deliver a total of 40 to 61 Gy at the reference point. Treatment can include a boost (using electrons, interstitial therapy, external beam or new techniques).

Types of outcome measures

Primary outcomes

Local recurrence in the ipsilateral breast and cosmesis.

Local recurrence will be defined as a recurrence of the same histological type of cancer within the same quadrant of the breast as the primary cancer.

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 radiotherapy, chemotherapy-related toxicity and surgical toxicity; individual protocol-based definitions).
3. New primary tumours in ipsilateral breast. A new primary will be defined as a lesion arising in a quadrant of the breast that is different from the original cancer or a tumour of a different histological subtype occurring anywhere within the breast.
4. Cause-specific mortality (deaths due to breast cancer at five years).
5. Distant metastases, in isolation or at the same time as local recurrence (the occurrence of metastases at five years).
6. Relapse-free survival (length of time after treatment during which no recurrence is found). Recurrence refers to breast cancer in the ipsilateral breast or elsewhere in the body, excluding a new breast cancer in the contralateral breast.
7. Subsequent mastectomy (ipsilateral partial mastectomy, modified radical mastectomy or radical mastectomy).
8. Compliance, defined as the number of women who commence treatment with APBI or conventional EBRT and complete the treatment course.
9. Costs (monetary costs of PBI versus EBRT) to women, government and insurance companies.
11. Consumer preference - do women prefer APBI or EBRT given the advantages and disadvantages of each approach?

Search methods for identification of studies

(1) Cochrane Breast Cancer Specialised Register

The specialised register maintained by the Cochrane Breast Cancer Group will be searched (details of search strategies used by the group for the identification of studies and the procedure used to code references are outlined in the group’s module (http://www.mrw.interscience.wiley.com/cochrane/clabout/articles/BREASTCA/frame.html)). Studies on the specialised register with keywords ‘early’ and ‘radiotherapy’ will be extracted for consideration.

(2) Electronic databases, no language restriction

(a) MEDLINE (host: OVID)

See Table 1.
(b) Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley InterScience) (via internet http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME)
(c) Cumulative Index to Nursing & Allied Health Literature (CINAHL) (host: EBSCO)
(d) Current Contents (host: ISI Web of knowledge)
The MEDLINE search strategy will be modified to search the above databases.

(3) Unpublished literature
We will search registers of ongoing clinical trials. These will include:
(a) US clinical trials registry (www.clinicaltrials.gov);
(b) International Standard Randomised Controlled Trial Number Register (www.controlled-trials.com/isrctn);
(c) UKCCR National Register of Cancer Trials (http://212.219.75.236/ukcccr/).

(4) Grey literature
(a) SIGLE (http://stneasy.fiz-karlsruhe.de/dbss/help.SIGLE.html)
We will contact researchers located from the grey literature and unpublished literature to ask if they are aware of any other trials on this topic.

Data collection and analysis

Selection of studies
All three authors (ML, BH, DF) will check the titles and abstracts retrieved by the searches. Each review author will independently assess the full text of the studies we think may be relevant to the review, resolving differences in assessment by discussion. Trial assessments will be performed with the results masked. In cases where data are limited, or information on study methods is limited, we will request further information from the study authors.

Data extraction and management
Three authors (ML, DF and BH) will perform data extraction, with disagreements resolved by discussion. Data will be entered into RevMan 4.2.8 for analysis. Where possible, we intend to extract data on tumour stage, nodal status, margin status, receptor status, hormonal manipulation, treatment allocation and surgery performed. The information extracted on radiotherapy will include overall treatment time, radiation dose, dose per fraction and method of PBI. We will extract outcome data on local recurrence, deaths (all-cause and breast cancer deaths), new ipsilateral primaries, mastectomy rate, distant metastases, treatment-related toxicity (including that related to acute and late effects of radiotherapy and to surgery), cosmesis, costs of treatment, consumer preference and quality of life.

Assessment of methodological quality of included studies
Trials will be assessed to check that they meet the inclusion criteria and the methodological quality will be assessed and graded. Any disagreement will be resolved by discussion between the review authors.

Methodological quality will be independently assessed by two review authors (BH and ML), the third author (DF) will be called in to resolve any discrepancies. Studies will be assessed according to the quality assessment tool based on the findings of Schulz 1995. This assesses whether treatment allocation was randomised, treatment allocation was concealed, patients were included in analyses using intention-to-treat principles and the adequacy of generation of the allocation sequence. Because of the nature of interventions used in the management of breast cancer, specifically those involved in this review for example whether radiation is delivered prior to chemotherapy, blinding of investigators or participants is not possible, therefore, assessment blinding will not form part of the quality assessment.

Sensitivity analyses will be performed on the basis of study quality. The analysis will be performed both with and without trials of low quality to assess the effect of quality on the results. Quality will be assessed empirically. Studies meeting 3 of the 5 criteria in Schulz 1994 will be deemed high quality.

Measures of treatment effect
Results for dichotomous outcomes will be presented as odds ratios (OR) with 95% confidence intervals (CI) (Deeks 2004). Results for continuous variables (such as quality of life) will be summarised using the mean difference or the standardised mean difference when different measurement scales are used (Deeks 2004).

Data synthesis (meta-analysis)
We will apply the intention-to-treat principle in analysing data from the trials and determine a weighted average treatment effect using the fixed-effect model to combine results, if appropriate (Mantel 1959), with RevMan 4.2. We will use the Mantel-Haenszel methods to calculate pooled results (Greenland 1985; Mantel 1959) if there is no significant heterogeneity, or otherwise the random-effects model of DerSimonian and Laird.

Subgroup analysis and investigation of heterogeneity
If data are available, we may perform subgroup analyses to investigate whether the effects of using PBI or conventional breast radiotherapy differ depending on nodal status, margin status, receptor status, hormonal manipulation or tumour stage. We will assess heterogeneity both visually and statistically using the chi-squared test of heterogeneity (Altman 1992; Walker 1988) and I² (Higgins 2002; Higgins 2003). The criterion for identification of heterogeneity is a P-value less than 0.10 for the chi-squared test, acknowledging the limitations of this process, and a value of I² greater than 50%. If we identify significant heterogeneity, the reasons for it will be explored and we will make a cautious attempt to explain the heterogeneity.
REFERENCES

Additional references

AIHW 2006

Altman 1992

Deeks 2004

EBCTCG 1995

Fisher 1995

Fisher 2002

Fleming 1997

Freeman 1981

Greenland 1985

Higgins 2002

Higgins 2003

Holland 1985

Jacobsen 1995

Krauss 2004

Lagios 1983

Mantel 1959

Montgomery 1978

ONS 1999

Poggi 2003

Ries 2006

Schoen 2005

Schulz 1994
Schulz KF, Chalmers I, Grimes DA, Altman DG. Assessing the quality of randomization from reports of controlled

**Schulz 1995**

**Smith 2000**

**Van Dongen 2000**

**Veronesi 1995**

**Veronesi 2002**

**Walker 1988**

**Wallner 2004**

**Whelan 2000**

* Indicates the major publication for the study

### APPENDICES

#### Appendix 1. Search Strategy - Medline (Ovid)(1966 to present)

1. RANDOMIZED CONTROLLED TRIAL.pt
2. CONTROLLED CLINICAL TRIAL.pt
3. RANDOMIZED CONTROLLED TRIALS.sh
4. RANDOM ALLOCATION.sh
5. DOUBLE BLIND METHOD.sh
6. SINGLE BLIND METHOD.sh
7. or/1-6
8. (ANIMALS not HUMANS).sh
9. 7 not 8
10. CLINICAL TRIAL.pt
11. exp CLINICAL TRIALS/
12. (clin$ adj25 trial$).ti,ab
13. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab
14. PLACEBOS.sh
15. placebo$ ti,ab
16. random$.ti,ab
17. RESEARCH DESIGN.sh
18. or/10-16
19. 18 not 8
20. 19 not 9

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21. 9 or 20
22. exp breast neoplasms/
23. exp "neoplasms, ductal, lobular, and medullary"/
24. exp breast/
25. exp neoplasms/
26. 24 AND 25
27 (breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or dcis or ductal or infiltrat$ or intraductal$ or lobular or medullary)).mp.
28 exp mammary neoplasms/
29 (mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or dcis or ductal or infiltrat$ or intraductal$ or lobular or medullary)).mp
30. or/22, 23,26-29
31. partial breast irradiation.sh,kw,ti,ab
32. partial breast.sh,kw,ti,ab
33. whole breast irradiation.sh,kw,ti,ab
34. whole breast radiotherapy.mp
35. less that whole breast rad$.mp
36. brachytherapy.sh,kw,ti,ab
37. high-dose-rate brachytherapy.sh,kw,ti,ab
38. accelerated partial breast irradiation.sh,kw,ti,ab
39. tumor bed boost.sh,kw,ti,ab
40. sole tumor bed irradiation.sh,kw,ti,ab
41. MammoSite.sh,kw,ti,ab
42. Breast Neoplasms/ rt.sh
43. Radiotherapy, Conformal/adverse events.sh
44. Radiotherapy, Conformal/methods.sh
45. Brachytherapy.sh
46. Balloon dilation.sh
47. Radiotherapy/.sh
48. or/31-47
49. 48 AND 30
50. 49 AND 21

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HISTORY

CONTRIBUTIONS OF AUTHORS
The protocol was written by Dr Margot Lehman, Dr Brigid Hickey and Mr Daniel Francis

DECLARATIONS OF INTEREST
Nil

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Internal sources
- No sources of support supplied

External sources
- Princess Alexandra Cancer Collaborative Group, Australia.