Post-operative Radiotherapy In Minimum-risk Elderly Phase II

A Randomised Breast Cancer Trial To Assess Local Control in Older Patients

(incorporating the PRIME Quality of Life Trial)

Under the auspices of the Scottish Breast Cancer Trials Group

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# Contents

1. Introduction  

2. Background  
   2.1 Breast cancer in older patients  
   2.2 Breast conserving therapy in older patients  
   2.3 Risk factors for local recurrence  

3. Aims of trial  

4. Plan of investigation  
   4.1 Objectives  
   4.2 Design  
   4.3 Primary end-point  
   4.4 Secondary end-points  
   4.5 Sub-studies  
   4.6 Size of trial  
   4.7 Analysis plan  

5. Eligibility Criteria  

6. Exclusions  

7. Consent  

8. Randomisation  

9. Surgical procedures  

10. Radiotherapy  

11. Oestrogen receptor status and hormonal treatment  

12. Clinical assessments  

13. Data collection  

14. Data monitoring  

15. Ethical considerations  

16. Financial support  

17. Presentation, Final Analysis, Publications  

18. References
1. Introduction

The PRIME II trial is a randomised controlled clinical trial to assess the role of radical breast irradiation in older “low-risk” women undergoing breast conservation and adjuvant endocrine therapy. It is being set up as a large multi-centre, international trial in order to recruit sufficient patients to have adequate power to detect small differences in local recurrence rates.

2. Background

2.1 Breast cancer in older patients – epidemiological aspects

The management of breast cancer among older patients places major and growing demands on NHS resources. Just over half the cases of breast cancer occur in older patients (65 years or older) with the peak incidence rate occurring in women in their ninth decade of life (Yancik et al, 1989). The incidence of the disease is set to rise due to an increase in the age-specific incidence of the disease (Brody and Cassell, 1990) and demographic changes in the population (Haynes and Feinleib, 1980). In Scotland a 12% rise in breast cancer between 1996-2006 is predicted in women 75 years or older (C. Thomson, Scottish Cancer Intelligence Unit, personal communication, 1997). Additional cases are likely to be detected as the age limit of the UK breast screening programme is extended up to the age of 70 in 2003. The Scottish Executive predicts a 41% rise in the annual number of cases of breast cancer, from 3312 per annum in 1995-7 to 4831 per annum by 2010-14 (Cancer Scenarios, 2001).

The differences between older and younger women in response to standard treatments are poorly defined since patients over 70 are frequently excluded from trials on the basis of age or comorbidity. The National Institute of Health Consensus Development Conference Statement (2000) on adjuvant therapies in breast cancer identified the need for trials of adjuvant therapies in older patients. It is also reported, for many malignancies, that patients aged 65 and older are under represented in clinical trials (Hutchins et al, 1999). Addressing the particular needs of older patients with cancer is one of the priorities of the Scottish National Cancer Plan (Cancer in Scotland, 2001). The conduct of randomised trials of cancer therapy among older patients in general and for breast cancer in particular is therefore an important priority of the NHS.

2.2 Breast conserving therapy in older patients.

Breast conserving surgery, adjuvant postoperative breast radiotherapy and systemic therapy has become standard treatment for increasing numbers of women with early breast cancer. In Scotland in 1993 44% of women 70 years or older with axillary node negative operable breast cancer underwent breast conserving surgery (P.Stroner, Scottish Cancer Intelligence Unit, personal communication, 1997). Nonetheless there is evidence of wide variation in the receipt of breast irradiation among older patients undergoing breast conserving surgery. Ballard-Barbash et al (1996) found among a cohort of 18,704 women aged 65 or older that the receipt of postoperative radiotherapy declined substantially with age, irrespective of comorbidity and disease stage. For the age groups 65-69 and 80 years or older, the use of irradiation fell from 77% to 24% in women with no comorbid conditions and 50% to 12% with two or more comorbid conditions. The reasons for the lower rates of breast irradiation with age are often not related to the stage of the disease. They may reflect the...
patient’s, carer’s or oncologist’s belief that breast irradiation will not be tolerated or is not worthwhile. Selecting older patients for irradiation is often made more difficult by the presence of comorbidity which may increase the risk of treatment complications (Cova et al, 1998) and can influence survival.

Postoperative radiotherapy has been shown in a number of randomised trials to reduce the risk of breast cancer recurrence following breast conserving surgery (Clark et al, 1992; Fisher et al, 1995; Veronesi et al, 1993; Lijegren, 1999; Forrest et al, 1996). A four fold reduction in risk of breast recurrence was shown in the Scottish Conservation trial (Forrest et al, 1996). No compromise in survival was demonstrated in these trials by the omission of breast radiotherapy. The addition of adjuvant tamoxifen would be expected to further reduce the risk of local recurrence. While distant metastases may develop in patients who develop local recurrence, it remains unclear whether or not these events are causally related (Koscielny and Tubiana, 1999) or coincidental (Fisher et al, 1991).

2.3 Risk factors for local recurrence

There is conflicting evidence as to whether breast radiotherapy may be safely omitted in some patients at low risk of local recurrence. The risk of local recurrence is raised two fold in patients with grade 3 histology or lymphatic/vascular invasion (Locker et al, 1989; Kurtz, 1992). However the major risk factor, which confers a 9 fold risk of local recurrence, is the involvement of resection margins (Smitt et al, 1995). The relative risks of age, tumour grade and lymphatic/vascular invasion have however largely been deduced from trials of breast conserving therapy in women under the age of 70. The importance of these factors for older patients is poorly defined.

Data on the impact of age on the risk of local recurrence following breast conserving surgery is conflicting. The Milan trial (Veronesi et al, 1993) suggests that local recurrence rates in older patients fall with age. This trial of quadrantectomy, axillary clearance and systemic therapy with or without breast irradiation, in the non-irradiated group, showed a 3.8% local recurrence rate in women over 55 compared to 8.7% in the 46-55 and 17.5% in the <45 age groups respectively.

In the Uppsala Orebro randomised trial, (Liljegren et al, 1997) 381 stage I patients were randomised after sector resection to breast radiotherapy or its omission. Patients over the age of 60 without comedo or lobular carcinoma were found to be at low risk of local recurrence (5.9% at 5 years). In contrast, neither the NSABP trial (Fisher et al, 1995) nor the Scottish conservation trial (Forrest et al, 1996) showed any impact of age on risk of local recurrence. However, in none of these trials are there large numbers of patients over the age of 65 and particularly few among the over 75 year age group.

More recently reported randomised trials provide conflicting conclusions on the risk of breast recurrence in low risk patients in whom breast radiotherapy is omitted. In the NSABP B21 trial (Wolmark et al, 2000), patients with ≤1cm, node negative tumours managed by breast conservation were randomised to tamoxifen alone, radiotherapy alone or radiotherapy plus tamoxifen. The ipsilateral breast recurrence rate in the tamoxifen alone group was 11.9% (40/336) compared to 5.7% (19/336) in the radiotherapy alone group and 1.8% (6/337) in the tamoxifen + radiotherapy group. Annual recurrence rates were 2.44%, 1.17% and 0.36% respectively. Average follow up was 73 months. However, this trial was not conducted in the elderly specifically.
In contrast the CALGB/RTOG/ECOG trial (Hughes et al, 2001) of lumpectomy and adjuvant tamoxifen, with or without breast radiotherapy in women 70 years and older had a very low rate of breast recurrence in the tamoxifen alone group (1.3%, 4/319) compared with 0/317 in the tamoxifen plus radiotherapy group. The median follow up was relatively short at 28 months. Of particular interest is the observation that, of the 39 deaths, only one was due to breast cancer (tamoxifen only group). This suggests that comorbidity rather than breast cancer becomes the major cause of death in older low risk women. Both trials have only been published in abstract form but their discrepant findings do suggest that there is still uncertainty about whether breast radiotherapy is needed.

Furthermore, the recent Oxford overview of trials (EBCTCG 2000) on the effects of post-operative radiotherapy (both post-mastectomy and post-conservation) suggests that non-breast cancer (mainly vascular) causes of death offset a reduction in breast cancer mortality from radiotherapy. Since randomised trials were, in the past, largely conducted in women under the age of 70, older women are relatively under represented in the overview. The over 70 group, with a higher probability of cardiovascular comorbidity, might be at even greater risk of radiation induced cardiac damage. It is therefore all the more important to determine whether breast radiotherapy can be safely omitted in some older patients.

Retrospective studies also suggest breast cancer in older patients may be less locally aggressive. In a study of 122 women with T1 and smaller T2 breast cancer treated by wide local excision without breast irradiation, Nemoto et al (1991) found a significantly lower recurrence rate 3% (1/31) in patients 70 years or older compared to younger age groups.

The study of Gruenberger et al (1998) among patients 60 years or older of quadrantectomy, axillary node clearance and adjuvant tamoxifen, with or without breast irradiation in ‘low risk’ (axillary node negative, oestrogen receptor positive) patients showed a 3% local recurrence without breast irradiation at a median follow up of 60 months, similar to 2.6% in the irradiated group.

More recently, a much larger study of 50,828 patients from the San Antonio breast cancer database and 256,287 patients from the Surveillance, Epidemiology and End Results (SEER) registry (Diab et al, 2000) has shown that patients 55 years or older have more favourable biological parameters (e.g. ER positivity, normal P53 and low proliferative rates). Observed survival for node negative patients and/or small tumours was similar to the expected survival in the general population.

However, the number of retrospective studies are few and potentially subject to selection bias. A large randomised trial is therefore needed to assess the role of breast irradiation in older women at low risk of local recurrence treated by wide excision and adjuvant endocrine therapy with or without breast irradiation. The importance of prognostic factors such as grade, tumour size and lymphatic/vascular invasion in this age group also requires examination.
3. Aims of the trial

It is the purpose of the proposed trial to determine the role of adjuvant breast irradiation on local control and overall survival. In addition, quality of life, functional status, cosmesis and cost-effectiveness will be measured, as approved in MREC /98/0/86 PRIME, in what will become a sub-study at specified centres; (see section 4.5).

4. Plan of investigation

Women aged 65 years or older with early breast cancer at low risk of recurrence, who are attending breast cancer clinics in participating centres will be invited to take part in the trial. Formal invitation to participate will take place after the patient has received breast conserving surgery to remove the cancer and once the pathology results are known, although the possibility of entering the trial may be raised earlier. Patients who are eligible and interested will be given a ‘Patient Information Leaflet’ and a ‘Consent Form’. Patients must be allowed at least 24 hours to consider participation before signed Consent Forms are collected. Patients will then be randomised to receive radiotherapy or no radiotherapy to the breast by telephoning a central office (this may be organised on a regional basis if more convenient).

Patients in both arms of the trial will be followed up in an identical manner according to local practice, to monitor clinical progress. An annual follow up form will be completed for the purposes of the PRIME II trial.

4.1 Objectives

To assess the role of post-operative breast radiotherapy in women aged 65 or older, with low risk breast cancer treated by breast conserving surgery and adjuvant endocrine therapy: in particular to estimate the difference in local recurrence rates between patients treated with and without radiotherapy.

4.2 Design

The PRIME II trial is a multi-centre randomised controlled clinical trial which incorporates a Quality of Life sub study named PRIME.

4.3 Primary end-point

- Ipsilateral breast recurrence rates.

4.4 Secondary end-points

- Regional recurrence
- Contralateral breast cancer
- Distant metastases
- Disease-free survival
- Overall survival

4.5 Sub-studies

1) Quality of Life, Functional Status, Cosmesis and Cost-effectiveness (the original PRIME Trial MREC /98/0/86)

The sample size which is required for adequate power to detect differences in recurrence rates (see section 4.6) is larger than may be required for other types of end-point. This
allows the possibility of conducting sub-studies within certain participating centres. Thus a quality of life, cosmesis and cost-effectiveness randomised trial has been initiated in the United Kingdom, with assessments being made at home by a research nurse up to 15 months post-surgery and at 3 and 5 years post-surgery by postal questionnaire. A detailed protocol may be obtained from the Trial Administrator.

2) Comprehensive Cohort Study
Centres participating in the Quality of Life trial (section 4.5.1) may also record the outcomes in patients who decline to be randomised, but who are willing to be followed-up for research purposes. In combination with the data from the randomised patients, this will form a Comprehensive Cohort Study, which will provide empirical information on the size of the treatment effects in randomised patients, and in those choosing their own treatment. It will also allow comparison of the outcome of patients who choose a particular treatment (e.g. radiotherapy) with those who are randomised to that treatment. The Comprehensive Cohort Study is likely to be particularly valuable as an adjunct to the quality of life and cost-effectiveness sub-study, for which the endpoints may be sensitive to the process by which treatment decisions have been reached. Cosmetic assessment is not undertaken in this sub-study. Long term follow up will follow the same procedure as with the randomised patients. Again, this protocol may be obtained from the Trial Administrator.

3) The Executive Committee will consider proposals from participating centres for further sub-studies.

4.6 Size of the trial
1176 patients (588 per arm) will be needed over the period of the trial to detect a difference between 2% and 5% in 5 year recurrence rates with 80% power at the 5% level of significance. To allow for attrition we aim to recruit 1300 patients.

4.7 Analysis plan
Analysis will be conducted in line with the principle of intent-to-treat. That is, all patients will be analysed according to their randomised treatment, irrespective of the treatment actually received. Patients randomised within the current PRIME Quality of Life and Cost-effectiveness trial (see section 4.5.1) will be included in the analysis of local control. Detailed reports on trial progress will be circulated to members of the Data Monitoring Committee (DMC) (see also section 14) at six-monthly intervals, or at any other time which the DMC deems appropriate. Although there are no formal rules for possible early termination of the trial, very highly significant differences in recurrence rates or survival (p<0.001) will cause trial entry to cease. Recommendations by DMC on continuing or stopping the trial would be referred initially to the Steering Committee and then to the Executive Committee. It is anticipated that such decisions would take into account the absolute recurrence/death rates, as well as differences between the treatment arms.

Only those conducting the analysis and the members of the DMC will be aware of the detailed results in each treatment arm until trial entry has ceased, or there has been a recommendation from DMC for closure. Advice on the timing of publishing trial findings will be provided by the Steering Committee.
The end-points of the main trial are all “survival” measures and standard methods of survival analysis will be used. In particular, Kaplan-Meier plots will be produced by treatment group, and hazard ratios and accompanying 95% confidence limits will be estimated using a Cox proportional hazards model. Two-tailed procedures will be used throughout.

5. Eligibility Criteria

1. Breast conserving surgery with an excision margin of a minimum of 1mm on histological assessment
2. Histologically confirmed unilateral breast cancer of pathological size 3cm or less
3. Oestrogen receptor or progesterone receptor positive and treated with adjuvant endocrine therapy (including pre-operative neo-adjuvant endocrine therapy)
4. No axillary node involvement on histological assessment
5. Medically suitable to attend for all treatment and follow up
6. Able and willing to give informed consent

6. Exclusions

1. Age younger than 65 years (date of issue of pathology results)
2. Grade III cancer combined with lymphatic/vascular invasion (because of higher risk of local recurrence)
3. Previous in situ or invasive carcinoma of either breast
4. Current or previous malignancy within the past five years, other than non-melanomatous skin cancer or carcinoma in situ of cervix

7. Consent

Entry to the trial is dependent upon obtaining fully informed patient consent. The concept of the trial may be introduced to the patient at any time, but a formal invitation to participate should not be made until pathology results are available, and trial eligibility is confirmed. Interested patients should be given a ‘Patient Information Leaflet’, and must be allowed to consider participation for at least 24 hours before written informed consent is obtained using the appropriate Consent Form.

8. Randomisation

Eligible consenting patients, treated by conservation surgery and adjuvant endocrine therapy, will be randomised to receive or not receive breast irradiation.

For those patients consenting, the randomised treatment allocation will be obtained by telephoning the appropriate randomisation centre. As the sample size is reasonably large, there will be no stratification of patients in the randomisation process, except for those centres participating in a specified sub-study.
9. Surgical procedures

The aim of the surgical procedure in patients entered into PRIME II is to excise the cancer with 1 cm rim of normal tissue. The preferred technique is to remove a cylinder of tissue from subcutaneous fat down to the pectoral fascia, the specimen orientated so that if disease is present at any of the radial margins then re-excision, if appropriate should be performed. Specimen radiography can be useful in ensuring the lesion has been adequately excised with a 1 cm margin. Older patients' breasts are often fatty. During surgical excision of the mass lesion and processing it is appreciated that fatty tissue from the margins is lost in preparation of the slides for the pathologist. To ensure that the lesion has been adequately excised at all margins there needs to be reported by the pathologist a 1 mm or greater margin of normal tissue beyond the edge of the cancer at all the radial margins.

Alternatively, in those centres which use cavity shavings, all the cavity shavings need to be free of disease so that complete excision can be reasonably guaranteed.

An ipsilateral four node, lower axillary node sample, sentinel node biopsy or axillary node clearance should be performed.

10. Radiotherapy

The total dose, number of fractions and overall treatment time will be according to local practice in each participating centre. As a guideline 40-50 Gy over three to five weeks will normally be given at megavoltage to the breast with a boost, if given, of electrons of 10-15 Gy at an appropriate energy or an iridium 192 implant (e.g. 20 Gy to 85% reference isodose).

While participating centres will not be asked to make any significant change to current practice it will be emphasised that every precaution should be taken to minimise any notable acute or late toxicity of treatment. Specifically the following recommendations are made:

1. The patient must be in the supine position in a stable position during planning simulation and treatment. Some form of immobilisation should be used (e.g. an arm pole). A breast board may be used. The set up should be confirmed by orthogonal lasers.
2. The clinical target volume is the whole breast down to the deep fascia.
3. The planned target volume is the whole breast with a margin of 1 cm. The medial extent of the field should extend to the midline, the lateral margin to 1 cm below the breast plate (or mid-axillary line). Superiorly, the volume should extend to the line of the second intercostal space at the level of the angle of Louis. Inferiorly, the volume should extend 1-2 cm below the inframammary fold.
4. All patients are simulated for radiotherapy to determine the volume of lung within the radiation treatment field. The maximum thickness of lung should not exceed 3 cm.
5. The peripheral lymphatics are not irradiated.
6. A minimum of one transverse outline, taken at the central axis of the length of the tangential fields should be taken.
7. All fields should be treated with megavoltage irradiation with wedged fields so that the dose homogeneity does not vary by more than 10%. All fields will be treated daily.
8. Doses should be prescribed to the reference point at or close to the centre of the target volume (ICRU-50). This point lies half way between the surface of the lung and the surface of the skin on the perpendicular bisector of the posterior beam edge.

9. The planning target volume for the boost will be the tumour bed with lateral margins of 2cm and a deep margin extending down to the underlying muscle.

10. Machine energy, total dose, fractionation and overall treatment time will be recorded for each patient.

11. Oestrogen receptor status and hormonal treatment

Patients classified as ER > 0 are eligible for entry. Patients who are ER 0, but with PgR scores of >0 are also acceptable.

Standard endocrine therapy is tamoxifen 20mg orally daily for five years. However, other forms of adjuvant endocrine therapy will be acceptable. Patients who have received pre-operative neoadjuvant endocrine therapy are also eligible.

12. Clinic assessments

The clinic visits for both arms of the trial will be made post-operatively to fit in with standard local clinical practice following radiotherapy. For the purposes of this trial a minimum of one annual assessment will be required for at least five years. Annual bilateral mammograms are required.

13. Data collection

1. Record of eligible and ineligible patients undergoing breast conserving surgery

In order to be able to describe the population of patients entering the trial, each centre is asked to keep a register of patients aged 65 or older who have undergone breast conserving surgery. This should note the reason for ineligibility, for eligible patients not being offered randomisation and if the patient refuse randomisation. A standardised template will be provided.

2. Registration of trial patients

A standardised form should be completed at entry giving baseline characteristics of the patient. Details of radiotherapy treatment will also be required in the radiotherapy arm of the trial. A follow-up form should be completed annually thereafter and returned to the Trial Administrator. If there has been a recurrence of disease, details of the date, site(s) and treatment initiated should be returned as soon as possible. If the patient ceases to attend the follow-up clinics (e.g. if the patient has moved), details of how to contact the relevant clinician, or the patient herself, should be sent to the Trials Office if at all possible. For any patient who dies, the follow-up form should be completed as fully as possible.

3. Recording of recurrence

Recurrences within the ipsilateral breast, axilla, or distant sites will be recorded. Histological confirmation of recurrence should be sought where possible.

The management of patient data will comply with the requirements of the current Data Protection Act.
14. Data monitoring

A Data Monitoring Committee will be established and will meet six monthly (or as often as they deem appropriate). This committee will be unblinded and will receive regular reports from the administrative centre. It will then pass on its comments and recommendations to the Steering Committee and the Executive Committee.

15. Ethical considerations

Ethical approval for the quality of life and cost-effectiveness sub-study was granted by the Multi-centre Research Ethics Committee (MREC) for Scotland on 15th October 1998. An extension to allow the assessment of patients who declined randomisation was granted on 13th January 2000. MREC approval for PRIME II was granted on 24th September 2001. All local investigators will be required to obtain local ethical and management approval before beginning recruitment.

16. Financial support

A grant has been awarded to undertake the quality of life and cost-effectiveness sub-study by the NHS Research and Development Health Technology Assessment Programme. Further national/international funding will be sought for the main trial described in this protocol.

17. Presentation, Final Analysis, Publications

The model which is proposed for publication is that authorship of peer-reviewed publications relating to PRIME II should be from the Steering Committee, with a named writing committee, and acknowledgement of all collaborators in PRIME II participating centres. Conference presentations arising from the trial should be approved by the Executive Committee, and should not divulge any information relating to treatment differences until entry to the trial is complete. The timing of analyses relating to the main trial, and the content and timing of corresponding publications will be determined by the Steering Committee.

The existing sub-studies will be monitored by their own steering committees, and will be subject to a similar policy with respect to publications.
References


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