

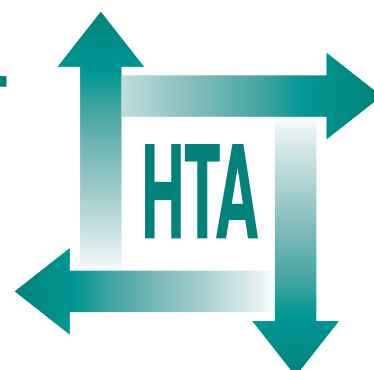
A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial

RJ Prescott, IH Kunkler, LJ Williams, CC King, W Jack, M van der Pol, TT Goh, R Lindley and J Cairns



August 2007

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Declared competing interests of authors: none

Published August 2007

This report should be referenced as follows:

Prescott RJ, Kunkler IH, Williams LJ, King CC, Jack W, van der Pol M, *et al.* A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial. *Health Technol Assess* 2007;11(31).

Health Technology Assessment is indexed and abstracted in *Index Medicus/MEDLINE*, *Excerpta Medica/EMBASE* and *Science Citation Index Expanded (SciSearch®)* and *Current Contents®/Clinical Medicine*.

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The research reported in this monograph was commissioned by the HTA Programme as project number 96/03/01. The contractual start date was in January 1999. The draft report began editorial review in March 2006 and was accepted for publication in January 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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ISSN 1366-5278

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Abstract

A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial

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Objectives: To assess whether omission of postoperative radiotherapy in women with 'low-risk' axillary node negative breast cancer (T0–2) treated by breast-conserving surgery and endocrine therapy improves quality of life and is more cost-effective.

Design: A randomised controlled clinical trial, using a method of minimisation balanced by centre, grade of cancer, age, lymphatic/vascular invasion and preoperative endocrine therapy, was performed. A non-randomised cohort was also recruited, in order to complete a comprehensive cohort study.

Setting: The setting was breast cancer clinics in cancer centres in the UK.

Participants: Patients aged 65 years or more were eligible provided that their cancers were considered to be at low risk of local recurrence, were suitable for breast-conservation surgery, were receiving endocrine therapy and were able and willing to give informed consent.

Interventions: The standard treatment of postoperative breast irradiation or the omission of radiotherapy.

Main outcome measures: Quality of life was the primary outcome measure, together with anxiety and depression and cost-effectiveness. Secondary outcome measures were recurrence rates, functional status, treatment-related morbidity and cosmesis. The principal method of data collection was by questionnaire, completed at home with a research nurse at four times over 15 months.

Results: The hypothesised improvement in overall quality of life with the omission of radiotherapy was not seen in the EuroQol assessment or in the functionality

and symptoms summary domains of the European Organisation for Research in the Treatment of Cancer (EORTC) scales. Some differences were apparent within subscales of the EORTC questionnaires, and insights into the impact of treatment were also provided by the qualitative data obtained by open-ended questions. Differences were most apparent shortly after the time of completion of radiotherapy. Radiotherapy was then associated with increased breast symptoms and with greater fatigue but with less insomnia and endocrine side-effects. Patients had significant concerns about the delivery of radiotherapy services, such as transport, accommodation and travel costs associated with receiving radiotherapy. By the end of follow-up, patients receiving radiotherapy were expressing less anxiety about recurrence than those who had not received radiotherapy. Functionality was not greatly affected by treatment. Within the randomised controlled trial, the Barthel Index demonstrated a small but significant fall in functionality with radiotherapy compared with the no radiotherapy arm of the trial. Results from the non-randomised patients did not confirm this effect, however. Cosmetic results were better in those not receiving radiotherapy but this did not appear to be an important issue to the patients. The use of home-based assessments by a research nurse proved to be an effective way of obtaining high-quality data. Costs to the NHS associated with postoperative radiotherapy were calculated to be of the order of £2000 per patient. In the follow-up in this study, there were no recurrences, and the quality of life utilities from EuroQol were almost identical.

Conclusions: Although there are no differences in overall quality of life scores between the patients treated with and without radiotherapy, there are several dimensions that exhibit significant advantage to the omission of irradiation. Over the first 15 months, radiotherapy for this population is not a cost-effective treatment. However, the early postoperative outcome does not give a complete answer and the eventual cost-effectiveness will only

become clear after long-term follow-up. Extrapolations from these data suggest that radiotherapy may not be a cost-effective treatment unless it results in a recurrence rate that is at least 5% lower in absolute terms than those treated without radiotherapy. Further research is needed into a number of areas including the long-term aspects of quality of life, clinical outcomes, costs and consequences of omitting radiotherapy.



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List of abbreviations

BNF	British National Formulary	LREC	Local Research Ethics Committee
CCS	comprehensive cohort study	LVI	lymphovascular invasion
CEAC	cost-effectiveness acceptability curve	MREC	Multicentre Research Ethics Committee
CI	confidence interval	PGCMS	Philadelphia Geriatric Center Morale Scale
COREC	Central Office for Research Ethics Committees	PRIME	Postoperative Radiotherapy In Minimum-risk Elderly
EORTC	European Organisation for Research and Treatment of Cancer	QALY	quality-adjusted life-year
ER	oestrogen receptor	QEO	quasi-experimental and observational
HADS	Hospital Anxiety and Depression Scale	QoL	quality of life
HCHS	Hospital and Community Health Services	RCT	randomised controlled trial
ICER	incremental cost-effectiveness ratio	RT	radiotherapy
ITT	intention-to-treat	RTOG	Radiation Therapy Oncology Group
		SHSC	Scottish Health Service Costs

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.



Executive summary

Background

Postoperative breast irradiation is the standard treatment following breast-conserving surgery and adjuvant endocrine therapy, irrespective of age. However, the differences between older and younger patients in response to treatment are poorly defined, since patients aged over 70 years are frequently excluded from trials.

The use of breast irradiation declines substantially with age, although just over half of the cases of breast cancer occur in women aged 65 years and older. Current data suggest that the risk of local recurrence after conservation surgery and endocrine therapy may decline with age. At the same time, there are competing risks of death, particularly vascular, in older patients.

Objectives

The objectives of this study were to assess whether omission of postoperative radiotherapy in women with 'low-risk' axillary node negative breast cancer (T0–2) treated by breast-conserving surgery and endocrine therapy improves quality of life and is more cost-effective.

Methods

Design

A randomised controlled clinical trial, using a method of minimisation balanced by centre, grade of cancer, age, lymphatic/vascular invasion and preoperative endocrine therapy, was performed. A non-randomised cohort was also recruited, in order to complete a comprehensive cohort study.

Setting

The setting was breast cancer clinics in cancer centres in the UK.

Participants

Patients aged 65 years or more were eligible provided that their cancers were considered to be at low risk of local recurrence, were suitable for breast-conservation surgery, were receiving

endocrine therapy and were able and willing to give informed consent.

Interventions

Interventions were the standard treatment of postoperative breast irradiation or the omission of radiotherapy.

Main outcome measures

Quality of life was the primary outcome measure, together with anxiety and depression and cost-effectiveness. Secondary outcome measures were recurrence rates, functional status, treatment-related morbidity and cosmesis. The principal method of data collection was by questionnaire, completed at home with a research nurse four times over 15 months.

Results

The hypothesised improvement overall in quality of life with the omission of radiotherapy was not seen in the EuroQol assessment or in the functionality and symptoms summary domains of the European Organisation for Research in the Treatment of Cancer (EORTC) scales. Some differences were apparent within subscales of the EORTC questionnaires, and insights into the impact of treatment were also provided by the qualitative data obtained by open-ended questions. Differences were most apparent shortly after the time of completion of radiotherapy. Radiotherapy was then associated with increased breast symptoms and with greater fatigue but with less insomnia and endocrine side-effects. Patients had significant concerns about the delivery of radiotherapy services, such as transport, accommodation and travel costs associated with receiving radiotherapy. By the end of follow-up, patients receiving radiotherapy were expressing less anxiety about recurrence than those who had not received radiotherapy.

Functionality was not greatly affected by treatment. Within the randomised controlled trial, the Barthel Index demonstrated a small but significant fall in functionality with radiotherapy compared with the no radiotherapy arm of the

trial. Results from the non-randomised patients did not confirm this effect, however. Cosmetic results were better in those not receiving radiotherapy but this did not appear to be an important issue to the patients. The use of home-based assessments by a research nurse proved to be an effective way of obtaining high-quality data.

Costs to the NHS associated with postoperative radiotherapy were calculated to be of the order of £2000 per patient. In the follow-up in this study, there were no recurrences, and the quality of life utilities from EuroQol were almost identical. Within this time frame, no radiotherapy is therefore the cost-effective choice. In the longer term, cost-effectiveness will depend on the extent of any greater recurrence rates in patients not receiving radiotherapy and the effect of the recurrence on their quality-adjusted life-years.

Conclusions

Although there are no differences in overall quality of life scores between the patients treated with and without radiotherapy, there are several dimensions that exhibit significant advantage to the omission of irradiation.

Over the first 15 months, radiotherapy for this population is not a cost-effective treatment. However, the early postoperative outcome does not give a complete answer and the eventual cost-effectiveness will only become clear after long-term follow-up. Extrapolations from these data suggest that radiotherapy may not be a cost-effective treatment unless it results in a recurrence rate that is at least 5% lower in absolute terms than those treated without radiotherapy.

Implications for healthcare

The results of this trial have the following implications for healthcare:

- The evidence suggests that there are significant differences in some dimensions of quality of life, although there is no significant overall

quality-of-life advantage in the omission of adjuvant radiotherapy.

- Although there is a short-term economic benefit from the omission of radiotherapy in this group of patients, the longer-term benefit has yet to be determined.
- Comprehensive capture of quality of life and co-morbidity data may be facilitated by nurse-led home assessment.
- Cosmesis, although impaired by radiotherapy, appears to be of limited importance to the majority of patients within the first 15 months following surgery.
- More needs to be done to improve access to hospitals for older patients.
- Older low-risk patients have significant concerns about recurrence of breast cancer, even following radiotherapy.

Recommendations for further research

The following are recommended for further research.

1. Long-term data on quality of life and clinical outcomes in PRIME or similar trials should be obtained.
2. Further economic modelling on the longer term costs and consequences of omitting radiotherapy is needed.
3. The application of novel methodologies (such as touch screen technology) for capturing and grading co-morbidity and quality of life at baseline and at clinical follow-up should be investigated.
4. The influence of specific types and degrees of co-morbid disease on quality of life requires study.
5. Methodologies to integrate the prediction of recurrence rates from breast cancer with the competing effects of mortality from other diseases need to be refined to improve clinical decision-making.
6. A validated questionnaire/scale to assess the impact of access to healthcare services should be developed.

Chapter I

Introduction and background

Breast cancer in older patients

Breast cancer is the commonest form of malignancy in women, accounting for 12% of all cancers, 18% of all female cancers, 10% of all cancer deaths and 20–25% of all female cancer deaths globally. Every year in the UK, there are 41,000 new cases and over 12,000 women die of the disease.¹ About 80% of breast cancers develop in postmenopausal women. The incidence of the disease increases with age, from one in 50 up to the age of 50 years rising to one in 10 up to the age of 85 years.² The number is set to increase due to demographic changes in the population³ and a rise in the age-specific incidence of the disease.⁴ By 2030, 20% of women will be 65 years or older (hereafter referred to as 'older') in the USA.⁵ Over half of all breast cancers occur in older women.⁶ There is evidence, though, that older women are less likely to receive therapy than younger women.⁷ Anticipated life expectancy, comorbidity and functional status all influence the decision on whether or not to offer adjuvant irradiation. With the maximum age for the UK breast screening programme extended from 64 up to the age of 69 years, more older women will be diagnosed with early-stage breast cancer. Most of these women will be candidates for breast-conserving surgery and postoperative radiotherapy. However, there is a paucity of data in older 'low-risk' patients on the impact of postoperative radiotherapy on local recurrence, quality of life (QoL) and health economics. The Postoperative Radiotherapy In Minimum-risk Elderly (PRIME) trial, which is the subject of this report, provides information on QoL and cost-effectiveness. It has led to the PRIME II trial, for which most patients in PRIME will be eligible for joint analysis, which will collect data on local control in a similar group of patients. At the time of this report, over 70% of the target accrual of 1000 patients in PRIME II has been reached.

Radiotherapy after breast-conserving surgery

Reviews of the literature both before and since the start of PRIME have shown results consistent with a 3–4-fold reduction in ipsilateral recurrence in

women treated with breast irradiation following breast-conserving surgery and systemic therapy.^{8–15} The only randomised trial restricted to an age group of 70 years or older (T1,NO ≤1 cm)¹⁶ shows a 5-year local recurrence risk of 4% in the lumpectomy plus tamoxifen arm compared with 1% in the lumpectomy plus tamoxifen plus radiotherapy arm. The absolute benefit of radiotherapy in reducing local recurrence is modest. In an accompanying editorial, Smith and Ross¹⁷ question the need for radiotherapy in this subset of patients.

The Oxford overview of randomised trials of postoperative radiotherapy¹⁸ provides information on nearly 23,500 patients participating in 46 trials. Patients were randomised to receive or not to receive radiotherapy, with or without adjuvant systemic therapy. Most of the long-term data, however, are derived from trials of postmastectomy radiotherapy rather than following breast-conserving surgery, with only 7311 women from 10 trials treated by breast-conserving surgery. Nonetheless, there are a number of general conclusions from the overview. First, radiotherapy reduces the risk of local recurrence by a factor of three. Second, there is a clear causal relationship between reducing loco-regional recurrence and improved survival. A 19% absolute reduction in loco-regional failure at 5 years was associated with a 5% increase in breast cancer-specific survival at 15 years. However, many of the patients in the older trials were treated with what – by current standards – would be considered inappropriate chemotherapy and radiotherapy, which was associated with excess contralateral breast cancer and non-cancer mortality (mainly heart disease and lung cancer). An overview restricted to patients treated by radiotherapy and systemic therapy is probably more pertinent to contemporary practice.⁸

A further overview of trials of postoperative radiotherapy in 6387 patients from 18 trials who received systemic therapy reported by Whelan and colleagues¹⁹ showed that radiation reduced the risk of local recurrence [odds ratio 0.25; 95% confidence interval (CI) 0.19 to 0.34] and mortality (odds ratio 0.83; 95% CI 0.74 to 0.94). However, the authors acknowledge that the

findings from trials initiated 25–30 years ago may not be generalisable to contemporary practice, and patients in the trial were treated by either conservation surgery or mastectomy.

At the time of the design of the PRIME trial (1998), there was no evidence that the omission of radiotherapy had an impact on breast cancer survival. Since then, Vinh Hung and Verschraegen²⁰ have reported a pooled analysis of published randomised trials of postoperative radiotherapy versus no radiotherapy after breast-conserving surgery. Fifteen trials with a pooled total of 9422 patients were analysed. The relative risk of ipsilateral breast tumour recurrence on comparing non-irradiated and irradiated patients was 3.00. The relative excess mortality from the omission of radiotherapy was 1.086 (95% CI 1.003 to 1.175). However, only three of the trials included patients over the age of 70 years.²¹ It therefore remains uncertain whether the omission of breast radiotherapy in older patients compromises survival. In this age group, co-morbidity is a major competing risk of mortality.

Vallis and Tannock²² commented that it was surprising, in view of the substantial gains in survival seen from the addition of postmastectomy loco-regional irradiation to systemic therapy, that the survival advantage from radiotherapy after breast-conserving surgery was not greater. They speculated that local recurrence may give rise to metastatic disease and considered that the effect of postoperative radiotherapy after breast-conserving surgery might be lower due to a greater impact of local recurrence on the chest wall than in the residual breast. However, the findings of Vinh Hung and Verschraegen are at variance with the lack of survival advantage of radiotherapy in any of the trials assessing its omission. One weakness in this analysis, identified by Vallis and Tannock, is that their paper is based on published data and not on survival data. Stewart and Palmer²³ have shown that meta-analyses of randomised controlled trials (RCTs) based on published material may overestimate the effects of treatment.

The need for clinical trials in older patients

Addressing the needs of older patients with cancer is one of the priorities of the Scottish National Cancer Plan.²⁴ The National Institutes of Health of the USA in their 2000 consensus statement²⁵ on adjuvant therapies in breast cancer also identified the need for clinical trials in older patients, a

population which is poorly represented. In large part, this is explained by the systematic exclusion of patients over the age of 70 years from clinical trials in the past. For example, only 550 (9%) of the 6097 patients with breast-conserving surgery and negative nodes included in the Oxford Overview¹⁸ were over the age of 70 years. Only 9% of the 16,396 patients entered into trials of the US South West Oncology Group between 1993 and 1996 were aged 65 years or older.⁶

In clinical practice, the results of trials in younger women have been extrapolated to older women, even in the absence of a solid evidence base in this age group. The Oxford Overview¹⁸ recently demonstrated, however, that the level of 5-year risk of local recurrence falls with age for both irradiated and non-irradiated patients (to 3% with radiotherapy vs 13% without radiotherapy at age ≥ 70 years), as does the absolute reduction (from 22% at age ≥ 50 to 11% at age ≥ 70 years). The Scottish Intercollegiate Guidelines Network²⁶ guideline on best practice for breast cancer, for example, sets no upper age limit for radiotherapy. It sets as a criterion the benefit of treatment outweighing the risk of radiation-induced morbidity.

Trials assessing the role of radiotherapy after breast-conserving surgery

Progress has been made in trials of radiotherapy in older women since the protocol was written, and there is now a wider but still limited evidence base for the use or omission of radiotherapy in low-risk older women.

In the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial,²⁷ 1009 patients with invasive node-negative breast cancer of less than 1 cm were randomised to tamoxifen alone ($n = 336$), radiotherapy plus placebo ($n = 336$) or tamoxifen plus radiotherapy ($n = 337$). Median follow-up was 8 years. The cumulative incidence of ipsilateral breast recurrence was 2.8% with tamoxifen plus radiotherapy, 9.3% with radiotherapy plus placebo and 16.5% with tamoxifen alone. Radiotherapy reduced the risk of local recurrence more than tamoxifen alone, regardless of oestrogen receptor (ER) status. There was no significant difference in survival in the three arms. Although the local recurrence rate in patients aged 70 years or older in the tamoxifen alone arm (13%) was lower than in the 50–59-years group (25.9%) or 60–69-years group (22.2%), the numbers in the over 70-years

group are too small to identify whether there is a statistically significantly lower risk of local recurrence in the older age group with or without breast radiotherapy.

The Cancer and Leukemia Group B (CALGB)¹⁶ trial is an important contributor to the debate about the role of breast radiotherapy in older patients, since it was confined to patients 70 years or older with T1, ER-positive, clinically node-negative breast cancer treated by lumpectomy and adjuvant tamoxifen (median follow-up 5 years). More than 55% of patients were over the age of 75 years. The main question posed was whether radiotherapy added significantly to the benefits of tamoxifen in older women with small ER-positive breast tumours. The results showed a 1% ipsilateral breast recurrence rate in the group receiving postoperative breast irradiation and 4% in the non-irradiated group.

With such doubt cast on the need for radiotherapy in older patients in relation to recurrence and survival, outcomes such as QoL and functional status become increasingly important measures in view of coexisting morbidity and the more limited life expectation of these patients relative to younger women. Although the majority of patients will choose treatments that maximise the probability of survival, considerations of QoL may be important to patients' decision-making.²⁸ These outcome measures have not been documented in a comprehensive way in older patients with breast cancer. PRIME was established in response to this need following a call for proposals from the Health Technology Assessment (HTA) Programme.

Morbidity from breast radiotherapy

In addition to the limited clinical evidence base of the need for radiotherapy in low-risk older patients, side-effects and complications from radiotherapy have not been well documented in this group and need to be taken into account by patients and clinicians.

The unwanted side-effects which may occur after breast irradiation include fatigue, skin effects, symptomatic pneumonitis, rib fracture, radiation-induced heart disease, soft tissue fibrosis or necrosis and secondary malignancy.²⁹

The occurrence of pneumonitis is related to the volume of lung irradiated, the use of adjuvant

systemic therapy and any pre-existing lung impairment. Its incidence is normally less than 1%.³⁰ Symptomatic pneumonitis may produce a dry cough, dyspnoea and low-grade fever developing within 6–12 weeks of postoperative radiotherapy.

The incidence of rib fracture after adjuvant breast irradiation is reported to be less than 5%. It is related to the beam energy, total radiation dose and use of adjuvant chemotherapy.²⁹ A 5.7% incidence of rib fracture was reported by Pierce and colleagues³¹ after a dose of 5000 cGy or more.

An increase in cardiac deaths identified in the meta-analysis of clinical trials of adjuvant radiotherapy was associated with left-side tumours and those who received orthovoltage or cobalt-60 irradiation.^{32–34} Part of the heart may be irradiated in patients undergoing adjuvant breast irradiation. Tangential irradiation of the left breast may encompass up to 10% of the left ventricle.^{35,36} With modern megavoltage radiotherapy and increasing access to three-dimensional treatment planning and respiratory gated radiotherapy, however, the dose to the heart can be significantly reduced.

Breast radiotherapy is known to induce fibrosis, which may impair the cosmetic outcome (cosmesis) from a patient and objective view. Cosmesis may be influenced by the extent of surgery and also the total dose, dose inhomogeneity, dose per fraction and overall treatment time. In addition, patient-related factors play a part, with increasing breast size correlating with worse cosmetic outcomes.³⁷ Little is known about the cosmetic effect of radiotherapy in older patients after breast-conserving surgery or its impact on QoL. We therefore included it as a secondary end-point in the PRIME trial.

For patients, radiotherapy imposes the burden of attendance for daily treatments for up to 6 weeks, with the potential for increase in fatigue. For some, this may involve staying away from home for prolonged periods and/or extensive travel. These, and other factors, may have an impact on the QoL of older patients.

Assessment of quality of life in clinical trials

A wide range of aspects of QoL have been identified and described within clinical, functional, psychosocial and financial domains.³⁸ All of these

may be influenced by life circumstances, coexisting illnesses and treatment. Health-related QoL assessment is now regarded as a key component in oncology clinical trials, but this is only a recent trend.³⁹ In trials where there may be minimal or no survival advantage from a particular treatment, information about how it affects QoL may be very important to women and to clinical decision-making. In our patient group, the potentially small benefits of radiotherapy in reducing the risk of local recurrence of cancer need to be weighed against the potential impact on patient QoL.

Quality of life measurement in cancer patients

In a review of QoL assessment within oncology, Sprangers⁴⁰ considered that, “health-related quality of life can be measured reliably and validly and that the ‘subjectivity’ will help clinicians to gain insight into the patient’s perspectives of their disease and treatment”. However, Sprangers and colleagues caution that, in adapting to their cancer diagnosis, patients may have changes in perspective or internal views during their disease experience – referred to as ‘response shift’.^{41,42} This may result in patients reporting a stable QoL over time, in standardised questionnaires, while concurrently exhibiting deteriorating clinical health.

Quality of life measurement in older cancer patients

There are potential methodological problems associated with measuring QoL in older patients: the scales available may not have been validated in older populations, there may be poor compliance with questionnaire completion and the coexistence of other disease is a further complicating factor. All of these factors may impact on both the quality of data and interpretation of results.⁴³ The need for specialised methodologies to capture the influence of non-cancer-related factors on outcomes has been emphasised.²⁸ In the PRIME trial, we addressed the issue of compliance in older patients by having a research nurse assist in the completion of the questionnaires with patients. We recorded baseline health problems and any new health problems from patients at each questionnaire. At each time point, clinicians were also asked to record any new co-morbidity which might impact on QoL.

Studies measuring quality of life in breast cancer patients with various treatment modalities

It has been reported in many small non-randomised studies that older patients, in

general, adjust more easily to breast cancer than younger women. This may apply both immediately after diagnosis and one or more years after surgery.^{44–48}

Vacek and colleagues⁴⁹ assessed the factors affecting quality of well-being at yearly intervals over 4 years in a longitudinal study of 195 women diagnosed with breast cancer. The mean age was 66 years with a range of 39–93 years. The majority had local disease, about half had breast conservation and around one-third had breast irradiation. They found that the well-being scores declined over time and, as age increased, the rate of decline increased. The presence of a spouse was identified as slowing the rate of decline, while co-morbidity was associated with significantly lower levels of well-being, while not affecting the rate of change.

Overall, breast cancer survivors have been reported to experience similar QoL levels, in the long term, to non-clinical populations, adjusted for age.^{50,51} Having a perceived choice in treatment has been identified as having a health benefit in both younger and older women with breast cancer.^{52,53}

Leedham and Ganz⁵⁴ reported some positive changes which women identified from breast cancer diagnosis. Other studies^{55,56} suggest that distress, common at diagnosis and during treatment, declines during the first year. Some have suggested that anxiety and depression levels increase in a proportion of patients.^{57,58} However, Burgess and colleagues,⁵⁹ in a 5-year observational cohort study, found that nearly 50% of women had anxiety/depression in the year from diagnosis, 25% in the following 3 years and 15% in the fifth year. Previous psychological treatment, young age, lack of confiding relationship and stressful life experience, rather than clinical factors, seemed to be associated with depression and anxiety.

Where multiple treatment modalities are involved (breast conservation, mastectomy, radiotherapy, systemic therapy), the contribution of each to QoL is difficult to quantify.

Randomised trial including quality of life assessment in patients treated with or without radiotherapy after breast-conserving surgery

Older patients are a heterogeneous population in terms of physiological and functional impairment. Clinical trials have a major advantage in balancing these factors in comparing irradiated and non-

irradiated patients. To our knowledge, there is only one published randomised trial where the effect of radiotherapy on patient QoL is evaluated.⁶⁰ In this Canadian trial by Whelan and colleagues, 837 women had a lumpectomy, axillary dissection, with or without radiotherapy, but no systemic therapy. It cannot be ascertained from their report how many were aged over 65 years. They used a modified Breast Cancer Chemotherapy QoL scale (BCQ),⁶¹ administered by a nurse at baseline (randomisation), 4 and 8 weeks after randomisation. The trial results suggested that radiotherapy had a statistically significant deleterious effect on QoL in the 2 months after randomisation. By this time, 88% of patients had completed radiotherapy. At 1 month, women in the group having radiotherapy had statistically higher scores in the physical symptom, inconvenience and fatigue domains. They found no significant difference between groups in the areas of emotional dysfunction, social support and attractiveness. In the no radiotherapy group, there was a steady increase in QoL from baseline to 2 months.

Longer term QoL was assessed in 75% of the group, by self-completion of questionnaires on a 3-monthly basis. These focused only on skin irritation, breast appearance and pain. The first was done at a median of 7 weeks after the last treatment. Radiotherapy significantly increased the proportion of women with skin irritation. This symptom gradually decreased over the assessment period with 7% reporting it at 2 years in both groups. A similar pattern was seen in the area of breast pain, 15% still having breast pain in both groups at 2 years. There was no statistical difference between groups in their rating of cosmetic appearance.

Non-randomised studies of quality of life in patients treated with or without radiotherapy

Rayan and colleagues⁶² reported on a non-randomised prospective postal questionnaire comparison of breast pain and its effect on QoL in a study of 86 patients. These women were recruited from patients offered trial participation in the final 2 years of accrual into a randomised trial of breast-conserving surgery plus tamoxifen with or without radiotherapy.⁶³ The authors acknowledge that the breast pain study did not itself involve a randomised comparison. The women were aged over 50 years, with a median age of 70 years. The European Organisation for Research in the Treatment of Cancer (EORTC) scales, QLQ-C30 and QLQ-BR23, were

administered at baseline and 3, 6 and 12 months. The only statistically significant difference found between the two groups was in the score for role function at 12 months, which was lower in the radiotherapy plus tamoxifen group than in the tamoxifen alone group. The scores generally suggested a good and stable QoL over four estimations, throughout the first year post-surgery. The symptoms most commonly reported were sleep disturbance and fatigue. Dyspnoea, appetite and financial impact scores decreased, indicating improvement in both groups over the same period. Scores for body image scales were high and sexual function component scores low. No statistical differences were found in pain or breast symptoms between the two groups. The authors acknowledge that the lack of statistical significance in the above study may be due to low statistical power, as a result of fewer than expected patients being recruited.

A recently reported study, assessing longer term health-related QoL in 370 women after breast-conserving surgery, axillary node dissection and radiotherapy, was conducted by Fehlauer and colleagues.⁶⁴ They used the EORTC QLQ-C30 and QLQ-BR23 scales to assess QoL at medians of 7 and 12 years after radiotherapy, by age group and adjuvant treatment. A significant improvement was noticed in patients in global QoL scores with longer follow-up.

In 1994, Graydon⁶⁵ reported on a non-randomised study of 53, mainly younger, patients (mean age 57 years, range 37–82 years). They had had a lumpectomy or other breast-conserving surgery. Her results suggested that, although stressful at the time, the QoL of women who had a course of radiation therapy after breast-conserving surgery was not adversely affected when measured at 7 weeks post-radiotherapy. Patients reported resuming many of their usual activities, although they were still experiencing fatigue. Alongside the tiredness, they experienced some reduction in their pastimes and home management activities.

In a further non-randomised study of 53 patients after breast-conserving surgery, Rahn and colleagues⁶⁶ assessed psychological distress resulting from post-operative radiotherapy treatment and surroundings, in addition to the coping strategies employed by women having radiotherapy. Twenty-four patients received adjuvant endocrine treatment and 20 had chemotherapy prior to radiotherapy. The ages of the patients were not specified. Assessments were made on the first and last day of treatment. Some

40% of patients were initially anxious about the treatment and 54% about possible side-effects of irradiation. Levels of fear, about the radiotherapy itself and its cosmetic and other effects, were reported to reduce gradually during the assessment period, although 19% remained anxious for the whole course of radiotherapy; 20% felt emotionally distressed by the radiotherapy-related breast changes. Various coping strategies were employed by the women, including seeking out information about radiotherapy, talking to physician or partner, repressing thoughts about radiotherapy or using distraction techniques.

A recent longitudinal study of 94 breast cancer patients, of whom one-third were 60 years or older, with varying treatment modalities was described by Deshields and colleagues.⁶⁷ They reported raised levels of depression, low anxiety scores and diminished QoL during the last week of radiotherapy treatment. At 2 weeks post-radiotherapy, the women were found to have improved in these domains, although around 25% still had depressive symptoms. A similar pattern was noted for functional and physical scores.

Amichetti and Caffo⁶⁸ retrospectively mailed questionnaires to 227 women who had had breast-conserving surgery and definitive breast irradiation 3 years earlier. Their median age was 56 years (range 28–75 years). Nearly 70% responded, with completed assessments from 156 patients. The questionnaire assessed six core areas of QoL. Subjective evaluations of the cosmetic effect were considered good to excellent by 56% of the women, with 8% having a negative perception of body image. Of the 139 responding to sexual life questions, fewer than 15% reported difficulties in this area. Some 25% reported feeling tense, 19% nervous, 27% anxious and 16% depressed; 11% considered that their treatment had affected their health status and less than 10% considered they had a worse QoL due to their disease or treatment. This study may be limited in value by the 3-year time delay between the completion of radiotherapy and the completion of the questionnaire.

Wengstrom and colleagues⁶⁹ described the side-effects and QoL of 134 women with breast cancer. Approximately two-thirds had had mastectomy and one-third breast conservation followed by radiotherapy. Almost half received chemotherapy and almost 60% received endocrine therapy. They underwent symptom and QoL assessments before radiation therapy and during the third and the end of the fifth week of treatment. Further assessments were made at 2 weeks and 3 months

from the completion of radiotherapy. Mild to moderate fatigue was found to be the most frequently reported symptom at all measurement times. However, 30% rated fatigue as severe to intolerable. The number of patients experiencing pain and swelling increased as treatment progressed. The global QoL score showed steady improvement throughout the 3-month follow-up period, while physical functioning decreased as treatment progressed.

Randomised trial of quality of life in older women with multimodal therapy

In the EORTC 10850 trial of de Haes and colleagues,⁷⁰ 236 patients aged 70 years or older were randomly allocated to mastectomy or tumour excision plus tamoxifen but no radiotherapy. In a subgroup of 136 patients, QoL was measured and showed that women with breast conservation did not differ significantly from those receiving mastectomy in QoL dimensions, apart from reporting fewer arm problems and a borderline significant benefit in body image.

Non-randomised studies of quality of life in older women with multimodal therapy

In a random cross-sectional sample of over 1800 breast cancer patients, aged 67 years and older, the physical and mental health of women was assessed by telephone survey at 3, 4 and 5 years after surgery.⁵³ Some 13% had breast-conserving surgery, 52% had breast conservation and radiotherapy with 34% receiving mastectomy. A total of 79% underwent axillary sampling. The only statistically significant surgical treatment found to affect QoL outcomes was the use of axillary dissection. This increased the risk of arm problems four-fold, which in turn had a negative effect on other outcomes. In addition, the effect of having axillary surgery and arthritis were compounded at 2 years after surgery.

Ganz and colleagues⁷¹ interviewed 691 patients who were aged 65 years or older, had undergone breast-conserving surgery or mastectomy and were taking tamoxifen. At 3 months after surgery, they had levels of physical and emotional functioning comparable to age-matched samples of women without breast cancer. They also demonstrated that, in the year of follow-up, mental and physical health scores declined significantly whereas scores on a cancer-specific QoL measure improved over time. Their conclusion was that age or type of surgical treatment does not seem to affect QoL outcomes adversely but physical, emotional and social outcomes do.

Other issues, such as potentially diminishing networks of social support and the likelihood of increasing social isolation, have also been shown to affect the QoL of postmenopausal women after mastectomy/lumpectomy plus radiotherapy.⁷²

A study of 222 recently diagnosed older women with varying breast cancer treatments⁷³ suggested that support and adjustment from partners/family members to the diagnosis independently predicted less depression and anxiety in the study participants.

Overview of quality of life issues

Radiotherapy in breast cancer patients, irrespective of age, tends to be stressful and may increase fatigue, skin irritation and breast pain in the short term and during the first year. QoL scores tend to be fairly stable in the first year, except perhaps in the domain of role function, which has been found by some investigators to be still reduced at 12 months. Levels of depression tend to increase in a proportion of patients in the first year and gradually decrease over the following 4 years. Rather than clinical factors affecting levels of depression and anxiety, previous stressful life experiences, young age and lack of close relationship seemed to be associated with higher levels.

Overall, breast cancer survivors have been reported to experience approximately similar, longer term QoL levels to non-clinical populations. Having a perceived choice in treatment may also have a health benefit. Some women also report on positive changes from breast cancer. We chose to supplement the formal QoL scales with several open-ended questions to capture the impact of the experience of the diagnosis and treatment of breast cancer in their own words.

Older patients may adjust to breast cancer more easily than younger women. Some studies have suggested that mental, physical and social health scores decline for the first year whereas QoL scores improve over the same period in this age group. The presence of a spouse has been suggested to slow the rate of decline and the presence of co-morbidity was associated with significantly lower levels of well-being. The use of axillary dissection has been shown to have a detrimental effect on arm function in older women and this may add to the effect of coexisting illnesses such as arthritis.

The applicability of much of the literature to our study population is limited, since so few studies

specifically address the impact of radiotherapy on QoL. It may not be appropriate to apply the results of studies in younger women to our patient group directly, when the issues of QoL may differ. The different time points, periods of follow-up and measurement scales also interfere with comparisons. These limitations underpin the rationale for the PRIME trial.

The only randomised trial on the impact on QoL of radiotherapy versus no radiotherapy, after breast conservation, provided only very short-term follow-up data. It suggested that radiotherapy had a significant negative impact on QoL in the 2 months after radiotherapy. We are not aware of any published randomised trials evaluating the effect of radiotherapy on QoL exclusively in older patients after breast-conserving surgery and endocrine therapy. Currently there are insufficient randomised data from which the impact of radiotherapy on QoL in breast-conserved, older women can be assessed accurately.

Health economic aspects of breast irradiation

Radical breast irradiation places substantial demands on the equipment and staff of the resources of a radiotherapy department. Indeed, one report estimated that breast cancer care accounts for one-third of the work of a radiotherapy department.⁷⁴ With the age-related increase in incidence of breast cancer, the radiotherapy workload is likely to rise over the next decade.⁷⁵ The impact on overall resource use is not clear, however, as withholding radiotherapy may increase local recurrence rates. It has been estimated that the marginal cost per recurrence prevented by irradiation is £4415 in younger women taking into account the costs of surgery. This figure does not take into account case mix factors such as co-morbidity. Older patients, for example, often place further demands on the NHS as a result of some requiring provision of transport, accommodation or nursing care during the course of their radiotherapy.

Given the potential impact on both resource use and health outcomes, it is important to assess the cost-effectiveness of radiotherapy. Limited evidence is available on this. The trial by Liljegren and colleagues⁷⁶ assessed the cost-effectiveness of postoperative radiotherapy alongside a prospective RCT carried out at six hospitals. A decision-tree model was used with a time horizon of 5 years. The direct costs included costs of

primary treatment, follow-up and treatment of recurrence. Patients' travel expenses and productivity costs were also included. The utility values used to estimate quality-adjusted life-years (QALYs) were elicited from eight health professionals. The incremental cost-effectiveness ratio (ICER) was equal to, in 1993 prices, 1.1–1.8 million Swedish kroner (£88,000–144,000) per QALY. This relatively high figure was due to higher costs of initial treatment and follow-up visits in the radiotherapy group compared with the no radiotherapy group combined with a relatively minor QALY gain. Moreover, no QALY gains were obtained from radiotherapy in the low-risk group (women aged 60 years and above and without comedo or lobular carcinoma).

Two further studies applied Markov modelling techniques to assess the cost-effectiveness of radiotherapy. Hayman and colleagues⁷⁷ applied a Markov model to a hypothetical cohort of 60-year-old women with early-stage breast cancer over a 10-year duration. Costs included treatment costs and patients' time and travel costs. The effectiveness data were taken from the National Surgical Adjuvant Breast and Bowel project B-06 trial. The utility values used to estimate QALYs were elicited from 97 breast cancer patients using the standard gamble method. The ICER was estimated, in 1995 prices, at US\$28,000 per

QALY. This estimate was particularly sensitive to the assumptions made regarding the cost of radiotherapy and the QoL following recurrence. Suh and colleagues⁷⁸ applied Markov modelling to a theoretical cohort of women aged 55 years with ductal carcinoma *in situ*. The cycle length was 1 year and the cohort was modelled using a lifetime horizon. The costs included were treatment costs and patients' time costs. The effectiveness data came from six different primary studies. The utility values used to estimate QALYs were elicited from 210 healthy women using the standard gamble method. The ICER was estimated, in 2002 prices, at US\$36,700 per QALY and increased as a function of age.

The limited evidence available demonstrates a clear need for comprehensive economic analyses to establish more fully the cost-effectiveness of radiotherapy in older breast cancer patients.

Aims and objectives

It was the purpose of the PRIME trial to determine whether adjuvant breast irradiation significantly changes the QoL of older women with breast cancer treated by breast-conserving surgery and adjuvant endocrine therapy, and whether this treatment is cost-effective.

Chapter 2

Methods

Objectives

The objectives were to assess whether the omission of postoperative radiotherapy in older women with 'low-risk', axillary node-negative breast cancer (T0–2, N0–1, M0) treated by breast conservation with wide local excision and endocrine therapy (1) improves QoL and (2) is more cost-effective.

Design

PRIME was an RCT comparing the QoL, functional status, cosmesis and cost-effectiveness of low-risk older breast cancer patients treated with or without breast radiotherapy. The original design envisaged the trial being conducted entirely within Scotland, over a recruitment and follow-up period of 5 years. The geographical restriction reflected the support of the trial by the Scottish Cancer Trials Breast Group and the feasibility of patient interviews by a research nurse located in Edinburgh. Multicentre Research Ethics Committee (MREC) approval was granted by the Scotland Committee on 15 October 1998.

Modifications to the design

Following a slow start in recruitment, with a lower acceptance of randomisation by patients than expected, the study was widened to include the follow-up of patients who did not want their treatment to be randomly allocated. This was viewed as an opportunity to complete a comprehensive cohort study (CCS),⁷⁹ and was granted MREC approval on 13 January 2000. The results from this are discussed in Chapter 11.

Trial recruitment continued to run below target in Scotland, often due to the lengthy process of applying for Local Research Ethics Committee (LREC) approval delaying centres coming on-stream. The trial was, therefore, extended to include centres in England. Initially, this only involved areas of northern England which were relatively accessible to the research nurse (Northumbria and Cumbria), but was broadened again in response to interest from centres further south. These centres provided their own interviewers, and worked to a set of instructions

provided by the trial research nurse. The consequences of this slow start resulted in a request for an unfunded extension to the original recruitment period, which was agreed by the HTA Programme. Despite this additional period, recruitment remained lower than expected, and a funded extension was granted by the HTA Programme in order to meet our required target, and the end of our recruitment period was deferred. A further funded extension was approved by the HTA Programme in order to meet the additional costs of continued recruitment until the rescheduled date for the end of recruitment, although we had, in fact, reached our target earlier.

In the original protocol, the research nurse was to be 'blinded' to the randomised treatment and patients were asked not to say which treatment they had been allocated. After the first few patients had completed the 2 weeks post-radiotherapy interviews, it was recognised that this was unhelpful to the women. While gaining some insight into their experience, particularly in their responses to the open questions, they were having to censor their comments about radiotherapy and how it had affected them. In attempting to keep bias to a minimum while encouraging the women to give as full responses as they wished, a change to the protocol was approved very early in the study, which did not require them to withhold information about their treatment.

In order to collect longer term QoL data, postal questionnaires at 3 and 5 years post-surgery were added, again with MREC approval (5 December 2000). These are not yet complete and will, therefore, not be discussed in this report.

Eligibility criteria

The eligibility criteria were as follows:

1. aged 65 years or more, receiving adjuvant endocrine therapy
2. medically suitable to attend for all treatments and follow-up
3. histologically confirmed unilateral breast cancer of tumour, node, metastasis (TNM) stages T0–2, N0, M0

4. no axillary node involvement on histological assessment
5. had breast-conserving surgery with complete excision on histological assessment
6. able and willing to give informed consent.

Exclusions

Patients with the following were excluded:

1. past history of pure *in situ* carcinoma of either breast or previous or concurrent malignancy within the past 5 years other than non-melanomatous skin cancer or carcinoma *in situ* of cervix
2. Grade III cancer with lymphatic/vascular invasion (because of the higher risk of local recurrence).

Centres were also allowed to narrow the entry criteria, based on local perception of risk, provided they did not exceed the trial criteria.

Primary end-points

Primary end-points were as follows:

1. QoL (see the section 'Cancer-specific quality of life', p. 11)
2. anxiety and depression (see the section 'Anxiety and depression', p. 13)
3. cost-effectiveness (see the section 'Cost-effectiveness analysis', p. 15).

Secondary end-points

Secondary end-points were as follows:

1. loco-regional and distant recurrence rate (see Chapter 9)
2. functional status (see the section 'Functional status', p. 13)
3. acute and late morbidity (see the section 'Morbidity and co-morbidity', p. 13)
4. cosmesis (see the section 'Cosmesis', p. 14).

Size of the study

The aim was to recruit 120 patients per arm, a total of 240 over 3 years. With allowances for attrition due to unrelated deaths or loss to follow-up, this was expected to yield 100 evaluable patients per group. The primary outcome

variables in this study were psychometric scales, from which an assessment of the QoL was made. Power calculations were made in terms of the residual standard deviation, σ , for each variable. There was 80% power to detect statistically significant differences at the 5% level when the difference in population means equals 0.4σ . Although the study was not powered to detect small differences in recurrence rates, there is 70% power to detect statistically significant differences at the 5% level if recurrence rates in the two treatment arms are 5 and 15%.

Randomisation

Consenting patients treated by conservation surgery and adjuvant endocrine therapy were randomised to receive or not receive breast irradiation.

The randomised treatment allocation was obtained by the investigator telephoning a randomisation service at the Health Services Research Unit in Aberdeen. This service was computerised. Patient data were obtained by a mixture of recording verbal information and the investigator using the keys on a touch-tone phone. Randomisation was balanced by centre, grade of cancer, age, lymphatic/vascular invasion and preoperative endocrine therapy using the method of minimisation. This process of randomisation had the advantages of being secure (not prone to entry bias), and allowed some checks on patient eligibility to be made at time of randomisation.

Surgical procedures

Primary surgery consisted of a wide local excision to obtain clear margins around the tumour and an ipsilateral four-node lower axillary node sample or clearance. Re-excision of the margins was carried out, if required, to obtain histologically clear margins.

Radiotherapy planning and technique

Patients underwent a radical course of radiotherapy to the breast alone, followed for a few patients in some centres by a 'boost' by electrons to the site of the excision. The total dose, number of fractions and overall treatment time were according to local practice in each participating centre and recorded for each patient.

As a guideline, 45–50 Gy over 4–5 weeks was normally given by megavoltage irradiation to the breast with or without a boost of electrons of 10–15 Gy at an appropriate energy or an iridium-192 interstitial implant, although this latter option was never utilised within the trial.

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

1. 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.
2. The peripheral lymphatics are not irradiated.
3. A minimum of one transverse outline, taken at the central axis of the length of the tangential fields, should be taken.
4. 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 should be treated daily.

During the final week of treatment, the post-radiotherapy form (see Appendix 1, third form) was completed and sent to the Administrator, to allow the timing of the first post-radiotherapy (or equivalent in the no radiotherapy patients) questionnaire to be calculated.

Hormonal treatment

Standard adjuvant endocrine therapy was tamoxifen 20 mg orally daily for 5 years. However, for trial purposes, all forms of adjuvant endocrine therapy were acceptable, including preoperative neoadjuvant therapy.

Implementation

Women aged 65 years or more with early breast cancer, assessed through the inclusion/exclusion criteria as being at low risk of local recurrence, were invited to participate in the trial (see *Figure 1*). Formal invitation to participate was offered after breast-conserving surgery and once the pathology results were known. Those who were interested were given a patient information leaflet and a consent form (see Appendix 1, first two forms). Those who verbally accepted were contacted by the research nurse, when the consent

form was signed and collected, and the baseline questionnaire administered. Also at this contact, the patient diary (see Appendix 1, fourth form) for documenting the use of health and social service resources was given to the patient, to be collected at the following visit. Patients were then randomly allocated to receive or not receive breast radiotherapy and informed of the outcome.

Data on how breast cancer and its treatment had affected the patient's QoL and functioning were collected at a further three home/hospital visits by the research nurses over a 15-month period using the standardised questionnaire. Their clinical status and radiotherapy-related morbidity were also assessed on three further occasions, at routine outpatient clinics over the year following surgery. Where facilities existed, a photograph of both breasts was taken shortly before radiotherapy (and the equivalent time for non-radiotherapy patients) to assess the cosmetic effects of the treatment. This was repeated at the 12-month post-surgery visit. For all patients, bilateral mammography was performed at 1 year post-surgery. Patients are being followed up longer term to monitor clinical progress in accordance with the clinics' normal procedure, as part of the international PRIME II trial of local recurrence and survival,⁸⁰ with postal questionnaires on QoL at 3 and 5 years post-surgery.

Questionnaire-based measures

It was decided that a broad range of standardised and validated assessment scales should be employed to capture information on QoL, physical functioning, anxiety and depression. In addition, a limited number of questions were included covering symptoms not included within the other assessment scales. Patients were also asked to keep a diary (see Appendix 1, fourth form) to monitor use of health services. These diaries were collected by the research nurses at each assessment.

Cancer-specific quality of life

The scales of the EORTC Study Group on Quality of Life were developed for use as brief standardised QoL measures which could be used in international cancer trials.

EORTC QLQ-C30

The model of QoL used for this scale⁸¹ is multidimensional and covers cancer-specific symptoms of disease, the side-effects of treatment, psychological distress, physical functioning, social

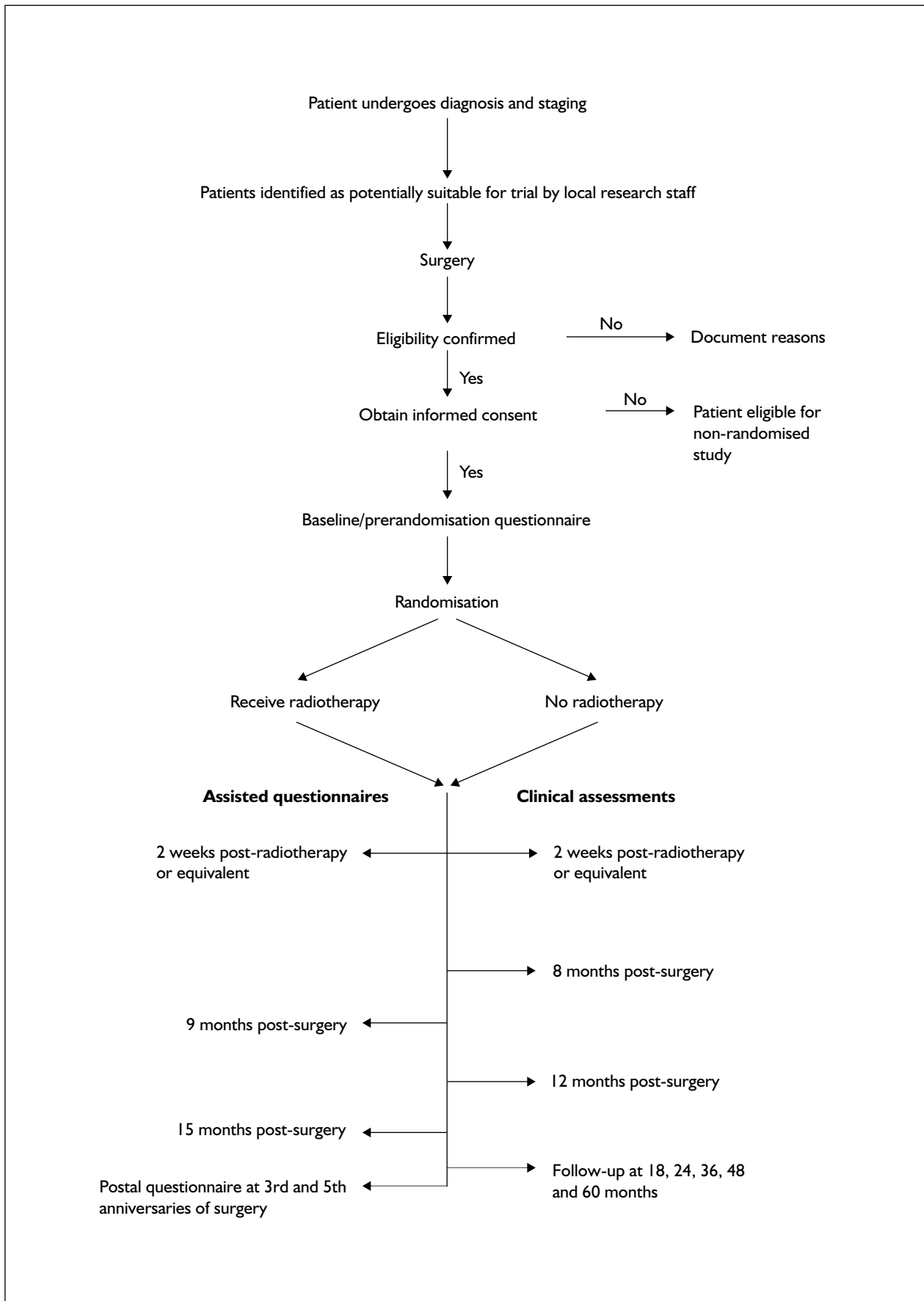


FIGURE 1 Summary of trial stages

interaction, global health and QoL. Most of the questions have a hierarchical response (not at all; a little; quite a bit; and very much), with two questions relying on the use of a visual analogue scale. The questions are summed to produce subscales. The EORTC QLQ-C30 scale has undergone extensive psychometric testing. In the light of these considerations, the QLQ-C30 was employed as a general cancer QoL scale.

EORTC QLQ-BR23

In addition to the QLQ-C30, the QLQ-BR23⁸² was used, which is the breast cancer module designed to supplement the QLQ-C30. This 23-item scale includes cancer-specific symptoms and also problems of the breast, axilla, arm, shoulder and skin. Three of the questions relate to sexual functioning and enjoyment, and could be omitted if the patient preferred. This scale has also undergone psychometric testing.

Anxiety and depression

Hospital Anxiety and Depression Scale (HADS)

It was recognised that many of the scales designed to investigate psychiatric conditions and psychological morbidity contained questions relating to physical illness. In order to avoid the influence of physical illness, the HADS was included in the study.⁸³ This scale, which is widely used in oncology, comprises 14 items with four-point response scales. The individual items are scored from zero to three or three to zero, depending on the direction of the item wording. Higher scores are indicative of problems. Cut-off points have been established for the anxiety and depression subscales. The reliability and validity of the scale have been tested by its developers.

Philadelphia Geriatric Center Morale Scale (PGCMS)

The PGCMS was developed specifically for use in the elderly⁸⁴ and has been found to be highly acceptable to them. A joint working party from the Royal College of Physicians and the British Geriatrics Society⁸⁵ recommended it as one of a series of research instruments for the assessment of the morale of older persons. It contains 17 questions which have a yes/no format. All questions within the scale are given equal weight, yielding a maximum possible score of 17 indicating a very high morale. The overall scale may be subdivided into three subscales: agitation, attitude towards own ageing and lonely dissatisfaction.

Functional status

Barthel index

The Barthel Index⁸⁶ is extensively used to assess

the primary activities of daily living. It is also one of the recommended scales of the joint working party from the Royal College of Physicians and the British Geriatrics Society for the assessment of older people. It comprises 10 questions, seven of which address self-care and the remainder mobility. The scores for the individual questions are summed and may range from 0 to 20, with higher scores indicating more independence. It is recognised that the scoring system is rudimentary and changes of a given number of points do not reflect equivalent changes in disability across different activities. The index is not sensitive to small impairments and is limited by ceiling effects.

Clackmannan Scale

To help overcome the ceiling effect identified in relation to the Barthel Index, the Clackmannan Scale⁸⁷ was included. This scale assesses the instrumental activities of daily living, and also the primary activities (self-care and mobility), giving three subscales. The subscales may be added together to give an overall score. Scores may range from 0 to 30, with lower scores being indicative of a higher level of functioning. It should have more sensitivity to detect functional differences between the two groups of our study population. The Clackmannan Scale was specifically constructed for the purpose of surveying elderly people in the community and in institutional care. The elderly find the scale acceptable and it has been widely used for community surveys in Britain. Considerable developmental work went into designing the scale and a limited amount of psychometric testing has been performed.

Morbidity and co-morbidity

During the first postoperative QoL assessment, acute morbidity such as cough or dyspnoea, and also those covered by the EORTC QLQ-BR32, were recorded. Skin and lung reactions were also recorded at a clinical visit 2 weeks post-radiotherapy (or equivalent time), using the simple four- or five-point scales devised by the Radiation Therapy Oncology Group (RTOG) and the EORTC.⁸⁸ Late morbidities such as telangiectasia and fibrosis were collected at 8, 12, 18, 24, 36, 48 and 60 months post-surgery, although complete data only currently exist for up to 12 months post-surgery. Co-morbidity information was collected with the questionnaire and at clinical assessments.

Any recurrences were documented on the follow-up form and details of treatment recorded on the

adverse events form (see Appendix 1, fifth form), which was sent out by the Administrator as required.

Cosmesis

At centres where there were suitable facilities, a photograph of both breasts was taken. These were taken before the radiotherapy simulation appointment and its equivalent for patients not receiving radiotherapy, and repeated at 12 months post-surgery. Patients were required to be photographed in colour, landscape format, standing with their hands on hips. The photographer was asked to ensure that the head was excluded from the image. A 10-cm scale was taped horizontally at the level of the suprasternal notch. Consent for photographs to be taken did not need to be obtained separately, since permission had already been given by their agreement to participate in the trial. Those patients who expressed a desire not to have a photograph taken were still entered into the trial, a note made in the trial records and their wishes respected.

The photographs were subsequently scanned and digitised, in order to assess any changes in nipple position and breast contour, as described by Van Limbergen and colleagues.⁸⁹ Measurements were made of the digital image using software developed in conjunction with the Department of Medical Physics in Edinburgh.⁹⁰

A variety of grading systems are available for the assessment of cosmesis based on a subjective comparison with the untreated breast. The simple four-point grading system devised by Harris and colleagues,⁹¹ which has been shown to be reliable and straightforward, was used in this case. This was carried out using the photographs mentioned above.

Data collection

Data were double-entered to minimise the risk of errors. Monthly reminders were sent to participating centres in order to flag any forthcoming or outstanding clinical visits or questionnaires.

Consistency

Detailed guidelines for completion of the questionnaire were sent to all centre interviewers to aid consistency of approach for patients whom

the trial nurse was not visiting. The timing of the post-radiotherapy questionnaire was dependent on the waiting time for radiotherapy in each centre. Interviewers were asked to keep the period between interviews similar in both arms of the trial, particularly for the 'post-radiotherapy' questionnaire, in order to maintain comparability within centres.

Structure of the questionnaire

The questionnaire used standardised introductory text, then information on demographics, current medications and health problems was gathered. This was followed by QoL questions using the scales described in the section 'Questionnaire-based measures' (p. 11) (and Appendix 2).

There were several open-ended questions which allowed the women to talk about how the diagnosis of breast cancer was affecting them and their relationships in a less constrained time frame than today, last week or last month, as required by specific components of the questionnaire. The recording of any other life-impacting events or questions/comments at the various time points also allowed us to understand their breast cancer experience within the wider context of their lives.

In the open-ended questions, the method of maintaining rapport and some eye contact with the patient was to inform the patient that the interviewer would write down key words and phrases as they answered. The responses were written out more fully immediately after the interview. This was done, with very few exceptions, within 1 hour and before interviewing another patient. In reporting the views of patients, these are presented in the third person and illustrated in italics.

Content analysis of open-ended questions

Analysis of the qualitative parts of the baseline questionnaire was not begun until all baseline and first and second 'post-treatment' questionnaires had been completed. The treatment was unknown to the coders although, particularly in the first post-treatment questionnaire, it was obvious from some responses which patients had received radiotherapy.

Principles described by Mason⁹² were used to categorise and organise the responses.

Categorical indexing

The following describes the baseline 'free form' question analysis but was similarly repeated

for all subsequent questionnaires. The content of the responses was analysed systematically into subject categories, corresponding to the patient descriptions. These were based on replies which, for example, might describe their experience within the category of diagnosis, surgery, endocrine or radiation treatment. Subcodes were then applied to each descriptive category. For example, replies suggesting a radiotherapy category might be further subdivided into smaller units or subcodes such as radiotherapy skin effects, physical, psychological or family effects. These codes and subcodes were used as retrieval devices, allowing all instances for a particular topic to be counted.

Process of defining categories and codes

The responses in the first 25 questionnaires were categorised and around 36 descriptive codes assigned, first by the trial nurse (first coder) and then by the statistician who had entered the data (second coder). At this early stage, only 60% congruence between coders was achieved. Discussion between the two coders ensued, to resolve disagreements in coding. Definitions for each code and subcode were refined and codes were added, to create subcodes which were distinguishable from each other. This produced 13 broad categories to which a total of 50 subcodes were attached. The coding process was repeated by both coders, using the adjusted definitions and codes, to check inter-coder reliability. A more satisfactory 94% congruence was reached between the two coders.

Further defining and clarification took place, and advice was sought from an experienced qualitative researcher who looked critically at the operational definitions and proposed system which had been generated. This resulted in a few minor adjustments to inadequately defined codes. A week later, the first coder repeated the coding on the same patient data. A level of 92% consistency was achieved. The first coder then progressed through the full set of baseline questionnaires. A few subcodes were added, on topics which had not occurred at all within the first 30 questionnaires.

Some marginal notes were made in the coding database, indicating potentially important or useful post-interview records, ideas or reactions to data. Around two-thirds of the way through the coding of each set of questionnaires a check-code of two sets of responses was done, to verify

consistency over time. The whole process was repeated for each period of the follow-up questionnaires. Minitab was used to tabulate the data into the subgroups once the coding was completed. Frequency counts were then made on specific topics/themes.

Statistical analysis

The main emphases of the trial are on QoL, which is multidimensional, and on the economic cost of alternative treatment policies. Accordingly, we focused the analysis on the estimation of treatment differences for all of the dimensions of QoL, together with their standard errors, with comparable analysis of the economic variables. The principal analysis is based on repeated measures methods, using baseline levels of each variable as a covariate. Analyses were conducted in SAS using mixed models (PROC MIXED), as this overcomes many of the problems associated with missing values, if these can be assumed to be missing at random.

During the period of this grant, it was found that mortality and recurrence remained too low to allow informative survival analysis. Variables reflecting morbidity are summarised and analysed using standard methods for contingency tables. The measurement of cosmesis by the method of Van Limbergen and colleagues⁸⁹ gives distance measures. As such, they were analysed using *t*-tests.

All analyses are based on the intention-to-treat (ITT) principle, and all CIs and significance tests are two-sided.

Cost-effectiveness analysis

Costs

The cost-effectiveness analysis adopted the health service perspective. The cost categories included were: (1) radiotherapy treatment; (2) NHS transport to radiotherapy sessions; (3) treatment of recurrence; (4) medication; (5) endocrine therapy; (6) primary care (GP and nurse visits) and secondary care (inpatient or outpatient hospital visits). The costs of follow-up visits were common to both arms and therefore not included. *Table 1* shows the sources used for the measurement and valuation of resource use. Further details on unit costs used and source of data are described in *Table 60* in Appendix 6.

TABLE 1 Methods of resource use data collection and outcomes

Cost category	Item	Quantity	Method of costing	Outcome reported
Radiotherapy	Radiotherapy	CF	HRGs	Cost per event/patient
	Investigation	CF	HRGs	Cost per event/patient
	Medication	CF	HRGs	Cost per event/patient
	Referral	CF	HRGs	Cost per event/patient
	Ward stay	CF	HRGs	Cost per event/patient
	NHS Transport	CF	SHSC	Cost per event/patient
Primary/secondary care	GP visits	PD	Curtis and Netten ⁹⁵	Cost per event/patient
	Nurse visits	PD	Curtis and Netten	Cost per event/patient
	Physiotherapist visits	PD	Curtis and Netten	Cost per event/patient
	OT visits	PD	Curtis and Netten	Cost per event/patient
	Home care	PD	Curtis and Netten	Cost per event/patient
	Other staff	PD	Curtis and Netten	Cost per event/patient
	Outpatient	PD	HRGs	Cost per event/patient
	Inpatient	PD	HRGs	Cost per event/patient
	Tests and Investigations	PD	HRGs	Cost per event/patient
	Procedures	PD	HRGs	Cost per event/patient
Recurrence	Treatment	TF	HRGs	Cost per event/patient
Endocrine therapy	Medication	PD	BNF	Cost per event/patient
Other medication	Medication	PD	BNF	Cost per event/patient

BNF, British National Formulary; CF, Completion of Radiotherapy Form; HRGs, Health Resource Groups from NHS Reference Costs; OT, occupational therapist; PD, patient diary; SHSC, Scottish Health Service Costs; TF, Treatment of Recurrence Form.

The 'Completion of Radiotherapy Form' was used to obtain information on dosage and number of fractions to the whole breast, boost, the number of journeys by hospital car/ambulance and the number of nights of accommodation in hospital ward or NHS-run accommodation. The 'Treatment of Recurrence Form' was used to obtain information on local or distant recurrence. The patient diaries were used to obtain information on appointments with GPs, nurses and other professionals and on use of social care services and medication (including name, dosage, frequency and duration). The resources were measured in physical quantities and combined with unit cost data. Radiotherapy treatment-related and ward stay costs were obtained from the nationally agreed NHS Reference Costs.⁹³ Unit costs of NHS transport costs were based on Scottish Health Service Costs (SHSC).⁹⁴ Unit costs for health professional contact during the follow-up were derived from the Unit Costs for Social Services⁹⁵ and SHSC. The costs for endocrine therapy and other medication used during the follow-up were obtained from the BNF.⁹⁶

All costs are presented in 2004–5 pounds sterling (£). The Hospital and Community Health Services

(HCHS) pay and price index was used to inflate any unit costs based in years other than 2004–5. Costs (and QALYs) occurring in the second year (months 12–15) are discounted at a 3.5% discount rate, in line with recent UK HM Treasury recommendations.

QALYs

QALYs were derived using the EQ-5D instrument.⁹⁷ The EQ-5D classifies patients into one of 243 health states (five dimensions, each with three levels). The five dimensions are mobility; self-care; usual activities; pain/discomfort; and anxiety/depression. The EQ-5D is of demonstrated validity and reliability, and the EQ-5D health states can be translated into 'utility scores' using the UK population tariff.⁹⁸ The number of QALYs is calculated by estimating the area under the lines that link the utility scores, obtained at the different time points. The method developed by Manca and colleagues⁹⁹ was used to control for baseline differences. The method uses regression analysis and models patient-specific QALY estimates as a function of the baseline EQ-5D utility score and arm of the trial. The coefficient arm of the trial represents the QALY differences adjusted for baseline differences.

The incremental cost per QALY was estimated by dividing the difference in mean total costs between the no radiotherapy and radiotherapy arms by the difference in QALYs between the two arms. The base case analysis includes complete cases only, that is, patients with missing data on costs and/or QALYs were excluded.

Statistical analysis of cost-effectiveness data

Cost data are often positively skewed, as there are frequently a small number of patients who incur relatively high costs. The non-parametric technique of bootstrapping was therefore used to estimate CIs for the individual cost items and for the differences in costs and QALYs between the two arms of the trial.

A distribution of the cost per QALY estimates was obtained using bootstrapping. The 1000 bootstrap samples were used to construct a cost-effectiveness acceptability curve (CEAC). This shows the probability that having no radiotherapy is cost-effective relative to current practice (having radiotherapy) at various thresholds of cost-effectiveness. The threshold represents the decision-maker's willingness to pay for an additional QALY.

Sensitivity analysis

Several one-way sensitivity analyses were performed. First, the main determinant of the differences in costs between the two arms was the cost of radiotherapy. Therefore, the analysis was repeated using the lower and upper quartile of the NHS reference cost for radiotherapy. Second, four patients who consumed a relatively high amount of healthcare resources, which were unlikely to be related to radiotherapy, were excluded. One patient required multiple normal human immunoglobulin intravenous infusions, and three patients required lengthy in-hospital stays, one each for swollen leg, urinary problems and fractured vertebrae. Third, missing data were common in both arms of the trial. In total, complete data were available for 203 out of 254 patients, 102 out of 125 patients in the radiotherapy arm and 101 out of 129 patients in the no radiotherapy arm. Two methods of imputation were used: mean imputation from the complete cases and regression imputation, which provides estimates for the missing data conditional on the patient's age, the distance from home to local hospital and arm of the trial. The analysis was repeated for both the full samples. A summary of the missing data is provided in *Table 61* in Appendix 6.

Chapter 3

Characteristics of the trial population

Recruitment and participant flow

By the close of recruitment, 255 patients had been randomised into the trial from 53 centres with ethical approval (*Figure 2*). Another 100 had been entered into the non-randomised cohort forming part of the Comprehensive Cohort Study (see Chapter 11).

Despite best efforts, it proved difficult to collect information on all patients who were eligible, but who were not offered or declined participation in the trial. Complete data are available from only Edinburgh, Aberdeen, Southend and Reading. *Figure 3* gives an estimation based on the data returned by these centres, extrapolated to the total number of patients randomised by the close of recruitment.

Protocol violations/deviations

Aspects recorded as protocol violations and/or deviations are given in *Table 2*.

Demographic data

The randomised group were well balanced between the treatment arms of radiotherapy and no radiotherapy with respect to centre, age, grade of cancer, lymphovascular invasion (LVI) and preoperative endocrine therapy, all of which were used in the minimisation programme. *Table 3* summarises these factors, along with axillary surgery and side of cancer, with *Table 59* in Appendix 3 summarising the recruitment in each centre. Good balance was achieved for all of these variables.

Quality of life scores at baseline

Although 255 patients were randomised, one patient died before the completion of the baseline questionnaire and one baseline questionnaire was lost in transit, leaving 253 evaluable questionnaires at baseline. Both patients had been allocated to receive radiotherapy. A summary of the interpretation of the QoL measures can be found in *Table 58* in Appendix 2.

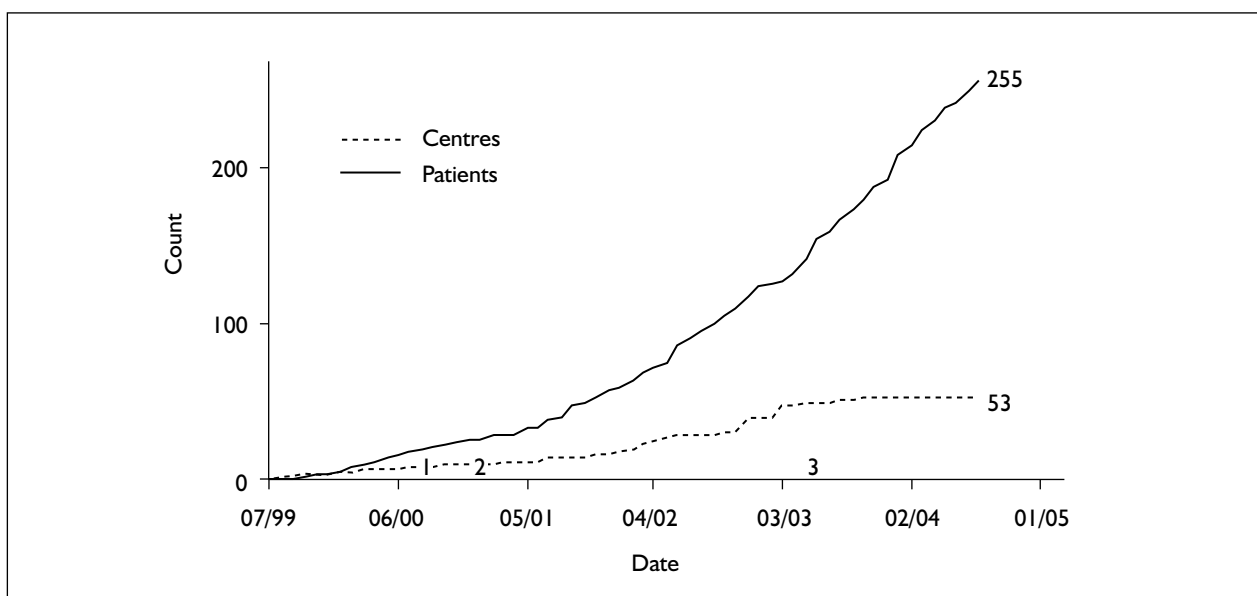


FIGURE 2 Trial recruitment over time. 1, Date of first LREC from centres in the North of England, within travelling distance for the trial nurse; 2, Date of first LREC from centres providing their own research nurses; 3, Principal funded extension granted.

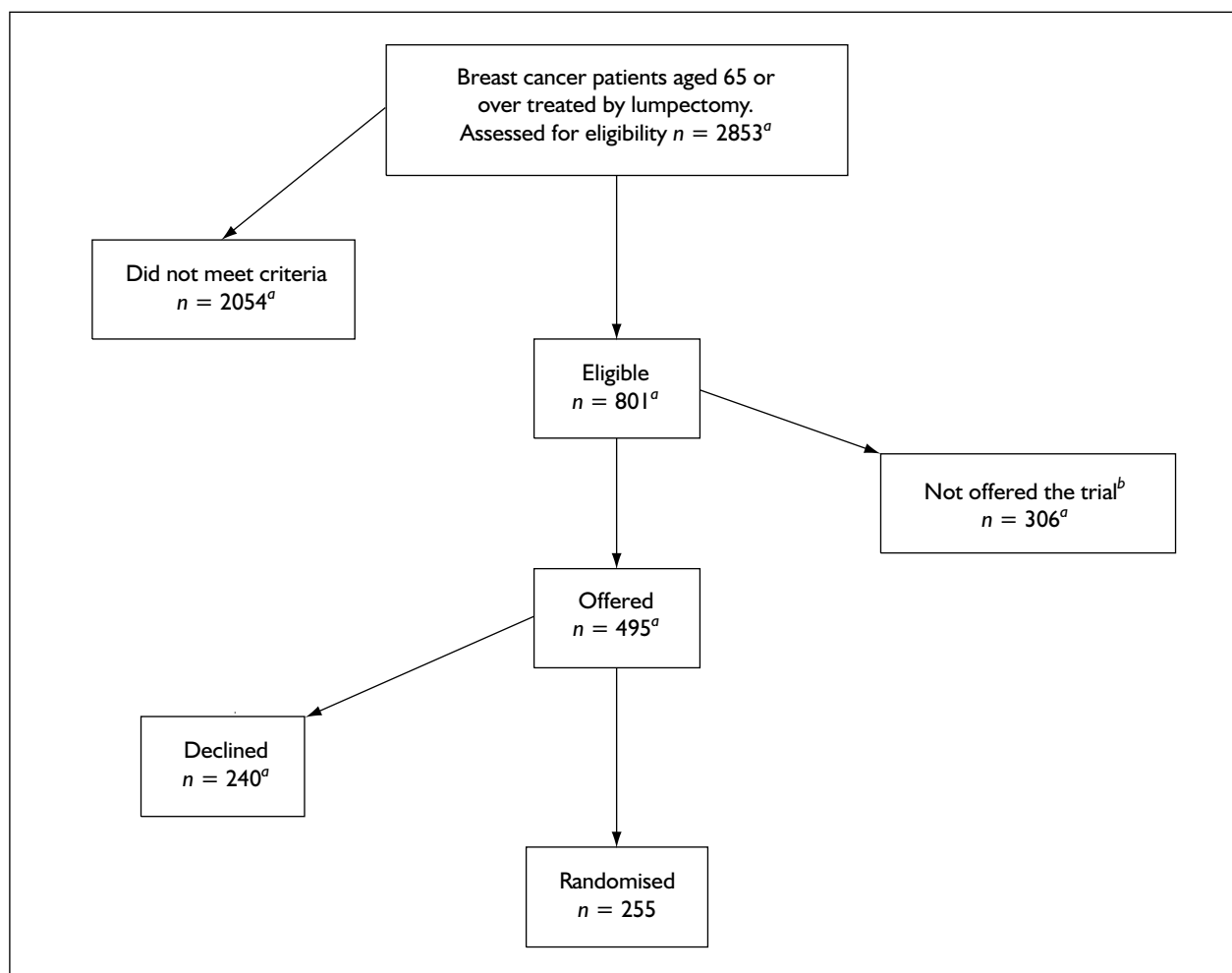


FIGURE 3 Participant flow, based on data received. ^a Estimated figure. ^b Includes local entry criteria.

TABLE 2 Protocol violations/deviations

Reason	Radiotherapy group	No radiotherapy group
Declined radiotherapy following randomisation	4	0
Died before treatment started and/or ended	3	0
Internal mammary chain irradiation	1	0
Randomised as having preoperative endocrine therapy, but did not	1	0
Were informed of their treatment before the baseline questionnaire was administered	3	6

EORTC scores

The mean scores at entry to the trial for the EORTC QLQ-C30 are shown for each dimension and for the combined functionality and symptom scores by the randomised treatment group in Table 4. There were no substantial differences in any variable between the randomised groups. Functionality and symptoms were summary variables of the mean scores of the other variables.

The mean scores at entry to the trial are shown in Table 5 for the variables obtained from the EORTC QLQ-BR23 for the two randomised treatment groups. The number of subjects answering the questions relating to sexual matters is substantially reduced and only for the few subjects who responded to the questions relating to sexual enjoyment are there substantial differences between the treatment groups. Similarly, both hair loss and cough are subject to a screening question,

TABLE 3 Information recorded at baseline

	Randomised (n = 255)	
	Radiotherapy (n = 127)	No radiotherapy (n = 128)
Mean age at surgery (SD) N (%)	72.3 (5.0)	72.8 (5.2)
Tumour grade		
1	48 (37.8)	48 (37.5)
2	72 (56.7)	71 (55.5)
3	7 (5.5)	9 (7.0)
LVI		
No	121 (95.3)	122 (95.3)
Yes	6 (4.7)	6 (4.7)
Pre-op ET		
No	110 (86.6)	106 (82.8)
Yes	17 (13.4)	22 (17.2)
Axillary surgery		(1 unknown)
Clearance	30 (23.6)	36 (28.1)
Sample	95 (74.8)	90 (70.3)
Sentinel node	2 (1.6)	1 (0.8)
Side		
Right	63 (49.6)	59 (46.1)
Left	61 (48.0)	67 (52.3)
Not given	3 (2.4)	2 (1.5)

Pre-op ET, preoperative endocrine therapy; SD, standard deviation.

TABLE 4 Baseline mean scores, with standard deviations in parentheses, by treatment group (EORTC QLQ-C30)

EORTC QLQ-C30	Radiotherapy (N = 125)	No radiotherapy (N = 128)
Functionality (mean PF – SF)	83.4 (14.3)	81.7 (15.7)
Symptoms (mean FA – FI)	14.0 (10.5)	14.9 (12.0)
Physical functioning (PF)	82.6 (17.2)	80.4 (19.1)
Role functioning (RF)	78.0 (23.6)	74.0 (28.3)
Emotional functioning (EF)	83.3 (19.2)	83.9 (18.4)
Cognitive functioning (CF)	84.5 (19.9)	85.3 (18.2)
Social functioning (SF)	88.4 (19.0)	85.0 (22.7)
Quality of life (QL)	72.4 (16.4)	70.3 (19.0)
Fatigue symptoms (FA)	26.8 (19.3)	27.7 (22.2)
Nausea and vomiting (NV)	4.8 (11.0)	5.3 (12.5)
Pain symptoms (PA)	24.7 (25.1)	29.0 (25.5)
Dyspnoea (DY)	12.0 (19.6)	10.9 (21.0)
Insomnia (SL)	28.8 (29.4)	28.9 (32.0)
Appetite loss (AP)	10.4 (20.5)	13.3 (23.0)
Constipation (CO)	12.5 (24.2)	9.1 (19.9)
Diarrhoea (DI)	3.7 (15.4)	6.0 (17.0)
Financial difficulties (FI)	1.9 (7.7)	3.4 (12.4)

TABLE 5 Baseline mean scores and standard deviations by treatment group (EORTC QLQ-BR23)

EORTC QLQ-BR23	Radiotherapy		No radiotherapy	
	N	Mean (SD)	N	Mean (SD)
Body image (BI)	125	94.7 (10.1)	128	93.5 (12.4)
Sexual functioning (SF)	78	10.3 (18.9)	81	6.6 (15.5)
Sexual enjoyment (SE)	18	51.9 (28.5)	9	63.0 (26.1)
Future perspective (FP)	125	21.9 (24.0)	128	26.0 (24.7)
Arm symptoms (AS)	125	15.3 (14.6)	128	17.5 (18.4)
Breast symptoms (BS)	125	23.1 (19.5)	128	19.8 (18.4)
Systemic therapy side-effects (ST)	125	12.1 (11.4)	127	12.9 (12.8)
Hair loss (HL)	20	21.7 (19.6)	14	16.7 (17.3)
Cough	37	35.1 (22.2)	40	36.7 (21.1)

TABLE 6 Baseline mean scores and standard deviations by treatment group (HADS)

HADS (max. score)	Radiotherapy (N = 125)	No radiotherapy (N = 128)
Depression (21)	2.4 (2.4)	2.8 (2.6)
Anxiety (21)	4.6 (3.5)	4.7 (3.4)

TABLE 7 Baseline mean scores and standard deviations by treatment group (PGCMS)

PGCMS (max. score)	Radiotherapy (N = 125)	No radiotherapy (N = 128)
Total score (17)	13.0 (3.3)	12.6 (3.5)
Agitation (6)	4.6 (1.6)	4.5 (1.6)
Attitude to own ageing (5)	3.2 (1.3)	3.0 (1.6)
Lonely dissatisfaction (6)	5.2 (1.2)	5.1 (1.3)

and only those patients who reported problems of this nature were asked the relevant question.

Hospital Anxiety and Depression Scale (HADS)

The results at entry to the trial for the HADS are summarised in *Table 6*. The two treatment groups are well balanced, with the levels of anxiety and depression generally low (a higher score indicates higher levels of anxiety or depression).

Philadelphia Geriatric Center Morale Scale (PGCMS)

The mean scores at entry in the PGCMS are also well balanced between the treatment groups (see *Table 7*), with a higher score indicating higher morale.

Clackmannan Scale

The Clackmannan Scale and Barthel Index were combined to remove the duplication of some questions. This made the data collection more complex, particularly for staff who were only infrequently completing the questionnaires with patients.

Possibly due to the complexity of the combined questionnaire, not all questions for the Clackmannan Scale were completed. However, the mean scores at entry are well balanced between the treatment groups (*Table 8*).

Barthel Index

The completion of the Barthel Index was also affected by the complexity of the combined questionnaires. However, as with the Clackmannan Scale, the mean scores at entry are well balanced (*Table 9*). It is interesting to note, however, that of the 225 responses available at baseline for the total score, 144 (70 radiotherapy and 74 no radiotherapy) scored the maximum of 20, 64%. This is indicative of the potential for this scale to suffer from a ceiling effect.

Co-morbidities

As part of the baseline questionnaire, patients were asked to describe any health problems they had, apart from the breast cancer. These were

TABLE 8 Baseline mean scores and standard deviations by treatment group (Clackmannan Scale)

Clackmannan Scale (max. score)	Radiotherapy		No radiotherapy	
	N	Mean (SD)	N	Mean (SD)
Total score (30)	100	3.9 (5.3)	105	4.3 (5.2)
Mobile (8)	111	0.8 (1.6)	120	1.1 (1.6)
House care (12)	106	1.9 (2.4)	110	2.2 (2.6)
Self-care (10)	123	0.9 (1.6)	121	0.9 (1.7)

TABLE 9 Baseline mean scores and standard deviations by treatment group (Barthel Index)

Barthel Index (max.)	Radiotherapy		No radiotherapy	
	N	Mean (SD)	N	Mean (SD)
Total score (20)	110	19.4 (1.1)	115	19.4 (1.2)
Mobile (8)	113	7.9 (0.4)	120	7.9 (0.4)
Self-care (12)	120	11.5 (0.8)	121	11.5 (1.0)

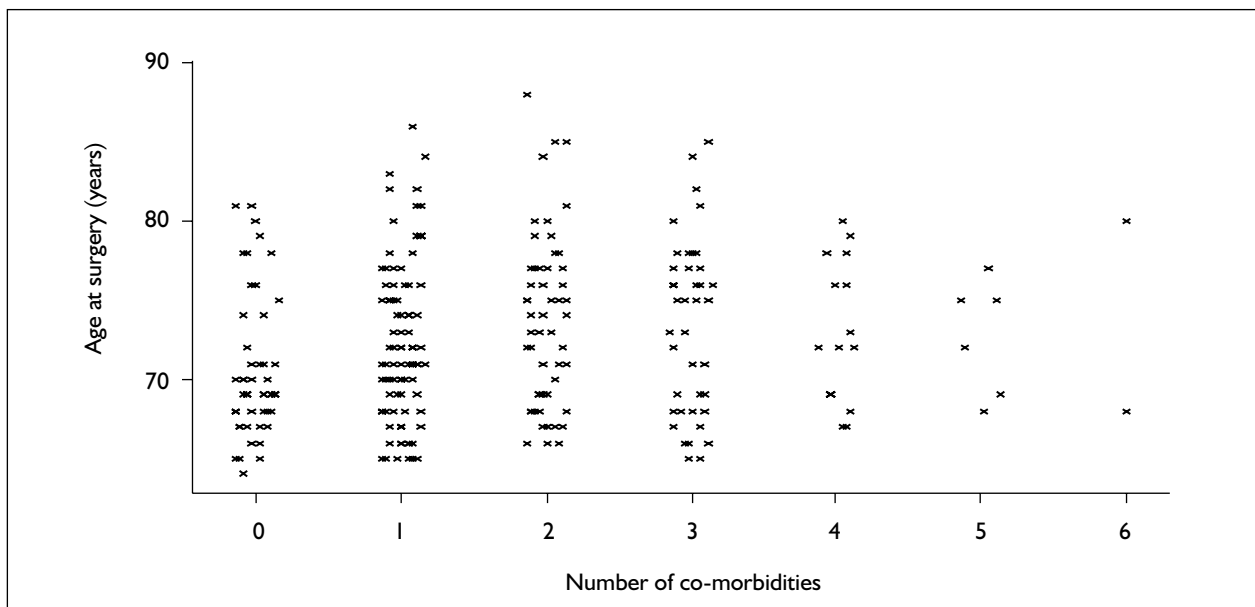


FIGURE 4 Relationship between age and number of co-morbidities

noted and subsequently coded. Since this is information given by the patient, no clinical diagnoses of severity have been incorporated. The patients' statements were reviewed by two clinicians and minor or transient diseases and conditions were excluded as being unlikely to have an impact on QoL.

Co-morbidities were categorised based on the Charlson list of co-morbid diseases.¹⁰⁰ However, since that list was more concerned with survival than QoL, and did not contain some of the co-morbidities specifically identified among the

present trial patients (e.g. depression, visual and auditory problems), we have added several new categories and subcategories. These are marked with an asterisk in *Table 10*.

There are few differences between treatment groups at baseline. As would be expected in this age group, the largest frequencies are in the rheumatological (including arthritis and gout) and hypertension categories (42 and 38%, respectively), with angina (10%), underactive thyroid (9%) and inflammatory bowel diseases (9%) the next nearest in terms of frequency.

TABLE 10 Co-morbidity types

Disease type	Radiotherapy (%)	No radiotherapy (%)
None	24 (19.0)	24 (18.8)
Myocardial		
Angina	14 (11.1)	11 (8.6)
Arrhythmia	4 (3.2)	7 (5.5)
Congestive heart failure	1 (0.8)	1 (0.8)
Myocardial infarction	4 (3.2)	3 (2.3)
Valvular	2 (1.6)	5 (3.9)
Vascular		
Cerebrovascular	1 (0.8)	4 (3.1)
Hypertension	56 (44.4)	42 (32.8)
Peripheral vascular	2 (1.6)	1 (0.8)
Pulmonary		
Asthma *	7 (5.6)	4 (3.1)
Chronic obstructive airways disease *	1 (0.8)	5 (3.9)
Tuberculosis *	0 (0)	1 (0.8)
Neurological		
Benign tumour *	1 (0.8)	0 (0)
Parkinson's disease *	1 (0.8)	1 (0.8)
Tinnitus *	0 (0)	4 (3.1)
Vertigo *	3 (2.4)	2 (1.6)
Other	1 (0.8)	2 (1.6)
Endocrine		
Diabetes	6 (4.8)	9 (7.0)
Underactive thyroid *	13 (10.3)	10 (7.8)
Renal	0 (0)	1 (0.8)
Gastrointestinal		
Inflammatory bowel disease	12 (9.5)	12 (9.4)
Peptic ulcer	1 (0.8)	1 (0.8)
Other	1 (0.8)	0 (0)
Mental health *		
Depression *	9 (7.1)	9 (7.0)
Nervous breakdown *	3 (2.4)	0 (0)
Schizophrenia *	1 (0.8)	0 (0)
Miscellaneous		
Haematological *	1 (0.8)	2 (1.6)
Hearing problems *	5 (4.0)	3 (2.3)
Musculoskeletal problems *	2 (1.6)	0 (0)
Osteoporosis *	4 (3.2)	8 (6.3)
Prolapse *	1 (0.8)	2 (1.6)
Rheumatological	43 (34.1)	50 (39.1)
Sight problems *	8 (6.3)	14 (10.9)

Table 11 illustrates the distribution of the number of co-morbidities experienced by patients. The randomisation resulted in the treatment groups being well balanced in terms of number of co-morbidities. However, the majority of patients had at least one disease other than breast cancer, which may have detracted from their QoL.

There is surprisingly little relationship between age and number of co-morbidities (Figure 4). The relationship had a correlation coefficient of 0.16 which, although being statistically significant ($p = 0.01$), is not strong.

TABLE 11 Tally of number of co-morbidities reported per patient

Co-morbidities	Radiotherapy (%)	No radiotherapy (%)
0	24 (19.0)	24 (18.8)
1	46 (36.5)	43 (33.6)
2	23 (18.3)	29 (22.7)
3	23 (18.3)	18 (14.1)
4	5 (4.0)	10 (7.8)
5	3 (2.4)	3 (2.3)
6	2 (1.6)	1 (0.8)

Chapter 4

Patient outcome – cancer-specific quality of life questionnaires

Figure 5 shows the number of questionnaires completed at each home visit.

The EORTC QLQ-C30 scale

The QLQ-C30 scale is a multi-item scale which may be collapsed into 15 subscales and two summary scales, and refers to the patient's QoL over the previous week. For each variable, the corresponding baseline score was used as a covariate, in a repeated measures analysis of covariance with an unstructured covariance pattern. The major scales, and those subscales with interesting or significant explanatory variables, are illustrated with a graph. In order to show changes over time as clearly as possible, only part of the scale on the y-axis is shown, and in the interpretation of the graphs the scales should be read carefully. As the treatment means at each time point have been adjusted for the baseline, a common baseline at the mean of all subjects is shown. Note that the timescale of the questionnaires is not to scale, due to the variability inherent in the baseline and post-radiotherapy visit times relative to surgery.

Functionality (mean of physical, role, emotional, cognitive and social functioning)

A decrease in score indicates a decrease in functionality. There is no evidence of any change in overall functionality over time in either treatment group (*Figure 6*, p. 29).

Symptoms (mean of fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties)

An increase in score indicates an increase in symptoms. The overall symptom scores show no evidence of any change over time in either treatment group (*Figure 7*).

Although there were no indications of any differences between the treatment groups for the summary scales, there was some evidence of a

treatment effect in some of the subscales, as detailed below.

Physical functioning (PF)

- Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?
- Do you have any trouble taking a long walk?
- Do you have any trouble taking a short walk outside of the house?
- Do you have to stay in a bed or a chair during the day?
- Do you need help with eating, dressing, washing yourself or using the toilet?

A higher score indicates a higher level of functioning. There is no evidence that the mean scores for physical functioning are significantly different between treatment groups (*Figure 8*). There is, however, a significant decline in score over time from baseline. The mean score has declined from 81.5 at entry to 76.4 at 15 months post-surgery.

Role functioning (RF)

- Were you limited in doing either your work or other daily activities?
- Were you limited in pursuing your hobbies or other leisure time activities?

There was no evidence of a time, treatment or time by treatment effect. The overall mean score was 76.8, with a standard error of 0.9.

Emotional functioning (EF)

- Did you feel tense?
- Did you worry?
- Did you feel irritable?
- Did you feel depressed?

Figure 9 suggests higher levels of emotional functioning in the radiotherapy group, particularly at 9 months post-surgery. The magnitude of the differences are small, however, and neither the treatment nor time by treatment differences are statistically significant. The overall small changes over time are also non-significant ($p = 0.07$).

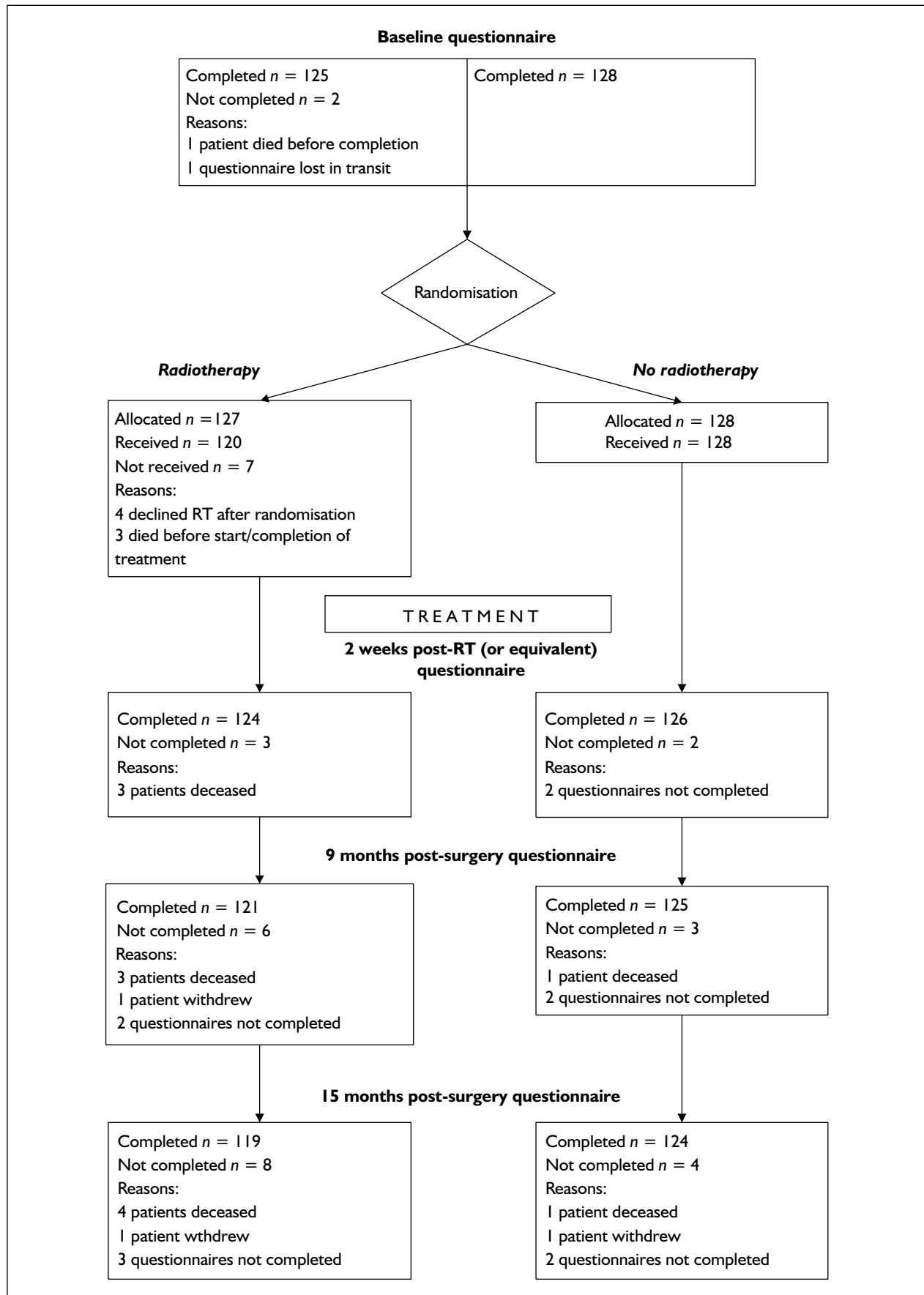


FIGURE 5 Number of evaluable questionnaires at each home visit by treatment. RT, radiotherapy.

Cognitive functioning (CF)

- *Have you had difficulty concentrating on things, like reading a newspaper or watching television?*
- *Have you had difficulty remembering things?*

There was no evidence of a time, treatment or time by treatment effect. The overall mean score was 82.7, with a standard error of 0.6.

Social functioning (SF)

- *Has your physical condition or medical treatment interfered with your family life?*
- *Has your physical condition or medical treatment interfered with your social life?*

Although there is no statistically significant evidence of a treatment or time by treatment effect, the mean scores over time for the radiotherapy group appear to lag one time period behind the no radiotherapy group (*Figure 10*), and are statistically significantly different over time.

Quality of life (QL)/global health status

- *How would you rate your health during the past week?*
- *How would you rate your overall quality of life during the past week?*

There was no evidence of a time, treatment or time by treatment effect. The scores for both groups decline slowly from baseline, although not significantly so (*Figure 11*).

Fatigue symptoms (FA)

- *Did you need to rest?*
- *Have you felt weak?*
- *Were you tired?*

There was no evidence of a time, treatment or time by treatment effect. *Figure 12* summarises these results, which may be contrasted with the results on fatigue presented in the section 'Radiotherapy' (p. 55).

Nausea and vomiting (NV)

- *Have you felt nauseated?*
- *Have you vomited?*

There was no evidence of a time, treatment or time by treatment effect. The overall mean score was 3.8, with a standard error of 0.3.

Pain symptoms (PA)

- *Have you had pain?*
- *Did pain interfere with your daily activities?*

Pain symptoms show signs of initial reduction from levels at randomisation, although at 15 months post-surgery the mean scores have returned to their previous levels (*Figure 13*). The reduction in the mean scores is greater in the radiotherapy group at 2 weeks post-radiotherapy, but neither the time by treatment interaction ($p = 0.68$) nor the time effect ($p = 0.09$) are statistically significant. However, the question is not specific to pain in the breast.

Dyspnoea (DY)

- *Were you short of breath?*

Figure 14 shows the no radiotherapy group reporting higher levels of breathlessness than the radiotherapy group until the final questionnaire, although the scores for both are increasing over time from baseline. Neither the time effect ($p = 0.07$) nor the time by treatment interaction ($p = 0.13$) reaches conventional levels of statistical significance. The average of post-baseline observations is, however, statistically significantly higher than the baseline level ($p < 0.001$).

Insomnia (SL)

- *Have you had trouble sleeping?*

Mean levels of insomnia tended to rise slightly in the no radiotherapy group, whereas insomnia levels were reduced in the radiotherapy group (*Figure 15*). The treatment difference is statistically significant ($p = 0.01$).

Appetite loss (AP)

- *Have you lacked appetite?*

There was no evidence of a time, treatment or time by treatment effect. The overall mean score was 9.1, with a standard error of 0.6.

Constipation (CO)

- *Have you been constipated?*

There was no evidence of a time, treatment or time by treatment effect. The overall mean score was 11.0, with a standard error of 0.7.

Diarrhoea (DI)

- *Did you have diarrhoea?*

There was no evidence of a time, treatment or time by treatment effect. The overall mean score was 4.7, with a standard error of 0.5.

Financial difficulties (FI)

- *Has your physical condition or medical treatment caused you financial difficulties?*

There are some fluctuations in the mean financial difficulties scores between the treatment groups over time. At 2 weeks post-radiotherapy, scores are higher in the radiotherapy group, with the position reversed at 9 months post-surgery. The scores are, however, all very low (*Figure 16*).

The EORTC QLQ-BR23 scale

This scale is specific to patients suffering from breast cancer and consists of 23 questions, which may be collapsed into eight subscales. In addition, a question on the presence of a cough was introduced by the trial team using the same format, in order to capture information on a potential side-effect of breast irradiation. As with the EORTC C30, each measure relates to the previous week, except for the questions dealing with sexual functioning and enjoyment, which relate to the previous 4 weeks.

Body image (BI)

- *Have you felt physically less attractive as a result of your disease or treatment?*
- *Have you been feeling less feminine as a result of your disease or treatment?*
- *Did you find it difficult to look at yourself naked?*
- *Have you been dissatisfied with your body?*

The treatment groups only appear to differ at 9 months post-surgery, with the no radiotherapy group reporting a higher self image (*Figure 17*). The time by treatment interaction is not, however, statistically significant ($p = 0.08$).

Sexual functioning (SF)

- *To what extent were you interested in sex over the last month?*
- *To what extent were you sexually active (with or without intercourse) over the last month?*

This question was optional, with patients being able to decline answering the whole section on sexual function or any part of it. Due to the nature of the analysis, a patient was only included in the analysis if she had provided an answer to this question at baseline. This was a total of 159 (78 radiotherapy and 81 no radiotherapy). Of the available post-randomisation observations from this subgroup, 184 were made in the radiotherapy group and 189 in the no radiotherapy group (numbers of observations at

each questionnaire are given on the graph).

Figure 18 shows a higher level of sexual functioning in the no radiotherapy group, with this difference being on the borderline of statistical significance ($p = 0.05$). The scores are low throughout.

Sexual enjoyment (SE)

- *To what extent was sex enjoyable for you?*

This question was only asked if the patient had indicated that they had been sexually active. As would be expected in this age group, only a relatively small proportion answered this question (18 radiotherapy and nine no radiotherapy at baseline). Again, only those patients for whom a baseline score had been recorded were included in the analysis. The number of responses from this subgroup are recorded in *Figure 19*. The effective sample size is too small to interpret the apparent pattern with any confidence.

Future perspective (FP)

- *Were you worried about your health in the future?*

There is no evidence that patients in one group or the other worried more in the previous week, and the changes over time are small and non-significant (*Figure 20*).

Arm symptoms (AS)

- *Did you have any pain in your arm or shoulder?*
- *Did you have a swollen arm or hand?*
- *Was it difficult to raise your arm or move it sideways?*

There is a substantial reduction in arm symptoms from the level at the time of randomisation in both treatment groups to the scores at 2 weeks post-radiotherapy. Thereafter, the no radiotherapy group appears to have a further small improvement, though neither the treatment ($p = 0.17$) nor time by treatment ($p = 0.20$) terms are statistically significant (*Figure 21*).

Breast symptoms (BS)

- *Have you had any pain in the area of your affected breast?*
- *Was the area of your affected breast swollen?*
- *Was the area of your affected breast oversensitive?*
- *Have you had skin problems on or in the area of your affected breast?*

In the no radiotherapy group, symptoms decline throughout the follow-up period. In the radiotherapy group, symptom scores are higher at

2 weeks post-radiotherapy than they were at randomisation. Subsequently, their breast symptom scores decline but remain higher than levels in the no radiotherapy group (Figure 22).

Systemic therapy side-effects (ST)

- Did you have a dry mouth?
- Did food and drink taste different than usual?
- Were your eyes painful, irritated or watery?
- Have you lost any hair?
- Did you feel ill or unwell?
- Did you have hot flushes?
- Did you have headaches?

There was a small but consistent increase in systemic therapy side-effects in the no radiotherapy arm (Figure 23), and this was statistically significantly different from the levels in the radiotherapy arm ($p = 0.03$).

Upset by hair loss (HL)

- Were you upset by the loss of your hair?

Where no loss of hair was reported, this question was not asked. However, in order to give a more representative view, where no loss was reported, a score of zero was recorded. Distress over hair loss is greater at the post-randomisation visits than at the time of randomisation, but there is no evidence of any influence of the treatment (Figure 24).

Frequency of hair loss

The level of hair loss is incorporated into the systemic therapy side-effects question discussed earlier. Figure 25 is a chart of the percentages of patients reporting any hair loss, regardless of level of loss. In other words, if a patient reported 'a little', 'quite a bit', or 'very much', it has been recorded as 'yes' for the purposes of the graph. There is little indication of any differences between the treatments.

Cough

This was a two-part question, added by the trial team as it did not appear to be covered by any other question, and was considered a potentially important side-effect of radiotherapy. The first part of the question generated a yes/no response, but the second part required the answer in the same format as the other questions in this scale: 'not at all', 'a little', 'quite a bit' and 'very much'.

Did you have a cough?

There is little evidence of any treatment effect (Figure 26).

How much has it affected you?

If it is assumed that anyone who did not report a cough had no effect from it (i.e. recorded 'not at all', which would give us a value of zero for the effect of the cough), there is still no evidence of treatment, time or time by treatment effects (Figure 27).

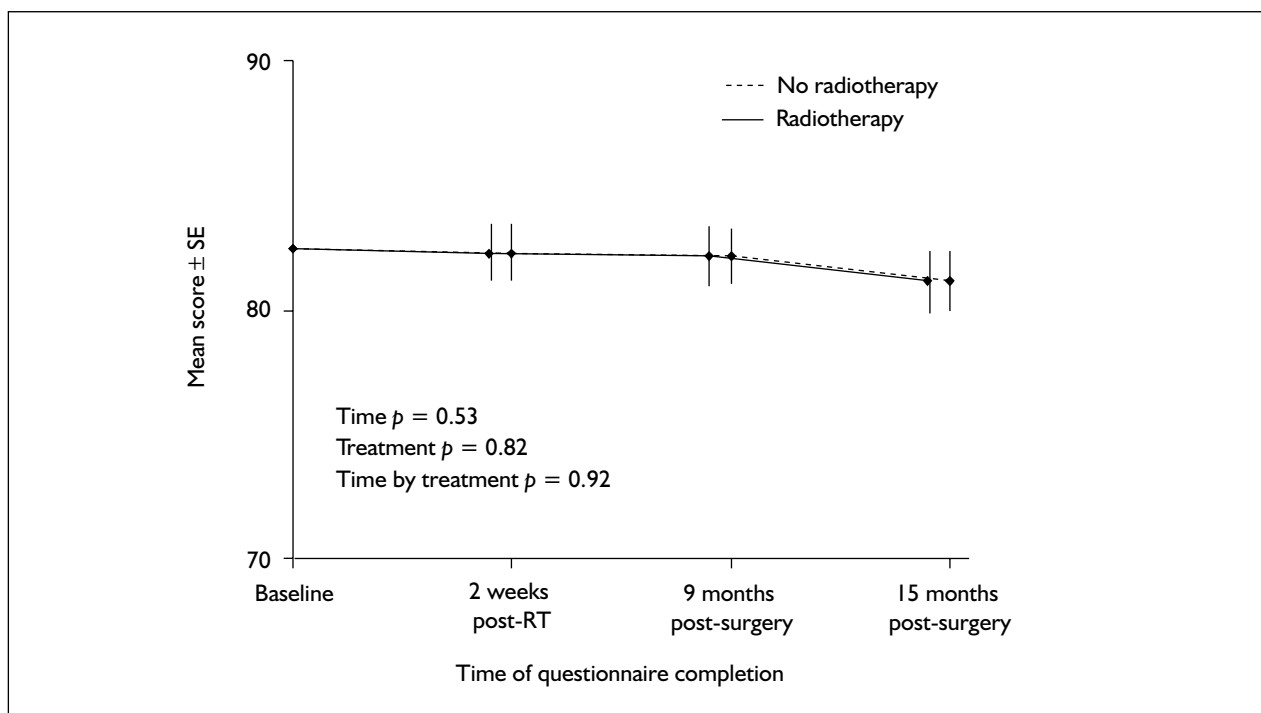


FIGURE 6 Mean scores of functionality by questionnaire

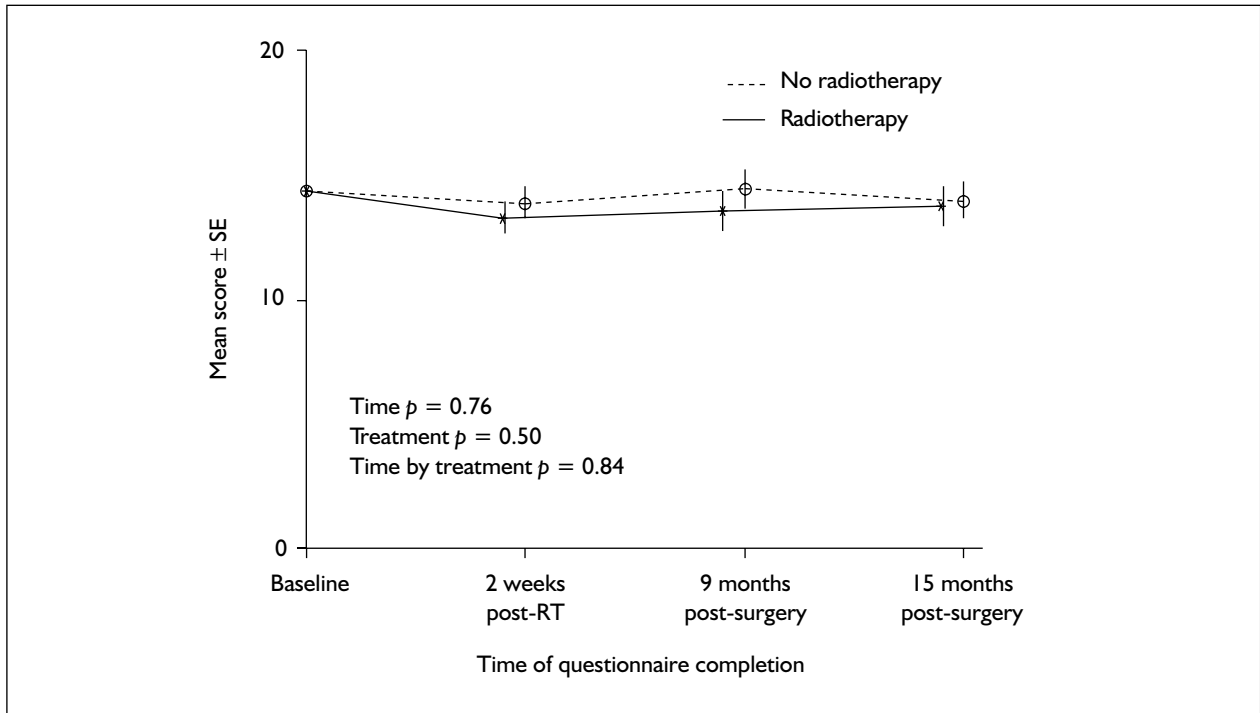


FIGURE 7 Mean scores of symptoms by questionnaire

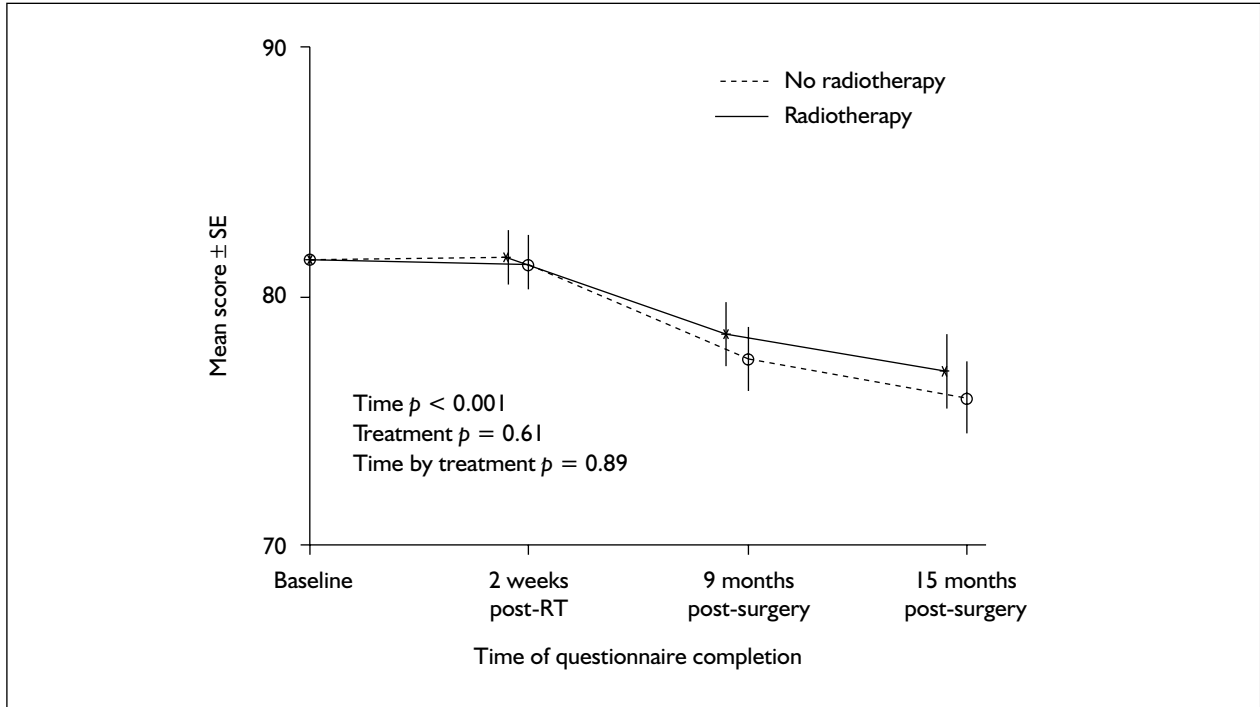


FIGURE 8 Mean score of physical functioning by questionnaire

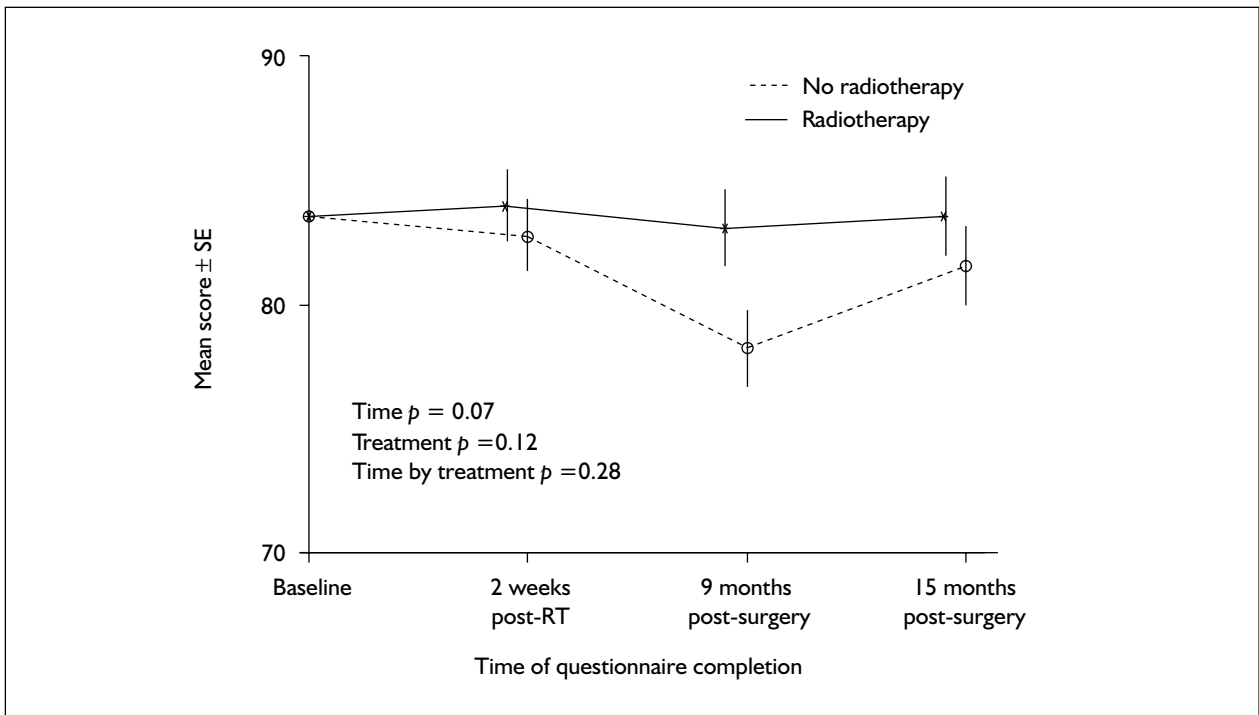


FIGURE 9 Mean score of emotional functioning by questionnaire

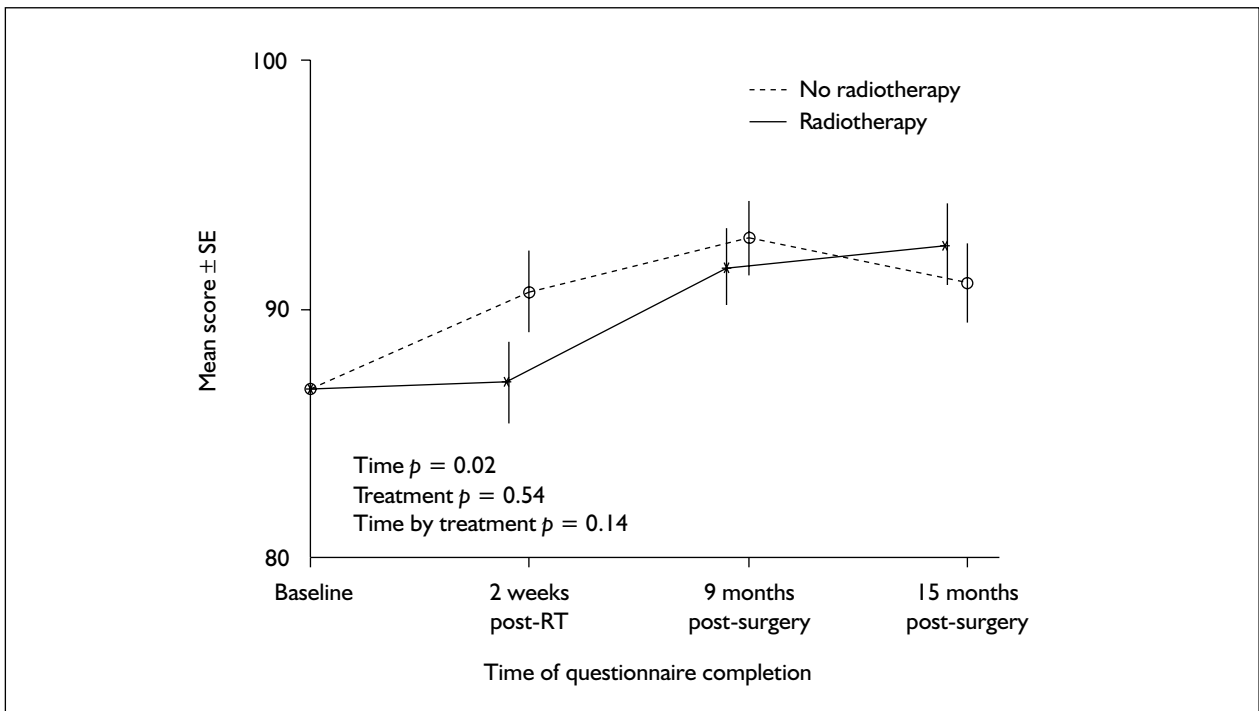


FIGURE 10 Mean score of social functioning by questionnaire

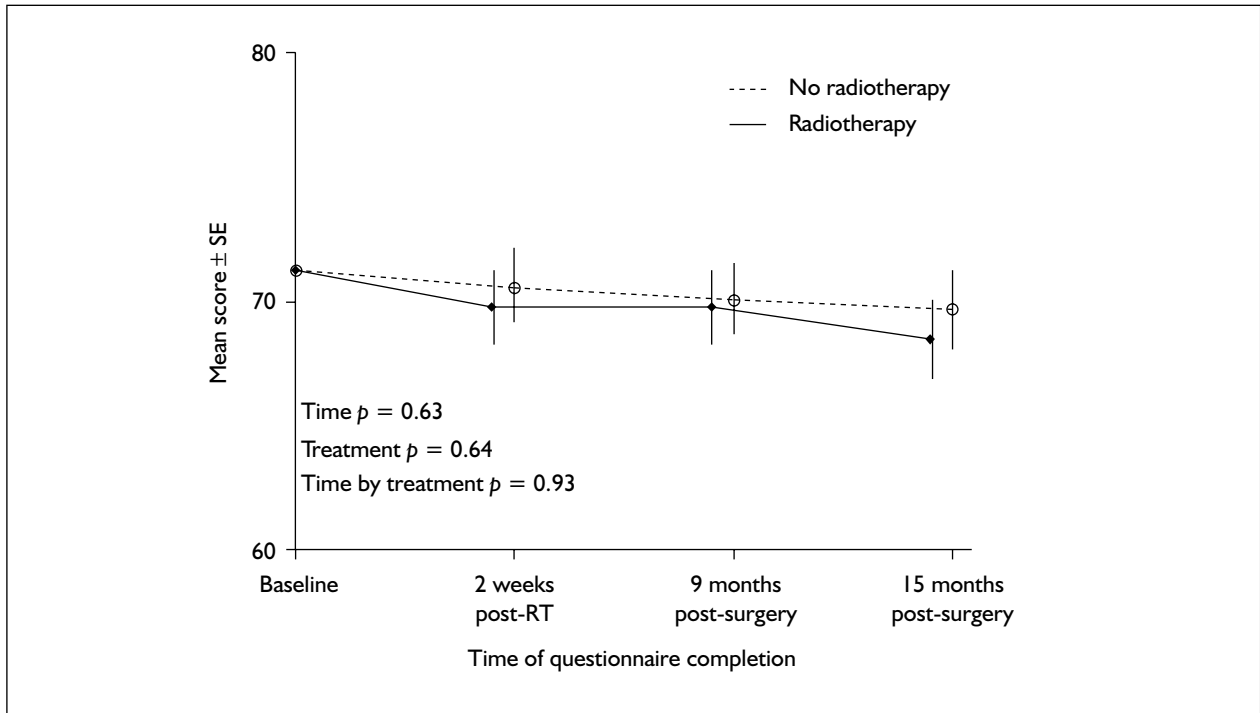


FIGURE 11 Mean score of global health status by questionnaire

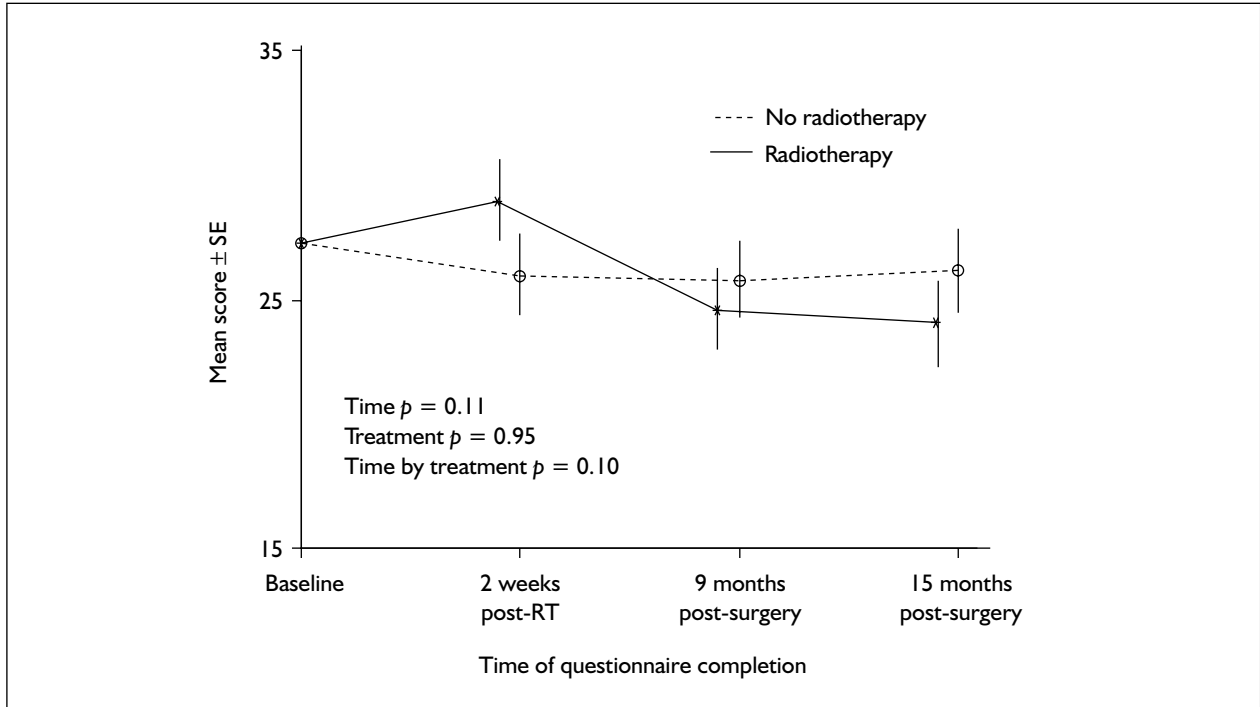


FIGURE 12 Mean score of fatigue symptoms by questionnaire

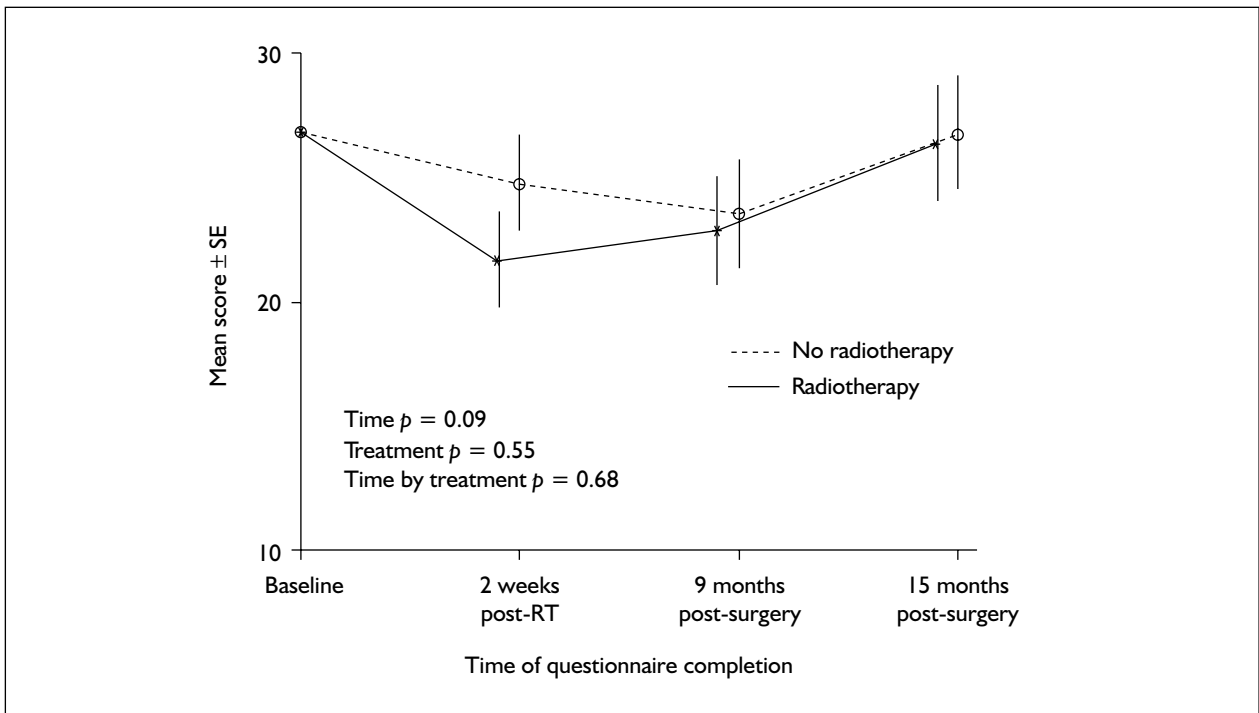


FIGURE 13 Mean score of pain symptoms by questionnaire

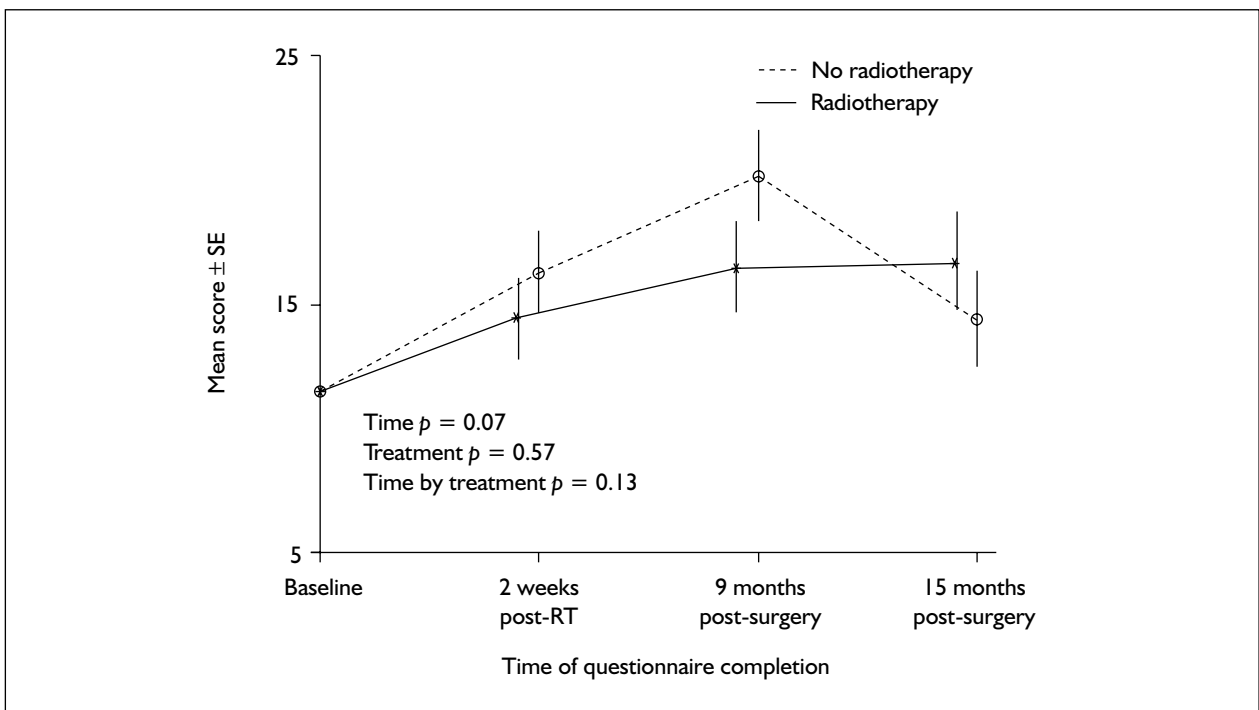


FIGURE 14 Mean score of dyspnoea by questionnaire

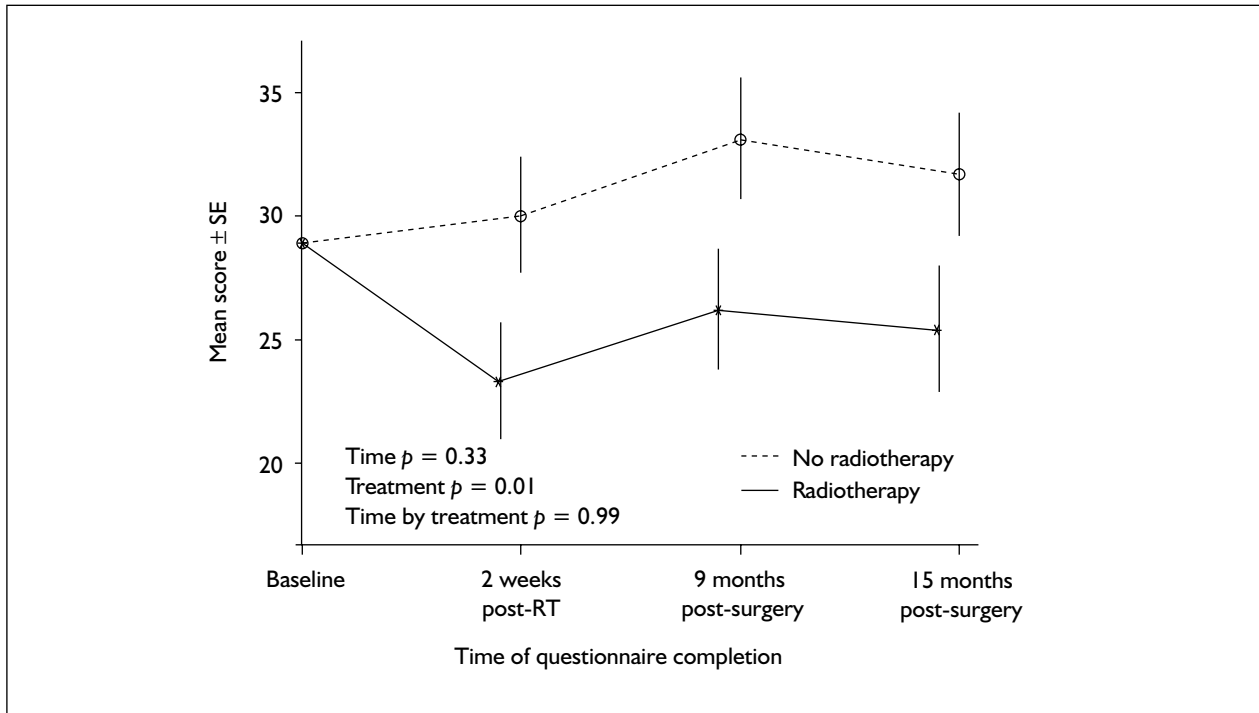


FIGURE 15 Mean score of insomnia by questionnaire

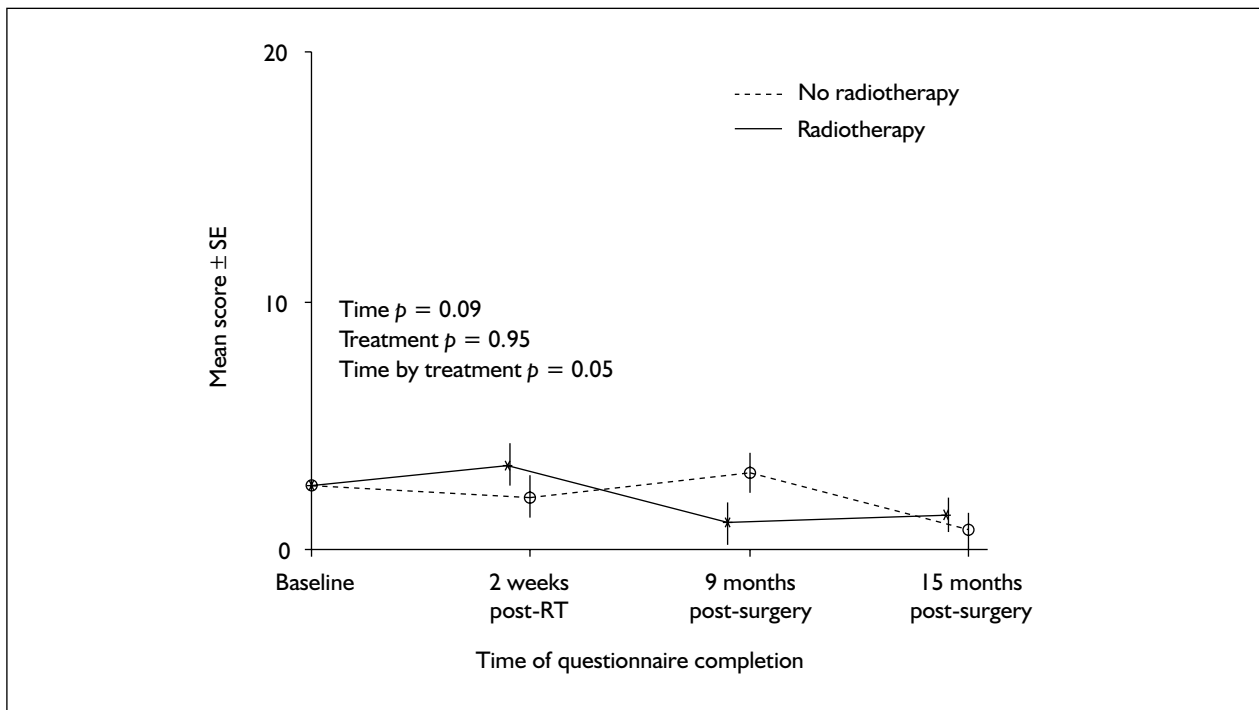


FIGURE 16 Mean score of financial difficulties by questionnaire

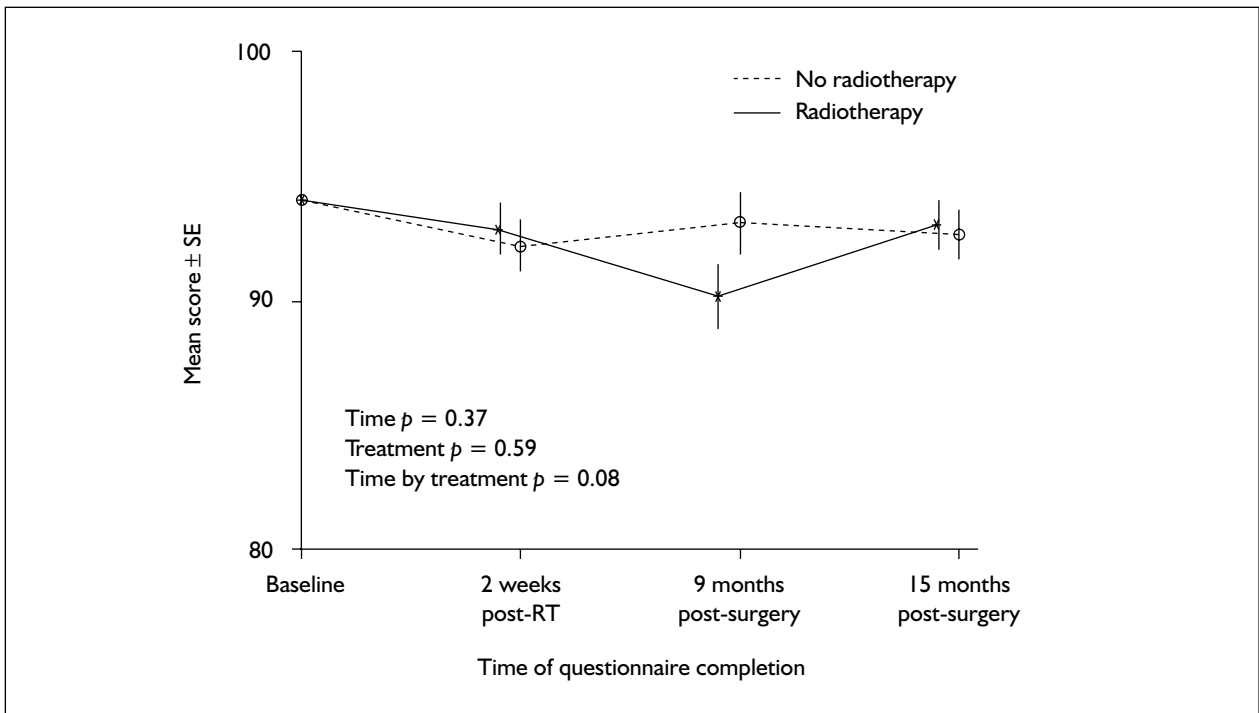


FIGURE 17 Mean scores of body image by questionnaire

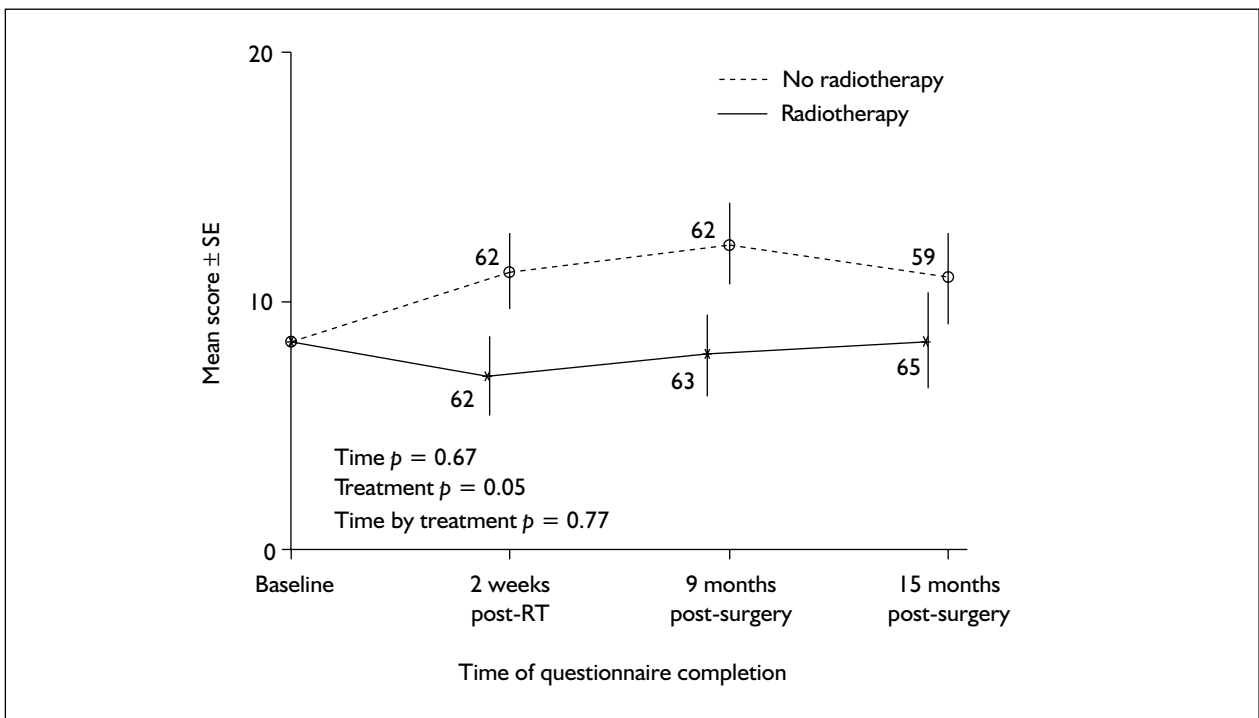


FIGURE 18 Mean score of sexual functioning by questionnaire. Numbers of observations available at each time point are given on the graph.

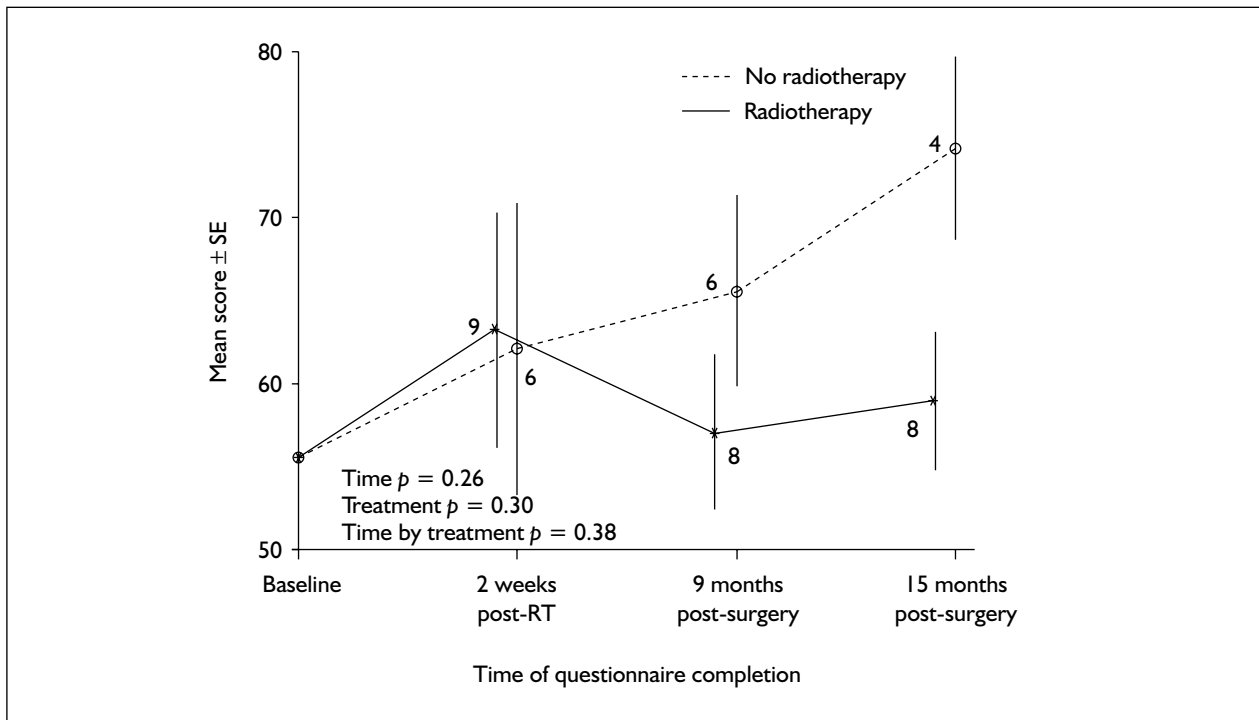


FIGURE 19 Mean score of sexual enjoyment by questionnaire. Numbers of observations available at each time point are given on the graph.

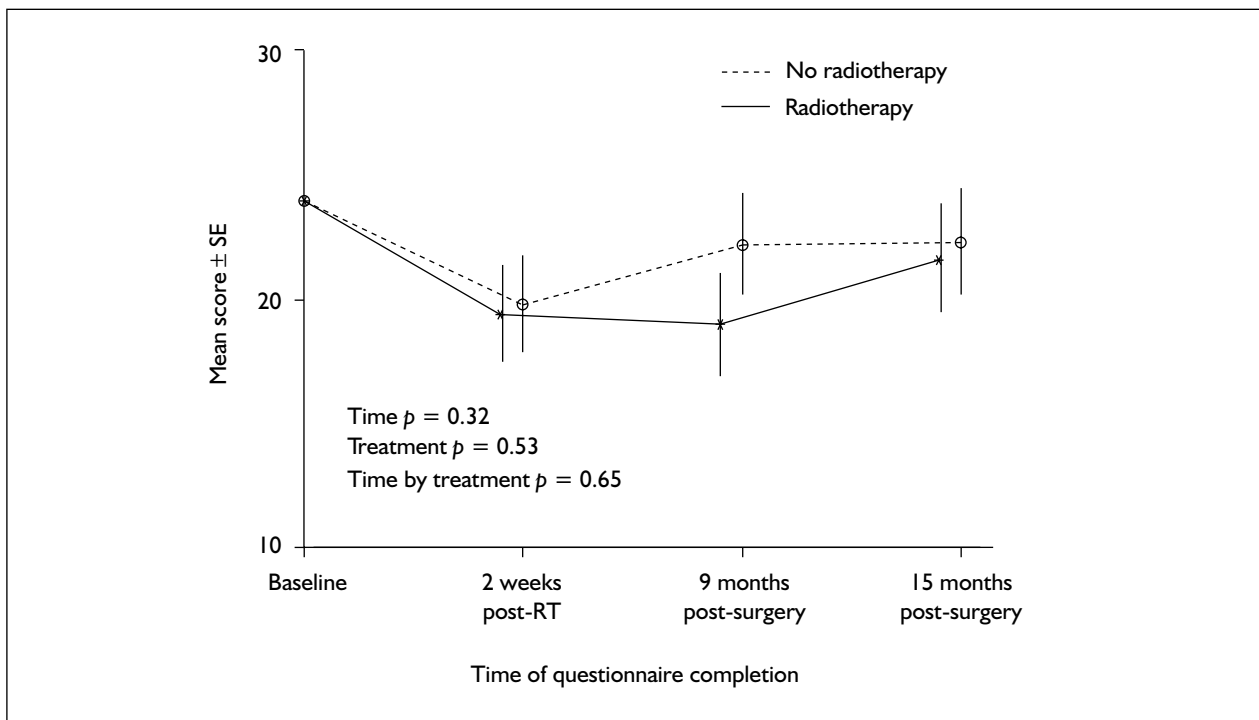


FIGURE 20 Mean score of future perspective by questionnaire

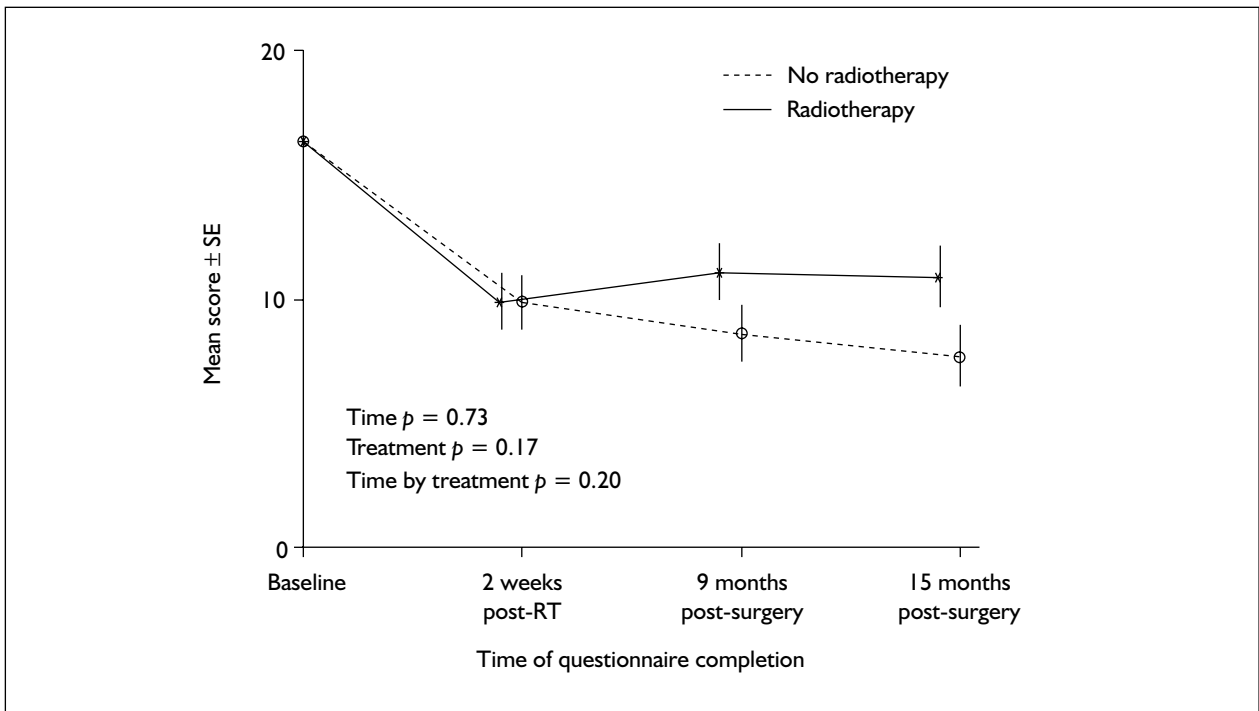


FIGURE 21 Mean score of arm symptoms by questionnaire

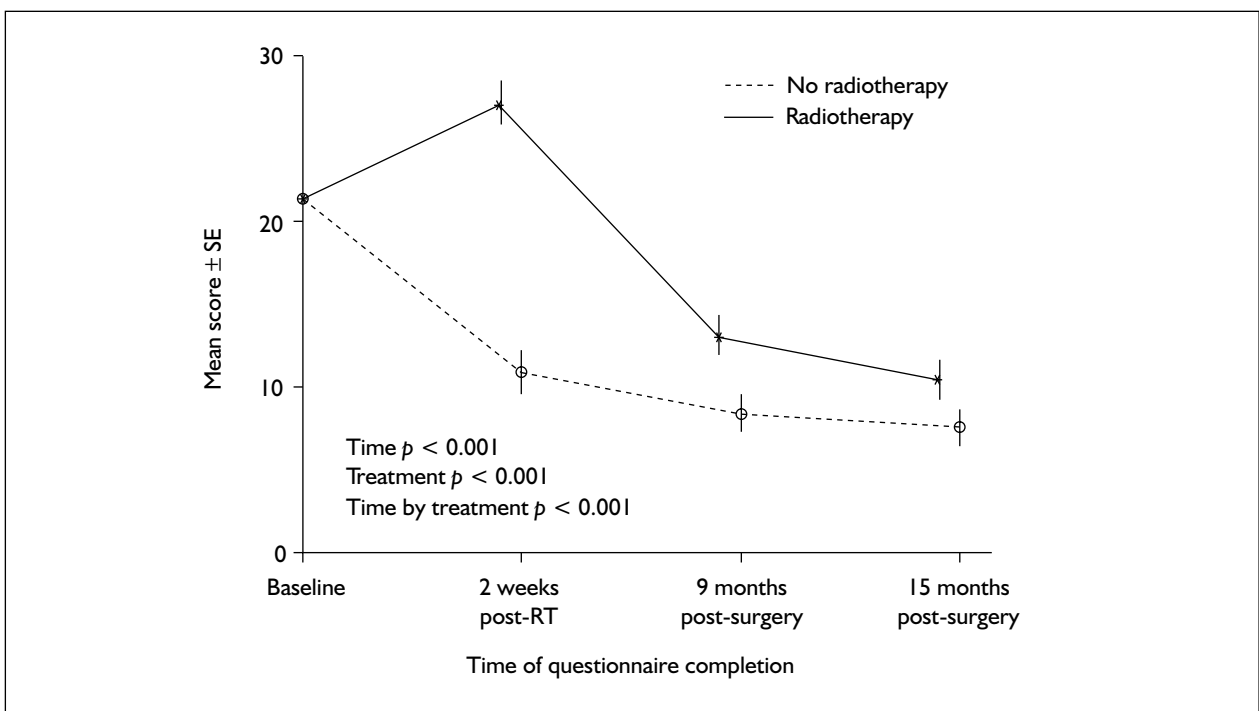


FIGURE 22 Mean score of breast symptoms by questionnaire

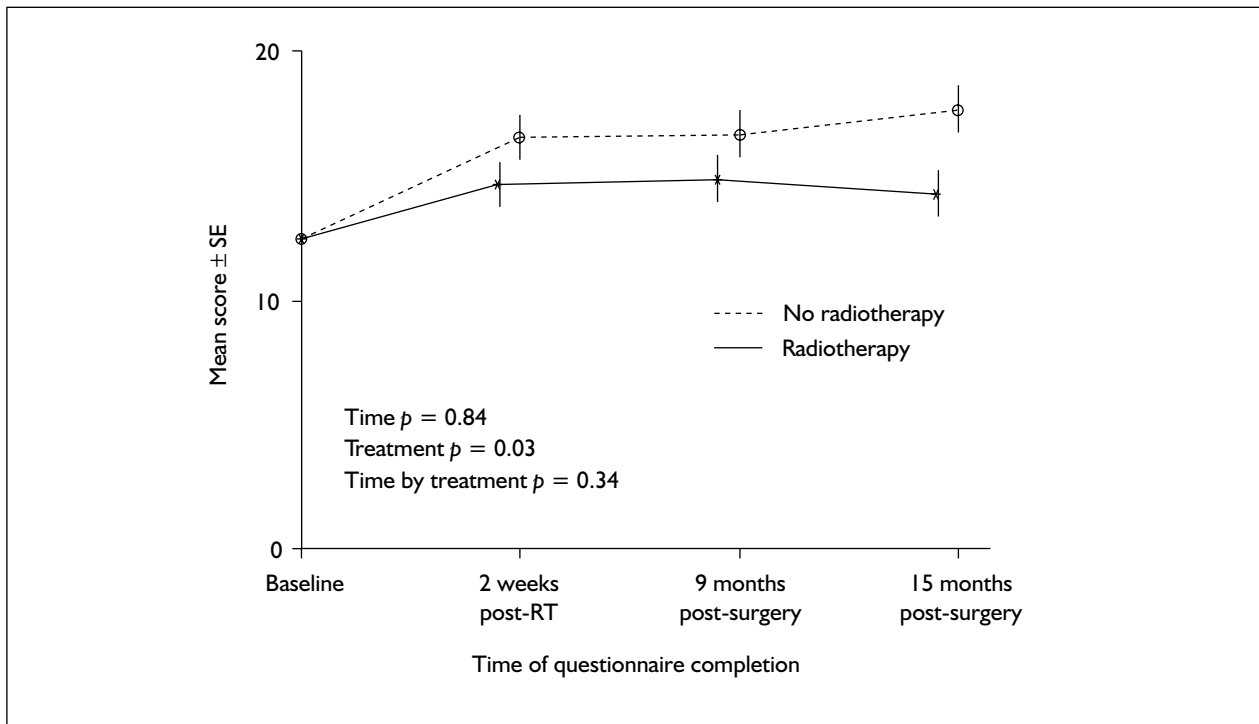


FIGURE 23 Mean score of systemic therapy side-effects by questionnaire

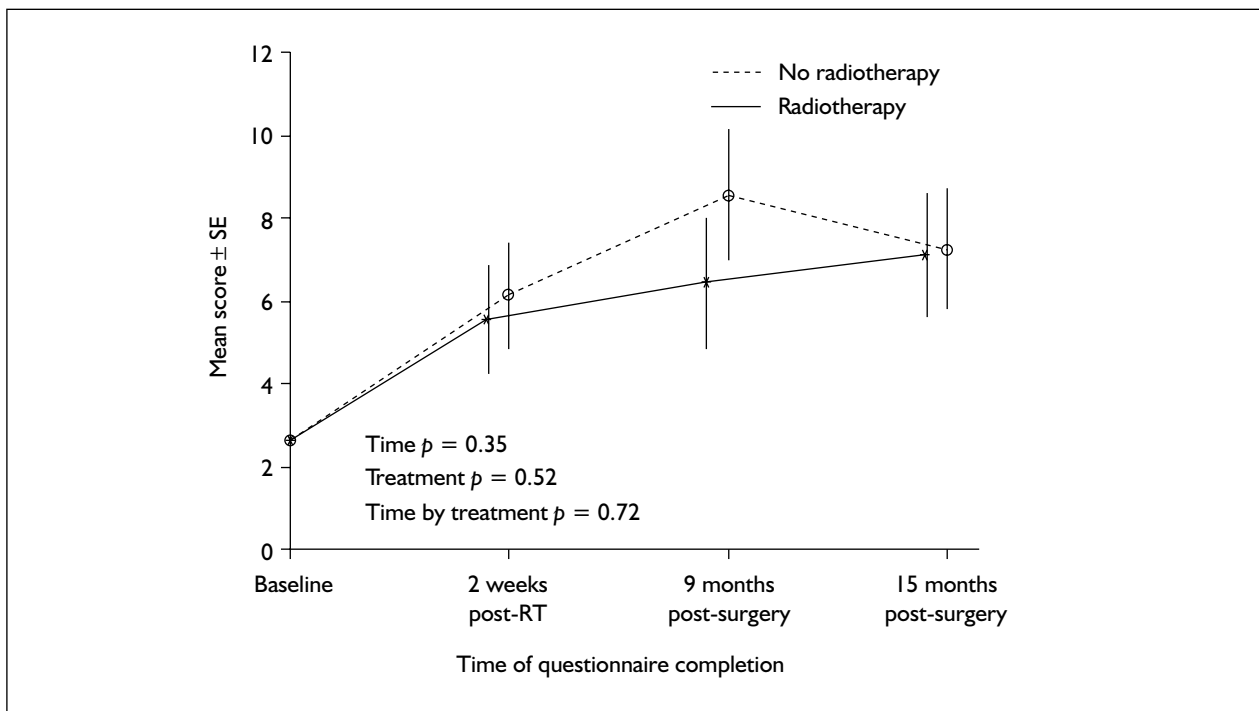


FIGURE 24 Mean score of distress at hair loss over all patients by questionnaire

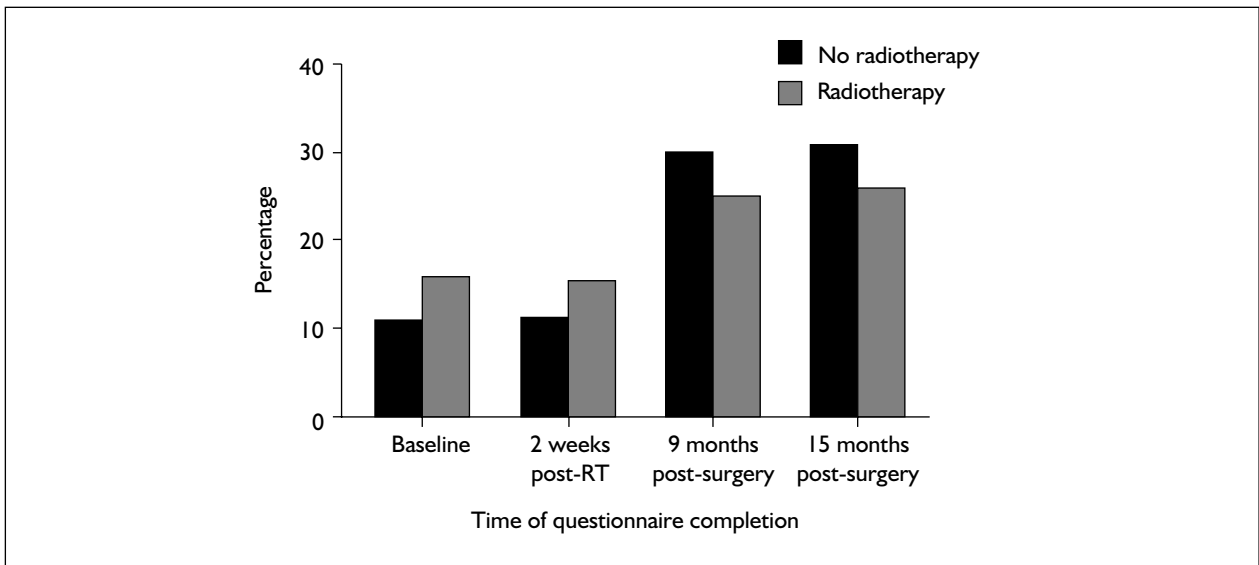


FIGURE 25 Percentage of patients reporting hair loss at each questionnaire

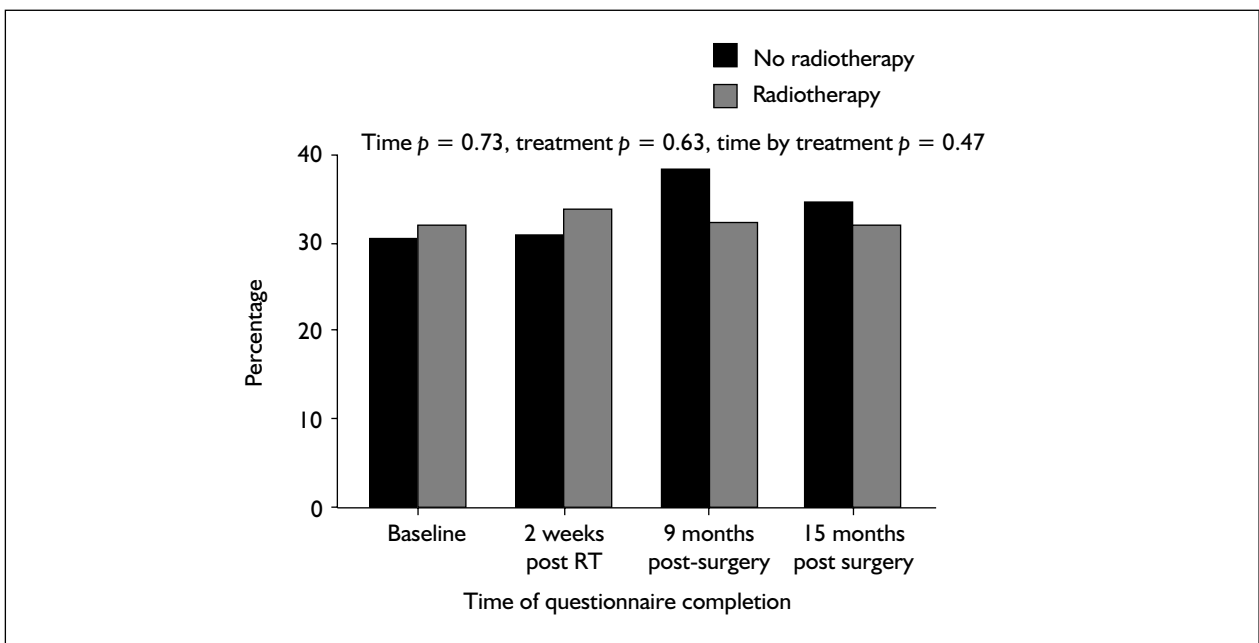


FIGURE 26 Percentage of patients reporting a cough at each questionnaire

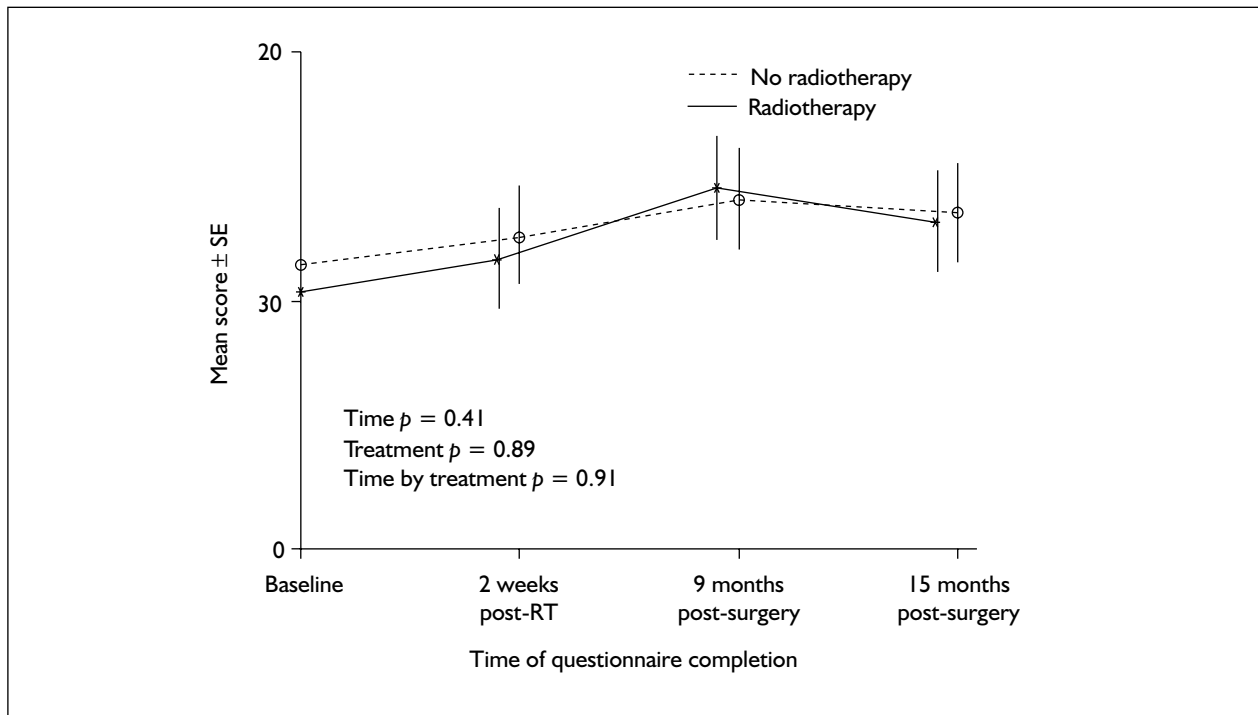


FIGURE 27 Mean score of effect of cough by questionnaire

Chapter 5

Patient outcome – anxiety and depression

Hospital Anxiety and Depression Scale (HADS)

HADS is a scale designed to investigate psychiatric and psychological morbidity, with respect to health. It comprises 14 questions, scored from zero to three, and is subdivided to provide separate scores for anxiety and for depression. Higher scores are indicative of higher anxiety/depression. Scores of more than 10 in either scale are indicators of significant problems, with a possible maximum of 21 for each scale. A list of the questions and their possible responses is given in Appendix 2.

Anxiety

Figure 28 suggests that anxiety levels may be slightly lower in the radiotherapy group, but the difference is not significant ($p = 0.17$).

Depression

There is evidence of increasing depression scores over time ($p = 0.04$), but there is no evidence of a treatment effect (Figure 29). Although the increase in mean depression scores is significant, the absolute change is small.

The Philadelphia Geriatric Center Morale Scale (PGCMS)

The PGMS is comprised of 17 questions with a yes/no answer, and yields a maximum of 17, indicating a very high morale. This score can also create three subscales. Maximum possible scores are given in parentheses.

Agitation

- Do little things bother you more this year?
- Do you sometimes worry so much you can't sleep?
- Are you afraid of a lot of things?
- Do you get angry more than you used to?
- Do you take things hard?
- Do you get upset easily?

Attitude to own ageing

- Do things keep getting much worse as you get older?
- Do you have as much energy as you did last year?
- As you get older do you feel less useful?
- As you get older are things better than expected?
- Are you as happy now as when you were younger?

Lonely dissatisfaction

- Do you feel lonely much?
- Do you see enough of your friends and relatives?
- Do you sometimes feel that life isn't worth living?

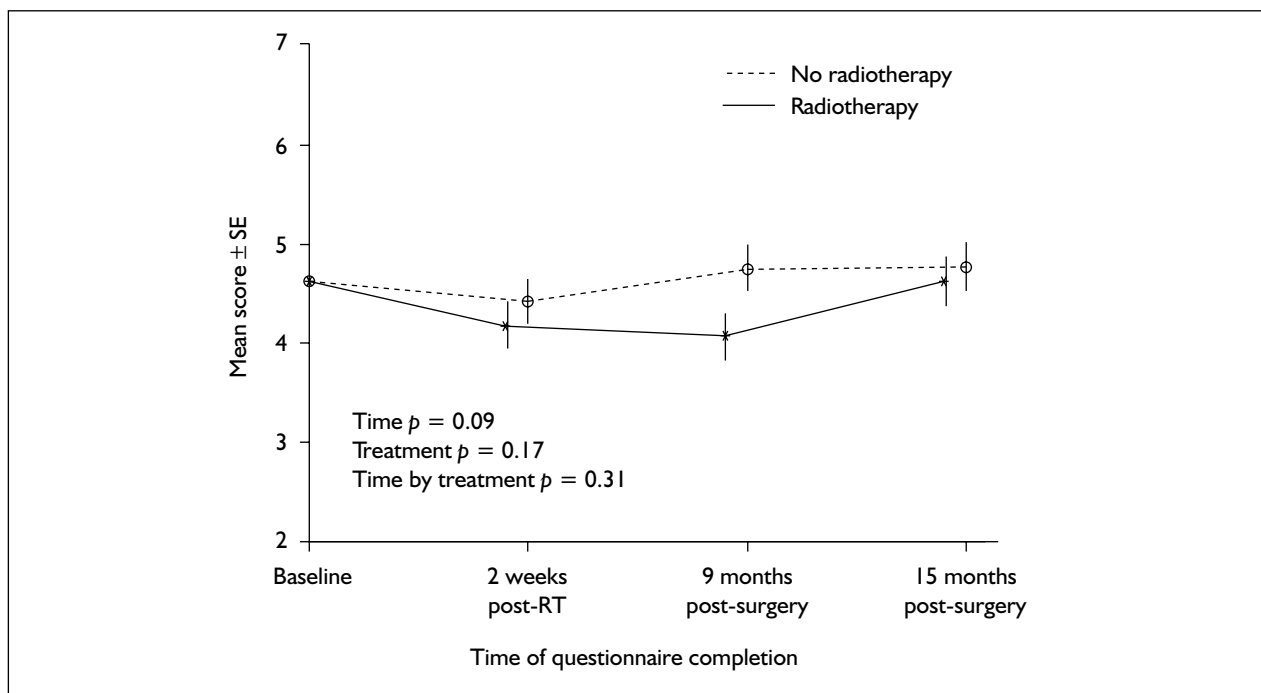


FIGURE 28 Mean score of anxiety by questionnaire

- Do you have a lot to be sad about?
- Is life hard for you most of the time?
- Are you satisfied with your life today?

Total score (17)

There is no evidence of any change over time, or any effect of treatment (Figure 30).

The three subscales show a similar lack of any changes (Figures 31–33). For the agitation subscale, the time by treatment interaction gives $p = 0.05$, but the differences are small and may be ascribed to multiple testing.

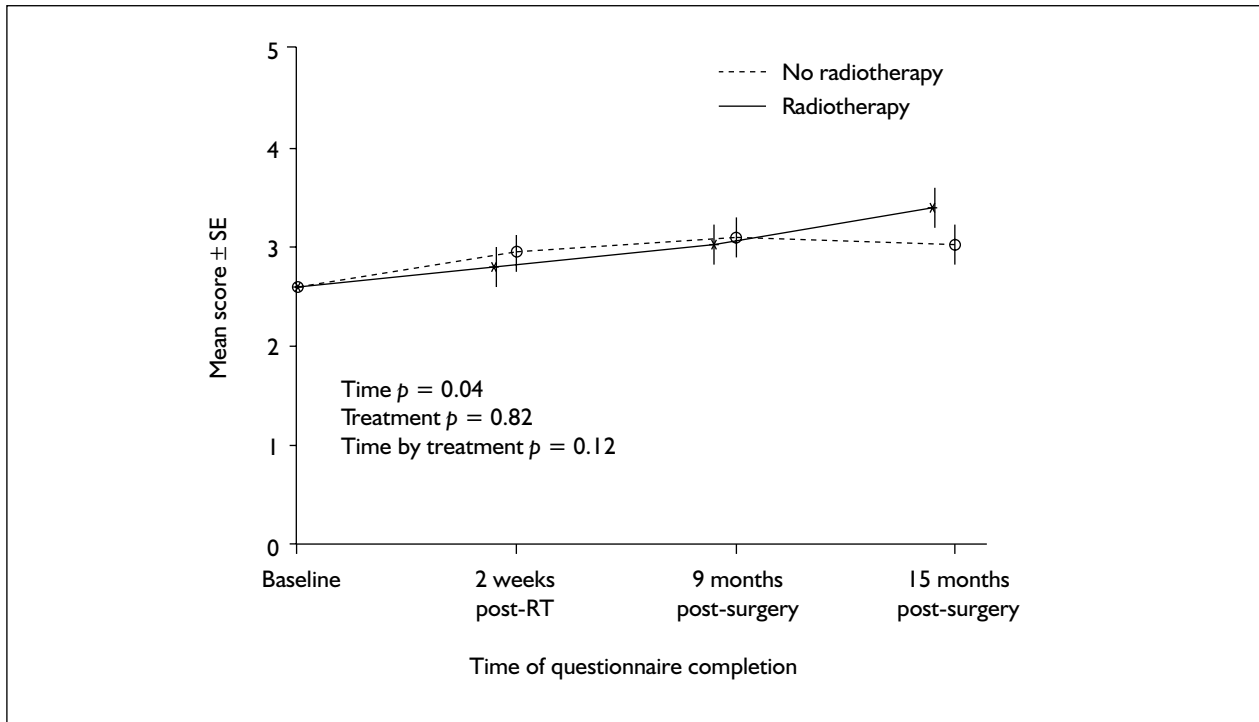


FIGURE 29 Mean score of depression by questionnaire

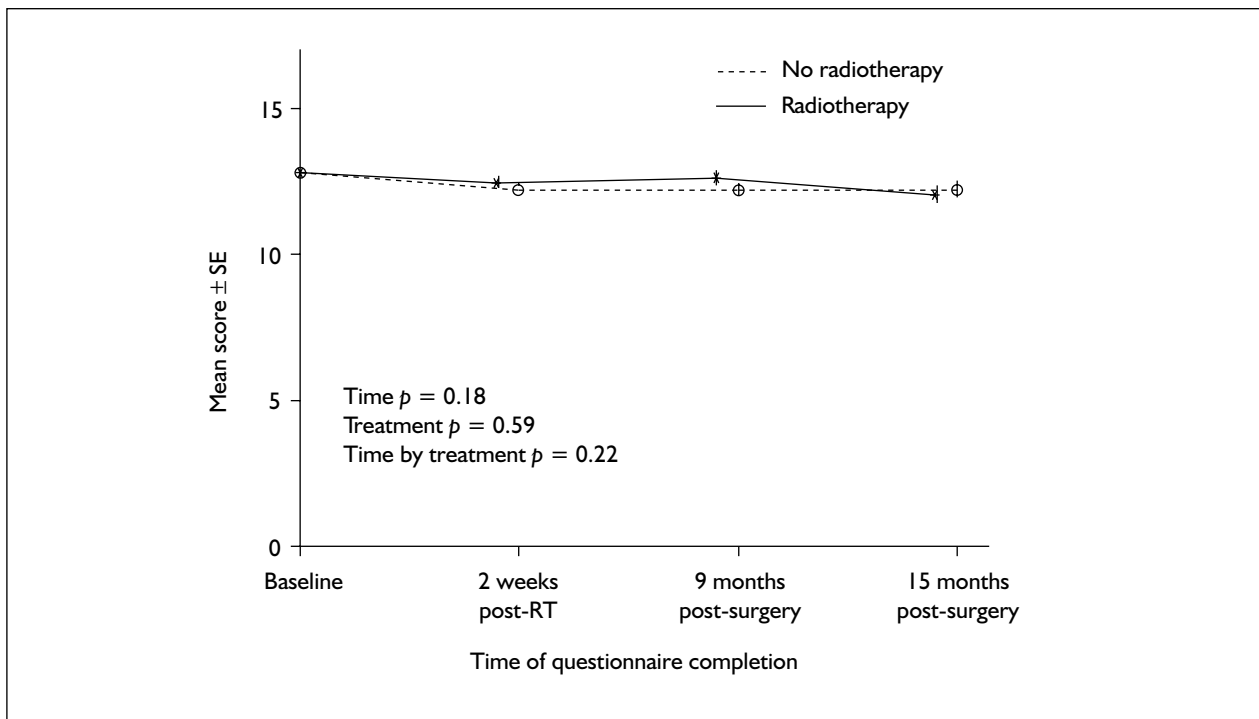


FIGURE 30 Mean scores for total (maximum 17) by questionnaire

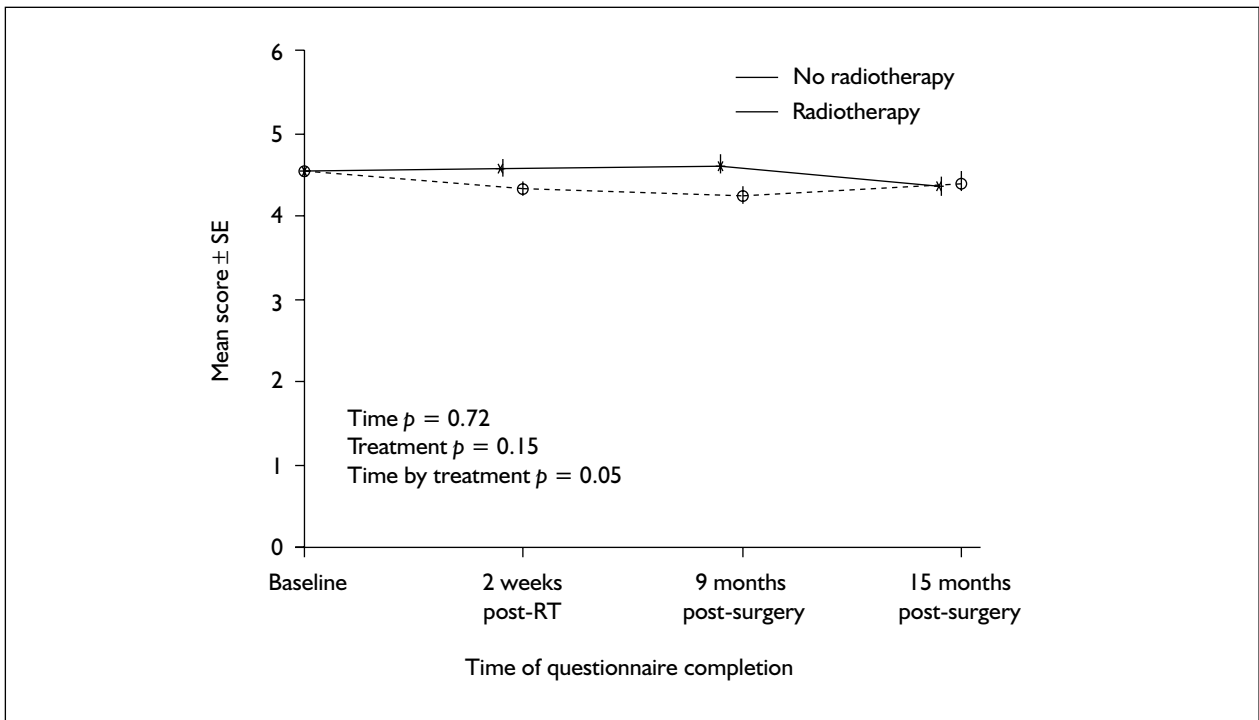


FIGURE 31 Mean score of agitation (maximum 6) by questionnaire

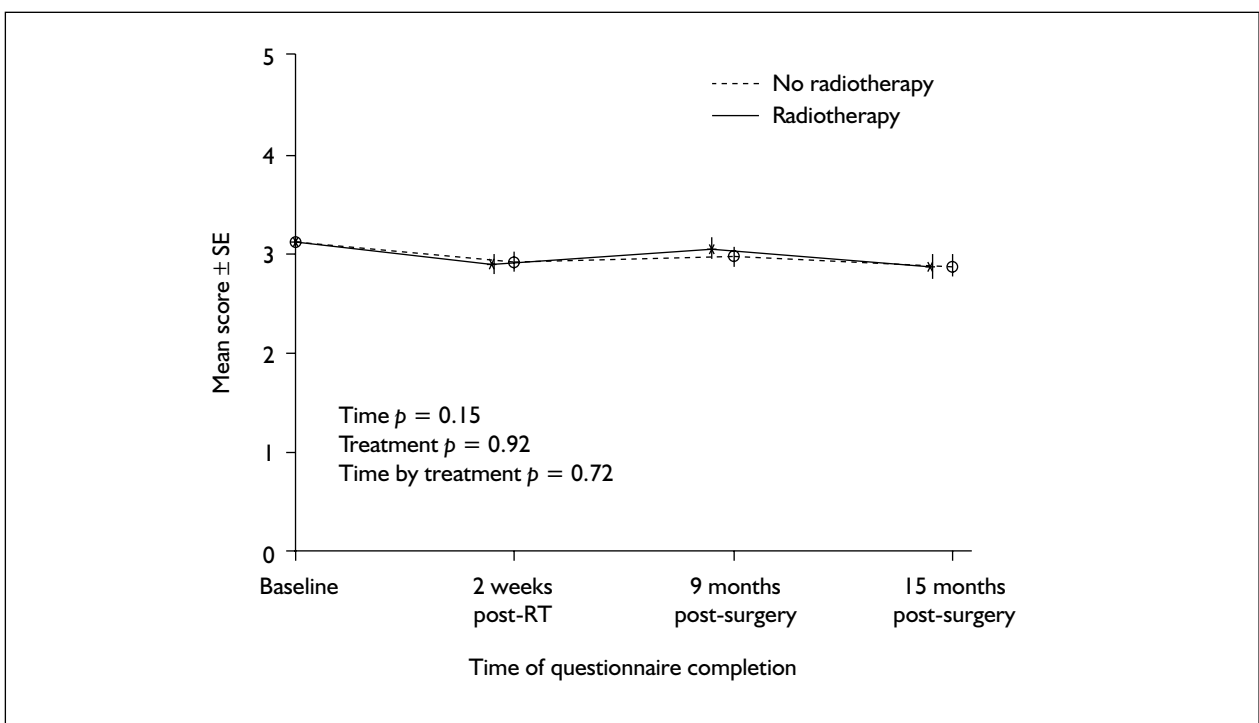


FIGURE 32 Mean score of attitude to own ageing (maximum 5) by questionnaire

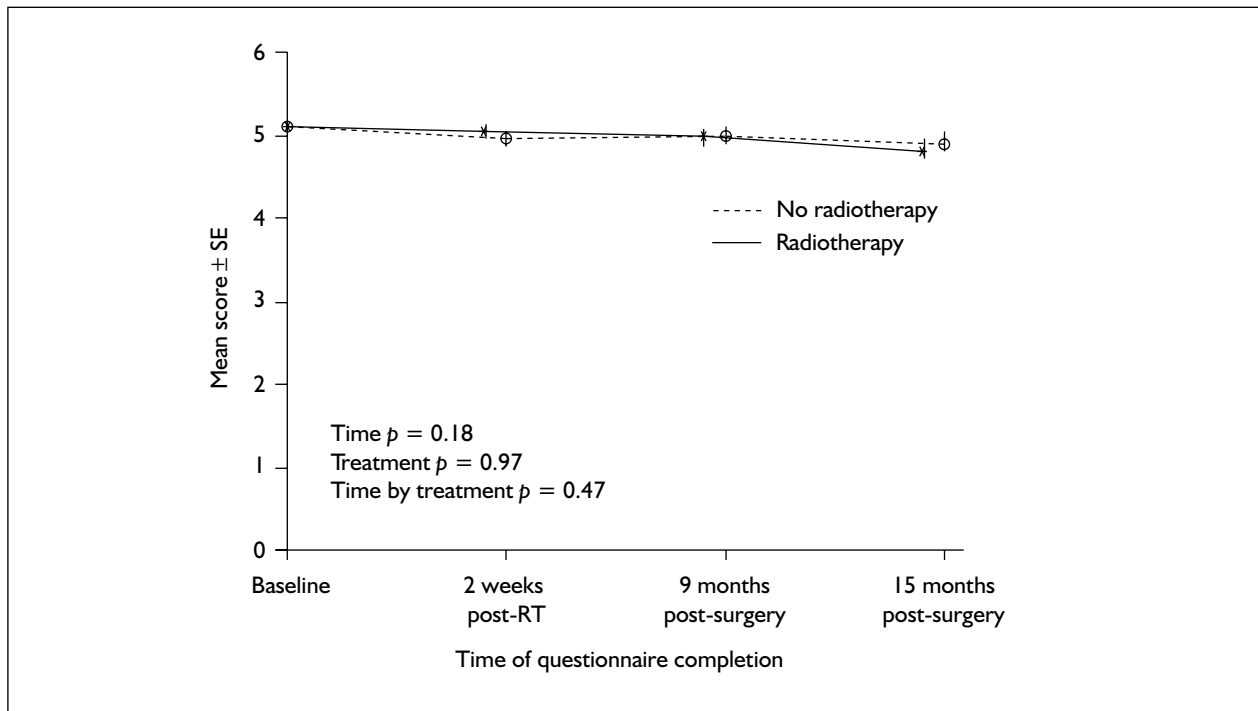


FIGURE 33 Mean scores of lonely dissatisfaction (maximum 6) by questionnaire

Chapter 6

Patient outcome – functional status

Clackmannan Scale

The Clackmannan Scale is a measure of the instrumental activities of daily living, covering such items as mobility, housework and self-care. Scores may range from 0 to 30, with a higher score indicative of a lower level of functionality. The full set of questions is given in Appendix 2.

Overall score (maximum score 30)

Although there is no evidence of a treatment effect, there is a highly significant time effect. Following an initial fall, there is a steady rise in score, which is indicative of an increase in problems (*Figure 34*). However, since this is a change from approximately 3.5 to 4.7 on a scale which reaches 30, this may not be a significant clinical change.

Mobility score (8)

As above, there is a significant time effect, although no evidence of a treatment effect (*Figure 35*). Again, any loss in mobility appears to be small when compared with the range available to the score.

House care (12)

As with the other scales in this index, there is no evidence that treatment is having an influence on the patient's ability to maintain their homes, although the time effect is again significant (*Figure 36*).

Self-care (10)

Again, there is no evidence of a treatment effect, although there are significant differences between the time points (*Figure 37*). However, as before, these fluctuations are not of a magnitude to be clinically significant.

Barthel Index

As with many of the previous scales, this measure may be subdivided into subscales, in this case self-care and mobility, in addition to the summary score. Higher scores are indicative of greater functionality. The full questionnaire is given in Appendix 2.

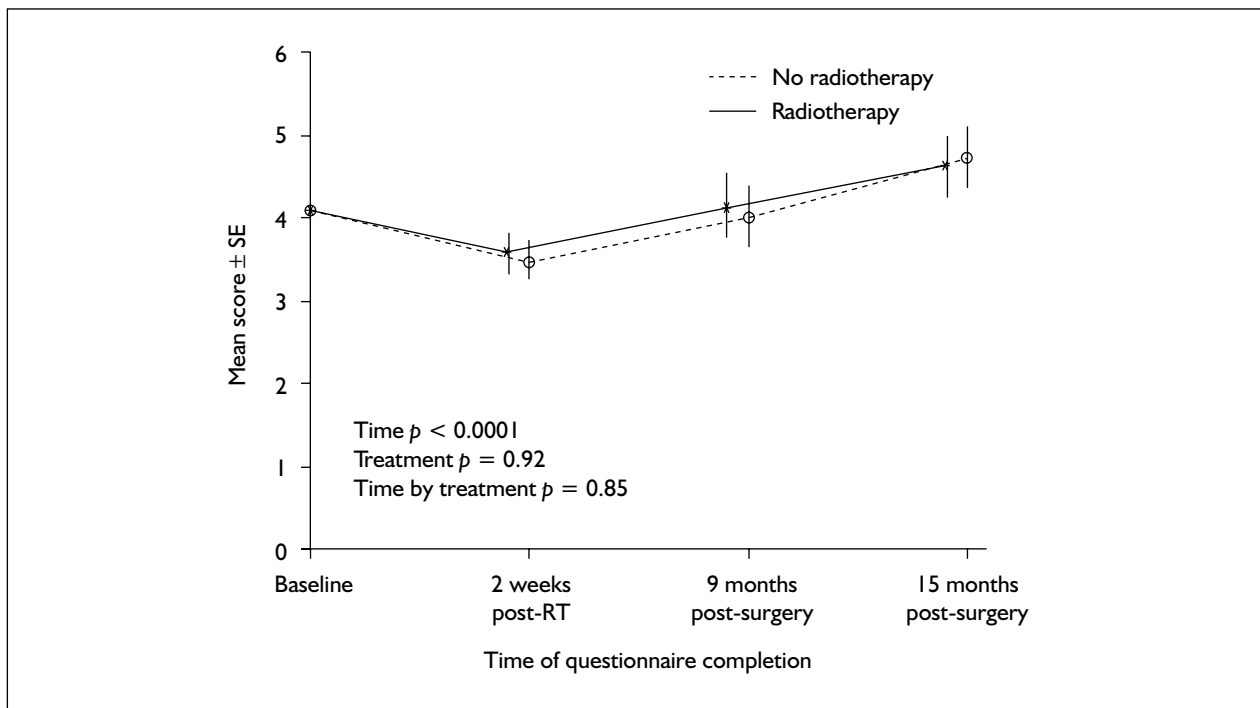


FIGURE 34 Mean of Clackmannan score (maximum 30) by questionnaire

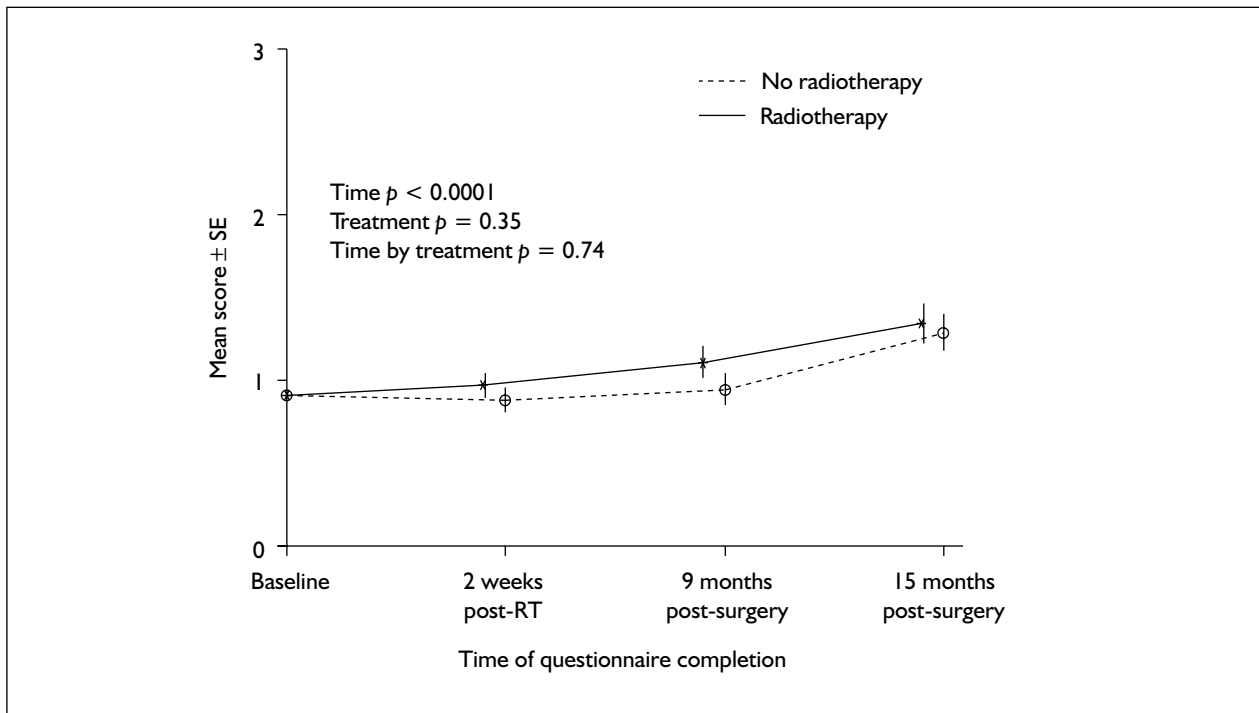


FIGURE 35 Mean of mobility score (maximum 8) by questionnaire

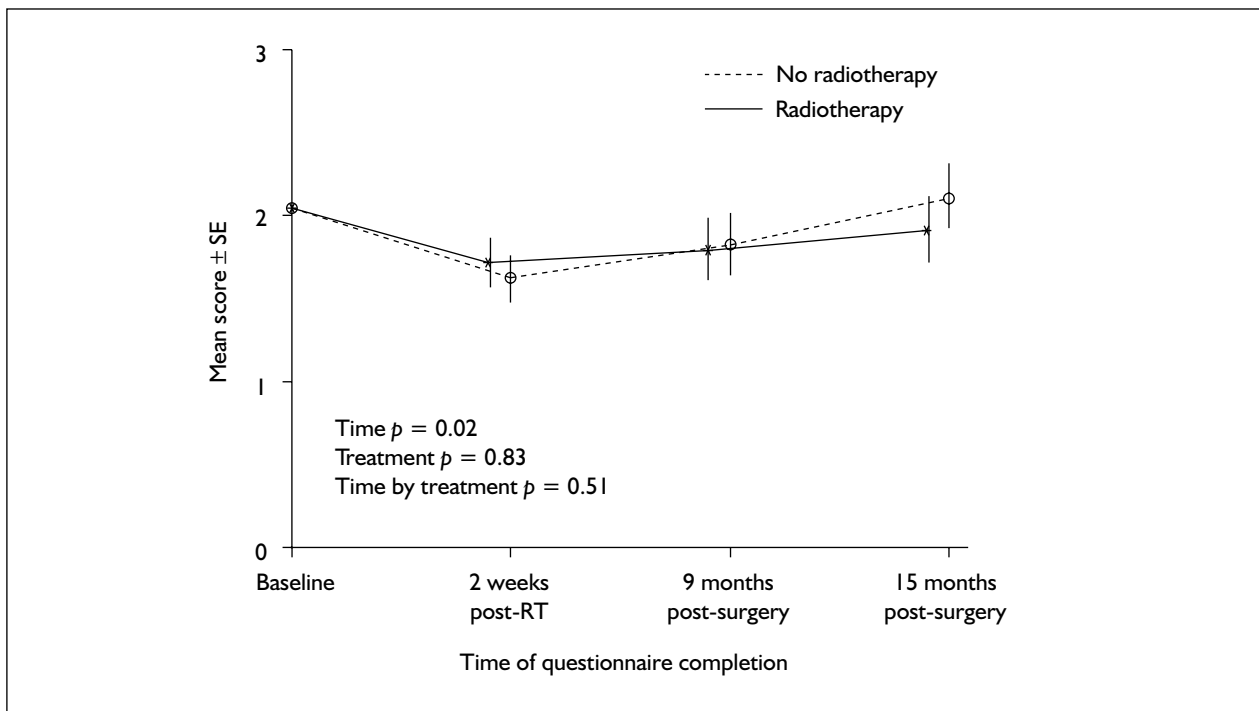


FIGURE 36 Mean of house care score (maximum 12) by questionnaire

Overall score

Figure 38 shows a pattern of little change in the mean of the Barthel Index in the no radiotherapy group, whereas a reduction of around 0.5 points is seen in the radiotherapy group by the end of the follow-up period. The widening gap between the two treatment groups

over time is confirmed by the statistically significant time by treatment interaction ($p = 0.04$).

Self-care

There is a large time effect evident for this subscale, and the difference between the

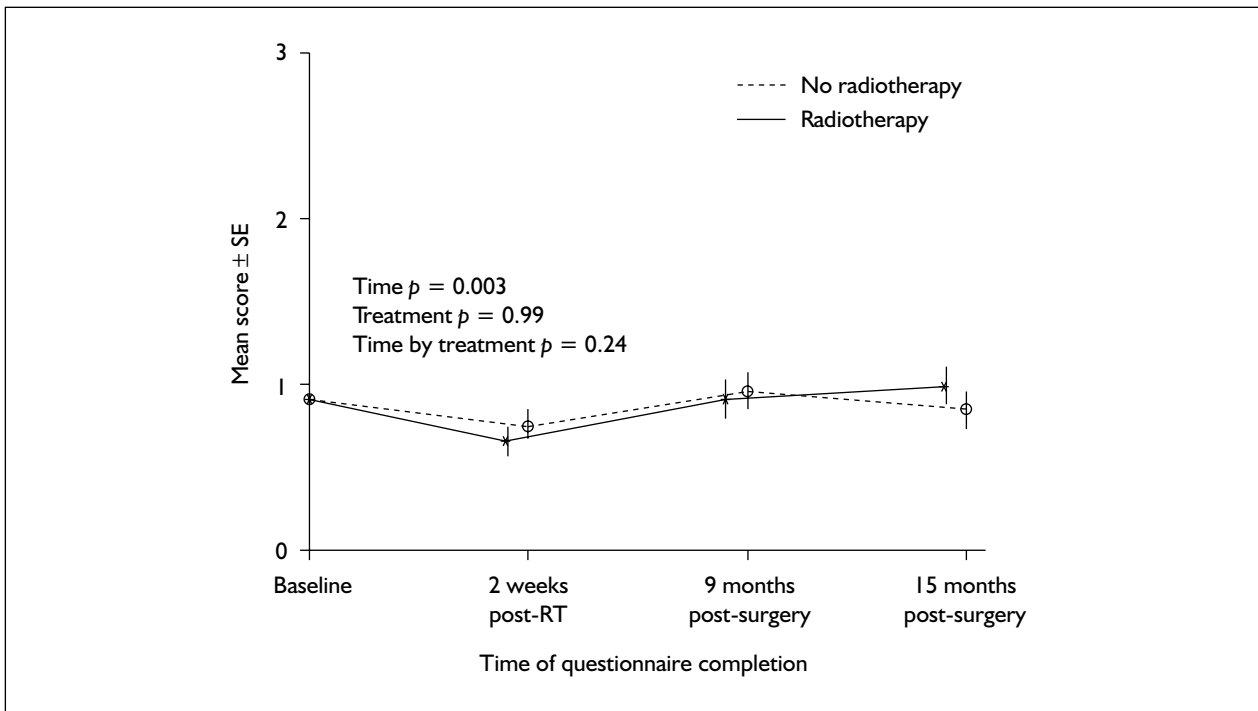


FIGURE 37 Mean of self-care score (maximum 10) by questionnaire

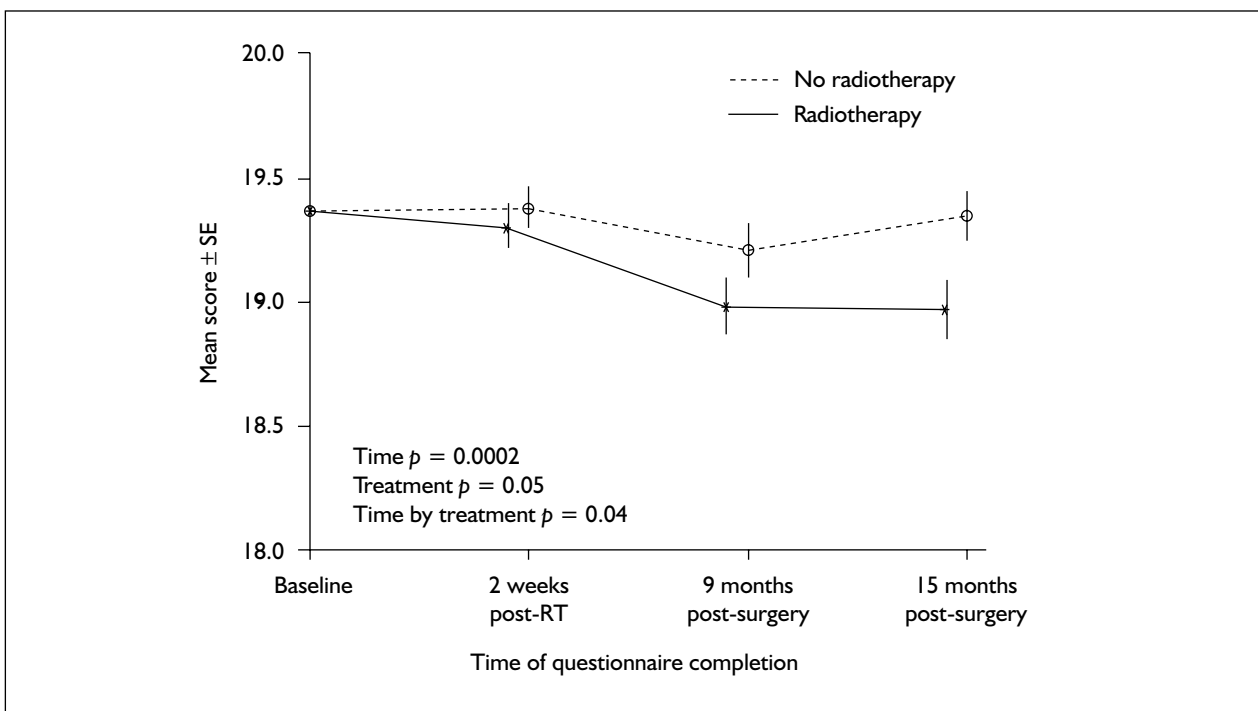


FIGURE 38 Mean of Barthel Index score (maximum 20) by questionnaire

treatments increases over time, with the no radiotherapy group evidencing higher self-care scores (Figure 39). The differences are not as marked as for the main scale and the treatment and time by treatment effects are not statistically significant.

Mobility

There is a small reduction in the mean mobility score in the radiotherapy group by 9 months post-surgery, but neither the treatment nor time by treatment effects are statistically significant (Figure 40).

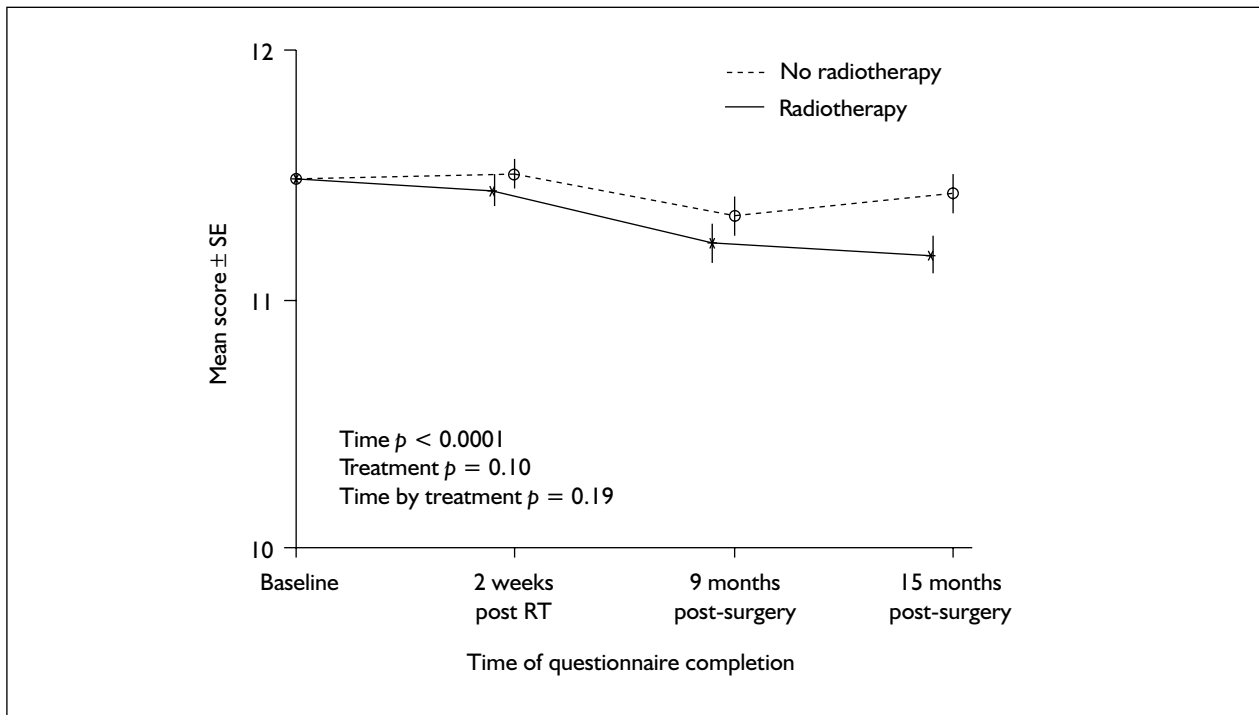


FIGURE 39 Mean of self-care score (maximum 12) by questionnaire

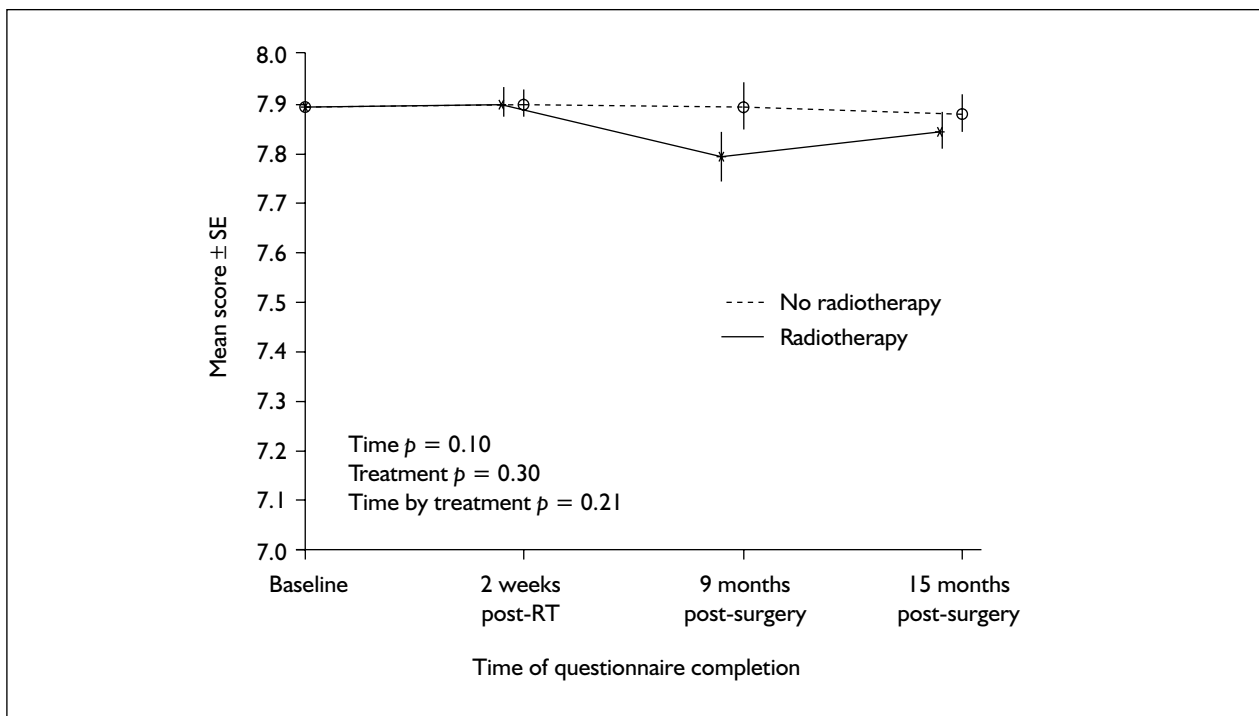


FIGURE 40 Mean of mobility score (maximum 8) by questionnaire

Chapter 7

Subjective views of patients (open-ended questions)

Introduction

The majority of QoL data were numerical, but there were some open-ended questions which allowed participating women to say something about how breast cancer had affected them or their relationships, or about additional life experiences which were having a major impact on their lives. At the end of each questionnaire, the women were also given the opportunity to make comments or to ask questions.

The full list of response categories can be found in Appendix 4. In this chapter, the headings reflect the coding frame used to organise the response content. At baseline, the radiotherapy and no radiotherapy groups were very similar in the way in which they responded to many of the free-form questions, as would be expected prior to knowing the outcome of randomisation. Thus the responses at baseline are considered as a single homogeneous group. A review of all the women's responses is included below, and only where significant differences were recorded between groups or interesting trends in the frequency of comments were observed over the follow-up period is further mention made in the text or in graphical form. The sections in italics (in the third

person) are illustrative excerpts from the responses given by the women.

Effects of breast cancer

- *Could I now ask you to say in your own words how your breast cancer has affected you?*

Some women gave lengthy replies which seemed completely spontaneous whereas others were observed to take some time to formulate their response. Some gave a short sentence in reply and appeared not to wish to say any more. A few were a little upset but seemed to want to say more and did so, when they recovered.

No effect

At baseline, 34 (13%) said they had experienced no effect from breast cancer and also that it had had no effect on relationships. No difference was noted between the group who had had radiotherapy and those not receiving radiotherapy in this respect. The proportion saying breast cancer had not affected them increased over time to around 25%, at 9 months from surgery. It then declined in both groups to around 20% (Figure 41) at the final assessment.

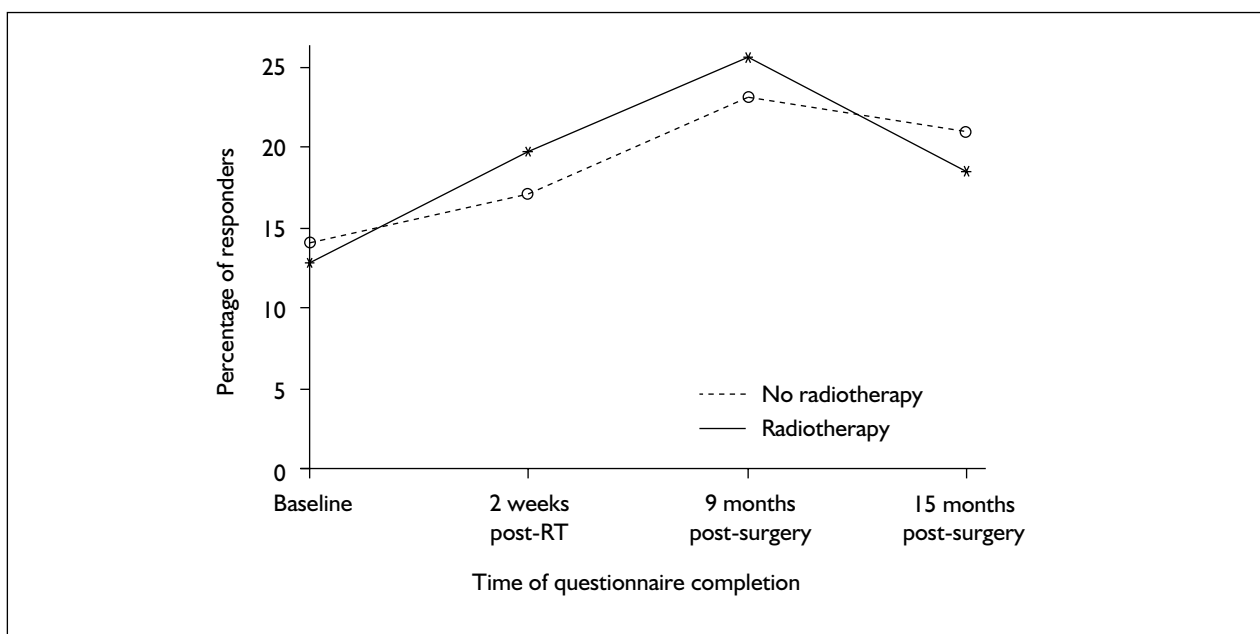


FIGURE 41 Percentage of patients replying that breast cancer had no effect on them

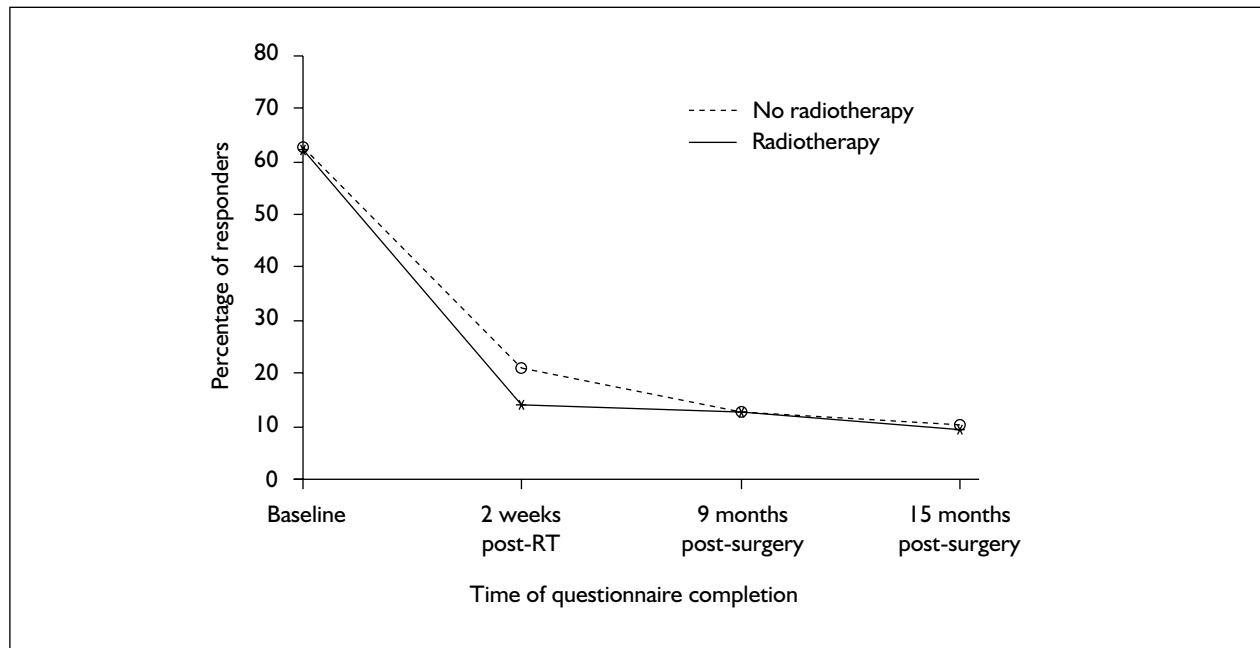


FIGURE 42 Percentage of patients who reported feelings of shock at the diagnosis

Diagnosis

Shock

In response to the question on how breast cancer had affected the patients, the first and most frequently mentioned reaction was one of shock at the diagnosis. A total of 198 women (78%) stated this while an additional 24 (9%) mentioned feeling shaky, sick or numb, possibly a physical effect of the same reaction. The comments of one patient were: *she had gone to the hospital fairly convinced she had a cyst. She had a core biopsy and a mammogram and an ultrasound and they all showed that it was cancer but when she was told, she couldn't speak at all. She just sat there and when they asked her if she was feeling very shocked she just couldn't answer them. They brought her some hot sweet drinks. She didn't know how many she had but she did remember then being able to ask some questions. She was on her own. She hadn't been prepared for getting the results all on the same day. She thought she asked the surgeon and the nurse about four times if they were sure she had cancer. She remembered them being very kind. They wanted to call someone to go home with her but she wouldn't let them. She wasn't really ready to tell anyone else yet. She didn't cry or anything and she found it difficult answering the phone to her family and friends and telling them she had breast cancer.*

As can be seen from *Figure 42*, the radiotherapy and no radiotherapy groups were almost identical in the frequency of shock, at baseline and over the whole follow-up period. There was much less mention of shock with increasing time from diagnosis.

Relief

In contrast, at baseline, 16 (6%) also reported some relief associated with breast cancer diagnosis, for example, that it had been discovered early or that the diagnosis had been made so speedily. There was no difference between groups and this effect was not mentioned at later time points.

Positive effect

In the baseline questionnaire, 51 (20%) mentioned some positive effect of diagnosis; deciding to do things they had always hoped to do, such as travelling more, visiting family or as a stimulus to mend a broken relationship. From *Figure 43*, it can be seen that no statistically significant differences were found in the proportions spontaneously reporting positive effects and, as with shock, mention of the effect diminished over the 15 months of follow-up.

Risk factors

Perhaps, in an attempt to understand how breast cancer had affected them in particular, 19 (7%) talked about breast cancer risk factors which they thought they might or might not have, for example, mentioning that they had no family history of the disease, or that they had breastfed several children or indeed that there were a number of family members who had had breast cancer.

Process of diagnosis

On being asked during the baseline questionnaire how breast cancer had affected them, 23 (9%)

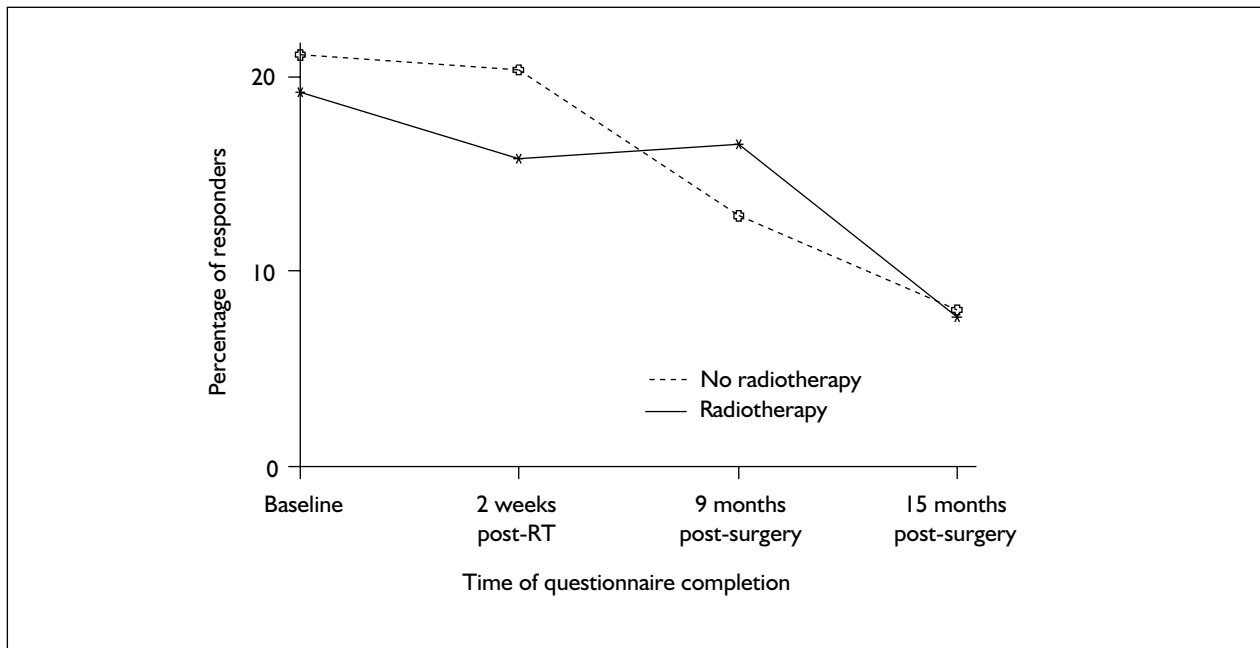


FIGURE 43 Percentage of patients who felt the diagnosis had had a positive effect on them

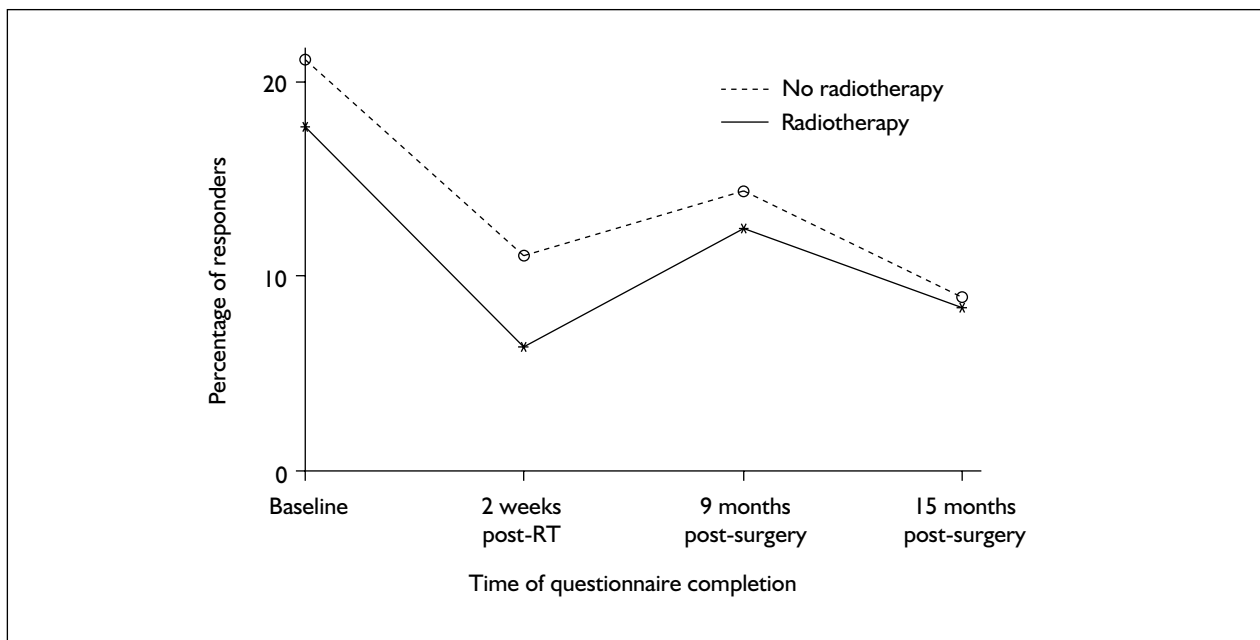


FIGURE 44 Percentage of patients who reported that surgery had had a negative physical effect on them

chose to describe the diagnostic process in a lot of detail. Sixty-four (25%) commented that diagnosis was made as a result of having some sign/symptom which had prompted them to visit their GP, while 40 (16%) mentioned that the cancer was detected at screening mammography. The remainder did not say how the diagnosis of breast cancer had come about. The process of diagnosis was hardly mentioned in later questionnaires.

Surgery

Negative physical effects

Before randomisation, 49 (19%) focused some of their response on difficult physical aspects relating to their surgery. These included symptoms such as nausea/vomiting, pain or the recommendation to have further surgery, either to stage the axilla or to ensure clear margins (Figure 44). Both groups displayed a similar trend over time, but

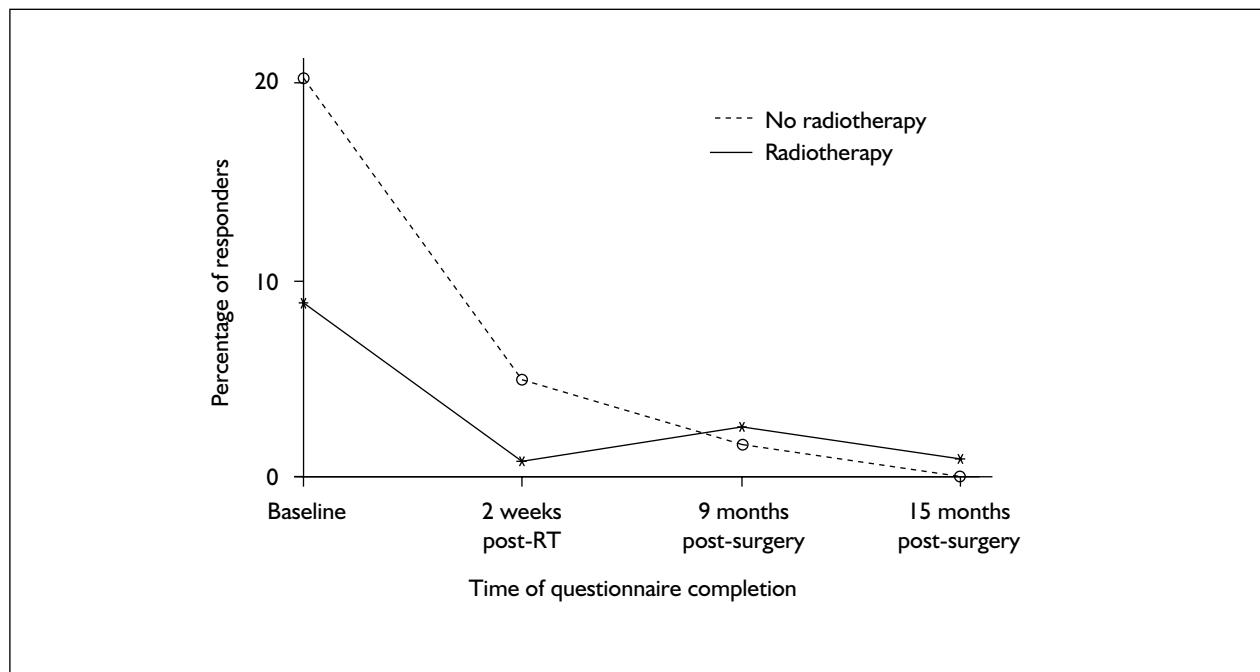


FIGURE 45 Percentage of patients who felt surgery had had a negative emotional effect on them

with no significant differences between them. Approximately 10% of patients continued to volunteer comments on this topic at 15 months post-surgery and these mainly referred to pain or discomfort in the breast or on arm movement.

Surgical complication

At baseline, 39 (15%) of respondents focused on a surgical complication which was affecting them: infection, haematoma or seroma that needed to be drained. The proportion commenting on this was similar in both groups but reducing at each follow-up point. At the three later time points, the complications also included arm lymphoedema.

Negative emotional effect of surgery

The women who mentioned this talked about feeling rather low in mood or experiencing an unreal feeling. A description of one interviewee is as follows: *at first she felt it wasn't happening to her. All of the appointments happened so quickly that her feet hardly had time to touch the ground. She was only in hospital for one day, discharged out the same evening. As far as she was concerned, she'd had cancer, she'd had the operation and wanted to carry on from then, whatever the next stage was to be. About 2 weeks after she was home, she thought it began to dawn on her that it was she who'd had breast cancer. She thought that some of that was to do with her not telling anyone but her husband at first. Once she was able to talk about it more widely it seemed more real.*

Figure 45 shows the proportion mentioning this effect over time. At baseline there was an appreciable difference in the proportion of responses on this subject with 11 (9%) in the radiotherapy group and 26 (20%) in the no radiotherapy arm of the trial. The magnitude of the difference is such that conventional significance testing would yield $p = 0.01$, although as the trial is randomised the difference is the result of chance. At later follow-up points, little further comment was made.

Positive emotions and thoughts

A slightly larger proportion during the baseline questionnaire, 50 (20%), described positive thoughts and emotions about their operation, for example, a sense of relief that the cancer was removed or that the surgery was over. The groups were similar at baseline and the trend over time almost identical, with steeply diminishing level of comment post-treatment, to almost no mention thereafter.

Change in attitude

On receipt of the prognostically good pathology results, 35 (14%) of the women specifically commented on a change in attitude from the time of diagnosis. One patient commented: *she certainly was shocked when they told her it was cancer. It knocked her for six. For days afterwards it was like a black cloud was pressing down on her then it gradually lessened. She was helped when told there had been no spread to*

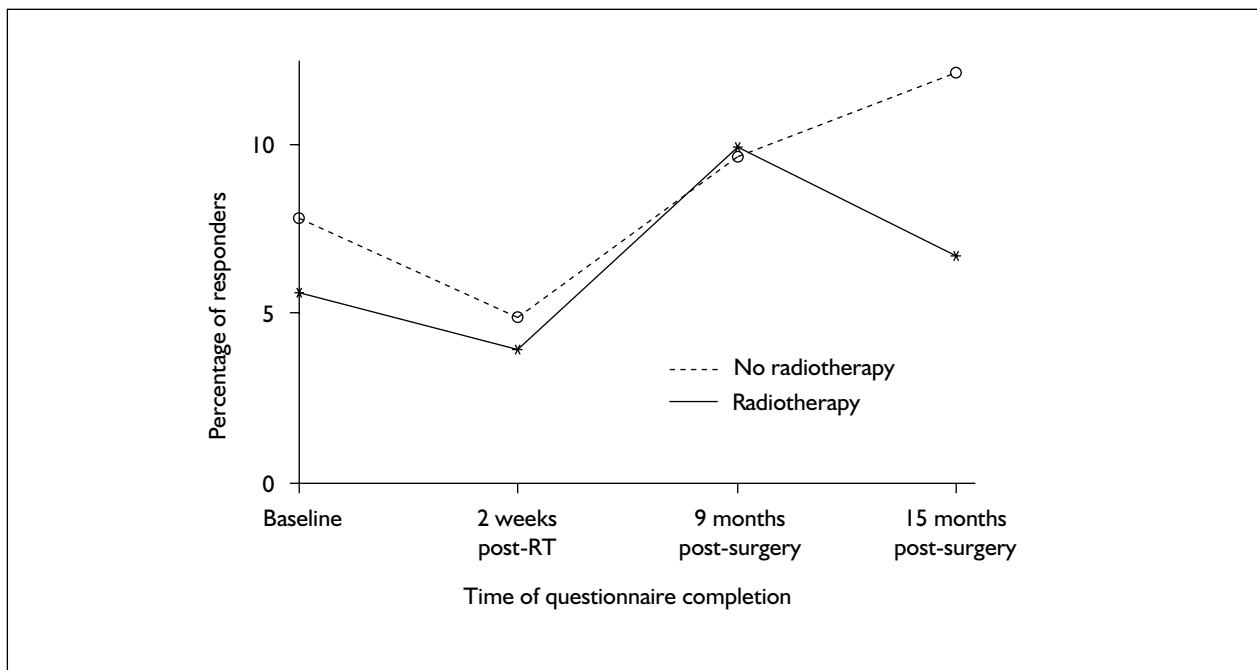


FIGURE 46 Percentage of patients reporting some form of coping mechanisms

the lymph glands and other results were good. Maybe she had blocked it out but the dark feeling didn't seem to be around any more.

Coping mechanisms

A similar small proportion in both groups described some coping mechanisms which they were using to get them through the experience. Examples were distraction, thought stopping, seeking out information or denial. The proportion mentioning these decreased similarly in both groups until 2 weeks after treatment, increased again to around 9 months after surgery when there was a non-significant divergence in the trend between groups (Figure 46).

Endocrine therapy

At the time of baseline questionnaire completion, most women (apart from the 39 who had preoperative endocrine therapy), had very recently started on endocrine therapy, while others were awaiting prescriptions. Of those having started adjuvant endocrine therapy, most (205) had commenced tamoxifen 20 mg daily. Seventeen patients were on anastrozole 1 mg, nine patients were taking letrozole 2.5 mg and two exemestane 25 mg. Eight patients were participating in another 'blinded' endocrine therapy trial and therefore the endocrine drug was not known to the patient or interviewer. In another 13 cases, the specific endocrine therapy was not stated.

Negative effects

At baseline, three patients (1%) expressed negative feelings about hormone treatment, expecting some side-effect, and at this early stage, seven (3%) had already experienced some symptom which they did not like.

During the follow-up period, a fairly representative comment from a patient was: *that she had been having quite bad hot flushes, mostly at night when she woke up soaking wet – not very pleasant, especially when she was a poor sleeper anyway with all the pain she had.*

The range of side-effects specifically raised in the follow-up period overall were typical endocrine therapy side-effects, including physical effects attributed by the women or professionals to therapy, in addition to negative psychological effects. The physical problems mentioned were hot flushes, night sweats, hair loss/changes, leg cramps, weight increase, vaginal discharge/bleeding, cracking nails, mouth ulcers, visual disturbances, sleep disturbance and effect on lifestyle, in cases with very severe side-effects. Adverse reactions included skin rashes, angioedema, taste changes, jaundice and liver damage, each of which had prompted discontinuation of the particular drug and, in most cases, prescription of an alternative.

The psychological side-effects mentioned were irritability, lethargy, weepiness, depression and

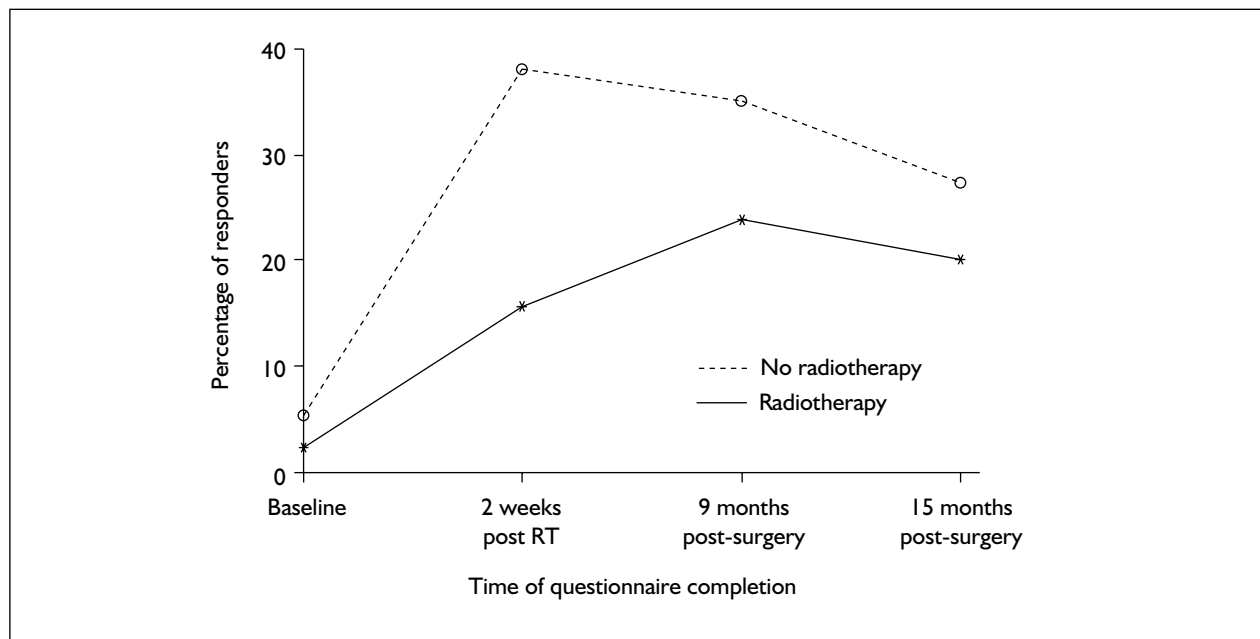


FIGURE 47 Percentage of patients reporting negative effects from the hormone therapy

food cravings. Comments similar to the following also were raised; one said that: *taking the tablet reminded her that she was still being treated for breast cancer and she didn't like being reminded.*

Both the radiotherapy and no radiotherapy groups commented negatively about endocrine therapy in small but similar proportions at baseline, and it can be seen that the trends between groups thereafter had some significant and initially surprising differences (Figure 47).

At 2 weeks post-treatment, significantly fewer women ($p = 0.0005$) who had undergone radiotherapy chose to mention endocrine therapy side-effects compared with those who had received no radiotherapy. The difference remained borderline significant ($p = 0.054$) at the 9-month questionnaire, reducing to a non-significant level at the final stage. At 15 months, around 25% overall were voluntarily commenting on endocrine side-effects.

Of the 39 (15%) who had had preoperative endocrine therapy, either letrozole or exemestane, there were both positive and negative comments. One patient said that: *taking the tablets for several months before surgery was really quite hard though, waiting to see if they would have a good effect and shrink the lump. She thought it would have been better for her to have got on with the surgery right away. However, she knew it meant much less of the breast had had to be removed and that had to be good.*

Radiotherapy

Negative emotions

At baseline, 10% volunteered negative attitudes or feelings in advance of any potential radiotherapy treatment. The comment of one patient illustrates this: *that she found it difficult to contemplate daily trips for radiotherapy, saying that it was almost worse for her than the diagnosis or the operation.*

Thereafter, the trends over time can be seen in Figure 48, with a statistically significant proportion of 18% in the radiotherapy group compared with, as would be expected, none in the no radiotherapy arm. Individual patient comments included phrases ranging from *anxious at first, agitated the week before, scary at first, to quite anxious and irritable during treatment*, all suggestive of fairly short-lived effects. Other comments implied a rather longer term impact, such as: *tense and easily weepy throughout, very anxious and irritable for weeks, emotionally exhausting, dreadful emotionally, saying she never wanted to go through that again and saying that it would take a while to put the experience behind her.*

Proportions relating negative emotions about irradiation steeply reduced towards the 9-month stage in the radiotherapy group and reached very similar minimal comment to the no treatment arm at the last two follow-up points. At the last two stages, comments were made by one patient on each occasion in the no treatment arm on lingering negative emotions relating to

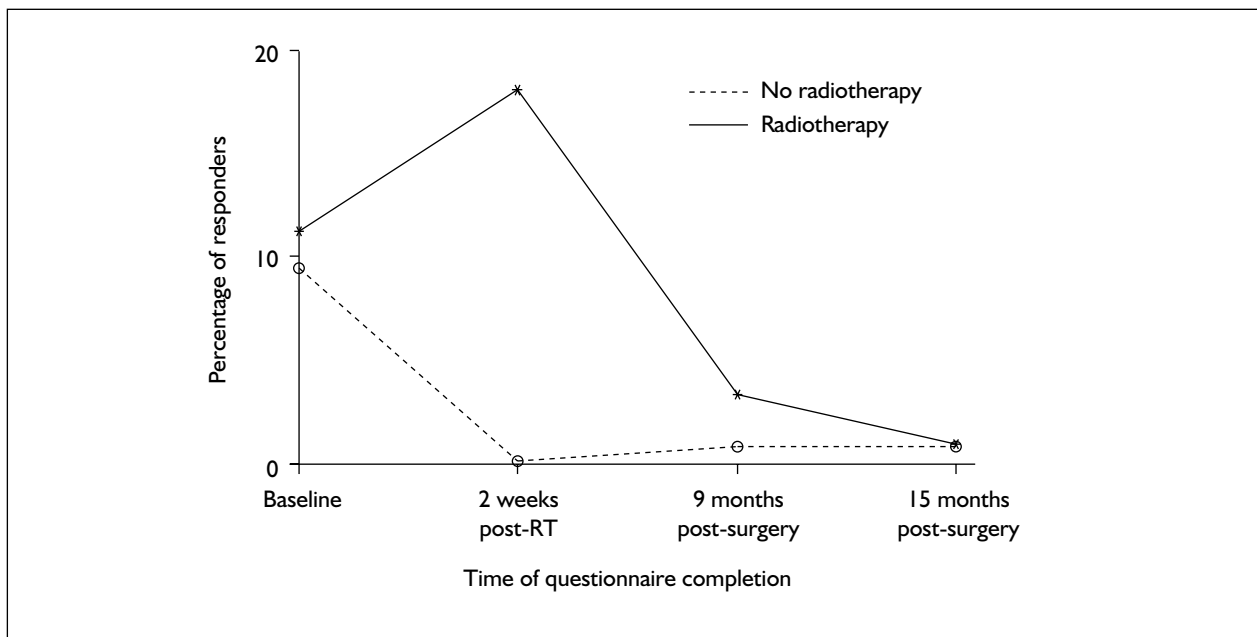


FIGURE 48 Percentage of patients reporting negative emotional effects associated with radiotherapy

radiotherapy, expressing gratitude that she had not had the treatment.

Fatigue

Comments made about fatigue were made by women in both groups. Statements included in this category ranged from *not too tired, slightly more tired, tiredness, so tiring, wearing, weariness, so tired towards end, quite tired to sleeping a lot, so exhausting it just sometimes overwhelmed her, so tired concentration was going* and *physically exhausting*.

A fuller statement by one patient highlights what, for a significant proportion, was a tiring experience: *during the last 2 weeks of treatment she felt as if she was sleep-walking! She really did very little else apart from spend 4–6 hours every day getting to and from the treatment and then recovering. She did very little else at weekends apart from one shopping and one church visit.*

As can be seen from *Figure 49*, approximately 30% of the women with radiotherapy volunteered comments about fatigue at 2 weeks post-treatment compared with 2% of the no radiotherapy patients at the post-treatment questionnaire ($p \leq 0.0001$).

At 9 months post-surgery, comments about fatigue were being made by around 10% of the women receiving radiotherapy and by 3% in the no treatment arm ($p = 0.008$) compared with 5% and none in the corresponding groups at 15 months.

Skin effects

Women in the radiotherapy group volunteered some concerns about skin effects (*Figure 50*), with almost 30% of them at the 2-week post-radiotherapy stage doing so, with a few in the no radiotherapy arm ($p \leq 0.001$). This steeply reduced to similar levels of skin irritation in the two groups at 9 months, suggesting that comments on skin effects from radiotherapy quickly diminished until 9 months and then decreased at a slower rate to 15 months, when the same level as the no radiotherapy patients was reached.

Breast pain

This symptom was mentioned and attributed to radiotherapy by less than 5% of radiotherapy patients in the early weeks after radiotherapy and only one patient in the no radiotherapy group at the same stage. It was not mentioned thereafter.

Nausea/appetite change

Just 2% of the radiotherapy group of women mentioned that nausea had affected them during or after radiotherapy, although there was no mention of it in the no radiotherapy group.

Cosmetic/breast texture effect

Approximately 2% wished to talk about the acute cosmetic effect of radiotherapy in the post-radiotherapy questionnaire. It was reported exclusively in a few women who had severe skin reactions requiring dressings and who could not, temporarily, wear a bra. Approximately the same

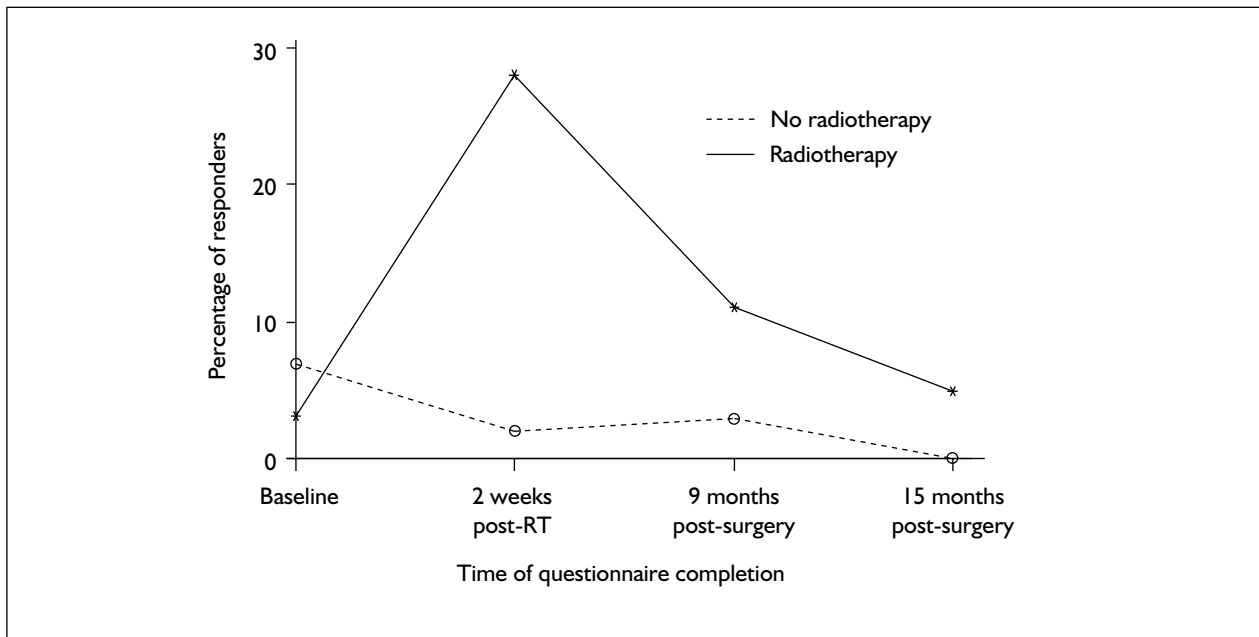


FIGURE 49 Percentage of patients reporting fatigue

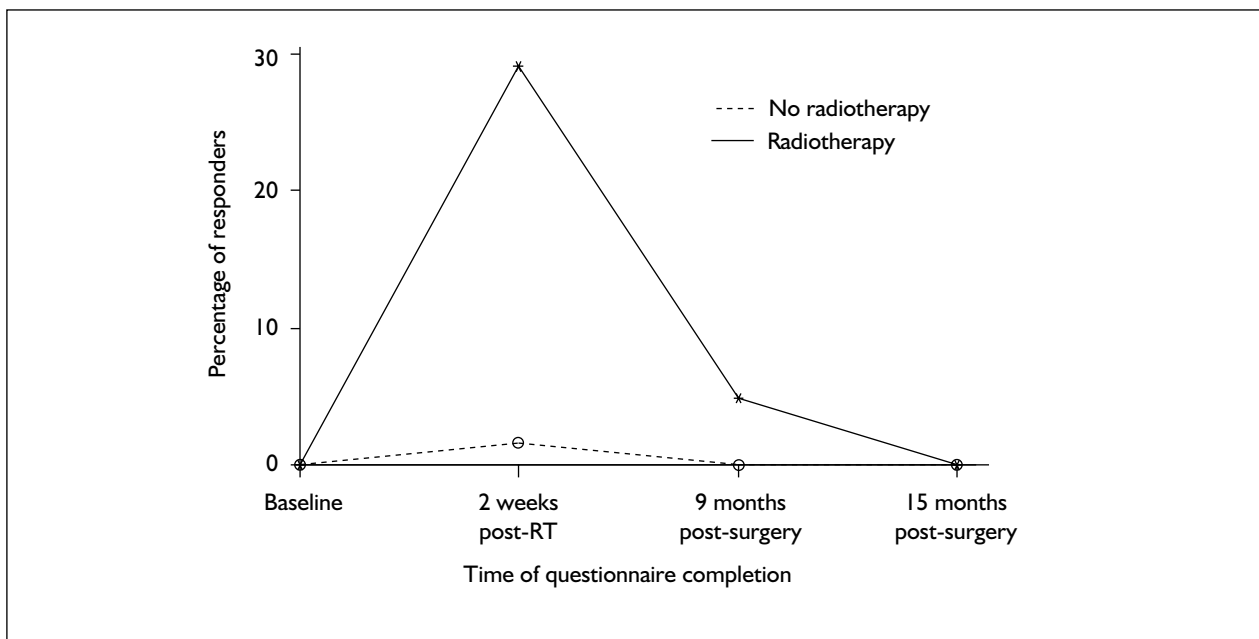


FIGURE 50 Percentage of patients reporting skin effects

proportion were concerned at the 9-month post-surgery stage about some change in the colour or texture of the breast and these effects were not mentioned at the final questionnaire.

Psychologically negative

Around 10% of patients in the radiotherapy group made reference to a psychologically negative effect of radiotherapy 2 weeks after completing radiotherapy treatment. This was highlighted by only one or two women at the 9- and 15-month follow-up stages.

Psychologically positive

Approximately 6% mentioned some positive psychological outcome of having had radiotherapy, although this was only reported at 2 weeks post-radiotherapy and is not mentioned at all at any other time point. One patient commented: *that in some ways she was quite grateful to have had radiotherapy, as perhaps a possible extra precaution, in what seemed to her to be quite a sneaky disease – where people like herself could feel quite well, not even knowing they had a problem. All the while it could be developing. She probably would have said no to*

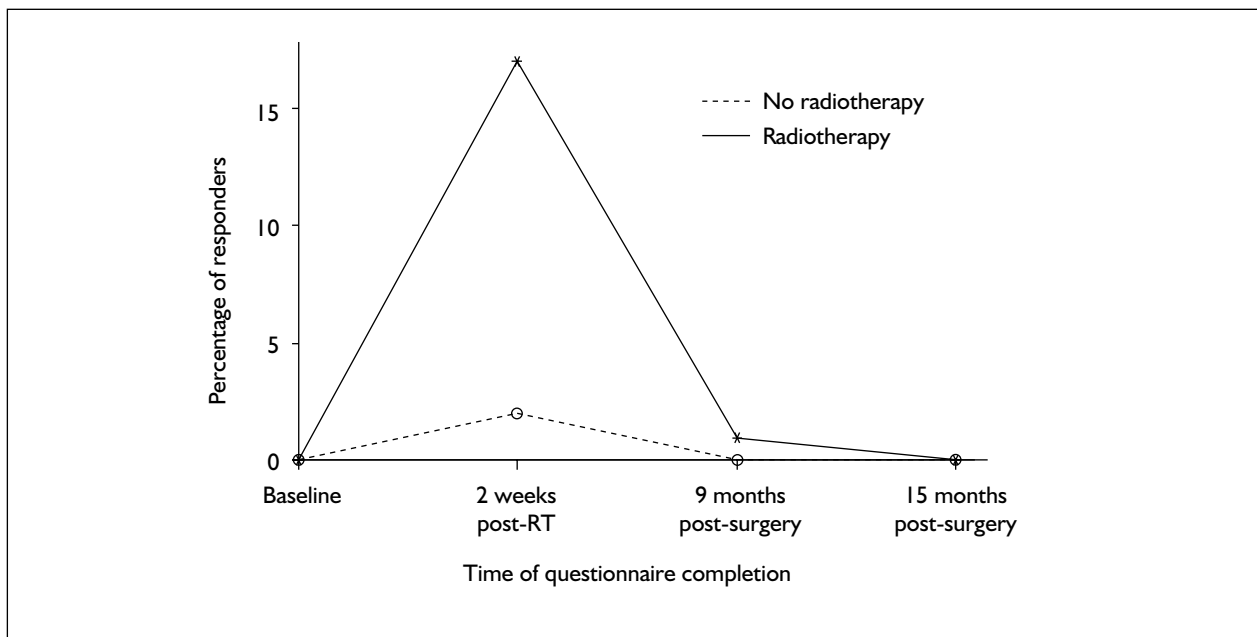


FIGURE 51 Percentage of patients reporting negative impact of hospital environment

radiotherapy had it not been for the trial. This sentiment was echoed by several patients.

Hospital environment negative

The significantly greater number of patients in the radiotherapy group commenting on the negative impact of the hospital environment is mainly a result of daily visits over several weeks (Figure 51). The women's comments largely related to feeling affected by seeing the number of people attending radiotherapy/oncology departments daily, the severity of illnesses noticed and the young age of some patients. Some of the comments referred to the environment of the radiotherapy simulator suite.

The following statement from one patient was typical: *she found lying on the low couch in the semi-darkness and having to keep so still for the measurements quite worrying – especially since she was a bit claustrophobic and kept imagining the machines were going to come closer than they actually did. She didn't like it when the staff went out of the room and was always so relieved when the little noise that came at the end of each treatment was to be heard. She said it wasn't so bad as time went on though – she got less anxious as she got used to it. She did get a bit down one day when she met this young, very attractive lady who had obviously had a recurrence and was having radiotherapy after chemotherapy. But overall it was okay.*

Travel to radiotherapy centre

There were only a few comments expressed on this potential problem at baseline.

At the time of the second questionnaire, occurring about 2 weeks after radiotherapy was complete, 29% of irradiated patients volunteered a negative effect related to travel. Most of these comments were made by women who were living a great distance away from the treatment centre or who were dependent on transport being provided, either by the Ambulance Service or a charity vehicle/volunteer driver.

Some of the women expressed discomfort from the whole experience of travel, with one saying that she thought: *the travelling in that dreadful minibus was awful – there were 11 of them jam-packed into the rickety thing and some of the drivers didn't even have a toilet stop. Some of the people had been travelling more than an hour before getting into it and then there was another 2 hours added on. They were just not comfortable.* This was not an isolated comment and similar spontaneous comments were made by women doing these lengthy journeys very early on a Monday morning and returning on Friday afternoon/evening. However, one patient who had fewer people travelling with her in this particular mode of transport said: *she had quite enjoyed the trips in the minibus.*

Some made use of transport provided by the NHS and the following excerpts might serve to illustrate their dissatisfaction: *very long waits; frustrating wait; second last day ordered a taxi; frustrating – hanging about when treatment took such a short time; waiting around needed a lot of patience; some days the whole*

process took 6 hours if the transport had to do a major detour.

Some women chose to make their way to treatment by public transport, particularly in the north of Scotland. For one patient this meant: *travelling took between 4 to 6 hours every day, she was stuck in snow for 4 hours one day.*

For others volunteering comments on travel effects, they either drove themselves or were driven by a friend or relative in their own transport. The effects described by these women were often about the difficulty of parking anywhere near the hospital: *a bit of a daily bind; her husband came because of parking.* Some looked at the problem more positively: *they soon got the knack of double parking and waited until someone came out of the earmarked spaces for treatment patients.*

Accommodation

Comments on this topic were made almost exclusively by women who required accommodation to be provided between the Mondays and Fridays of their treatments, and who then travelled home at weekends.

About 4% of the women commented on the excellent quality of the accommodation provided, but 11% of the total volunteered negative comments about the location of the accommodation. What affected all of the women who commented about the location was that: *the pavements and bus stops were very narrow and dangerous from the accommodation and they needed to change buses to reach the hospital.* Another commented that: *the pavements were narrow and the traffic scary.*

Lack of communication about the accommodation arrangements was, for some patients, a source of distress. One of several comments was that: *she had set off on the first day not knowing where she would be staying, which was not a nice feeling.* After one patient's first treatment: *she was told to go to a particular house within the grounds of the hospital but as she was settling in, she was informed she'd been put in the wrong room and as a result had to move to a ward.*

For some, it was other patients who caused them distress, either because of sharing a room or being in a ward: *for the first week she hardly slept at all. By the Friday she was in tears with exhaustion. She was on the verge of giving up treatment because of it. Each week she didn't know where she was to be. Sometimes she was in a ward overnight and on one of them she was put*

opposite a lady who looked very ill and was calling out in distress. She told one of the nurses she was finding this too difficult. They understood but were not able to move her until much later in the day. The nights she was in a ward she didn't sleep much either.

One patient commented positively about the ward accommodation, saying that: *the ward was OK and that she was able to come and go as she liked as long as she told someone.*

Effect on lifestyle

From Figure 52, it can be seen that nearly 20% of the radiotherapy group spontaneously gave information on the impact of radiotherapy on their lifestyle in the preceding few weeks.

Comments, in the case of those near enough the treatment centre to attend daily, ranged from: *difficulty planning anything, disruption to life, quite a chunk out of every day,* to one of several comments from women around 30 miles distant, saying that: *it just seemed to take over her life for several weeks – travelling back and forward to the hospital every day.*

Ongoing lifestyle effects of radiotherapy were not mentioned during later questionnaires, suggesting that the impact of radiotherapy in this respect was short term.

Effect of breast cancer/radiotherapy on family and friends

At baseline, 41 (16%) considered there had been negative effects on their family and friends, causing them to be anxious or worry, and five (2%) thought there were some positive effects such as increased contact with them.

In the radiotherapy group, just over 15% of the women related the impact (as they perceived it) which radiotherapy had had on their family, such as driving them to hospital, making arrangements to have spouses cared for if the patient was the main carer and rearranging holidays. The impact was in most cases of short duration and not mentioned at later assessments.

Overall professional care

Negative

At baseline, only five (2%) mentioned some negative aspect about the professional care received.

Positive

At baseline, in contrast, 39 (15%) commented positively on the professional care they had received, many praising the staff who had looked after them. One patient stated: *she'd been very*

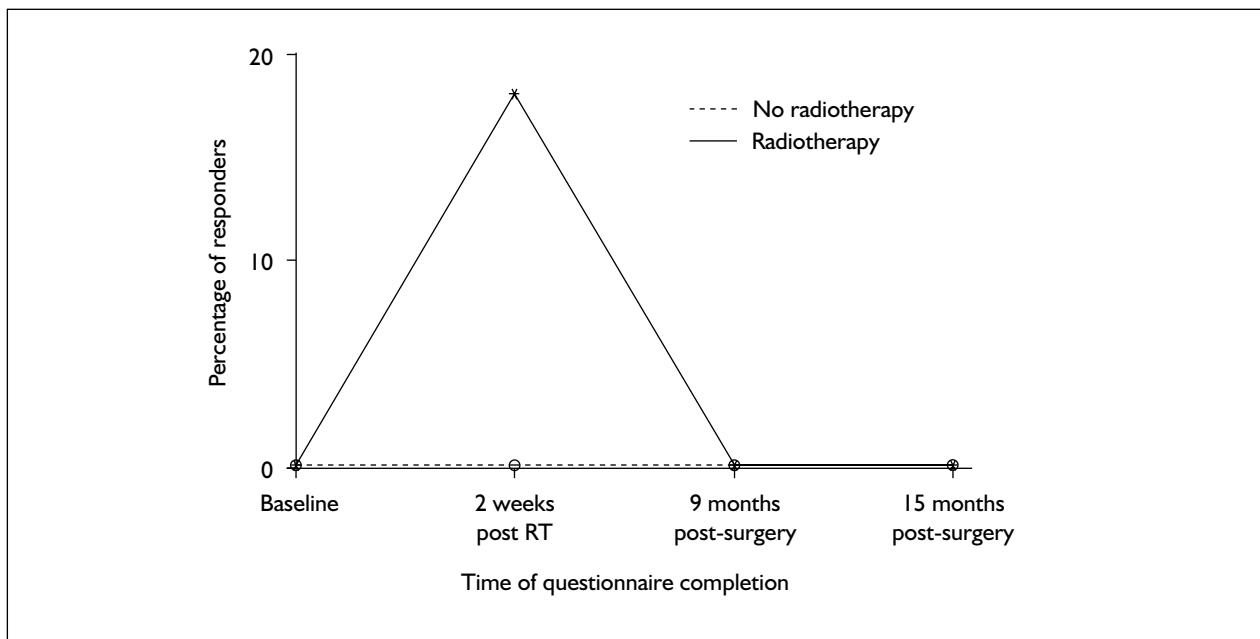


FIGURE 52 Percentage of patients reporting adverse impact of radiotherapy on their lifestyle

TABLE 12 Positive professional care at 2 weeks post-treatment

Professional care positive	
Treatment	2 weeks post-treatment
Radiotherapy	31/127
No radiotherapy	4/123
	$p < 0.0005$

impressed with the efficiency, professional yet caring and friendly attitude with which she'd been treated. She had been particularly amazed that medical and nursing staff offered someone of her age (late 70s) surgery: but it had been pleasing that she had been valued even at her age. She had been involved in all the decisions made and her questions and opinions respected and she'd liked that.

Although starting at very similar proportions in both groups, at 2 weeks post-treatment, the number of comments on positive professional care was significantly higher in the radiotherapy group, following the daily opportunity of contact with professionals which was not available to those in the no radiotherapy arm of the trial (Table 12).

This difference was not evident at 9 and 15 months.

Care received by women from family and friends

At completion of the first questionnaire, 46 (18%) commented on very positive attention from

friends and family, describing both emotional and practical support. This was mentioned at 2 weeks after treatment by a higher, but not statistically significant, proportion (13%) in the radiotherapy arm compared with the no radiotherapy group (7%). At later questionnaires there was little reference to this.

Sexual issues

At baseline, two (1%) volunteered that breast cancer diagnosis had reduced their interest in sexual relationships and approximately the same small proportion of comment was observed at each follow-up point in both groups.

Spirituality

Seven (3%) chose to mention spiritual issues during the first and second questionnaires, either because they noticed these had not been mentioned in the questionnaire and/or because their faith had been important and helpful during their experience of breast cancer.

Mortality/life expectancy/vulnerability

At baseline, 19 (8%) women commented that the diagnosis had made them think about these issues.

The comments of one patient were: *it hadn't really affected her that much physically on a day-to-day basis but it had given her an awareness of her vulnerability. When she was young she thought that nothing like this would happen to her. It had given her a bit of an awakening.*

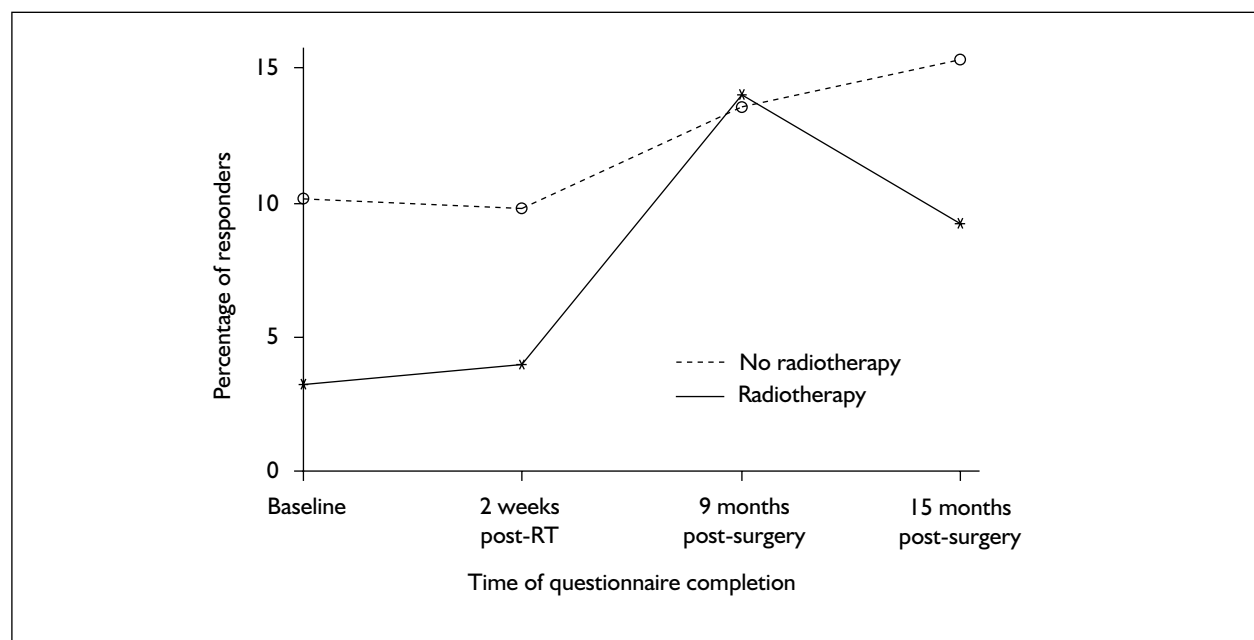


FIGURE 53 Percentage of patients reporting co-morbidities exceeding the effect of breast cancer

There were no significant differences between the groups and mention of this was made in smaller but ongoing proportions during the follow-up period.

Co-morbidities

There was a difference at baseline, despite randomisation, between the groups in the proportions choosing to comment on another significant illness or condition which they were managing in addition to breast cancer, for example loss of vision, arthritis and cardiac or respiratory problems. Invariably, when highlighted here, the other condition was stated to be having more life impact than breast cancer had so far (Figure 53). There were no significant differences between groups at any of the later follow-up points. The radiotherapy group commented less frequently on coexisting diseases initially. Interestingly, they showed a larger increase at 9 months after treatment before a fall in the proportion reporting co-morbidities at 15 months whereas the no radiotherapy group continued to increase gradually to 15 months.

Additional life circumstances

For some women, the diagnosis and surgery had been a very stressful time, but 42 (17%) volunteered that they were dealing with a serious additional life circumstance at the time of diagnosis (Figure 54). For some, this was a serious illness, recent bereavement of a close family member, divorce or moving house. Being a carer

for a husband or other relative was also mentioned and these women felt that breast cancer was affecting them less than the other circumstance. One patient reported that: *compared to a lot of other things that were happening in her life, breast cancer had been relatively straightforward.*

There were no differences between groups and this was mentioned by only a few patients at later stages, presumably since it had been mentioned at the beginning and had an ongoing effect for most of those who had raised it. In a small proportion (<2%), a serious adverse life circumstance arose and was commented on during the follow-up period.

Concern about cancer recurrence

At baseline, six (2%) mentioned the possibility of the cancer coming back as being something which affected them. One whose cancer had not been discovered by herself commented: *that she hadn't had any symptoms before it was diagnosed and therefore it could easily come back without her knowing.*

At 2 weeks after treatment, a significantly smaller proportion in the radiotherapy group ($p = 0.013$), commented on cancer recurrence. This may reflect the fact that the group who had recently received several weeks of treatment were feeling 'protected' by the irradiation. As can be seen from Figure 55, the proportions thereafter were similar between groups and at 15 months around 15% were mentioning concern about recurrence.

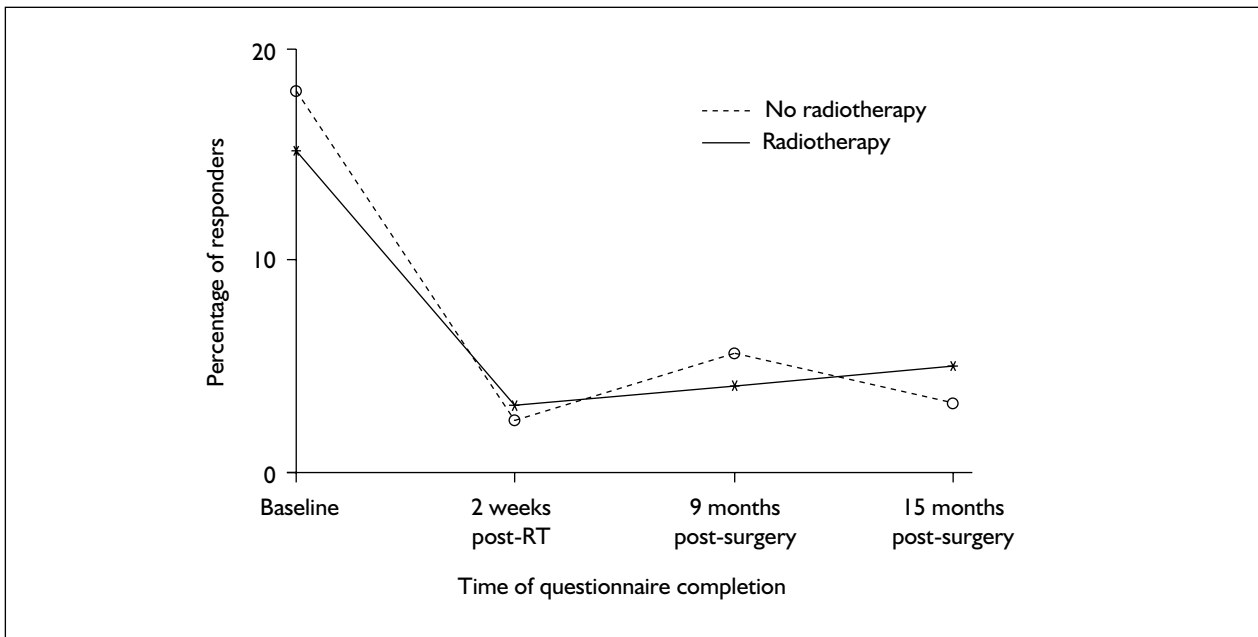


FIGURE 54 Percentage of patients dealing with additional serious life circumstances

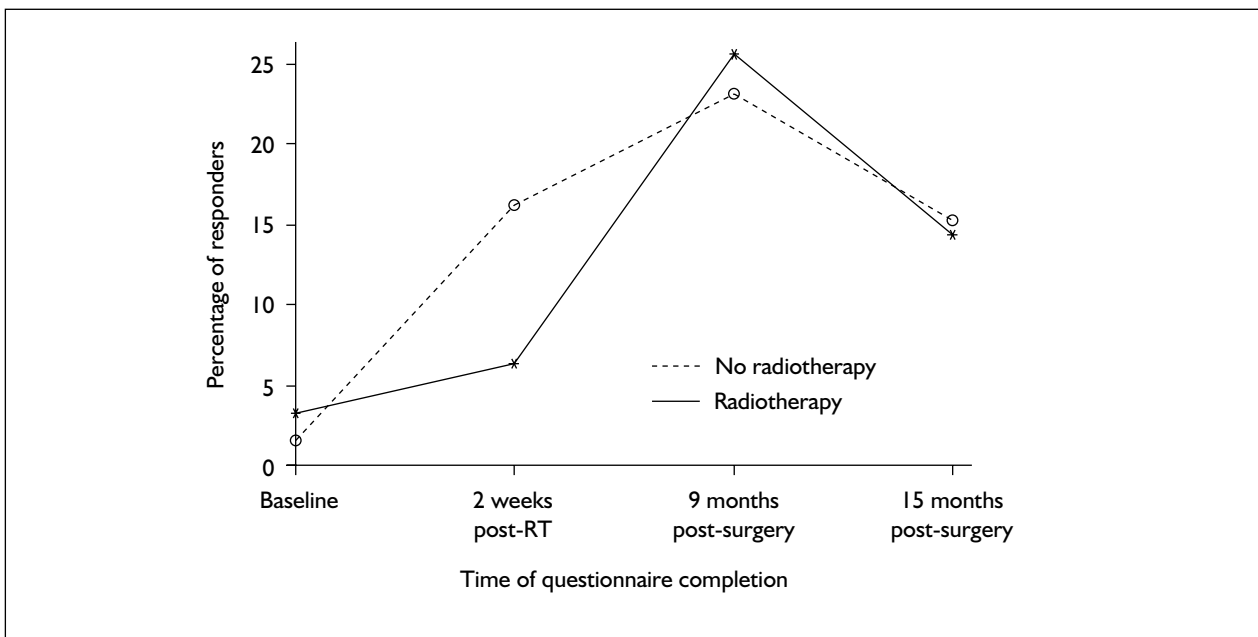


FIGURE 55 Percentage of patients expressing concern about cancer recurrence

Anxiety about the process of clinical follow-up

As follow-up progressed, an increasing proportion of patients spontaneously volunteered anxiety about the process of clinical follow-up. The proportions were consistently higher in the no radiotherapy group (Figure 56). Some of the anxiety mentioned here in relation to follow-up may arise from concern about recurrence.

Investigations for potential recurrence

Figure 57 illustrates the proportion of patients who mentioned some form of investigation. These were only mentioned at the 9- and 15-month stages, usually in conjunction with symptoms which could potentially be attributed to recurrences. As can be seen, there was no difference between groups but at 9 months around 10% related some procedure for investigation of

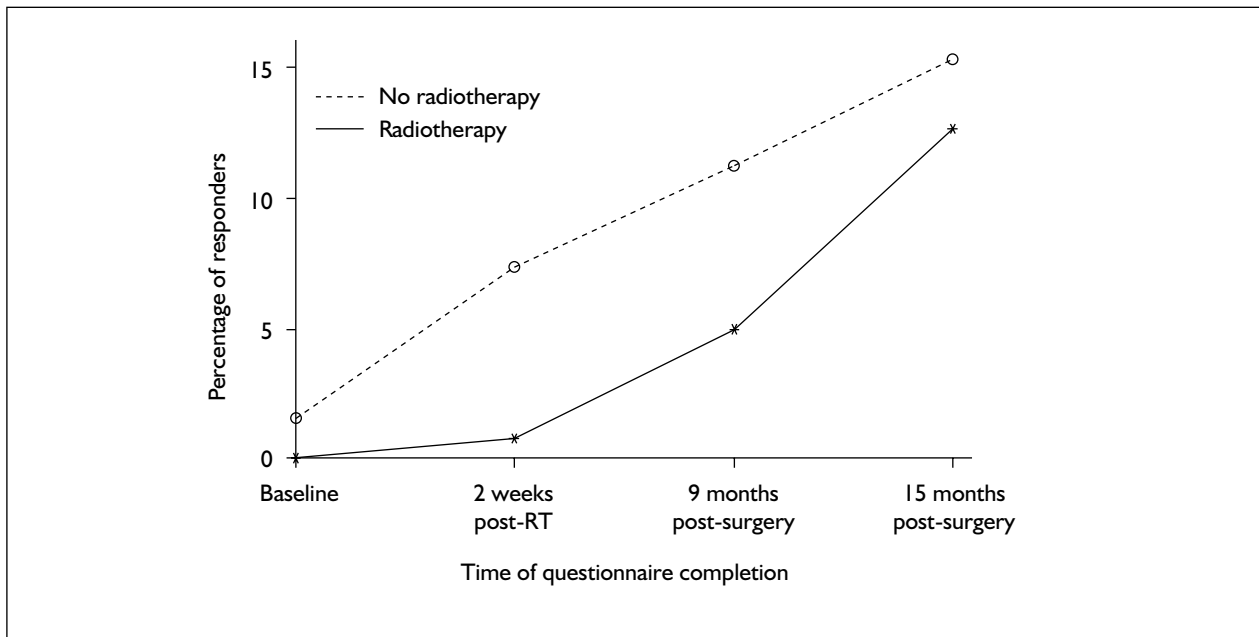


FIGURE 56 Percentage of patients expressing anxiety about clinical follow-up

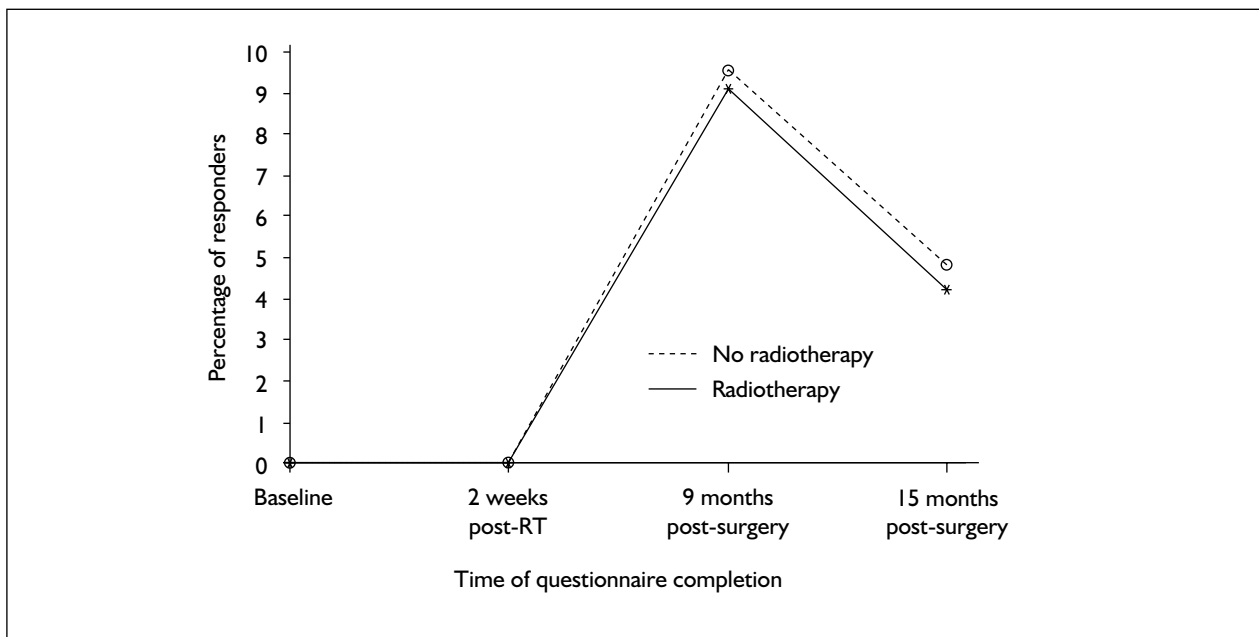


FIGURE 57 Percentage of patients reporting investigation of symptoms potentially related to recurrence

potential recurrence (although none were detected).

Activities

At baseline, approximately 7% volunteered that breast cancer had had a negative effect on their activities to date. This proportion gradually reduced to less than 3% in both groups, without significantly different proportions in either arm of the trial. For example: *swelling under the arm has*

stopped me doing things. I can't move my arm comfortably or blow dry my hair.

Media

Three patients (1%) at baseline mentioned some aspect of the media which had affected them, with a slightly higher proportion at later follow-up points (4%). Some made comments like: *she would perhaps see an advert about breast cancer or an item in a newspaper or magazine and she would think – oh*

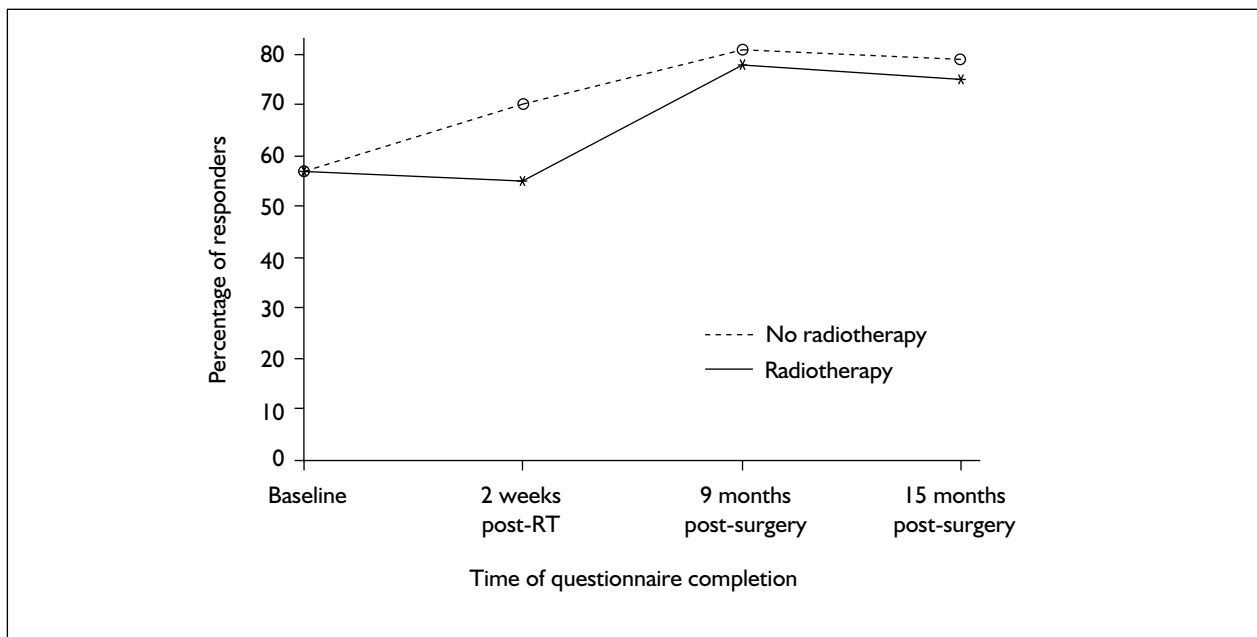


FIGURE 58 Percentage of patients reporting that their cancer had had no effect on their relationships

she'd got that and then she would forget about it again and get on with life.

Research

At baseline, 24 patients (9%) raised some negative aspect related to the research study, usually with regard to their decision about whether or not to participate. One patient illustrated: *that she had received confusing messages about the radiotherapy. Her GP had really advised her to have it, the surgeon thought she didn't need it and the cancer specialist was unsure. She had found it quite difficult having the decision left to her.*

Another commented that: *she couldn't decide whether to take part in the research or not but decided to go for it because she was terrified to have the radiotherapy but also scared to miss it out. So she was going to let the computer decide and accept the decision.*

Thirty-four patients (13%) mentioned some positive aspect to the research, often about being able to provide better information for women or female family members and staff in the future. Others commented on: *doing her bit for medical science or participating in appreciation of the professional care she had received.*

Another patient thought: *that somebody had to help with research to improve things and so she was prepared to accept either treatment. She didn't feel strongly about one or the other.*

Relationships

- *Do you think that your diagnosis of breast cancer has affected your relationship with others?*

No effect on relationships

More than half of the patients at baseline (144, 57%) stated that breast cancer had had no effect on their relationships (Figure 58). The proportions reporting "no effect" at 2 weeks after treatment time were significantly lower in the radiotherapy arm ($p = 0.016$) and then the proportion increased substantially to around 80% at the 9-month stage in both groups, remaining at around the 75% point at 15 months. The following sections shed light on these data.

Positive effect on relationships

Despite proportions of around 30% reporting on this from both groups at baseline, at 2 weeks post-treatment or equivalent, women who had received radiotherapy reported significantly more instances of breast cancer having a positive effect on relationships ($p = 0.001$, Figure 59). In many instances, this may be attributable to patients having daily escorts, who might be family, friends or ambulance staff. A few women reported developing friendships with other patients also. The effect was later commented on much less often in both groups.

One lady suggested: *they had all talked a lot more as a family – about the past and the future and that can only be good.*

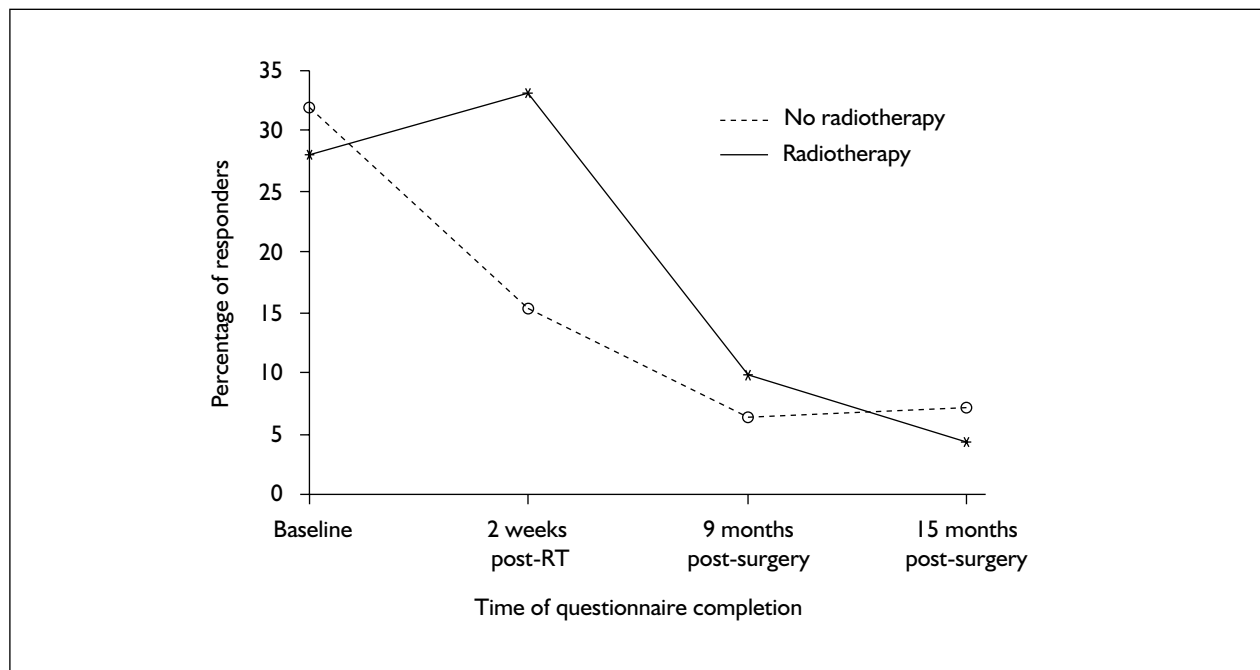


FIGURE 59 Percentage of patients reporting that their cancer had had a positive effect on their relationships

Another considered that: *some people she had become much closer to – to God and especially one of her daughters who had been very supportive.*

whatever and some had been very dramatic and tearful. She said she hadn't expected to be affected by the different reactions as much as she had been.

Negative effect on relationships

Forty-four (17%) at baseline replied that breast cancer had had a negative effect on relationships and in how they felt they could interact with other people: *she felt at first that she wanted to cut herself off from people until she got things sorted out in her own mind. Then, when she managed to get over that hurdle, she talked to the people she thought would be easiest to tell first and then gradually got better at it. It really hadn't been so difficult.*

Others found it took longer for them to return to other than close family relationships: *she had been completely floored at first. She had wanted to hide away from everyone. She had been afraid she would cry when people spoke to her. At first she had avoided people – for about 4 months (during preoperative endocrine therapy). She had been very emotional and hadn't wanted people to see her like that. Apart from her husband and daughters, she hadn't wanted to see anybody. Only recently had she been able to relax with people other than her family.*

Some perceived differences in how others related to them. One had found: *it was surprising to learn how different the reactions of friends and family were to the news of her illness. Some had changed the subject, others had hesitated and carried on with their lunch or*

Other events

After completion of the standardised scales, a question was posed to put the QoL questionnaire into the wider context of the women's lives rather than focusing on their breast cancer experience alone. Some women had mentioned additional life circumstances earlier in the questionnaire, but the opportunity was given at the end to mention anything which they considered was having a major impact.

- *Apart from your recent breast cancer, have there been any events in the last six months that have had a major impact on your life?*

Other major impacting events

At baseline, the majority 160 (63%) reported they had had no major life-impacting experience in the last 6 months. Despite randomisation, there was a difference in the number of patients who answered they had had no major impacting events in the previous 6 months, with fewer allocated to no radiotherapy reporting no events (54 versus 76%). In no other questionnaire did this variable show statistically significant differences.

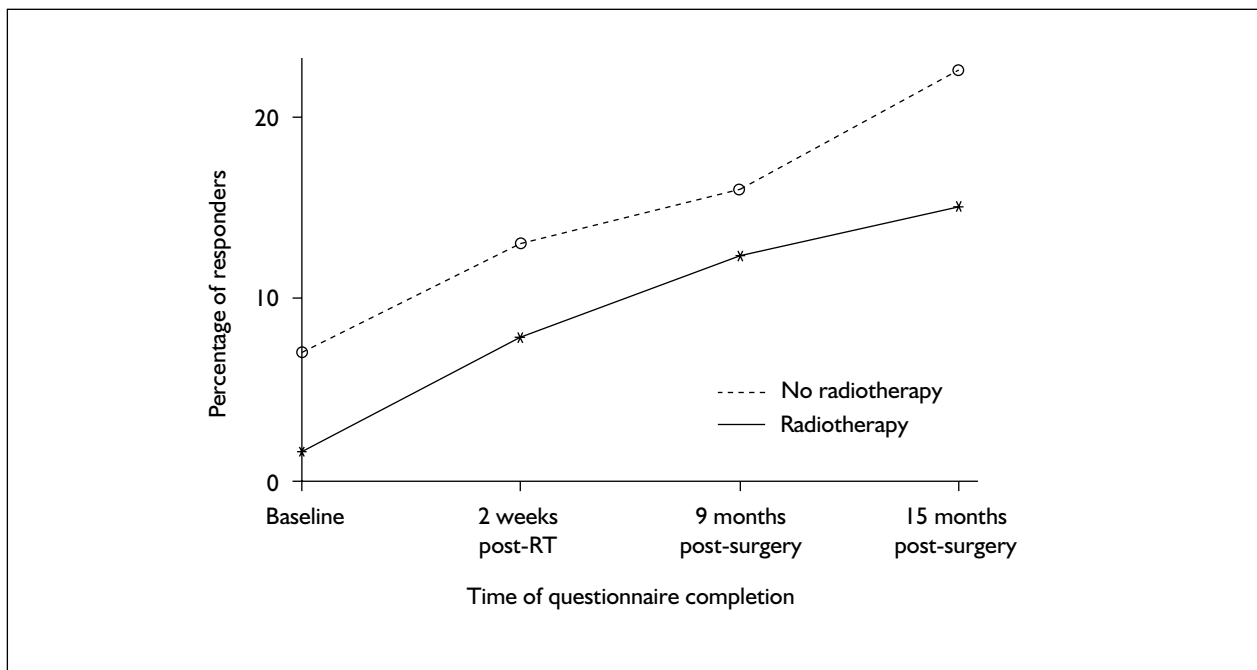


FIGURE 60 Percentage of patients reporting co-morbidity to have a major impact on life

Positive impact event

Six (2%) reported an event which had had positive impact on their lives, such as a first grandchild being born or a 'holiday of a lifetime'.

Negative impact event

Eighty patients (32%) cited some major impacting negative event at baseline, such as a significant and recent bereavement, serious illness of a close relative/friend, co-morbidity or moving house. Less frequently mentioned life-impacting events were, for some patients in rural areas, the 'foot and mouth' crisis. Severe problems in relationships either with family or neighbours or of their close family were also mentioned.

A difference in the total number of patients reporting negatively impacting events was observed between the groups at baseline, with a lower proportion reporting these in the radiotherapy group. This might have affected the QoL scores within the formal scales. For example, the majority of the difference at baseline was accounted for by incidences of a life-impacting co-morbidity and of bereavement. These differences were not observed to be significant at the two intermediate questionnaires. However, at the 15 months from surgery questionnaire, the women in the radiotherapy arm reported a significantly lower number of life-impacting co-morbidities ($p = 0.04$) (Figure 60).

Comments

- *I would like to give you the opportunity to ask any questions or to make any comments about the study*

Questions or comments about the questionnaires/research

At baseline, 183 (64%) made comments or had questions about the study.

Forty-six (18%) had comments/questions about particular items in the questionnaire or about difficulty in coming to a 'yes' or 'no' answer in the PGCMS.

Thirty-eight (15%) asked for more detail about how the randomisation process was done or when the outcome would be known. Ten (4%) of the comments were positive ones about having the opportunity to ask questions in relation to the patient information sheet or oncology consultation prior to consent.

A few women wanted more information about the clinical photography aspect of the trial and 21 (8%) wished these were reminders about the timing of future clinical follow-up or QoL questionnaires.

Small numbers of women were interested to know about some aspect of methodology in the research,

how the analysis of all the data would be done or by whom. This query increased to the level of 7% over time.

Some commented positively on the research nurse contribution or expressed appreciation of the home visit. This appreciation was expressed by 30% at the last questionnaire compared with less than 5% at the baseline.

There were two (1%) negative comments about the research, which referred to waiting for the randomisation outcome. Twenty-three (9%) positive comments were made, mainly about pleasure in helping people in the future. Finally, three (1%) of the women commented on or objected to the use of the word 'elderly' in the research title.

Questions or comments about radiotherapy

Sixty-five women in total (26%), at the first assessment, asked about some aspect of radiotherapy, with 40% of the radiotherapy group compared with 15% in the no radiotherapy arm; some of these questions were asked of the interviewer after the outcome of the randomisation had been given to the patient.

Ten women (4%) questioned when or how they would be informed of dates for radiotherapy (if they were to have it) or waiting times for their centre. Twenty-one (8%) wished to know more about the radiotherapy procedures. Eight (3%) wanted further clarification about potential side-effects from radiotherapy, 20 (8%) asked about some aspect of transport and six (2%) about accommodation, if having radiotherapy treatment. That such a high proportion asked about some aspect of radiotherapy at baseline probably reflects the well-known fact that information is difficult to absorb while potentially anxious at hospital appointments and that, unlike patients not participating in the trial, they would not have known whether they were to have radiotherapy and might have asked more at the appointment, if known.

Endocrine therapy questions

Thirty-one (12%) had questions about some aspect of hormone treatment, with the proportions consistently but non-significantly higher over time in the no radiotherapy arm.

Other questions/comments

At baseline, a few women asked the interviewer about their breast or axillary wound, about

benefits or about home aids. A small number at this point made very positive comments about the professional care they had received by the interviewer or other staff. One had a question about mammography and 3% asked about causes or risk factors for breast cancer. Where the interviewer had competence to answer the questions, she did so. In some situations, for example, after observing a breast wound at the request of the patient, advice might be given to contact a GP or appropriate hospital professional to assess and treat symptoms suggestive of infection.

Interviewer comments

• Interviewer's comments

In 117 (46%) of baseline questionnaires, 92 (37%) of second, 105 (43%) of third and 112 (46%) of fourth questionnaires, there were no interviewer comments. There were no differences between groups.

At baseline, 65 incidences (26%) of some action taken by the interviewer were recorded, either answering a question, giving information or advice about follow-up appointments, looking at a patient's wound when requested or giving direction on appropriate referrals. This increased to 36% at the post-treatment questionnaire in approximately the same proportions in each group. The actions mainly consisted of making sure subsequent follow-up appointments were arranged or answering patient questions. At the 9-month questionnaires, interviewer actions were recorded at around 30%, exactly the same in each group. At the final questionnaire, the proportion was 33%.

At baseline, 25 interviewers (10%) recorded that another person was present but remained silent during questionnaire completion and two (1%) commented that the other person occasionally interrupted. The proportion at later questionnaires gradually reduced to less than 1%.

On nine occasions (3.5%), interviewers mentioned a protocol error at baseline, in which the patient had been told the outcome of randomisation, prior to questionnaire completion.

In 14 questionnaires (6%), there was comment on a longer or shorter than expected time gap from surgery to questionnaire completion.

Chapter 8

Clinical outcomes

Acute and late morbidity

Figure 61 records the number of forms returned to the trial office at each of the standard clinical follow-up visits.

Acute morbidity

Acute morbidity was collected at the first clinical visit after radiotherapy (or equivalent), using the RTOG/EORTC scales for soft tissue and lung complications (see Appendix 5). A score of zero indicated no complications, while a score of four indicated serious complications. A score of five was recorded when death resulted from the complications, although this never occurred in the trial. The Cochran–Armitage test for trend or Fisher’s exact test was used for analysis.

Skin

Table 13 shows the number of patients with each level of acute skin reaction (approximately 2 weeks after the end of radiotherapy or equivalent).

Treatment had a significant effect on the score ($p < 0.0001$).

Lung

Table 14 shows the scores recorded for the lung reactions (cough, etc.) at the first clinical visit.

We observe that although lung morbidity in the no radiotherapy groups was reported in two cases, there is no statistically significant difference between the treatment groups ($p = 0.26$, Fisher’s exact test). Mild problems (“dry cough, dyspnoea on exertion”) were observed in 5% of those in the radiotherapy group.

Late morbidity

The late effects of radiotherapy were recorded at 8 and 12 months after surgery, again using the RTOG/EORTC scales (see Appendix 5). As with the acute morbidity scales, a score of zero indicates no problems, and a higher score would illustrate increasing problems. For the scales assessing management (i.e. oedema management, ulcer management and atrophy management), only cases where medical or surgical intervention had been necessary were recorded. The number of entries in the tables for late morbidity are less than the number of patients attending the corresponding clinic visits. The discrepancy arises from forms that were not returned or were not fully completed.

As with the acute data, the Cochran–Armitage test for trend or Fisher’s exact test were used to analyse the data.

TABLE 13 Skin morbidity at the first clinical visit after radiotherapy (or equivalent)

Skin score	Radiotherapy (121)	No radiotherapy (124) ^a
0: None	31	120
1: Faint/dull erythema	63	4
2: Tender erythema, moderate oedema	25	0
3: Confluent desquamation	2	0
	$p < 0.0001$	
^a Score not recorded for one patient.		

TABLE 14 Lung morbidity at the first clinical visit after radiotherapy (or equivalent)

Lung score	Radiotherapy (121)	No radiotherapy (125)
0: None	115	123
1: Dry cough, dyspnoea on exertion	6	2
	$p = 0.26$	

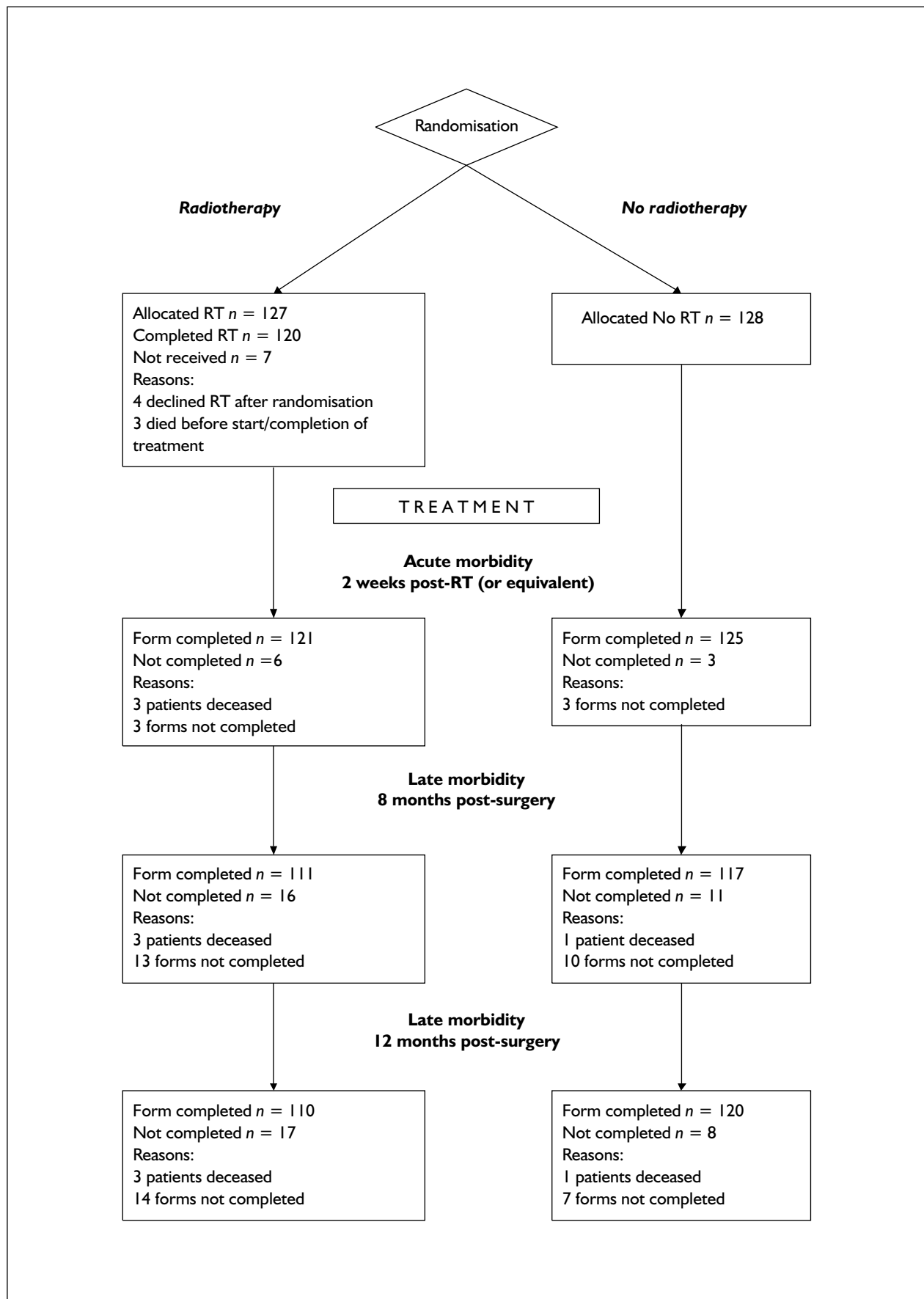


FIGURE 61 Number of morbidity forms completed

Breast oedema

This is defined as an abnormal collection of fluid in the tissues, causing a puffy swelling.

At both time points (Tables 15 and 16), there is a significant effect from radiotherapy on the oedema score ($p < 0.0001$). One year after surgery, 26% of the radiotherapy group still have some degree of breast oedema compared with 6% of the no radiotherapy group.

Despite the differences in the oedema scores, there was no evidence of any treatment effect in oedema management at either 8 or 12 months or post-surgery.

Telangiectasia

This is the formation of a lesion in the breast consisting of a number of dilated capillaries which have a web-like appearance. The categories are based on the size of area affected.

At both time points (Tables 17 and 18), there is a similar and statistically significant effect from radiotherapy on the telangiectasia score ($p = 0.04$ and 0.01 , respectively).

Fibrosis

This is a measure of the formation of fibrous connective tissue in the breast.

At both time points (Tables 19 and 20), a significant effect is seen in the group receiving radiotherapy ($p < 0.0001$). At one year after surgery the prevalence of fibrosis was 44% in

TABLE 15 Breast oedema at 8 months post-surgery

Oedema score	Radiotherapy (111)	No radiotherapy (117)
0: None	76	109
1: Asymptomatic	28	7
2: Symptomatic	6	1
3: Secondary dysfunction	1	0
	$p < 0.0001$	

TABLE 16 Breast oedema at 12 months post-surgery

Oedema score	Radiotherapy (110)	No radiotherapy (120)
0: None	81	113
1: Asymptomatic	25	6
2: Symptomatic	4	1
	$p < 0.0001$	

the radiotherapy group compared to 6% in the no radiotherapy group.

Retraction/atrophy

This is defined as a wasting of the tissues, pulling back from the wound. Again, the categories are based on the proportion of the breast affected.

There is no evidence of a treatment effect at 8 months ($p = 0.46$, Table 21), but there is a highly significant difference at 12 months post-surgery

TABLE 17 Telangiectasia at 8 months post-surgery

Telangiectasia score	Radiotherapy (108)	No radiotherapy (116)
0: None	102	115
1: $< 1 \text{ cm}^2$	3	1
2: $1-4 \text{ cm}^2$	1	0
3: $> 4 \text{ cm}^2$	2	0
	$p = 0.04$	

TABLE 18 Telangiectasia at 12 months post-surgery

Telangiectasia score	Radiotherapy (107)	No radiotherapy (119)
0: None	101	119
1: $< 1 \text{ cm}^2$	1	0
2: $1-4 \text{ cm}^2$	2	0
3: $> 4 \text{ cm}^2$	3	0
	$p = 0.01$	

TABLE 19 Fibrosis at 8 months post-surgery

Fibrosis score	Radiotherapy (110)	No radiotherapy (117)
0: None	63	108
1: Barely palpable	30	4
2: Definite increased density	17	5
	$p < 0.0001$	

TABLE 20 Fibrosis at 12 months post-surgery

Fibrosis score	Radiotherapy (110)	No radiotherapy (120)
0: None	62	113
1: Barely palpable	32	5
2: Definite increased density	16	2
	$p < 0.0001$	

($p = 0.003$, Table 22). The prevalence of retraction was 20% in the radiotherapy group compared with 5% in the no radiotherapy group.

No form of atrophy management was required at either 8 or 12 months post-surgery.

Ulcer

This is a region where there is a breach in the continuity of the epithelium.

Only one ulcer was recorded in a patient in the radiotherapy group at 8 months post-surgery. The ulcer required medical intervention but had healed by the 12-month assessment.

TABLE 21 Retraction at 8 months post-surgery

Retraction score	Radiotherapy (107)	No radiotherapy (113)
0: None	95	104
1: 10–25%	11	8
2: >25–40%	1	1
$p = 0.46$		

TABLE 22 Retraction at 12 months post-surgery

Retraction score	Radiotherapy (105)	No radiotherapy (116)
0: None	84	110
1: 10–25%	21	5
2: >25–40%	0	1
$p = 0.003$		

TABLE 23 Pain management at 8 months post-surgery

Pain management score	Radiotherapy (110)	No radiotherapy (115)
0: None	88	105
1: Occasional non-narcotic	19	8
2: Regular non-narcotic	3	2
$p = 0.03$		

TABLE 24 Pain management at 12 months post-surgery

Pain management score	Radiotherapy (110)	No radiotherapy (120)
0: None	103	113
1: Occasional non-narcotic	6	7
2: Regular non-narcotic	1	0
$p = 0.68$		

Pain management

This records the steps to which a patient had to resort to control any breast pain which they may have experienced.

At 8 months post-surgery there was a significantly higher level of pain management in the radiotherapy treatment arm ($p = 0.03$, Table 23). By the 12-month visit the levels of pain management were similar in the two treatment groups (Table 24).

Lung

This is similar to, but not exactly the same as, the scale used for lung function in the acute morbidity form.

At 8 months post-surgery (Table 25) the only cases of lung morbidity were in the radiotherapy group (7%, Fisher’s exact test: $p = 0.005$). Most had resolved by 12 months post-surgery (Table 26), when there were only two cases in the radiotherapy group and one in the no radiotherapy group ($p = 0.94$).

Bone

This variable measures changes in bone structure, although it should be treated with caution as no bone scans were required. Any reports of problems were therefore symptomatic.

At 8 months post-surgery, there were three cases with grade two bone morbidity (moderate pain or tenderness, irregular bone sclerosis) (two radiotherapy, one no radiotherapy) but at 12 months there was only a single case with grade one morbidity (asymptomatic, reduced bone density) ($p = 0.95$ and 0.95 respectively).

TABLE 25 Lung at 8 months post-surgery

Lung score	Radiotherapy (110)	No radiotherapy (117)
0: None	102	117
1: Asymptomatic or mild symptoms	8	0
$p = 0.005$		

TABLE 26 Lung at 12 months post-surgery

Lung score	Radiotherapy (110)	No radiotherapy (119)
0: None	108	118
1: Asymptomatic or mild symptoms	2	1
$p = 0.94$		

TABLE 27 Proportion of surgical morbidities reported

Surgical morbidity	Radiotherapy	No radiotherapy	p-Value
2 weeks post-radiotherapy	7/126	9/128	0.80
8 months post-surgery	6/113	2/119	0.16
12 months post-surgery	2/111	4/123	0.68

TABLE 28 Proportion of endocrine morbidities reported

Endocrine morbidity	Radiotherapy	No radiotherapy	p-Value
2 weeks post-radiotherapy	1/126	8/128	0.04
8 months post-surgery	8/113	4/119	0.24
12 months post-surgery	6/111	2/123	0.15

TABLE 29 Proportion of radiotherapy morbidities reported

Radiotherapy morbidity (general)	Radiotherapy	No radiotherapy	p-Value
2 weeks post-radiotherapy	5/126	6/128	1.00
8 months post-surgery	10/113	2/119	0.02
12 months post-surgery	3/111	1/123	0.35

Reported treatment-related morbidity

In addition to the acute and late morbidity forms, a section in the follow-up form asked clinicians to record any morbidity which was potentially related to treatment. It is likely, however, that these have been under-reported. These were then categorised by the possible causes of the morbidity – surgery, endocrine and radiotherapy, with the radiotherapy category subdivided by type of morbidity (tiredness, breast pain, cough, etc.). Morbidities could be included in more than one category where the cause was unclear. Categorisation was conducted blind, such that the coders were unaware of whether the patient had received radiotherapy. The *p*-values were calculated using Fisher's exact test, due to the relatively small numbers involved.

Surgical morbidity

Surgical morbidity could include hand/arm lymphoedema, shoulder pain, infection in the surgical wound and general breast pain (although the last could also be due to radiotherapy).

There is no evidence of a difference between the treatment groups in terms of surgical morbidities, which is as expected (*Table 27*).

Endocrine therapy morbidity

Morbidity potentially related to endocrine therapy was more varied, and could include hot flushes,

tingling sensations, joint stiffness/pain, weight gain, vaginal irritation, skin rash and mood changes.

There are statistically significantly more reports of endocrine therapy side-effects at 2 weeks post-radiotherapy (*Table 28*) in the group not receiving radiotherapy, which concurs with the comments reported in the section 'Endocrine therapy', (p. 53). However, the reports at 8 and 12 months are at variance with the number of comments made (*Figure 47*).

Radiotherapy morbidity

These were selected as being common side-effects of radiotherapy, although some may also have been attributable to other causes (for example, breast pain and tiredness). *Table 29* summarises all the radiotherapy-related morbidities reported during the trial. The subcategories of radiotherapy morbidity are given in *Tables 30–36*.

By 8 months post-surgery, there is some evidence that there are statistically significantly more morbidities generally associated with irradiation in the group which received radiotherapy. However, this may be heavily influenced by the reports of a cough in *Table 36*.

Radiotherapy morbidity subcategories

Tables 30–36 show the individual types of morbidity commonly seen following radiotherapy.

TABLE 30 Proportion of radiotherapy (tiredness) morbidities reported

Radiotherapy morbidity (tiredness)	Radiotherapy	No radiotherapy	p-Value
2 weeks post-radiotherapy	0/126	1/128	1.00
8 months post-surgery	1/113	0/119	0.49
12 months post-surgery	0/111	1/123	1.00

TABLE 31 Proportion of radiotherapy (breast pain) morbidities reported

Radiotherapy morbidity (breast pain)	Radiotherapy	No radiotherapy	p-Value
2 weeks post-radiotherapy	1/126	3/128	0.62
8 months post-surgery	3/113	0/119	0.11
12 months post-surgery	0/111	0/123	–

TABLE 32 Proportion of radiotherapy (skin effect) morbidities reported

Radiotherapy morbidity (skin effect)	Radiotherapy	No radiotherapy	p-Value
2 weeks post-radiotherapy	3/126	0/128	0.12
8 months post-surgery	2/113	1/119	0.61
12 months post-surgery	0/111	0/123	–

TABLE 33 Proportion of radiotherapy (other breast symptoms) morbidities reported

Radiotherapy morbidity (breast other)	Radiotherapy	No radiotherapy	p-Value
2 weeks post-radiotherapy	2/126	1/128	0.62
8 months post-surgery	0/113	0/119	–
12 months post-surgery	1/111	0/123	0.47

TABLE 34 Proportion of radiotherapy (arm/shoulder) morbidities reported

Radiotherapy morbidity (arm/shoulder)	Radiotherapy	No radiotherapy	p-Value
2 weeks post-radiotherapy	0/126	1/128	1.00
8 months post-surgery	1/113	1/119	1.00
12 months post-surgery	0/111	0/123	–

TABLE 35 Proportion of radiotherapy (rib pain) morbidities reported

Radiotherapy morbidity (rib pain)	Radiotherapy	No radiotherapy	p-Value
2 weeks post-RT	0/126	1/128	–
8 months post-surgery	0/113	1/119	1.00
12 months post-surgery	0/111	0/123	–

TABLE 36 Proportion of radiotherapy (cough) morbidities reported

Radiotherapy morbidity (cough)	Radiotherapy	No radiotherapy	p-Value
2 weeks post-radiotherapy	0/126	0/128	–
8 months post-surgery	5/113	0/119	0.03
12 months post-surgery	2/111	0/123	0.11

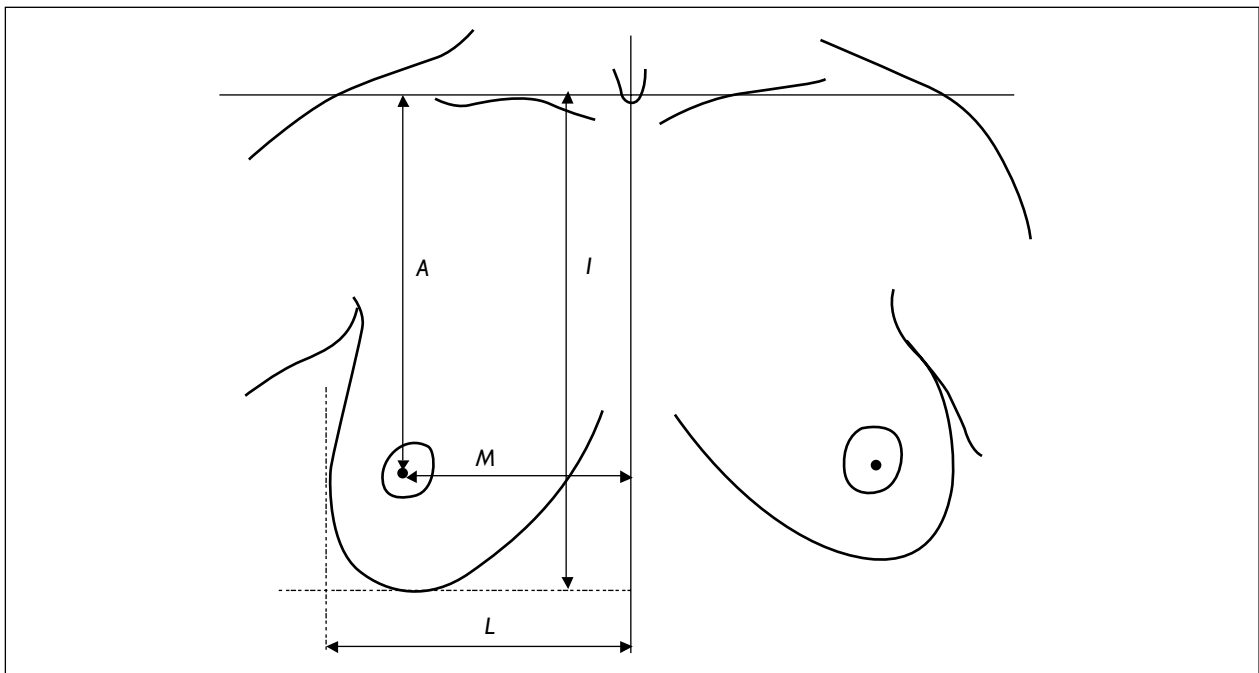


FIGURE 62 Diagram of measurements as defined by Van Limbergen and colleagues

The numbers reported for each of the submorbidities are small in most cases, and only cough at 8 months post-surgery shows any indication of a treatment difference between the two groups.

Cosmesis

A deadline of the end of September 2005 was set for the receipt of the cosmesis photographs to allow sufficient time for these to be scanned, digitised and assessed by both objective measurement (the Van Limbergen method) and subjective grading (the Harris scale). By this point, photographs from 140 patients had been returned, although not all included both photographs. Of the 140, 10 returned only the first photograph (before radiotherapy or equivalent), and nine returned only the second photograph (12 months after surgery). There were 121 complete pairs.

Objective measurement

Photographs were scanned and digitised, then the positioning of various features (e.g. nipple displacement, distortion) was analysed in accordance with a method proposed by Van Limbergen and colleagues,⁸⁹ using software developed with the Department of Medical Physics in Edinburgh. Several photographs were unusable, due to the position of the patient on the photograph and other technical problems.

Van Limbergen and colleagues proposed a method by which four measurements were taken of each breast (the 'treated' breast which had contained the cancer and the untreated breast). These were defined as:

- A* distance from the incisura jugularis to the nipple level
- I* distance from the incisura jugularis to the projection of the inferior breast contour
- M* distance from the midline to the nipple
- L* distance from the midline to the projection of the lateral breast contour.

A graphical illustration is presented in *Figure 62*.

The differences in each of the measures was calculated as the difference between the treated breast and the untreated breast. Van Limbergen and colleagues also described a measurement proposed by Pezner and colleagues¹⁰¹ to measure nipple asymmetry: $BRA = \sqrt{[(\text{difference in } M)^2 + (\text{difference in } A)^2]}$. All these measurements were calculated for both the baseline photograph ($n = 97$) and the one taken at 12 months post-surgery ($n = 98$).

Due to displacement appearing to occur in both directions, the absolute difference was calculated for each variable, as was the case for some of the variables reported by Van Limbergen and colleagues. There were no appreciable differences between the treatments for any of the variables measured in the baseline photograph.

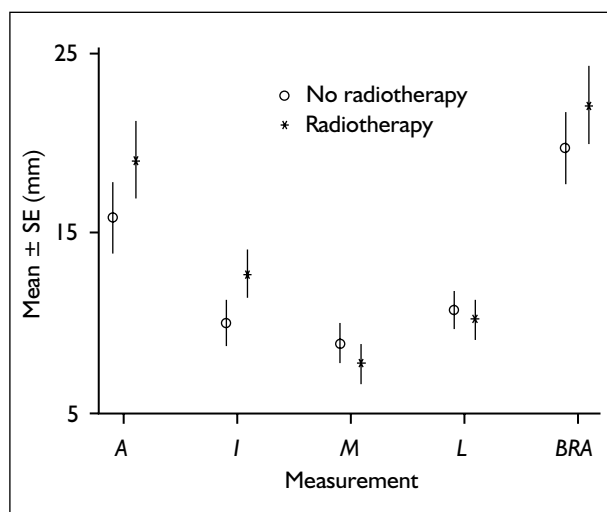


FIGURE 63 Mean differences between treated and untreated breasts at 12 months post-surgery

Figure 63 shows the mean absolute differences for each measurement variable taken from the 12 months post-surgery photograph. There was no significant difference between treatment groups for any of the variables. The greatest observed differences were for the changes in the y-distances (A and I), which were greater in the group treated with radiotherapy: 15.9 versus 19.1 mm for A ($p = 0.28$) and 10.1 versus 12.8 mm ($p = 0.16$) for I.

Subjective grading

This was performed by three observers; a male clinician, a female clinician and a female non-clinical scientist. The grading was performed in two sessions, with each observer completing their observations independently before reaching a consensus decision.

The Harris scale grades the appearance of the treated breast in comparison with the untreated breast using a simple four-point scale: Excellent, Good, Fair, Poor. The observers were asked to grade the post-treatment photograph independently first, and then

grade the baseline photograph. In this way, the nine patients who only had the second photograph returned would be included in the analysis. From the pre- and post-treatment assessments, the change in rating could also be determined.

The data were analysed using the Cochran–Armitage test for trend, counting the number of instances of Excellent, Good, Fair and Poor in each treatment group.

Agreement between coders was calculated using the kappa statistic, a measure of the amount of agreement between the coders over that which would be expected by chance.

Baseline photographs (N = 114)

There is no underlying difference between treatment groups at the time of the baseline photograph (Table 37). Agreement between the observers was moderate, with kappa coefficients for pairs of observers between 0.3 and 0.4 (Table 38).

Post-treatment (12 months post-surgery) photographs (N = 123)

All observers tended to rate cosmesis better in the no radiotherapy group, and this was statistically significant for two of the three observers and for the consensus rating (Table 39). As at baseline, agreement between observers was moderate (Table 40).

Change in rating (N = 114)

Change was initially calculated as the number of ratings that the photograph changed between the rating of the second photograph only, and then the first photograph. Due to the infrequency of values greater than |1|, these were collapsed into the next nearest group (e.g. ‘2’ was amalgamated into ‘1’). A negative value indicates a deterioration from baseline; a positive value indicates an improvement.

TABLE 37 Summary of treatment effect on Harris scores at baseline

Rating	Observer 1		Observer 2		Observer 3		Consensus	
	RT	No RT	RT	No RT	RT	No RT	RT	No RT
Poor	4	3	3	4	5	4	4	4
Fair	20	22	28	19	24	28	25	24
Good	23	25	19	23	24	24	24	25
Excellent	9	8	6	12	3	2	3	5
p-Value	0.97		0.12		0.80		0.61	

RT, radiotherapy.

TABLE 38 Measure of agreement between observers at baseline

	Observer 1	Observer 2	Observer 3	Consensus
Observer 1		0.30	0.37	0.59
Observer 2	0.30		0.37	0.59
Observer 3	0.37	0.37		0.71
Consensus	0.59	0.59	0.71	

TABLE 39 Summary of treatment effect on Harris scores on photograph taken at 12 months

Rating	Observer 1		Observer 2		Observer 3		Consensus	
	RT	No RT	RT	No RT	RT	No RT	RT	No RT
Poor	4	2	7	3	7	1	6	3
Fair	27	18	30	14	26	18	30	15
Good	24	30	21	26	29	35	25	34
Excellent	10	8	7	15	2	4	4	6
p-Value	0.31		0.002		0.02		0.02	

TABLE 40 Measure of agreement between observers on photograph taken at 12 months

	Observer 1	Observer 2	Observer 3	Consensus
Observer 1		0.31	0.39	0.56
Observer 2	0.31		0.36	0.60
Observer 3	0.39	0.36		0.68
Consensus	0.56	0.60	0.68	

In each case, more radiotherapy patients' cosmesis scores deteriorated than would be expected by chance and the differences between the treatment groups were statistically significant for one of the three observers and for the consensus assessment. The two instances of an improvement of two in a

rating from observer 1 were both from patients who did not receive radiotherapy. One of these was also recorded by observer 2 as an improvement of two rating points (Table 41). Observer agreement was again low (Table 42).

TABLE 41 Summary of treatment effect on change of Harris scores

Change	Observer 1		Observer 2		Observer 3		Consensus	
	RT	No RT	RT	No RT	RT	No RT	RT	No RT
-1	7	6	12	3	9	0	9	1
0	41	42	34	43	37	40	37	44
+1	8	10	10	12	10	18	8	13
p-Value	0.6		0.07		0.004		0.02	

TABLE 42 Measure of agreement between observers on change of Harris scores

	Observer 1	Observer 2	Observer 3	Consensus
Observer 1		0.20	0.28	0.27
Observer 2	0.20		0.35	0.54
Observer 3	0.28	0.35		0.54
Consensus	0.27	0.54	0.54	

Chapter 9

Recurrence and deaths

Although patients in the trial have been followed up for a median of 1506 days (4 years 1.5 months, as of 24 May 2007), we only report incidents which occurred during the 15 months of follow-up corresponding to the assessments reported here. Almost all of the patients in this trial are contributing to an ongoing follow-up trial (PRIME II), in which 1000 patients are being recruited, and where local/regional recurrence is the primary outcome variable. This will be reported when that trial is mature.

Loco-regional and distant recurrence rate

There have been no reported occurrences of local or distant recurrence within the 15-month follow-up period other than the protocol violation reported earlier (liver metastases discovered immediately after randomisation).

Other cancers

Three patients have been reported as developing other cancers during the follow-up period. These were in radiotherapy patients:

- basal cell carcinoma of the nose

and in the non-radiotherapy patients:

- peritoneal metastases, primary unknown (cause of death)
- cancer of the head of the pancreas.

Deaths

During the 15-month follow-up period, five deaths were recorded. Of these, four had received radiotherapy and one had not. The causes of death of those who were randomised to receive radiotherapy were as follows:

- hypertensive heart disease (died before receiving radiotherapy)
- osteoporotic fracture of the hip, followed by a chest infection (died part way through course of radiotherapy)
- liver metastases (died before receiving radiotherapy)
- cardiac arrest, following long-term ischaemic heart disease.

Of the one who did not receive radiotherapy, the cause of death was peritoneal metastases, primary unknown.

Chapter 10

Cost-effectiveness analysis

Table 43 (with *Table 62* in Appendix 6) reports the mean costs (quantity) of healthcare resources for the different categories. Radiotherapy was the main cost driver for the radiotherapy arm, contributing to 61% of the total cost. On average, the patients attended 20 sessions of radiotherapy, with a mean cost of £2128 per patient.

Patients in the no radiotherapy arm tended to receive relatively more expensive endocrine therapy (£293 for the no radiotherapy arm versus £215 for the radiotherapy arm), although the difference was not significant. Other medication costs were also higher (£915 for the no radiotherapy arm versus £402 for the radiotherapy arm), but again, not significantly so. This difference seems to be driven by one patient in the no radiotherapy arm who had been receiving long-term ongoing high-cost treatment (this was further explored in the sensitivity analysis). In terms of other primary and secondary care, the mean costs were broadly similar (£685 for the no radiotherapy arm and £755 for the radiotherapy arm).

The mean total costs were £1893 for the no radiotherapy arm and £3501 for the radiotherapy arm and the mean difference was therefore £1607. The 95% CI (£474 to £2741) indicates that this difference was statistically significant at the 5% level.

QALYs

Table 44 reports the utility scores at the different time points. The utility scores were higher at baseline for the radiotherapy arm than the no radiotherapy arm. The estimated difference in QALYs between the two arms of the trial is adjusted for this baseline difference. The difference in adjusted QALYs was extremely small (-0.0075) and the 95% CI of the difference indicates that this difference was not statistically significant at the 5% level.

Cost-effectiveness

The cost-effectiveness of no radiotherapy compared with radiotherapy is dependent on

whether the difference in QALYs is considered to be important. The difference is close to zero and it could therefore be argued that no radiotherapy is dominant in that it produces a similar number of QALYs and is less costly. However, if the difference in QALYs is taken to be of importance, then it should be concluded that no radiotherapy produces fewer QALYs and is less costly. The ICER was estimated at £215,160 per adjusted QALY. It should be noted that it is a ratio of two negatives, that is, the no radiotherapy option is less costly but also less effective. The ratio indicates that withholding radiotherapy saves £215,160 at a loss of one QALY.

Figure 64 presents the uncertainty surrounding the ICER by showing the 1000 bootstrap estimates of this ratio on a cost-effectiveness plane. In 26.7% of the 1000 samples no radiotherapy produced more QALYs and was less costly than radiotherapy. In those cases no radiotherapy is dominant. In 72.3% of the 1000 samples no radiotherapy produced less QALYs and was less costly than radiotherapy.

Figure 65 shows the CEAC, which indicates the probability that no radiotherapy is cost-effective relative to radiotherapy against the maximum that decision-makers might be willing to pay for an additional QALY. When a QALY is worth £30,000 (conventional threshold), the probability that no radiotherapy is cost-effective is 94.1%. This probability is around 62.3% when the QALY estimates are not adjusted for baseline differences in EQ-5D scores.

Sensitivity analysis

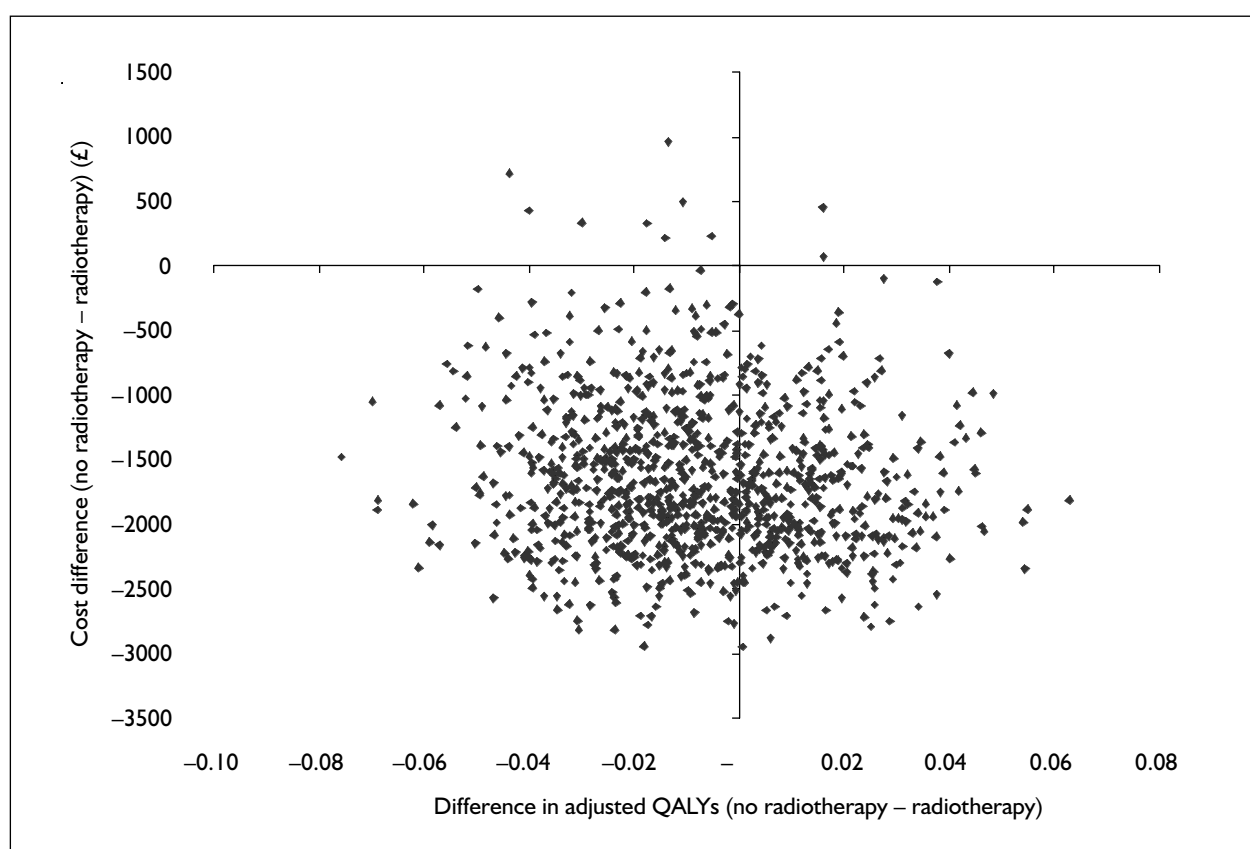
Table 45 and *Figure 66* present the results of the sensitivity analysis. Using the lower quartile and upper quartile of the Health Resource Group unit costs for radiotherapy resulted in a smaller and larger cost difference between the two arms, respectively. Excluding the four patients who were outliers in terms of healthcare use resulted in lower mean cost for both arms of the trial. The net effect was a larger cost difference between the two arms. Imputation of missing data resulted in higher costs for the radiotherapy arm and lower

TABLE 43 Mean cost per patient

Variable	Radiotherapy (n = 102) mean (95% CI) (£)	No-radiotherapy (n = 101) mean (95% CI) (£)	Difference cost: mean (95% CI) (£)
Radiotherapy	2128.32 (2074.28 to 2182.36)	–	-2128.32 (-2182.36 to -2074.28)
Sessions	1960.39 (1930.03 to 1990.75)	–	-1960.39 (-1990.75 to -1930.03)
NHS Transport	111.11 (76.09 to 146.13)	–	-111.11 (-146.13 to -76.09)
Accommodation	56.58 (24.48 to 88.68)	–	-56.58 (-88.68 to -24.48)
Referral/investigation	0.22 (0.15 to 0.43)	–	-0.22 (-0.43 to -0.15)
Endocrine therapy	215.31 (141.62 to 289.00)	292.61 (201.98 to 383.24)	77.30 (-35.94 to 190.53)
Other medication	402.45 (322.06 to 482.84)	915.35 (-141.63 to 1972.32)	512.90 (-499.91 to 1525.71)
Primary/secondary care	754.57 (404.84 to 1104.31)	685.28 (506.21 to 864.34)	-69.30 (-449.43 to 310.84)
GP – home visits	43.82 (5.21 to 82.42)	29.30 (12.41 to 46.19)	-14.52 (-55.41 to 26.37)
GP – surgery visits	76.34 (62.65 to 90.03)	87.98 (72.70 to 103.26)	11.64 (-9.42 to 32.69)
GP – telephone	4.21 (2.06 to 6.36)	1.89 (0.23 to 3.55)	-2.32 (-5.02 to 0.39)
Nurse – home visits	50.14 (-27.09 to 127.38)	13.33 (3.29 to 23.37)	-36.81 (-114.30 to 40.68)
Nurse – surgery visits	38.55 (22.34 to 54.77)	46.40 (10.54 to 82.25)	7.84 (-32.30 to 47.98)
Nurse – hospital visits	3.53 (1.58 to 5.47)	6.39 (0.66 to 12.13)	2.87 (-3.05 to 8.78)
Physiotherapist – home	7.53 (-3.38 to 18.44)	5.23 (-3.87 to 14.33)	-2.30 (-16.88 to 12.27)
Physiotherapist – surgery	1.76 (-0.57 to 4.10)	3.90 (0.12 to 7.69)	2.14 (-2.21 to 6.49)
Physiotherapist – hospital	5.63 (-0.21 to 11.47)	14.07 (-0.92 to 29.06)	8.44 (-7.15 to 24.04)
Occupational therapist	10.76 (0.56 to 20.96)	6.00 (-0.32 to 12.33)	-4.76 (-16.25 to 6.73)
Homecare	49.68 (-9.90 to 109.27)	55.31 (-21.08 to 131.69)	5.63 (-90.45 to 101.70)
Other staff	7.93 (2.44 to 13.42)	11.30 (2.82 to 19.77)	3.36 (-6.84 to 13.56)
Outpatient consultant visit	159.84 (120.48 to 199.20)	186.36 (132.78 to 239.93)	26.52 (-37.72 to 90.76)
Inpatient bed-day	220.99 (36.33 to 405.64)	194.76 (92.50 to 297.02)	-26.22 (-233.85 to 181.40)
Investigations/procedure	46.81 (20.60 to 73.02)	23.07 (11.90 to 34.23)	-23.74 (-52.34 to 4.85)
Total cost	3500.66 (3066.96 to 3934.35)	1893.24 (759.49 to 3026.99)	-1607.42 (-2741.31 to -473.53)

TABLE 44 Mean quality of life scores (EQ-5D) and adjusted QALYs

	Radiotherapy (n = 102) mean (95% CI)	No-radiotherapy (n = 101) mean (95% CI)
EQ-5D		
Baseline	0.77 (0.73 to 0.80)	0.74 (0.70 to 0.77)
3.5 months	0.78 (0.74 to 0.81)	0.76 (0.73 to 0.79)
9 months	0.76 (0.71 to 0.81)	0.72 (0.68 to 0.76)
15 months	0.74 (0.70 to 0.78)	0.73 (0.69 to 0.77)
Unadjusted QALYs	0.95 (0.90 to 0.99)	0.92 (0.88 to 0.95)
Difference in unadjusted QALYs:	-0.03 (-0.09 to 0.03)	
Difference in adjusted QALYs:	-0.01 (-0.05 to 0.04)	

**FIGURE 64** Cost-effectiveness plane**TABLE 45** Sensitivity analysis

	Mean total cost (£)		Difference		ICER (£ per QALY)
	Radiotherapy	No radiotherapy	Cost (£)	QALY	
Unit cost of radiotherapy					
Lower quartile	3,062.37	1,893.24	-1,169.13	-0.0075	156,493.28
Upper quartile	4,066.42	1,893.24	-2,173.19	-0.0075	290,890.53
Excluding 4 outliers	3,194.23	1,350.55	-1,843.68	-0.0173	106,571.10
Mean imputation	3,428.91	1,737.70	-1,691.21	0.0052	- ^a
Regression imputation	3,436.51	1,731.54	-1,704.97	0.0076	- ^a

^a No radiotherapy dominant.

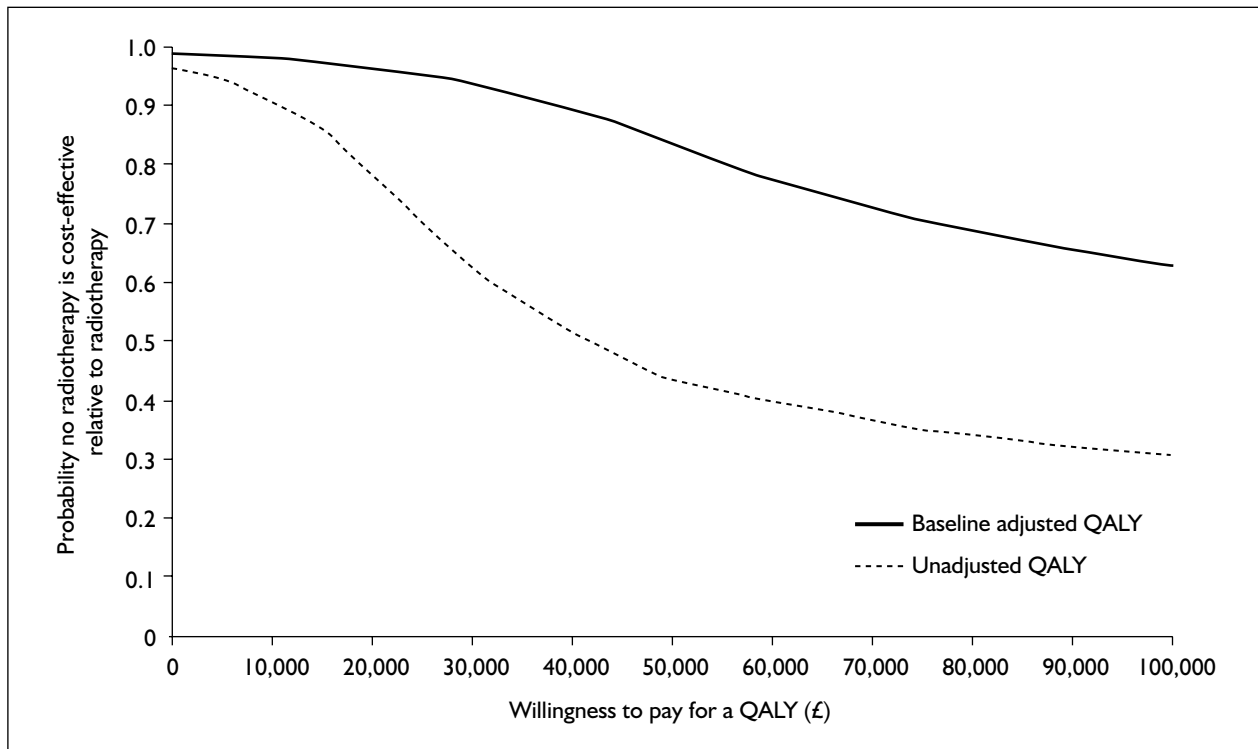


FIGURE 65 CEAC – baseline

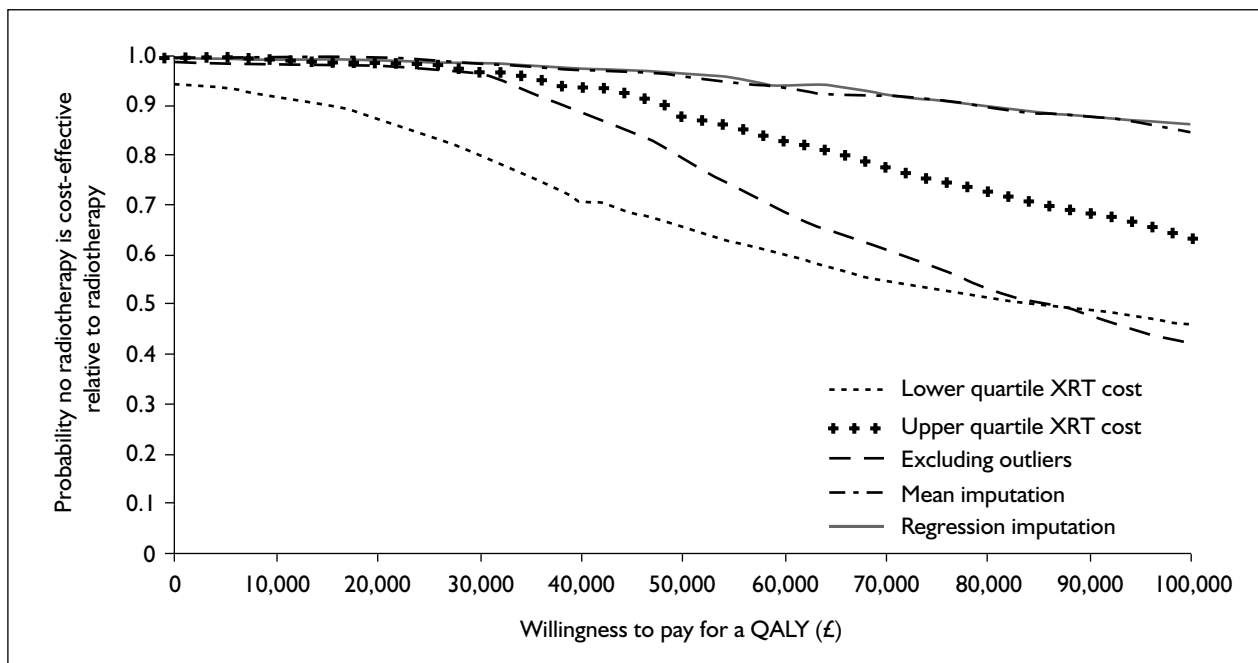


FIGURE 66 CEAC – sensitivity analysis. XRT, radiotherapy treatment.

costs for the no radiotherapy arm. The difference in mean costs between the two arms was therefore larger. The estimated difference in QALYs between the two arms was positive rather than negative, but still very close to zero.

Figure 66 shows the CEAC under the different assumptions. At £30,000 per QALY, no radiotherapy is highly likely to be cost-effective under all assumptions. Using the lower unit cost for radiotherapy had the largest impact on results

but the conclusions regarding cost-effectiveness of no radiotherapy relative to radiotherapy are very similar.

In this study, no recurrence was reported. To explore the possible impact of recurrence on the cost-effectiveness results, a crude threshold analysis can be performed. This threshold analysis identifies, for the study's time horizon of 15 months after surgery, the critical value for the recurrence rate at which radiotherapy becomes

cost-effective. Assuming that diagnosing and treating recurrence costs £20,000 (Cameron D, Western General Hospital, Edinburgh: personal communication, January 2006), and that recurrence decreases QoL by 9%⁷⁷ and has no impact on life expectancy,¹⁸ then withholding radiotherapy would have to result in a 5.5% increase in local recurrence before radiotherapy would be considered cost-effective at the £30,000 threshold.

Chapter 11

Comprehensive cohort study

Background and aim of the study

Early in the trial, it was discovered that the randomisation options of radiotherapy or no radiotherapy were perceived by patients to be so markedly different that we were finding that many women had a strong preference for one or other option. This led them to reject randomisation, although they had indicated that otherwise they would have been happy to take part in assessments of QoL and clinical follow-up. This led to an application for an amendment to the original trial, in order to allow the follow-up of non-randomised patients.

This extension to the original design, to allow non-randomised patients to be followed up in the same manner as the randomised patients, has been termed a comprehensive cohort study (CCS).⁷⁹ Formal methods for the analysis of such a design have been proposed,¹⁰² but these have some disadvantages.¹⁰³ Our own approach to analysis has two components. Firstly, there is the aim to examine whether the QoL assessments differ systematically between patients who are randomised to a treatment and those who make their own choice of that treatment. It was unlikely that a randomised study to answer that question could ever be undertaken, and the information from a CCS should provide the best comparison possible.

Second, we wished to examine and compare the estimates of treatment effect of radiotherapy between the randomised and non-randomised patients. There was, at the time, much debate about the extent to which quasi-experimental and observational (QEO) data could contribute to the assessment of the size of treatment effects. As RCTs are not feasible in many areas, it is of great importance to know more about the comparability of findings from RCT and QEO studies. A systematic review commissioned by the HTA Programme recommended that there is a need for more evidence about this comparability, and they believe that the CCS is the best study design to use to obtain such evidence.¹⁰⁴ Our results will contribute to that evidence.

Plan of investigation

Women who declined an invitation to participate in the PRIME trial were offered the opportunity to take part in the non-randomised QoL study by the oncologist or research nurse. If agreeable, the patients were then monitored in the same way as those in the randomised arm of the trial (although the clinical photograph was not offered to these patients).

Objectives

The objectives were as follows:

1. to compare the QoL in older women with low-risk axillary node-negative breast cancer treated by wide local excision and adjuvant endocrine therapy who choose the omission of postoperative breast radiotherapy with the QoL in comparable women who choose to be treated with postoperative radiotherapy.
2. to compare the QoL of patients who choose their treatment modality with that of patients receiving the same treatment as the result of randomisation.

Recruitment

Of the 96 patients who declined randomisation in Scotland and the north of England (Northumbria and Cumbria) for whom there was a complete set of data, nine (9%) were not offered the non-randomised follow-up (as this was before MREC approval was granted), 51 (53%) declined all non-standard follow-up and did not enter the non-randomised study and 36 (38%) consented to enter the study. If the nine patients who were not given the choice were excluded, 41% of patients who had declined the randomised trial accepted the non-randomised study in this area. There is not sufficiently detailed information to provide similar information for the whole study. The distribution of randomised and non-randomised patients is presented in *Table 59* in Appendix 3.

TABLE 46 Information recorded at baseline for randomised and non-randomised patients

	Randomised (n = 255)		Non-randomised (n = 100)	
	Radiotherapy (n = 127)	No radiotherapy (n = 128)	Radiotherapy (n = 63)	No radiotherapy (n = 37)
Mean age at surgery (SD) (years)	72.2 (4.9)	72.9 (5.3)	70.9 (4.5)	75.4 (6.2)
N (%)				
Tumour grade				
1	47 (37.6)	49 (37.7)	23 (36.5)	17 (45.9)
2	71 (56.8)	72 (55.4)	36 (57.1)	19 (51.4)
3	7 (5.6)	9 (6.9)	1 (1.6)	1 (2.7)
LVI				
No	119 (95.2)	124 (95.4)	62 (98.4)	37 (100)
Yes	6 (4.8)	6 (4.6)	1 (1.6)	0 (0)
Pre-op ET				
No	109 (87.2)	107 (82.3)	55 (87.3)	31 (83.8)
Yes	16 (12.8)	23 (17.7)	8 (12.7)	6 (16.2)
Axillary surgery		(1 unknown)		
Clearance	30 (23.6)	36 (28.1)	16 (25.4)	9 (24.3)
Sample	95 (74.8)	90 (70.3)	46 (73.0)	27 (73.0)
Sentinel node	2 (1.6)	1 (0.8)	1 (1.6)	1 (2.7)
Side				
Right	63 (49.6)	59 (46.1)	34 (54.0)	16 (43.2)
Left	61 (48.0)	67 (52.3)	29 (46.0)	21 (56.8)
Not given	3 (2.4)	2 (1.5)	0	0

Pre-op ET, preoperative endocrine therapy.

Results

Comparability of treatment and cohort groups

Demographic results

Table 46 summarises the demographic data by treatment in randomised and non-randomised patients. The most interesting difference is between the ages of the patients at surgery. Within the non-randomised group, the mean difference is nearly 5 years (Figure 67). If it is assumed that the randomised arm is a homogeneous group, irrespective of assigned treatment, then the differences between the randomised group, the group which chose radiotherapy and the group which chose no radiotherapy are significantly different ($p < 0.001$). This would imply that younger patients may still choose radiotherapy if given a choice, whereas their older counterparts are more likely to opt for the omission of radiotherapy.

Quality of life at baseline

Although a full analysis of the results from all 355 patients (randomised and non-randomised) was completed, only those baseline variables where the results differ substantially from those obtained in

the randomised arm will be reported here. Cohort is used as a variable name defining whether a patient was in the randomised or non-randomised group. The p -value is for the comparison of all randomised patients with non-randomised radiotherapy with non-randomised no radiotherapy – a trinomial variable.

EORTC scales

Only the subscale in Table 47 showed any baseline differences between the mean scores of the randomised patients and the two self-selected treatment groups.

For emotional functioning, a higher score is indicative of a higher level of emotional well-being. This would imply that those with a lower score (the more anxious/depressed) are more likely to choose not to have their treatment allocated randomly, although there is no indication that it then influences their choice of treatment.

Patients choosing their own treatment had higher levels of sexual function than the randomised patients, but the means scores remain low (Table 48).

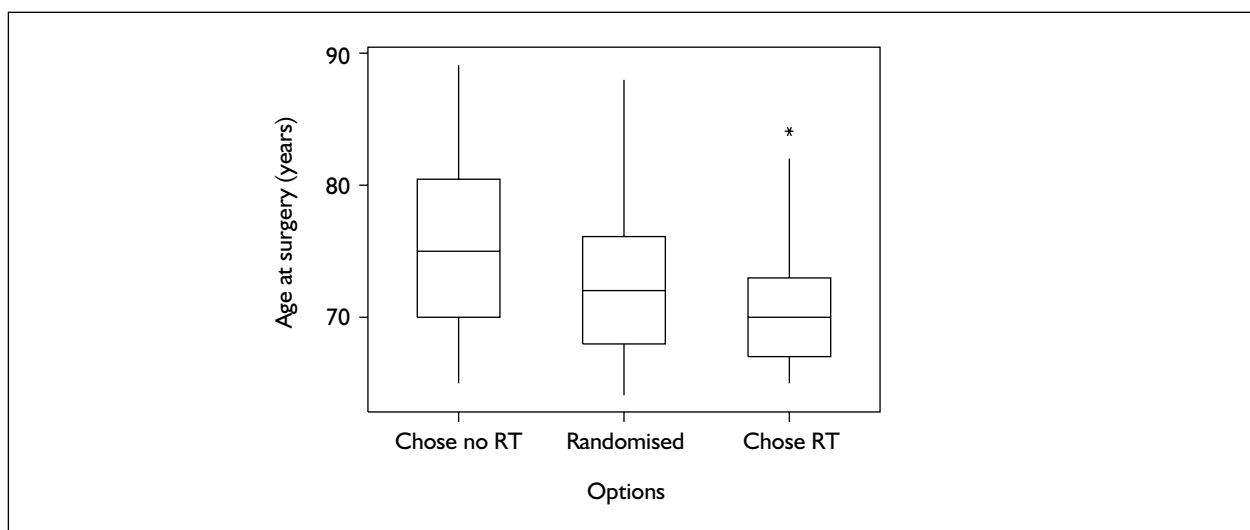


FIGURE 67 Comparison of ages at surgery

TABLE 47 Mean and standard deviation by cohort and treatment (EORTC QLQ-C30)

EORTC QLQ-C30	Randomised		Non-Randomised		p-Value
	Radiotherapy (N = 125)	No radiotherapy (N = 128)	Radiotherapy (N = 63)	No radiotherapy (N = 37)	
Emotional functioning (EF)	83.3 (19.2)	83.9 (18.4)	79.0 (17.4)	76.1 (21.5)	0.03

TABLE 48 Mean and standard deviation by cohort and treatment (EORTC QLQ-BR23)

EORTC QLQ-BR23	Randomised		Non-randomised		p-Value
	Radiotherapy (N = 125)	No radiotherapy (N = 128)	Radiotherapy (N = 63)	No radiotherapy (N = 37)	
Sexual function (SF)	10.3 (18.9) n = 78	6.6 (15.5) n = 81	15.9 (21.0) n = 45	11.1 (20.1) n = 24	0.05

TABLE 49 Mean and standard deviation by cohort and treatment (PGCMS)

PGCMS	Randomised		Non-randomised		p-Value
	Radiotherapy (N = 125)	No radiotherapy (N = 128)	Radiotherapy (N = 63)	No radiotherapy (N = 37)	
Lonely dissatisfaction (maximum 6)	5.2 (1.2)	5.1 (1.3)	5.5 (1.0)	4.8 (1.6)	0.03

Hospital Anxiety and Depression Scale

There is no evidence that the HADS anxiety and depression scores are influenced by treatment group or the ability to choose their own treatment.

Philadelphia Geriatric Center Morale Scale

For the PGCMS, a higher score is indicative of higher morale. Only in the lonely dissatisfaction

subscale were there statistically significant differences, with the highest score in those choosing radiotherapy and the lowest in those choosing no radiotherapy (Table 49).

Clackmannan Scale

There was no evidence of any differences between the cohorts (randomised versus non-randomised).

TABLE 50 Tally of number of co-morbidities reported per patient

Co-morbidities	Randomised (%)		Non-randomised (%)	
	Radiotherapy	No radiotherapy	Radiotherapy	No radiotherapy
0	24 (19.0)	25 (19.5)	22 (34.9)	4 (10.8)
1	48 (38.1)	42 (32.8)	14 (22.2)	17 (45.9)
2	23 (18.3)	29 (22.7)	14 (22.2)	10 (27.0)
3	21 (16.7)	20 (15.6)	11 (17.5)	5 (13.5)
4	5 (4.0)	9 (7.0)	1 (1.6)	0 (0)
5	3 (2.4)	3 (2.3)	0 (0)	0 (0)
6	2 (1.6)	0 (0)	1 (1.6)	1 (2.7)

Barthel Index

There was no evidence of any differences between the cohorts (randomised versus non-randomised).

Co-morbidities

As with the randomised patients, the co-morbidities of the non-randomised patients were recorded at baseline.

If we examine only the non-randomised patients, there are too few patients with four or more co-morbidities to be able to rely on the result of the χ^2 analysis (Table 50). However, if those results are collapsed into a category labelled “three or more”, there is evidence of an association between the number of co-morbidities a patient has and the treatment she chose ($p = 0.019$).

Quality of life outcomes

As with the comparison of baseline results, only those results that differ between the randomised and non-randomised groups (“cohort”) will be discussed in detail here. The error bars have been omitted to maintain the clarity of the graphs. Due to the influence of multiple testing, only those interactions which involve the cohort and have a p -value of <0.01 will be considered significant.

EORTC Scales: QLQ-C30**Physical functioning (PF)**

There is little evidence to suggest a systematic difference in physical functioning between the treatment groups, as the only appreciable difference between the randomised and non-randomised groups is an isolated observation at the final questionnaire (Figure 68).

Fatigue symptoms (FA)

Although there is no evidence of a difference between the randomised and non-randomised groups, the time by treatment interaction has become significant (Figure 69). This was not the case in the section ‘The EORTC QLQ-C30 scale’,

($p = 0.25$) when only the randomised group was analysed. Thus fatigue is a greater problem for the patients receiving radiotherapy when measured 2 weeks after the completion of radiotherapy, but differences have disappeared by 9 months post-surgery.

EORTC QLQ-BR23**Body image (BI)**

As with the randomised group alone, there is little consistency between the treatments or cohorts. The significant time by treatment by cohort interaction (Figure 70) is not readily interpretable and may be a false positive resulting from multiple testing.

Sexual functioning (SF)

Here, the non-randomised group display consistently higher mean scores for both treatment options (Figure 71). As earlier, patients are given the option to decline to answer this and the following question.

Sexual enjoyment

Again, there are differences between the randomised and non-randomised groups, and also treatment differences (Figure 72). However, the sample size is small and other factors may play a part in these results.

Systemic therapy side-effects

The inclusion of the non-randomised group has obscured the treatment difference observed in the randomised group, as the trend for the non-randomised patients appears to be the antithesis of that of the randomised group (Figure 73).

Anxiety and depression**Hospital Anxiety and Depression Scale (HADS)****Anxiety**

With the addition of the non-randomised patients, treatment becomes statistically significant (Figure 74). Patients who do not receive

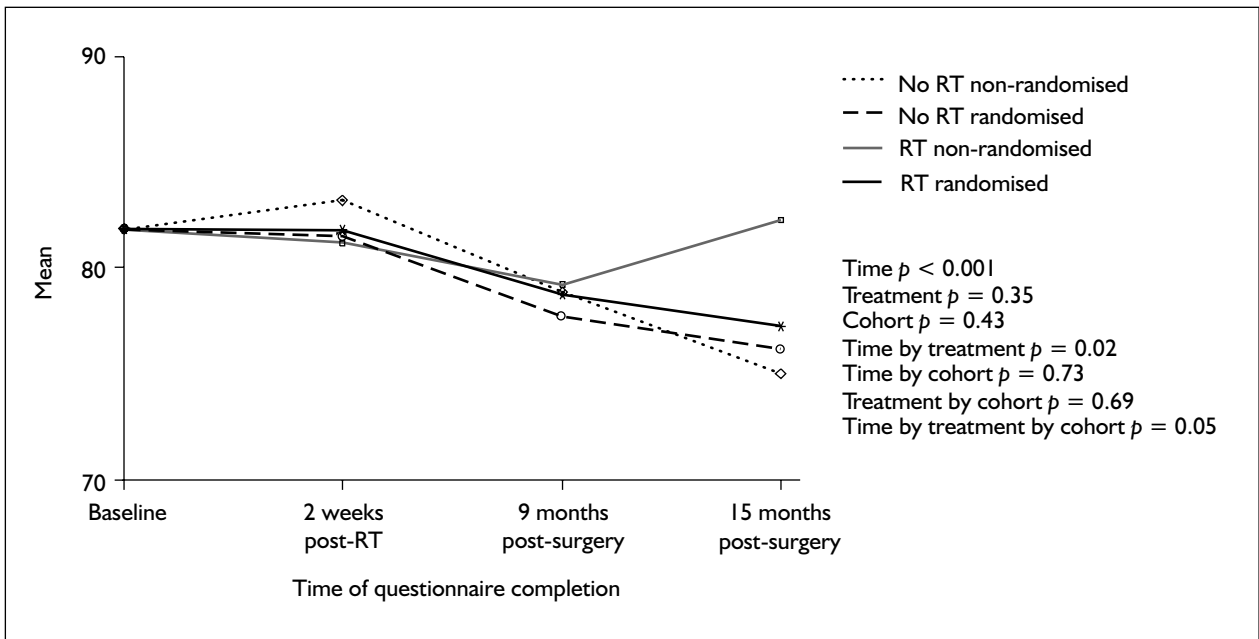


FIGURE 68 Mean score of physical functioning by questionnaire

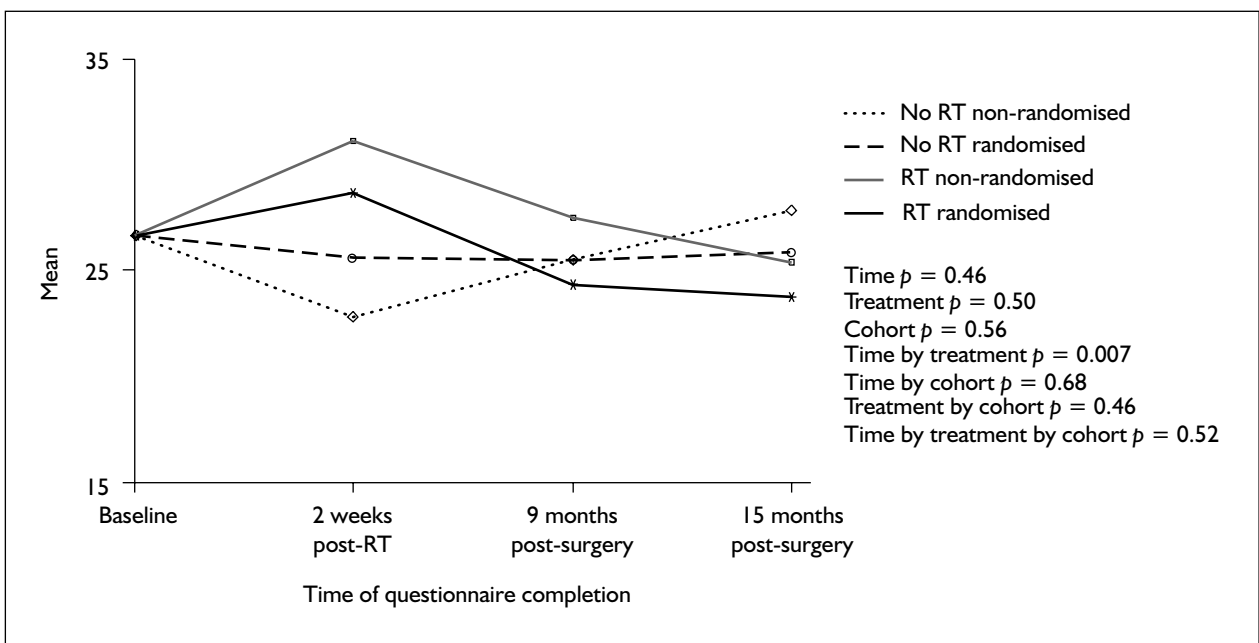


FIGURE 69 Mean score of fatigue symptoms by questionnaire

radiotherapy are, on average, more anxious than those who do receive radiotherapy. Also, those accepting randomisation are showing significantly less anxiety than the non-randomised patients. However, these differences do not extend to higher levels of anxiety at which anxiety would be considered a clinical problem (scores >10; Figure 75), where the excess proportion in the no radiotherapy group is small.

Depression

As for the randomised patients alone, time is again significant, implying that patients are becoming slightly more depressed over time (Figure 76). Although the time by treatment by cohort interaction is nearly significant, there appears to be no difference between the treatments or cohorts (randomised versus non-randomised).

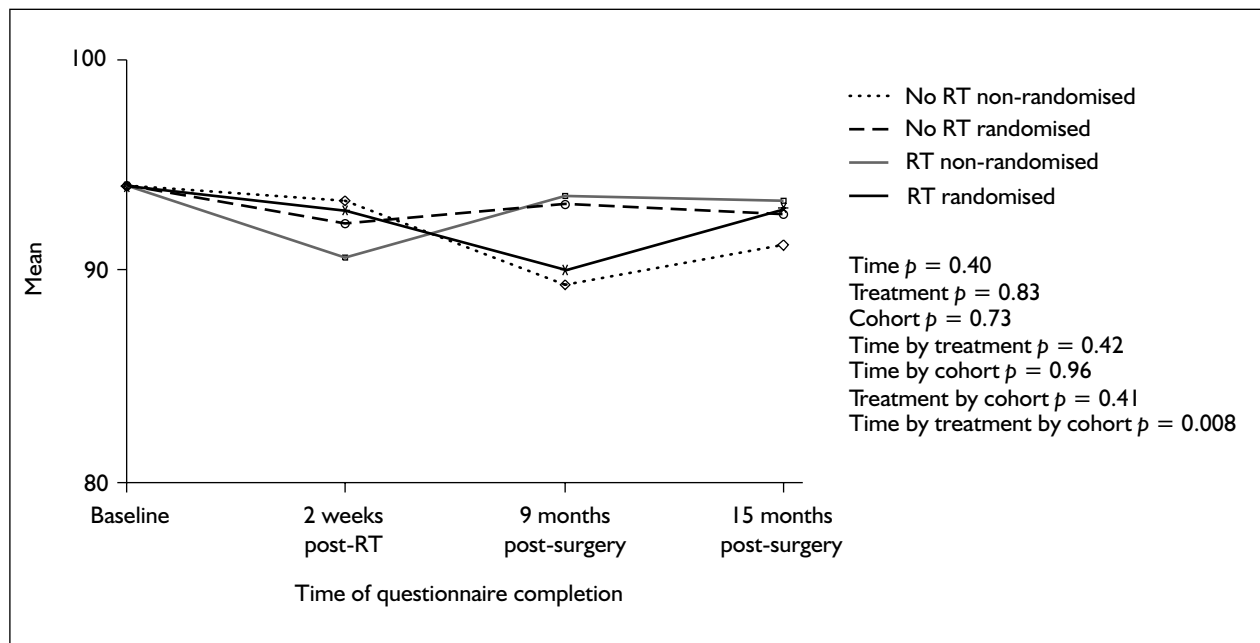


FIGURE 70 Mean score of body image by questionnaire

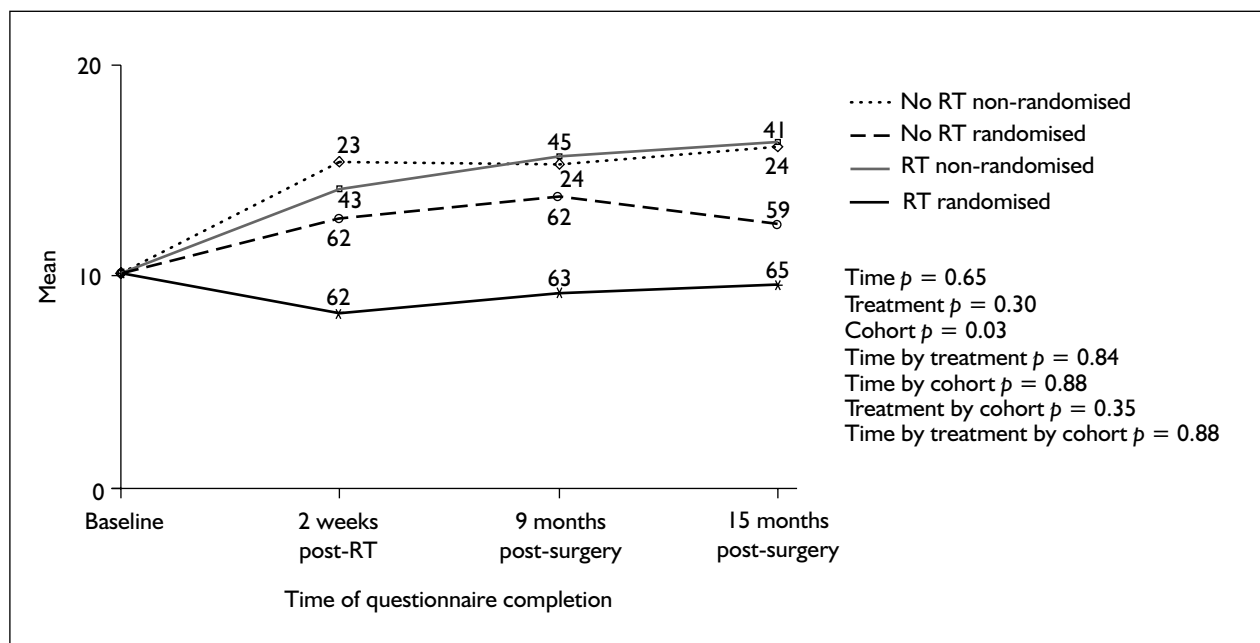


FIGURE 71 Mean score of sexual functioning by questionnaire (n available)

The suggestion of a possible three-way interaction in the mean depression scores is reflected in the percentage of patients with clinical depression. The pattern is not consistent (Figure 77), with no particular group consistently producing the highest proportion with clinical depression.

The Philadelphia Geriatric Center Morale Scale Total score

There was no evidence of any differences between

the cohorts (randomised versus non-randomised), in either the total score or in any of the subscales (Figure 78).

Functional status Clackmannan Scale

There was no evidence of any differences between the cohorts in the overall score (randomised versus non-randomised) and no consistent patterns in any of the subscales.

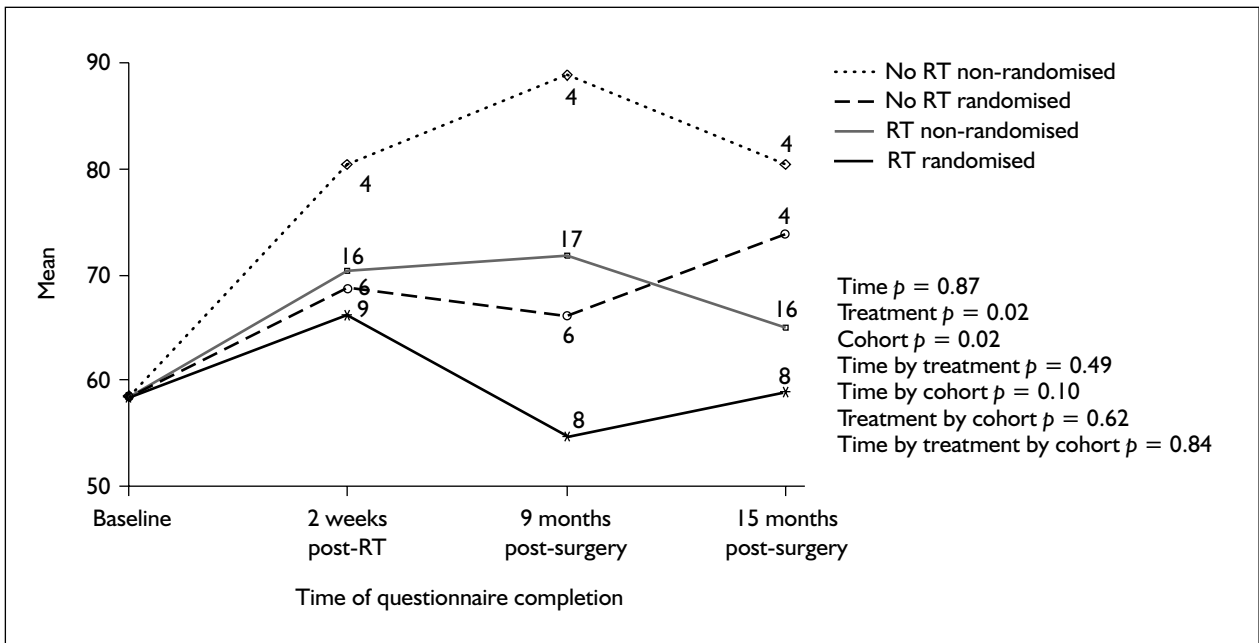


FIGURE 72 Mean score of sexual enjoyment by questionnaire (n)

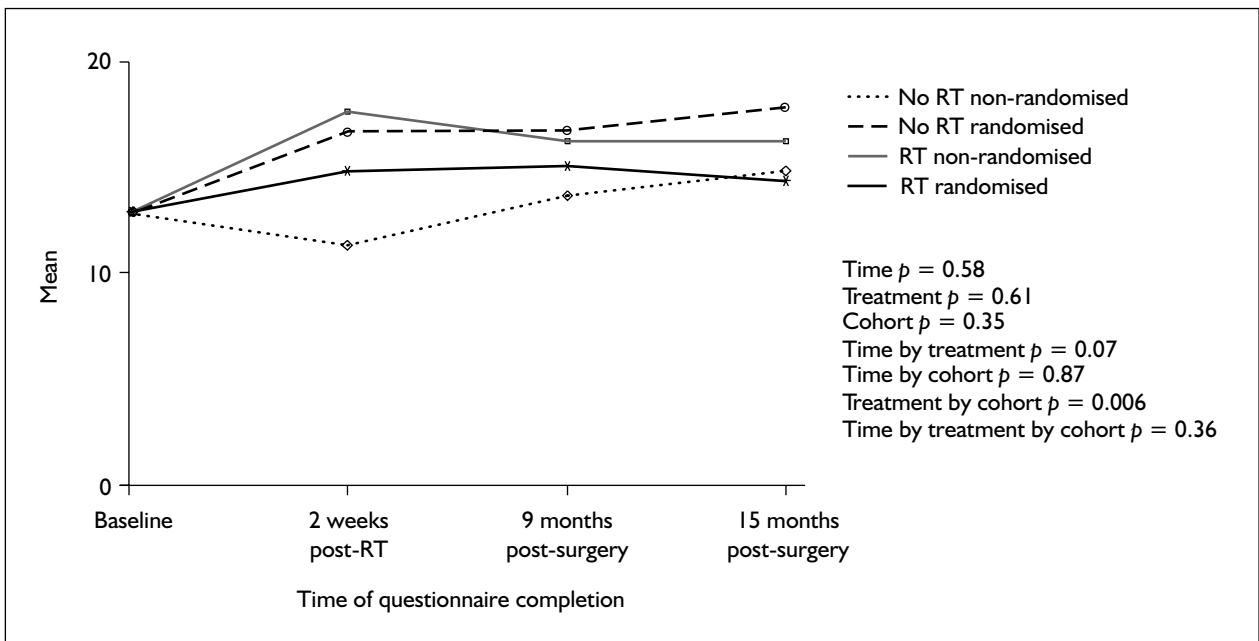


FIGURE 73 Mean score of systemic therapy side-effects by questionnaire

Barthel Index

There was no evidence of any differences between the cohorts in the total Barthel Index (randomised versus non-randomised), although the relative advantage of no radiotherapy seen in the analysis of the randomised patients was not observed in those choosing their own treatment (Figure 79).

There was no evidence of any differences between the cohorts (randomised versus non-randomised) for either of the subscales of the Barthel Index.

Summary of quantitative measures

In order to provide comparative data on estimates of differences between no radiotherapy and radiotherapy from randomised and non-randomised studies, the average differences over all post-treatment visits are summarised in Table 51. The standard errors are larger for the non-randomised comparisons, reflecting the smaller sample size. The standard errors of the difference are, of course, still larger. The conclusions that can be drawn are limited by this

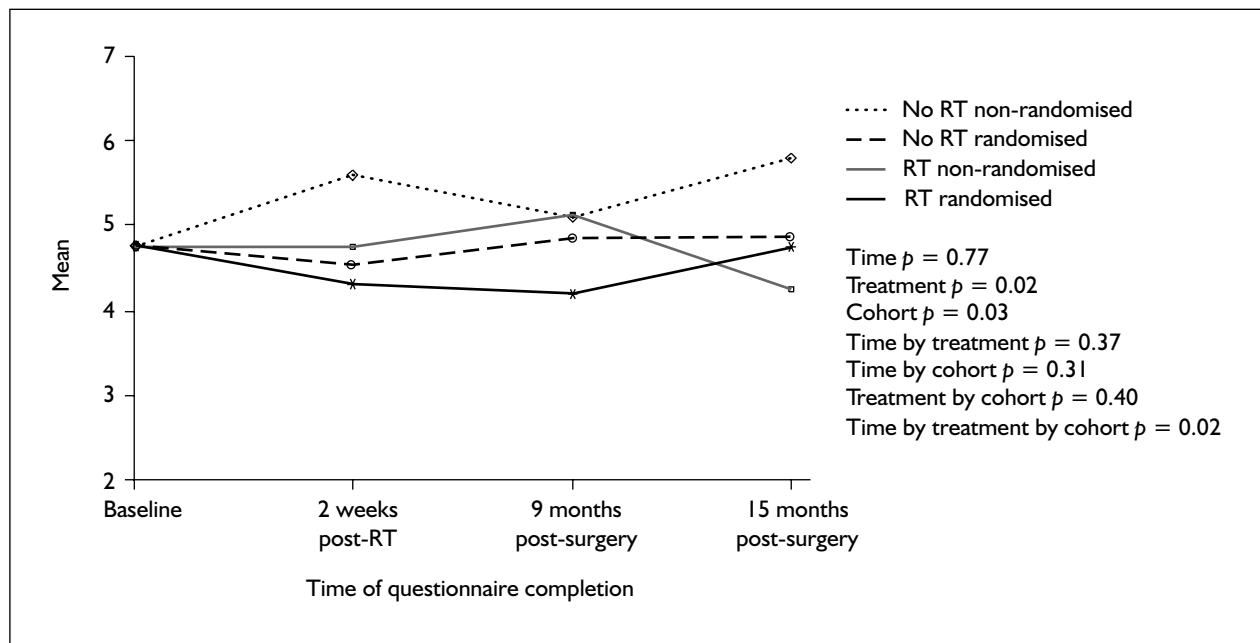


FIGURE 74 Mean score of anxiety by questionnaire

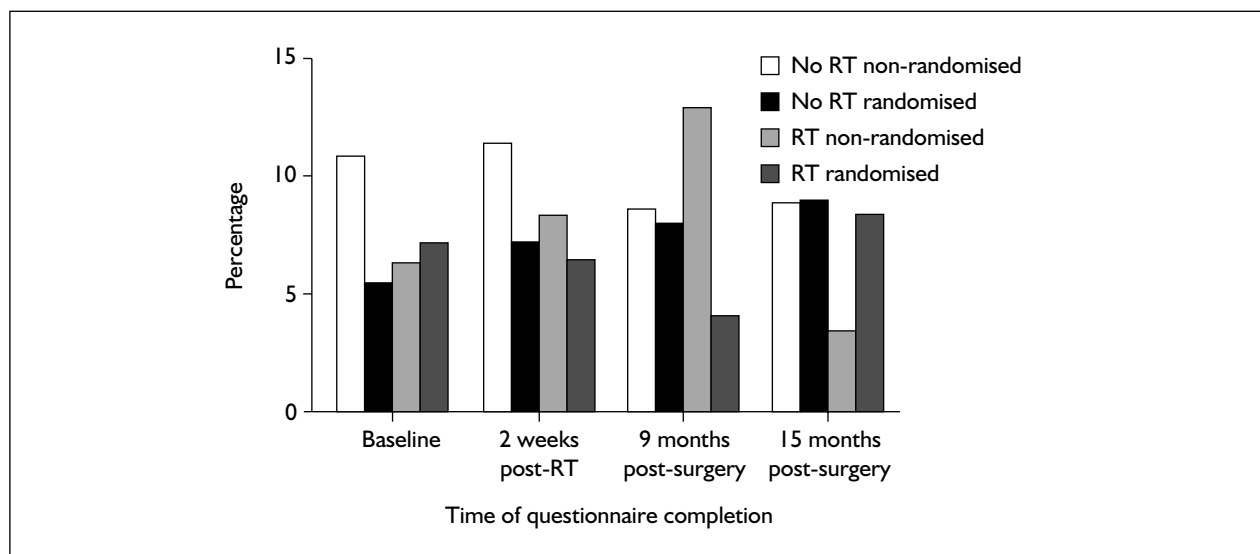


FIGURE 75 Percentage of patients with anxiety scores > 10

lack of precision. The only variable with significantly different estimates for the randomised and non-randomised comparisons is systemic side-effects. In the randomised comparison this variable has significantly higher levels in the no radiotherapy arm. In the non-randomised comparison, there is a greater (but non-significant) difference in the opposite direction. Among the 37 variables reported, a single significant finding is compatible with the hypothesis that the estimates from the randomised and non-randomised comparisons do not differ systematically in this context.

Means and standard errors in bold indicate significant differences between the treatments.

Subjective responses of patients (open-ended questions)

This parallels the results in Chapter 7 for the randomised group. This section compares the spontaneous baseline responses on how breast cancer was affecting the group of patients having their treatment randomly allocated with those who chose their treatment. Similarities and differences

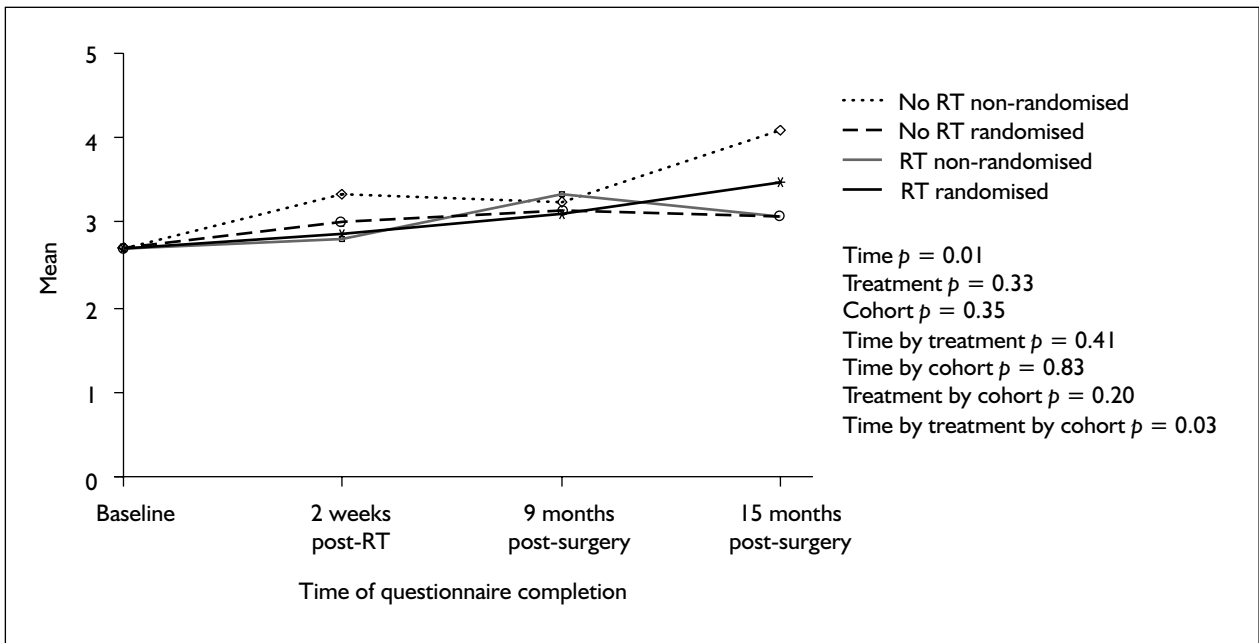


FIGURE 76 Mean score of depression by visit

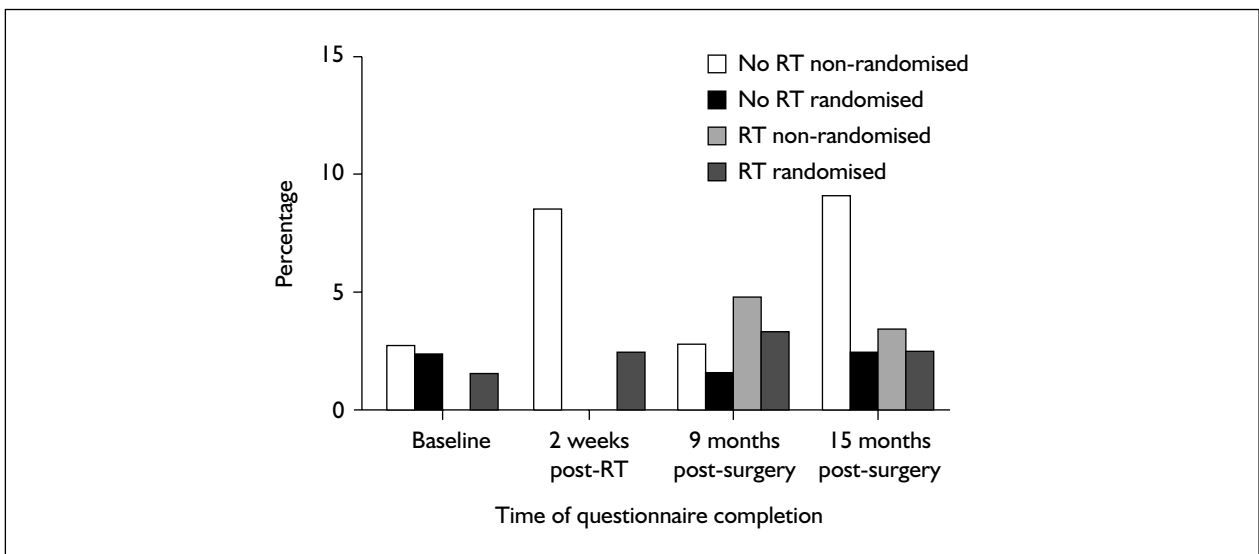


FIGURE 77 Percentage of patients with depression scores > 10

in response over time between the group randomly allocated a treatment and those who chose the same treatment are highlighted but the results are not presented in full detail.

Baseline responses in the randomised and non-randomised groups

At baseline, the themes and frequency of the women’s responses on how breast cancer was affecting them were extremely similar to those of the group who had their treatment randomly allocated. There were, however, some significant

differences in the distribution of responses, although they involved small proportions in most cases.

Negative feelings about surgery

Statistically significant differences in the responses between the two cohorts were noted, first in the number of women agreeable to randomisation who also mentioned negative feelings about their surgery (Table 52). These emotions included feeling rather low or anxious about some aspect of their operation.

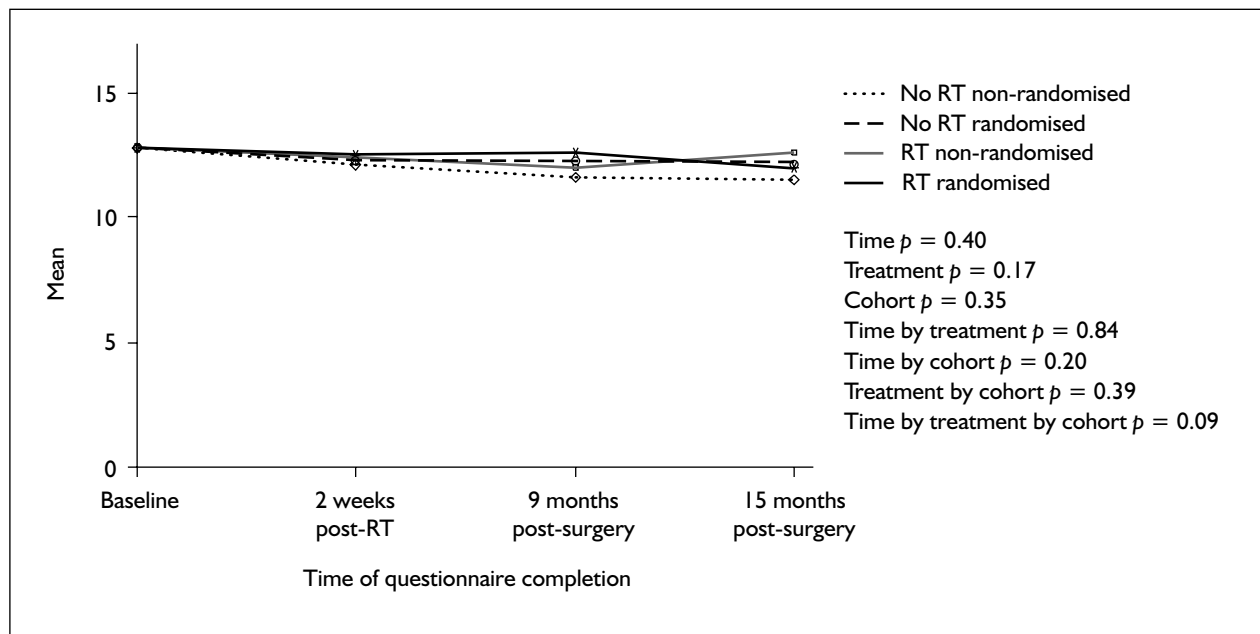


FIGURE 78 Mean score of PGCMS total by questionnaire

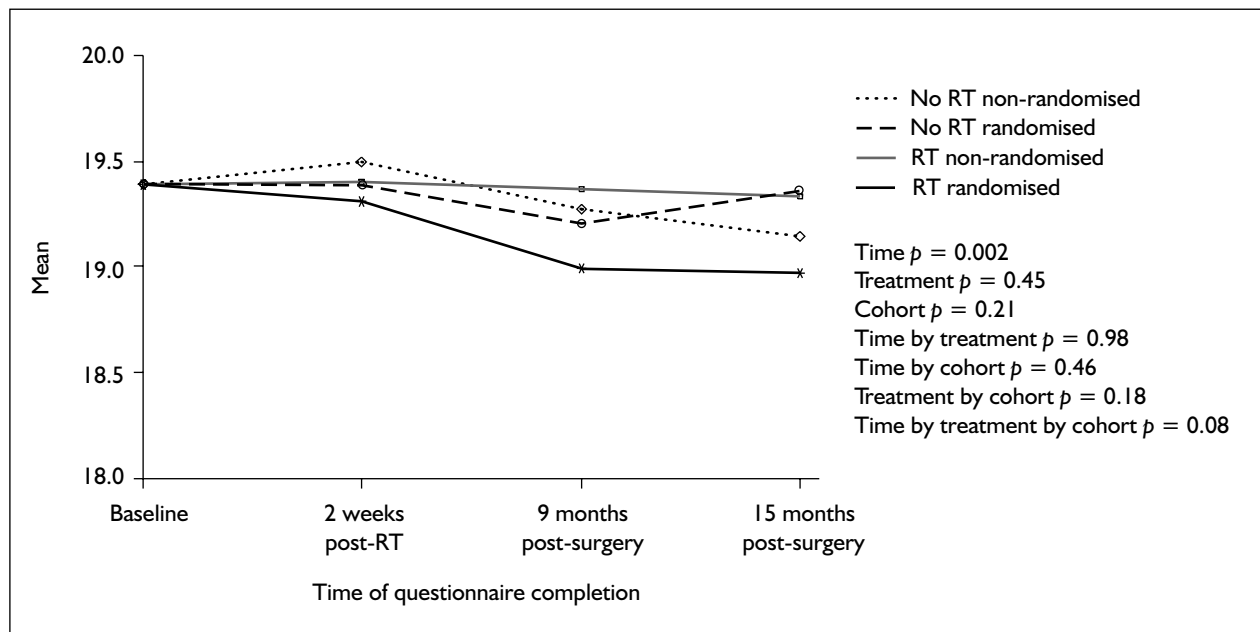


FIGURE 79 Mean score of Barthel Index by questionnaire

Positive attitude to radiotherapy

Significantly fewer in the randomised group voluntarily expressed positive attitudes towards radiotherapy treatment (Table 53). This may only reflect the fact that women in the randomised group did not yet know which treatment they were to have.

Research positive

Significantly more in the randomised trial volunteered positive statements about the research (Table 54).

Trends over time between the randomised and non-randomised groups

This section highlights areas of similarity or difference over the 15 months of follow-up, incorporating the non-randomised group responses.

Effect of breast cancer

- Could I now ask you to say in your own words how your breast cancer has affected you?

Although all groups were similar at baseline, there was a greater tendency for those who chose no

TABLE 51 Mean difference (no radiotherapy – radiotherapy) and standard error of all QoL measures

Measure	Randomised: mean difference (SE)	Non-randomised: mean difference (SE)
EORTC QLQ-C30		
Physical functioning (PF)	-0.77 (1.47)	-1.90 (2.45)
Role functioning (RF)	-0.24 (2.67)	-5.88 (4.43)
Emotional functioning (EF)	-2.66 (1.70)	-0.76 (2.82)
Cognitive functioning (CF)	0.44 (1.63)	1.18 (2.72)
Social functioning (SF)	1.11 (1.74)	3.16 (2.88)
Quality of life (QL)	0.84 (1.62)	-1.72 (2.69)
Fatigue symptoms (FA)	0.13 (1.89)	-2.61 (3.14)
Nausea and vomiting (NV)	-1.00 (0.81)	-1.62 (1.35)
Pain symptoms (PA)	1.18 (2.34)	-0.52 (3.87)
Dyspnoea (DY)	1.02 (1.99)	-4.02 (3.31)
Insomnia (SL)	6.60 (2.59)	7.75 (4.31)
Appetite loss (AP)	-0.13 (1.64)	-0.16 (2.72)
Constipation (CO)	0.05 (1.97)	1.43 (3.26)
Diarrhoea (DI)	-0.13 (1.14)	-0.63 (1.89)
Financial difficulties (FI)	-0.02 (0.86)	1.78 (1.42)
Functionality (mean PF – SF)	-0.27 (1.34)	-0.73 (2.22)
Symptoms (mean FA – FI)	0.61 (0.88)	-0.13 (1.46)
EORTC QLQ-BR23		
Body image (BI)	0.72 (1.23)	-1.25 (2.05)
Sexual functioning (SF)	4.03 (2.17)	0.23 (3.42)
Sexual enjoyment (SE)	9.62 (6.23)	14.22 (6.95)
Future perspective (FP)	1.41 (2.21)	-0.16 (3.68)
Arm symptoms (AS)	-1.94 (1.31)	-2.16 (2.18)
Breast symptoms (BS)	-7.94 (1.26)	-10.11 (2.09)
Systemic therapy side-effects (ST)	2.37 (1.08)	-3.45 (1.81)
Hair loss (HL)	7.74 (6.26)	-6.74 (12.52)
Cough	-2.64 (5.55)	12.33 (12.62)
HADS (maximum score)		
Depression	-0.07 (0.22)	0.49 (0.37)
Anxiety	0.35 (0.25)	0.77 (0.42)
PGCMS (maximum score)		
Total score (17)	-0.15 (0.28)	-0.62 (0.47)
Agitation (6)	-0.19 (0.13)	-0.06 (0.22)
Attitude to own ageing (5)	-0.01 (0.13)	-0.25 (0.21)
Lonely dissatisfaction (6)	0.009 (0.12)	-0.34 (0.20)
Clackmannan Scale		
Total score (30)	-0.04 (0.39)	0.69 (0.65)
Mobile (8)	-0.10 (0.11)	0.39 (0.19)
House care (12)	0.04 (0.20)	0.25 (0.34)
Self-care (10)	-0.001 (0.12)	0.12 (0.20)
Barthel Index		
Total score (20)	0.23 (0.11)	-0.06 (0.18)
Mobile (8)	0.04 (0.04)	-0.08 (0.07)
Self-care (12)	0.14 (0.08)	0.008 (0.13)

TABLE 52 Numbers reporting negative feelings about surgery

Group	Baseline
Randomised	37/253
Non-randomised	0/100
	$p < 0.001$

TABLE 53 Numbers reporting a positive attitude to radiotherapy

Group	Baseline
Randomised	1/253
Non-randomised	8/100
	$p = 0.001$

TABLE 54 Numbers reporting a positive attitude to the research

Group	Baseline
Randomised	13/253
Non-randomised	1/100
	$p < 0.001$

radiotherapy to say breast cancer had no effect on them (Figure 80).

Shock at diagnosis

At baseline, more patients who chose radiotherapy volunteered that they had been shocked by the diagnosis of cancer than those who chose no radiotherapy ($p = 0.002$, Figure 81).

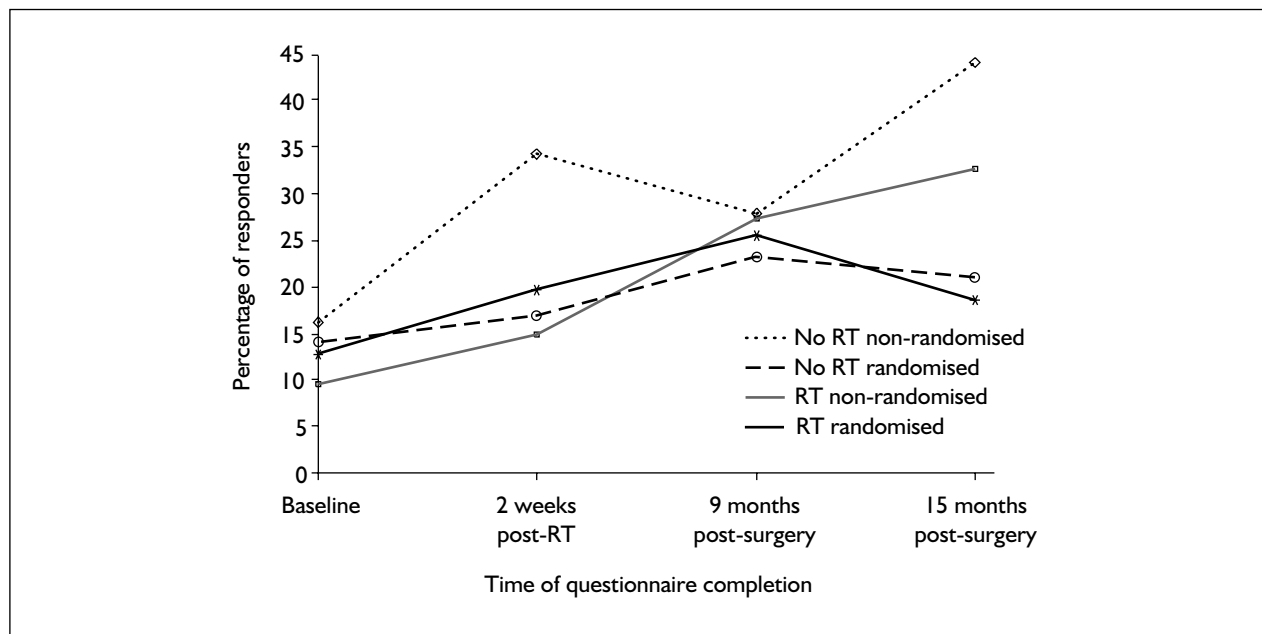


FIGURE 80 Percentage of patients reporting that their breast cancer had had no effect on them

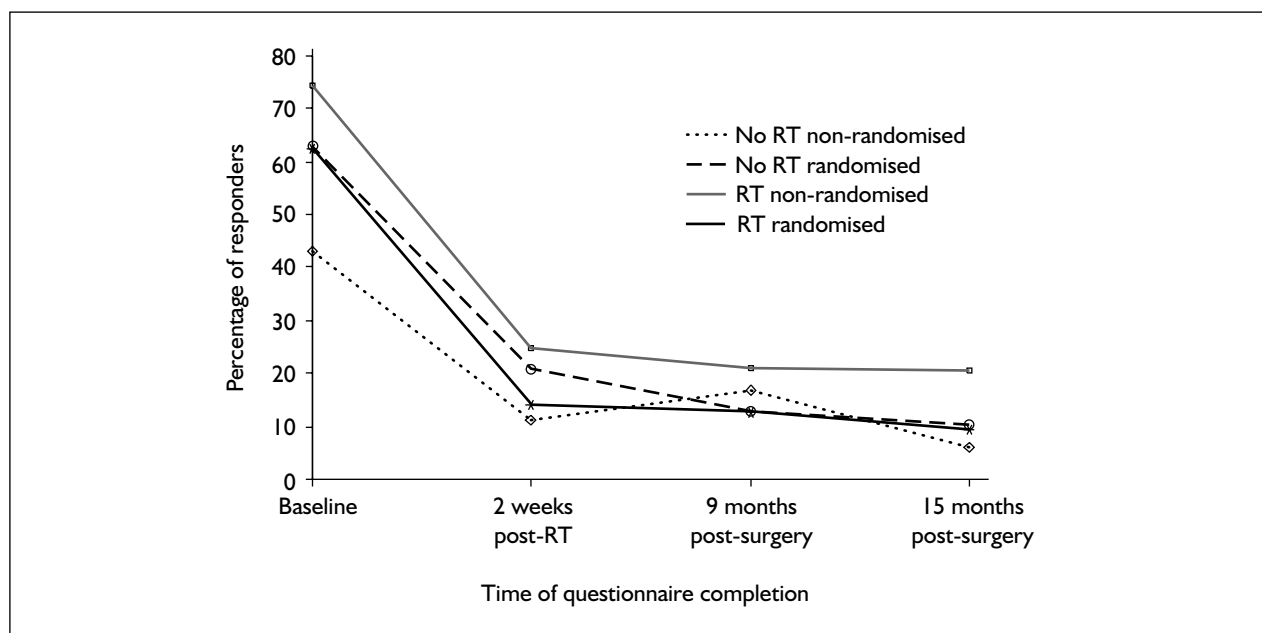


FIGURE 81 Percentage of patients reporting shock at their diagnosis of cancer

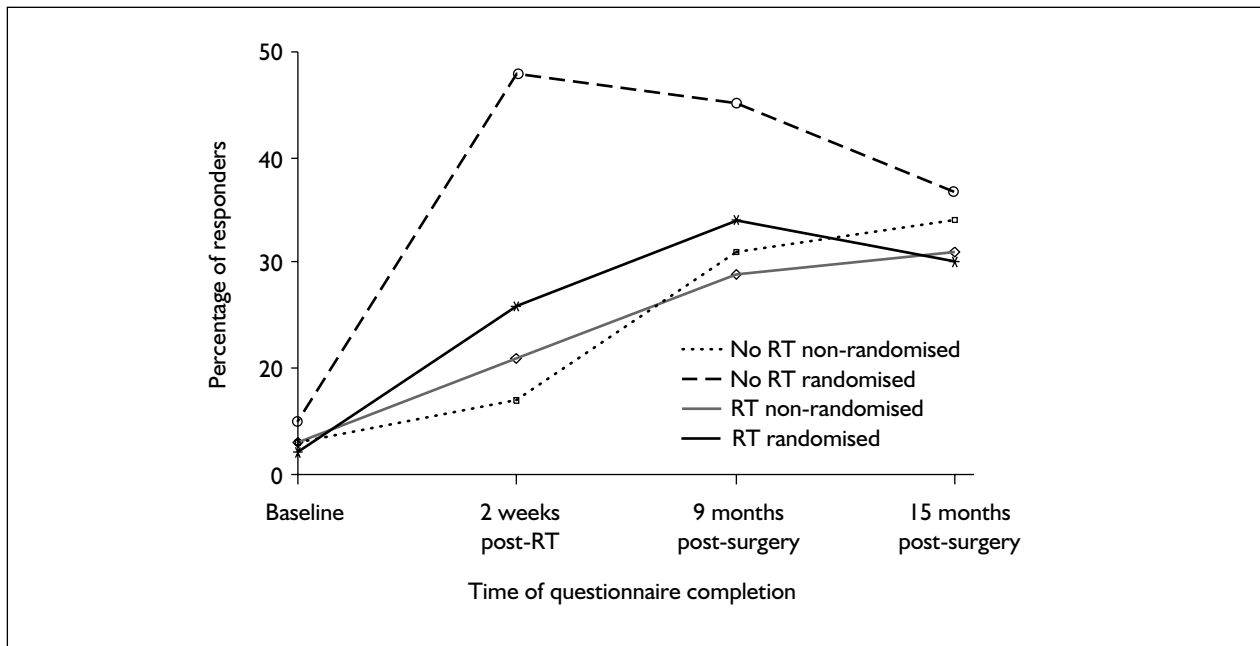


FIGURE 82 Percentage of patients reporting negative effects from endocrine therapy

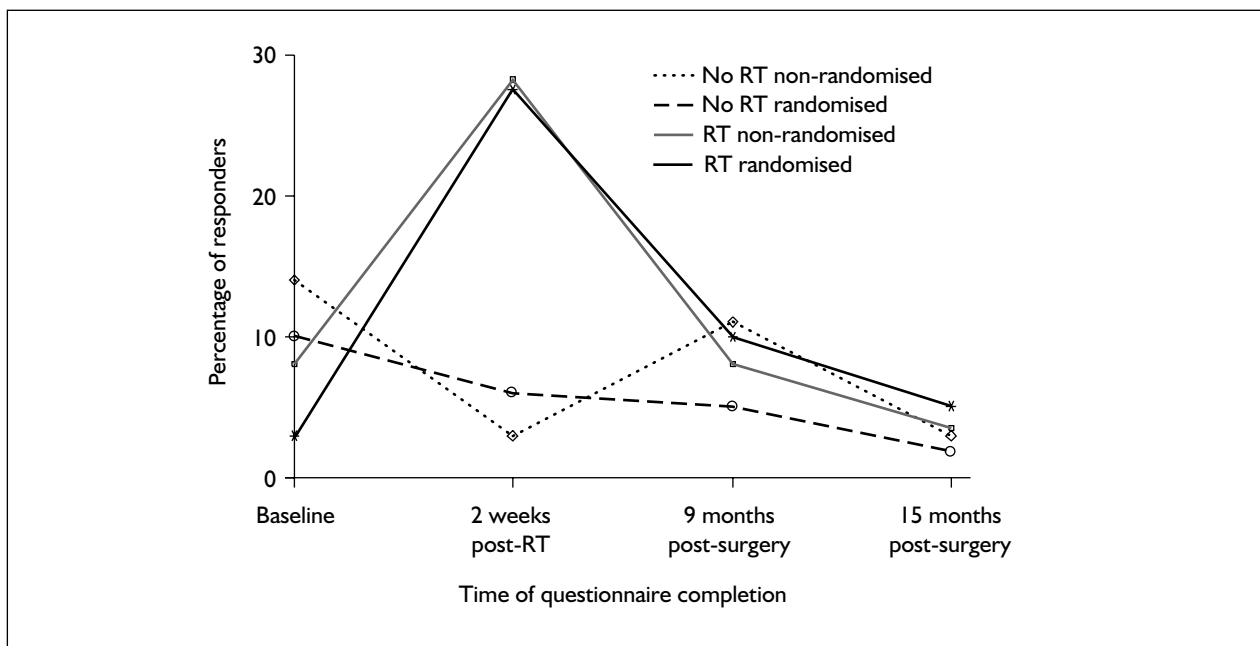


FIGURE 83 Percentage of patients reporting fatigue

Endocrine therapy negative effects

As is evident from *Figure 82*, both non-randomised groups of patients (those choosing radiotherapy and those who chose not to receive it) made proportionally fewer negative comments on endocrine therapy side-effects. However, at the equivalent time to 2 weeks after treatment, a significantly higher proportion of the group ($p = 0.003$) randomly allocated to no radiotherapy described negative effects of endocrine therapy

than in the group selecting no radiotherapy. At later stages there were no statistically significant differences.

Fatigue

As can be seen from *Figure 83*, at 2 weeks after radiotherapy or no radiotherapy, there were significant differences between treatment groups in the proportions of women volunteering comments about tiredness. In the groups receiving

radiotherapy, more than one-quarter commented on this effect. At the same time point, choosing to have radiotherapy, as opposed to being randomly allocated it, does not appear to alter the proportion of women reporting this effect. In later questionnaires, all groups become very similar in the frequency of this response, with around 10 and 5% at 9 and 15 months, respectively, volunteering this effect from breast cancer.

Skin effects

The trend over time and frequency of responses between groups on this theme were very similar to *Figure 83*. Approximately 25% of the women in each of the radiotherapy groups mentioned some skin effect at 2 weeks after treatment. By the time of the 15-month post-surgery questionnaires, this proportion was less than 5% in all groups.

Travel to radiotherapy centre

At the second questionnaire, those choosing radiotherapy mentioned negative aspects of transport less frequently than those randomly allocated to receive radiotherapy (7 versus 29%, $p = 0.0003$ by Fisher's exact test).

Radiotherapy effects

Accommodation provision and arrangements

There were no significant differences in their spontaneous comments on these topics.

Adverse lifestyle effect

At baseline there was a significantly higher proportion ($p = 0.002$, Fisher's exact test) of women who selected to have no radiotherapy than those who were randomised to it, who described some anticipated negative effect on their lifestyle. The proportion was approximately 11% and was not mentioned at baseline by any other group. The actual effects on lifestyle volunteered at 2 weeks after surgery were similar in proportion (approximately 18%) in both groups receiving radiotherapy, and were not mentioned again.

Psychologically negative

The proportions and trends almost exactly paralleled the adverse lifestyle effects (anticipated and actual) which were described in the previous section.

Psychologically positive

The proportions and trend in the positive effects of radiotherapy mirrored the adverse lifestyle and negative psychological impact of radiotherapy above. The proportion commenting positively at baseline was statistically significantly higher

($p = 0.001$) in those selecting radiotherapy than in those allocated to radiotherapy. This may reflect the fact that those in the randomised group did not know which treatment they were having at this point.

Professional care: positive

At baseline, a statistically significant and smaller proportion ($p = 0.002$) of those choosing to have radiotherapy commented on some aspect of professional care which they had appreciated. This was mentioned less frequently at 2 weeks after radiotherapy except in the group who chose radiotherapy (*Figure 84*).

Concern about cancer recurrence

The proportions of comments on this topic at baseline were similar in all groups, with between 2 and 12% of women volunteering some concern about this (*Figure 85*). The proportions continued to be similar at the next two stages but between the 9- and 15-month follow-up period, a significantly higher proportion ($p = 0.003$) of the group who chose to have no radiotherapy were describing concern compared with those who chose radiotherapy. This corresponds to concern increasing in the group choosing not to have the current standard treatment.

Relationships

- *Do you think that your diagnosis of breast cancer has affected your relationship with others?*

The proportions answering that breast cancer was having no effect on relationships were similar in all groups at each questionnaire and gradually increased from approximately 55% at baseline to more than 70% at 15 months.

Patient questions/comments

- *I would like to give you the opportunity to ask any questions or to make any comments about the study*

There was only one significant difference at baseline, with more questions/comments about some aspect of randomisation being made by the women consenting to having their treatment randomly allocated (15 versus 4%, $p = 0.004$).

At the 2 weeks after treatment questionnaire, significantly fewer patients (6%) in the randomised group made comments or had questions about specific questions/items in the questionnaire compared with 15% of women selecting their treatment ($p = 0.014$).

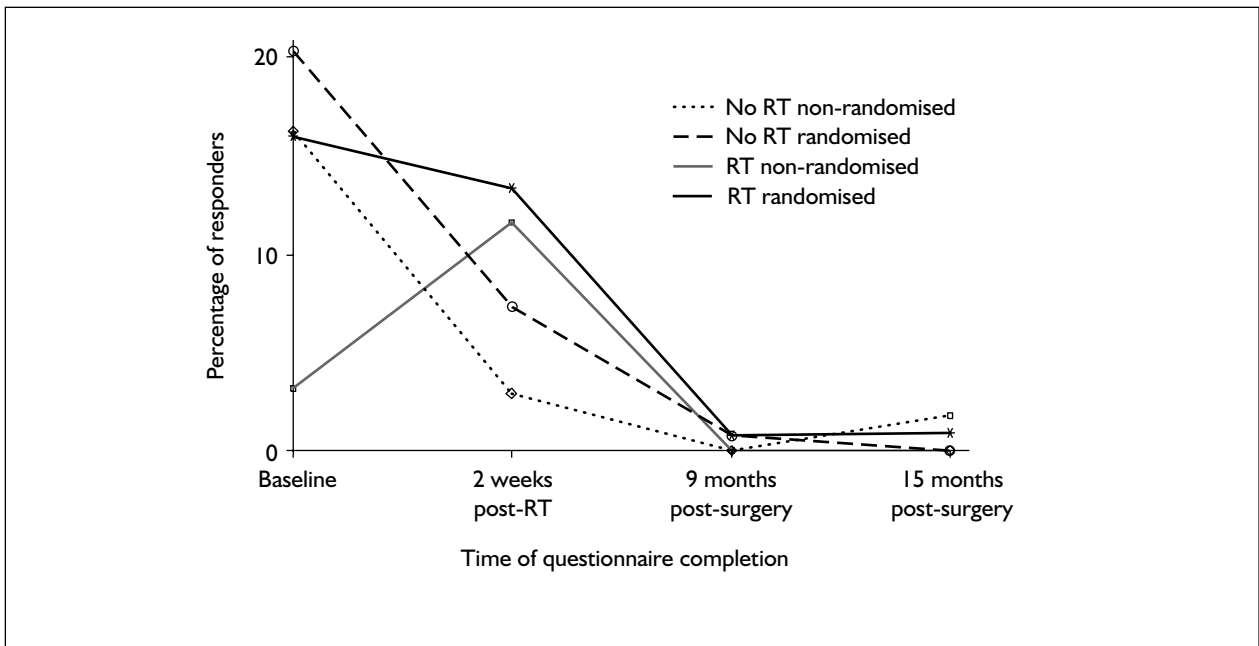


FIGURE 84 Percentage of patients reporting positive professional care

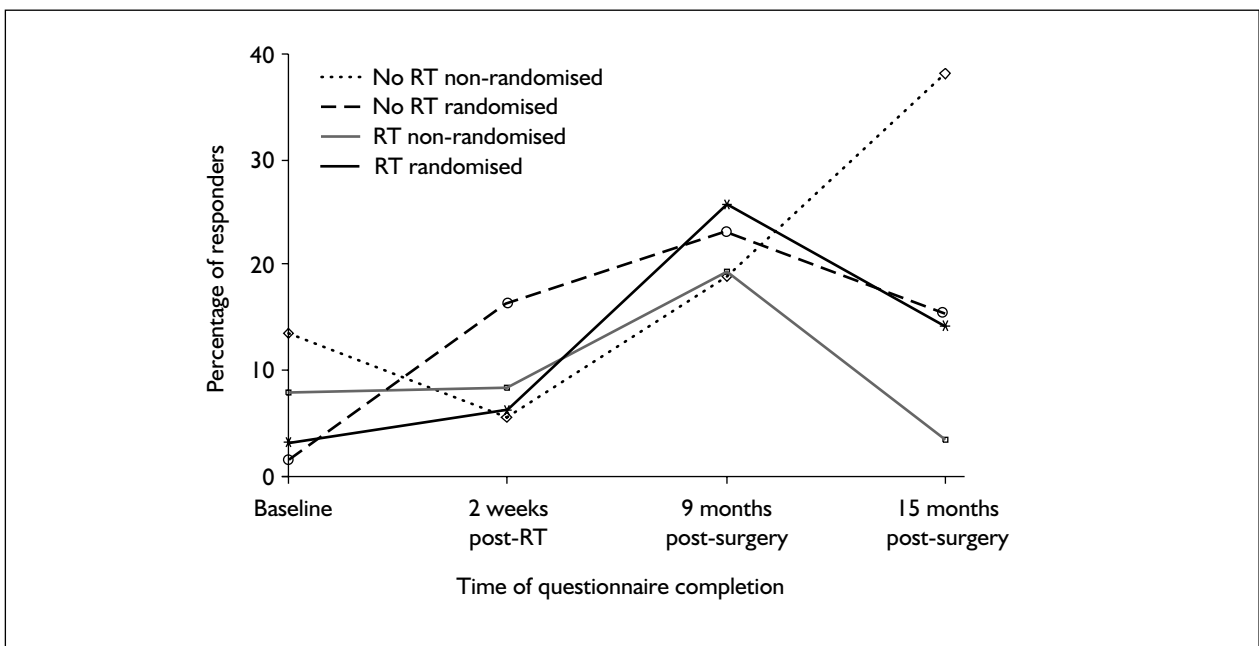


FIGURE 85 Percentage of patients reporting concern over cancer recurrence

At the 9 and 15 months post-surgery stage, significantly fewer women in the randomised group had no questions or comments; 42 versus 57% ($p = 0.006$) at 9 months and 32 versus 46% ($p = 0.02$) at our final questionnaire.

The above suggests that those selecting their treatment may be rather more enquiring or assertive.

Interviewer comments

At baseline, no significant differences were found between groups.

At the 2 weeks post-treatment questionnaire, “no interviewer comments” was recorded for 37% of women participating in the randomised arm versus 49% in the non-randomised study ($p = 0.001$). The above difference was mainly

accounted for by the number of interviewer actions recorded in the randomised patients: 36 versus 24% in those women choosing their treatment. This predominantly consisted of arranging patient follow-up appointments, when they had been omitted or wrongly timed for the purposes of the research.

This may suggest that the normal systems for follow-up are interrupted in a slightly higher proportion of patients participating in the

randomised versus self-selecting treatment group.

Acute and late morbidity

Tables 55, 56 and 57 show the clinical morbidity variables recorded at 2 weeks post-radiotherapy and at 8 and 12 months post-surgery, respectively. These findings are consistent with those in Chapter 8 for the randomised patients alone.

TABLE 55 Acute morbidity at 2 weeks post-radiotherapy or equivalent

	Randomised		Non-randomised	
	Radiotherapy	No radiotherapy	Radiotherapy	No radiotherapy
Acute skin	<i>n</i> = 121	<i>n</i> = 124	<i>n</i> = 60	<i>n</i> = 35
0: None	31	120	10	34
1: Faint/dull erythema	63	4	43	1
2: Tender erythema, moderate oedema or worse	27	0	7	0
Acute lung	<i>n</i> = 121	<i>n</i> = 125	<i>n</i> = 59	<i>n</i> = 35
0: None	115	123	47	34
1: Dry cough, dyspnoea on exertion or worse	6	2	12	1

TABLE 56 Late morbidity at 8 months post-surgery

	Randomised		Non-randomised	
	Radiotherapy	No radiotherapy	Radiotherapy	No radiotherapy
Oedema	<i>n</i> = 111	<i>n</i> = 117	<i>n</i> = 57	<i>n</i> = 32
0: None	76	109	41	32
1: Asymptomatic	28	7	13	0
2: Symptomatic or worse	7	1	3	0
Telangiectasia	<i>n</i> = 108	<i>n</i> = 116	<i>n</i> = 55	<i>n</i> = 31
0: None	102	115	53	31
1: <1 cm ²	3	1	1	0
2: ≥1 cm ²	3	0	1	0
Fibrosis	<i>n</i> = 110	<i>n</i> = 117	<i>n</i> = 57	<i>n</i> = 32
0: None	63	108	39	32
1: Barely palpable	30	4	11	0
2: Definite increased density	17	5	7	0
Retraction	<i>n</i> = 107	<i>n</i> = 113	<i>n</i> = 55	<i>n</i> = 29
0: None	95	104	49	27
1: 10–25%	11	8	5	1
2: >25–40%	1	1	1	1
Pain management	<i>n</i> = 110	<i>n</i> = 115	<i>n</i> = 58	<i>n</i> = 33
0: None	88	105	46	30
1: Occasional non-narcotic	19	8	12	3
2: Regular non-narcotic	3	2	0	0
Lung	<i>n</i> = 110	<i>n</i> = 117	<i>n</i> = 57	<i>n</i> = 33
0: None	102	117	51	33
1: Asymptomatic or mild symptoms or worse	8	0	6	0

TABLE 57 Late morbidity at 12 months post-surgery

	Randomised		Non-randomised	
	Radiotherapy	No radiotherapy	Radiotherapy	No radiotherapy
Oedema	<i>n</i> = 109	<i>n</i> = 119	<i>n</i> = 57	<i>n</i> = 33
0: None	80	112	46	33
1: Asymptomatic	25	6	11	0
2: Symptomatic or worse	4	1	0	0
Telangiectasia	<i>n</i> = 106	<i>n</i> = 118	<i>n</i> = 56	<i>n</i> = 32
0: None	100	118	54	31
1: <1 cm ²	1	0	2	1
2: ≥1 cm ²	5	0	0	0
Fibrosis	<i>n</i> = 109	<i>n</i> = 119	<i>n</i> = 57	<i>n</i> = 33
0: None	61	112	36	32
1: Barely palpable	32	5	14	1
2: Definite increased density	16	2	7	0
Retraction	<i>n</i> = 104	<i>n</i> = 115	<i>n</i> = 56	<i>n</i> = 32
0: None	83	109	52	30
1: 10–25%	21	5	2	2
2: ≥25%	0	1	2	0
Pain management	<i>n</i> = 109	<i>n</i> = 119	<i>n</i> = 56	<i>n</i> = 33
0: None	102	112	52	32
1: Occasional non-narcotic or stronger	7	7	4	1
Lung	<i>n</i> = 109	<i>n</i> = 118	<i>n</i> = 57	<i>n</i> = 32
0: None	107	117	54	32
1: Asymptomatic or mild symptoms or worse	2	1	3	0

Chapter 12

Discussion

Introduction

RCTs have been the gold standard for the evaluation of alternative treatments for several decades, but until recently it has been common to restrict the maximum age of patients entering trials. In the absence of level I evidence in older patients, guidelines, if they exist, are usually based on an extrapolation of the evidence obtained on younger patients. In view of the physiological changes that accompany ageing, and the impact of coexisting diseases that are more prevalent in the older patient, such an extrapolation may not be warranted. The paucity of evidence is of particular concern in countries such as the UK, where demographic changes and improved survival point to a substantial rise in the proportion of older people in the population.

In breast cancer, these problems are compounded by the rising incidence in older patients.² There is already an indication that inadequate treatment of older patients with breast cancer compromises survival,¹⁰⁵ and an evidence base for treating such patients is needed.

In parallel with increasing awareness of the need for RCTs involving older patients there has been a move towards assessing 'softer' end-points such as QoL in addition to the purely 'hard' end-points such as recurrence and mortality. The economic issues of the cost of providing treatment in relation to the patient benefit have also gained prominence, especially in the UK, as budgetary constraints have been imposed. These issues came together in the NHS R&D HTA Programme 96/03 call for research on adjuvant therapies for older women with breast cancer.

PRIME was designed in response to that call and focused on the issue of whether postoperative radiotherapy could be avoided in low-risk older women who were receiving adjuvant endocrine therapy. A complete answer to that question cannot be given until long-term follow-up is completed, but level I evidence has been obtained on the impact on QoL for the first 15 months postoperatively, and the costs of the initial treatment with radiotherapy have been determined.

Recruitment

Recruitment to the trial was not without its difficulties. The explanation is probably multifactorial. In part, this related to the significant proportion of patients 65 years or older treated by breast-conserving surgery who did not meet the entry criteria for the trial (72%). Of those eligible, 62% were offered entry to the trial (see the section 'Recruitment and participant flow', p. 19). In part, this may reflect lack of individual or group equipoise among surgeons and oncologists. We know anecdotally that some patients with a tumour of higher pathological grade or lymphovascular invasion in the primary tumour were assessed as requiring radiotherapy whereas others who were frail or geographically disadvantaged were not offered radiotherapy.

We did not succeed in collecting data about why eligible patients were not offered the trial in all centres, so we cannot identify or quantify the extent to which this was related to physician- or patient-related reluctance to participate. Of those who were offered entry into the trial, 52% agreed to randomisation. In the context of a trial where the non-standard intervention involved less treatment, we feel that this acceptance rate is satisfactory and is similar to that in trials in younger patients.

The trial illustrated the gulf that can exist between overall professional equipoise on treatment choice and individual equipoise. At least one centre did not participate because the clinicians felt that all of the eligible patients should receive radiotherapy, whereas another did not participate because radiotherapy was considered inappropriate in our eligible patient population.

A further obstacle was the delay in the submitting and granting of LREC approvals. This slowed the opening of new centres. During most of the recruitment period of the trial, there was no time limit between the receipt of LREC application and a decision on approval. These concerns have since been addressed by strict time limits introduced in 2004 by the Central Office for Research Ethics Committee (COREC) on the interval between submitting of the protocol to an ethics committee and their decision.

Non-randomised study

The concept of the CCS is no longer new,⁷⁹ but few such studies are undertaken. Our own experience was mixed. Uptake was lower than we would have wished, but it is unsurprising that a substantial proportion of patients with a diagnosis of cancer will not wish to take part in any research. Overall, an estimated 44% of eligible patients (72% of those offered the trial) were either randomised or entered the non-randomised cohort. On the other hand, it did allow to a limited degree, investigation of the influence of patient choice of treatment on QoL outcomes. Although the ages were appreciably different in those choosing radiotherapy and those choosing not to have radiotherapy, overall the differences in outcome between the randomised and correspondingly treated non-randomised patients were small, even though the limited sample size meant that the standard errors were high. Similarly, the difference between the two treatment arms was generally comparable in the randomised and non-randomised cohorts. In this context, any bias from non-randomised comparisons may be relatively small. The non-randomised comparisons were helpful in forming a subjective judgement of whether a surprising observed difference in the randomised trial was likely to be genuine, or an artefact generated by multiple testing.

Missing data and compliance

QoL trials may be handicapped by missing data, particularly if postal questionnaires are utilised. The strategy of employing research nurses to collect QoL data in the patients' homes proved to be invaluable in addressing this problem. The compliance of the patients in completing the questionnaires with the assistance of the research nurse was high, with 98.5% of questionnaires completed at their scheduled time. This would undoubtedly have been considerably lower without input from the research nurse, and the robustness of our conclusions on the impact of the omission of radiotherapy on QoL significantly diminished as a consequence. In addition, the deployment of the research nurses allowed us to collect a rich source of qualitative data from patients using open-ended questions on the impact of breast cancer on their individual lives. This allowed the identification of issues such as the inconvenience and disruption of travelling to the cancer centre daily over 3–6 weeks, difficulties in parking, lack of accommodation close to the cancer centre and concern over recurrence. These and other issues

were not captured by any of the formal measures we adopted, and enhanced our understanding of issues that really matter to the patients.

The study showed the feasibility of a dedicated research nurse in a small trial covering a reasonably wide geographical area. All of Scotland and northern England were covered within PRIME by a single person. A limited number of research nurses covering regions of England and Wales might prove similarly effective, depending on the rate of accrual.

The possibility cannot be excluded that the presence of the research nurses may have influenced how patients responded to the questionnaire. However, we think that the effect is likely to be small and would be similar in degree in both arms of the trial by virtue of the randomisation process. Blinding of the research nurses to the treatment would have guaranteed an absence of bias, but this proved to be incompatible with patients reporting in detail on how the disease and treatment affected their lives. Any disadvantage in this regard was outweighed by the achievement of high levels of compliance by patients with what was a lengthy questionnaire. Overall, feedback from patients on the involvement of the research nurse was very positive.

Co-morbidity

In any trial of older patients, evaluation of treatments may be affected by co-morbidity. More than 80% of patients in the trial reported some form of co-morbidity at baseline (see the section 'Co-morbidities', p. 22). In our original plan, it was not considered feasible to obtain detailed clinical information on the severity of patient co-morbidities, and so many of the common measures of co-morbidity^{106–108} were not considered suitable. However, the Charlson Co-morbidity Index¹⁰⁰ was used to establish a framework for coding the types of co-morbidity, although this was supplemented by other co-morbidities considered more important in terms of QoL (for example, Parkinson's disease, visual difficulties, mental health problems).

This is an important area that requires a consistent method of recording relevant information on an ongoing basis. It is information that would be valuable outwith the clinical trials setting, in addition being highly relevant within it. Capture of these data might be facilitated by new

approaches based on touch-screen technology. Such approaches have been useful in recording depression in cancer patients, although in a younger population,¹⁰⁹ and in recording QoL.¹¹⁰ Acceptability to older patients is still to be established.

In our study, there was only a weak relationship between age and number of co-morbidities. This may have been influenced by older patients with high levels of co-morbidity not being entered into the trial, either through clinician reluctance to impose the additional burden of treatment or patient decision. Although the frequency of co-morbidities was similar in both arms of the randomised trial, there was a significant difference where the patients chose their treatment, with a higher proportion of patients without any co-morbidities opting to receive radiotherapy (see the section 'Comparability of treatment and cohort groups', p. 86).

In the combined cohort of randomised and non-randomised patients, 42% of patients reported some vascular morbidity (hypertension, cerebrovascular, peripheral vascular), 35% had rheumatological co-morbidity and 17% had cardiac morbidity. These accounted for the majority of co-morbidity sources.

Throughout the study, more than 10% of patients in the no radiotherapy group spontaneously reported that the effect of co-morbidities exceeded the effect of breast cancer, with lower proportions in the radiotherapy group (see the section 'Co-morbidities', p. 60). When asked directly about events having a major impact on life in the previous 6 months, a consistently increasing proportion reported negative events, with co-morbidities (see the section 'Negative impact event', p. 65) and bereavement prominent. The excess of such events in the no radiotherapy arm (*Figure 60*) may well have had a differentially negative effect on the QoL of these patients.

In any study of older patients, the impact of these factors needs to be considered. In an age group where health is declining and the death of contemporaries is frequent, these problems will occur with greater frequency than in younger patients.

Instruments employed

The scales chosen for use in the questionnaire were selected to reflect the age of the patients,

their diagnosis and the research question. Thus, the general cancer and breast cancer-specific QoL scales developed by EORTC were employed. EuroQol was chosen so that QALYs could be calculated readily. The recommendations of the British Geriatrics Society and Royal College of Physicians for the assessment of older subjects led to the adoption of the Barthel Index and the PGCMS. A broad range of instruments was used to reflect the multidimensional aspects of 'quality of life' and to ensure that any important differences in QoL were likely to be captured.

With hindsight, we would not have used the PGCMS (see the section 'The Philadelphia Geriatric Center Moral Scale (PGCMS)', (p. 41)). A number of patients commented that some of the questions were too vague about the specific aspect of their lives that they were intended to explore. An example is the first question in the scale, which asks 'Do *things (our italics)* keep getting worse as you get older?' Patients found the word 'things' too non-specific to be able to reply meaningfully. Further questions referring to current expectation, fear and personal difficulties employ similar phraseology. Patients also found it difficult to respond in the yes/no format to some of the questions.

Within the study, it may be that the sample size was too small to detect an important difference in QoL between irradiated and non-irradiated patients. Alternatively, the QoL instruments may have been insufficiently sensitive to identify clinically significant differences in QoL. We believe neither to be the case. The size of the standard error of the treatment difference is less than three units for all of the main EORTC scales. The EORTC and EuroQol QoL instruments were specifically designed for cancer patients. The EORTC QoL scales have undergone extensive field testing and have been widely applied in breast cancer trials. One limitation of the EORTC BR23 QoL scale is that it does not specifically capture the presence or level of concern about recurrence of breast cancer. This concern was identified by patients, as recorded in their spontaneous comments (see the section 'Concern about cancer recurrence', p. 60). Fear of recurrence is likely to be a particular worry among patients who received less than the standard treatment and the results suggest that concern was increasing in the group choosing no radiotherapy (see the section 'Concern about cancer recurrence', p. 98).

The HADS is still widely used among breast cancer patients in routine practice and in research

to assess levels of anxiety and depression, although its limited sensitivity and specificity have been criticised.^{111,112} In addition, at its cut-off score of 11, it may underestimate the level of psychiatric morbidity in individuals below the cut-off level. As a result, it is possible that clinically important levels of anxiety and depression may have been underestimated in both arms of the trial (see the section 'Hospital Anxiety and Depression Scale (HADS)', p. 41).

In the study, the two functional scales (Barthel Index and Clackmannan Scale) were less informative than expected (see Chapter 6). The study population was in relatively good health and the ceiling effects of the Barthel Index were evident. In addition, a number of patients commented that the questions on the activities of daily living studied needed updating to include the use of a washing machine or a vacuum cleaner. Also, the question about heavy shopping was now less relevant to older people due to easier access to private cars, home delivery services and shopping trolleys.

Cosmesis

Cosmesis is an important end-point of breast-conserving surgery and radiotherapy. However, it is limited by the subjective nature of the assessment.¹¹³ Most studies of cosmesis have involved assessment by one or more observers. We used measures of distortion of the breast using displacement of the nipple on the irradiated side⁸⁹ and the more global scale of Harris,⁹¹ which takes into account the overall appearance of the breast. No statistically significant difference was found in the treatment groups for any of the quantitative variables (see the section 'Objective measurement', p. 73). By contrast, two of the three observers who independently rated the cosmesis of the breast on the Harris scale did detect a higher than expected number of patients with fair and poor cosmesis in the irradiated group 1 year after surgery (see the section 'Subjective grading', p. 74). This difference in the findings may reflect differences in breast appearance not attributable solely to nipple displacement, such as the appearance of the scar, skin oedema or skin telangiectasia.

The results are consistent with the findings of Vrieling and colleagues,¹¹⁴ in which nipple displacement and a more global assessment of breast cosmesis were made as part of the EORTC boost versus no boost trial after breast-conserving

surgery and whole breast irradiation. They showed that nipple position is only moderately representative of overall cosmetic outcome. A recent study¹¹⁵ showed that the measurement of nipple displacement improved in its reproducibility with the number of observers and the number of photographs. Maximum precision was achieved with five observers and five photographs. The relatively poor result of the nipple displacement method in the study may relate to the trial comparing only two photographs. In addition, the follow-up at 1 year may have been too short for the nipple to be significantly displaced by breast fibrosis. However, the value of the comparison of the baseline photograph to the postoperative photograph at 1 year is corroborated by a randomised trial at the Royal Marsden Hospital/Gloucestershire Royal Infirmary,¹¹⁶ in which a similar approach to ours was able to discriminate a 10% difference in dose per fraction. On the basis of our experience, it would seem appropriate to use the subjective, more global assessment, of cosmesis rather than the objective measure of nipple displacement in future studies in older patients, if this needs to be assessed at all.

We would hypothesise that older patients would be less concerned about cosmesis than younger women. This notion is supported by the fact that only 2% of patients who received radiotherapy volunteered comments about any cosmetic effects at the 2 weeks postradiotherapy stage and about changes in colour or texture at 9 months and there was no mention at all by 15 months post-surgery (see the section 'Radiotherapy', p. 54). It therefore seems unlikely that measuring cosmesis is a relevant end-point in most older patients.

Treatment differences

Over the 15 months of follow-up, differences emerged between the two treatment groups in some dimensions of QoL whereas other dimensions showed temporal changes that were similar in both treatment arms.

Social functioning

Randomised patients who did not receive radiotherapy had increased their level of social functioning by the time of the first post-randomisation assessment, whereas those receiving radiotherapy remained at their post-surgery level. By 9 months post-surgery, both groups had reached high mean levels of social functioning (see the section 'the EORTC QLQ-C30 scale', p. 25).

This is in accord with a small study⁶⁵ which reported a short-term reduction in pastime activities after radiotherapy. Irradiated patients also commented on issues such as the need to cancel holidays and other lifestyle effects.

Breast symptoms

Non-irradiated patients also recovered more quickly from breast symptoms, whereas those receiving radiotherapy experienced an increase in these symptoms (pain, swelling and skin problems) at 2 weeks following radiotherapy (see the sections 'The EORTC QLQ-BR23 scale', p. 28 and 'Acute morbidity', p. 67). These findings are entirely consistent with the normal course of acute radiotherapy reactions following radical radiotherapy of 40–50 Gy over 3–5 weeks.¹¹⁷ The findings are corroborated by the open responses, where the proportion of comments relating to side-effects on the skin was significantly higher in the group randomised to radiotherapy and in the non-randomised group choosing radiotherapy (see the section 'Radiotherapy', p. 54).

The acute and late morbidities were very much as expected, given the range of dose and fractionation regimes used in the study. Breast erythema was significantly less common in the no radiotherapy arm. At 2 weeks after treatment, almost 75% of the radiotherapy group were recorded by clinicians as having some degree of erythema (see the section 'Acute morbidity', p. 67).

In both groups and for most patients at 2 weeks post-treatment, an absence of lung morbidity was recorded on the acute morbidity forms (see the section 'Acute morbidity', p. 67). This was as expected, since the thickness of lung exposure was to be kept to a minimum of 3 cm, in accordance with the study protocol. However, at a similar time point, the very low levels of dyspnoea/cough recorded by clinicians were at variance with the patient-levels, with dyspnoea in the QLQ-C30 (around 15% in both groups; see the section 'The EORTC QLQ-C30 scale', p. 25) and cough (around 30% in both groups; see the section 'The EORTC QLQ-BR23 scale', p. 28), perhaps reflecting under reporting to the clinical staff.

Breast oedema was recorded significantly less frequently in the no radiotherapy arm at 8 months (7 versus 32%) and at 12 months (6 versus 26%) from surgery (see the section 'Late morbidity', p. 67).

As might be expected, at 8 and 12 months post-surgery there were significant effects from

radiotherapy on the scores for telangiectasia and breast fibrosis and at 12 months on retraction of the breast. However, it is recognised that follow-up at 12 months is too short to assess the maximum extent of such late effects.

Fatigue

Only from the volunteered responses on the effects of breast cancer was there an advantage to the no radiotherapy group in terms of fatigue demonstrated (see the section 'Radiotherapy', p. 54). At the 2-week post-radiotherapy questionnaire, 28% of those receiving radiotherapy spontaneously commented on this effect compared with 2% in the no radiotherapy group. This is consistent with the findings of some small non-randomised studies,^{65,69,118} in which fatigue was the most commonly reported symptom after radiotherapy. Significantly higher levels of fatigue in the radiotherapy group were also found in the large trial reported by Whelan and colleagues.⁶⁰ However, they used different instruments and their measurements of fatigue took place during or very near completion of radiation treatment and not thereafter.

In the PRIME trial, lower fatigue scores in the non-irradiated patients were, surprisingly, not detected by the EORTC fatigue subscale (see the section 'The EORTC QLQ-C30 scale', p. 25). This latter finding concurs with Rayan and colleagues' study results⁶² of postmenopausal women (mean age 70 years). They found no statistical difference in fatigue levels, using the same EORTC instruments, between the group receiving and not receiving radiotherapy, although fatigue and sleep disturbance were the most commonly reported symptoms.

Concern about recurrence

The above sections report areas where there was an advantage to the omission of radiotherapy. There were other areas where the outcome was more favourable in the radiotherapy arm of the trial. For concern about recurrence, the between-group differences were seen more clearly in the responses to the open-ended questions (see the section 'Concern about cancer recurrence', p. 60) than shown in the anxiety levels recorded by HADS (see the section 'Hospital Anxiety and Depression Scale', p. 41). Two weeks after radiotherapy, concern over cancer recurrence was expressed by 16% of those not receiving radiotherapy compared with only 6% of those irradiated. The similar and higher proportions expressing concern at later assessments imply that any reassurance provided by radiotherapy is

short-lived. The non-irradiated patients also expressed more anxiety about the clinical follow-up (see the section 'Anxiety about the process of clinical follow-up', p. 61), which in turn probably reflects concern about recurrence. Interestingly, over one-third of the patients who did not accept randomisation and chose to omit radiotherapy expressed concern about cancer recurrence at their last assessment. It may be that patients who had chosen to have no radiotherapy grew more concerned over time (see the section 'Concern about cancer recurrence', p. 60). It is possible that the level of concern in this group would have been lower if no radiotherapy had been the standard treatment.

Insomnia

The insomnia scale results (see the section 'The EORTC QLQ-C30 scale', p. 25) showed a significant advantage to the radiotherapy group with lower mean scores, which remained consistent throughout follow-up. It may be speculated that fatigue and/or systemic therapy side-effects (see below) are partial contributors to this result. They may also be associated with the greater levels of concern about cancer recurrence that were seen in the no radiotherapy group.

Systemic therapy side-effects

A significantly higher level of systemic therapy (endocrine) side-effects was recorded from the EORTC scale in the no radiotherapy arm of the trial, with a small but consistent increase over the 15 months of follow-up (see the section 'The EORTC QLQ-BR23 scale', p. 28). This effect was replicated and accentuated in the spontaneous comments (see the section 'Endocrine therapy', p. 53), with nearly 40% of non-irradiated patients offering negative comments on endocrine therapy at 2 weeks post-radiotherapy assessment compared with 15% in the radiotherapy group. Even at 15 months post-surgery, 28% of non-irradiated patients in the trial mentioned endocrine side-effects compared with 21% of irradiated patients. The explanation for these differences is unclear. In general, adjuvant endocrine therapy was started at the same time in both arms of the trial. Some of the patients (3.5%) were participating in other studies of neoadjuvant endocrine therapy comparing tamoxifen with aromatase inhibitors (anastrozole and letrozole). However, by virtue of randomisation these patients should have been equally distributed between the two arms of the trial. One possible explanation is that patients while on radiotherapy are normally seen at a weekly review clinic by a nurse, therapy radiographer or doctor. These professionals may

enquire about endocrine symptoms as a routine procedure. These patients may thus be reassured about their symptoms and make less comment about them. However, it might not be expected that this possible explanation would continue through the 15 months.

The numbers of endocrine-related side-effects reported by the clinicians were small (see the section 'Endocrine therapy morbidity', (p. 71), although there are statistically significantly more reports in the no radiotherapy group at 2 weeks after treatment. This concurs, although on a much smaller scale, with the EORTC scales and the open comments reported by patients in the section 'Endocrine therapy', (p. 53).

Physical functioning

In both arms of the trial, the EORTC assessment of physical functioning showed a progressive decline with an overall mean drop of five points during the follow-up (see the section 'The EORTC QLQ-C30 scale', (p. 25). Among any cohort of older subjects, some mean decline would be expected over a 15-month period, but this decline is surprisingly large. Evidence of physical decline was also seen in the Barthel Index (see the section 'Barthel Index', p. 45), and here there was an indication from the trial patients that the decline was greater in patients randomised to radiotherapy. This pattern was not seen in the non-randomised cohort, however, and it may well be a false-positive finding resulting from multiple testing (see the section 'Quality of life outcomes', p. 88).

General pain symptoms (see the section 'The EORTC QLQ-C30 scale', p. 25) showed initial reductions in both treatment arms but, at the end of follow-up, mean levels were similar to those recorded prior to randomisation, and soon after surgery. This may be unrelated to breast cancer and its treatment, and may reflect the influence of co-morbidities, particularly rheumatological. Lower levels of activity and prescribed analgesia in the post-surgical phase may also be an explanation of the patterns observed.

Global quality of life

In view of the significant differences that have emerged from consideration of the qualitative aspects of the questionnaire data, it is perhaps surprising that these differences are not reflected in the global assessments of QoL, through either EORTC or EuroQol. Any observed differences are tiny and non-significant. These agree with the findings of Rayan and colleagues,⁶² using the

same EORTC instruments in a non-randomised study and comparing breast-conserving surgery and tamoxifen with or without radiotherapy. However, any differences in favour of no radiotherapy may have been masked by the excess number of negatively impacting non-breast cancer events (see the section 'Negative impact event', p. 65).

Open-ended questions

From the qualitative data, it is clear that there are specific issues for some patients in the organisation and delivery of radiotherapy services that the formal scales failed to capture. These issues include dissatisfaction with lengthy and sometimes uncomfortable hospital transport from home to the radiotherapy and back, inadequate information about provision of accommodation at or close to the radiotherapy centre and inadequate hospital parking. If these issues had been captured by the QoL instruments, this might have resulted in a significant disadvantage in terms of QoL in the radiotherapy arm. The issues of hospital transport (lengthy journeys and long waits for transport at home or at the radiotherapy centre) and travel costs are particularly pertinent to patients in rural areas, and especially to the older and more frail.

Cost-effectiveness

The estimated difference in QALYs between no radiotherapy and radiotherapy was close to zero (see the section 'QALYs', p. 79). The cost-effectiveness of no radiotherapy compared with radiotherapy is dependent on whether this difference is considered to be important. If it is not important, then no radiotherapy is dominant in that it produces a similar number of QALYs and is less costly. If it is considered important, then no radiotherapy produces fewer QALYs and is less costly. The ICER was £231,449 per QALY. The ratio indicates that withholding radiotherapy saves £231,449 at a loss of one QALY (see the section 'Cost-effectiveness', p. 79). This is well above the conventional threshold of £30,000 per additional QALY and no radiotherapy is therefore highly likely to be considered cost-effective. The CEAC indicated that the probability that no radiotherapy is cost-effective relative to radiotherapy was 94%.

The decision rule used in cost-effectiveness analyses is generally based on a threshold which

represents the decision-maker's willingness to pay for an additional QALY. This was also applied in this study. However, in most situations the new intervention is more effective and more costly than current practice. In this study, the 'new' intervention was less effective and less costly. There is some debate as to whether the same threshold should be applied in those circumstances.¹¹⁹ A higher threshold would reduce the probability that no radiotherapy is cost-effective but it would have to be substantially higher before the conclusions regarding cost-effectiveness would change.

This study adopted a health service perspective and costs to patients and their families were not included. Patients may incur substantial travel and accommodation costs when attending the radiotherapy sessions. This suggests that the cost difference between the two arms would probably have been even larger if a societal perspective had been adopted.

The main limitation of the economic analysis has been the reliance on patient diaries to estimate resource use. With self-report diaries there are concerns over accuracy because of recall error, questionnaire response and completion rates. Attempts were made to increase the accuracy of the data through encouragement and checks by the trial research nurse. Also, evidence is mixed as to whether patient records and self-report diaries produce different estimates of healthcare use.^{120,121} The self-report data on travel to radiotherapy sessions were particularly problematic as the number of journeys did not add up and because of the use of several modes of transport within one journey. Several assumptions therefore had to be made regarding travel costs. The potential impact of this will be explored in further sensitivity analyses.

There were some missing data both from the diaries and for the EQ-5D. Mean and regression imputation was therefore used in the sensitivity analysis (see the section 'Sensitivity analysis', p. 79). Although the difference in QALYs between no radiotherapy and radiotherapy remained close to zero, imputation did result in the difference becoming positive rather than negative. This suggests that patients with relatively low QoL are more likely to drop out in the radiotherapy arm than in the no-radiotherapy arm. It should be noted that several other imputation methods exist and it would be desirable to explore the impact of the different methods on the cost-effectiveness results.

All of the evidence suggests that the ultimate recurrence rate will be higher in the no radiotherapy arm, but the magnitude of any difference is unknown, although likely to be small. This question is one that will be answered by PRIME II. This trial is larger and focuses on recurrence and survival. PRIME is embedded within PRIME II, so the data from the majority of patients included in the present report will also be contributing to PRIME II. By 28 February 2006, 630 patients, including those from PRIME, had been recruited to PRIME II (for which the target is 1000 patients).

To assess fully and robustly the impact of recurrence on the cost-effectiveness of withholding radiotherapy, a Markov model is required to model the longer term costs and consequences. As such an analysis is beyond the remit of this study, only a crude threshold analysis was performed. The results of this analysis showed that withholding radiotherapy would have to result in at least a 5.5% increase in local recurrence before radiotherapy would be considered cost-effective at the £30,000 threshold.

Chapter 13

Conclusions

This study provides the first level I evidence evaluating the QoL of low-risk older women with breast cancer, following wide local excision, axillary surgery and adjuvant endocrine therapy. Although there were no clinically significant differences in overall QoL scores, within the first 15 months postoperatively, significant differences were detected between patients receiving or not receiving adjuvant breast radiotherapy within several QoL subscales, including breast symptoms, social functioning, fatigue, insomnia and systemic therapy side-effects.

The acute morbidity recorded by clinicians showed that breast erythema was significantly more common in the radiotherapy arm, at 2 weeks from completion of treatment. At 8 and 12 months after surgery, breast oedema and telangiectasia were observed significantly more in women who had radiotherapy. At 12 months, breast retraction scores were significantly higher in the radiotherapy group. The extent of late morbidity effects will be further assessed as follow-up continues.

There was an indication from the observer-rated breast photographs, at 12 months after surgery, that a significant excess of patients with fair and poor cosmesis was observed in women who had radiotherapy treatment. Very few women, however, expressed concern about cosmetic outcome.

As is often the case with less aggressive forms of cancer, the early postoperative outcome does not give a complete answer to treatment effectiveness. Over the time horizon of the trial, radiotherapy for this group of patients is not a cost-effective treatment. The eventual benefit to the patient and cost-effectiveness will only become apparent when the magnitude of any excess local recurrence in patients not receiving radiotherapy in the PRIME trial becomes clear. An appropriately powered trial to assess the longer term clinical outcome in this patient population is required, and PRIME II, which is currently recruiting, will meet this need.

At present, the cost of treating local recurrences is not known for older patients as none have occurred within PRIME, and research is needed to

establish this cost. In the absence of such data, only relatively crude extrapolations can be made. These suggest that radiotherapy in this population may not be a cost-effective treatment unless it results in a recurrence rate that is at least 5% lower in absolute terms than those treated without radiotherapy.

Our qualitative data have revealed QoL issues important to patients which were not identified by any of the standard instruments we used. This argues for the inclusion of qualitative data to complement standard QoL scales in future studies. Issues include transport to and from a radiotherapy clinic, lack of information about residential accommodation and concern over cancer recurrence. The information on QoL outcomes that we have obtained in PRIME may be helpful in designing patient-focused care plans until such time as longer term follow-up establishes an overall advantage or disadvantage to the use of postoperative adjuvant radiotherapy. The issue of the extent to which patients wish to be involved in the design of their care plan is important, but outwith the scope of this trial.

We confirmed a substantial level of co-morbidity within the study population, and this is a competing risk of mortality. It also has a major impact on QoL for an appreciable proportion of patients. It is, therefore, important in QoL studies, particularly in older patients, that co-morbidity data are collected in a systematic way. Our ability to quantify the impact of co-morbidity on the measured QoL was restricted by the present focus on mortality displayed by the co-morbidity instruments.

Implications for healthcare

In the study population of older, low-risk patients with early breast cancer, following treatment with breast-conserving surgery and adjuvant endocrine therapy, the following implications for healthcare were identified:

- The evidence suggests that there are significant differences in some dimensions of QoL, although there is no significant overall QoL

advantage in the omission of adjuvant radiotherapy.

- Although there are clear indications that there is a short-term economic benefit from the omission of radiotherapy in this group of patients, the evidence for the longer term benefit has yet to be determined.
- Comprehensive capture of QoL and co-morbidity data may be facilitated by nurse-led home assessment.
- Cosmesis, although impaired by radiotherapy, appears to be of limited importance to the majority of patients within the first 15 months following surgery.
- More needs to be done to improve access to hospitals for older patients, as inadequate patient transport, hospital parking and accommodation during treatment (when required) are significant sources of stress.
- Older low-risk patients have significant concerns about the recurrence of breast cancer, even following radiotherapy.

Recommendations for further research

The following recommendations are made for further research:

- Obtain long-term data on QoL and clinical outcomes in PRIME or similar trials.
- Further economic modelling on the longer term costs and consequences of omitting radiotherapy
- Investigate the application of novel methodologies (such as touch-screen technology) for capturing and grading co-morbidity and QoL at baseline and at clinical follow-up.
- Investigate the influence of specific types and degrees of co-morbid disease on QoL.
- Refine methodologies and develop software to integrate the prediction of recurrence rates from breast cancer with the competing effects of mortality from other diseases to improve clinical decision-making.
- Develop a validated questionnaire/scale to assess the impact of access to healthcare services.



Acknowledgements

We would like to thank all the research nurses/radiographers and clinicians in each trial centre for all their hard work and patience in this labour-intensive trial. We would especially like to thank all the patients who gave their time to participate in the trial. Thanks must also go to the HTA, who were supportive and encouraging, particularly during the early days when recruitment was slower than expected. Without their support and understanding, this trial would not have been completed so successfully.

We would also like to thank the following for their assistance: Mr Ronnie Robertson, Mr Colin Ferrington and Ms Carol Miller, for their help in the digitisation and measurement of the cosmesis photographs; Ms Alison Finney, who covered for Mrs Cecilia King during holiday periods; Dr Pamela Warner, who commented on an early draft of the qualitative aspects; and Dr Angus Bancroft, who critically assessed the operational definitions and proposed system for categorising the open-ended question responses.

Thanks are also due to the other grantholders who, despite involvement in the setting up of the trial, were unable to contribute to the final report: Mr JM Dixon, Dr Sue Shepherd and Professor David George. We also gratefully acknowledge the support and guidance of the Steering Committee and Data Monitoring Committee (see Appendix 7 for membership lists).

Contribution of authors

Robin J Prescott (Professor of Health Technology Assessment, Statistician) was the Principal Grantholder, was involved in all stages of the study

and report development and provided guidance on the statistical analysis. Ian Kunkler (Consultant Clinical Oncologist) was a grantholder and the Principal Clinical Investigator who was deeply involved in the trial from conception to publication, including design, organisation, entering patients, interpreting results and preparing the report. Linda Williams (Research Fellow, Statistician/Administrator) administered the trial, conducted the statistical analysis, undertook much of the preliminary drafting and prepared the report for publication. Cecilia C King (Research Nurse) was responsible for much of the data collection, was a member of the management team, wrote the first draft of the quality of life background section and the results from the open-ended questions and was a member of the writing team. Wilma Jack (Clinical Research Fellow) was involved in the trial from conception, gave advice on patient-related matters, was a member of the management team and was a member of the writing team. Marjon van der Pol (Senior Research Fellow, Health Economics) was responsible for the economic evaluation and contributed to the preparation of the report. T Goh (Research Assistant, Health Economics) conducted the economic analysis and prepared the economic evaluation for the report. Richard Lindley (Professor of Geriatric Medicine) was a grantholder, gave expert advice on aspects of the trial from the perspective of a geriatrician and made detailed comments on later drafts of the report. John Cairns (Professor of Health Economics) was a grantholder, wrote the health economics section in the protocol, and commented on later drafts of the report.



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Appendix I

Forms

The following forms are presented:

1. Informed consent form
2. Patient information sheet
3. Completion of radiotherapy form
4. Health service resource diary
5. Adverse events form.

**PRIME (Post-operative Radiotherapy In Minimum-risk Elderly)
Breast Cancer Trial**

Informed Consent Form

Name of patient:

Name of clinician:

Hospital:

The aims and procedures of the clinical trial I have been asked to take part in have been explained to me by I have read and understood the patient information leaflet provided. I have been informed about the possible benefits to myself and about any reasonably foreseeable risks or discomfort, and have had sufficient time to decide.

I have had the opportunity to ask questions and consider the answers given.

I understand that participation in the trial is voluntary and that I may withdraw from the trial at any time of my own accord and that if I do, it will not affect the future care and attention which I receive from my doctors.

I understand that all records relating to this trial will be kept confidential and all data will be secure against unauthorised access.

I understand that my General Practitioner will be informed of my participation in this study and will be advised of any clinically significant information that comes to light.

I hereby freely give my consent to take part in this clinical trial.
(Signature on this form does not affect your legal rights).

Patient's signature: **Date:**

I confirm that I have explained the nature of this clinical trial to the above named patient and that she has understood the explanation given to her.

Investigator's signature: **Date:**

Witness to written consent

Name: **Signature:**

Relationship to patient: **Date:**

Further information is available from: Cancer BACUP on 0808 800 1234, Monday to Friday, 9am – 7pm. or Dr. I. Kunkler, Department of Clinical Oncology, Western General Hospital, Crewe Road, Edinburgh EH4 2XU. Telephone: 0131 537 2214

Invitation to participate in the PRIME Trial

Patient Information Sheet

We would like to invite you to take part in the PRIME (Post-operative Radiotherapy In Minimum-risk Elderly) Breast Cancer Trial. To help you decide if you would like to take part we have prepared this information sheet to give you some further details about the trial which you can keep.

Introduction

You have recently been diagnosed with early breast cancer which has been completely removed by surgery. An anti-cancer drug, often Tamoxifen, will also be given as part of your treatment for five years and reduces the risk of the cancer returning. Another therapy which is currently routinely offered is radiotherapy to the breast. The radiotherapy is given to the affected breast and it is thought that it reduces the chances of the cancer coming back within the breast.

There is some evidence that in older women radiotherapy may not always be needed and, like many treatments, it also has both short and long term side effects. Apart from the evidence that radiotherapy might not be needed in older women, it may not be required in women such as yourself who are at low risk of their cancer returning because your cancer: (1) has been removed with a generous margin of normal breast tissue; (2) did not have any bad features when examined by the pathologist under the microscope; and (3) has not spread to the lymph glands under your arm.

On this basis we would like to ask you to take part in our trial to help us decide whether radiotherapy is necessary for women with your particular type of cancer. Your specialist has indicated that he thinks that you are suitable to take part in the PRIME trial.

What will I have to do if I take part?

The trial will involve 240 women who will each be followed up for 5 years. If you agree to take part you will be reviewed by a nurse either at home or in the clinic whichever is most convenient to you and you will be asked to complete a questionnaire. To determine whether or not you will receive radiotherapy, your specialist will telephone a central office which runs the PRIME trial, to enter you in the trial. The trial office will check some details about you, your disease and the treatment you have been prescribed and will use a computer to allocate your treatment. You will have the same chance of receiving radiotherapy as you will of not receiving it. Your specialist will be told whether you have been allocated a course of radiotherapy.

The nurse will arrange three visits over 15 months and on each visit you will again be asked to complete a questionnaire which will monitor how you are coping with your condition and how you are feeling and managing at home. In addition, a short version of the questionnaire will be sent to you by post for self-completion at 3 and 5 years after surgery. You will also be seen three times during the first 15 months in hospital clinics for a routine examination by your specialist. This is to check that the cancer remains under control. It is also hoped to arrange a photograph of your breasts at two of your clinic visits. This will allow us to look at changes in the breast which have occurred as a result of your treatment. At the end of the trial you will continue to be reviewed by your specialist on a regular basis. A mammogram will be done at one year after your surgery. During the trial you will be asked to keep a record of all health and social services that you received.

If you decide not to take part in the trial you will receive the usual high standard treatment that is currently employed for patients with early breast cancer. You will be offered radiotherapy and be followed up at the surgical outpatient clinics in the usual way.

What does radiotherapy involve?

Radiotherapy to the breast is usually carried out over four to five weeks, usually as an outpatient. For the first attendance a series of breast measurements are taken to plan your further treatment. The radiotherapy is normally given to the breast in a small dose each day. Treatments are given for 10 to 15 minutes per day on weekdays. No treatment is given over the weekends. Four to five additional daily treatments may also be given to the site where the original cancer was excised. This extra treatment is normally given in the week following the initial course of radiotherapy to the whole breast.

What are the possible risks of taking part?

Like all treatments there may be side effects with radiotherapy. Radiotherapy may cause skin reactions leading to breast tenderness and itching. These develop in the latter part of the course of radiotherapy and usually settle within one month of the treatment finishing. Breast pain, which is usually mild and intermittent, commonly occurs up to two years post-radiotherapy, but is less troublesome thereafter. Rarely radiotherapy may cause inflammation of the lung causing shortness of breath or it may cause ribs to fracture.

The possible risk of not being given radiotherapy is that there may be a slightly higher chance of the breast cancer coming back compared to women who have received radiotherapy. However, in women aged 65 or more, we know that the chance of the breast cancer returning is lower than in younger women. Also, from our knowledge of the results of your surgery and the type of your particular tumour we believe that the risk of your cancer coming back in the treated breast is much lower than average. If your cancer did recur in your breast further surgery would be considered.

Are there any benefits from taking part?

Whether or not you take part in the trial you will receive the highest standards of care. The information that we get from the trial will help us gain knowledge about the best way of treating breast cancer. It will help us to measure the advantages and disadvantages of radiotherapy for women aged 65 or more who are diagnosed with early breast cancer, using assessments that are relevant to them.

Do I have to take part?

No, taking part is voluntary. If you would prefer not to take part you do not have to give a reason. Your doctor would not be upset and your treatment would not be affected. If you take part but later change your mind you can withdraw from the trial without hindrance or detriment to your future treatment. We will give you a copy of your consent form to keep.

We would want to inform your GP that you are taking part with your permission and will send him/her a copy of your consent form.

Confidentiality

All the trial data will be confidential to the research team. You will not be identified in any published results.

What do I do now?

The research sister for the trial will contact you in a day or so. She can answer any questions and you can let her know if you are interested in taking part.

Thank you very much for considering taking part in our research. Please discuss this information with your family, friends or GP if you wish.

Local investigator:

If you would like to obtain independent advice about this research you may contact:

Please arrange the next oncology appointment for 2 weeks post-radiotherapy

Patient's surname: First Names:
Trial no.:
Hospital/Clinic:
Consultant's name:
Date:

Radiotherapy treatment

1) Whole breast Target absorbed dose Gy Number of fractions
Date of start Date of completion

2) Boost None
Electrons Max dose Gy Number of fractions
Implant 80% Reference isodose
Date of start Date of completion

Other investigations/treatment during radiotherapy YES / NO

If YES, specify:

.....
.....
.....
.....

Referral to other consultants/hospitals during treatment YES / NO

If YES, specify:

.....
.....
.....
.....

PRIME
Post-operative Radiotherapy In Minimum-risk Elderly
 Breast Cancer Trial

Please complete this section in addition to the table inside.

Date	Medication	Dose	Frequency

PLEASE FOLD HERE

Diary number:

Patient Initials: _____

Patient Trial No: _____

PATIENTS – Please ask any medical or nursing personnel whom you see for any reason during this study to complete the details overleaf. If you forget, please fill in as best you can. **THERE IS NO NEED TO RECORD VISITS TO THE RADIO THERAPY DEPARTMENT (IF APPLICABLE) AS THIS WILL BE RECORDED AT THE END OF RADIO THERAPY.**

Doctors, Nurses etc. – Please complete this Diary at every contact with this study patient (excluding radiotherapy treatments). It will only take a few seconds but is vitally important for this study. Thank you for your co-operation

Hospital:
 Study Nurse:

Study Co-ordinator: Dr Linda Williams
 0131 651 1631 (tel/fax)

Adverse Events form

Patient's surname: First Names:

Trial no.:

Hospital/Clinic:

Consultant's name:

Date of examination (dd/mm/yy): / /

Cytological/histological confirmation

Details of recurrence	Confirmation?	DATE dd/mm/yy
Local recurrence (LR)	YES / NO / /
Regional recurrence (RR)	YES / NO / /
Contralateral breast primary	YES / NO / /

Further Investigation (please tick)

Mammogram	<input type="checkbox"/>	Liver Function Test	<input type="checkbox"/>
Fine Needle Aspiration	<input type="checkbox"/>	Chest X-ray	<input type="checkbox"/>
Core Biopsy	<input type="checkbox"/>	Bone Scan	<input type="checkbox"/>
Breast Ultrasound	<input type="checkbox"/>	Liver Ultrasound	<input type="checkbox"/>
Full Blood Count	<input type="checkbox"/>	MRI scan	<input type="checkbox"/>
		CT scan	<input type="checkbox"/>

Further Treatment required (please tick)

Breast surgery – Wide Local Excision	<input type="checkbox"/>	Date of surgery:	/.....	/
– Mastectomy	<input type="checkbox"/>	Date of surgery:	/.....	/
Axillary surgery – Sample	<input type="checkbox"/>	Sentinel node	<input type="checkbox"/>	
– Clearance	<input type="checkbox"/>	None	<input type="checkbox"/>	
Pathology: Grade:		Type:		
		Specify:		
Systemic Therapy – Endocrine	<input type="checkbox"/>		
Systemic Therapy – Cytotoxic	<input type="checkbox"/>		
			
Radiotherapy – Breast	<input type="checkbox"/>	If Radiotherapy is required:		
Radiotherapy – Breast and axilla	<input type="checkbox"/>	Number of fractions:		
		Number of days as outpatient:		
		Number of days as inpatient:		

Transport		Number of journeys
Own	<input type="checkbox"/>	_____
Hospital Car	<input type="checkbox"/>	_____
Hospital Ambulance	<input type="checkbox"/>	_____
Other (specify)	<input type="checkbox"/>	_____
Palliative care	<input type="checkbox"/>	

Appendix 2

Quality of life measures

The following forms are presented:

1. EORTC QLQ-C30
2. EORTC QLQ-BR23
3. Hospital Anxiety and Depression Scale
4. EuroQol
5. Philadelphia Geriatric Center Morale Scale
6. Clackmannan Scale
7. Barthel Index
8. Summary of variables

EORTC QLQ-C30

Responses to these questions (other than questions 29 and 30) were on a four-point scale of “Not at all”, “A little”, “Quite a bit” and “Very much”, and were asked in relation to the week prior to the interview.

1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?
2. Do you have any trouble taking a long walk?
3. Do you have any trouble taking a short walk outside of the house?
4. Do you have to stay in a bed or a chair during the day?
5. Do you need help with eating, dressing, washing yourself or using the toilet?
6. Were you limited in doing either your work or other daily activities?
7. Were you limited in pursuing your hobbies or other leisure time activities?
8. Were you short of breath?
9. Have you had pain?
10. Did you need to rest?
11. Have you had trouble sleeping?
12. Have you felt weak?
13. Have you lacked appetite?
14. Have you felt nauseated?
15. Have you vomited?
16. Have you been constipated?
17. Have you had diarrhoea?
18. Were you tired?
19. Did pain interfere with your daily activities?
20. Have you had difficulty concentrating on things, like reading a newspaper or watching television?

21. Did you feel tense?
22. Did you worry?
23. Did you feel irritable?
24. Did you feel depressed?
25. Have you had difficulty remembering things?
26. Has your physical condition or medical treatment interfered with your family life?
27. Has your physical condition or medical treatment interfered with your social life?
28. Has your physical condition or medical treatment caused you financial difficulties?

The following two questions were to be rated on a seven-point scale from “Poor” to “Excellent”.

29. Could I now ask you to rate your overall health during the past week?
30. How would you rate your overall quality of life during the past week?

EORTC QLQ-BR23

As for the C30, responses to these questions were on a four-point scale of “Not at all”, “A little”, “Quite a bit” and “Very much”, and were asked in relation to the week prior to the interview. Questions X1 and X2 were added by the trial team to record any instances of a cough, X3 was included to allow patients the option to decline the sexual questions and X4 was added to record in which breast the cancer had been found.

- X1. Did you have a cough? (Answered Yes/No).
If yes: X2. How much has it affected you?
1. Did you have a dry mouth?
 2. Did food and drink taste different than usual?
 3. Were your eyes painful, irritated or watery?
 4. Have you lost any hair?
 5. Were you upset by the loss of your hair?
 6. Did you feel ill or unwell?
 7. Did you have hot flushes?
 8. Did you have headaches?
 9. Have you felt physically less attractive as a result of your disease or treatment?
 10. Have you been feeling less feminine as a result of your disease or treatment?
 11. Did you find it difficult to look at yourself naked?

12. Have you been dissatisfied with your body?
13. Were you worried about your health in the future?
- X3. The questionnaire that we are using has 3 questions on sexual matters. We realise that this can be a sensitive area, but are you willing for me to ask you these questions?
14. To what extent were you interested in sex?
15. To what extent were you sexually active? (with or without intercourse)
16. To what extent was sex enjoyable for you?
17. Did you have any pain in your arm or shoulder?
18. Did you have a swollen arm or hand?
19. Was it difficult to raise your arm or to move it sideways?
20. Have you had any pain in the area of your affected breast?
21. Was the area of your affected breast swollen?
22. Was the area of your affected breast oversensitive?
23. Have you had skin problems on or in the area of your affected breast (e.g. itchy, dry, flaky)?

Hospital Anxiety and Depression Scale

All of the questions relate to how you have been feeling over the past week. Please give the response which comes closest to how you have been feeling. Don't take too long over your replies; your immediate reaction to each question will probably be more accurate than a long thought-out response.

1. Would you say that you feel tense or 'wound up':
 - Most of the time
 - A lot of the time
 - From time to time, occasionally
 - Not at all
2. Would you say that you still enjoy the things you used to enjoy:
 - Definitely as much
 - Not quite as much
 - Only a little
 - Hardly at all
3. Would you say that you get a sort of frightened feeling as if something awful is about to happen:
 - Very definitely and quite badly
 - Yes, but not too badly
 - A little, but it doesn't worry me
 - Not at all
4. Would you say that you can laugh and see the funny side of things:
 - As much as I always could
 - Not quite so much now
 - Definitely not so much now
 - Not at all
5. Would you say that worrying thoughts go through your mind:
 - A great deal of the time
 - A lot of the time
 - From time to time but not too often
 - Only occasionally
6. Would you say that you feel cheerful:
 - Not at all
 - Not often
 - Sometimes
 - Most of the time
7. Would you say that you can sit at ease and feel relaxed:
 - Definitely
 - Usually
 - Not often
 - Not at all
8. Would you say that you feel as if you are slowed down:
 - Nearly all the time
 - Very often
 - Sometimes
 - Not at all
9. Would you say that you get a sort of frightened feeling like 'butterflies' in the stomach:
 - Not at all
 - Occasionally
 - Quite often
 - Very often
10. Would you say that you have lost interest in your appearance:
 - Definitely
 - I don't take as much care as I should
 - I may not take quite as much care
 - I take just as much care as ever
11. Would you say that you feel restless as if you have to be on the move:
 - Very much indeed
 - Quite a lot
 - Not very much
 - Not at all

12. Would you say that you look forward with enjoyment to things:
 As much as I ever did
 Rather less than I used to
 Definitely less than I used to
 Hardly at all
13. Would you say that you get sudden feelings of panic:
 Very often indeed
 Quite often
 Not very often
 Not at all
14. Would you say that you can enjoy a good book or radio or TV programme:
 Often
 Sometimes
 Not often
 Very seldom

EuroQol

1. Would you say that:
 you have no problems in walking about
 you have some problems in walking about
 you are confined to bed
2. Would you say that:
 you have no problems with self-care
 you have some problems washing or dressing yourself
 you are unable to wash and dress yourself
3. Would you say that:
 you have no problems performing your usual activities
 you have some difficulty performing your usual activities
 you are unable to perform your usual activities
4. Would you say that:
 you have no pain or discomfort
 you have moderate pain or discomfort
 you have extreme pain or discomfort
5. Would you say that:
 you are not anxious or depressed
 you are moderately anxious or depressed
 you are extremely anxious or depressed
6. We would like you to indicate on this scale (0 = worst imaginable health state, 100 = best imaginable health state) how good or bad is your own health today, in your opinion.

Philadelphia Geriatric Center Morale Scale

1. Do things keep getting much worse as you get older?
2. Do you have as much energy as you did last year?
3. Do you feel lonely much?
4. Do you see enough of your friends and relatives?
5. Do little things bother you more this year?
6. As you get older do you feel less useful?
7. Do you sometimes worry so much you can't sleep?
8. As you get older are things better than expected?
9. Do you sometimes feel that life isn't worth living?
10. Are you as happy now as when you were younger?
11. Do you have a lot to be sad about?
12. Are you afraid of a lot of things?
13. Do you get angry more than you used to?
14. Is life hard for you most of the time?
15. Are you satisfied with your life today?
16. Do you take things hard?
17. Do you get upset easily?

Clackmannan Scale

1. Do you have difficulty getting in or out of a chair?
 No
 Some difficulty
 Unable to do it alone
2. Do you have difficulty walking around inside on a level surface?
 No
 Some difficulty
 Unable to do it alone
 Wheelchair user – able
 Wheelchair user – unable
3. Do you have difficulty getting about outside on a level surface?
 No
 Some difficulty
 Unable to do it alone
 Wheelchair user – able
 Wheelchair user – unable
4. Do you have difficulty travelling by bus?
 No
 Some difficulty
 Unable to do it alone
 Wheelchair user – able
 Wheelchair user – unable

House care

5. Do you usually do the light housework like dusting or washing up?
 Yes No
 If yes: Do you have any difficulty doing it?
 No difficulty
 Some difficulty
 If no: Did someone do it for you?
 Yes No
 If you had tried doing the light housework would you have had difficulty with it?
 Yes No
 If yes: Would you have been able do it on your own or would you have been unable to do it alone?
 Would be able to alone
 Unable to do it alone
6. Do you usually make your bed?
 Yes No
 If yes: Do you have any difficulty doing it?
 No difficulty
 Some difficulty
 If no: Did someone do it for you?
 Yes No
 If you had tried making your bed would you have had difficulty with it?
 Yes No
 If yes: Would you have been able do it on your own or would you have been unable to do it alone?
 Would be able to alone
 Unable to do it alone
7. Do you usually iron your clothes?
 Yes No
 If yes: Do you have any difficulty doing it?
 No difficulty
 Some difficulty
 If no: Did someone do it for you?
 Yes No
 If you had tried ironing your clothes would you have had difficulty with it?
 Yes No
 If yes: Would you have been able do it on your own or would you have been unable to do it alone?
 Would be able to alone
 Unable to do it alone
8. Do you usually wash your clothes?
 Yes No
 If yes: Do you have any difficulty doing it?
 No difficulty
 Some difficulty

- If no: Did someone do it for you?
 Yes No
 If you had tried to wash your clothes would you have had difficulty with it?
 Yes No
 If yes: Would you have been able do it on your own or would you have been unable to do it alone?
 Would be able to alone
 Unable to do it alone

9. Do you usually prepare and cook your meals?
 Yes No
 If yes: Do you have any difficulty doing it?
 No difficulty
 Some difficulty
 If no: Did someone do it for you?
 Yes No
 If you had tried preparing and cooking your meals would you have had difficulty with it?
 Yes No
 If yes: Would you have been able do it on your own or would you have been unable to do it alone?
 Would be able to alone
 Unable to do it alone
10. Do you usually do heavy shopping?
 Yes No
 If yes: Do you have any difficulty doing it?
 No difficulty
 Some difficulty
 If no: Did someone do it for you?
 Yes No
 If you had tried doing heavy shopping would you have had difficulty with it?
 Yes No
 If yes: Would you have been able do it on your own or would you have been unable to do it alone?
 Would be able to alone
 Unable to do it alone

Self-care

11. Do you have difficulty putting on your shoes and socks or stockings?
 No
 Some difficulty, but could do it alone
 Unable alone
12. Do you wash your hair or do you rely on someone else to do this for you all the time?
 By self By other(s)
 If by self: Do you have any difficulty?
 Yes No

If by other(s): Would you have difficulty if you had tried?

Yes No

If yes: Could you do it on your own or were you unable to do it on at all alone?

Able alone
Unable alone

13. Do you have difficulty washing your hands and face?
No
Some difficulty, but could do it alone
Unable alone
14. Do you have difficulty having a bath or shower?
No
Some difficulty, but could do it alone
Unable alone
15. Do you have difficulty dressing (other than buttons and zips)?
No
Some difficulty, but could do it alone
Unable alone

Barthel Index

Mobility

1. Are you able to move from a bed to a chair –
Without help
With a little help from one person
With a lot of help from one or more people
Not at all
2. Are you able to walk around inside on a level surface –
Without help
With help from one person
Wheelchair independent, including corners
Immobile
3. Are you able to climb stairs –
Without help
With a little help
Not at all
- Self-care**
4. Do you have any difficulty feeding yourself?
No difficulty
With help cutting up food or spreading butter
With more help
5. Do you have difficulty brushing your hair and teeth, washing your face and applying make-up?
No difficulty
Needs some help
6. Do you have difficulty dressing?
No difficulty
Just help with buttons and zips
With someone helping you most of the time
7. Do you have any difficulty using the toilet or commode?
No difficulty
With some help but able to do some things by self
With quite a lot of help
8. Which of the following best describes how you control your bowels?
Never any problems
Occasional accident
Problems all the time
9. Are you always able to control your bladder?
Always
Occasional accident (less than once a day)
Daily accidents
10. Do you have any difficulty having a bath or a shower?
No difficulty
Needs some help

Summary of scores and their interpretation

TABLE 58 Summary of scores and their interpretation

Variable	No. of items	Range	Higher value indicates
Physical functioning	5	0–100	Higher level of functioning
Role functioning	2	0–100	Higher level of functioning
Emotional functioning	4	0–100	Higher level of functioning
Cognitive functioning	2	0–100	Higher level of functioning
Social functioning	2	0–100	Higher level of functioning
Quality of life	2	0–100	Higher level of QoL
Fatigue symptoms	3	0–100	Higher level of fatigue
Nausea and vomiting	2	0–100	Higher level of problems
Pain symptoms	2	0–100	Higher level of pain
Dyspnoea	1	0–100	Higher level of problems
Insomnia	1	0–100	Higher level of problems
Appetite loss	1	0–100	Higher level of problems
Constipation	1	0–100	Higher level of problems
Diarrhoea	1	0–100	Higher level of problems
Financial difficulties	1	0–100	Higher level of problems
Body image	4	0–100	Higher self image
Sexual functioning	2	0–100	Higher level of functioning
Sexual enjoyment	1	0–100	Higher level of enjoyment
Future perspective	1	0–100	Higher level of worry
Arm symptoms	3	0–100	Higher level of problems
Breast symptoms	4	0–100	Higher level of problems
Systemic therapy	7	0–100	Higher level of problems
Hair loss (distress)	5	0–100	Higher level of distress
Cough	1	0–100	Higher level of problems
HADS – anxiety	7	0–21	Higher level of problems
HADS – depression	7	0–21	Higher level of problems
PGCMS – total	17	0–17	Higher level of morale
PGCMS – agitation	6	0–6	Higher level of morale
PGCMS – attitude towards own ageing	5	0–5	Higher level of morale
PGCMS – lonely dissatisfaction	6	0–6	Higher level of morale
Barthel Index – total	10	0–20	Higher level of independence
BI – mobility	3	0–8	Higher level of independence
BI – self-care	7	0–12	Higher level of independence
Clackmannan Scale	15	0–30	Lower level of functionality
CS – mobility	4	0–8	Lower level of functionality
CS – house care	6	0–12	Lower level of functionality
CS – self-care	5	0–10	Lower level of functionality

Appendix 3

Recruitment

Table 59 illustrates the number of patients recruited at each centre, for both the randomised and non-randomised arms of the study.

TABLE 59 List of centres which entered patients

Referring hospital	Centre by treatment		
	Randomised	Non-randomised, radiotherapy	Non-randomised, no radiotherapy
Edinburgh	73	11	8
Aberdeen	13	1	0
Exeter	3	1	0
Dunfermline	7	0	0
Dumfries	26	5	5
Inverness	8	0	1
Southend	15	5	0
Gateshead	8	2	0
Colchester	5	0	0
Shrewsbury	8	10	1
Newcastle	1	0	0
South Cleveland	1	0	0
South Durham	4	0	0
Portsmouth	1	1	1
Cumbria	6	0	1
Worthing	4	2	0
Brighton	4	0	0
Hartlepool	1	0	0
Basildon	1	0	0
Bath	6	0	0
Bristol Oncology Centre	0	1	0
Taunton	2	1	2
North Bristol	5	3	5
Weston-super-Mare	0	0	3
Swindon	1	0	0
Winchester	3	0	0
Torquay	2	0	0
Reading	5	1	0
Harrogate	0	3	1
Leeds General Infirmary	3	1	1
Pinderfields	1	3	0
St James, Leeds	1	1	0
York	2	1	1
Tyne and Wear	0	0	1
Plymouth	4	6	0
Eastbourne	1	0	0
Oxford	13	2	4
Blackpool	6	1	1
Sunderland	0	1	0
Lancaster	6	0	0
Blackburn	0	0	1
Furness	3	0	0
Burnley	1	0	0
Preston	1	0	0

Appendix 4

Subjective response codes

Could I now ask you to say in your own words how your breast cancer has affected you?

No effect

Diagnosis

Diagnosis negative impact
Diagnosis positive impact
Diagnosis physical effect
Diagnosis relief
Risk factors
Attitude change after pathology results
Coping mechanisms used
Diagnostic process described
Mentioned symptomatic breast cancer
Mentioned screen detected breast cancer

Surgery

Surgery negative physical
Surgery positive physical
Surgery negative emotions
Surgery positive emotions
Surgical complications (e.g. haematoma, seroma, infection)
Surgery negative cosmetic

Endocrine therapy

Hormone negative comments
Hormone positive comments
Hormone treat complications

Radiotherapy

Radiotherapy negative feelings
Radiotherapy positive feelings
Radiotherapy attitude change
Radiotherapy environment negative
Schedule information negative
Schedule interrupted
Radiotherapy physically negative
Psychologically negative
Psychologically positive
Radiotherapy transport negative
Radiotherapy transport positive
Transport arrangements negative
Transport arrangements positive
Radiotherapy car parking
Accommodation location negative
Accommodation quality positive
Radiotherapy family impact
Skin effects
Nausea/appetite change
Radiotherapy complication

Cosmetic/breast density effect
Breast pain
Radiotherapy lifestyle effect

Professional care received

Professional care negative
Professional care positive

Hospital general environment effect

Negative impact
Positive impact

Effect on family/friends

Family/friends effect negative
Family/friends effect positive

Care from family/friends

Care from family/friends negative
Care from family/friends positive

Research

Research negative
Research positive
Participation in other trials
Clinical photograph
Research randomisation

Other effects

Sexual issues negative
Discomfort in bra
Feminine self-image
Spirituality
Mortality/life expectancy
Change in life perspective
Complementary medicine
Co-morbidities
Additional life circumstances
Activities negative
Activities positive
Clinical follow-up anxiety
Media
Cancer recurrence anxiety
Travel insurance
Lifestyle effects
Nutritional/dietary changes
Charity fund raising/donation
Genetic testing/counselling
Hormone replacement therapy
Investigations for potential recurrence

Effect on relationships

No effect
Negative effect
Positive effect

Apart from your recent breast cancer, have there been any events in the last 6 months that have had a major impact on your life?

No events
Positive major impact
Co-morbidity *
Bereavement *
Illness of relative/friend *
House move *
House refurbishment *
Retirement *
Accident *
'Foot and mouth' crisis *
Patient relationship problem *
Relationship problem of family *
Burglary *
* Combined to create 'Negative major impact'

Now, I have asked you a lot of questions and I would like to give you the opportunity to ask any questions or make any comments about the study.

No questions/comments

Research

Questionnaire items
Randomisation process
Opportunity to talk/ask quest
Methodology
Research nurse/interviewer
Home visit
Negative comments study
Positive comments study
Research title
Research follow-up appointments

Radiotherapy questions/comments

Radiotherapy schedule
Radiotherapy procedures
Radiotherapy side-effects
Radiotherapy transport
Radiotherapy accommodation
Radiotherapy skin effects

Other questions/comments

Endocrine therapy
Breast/axilla
Activities
Mammography
Benefits/home aids
Professional care comments positive
Cancer recurrence
Media comments
Changed life perspective
Breast cancer risk factors
Spirituality

Interviewer's comments

No interviewer comments
Other person present and silent

Other person present and interrupting occasionally
Self-completed questionnaire
Time gap longer/shorter
Interviewer action
Answers atypical because of other recent health problems
Usual activities resumed
Other trials

Appendix 5

Morbidity

The following forms are presented:

1. Acute morbidity form
2. Late morbidity form

Patient's surname: First names:
Trial No.:
Hospital/Clinic:
Consultant's name:
Date of examination: / /

Acute morbidity (EORTC/RTOG radiation morbidity criteria)

Tick one box in each category for all patients (including those not having radiotherapy)

- Skin**
- 0 : None
 - 1 : Follicular, faint or dull erythema, epilation, dry desquamation, decreased sweating.
 - 2 : Tender or bright erythema, patchy moist desquamation, moderate oedema
 - 3 : Confluent, moist desquamation other than skin folds, pitting oedema
 - 4 : Ulceration, haemorrhage, necrosis

- Lung**
- 0 : None
 - 1 : Mild symptoms of dry cough or dyspnoea on exertion
 - 2 : Persistent cough, antitussive agents, dyspnoea with minimal effort but not at rest
 - 3 : Severe cough unresponsive to narcotic antitussive agent or dyspnoea at rest, clinical or radiologic evidence of acute pneumonitis, intermittent O₂ or steroids may be required
 - 4 : Severe respiratory insufficiency; continuous oxygen or assisted ventilation

Patient's surname: First names:
 Trial No.:
 Hospital/Clinic:
 Consultant's name:
 Date of examination: / /

Late morbidity (SOMA radiation morbidity criteria)

Tick one box in each category for all patients (including those not having radiotherapy)

Breast (Objective) Grade

- oedema 0 : None
 1 : Asymptomatic
 2 : Symptomatic
 3 : Secondary dysfunction

- telangiectasia 0 : None
 1 : <1 cm²
 2 : 1 cm² – 4 cm²
 3 : >4 cm²

- fibrosis 0 : None
 1 : Barely palpable increased density
 2 : Definite increased density and firmness
 3 : Very marked density, retraction and fixation

- retraction/atrophy 0 : None
 1 : 10% – 25%
 2 : >25% – 40%
 3 : >40% – 75%
 4 : Whole breast

- ulcer 0 : None
 1 : Epidermal only, ≤ 1 cm²
 2 : Dermal, >1 cm²
 3 : Subcutaneous
 4 : Bone exposed, necrosis

Breast (Management)

- pain 0 : None
 1 : Occasional non-narcotic
 2 : Regular non-narcotic
 3 : Regular narcotic
 4 : Surgical intervention

- Grade
 oedema 3 : Medical intervention
 4 : Surgical intervention/mastectomy

- atrophy 4 : Surgical intervention/mastectomy

- ulcer 2 : Medical intervention
 3 : Surgical intervention/wound debridement
 4 : Surgical intervention/mastectomy

RTOG/EORTC criteria

- Lung 0 : None
- 1 : Asymptomatic or mild symptoms (dry cough). Slight radiographic appearance
- 2 : Moderate symptomatic fibrosis or pneumonitis (severe cough). Low grade fever; patchy radiographic appearances
- 3 : Severe symptomatic fibrosis or pneumonitis. Dense radiographic changes
- 4 : Severe respiratory insufficiency/continuous O₂/assisted ventilation
-
- Bone 0 : None
- 1 : Asymptomatic, reduced bone density
- 2 : Moderate pain or tenderness, irregular bone sclerosis
- 3 : Severe pain or tenderness, dense bone sclerosis
- 4 : Necrosis, spontaneous fracture

Appendix 6

Health economics

Tables are presented for the following:

1. Unit costs used in economic evaluation by cost category
2. Summary of frequency of missing data
3. Mean quantity of resource use

Unit costs used in economic evaluation by cost category

TABLE 60 Unit costs used in economic evaluation by cost category

Cost category	Mean cost (£)	Description	Source
Radiotherapy			
> 12, < 24 sessions	1879.77	Teletherapy with technical support > 12, < 24 fractions	NHS Reference Costs, 2004
> 25 sessions	2253.54	Teletherapy with technical support > 23 fractions	NHS Reference Costs, 2004
NHS transport			
Patient transport service	14.32	PTS cost/trip	Scottish Health Service Costs, 2004
Ambulance car	5.31	Ambulance car service cost/journey	Scottish Health Service Costs, 2004
Ward stay	29.00	Ward attenders RADY (no treatment)	NHS Reference Costs, 2004
General illness/follow-up			
Health professional contact			
GP ^a			
Surgery visit	21.00	Per surgery consultation lasting 9.36 minutes	Curtis and Netten, 2004 ⁹⁵
Home visit	65.00	Per home visit lasting 13.2 minutes (plus travel time)	Curtis and Netten, 2004
Telephone consultation	24.00	Per telephone consultation lasting 10.8 minutes	Curtis and Netten, 2004
Nurse ^d			
Surgery visit	14.00	Nurse practitioner H/I grade	Curtis and Netten, 2004
Home visit	20.00	District nurse G grade	Curtis and Netten, 2004
Hospital visit	9.00	Practice nurse F grade	Curtis and Netten, 2004
Physiotherapist ^d			
Home visit	48.00	Per community physiotherapist home visit	Curtis and Netten, 2004
Clinic visit	18.00	Per community physiotherapist clinic visit	Curtis and Netten, 2004
Hospital visit	41.00	Per hour of client contact	Curtis and Netten, 2004
Occupational therapist ^d			
Home visit	48.00	Per community occupational therapist home visit	Curtis and Netten, 2004
Speech therapist ^{d,b}	41.00	Per hour of client contact	Curtis and Netten, 2004
Chiroprapist/podiatrist ^{a,b}	10.00	Per community chiroprapist clinic visit	Curtis and Netten, 2004
Health visitor ^b	31.00	Per home visit	Curtis and Netten, 2004
Healthcare assistant ^b	18.00	Per hour spent on home visit	Curtis and Netten, 2004
Orthoptist ^b	27.00	Net total cost per attendance – hospital visit	Scottish Health Service Costs, 2004
Audiologist/audiometry ^b	43.00	Net total cost per attendance – hospital visit	Scottish Health Service Costs, 2004
Hearing aids ^b	32.00	Net total cost per attendance – hospital visit	Scottish Health Service Costs, 2004
Dietician ^b	32.00	Per hour in clinic – hospital visit	Curtis and Netten, 2004
Dentist ^b	94.00	Net total cost per attendance – consultant outpatient	Scottish Health Service Costs, 2004
Local authority			
Social worker (adult)	99.00	Per hour face-to-face contact	Curtis and Netten, 2004
Home care worker	14.00	Per hour face-to-face weekday contact	Curtis and Netten, 2004
	21.00	Per hour face-to-face contact Saturdays	Curtis and Netten, 2004

continued

TABLE 60 Unit costs used in economic evaluation by cost category (cont'd)

Cost category	Mean cost (£)	Description	Source
Day care for older people	27.00	Per hour face-to-face contact Sundays	Curtis and Netten, 2004
Residential care	28.00	Per session at the daycare facility	Curtis and Netten, 2004
Shower	676.00	Care package costs per short-term resident week	Curtis and Netten, 2004
Community alarm system	2036.00	Shower replacing bath (mean cost)	Curtis and Netten, 2004
Meals on wheels	300.00	Individual alarm systems (mean cost)	Curtis and Netten, 2004
Medication	2.30	Cost per meal (2000–1 price inflated)	City of Edinburgh Council, 2001
Hospital visits		Medication and endocrine therapy costs	BNF 49, March 2005
Hospitalisation			
Outpatient	132.55	Geriatric medicine – follow-up attendance	NHS Reference Costs, 2004
Inpatient	166.00	Cost per bed day (NHS Reference Cost 2002–3 inflated)	Curtis and Netten, 2004
A&E services	26.87	Minor injury attendance	NHS Reference Costs, 2004
Investigations and procedures			
Radiology			
X-rays	16.26	Band A	NHS Reference Costs, 2004
Ultrasound	32.23	Band B3 – other ultrasound	NHS Reference Costs, 2004
CT	49.01	Band C5 – CT other	NHS Reference Costs, 2004
Barium enema	68.14	Band C6 – other band C tests	NHS Reference Costs, 2004
MRI	219.52	Band F1 – MRI	NHS Reference Costs, 2004
Bone scan	142.16	Band H – radionuclide [isotope] tests	NHS Reference Costs, 2004
Whole body scan	687.44	Band L – radionuclide [isotope] tests	NHS Reference Costs, 2004
Other radiology	55.62	Net cost per attendance	NHS Reference Costs, 2004
Tests			
ECG	23.04	ECG (12 lead)	NHS Reference Costs, 2004
Echocardiogram	56.63	Echocardiogram	NHS Reference Costs, 2004
Diagnostic endoscopy	152.82	Diagnostic endoscopy	NHS Reference Costs, 2004
Breathing test	25.44	Spirometry test and bronchodilator response test	NHS Reference Costs, 2004
Phlebotomy	4.89	Cost per phlebotomy	NHS Reference Costs, 2004
Microbiology/bacteriology	7.04	Cost per test	NHS Reference Costs, 2004
Procedures			
Bronchoscopy	671.34	Fibre-optic bronchoscopy	NHS Reference Costs, 2004
Other tests	74.06	(For 24-hour BP monitoring, etc.)	NHS Reference Costs, 2004
Sigmoidoscopy	143.42	Gastroenterology: flexible sigmoidoscopy examination alone	NHS Reference Costs, 2004
Skin biopsy	113.40	Dermatology: other excision/biopsy of skin	NHS Reference Costs, 2004
Breast biopsy	122.00	Breast and endocrine surgery: excision biopsy	NHS Reference Costs, 2004
Cystoscopy	361.76	Urology: bladder minor endoscopic procedure	NHS Reference Costs, 2004

BP, blood pressure; CT, computerised tomography; ECG, electrocardiogram; MRI, magnetic resonance image.

Scottish Health Service Costs, 2004, ISD Scotland NHS National Services Scotland.

NHS Reference Costs, 2004, Department of Health.

^a All with qualification costs included.

^b Included in other staff category.

Summary of frequency of missing data

TABLE 61 Summary of frequency of missing data

Variable	Number of missing values		
	Radiotherapy	No radiotherapy	Total ^a
Radiotherapy	0	–	0
Endocrine therapy	2	2	4 (1.6%)
Other medication	5	5	10 (3.9%)
Primary/secondary care	11	22	33 (13.0%)
Total cost	16	27	43 (16.9%)
EQ-5D scores			
Baseline	1	0	1 (0.1%)
3.5 month	1	3	4 (1.5%)
9 month	4	4	8 (3.1%)
15 month	7	5	12 (4.7%)
QALYs	10	8	18 (7.1%)

^a Total number of subjects available for analysis: 254.

Mean quantity of resource use

TABLE 62 Mean quantity of resource use

Variable	Radiotherapy (n = 102) Mean (95% CI)	No radiotherapy (n = 101) Mean (95% CI)	Difference Mean (95% CI)
Radiotherapy			
Sessions	20.30 (19.54 to 21.07)	0	-20.30 (-21.07 to -19.54)
Ambulance car	6.30 (3.54 to 9.07)	0	-6.30 (-9.07 to -3.54)
Hospital car	5.42 (3.06 to 7.78)	0	-5.42 (-7.78 to -3.06)
NHS accommodation	1.95 (0.84 to 3.06)	0	-1.95 (-3.06 to -0.84)
Primary/secondary care			
GP – home visits	0.68 (0.08 to 1.27)	0.46 (0.19 to 0.72)	-0.22 (-0.85 to 0.41)
GP – surgery visits	3.66 (3.00 to 4.31)	4.22 (3.48 to 4.95)	0.56 (-0.45 to 1.57)
GP – telephone	0.18 (0.09 to 0.27)	0.08 (0.01 to 0.15)	-0.10 (-0.21 to 0.02)
Nurse – home visits	2.51 (-1.36 to 6.38)	0.67 (0.16 to 1.18)	-1.84 (-5.72 to 2.04)
Nurse – surgery visits	2.42 (1.41 to 3.44)	2.92 (0.67 to 5.17)	0.50 (-2.02 to 3.02)
Nurse – hospital visits	0.39 (0.18 to 0.61)	0.71 (0.07 to 1.35)	0.32 (-0.34 to 0.98)
Physiotherapist – home	0.16 (-0.07 to 0.38)	0.11 (-0.08 to 0.30)	-0.05 (-0.35 to 0.26)
Physiotherapist – surgery	0.10 (-0.03 to 0.23)	0.22 (0.01 to 0.43)	0.12 (-0.12 to 0.36)
Physiotherapist – hospital	0.14 (-0.01 to 0.28)	0.35 (-0.02 to 0.71)	0.21 (-0.17 to 0.59)
Occupational therapist	0.23 (0.01 to 0.44)	0.13 (-0.01 to 0.26)	-0.10 (-0.34 to 0.15)
Home care	1.12 (-0.12 to 2.35)	1.67 (-0.69 to 4.03)	0.56 (-2.13 to 3.24)
Other staff	0.24 (0.08 to 0.39)	0.28 (0.11 to 0.44)	-0.04 (-0.18 to 0.27)
Outpatient consultant visit	1.21 (0.91 to 1.50)	1.41 (1.00 to 1.81)	0.20 (-0.28 to 0.68)
Inpatient bed day	1.22 (0.19 to 2.24)	1.20 (0.52 to 1.88)	-0.02 (-1.24 to 1.20)
Investigations/procedure	0.53 (0.33 to 0.73)	0.51 (0.31 to 0.72)	-0.02 (-0.30 to 0.27)

Appendix 7

Membership of committees

Steering committee

Dr Rajiv Agrawal
Dr Peter Bliss
Dr Antony Branson
Professor John Cairns
Dr Peter Canney
Mr J Michael Dixon
Dr Paul Dyson
Professor David George
Dr John Hardman
Dr Adrian Harnett
Professor Steven Heys
Dr Wilma Jack
Mrs Celia King
Dr Ian Kunkler
Professor Robert Leonard
Professor Richard Lindley
Dr Helen Lucraft
Professor William Miller

Dr Phil Murray
Professor Robin Prescott
Dr Anne Robinson
Professor Alan Rodger
Mr Richard Sainsbury
Dr Tarun Sarkar
Dr Sue Shepherd
Professor Alastair Thompson
Dr Andrew Walls
Mr Patrick Walsh
Dr Pam Warner
Dr Linda Williams
Dr Frances Yuille

Data monitoring committee

Dr Helen Brown
Professor Alasdair Munro
Professor Elaine Rankin



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A review by Chamberlain J, Melia J, Moss S, Brown J.

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A review of near patient testing in primary care.

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Systematic review of outpatient services for chronic pain control.

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Neonatal screening for inborn errors of metabolism: cost, yield and outcome.

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Preschool vision screening.

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A critical review of the role of neonatal hearing screening in the detection of congenital hearing impairment.

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Screening for gestational diabetes: a systematic review and economic evaluation.

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<p>Dr Mahmood Adil, Deputy Regional Director of Public Health, Department of Health, Manchester</p> <p>Dr Aileen Clarke, Consultant in Public Health, Public Health Resource Unit, Oxford</p>			

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Feedback

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The Correspondence Page on the HTA website (<http://www.hta.ac.uk>) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.