For office use only Grant ID: **006**

The College of Radiographers Research Awards
Final Report

1. Principal Investigator	Nick Courtier
2. Project Title	Fatigue during radiotherapy for early-stage breast cancer and its relationship to irradiated volumes, IL-6sR and anxiety and depression: towards a prognostic model
3. Amount of Award	£5,000
4. Did you spend the money as indicated in your proposal (if not why)?	
Yes, apart from one deviation. The Actigraph equipment and software was not purchased (budget £380) This under-spend was offset by a higher than estimated use of laboratory consumables	
5. Did you reach your intended project outcomes (if not why)?	
The ultimate project outcomes were met. There were, however, differences between the original objectives and the final research questions. These relatively minor changes entailed a narrower focus on one inflammatory marker, and increased emphasis on the development of a prognostic model. The original and final objectives are included for comparison Original Objectives • Evaluate the relative contributions of the potential risk factors BMI, differential blood counts, peripheral inflammatory cytokine levels, anxiety and depression, activity levels, smoking history and demographic and socioeconomic factors to baseline fatigue. • Determine whether a relationship exist between increasing adiposity and elevated baseline fatigue, via a theoretical causal pathway between higher depression and lower activity levels increasing BMI, thereby upregulating expression of IL-6. • Investigate the strength of any correlation between the planning target volume and volumes of heart, ipsilateral lung, liver and sternum and ribs irradiated to the 10%, 50% and 90% isodose level, and longitudinal measures of (i) circulating cytokine receptors Il-1ra, sIl-6R and sTNF-RII. (ii) self-reported fatigue. • Evaluate the relative contributions of the potential risk factors baseline fatigue, volumes of normal tissue irradiated, BMI, differential blood counts, peripheral activity of cytokines IL-1ß, IL-6 and TNF, anxiety and depression, activity levels and demographic and socio-economic factors to fatigue during adjuvant radiotherapy. • Estimate the impact the individual patient characteristics of age, menopausal status, WHO performance status, treatment travel mode and time to treatment, smoking history and employment/dependent children status have on radiotherapy related fatigue. Final research questions 1. What are the intensity, prevalence and course of fatigue for radiotherapy patients with early invasive breast cancer and ductal carcinoma in situ, receiving no prior systemic therapies, undergoing a 40Gy/ 15#/ 3weeks fractionation schedule? 2. What is the impact of BMI on self-reported fatigue before radiotherapy for: (i) Three cumulative anxiety and depression categories? (ii) Three physical activity categories? 3. What risk factors – such as age, menopausal status, smoking history, tumour size, BMI, anxiety and depression and physical activity levels, leukocyte and IL-6sR concentrations – contribute to self-reported fatigue before radiotherapy?	

4. What is the relationship between the volume of irradiated tissue within the 10, 50 and 90% isodoses (V10, 50 & 90) and longitudinal measures of:
   (i) Sera concentration of circulating IL-6sR?
   (ii) Self-reported fatigue?
5. What risk factors – such as age, travel time for radiotherapy treatment, smoking pack-years, employment status, anxiety and depression and physical activity levels, irradiated tissue volumes (V10, 50 & 90), BMI, leukocyte and IL-6sR concentration – contribute to self-reported fatigue during radiotherapy treatment?
6. Which parsimonious set of pre-treatment variables best predicts a high risk of experiencing significant fatigue during breast radiotherapy treatment?

6. What are your significant findings?

- 38% of women undergoing radiotherapy for early breast cancer experience significant fatigue. The remainder report minimal fatigue before, during or after treatment.
- The current UK NICE recommended 40gy/15#/3 weeks schedule appears to attenuate fatigue as compared to longer international regimens.
- BMI did not significantly affect fatigue status, either directly or via associations with decreased psychological mood or physical activity.
- Depression level uniquely accounted for 34% of the variance in pre-treatment fatigue.
- During radiotherapy, depression level and interleukin-6 soluble receptor concentration were significantly elevated in the fatigued group compared to the non-fatigued group ($p < 0.0001$, $p = 0.01$, respectively).
- The volume of tissue irradiated significantly affected peripheral interleukin-6 soluble receptor concentration ($p = 0.003$), but was not strongly associated with fatigue level. Liver irradiation was associated with an increase in interleukin-6 soluble receptor, after controlling for BMI. Small to moderate positive correlations were evident between lung irradiation and fatigue. Cardiac irradiation had no association with either interleukin-6 soluble receptor concentration or fatigue.
- A model comprising pre-treatment fatigue, anxiety and activity level (as measured by the International Physical Activity Questionnaire) reliably classified 82% of the study participants to the correct fatigue outcome (sensitivity 71.1%; specificity 88.7%).

7. Have you submitted the work for publication (if so where)?

1. Psychological and immunological characteristics of fatigued women undergoing radiotherapy for early-stage breast cancer. (Supportive Care in Cancer)

2. A prognostic model for fatigue in women with early-stage breast cancer undergoing radiotherapy.

3. Fatigue during radiotherapy for early-stage breast cancer and its relationship to irradiated volumes, BMI and immunological factors

Presentations

- 04/11 UK Radiation Oncology Conference [Oral presentation] 'Hepatic irradiation during modern radiotherapy protocols after breast conservation' Abstract Clinical Oncology
- 05/10 Inter-disciplinary Cancer Research Group Symposium [Oral presentation] 'Is fatigue a biologically appropriate response to radiotherapy for patients with breast cancer?'
- 04/09 UK Radiation Oncology Conference [Oral presentation]
Abstract Clinical Oncology 21 Supp. 1, S32.
'Fatigue, depression and physical activity in breast radiotherapy patients: Are they explained by sickness behaviour?'
- 02/09 Society & College of Radiographers Radiotherapy Conference [Oral presentation] 'Acute fatigue in a breast radiotherapy cohort'.
- 10/08 National Cancer Research Institute Conference [Poster] 'Acute fatigue in a breast radiotherapy cohort and its relationship to irradiated volumes, body mass index and biological factors.'
- 02/08 Society & College of Radiographers Radiotherapy Conference [Oral presentation] 'Joy in repetition: the effect of advances in statistical software on the analysis of repeated measures studies in radiotherapy research.'
- 11/07 School of Healthcare Studies Research Conference [Oral presentation] 'Assessing fatigue in breast radiotherapy patients'
- 02/07 Society & College of Radiographers Radiotherapy Conference, Brighton [Poster (1st prize)] 'The volume of the liver irradiated during breast radiotherapy'

8. Please provide an executive summary of your work (two sides of A4 maximum)
N.B. If you already have a draft or final version of the proposed publication can you please attach.

Background

Patients rate fatigue as both the most prevalent and severe untreated symptom during radiotherapy treatment (1,2). Between 20 and 30% of women who undergo radiotherapy for early breast cancer report chronic fatigue that can be sustained even years after active treatment (3,4). Despite the potential for amelioration, through both pharmacological (5) and non-pharmacological pathways (6) management of radiotherapy-related fatigue (RRF) remains the exception. This deficiency is due to a complex aetiology (that may vary with tumour site) and uncertainty regarding which patients will experience significant fatigue.

The study sought to characterise fatigued patients, based on disease, treatment and patient-related factors, and to develop a prognostic model to identify women at a high risk of significant fatigue

Methods

The study cohort comprised 100 women, diagnosed with Stage 0 to IIA breast cancer, and prescribed whole breast irradiation to 40Gy in 15 fractions over three weeks. Exclusion criteria included systemic therapies, inflammatory conditions, unstable co-morbidities and a history of depression. The primary outcome fatigue was assessed before, during and four weeks after radiotherapy using the Functional Assessment of Chronic Illness Therapy Fatigue Subscale (FACIT-F). Psychological mood was measured via the Hospital Anxiety and Depression Scale (HADS); the International Physical Activity Questionnaire (IPAQ) recorded physical activity over the previous seven days; volumes of tissue irradiated were derived from dose-volume histogram analysis; concentrations of the cytokine interleukin-6 soluble receptor (IL-6sR) were established via enzyme-linked immunosorbent assay. Multivariable analysis determined the contribution of factors to fatigue and generated a prognostic model that classified participants to fatigued or non-fatigued groups.

Results

38% of participants experienced significant fatigue during radiotherapy, with the remainder little affected. 30% of participants showed no improvement or a deterioration in fatigue score from week three of treatment to the a four weeks post-treatment follow-up.

Depression uniquely accounted for 34% of the variance in pre-treatment fatigue. The reported levels of depression were relatively modest with 4% and 7% of respondents classified as a probable case at baseline and week three, respectively. BMI was not statistically associated with fatigue, either directly or via associations with depressed mood or physical activity.

During radiotherapy, depression level and interleukin-6 soluble receptor concentration were significantly elevated in the fatigued group compared to the non-fatigued group ($p < 0.0001$, $p = 0.01$, respectively). The volume of tissue irradiated significantly affected peripheral interleukin-6 soluble receptor concentration ($p = 0.003$), but was not significantly associated with fatigue.

After controlling for baseline fatigue level, anxiety made the strongest unique contribution to fatigue level during treatment. A model comprising pre-treatment fatigue, anxiety and activity level reliably classified 82% of the study participants to the correct fatigue outcome (sensitivity 71.1%; specificity 88.7%).

Implications for research and practice

Healthcare professionals need to acknowledge the reality and impacts of RRF – whether physical, cognitive or affective. An increased recognition of fatigue through the use of screening prognostic factors could enable timely prophylactic treatment. Therefore, it is vital that fatigue is evaluated prior to radiotherapy, and where indicated proactive measures taken to minimise the impacts. Additionally, radiographers can more reliably inform patients of the likelihood of fatigue during treatment. The majority of women can be reassured that significant fatigue is unlikely and transitory.

As the majority of women have a very low level of fatigue (and anxiety and depression) both before and during radiotherapy, interventions to reduce fatigue are unlikely to show much promise. The targeting of women at a high risk of experiencing fatigue is therefore indicated. This approach is consistent with the practical delivery of treatments that address an unmet clinical need.

The study data is consistent with the hypothesis that anxiety acts as a trigger for subsequent heightened fatigue, depression and inflammatory response. Future treatment strategies should concentrate on

anxiety/stress reduction in this patient group. Initially, psychosocial approaches should be preferred to pharmacological remedies. Differing aspects of the stress response – either waking or diurnal cortisol profile – provide a valuable objective marker to supplement self-reported outcomes. Younger patients and those with a diagnosis of DCIS may be particularly vulnerable to an anxiety-based fatigue syndrome and additional support should be available for these patient groups.

A relatively high threshold of activity is required to modulate acute fatigue significantly. Therefore, no single activity strategy will be effective for all patients and all degrees of fatigue. Patients should be reassured that continuing activities is desirable, but to 'listen to one's body'. This rather trite phrase encapsulates an adaptive approach that discourages succumbing to – internal or external – pressure to be 'ill', or conversely maximising physical and cognitive activity at the cost of overexertion. The concepts of pacing, developed from chronic fatigue research, provide a self-management model equally applicable to the breast radiotherapy context. The involvement of partners and family members may also aid the communication of a realistic message.

Patient benefit must ultimately be the yardstick by which technical developments in radiotherapy are judged. Study results imply that a reduction in the volume of normal tissue irradiated has the potential to reduce the induction of IL-6sR. The little considered issue of hepatic irradiation may be of particular importance in this respect. The use of prone positioning for women with pendulous breasts and a wider adoption of partial breast irradiation may thus reduce the release of adverse bioactive agents. The possibility remains for adverse fatiguing effects of IMRT approaches due to dose bath effects. Trials of adaptive radiotherapy techniques should therefore incorporate a careful evaluation of acute effects, such as fatigue. More generally, positive findings from this study should encourage further research to better define the role of IL-6sR in CRF.
The prognostic model developed demonstrated potential to reliably identify participants at a high risk of fatigue. In terms of prognostic ability, psychological factors supplanted objective laboratory data and treatment-related characteristics. Haematological factors and irradiated volumes of tissue were not good predictors of RRF, whereas three self-reported measures correctly classified 82% of the participants to the correct fatigue group. Additional variables can now be evaluated against this tight set of variables. To avoid over-fitting of the data, this model requires validation with an external dataset. A stable model would enable the targeting of high-risk women, which coupled with aetiological insights would form the bases for the development of prophylactic treatment interventions. It is widely acknowledged that the assessment and treatment of fatigue is inadequate. These considerations are vital if treatment approaches are to be initiated and the burden of patients with breast cancer reduced.

References

1. Hickok JT, Morrow GR, Roscoe JA, Mustian K, Okunieff P. Occurrence, severity, and longitudinal course of twelve common symptoms in 1129 consecutive patients during radiotherapy for cancer. J Pain Symptom Manage 2005;30:433–442.
2. Curt GA, Breitbart W, Cella D, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. Oncologist 2000;5:353–360.
3. Geinitz H, Zimmermann FB, Thamm R, Keller M, Busch R, Molls M (2004) Fatigue in patients with adjuvant radiation therapy for breast cancer: long-term follow-up. J Cancer Res Oncoly 130: 327–333.
4. Bower JE, Ganz PA, Desmond KA, Bernaards C, Rowland JH, Meyerowitz BE, Belin TR (2006) Fatigue in long-term breast carcinoma survivors. Cancer 106(4): 751–758.
5. Carroll JK , Kohli S, Mustian KM, Roscoe JA, Morrow GR. Pharmacologic treatment of cancer-related fatigue. Oncologist 2007;12:43–51.
6. Mustian KM, Morrow GR, Carroll JK, Figueroa-Moseley CD, Jean-Pierre P, Williams GC. Integrative nonpharmacologic behavioural interventions for the management of cancer-related fatigue. Oncologist 2007;12:52–67.