Acute fatigue in a breast radiotherapy cohort and its relationship to irradiated volumes, body mass index and biological factors: towards a predictive model.

Background

Advances in mammography and treatment techniques have rendered breast cancer more curative, and associated treatment morbidity an important consideration. Fatigue is the most commonly reported acute effect of breast radiotherapy with approximately 40-45% of patients suffering significant fatigue, and the remainder little affected (Fiets et al., 2003; Wratten et al., 2004). Studies have consistently emphasised the central impact of fatigue on patient's quality of life, with burden on physical, cognitive and affective domains (Olson, 2007). Curt et al. (2000) highlight the disparity between patient's perception of the impact of fatigue and the absence of evaluation and treatment of the symptom by health professionals. In the radiotherapy context this deficiency of treatment is largely due to the multitude of factors that contribute to CRF and the current imprecise understanding of the mechanisms underlying radiation induced fatigue. If it is known which patients are at higher risk of becoming fatigued, at what point in their treatment trajectory and the most likely aetiological factors then efficiently targeted evidence-based treatment be implemented. CRF treatment strategies are outside the scope of this study, which will evaluate the relative contribution of risk factors for the outcome of fatigue, as a precursor to developing a prognostic model for radiation-induced fatigue in breast cancer patients.

A number of biological pathways have been suggested whereby a localised treatment causes a systemic effect. Evidence implicates an inappropriate acute phase inflammatory response, largely mediated via the induction and release of normal tissue cytokines (Gutstein, 2001; Collado-Hidalgo et al., 2006). Cytokines are regulatory proteins that mediate intracellular responses. The principle inflammatory regulators being interleukin-1beta (IL-1ß), interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF_). As proinflammatory cytokines are known to be released in response to radiation and have been shown to be a principal mediator of sickness behaviour and fatigue (Greenberg et al., 1992; Dantzer, 2001) this study will longitudinally track activity of IL-1ß, IL-6 and TNF_ at points throughout participant's radiotherapy. Furthermore, Collado- Hidalgo et al. (2006) found fatigued survivors of

breast radiotherapy to have 28% more circulating T lymphocytes than non-fatigued controls. Blood cell counts will therefore be recorded prior to and during treatment.

Pre-radiotherapy fatigue appears to be a major contributor towards fatigue development during treatment, with 31% of variance in post treatment fatigue being accounted for by baseline fatigue levels (Smets 1998). During treatment, irradiated normal tissues include skin, mammary gland & adipose tissue, ribs & sternum, lung, heart and the liver. The dysregulated inflammatory response theory implicates cytokines released locally in irradiated thoracic and abdominal organs (liver, lung, heart etc.) activating terminating visceral vagal afferent nerves (Morrow et al., 2002). The result being a reflex depression of somatic body tone, and the ultimate perception at the behavioural level would be that extra ordinary effort would be required to accomplish a motor task. This mechanism is analogous to an animal which centrally reduces energy expenditure to combat infectious pathogens (Armes et al., 2004). In radiotherapy patients a necessity or tendency to continue with everyday tasks may result in a discrepancy between the expected and actual effort required; which may be experienced as fatigue.

A consequence of the subjective nature of fatigue is that it cannot be measured directly. Therefore, the incorporation of objective fatigue markers or risk factors into a prognostic tool would be particularly desirable. Candidate risk factors identified in the literature include body mass index (BMI), dose-volumetric factors and baseline and on treatment biochemical parameters. Studies have demonstrated connections between increasing BMI and baseline fatigue (Wratten et al., 2004), on treatment fatigue (Geinitz et al., 2001) and chronic fatigue post treatment (Bower et al., 2003). It is plausible that increasing BMI may affect fatigue status by two distinct mechanisms,

(i) By the correlation of BMI with larger more pendulous breasts (for breast conserving surgery) and hence increased volumes of irradiated normal tissue.

(ii) Due to inherent metabolic differences or associations with depressed mood and decreased activity levels.

Physical activity levels, smoking history and psychological and socio-economic behaviours will also be considered as potential confounders or interactions.

Basic immunological and neurological science has begun to unravel the biological basis of CRF (Gutstein, 2001), in parallel to advances in the management of this debilitating symptom (Mitchell, 2006). The proposed study - aiming to identify the most important risk factors in order to generate a prognostic model of fatigue over the course of breast radiotherapy treatment – is both timely and novel. Current studies that have sought correlates of breast radiotherapy related fatigue are characterised by methodological limitations that the proposed study will address. These include samples that are heterogeneous with regard to treatment(s) and a lack of objective measures and/or basic treatment related factors such as travel times for treatment. Only one study to date, (Geinitz et al., 2001), has considered volumes of normal tissue irradiated. Furthermore, even desirable longitudinal studies rarely take into account the temporal dimension.

A reliable model of prognostic factors for fatigue generation would be beneficial for three main reasons. Identified risk factors may help elucidate the aetiology of this complex symptom. Secondly, if prognostic factors can are identified it may be possible to predict a group of patients at higher than average risk of becoming fatigued from radiotherapy treatment, and those with the biggest change in fatigue status. Targeted clinical interventions and advice may then lead to improvements in patients' quality of life. Moreover, a parsimonious predictive model can simplify the multitude of variables that may covary with fatigue and identify important main factors that new or additional factors can be evaluated against, for example systemic treatment prior to radiotherapy.

Study aims and objectives

Aims

- To identify risk factors and develop a parsimonious predictive model for pre-radiotherapy fatigue in early stage female breast cancer patients receiving no prior systemic treatment.
- To analyse dose-volumetric data to evaluate correlations, independent of BMI, between volumes of normal tissue irradiated and repeated measures of levels of proinflammatory mediators of fatigue and fatigue at the behavioural level.

- To identify risk factors and develop a parsimonious prognostic model to determine which subset of early stage female breast cancer patients become most fatigued and which patients experience the biggest change in fatigue levels during adjuvant radiotherapy treatment.
- Determine the importance in a prognostic radiotherapy-related fatigue model of demographic and socio-economic factors.

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 socio-economic 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.

Study design and methodology

Study Design

The chosen study design is a correlational longitudinal study with repeated measures. This observational approach allows the estimation of the change over time of an adverse clinical outcome, with normal clinical practice and protocols remaining unaffected.

Patient population

The study cohort comprises 100 women diagnosed with early stage carcinoma of the breast (Tis to T2), which have undergone either wide-local excision or mastectomy and subsequently referred to Velindre Cancer Centre (VCC) for standard radiotherapy protocols. A power calculation suggested that a sample size of 100 would have a power of 0.83, assuming a moderate effect size.

In light of the study aims, breast radiotherapy patients are of particular interest, as theoretically there is negligible tumour contribution to neither cytokine release nor fatigue. As the specific focus of the proposed study is the effect of radiotherapy on fatigue, and it is feasible to do so in terms of numbers of eligible patients, those prescribed systemic cytotoxic or hormonal treatment prior to, or concurrent with radiotherapy will be excluded. Eligibility criteria are framed so as to exclude concommitant pathologies and extraneous treatment variables that may confound the effect of radiotherapy on fatigue.

Measurement of variables

Fatigue: Will be measured by the cumulative score on the Functional Assessment of Cancer Therapy Fatigue subscale (FACT-F). The FACT-F subscale is a brief and simple discriminative tool to assess fatigue severity and impact, derived from the longer FACT-G general scale (Cella et al., 1993).

Schedule: Patients who declined to participate in the study will be requested to fill in the FACT-F questionnaire to assess bias in the study sample. Participants will complete the questionnaire at baseline (2 weeks pre-treatment), at the ends of treatment weeks three and four and four weeks post treatment.

Irradiated volumes and treatment parameters: Volumes of interest will be delineated using the OMP 3D planning system outlining tool and dose volume histogram data generated. The volumes of the planning target volume (PTV),

ipsilateral lung, heart (left-sided), liver (right-sided) and ribs and sternum within the 10%, 50% and 90% isodose levels will be determined.

Body Mass Index (BMI): Is defined as the patient's body weight divided by the square of their height.
Schedule: Pre-treatment weight will be as recorded in patients' medical notes. Patients will be re-weighed at review clinic appointments, during treatment weeks two and four.

Full differential blood counts: Phlebotomists will draw 5ml of blood by antecubital venesection from the contralateral arm to the diseased breast. Full blood counts with differential white cell counts will be performed using standard techniques.
Schedule: To minimise hospital trips baseline blood tests will be performed after the patients CT planning scan. Subsequent blood samples will be taken at the end of weeks three and four of treatment and four weeks post treatment.

Cytokine assays: Commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D systems, Minneapolis, USA) will determine circulating levels of soluble receptors IL-1ra, sIL-6R and sTNF-RII. The rationale for measuring levels of cytokine receptor is that whilst cytokine production may be significantly elevated in irradiated tissues, circulating plasma cytokines work at very low concentrations. Soluble receptors form a more reliable marker in serum than the cytokines that induced their release (Bower et al., 2002).
Schedule: As for the differential blood counts above.

Anxiety and depression: The Hospital Anxiety and Depression Scale (HADS) is widely used to quantify the presence and severity of mild degrees of anxiety and depression
Schedule: At baseline (after CT scan), at the ends of treatment weeks three and four.
***Physical activity levels*:** The International Physical Activity Questionnaire (IPAQ) has been designed to provide data on health-related physical activity, and has been extensively validated in a variety of settings (Booth, 2000).

Sch*edule:* At baseline (after CT scan), at the ends of treatment weeks three and four.

Demographic and socio-economic data: Age and menopausal status and WHO status will be recorded from patients' medical notes. Interview will determine employment status, dependent child status, smoking history (recorded in pack years), travel time to VCC and intended travel mode for treatment.
Schedule: After consent process.

Patient diaries: A patient diary will be provided for all participants in the study, the completion of which will be entirely at the individuals' discretion. The diary will allow patients to express their feelings regarding the impact of CRF. Data from the diaries will help define CRF and facilitate the development of a theoretical framework centred on the postulated physical, affective and cognitive domains.

Data	**Timing**					
	Baseline (CT scan)	week 1*	week 2	week 3	week 4	4 weeks post trt.
3D DVH data						
Socio-demographics	X					
BMI	X		X		X	
FACT-F	X			X	X	X
HADS	X			X	X	
Blood samples	X			X	X	X
Activity levels	X			X	X	

Summary of assessment schedule

Data analysis
Multivariable regression analyses will determine the relative contribution of different causes to the outcome of fatigue, whilst adjusting for differences in baseline characteristics. Initially, logistic regression output will be utilised to generate a model to predict the dichotomous outcome of fatigued or not fatigued. A linear regression analysis will be performed to determine which exposures contribute most to baseline fatigue. Baseline fatigue score will then be included as a risk factor in a main linear

regression analysis to determine which exposures contribute to 'on treatment' fatigue.

To allow for the longitudinal data in the analysis two different methods will be used. A simple subject specific approach considers individuals as a basic unit (Griffiths, Parmar and Bailey, 1999). For each participant the FACT-F fatigue score will be plotted against the assessment time, and a standardised area under the curve calculated. The second approach is to develop a predictive linear model at timepoint 1 and evaluate the stability of this model at all other timepoints. That is, compare the predicted values of fatigue with the actual values. An iterative process of including and excluding variables from the predictive model will then determine which combination of variables has most impact on fatigue, before and during treatment.

Textual data emerging from the diaries will be explored inductively using content analysis to generate categories and explanations. Initially the data will be read and reread and coded into broad themes. Themes will be formed and refined through repetitive scanning of the data for exemplars of themes, attributes and negative cases (Lincoln and Guba, 1985). Relations between the different themes will be mapped, both for individual subjects and collectively.

Ethical considerations

Applications will be made to the Velindre NHS Trust R&D committee and an NHS LREC. Participants will only be consented to enter the study after full verbal and written information has been given to the patient's satisfaction. Patients will be free to withdraw from the study at any time without giving a reason, and without medical care or legal rights affected. Data will be anonymised and referenced with a serial number. No individual will be identifiable in any reports. No patient's treatment will be affected or altered due to the study procedures. As future patient management protocols may be influenced, the results will be disseminated to the relevant multidisciplinary team members.

Efforts have been made to reduce the burden on participants in the proposed study. This burden essentially has two components: Three self-reported instruments and blood testing. Pilot work suggests the average time taken to fill in the three documents is approximately 10-15 minutes. The minimum blood sample size,

consistent with the study aims, of 14ml will be drawn. Patients will be free to refuse any of these scheduled blood samples.

Whilst of no direct benefit for participants, study results may help to decide how to identify future patients who may become fatigued during breast radiotherapy. Patient diaries may offer therapeutic value for some patients in terms of expression of feelings and recognising patterns of fatigue and behaviour.

Administrative procedures

Evaluation Strategy

The study will undergo continuous peer review by the multidisciplinary team at Velindre Hospital, including breast consultant oncologists, lead breast planning physicists, review radiographers and patients. As this research constitutes a PhD level of study, progress will be continuously evaluated by academic staff and a supervisory team. Monitoring by first and second supervisors occurs every second week and month respectively.

Dissemination strategy

Interim and final findings will be disseminated locally and nationally/internationally. Locally, presentations and lectures will be made both to the academic school research groups - and to the full clinical staff at Velindre Hospital. Abstracts and posters will be submitted for presentation at major conferences such as the CoR Radiotherapy Weekend and UKRC 2008. Dissemination has already commenced with a poster - detailing pilot work that is informing the current study – winning 1st prize at the 2007 Radiotherapy weekend. Papers will be submitted for publication in CoR/SoR titles and high impact peer reviewed journals such as International Journal of radiation Oncology Biology Physics (impact factor 4.6) and Radiotherapy and Oncology (3.3).

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