Fatigue during radiotherapy for early-stage breast cancer and its relationship to irradiated volumes, IL-6sR and anxiety and depression: towards a prognostic model

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Abstract

Introduction

Fatigue is the most troublesome untreated symptom during radical breast radiotherapy. This situation persists due to an uncertain aetiology and an inability to identify patients at high risk of experiencing significant fatigue during subsequent radiotherapy. Aetiological investigations of the current study concentrated on discriminating the radiotherapy-specific effects on fatigue, in a context encompassing multiple psychological and physiological covariates. Prognostic aspects sought to characterise a 'high-risk' patient.

Methods

The study cohort comprised 100 women, diagnosed with Stage 0 to IIA breast cancer, and prescribed standard whole breast irradiation to 40Gy in 15 fractions over three weeks. The use of systemic therapies was an exclusion criterion. A cytokine-induced sickness behaviour model framed the study investigations, and provided a theoretical link between localised radiotherapy and systemic fatigue. The outcome fatigue was assessed before, during and four weeks after radiotherapy, using the Functional Assessment of Chronic Illness Therapy Fatigue Subscale. Volumes of tissue irradiated were derived from dose-volume histogram analysis; concentrations of the cytokine interleukin-6 soluble receptor were established via enzyme-linked immunosorbent assay. Multivariable analysis determined the factors that contributed 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. The fatigued group recorded relatively elevated pre-radiotherapy levels of depression, and particularly anxiety, as measured by the Hospital Anxiety and Depression Scale. Depression 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 significantly associated with 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%).

Conclusion

Psychological mood is the strongest predictor of fatigue before and during radiotherapy. Inter-related data is consistent with the concept that a lower psychological mood prior to radiotherapy relates to a distinct immunological and behavioural response during radiotherapy. These aetiological insights may inform fatigue treatment pathways, and ensure the targeting of future interventions at early breast cancer patients at a high risk of experiencing fatigue.

Glossary of terms and acronyms

$5\text{-}HT_3$	5-hydroxytryptamine$_3$ receptor antagonist
AI	aromatase inhibitor
APR	acute phase response
BCS	breast conservation surgery
BCT	breast conservation therapy
BED	biologically equivalent dose
BMI	body mass index
CFS	chronic fatigue syndrome
CI	confidence interval
CLE	consequential late effects
CNS	central nervous system
CRF	cancer-related fatigue
CRT	conformal radiotherapy
CT	computed tomography
CTV	clinical target volume
DCIS	ductal carcinoma in situ
DFS	disease free survival
DVH	dose-volume histogram
EBC	early breast cancer
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
ELISA	enzyme-linked immunosorbent assay
ER	oestrogen receptor status
FACIT-F	Functional Assessment of Chronic Illness Therapies Fatigue Subscale
FAST	UK Faster Radiotherapy for Breast Cancer Patients Trial
gp130	cell-surface glycoprotein 130 receptor subunit
Gy	Gray (SI unit of absorbed radiation)
HADS	Hospital Anxiety and Depression Scale
HER-2	human epidermal growth factor receptor 2 status
HPA	hypothalamic-pituitary-adrenal axis
HRT	hormone replacement therapy
ICD-10	International Classification of Diseases Code -10th Revision diagnostic criteria
IL-1ß	interleukin 1 beta
IL-6	interleukin 6
IL-6sR	interleukin 6 soluble receptor
IMC	internal mammary chain
IMPORT	UK Intensity Modulation and Partial Organ Radiotherapy Trial
IMRT	intensity modulated radiotherapy treatment
IPAQ	International Physical Activity Scale
IQR	inter-quartile range
MET	metabolic equivalent of task
ng/dL	Nanograms per decilitre
NICE	National Institute for Clinical Excellence
OB	oestrogen receptor blocker
OS	overall survival
PgR	progesterone receptor status
PTV	planning target volume
QoL	(health-related) quality of life

RCT	Randomised controlled trial
RILD	radiation-induced liver disease
RRF	radiotherapy-related fatigue
RT	radiotherapy
SCF	supraclavicular fossa
SNB	sentinel node biopsy
START	UK Standardisation of Breast Radiotherapy Trial
TDLU	terminal duct lobular unit
TNFα	tumour necrosis factor alpha
$V_{(10, 50 \& 90)}$	volume of irradiated tissue within the (10, 50 and 90% isodoses)
VCC	Velindre Cancer Centre
WLE	wide local excision

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CHAPTER ONE **Introduction**

This thesis is about fatigue: specifically acute fatigue in early-stage breast cancer patients undergoing adjuvant radiotherapy treatment. The study is distinct from much extant work in that the rationale underlying the investigations adopts a radiotherapy-based perspective, as opposed to a broader cancer-related fatigue (CRF) approach. The aim was to develop a prognostic model, capable of predicting patients at a high risk of experiencing significant fatigue during radiotherapy treatment. A series of research questions precede this study endpoint, framed to elucidate uncertainties in the current science of radiotherapy-related fatigue (RRF), and hence extend the utility of models of fatigue in breast cancer patients. The focus of the research questions was an attempt to discriminate and evaluate the component of fatigue attributable to the iatrogenic effects of the radiotherapy, in a contextual environment encompassing numerous putative contributory factors.

The complex aetiology of RRF necessitated a guiding theoretical framework, which could define the scope of the study and provide coherency between inter-related concepts and variables. The sickness behaviour framework, as described by Dantzer and Kelley (2007), fulfilled this function. In brief, this framework seeks to explain the behavioural response to non-specific tissue injury through immunologically initiated pathways, which integrate inflammatory, neurological and psychological responses. This study applies the principles of the sickness behaviour framework to a radio-biological/oncological setting. Scientific aspects of the framework inform a mechanistic explanation whereby a localised treatment can cause a centrally driven sensation such as fatigue. Full explanation of the framework and justification for its relevance for RRF is provided in chapter three.

Contexts of the fatigue problem

Enhancements in the diagnosis and treatment of non-metastatic breast cancer have yielded discernible improvements in disease free and overall survival (Early Breast Cancer Trialists' Collaborative Group 2005). One consequence of these welcome advances has been the emergence of research focussed on health-related quality of life (QoL) issues. At a UK health policy level, one of the foci has been improving

patient's experience of treatment (Department of Health 2005). Oncology patients themselves are concerned with the restoration of normal life and functioning (Kvale 2007). This normalisation process necessitates the amelioration of adverse symptoms associated with the disease and its treatment. Indeed, in some oncological settings, toxicity and QoL may be relatively interchangeable (Stephens et al. 1997).

More than 45,000 women annually receive a diagnosis of breast cancer in the UK, and the incidence rates are rising (Cancer Research UK 2006). Approximately two thirds of these women are prescribed radiotherapy, adjuvant to primary surgery. RRF is a widespread and well documented problem associated with this treatment (Munro et al. 1989, Smets et al. 1998a, Vogelzang et al. 1997), with best estimates suggesting 30 to 50% of patients suffering significant fatigue during treatment (Fiets et al. 2003, Wratten et al. 2004). By common consent, RRF affects physical, cognitive and emotional aspects of patients' daily functioning (Irvine et al. 1998, Jereczek-Fossa et al. 2002, Smets et al. 1998a, Whelan et al. 2000b). Curt et al. (2000) highlight the disparity between patient's perception of the significant impact of CRF with the absence of assessment and treatment of the symptom by health professionals. This deficiency persists despite increased acknowledgment that CRF has the potential for prophylactic amelioration, through both pharmacological (Carroll et al. 2007) and non-pharmacological interventions (Mustian et al. 2007).

The clinical problems behind the somewhat stygian lack of fatigue management in the radiotherapy setting are two-fold. Firstly, the *aetiology* of RRF is unclear, and may vary in accordance with cancer site. Secondly, it is unknown *which* patients will experience significant fatigue during radiotherapy. A brief introduction of the contexts to these two problem areas serves as a prologue to a thorough assessment of relevant literature in chapter three.

The aetiology of radiotherapy-related fatigue

The conceptualisation of CRF as a multi-dimensional syndrome (Cella et al. 2002a), suggests the aetiological aspect is complex. However, researchers have implicated the induction and release of pro-inflammatory cytokines – in response to peripheral tissue damage caused by cancer treatments – in the generation and/or potentiation of

CRF (Bower 2007, Gutstein 2001, Jager et al. 2008). Cytokines are pleiotropic proteins, one role being the co-ordination of the acute-phase response to non-specific toxic insult. A recent review, incorporating a weighted pooled analysis (Schubert et al. 2007), indicated significant associations between the cytokine interleukin 6 (IL-6) and CRF, however individual results have been conflicting. That definitive proof of concept for cytokine-induced CRF has remained elusive may be due to issues of methodological sophistication rather than validity of the theory. Specifically, basic immunological research (Kallen 2002, Marz et al. 1999, Scheller et al. 2006) has revealed that many of the biological actions (and consequential behavioural effects) of IL-6 depend largely on local levels of the agonistic interleukin 6 soluble receptor (IL-6sR), via a process called transsignalling. Section 3.3 includes a discussion of how the action of a dimerised IL-6/IL-6sR compound provides a mechanistic link between peripheral cellular damage during breast radiotherapy and the centrally driven behavioural response of fatigue. The current study synthesises the concepts of transsignalling and the sickness behaviour framework with breast radiotherapy theory and practice. As such, the role of IL-6sR in acute RRF is established.

A fuller understanding of the aetiology of RRF has three main benefits. Firstly, aetiological evidence will help formulate specific hypotheses, and thereby directly inform the nature and content of clinical interventions. Secondly, a tighter set of established risk factors for RRF is established, against which additional factors such as poly-chemotherapies can be evaluated. Thirdly, the identification of objective fatigue surrogates would strengthen the evaluation of fatigue by self-reported tools. Inflammatory biomarkers – such as cytokines – are prime candidates for this role, as their release is a component of the physiological response to radiation and theoretical and empirical evidence links them to fatigue generation.

Fatigue risk

An elegant epidemiological discourse by Rose (1985) highlights why attempts to explain the cause of individual cases of RRF are likely to be unproductive. Genetic, environmental and stochastic factors will all contribute to individual variance in fatigue. Instead, this study considers the causes of fatigue at a group level. The employment

of a prognostic (or probabilistic) approach then yields utility at the individual level. That is, a prognostic model is developed that characterises participants at high risk of experiencing fatigue during radiotherapy treatment.

A reliable estimate of the risk of fatigue has translational implications both for breast radiotherapy research and for practice. More personalised lifestyle advice may be available to breast radiotherapy patients. The ability to inform patients of the likelihood of toxicities is set to become an increasingly important aspect of the patient consent process, as the range of breast cancer treatments with equivalent actuarial survival rates expands. Moreover, fatigue management programmes can be targeted at the subgroup of patients most likely to benefit. Similarly, pre-treatment fatigue risk-status provides a basis to purposively recruit/ stratify research participants. Research and treatments both involve opportunity costs, whether expressed financially or in terms of inconvenience and adverse effects. Absolute benefits versus costs will vary for different risk groups (Haynes et al. 2006).

Limitations and evidence gaps in radiotherapy-related fatigue research

Limitations in research design and evidence gaps become apparent when applying the methodology and findings of the body of CRF research to the radiotherapy setting. The first limitation is the relative paucity of longitudinal studies. The fractionated delivery of radiotherapy and the cumulative nature of related adverse effects are particularly suited to the investigation of inter-related variables over time. Whilst there is now a growing body of studies employing longitudinal designs, they are heterogeneous regarding the sample composition and/or the treatments under consideration. This introduces variables that confound the relationship between radiotherapy, intervening biological players and fatigue. Indeed, the high ratio of background noise relative to the (fatigue) signal is probably the most significant methodological issue in CRF research. Therefore, the eligibility criteria of the study are framed to provide as homogenous a sample as possible as regards to co-morbidities and disease-related characteristics.

It is plausible that the mechanisms underlying fatigue may vary in different cancers. For example, depression appears to play a significant role in the fatigue experienced

by patients with breast cancer (Bennett et al. 2004, Burgess et al. 2005, De Vries et al. 2009, Goldstein et al. 2006). However, if fatigue is a generalised systemic effect of radiotherapy then why does only a subgroup of patients suffer? A standard principle of radiobiology is that adverse effects caused by radiotherapy treatment will vary as a function of the type and volume of normal tissue irradiated; as well as the dose distribution, the dose per fraction and the duration of the treatment. Latterly, it has also become apparent that genetic polymorphisms pre-dispose certain patients to particular toxicities. In the future, it is envisaged that radiotherapy prescriptions will become increasingly personalised based on multiple genetic signatures (Dowsett and Dunbier 2008). In this context, the danger exists to misinterpret generic dose-volume and dose distribution effects as the manifestation of individual radiotherapy sensitivities. The rigorous evaluation of radiotherapy parameters, as covariates of RRF, is therefore a research priority.

Evidence to support or refute the hypothesis that the type (and volume) of tissue irradiated modulates fatigue has been obfuscated by a preponderance of small-scale studies with mixed anatomical site samples. Limited site-specific studies suggest that patients undergoing radiotherapy for brain cancers (Faithfull and Brada 1998), head and neck cancers (De Graeff et al. 1999a) and lung cancers (Hicock et al. 1996) may experience an increased prevalence and/or severity of fatigue symptoms, as compared to breast cancer (Fiets et al. 2003, Wratten et al. 2004). Operable breast cancer provides a uniquely efficient model to study RRF as complete excision of the tumour is ubiquitous, and the prevalence of other confounding treatment-related toxicities is very low. This treatment background enables a relatively clear evaluation of the biological and behavioural effects of adjuvant radiotherapy.

The genesis of the current study was the author's undergraduate research study (Courtier 2006), which investigated the volume of liver and stomach irradiated during radical breast radiotherapy. The results of this small exploratory study were consistent with primary irradiation of up to 5% of the liver, and a maximum hepatic dose equivalent to 102% of the prescription dose. A logical research direction indicated by these findings was to investigate if irradiating small volumes of the liver to high doses resulted in damaged hepatocytes releasing novel mediators of fatigue and/or affected reported toxicities. The result of many modifying iterations is the current study, which

investigates the relative contribution of volumes of normal tissue irradiated to fatigue. With respect to the literature, only one published (German) study was identified that had previously considered this association (Geinitz et al. 2001). The current study will consider both the total volumes of tissue irradiated to different dose levels and the sub-volumes of individual organs irradiated.

Studies have linked increasing body mass index (BMI) with elevated 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 (at least) three distinct mechanisms: by the correlation of BMI with increased volumes of irradiated tissue, through associations with depressed mood and decreased activity levels or via the release of IL-6 by adipocytes. This study seeks to clarify the role of BMI in breast RRF in relation to the contribution of psychological mood and activity levels.

The duration of radiotherapy has long been identified as a modifying factor for fatigue (Haylock and Hart 1979). The accepted course of fatigue has been established using historic international fractionation schedules, typically of five to six weeks duration. Until now, no studies have plotted the intensity, prevalence and course of fatigue during the 40 Gray in 15 fractions over 3 week schedule (40Gy/15#/3 weeks) recommended by the UK National Institute for Clinical Excellence (NICE) 2009 guidelines.

Broad study aims and specific research questions designed to address the aforementioned evidence gaps and methodological limitations are now detailed.

1.1 Study aims and research questions

Aims

- To characterise the fatigue response over a 40Gy/ 15#/ 3 weeks dose-fractionation schedule.
- To quantify the contribution of patient, disease, psychological, haematological, immunological and radiotherapy-related risk factors for fatigue, both before and during radiotherapy treatment.
- To evaluate the longitudinal relationships between body size (BMI and volumes of normal tissue irradiated), IL-6sR (a biomarker of inflammation), and fatigue.
- To identify pre-radiotherapy risk factors for fatigue, as a precursor to developing a parsimonious prognostic model to determine which subset of early-stage female breast cancer patients are at a high risk of fatigue during adjuvant radiotherapy.

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 ($V_{10, 50 \& 90}$) 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 ($V_{10, 50 \& 90}$), 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?

CHAPTER TWO **Background to breast cancer and its treatment**

This chapter summarises the pathology of breast cancer and introduces terms and concepts that are relevant to the study investigations. An historical perspective to breast cancer treatment provides a background context to the current use of adjuvant radiotherapy and the role of multi-modal therapies.

2.1 Incidence and aetiology

Breast cancer is the most common malignancy in women in the UK, with more than 45,000 new cases diagnosed in 2006 (Cancer Research UK 2009). The incidence in Wales is approximately 2,500 per year, which equates to a crude rate of 160 women per 100,000 of population. Between 1996 and 2006, the UK incidence rate, adjusted for regional age-structure, has increased by 6% (Cancer Research UK statistics 2009). The increases in incidence are currently unexplained: as is the associated social gradient, whereby women from higher social class report a disproportionately high incidence.

Research estimates that up to 10% of breast cancers are attributable to an inherited genetic predisposition (McPherson 2000). Hereditary cancers tend to be aggressive and present at an early age (Sivell et al. 2007). Functional defects in the BRCA1 and BRCA2 tumour suppressor genes are the most commonly involved mutation, although additional genetic pathways have been more recently identified (Chua et al. 2005, Renwick et al. 2006, Seal et al. 2006). The remaining 90% of breast cancer incidence arises spontaneously. Whilst case-specific aetiology remains uncertain, the bases may be some combination of exogenous and/or endogenous endocrine agents, or possibly environmental carcinogens, that initiate dysregulated differentiation of mammary-specific stem cells (Trichopoulos et al. 2008). The estimated relative risks for established risk factors for breast cancer are included below in Table 2.1.

Risk factor	Estimated relative risk
Increased age	15.0
Socio-economic groups I and II	2.0
Younger age at menarche (before 11)	3.0
Late natural menopause (after 54)	2.0
Age at first birth greater than 40 years	3.0
Nulliparity	3.0
Obesity (in postmenopausal women)	3.0
Oral contraceptive	1.3
Exogenous hormone replacement therapy	1.7
Alcohol consumption	1.2
Exposure to ionising thoracic irradiation	3.0+
Family history in a younger first-degree relative	2.0+
Atypical ductal hyperplasia	4.0
Atypical ductal hyperplasia plus a first-degree relative	9.0

Table 2.1 Risk factors for breast cancer.

The strongest risk factor for breast cancer is increasing age. Under the age of 30, the risk is one in 1900. By age 50, the risk is one in 50 (Cancer Research UK 2009). The rate of rise in incidence decreases after the menopause. Despite criticisms regarding selection bias (Shapiro 2004), the sheer size and scope of the ongoing Million Women Study should enable an evaluation of the currently controversial influences of diet, physical activity and smoking.

2.2 The anatomy and pathology of breast carcinoma

The female breast extends superiorly from the sixth rib to the second rib. Anatomically, the breast is conceptualised as comprising a central portion and four quadrants. The upper outer quadrant encompasses the axillary tail. Internally, the breast divides into 15 to 20 lobes consisting of glandular sub-units called lobules. The functional unit of the breast is called the terminal duct lobular unit (TDLU). A series of progressively larger ducts traverse the breast until reaching the nipple areola complex. A connective tissue framework called the stroma secures the glandular tissue and surrounding adipose tissue. The stroma contains a network of nerves, blood vessels

and lymphatic vessels. Lymphatic drainage is predominantly towards the axilla, with additional pathways to medially placed nodes.

Almost all breast cancers are adenocarcinomas, involving the transition of normal epithelium lining the TDLU to atypical cells. The Nottingham combined histological grade classifies the grade of differentiation (from normal mammary cells) (Elston and Ellis 1991). Pathologists refer to early morphological changes confined to the lobes as in situ disease. As tumour progression ensues, cells that are frankly malignant may penetrate the basement membrane of the glandular tissue and become invasive carcinoma. Approximately 80% of invasive breast carcinoma is ductal carcinoma, 10% lobular carcinoma, with the remainder comprising numerous histopathologies. The natural course of invasive disease involves direct invasion of local structures and/or infiltration of the capillary walls of blood and/or lymph vessels.

Pre- widespread mammographic screening, approximately 40% of patients diagnosed with early breast cancer had histopathologically confirmed involvement of the regional (Levels I and II) axillary lymph nodes (Perez et al. 1998). The increasing presentation of small screen-detected cancers has seen this proportion effectively halved (Arnesson and Ahlgren 2000). Additional ipsilateral nodal groups classified as regional are the apical axillary (Level III), infraclavicular, supraclavicular fossa (SCF) and the internal mammary chain (IMC) groups (Sobin et al. 2010). Lymphatic spread to any other nodal group is distant metastases. Haematogenous dissemination occurs both by local vascular infiltration and/or through diverse lymphatic-venous communication. Common sites of subsequent metastasis are bone, lung and liver.

The International Union Against Cancer (UICC) provides a staging classification for breast cancer, based on the tumour-node-metastasis (TNM) system (Sobin et al. 2010). The current version of the TNM categories are summarised in Table 2.2. Stage groupings, based on prognosis, are shown in Table 2.3. It had been speculated that the recently published seventh edition would incorporate additional prognostic and predictive factors, such as Human Epidermal growth factor Receptor 2 (HER-2) status (Bonnefoi 2007). This was not the case, but should appear in the following edition.

TNM categories	Description
T category	primary *Tumour* extent
Tis	In situ disease
T1	≤ 2 cm
T1mic	Microinvasion ≤ 0.1 cm
T1a	> 0.1 to 0.5 cm
T1b	> 0.5 to 1 cm
T1c	> 1 to 2 cm
T2	> 2 to 5 cm
T3	> 5 cm
T4	Extension to the chest wall and/or skin; or inflammatory carcinoma
N category	pathological *Nodal* staging
pN0	No regional lymph node metastasis
pN1mi	Micrometastasis > 0.2 mm ≤ 2 cm
pN1	Metastasis in 1-3 axillary node(s) and/or in ipsilateral internal mammary nodes with microscopic metastasis detected by sentinel node biopsy but not clinically apparent
pN2	Metastasis in 4-9 axillary nodes, or in clinically apparent ipsilateral internal mammary nodes, without axillary nodes
pN3	Metastasis in ≥ 10 axillary nodes; or infraclavicular; or supraclavicular; or clinically apparent internal mammary nodes with axillary node(s); or > 3 axillary nodes with microscopic but not clinical internal mammary nodes
M category	presence of distant *Metastasis*
M1	Distant metastasis microscopically confirmed

Table 2.2 TNM classification of breast cancer

Stage group	T category	N category	M category
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T0, T1	N1mi	M0
Stage IIA	T0, T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0, T1, T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	N0, N1, N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Table 2.3 TNM stage groupings of breast cancer

2.3 Principles of the treatment of breast cancer

Early detection and incremental improvements in the multimodal treatment of breast cancer account for an increase in five-year survival from 52% in 1971 to 82% in 2006 (Cancer Research UK 2009). The standard annotation of medical notes prior to biopsy-led diagnosis provides an historical perspective for the role of radiotherapy in the treatment of operable breast cancer. Typical 1970s notation might simply state,

'Consented to excision biopsy. Frozen section. Proceed to mastectomy?'

Following theatre, the woman would awake with or without a breast, with no prior knowledge of the outcome, and without the various forms of supportive care available today.

The standard treatment for all operable breast cancer into the second half of the twentieth century has latterly been termed the Halstedian paradigm. This treatment model supposed that the tumour would disseminate to adjacent tissues in an anatomically predictable manner. The regional lymphatics were conceptualised as providing a sequential mechanistic defence to this centrifugal spread (Benson 1998). This centrifugal model provided the justification for the radical mastectomy procedure – originally performed by William S. Halstead –which removed the breast, underlying chest muscle and axillary nodes en bloc. The radical mastectomy did achieve good local disease control, but at the cost of formidable physical and psychological morbidity, and without proven improvement in survival (Baum 1988, p. 3–5).

By the early 1970s, the radical mastectomy (and the underpinning rationale) was obsolete. Adoption of the less extensive modified mastectomy was the initial evolution. Earlier detection of primary tumours, twinned with advances in radiotherapy (and endocrine and chemotherapy) subsequently facilitated the progression towards breast conservation therapy (BCT), without compromising local control. BCT (wide local excision plus adjuvant radiotherapy) has now become the standard adjuvant treatment for operable breast cancer: the rationale of the radiotherapy component being to minimise loco-regional recurrence. Contemporaneous adoption of biopsy-led diagnosis enabled the clinician and patient to agree a definitive surgical approach. The refinement of loco-regional therapy is ongoing, with the development of sentinel-node mapping, randomised trials investigating the role of partial breast irradiation (National

Surgical Adjuvant Bowel and Breast Project (NSABP) -B-39) and the TARGIT trial investigating intra-operative radiotherapy (Holmes et al. 2007).

Improved local disease control is, however, only part of the story. As previously noted, the Halstedian era had not rendered an increase in survival. Prompted by this, the Bernard Fisher group (and other researchers) investigated an area not adequately explained by the prevailing mechanical orthodoxy; namely unpredictable regional nodal involvement, advanced metastatic spread and hence mortality (Fisher 1980). By 1970, these investigations led to the formulation of an alternate paradigm proposing that breast cancer is a biologically heterogeneous disease that is intrinsically systemic. Here, metastasis occurs according to biological, not anatomical criteria. Hence, negative regional lymph nodes might not always be interpreted as evidence of localised disease, but rather the existence of an immunological host-tumour biology that both eradicates regional nodal involvement and inhibits distant metastasis (Fisher 1980). Subsequent randomised controlled trials (Fisher et al. 1980) – designed by the NSABP to clarify the respective roles of loco-regional treatment and systemic therapies – broadly upheld the biologically determined hypothesis, the continuum of which is evident in modern systemic therapies.

Current treatment practice integrates elements of both paradigms. Oncologists consider some disease truly localised, spreading in a progressive manner and curable by loco-regional treatment. Indeed, meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG 2000, 2005) has provided compelling evidence that loco-regional control can prevent distant metastases and thereby improve survival. Also situated within this model is the concept of predictable lymphatic progression via a sentinel node. Conversely, much disease is overtly systemic at presentation, or is considered to be due to the likelihood of distant micro-metastatic disease (Helman 1994), and therefore indicating systemic therapy.

A complex of established prognostic host-tumour related factors provide the bases for an estimate of the likelihood of micro-metastatic disease. Namely, regional nodal status, tumour size, histological grade and type, patient age, oestrogen (ER) and progesterone (PgR) receptor status, Human Epidermal growth factor Receptor 2 (HER-2) receptor status and the presence of vascular invasion. Furthermore, factors

such as ER and HER-2 status predict the individual response to adjuvant therapy (Cianfrocca and Goldstein 2004). The identification of novel predictive factors will further refine 'personalised' therapy. A wide range of molecular markers is under investigation, including angiogenic, proliferative and immunological factors. In clinical practice, estimates of the benefit from systemic therapies for individual patients are routinely calculated using the web-based tool Adjuvant! (available from www.adjuvantonline.com).

A dynamic initiative to reach a consensus on the optimal adjuvant systemic treatment of early breast cancer (EBC) is the international recommendations formulated at the St. Gallen Breast Cancer Conference. The most recently published update was in 2007 (Persing and Große 2007). A classification system based on the risk of relapse and mortality has been devised (Table 2.4), and systemic therapy recommendations advanced according to risk group (Table 2.5). The treatment selection algorithm reflects the current centrality of endocrine responsiveness of the tumour.

Low risk	**Intermediate risk**	**High Risk**
pN0 and *all* of the following criteria:	pN0 and *at least 1 further* criterion:	p(N1–3) and Her2 positive *or* p(N ≥ 4)
tumour ≤ 2 cm (Tis - T1)	Tumour > 2cm	
Grade 1	Grade 2 to 3	
no vascular invasion	vascular invasion present	
ER/PgR positive		
HER2-negative	HER2 over expression	
age ≥ 35 years	age < 35 years	
	or	
	p(N1–3) and HER2 negative	

Table 2.4 St. Gallen 2007 risk classification for early breast cancer patients

Low risk	Intermediate risk	High Risk
endocrine therapy *or* no therapy	*endocrine responsive* endocrine therapy *or* chemotherapy then endocrine therapy trastuzamab where appropriate	*endocrine responsive* chemotherapy then endocrine therapy
	uncertain endocrine responsiveness chemotherapy then endocrine therapy trastuzamab where appropriate	
	endocrine non-responsive chemotherapy trastuzamab where appropriate	*endocrine non-responsive* chemotherapy trastuzamab where appropriate

Table 2.5 St. Gallen 2007 therapy recommendations for early breast cancer patients

2.3.1 The role of adjuvant systemic therapies for early breast cancer

Chemotherapy

Broadly, low-risk patients are endocrine sensitive and high-risk patients are chemotherapy sensitive. Although ER status is limited as a predictor of chemotherapy response, the benefit of adjuvant chemotherapy varies inversely as a function of age and endocrine sensitivity. Meta-analysis by the EBCTCG (2005) found anthracycline-based poly-chemotherapy reduced breast cancer mortality by 38% and 20%, for the under 50s and those 50–59 respectively. After the age of 60, the benefit of chemotherapy decreases. With reference to the risk classifications above, adjuvant chemotherapy would be indicated for pre-menopausal women except those at low-risk, and for intermediate and high-risk post-menopausal women, unless they are endocrine responsive.

Anthracycline-based regimens (e.g. FEC) have demonstrated an 11% improvement in the likelihood of recurrence, when compared to gold-standard non-anthracycline regimens, such as CMF (EBCTCG 2005). Latterly, much research interest has

focused on a class of cytotoxic agents called taxanes. The addition of the taxane docetaxel is now indicated for younger node positive women (Martin et al. 2005). The sequence of radiotherapy and chemotherapy is conceivably unimportant, however, until all modern systemic therapies are evaluated for long-tem toxicity outcomes, it is recommended chemotherapy be given prior to radiotherapy.

Endocrine therapy

Broadly, aromatase inhibitors (AI), such as Arimidex, are indicated for endocrine responsive post-menopausal women and oestrogen receptor blockers (OB), such as Tamoxifen, for endocrine responsive pre-menopausal women. The EBCTCG (1992) review established the benefit of Tamoxifen in sensitive pre- and postmenopausal women. The subsequent BIG 1-98 (Letrosole v Tamoxifen) and ATAC (Armidex, Tamoxifen, Alone or in Combination) trials of post-menopausal women both indicated a lower occurrence of metastases and improved disease-free survival – of approximately 2.8% at 5 years and 4.8% at 10 years – for AI as compared to Tamoxifen. Furthermore, AI demonstrated a superior toxicity profile compared to OB, but were associated with increased bone pain and fracture. The IBIS-II trial is currently investigating the benefit of prophylactic AI administration in post-menopausal women at high risk of developing invasive breast carcinoma.

Oncologists can prescribe endocrine therapy concurrently or sequentially with radiotherapy (Harris et al. 2005) although in practice endocrine therapy may follow radiotherapy. The twin rationales for the latter sequencing are that hormones may decrease radiosensitivity by arresting tumour cells in the G_1 state (Osborne et al. 1983), and a hypothetical enhanced risk of radiation-induced lung or skin fibrosis through the induction of transforming growth factor-ß (Bentzen et al. 1996).

Trastuzamab

Approximately 25% of patients over-express the cell membrane surface-bound protein HER2/neu. Over-expression is associated with recurrence, but this is roughly halved by the administration of the targeted monoclonal antibody Trastuzamab (trade name Herceptin) (Slamon et al. 2001). Initial evidence from the HERA and NCCTG N9831

trials characterises associated cardiac toxicity to be predictable, acceptable and treatable. NICE has recently licensed the use of adjuvant Trastuzamab for all HER-2 positive tumours (NICE 2006).

2.3.2 Disease recurrence

Five years after the completion of adjuvant treatment, approximately 10% of disease will recur (Brewster et al. 2008). Depending on previous treatments, loco-regional recurrence may be treated by mastectomy and/or radiotherapy. The benefit of additional systemic treatment in this patient group is unproven (Rauschecker et al. 2001). Clinicians may consider multi-modal systemic regimens for distant relapse. Novel treatments targeted at genetic sub-types, such as PARP inhibitors targeted at BRCA2 mutations, show promise in treating some EBC recurrence (Geddes 2008).

CHAPTER THREE **Literature review**

A literature search was conducted to connect and contextualize the study topics to existing research, and provide an overview of three subject areas:

- Scientific and clinical aspects of radiotherapy for breast cancer
- The science of radiotherapy-related fatigue (RRF)
- The role of inflammatory cytokines in breast CRF and RRF, via the sickness behaviour framework.

Search strategy

The structure of the literature review was split into three stages. The first stage was a broad exploratory Ovid Medline search, designed to identify appropriate medical subject headings (MeSH). The keywords used at this stage were breast neoplasms, radiotherapy, fatigue, and inflammatory cytokines. A search history is included in Appendix 1.

The second stage of the process was the application of the generated MeSH terms and keywords in a comprehensive search of the following databases: AMED, all EBM Reviews (comprising ACP, CDSR, and DARE), EMBASE, Ovid Medline and Web of Science. Subject headings were modified as required by individual databases. A list of the MeSH terms used is included in Appendix 1. The comprehensive search was limited to publications between 1997 and 2009, as the preliminary search had identified very few relevant results prior to this date. Duplicates were removed prior to screening the resultant publications for relevance based on subject headings, title, abstract and the application of the following methodological criteria: case studies, non-English language papers, adolescent studies, studies of male breast cancer, chemotherapy-specific studies, exercise or muscle-related fatigue and chronic-fatigue syndrome studies were all excluded from review. Animal studies were also excluded, except where they provided evidence directly related to the vagal-afferent theory (section 3.2.6). Reviews and studies of all other types, considering the aetiology,

measurement, prediction or covariates of CRF and RRF were retained. Table 3.1 details the search results from the comprehensive search and the filtering process.

Database	Results	Relevant after reviewing
AMED	11	5
EBM reviews	37	12
EMBASE	90	24
Ovid Medline	135	75
Web of Science	181	38
Totals	454	154

Table 3.1 The number of references retrieved for each database searched

The third stage of the search process was to review the references cited in the 154 retained publications to broaden the search strategy, regardless of years of publication or eligibility criteria. This snowballing of citations rendered 51 further publications, and a total of 205 references retained for critical review.

The articles related to clinical breast radiotherapy practice were predominately well-designed randomised controlled trials (RCT), many of which were large, multi-centre and multi-national. The replication of findings and the availability of authoritative systematic reviews and meta-analyses emphasize the importance of the underlying clinical questions. The papers focussing on CRF and RRF were of more mixed methodological quality, although the general level was acceptable. These studies were almost exclusively observational, often with no obvious comparison group available. A small number of trials of fatigue treatment were evident. Generally, an improvement in quality was evident over time, with earlier (pre-2000) studies characterised by cross-sectional designs or a lack of baseline measurements. Longitudinal studies are more common in latter studies; however, cohorts were rarely homogenous or recruited at a uniform point in the treatment pathway. Diversity of outcome measures is also a common feature. The studies reporting cytokine bioactivity were generally of good quality, with standardised laboratory techniques

used. Relatively small sample sizes were common, which may have been inadequate to demonstrate subtle effects. Power calculations were absent, possibly due to the constraints of journal word limits.

3.1 Radiotherapy for breast cancer

3.1.1 Loco-regional treatment for operable breast cancer

Surgery to the breast

The primary treatment for EBC, including ductal carcinoma in situ (DCIS), is the surgical removal of the macroscopic tumour. Current surgical procedures are the modified radical mastectomy and wide local excision (WLE). Influential randomised trials with 20-year follow-up (Fisher et al. 2002a, Fyles et al. 2004, Veronesi et al. 2002) and comprehensive systematic reviews of randomised trials (EBCTCG 1995, Morris et al. 1997) have consistently demonstrated the equivalency of BCT and mastectomy, in terms of local recurrence, disease-free survival (DFS) and overall survival (OS).

The importance of histologically clear surgical resection margins is reflected in the recent update from NICE (2009, p. 13), which increased guidelines on disease-free margins from 1 to 2mm for DCIS. Involved margins necessitate surgical resection. If this is unachievable, or unacceptable to the patient, mastectomy is indicated. Other factors that may contraindicate breast-conserving surgery (BCS) include tumours that are larger than 50mm, multi-focal or multi-centric, or have an extensive intraductal component (Barrett-Lee and Iqbal 2008, p. 198).

Surgery to the axilla

Historically, surgical clearance of the axillary nodes had the twin aims of eradicating nodal disease and providing prognostic information to guide adjuvant therapy for invasive carcinoma patients. The arm morbidity associated with axillary clearance has prompted a move to increasingly minimal surgery over the last 10 years. Axillary sampling of the four most palpable nodes causes less morbidity, but does involve further surgical clearance (or axillary radiotherapy) for positive cases (Adwani et al. 2005). A consequence of population screening is a lower prevalence of nodal disease. This has led to a shift towards even less invasive investigation by sentinel node biopsy (SNB), with axillary clearance performed only when indicated. In a large randomised trial, Veronesi et al. (2003) demonstrated similar diagnostic reliability for the SNB

procedure (sensitivity of 91% and specificity of 100%) compared to axillary dissection. Despite challenges to the concept of a sentinel node (Adwani et al. 2005), SNB offers an accurate, non-invasive procedure, associated with minimal morbidity (Mansel et al. 2006), and is now the officially preferred UK axillary surgical procedure (NICE 2009, p. 14). The prognostic significance of axillary micrometastases is a matter for debate. As regards the current study, isolated micrometastatic deposits should not impose any substantive systemic tumour burden, and as such, patients with micrometastases were not excluded. The clinical significance of the 12% of the sentinel nodes Van Rijk et al. (2006) visualised external to the axilla and IMC remains ambiguous.

Adjuvant radiotherapy after breast conservation

The rationale of whole breast radiotherapy after BCS is to eradicate residual microscopic disease present in the breast tissue, chest wall or loco-regional nodes. Local recurrence tends to present in the residual breast tissue, and within the first five years following primary treatment (EBCTCG 2000). Well designed randomised trials (NSABP B-06, NSABP B-21, Swedish BCCG) comparing BCT with BCS alone have consistently shown an increased risk of local recurrence of approximately two-thirds if radiotherapy is omitted. The authoritative EBCTCG meta-analyses (2005) of patient-specific data pooled from 78 randomised trials confirmed the benefit; quantifying the five-year risk of local recurrence at 7% for radiotherapy patients and 26% for the non-radiotherapy patients. The absolute reduction in recurrence risk is essentially a function of the inherent risk-status of patient subgroups: the higher the risk of recurrence, the more beneficial radiotherapy is. Nodal status was the strongest determinant of risk, with younger age and increased tumour size and grade conferring elevated risk for node-negative controls not allocated radiotherapy.

The UK standardisation of breast radiotherapy (START) fractionation trials (Bentzen et al. 2008a, Bentzen et al. 2008b) reported mean five-year recurrence risks after BCT of 3.5%, for over 4000 EBC patients. The lower than predicted rate was attributable to some combination of improvements in screening, local therapies, endocrine and cytotoxic agents and patient-related factors such as age (Mannino and Yarnold 2009). The identification of a subgroup that inhere a sufficiently low risk of recurrence to omit radiotherapy constitutes a fundamental and fertile research direction. To this end, the

CALG C9343 trial (Hughes et al. 2004) recruited 319 low-risk women older than 70, who were ER-positive, with T1 stage tumours. The absolute difference in five-year recurrence risk was marginal, being 4% for BCS plus Tamoxifen, and 1% for the addition of radiotherapy. Based on such data, Smith and Ross (2004) argue the ubiquitous prescription of radiotherapy to BCS patients, regardless of risk status, is illogical. However, until longer-term data is available and fully evaluated for recurrence and survival endpoints, omission of radiotherapy remains investigational.

Despite many randomised trials (NSABP-06, Overgaard et al. 1990, Arriagada et al. 1995) with the potential to address the question, the effect of adjuvant radiotherapy on survival has until recently been uncertain. The reasons why this situation has persisted are three-fold. Differences in survival between patients randomised to radiotherapy and those not may take 10 to 15 years (or more) to become apparent. Furthermore, with apparently small effect-sizes, the numbers required to demonstrate reliably any difference between study arms are large. Finally, the evolution of radiotherapy techniques, over the long period to outcome, has meant that early data was established using anachronistic techniques associated with increased radiation-induced morbidity and mortality, particularly cardiac disease.

An evolving story is evident in the survival findings of the ECBTCG meta-analyses of randomised trials. The 1995 meta-analyses of trials commenced before 1985 found no statistically significant difference in 10-year survival between patients allocated radiotherapy and patients without radiotherapy ($p = 0.3$): all-cause mortality was 40.3% and 41.4% respectively. The 2005 update, comprising 76 trials commenced before 1995, still found no individual trial demonstrated a definitive survival benefit for radiotherapy, but the pooled meta-analysis revealed a highly significant absolute reduction in 15-year breast cancer-specific mortality of 5.4% ($SE = 1.7$, $p = 0.0002$). All-cause mortality at 15 years follow-up was now 35.2% for radiotherapy patients and 40.5% for non-radiotherapy patients. The divergence in mortality over time is evident below in Figure 3.1.

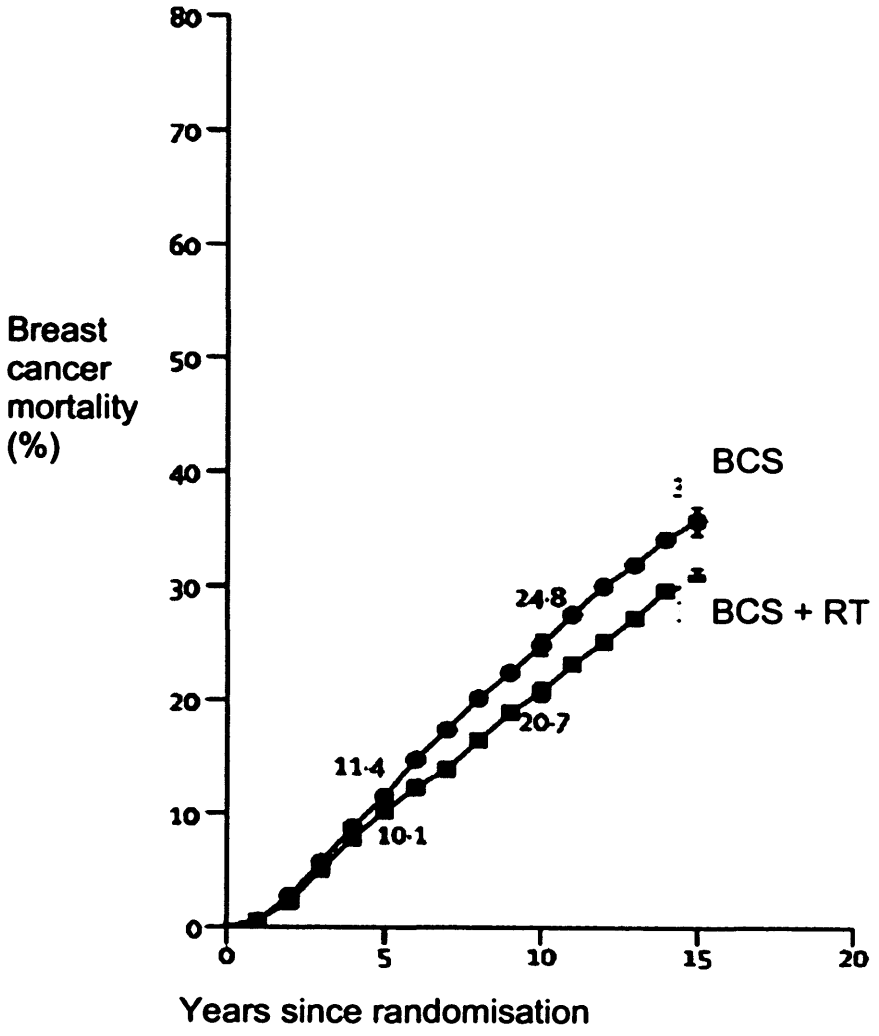


Figure 3.1 Effect of radiotherapy on breast cancer mortality for 7311 patients with early breast cancer (adapted from ECBTCG 2005). (BCS = breast conserving therapy; RT = radiotherapy.)

The long period covered by the comprehensive ECBTCG overviews has rendered their pooled-data subject to variations in a number of treatment-related variables that may confound the radiation effect. For example, management of the axilla was not consistent for all 7311 women included in the BCS data, with the sample described as 'generally' having undergone axillary clearance. Furthermore, developments over the last twenty years in screening and imaging have meant that the most common clinical presentation is now a T1 stage tumour. Whilst the introduction of novel adjuvant systemic therapies may conceivably act agonistically (or synergistically) with the radiotherapy to prevent local and distant recurrence (Whelan et al. 2000a), trials have clearly demonstrated endocrine and chemotherapy are not appropriate alternative adjuvant therapies to radiotherapy (Fisher et al. 2002b, Fyles et al. 2004, NSABP-06,

NSABP-B21). Radiotherapy is therefore likely to remain a central adjuvant treatment for breast cancer, and the assessment of iatrogenic toxicities needs to keep pace with developments in the delivery of breast radiotherapy.

Adjuvant radiotherapy after mastectomy

Post-mastectomy radiation may be given to eradicate residual disease in the chest wall or loco-regional nodes. As for BCS, the EBCTCG (2005) meta-analyses found post-mastectomy radiotherapy reduced the five-year local recurrence risk by approximately two-thirds. Confirmation of nodal status was via axillary clearance for all the 8300 women participating. The absolute benefit was small for node-negative women, but for node-positive women radiotherapy reduced the recurrence risk from 23% to 6%. Based on this data, radiotherapy is currently given to women with four or more involved lymph nodes. This four-node distinction is somewhat arbitrary. The role of post-mastectomy radiotherapy for women with one to three positive nodes (or an advanced primary cancer) is under investigation in the ongoing SUPREMO trial (Kunkler et al. 2008).

Evidence suggests that initial demonstrable benefits in loco-regional control and reduced breast cancer mortality in post-mastectomy radiotherapy patients were achievable, but at the cost of higher non-breast cancer deaths (Cuzick et al. 1994, EBCTCG 1995). The excess mortality was largely attributable to the pathological effects of cardiac – and to a lesser degree pulmonary – irradiation, exacerbated by now outmoded radiotherapy techniques. Randomised trials (Overgaard et al. 2004, Ragaz et al. 2005) and meta-analysis (Whelan et al. 2000a) of post-mastectomy trials using modern megavoltage radiotherapy techniques and dose-fractionation regimes, confirmed a 10-year OS benefit for radiotherapy of approximately 17%. The EBCTCG (2005) pooled-data analysis of 8300 women extended the post-mastectomy survival findings, reporting significant 15-year breast cancer mortality reduction of 5.4% ($p = 0.0002$), and an all-cause mortality reduction of 4.4% ($p = 0.0009$) for radiotherapy patients (Figure 3.2).

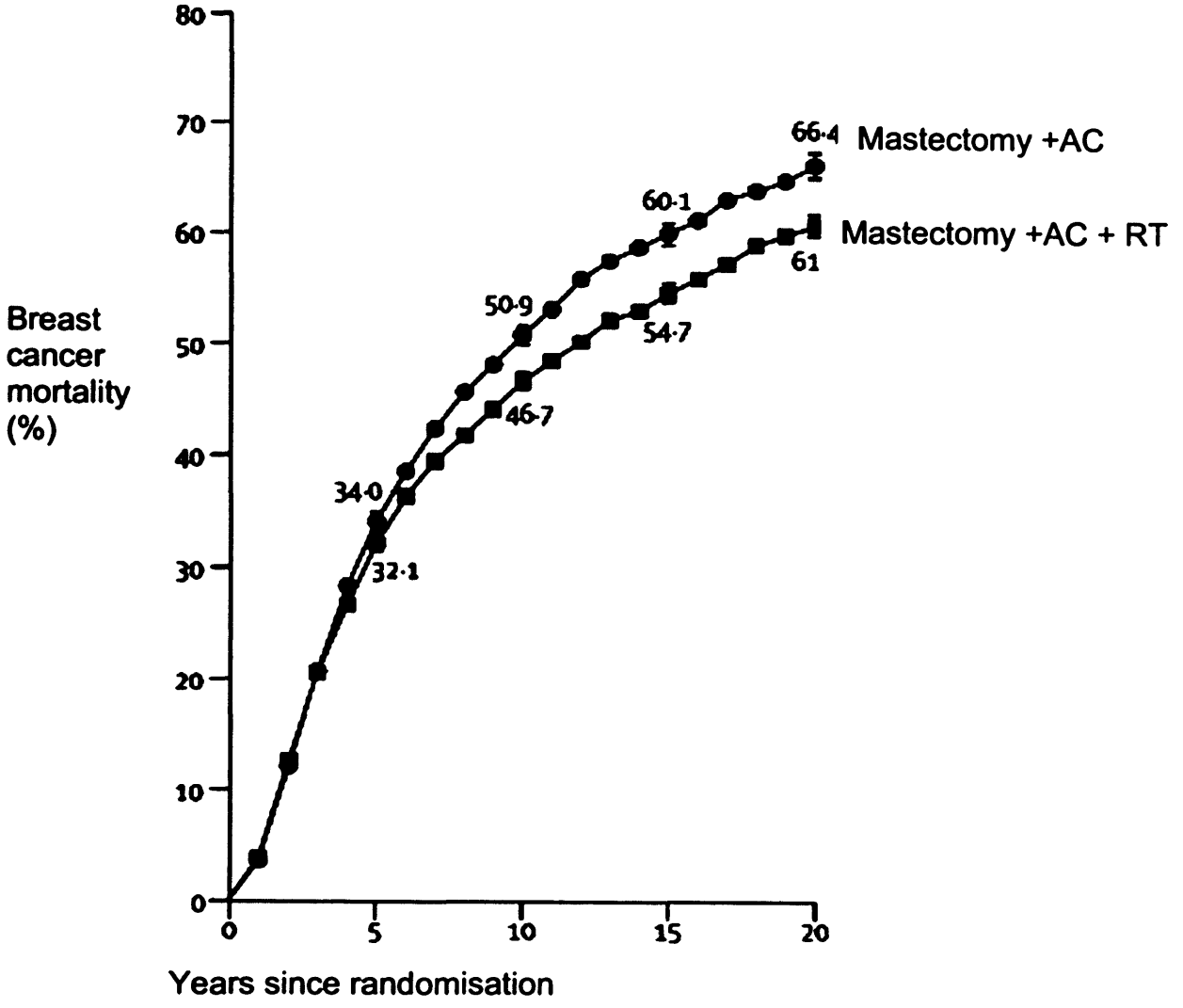


Figure 3.2 Effect of radiotherapy on breast cancer mortality for 8300 patients with early breast cancer undergoing mastectomy (adapted from ECBTCG 2005). (AC = axillary clearance; RT = radiotherapy.)

The relationship between recurrence and survival

The EBCTCG (2005) overview suggests that breast radiotherapy reduces the absolute risk of recurrence by approximately 20%, and the risk of mortality by approximately 5%. Therefore, statistically, the prevention of four local recurrences prevents one death due to distant metastasis. According to Kurtz (2000), this ratio is the minimum expected benefit, due to the underestimation of survival benefit caused by the inclusion of findings based on out-dated radiotherapy techniques and technology. The generalisability of the overview results to current clinical practice is potentially hindered by this factor, although the EBCTCG Group maintain the four-to-one ratio

may reasonably be inferred to the breast cancer population. The less optimistic aspect is the continued potential for radiation-induced vascular damage in low-risk women, causing a net-increase in mortality.

Radiotherapy to the loco-regional lymphatics

If axillary nodes are negative or axillary clearance is adequate, the omission of radiotherapy prevents increased arm morbidity. Where necessary axillary clearance is contra-indicated, axillary radiotherapy confers an equivalent preventative effect on axillary recurrence (Hetelekidis 2000). Positive axillary nodes are associated with an increased risk of SCF nodal recurrence. Therefore, the presence of four or more positive axillary nodes is an indication for irradiation of the ipsilateral SCF. Patients with one to three positive nodes and other adverse prognostic factors may also benefit, although reduction in SCF recurrence must be balanced against late morbidity (McKinna et al. 1999).

Irradiation of the IMC has fallen from favour. The position of the medially sited node group is difficult to localise exactly, and radiation fields that encompass the IMC irradiate increased volumes of deep-lying heart and lung tissue (Freedman et al. 2000). The uncertain role of IMC irradiation using modern techniques in a high-risk subgroup with medially sited tumours is under investigation in the EORTC 22922 trial.

External radiotherapy boost

An additional external beam radiation boost to the tumour bed is not routinely recommended (Barrett-Lee and Iqbal 2008, p. 200), despite two randomised trials showing that this procedure reduces the risk of local recurrence from 4.6 to 3.6% ($p = 0.04$) at three years (Romenstaing et al. 1997), and 7.3% to 4.3% ($p < 0.001$) at five years (Bartelink et al. 2001). Increased morbidity and inferior cosmesis offset the potential benefits for patients at a low-risk of relapse. For higher risk patients, such as those younger than 50 years or where surgical margins are inadequate, oncologists consider an electron or conformal photon boost of 10 to 16Gy.

Radiotherapy for ductal carcinoma in situ

Four high quality randomised-controlled trials (EORTC-10853, NSABP B-17, UKCCCR-DCIS trial, SweDCIS) have shown radiotherapy reduces the risk of ipsilateral breast events after BCS by at least 50% in women with DCIS (Goodwin et al. 2009). Approximately half of these events were invasive disease with metastatic potential, although impact on survival is speculative. Based on this evidence radiotherapy is routinely prescribed for all DCIS patients, even though this course leads to 'overtreatment' of ER positive, low-risk patients. Compared with invasive disease, patients with DCIS benefit less as a group from radiotherapy, but experience identical treatment-related acute and chronic toxicities such as RRF. Current randomised trials (ECOG E5194, RTOG 98-04) are attempting to identify a subgroup whose post-BCS prognosis is sufficiently favourable to omit radiotherapy safely. Current practice does not recommend post-mastectomy radiotherapy in this patient group.

3.1.2 Target volume localisation for breast and chestwall radiotherapy

As the tumour has been surgically removed, a conventional planning target volume (PTV), based on an expanded gross tumour volume (GTV), is not identifiable. Instead, the glandular breast tissue constitutes a clinical target volume (CTV). The addition of an isotropic margin of approximately 10mm then forms a proxy PTV.

Conventional two-dimensional (2D) planning utilises orthogonal X-ray films to localise field margins in accordance with a pre-set protocol. As the CTV cannot be wholly visualised, the definition of individual margins is via palpation and with reference to surface anatomy. Typical margins are midline medially, the mid-axillary line laterally, the suprasternal notch superiorly, and 10 mm below the inframammary fold inferiorly, with the pectoral fascia forming the deep margin (Figure 3.3).

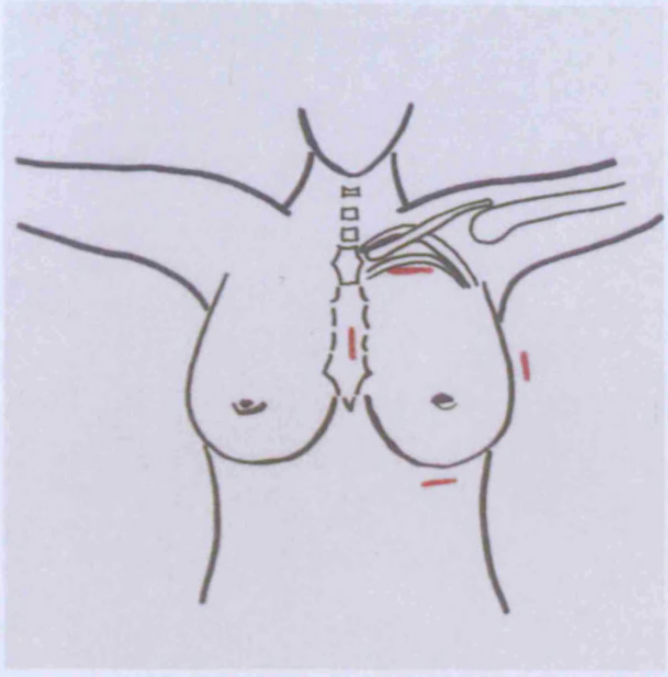


Figure 3.3 Typical field margins for conventional orthogonal film planning

The last 10 years has seen the advent of computed tomography (CT) scanners with sufficient bore-width to accommodate patients in the standard treatment position. Coupled with sophisticated computerised planning software, CT planning has become the gold standard for breast radiotherapy planning. This has enabled three-dimensional (3D) CTV visualisation and full PTV localisation in accordance with individual patient anatomy. Although not universally agreed (van der Laan et al. 2008), the CTV after BCS consists of the glandular breast tissue, excluding pectoralis muscle, ribcage and skin. After mastectomy, the skin (including surgical scar) to the deep fascia is included (Donovan et al. 2006, p. 49).

The standard CT patient position is supine, often on an inclined board to flatten the chestwall in relation to the horizontal, with either the ipsilateral or both arms raised and abducted to 90 degrees. Whilst this position is relatively stable, it does raise the sub-diaphragmatic organs superiorly towards the radiation field (Eddy 1999). A study objective is therefore to determine the volume of liver irradiated during breast radiotherapy, and evaluate evidence of any related acute effects.

A prone position appears to be beneficial for large pendulous breasts in terms of dose homogeneity and distribution (Buijsen et al. 2007). Neal et al. (1995) carried out a

study designed specifically to evaluate the effect of breast size (represented by three different surrogates) on dose heterogeneity. A methodological limitation of the study was that the aperture of the CT scanner limited the size of patient eligible for the study. DVH analysis revealed that the degree of dose heterogeneity was correlated positively and most strongly with breast volume (r = .70). Wilks and Bliss (2002) conducted a dose-positional analysis, concluding that dose is highest at the inframammary fold – a level at which the superior portion of the liver may be present. Their positional findings corroborate previous results by Delaney et al. (2000), who took a simple approach by utilising a phantom with two different breast sizes. The highest absolute dose was located in the inferior plane of the large breast, and the greatest dose deviation and highest measured doses occurred in the inferior aspects of both the small and large breast phantoms. This was a multi-centre study. Local clinicians placed the medial and lateral entry points, so the reliability is uncertain, though this situation does arguably reflect real practice. Furthermore, the sensitivity of the dosimetry is questionable, being based on an anthropomorphic phantom with only two breast sizes and nine thermoluminescent dosimeter positions. Consequently, any other heterogeneous dose areas in the breast were unknown.

Further rationale for a prone patient position for patients with large breast sizes are a reduction in positional errors during treatment, poor cosmesis after treatment and evidence that the volume of dose-limiting structures irradiated can be significantly reduced by a prone patient position in this patient group (Formenti et al. 2007). It is notable that the treatment plans produced for the Formenti et al. study were subjected to more stringent dose constraints than are common in the UK. The UK SuPr Study is currently investigating the relative reproducibility of the tumour bed position and volumes of healthy tissue irradiated in breast radiotherapy patients treated in supine and prone positions (details available from Clinical Trials.gov http://clinicaltrials.gov/ct2/results?term=SupR). Prone breast irradiation is not currently common practice, and is unavailable at the study centre. However, the current study will assess the impact of breast size on fatigue during supine radiotherapy.

As discussed in the following sections, the application of CT localisation has many potential advantages for breast planning, but does, intrinsically confer geometric uncertainty due to diaphragmatic, cardiac and hence abdomino-thoracic organ motion

(Caldwell et al. 2003). The CT body data captures a snapshot of the free-breathing cycle that may not be representative of the average regional tissue location on treatment. In this case, a systematic error will be present that may be exacerbated by the introduction of random and systematic treatment-based errors. Thus, the potential exists for the creation of net discrepancies between the dose-volume distribution data generated during planning and the actual organ doses received during treatment.

The standard beam-patient geometry for breast radiotherapy is two tangentially opposed beams, often angled to align the posterior margins to minimise lung dose (see Figure 3.4 below). To ensure the PTV is neither under-dosed nor over-dosed, the dose-distribution variation should be within 95–107% of the prescribed dose, in accordance with ICRU guidelines 50 (1993). An optimised plan aims to meet these criteria whilst keeping the dose to normal tissue volumes below critical constraints and as low as is practicable. Dose-limiting structures are the heart and lungs.

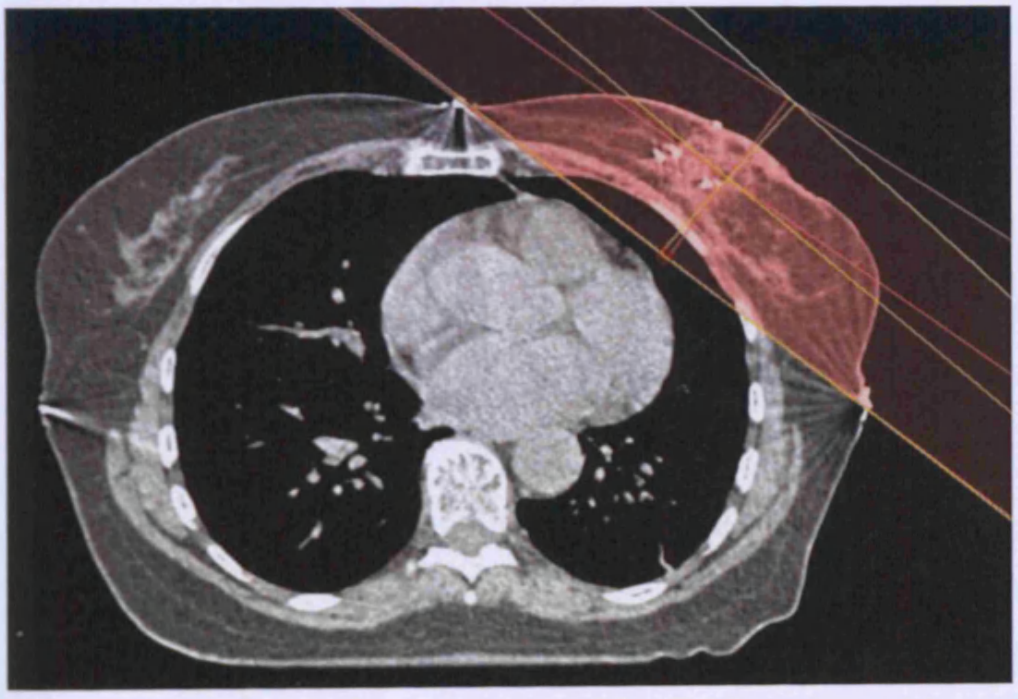


Figure 3.4 Opposed tangential breast radiotherapy fields with non-divergent posterior border

3.1.3 Modern dosimetry planning systems

The inherent accuracy of a planning system (and resultant dose-volume data) will depend on the accuracy of the beam calibrations, dose algorithms, data transfer systems and ultimately treatment delivery. All contributing components of the system are subject to a rigorous verification process as part of the standard quality assurance process (IPEM-81 1999).

Modern planning systems utilise the density variation of tissues acquired from CT data to produce accurate (iso)dose maps for each patient. Increasingly sophisticated convolution algorithms, such as the collapsed cone algorithm, model dose deposition at the voxel level incorporating broadened penumbra due to increased lateral secondary electron scatter through lower density lung tissues (Hasenbalg et al. 2007). When evaluated against the gold standard of Monte Carlo simulation dose modelling, such algorithms display increased validity compared to simpler pencil-beam algorithms (Wills et al. 2009). The study dose-volume data was derived used a collapsed cone algorithm.

The calculated 3D dose-distribution can be displayed as a dose-volume histogram (DVH). This graphical output displays the sub-volumes of a volume irradiated to differing levels of the applied dose. DVHs summarise a huge quantity of data and are widely used in the interpretation of 3D plans. An inherent limitation of DVH analysis is that they yield no information regarding location of dose deposition within a volume (Bentel 1996).

3.1.4 Clinical applications of 3D beam-patient geometry

When planning in 2D, the ICRU 50 dose homogeneity requirement is usually achievable with the aid of wedge compensators. However, when planning is undertaken in 3D, the complex double-contours of the breast and variations in tissue density render this criteria exacting; particularly when using a collapsed cone algorithm that models tissue density effects accurately (Irvine et al. 2004). Nonetheless, the ability to model the true dose distribution throughout the entire CTV is a fundamental evolution (Delaney et al. 2000, Donovan et al. 2002).

Clinical applications of 3D data include 3D conformal radiotherapy (3D-CRT) (Zackrisson et al. 2000) and intensity modulated radiotherapy (IMRT) (Vicini et al. 2002). These advanced techniques both rely on an accurate 3D localisation of target volumes to reduce dose to normal tissues and/or boost the dose to select (tumour) tissues. The clinical benefits of such applications may become apparent through trials such as the current UK Intensity Modulation and Partial Organ Radiotherapy (IMPORT) trial (Coles and Yarnold 2006). A brief overview of this trial will now serve to highlight a number of related scientific and clinical aspects of modern breast radiotherapy.

IMPORT is two randomised trials running in parallel: IMPORT Low and IMPORT High. In the Low trial, the application of prognostic and predictive factors has identified a subgroup of women at a statistically low risk (less than 1%) of local recurrence. This subgroup benefits less in terms of absolute survival reduction, but shares the same early and late-toxicity from standardised radiotherapy delivery. Furthermore, randomised trials indicate that approximately 70% of recurrences occur in the same quadrant as the original tumour (EBCTCG 2005). The aim of IMPORT Low is to test if the application of simple IMRT both retains recurrence benefit and reduces normal tissue sequelae that take months or years to manifest. Normal tissues that respond to irradiation in accordance with this chronology are referred to as late-reacting tissues. Figure 3.5 below, clarifies the dose-volume regimens for three IMPORT Low treatment allocations.

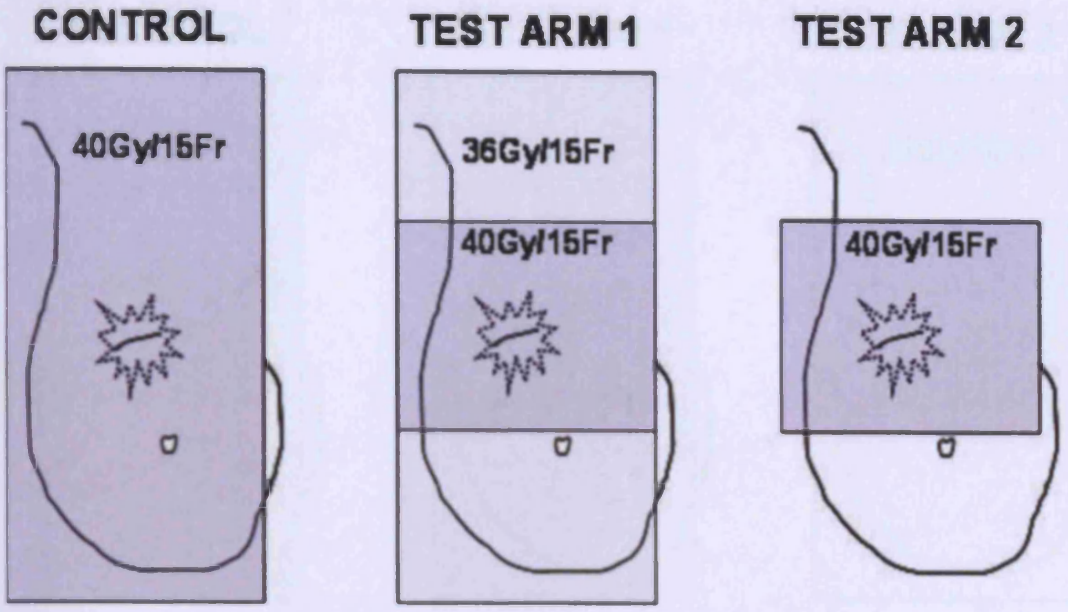


Figure 3.5 Schema summarising the trial arms in the Intensity Modulation and Partial Organ Radiotherapy (IMPORT) Low trial (Coles and Yarnold 2006). (Gy = gray; Fr = fractions.)

As the risk of relapse is low in the IMPORT Low patient group, local control must be achieved at the cost of acceptable acute toxicities. The current study will provide initial evidence of the impact of dose-volumetric parameters on fatigue. The design of IMPORT low is ideal to incorporate a translational study of the effect of irradiated volume on acute (and chronic) fatigue.

The rationale of the Import High trial is to target EBC patients at a higher risk of relapse. The aim is to investigate the impact of modulating the dose across the PTV, concentrating sequential or concomitant dose escalation on the tumour bed (see Figure 3.6 below). The primary study endpoint is breast cosmesis, with secondary endpoints including late normal tissue toxicity, QoL and local control.

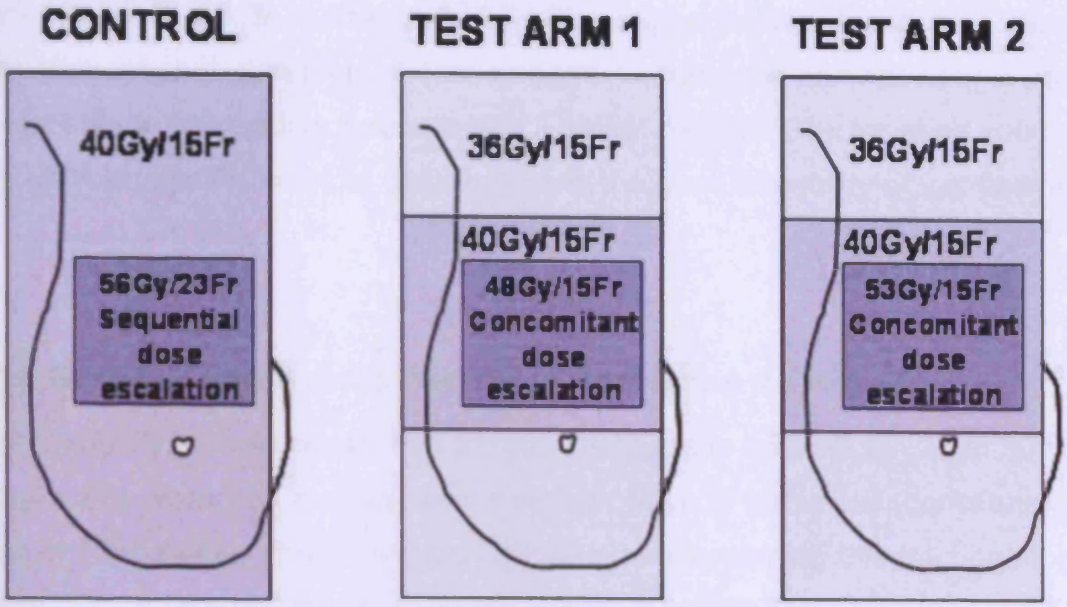


Figure 3.6 Schema summarising the trial arms in the Intensity Modulation and Partial Organ Radiotherapy (IMPORT) High trial (Coles and Yarnold 2006). (Gy = gray; Fr = fractions.)

Two extant technical issues that take on increased importance in the breast IMRT setting are tumour bed localisation and uncertainty in beam-patient geometry. First, as the breast scar does not relate well to the resected tumour cavity (Salvadori et al. 1999) the IMPORT trial protocol specifies the surgical implantation of titanium or gold fiducial markers (Coles et al. 2009) that enable radiographic visualisation, and thereby target localisation. Ideally, this development will become adopted as standard surgical practice. Second, modern helical CT scanners minimise scan times but inherently suffer from the aforementioned problem of geometric uncertainty due to abdomino-thoracic organ motion (Caldwell et al. 2003). The potential exists for geometrical misses, enlarged PTV margins and increased volumes of normal tissue irradiated. Paradoxically, the superseded conventional planning technology could utilise fluoroscopy to account for organ movement. Generating an 'average' organ position via slow CT-scanning (Lagerwaard et al. 2001) is one possible technical solution. Gating of the breathing cycle is a different approach (Remouchamps et al. 2003). However, the introduction of intra-fractional and inter-fractional errors may also occur during treatment, through variation in organ topography, breast inflammation, weight loss, patient movement and inaccurate treatment set-up (Hurkmans 2001). Reported mean cumulative errors are of the order of 2 to 4.5mm in the anterior-posterior plane and 3.5 to 6.5mm in the cranio-caudal plane (Frazier et al. 2004, Hector et al. 2000,

Korreman et al. 2005). Although IMRT offers superior dose-distribution characteristics than conventional planning, evidence suggests that dose homogeneity is particularly susceptible to cumulative errors in IMRT breast patients (Hector et al. 2000). The relatively small sample of 36 datasets limits the generalisability of this finding.

3.1.5 Radical breast radiotherapy fractionation schedules

Internationally, radical breast radiotherapy is typically delivered in 25 to 30 treatments, using a 2Gy dose per fraction, over a period of five to six weeks, constituting a total dose of 50 to 60Gy. The conventional thinking underpinning this fractionation regime is that late-reacting normal tissues are sensitive to both total dose and dose per fraction, whereas tumours (and early-reacting tissues such as the epidermis) are relatively insensitive to dose per fraction (Tutt and Yarnold 2006). Consequently, high total doses in small fractions of 2Gy or less spare normal tissues relative to the tumour. Published data from two randomised trials contradict such assumptions. The first found that local recurrence rates to be similar for biologically equivalent doses (BED) from 16 and 25 fraction regimes (Whelan et al. 2002). The second suggested that breast adenocarcinomas are as sensitive to fraction size as late-reacting normal tissues (Owen et al. 2006). Considered together, the implication of these findings is that small fraction sizes spare the tumour and normal tissues equally, and a lower total dose delivered at a higher dose per fraction over a shorter duration would yield a radiobiologically equivalent effect.

The UK START trial – developed from the Owen et al. (2006) trial – has evaluated the benefits for EBC patients of fraction sizes bigger than 2Gy (called hypofractionation). End-points included local tumour control, late-normal tissue responses and QoL. Two concurrent randomised trials (A and B) tested three experimental schedules against an international standard control of 50Gy over five weeks (Figure 3.7).

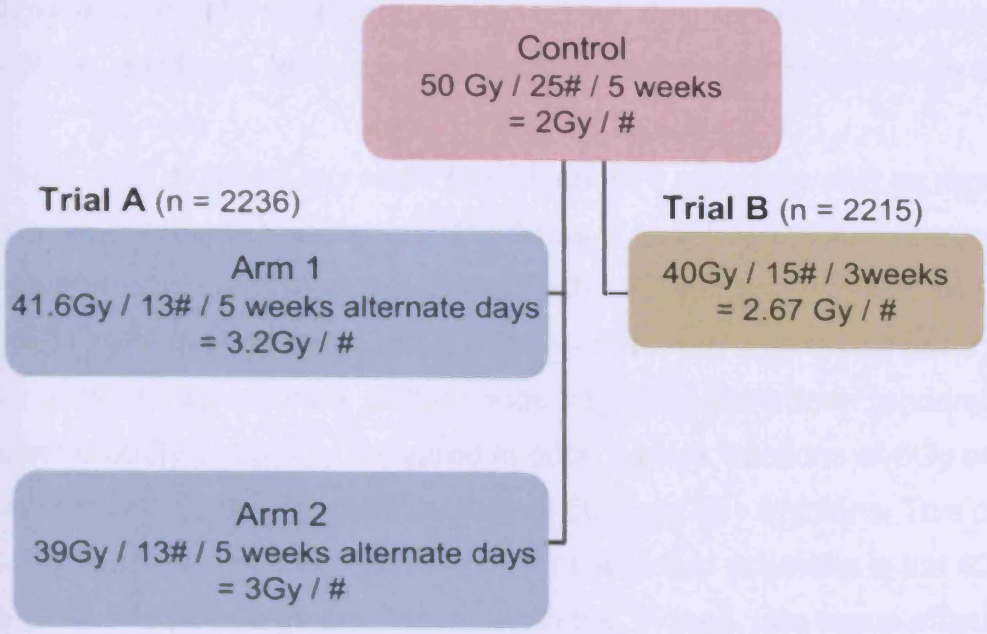


Figure 3.7 Schema summarising the study design in the UK Standardisation of Breast Radiotherapy (START) Trials A and B

When compared to the control schedule, absolute differences in five-year recurrence rates were statistically non-significant, being 0.2% (95% CI -1.3% to 2.6%) for 41.6Gy, 0.9% (95% CI -0.8% to 3.7%) for 39Gy and -0.7% (95% CI -1.7% to 0.9%) for 40Gy (START Trialists' Group 2008a, 2008b). Additionally, the incidence of severe radiotherapy normal tissue side effects was low (range 3% to 5%) for all schedules, with the 40Gy arm marginally outperforming the control (3% and 4% respectively). The findings support the hypothesis that breast adenocarcinoma cells are similarly sensitive to fraction size as local late-reacting normal tissues. It is notable that the published estimates of tissue-sensitivity are specific to breast tissue and the ribcage, rather than adjacent organs such as the heart or lung. Furthermore, participant and clinician-reported measures, collected via non-standardised methods, informed the estimates.

In light of favourable START findings and subsequent NICE recommendation (2009, p. 20), the 40Gy in 15 fractions schedule has become widely adopted in the UK for EBC patients. Further international adoption of this schedule is to be expected. The current study will establish how the course, intensity and prevalence of fatigue over

the new hypofractionation schedule compares to longer schedules. The alternate days schedules are still considered experimental, despite performing equally well and offering significant resource benefits. Mature data will inform future directions.

The START findings represent the advent of a paradigm shift as regards the delivery of optimal breast radiotherapy. The limits of hypofractionation are under test in the UK National Cancer Research Network Faster Radiotherapy for Breast Cancer Patients (FAST) trial (Yarnold et al. 2004). 900 women with a relatively good prognosis (age > 50, tumour size < 30mm, axillary node negative) have been randomly allocated to receive 30Gy or 28.5Gy delivered in once a week fractions of 6Gy and 5.7Gy respectively, or the control schedule of 50Gy in 2Gy fractions. This control appears somewhat illogical given that the current standard schedule is the 40Gy in 15-fraction regime. Initial findings are not yet available. Indeed, late tissue effects, especially pulmonary and cardio-toxicity, and survival need to be followed-up for at least 10 to 15 years before hypofractionation can be adequately evaluated (Munshi and Budrukkar 2007). However, to speculate, it may ultimately be higher risk patients who will benefit most from an aggressively tumourcidal dose. If proved safe, the benefits of hypofractionation in terms of decreased patient burden during treatment are tangible.

Whatever the future, the aim of breast radiotherapy will continue to centre on control of local relapse and minimising late normal tissue effects, but this balance must be achieved at the cost of acceptable acute toxicity. It may appear reasonable to assume that shorter treatment duration may reduce acute cumulative effects such as RRF, although the effects of larger daily doses render this uncertain. Certainly, evidence exists that demonstrates the duration of radiotherapy modulates the fatigue response (Haylock and Hart 1979). Acute effects during radiotherapy from the START trial are not directly reported. However, the range of technical, clinical and QoL outcomes that the START trial has disseminated provides invaluable comparative data for a comparable EBC cohort. This data includes a comprehensive range of published pre-radiotherapy and longitudinal QoL and psychosocial outcomes for a subset of 2,208 women with EBC (Hopwood et al. 2007, Hopwood 2010), which provide a valuable comparator to the findings of the current study.

3.1.6 Adverse effects of breast radiotherapy

Normal tissue complications after radiotherapy are normally classified as being acute (up 30 days after the cessation of radiotherapy), subacute (between one and three months after radiotherapy) and chronic (more than three months after radiotherapy). Late tissue reactions occurring in the chronic phase are primarily related to radiation-induced damage to endothelial cells that line the lumen of blood vessels. Late effects may also arise as a consequence of preceding symptomatic acute effects (Dörr and Hendry 2001). Consequential late effects (CLE) predominate in tissues where radiation causes an acute loss of integrity of functional or protective lamina, for example, the skin. The severity of acute radiotherapy reactions may therefore be predictive of late effects in such tissues. A second important clinical implication of CLE is that, depending on the relative sensitivity to fraction size of regional normal tissues, both hypofractionation and overall treatment time have the potential to modulate acute effects and thereby potentiate late effects (Fowler et al. 2003).

The low incidence of additional somatic symptoms – such as nausea, oesophagitis, pain – that may confound the relationship between the radiotherapy and fatigue make breast radiotherapy a useful model to examine. Symptomatic acute effects of breast radiotherapy may be limited to skin and fatigue reactions. Skin sequelae range from mild erythema to moist desquamation. Acute skin reactions are related to increased breast volume, dose inhomogeneity and genetic factors, and may lead to consequential poor cosmesis. Fatigue can be considered a bystander (out-of-field) effect that 'spreads' from the site of tissue damage mediated by bioactive agents.

Clinical and experimental models are increasingly elucidating the importance of the complex humoral responses to normal tissue irradiation, involving leukocytes, inflammatory agents, stromal functional cells and later profibrotic changes (Herskind et al. 1998, McBride et al. 2004, Miller et al. 2005). Due to the anatomical positions of the ipsilateral lung, heart (left-sided tumours) and liver (right-sided tumours) relative to the radiation portal, a proportion of these regional abdomino-thoracic organs may be irradiated by the primary beam during breast radiotherapy. Individual patient organ topography, the natural rise of the organs when supine with arms raised, deep expiration and/or the radiotherapy technique utilised will modulate this effect. Although not widely addressed in the literature, organ-specific acute morphological responses

to radiation will now briefly be discussed. The relevance of this section is that basic evidence is introduced for the activation of immunological pathways that have been implicated in the aetiology of RRF (Bower 2007, Collado-Hidalgo et al. 2006, Gutstein 2001, Schubert et al. 2007). This literature also informed the choice of immunological study variables and dose-volume structures to analyse.

Lung

The functional unit of the lung comprises branching bronchioles, alveolar ducts and alveoli. The alveolar wall is composed of vascular endothelium and Type I and Type II epithelial pneumocytes sharing a common basement membrane. The interalveolar interstitial space comprises fibroblasts, alveolar macrophages and extracellular matrix (Jenkins et al. 2007). Early radiation-induced changes in the lung are characterised by alveolar wall damage and infiltration of the interstitial space by inflammatory cells (Tsoutsou and Koukourakis 2006). Apoptotic mechanisms deplete the Type I cells that line the alveoli, leading to hyperplasia of Type II cells to maintain the epithelial basement. Activated alveolar macrophages rapidly induce and release a wide range of inflammatory cytokines (e.g. IL-1ß, IL-2, IL-6, IL-10, TNFα) and growth factors (e.g. TGF-ß, FGF, PDGF). Whilst the inter-play of these proteins is complex, the key physiological changes observed in experimental models are vasodilation and associated extravasation of leukocytes and proteins into the interstitial space (Tsoutsou and Koukourakis 2006).

Inflammatory processes are central to the regulation of leukocytes and hence an immunological acute-phase response. Evidence suggests the inflammatory cytokine IL-6, produced by activated macrophages, T helper lymphocytes, fibroblasts and Type II pneumocytes (Kotloff et al. 1990), is a principal regulator of lymphocytic alveolitis (Yoshida et al. 1995). The interstitial space in the healthy lung comprises approximately 30 to 40% – mostly B – lymphocytes, in contrast to 60 to 70% – predominately activated T cells – in the pneumonitic irradiated lung (Morgan and Breit 1995). A positive correlation is evident between concentrations of peripheral IL-6 during radiotherapy and the development of acute radiation pneumonitis (Arpin et al. 2005, Chen et al. 2001).

Proinflammatory and profibrotic cytokines also induce a proliferation of fibroblasts and collagen deposition in the intra-alveolar and interstitial spaces. Such changes deform the normal alveolar architecture, with fibrosis radiologically evident in a period of weeks within the radiation field (Tsoutsou and Koukourakis 2006). Consequential late fibrotic changes are clinically termed radiation pulmonary fibrosis. Risk of both early and late radiation-induced lung sequelae in EBC is dependent on patient age, volume of lung irradiated and the radiation dose (Kahan et al. 2007). It is interesting to note that smoking has a suppressive effect on the inflammatory response of the lung parenchyma to irradiation (Bjermer et al. 1990).

Heart

The initial response to cardiac irradiation is acute inflammation of endothelial cells within capillaries and small arteries. Within 6 hours of radiation exposure, epithelial swelling leads to a progressive narrowing of the vascular lumen and leukocytic infiltration of the heart wall lamina (Stewart et al. 1995). This acute inflammatory phase involves the activation of local macrophages and monocytes, which in turn release inflammatory cytokines and subsequently adhesion molecules and growth factors, which are chemotactic for neutrophils and macrophages (Gyenes 1998).

All cardiac structures are susceptible to radiation-related morbidity, although myocardial injury is the most evident (Adams et al. 2003). Microvascular damage, rather than direct myocardial radiation-induced cell death appears to be the initiating event that leads to consequent symptomatic heart disease. Morphological changes in the vasculature involve a progression from a decrease in vessel patency leading to ischemia and a subsequent decrement in diastolic functioning due to the replacement of local myocytes with fibroblasts (Schultz-Hector and Trott 2007). Dose and time dependent inflammatory responses in larger vessels, leading to a macrophage-rich environment and deposition of atherosclerotic lesions have been demonstrated in animal models (Stewart 2006), and as a CLE in breast radiotherapy patients (Gyenes et al. 1994).

Most cardiac damage related to breast radiotherapy is located within the radiation portal and is associated with an increased volume of tissue irradiated, dose

fractionation schedules (Adams et al. 2003, Recht 2006) and cardiotoxic systemic therapies such as anthracyclines (Shapiro et al. 1998) and trastuzamab (Shapiro and Recht 2001). There is also evidence of low dose effects, possibly related to the potentiating effect of proinflammatory agents (such as IL-6) on artherosclerosis development (Hayashi et al. 2003, Ross 1999).

Liver

Subacute disease is the most studied toxicity (Lawrence et al. 1992), with its own recognised clinical syndrome: radiation-induced liver disease (RILD). Scant literature is concerned with the acute period as clinical symptoms tend not to be dramatic and the understanding of underlying mechanisms is incomplete. However, Cheng and Huang (2004, p.1589–1596) point to progressive damage in the fine vasculature of parenchymal hepatocytes that leads to clinically significant secondary degeneration late in the acute period. Liver irradiation is thought to selectively damage endothelial cells which line the hepatic venules and cytokine producing Kupffer cells (hepatic macrophages) that line the venous sinusoids (Kmiec 2001, Quaia et al. 2002). Ensuing acute-phase inflammation distorts the lobular structure and may lead to collapse of the lobules (Lawrence et al. 1995). Between 24 and 48 hours post-irradiation lipometabolism appears sub-optimal, with evidence of abnormal retention of lipids (called steatosis) in periportal hepatocytes (Christiansen et al. 2004). CT scans indicate discernable regions of low density, corresponding to volumes that received high dose radiation (Lawrence et al. 1995).

Hepatocytes are considered to be relatively radio-resistant, although recent work has indicated that radiation can temporarily render the cells susceptible to tumour necrosis factor alpha (TNF-α) induced apoptotic cell death (Christiansen et al. 2004). Late effects are characterised by a veno-occlusive disease, involving early activation of hepatic stellate cells followed by progressive changes involving fibrotic changes and subsequent collagen deposition (Fajardo and Colby 1980, Sempoux et al. 2002). As whole-liver dose increases, a shift is evident towards liver fibrosis, rather than regeneration (Geraci and Mariano 1993). As IL-6 plays a central role in hepatocyte regeneration (Taub 2004), Christiansen et al. (2004) propose that the dysregulation of IL-6sR may play a role in impairing the ability of the liver to regenerate.

Hepatic tolerance dose has been the subject of much debate, but data consistently stresses the importance of volume as well as dose (Cheng and Huang 2004, p. 1593, Cox and Ang 2003, Dawson and Ten Haken 2005). Inconsistencies between study findings may stem from differing irradiation protocols and varying observation periods. For conventional fractionation, the whole liver can conservatively receive 20 to 30 Gy, whereas a third to half of the liver volume can receive 30 to 40 Gy without severe complication (Cheng and Huang 2004, p. 1593). Dawson and Ten Haken (2005) suggest that the irradiation of less than 25% of the liver to 90Gy is consistent with only a 5% risk of RILD.

Late radiation effects

Late effects are ultimately attributable to events localised to the radiation portal. Whilst the incidence of severe late effects is relatively low, documented late effects in EBC radiotherapy patients include (Pierce et al. 1992): poor cosmesis involving telangectasia, induration or shrinkage; breast or rib tenderness/pain; cardiac toxicity in left-sided cancers including cardiomyopathy, valve dysfunction and coronary artery disease; lung morbidity, with an elevated risk of pulmonary fibrosis associated with concurrent smoking; effects due to lymphatic irradiation, e.g. Lymphoedema, functional morbidity of the arm and shoulder (after axillary irradiation) and stroke (after SCF irradiation); secondary malignancies.

3.2 Radiotherapy-related fatigue

3.2.1 Cancer-related fatigue concept map

Alternate definitions of CRF abound in the published literature (Dalakas et al. 1998, Krishnasamy 2000, Piper et al. 1998, Spazzapan et al. 2004). Current US National Comprehensive Cancer Network (NCCN) CRF guidelines (2000) appear to provide some consensus on the issue, defining CRF as:

> A distressing persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning (Mock et al. 2000).

This definition incorporates the main concepts associated with CRF in a pragmatic form that is suitable for universal application to research and clinical settings, and will be adopted for the current study. Cella et al. (2002a) draw a further useful distinction between fatigue conceptualised as a symptom (weakness, tiredness) and as a syndrome (overwhelming exhaustion and decreased capacity for physical and mental work).

To merit scientific study (and treatment), the intensity and/or quality of CRF should be distinct from 'normal' tiredness. Tiredness as a protective response to stressors is certainly common in the general population. Cross-sectional surveys in the UK (Cox et al. 1987, Meltzer et al. 1995) and internationally (Hjermstad et al. 1998, Kroenke and Price 1993) have consistently found the prevalence of tiredness over the preceding month to be approximately 20% for men and 30% for women. However, patient experiences of CRF suggest it is a substantively different state from 'normal' tiredness (Olsen 2007, Poulson 2001, Wu and McSweeney 2007), being akin to exhaustion and distinguishable by increased intensity and duration, not alleviated by rest, and characterised by debilitating weakness that can make any task onerous. Studies have emphasised the central and profound impact of CRF on patient's QoL (Dagnelie et al. 2007, Curt et al. 2000, Munro et al. 1989, Vogelzang et al. 1997).

As with most symptoms of illness, fatigue is understandable on a continuum of severity. However, Olsen (2007) argues that CRF is not a continuum in itself, but rather a state along a continuum (that they label adaptation). The clinical implication of this seemingly subtle distinction is that tiredness, fatigue and exhaustion can be considered as distinct states, associated with decreasing ability to adapt to stressors. A non-adaptive approach to tiredness would thus be the antecedent to fatigue (and ultimately exhaustion), but importantly, timely clinical interventions may render the patient state reversible to 'normal' tiredness.

CRF is commonly conceptualised as encompassing and affecting three domains: physical (weakness, tiredness, reduced energy), cognitive (reduced concentration, memory and mental capacity) and affective (vulnerability, distress, impatience, anxiety, emotional numbness or lability) (NCI 2007, Schwartz et al. 1998, Mitchell and Berger 2006). Whilst this is undoubtedly true, the relative impact on these postulated domains, particularly in site-specific and treatment-specific oncology patients, has been little reported. Therefore, the current study incorporated a protocol-specific patient diary, designed with the potential to capture the impacts of radiotherapy across the three domains.

Attempts have been made to frame the complex multi-dimensional construct of CRF in theoretical models (Mock et al. 2007, Piper et al. 1987). Both models include numerous biological, psychological and sociological factors, but the relationships between variables are both overly complex and insufficiently specific to generate testable hypotheses. The four directional pathways in Wessley et al.'s (1998) model (Figure 3.8) arguably have more utility in the breast cancer treatment context, despite being derived from Chronic Fatigue Syndrome (CFS) research. The feedback loop between fatigue and behavioural avoidance and deconditioning implies that fatigue may persist after the cessation of the disease and treatment. Chronic CRF is conventionally defined as lasting six months or more, again based on CFS work (Fukuda et al. 1994).

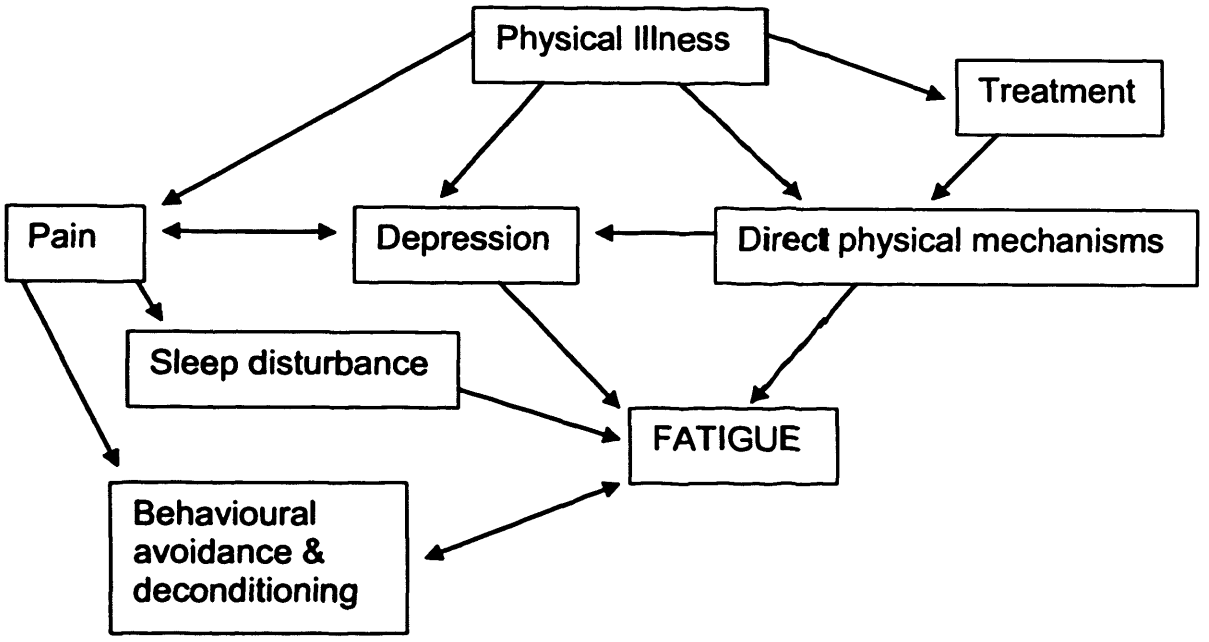


Figure 3.8 Schematic cancer-related fatigue model – adapted from Wessley et al. (1998).

The sickness behaviour framework (detailed in section 3.3.3) provided a useful guide to the current study for three main reasons. It establishes a theoretical link between a localised intervention and a systemic effect; it provides an overarching conceptual basis for the cognitive, affective and depressive aspects of women undergoing adjuvant treatment for breast cancer; it provides a theoretical basis for hypothesis generation.

3.2.2 Prevalence of cancer-related fatigue

Estimates for the prevalence of CRF vary between a third (Mendoza et al. 1999) and more than 90% (Richardson and Ream 1996). The wide range is due to the mix of cancer sites, stages of disease, treatments undertaken, plus the timing and method of assessment. Three of the larger studies of mixed-site and stage cancer patients provide the best evidence for a global point estimate. Ashbury et al. (1998) (n = 913), Kurtz et al. (1994) (n = 208) and Vogelzang et al. (1997) (n = 419) concurred that the prevalence of CRF was 78%. Studies of homogenous patient groups produce estimates that are more meaningful. For example, EBC patients who receive

chemotherapy prior to radiotherapy report a higher prevalence of fatigue than those receiving radiotherapy alone, but the latter group experience a greater increase of fatigue over the treatment course (Donovan et al. 2004). Advanced stage or palliative patients report an almost ubiquitous prevalence of fatigue (Stone et al. 1998).

The interpretation of prevalence statistics is enhanced by the inclusion of a 'normal' control population or, if available, comparison with normative population data. A recent review of CRF (Prue et al. 2006) identified five studies incorporating a non-cancerous control arm. In all studies, cancer patients experienced significantly more fatigue than controls. Cella et al. (2002a) have compared fatigue in the US general population to a mixed cancer group receiving chemotherapy, via the administration of the Functional Assessment of Chronic Illness Therapies Fatigue Subscale (FACIT-F). Whilst the generalisability of the cancerous group data is limited by a preponderance of anaemic patients, the establishment of normative FACIT data, median 47, mean (SD) 43.6 (9.4) for 1010 participants is an important progression. Age and gender-stratified distributions of the cancer patients were all significantly shifted towards the more fatigued portion of the scale, compared to the normal population. For the 544 female members of the normal population cohort, the mean (SD) age was 46 (16.6), 75.9% were white and 87.8% had at least a high school education. The median score for women less than 50 years of age (n = 310) was 47, and 45 for 50 years and above (n = 209).

3.2.3 The assessment of cancer-related fatigue

As previously suggested, estimates of CRF prevalence and incidence will depend on the assessment metric used. The ideal of cross-study interpretation via a reliable, universally accepted measurement and diagnostic tool unfortunately does not exist. Instead, a multitude of self-reported scales have been utilised to measure the presence, intensity, severity or frequency of CRF. Commonly used scales include, European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30), Functional Assessment of Chronic Illness Therapies Fatigue Subscale (FACIT-F), Fatigue Severity Scale (FSS), The Multidimensional Fatigue Inventory (MFI-20), Piper Fatigue Scale (PFS) and the Schwartz Cancer Fatigue Scale, although many others exist (Minton and Stone 2009). In order of increasing complexity, these tools range

from single-item measures (visual analogue scales) to aggregated multiple-item scales and then multi-dimensional scales (i.e. physical, cognitive, affective dimensions). Some researchers have postulated that only multi-dimensional scales can capture a complex symptom like CRF (Jacobsen and Thors 2003) but as Jean-Pierre et al. (2007) point out, the complexity of scales is often inversely related to validity, interpretability and utility. For many research purposes, a reliable fatigue intensity value is adequate.

A recent well-designed review (Minton and Stone 2009), systematically appraised the quality of cancer-specific fatigue scales using an a priori system. In conclusion, the authors recommend the use of the EORTC QLQ-C30 fatigue subscale or the FACIT-F: the former being suitable for clinical screening, with the latter considered more appropriate in the CRF research setting. The FACIT-F is a 13-item scale that measures the intensity of fatigue, incorporating physical, cognitive and affective aspects, plus the impact on normal functioning. It has been widely validated in cancer populations (Cella et al. 2002c, Hwang et al. 2003, Yellen et al. 1997). Furthermore, it is one of the few instruments demonstrated to be capable of detecting changes over time in relation to associated criteria, such as haemoglobin and performance status (Berndt et al. 2005, Cella et al. 2002b). Minimal clinically important differences are also quantified (Cella et al. 2002c). The FACIT-F will be used to assess fatigue in the current study, and comparisons made with the available normative data.

An alternate CRF assessment approach, which enables consistent definition of cases, is the WHO accepted International Classification of Diseases code-10th Revision (ICD-10) diagnostic criteria (Porternoy and Itri 1999). Cases of fatigue are defined by the presence of fatigue, plus five additional symptoms that have caused clinically significant distress or impairment for a minimum period of two preceding weeks. The stringency of such criteria is likely to render lower prevalence estimates when compared to definitions based on arbitrary scale cut-off points. For example, Andryowski et al. (2005) found 26% of EBC patients met the ICD-10 criteria, compared to scale-based study estimates of 40 to 45% in comparable study populations (Wratten et al. 2004, Fiets et al. 2003). Two disadvantages of the ICD-10 criteria that militated against its use in the current research setting are the relatively long administration time – with an associated requirement to assess psychiatric

comorbid conditions clinically as part of the exclusion process – and the lack of a resultant intensity score.

A third and under-used assessment resource are symptom diaries. Diaries offer value in terms of elucidating the temporal dimension, patterns and impacts of CRF in relation to treatment pathways. Relevant contextual factors and co-existing symptoms not measurable by other assessment tools may become overt. Additionally, symptom diaries have potential for a therapeutic effect, helping patients recognise and express their feelings regarding the impacts of CRF in their lives (Magnusson et al.1997).

3.2.4 Inherent methodological issues in the measurement of fatigue

CRF is a subjective experience, mediated through an individual's personal understanding and experiences. Therefore, self-report tools are the appropriate CRF measure (Jean-Pierre et al. 2007). The supplementation of subjective CRF reports by objective physiological, biological or behavioural correlates would be particularly welcome for homogenous patient subgroups. For example, motion sensitive accelerometers have been used in CFS research to correlate activity reduction with fatigue and Wratten et al. (2004) conducted major correlation analysis of an array of immunological and haematological factors and fatigue in EBC patients (see section 3.2.5). The current study assesses the utility of the cytokine IL-6sR as a novel objective marker of acute fatigue.

A methodological issue related to the subjectivity of fatigue is that of response shift. This occurs when patients who become severely fatigued during treatment retrospectively downgrade their assessment of earlier symptoms, as compared to their current experiential state. The upper boundary of an individual's internal fatigue response is effectively recalibrated upwards (Andrykowski et al. 2009). Conversely, patients receiving prior chemotherapy may become accustomed to a level of fatigue (Donovan et al. 2004). The effect of both changes can be an underestimation of the impact of treatment-related fatigue. Pre–post treatment study designs have identified response shift in EBC patients undergoing radiotherapy (Jansen et al. 2000, Visser et al. 2000) and chemotherapy (Andykowski et al. 2009). All three studies used

retrospective scoring of the pre-treatment state, rendering the data susceptible to recall and social desirability bias. Approximately one-third (n = 57) of participants in the Visser et al. study reported stable fatigue scores before and after radiotherapy. Assuming the validity of the response shift concept, presumably this subgroup was unaffected by this effect. Response shift is not an easy effect to counter, however, the timing of the observations in the current study have been informed by the likely trajectory of fatigue during radiotherapy suggested by the literature (Graydon 1995, Greenberg et al. 1992, Irvine et al. 1998, Smets et al. 1998a, Hickok et al. 2005a).

A further methodological issue in the assessment of CRF is that some multi-item assessment tools conflate the symptoms and functional impacts of CRF in a composite score (Winningham et al. 1994): a resultant problem being that distinct CRF experiences may yield indistinguishable scale scores. Such criticism must be less applicable for scales – such as the FACIT-F – which have demonstrated convergent and discriminant validity against established markers of fatigue (Cella 1997b), and have been validated against established uni-dimensional tools (Van Belle et al. 2005). However, the supplementation of scale scores by qualitative responses would enable a correlative analysis of the degree to which scale scores reflect the underlying experiences. The fatigue diary has been designed to fulfil this function in the current study.

Dodd et al. (2001) raised a final and fundamental issue, when they queried whether CRF should be considered as a single symptom, correlated with co-existing symptoms, or seen as a component of a symptom cluster. The authors identified a generic cluster of concurrent symptoms – fatigue, aches and impaired sleep hygiene – in mixed-site cancer patients. However, the study of treatment and site-specific clusters is likely to be more informative, as most effects of radiotherapy are localised, whereas chemotherapy may more predictably induce nausea and anaemia. Bender et al. (2005) used hierarchical cluster analysis to derive symptom clusters in EBC patients, after surgery, after adjuvant therapy, and in women with metastatic disease. Symptoms that were common across groups were fatigue, cognitive impairment and depressed mood. Kim et al. (2008) identified a psychoneurological cluster in an, n = 282, mixed-stage breast cancer cohort, which comprised the previous three symptoms plus insomnia and pain. Further interpretations of the results are impaired by the

diversity across groups in terms of disease stage, point in treatment pathways and tools used to assess symptoms. Future directions for research and practice may be most productive when focussing on the uncertain extent to which concurrent symptoms share a common underlying biological mechanism (Miaskowski and Aouizerat 2007, Kim et al. 2008). To this end, the current longitudinal study aims to determine the patterns of covarying symptoms, and analyses the relationships with biological correlates over time.

3.2.5 Radiotherapy-related fatigue

Literature searches centred on CRF identify much review, commentary and opinion, but rather less primary research. Of the extant CRF research, surprisingly little is specific for radiotherapy patients, with less pertaining to the acute-period. This discussion will be limited to external bream radiotherapy, although reports regarding brachytherapy are virtually non-existent.

A cumulative fatigue dose-response to radiotherapy has been widely reported (Graydon 1995, Greenberg et al. 1992, Irvine et al. 1998, Smets et al. 1998a, Hickok et al. 2005a). Hickcok et al. (2005a) conducted a longitudinal study of a mixed sample of 1,129 patients undergoing radiotherapy at a single US location. Fatigue was the most common symptom reported at fraction one, with 33% classified as moderate or severe. A subset of 419 participants was followed throughout their treatment. At week five of radiotherapy, fatigue had increased for approximately half the patients, and decreased for 20%. Greenberg et al. (1992) plotted the daily course of fatigue throughout radiotherapy in EBC patients. The longitudinal fatigue response was not linear. Instead, fatigue reduced slightly between weeks one and two, rose in week three, before reaching a plateau in week four which was maintained to the end of treatment (between 9 and 21 more treatments). Symptoms had generally returned to initial levels three weeks post treatment. The small sample size of 15 aided daily recording of fatigue, but limits the generalisability of the findings. The relevance of the study is questionable on the basis that the techniques associated with the cobalt treatment machines used were likely to irradiate increased volumes of normal tissue compared to current protocols. A more fundamental methodological shortcoming

(shared by Hickcok et al. 2005a) is the failure to record a pre-treatment fatigue score. Nevertheless, the general course of fatigue – increasing after approximately one week of radiotherapy, peaking at or near the end of radiotherapy before returning to pre-treatment levels over a period of weeks or months – has been replicated in larger, more recent studies of EBC patients (Geinitz et al. 2001, Irvine et al. 1998, Smets et al. 1998a, Wratten et al. 2004).

Researchers have hypothesised that if radiotherapy has a direct effect on fatigue a reduction might be discernable on weekends, when treatment is not routinely scheduled. Evidence for this pattern is not in accordance (Greenberg 1992) but at least three methodologically rigorous studies have to some extent reported such a phenomenon (Haylock and Hart 1979, Irvine et al. 1994, Smets et al. 1998a). Of the 250 patients investigated by Smets et al. (1998a), 28% reported reduced fatigue on non-treatment days. The concept that an acute effect, that has progressively accumulated, will decrease significantly on weekends may itself be erroneous.

Despite clear evidence of increasing fatigue during radiotherapy, crude attempts to correlate radiotherapy-related parameters with fatigue have yielded mixed results. Smets et al. (1998a) found no significant association between fatigue and either prescribed dose or fractionation schedule. The evaluation of such findings should be cautious, due to the likely confounding effect of the heterogeneous cancer sites under investigation. Two studies have demonstrated a site-specific dose-fatigue relationship, both in cerebral glioma patients (Kiebert et al. 1998, Lovely et al. 1999). The current study will assess the uncertain role of dose-volumetric effects on fatigue responses for patients with EBC.

Limited evidence supports the hypothesis that the type of tissue irradiated modulates the fatigue response. Hickok et al. (2005b) report fatigue levels for a mixed sample of 372 patients prescribed radiotherapy. Measurements were conducted before radiotherapy, at week three and week five of radiotherapy using an institution-specific symptom inventory. The bespoke assessment tool hinders cross-study comparisons and is of questionable validity. Patients with breast (57%) and prostate (42%) cancer, reported lower levels of pre-treatment fatigue than patients with head and neck (64%), gastro-intestinal (78%) and lung (78%) carcinoma. The authors speculate that the

relatively good prognosis of radical breast and prostate patients may contribute to lower fatigue levels. Presumably, this postulated relationship is attributable to an improved mood state or coping mechanisms, but it may also be due to differential tumour burden or toxicity of treatment. During radiotherapy, the relative increases in fatigue for breast and prostate cancer patients were large compared to other sites, being 25% and 40% respectively. It is conceivable that high pre-treatment fatigue in the lung cancer patients was related to obstructed airways that were subsequently ameliorated by radiation-induced tumour shrinkage.

The previous change score data may simply be attributable to regression to the mean. However, site-specific studies suggest that patients undergoing radiotherapy for brain cancers (Faithfull and Brada 1998), head and neck cancers (de Graeff et al. 1999a, de Graeff et al. 1999b) and lung cancers (Hickok et al. 1996) report an increased prevalence of fatigue, as compared to both breast (Fiets et al. 2003, Wratten et al. 2004) and prostate cancers (Beard et al. 1997, Lilleby et al. 1999, Monga et al. 1999). Interestingly, the Beard et al. (1997) study indicated that whole-pelvis irradiation was associated with increased levels of fatigue, as compared to smaller conformal radiotherapy fields. Initial findings from the current Parsport Study (Nutting et al. 2009), are also consistent with the hypothesis that the type (and volume) of tissue irradiated modulates fatigue. Parsport is a phase III RCT of patients with head and neck cancers, comparing conventional parallel-opposed field irradiation and an IMRT technique. IMRT modulates the intensity of the radiation beam to spare critical structures and/or deliver a higher tumour dose. In this case the dose to the parotid glands was reduced. The only acute toxicity to demonstrate a significant difference between arms was fatigue (chi-squared, $p < 0.01$). The incidence of at least a grade-two fatigue criterion was 41% for the conventional radiotherapy allocation compared to 76% in the IMRT arm. The reason for this difference is speculative, but may plausibly be a consequence of increased low doses to larger volumes of normal tissues (integral doses) associated with IMRT. Chemotherapy effects do not cause the fatigue, as concomitant therapies were an exclusionary criterion. Whether the findings reflect a brain-specific effect is unclear. The dose-volumetric analysis undertaken in the current study incorporated an evaluation of low-dose effects during breast radiotherapy.

In conclusion, theoretical and empirical evidence suggests that different mechanisms of fatigue may be responsible in different types of cancer, and by extension different sites of radiotherapy. A consideration of the theoretical mechanisms underlying RRF follows in the next section. Additional to a direct radiation effect, it is reasonable to assume that the repetitive travelling times, disruption to working patterns, waiting time for treatment and daily confrontation with disease that radical outpatient radiotherapy entails may exacerbate RRF (Junor et al. 1992). Indeed, spouses of patients receiving radiotherapy report increased fatigue and impaired mood (Jason et al. 1997). The current study will therefore consider the impact of the travel time for treatment and the mode of transport.

3.2.6 The aetiology of radiotherapy-related fatigue

Outlined below are three models of inflammatory-induced CRF. They are not mutually exclusive and additional relationships are conceivable. As the focus of the current study is on the effect of radiotherapy on fatigue, only the first model will be considered in this chapter.

1. radiotherapy → cytokines → fatigue
2. cancer → cytokines → fatigue
3. inflammation → cancer
   inflammation → fatigue

Incidents of accidental radiation provide basic evidence that radiation doses of the magnitude prescribed in radiotherapy cause fatigue in the absence of cancer (Anno et al. 1989). Any robust model of RRF must not only seek to explain both subjective and objective measures of this symptom (Morrow et al. 2002), but also elucidate the biological pathways whereby a localised treatment causes a systemic effect. Gutstein (2001) classifies fatigue-inducing mechanisms into the useful division of peripheral (signalling of energy imbalance in the peripheral neuromusculature) and central (activation of the central nervous system (CNS)). This conceptual division could be considered somewhat arbitrary, as in reality, peripheral activators may have effects on

central mechanisms, and vice versa. Ultimately, at some level the generation and perception/sensation of fatigue must be central.

Parallels have been drawn between the current understanding of the pathophysiology of RRF and that of chemotherapy-induced nausea and vomiting 20 years ago (Morrow et al. 2002). A shift in the perception of the latter symptom saw it become considered as an inappropriate activation of the cleansing emetic system and treatment was subsequently revolutionised by the development of 5-hydroxytryptamine$_3$ receptor antagonists (5-HT$_3$). RRF may be due to an analogous inappropriate activation of the innate immune system. The adaptive system may also be involved, or a combination of both systems.

Researchers in both CRF and CFS have advanced a number of alternate mechanisms underlying fatigue sensations. Namely, peripheral muscle metabolism modulation (Cella et al. 1998); anaemia (Morant 1996); and an inappropriate acute phase inflammatory response, largely mediated via the induction and release of normal tissue cytokines (Cleeland et al. 2003, Collado-Hidalgo et al. 2006, Gutstein 2001, Miller et al. 2008). Weakness due to skeletal muscle fatigue associated with defects in the mechanisms regenerating adenosine triphosphate has been reported in CFS patients (Wessley et al. 1998, Forsyth et al. 1999). Anaemia is primarily a chemotherapy-induced pathology. In the radiotherapy setting, the weight of current evidence broadly supports the latter dysregulated inflammatory response theory (Bower et al. 2002, Bower 2007, Coldo-Hidalgo et al. 2006, Greenberg et al. 1993, Morrow et al. 2002, Standish et al. 2008, Wratten 2004); although some evidence is equivocal (Ahlberg et al. 2004, Geinitz et al. 2001). An aetiological model of RRF that may have particular relevance for the (breast) radiotherapy setting is the vagal-afferent theory (Andrews et al. 2004, p. 64). The theory and supportive evidence are set out below.

The vagal-afferent theory

There are a number of variants of the vagal-afferent theory, but the common facet is that the induction and release of cytokines mediates the response to irradiation. Cytokines are the subject of section 3.3 of this chapter but will be briefly discussed

here. Cytokines are regulatory proteins that mediate the intracellular immune response. The principle inflammatory regulators are interleukin-1beta (IL-1 ß), IL-6 and TNFα. Proinflammatory cytokines are demonstrably released in response to low-dose radiation (Herskind 1998, Miller et al. 2005) and are known to be a mediator of behavioural responses, such as fatigue (Dantzer and Kelley 2007, Greenberg et al. 1992, Vollmer-Conna et al. 2004). Figure 3.9 summarises the theoretical inflammatory link between a localised (breast radiotherapy) treatment and a systemic fatigue reaction.

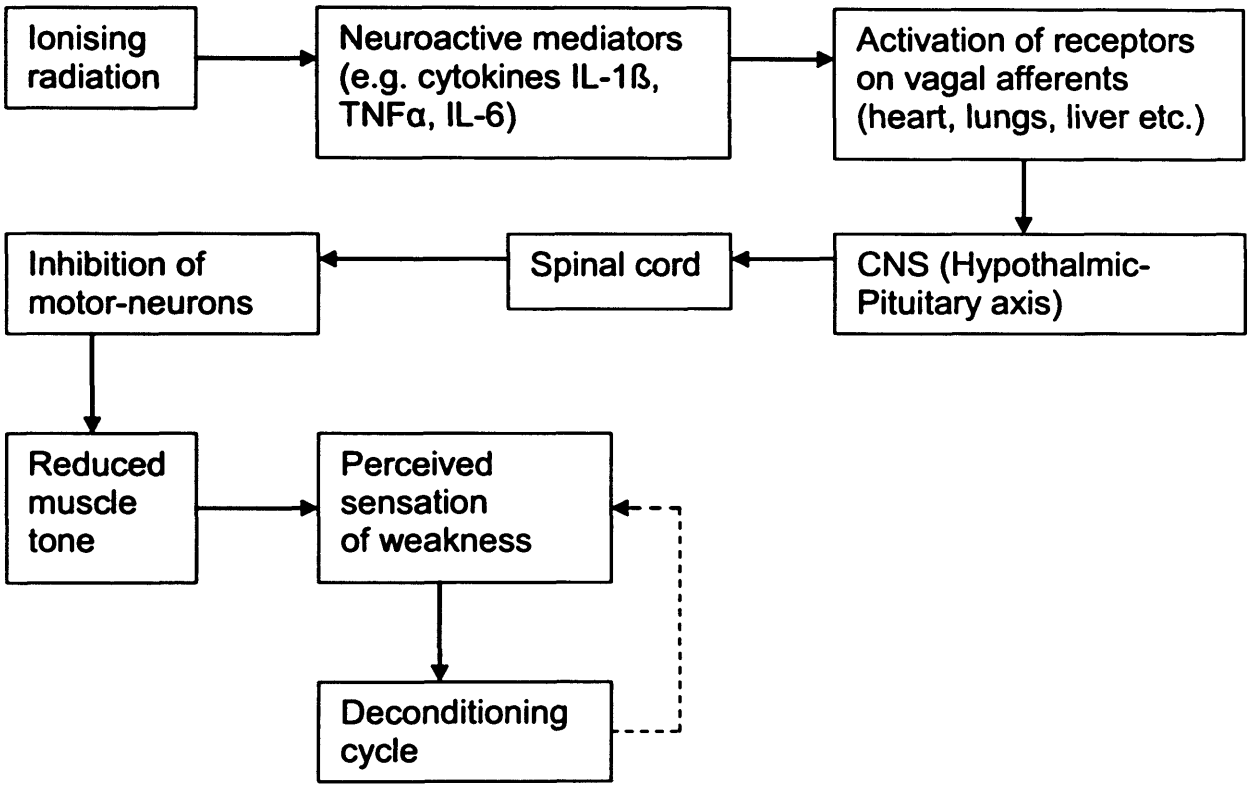


Figure 3.9 Schema showing the vagal-afferent theory of radiotherapy-related fatigue (adapted from Andrews et al. 2004, p. 64). (IL-1 ß = interleukin-1beta, TNFα = tumour necrosis factor alpha, IL-6 = interleukin 6.)

With reference to Figure 3.9, incident radiation is deposited in normal tissues. In the case of breast irradiation this would include, the skin, adipose tissue, haematopoietic tissue, lung, heart and liver. Cell-death is initiated by necrosis and apoptosis (McMillan 2003, p. 290). This non-specific toxic insult activates the innate immune system, which directly engages the products of cell-death (collectively referred to as 'bleb'). A

response to local tissue damage is the release of inflammatory cytokines by recruited cells, including monocytes and macrophages (Dantzer 2001a, Seruga et al. 2008). The cytokines subsequently activate receptors of afferent vagal nerves that innervate thoracic and abdominal organs (Paintal 1995, Morrow et al. 2002). An important implication of this mechanism is that the volumes of tissue irradiated may relate to cytokine concentrations. Subsequent neuroimmunological signalling via vagal (and/or alternate neural) pathways induces proinflammatory cytokines in several areas in the brain, including the hypothalamus (Bower et al. 2007, Miller et al. 2008). Hypoactivity of the hypothalamic-pituitary-adrenal (HPA) axis has been implicated in the aetiology of CFS (Scott and Dinan 1999) and CRF (Miller et al. 2008). The physiological response is now central. An efferent message to inhibit motor-neural activity (Gandevia 2001) causes a reduction in somatic body tone.

The ultimate perception of the preceding bioactivity at the behavioural level would be that an extra-ordinary effort would be required to accomplish a motor task. This mechanism is analogous to an animal that upon ingesting a bacterial or viral toxin instinctively exhibits depressed behaviour in a coordinated response to overcome the insult by reduction in energy expenditure (Andrews et al. 2004, p.66). It is plausible that humans have a teleologically equivalent adaptive host response, but the psychosocial demands that humans are subject to, often demands the maintenance of activities. The discrepancy between the energy anticipated to undertake any motor task and the (new) actual level required may be how the fatigue sensation is perceived. The first implication of this theory is that a positive correlation may exist between cytokine concentration and fatigue intensity. This relationship will be analysed in the current study. A further implication of this theory would be that, at least to some degree, fatigue could be considered as a biologically appropriate response to the radiotherapy.

Whilst the vagal-afferent model of breast RRF remains theoretical, several levels of supportive evidence from a series of animal studies are relevant for abdomino-thoracic irradiation. Activation of vagal afferents innervating the lungs, called the J-(juxta-pulmonary capillary) receptors or the pulmonary C-fibre receptors, in conscious, and anaesthetised cats and dogs causes a reflex reduction in somatic motor activity (Paintal 1995). As increases in pulmonary capillary capacity during exercise stimulate

the C-fibres, the purpose of the reduction in somatic muscle activation may be to suppress further exertion. Pickar et al. (1993) described how the stimulation of pulmonary vagal afferents inhibited walking in mesencephalic cats. Abdominal vagotomy attenuates the behaviourally depressing affects of both IL-1ß (Opp and Toth 1998) and bacterial lipopolysaccharide administration in rats (Kapas et al. 1998). Shielding the dog from abdominal irradiation has prevented acute decrement in functioning and behaviour (Malakhovski et al. 1990). Interestingly, pharmacological blockade of the vagal innervations of the abdomen also prevented the decrement in physical capacity.

As a composite, the body of evidence is indicative of a major role of the reflex mechanism in motor somatic inhibition by vagal-afferent stimulation in animal studies. The necessary inference from a reduction in activity/behavioural changes to fatigue in animals limits the relevance of this work to CRF. Comparable models in humans do not yet exist. However, on teleological grounds it is reasonable to assume analogous reflex mechanisms may be present in man. The current study will generate indirect evidence for this mechanism by analysing the relationships between the volumes of tissue (and the lung, heart, and liver) irradiated and concentrations of a neurally acting cytokine and fatigue.

3.2.7 Breast radiotherapy-related fatigue

Fatigue studies of breast cancer have focussed primarily on women – labelled survivors – who have completed adjuvant radiotherapy months or years previously (Alexander et al. 2009, Andryowski et al. 1998, Bower et al. 2000, Bower et al. 2006, Servaes et al. 2009). Prospective studies with key findings that report on acute RRF in breast cancer patients are summarised in Table 3.2.

Table 3.2 Prospective studies with key findings that are specific to radiotherapy-related fatigue in breast cancer patients.
(CT = chemotherapy; RT = radiotherapy; HT = hormone therapy; EBC = early breast cancer; HADS = Hospital Anxiety and Depression Scale)

Study	Patient characteristics	Data collection schedule	Fatigue assessment tool	Key findings
Donovan et al. (2004)	N = 134, (57 CT+RT , 77 RT only), EBC Two centres	*3* (1^{st}#, 15^{th}# , final #) No pre-RT	Fatigue Symptom Inventory (FSI)	Patients receiving CT prior to RT were more fatigued at beginning of RT; RT only patients experience larger increase in fatigue during RT. No correlation for age, menopausal status, disease stage.
Fiets et al. (2003)	N =154 (112 CT+RT, 42 RT only) 50Gy/25#, plus a 14–20Gy boost	*8* (Pre-RT, every two wks during RT, 3 and 6 wks, 3 and 6 months post-RT)	Common Toxicity Criteria (CTC)	RT patients reported 40% CTC Grade 2, 5% Grade 3 malaise; CT+RT patients reported 62% Grade 2, 21% Grade 3 malaise.
Geinitz et al. (2001)	N = 41 (61% received HT and 10% received CT during study), EBC, Median age 54 (range 34–77)	*7* (Pre-RT, end wks 1-5 of RT, 2 month post-RT)	Fatigue Assessment questionnaire (FAQ) and Visual analogue scale (VAS) on fatigue intensity	The FAQ did not increase sig. during RT; the VAS increased sig. at wk 4, and remained elevated at wk 5. Positive correlations with cumulative HADS score, though HADS remained stable during RT. Anxiety reduced during RT. Correlation with BMI (and volume of tissue irradiated at wk 5 of RT) No correlations with immunological (IL-1ß, TNFα, IL-6) or haematological factors.

Greenberg (1992)	N = 15, EBC 28# , plus 7–10# electron boost	Daily during RT, 3 and 20 wks post-RT No pre-RT	Profile of Moods States (POMS) and Pearson Byers Fatigue List	Fatigue increased wks 2–4, then remained stable to end of treatment. Fatigue not reduced on weekends, but resolved 3 wks post-RT. No correlation with cardio-pulmonary exercise capacity or pulse change with orthostatic stress.
Hicock et al. (2005b)	N = 372, mixed sample with 156 female breast patients	*5* (each of 5 weeks of RT) Inconsistent baseline	Protocol-specific Symptom Inventory	78% of patients reported fatigue by wk 5. Cancer-site was the only factor sig. correlated with fatigue.
Irvine et al. (1998)	N = 76, EBC Mean age 60 (SD 11)	*6* (Pre-RT, wks 1 and 2, during last wk of RT, 3 and 6 months post-RT)	Pearson Byers Fatigue Checklist	Fatigue increased sig. over the course of RT, peaked at last wk, returning to pre-RT level at 3 months. Positive correlations with symptom and psychological distress. Self-help strategies of rest and reduced activity were successful.
Jacobsen et al. (2004)	N = 90 Mean age 55 Two centres	*2* (pre-RT, final #)	Fatigue Symptom Inventory (FSI)	Greater catastrophising was related to increased fatigue
Lee et al. (2008)	N = 61, (34 had prior CT), EBC Mean age 54 (SD 12)	*3* (Pre-RT, end of RT, 7 months post-RT)	EORTC QLQ-C-30 and BR-23 QoL questionnaires	No sig. difference in QoL at any time-point. Fatigue was the strongest predictor of poor QoL post-RT.

Table 3.2 (Continued)

Stone et al. (2001)	N = 67, (34 breast, 35 prostate) Median age 63 (range 41–79) 50Gy/25# plus 11Gy boost	*2* (Pre-RT, 1 wk of RT end)	Fatigue Severity Scale (FSS) and Bi-dimensional Fatigue Scale (BDS) and QLQ-C-30	Fatigue severity increased significantly on 3/5 fatigue measures. RT associated with a decline in QoL, cognitive and social functioning. Fatigue and anxiety scores predicts 54% of the variation at the end of RT
Whelan et al. (2000b)	N = 837 (416 randomised to RT, 421 no RT), node-negative EBC	*3* (Pre-RT, 1 and 2 months after randomisation)	(modified) Breast Cancer Chemotherapy Questionnaire (BCQ)	Change in QoL from pre-RT to 2 months was -0.05 for RT and +0.3 for non-RT ($p = 0.0001$).
Wratten et al. (2004)	N = 54, EBC Mean age 58 (SD 10)	*8* (Pre-RT, weeks during RT, 2 and 6 wks post-RT	FACIT-F	43% of patients developed sig. fatigue RT; 54% developed minimal or no fatigue. Fatigue plateaued between wk 4 and 2 wks post-RT. Best predictors of fatigue during RT were higher baseline fatigue, neutrophils and red blood counts. BMI was positively correlated with baseline fatigue. IL-6 positively correlated at wk5, but insig. when BMI controlled for.

Table 3.2 (Continued)

In concordance with previous evidence that fatigue may reach a peak prior to treatment completion (Greenberg 1992, Geinitz et al. 2001, Hickcock et al. 2005b, Wratten et al. 2004), all reported fatigue levels during breast radiotherapy plateaued between weeks three and five, implying some form of physiological adaptation to stressors or response shift in internal standards. That all studies used different fatigue assessment tools highlights the problem of cross-study comparisons. Despite this methodological deficiency, and additional patient-related disparities in the respective samples, the consistency of findings provides confidence in the findings relating to fatigue course. However, no studies were identified that reported the course of fatigue over a 40Gy in 15 fractions over three weeks fractionation schedule.

Wratten et al. (2004) and Stone et al. (2001) both identified baseline fatigue as a useful predictor of fatigue level during treatment. The Stone et al. (2001) study reported baseline fatigue and baseline anxiety explained 54% of the variability of fatigue at the end of treatment. The treatment preceding radiotherapy therefore constitutes a logical starting point to consider baseline fatigue. Evidence relating to fatigue after primary surgery is scant. Cimprich (1992) evaluated cognitive functioning post either mastectomy or BCS in 32 women with EBC. No significant group differences were evident. Jacobsen et al. (1999) recorded fatigue post surgery/pre chemotherapy for 24 patients receiving BCS and 24 undergoing mastectomy. Fatigue severity did not differ significantly between surgical procedures. The sample represented a slightly different patient group than the current study, comprising a preponderance of TNM stage group II and III patients. This disparity should not materially affect the relevance of the finding for the current study. An earlier study by Maraste et al. (1992) had analysed HADS anxiety and depression scores post mastectomy or BCS, for 133 patients with EBC. No significant differences were found ($p = 0.13$), except for an increased intensity of anxiety in women who had undergone a mastectomy in their 50s. Despite the incomprehensive evidence base, surgical procedure does not appear to be a strong determinant of baseline fatigue. Therefore, one aim of the current study is to determine the risk factors that contribute to fatigue prior to radiotherapy.

Studies that have attempted to correlate radiotherapy-related variables to fatigue have almost exclusively used rather crude parameters. For example, receiving radiotherapy or not (Donovan et al. 2004), or dose and fractionation which are unlikely to exhibit sufficient variability in a relatively homogenous sample to yield statistically significant contributions (Smets et al. 1998a). The notable exception is a longitudinal study by Geinitz et al. (2001). They measured fatigue in an n = 41 cohort of EBC patients before treatment, during weeks one to five of radiotherapy, and two months after the completion of radiotherapy. Confidence in the reliability of their primary outcome (fatigue) is boosted by the use of two fatigue assessment tools: a visual analogue scale and the multi-dimensional Fatigue Assessment Questionnaire. Additionally, subjects with co-morbidities with the potential to confound relationships between radiotherapy and fatigue care were excluded. DVH analysis enabled the calculation of the total volumes of tissue, and chestwall irradiated within the 50% and 90% isodoses, and the correlation with fatigue scores. A significant correlation was revealed at week five of radiotherapy, $\rho = .48$. Additionally, a highly significant correlation was reported between the total irradiated volume parameter and IL-6 concentration at the same time-point. Both results were presumed to be secondary to relationships between BMI and both fatigue and IL-6. Based on the data presented, it is equally plausible that a primary relationship existed between irradiated volumes and both fatigue and IL-6.

As previously discussed, larger breasts that are more pendulous are associated with dose inhomogeneity and high-dose regions, modifiable by radiotherapy technique. Therefore, evidence of positive correlations between BMI and fatigue (Geinitz et al. 2001, Wratten et al. 2004) may be related to dose-volume characteristics. It is also conceivable that associations between fatigue and BMI are related to depressed mood and decreased activity levels in more obese patients. Furthermore, increased adiposity is known to be correlate positively to IL-6 concentration. The extent to which these factors impact on fatigue requires clarification, as all three mechanisms are modifiable through different measures. The current study is designed to evaluate the inter-relationships between these variables.

A comparison of whole breast photon irradiation and a subsequent electron boost may provide indirect evidence to support or refute a relationship between irradiated volumes and fatigue. It is conceivable that the electron irradiation, limited to the former

tumour region, does not encompass a sufficient volume to cause fatigue. That Greenberg et al. (1992) found no evidence for this hypothesis is noteworthy, but the sample size calls into question the conclusions. The comparison involved only 11 patients receiving the boost and four without. The non-parametric Wilcoxon test used, based on a rank order, are unlikely to detect a significant difference even if a real difference exists due to an inadequate sample size. The plateauing effect of RRF described previously may also account for the lack of difference, irrespective of any dose-volumetric effects. Furthermore, delivery of the radiotherapy treatment was via a cobalt machine, which has different depth-dose and penumbra characteristics than current megavoltage machines.

Only three studies specific to breast radiotherapy patients were identified that studied biological covariates of fatigue, during the intervention of breast radiotherapy. The earliest study, (Greenberg et al. 1992), investigated relationships between fatigue and albumin, hematocrit, glucose, thyroxine (T4), triiodothyronine (T3) reverse triiodothyronine (rT3) and thyroid stimulating hormone in 15 EBC patients. The relevance of the thyroxine-derived agents is that under stress conditions, increased cortisol inhibits the conversion of T4 to T3, resulting in hypothyroid-like symptoms, including fatigue. Fatigue did not covary with any of the biological variables. Although generally well designed to reduce bias and comorbidities, the small sample size and failure to record before treatment data both limit the utility of the findings.

A later study (Geinitz et al. 2001) considered the relationships between fatigue and the serum cytokines IL-1, IL-6 and TNF-α and differential blood counts, in 41 women with EBC. They concluded that cytokines were not responsible for the increase in fatigue recorded in these patients, although (unfortunately), 57% of the TNF-α samples were below the lower limit of the assay range. 61% of the 41 participants received endocrine therapy during radiotherapy, and 8% received chemotherapy. According to expert opinion, the potential for endocrine effect on acute fatigue is arguably low, as this would probably be a longer acting cumulative effect. However, white blood counts may be affected. Certainly, Geinitz et al. report a significant decline in peripheral blood counts during radiotherapy: lymphocytes by approximately 50%. The volume of haematological tissue irradiated appeared to be insufficient to explain the lymphocytepenia. Bower et al. (2003) advance an alternate biologically plausible

theory for this effect. They suggested that depleted levels of circulating lymphocytes and myeloid dendritic cells are due to increased recruitment of the cells to inflammatory tissue sites. Whatever the mechanisms, radiotherapy had a significant effect on white blood counts in the Geinitz study. Presumably, leukocyte counts were not a reliable marker of fatigue, as this relationship was not reported. The current study seeks to characterise any relationship between differential white blood counts and fatigue, both before and during radiotherapy.

A third study (Wratten et al. 2004) recorded a wide range of peripheral biochemical factors – electrolytes, liver function tests, lipids, differential blood counts, cytokines and coagulation factors – before, during and after breast radiotherapy. The FACIT-F was used to assess fatigue. The authors attributed correlations between IL-6 and fatigue at week five of radiotherapy to correlations with BMI. As commented previously, it is equally conceivable that the volumes of tissue irradiated are a factor; however, dose-volumetric data was not collected in this study. Multiple regression analysis concluded the factors most predictive of fatigue during radiotherapy were baseline fatigue and higher baseline neutrophil and erythrocyte counts. Conceivably, selection bias may be present due to the relatively onerous battery of measurement scales, additional inflammatory response tests (reflectance spectrophotometry and cutaneous ultrasound) and blood tests required by the methodology. Those with higher baseline fatigue levels may have been disinclined to enter the study, either through self-selection or on clinician advice. Conversely, this potential drawback should be viewed as an inherent consequence of the comprehensive breadth and extent of the assessment schedule.

One research centre has generated an important body of work that examines the biologic basis of fatigue after the completion of breast radiotherapy. Progress is evident from an investigation of the immunological and neuro-endocrine bases of fatigue (Bower et al. 2002, Bower et al. 2005a, Bower et al. 2005b), via an increasingly focussed characterisation of inflammatory processes underlying fatigue (Bower et al. 2007, Collado-Hidalgo et al. 2006) to a consideration of the genetic polymorphisms that may drive variance in inflammatory response (Colado-Hidalgo et al. 2008). The data generated has been established for EBC patients, years after the completion of radiotherapy. Logic suggests that long-term fatigue relates to events

connected to the disease and its treatment. Therefore, a number of promising directions are suggested for parallel investigations linking the acute adjuvant treatment phase to the longer-term. For all six studies referenced, participants were classified as fatigued or non-fatigued based on responses to the SF-36 vitality subscale. Scores ≤ 50 were classified as fatigued and scores 70 to 100 were classified as non-fatigued. Potential participants with intermediate scores were excluded. Significant differences between groups were found in profiles of peripheral cortisol and inflammatory cytokines. The fatigued group had significantly higher plasma concentrations of IL-6sR than the non-fatigued group (40.1 ng/mL and 30.6 ng/mL, respectively). Furthermore, the monocyte cell-surface expression of IL-6R was negatively correlated with circulating IL-6sR, consistent with the concept of IL-6sR being a specific marker of IL-6 bioactivity.

Whilst the findings are impressive, it is noteworthy that participants were not at a common point after the completion of radiotherapy; with durations ranging from one to five years post treatment. As the duration since treatment appears to be a significant factor in fatigue intensity/prevalence (Hopwood et al. 2007), this relatively common source of heterogeneity in CRF studies may be a substantive methodological limitation. By design, the current study will recruit women at a uniform point in their treatment pathway.

3.2.8 Covariates of breast radiotherapy-related fatigue

Depression

A wealth of literature has shown varying degrees of correlation between psychological mood and CRF. Depression appears to be particularly strongly associated with fatigue in patients with breast cancer (Bennett et al. 2004, Burgess et al. 2005, De Vries et al. 2009, Goldstein et al. 2006, Mose et al. 2001). The relationship between anxiety, depression and fatigue is likely to be complex. Although the two symptoms share a degree of conceptual similarity, a key feature of RRF that distinguishes it from depression is a generalised sensation of weakness, which is associated with an extra-ordinary amount of effort to complete motor tasks. Bennett et al. (2004) found that fatigue (37%) and psychological distress (31%) were common symptoms in 109

patients with EBC. Furthermore, the more fatigued participants were more likely to exhibit depressive symptoms, suggesting the two symptoms may covary. When the presence of a mood disorder is determined via diagnostic criteria, depression is not as prevalent as fatigue (Goldstein et al. 2006), suggesting that the two variables may coexist/covary rather than share a causative relationship.

A cross-sectional design and inclusion of women both during and after the completion of adjuvant treatment limit the ability of the Bennett et al. study to illuminate the relationship between fatigue and depression. Goldstein et al. (2006) examined the longitudinal course of depression and fatigue after adjuvant treatment in 176 patients with EBC. The time-courses of the two symptoms suggested that both symptoms were attributable to events surrounding the treatment. Fatigue was a relatively stable symptom, unlikely to evolve into a later mood disorder. The authors concluded that fatigue and depression have independent determinants, however, women experiencing a combination of fatigue and mood disorder reported significantly more sustained fatigue symptoms. A generic disadvantage of longitudinal studies was evident in declining response rates. At the final follow-up, the response rate was 66% of the original cohort. It is plausible that the more depressed/fatigued participants were non-responders. According to the authors, 9% of the cohort had relapsed or died at this time-point.

Morrow et al. (2003) showed that the anti-depressant SSRI paroxetine reduced depressive symptoms but not fatigue scores, providing strong argument that the two symptoms are pathologically distinct. The findings are noteworthy, being derived from a well-designed randomised double blind trial. However, it remains possible that CRF will not be modifiable by a reduction in 5-HT levels, but still share a degree of common underlying aetiology. Furthermore, a number of methodological factors suggest a degree of caution when considering the conclusions. The authors acknowledge the chosen fatigue outcome measure, the Multi Dimensional Assessment of Fatigue, was 'relatively untested'. Problems with the reliability of the scale led to the replacement of the entire questionnaire by a single question from the same questionnaire. This was effectively a Likert-like item, asking about the degree of fatigue experienced during the previous week. Whilst the decrease in depression, as measured by the Center for Epidemiological Studies Depression (CES-D) scale, was statistically significant, a

relatively small absolute difference in post intervention scores was evident, being 12.0 versus 14.8 for the paroxetine and placebo groups respectively. The generalisability of the study to the current situation is also questionable, as the sample comprised only chemotherapy patients, both men and women, and mixed-anatomical sites. The current study sought to elucidate the relationship between fatigue and depression, via an analysis of the courses of fatigue and anxiety and depression before and during breast radiotherapy.

Geinitz et al. (2001) found that anxiety, as measured by the HADS, fell slightly during the five-week course of radical breast radiotherapy, whereas depression did not change significantly from baseline score. Fatigue increased significantly during the same period, supporting the theory that psychological mood and fatigue exhibit different chronologies or are distinct entities. Knobf and Sun (2005) subsequently replicated this pattern of symptoms using an alternate outcome tool: the POMS. The sample was small, being 30 women with EBC undergoing radiotherapy.

Considering anxiety, Mose et al. (2001) identified a group of women at high risk of radiotherapy associated distress. They included younger women (≤ 58) who were initially anxious about treatment and did not benefit from distraction techniques. For this subgroup, daily confrontation with their disease may be particularly debilitating. A similar finding was reported by Hopwood et al. (2007) for an n = 2,208 subset of the START trial participants. They reported that women less than the age of 50 experienced heightened anxiety but not depression, as measured by the Hospital Anxiety and Depression Scale (HADS). Similarly, Burgess et al. (2005) reported younger age to be a risk factor for anxiety in women with EBC. De Vries et al. (2009) found that personality-related trait anxiety was the sole significant predictor of depression after treatment for breast cancer and was also related to elevated fatigue.

A number of studies have investigated the theory that depression and fatigue are components of a treatment-related symptom cluster (Kim et al. 2008, Cleeland et al. 2003), and as such, should be considered as behavioural manifestations of sickness behaviour. Studies of the response to the therapeutic use of interleukin-2 and interferon-α provide basic evidence for this concept (Capuron et al. 2002, Capuron et al. 2004). The administration of supraphysiological concentrations of cytokines as an anti-cancer therapy results in symptom clusters involving fatigue, pain and depression.

Interestingly, the appearance of fatigue preceded depression suggesting the possibility of alternate neuro-immuno mechanisms for the two symptoms.

Physical activity

Research suggests that moderate intensity physical activity, coupled to a low-fat high vegetable diet, results in better survival characteristics for women with EBC (Holmes et al. 2005, Pierce et al. 2007). The negative feedback loop shown in Figures 3.8 and 3.9 indicates the possibility of a deconditioning cycle during cancer treatment. Reduced activity may lead to a decrement in physiological function (muscular, cardiovascular, increased fatigue on exercise) and detrimental psychological effects (reduced desire to perform activity, poor sleep hygiene and lowered mood). As such, a decline in physical functioning may be a covariate of fatigue in radiotherapy patients.

Only two studies were identified that assessed the effect of physical activity programmes in breast radiotherapy-specific samples. Flinton et al. (2002) assessed fatigue in 123 women undergoing breast radiotherapy. 54 received the local standard advice, to 'rest and take things easy'; 69 received modified advice that stressed the importance of daily light activity, such as a daily 10 to 15 minute walk. As the advice was provided by the therapeutic radiographers in a busy clinical setting, it is possible the intervention was not administered in a consistent manner. Although fatigue increased significantly from baseline to the end of treatment, no significant difference was discernable for the two advice arms. As the study design involved a non-randomised allocation, the lack of a pre-treatment measure of activity renders it impossible to assess baseline differences. An indication that adherence problems may have been present was that the self-reported change in activity from a 'normal' level was also comparable between arms.

Mock et al. (1997) also evaluated a walking programme during breast radiotherapy. 46 women with EBC were assigned either to a 20 to 30 minute, 4 or 5 times per week aerobic walking programme or to a control group of no intervention. The walking group reported significantly lower levels of fatigue than the control group. A comparative reduction in sleep disturbance, anxiety and depression was also reported for the intervention group.

A number of clinical trials have additionally assessed the effect of exercise on CRF in breast cancer patients receiving chemotherapy. The results of two systematic reviews of the effects of CRF in patients with breast cancer have been equivocal. The first review (McNeely et al. 2006) included only RCTs and incorporated studies of survivors and all disease stage groups. The authors concluded that exercise led to significant reductions in fatigue levels. The results of a Cochrane Review (Markes et al. 2006) should (in principle) be more relevant for the current study, as only patients with EBC undergoing adjuvant treatment were included. Meta-analysis suggested that exercise improves key physiological markers, but the slight improvement in fatigue for exercisers was statistically non-significant (standardised mean difference = -0.12, 95% CI = -.37 to 0.13).

In light of the previously mentioned relationships evinced between BMI and fatigue (Geinitz et al 2001, Wratten et al. 2004) it might appear intuitive to expect a negative relationship between BMI and physical activity that may have relevance for RRF. No evidence was identified to evaluate this putative relationship, which will be examined formally as research question two in the current study.

3.3 Cytokines

3.3.1 Background to cytokine bioactivity

Cytokines are a diverse group of soluble proteins that act as intracellular signallers of the immune system. They share a common complex of receptor networks, exhibiting a high degree of redundancy and functional pleiotropy. When cytokine and cell-surface receptor are bound, signal transduction can modulate the metabolism of cell division or clonal proliferation of the target leukocyte (Madigan et al. 2003, p. 827). Roles include wound repair and the immune-inflammatory response involved in acute-phase reactions (APR) and septic shock (Madigan et al. 2003, p. 826–828). The resultant biological action reflects complex agonistic, synergistic and antagonistic regulatory interactions.

Virtually all nucleated cell types produce cytokines, including monocytes, macrophages, lymphocytes, epithelial cells and fibroblasts. Activation is in response to infection, tissue injury or other immunological stress, and is characterised by a short half-life (Roitt and Delves 2001, p.177–180). Cytokines themselves are therefore transient in the bloodstream, but their effects can be long lasting. Using both paracrine (adjacent stimulation) and autocrine (self-stimulation) pathways, cytokines normally act over a short radius, acting via adjacent membrane bound cell-surface receptors on immune cells. Exceptions to the locally acting norm are the acute phase cytokines, IL-1ß, TNF-α and IL-6. In sufficient concentrations, these can act systemically, often with pathogenic effects (Roitt and Delves 2001, p. 177). Furthermore, some cytokines, such as IL-6, can activate signal transduction through receptors that are both membrane-bound and in a soluble form (Jones et al. 2005).

3.3.2 Interleukin 6 and the acute phase response

Interleukin 6 (IL-6) is a highly potent leukopoietic cytokine that acts at low picogram concentrations. IL-6 producer cells include activated T cells, macrophages, monocytes, endothelium, bone marrow stroma and adipocytes. In normal populations, up to 30% of circulating IL-6 is estimated to be derived from adipocytes (Fried et al. 1998, Mohamed-Ali 1997).

The principal target of IL-6 is B-cells and actions include T and B lymphocyte activation and differentiation and initiation and regulation of the APR. The primary affects of IL-1 and TNF-α are reflected in the activity of the subsequently produced IL-6, which in turn elevates the levels of the acute phase proteins Serum Amyloid A (SAA) and C-reactive protein (CRP). The effect of selective receptor knockout or IL-6 antagonism is the inhibition of the APR (Janeway et al. 2001, appendix III). IL-6 therefore, plays a major role in the mediation and resolution of the inflammatory response initiated by infection and cell damage. It is also found to be elevated in much chronic inflammatory pathology, including autoimmune diseases, rheumatoid arthritis and CFS (März et al. 1999). What causes IL-6 to play a detrimental role in some patients is uncertain (Jones et al. 2005).

3.3.3 A cytokine-induced sickness behaviour framework

Since 1988, a body of research has evolved concerned with the (cytokine-mediated) interface between the brain and the immune system (Dantzer and Kelley 2007). A key concept of this work is the bi-directional nature of the communication between the CNS and the peripheral immune system (Dantzer 2001b, Irwin 2008, Jager et al. 2008, Watkins et al. 1995). A peripheral immunogenic event produces a cytokine-mediated APR that induces bioactivity locally and then centrally. Cytokine production in the brain can induce a cluster of symptoms including fever, fatigue, hyperalgesia, depressed mood, reduced social interaction and cognitive deficits (Dantzer and Kelley 2007, Hart 1988, Konsman et al. 2002, Vollmer-Conna et al. 2004). The expression of such symptoms as part of a coordinated psychoneuroendocrine response has been termed sickness behaviour. An implication of the sickness behaviour framework is that proinflammatory cytokines have the potential to act as an objective marker for subjective behaviours.

The highly organised nature of the sickness behavioural response is considered to be appropriate and thus distinct from a generalised malaise in response to pathology (Konsman et al. 2002). However, if the response is not proportionate to the initiating stressor, or is too sustained the effect may become inappropriate, non-adaptive and

pathological (Dantzer and Kelley 2007). Like fear or hunger, the behavioural depression associated with sickness behaviour is considered to reflect a motivational state, which leads to a reorganisation of priorities. That is, behaviour change is less likely to happen if the consequences of the change are adverse (Larson and Dunn 2001). This conception implies the importance of contextual, environmental and internal factors/pressures that may serve to constrain behavioural adaptations. In the RRF context, this might mean the necessity to continue work, when rest is desirable.

Peripheral IL-1, IL-6 and TNF-α communicate with the CNS via two pathways: (i) a fast neural route, and (ii) a slower humoral route. The neural pathway involves the stimulation of vagal afferent neural targets by local inflammatory cytokines (Dantzer 2001b, Kelley et al. 2003, Konsman et al. 2002). This mechanism enables local paracrine signalling – involving short half-lives and physiological concentrations – to cause systemic effects via the CNS. Evidence suggests the neural pathway is primarily responsible for the behavioural depression and fatigue associated with inflammatory cytokine cascades, whereas the humoral route is more important for febrile symptoms (Konsman et al. 2002). This specificity of routes may have particular relevance for the composition of the symptom clusters identified in breast radiotherapy patients. Fatigue and depression are prevalent whereas fever is not, implicating activation of the neural route as the principal pathway during radiotherapy. It is important to note that the proof of concept of the neural route has been established largely by investigation of sub-diaphragmatic vagal afferents (Bluthe et al. 1996, Opp and Toth 1998). The role of vagal afferents outside the abdomen and alternate neural routes is uncertain (Watkins et al. 1995).

The humoral pathway involves the induction and slow diffusion of cytokines at sites where the blood-brain barrier is permeable. This leads to a subsequent induction of CNS cytokines by cerebral phagocytes and macrophages called microglia (Dantzer 2001b, Kelley et al. 2003, Konsman et al. 2002). For example, IL-1ß is synthesised by microglia in the circumventricular organs and the choroid plexus (Konsman et al. 1999, Kelley et al. 2003) in response to peripheral immunogenic stress. Receptors for IL-1, TNF and IL-6 have all been localised in the brain (Watkins et al. 1995), however, evidence suggests IL-1 to be the principal CNS cytokine synthesised (Dantzer 2001b,

Konsman et al. 2002, Larson and Dunn 2001). IL-6 plays a secondary role in the CNS, potentiating the behaviourally depressing effects of IL-1ß.

3.3.4 Transsignalling via the interleukin 6/interleukin 6 receptor complex

An important step in the feedback loops that counter-regulate cytokines is the ability of cells to shed the extracellular domain of a membrane-bound receptor complex to form a soluble product. The soluble receptor retains the ability to bind (neutralise) circulating cytokines, but the remaining portion of the membrane-bound receptor is unable to bind ligands, and thereby induce cellular responses. Therefore, most soluble cytokine receptors (eg. sIL-1R and sTNF-α) act as natural antagonists of their parent cytokine (Janeway et al. 2001, appendix III). Conversely, interleukin-6 soluble receptor (IL-6sR) acts an agonist to IL-6. IL-6 activation is reflected in increased IL-6sR concentrations. IL-6 and IL-6sR dimerise, and the formed IL-6/sIL6R complex then binds to a second high affinity cell-surface glycoprotein (gp130) receptor subunit. This activity enables the initiation of intracellular signal transduction, called transsignalling (Hong et al. 2007, Jones 2005, Scheller et al. 2006). An illustrative model of transsignalling is included in Figure 3.10.

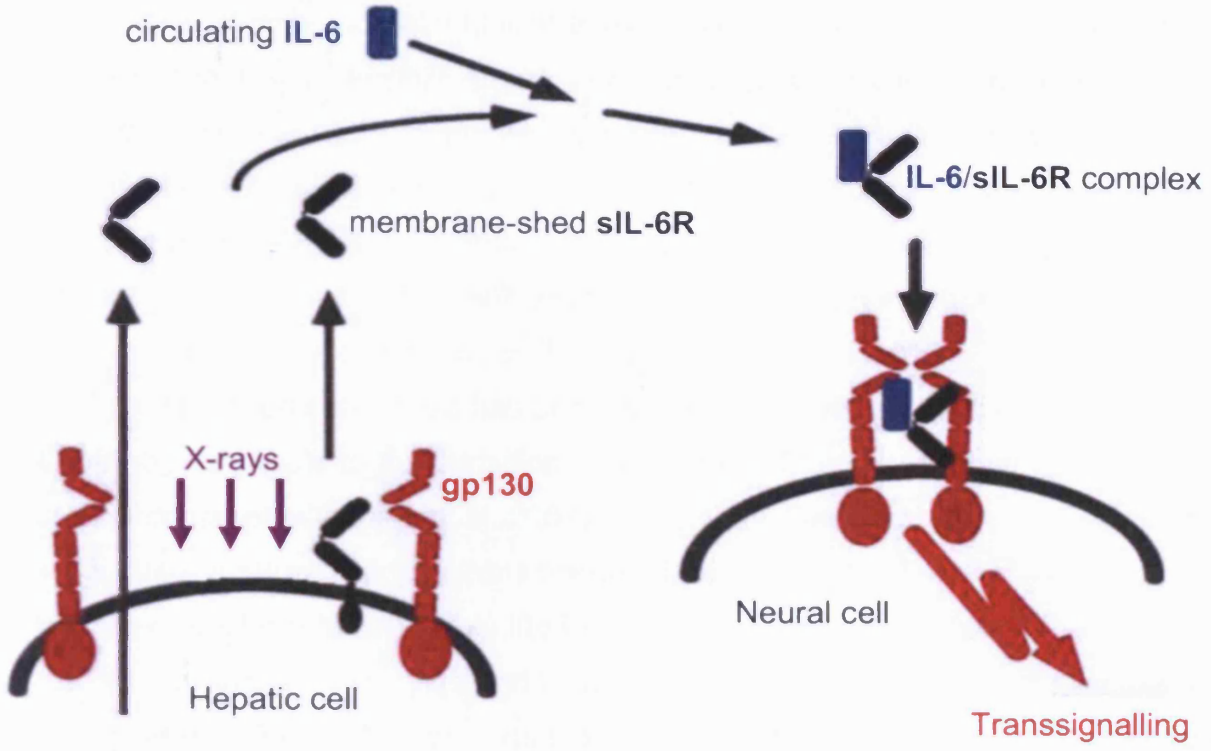


Figure 3.10 A schematic model of IL-6 transsignalling (adapted from März et al. 1999). (Incident X-rays induce the shedding of the membrane-bound interleukin-6 receptor from a hepatocyte. The resultant soluble interleukin-6 receptor (sIL-6R) is bound by free interleukin 6 (IL-6). Dimerisation of the IL-6/sIL-6R complex with the cell-surface gp130 subunit enables neural activation of protease pathways via transsignalling.)

The physiologically important aspect of transsignalling is that only a relatively limited range of leukocytes and hepatocytes express the membrane-bound receptor (mIL-6R), whereas gp130 is expressed ubiquitously throughout the body (Jones et al. 2005, März et al. 1999). Therefore, transsignalling enables IL-6 to activate cells that lack mIL-6R, such as embryonic stem cells, endothelial cells, and crucially for the vagal-afferent theory, neural cells (März et al. 1998, März et al. 1999). Through the activation of diverse cellular pathways, many of the pathophysiological effects of IL-6 ultimately depend on sIL-6R levels. The current study will therefore measure the peripheral concentrations of IL-6sR. Soluble gp130 is the naturally occurring antagonist of the IL-6/sIL-6R complex that selectively inhibits transsignalling (Richards 2006).

IL-6/IL-6sR transsignalling plays a central role in the outcome of an acute inflammatory episode. An effectively resolved inflammatory event is characterised by

an initial stromal infiltration of neutrophils by a process of chemotaxis. IL-6 bioactivity determines that the neutrophils quickly undergo apopotosis and are replaced by mononuclear cells such as monocytes and lymphocytes, which remain until resolution of the inflammatory episode (Jones 2005). As stromal cells lack the membrane bound IL-6 receptor (mIL-6R), IL-6 controlled leukocytic recruitment and clearance is dependent on local levels of IL-6sR. Hurst et al. (2001) demonstrated empirically that a positive correlation exists between IL-6sR concentrations and the level of neutrophil infiltration. Neutrophil apoptosis has been demonstrated to induce IL-6sR shedding and thereby contribute to the transition from neutrophil to mononuclear cells during acute inflammation (Chalaris et al. 2007). When the inflammatory processes become dysregulated, neutrophil populations become unduly sustained and/or activated monocytes may be retained within the local tissues (Savill et al. 2002). The relative ratios of neutrophils, monocytes and lymphocytes may therefore be more indicative of a dysregulated inflammatory episode than the absolute differential counts. Evidence for sustained leukocyte profiles will be sought in the current study.

Evidence from both therapeutic and accidental radiation exposure settings has demonstrated that the irradiation of normal tissues at therapeutic dose levels induces the local release of acute phase cytokines, including IL-6 (Cengiz et al. 2001, Galdiero et al. 1994, Herskind et al. 1998, Ibuki and Goto 1999, Kusunoki and Hayashi 2008, McBride et al. 2004, Miller et al. 2005). Furthermore, the systemic administration of therapeutic cytokines such as IL-2 and interferon-α to augment the immune system of cancer patients is known to induce an inflammatory syndrome comprising elevated depression and severe fatigue (Capuron et al. 2000). Direct evidence specific to breast radiotherapy patients is scant, however, monocytes isolated from breast cancer patients after radiotherapy released significantly elevated levels of in-vivo IL-1 when compared to pre-radiotherapy samples (Wasserman et al. 1991).

The preceding science prompts two currently unanswered questions: One, are the effects of tissue irradiation measurable via elevated concentrations of peripheral IL-6sR during radiotherapy? Two, does IL-6sR (or IL-6) act as an objective surrogate of RRF? The evidence relevant to IL-6 and RRF will now be considered.

3.3.5 Relevance of the interleukin 6/interleukin 6 receptor complex for radiotherapy-related fatigue

Schubert et al. (2007) conducted a review of studies that have investigated the association between fatigue and inflammation in cancer patients. Eighteen studies – encompassing 1,037 participants – were included in the review. 17 of the studies were published in the period after 2000. Weightings based on eight objective quality criteria were applied prior to the pooling of statistics. Correlation coefficients were used to assess the level of association between fatigue and multiple inflammatory biomarkers. Imputation was utilised to ascribe a correlation coefficient value of zero and a p-value of 0.5 in the 32 of 58 cases where results were statistically non-significant but a relevant statistic was not quoted. The effect of this approach on a pooled point estimate would be to underestimate the association between fatigue and the inflammatory marker. When studies (Ahlberg et al. 2004, Mills et al. 2004, Wratten et al. 2004) reported more than one correlation between fatigue and IL-6, the lowest reported correlation coefficients and the highest p values were included in the pooled analysis.

The data revealed significant positive associations between fatigue and all inflammatory markers combined ($r = .11$, $p < 0.0001$), IL-6 ($r = .12$, $p < 0.004$), IL-1ra ($r = .24$, $p < 0.0005$) and neopterin ($r = .22$, $p = 0.0001$). No significant correlations were found between fatigue and IL-1ß ($r = .05$, $p = 0.42$) or TNF-α ($r = .04$, $p = 0.34$). It is notable that whilst the correlations were highly significant the effect sizes were small. The conservative analytical approach adopted by the reviewers may serve to under-estimate the strength of the associations. Furthermore, the pooled values reflected large heterogeneity in individual study values. Limitations that are more fundamental are the heterogeneous nature of the cancer sites, therapies involved, measurement timescales in relation to treatment and biomarkers considered.

Whilst evidence has established that IL-6/IL-6sR transsignalling is associated with increased fatigue and sleep in healthy subjects (Dimitrov et al. 2006, Irwin et al. 2006), only one study (Collado-Hidalgo et al. 2006) has evaluated the association between IL-6sR and fatigue in breast cancer patients. Based on previous work (Bower et al. 2002), a practical aspect of their rationale for investigating the soluble receptor was

that physiological levels of cytokine receptors exist in much higher (thousand-fold) concentrations than their parent cytokines (Dimitrov et al. 2006), and are longer-lived in the bloodstream. Thus, receptor measurement in serum and plasma may be more reliable than the progenitor cytokines whose actions they reflect. The Collado-Hidalgo et al. (2006) study, reported on 50 breast cancer survivors who were at least two years post primary treatment. Persistently fatigued survivors and non-fatigued controls were identified, based on scores on the SF-36 vitality scale. Although relatively robust as a QoL tool, it is unfortunate for cross-comparison purposes that a fatigue-specific assessment tool was not used. 32 women were in the fatigued group and 18 in the non-fatigued group. Fatigued participants showed significantly higher IL-6sR plasma concentrations (40.1ng/mL) than non-fatigued participants (30.6ng/mL), $p = 0.05$. The differences between groups remained significant after controlling for age, time elapsed since diagnosis, depression level and type of treatment. Additionally, monocyte expression of membrane bound IL-6R was negatively correlated with circulating levels of IL-6sR ($r = -.30$, $p = 0.06$) consistent with the hypothesis that receptor shedding is induced by elevated peripheral concentrations of IL-6 (Bower et al. 2006). With respect to the literature, no studies were identified that evaluated the relationship between IL-6sR and fatigue during radiotherapy treatment.

More evidence exists for a positive relationship between IL-6 and fatigue in breast radiotherapy patients, but findings remain limited and equivocal. The small effect sizes evident in the Schubert et al. (2007) review suggest samples may have been underpowered to detect significant changes. Furthermore, different types of breast cancer, non-standardised treatments outcome measures may contribute to inconsistent findings. Geinitz et al. (2001) reported a positive correlation between fatigue and IL-6 concentration at week five of radiotherapy, but this association disappeared upon controlling for BMI. Moreover, IL-6 did not increase during radiotherapy. Wratten et al. (2004) broadly replicated these findings. Collado-Hidalgo et al. (2006) found no significant difference between IL-6 concentrations in fatigued and non-fatigued breast cancer survivors.

3.4 Summary of the literature and gaps in the evidence

Breast cancer affects a large and increasing number of women every year, approximately two thirds of whom will undergo radiotherapy. The most troublesome untreated symptom during radiotherapy treatment is fatigue. The acute fatigue response to the current UK breast radiotherapy fractionation schedule remains to be clarified. A prospective longitudinal design has therefore been used to capture this response before, during and after radiotherapy. These fatigue data will depend on the fatigue assessment tool used. Here the FACIT-F has been used. A movement towards a consensus on the optimal method of assessment would be a significant development in the field. Further common methodological limitations centre on issues of sample, cancer-site and type and treatment-related heterogeneity. This study has incorporated a more defined sample, which should enhance the ability to predict patients at elevated risk of experiencing RRF. A modelling approach has been adopted to achieve this study aim. A simple model will be sought that has the potential to be integrated into clinical practice, and hence facilitate targeted fatigue interventions.

The aetiology of CRF is currently uncertain. Few existing studies underpin investigations with conceptual theory. Furthermore, the complexity of existing models of fatigue may hinder the development and testing of hypotheses. In this study, the empirically based (cytokine-induced) sickness behaviour framework has been used to define the scope and organise the structure of inter-related concepts.

Several levels of evidence indicate a pathological involvement of the pro-inflammatory cytokine IL-6 in the aetiology of CRF (Bower et al. 2007, Capuron et al. 2004, Collado-Hidalgo et al. 2006, Jager et al. 2008, Schubert et al. 2007). The behavioural effects of IL-6 depend largely on the presence of its soluble receptor. IL-6sR may play a central role in RRF as it forms a neuro-immunological link between a localised treatment and a systemic effect, and has been shown to be elevated in fatigued survivors of breast radiotherapy. The role of IL-6sR as a biomarker of acute fatigue will be assessed for the first time.

An issue related to IL-6sR concentrations is that of the volumes of tissue irradiated. Although radiation oncology research routinely relates dose-volume effects to toxicities, only one published study was identified that considered the volumes of tissue irradiated (Geinitz et al. 2001). Although generally well designed, this was a relatively small non-UK study, using the international fractionation schedule. The evaluations of novel parameters in the current study are cardiac and hepatic irradiation, and the role of low-dose effects. Relevance of irradiated volumes may increase as ongoing investigations of partial breast irradiation, such as IMPORT, mature. The Geinitz et al. study, and Wratten et al. (2004), found a positive relationship between BMI and fatigue. This relationship demands clarification, and the related influences of irradiated volumes, depression and exercise and IL-6 elucidated.

It is known that anxiety and depression appear to be related to breast CRF. Whether fatigue causes depression, fatigue is a symptom of depression or the two symptoms co-exist is less clear. The possibility that the two symptoms form part of a symptom cluster sharing a common aetiology involving inflammation has implications for the prophylactic treatment of breast RRF. Therefore, the current study will trace the longitudinal course of fatigue and psychological mood.

CHAPTER FOUR **Methods**

4.1 Study Design

4.1.1 Methodological approach

Although fatigue is a subjective experience, interpreted through individual experience, the epistemological viewpoint underpinning the chosen methodology is one of positivism (Bowling 2002, p. 126). That is, mathematical relationships were sought between variables that explained the empirical data, and aetiological hypotheses generated from these data. This study adopts an integrated scientific approach to reflect the multi-factorial nature of fatigue. Theory and practice from the fields of radiation oncology, psycho-oncology, and immunology has shaped the study investigations. The integrated approach is essentially quantitative, although a patient diary constitutes a subsidiary element of qualitative enquiry. This qualitative data reinforces the main quantitative approach, but does not answer specific research questions (Denscombe 2007). CRF is a complex and poorly defined phenomenon. Therefore, even in a relatively small-scale project such as the current study, a conceptual framework is necessary. The cytokine-induced sickness behaviour model was invaluable when seeking conceptual coherency at the study planning stage, in guiding the selection of a set of variables for inclusion in multivariable analysis and in the interpretation of study results.

4.1.2 Study design

The study design was a prospective, longitudinal, cohort study with repeated measures. That is, measurements were taken from the same subjects, on a number of occasions, over the forward passage of time. In the context of the study aims and research questions, a cohort study offered manifold advantages. Intensity, prevalence over a period, and the risk of the adverse outcome fatigue, could all be measured directly (Martin 2005, p. 103). Quantitative measurements could be made from a wide range of exposure factors, some of which varied over time (e.g. IL-6sR concentration) while others were fixed (e.g. irradiated tissue volumes). A prospective design ensured the collection of the requisite data at optimal time-points in relation to anticipated changes in fatigue. Repeated measurements on the same individuals captured the

timelines of related risk factors. Such analytical data allowed the assessment of relationships between variables and could provide temporal and dose-response evidence for causality (in accordance with Hill's (1965) criteria for causality). For example, changes in IL-6sR concentration were analysed in relation to both the clinical intervention of radiotherapy and the outcome of fatigue.

Many of the disadvantages associated with cohort studies are artefacts of the often long periods of time over which subjects are followed. Examples include costly follow up, sample attrition, measurement bias due to inconsistent observations over time and changes in the intrinsic aetiology or incidence of an outcome (Rothman et al. 2008). The relatively short timeframe from intervention to symptom resolution in the current study obviates such disadvantages.

The retrospective nature of a case-control study would have precluded the observation of many relevant exposure factors not routinely assessed in the clinical setting. Consideration was given to the more exotic variants of cohort/case-control studies. Indeed, the current study is akin to a case-control nested within a cohort study. That is, all the measurements were prospective, and when outcome status was established, the exposure factors of cases (fatigued participants) and controls (non-fatigued participants) were then analysed retrospectively. Where researcher manipulation of patients' radiotherapy treatment parameters would clearly be unethical, it is difficult to envisage how an interventional study might be employed to answer the study research questions. An observational design, where exposure status of participants is recorded but not manipulated, was therefore appropriate. Patients inherently have variation in a range of exposure factors such as BMI, length of travel for treatment, etc. Similarly, patients treated for disease of the left breast may have a clinically significant volume of heart irradiated, compared to a right-sided patient with negligible cardiac irradiation. Social scientists refer to such studies as natural experiments (Martin 2005, p. 201, Alvarez-Dardet 2000). Compared to a true experiment, the lack of control over exposures makes it more difficult to assess causality and/or unequivocally answer research questions.

4.1.3 Consideration of cohort subgroups and control groups

When considering one main exposure factor, for example BMI, it would be possible to stratify patients to determine the relative risk of high/low BMI patients becoming fatigued during radiotherapy. However, many other factors are correlated to fatigue, and may moderate the relationship between BMI and fatigue. The multi-factorial aetiology of CRF determined that the cohort was not assembled on one particular characteristic, such as BMI. The study cohort is well defined as regards sex, geographical location and disease characteristics, with all patients at an early and common point of their treatment.

Cases of fatigue arose as the cohort was followed prospectively, with the non-fatigued members of the cohort acting as an internal comparison group (Rothman et al. 2008, p. 79–80, Martin 2005, p. 138). The individual impact of multiple exposure factors on CRF was then assessed by a retrospective multivariable analysis. Multivariable analysis[1] reduces the need for an external control group by simultaneously adjusting for the confounding effects of multiple variables (Katz 2006, p. 14–15).

The fact that early breast cancer patients almost uniformly receive radiotherapy as the primary component of their adjuvant treatment severely hinders the selection of a meaningful external control group. A number of control populations were considered: namely, breast cancer patients receiving no radiotherapy, women attending breast-screening units with a benign breast abnormality, patients who had recently undergone a minor non-oncological surgical procedure and 'healthy' subjects. In practice such groups were too small, inaccessible or so heterogeneous regarding other confounding factors to be of substantive value. Approaching a relatively small number of 'healthy' subjects with an outcome measure designed for chronically ill patients was considered to be too lacking in context. Instead, comparisons were made with available normative population fatigue data (Cella et al. 2002a).

[1] As multiple explanatory variables were considered, the general term multivariable analysis is used, (as opposed to multivariate, which strictly refers to multiple outcomes).

4.2 Study sample

4.2.1 Study population

The study population comprised women diagnosed with histologically confirmed early-stage carcinoma of the breast, having undergone primary surgery and subsequently referred to Velindre Cancer Centre (VCC) for adjuvant radiotherapy. The definition of early-stage disease here follows the conventions of confinement to the breast and disease that is completely removable by surgery (Cassidy et al. 2006, p. 250). That is, Tis to T2N1mi stage tumours, as expressed in the TNM staging taxonomy 7th edition (Sobin et al. 2010).

In light of the study aims and research questions, an important consequence of the surgical removal of the macroscopic tumour was that, theoretically, no paraneoplastic effects should be present. These are substances produced by the tumour that act remotely through endocrine, neuromuscular, haematological or other routes, and thereby contributing to either cytokine release and/or fatigue. Axillary micrometastatic disease was deemed unlikely to add substantively to tumour burden. It is also conceivable that significant biological differences exist between invasive and in situ carcinoma, with increased cytokine activity associated with the latter category. Therefore, the effect of diagnosis on fatigue will be evaluated.

The study location was expedient, as the vast majority of breast cancer patients in South East Wales (and some from a wider geographical area) undergo treatment there. VCC has a catchment area of 1.5 million people. The two lead clinical oncologists for breast patients at the centre agreed to their patients being approached to consider participation in the study, providing an adequate throughput of eligible patients. The patients under 'clinician one' were referred from primary care predominantly in the South Wales Valleys (North West of Cardiff) and Newport areas, with the remainder (under 'clinician two') referred from the Cardiff and Vale of Glamorgan regions. This geographical coverage ensured a diverse range of ethnic and socio-economic backgrounds. Whilst single location studies have limitations in terms of ecological validity, they are appropriate for studies that are assessing the relationships between multiple variables (Bland 2000).

At VCC, adjuvant endocrine therapy for early-stage breast cancer patients normally commences after the completion of radiotherapy. This scheduling of therapies enabled framing of study eligibility criterion to exclude all prior adjuvant systemic therapies. Furthermore, this centre is notable for all the breast radiotherapy treatment plans using three dimensional (3D) body data generated by a CT simulator with a sufficiently wide bore to accommodate patients in the standard treatment position. This 3D data was necessary for the determination of the dose-volumetric data, consistent with the study aims.

4.2.2 Study sample

Commencing in November 2007, a consecutive sample of women was recruited. A sample size of 100 was decided upon, with the aim to recruit women equally from the two referring clinicians. The following estimations were made to guide sample recruitment. The two referring clinicians would prescribe adjuvant radiotherapy to approximately eight new patients per week. Approximately 40% of these radiotherapy patients would be rendered ineligible due to the prescription of systemic poly-chemotherapies. After allowing for confounding co-morbidities and/or study eligible patients declining entry, a conservative actuarial accrual rate of two patients a week was projected. Therefore, a year was allocated for sample recruitment. If actual accrual rates were insufficient, then additional clinicians' new patient clinics were available to boost recruitment.

Participants were sought whose pathology report indicated ductal carcinoma in situ or axillary node-negative or micrometastatic invasive breast cancer, with an associated TNM staging included within the range Tis–T2 N1mi. Eligible participants had undergone a resection of the primary breast cancer by either wide local excision or mastectomy. Surgical margins were disease free, with re-excision performed if excision margins were initially inadequate. Either sentinel node biopsy or axillary node sampling (with a minimum of four sampled nodes) had assessed axillary lymph node status.

4.2.3 Eligibility criteria

Eligibility criteria were framed to provide a homogenous cohort regarding disease and treatment-related characteristics, and to restrict potentially confounding effects of concomitant pathologies. As the specific focus of the proposed study was the effect of radiotherapy on fatigue, those prescribed neo-adjuvant or concurrent systemic cytotoxic and/or hormonal therapeutic agents were excluded. This narrowing of the set of contributory factors for fatigue inherently renders the study results less universal.

The ICD-10 diagnostic criteria for CRF (Portenoy and Itri 1999) exclude patients, whose fatigue is, '—primarily a consequence of comorbid psychiatric disorders such as major depression'. As the endpoint of the study was to develop a fatigue model capable of application to external samples of breast radiotherapy patients, variance in depression scores was desirable. Potential participants who had a history of depression, which had been treated and were now stable, were included unless the depressive episode had been significant and/or had arisen since the breast cancer diagnosis. The treating clinician decided the classification of significant depression.

Exclusion criteria

- Pre-existing uncontrolled heart, lung or liver disease.
- Any previous history of chronic fatigue syndrome, chronic autoimmune or inflammatory disease (including rheumatoid arthritis and inflammatory bowel disease) or untreated thyroid dysfunction.
- A history of untreated or significant depression.
- Concurrent systemic chemotherapy or endocrine therapy.
- Prior adjuvant/neoadjuvant systemic chemotherapy or endocrine therapy.
- Locally advanced disease (Stages IIB to IIIC).
- Evidence of metastatic breast disease (Stage IV).
- Previous history of radiotherapy.

Inclusion criteria

- Females >18 years.
- Not pregnant.

- Histological confirmation of insitu breast disease or early invasive breast carcinoma (Stages 0 to IIA).
- Complete macroscopic excision of the tumour by either wide local excision or mastectomy ± sentinel node biopsy or axillary node sampling.
- Axillary micrometastases.
- Standard local radiotherapy dose-fractionation schedule of 4000cGy in 15 fractions over 3 weeks.
- Ability and willingness to undergo blood tests and complete self-report tools.

4.2.4 Sample size

Three logistical factors largely dictated a pragmatic sample size of 100. The prohibitive cost of cytokine assay kits, the rationing of departmental computer terminal time necessary to generate the requisite dose-volume data and the time-frame of a full-time PhD study. A sample size of approximately 140 plus would have allowed the splitting of the sample into an exploratory and confirmatory dataset (Tabachnick and Fidell 2007, p. 141). The aforementioned factors precluded this ideal.

Statistical power varies as an inverse function of the number of independent variables (IV) included in multivariable analyses (Field 2006, p. 172, Tabachnick and Fidell 2007, p. 123). Furthermore, to achieve an equivalent power in a multivariate setting requires more subjects than for the bivariate setting (Katz 2006, p. 77). One rule of thumb of the required sample size for multivariable analysis is given by the equation:

$$n > 50 + 8K \quad \text{.....Equation 4.1 (Green 1991)}$$

where n = sample size and k = number of independent variables

Assuming a sample size of 100, equation 4.1 suggested up to six IVs. However, the type of multivariable analysis undertaken also affects statistical power. An alternative guide for multiple linear regression is, approximately 20 individuals are required per variable entered into the regression model (Katz 2006): suggesting five IVs. For logistic regression a requirement of 10 adverse outcomes for each IV is suggested by Haynes et al. (2006). Published research (Wratten et al. 2004) and pre-experimental focus groups (see section 4.8.1) suggested approximately 40% of patients become

fatigued during breast RT. This equates to 40 adverse outcomes in a sample of 100 and following the Hayne's et al. guidelines would suggest up to four IVs for a logistic regression analysis.

To estimate the power for the current study an a priori calculation was performed using the GPower3 software program (Faul et al. 2007). The calculation was based on a multiple regression test. Assuming a model with five IVs, a moderate effect size of $f^2 = 0.15$ (which corresponds to a modest increment in $R^2 = 0.13$), a sample size of 100 and significance level set at $\alpha = 0.05$ the study would have power of 84%. The relationship between sample size and statistical power is represented graphically in Figure 4.1. If due to missing data, 10 or more subjects were excluded from analysis then statistical power – to correctly reject the null hypothesis that the IVs are not related to fatigue – would drop below the 80% conventional benchmark of adequacy for an observational study.

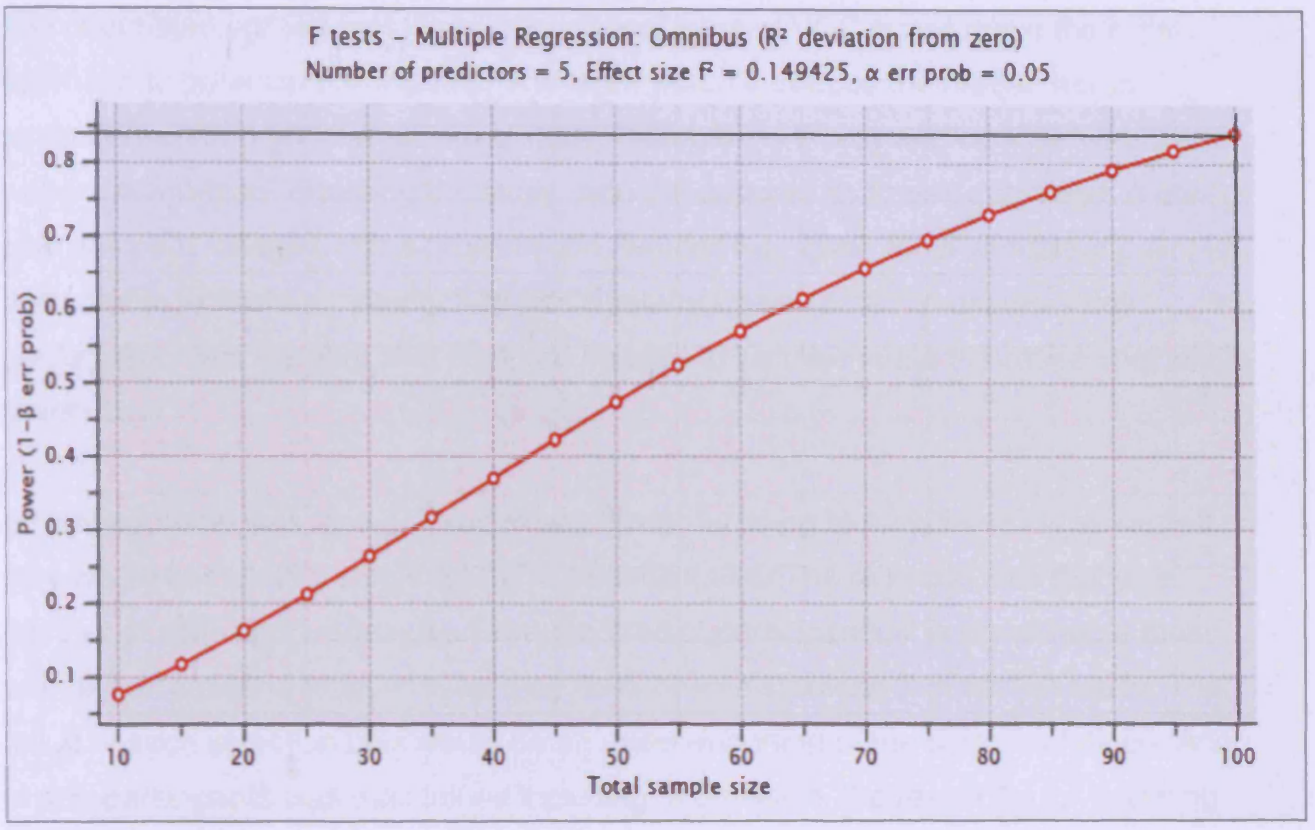


Figure 4.1 Statistical power as function of sample size for multiple regression analysis (for five independent variables, moderate effect size and $\alpha = 0.05$).

4.3 Ethical considerations

A South East Wales research Ethics Committee granted the study ethical approval on 8 October 2007. The letter of approval is included in Appendix 2. In summary, the committee report noted the following: Patients' standard treatment remained unchanged as a result of study participation and patient confidentiality was maintained at all times – other than in the reporting of serious adverse events – by the substitution of patient identifiers with an anonymised project code. This applied both to study documents and biological samples. Cardiff University was/is the data controller. In this capacity, the School of Healthcare Studies Cardiff University will retain all data collected during the research for 15 years, in accordance with the Data Protection Act (1998).

The committee agreed that the normal clinical team at VCC would make the initial approach to potential participants. The team would introduce the researcher to patients declaring an interest in the study. Patients were provided concise verbal and written information regarding the study, with the opportunity to ask questions. A pre-paid postcard labelled with a project code number was given to all interested patients, designed to indicate an intention to participate/not participate. To ensure study participation was feasible, this postcard needed to be returned to the researcher within seven days.

Ethical approval was also granted to ask those declining to participate in the study if they would complete a single FACIT-F questionnaire. The rationale was that as a number of self-report measures were required of participants, it is conceivable those with higher baseline fatigue levels may have been disinclined to enter the study. The result of such selection bias would be an under-reporting of the outcome fatigue. A log of non-participants was maintained including, if proffered, the reason(s) for declining entry).

Throughout the recruitment process, the researcher strove to maintain a position of equipoise regarding study participation.

4.4 The recruitment process

The recruitment process is illustrated below in Figure 4.2. Copies of the recruitment documents italicised in the flowplan are included in Appendix 2. The initial researcher-patient contact was at new patient clinics at VCC. Study eligibility was initially checked with reference to hospital notes and then verified in a face-to-face interview.

The researcher met patients expressing an interest (by postcard) directly after their CT treatment planning scan, at the radiotherapy-planning department of VCC. This occurred approximately 10 to 14 days after the initial contact. After an opportunity to ask any questions, patients who wished to participate in the study were formally consented. One copy of the consent form was given to the participant, one copy was filed in the VCC radiotherapy research department and the researcher retained one

copy. Details regarding study participation were included in a subsequent letter sent to the relevant general practitioner (Appendix 2).

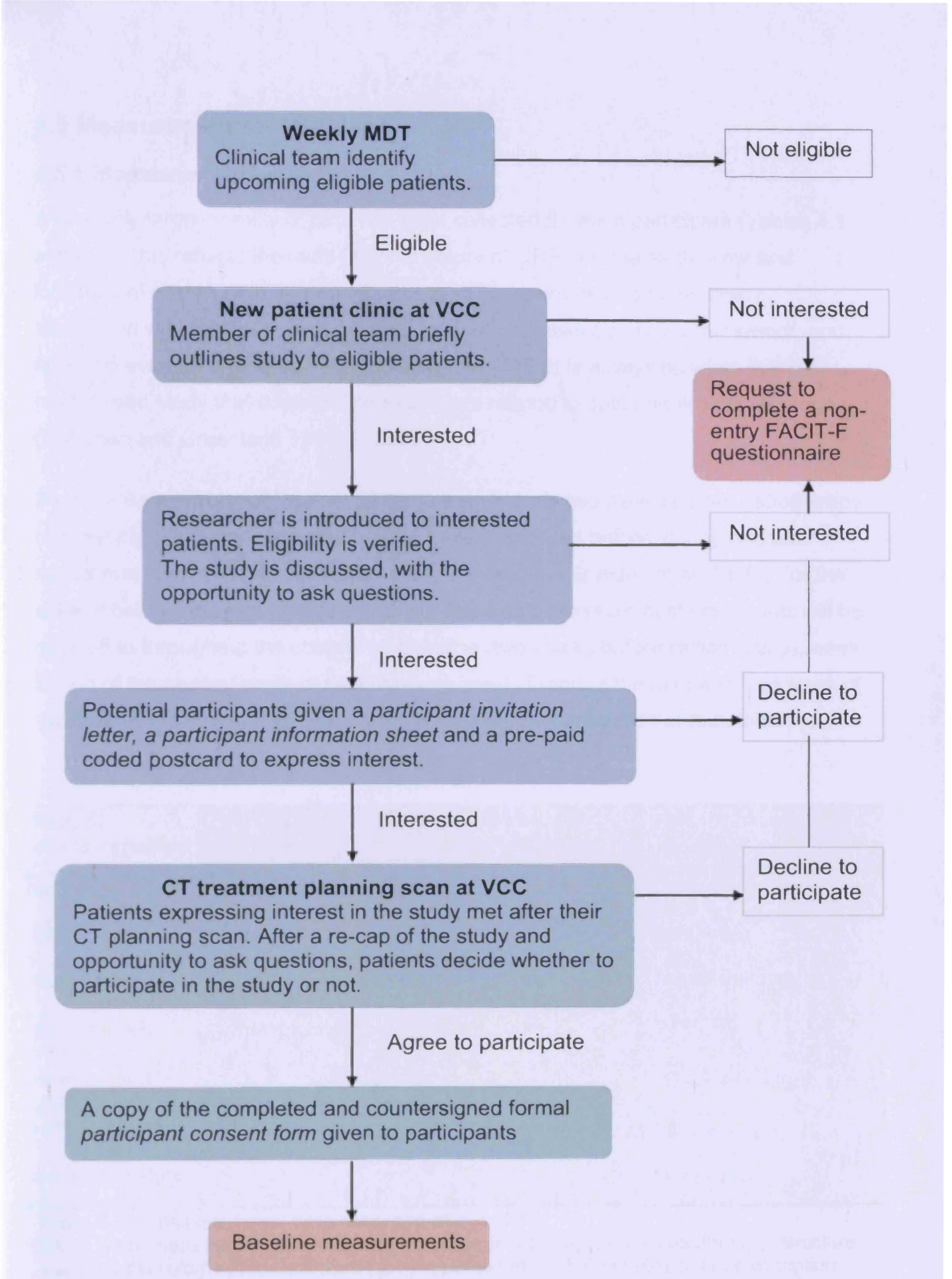


Figure 4.2 Flow-plan outlining the recruitment process

4.5 Measurement of variables

4.5.1 Measurement schedule

A relatively large quantity of data has been collected for each participant (Tables 4.1 and 4.2). This reflects the multi-factorial nature of CRF and the study aims and longitudinal design. The aim was to record all exposure factors theoretically associated with fatigue via the cytokine induced sickness behaviour framework, and factors previously shown to be associated with CRF. It is always possible in a non-randomised study that confounding exposures related to outcome are not recorded (Rothman and Greenland 1998, p. 255).

Baseline data (Table 4.1) was recorded approximately two weeks before radiotherapy commenced. Longitudinal data (Table 4.2) was recorded before, during and after radiotherapy, to reflect the assumed course of fatigue (Graydon et al. 1995). For the sake of brevity, the four chronologically ordered data measurement time-points will be referred to throughout the chapter as baseline (two weeks before radiotherapy), week 2 (end of the second week of radiotherapy), week 3 (end of the third and final week of radiotherapy) and 4 weeks post (four weeks after the completion of radiotherapy).

Patient characteristics	Disease characteristics	Surgical characteristics	Radiotherapy variables
age	histological diagnosis	surgical procedure	tangential separation
BMI	tumour size	laterality	field area
work status	histopathological grade	time from surgery to radiotherapy	breast volume
travel time & mode	pathological stage		$PTV_{10, 50, 90}$
menopausal status			ipsilateral $lung_{10, 50, 90}$
HRT history			$heart_{10, 50, 90}$
smoking history			$liver_{10, 50, 90}$

Table 4.1 Cross-sectional data recorded at baseline
(BMI = Body mass index; HRT = hormone replacement therapy; RT = radiotherapy; structure $_{10, 50, 90}$ = total volume of the structure (cm^3) irradiated to 10, 50 and 90% of the prescription dose.)

	Pre-radiotherapy	During radiotherapy		Post radiotherapy
	(Baseline)	(Week 2)	(Week 3)	(4 weeks post)
FACIT-F (fatigue)	x	x	x	x
HADS (anxiety & depression)	x	x	x	
IPAQ (physical activity)	x	x	x	
Full Blood Count	x	x	x	x
Serum IL-6sR concentration	x	x	x	x
Weight/BMI	x		x	

Table 4.2 Longitudinal data recorded at four time-points
(FACIT-F = functional assessment of chronic illness therapy fatigue scale; HADS = hospital anxiety and depression scale; IPAQ = international physical activity questionnaire; IL-6sR = interleukin 6 soluble receptor; BMI = body mass index.)

As radiotherapy toxicities are cumulative, it was felt that little information would be gained from fatigue observations after one week of radiotherapy (Graydon et al. 1995, Wratten et al. 2004). Eliminating this time-point also served to reduce participant burden as they familiarised themselves with the actuality of treatment. The rationale behind the 4 weeks post time-point was that both published (Geinitz et al. Wratten et al. 2004) and expert opinion suggested acute fatigue commonly resolves four weeks post treatment, in the study patient population. This time-point was therefore of scientific interest to elucidate fatigue radiation dose-time response patterns, and provide a potential indicator of chronic fatigue problems.

A flowplan (Figure 4.3 below) clarifies how the cross-sectional and longitudinal measurements relate to the study time-points. Italicised text refers to study documents included in Appendix 3.

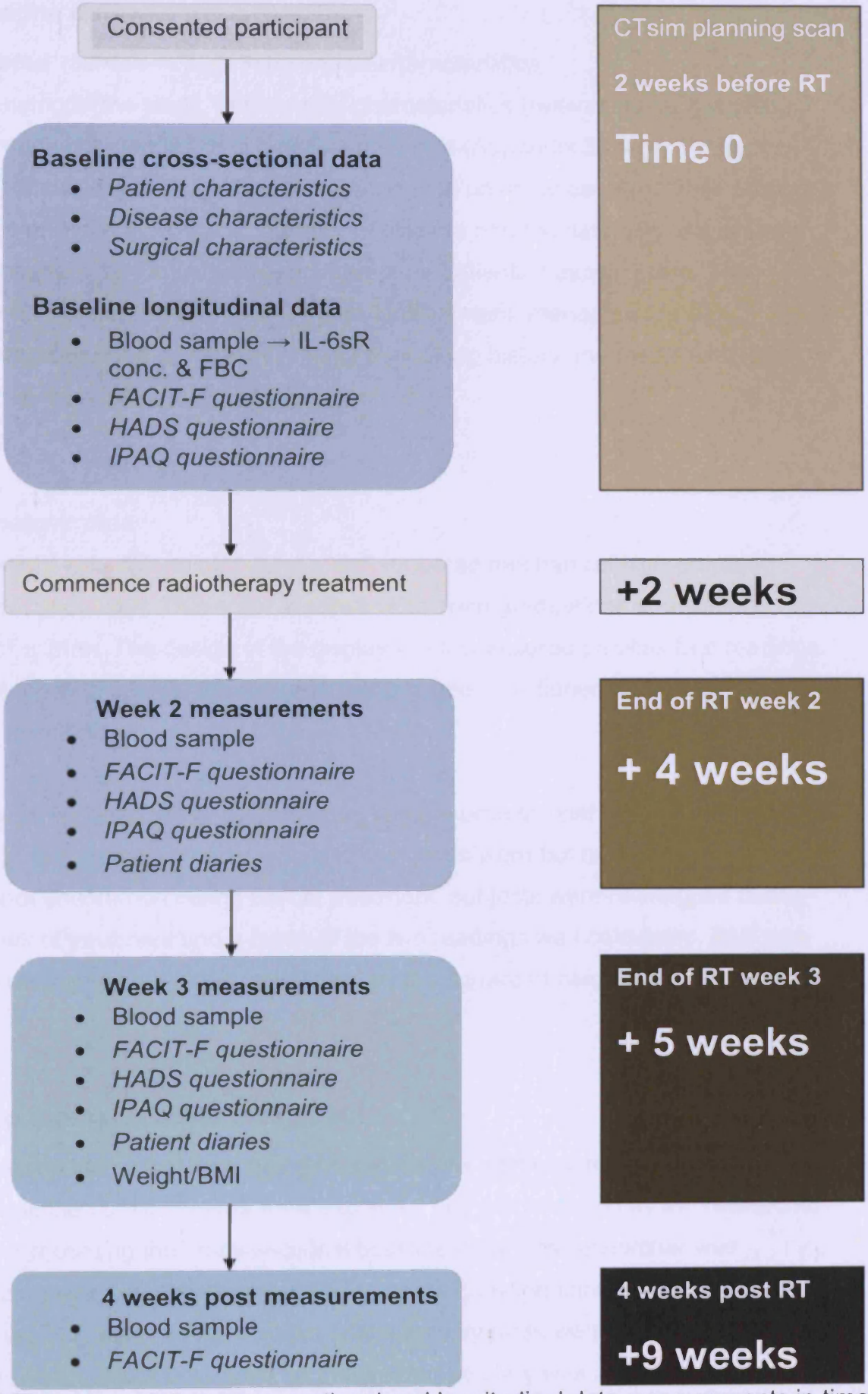


Figure 4.3 Flow-plan relating cross-sectional and longitudinal data measurements in time

4.5.2 Baseline data

Patient-related, disease-related and surgical characteristics

After consenting to the study, participants' characteristics (relevant to fatigue status) were recorded on a standardised baseline proforma (Appendix 3). Age, histological diagnosis, tumour size, histopathological grade, and pathological stage were obtained from electronic medical records. Laterality of disease and the date and nature of the surgical procedure performed were recorded from patients' hospital notes. The variables work status, travel time and mode for treatment, menopausal status, hormone replacement therapy (HRT) history, smoking history and medication taken were gleaned from participant interview.

Anthropomorphic data

Barefoot height was determined using a wall-mounted mechanical high-precision stadiometer (Seca 240). This scale is sensitive to 1mm graduations and states a precision of ± 2mm. The design of the display window ensured parallax free readings. Subjects stood with back to the rod, and feet in a heel 'positioner' to maintain consistent positioning.

Subjects were weighed to the nearest gram using a professional digital floor scale (Seca 888) sited on a solid base. Indoor clothing was worn but not shoes. As weight change is not uncommon during cancer treatment, subjects were re-weighed during the last week of treatment and a mean of the two readings was calculated. BMI was calculated by dividing the mean weight (kg) by the square of height (m^2).

4.5.3 Longitudinal questionnaire data

To minimise measurement bias, questionnaires were administered in a standardised manner. Baseline questionnaires were explained and administered by the researcher directly after recording the cross-sectional baseline data. The researcher was available to answer any queries regarding baseline questionnaire completion. The remaining week 2, week 3 and 4 weeks post questionnaires were given to participants at this time, as a colour-coded pack. A patient fatigue diary was included.

The validity and successful analysis of longitudinal cohort studies is largely dependent on the completeness of the data (Katz 2006, p. 87). In an effort to maintain response rates, the researcher scheduled brief meetings with participants on the days the week 2 and week 3 questionnaires were due. If questionnaires had not been returned within a week, a follow-up telephone call was scheduled to prompt their completion and return. A log was maintained recording response rates and deviations from the measurement schedule.

Whilst participants were informed in broad terms about the aims of the study, where possible, participants were unaware of specific study research questions whilst completing the self-reported questionnaires. The concern was Hawthorne-type effects (Adair 1984). Conversely, the researcher remained blind to the fatigue status of the participant until all other measurements had been taken. These strategies acted as important safeguards against information and observer bias respectively, that could have weakened the observational study design (Davey Smith and Ebrahim 2002).

Fatigue (FACIT-F)

Fatigue was measured the using the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F). Permission was granted for its use in July 2007. Previously known as the Functional Assessment of Cancer Therapy Fatigue subscale (FACT-F), FACIT-F is a multi-dimensional discriminative tool to assess fatigue severity over the previous seven days. As the former name implies this tool was originally developed specifically for cancer populations (Cella et al. 1997a). It has been used in over 200 published studies (Webster et al. 2003) including numerous breast cancer (Chang et al. 2005, Fan et al. 2005, O'Shaughnessy et al. 2005, Tchen et al. 2003) and radiotherapy studies (Shafqat et al. 2005, Wratten et al. 2004). The widespread use of the FACIT-F allows cross-comparison of study results with numerous published studies and importantly, normative data (Brucker et al. 2005, Cella et al. 2002a).

The format of the scale is a 13-item questionnaire using a Likert-type scale. The brevity of the subscale is desirable as reduced questionnaire response rates have been reported as fatigue levels rise (Dittner et al. 2004). Scores for negatively worded items are reversed, and the items then summed to generate a cumulative score

between zero (maximum fatigue) and 52 (no fatigue). That is, FACIT-F is an inverse scale, with lesser scores representing increased fatigue. A logarithmic transformation can be applied (Cella et al. 2002a) that transposes raw scores (scores 0 to 52) into true interval data (scores 0 to 100), thereby extending the range of appropriate statistical analyses and enhancing interpretation/comparison of results. A conversion table for raw and interval scores is included in Appendix 4. The quantification of a minimally clinically important difference as three to four points (Cella et al. 2002c). further enhances the interpretation of results.

The scale has demonstrated good validity, test-retest reliability (r = .90), internal consistency (α = 0.93–0.95) (Cella 1997b) and sensitivity to change in related parameters, such as haemoglobin (Berndt et al. 2005) and performance status (Cella et al. 2002a). Published research also informs the definition of what cut-point constitutes fatigue 'caseness'. Wratten et al. (2004) define 'significant fatigue' as a score < 37, compared to the cut-point of 34 for the diagnosis of fatigue proposed by Van Belle et al. (2005). The more stringent cut-off score of ≤ 34 will be adopted for this study. In an effort to minimise classification bias, only participants whose average of scores at week 2 and week 3 was ≤ 34 were categorised as a fatigued participant. Conversely, participants whose average FACIT-F score over week 2 and week 3 scores was 35 and above were categorised as non-fatigued.

Anxiety and depression (HADS)

The Hospital Anxiety and Depression Scale (HADS) was used as a self-reported measure of anxiety and depression over the previous seven days. An institutional licence for use of the HADS scale was registered. The scale's psychometric properties and sensitivity to medical interventions have been validated in diverse settings (Hermann 1997) including cancer patients (Moorey et al. 1990), and used to assess mood disorders in breast radiation oncology studies (Geinitz et al. 2001, Maraste et al. 1992). The format of the questionnaire is 14 questions alternately pertaining to anxiety or depression (included in Appendix 3). Responses to the questions are scored between 0 (none) to 3 (severe), yielding a total score between 0 and 21, for each symptom. According to Zigmond and Snaith (1983), symptom scores can be categorised as normal (0–7), borderline (8–10) and significant (11–21). Individual

symptom scores can also be combined to render a cumulative HADS score indicative of psychological mood (Le Fevre et al. 1999, Lloyd-Williams et al. 2001).

As part of the consent process, participants were specifically asked to assent to their GP being notified on obtaining a cumulative HADS scale score of 20 or more. This figure has been identified as a clinically important interface between moderate and more severe symptoms (Le Fevre et al. 1999, Lloyd-Williams et al. 2001).

Physical activity (IPAQ)

Physical activity was measured using the self-reported International Physical Activity Questionnaire (IPAQ) Long Form (Appendix 3). The IPAQ has been used widely for population surveillance (Craig et al. 2003, Rutten and Abu-Omar 2004) in health-related studies (Booth 2000) and breast cancer studies (Johnson-Koslow et al. 2006). The Long Form version of the IPAQ assesses physical activity level across a comprehensive set of life domains, namely: work-related activities, transport-related activities (getting from place to place), home-based activities (in the house and garden) and leisure activities. This allowed sub-analysis of adaptations in activities, as theorised in the sickness behaviour model. The time spent sitting is also recorded as an additional item. A total physical activity score is produced by summation of the individual domain scores.

All IPAQ activity scores are expressed as Metabolic Equivalent Task-minutes per week (MET-min/wk). An MET is a standard unit equivalent to the ratio of the rate of energy expended during an activity to the rate of energy expended at rest (Ainsworth et al. 2000). Each type of activity asked about in the IPAQ is weighted according to its energy requirements defined in METS (Craig et al. 2003). By multiplying this figure by the time spent doing this activity over the previous week renders a continuous score in MET-min/wk. The continuous score can also be ranked as a low, moderate or high level of activity based on a standardised scoring protocol (included in Appendix 4).

4.5.4 Cytokine data

Cytokine blood processing

Qualified phlebotomists at VCC drew five mL of blood by venepuncture at the antecubital fossa, contra-lateral to the disease site. This measure avoids further tissue damage and the associated risk of lymphoedema in the affected limb. The samples were collected in serum separation tubes (BD Vacutainer, New Jersey, US) labelled with participant's project code number. Serum separation tubes are coated with a silica clot activator and contain an inert gel that (when centrifuged) forms an impermeable barrier between the serum and red cells, preventing contamination by intracellular material. All samples were stored for one hour at room temperature to ensure standardised sample handling and to allow clotting to proceed. Cellular material was separated by centrifugation at 1500 x g for 15 minutes at room temperature. The resultant sera were transferred to coded sterile screw capped polypropylene tubes (Molecular BioProducts, Thermo Fisher Scientific, San Diego, US) in 300 µL aliquots. Samples were then immediately stored on-site at -70°C until analysed.

Interleukin 6 soluble receptor assay materials

Commercially available enzyme-linked immunosorbent assay (ELISA) kits, optimised for use with human serum, determined circulating levels of IL-6sR (R&D Systems Quantikine Colorimetric Sandwich ELISA kits, Minneapolis, USA). ELISA inter-assay variation can occur due to an array of environmental and laboratory technique-related variables (De Jongh et al. 1997, Flower et al. 2000). To minimise this variability, samples were assayed in batches of the maximum numbers deemed logistically prudent. In total, 10 separate experimental IL-6sR ELISAs were conducted. All experimental kits were purchased as a multiple batch with common lot numbers, as heterogeneity has previously been demonstrated between manufacturers' lots (Aziz et al. 1999). The sensitivity of the ELISA kits was quoted as a minimum detectable IL-6sR concentration of 15.1pg/mL. This detection threshold was below the lower ranges observed from pilot work (4.8.2), and as indicated from previous studies (Collado-Hidalgo et al. 2006, Klabusay et al. 2006).

All ELISA assays were conducted at the Cardiff University laboratory, based in the Cancer Research Wales building, at VCC.

Interleukin 6 soluble receptor assay procedure

All assays were conducted in accordance with the manufacturer's instructions (available from < http://www.rndsystems.com/pdf/dr600.pdf >).

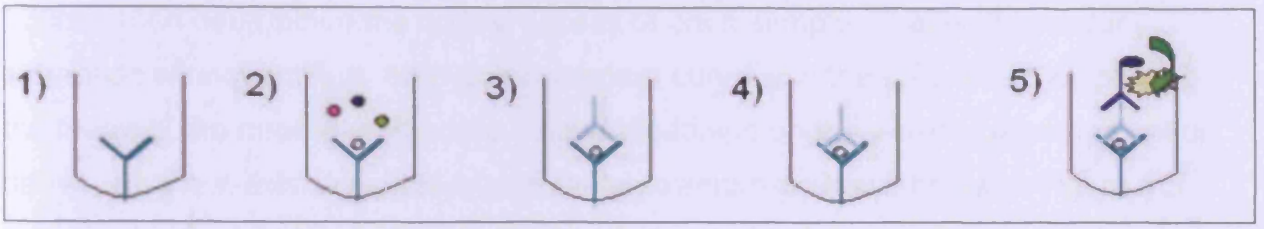


Figure 4.4 Principle of a sandwich enzyme-linked immunosorbent assay (ELISA)

With reference to Figure 4.4 above, the procedure of the IL-6sR ELISA assay was as follows:

1. The microplate was pre-coated with monoclonal antibody specific for human IL-6sR.
2. Eight standard dilutions of 2000, 1000, 500, 250, 125, 62.5, 31.2 pg/mL and 0 pg/mL were prepared. Serum sample was diluted by a factor of 120 in a Calibrator Diluent, as determined by pre-experimental work (4.8.2). A sample of known concentration, established from the pre-experimental work, was added to each plate to act as a reference set. This enabled inter-assay variability to be characterised. 100 µL of standard, sample, or reference sample was added to each well. All samples were run in duplicate. After incubation of two hours all unbound antigen was washed off.
3. 200 µL of a polyclonal detection antibody was added to each well.

4. The detection antibody was conjugated to the enzyme horseradish peroxidise.
5. After incubation and washing, a substrate was added that reacts chemically with the enzyme to create a detectable (coloured) signal. After 20 minutes, the addition of a stop solution rendered the reaction stable.

The endpoint of a (colorimetric) ELISA is that each individual well-plate sample inheres a specific colour saturation, which is a function of the concentration of IL-6sR present. A microplate reader, set to wavelength 450nm and wavelength correction 570nm, then determined the optical density of each sample. That is, the colour saturation was quantified. An 8-point standard curve was then produced, by plotting the mean of the duplicate standard (known) readings on the y-axis against the optical density on the x-axis. A typical experimental example is shown below in Figure 4.5. Empirical optical density values were then converted to (previously unknown) sample concentrations, using the second order polynomial equation describing the standard curve.

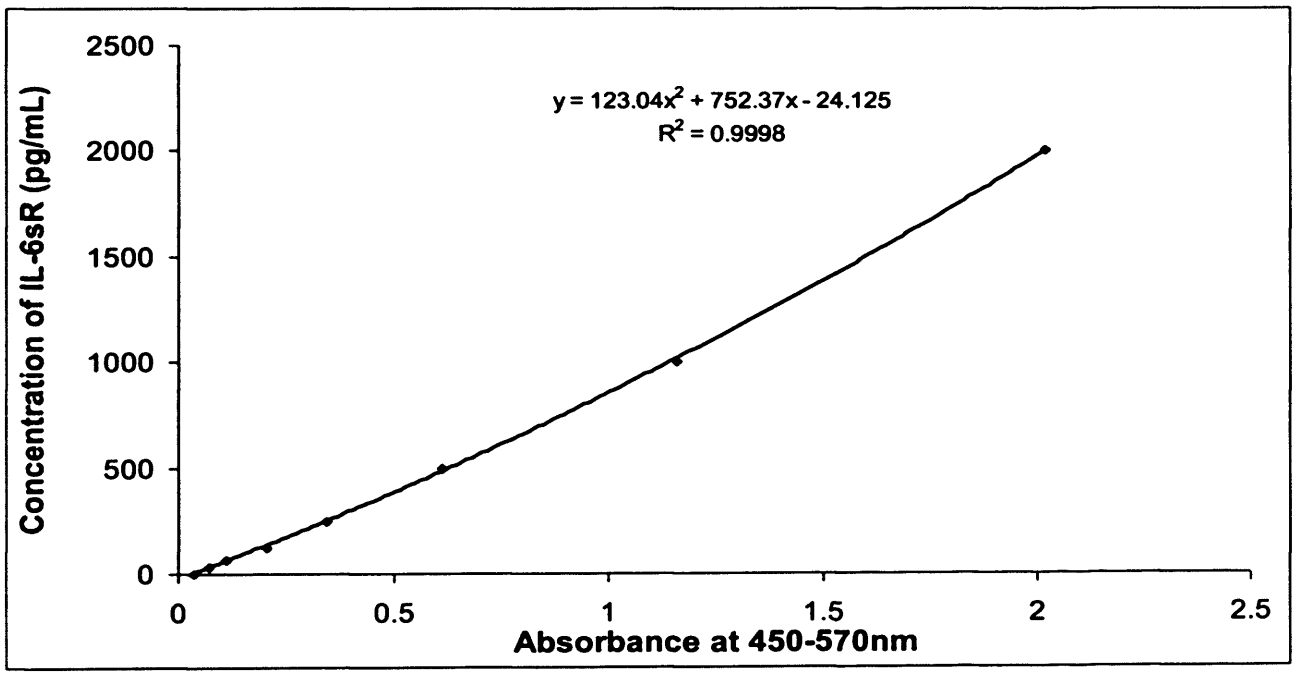


Figure 4.5 The concentration of standard interleukin-6 soluble receptor (IL-6sR) concentrations (pg/mL) plotted against optical absorbance using a wavelength of 450nm and a wavelength correction filter of 570nm

Interleukin 6 assay materials

A commercially available ELISA kit, optimised for use with human serum, determined circulating levels of IL-6 (R&D Systems Quantikine Colorimetric Sandwich ELISA kits, Minneapolis, USA). In man, IL-6 is present in the bloodstream at low picogram (pg) concentrations: potentially less than the lower detection range (3.1 pg/mL) quoted for a standard IL-6 ELISA kit (R&D Systems). Therefore, a high sensitivity kit was used, with an associated threshold of detection of 0.156 pg/mL.

Interleukin 6 assay procedure

The assay was conducted in accordance with the manufacturers' instructions (available from < http://www.rndsystems.com/pdf/hs600b.pdf >). Two procedural distinctions from the IL-6sR assay, both related to the high-sensitivity of the kit, were that to avoid sample contamination the assay was conducted in a class 2 safety cabinet, and the sera samples were assayed neat.

4.5.5 Full differential blood counts

Qualified phlebotomists drew six mL of blood by contra-lateral antecubital venepuncture into haematology tubes (BD Vacutainer). These polyethylene terepthalate tubes are coated with the anticoagulant K_2EDTA, to prevent sample clotting. Samples were auto-analysed (Pentra XL 80, Horiba ABX, Montpellier, France) by technicians in accordance with standard VCC procedures.

A full blood count with a five-part leukocyte differential was recorded. The results for any study participant outside normal ranges were circulated to the treating clinical treatment team.

4.5.6 Radiotherapy data

Radiotherapy treatment simulation and planning process

The treatment planning process, based on the preceding CT-simulation procedure is now summarised. Briefly, patients were scanned using a 2mm slice thickness on a

Siemens Somatron Sensation Open CT Simulator (Siemens Healthcare, Erlangen, Germany). The resultant 3D body data was imported via a Dicom into ProSoma virtual simulation software (Medcom, Darmstadt, Germany), where a breast planning radiographer localised the CTV. An isotropic margin of 10mm was then added to form a PTV. The application of opposed tangential fields created a non-divergent posterior field border and achieved adequate coverage of the clinical volume. This data was imported into the Oncentra MasterPlan (OMP) version 3.1 treatment planning system (Nucletron, Veenendaal, Netherlands). A member of the medical physics team then created a 2D treatment plan to ensure the central slice dose distribution was between 95–107% of the prescribed dose in accordance with ICRU guidelines 50 (1993) and 62 (1999). These were the standard procedures at VCC for the duration of the study.

Dose-volume histogram data extraction

To extract the required 3D dose-volumetric data for each participant, the researcher undertook the following procedure. The CT body structure and treatment plan datasets were re-imported from ProSoma into a standalone OMP system. A non-clinical copy was created and anonymised with the appropriate participant code. The imported clinical plan was then deleted.

The organs of interest were outlined on each contiguous transverse body structure slice using a segmentation tool. Figure 4.6 below shows a typical study screenshot of a CT slice with the heart (red), lungs (green) and the external body (beige) delineated.

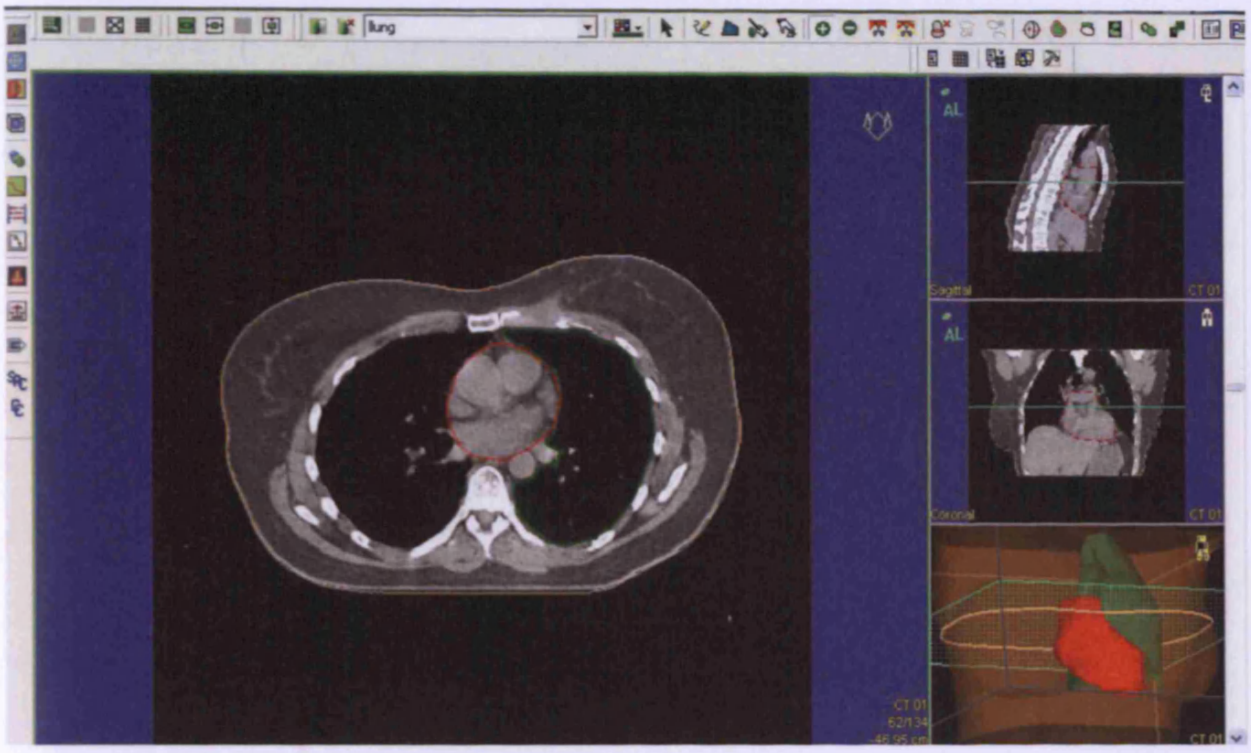


Figure 4.6 Screenshot from Oncentra MasterPlan 3D planning system (showing a transverse CT slice on the left-hand portion of the screen and alternate sagittal, coronal and reconstructed 3D views in the right-hand portion)

The next step was to model the beam data. The appropriate treatment machine and photon beam energy were specified. The beam weightings specified on the treatment plan were applied. Similarly, the orientation and angle of specified wedge filters were applied.

To maximise the accuracy of dose-calculations, the minimum calculation grid voxel size of 3mm was selected. The calculation grid was extended axially by 50mm, superiorly and inferiorly, to allow for scattered dose. A dose normalisation point was defined – in accordance with ICRU 50 (1993) and 62 guidelines (1999) – that was both on the plane that bisected the tangential separation on central slice, and was the perpendicular midpoint between the chest wall and skin. Gray et al. (1991) define tangential separation as, 'The linear distance between the lateral and medial tangential field entry points on the central slice'. The beam-anatomy geometry is clarified below, in Figure 4.7.

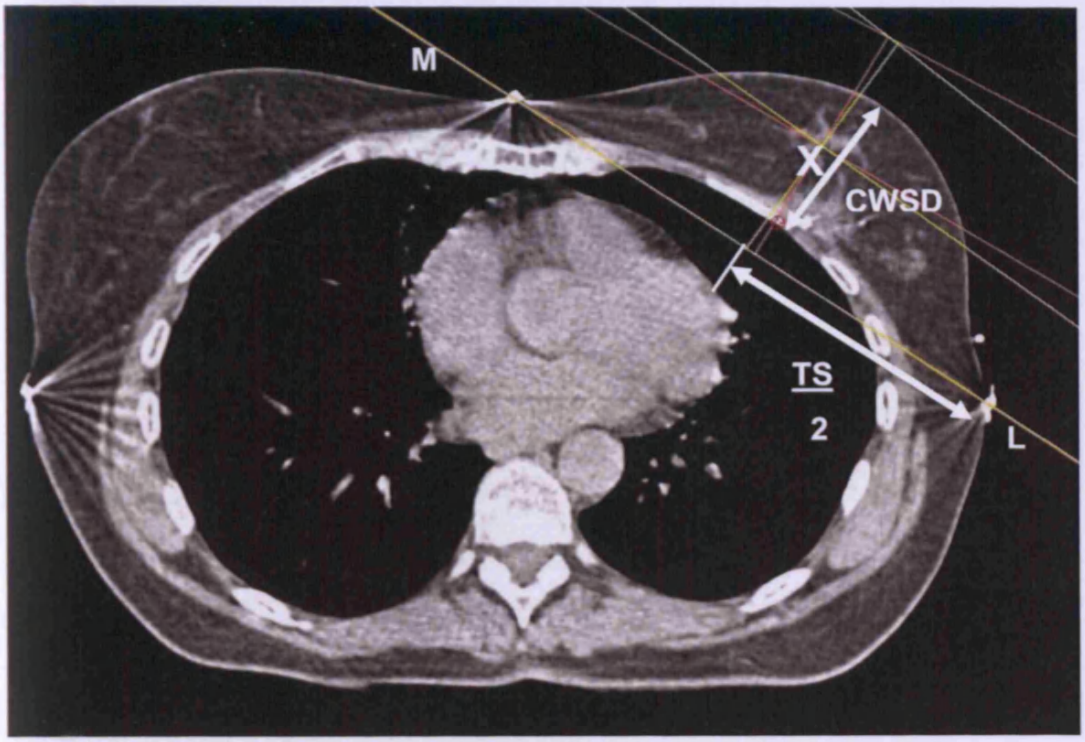


Figure 4.7 Beam-anatomy geometry for the central transverse CT body structure slice. The red lines are the medial field, the yellow lines are the lateral field. (M = medial; L = lateral; TS = tangential separation; CWSD = chest wall skin distance X = location of dose normalisation point.)

The planning system calculated the dose distribution throughout the 3D body volume, using a collapsed cone convolution algorithm. The resultant dose distribution was displayed as a DVH. The minimum, maximum and mean tissue doses were also automatically generated. A typical example of a study DVH is illustrated below in Figure 4.8:

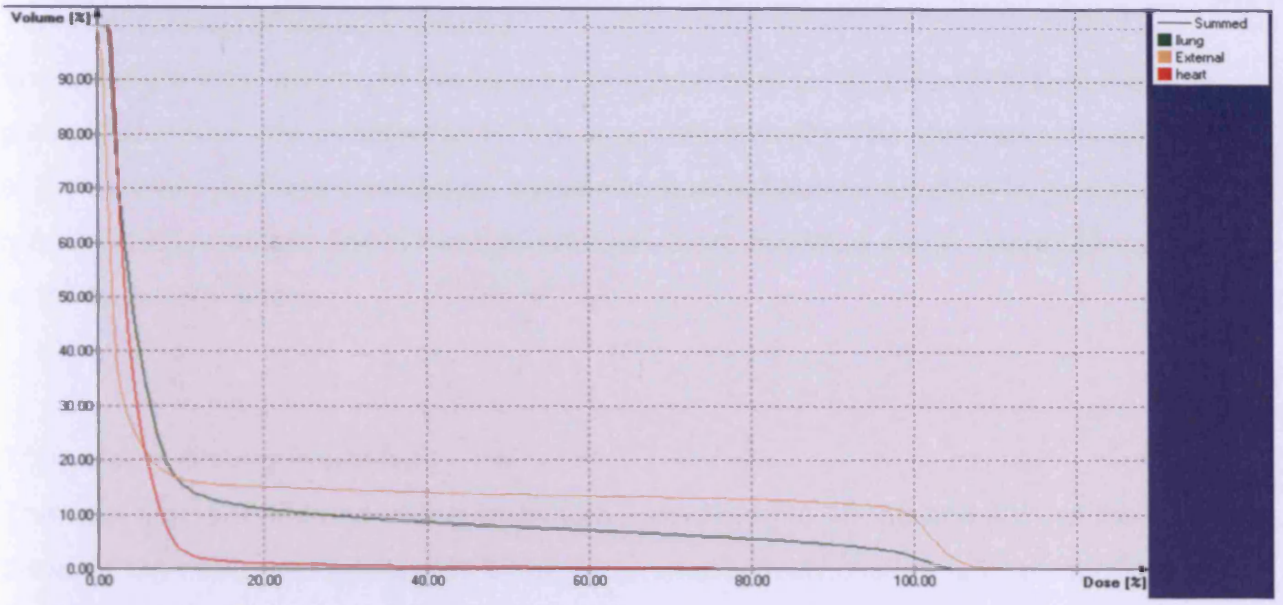


Figure 4.8 Screenshot from Oncentra MasterPlan 3D planning system output, showing an example of a dose-volume histogram (DVH). The percentage volumes of tissue (y-axis) irradiated to percentages of the applied dose (x-axis) are displayed for the body outline (yellow line), lung (green line), and heart (red line)

Brief definition of the radiotherapy parameters recorded will now follow. Where appropriate, the rationale for measuring and/or specific procedure involved in calculating the parameter is detailed.

Breast volume

For the purposes of the study, the breast volume was considered to consist of the volume of tissue within the 95% isodose. This surrogate is valid as the treatment was planned such that this dose level conforms to the PTV and hence the extent and contours of the breast tissue. As the treatment was not optimised three dimensionally there will inevitably be some discrepancy in off-axis contours and a small portion of non-breast tissue irradiation (for example, lung). The latter affect will be to some extent counter-balanced by a slight underestimation in the most superficial 3–5mm of breast tissue, as this corresponds to the rapid dose build up region for a 6MV linear accelerator (Lacey et al. 2007).

The total volume of tissue irradiated

The absolute total volume of the tissue (cm^3) irradiated to 10, 50 and 90% of the prescription dose are denoted as $PTV_{10, 50, 90}$, respectively. The steep density gradient at the skin/air interface enabled an automatic external outline function to generate the required body outline. Any CT image artefacts were modified as necessary to conform to the true body shape.

The volume of lung irradiated

The total absolute volume of the lungs (cm^3) irradiated to 10, 50 and 90% of the prescription dose are denoted as $lung_{10, 50, 90}$, respectively. As the full extent of the lung was always included in the CT scan, percentage volumes of the whole lung irradiated were also calculated. The contrast in density between lung and surrounding mediastinal tissue created a distinct pleural border on the CT image. This allowed the use of an internal automatic contouring tool when outlining the lung volumes. Any discrepancies were modified to conform to the true organ boundary.

The volume of liver irradiated

The liver extent was outlined as visualised on the CT image. The total absolute volume of the liver (cm^3) irradiated to 10, 50 and 90% of the prescription dose are denoted as $liver_{10, 50, 90}$, respectively. As the full extent of the liver was not always included in the CT scan only absolute volume (cm^3) data could be universally generated.

The volume of heart irradiated

The heart was defined as the extent of the pericardial sac, including the inner pericardial fat and coronary arteries. This definition theoretically included all the important structures as regards acute radiation effects (and cytokine release). The pericardium has a ragged upper limit that may extend as far superiorly as the arch of the aorta (see Figure 4.9 below). To ensure consistency, the upper border corresponded to the first CT slice to include the left pulmonary artery; which appears slightly superior to the branching of the pulmonary trunk. The roots of the great

vessels were considered as pericardial structures, including the origin of the aorta. These structures were excluded when they became separate elements that could only be connected by an island in the outlining procedure. The Hila, where the lung and heart abut, were also excluded as these are mixed tissue structures. The inferior margin was the apex of heart.

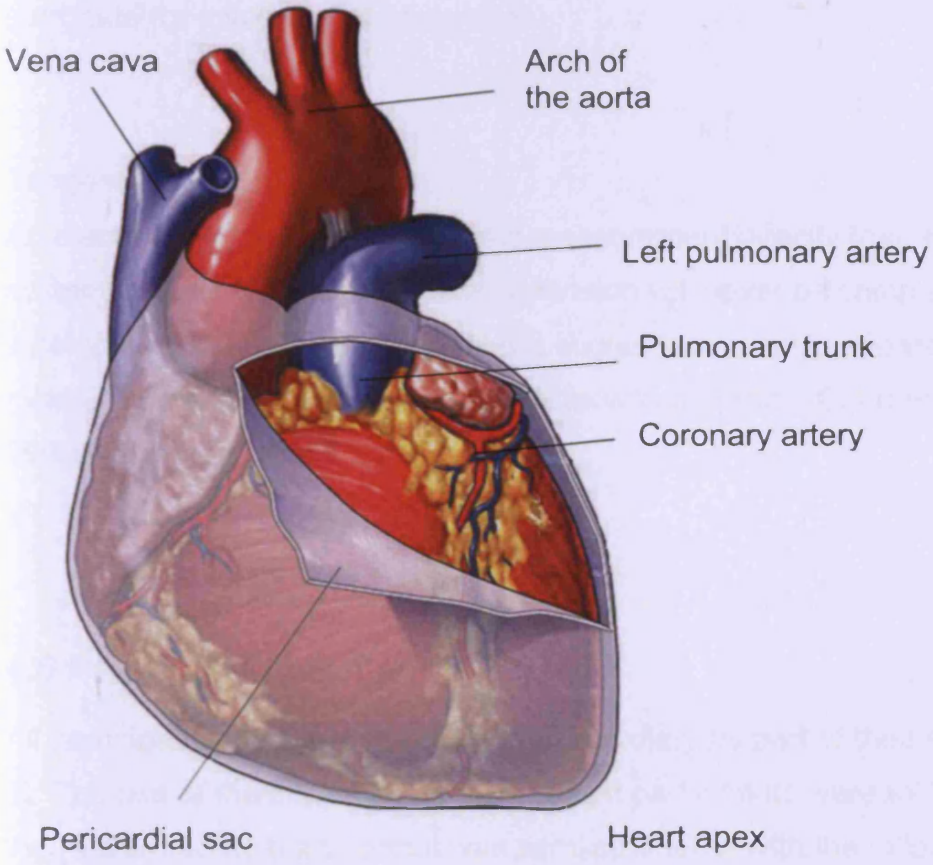


Figure 4.9 Anatomy of the heart and cardiac structures (image adapted from http://www.lausd.k12.ca.us/Figueroa_EL/images/Mystery%20to%20Medicine/pericardium.jpg)

In practice the thinness of the pericardial membrane, and the limited soft tissue contrast resolution on some CT images rendered cardiac outlining susceptible to reliability issues (see section 4.5.3). The full use of sagittal, coronal and 3D reconstructed views, whilst scrolling between contiguous slices, combined with

manipulation of window level to reveal fine detail, greatly expedited interpolation of cardiac structures.

Radiation field area

The field area was the product of the field width and field length (Figure 4.12). This parameter was a simple 2D construct that was easy to calculate. In a clinical prognostic model, these qualities potentially make field area a potentially useful surrogate for a volumetric parameter.

Tangential separation

An electronic ruler tool captured this measurement directly from the OMP planning system images. Although a linear dimension will never be completely representative of a complex shape, correlation analysis suggests tangential separation (Figure 4.7) retains a degree of utility as a breast size/volume proxy (Courtier 2006, Law et al. 2000, Neal et al. 1995).

4.6 Patient fatigue diaries

All participants were given a patient fatigue diary as part of their study pack (Appendix 3). The use of the diary was optional, albeit participants were told it would be useful for the research. The diary format was semi-structured with the following three questions (and brief guidance) posed for each week of treatment:

i. How do you feel physically?
   (e.g. Describe how your body feels and the kind of fatigue feelings you experience. When do you feel better or worse?)
ii. How does fatigue affect the way you think?
   (e.g. Do you have difficulty thinking or concentrating? Are you more forgetful than normal?)

iii. How does fatigue affect your mood and emotions?
(e.g. Are you more up and down than normal? Does fatigue make you impatient with the people around you?)

During the planning stage of the project a wider role was anticipated for the fatigue diaries. Envisaged diary functions included the provision of a concept map encompassing the three postulated – physical, cognitive and affective – domains, a systematic analysis of fatigue group differences and an investigation of behavioural adaptations over time. The realities of time constraints determined that, for the purposes of the PhD, the function of the diaries was more limited. The first function was to provide a comparator with the FACIT-F data. For example, did fatigued patients recount differing intensities/impacts of fatigue as compared to non-fatigued patients? Secondly, diary entries provided valuable contextual information (transient illness, social factors, etc.) that may elucidate some of the variance in individual's fatigue scores.

4.7 Data handling and analysis

4.7.1 Data handling

A priori data processing rules (Appendix 4) were formulated to ensure consistent handling of data. Prior to statistical analysis, the dataset was screened to identify outliers, missing data, out of range values and other anomalies. Identified errors were corrected. All analysis was carried out using SPSS version 16, with the option of excluding cases pairwise selected as a default.

4.7.2 Statistical analysis approach

Evaluating quality of life type outcomes has a tendency to become complex (Cox et al. 1992), especially when the data is longitudinal (Griffiths 1999). In an effort to establish clarity of analysis and interpretation, the (quantitative) data analysis was conducted in five discrete phases that reflect the research questions, (and are subsequently

mirrored in the presentation of results in chapter five and a discussion results in chapter six), namely:

- A fatigue overview
- Relationships between baseline variables
- Changes from baseline in longitudinal variables and relationships between these longitudinal variables
- Fatigue during radiotherapy
- A prognostic model.

The *fatigue overview* considered three aspects of the longitudinal course of fatigue to provide a facetted overview of the cohort fatigue response. Time-series charts were plotted summarising each of these aspects. Non-parametric statistics were used throughout this section: the Friedman Test (with post-hoc tests to see where differences occur) for within group comparisons and Mann–Whitney test at time-points to compare between group fatigue responses.

In the second section, independent-samples t-tests and one-way between-groups analysis of variance (ANOVA) were conducted to determine if significant differences existed in baseline fatigue scores between categories of *baseline variables.* The impact of BMI on baseline fatigue – and theoretical interactions with anxiety and depression and physical activity – was explored by the use of two-way between groups ANOVAs. A series of Spearman's Rank Order correlations were then performed to determine the strength and direction of bivariate associations between baseline IVs[2] and baseline fatigue. Based on the correlation results, and more importantly theoretical bases, baseline variables were selected for forced entry into a multiple regression model. This modelling technique determines the relative contribution of each risk factor to the outcome baseline fatigue, whilst simultaneously adjusting for the effect of the other multiple risk factors. Multiple regression analysis is commonly reported in a rather crude manner, with inadequate disclosure and testing

[2] The following sets of words are used synonymously throughout the text: 'exposure factor', 'independent variable' and 'risk factor'; 'measurement' and 'observation'; 'dependant variable' and 'outcome'. The term 'predictor' is reserved for discussions of the performance of the prognostic model in the context of how well the model accounts for a subject's outcome.

of the assumptions that underlie the technique. The current study placed emphasis on rigorous analysis of the model residuals to check whether the study data fits the stated assumptions of the regression model. Residuals are the difference between the observed value of the dependent variable (DV) and the value estimated by the regression model. They are therefore indicative of the error in the estimated values of fatigue, or, in other words, the model accuracy. An indication of how well the model would perform using a different sample was also provided.

In section three, *the changes in longitudinal variables* were considered. Three linear fixed models with repeated measures were conducted. This technique accounts for the fact that multiple measurements on the same individuals are not independent observations. The first analysis assessed changes in concentration of the cytokine IL-6sR; the second analysis evaluated the impact of the volume of normal tissue irradiated on the cytokine concentration (biochemical level); the third analysis evaluated the impact of the volume of normal tissue irradiated on fatigue (behavioural level). Major correlational analyses supplement the repeated measures analysis, by considering the strength of the relationships between longitudinal variables, at time-points.

Results from the preceding correlational analyses inform the fourth section that reports on a second multiple regression model, formed to determine the contribution of multiple IVs to the variance in *fatigue during radiotherapy*. A hierarchical entry method was utilised that allows baseline fatigue to be entered prior to 'on-treatment' risk factors. This procedure controls for the effect of baseline fatigue on the DV. The DV was the average fatigue score at week 2 and week 3. The use of a summary measure to represent the fatigue response during radiotherapy overcame the problem of correlated observations at the individual level and an associated inflation of statistical significance (Katz 2006, p. 162, Twisk 2003, p.1).

The last section details the inclusion of pre-treatment IVs to form a stochastic model, *prognostic for fatigue status during treatment*. A prognostic model articulates risk of an outcome, which is distinct from diagnostic information from a predictive model (Byar 1984). A dichotomised outcome (fatigued or non-fatigued) was chosen, as simple models possess enhanced utility in a clinical setting. The categorical outcome

determined that a logistic regression model was appropriate. As the model purpose was prognostication, a forward stepwise algorithm was used that selects variables solely on statistical association. As previously, for multiple regression, the accuracy and the assumptions underlying the model are fully evaluated. The performance of the model was assessed in a four-step process, which is represented below in schematic form (Figure 4.10):

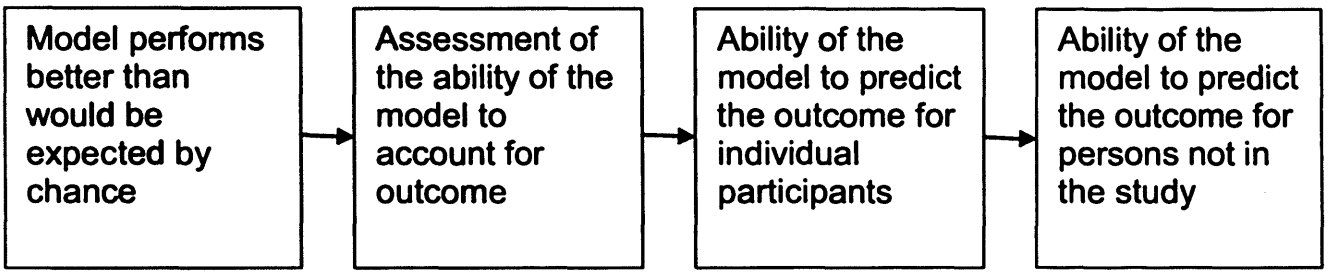


Figure 4.10 Tests for assessing the quality of a prognostic model (adapted Katz 2006, p. 180)

The generated model will fit the study data better than data collected from a different source. This is called 'over-fitting' of the data to the model. Ideally, the decrement in model performance would be validated in a separate confirmatory dataset (step four above). As the sample size precluded a separate confirmatory dataset, a jackknife cross-validation was employed. This procedure involves sequentially removing individual subjects from the dataset from which the model is derived. The derivation dataset becomes the dataset minus one case, and the confirmatory set is the missing case.

Finally, optimum cut-points were established in prognostic IVs that most accurately characterise a subgroup of participants at high risk of experiencing fatigue during treatment.

4.7.3 Diary data

Textual diary data was explored inductively using content analysis to generate categories and explanations. Initially the data was read and reread prior to being

coded into broad themes and for the two fatigue groups. It had been planned to refine the themes through repetitive scanning of the data for exemplars, attributes and negative cases (Lincoln and Guba 1985). Additionally, relations between the different themes were to be mapped, both for individual subjects and collectively.

4.8 Pre-experimental work and concerns relating to reliability of methods

4.8.1 Focus groups

The planning of the study was informed by input from two focus groups, formed from attendees at two South Wales breast cancer support groups. The groups were based in areas of contrasting socio-economic composition. Two meetings were convened with each group.

At the first meetings, a sequence of planned open questions explored the prevalence and experiences of CRF with survivors of breast cancer. Responses suggested approximately 40% (11 of 28) of patients suffered (at least) moderate fatigue during radiotherapy. A number of responses alluded to the difficulty in describing the experience of fatigue, though a number of descriptions intimated a systemic experience; for example, 'tired from the inside out'. Factors that participants perceived might have contributed to their fatigue were then elicited. The cumulative burden of travelling everyday for treatment was the most common factor mentioned. Questions that patients would like to be addressed in a fatigue study were compiled. The aim was to avoid the dissonance that can arise between researchers' aims and what is important to service users (Gary Rolfe 1998). Most proposed questions related to the individuals' uncertainty regarding the incidence, patterns and functional impacts of fatigue.

The purpose of the latter meetings was broadly to identify potential practical and ethical issues, and to assess the acceptability of the proposed study measures and questionnaires. For example, following suggestions, the follow-up blood sampling was made an optional element. Additionally, the consensus view was that using more than one self-reported measure of fatigue could be counterproductive, involving replication

that may consequently be construed as a 'paper exercise'. The researcher's concerns regarding the administration of the somewhat unwieldy Long Form IPAQ were mitigated because of focus group input.

These sessions were particularly useful in shaping the embryonic fatigue diary into a simple document with mutual utility for both study participants and the researcher. Descriptions of how women felt during radiotherapy were used directly as entry examples in the final diary.

4.8.2 Concerns regarding reliability of ELISA assay methodology

Limited results are reported in the following two subsections when they relate directly to methodological concerns.

Cardiff University biochemical researchers at the Cancer Research Wales laboratory, at VCC, provided training in laboratory techniques and specifically the ELISA procedure. Two pre-experimental IL-6sR ELISA assays were conducted. One was using sera from six healthy female volunteers, and the second using sera from six patients with prostate cancer, collected before radiotherapy, after one fraction and after 20 fractions.

The rationale of the pre-experimental assays was five-fold. Of primary importance was to attain proficiency in the assay procedure. Secondly, limited evidence was gleaned regarding the effect of irradiation on peripheral IL-6sR concentrations. The median (inter-quartile range (IQR)) concentration in the prostate cancer patients decreased from Md = 54.5 ng/mL (35.6–66.0 ng/mL) at baseline, to Md = 36.8 ng/mL (36.8–64.0 ng/mL) at fraction 20. Additionally, comparative IL-6sR concentrations for six healthy females were generated. The median (IQR) concentration was Md = 30.6 ng/mL (25.5 –38.5 ng/mL). Other significant advances included optimisation of the serum sample dilution factor (x 120), to ensure that study readings were on a linear portion of the standard curve. Serial sample dilutions also allowed sensitivity investigations of serum-binding effects. Finally, the IL-6sR concentration of a reference sample set was established and replicated, which could be added to subsequent plates to assess

inter-assay variation. Unfortunately, due to the high cost of the ELISA kits, the reference sample was only added to eight of the 10 plates assayed.

Intra-assay reliability

Intra-assay precision for the experimental ELISAs was calculated using the formula:

$$\text{Intra-assay coefficient of variation} = \frac{\text{Mean of the SD of the duplicate samples}}{\text{Grand mean of the duplicates}} \times 100$$

.....Equation 4.1 (www.poultry-health.com/library/serdiss/assayqc.htm)

The intra-assay coefficient of variation (ICC) was less than 8% for all assays. The mean (SD) ICC for all 10 assays was M = 3.7% (1.3).

Inter-assay reliability

The inter-assay reliability was assessed by comparison of the experimental IL-6sR ELISA standard curves. A visual inspection of the 10 standard curves and the reference set assay standard curve (Figure 4.11) indicated a high degree of inter-assay reliability.

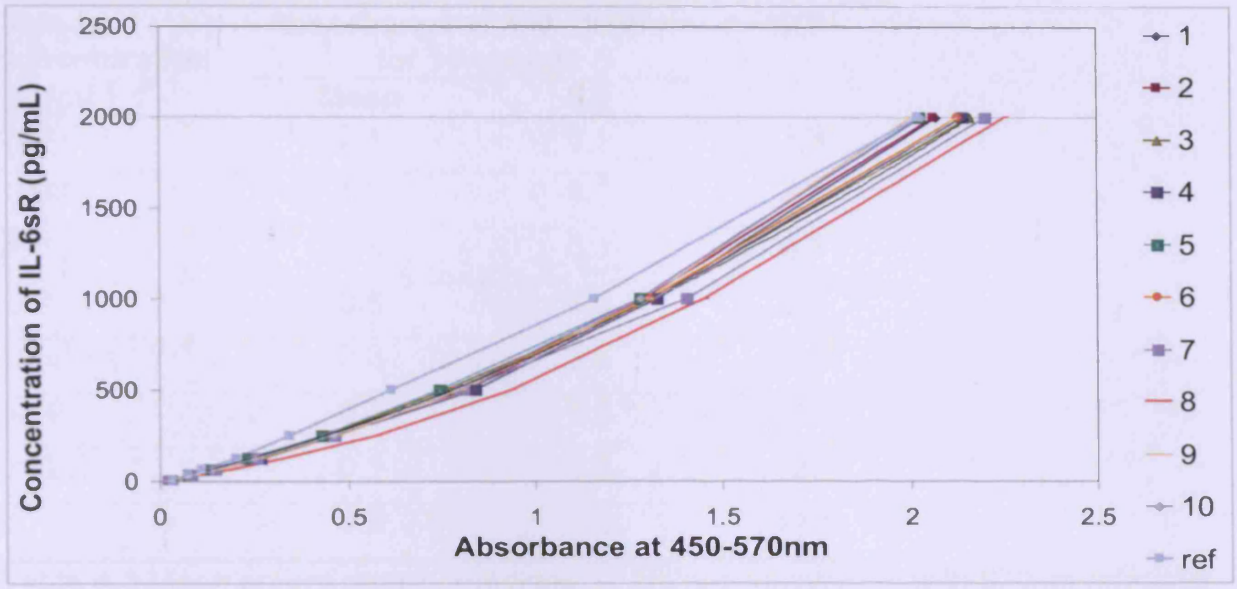


Figure 4.11 Comparison of standard curves from 10 experimental interleukin-6 soluble receptor (IL-6sR) ELISA assays and one ELISA assay with a reference sample

Inter-assay precision was calculated using the formula:

$$\% \text{ Coefficient of variation} = \frac{\text{SD of the means of the duplicate samples}}{\text{Grand mean of the duplicates}} \times 100$$

.....Equation 4.2 (www.poultry-health.com/library/serdiss/assayqc.htm)

The results summarised below in Table 4.3 indicated good inter-assay precision with a percentage coefficient of variation (%CV) of ≤ 4% at physiological levels of IL-6sR.

Standard concentration (pg/mL)	Absorbance at 450 - 570nm for 10 assays		%CV
	Mean	SD	
2000	2.1	0.1	3.9
1000	1.3	0.1	4.2
500	0.8	0.1	6.5
250	0.5	0.0	8.9
125	0.3	0.0	10.0
62.4	0.1	0.0	11.3
31.2	0.1	0.0	12.5
0	0.0	0.0	12.8

Table 4.3 Mean optical density readings, at 450nm wavelength with 570nm reference filter, for 10 IL-6sR ELISA assays, and associated percentage coefficient of variation (%CV)

An additional level of inter-assay reliability verification was provided by considering the variance of the reference sample of known IL-6sR concentration. The pre-experimental concentration measurement was 46.9 ng/mL. The mean (SD) experimental concentration, assayed on eight separate plates, was M = 44.59 ng/mL (3.0), and %CV = 7%, again indicating good inter-assay reliability.

4.8.3 Concerns regarding reliability of dose-volume histogram methodology

Pre-experimental work focussed on two areas:

- The procedural *generation* of the planned DVH data
- The development of a verification process to quantify *discrepancies* between the planned dose-distribution data and the treatment actually delivered.

Dose-volume histogram data generation

This area of concern was comprised of two main elements. Firstly, pre-experimental work was undertaken to establish the feasibility and logistics of – the unorthodox procedure of – recreating a 3D plan from CT body data and a 2D plan. Staff in the

medical physics department at VCC deemed the devised procedure yielded 3D plans that were both representative of the 2D versions and, an accurate simulation of the planned treatment.

The second element of concern was regarding the reliability of the organ delineation used to generate the DVH data. The definition of the perimeters of organs was determined pre-experimentally under the guidance of an experienced consultant radiologist, to ensure outlining was executed in a consistent manner. At this stage, an intention to outline volumes of haemopoeitic tissue was abandoned, due to technical problems outlining multiple, small, neighbouring structures. To verify there were no gross errors in organ delineation, breast planning radiographers and/or the radiologist reviewed outlining work prospectively. Additionally, 5% of the cases were retrospectively selected at random to assess the reliability of the outlining. Both the researcher and the consultant radiologist repeated the structure outlining throughout the volumes. The delineated volumes were re-calculated, with the radiologist's values considered the gold standard reference data.

The experimental (study) volumes for the external body and the lung were the reference value ± 1% and ± 1.5%, respectively. This close agreement was expected given the high degree of automated segmentation tools utilised. More heterogeneity was evident for the liver and heart volumes, being the reference value ± 6% and ± 8%, respectively. The volumes repeated by the researcher were all within 5% of the experimental values.

Discrepancies between planning and treatment data

Two approaches were used to assess the extent of geometric uncertainties that could contribute to discrepancies between the DVH data generated during planning and the actual organ doses received during treatment. The first quantifying the gross impact of diaphragmatic motion on patient/beam geometry and the second verifying the global agreement between planning and on-treatment data.

Pre-experimentally, a series of medial field planar MV electronic portal images (EPI) were captured every 10 monitor units throughout the duration of a single fraction for

10 breast radiotherapy patients. Sequencing of the EPIs rendered a pseudo 'moving cine' image. An electronic ruler tool was used to estimate the movement in the anterio-posterio (a–p) and cranio-caudal (c–c) planes due to breathing. The parameters recorded were the flash distance (FD), the central axis inferior distance (CxID) and the central lung distance (CLD) (see Figure 4.12 below).

The median maximum variance in FD was Md = 2.0 mm, (range = 1–5 mm), and the median maximum variance in the CxID was Md = 2.5 mm, (range = 1–5 mm).

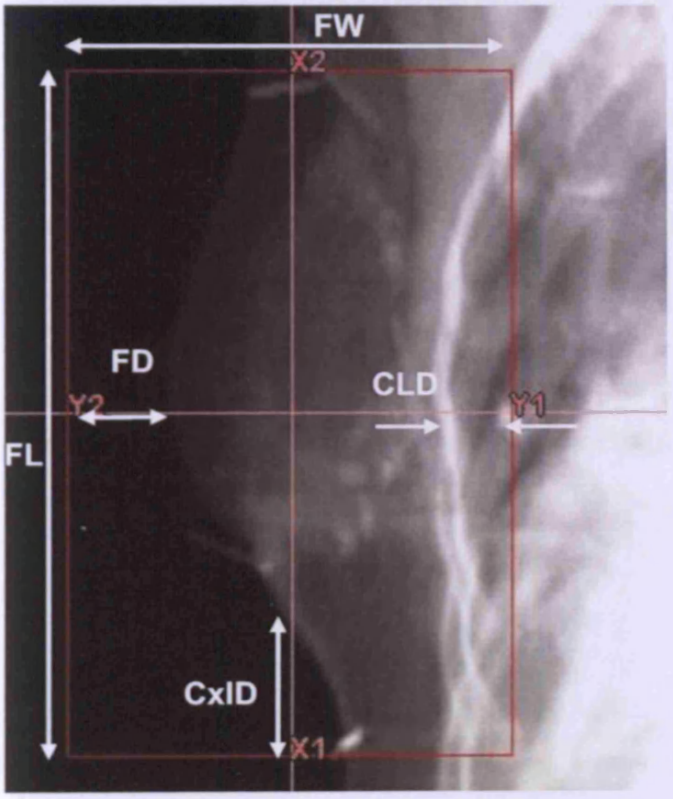


Figure 4.12 Beams-eye view defining beam-anatomy geometry and relevant parameters. (FW = field width, FL = field length, FD = flash distance, CLD = central lung distance, CxID = central axis inferior distance.)

To evaluate the volumetric effects of a–p respiratory movements, the impact of variance in central lung distance (CLD) on lung volume was estimated using the following quadratic equations:

% Lung (left) = $0.01CLD^2 + 0.16\ CLD - 0.18$ .....equation 4.3 (Neal and Yarnold 1995)

% Lung (right) = $0.01CLD^2 + 0.17\ CLD + 0.19$.....equation 4.4 (Neal and Yarnold 1995)

Where CLD = central lung distance measured in mm

Substituting median, minimum and maximum experimental CLD values into equations 4.3 or 4.4 as appropriate, yielded an estimate that the median maximum variance (due to breathing) in the volume of lung within the radiation field was Md ≈ 0.6%. The volumetric data was consistent with a range of Md ≈ 0.2%–1.3%.

The second verification method was to compare the reference digitally reconstructed radiograph, generated from the CT-simulator data, to an EPI acquired as part of the standard treatment verification process. The RD and CxID was measured for the first 14 study participants. Bland-Altman plots were used to compare the reference (CT) and on-treatment (EPI) values. This method is appropriate when comparing two measurements that are both subject to errors in their measurement (Hanneman 2008). Figures 4.13 and 4.14 below indicated acceptable agreement between the CT planning data and the on-treatment verification data.

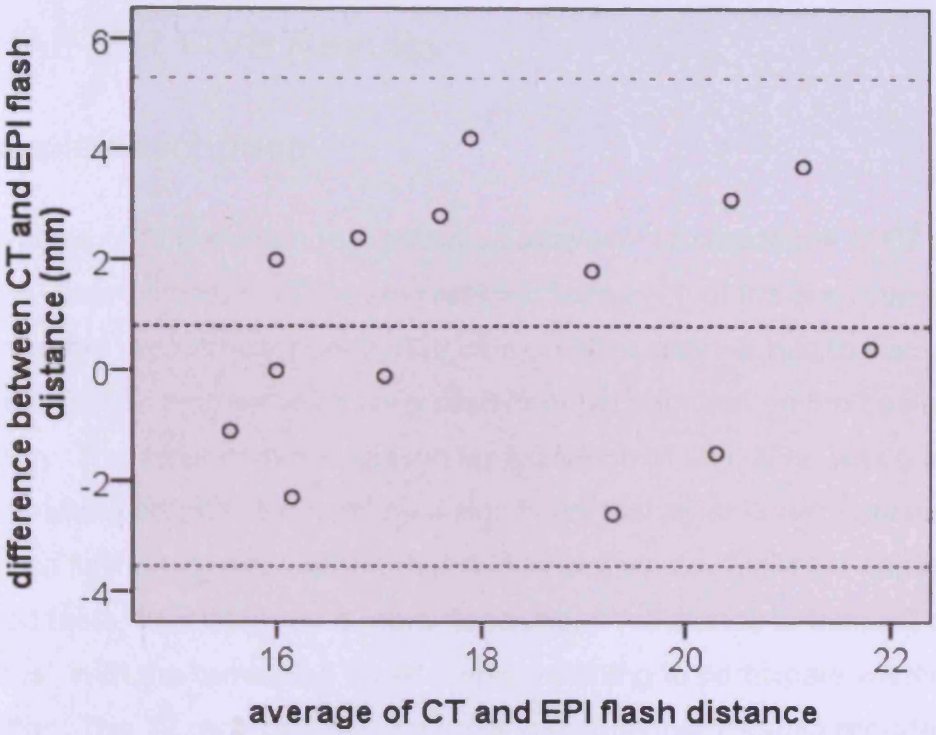


Figure 4.13 Bland-Altman plot comparing the flash distance (mm) as measured during CT planning and an on-treatment electronic portal image

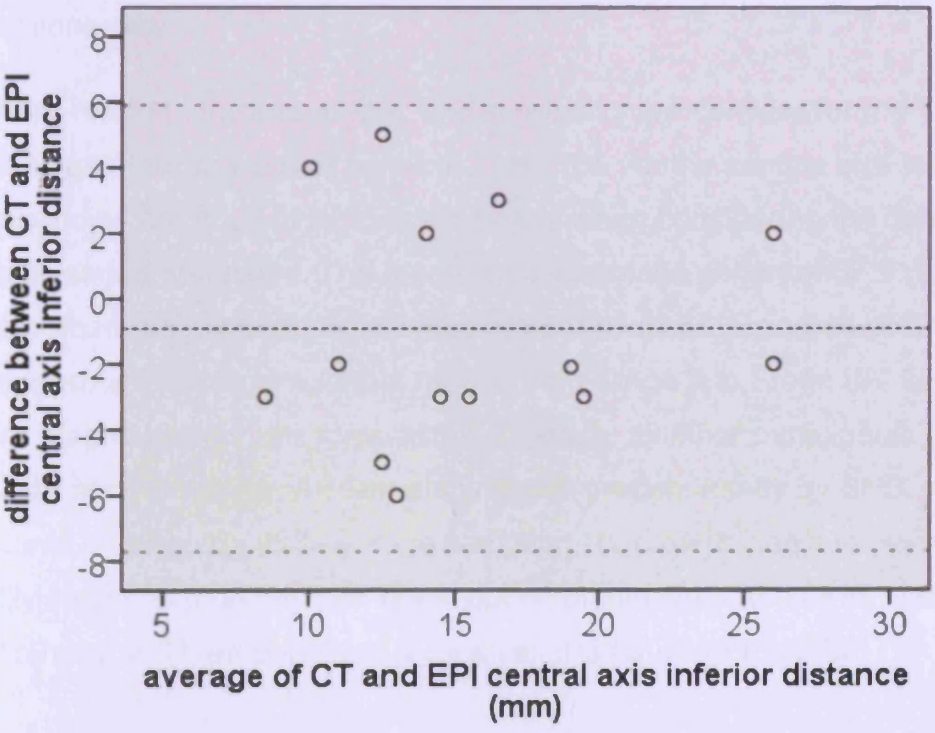


Figure 4.14 Bland-Altman plot comparing the central-axis inferior distance (mm) as measured during CT planning and an on-treatment electronic portal image

CHAPTER FIVE **Results**

Sample description

A sample of 100 women was recruited between 15 November 2007 and 16 October 2008. Approximately 50% were recruited from each of the two referring clinicians. During the recruitment period, 130 women were approached to participate in the study. Fifteen women were precluded from participation on the basis of a full medical history. The most common reason for exclusion at this stage was a history of rheumatoid arthritis, followed by a significant history or current episode of depression. Fifteen further eligible women declined to participate. Eight did not wish to undergo blood tests, four declared a more generalised resistance to thinking about 'extra things', with the remaining three simply declining to participate without volunteering a reason. The 12 recorded non-entrants and study participants reported mean (SD) pre-treatment FACIT-F scores of 40.5 (5.9) and 41.0 (9.8), and mean (SD) ages of 57.1 (7.4) and 57.9 (8.8), respectively. No details were available for the further three patients who declined both to enter the study and complete the non-entry FACIT-F questionnaire.

Patient-related, disease-related and surgical characteristics for the 100 study participants are presented below in Table 5.1. As the sample size was 100, frequencies are equivalent to percentages when considering the cohort as one entity, unless stated otherwise. The mean (SD) age of the cohort of 57.9 (8.8) was marginally higher than the national UK average of 56.9 (Cancer Research UK 2009). The TNM stage-groupings of participants ranged from Stage 0 to Stage IIA. Two participants were diagnosed with micrometastatic disease; all other participants were classified as axillary node-negative. Axillary staging was predominantly by SNB, with 10% of patients undergoing axillary node sampling. Two participants received an additional 10Gy in five fraction electron boost upon completion of the three weeks of photon radiotherapy. Three participants received irradiation of the SCF.

Characteristics	Sample (n = 100)
Patient-related	
Age (years)	57.9 (8.8)
BMI (Kg/m^2)	28.2 (4.7)
Menopausal status	
Post-menopausal	73
Peri-menopausal	16
Pre-menopausal	11
HRT history	
Never	70
Previous	30
Travel mode for radiotherapy	
Driven	62
Self drive	22
Other	16
Travel time (mins) [a]	35 (29)
Smoking history	
Never	50
Past	32
Current	18
Smoking pack- years [a]	0.5 (14.7)
Disease-related	
Histological diagnosis	
Ductal carcinoma in-situ	13
Invasive ductal carcinoma	61
Invasive lobular carcinoma	12
Other	14
Histopathological grade	
Grade 1	31
Grade 2	51
Grade 3	18
TNM stage	
0	13
I	70
IIA	17
Tumour size (mm) [a]	15 (10.3)
Surgical characteristics	
Laterality	
Right	52
Left	48
Surgical procedure	
WLE	98
Mastectomy	2
Time from surgery to radiotherapy (days)	61.2 (15.1)

Table 5.1 Characteristics of the n = 100 study sample of breast radiotherapy patients
Normally distributed continuous variables are means (standard deviation)
[a] Non-normally distributed continuous variables are medians (inter-quartile range)
Categorical variables are numbers (and percentages) of patients.
(BMI = body mass index; HRT = hormone replacement therapy; WLE = wide local excision.)

5.1 Fatigue overview

As the raw FACIT-F (fatigue) data was not normally distributed, median (IQR) data is presented. To maintain consistency with the median data, non-parametric statistical tests were used throughout section 5.1. Significance values were set at $p = 0.05$, and the sample size was $n = 100$ unless otherwise stated. Effect sizes were interpreted as being small ($d \cong 0.2$), medium ($d \cong 0.5$) and large ($d \cong 0.8$), as suggested by Cohen (1988, p 22).

5.1.1 Whole cohort response

The median FACIT-F fatigue scores for the cohort (Figure 5.1) decreased from 44 at baseline, to 41.5 at week 2, reaching a peak of 37 at week 3, with a subsequent improvement to 42 at the 4 weeks post follow-up. The proportion of the cohort falling into the fatigued category at each time-point, (threshold ≤ 34 scale-points), is also detailed to highlight temporal changes in the prevalence of fatigue.

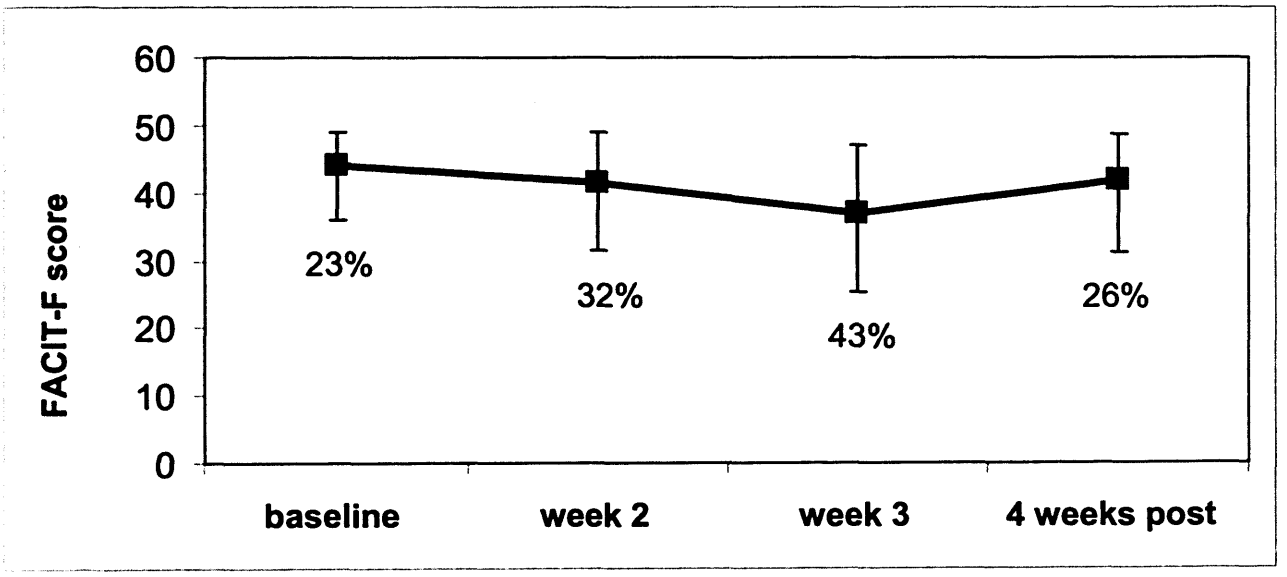


Figure 5.1 Median longitudinal Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F) score, for the n = 100 sample of breast radiotherapy patients. (Error bars = inter-quartile range; percentages = the proportion of the cohort with FACIT-F score ≤ 34.)

Longitudinal changes within the cohort were evaluated using the Friedman Test. The test results indicated that there was a statistically significant difference in FACIT-F

score across the four time-points, χ^2 (3,100) = 27.17, $p < 0.001$. To determine which time-points were statistically significant, post-hoc testing was conducted using the Wilcoxon Signed Ranks Tests (using a Bonferonni adjusted alpha value to control for Type 1 errors). Comparisons were made between scores at baseline and week 3, and week 3 and 4 weeks post. To account for multiple comparisons, the alpha level was revised downwards to 0.05/2 = 0.025. The changes between baseline and week 3, and week 3 and 4 weeks post were both statistically significant, z = -4.65, $p < 0.001$, effect size d = 0.33 (small to medium) and z = -3.64, p = 0.001, effect size d = 0.27, respectively.

Cochran's Q Test was used to analyse the differences in fatigue point prevalence. The test results indicated the statistically significant changes over time in the proportion of the cohort that recorded a FACIT-F score that was classified as fatigued, Q (3,100) = 18.97, $p < 0.001$.

Whilst a group trend is evident in Figure 5.1, for participants to return to near pre-treatment fatigue levels after treatment, 30% of participants showed no improvement in fatigue score from week 3 to the 4 weeks post follow-up. Of these subjects, 10 recorded deterioration in their FACIT-F score of more than 4 points. As evidence exists for associations between chronic RRF and elevated IL-6sR concentrations (Collado-Hidalgo et al. 2006), an exploratory analysis, using Mann–Whitney U Tests, was performed to check whether these 10 atypical cases exhibited an aberrant IL-6sR profile. The mean IL-6sR concentrations of the 10 cases were not significantly different from the residual cohort at week 3 (n = 100, p = 0.6), or at 4 weeks post (n = 88, p = 0.9). The 10 cases will be further discussed hereafter in section 6.1.

5.1.2 Grouped subject-specific response

Subject-specific responses were examined to divide participants into fatigued and non-fatigued groups, based on an a priori cut-off point. If the average of participant's FACIT-F scores at weeks 2 and 3 was ≤ 34, that subject was categorised as fatigued. In this way, 38% of participants were categorised as fatigued, with the remaining 62%

classified as non-fatigued. The course of median fatigue for the two groups is shown below in Figure 5.2.

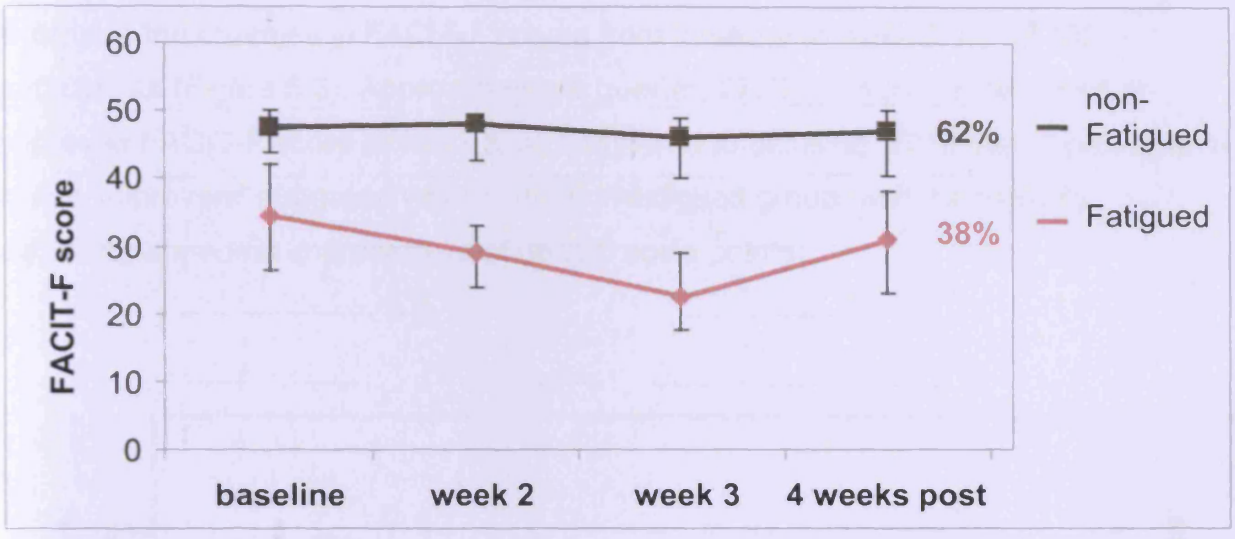


Figure 5.2 Median longitudinal Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F), for fatigued and non-fatigued groups of breast radiotherapy patients. (Error bars = inter-quartile range; percentages = the proportion of the cohort classified in each group.)

The discrete nature and relative stability of the two groups was indicated by the results of Mann–Whitney U Tests, which revealed significantly lower median FACIT-F score in the fatigued group compared to the non-fatigued group at all time-points; all results $p < 0.001$ and associated large effect sizes of ≥ 0.7. Furthermore, the Friedman Test revealed statistically non-significant differences between longitudinal FACIT-F scores of the non-fatigued group, $\chi^2 (3, 62) = 7.7$, $p = 0.06$. The same test revealed a statistically significant difference in the longitudinal FACIT-F scores for the fatigued group, $\chi^2 (3, 38) = 36.0$, $p < 0.0005$. For the fatigued group only, post-hoc testing was conducted using the Wilcoxon Signed Ranks Tests. This revealed statistically significant changes between all pairs of consecutive time-points. For baseline to week 3, $z = -4.6$, $p < 0.0001$, effect size $r = 0.5$; for week 3 to 4 weeks post, $z = -3.9$, $p < 0.0001$, effect size $r = 0.5$.

5.1.3 Subject-specific changes in fatigue from baseline to week three

The previous grouped analysis obscures the fact that, for a minority of participants, reported fatigue actually lessened during treatment, as compared to baseline level. To distinguish this signal from the underlying noise, a waterfall plot was graphed that illustrates the changes in FACIT-F scores from baseline to week 3, for all 100 participants (Figure 5.3). Approximately a quarter, 27(%), of subjects recorded an improved FACIT-F score at week 3, as compared to baseline. 22 of the 27 participants in this 'improvers' subgroup were in the non-fatigued group, with the majority exhibiting a modest improvement of up to 5 scale points.

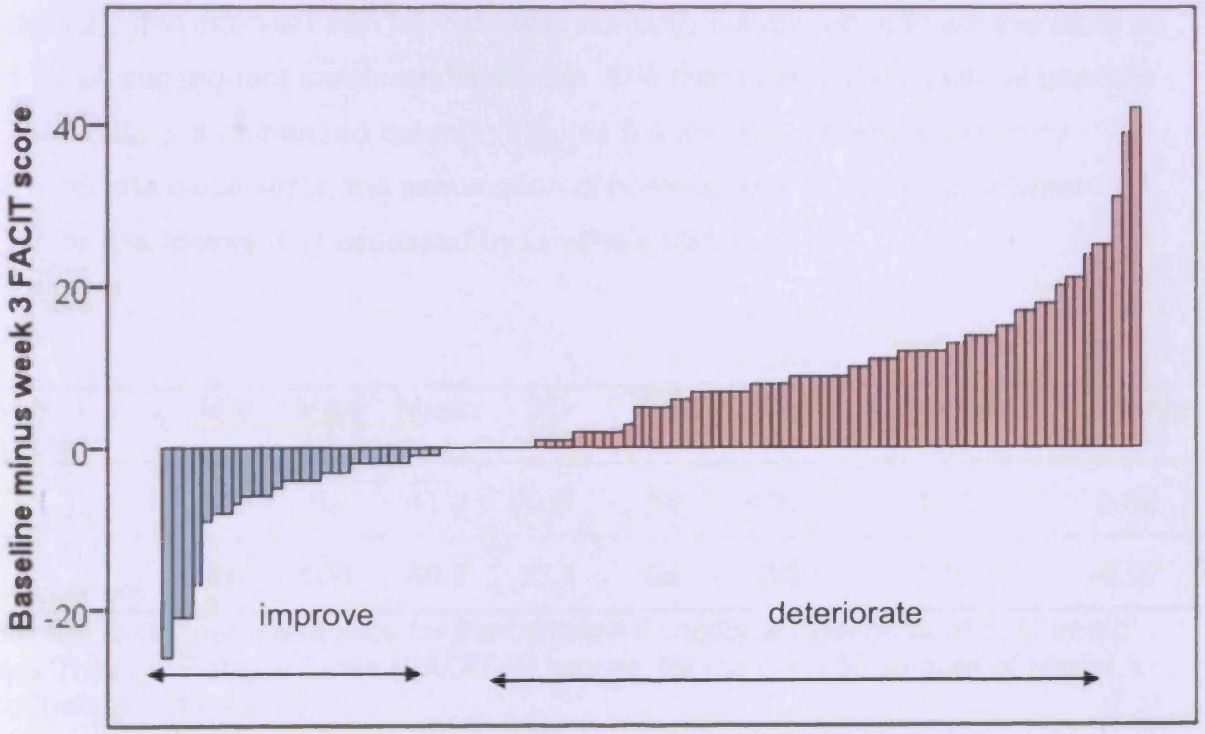


Figure 5.3 Waterfall plot of change in Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F) score from baseline to week 3 for the n = 100 cohort of breast radiotherapy patients (negative scores indicate an improvement in fatigue)

5.2 Baseline variables

Prologue to statistical analysis

Prior to conducting substantive analyses of baseline variables, distribution histograms, Q-Q plots, skewness and Kolmogorov–Smirnov statistics were generated for all non-categorical variables to assess the normality of distribution. Significance value for normality was set at $p > 0.05$. Symmetry of distribution was assessed by dividing the skewness statistic by standard error to calculate a z-value. Symmetry was defined by the range $-1.96 < z > 1.96$. Kolmogorov–Smirnov and skewness statistics for baseline variables are included in Appendix 4.

The raw FACIT-F data did not meet the assumptions of normally distributed data (Table 5.2). The interval FACIT-F data was normally distributed, and will therefore be used for all subsequent parametric analyses. The distribution of the interval baseline FACIT-F data is summarised below in Figures 5.4 and 5.5. Where required by parametric statistical tests, the assumption of homogeneity of variance between groups or time-points was assessed by Levene's test.

Baseline variable	Min	Max	Mean	SD	K-S	Sig.	skewness	kurtosis
FACIT-F raw score	12	52	41.0	9.8	.16	<.001	-1.15	0.62
FACIT-F interval score	40	100	69.7	13.1	.06	0.2	0.10	-0.07

Table 5.2 Distribution statistics for the baseline Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F) scores, for the n = 100 sample of breast radiotherapy patients

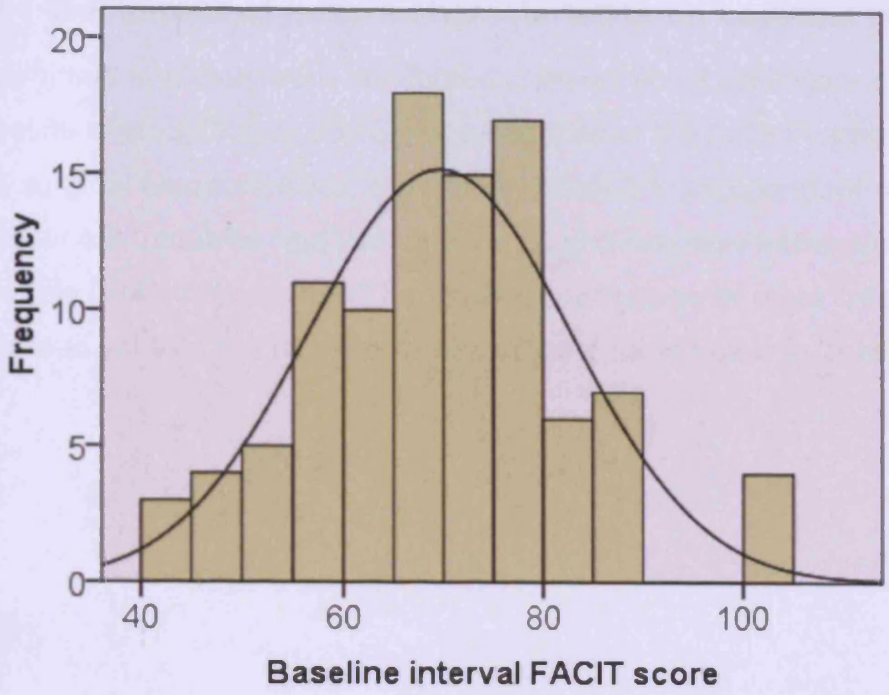


Figure 5.4 Histogram of interval (logit transformed) baseline Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F) score for the n = 100 sample of breast radiotherapy patients

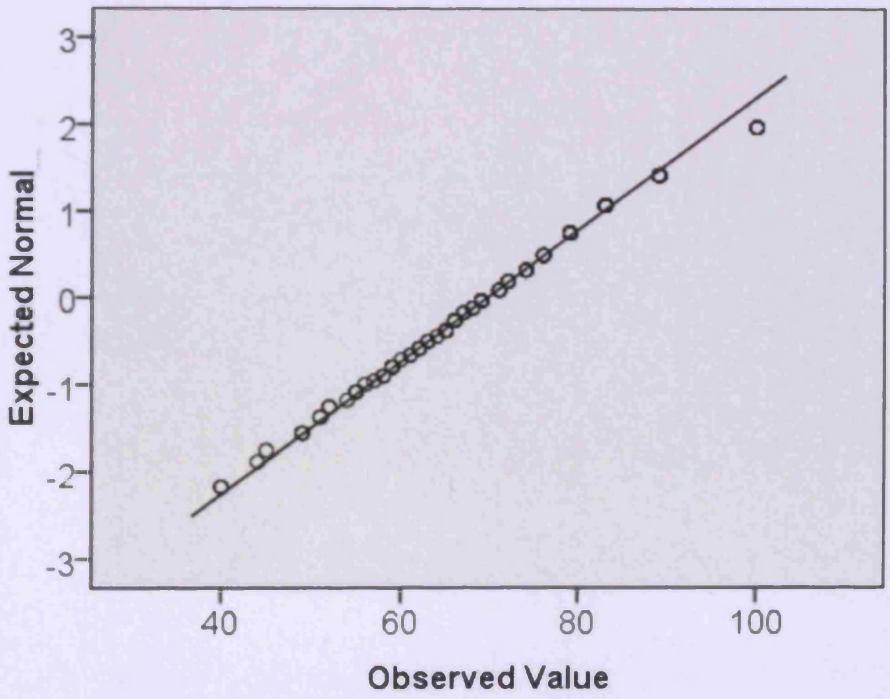


Figure 5.5 Normal Q-Q plot of interval (logit transformed) baseline Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F) score, for the n = 100 sample of breast radiotherapy patients

5.2.1 The impact of patient characteristics on baseline fatigue

Preliminary analyses were conducted to determine if significant differences existed in baseline interval fatigue scores for categories of the patient-related, disease-related and surgical characteristics, reported in Table 5.1. Independent-samples t-tests were used where variables had two categories, and one-way between-groups analysis of variance (ANOVA) was used for variables with three or more categories. Significance level was set to $p = 0.05$. The results are tabulated below in Table 5.3.

Baseline characteristic	Mean fatigue score (SD)	Test statistic	Sig.
Patient-related			
Age (years)		F = 3.0	p = 0.05
≤ 54	68.0 (12.8)		
55–61	74.1 (12.4)		
62+	66.8 (13.4)		
Menopausal status		F = 0.72	p = 0.5
Post-menopausal	65.2 (13.3)		
Peri-menopausal	70.5 (10.0)		
Pre-menopausal	70.16 (13.3)		
HRT history		t = 0.05	p = 0.9
Never	69.7 (12.6)		
Previous	69.6 (14.4)		
Smoking history		F = 0.07	p = 0.9
Never	69.6 (13.0)		
Past	69.2 (12.7)		
Current	70.7 (14.9)		
Disease-related			
Histological diagnosis		F = 1.33	p = 0.3
Ductal carcinoma in-situ	66.7 (10.9)		
Ductal carcinoma	71.1 (14.1)		
Lobular carcinoma	72.0 (11.7)		
Other	64.4 (10.9)		
Tumour size (mm)		F = 1.37	p = 0.3
≤ 10	66.5 (13.8)		
11–20	69.2 (13.0)		
21+	73.4 (12.4)		
Histopathological grade		F = 0.30	p = 0.7
Grade 1	68.9 (13.1)		
Grade 2	70.7 (12.6)		
Grade 3	68.1 (14.5)		
TNM stage		F = 1.74	p = 0.2
0	64.0 (11.9)		
I	69.9 (13.2)		
IIA	72.7 (13.0)		
Surgical-characteristics			
Laterality		t = 0.04	p = 0.9
Right	69.6 (13.1)		
Left	69.7 (13.2)		
Time from surgery to RT (days)		F = 0.17	p = 0.8
≤ 55	69.1 (14.1)		
56–67	70.7 (12.9)		
68+	69.0 (12.5)		

Table 5.3 Impact of categories of pre-treatment characteristics on mean interval baseline Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F) scores, for the n = 100 sample of breast radiotherapy patients. (HRT = hormone replacement therapy; RT = radiotherapy.)

The only pre-treatment characteristic exhibiting (borderline) statistical significance was age, $F(3, 96) = 3.0$, $p = 0.05$. Tukey's HSD post-hoc test indicated that the middle age group (55 to 61) was significantly different from the other two groups. The older and younger age groups were not significantly different from each other. An approximate effect size for the significant group difference was evaluated using the partial eta squared (η^2) statistic – in accordance with Cohen's (1988) convention of small, $\eta^2 \cong 0.01$, medium $\eta^2 \cong 0.06$ and large $\eta^2 \cong 0.14$ – which reflects the proportion of variance of an outcome explained by levels of an IV (Tabachnick & Fidell 2007, p 55). The effect size for age was moderate, being $\eta^2 = 0.06$.

5.2.2 The impact of BMI (and baseline HADS score) on baseline fatigue

To clarify the impact of BMI on baseline fatigue, a two-way between-groups ANOVA was conducted. The DV was the baseline interval FACIT-F score. The first IV was BMI, collapsed into low (< 25), medium (25–29.99) and high (≥ 30) categories. These sub-divisions were based on 33.33% tertiles, rounded-off so as to approximate to the WHO classifications of normal, overweight and obese, respectively (WHO 2000). Cumulative baseline HADS score was incorporated into the analysis as a second IV, and to identify any interaction effect between the HADS and BMI categories. The HADS cumulative score was split into thirds again based on 33.33% tertiles, of 0–5, 6 –10 and 11–21.

A non-significant Levene's test of homogeneity, $p = 0.2$, indicated that the assumption of equality of variances was met. The interaction effect between BMI and HADS groups was not statistically significant, $F(4, 91) = 0.14$, $p = 1.0$. The main effect for BMI, $F(2, 91) = 1.58$, $p = 0.2$, was also not statistically significant. The main effect for HADS group was statistically significant, $F(2, 91) = 24.69$, $p < 0.001$, with an associated (very) large effect size ($\eta^2 = 0.4$). Post-hoc comparisons, using the Tukey HSD test, indicated that the mean (SD) baseline FACIT-F scores of the low, M = 77.48 (10.31), medium, M = 70.33 (11.40) and high, M = 59.67 (10.90) HADS groups were all significantly different. Figure 5.6 graphically illustrates the relationship between variables, indicating that the participants with higher baseline HADS scores were more fatigued at all levels of BMI.

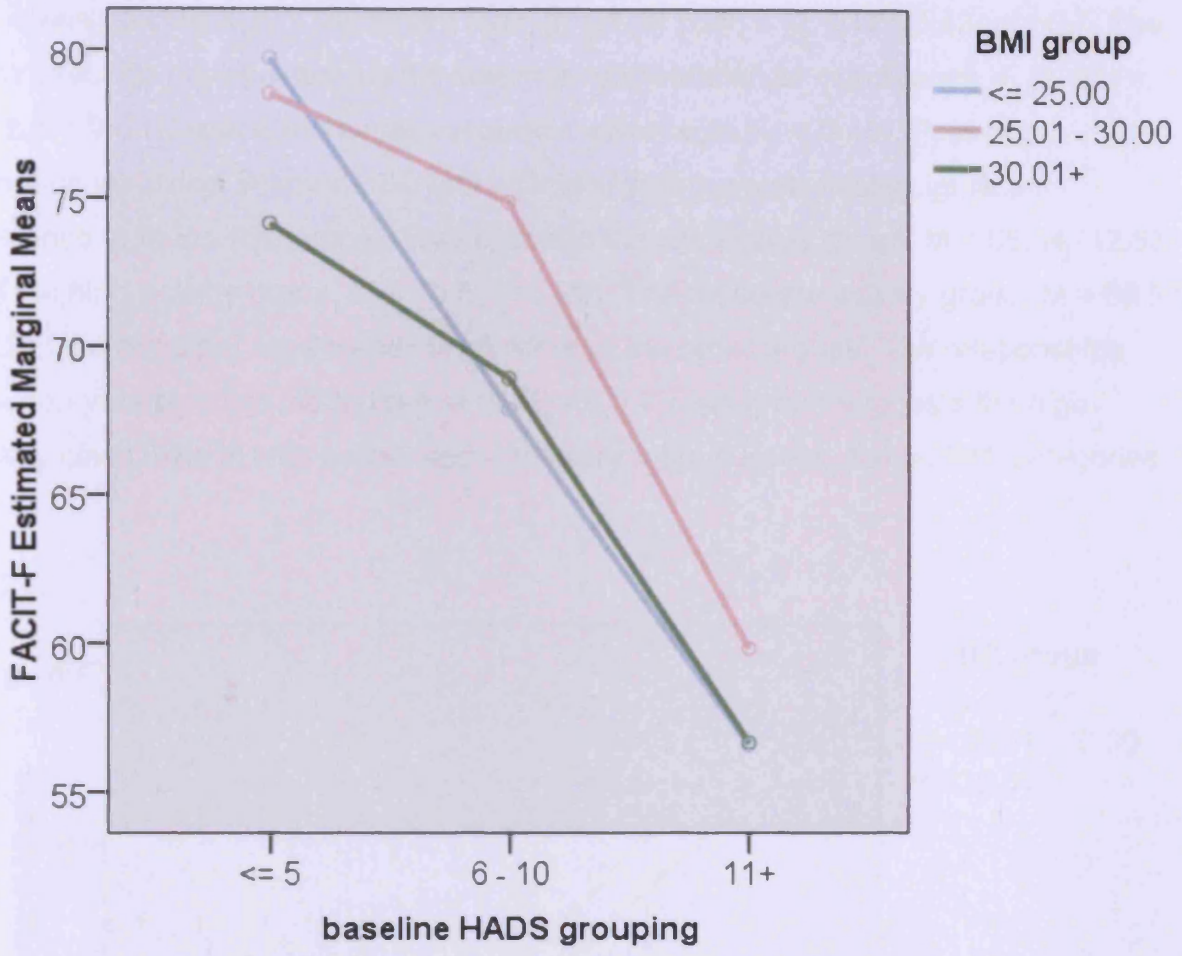


Figure 5.6 Interaction plots of interval Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F) baseline score across three HADS groupings and three BMI categories. (HADS = Hospital Anxiety and Depression Scale; BMI = body mass index.)

5.2.3 The impact of BMI (and baseline IPAQ score) on baseline fatigue

It is conceivable that the lack of impact of BMI on baseline fatigue was influenced by an interaction effect with physical activity level. Therefore, a second two-way between-groups ANOVA was conducted to investigate this theoretical effect whilst simultaneously considering physical activity level as a main effect. Physical activity was represented by the baseline IPAQ categories of low, medium and high activity level. The BMI grouping and the DV were the same as in the preceding section 5.2.2.

Levene's test for homogeneity confirmed that the assumption of equality of variances was met, $p = 0.4$. No statistically significant interaction effect was found between

physical activity level grouping and BMI group, F (2, 91) = 0.65, p = 0.6. As before, there was no statistically significant main effect for BMI, F (2, 91) = 0.43, p = 0.7. The main effect for physical activity did however reach statistical significance, F (2, 91) = 5.23, p = 0.007, with a moderate associated effect size ($\eta^2 = 0.10$). Post-hoc comparisons using Tukey's HSD test indicated that the statistically significant difference in mean (SD) scores was between the low activity group, M = 65.04 (12.53) and the high activity group, M = 76.57 (13.26). The moderate activity group, M = 69.57 (12.22) did not differ significantly from either of the other groups. The relationships between variables are plotted below in Figure 5.7. This graph suggests the high activity classification was associated with lower fatigue levels, across BMI categories.

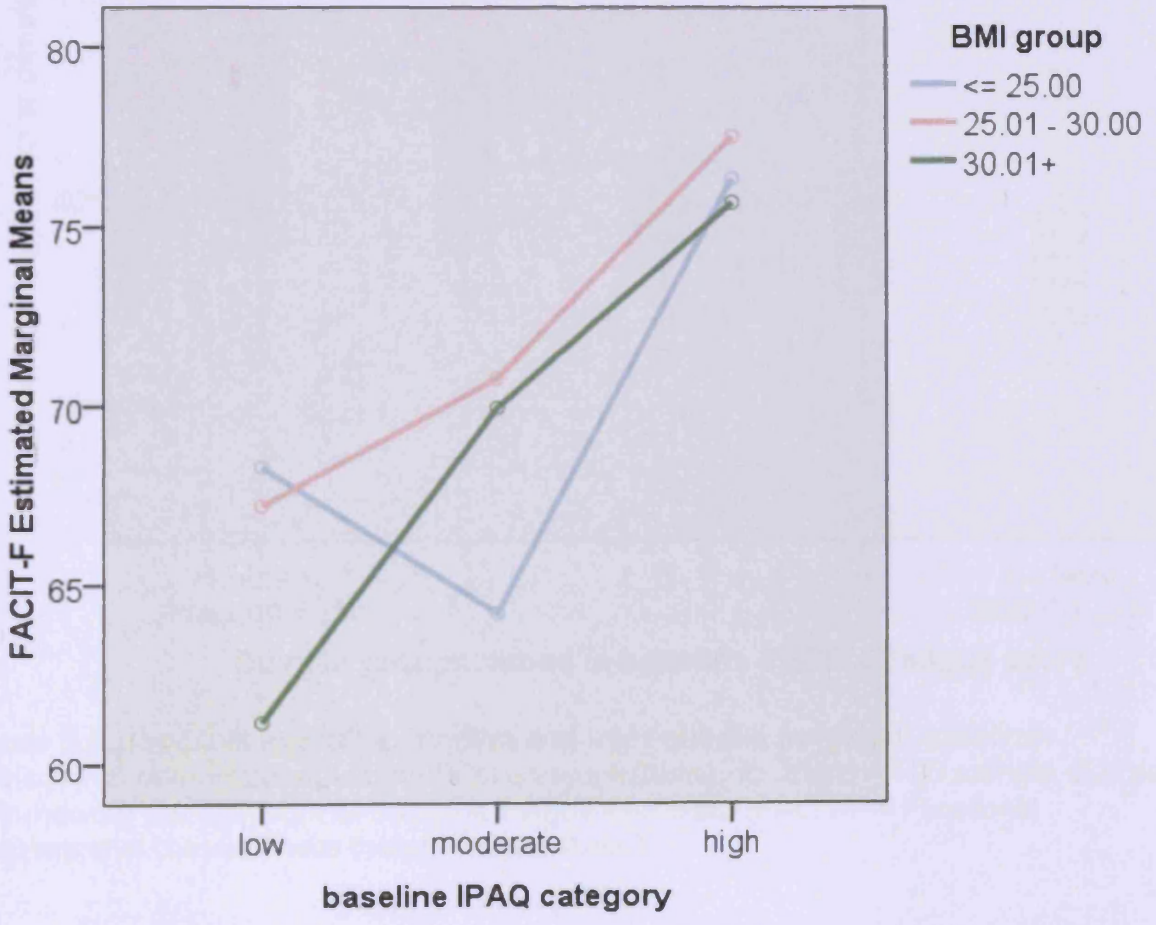


Figure 5.7 Interaction plots of interval Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F) baseline score across three IPAQ groupings and three BMI categories. (IPAQ = International Physical Activity Questionnaire; BMI = body mass index.)

5.2.4 The relationship between IL-6sR concentration and baseline fatigue

The median (IQR) and mean (SD) baseline IL-6sR concentrations were 39.5 ng/dL (31.9–49.2) and 41.2 ng/dL (11.6), respectively. To gain an understanding of any relationships between IL-6sR concentration and fatigue at baseline, the cohort was split into fifths based on baseline FACIT-F fatigue score. The IL-6sR concentrations for the five ordinal groups are illustrated below in Figure 5.8.

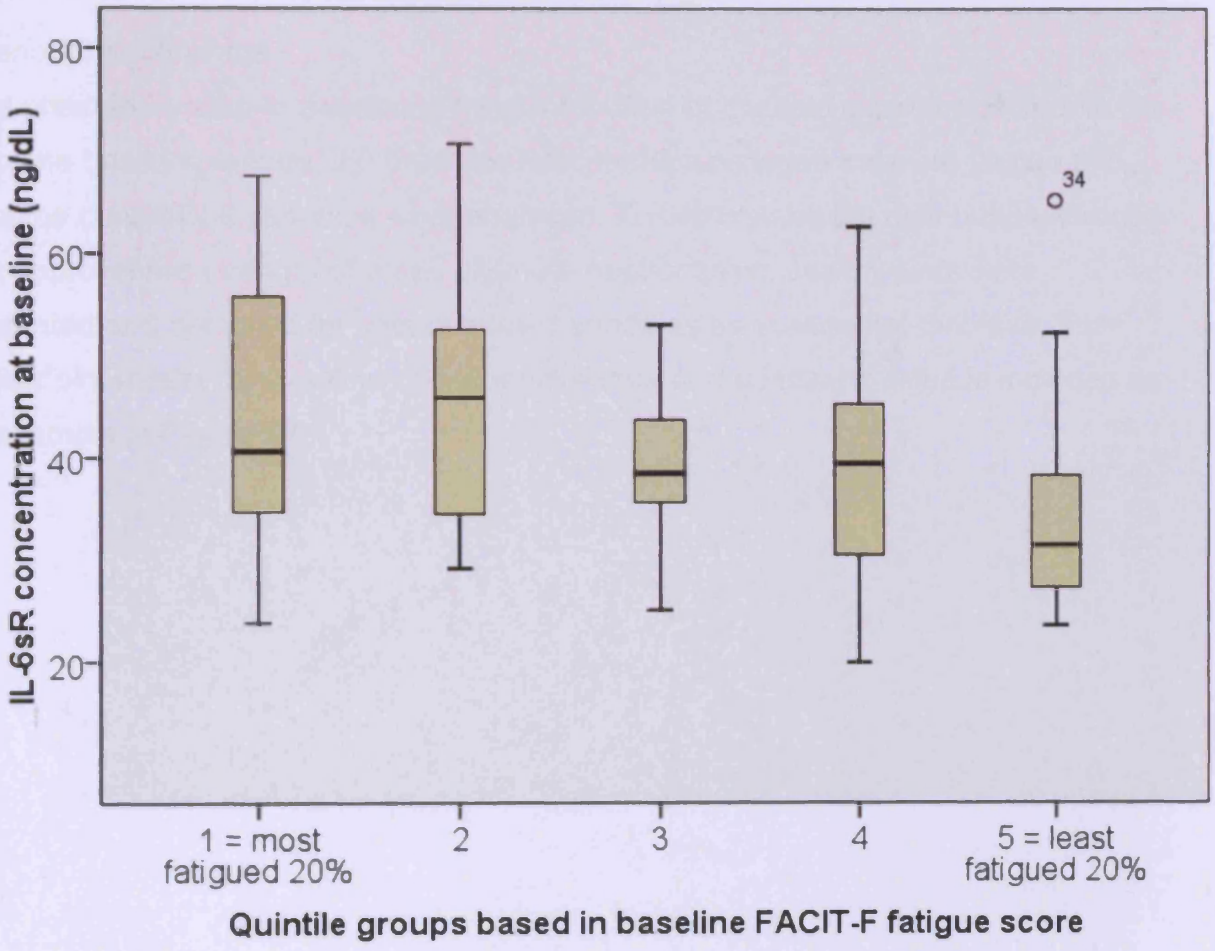


Figure 5.8 Box-plots indicating median and inter-quartile ranges of baseline interleukin 6 soluble receptor (IL-6sR) concentrations, for the n = 100 sample of breast radiotherapy patients split at baseline fatigue quintiles. (FACIT-F = Functional assessment of chronic illness therapy fatigue scale.)

An exploratory between-groups ANOVA was conducted to explore the impact of baseline fatigue level on IL-6sR concentration. Levene's test indicated the homogeneity of variance assumption was fulfilled, $p = 0.28$. Statistically significant

differences in mean IL-6sR concentration between fatigue quintile groups were revealed, $F(4, 95) = 2.8$, $p = 0.03$, effect size $\eta^2 = 0.11$. Post-hoc comparisons using the Tukey HSD test indicated that only the mean scores for both the first and second most fatigued fifths and the least fatigued fifth were significantly different. This suggests the possibility that IL6sR levels could co-vary with extreme levels of fatigue.

5.2.5 Factors that contribute to baseline fatigue

Bivariate relationships

As a preliminary step to assessing the contribution of multiple exposure factors to the outcome baseline fatigue, the bivariate relationships between baseline fatigue and baseline continuous variables were analysed. To understand the distribution, direction and approximate strength of these bivariate relationships, scatter-plots were generated and compiled for sets of related variables as scatter plot matrices. The scatter plot matrix for baseline questionnaire data and baseline fatigue is included as an example in Figure 5.9.

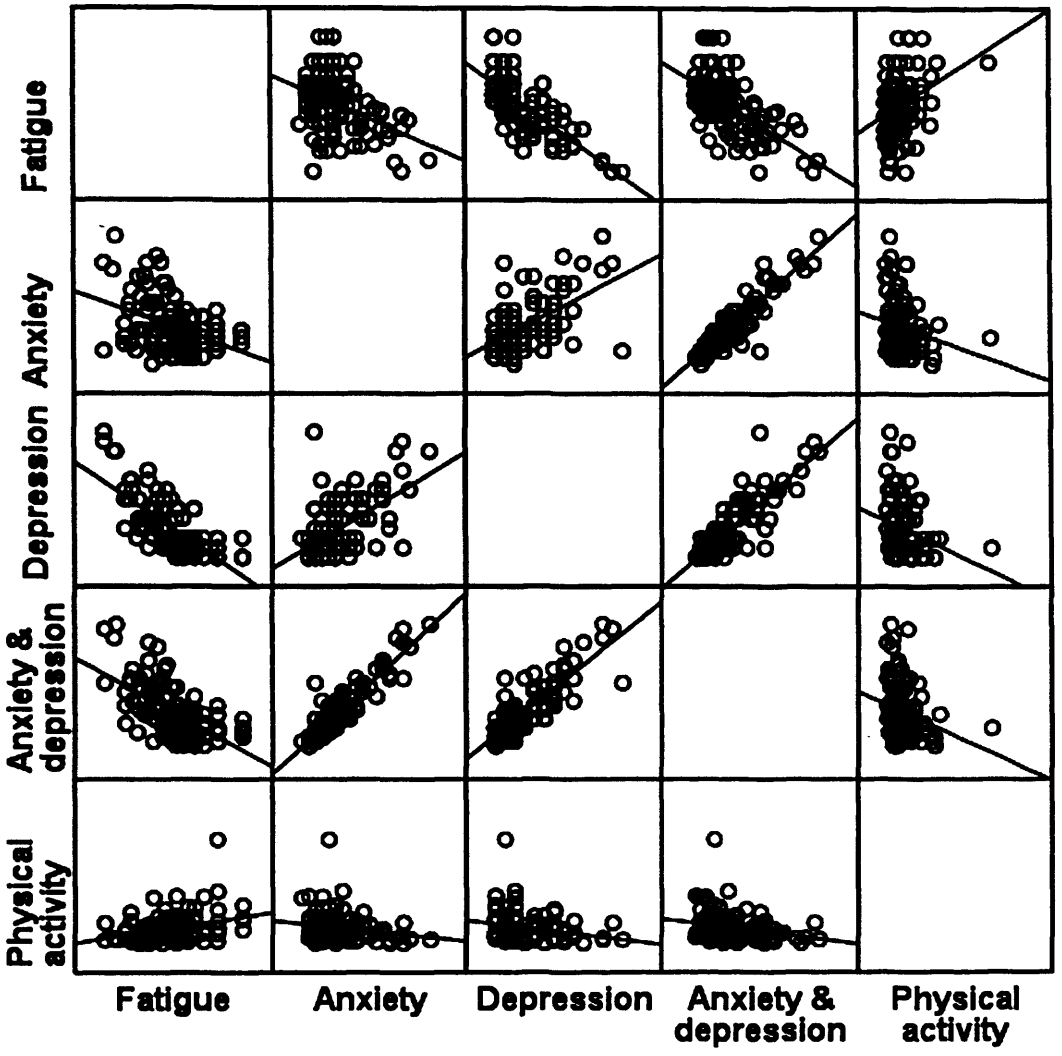


Figure 5.9 Scatter-plot matrix of correlations between baseline questionnaire variables

As a number of variables exhibited non-linear relationships, correlations between variables were investigated using the non-parametric Spearman's Rank Order Correlation. Data was missing for two subjects' full blood counts due to technical problems drawing the sample: otherwise, the sample size was n = 100 throughout. All p-values were two-tailed, and the strength of relationships was interpreted using Cohen's (1988, p. 79) guidelines of small (ρ = .1–.29), medium (ρ = .3–.49) and large (ρ = .5–1.0). The correlations between important baseline variables are presented below as a matrix table (Table 5.4):

Baseline variable	1	2	3	4	5	6	7	8	9	10	11	12	13
1. FACIT-F interval	1.00												
2. age	.045	1.00											
3. BMI	-.096	.254*	1.00										
4. Tumour size	.170	.054	.057	1.00									
5. HADS anxiety	-.353**	-.274**	.015	-.065	1.00								
6. HADS depression	-.710**	-.009	.09	-.096	.504**	1.00							
7. HADS sum	-.597**	-.161	.055	-.095	.886**	.817**	1.00						
8. IPAQ sum	.286**	-.193	-.005	.104	-.174	-.286**	-.284**	1.00					
9. IL-6sR conc.	-.294**	.158	.218*	-.156	.222*	.290**	.284**	.059	1.00				
10. lymphocytes	.051	-.043	.276**	-.092	-.143	-.124	-.168	.058	.051	1.00			
11. neutrophils	-.067	.221*	.218*	.074	.006	-.112	-.034	-.191	.028	.304**	1.00		
12. monocytes	-.159	.096	.330**	.071	-.091	.092	.006	-.115	.116	.467**	.371**	1.00	
13. haemoglobin	.075	-.06	.104	.073	.004	.005	-.014	.078	.304**	.202*	.136	.137	1.00

Table 5.4 Spearman's Rank correlations between baseline fatigue and select baseline variables. ** correlation is significant at the 0.01 level (2-tailed); * correlation is significant at the 0.05 level (2-tailed). (FACIT-F = Functional Assessment of Chronic Illness Therapy Fatigue Scale; BMI = body mass index; HADS = Hospital Anxiety and Depression Scale; IPAQ = International Physical Activity Questionnaire; IL-6sR = interleukin 6 soluble receptor.)

The strongest statistical correlation with baseline FACIT-F score was a strong negative correlation with depression, $\rho = -.71$, $n = 100$, $p < 0.001$. Converting the correlation to a coefficient of determination indicated that, at the bivariate level, depression score explained approximately 50% of the variance in self-reported fatigue before treatment. Compared to depression, the relationship between anxiety and baseline fatigue was approximately half the strength, $\rho = -.35$, $p < 0.001$. Older age was significantly associated with lower anxiety, $\rho = -.27$, $p = 0.004$, but not with depression level, $\rho = -.009$, $p = 0.9$. Higher physical activity correlated with both lower fatigue, $\rho = .29$, $p = 0.005$, and lower levels of depression, $\rho = -.29$, $p = 0.005$.

The major correlation analysis also revealed IL-6sR concentration had statistically significant associations with baseline fatigue, $\rho = -.30$, $p = 0.003$; BMI, $\rho = .22$, $p = 0.03$; anxiety, $\rho = .22$, $p = 0.03$; depression, $\rho = .29$, $p = 0.003$; haemoglobin, $\rho = .30$, $p = 0.002$. No other baseline blood counts exhibited statistically significant associations with IL-6sR concentration.

To determine if the correlation between baseline fatigue and IL-6sR was influenced by associations between the latter and BMI and/or depression, two exploratory Pearson's partial correlation analyses were undertaken. Histograms and scatter plots suggested assumptions of normality, linearity and homoscedasticity were reasonably met. The medium strength negative relationship between baseline fatigue and IL-6sR concentration when controlling for BMI, $r = -.30$, $p = 0.002$, was only slightly diminished from the zero order correlation, $r = -.32$, $p = 0.002$. However, when controlling for depression level the correlation between fatigue and IL-6sR concentration was rendered statistically non-significant, $r = -.07$, $p = 0.5$.

The apparent influence of depression on the relationship between baseline fatigue and IL-6sR concentration instigated two further exploratory analyses. First, a sensitivity analysis was conducted to investigate the change in correlation coefficient between baseline IL-6sR concentration and fatigue when the most depressed patients were excluded from the analysis. The excluded subgroup comprised the fifth of the sample with the highest baseline score on the HADS depression scale, leaving a sample size of $n = 81$ for analysis. The Spearman correlation was slightly reduced, from $\rho = -.30$, $p = 0.003$ to $\rho = -.24$, $p = 0.03$.

In the second exploratory analysis, one-way between-groups ANOVAs were conducted to examine differences in IL-6sR concentration for both anxiety and depression levels. Low, medium and high depression groups were formed by dividing the cohort into ordinal thirds based on baseline depression scores. Levene's test indicated that the assumption of homogeneity of variances for the groups was met. There was a statistically significant difference in IL-6sR concentration for the three groups: $F(2, 97) = 4.5$, $p = 0.01$. The eta squared effect size was $\eta^2 = 0.9$, indicating a moderate effect. Post-hoc comparisons, using the Tukey HSD test, indicated that the mean (SD) concentration for the high group, M = 46.3 ng/mL (11.6), was significantly different from the low group, M = 37.9 ng/mL (11.5), but the moderate group, M = 41.2 ng/mL (9.2) did not differ significantly from the other two groups. An equivalent analysis was conducted for baseline anxiety: no significant difference was found between any groups: $F(2, 97) = 2.1$, $p = 0.1$. This pattern of findings is suggestive of a positive relationship between baseline IL-6sR and depression, but not anxiety.

Multivariable relationships

A standard multiple regression analysis determined the relative contribution of multiple risk factors to baseline fatigue. IVs were chosen for inclusion into the regression model on a hypothesis-driven basis. Additionally, variables exhibiting a bivariate association with baseline fatigue of the order of correlation coefficient ≥ 0.25 were considered for inclusion (Katz 2006, p. 74). IVs were entered simultaneously into the model by a forced-entry selection process, which makes no assumptions regarding the importance of variables to the model. Ordinal or nominal variables were transformed to create multiple dichotomous categorical variables prior to inclusion in the regression model.

Baseline fatigue, as measured by the interval FACIT-F score, was the DV. An initial multiple regression model was computed with age, HADS anxiety, HADS depression, IPAQ sum, IL-6sR concentration, BMI and pathological diagnosis as IVs. There was no missing data. Violations of the assumptions of normality, linearity, homoscedasticity and evidence of outliers were identified by inspection of the scatterplot of the standardised residuals. To reduce these problems a square root transformation was

undertaken on both the depression and IL-6sR variables, and a logarithmic transformation was used on the physical activity variable.

Following the transformations, the residual plots were enhanced and no outliers were identified. The absence of outliers was verified, as the maximum Mahalanobis distances were less than the critical chi-square value of 24.32 (for seven IVs), when using an alpha level of 0.001 as recommended by Tabachnick and Fidell (2007, Table C4). Anxiety was excluded from subsequent model computations as its additive value was found to be negligible above that shared with depression. Similarly, BMI (ß = 0.09), pathological diagnosis (ß = 0.07) and age (ß = 0.07) made virtually no contribution to the regression equation and were therefore excluded from subsequent model iterations. The final model therefore comprised baseline depression, physical activity and IL-6sR concentration.

The results of the final multiple regression equation are summarised below in Table 5.5. Parameters detailed are: the bivariate correlations between the variables; the standardised regression coefficients (ß) indicating the strength of the relationship between an IV and the DV whilst controlling for other factors; the statistical significance of the contribution of each variable to the equation (Sig.); the percentage of the variance in the DV uniquely explained by each variable (% R^2). The shaded, inset cells detail the multiple correlation coefficient (R) and the adjusted coefficient of determination (R^2), the proportion of the variance in the DV that is explained by the model.

Variables	Fatigue (DV)	Depression (sq. root)	Physical activity (log)	IL-6sR conc. (sq. root)	**ß**	**Sig.**	**% R^2 unique to IV**
Depression (square root)	-.714				-.64	<0.001	34.22
Physical activity (log)	.290	-.256			.13	0.08	1.61
IL-6sR conc. (square root)	-.316	.309	.055		-.13	0.1	1.40
Means	69.67	1.45	3.23	6.36			R = .73**
SD	13.13	0.95	0.38	0.90			Adj R^2 = .52

Table 5.5 Standard multiple regression of the dependent variable baseline fatigue, as expressed by the Functional Assessment of Chronic Illness Therapy Fatigue Scale. ** = significant at the 0.01 level. (IL-6sR = Interleukin 6 soluble receptor.)

Statistically, the model was significantly different from zero, F (3, 96) = 35.5, p < 0.00001. The adjusted R^2 = .52, revealing that just over 50% of the variance in baseline fatigue was explained by the variables depression, physical activity level and IL-6sR concentration. When the other two model variables were controlled for, depression was the strongest statistical predictor of fatigue (ß = -.64). In contrast, physical activity and IL-6sR made much smaller and statistically non-significant unique contributions to the model. Calculating semi-partial correlations (squared) parameters, revealed depression uniquely accounted for approximately 34% of the variance in baseline fatigue. Semi-partial correlations represent the contribution of an IV with any shared variance removed.

Multivariable model accuracy

Post-hoc diagnostic analyses of the regression residuals were undertaken to check for significant violations of the assumptions underlying the final multiple regression model, namely: an absence of a very high degree of correlation between IVs, called

multicollinearity; the distribution of the residuals is normal; no individual subjects values exert a disproportional leverage on the model; the variance of the residuals is equal at all levels of the predicted scores (absence of homoscedasticity); the DV varies linearly both with multiple IVs and each individual IV.

Maximum inflation factor (VIF) values confirmed none of the variables displayed multicollinearity. Four cases were found to have a standardised residual (z) beyond the range $-2 < z > 2$. This situation provided assurance that the residuals were normally distributed, as it would be expected that 95% of cases would be within this range for a normal distribution. The maximum Mahalanobis distance value of 10.37, was less than the critical chi-square value of 16.27 for three IVs (Tabachnick & Fidell 2007, Table C4), suggesting an absence of outliers. The maximum Cook's distance of 0.193, suggested no single case had an undue influence on the model. That would be, for example, a case with a very high activity level, and by chance an unusually high fatigue level, leading to a Type 1 error. Further evidence for an absence of undue case influence was reinforced by an analysis of the leverage values. Taken together the above diagnostic statistics gave confidence that the regression model was accurate for the sample, and free from disproportional influences.

The pattern of a standardised residual scatter-plot (Figure 5.10) indicated that the assumptions of linearity and homoscedasticity were met. Additionally, partial regression scatter-plots for each of the three IVs suggested no significant violations of the (above) stated assumptions regarding individual IVs (see Appendix 4).

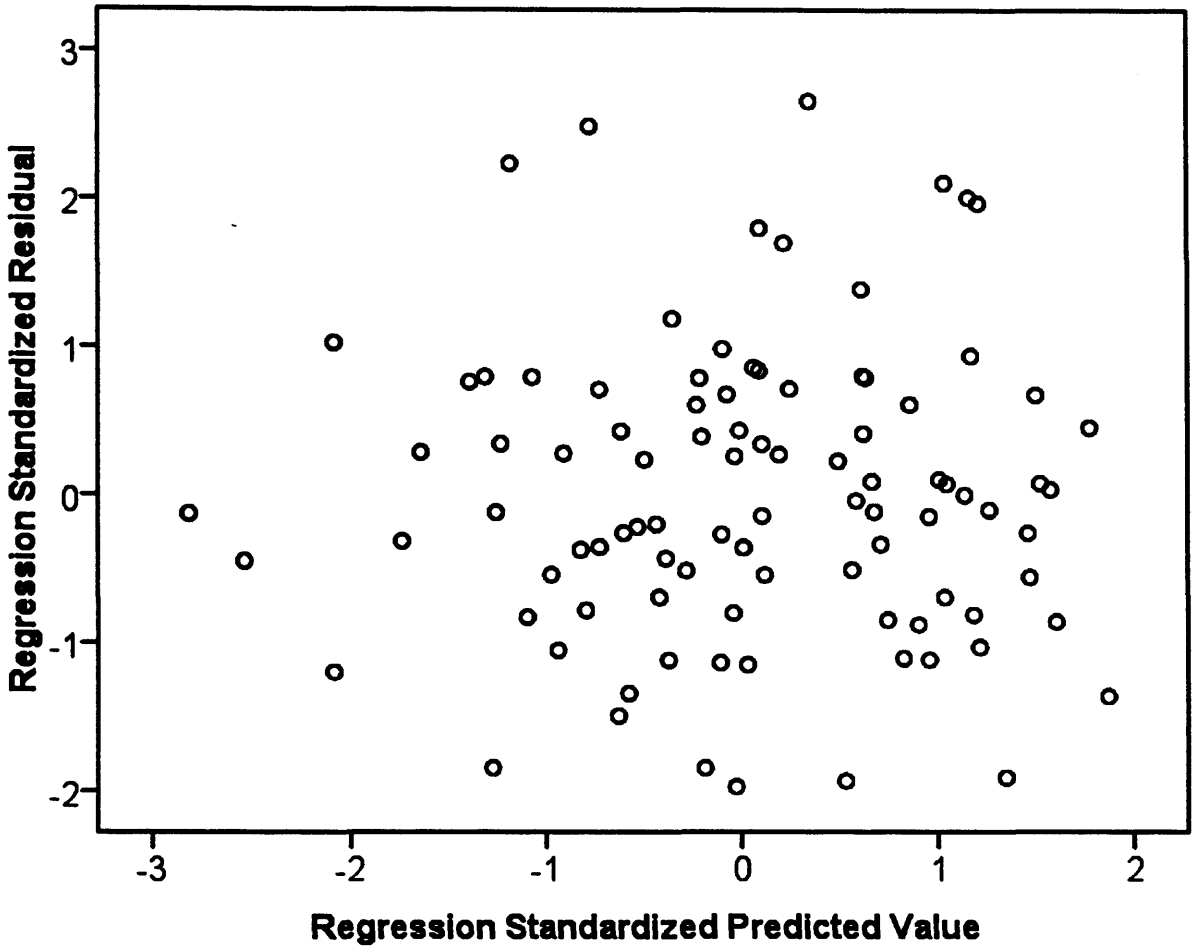


Figure 5.10 Residual scatter-plot of standardised residuals against the predicted residual values for the dependent variable baseline fatigue

A distribution histogram and P-P normal probability plot for the standardised residuals are shown below in Figure 5.11 and 5.12 respectively; indicating the assumptions regarding residual normality were reasonably met.

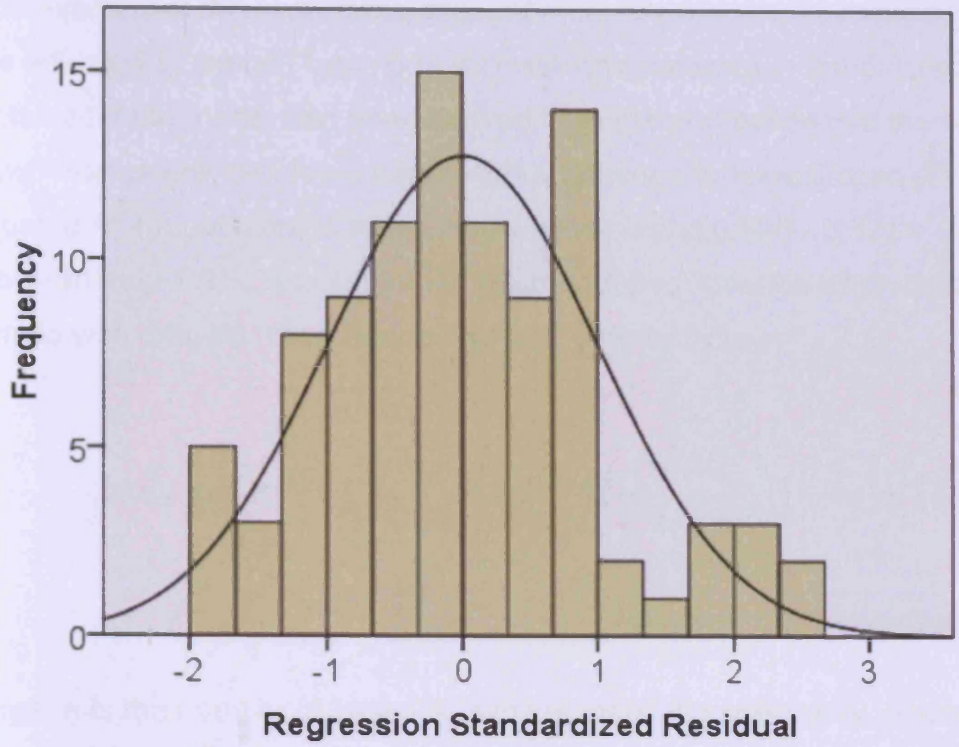


Figure 5.11 Distribution histogram of regression standardised residual for the dependent variable baseline interval fatigue score, for the n = 100 sample of breast radiotherapy patients

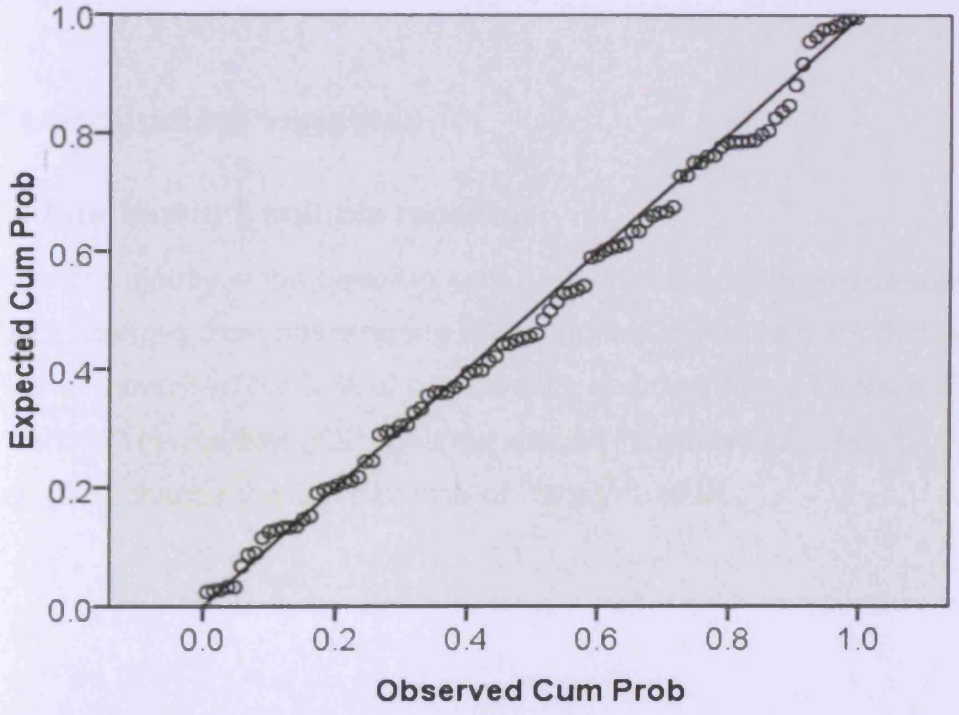


Figure 5.12 Normal P-P plot of regression standardised residual for the dependent variable baseline interval fatigue score, for the n =100 sample of breast radiotherapy patients

Cross-validity of the multivariable model

The adjusted R^2 value (Table 5.5) indicates the variance in the outcome that would be explained if the model had been derived from the population that the sample was drawn from. Here, the decrement in value between the unadjusted R^2 (sample) and adjusted R^2 (population) is reassuringly small, being 0.536 - 0.521 = 0.015, or approximately 1.5%. An estimate of the model performance when using a different sample was derived using Stein's formula, defined below:

$$\text{adjusted } R^2 = 1 - \left[\left(\frac{n-1}{n-k-1}\right)\left(\frac{n-2}{n-k-2}\right)\left(\frac{n+1}{n}\right)\right](1 - R^2)$$

.....**Equation 5.1** (Stevens 2002, p. 118)

Where n is the number of cases, k is the number of explanatory variables and R^2 is the unadjusted R^2 value from the model summary. The formula rendered a Stein's adjusted R^2 of 0.501. The decrement in the variance explained was 0.521 - 0.501 = .2, or 2%, suggesting excellent model cross-validity.

5.3 Longitudinal variables

5.3.1 Interleukin 6 soluble receptor

The heterogeneity in the baseline sera IL-6sR level and the wide variation in individual subject changes from baseline are both manifest in Figure 5.13. In this period, the IL-6sR level increased for 68% of participants, and decreased for the remaining 32% of the cohort. The median (IQR) change was an increase of 2.5 ng/dL (-2.4–6.9), the mean (SD) change was an increase of 2.6 ng/dL (6.9).

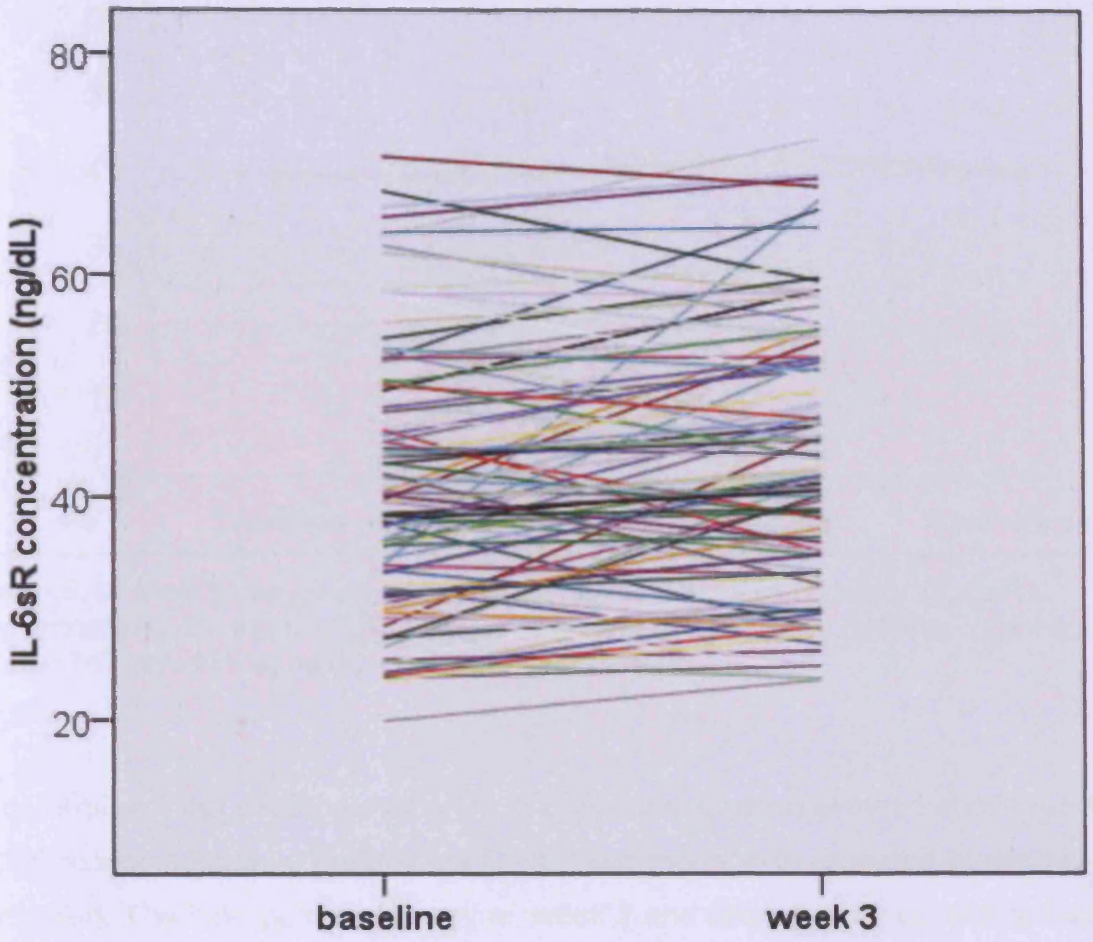


Figure 5.13 Individual subject changes in sera interleukin-6 soluble receptor (IL-6sR) concentration between baseline and week 3, for the n = 100 cohort of breast radiotherapy patients. (ng/dL = nanogram per decilitre.)

To distinguish the signal of the change from baseline from the noise generated by the underlying heterogeneity, the median cohort concentrations of IL-6sR over the four time-points are presented below in Figure 5.14.

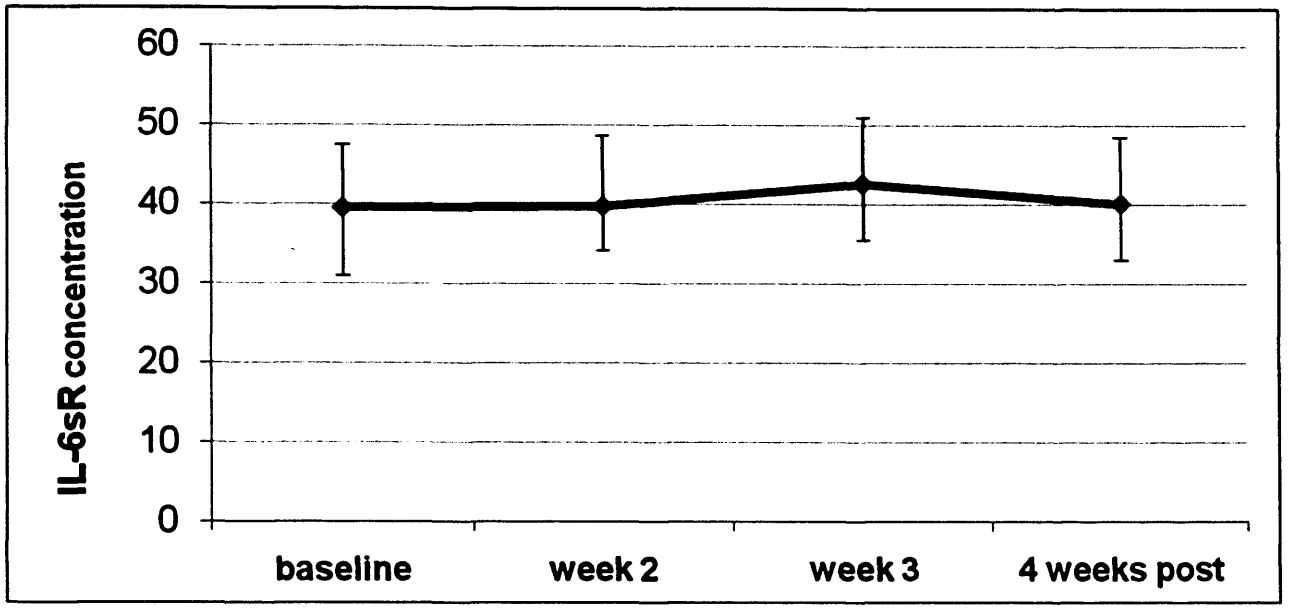


Figure 5.14 Median longitudinal sera interleukin-6 soluble receptor (IL-6sR) concentrations, for the n = 100 sample of breast radiotherapy patients. (Error bars = 25th and 75th percentiles; ng/dL = nanogram per decilitre.)

To determine if the partial elevation in IL-6sR concentration evinced above reached statistical significance, a preliminary linear fixed model with repeated-measures was conducted. The time-points of baseline, week 2 and week 3 were considered as a time factor and the IL-6sR concentrations at the time-points were the DVs. As 12 subjects had missing data for the 4 weeks post measurements, this time-point was excluded from the analysis. Although the IL-6sR data at week 2 indicated a modest degree of departure from a normal distribution, the variable was not transformed as a repeated-measures ANOVA is considered 'relatively tolerant' of violations of this assumption (Field 2005, p. 324, Pallant 2007, p. 204).

The mean (SD) IL-6sR concentration was 41.21 ng/dL (11.6) at baseline, increasing to 41.64 ng/dL (10.7) at week 2 and 43.84 ng/dL (11.8) at week 3. Although not included in the repeated-measures analysis, for reference purposes the mean IL-6sR concentration at 4 weeks post was 40.32 ng/dL (11.4). Mauchly's Test of Sphericity was met, $W = 0.97$, $p = 0.2$. There was a significant effect for time, Wilks' Lambda = .84, $F(2, 98) = 9.2$, $p < 0.0005$, and a large effect size denoted by a partial eta squared, $\eta^2 = .16$. Pairwise comparisons indicated that the differences in IL-6sR concentrations between baseline and week 3 ($p = 0.01$) and week 2 and week 3 ($p = 0.01$) were significant but not baseline to week 2 ($p = 1.0$).

To evaluate more fully if the partial elevation of peripheral IL-6sR displayed in Figure 5.14 is a real dose-effect, a subset of 24 sera samples were re-analysed to determine the concentrations of IL-6 at time-point week 3. The rationale being that when activated, IL-6sR only increases by a small factor – say up to two-fold – whereas IL-6 concentration may increase by many times. To ensure a spread of values the re-analysis subset was purposively selected by dividing the cohort into quarters based on IL-6sR concentrations, and then randomly choosing six samples from each quarter. The relationship between the concentrations of the IL-6 and IL-6sR was explored using a two-tailed Spearman's Rank Order correlation. The variables were strongly positively correlated, $n = 24$, $\rho = .7$, $p = 0.01$.

Relationships between IL-6sR concentration and fatigue

The median (IQR) IL-6sR concentrations for the two fatigue groups are plotted below in Figure 5.15.

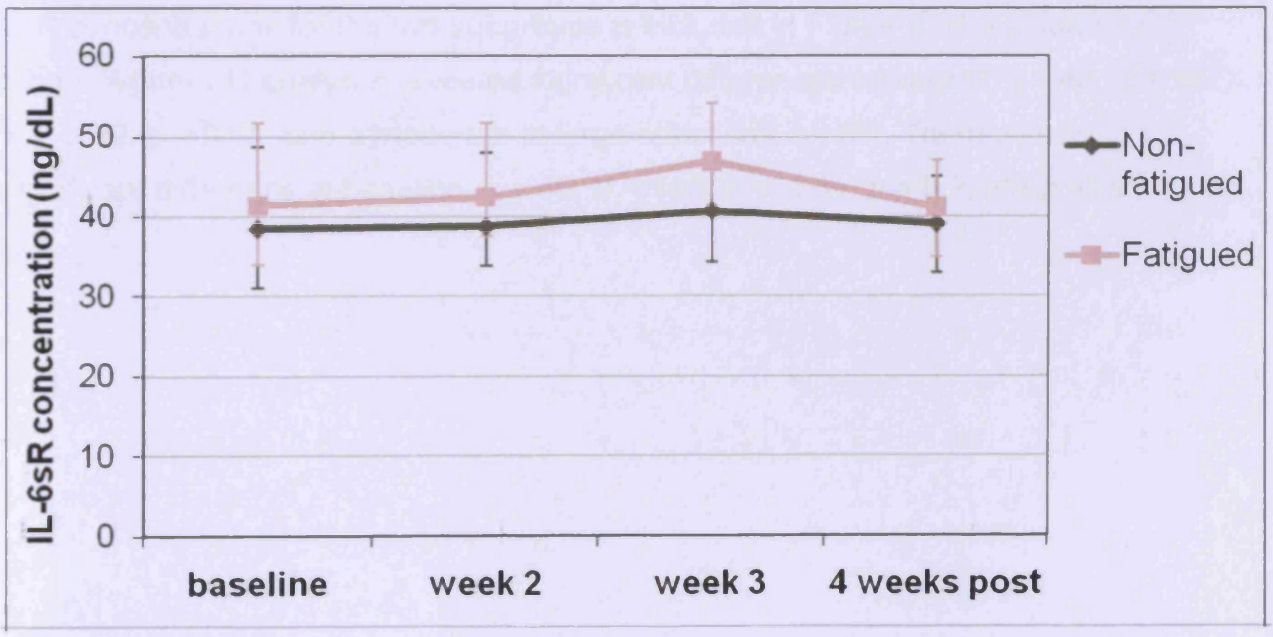


Figure 5.15 Median longitudinal sera interleukin-6 soluble receptor (IL-6sR) concentrations for fatigued and non-fatigued groups of breast radiotherapy patients. (error bars = 25th and 75th percentiles; ng/dL = nanogram per decilitre.)

A series of Mann–Whitney U tests revealed significant differences in the IL-6sR concentrations of the fatigued and non-fatigued groups at weeks 2 and 3, but not pre or post-treatment. At week 2, fatigued participants had higher IL-6sR concentrations, n = 38, Md = 42.39 ng/dL, than non-fatigued, n = 62, Md = 39.79 ng/dL, U = 854, z = -2.30, p = 0.02. At week 3, the fatigued group again had higher IL-6sR concentrations, n = 38, Md = 46.86 ng/dL than the non-fatigued group, n = 62, Md = 40.61 ng/dL, U = 837, z = -2.42, p = 0.01. The following equation yielded moderate effect sizes of approximately 0.3:

$$r = z / \sqrt{n} \quad \text{..... Equation 5.2 (Pallant 2007, p. 223)}$$

where n = total number of cases

To clarify the extent that more fatigued participants exhibited distinct longitudinal IL-6sR profiles from less fatigued participants, the cohort was divided into fifths based on quintile week 3 fatigue scores. Participants with intermediate fatigue scores were excluded from the analysis, rendering a subgroup sample of n = 40 comprised of the most and least fatigued participants. A graphical comparison of the median (IQR) IL-6sR concentrations for the two subgroups is included in Figure 5.16. Exploratory Mann–Whitney U analyses revealed significant differences at week 3, n = 40, U = 107, z = -2.32, p = 0.01, and a moderate to large effect size r = 0.4. There was no significant difference at baseline, n = 40, U = 140, z = -1.41, p = 0.2, effect size r = 0.2.

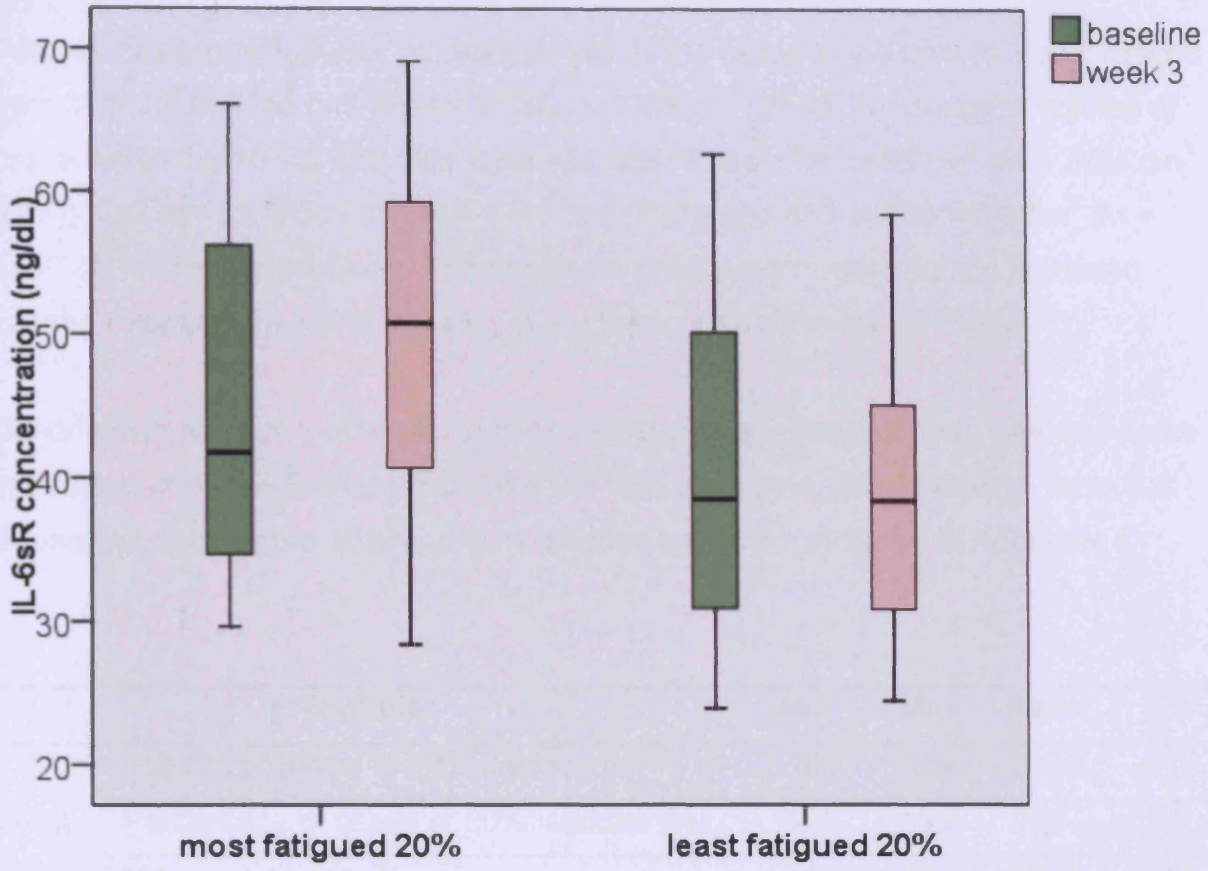


Figure 5.16 Box-plots indicating median and inter-quartile ranges of baseline interleukin-6 soluble receptor (IL-6sR) concentrations for the most and least fatigued fifths, of the n = 100 sample of breast radiotherapy patients. (ng/dL = nanogram per decilitre.)

In light of the results at baseline (section 5.2.4), a partial correlation controlling for depression level was undertaken to further explore the bivariate relationship between fatigue and IL-6sR concentration. In contrast to the baseline data, the zero order Pearson's correlation between IL-6sR and fatigue at week 3 ($r = -.28$, $p = 0.005$) was almost unchanged ($r = -.28$, $p = 0.006$) when controlling for week 3 depression level. Additional partial correlation analyses indicated age, BMI or physical activity levels (data not shown) did not significantly influence associations between IL-6sR and fatigue.

5.3.2 Volumes of irradiated tissue

Participant's breast volume, as represented by the tissue in the 95% isodose, ranged from 382 cm^3 to 4158 cm^3 (mean M (SD) = 1359cm^3 (593)). The range of volume of tissue within the 10, 50 and 90% isodoses was, 792 cm^3 to 5865 cm^3 (M = 2164 cm^3 (848)), 582 cm^3 to 4956 cm^3 (M = 1748 cm^3 (722)) and 458 cm^3 to 4378 cm^3 (M = 1498 cm^3 (633), respectively. The maximum dose point throughout the irradiated volume ranged from 110% to 138% of the prescribed dose (M = 113% (4.1)).

Descriptive statistics for the absolute and percentage volume of lung, liver and heart irradiated within the 50% isodose level (PTV_{50}) are summarised below in Table 5.6. Equivalent data for the 10% and 90% isodose levels are included in Appendix 4.

	Variable	Min	Max	Mean	SD
Lung	Volume of tissue in 50% isodose (cm^3)	10	204	100.6	40.2
	Percentage of tissue in 50% isodose (%)	0.6	13.5	7.6	2.5
	Max organ dose (%)	13	121	106.3	12.1
Heart	Volume of tissue in 50% isodose (cm^3)	0	32	4.5	7.3
	Percentage of tissue in 50% isodose (%)	0	4.7	0.7	1.1
	Max organ dose (%)	2.5	110.7	46.7	46.5
Liver	Volume of tissue in 50% isodose (cm^3)	0	92	11.7	19.5
	Max organ dose (%)	0.8	113.1	49.1	47.3

Table 5.6 Absolute (cm^3) and percentage volumes of individual organs irradiated within the 50% isodose.

Relationships between volumes of irradiated tissue and IL-6sR concentrations

To evaluate the impact of radiotherapy dose-volumetrics on the longitudinal IL-6sR concentrations, a second linear fixed-model with repeated-measures was conducted. The time-points of baseline, week 2 and week 3 were considered as a time factor, the IL-6sR concentrations at the time-points were the DVs and the volume of tissue irradiated to 10% (PTV_{10}), 50% (PTV_{50}) and 90% (PTV_{90}) of the prescribed dose were included as a covariate. There were no missing data.

Mauchly's assumption of sphericity was met, W (2, 98) = 0.97, p = 0.2. The results, summarised below in Table 5.7, indicated that the volume of tissue irradiated had a significant effect on IL-6sR concentration at all three isodose levels, with associated p-values < 0.005. The partial eta values represent moderate effect sizes (Cohen 1988, p 284).

Irradiated volume	Effect	F	Sig.	Effect size (η^2)
PTV_{10}	Time-point	.51	.6	.03
	Time*PTV_{10}	.53	.6	.005
	PTV_{10}	8.73	.004**	.082
PTV_{50}	Time-point	.68	.5	.014
	Time*PTV_{50}	.59	.6	.012
	PTV_{50}	9.15	.003**	.085
PTV_{90}	Time-point	.286	.8	.006
	Time*PTV_{90}	1.31	.3	.026
	PTV_{90}	8.65	.004**	.081

Table 5.7 The effect of irradiated volumes of tissue on IL-6sR concentrations over three time-points, under three different isodose levels. ($PTV_{10,\ 50\ and\ 90}$ = the gross volume of tissue irradiated within the 10%, 50% and 90% isodose, respectively.)

BMI and PTV_{50} were strongly correlated: the Spearman's correlation between the two variables was, ρ = .72, p < 0.0001. It was therefore difficult to discriminate between the relative effects on IL-6sR of BMI and the dose-volume variables during treatment. In an attempt to elucidate these relationships further, box plots were plotted for IL-6sR concentrations across three BMI categories (Figure 5.17). A trend for an increase in median IL-6sR concentration from baseline to week 3, with increasing BMI was evident. An exploratory one-way between-groups ANOVA was conducted to statistically investigate this trend. Between-groups differences were not significant at baseline, F (2, 97) = 1.62, p = 0.2, effect size η^2 = 0.2, nor at week 3, F (2, 97) = 2.2, p = 0.1, effect size η^2 = 0.4 (small to medium).

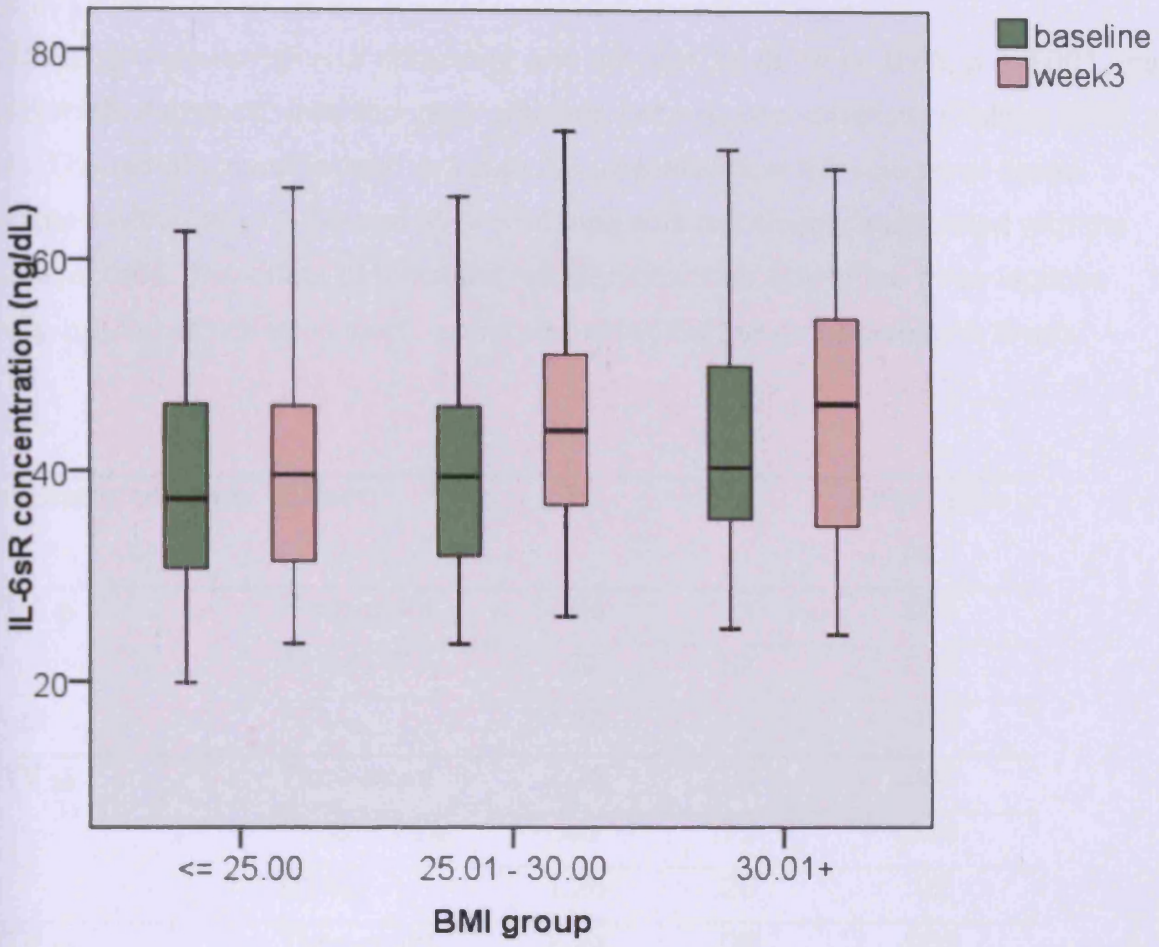


Figure 5.17 Change in interleukin-6 soluble receptor (IL-6sR) concentration from baseline to week 3 across three BMI groups. (BMI = body mass index.)

The degree of association between IL-6sR concentrations and dose-volume data for the individual organs was analysed by Spearman's correlation. The lone statistically significant result was the volume of liver irradiated within the 10% isodose for the right-sided participants, $\rho = .3$, $p = 0.03$.

Relationships between volumes of tissue irradiated and fatigue

To determine the effect of the volumes of tissue irradiated on longitudinal fatigue, a third linear fixed-model with repeated-measures was analysed. Interval FACIT-F scores at baseline, week 2, week 3 and 4 weeks post were the DVs, the four time-points were considered as a time factor and the irradiated volumes ($PTV_{10, 50 \& 90}$) were incorporated as a covariate. There were no missing data.

As Mauchly's assumption of sphericity was not met, W (2, 98) = 0.65, p < 0.001, the multivariate statistics were reported which do not assume sphericity (Pallant 2007, p. 254). The results, summarised in Table 5.8, revealed that the volume of tissue irradiated within the 10, 50 and 90% isodoses was not closely associated with the fatigue scores. The effect of time was not significant for any of the three isodose levels, but the effect sizes were moderate under the three dose-volume levels.

Irradiated volume	Effect	F	Sig.	Effect size (η^2)
PTV_{10}	Time-point	2.08	.11	.061
	Time*PTV_{10}	.59	.62	.018
	PTV_{10}	1.84	.18	.018
PTV_{50}	Time-point	2.28	.08	.064
	Time*PTV_{50}	.40	.75	.018
	PTV_{50}	1.26	.26	.02
PTV_{90}	Time-point	2.24	.09	.065
	Time*PTV_{90}	.59	.62	.018
	PTV_{90}	1.96	.16	.02

Table 5.8 The effect of irradiated volumes of tissue on fatigue over four time-points, under three different isodose levels. ($PTV_{10, 50 \text{ and } 90}$ = the gross volume of tissue irradiated within the 10%, 50% and 90% isodose, respectively.)

Analysis by Spearman's correlation indicated that, the volume of lung irradiated within the 10% and 50% isodose levels, and the maximum lung dose, all correlated negatively with fatigue score at week 3 and 4 weeks post. Correlation coefficients in the range ρ = -.20 to -.29 suggested a small association between larger volumes of lung irradiated and increased fatigue. No significant relationships with fatigue were evident for the dose-volume data for the liver or heart.

5.3.3 White blood counts

White blood counts (WBC) reduced during treatment, and at 4 weeks post radiotherapy had only partially recovered from their nadir. Mean concentrations of differential WBC after treatment were approximately 20% lower than at baseline.

Relationships between white blood counts and fatigue

Figure 5.18 presents the longitudinal concentration of lymphocytes for the two fatigue groups. Mann–Whitney U tests revealed no significant differences in concentrations of the fatigued and non-fatigued at any time-point (U range = 918–1030, p range = 0.07–0.4). The pattern indicated – a non-significant trend for the fatigued group having lower mean levels of WBC at all time-points and the two groups exhibiting a parallel rate of decline from baseline – was typical for the other differential WBC.

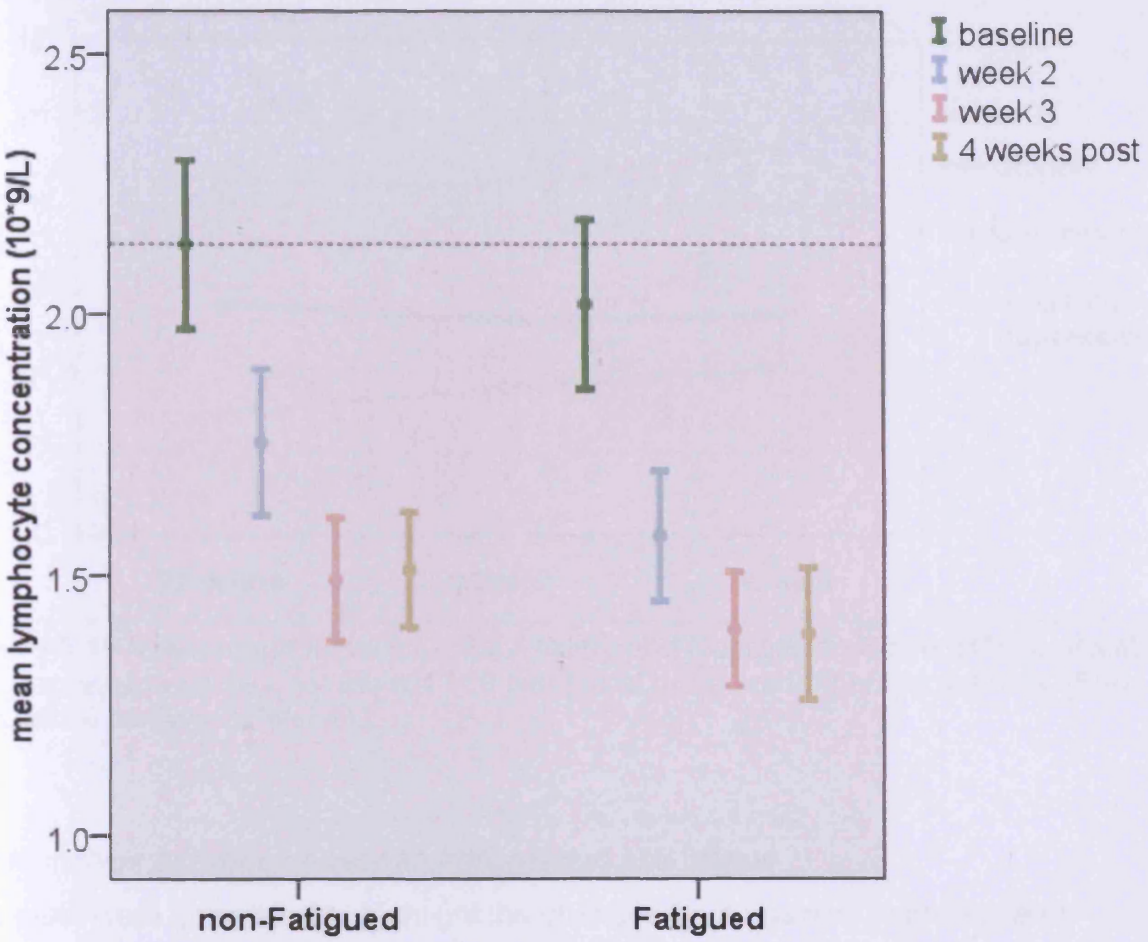


Figure 5.18 Error bars displaying mean longitudinal lymphocyte concentration and 95% confidence interval for non-fatigued and fatigue groups of breast radiotherapy patients

5.3.4 Anxiety and depression levels

The mean HADS anxiety, depression and cumulative scores for the study cohort are illustrated below in Figure 5.19.

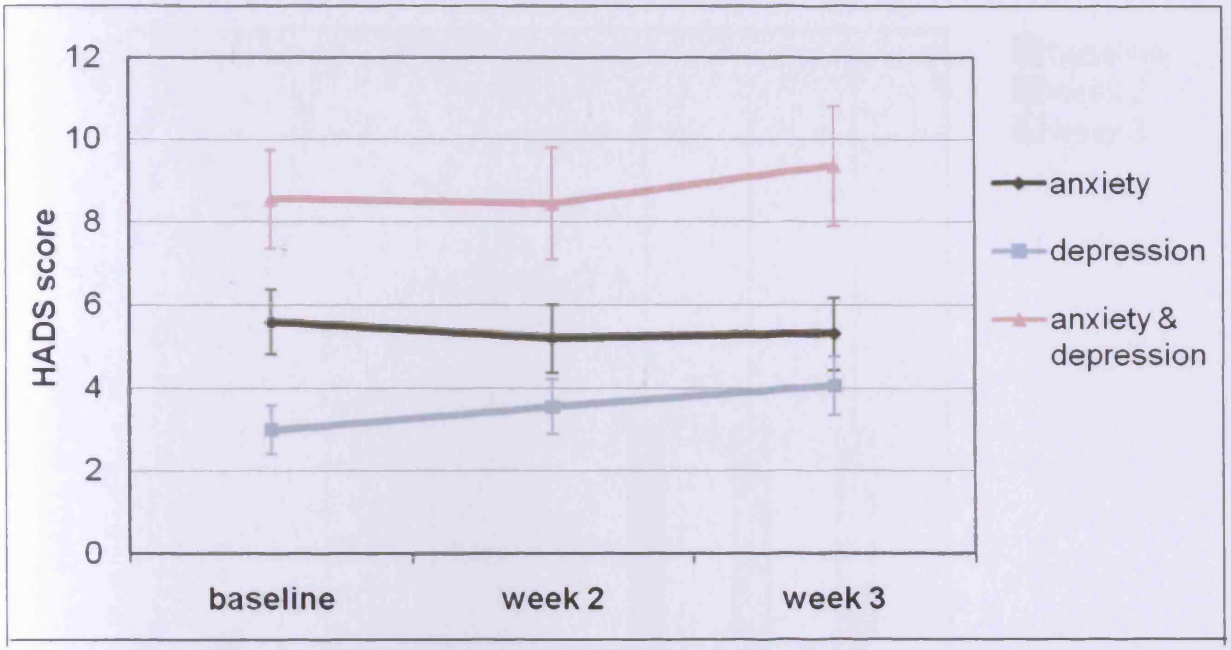


Figure 5.19 Mean longitudinal Hospital Anxiety and Depression Scale (HADS) anxiety and depression scores, for the n = 100 sample of breast radiotherapy patients. (Error bars = 95% confidence interval.)

Relationships between anxiety and depression and fatigue

Box-plots were generated to highlight the changes from baseline in anxiety and depression levels for the fatigued and non-fatigued groups (Figures 5.20 and 5.21). The median anxiety levels fell by one HADS scale point from baseline to week 3 for both groups. In the same period, the median depression level of the fatigued patients continued to increase, from 3.8 to 7.2, as compared to no change in the non-fatigued group.

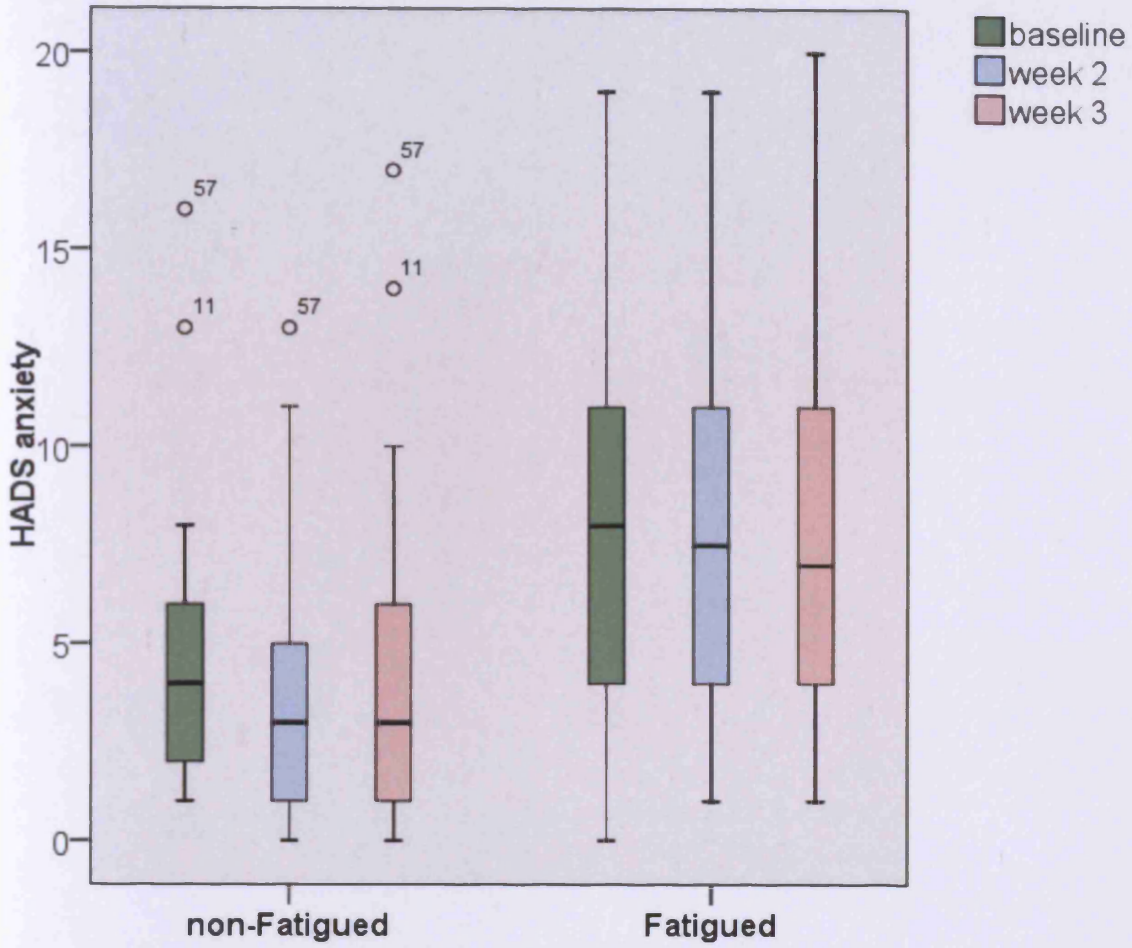


Figure 5.20 Box-plots representing median and inter-quartile ranges of longitudinal Hospital Anxiety and Depression Scale (HADS) anxiety scores for non-fatigued and fatigued groups of breast radiotherapy patients. (Numbered markers = outlier cases.)

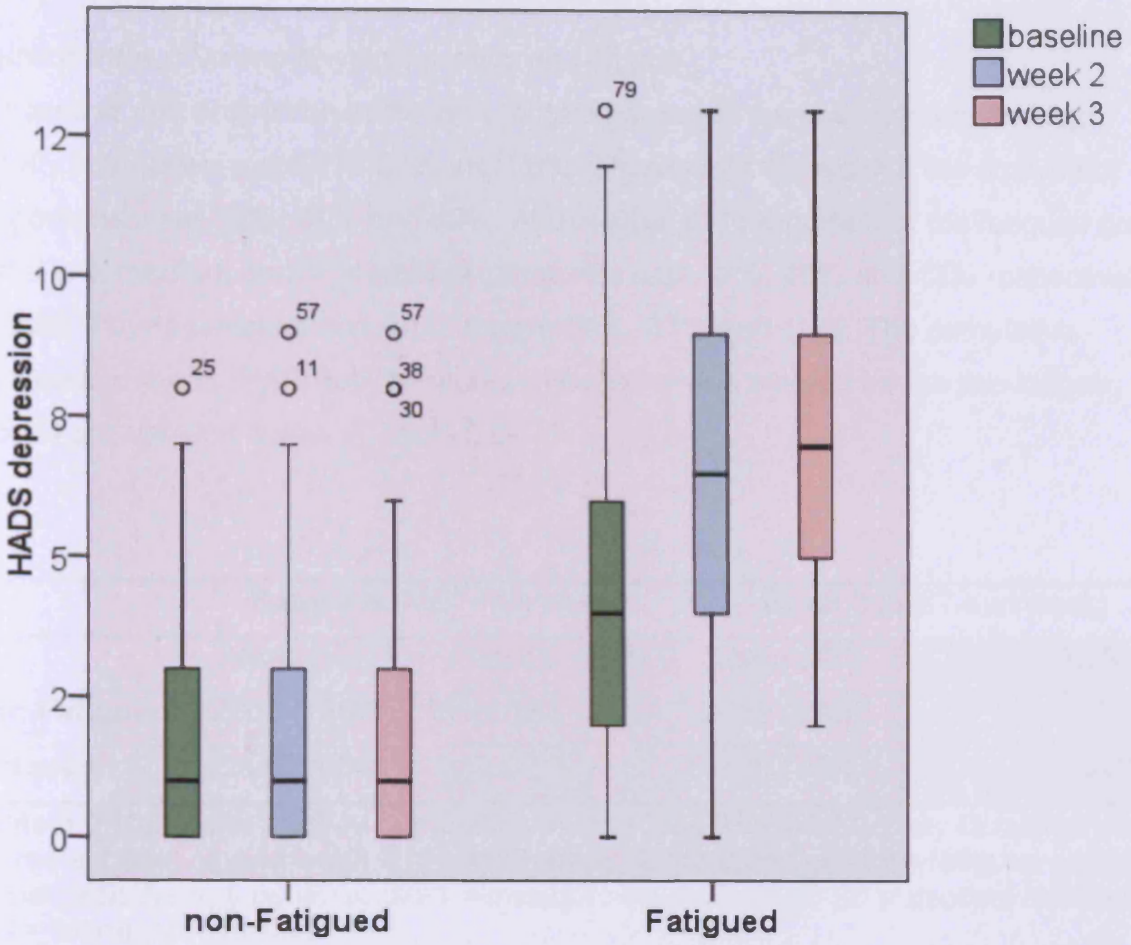


Figure 5.21 Box-plots indicating median and inter-quartile ranges of longitudinal Hospital Anxiety and Depression Scale (HADS) depression scores for non-fatigued and fatigued groups of breast radiotherapy patients. (Numbered markers = outlier cases.)

5.3.5 Physical activity levels

One participant, (from the non-fatigued group), was excluded from all physical activity analyses as she was confined to a wheelchair. The cumulative median (IQR) IPAQ score for the remaining 99 participants was 1692 MET-min/week (852–3257) at baseline, decreasing to 1553 MET-min/week (823–3378) at week 3. In addition, the continuous data was classified as low, medium and high levels of physical activity, in accordance with the data processing rules detailed in Appendix 4. At baseline, 37% of participants reported low activity, 40% medium activity and 23% high activity. By week 3 slightly more participants (44%) were in the low activity category, slightly less (33%) were in the medium category and the same percentage (23%) were in the high category.

Relationships between physical activity and fatigue

At baseline, the proportion of the non-fatigued group in the low, medium and high activity categories was 34%, 37% and 29% respectively. By week 3 the equivalent proportions were 39%, 31% and 30%. At baseline, the proportion of the fatigued group in the low, medium and high activity categories was 42%, 45% and 13% respectively: at week 3 the equivalent proportions were 50%, 37% and 13%. The cumulative median and mean IPAQ activity scores at baseline and week 3 for the two fatigue groups are detailed below in Table 5.9:

	Baseline (MET-min/week)		**Week 3** (MET-min/week)	
	Mean (SD)	*Median (IQR)*	*Mean (SD)*	*Median (IQR)*
Non-Fatigued	2302 (1867)	1653 (881–3623)	2643 (2345)	1657 (928–3534)
Fatigued	2305 (2606)	1759 (705–2871)	1696 (1668)	1179 (497–2411)

Table 5.9 Mean and median cumulative International Physical Activity Questionnaire scores at baseline and week 3 of radiotherapy, for fatigued and non-fatigued groups of breast radiotherapy patients. (MET = metabolic equivalent task; SD = standard deviation; IQR = inter-quartile range.)

At baseline, the cumulative IPAQ scores for the two fatigue groups were comparable. By week 3, the group difference was 950 MET-min/week for mean scores, and 584 MET-min/week for median scores.

To reveal finer detail of the nature of the changes in activity for the two groups, the cumulative IPAQ data was broken down into the four activity domains. Figures 5.22 and 5.23 represent the median and IQR of the physical activity levels across the comprehensive set of IPAQ domains, at baseline and week 3 respectively. Additionally, the time spent sitting per day was recorded. At baseline, the median time spent sitting was 300 minutes for the non-fatigued group and 292 minutes for the fatigued group. At week 3, the respective times were 300 minutes, and 360 minutes.

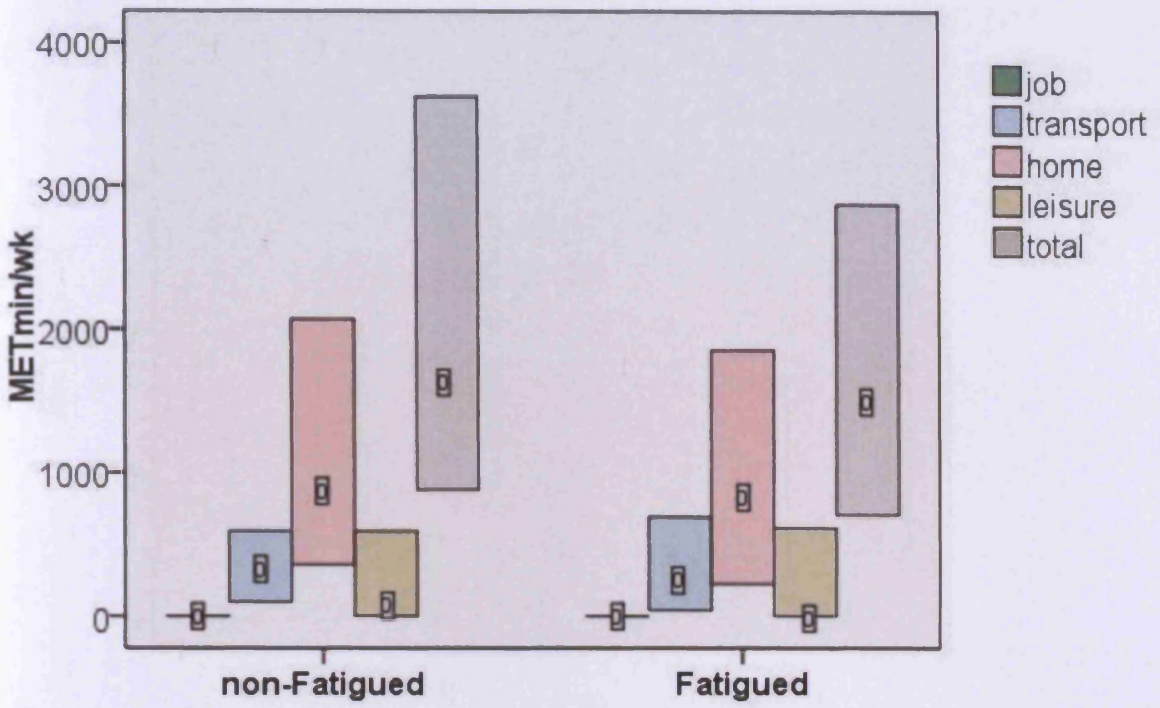


Figure 5.22 Baseline median and inter-quartile range International Physical Activity Questionnaire domain-specific scores for fatigued and non-fatigued groups of breast radiotherapy patients. (METmin/wk = minutes of metabolic equivalent tasks per week.)

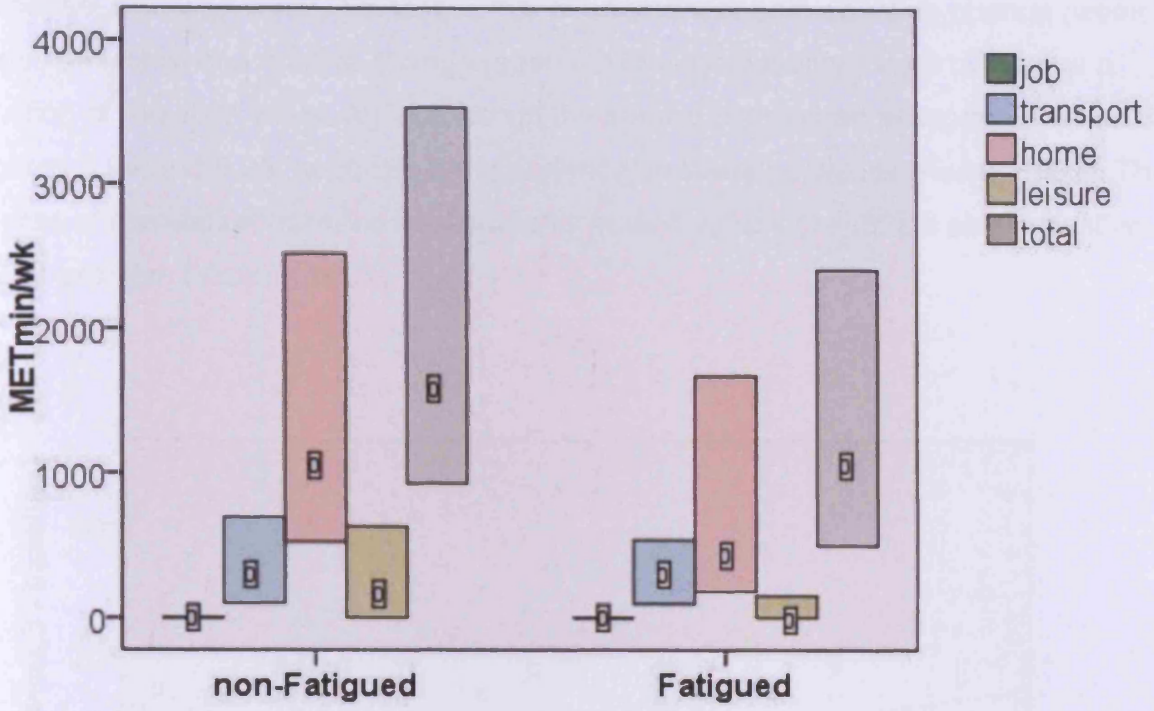


Figure 5.23 Week 3 median and inter-quartile range International Physical Activity Questionnaire domain-specific scores for fatigued and non-fatigued groups of breast radiotherapy patients. (METmin/wk = minutes of metabolic equivalent tasks per week.)

5.4 Factors that contribute to fatigue during radiotherapy treatment

Consideration of the most appropriate dependent variable

Prior to conducting multiple regression analysis, the most appropriate summary measure to represent the 'average' fatigue response during radiotherapy was considered. The chosen DV was the mean of the interval FACIT-F scores at week 2 and week 3. The interval FACIT-F data was again preferred, as it exhibited enhanced normality, skewness and homoscedascity of distribution as compared to the raw FACIT-F scores. Distribution, normality and skewness data for the chosen DV are included in Appendix 4.

An alternate summary DV, of the change score from baseline to week 3, was considered. The use of change scores as outcome measure has been criticised (Cronbach and Furby 1970), largely relating to the inherent problem of regression to the mean effects. That is, those with high baseline scores experience a bigger change

response, and vice versa. To assess this phenomenon, both absolute change (week 3 minus baseline) and relative change (absolute change/baseline) were plotted as a function of baseline value. An increase in the spread of the change scores, evinced in Figures 5.24 and 5.25, suggests a dependency on baseline values (Kaiser 1989). The degree of correlation between baseline and week 3 values (r = .52) is also indicative of this problem (Vickers 2001).

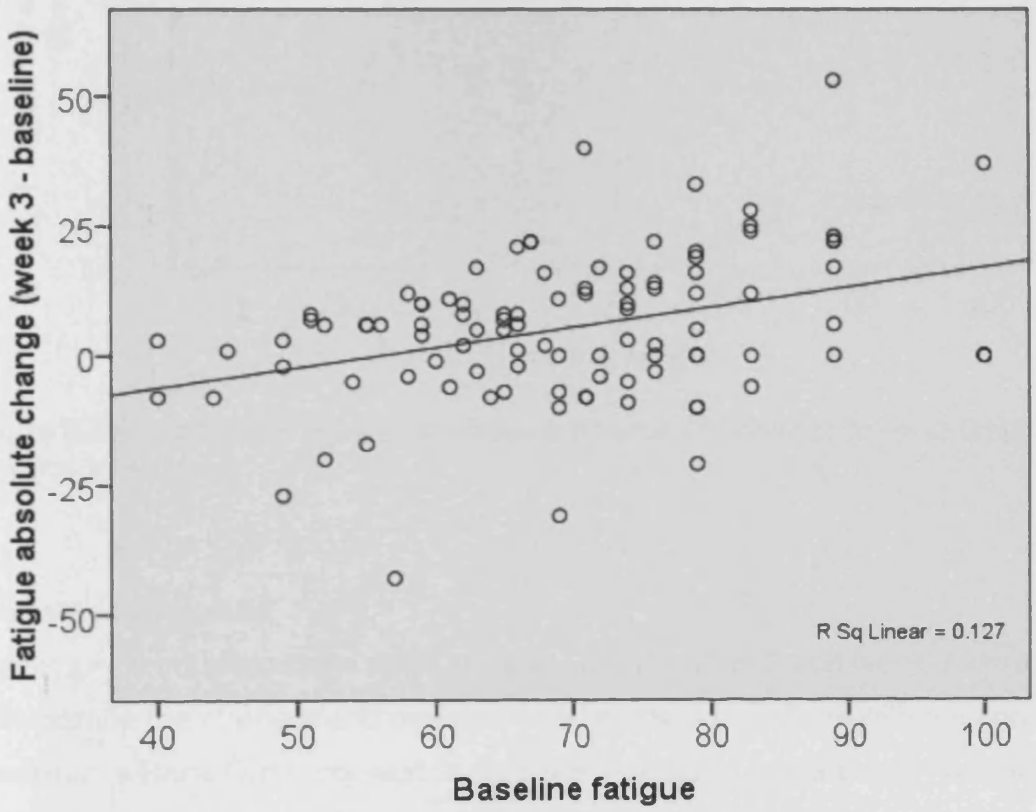


Figure 5.24 Scatterplot of baseline fatigue against absolute change in fatigue from baseline to week 3

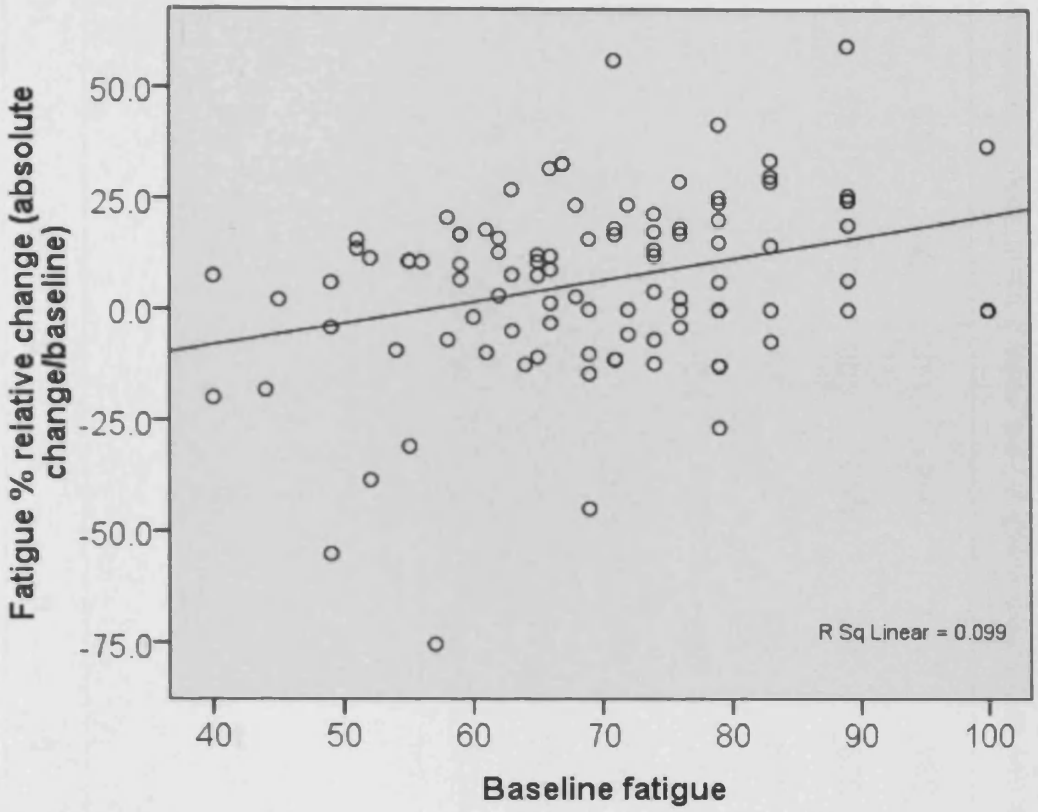


Figure 5.25 Scatterplot of baseline fatigue against absolute change in fatigue from baseline to week 3

Bivariate relationships

Preliminary to multiple regression analysis, IVs for week 2 and week 3 were screened to determine the strength and direction of bivariate correlations with the chosen DV. Spearman's Rank Order correlation was used to accommodate non-normally distributed data. Results of some of the important variables are summarised below as a correlation matrix (Table 5.10).

Variable	1	2	3	4	5	6	7	8	9	10	11
1. Mean of weeks 2 & 3 FACIT-F interval score	1.00										
2. FACIT-F baseline	.622**	1.00									
3. age	.200*	.045	1.00								
4. BMI	-.188	-.096	.254*	1.00							
5. PTV50	-.153	-.169	.092	.689**	1.00						
6. max lung dose	-.222*	.010	-.153	-.325**	-.088	1.00					
7. anxiety week 3	-.571**	-.269*	-.405**	-.027	-.002	.140	1.00				
8. depression week 3	-.835**	-.499**	-.228*	.041	.037	.276**	.678**	1.00			
9. IPAQ sum week 3	.309*	.259**	-.067	-.062	-.038	-.128	-.087	-.190	1.00		
10. IL-6sR concentration week 2	-.203*	-.324**	.160	.259**	.329**	-.162	.052	.106	-.065	1.00	
11. IL-6sR concentration week 3	-.265**	-.313**	.117	.253**	.334**	-.111	.094	.140	-.08	.869**	1.00

Table 5.10 Spearman's rank correlations between fatigue during radiotherapy and select week 2 and week 3 variables. ** correlation significant at the 0.01 level (2-tailed); * correlation significant at the 0.05 level (2-tailed). (FACIT-F = Functional Assessment of Chronic Illness Therapy Fatigue Scale; BMI = body mass index; PTV_{50} = volume of tissue irradiated within the 50% isodose; IPAQ = International Physical Activity Questionnaire; IL-6sR = interleukin 6 soluble receptor.)

Multivariable relationships

Hierarchical multiple regression analysis was performed to determine the factors that contribute to on-treatment fatigue, whilst controlling for baseline fatigue level. The DV was the mean of the interval FACIT-F scores on weeks 2 and 3. IVs were selected for entry on a substantive theoretically driven basis. Factors, such as travel time for radiotherapy that conceivably may have been associated with fatigue during treatment, but exhibited no bivariate association with the outcome, (ρ = -.02, p = 0.8) were excluded from the model. Conversely, factors that exhibited a correlation with the DV of $\rho > .25$ were considered for inclusion. Variables were transformed as required to enhance normality, skewness and homogeneity of variance prior to entry into the model.

An initial standard hierarchical regression model was formed with interval baseline FACIT-F fatigue score entered at step one. Subsequently, the exposure factors: age, BMI, PTV_{50}, week 3 depression (square root), week 3 physical activity (square root) and week 3 IL-6sR concentration (square root) were entered simultaneously at step two. There were no missing data.

Age was excluded from subsequent iterations as neither its additive value, nor substantive bases for inclusion was strong. Variance inflation factor (VIF) values for BMI and PTV_{50} increased the average VIF value above 1.5; a threshold that may potentiate the risk of biased results according to Bowerman and O'Connell (1990). PTV_{50} was retained on a substantive basis, thereby excluding BMI (ß = .09) from subsequent iterations. The results of the final multiple regression equation are summarised in Table 5.11.

Variable	ß	Sig.	% R^2	ΔR^2
Step 1				R^2 = .37 for step1
Baseline fatigue (interval)	.61	<.001	37.21	
Step 2				ΔR^2 = .40 for step2
Baseline fatigue (interval)	.19	.003	2.25	
IL-6sR concentration week 3 (sqrt)	-.08	.18	0.46	
Physical activity week 3 (sqrt)	.14	.01	1.72	
Depression week 3 (sqrt)	-.69	<.001	35.52	
PTV_{50}	-.09	.094	0.71	
				Total R^2 = .77

Table 5.11 Hierarchical multiple regression for fatigue during radiotherapy treatment. (sqrt = square root; IL-6sR = interleukin 6 soluble receptor; PTV_{50} = volume of tissue irradiated within the 50% isodose.)

Baseline fatigue, entered at Step 1, explained 37.2% of the variance in on-treatment fatigue. PTV_{50}, week 3 depression (sqrt), week 3 physical activity (sqrt) and week 3 IL-6sR concentration (sqrt), entered simultaneously at Step 2, explained an additional 40% of the variance in on-treatment fatigue, R^2 change = .40, F change (1, 99) = 40.23, $p < 0.001$. Hence, the total variance explained by the model as a whole was 77%, F (5, 95) = 62.39, $p < 0.001$. After controlling for baseline fatigue, two IVs were statistically significant: namely, week 3 physical activity (ß = 0.14, p = 0.01) and week 3 depression (ß = -0.69, $p < 0.001$). Week 3 depression makes a considerably larger unique contribution (35.5%) to the total R^2 than physical activity (1.7%).

Multivariable model accuracy

The regression residuals were analysed to check for significant violations of the assumptions underlying the multiple regression analysis (as before for the baseline multiple regression model section 5.2.5). None of the variables displayed multicollinearity. The maximum Mahalanobis distance value of 16.11 was less than the critical chi-square value of 20.52, for five IVs (Tabachnick and Fidell 2007, Table C4); indicating an absence of outliers in the data. A maximum Cook's distance of 0.191, and inspection of leverage values indicated no cases had a disproportional leverage on the model.

A standardised residual (z) scatter-plot (Figure 5.26) indicated that the assumptions of linearity and homoscedasticity were reasonably met. The plot indicated four residual values beyond the range -2 < z > 2, which is consistent with a normally distributed statistic from a sample size of 100. Equivalent partial regression scatter-plots for all three IVs are included in Appendix 4.

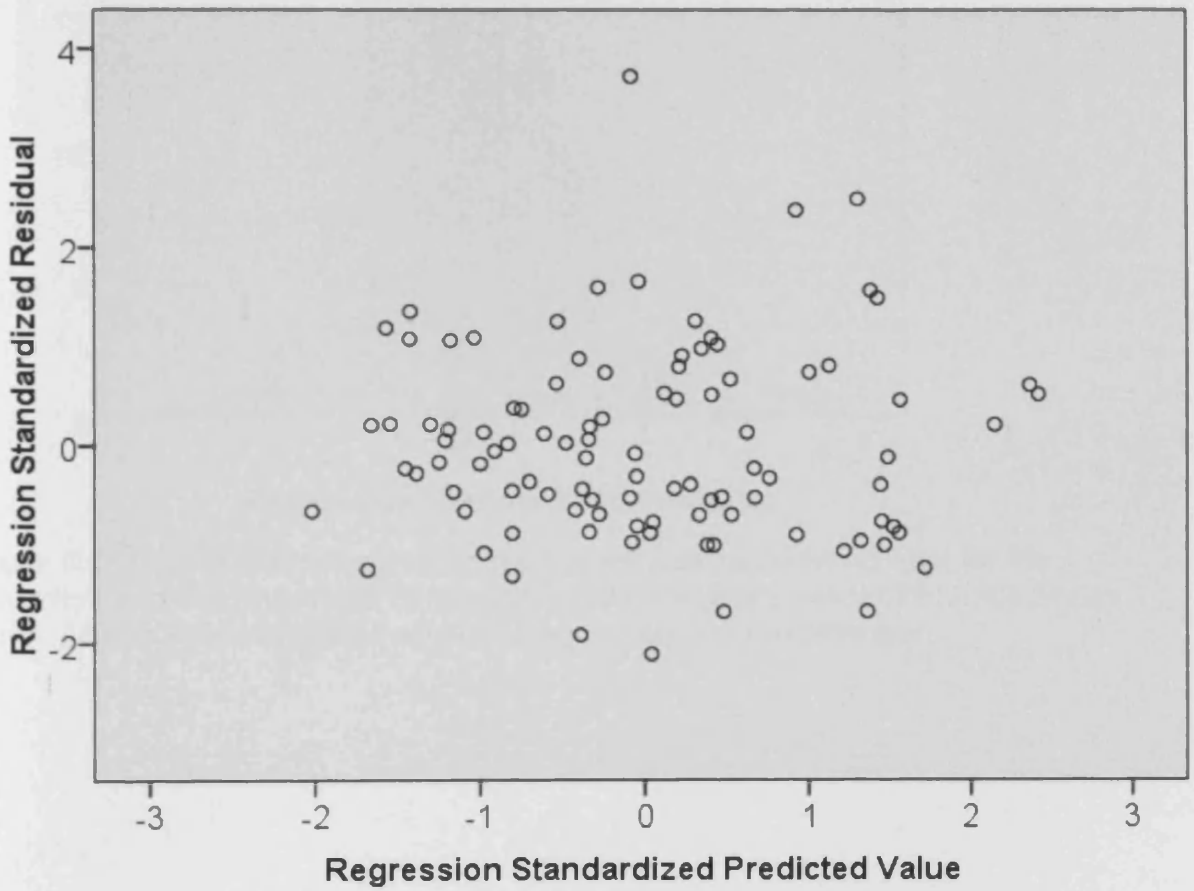


Figure 5.26 Residual scatterplot of standardised residuals against the predicted values for the dependent variable, the mean of interval Functional Assessment of Chronic Illness Therapy Fatigue Scale score at week 2 and week 3 of radiotherapy

A distribution histogram and P-P normal probability plot for the standardised residuals, below in figure 5.27 and 5.28 respectively, indicated the assumptions regarding residual normality were reasonably met.

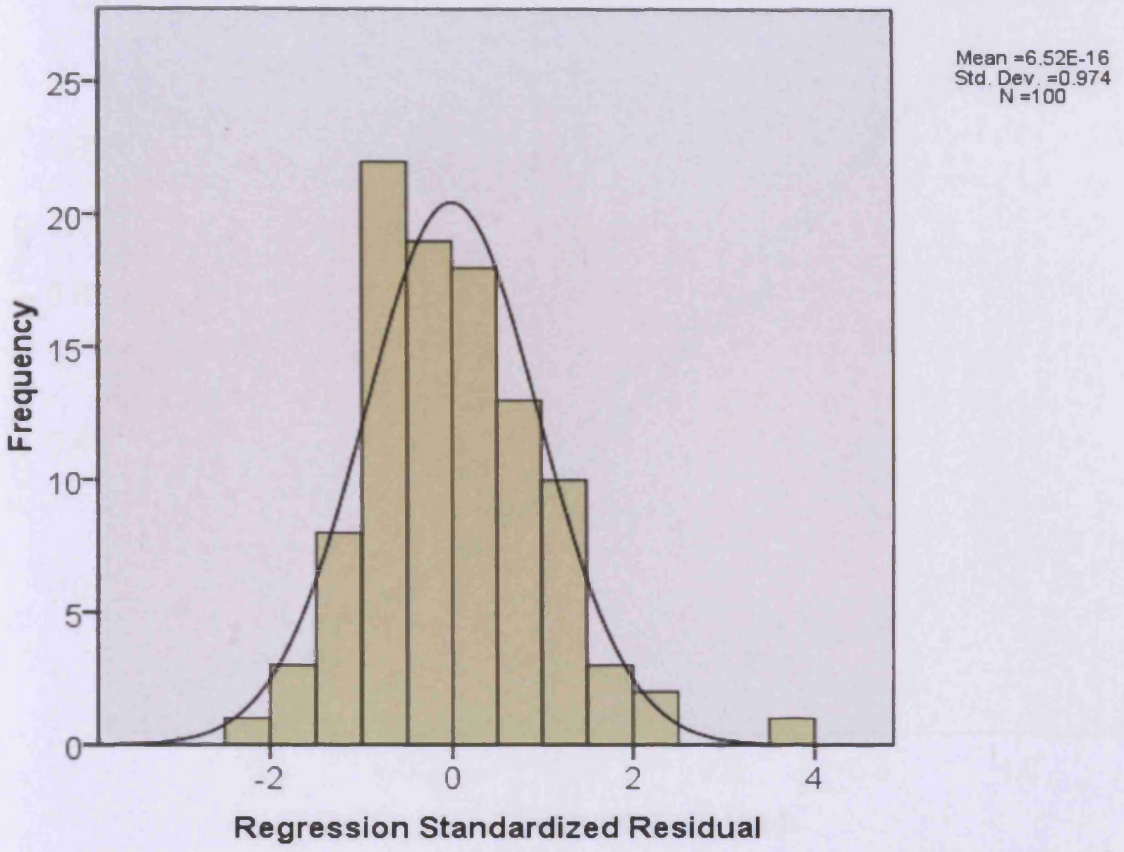


Figure 5.27 Distribution histogram of regression standardised residual for the dependent variable, the mean of interval Functional Assessment of Chronic Illness Therapy Fatigue Scale scores at week 2 and week 3 of radiotherapy

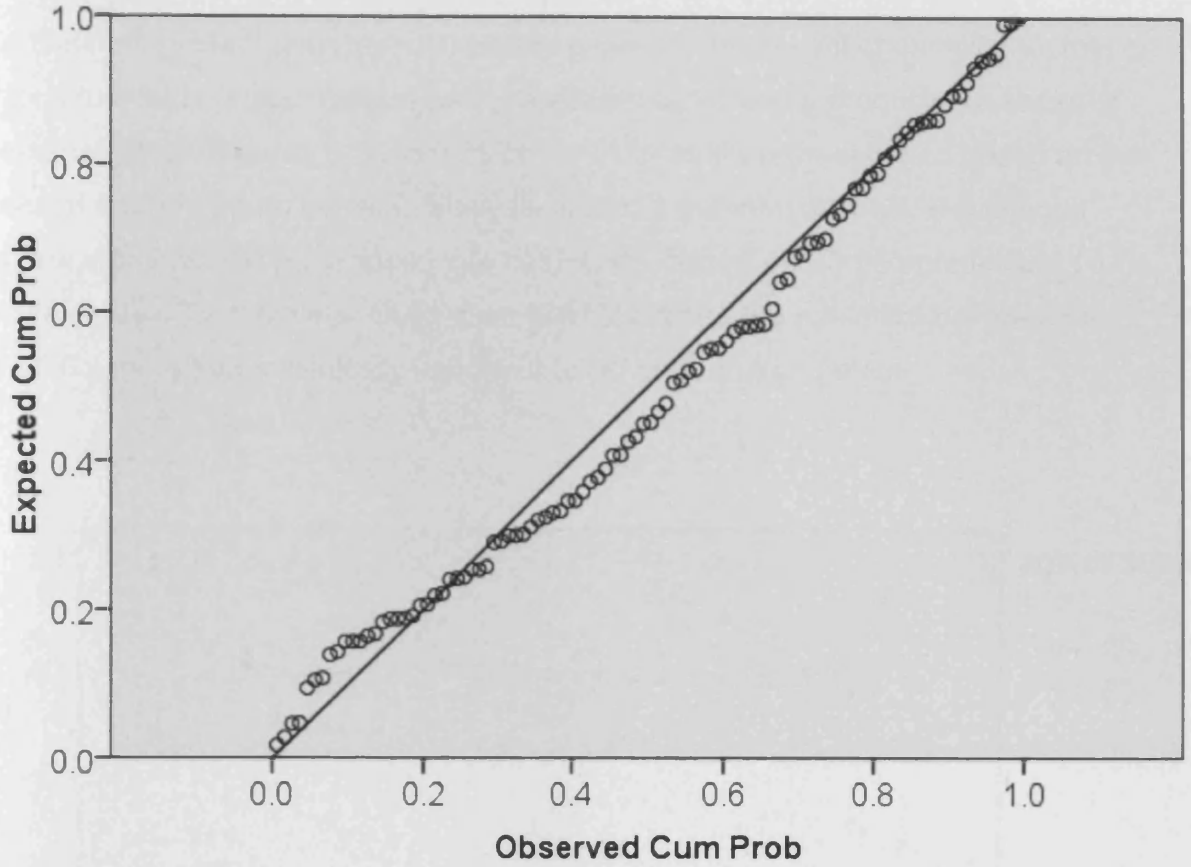


Figure 5.28 Normal P-P Plot of regression standardised residual for the dependent variable, the mean of interval Functional Assessment of Chronic Illness Therapy Fatigue Scale scores at week 2 and week 3 of radiotherapy

Cross-validity of the multivariable model

The adjusted R^2 coefficient of determination was only .01 reduced from the unadjusted value, suggesting a decrement of only about 1% in performance if the model had been derived from the sample population. The value of R^2 rendered by Stein's formula (Equation 5.1, section 5.2.5) was close to the unadjusted model summary R^2, being 0.75 and 0.77 respectively. The decrement in the variance explained by the model for an external dataset was therefore estimated to be approximately 2%, suggesting good model cross-validity if applied to an external dataset.

5.5 Baseline variables that are prognostic of fatigue during radiotherapy

As a preliminary step, prior to multivariable analysis, the impact of baseline factors on the longitudinal course of fatigue was graphically explored by producing a series of time-series plots (Figures 5.29 to 5.38 below). Variables were selected based on the results of the (previous) baseline analysis and/or a theoretical basis. Continuous baseline variables were collapsed into categories, based on 33.33 percentiles. To provide context for the plots, Cella et al. (2002b) define the minimum difference in FACIT-F scores that is clinically important to be three to four points.

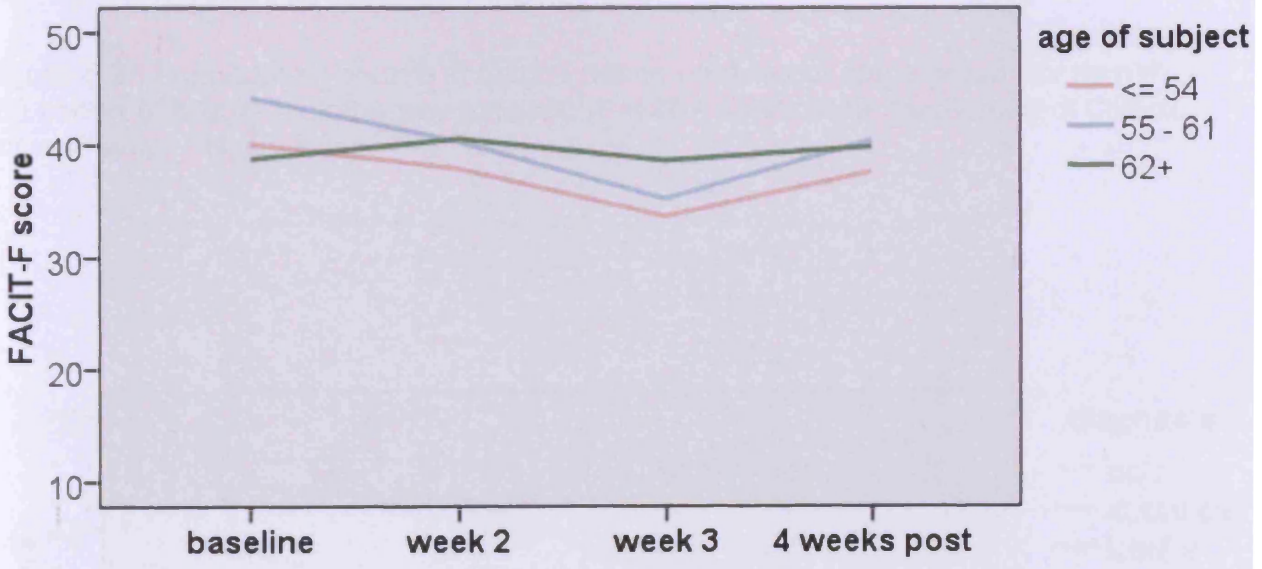


Figure 5.29 Longitudinal course of fatigue for three categorised age groups, of an n = 100 cohort of breast radiotherapy patients. (FACIT-F = Functional Assessment of Chronic Illness Therapy Fatigue Scale.)

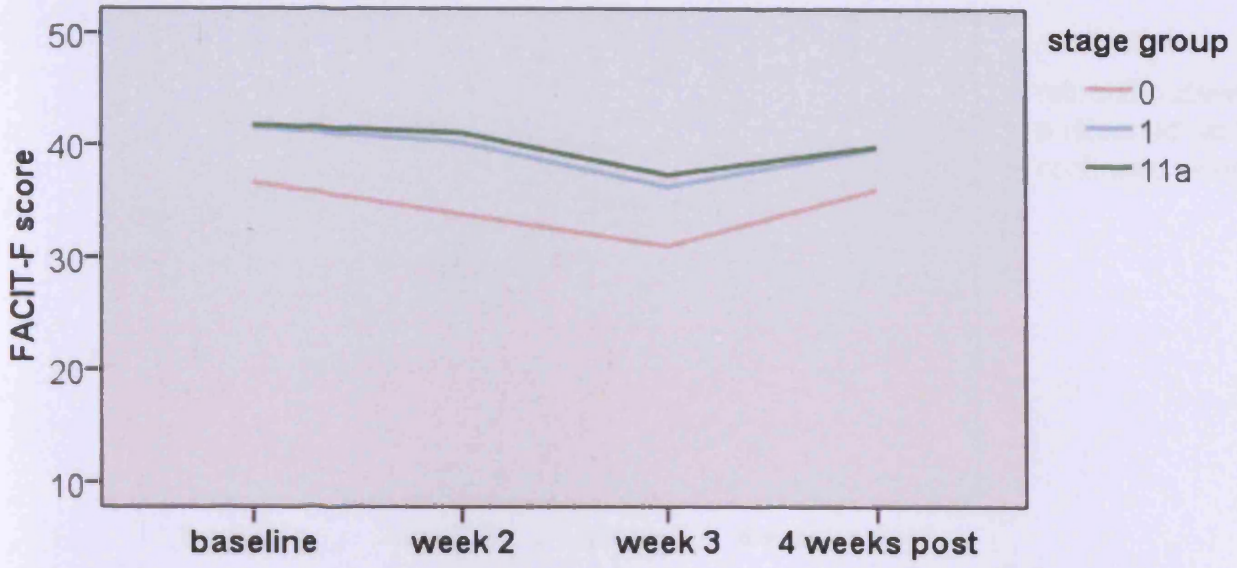


Figure 5.30 Longitudinal course of fatigue based on disease stage group, for an n = 100 cohort of breast radiotherapy patients. (FACIT-F = Functional Assessment of Chronic Illness Therapy Fatigue Scale.)

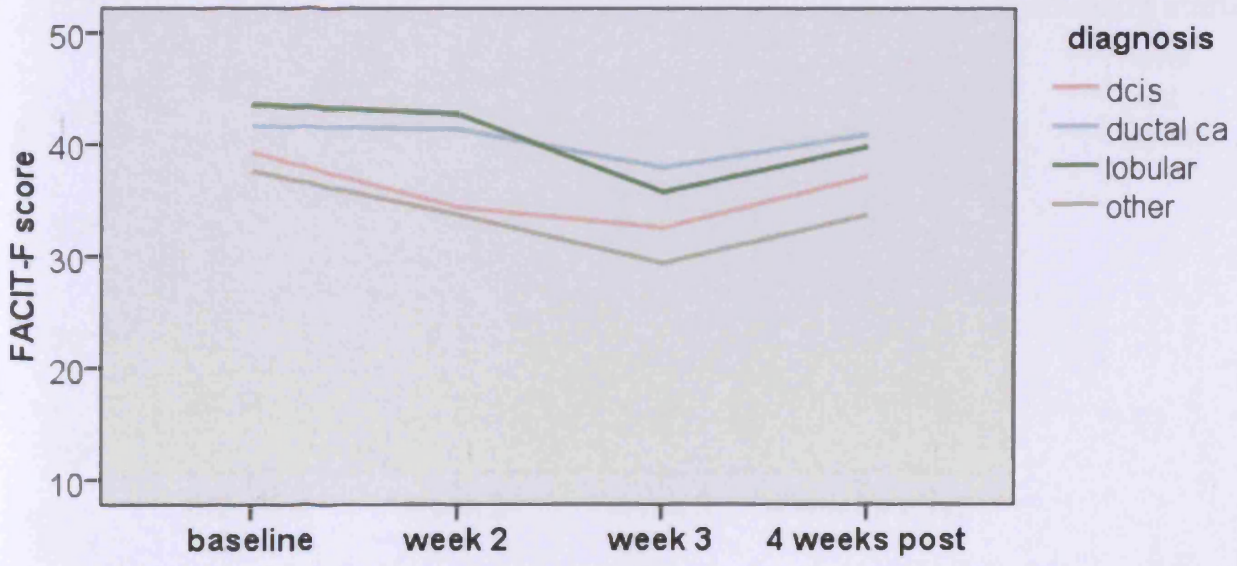


Figure 5.31 Longitudinal course of fatigue based on pathological diagnosis, for an n = 100 cohort of breast radiotherapy patients. (FACIT-F = Functional Assessment of Chronic Illness Therapy Fatigue Scale.)

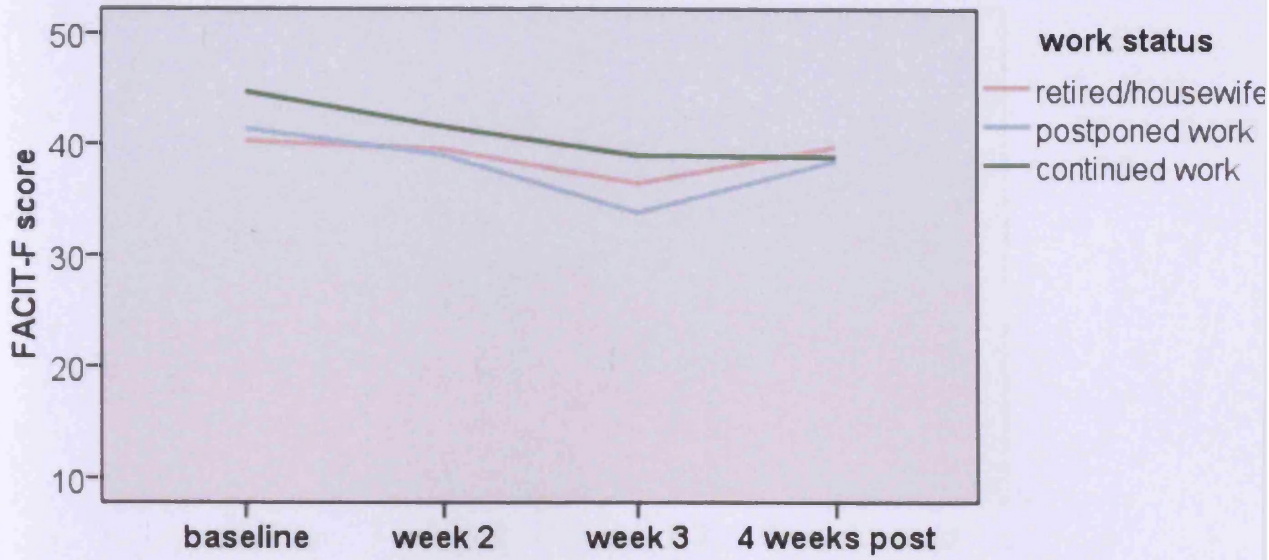


Figure 5.32 Longitudinal course of fatigue based on three work status groups, for an n = 100 cohort of breast radiotherapy patients. (FACIT-F = Functional Assessment of Chronic Illness Therapy Fatigue Scale.)

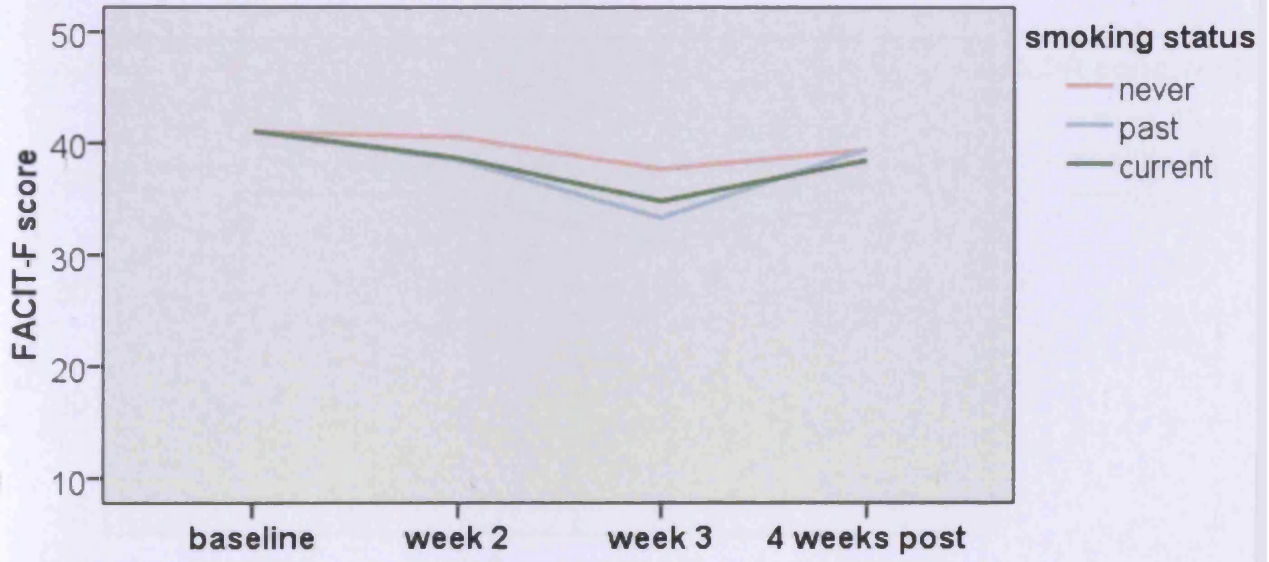


Figure 5.33 Longitudinal course of fatigue based on smoking status, for an n = 100 cohort of breast radiotherapy patients. (FACIT-F = Functional Assessment of Chronic Illness Therapy Fatigue Scale.)

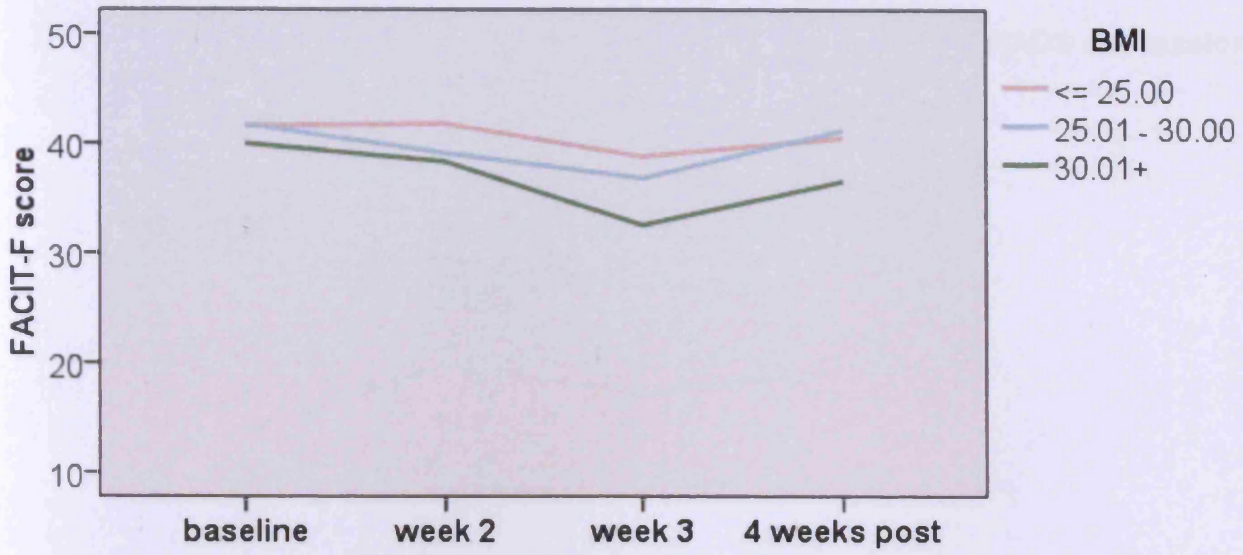


Figure 5.34 Longitudinal course of fatigue based on three BMI groups, for an n = 100 cohort of breast radiotherapy patients. (FACIT-F = Functional Assessment of Chronic Illness Therapy Fatigue Scale.)

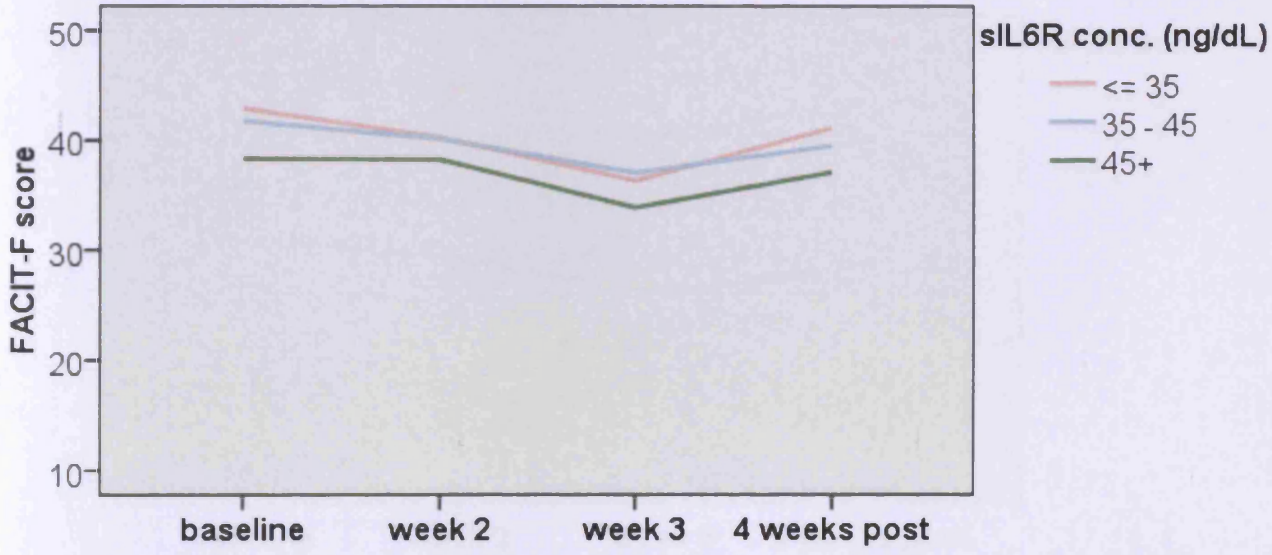


Figure 5.35 Longitudinal course of fatigue based on categorised baseline interleukin-6 soluble receptor (sIL-6R) concentration, for an n = 100 cohort of breast radiotherapy patients. (FACIT-F = Functional Assessment of Chronic Illness Therapy Fatigue Scale.)

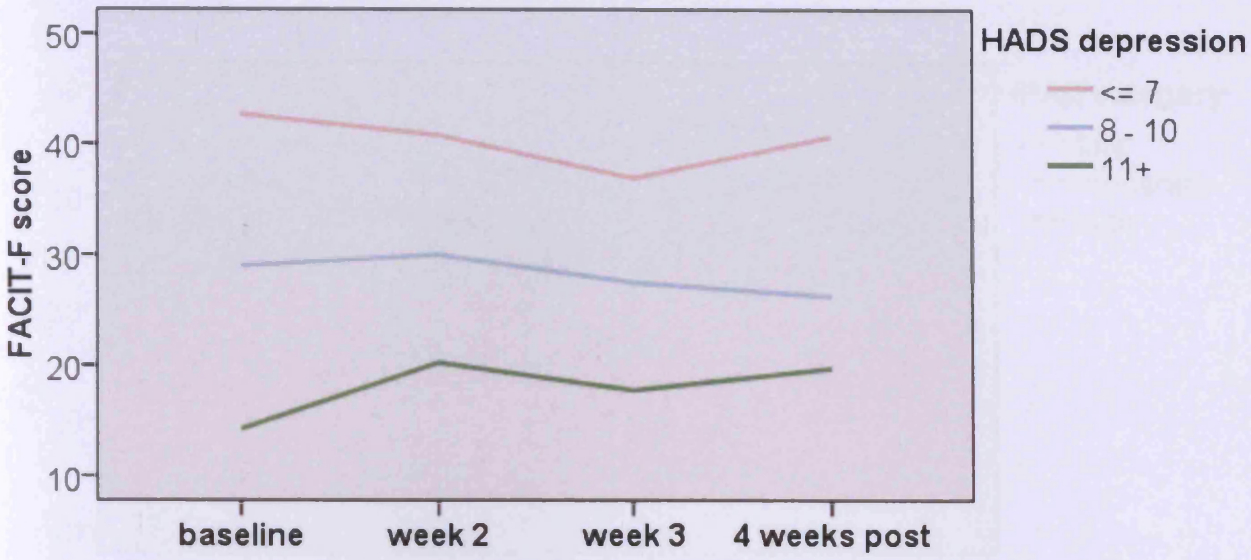


Figure 5.36 Longitudinal course of fatigue based on categorised baseline Hospital Anxiety and Depression Scale (HADS) depression score, for an n = 100 cohort of breast radiotherapy patients. (FACIT-F = Functional Assessment of Chronic Illness Therapy Fatigue Scale.)

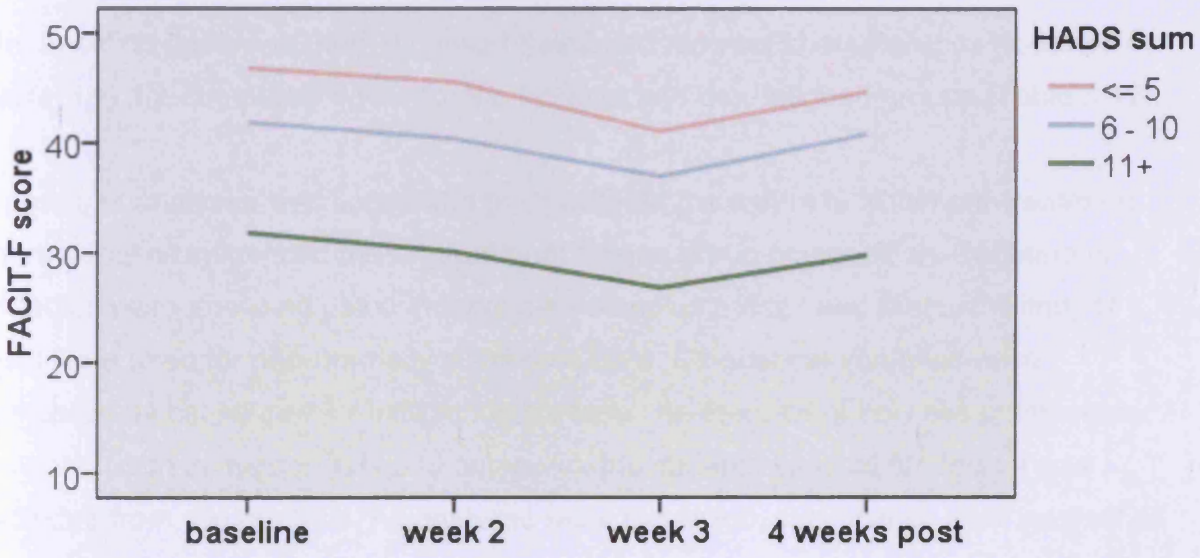


Figure 5.37 Longitudinal course of fatigue based on categorised baseline Hospital Anxiety and Depression Scale (HADS) cumulative anxiety and depression groups, for an n = 100 cohort of breast radiotherapy patients. (FACIT-F = Functional Assessment of Chronic Illness Therapy Fatigue Scale.)

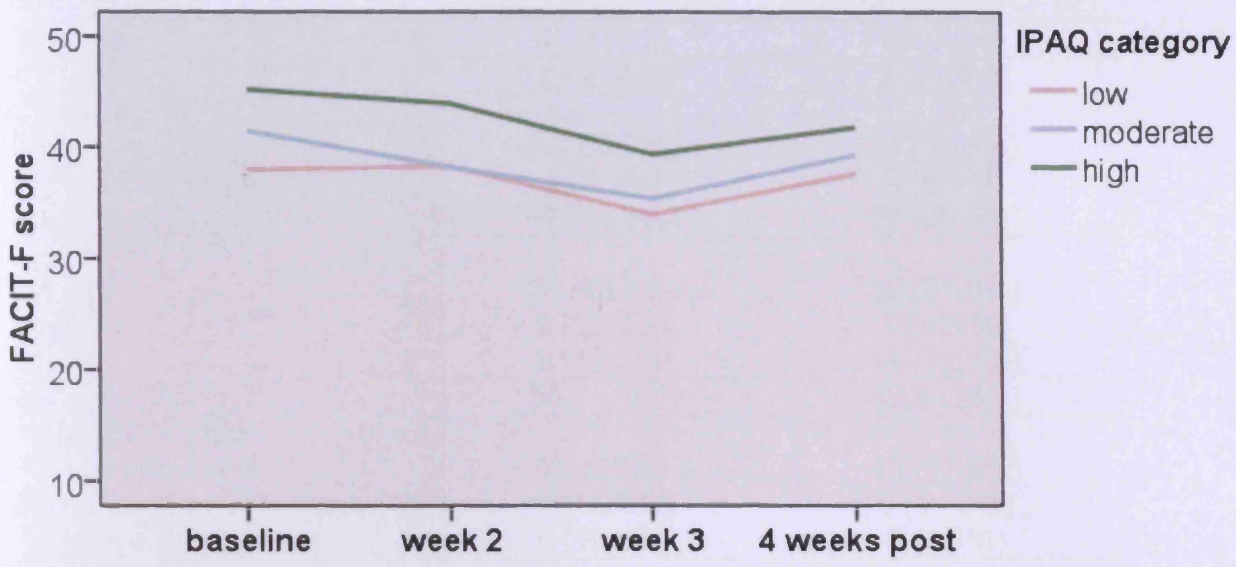


Figure 5.38 Longitudinal course of fatigue based on International Physical Activity Questionnaire (IPAQ) categories, for an n = 100 cohort of breast radiotherapy patients. (FACIT-F = Functional Assessment of Chronic Illness Therapy Fatigue Scale.)

Bivariate analysis of baseline sample characteristics by fatigue group

The baseline patient-related, disease-related and surgical characteristics (reported in Table 5.1) are compared below for the fatigued and non-fatigued groups (Table 5.12).

A series of analyses was conducted to investigate the extent to which pre-treatment characteristics influenced the on-treatment fatigue group composition. Continuous variables were analysed using independent-samples t-tests, and Mann–Whitney U tests were used for non-normally distributed data. Categorical variables were compared by chi-square for independence tests. As there were only two mastectomy patients, (both in the non-fatigued category), the variable surgical procedure was excluded from this analysis. All analyses were two-tailed, significance level was set at $p = 0.05$ and sample size was $n = 100$.

Characteristics	**Fatigued** (n = 38)	**Non-fatigued** (n = 62)
Age (years)	55.9 (9.3)	59.0(8.5)
BMI (Kg/m^2)	29.2 (4.8)	27.6 (4.6)
Work status		
Retired/Housewife	24 (63.2%)	34 (54.8%)
Continued to work during RT	2 (5.3%)	6 (9.7%)
Postponed work for RT	12 (31.6%)	22 (35.5%)
Travel mode for RT		
Driven	24 (63.2%)	38 (61.3%)
Self drive	9 (23.7%)	13 (21%)
Other	5 (13.2%)	11 (17.7%)
Travel time[a] (mins)	36.7 (19.1)	39.8 (34.4)
Menopausal status		
Post-menopausal	25 (65%)	48 (77.4%)
Peri-menopausal	7 (18.4%)	9 (14.5%)
Pre-menopausal	6 (15.8%)	5 (8.1%)
HRT history		
Never	25 (65.8%)	45 (72.6%)
Previous	13(24.2%)	17 (27.4%)
Smoking history		
Never	16 (42.1%)	34 (54.8%)
Past	14 (36.8%)	18 (29%)
Current	8 (21.1%)	10 (16.1%)
Pack-years[a]	12.6 (16.4)	6.2 (9.7)
Histological diagnosis		
Ductal carcinoma in-situ	6 (15.8%)	7 (11.3%)
Invasive ductal carcinoma	18 (47.4%)	43 (69.4%)
Invasive lobular carcinoma	5 (13.2%)	7 (11.3%)
Other	9 (23.7%)	5 (8.1%)
Tumour size[a] (mm)	17 (10.1)	18.4 (10.4)
Histopathological grade		
Grade 1	14 (36.8%)	17 (27.4%)
Grade 2	17 (44.7%)	34 (54.8%)
Grade 3	7 (18.4%)	11 (17.7%)
TNM stage		
0	7 (18.4%)	6 (9.7%)
I	25 (65.8%)	45 (72.6%)
IIA	6 (15.8%)	11 (17.7%)
Laterality		
Right	20 (52.6%)	32 (51.6%)
Left	18 (47.4%)	30 (48.4%)
Time from surgery to RT (days)	61.5 (12.2)	61.0 (16.7)

Table 5.12 Pre-radiotherapy sample characteristics for fatigued and non-fatigued groups, of the n = 100 study sample of breast radiotherapy patients.
Normally distributed continuous variables are means (standard deviation).
[a] Non-normally distributed continuous variables are medians (inter-quartile range).
Categorical variables are numbers (and percentages) of patients in that group.
(BMI = body mass index; HRT = hormone replacement therapy; RT = radiotherapy; WLE = wide local excision.)

Independent-samples t-tests revealed no significant differences in age ($p = 0.1$), or BMI ($p = 0 .1$), between fatigue groups. Mann–Whitney U tests revealed no significant difference in the time surgery to radiotherapy ($p = 0.2$), travel time for radiotherapy ($p = 0.9$) or tumour size ($p = 0.5$). Although not reaching statistical significance in the bivariate context, ($U = 952$, $z = -1.72$, $p = 0.09$) smoking history, expressed as pack-years, may be of substantive significance: as such it was considered as a potential candidate exposure factor for multivariable analysis.

Chi-square tests for independence (with Yates' Continuity Correction for dichotomous variables) indicated no significant differences between fatigue groups for the variables HRT history, laterality, travel mode, menopausal status, smoking history, histopathological grade and TNM stage. Violations of the minimum expected cell frequency were found for the variables work status and histological diagnosis. These categorical variables were consequently collapsed into the dichotomous forms of 'job/no job' and 'invasive ductal carcinoma/other' respectively. A significant association was then found between diagnosis and fatigue group, $\chi^2 (1, n = 100) = 3.91$, $p = 0.05$, with an associated small to moderate effect size, phi = 0.22. Cross-tabulation revealed that only 29 % of invasive ductal carcinoma patients were in the fatigued group, as opposed to 51% of patients with other diagnoses. No significant association between dichotomised work status and fatigue group was found.

The baseline values of longitudinal variables were also contrasted for the two fatigue groups. Continuous variables were compared using independent-samples t-tests for normally distributed data and Mann–Whitney U tests if non-normality was indicated. The results are summarised below in Table 5.13:

Baseline variable	Fatigued (n = 38)	Non-fatigued (n = 62)	Test
Questionnaire data			
HADS anxiety [a]	8 (7.5)	4.3 (2.8)	U = 711, p = 0.001
HADS depression [a]	4 (4.5)	1.9 (2.1)	U = 543, p < 0.001
HADS sum (A+D) [a]	12.5 (9.5)	6.2 (4.1)	U = 541, p < 0.001
IPAQ total (MET-min/wk) [a]	1759 (2742)	1752 (2166)	U =1124, p = 0.9
Immunological			
IL6-sR concentration (ng/dL)	43.5 (11.6)	39.8 (11.5)	t = -1.55, p = 0.1
Haematological			
Red blood count (10*12/L)	4.41 (0.32)	4.42 (0.34)	t = 1.96, p = 0.2
haemoglobin (g/dL)	13.4 (1.1)	13.7 (0.9)	t = 1.49, p = 0.2
haematocrit	(0.40 (0.03)	0.41 (0.03)	t = 1.08, p = 0.3
mean corpuscular volume	91.5 (5.9)	92.9 (4.7)	t = 1.28. p = 0.2
mean corpuscular haemoglobin	30.3 (2.3)	31.0 (1.7)	t = 1.76, p = .08
platelets (10*9/L)	264.2 (60.5)	270.0 (69.3)	t = 0.42, p = 0.7
White blood count (10*9/L) [a]	6.3 (2.2)	6.8 (1.9)	U = 985, p = 0.2
neutrophils (10*9/L) [a]	3.6 (1.3)	3.9 (1.5)	U = 996, p = 0.3
lymphocytes (10*9/L) [a]	2.0 (0.7)	2.1 (0.8)	U = 1030, p = 0.5
monocytes (10*9/L) [a]	0.52 (0.20)	0.46 (0.17)	U = 1070, p = 0.7
eosinophils (10*9/L) [a]	0.19 (0.16)	0.19 (0.15)	U = 1100, p = 0.8
basophils (10*9/L) [a]	0.03 (0.02)	0.03 (0.02)	U = 945, p = 0.2

Table 5.13 Baseline value of longitudinal variables for fatigued and non-fatigued groups, of the n = 100 study sample of breast radiotherapy patients.
Normally distributed continuous variables are means (standard deviation)
[a] Non-normally distributed continuous variables are medians (inter-quartile range).
(HADS = Hospital Anxiety and Depression Scale; IPAQ = International Physical Activity Questionnaire; IL-6sR = interleukin 6 soluble receptor.)

Mann–Whitney U tests revealed significant differences in the baseline anxiety, depression and cumulative HADS scores for the two fatigue groups, but not for physical activity levels. A series of Mann–Whitney U tests (n = 98), revealed no significant differences in baseline WBC or IL-6sR concentrations. Similarly, a series of

two-tailed independent-samples t-tests indicated no significant differences in red blood counts or platelets for the two fatigue groups.

Multivariable analysis

A logistic regression analysis was undertaken to determine the combination of pre-treatment exposure factors that best predict fatigue group during treatment. The aim of this analysis was to generate the simplest model (least number of variables that retained prognostic utility). As the objective was prognostic, a selection algorithm was used. A backward method of entry was chosen as forward selection has been linked with an increased risk of Type II errors (Field 2005, p. 161).

Ordinal and nominal variables with more than two groups were transformed into multiple dichotomous variables prior to entry to the model. No transformations of variable distribution were used in this analysis to render clear results. Helpfully in this respect, logistic regression makes no assumptions regarding the distribution of IVs. The assumptions made regarding the logistic regression model were: that the logit of the outcome varied linearly with multiple IVs; the distribution of the DV was dichotomous; an absence of multicollinearity between IVs.

IVs entered into an initial model were: age, pathological diagnosis, work status, smoking pack-years, BMI, tangential separation, field area, PTV_{50}, maximum lung dose, and baseline fatigue, anxiety, depression, physical activity, IL-6sR concentration and blood counts. The significance level criterion for exclusion of variables, after the application of the likelihood ratio test, was set to $p = 0.01$ to reflect the number of IVs included at Step 1 of the analysis. After seven iterations the variables comprising an initial model were – in decreasing order of statistical significance – baseline fatigue, anxiety, smoking pack-years, maximum lung dose, tangential separation, physical activity sum, PTV_{50}. The initial model correctly classified 88.5% of patients overall. The sensitivity of the model was 73.7%, and the specificity was 82.8%.

After the preliminary run, all haematological variables were excluded from further iterations as they added little to the prognostic ability of the model whilst reducing the

sample size to 98, due to two cases with missing data. PTV_{50} and maximum lung dose were also excluded as they were considered overly complex parameters to be of utility in a 'simple' prognostic model. Because of these adjustments, a second backward stepwise logistic regression analysis was performed, and the results after seven iterations are summarised in Table 5.14.

Baseline variable	β	SE	Wald	Sig.	Odds ratio	95% CI for Odds ratio	
						Lower	Upper
Fatigue	-.16	.04	18.72	<.0001	1.19	1.09	1.27
Anxiety	.17	.08	4.77	.03	1.18	1.02	1.38
Physical activity	.001	.00	4.65	.05	1.0	1.0	1.0
Constant	4.6	1.63	7.96	.005			

Table 5.14 Final logistic regression model for the dichotomous outcome, fatigued or non-fatigued group during radiotherapy treatment.

The final model, comprising the raw (untransformed) FACIT-F fatigue baseline score, baseline anxiety and baseline physical activity was statistically significant, χ^2 (3, N = 100) = 45.63, $p < 0.0001$, indicating that the model had utility in classifying patients to the fatigued/non fatigued groups. The model correctly classified 82% of patients overall. The positive predictive value was calculated as 80%. The sensitivity of the model was 71.1%. The specificity of the model was 88.7%.

The Wald statistics indicates the contribution of an IV to the predictive ability of a model. Of the three predictors, baseline fatigue has the largest individual contribution, W = 18.72, $p < 0.001$. An approximate effect size (R) for individual predictors can be derived - from the Wald statistic - using the following equation:

$$R = \pm\sqrt{\left(\frac{Wald - (2 \times df)}{-2\,LLH\ for\ step\ 1}\right)}$$

.....**Equation 5.3** (Field 2005, p 223)

Where df = degrees of freedom; LLH = *log-likelihood* statistic (an indicator of how much unexplained information remains after the model has been fitted to the data.)

Applying this formula generated a large effect size for baseline fatigue of, R = 0.45. Additionally, baseline fatigue had a modest Exp(*B*) of 0.84. This statistic can be inverted – for easier interpretation – rendering a point estimate odds ratio of 1.19. Therefore, for every additional point increase in FACIT-F baseline fatigue score (less fatigued), participants were 1.19 times (19%) less likely to be classified as fatigued during treatment. The data was consistent with a reduced likelihood of up to 27%. Although anxiety (Wald = 4.77, p = 0.03, R = 0.18, OR ≅ 1.38) and physical activity (Wald = 4.65, p = 0.05, R = 0.18, OR ≅ 1) are only marginally significant, their joint inclusion enhances the sensitivity of the model by approximately 8%.

Multivariable model accuracy

The primary consideration in terms of assessing the accuracy of the model is how well the model fits the study data. The goodness of fit of the model as a whole is indicated by the Homer-Lemeshow Test, (χ^2 = 9.35, p = 0.3). The hypothesis under test here is that the observed values are significantly different from the predicted values. Therefore, the non-significant result indicates that values predicted by the model were not significantly different from the observed data (Field 2005, p. 254). Additionally, pseudo R^2 values estimated that the model as a whole explained between 36.6% (Cox and Snell R^2) and 49.8% (Nagelkerke R^2) of the variance in fatigue group classification.

Considering individual subjects, 94 cases had standardised residual values (z) in the range -2 < z > 2. Four cases had a standardised residual value outside the range -2.5 < z > 2.5. These cases represented outlying data that the model does not fit well. Two of these participants (17 and 64), were predicted to be in the non-fatigued group but in actuality both became fatigued during treatment, and the other two participants (14

and 89) were in the converse situation. The diary entries of all four cases were further investigated to establish if there were any factors that might explain their atypical response. A discussion of these cases can be found in Chapter section 6.5. The four outlier cases were not excluded from analysis as all values of Cook's distance were significantly less than 1 (range .25–.56), indicating none of the cases exerted an undue influence over the model (Field 2005, p. 200). Further confidence in this course of action was provided by leverage (hat) values for the four cases. The average hat value can be approximated by the following formula:

Average hat value = (k+1)/n..... **Equation 5.4** (Field 2005, p 165)

where k is the number of explanatory variables and n is the number of cases.

Hoaglin and Welsch (1978) specify that hat values greater than two times the average are indicative of a case exerting an unduly large influence on the regression equation. Here, as the values for the four cases (0.02, 0.04, 0.02 and 0.03) are very close to the average of 0.03, no cases were removed prior to further iterations.

Cross-validity of the multivariable model

The first step in assessing how well the model would perform when applied to other data was to check the assumption of no multicollinearity between IVs. Tolerance values of less than 0.1 (Menard 1995) and VIF values greater than 10 (Myers 1990) are considered to be indicative of problems with multicollinearity. The minimum study tolerance value was 0.78, and maximum VIF value was 1.28, signifying an absence of multicollinearity.

A jackknife procedure was used to assess the cross-validity of the model. Each subject was removed sequentially from the derivation dataset and the model re-calculated. That is, 100 iterations in total. This procedure allowed the robustness of the model to individual cases to be assessed and the probability of the subject's outcome could be predicted from the remaining derivation dataset (Katz 2006, p. 182).

The statistics summarising the accuracy of the model are tabulated below in Table 5.15. The close agreement between the final model values and the mean values for the jackknife validation sets suggested good cross-validity properties of the final model.

	Cox & Snell R^2	Nagelkerke R^2	% correctly predicted	Sensitivity %	Specificity %
Final model	.366	.498	82.0	71.1	88.7
Validation datasets	.365 (0.01)	.498 (0.01)	82.0 (0.43)	70.9 (0.87)	88.5 (0.78)

Table 5.15 Comparison of model accuracy parameters for the final model and the jackknife validation dataset. (R^2 validation values are means (SD); discrimination validation values are percentages (SD).)

Towards a prognostic model

The general form of the logistic regression equation is:

$$\text{logit}(p) = b_0 + b_1X_1 + b_2X_2 + \ldots\ldots b_nX_n \quad \ldots\ldots\ldots\ldots \textbf{Equation 5.5} \text{ (Field 2005, p266)}$$

where p is the probability of an outcome, b_0 is a constant and b_n is the regression coefficient of variable X_n.

logit(p) can be transformed to p by the following equation:

$$p = \frac{1}{1+e^{-\text{logit}(p)}} \quad \ldots\ldots\ldots\ldots \textbf{Equation 5.6}$$

Substituting the final model logistic regression β coefficients into equation 5.5 rendered the following equation:

logit (fatigued) = 4.6 – .16 x baseline fatigue + .17 x anxiety + .001 x physical activity
..... **Equation 5.7**

Equations 5.6 and 5.7 were used to predict the probability of fatigue group status for each case excluded from the jackknife set. The derivation dataset displayed good discrimination, correctly predicting the correct fatigue group for 80% of the confirmatory cases.

To extend the utility of equation 5.7, a high-risk (for fatigue) group was defined. The SPSS 'optimal binning' function was used to yield the cut points that maximised the differences between fatigue groups. This procedure indicated that, the fatigued group was characterised by a baseline FACIT-F fatigue score < 40, a HADS anxiety score ≥ 5 and low or medium IPAQ physical activity categories.

CHAPTER SIX **Discussion of results**

Prior to a discussion of the study results, it is worthwhile revisiting the broad study aims, which were framed in response to reviewing the literature:

- To determine the course and intensity of fatigue over a 40Gy/ 15#/ 3 weeks dose-fractionation schedule.
- To quantify the contribution of patient, disease, haematological, immunological and treatment-related risk factors for fatigue, both before and during radiotherapy treatment.
- To evaluate the longitudinal relationships between body size (BMI and volumes of normal tissue irradiated), IL-6sR (a bio-marker of inflammation) and fatigue.
- To identify pre-radiotherapy risk factors for fatigue, as a precursor to developing a parsimonious prognostic model to determine which subset of early-stage female breast cancer patients are at high risk of fatigue during adjuvant radiotherapy.

This chapter has been structured into five subsections that reflect the order of the results. After brief comments regarding the study sample, section *6.1* provides an overview of the aggregated cohort fatigue response, in terms of the course, intensity and prevalence. Interpretation is inter-woven throughout the text to provide an evaluation of the clinical significance of these data. Fatigue diary quotes supplement a discussion of the impacts of the reported fatigue levels. As the diary data were not subjected to a full analysis, the use of quotes was limited to the support of empirical data and is attributed to as specific a group of patients as possible. Diary entries also illuminate contextual issues for atypical subjects. Section 6.1 concludes with a comparison of the fatigue group data and substantive differences are examined.

The second *section (6.2)* discusses baseline variables and their relationship to baseline fatigue. The emergent importance of psychological factors focussed this discussion on the HADS data and the pathways that relate anxiety and depression to fatigue. Extant published data provides the context for this discussion. The relative

role of other relevant baseline variables is evaluated, both as bivariate and multivariable relationships.

Section 6.3 characterises the changes from baseline of the longitudinal variables. The course of variables over time is then related to fatigue and the implications for the treatment of RRF considered. This work encompasses an evaluation of the impact of dose-volume parameters on both IL-6sR concentrations and fatigue.

The fourth *section (6.4)* is concerned with the factors that contribute to fatigue during treatment. The large contribution of baseline fatigue will be discussed in relation to patient and radiotherapy-related factors that may plausibly influence RRF.

The last *section (6.5),* considers the development of the prognostic model comprising baseline factors that are predictive of fatigue during treatment. The accuracy of the model, both in terms of how well it fits the data and the predictive value at an individual level, is scrutinised. Out of trend subjects are evaluated to determine if reasons for poor model precision can be identified. The chapter concludes with a discussion of the clinical utility of the model.

The sample

The projected recruitment rate of two per week was successfully realised. Women declining to enter the study did not appear to be intrinsically different in terms of age and fatigue level, when compared to study participants. Moreover, the age distribution of the study sample was comparable to the UK female EBC population, apart from a lower proportion of women older than 70 years. This was largely a consequence of the increased incidence of exclusionary comorbidities with increasing age. The generalisability of the study findings to women older than 70 is therefore uncertain. The statistical power of the study was based on a medium effect size for multivariable regression analysis. This assumption was justified by the subsequent data: indeed, it was conservative for the multiple regression data. The sample size was therefore adequate for the principal statistical tests.

6.1 Fatigue overview

The study cohort of 100 women recorded a relatively modest but statistically significant increase in median self-reported fatigue, as measured by the FACIT-F, from pre-treatment baseline (44) to the final week of radiotherapy (37). The decrease in fatigue from week three to four weeks post treatment was also statistically significant, although the effect size was relatively small. This is the first time the acute fatigue response has been reported for the current UK standard breast radiotherapy schedule of 40Gy in 15 fractions over three weeks. As such, these data reflect contemporary surgical and radiotherapy protocols used in the UK.

The largest increase in fatigue occurred between the second and third weeks of treatment. Maximum fatigue was typically recorded at week three of treatment. This constitutes a departure from the pattern consistently evident in previous reports of longer fractionation schedules. That is, the maintenance of a peak level of fatigue (or slight increase) throughout the last weeks of treatment (Donovan et al. 2004, Geinitz et al. 2001, Wratten et al. 2004). No plateauing effect is apparent with the current cohort, suggesting that peak fatigue may be avoided with the shorter schedule. This conclusion is supported by the fact that Geinitz et al. (2001) and Wratten et al. (2004) both reported increases in fatigue of the same magnitude between week three and the last week of treatment, as between baseline and week three. Assuming that fatigue is in some way part of the acute radiotherapy response, it might seem self-evident that a shorter fractionation schedule would be less tiring than a longer schedule. Indeed, in broad terms the reduction of treatment impact is implicit in the hypofractionation rationale of the START trial, although as a tertiary outcome given the apparent disease-relapse equivalency of the study schedule (START Trialists' Group 2008b). However, it is noteworthy that the mean FACIT-F score of the current study indicated a greater mean intensity of fatigue at baseline (41.0 v 45.7) and at peak fatigue (35.8 v 40.8) than in the Wratten et al. study. The current study sample is twice the size of the Wratten et al. study, which has resulted in tighter confidence intervals around the central measure. Furthermore, the ecological validity of comparing findings from an Australian-based study is uncertain, with the potential for multiple differences in healthcare settings that confound fatigue. Despite this limitation, the Wratten et al. study is useful as it provides the most direct comparison with the current data, utilising

a common outcome measure and sampling participants' with comparable disease characteristics.

Comparing FACIT-F data across studies raises the question of which measure of central tendency best represents the data distribution. Generally, the stability of the mean is increased over repeated measures (Osborn 2008, p. 115), but it is still affected by skewed distributions. The median is insensitive to extremes. An appraisal of the study raw data suggests that as the mean and median fatigue scores are virtually concordant, either provides a good representation of the data in this case. The median measure was favoured as it exists as a scale score, and as such interpretation was rendered more meaningful. Where other studies have only reported means, that statistic from the current study was available for comparison.

The average change score between baseline and week three was seven points: double the minimum clinically important difference, of three to four scale-points, as defined by Cella et al. (2002c). The Cella et al. definition implies changes of this magnitude would be reflected in discernable impacts on QoL, even allowing for the variability in baseline scores. Certainly, participants who recorded changes (in the more fatigued direction) of the order of the study average commonly reported profound impacts on physical, cognitive and affective aspects of functioning. This diversity of functional impacts is widely postulated (Mitchell and Berger 2006, NCI 2007, Schwartz et al. 1998), but little primary evidence has been presented to characterise the effects. The following exemplars were diary entries recorded during week three of treatment by four separate individuals who self-reported deterioration in fatigue score of the average, or slightly above:

'Some days I feel everything is too much trouble.' (participant 033GD)

'Hit a brick wall Wednesday and Thursday. Complete exhaustion.' (participant 047EN)

'I have been forgetful & lack concentration, if anything this seems to be getting worse.' (participant 007HP)

'Tiredness makes me moody and I sometimes explode for really silly things.' (participant 064PN)

Subjective data is, by definition, (re)constructed and expressed in relation to individual experiences (Morgan and Drury 2003). However, the content and representative nature of the qualitative data reinforces the clinical significance of the self-reported FACIT-F change scores evinced in the study. Of the 74 diaries returned, 49 (66%) were from participants in the non-fatigued group, and the remaining 34% from the fatigued group. Therefore, neither subgroup disproportionately completed the diaries.

Two studies that have previously utilised multi-dimensional scales to assess RRF have reported significant increases in the general or physical fatigue scales, but lesser changes in the cognitive and particularly affective scales (Geinitz et al. 2001, Smets et al. 1998a). This is somewhat at odds with the affective state of many of the fatigued participants.

A prominent and recurring motif of diary entries from participants classified as fatigued was the sometimes overwhelming turbulence of emotional states, characterised by unforeseen and non-specific swings from numbness to heightened emotion:

> *'I find that these moods fluctuate progressing throughout the day and at its worst in the evening, probably when I am more fatigued.'* (participant 037DR, week three)

> *'I seem to be quite emotional. Short tempered at times and taking offence at innocent comments from my family.'* (participant 049PK, week three)

> *'Thursday was my worst day (eigth treatment !!) Very, very low and emotional – very snappy and sorry for myself ... Friday - felt really great and happy - really surprised after not such a good day Thursday.'* (participant 078AW, week two)

> *'Roller-coastering. I do feel far more emotional & sensitive. Also, feelings of "doom & gloom" fly in & out: but mostly, not too bad!'* (participant 099LG, week three)

Emotional lability was clearly an unpleasant aspect for some. Methodological reasons may exist for seeming inconsistencies between the diary entries and the published data from the multi-dimensional scales. The latter may be useful in distinguishing domain-specific impacts, but (because of their complexity) the validity of multi-dimensional scales has been questioned (Jean-Pierre et al. 2007). The scales may

therefore be measuring different constructs to the diary questions. The interpretation of multi-dimensional scales is also complex. How does one interpret scale findings that do not converge? For example, VAS scores utilised in the Geinitz et al. (2001) study correlated with the general scale at all time-points, but not the affective domains.

Considering the current data, profound impacts for a proportion of participants seem unambiguous. However, fatigue is also prevalent in non-cancerous populations. Any evaluation of the clinical significance of CRF scores is dependent on the availability of reliable and valid normative data. The median fatigue levels revealed in the current study were higher at all time-points than the normative FACIT-F scores for US females of median 47 and 45 for women above and below 50, respectively (Cella et al. 2002a). Before radiotherapy, the difference in the fatigue levels for the two datasets was relatively small. Indeed, approximately half of the study cohort reported fatigue levels of the same order or less than the normal population data, when matched for age group. By week three of treatment this proportion had reduced to a third. At this time-point, the difference between median scores for the cohort and the normal population was three times the previously defined minimal clinically important difference.

The lack of normative comparison data is a common methodological limitation of CRF studies (Prue et al. 2006). In this study it was felt that collecting a relatively small quantity of data with little context was of limited value. Unless administered in a careful manner, the validity of using a chronic illness scale in the general population is uncertain. For example, respondents have no event to relate to questionnaire items such as 'I am unable to do my usual activities'. Where normal data is not collected, the availability of a valid healthy population dataset is crucial. The headline conclusion of a recent comprehensive review of fatigue measurement tools (Minton and Stone 2009) recommended the use of the FACIT-F scale in the research setting, suggesting the use of this tool may increasingly become the norm. In these contexts, establishing reliable and valid FACIT-F data for healthy UK populations would be a welcome advance: ideally, both normal population and cancer population data would be established. The sample sizes would need to be sufficiently large to enable stratified analysis and matching for age, sex and site-specific cancers. A pragmatic approach might indicate the desirability of additionally establishing equivalent normative data for the QLQ-C30. The widespread use of this health-related QoL tool in multicentre breast

cancer trials has built up a body of comparative evidence that includes (limited) fatigue information. Moreover, Minton and Stone (2009) have recommended its use as a clinical screening tool.

Given the relative elevation and apparent impact of cohort fatigue scores at the end of radiotherapy, it is reassuring that aggregated cohort fatigue was returning to baseline levels four weeks post treatment. This pattern replicates trends evident in previous studies (Greenberg et al. 1992, Irvine et al. 1998, Smets et al. 1998a, Wratten et al. 2004). Whilst a decrease in fatigue was evident for the majority, 26% of study participants were still categorised as fatigued at four weeks follow-up. Indeed, 10 (% of) subjects exhibited a clinically significant deterioration of four points or more between the end of radiotherapy and follow-up. Seven of the 10 cases had completed a diary, and the entries for these cases were reviewed to consider if they could elucidate further potential reasons for the individuals' lack of recovery. Specific contextual entries were that one participant's husband was concurrently undergoing major surgery, whilst another mentioned the demands of being self-employed throughout treatment. A feature that was common for all seven cases was significant impacts on the cognitive and affective domains in addition to the physical domain. Expressions of concern regarding future uncertainties were common, suggesting non-adaptive coping mechanisms may play a role in a poor fatigue response after treatment for these participants.

The problem of persistent fatigue in a minority of patients long after curative breast treatment has been identified in numerous studies (Andrykowski et al. 1998, Bower et al. 2000, Bower et al. 2006, Servaes et al. 2009). Associated estimates of the prevalence of long-term fatigue range up to 34% of patients. Non-standardised measurement tools and inconsistencies in the methods of defining fatigue have probably over-inflated this figure, with a more conservative estimate being 15 to 20% (Goldstein et al. 2006). The prevalence of chronic fatigue appears to decrease as the interval from the completion of radiotherapy increases. Of the 28% of START trial QoL substudy participants who reported high levels of fatigue at baseline, half were still experiencing fatigue at six months (start of the chronic period), with 12% still reporting fatigue at 5 years follow-up. It is reasonable to assume that events surrounding the adjuvant treatment act as a trigger of fatigue.

It was evident from the current data that the correlation between fatigue at baseline and at four weeks follow-up was strong and highly significant. This (acute-phase) study cannot answer the question of whether the participants whose fatigue levels did not improve post treatment continued on a downward trajectory. However, evidence does exist to suggest that fatigue levels during the acute phase are a strong risk factor for experiencing chronic fatigue (Geinitz et al. 2004, Smets et al. 1998b). The latter study reported that 30% of the variance in fatigue nine months post radiotherapy was explained by the treatment fatigue level. The Geinitz et al. (2004) study revealed that pre-treatment fatigue and depression level explained between 49% and 60% of the variance in fatigue, two and a half years after the completion of radiotherapy. This surprisingly high figure suggests that patients with the most elevated pre-treatment and on-treatment fatigue may be at risk of chronic fatigue.

The Geinitz et al. and Smets et al. studies are rare exemplars that have the extended individual changes in RRF from the acute into the chronic period. Further research is needed to more definitively trace the long-term impacts of adjuvant treatments. The time constraints imposed on a PhD meant this was not feasible here. With hindsight, the postal administration of FACIT-F and HADS questionnaires at six months post radiotherapy would have provided a valuable indicator of recovery that would additionally have allowed comparison with a limited portion of the START data. Ideally, the measurement of objective biological data would be incorporated. Resource implications of longitudinal studies may determine that, where suitable samples are available, 'bolting' sub-studies onto ongoing multi-centre trials proves a pragmatic solution. The current inclusion of QoL-type outcomes into multicentre RCTs such as IMPORT is to be welcomed, as long as measures are not overly crude to discern specific behavioural effects.

Rationale for the prospective collection of biological samples is provided by Collado-Hidalgo et al. (2006), who have revealed evidence for associations between persistent CRF and elevated IL-6sR concentrations in breast cancer patients. Whether the 10 study subjects recording deteriorating fatigue scores post treatments continue to suffer long-term chronic fatigue is speculative. Certainly, the current data did not provide evidence of an aberrant cytokine profile in these patients. The concentrations of IL-

6sR were not significantly different from the remainder of patients at the end of treatment, nor at four weeks follow-up.

A wider clinical point regarding long-term iatrogenic effects of radiotherapy is that after the intensive monitoring during daily radical treatment the next follow-up appointment may be up to six months hence, with minimal contact with specialist oncologists after that. Such a care plan may be adequate for the majority of patients, but risks overlooking significant related symptoms in a minority, who may be readily identifiable from acute data.

A final and potentially important implication of the fatigue data is suggested by Gutstein (2001). If inappropriately activated inflammatory mechanisms that sustain CRF also correlate with patients clinical and biochemical status, then response to therapies and thereby prognosis may be modulated. Certainly, it is known that inflammatory processes play a role in the complex interactions that initiate and progress cancers (Coussens and Werb 2002). More specifically, biomarkers of inflammation have been identified as risk factors for reduced survival in breast cancer patients (Pierce et al. 2009).

Comparison of the fatigue group data

The comparison of fatigued and non-fatigued participants requires the definition of a precise scale cut-off point. The method of classification is a crucial, but somewhat arbitrary progression, which will modulate the prevalence statistics. Van Belle et al. (2005) used a logistic regression analysis to assess the ability of various FACIT-F scores to predict the classification of fatigued or not fatigued, as defined by the ICD-10 diagnostic criteria. The ensuing cut-off point of 34 for the diagnosis of fatigue, as proposed by Van Belle et al. was adopted for this study. Confidence in this value is increased as it equates to an interval FACIT-F score of 60 (from 100), which corresponds with a score of 4 or more on a 10-point scale. Many scales of this type categorise scores of 0 to 3 as mild and 4 to 6 as the moderate fatigue range (Mendoza et al. 1999). The magnitude of difference in fatigue level between the two groups and their stability justify the use of a cut point as a way of investigating the role of other characteristics.

A related issue is whether patients should be classified as fatigued as a result of a low scale score over a short period? To minimise classification bias, an average score at week two and week three of ≤ 34 was categorised as a fatigued participant. The converse of this scenario was that an average week two and week three score of 35 and above was categorised as non-fatigued. An alternate diagnostic criterion of only classifying participants as fatigued with scores ≤ 34 over both weeks is attractive, but does not tally well with the cumulative course of fatigue; characterised by a steeper increase in the final week of treatment. Furthermore, the FACIT-F is a comparative scale. An average score over two weeks may serve to counteract the effects of response shift and recency, whereby undue weight is given to the current experiential state. The FACIT-F scale scores fatigue over the previous week. Even such a short-term retrospective measurement is susceptible to the vagaries of memory, but should reduce sensitivity to random or episodic fluctuations in fatigue.

The relatively modest increase of the aggregated median cohort fatigue score seems somewhat at odds with the significant increase in the prevalence of fatigued participants from 23% at baseline to 43% at week three: an incidence rate of 20%. On division of participants into two groups based on the adopted cut-off point, 38% of participants were categorised as fatigued, with the remaining 62% categorised as non-fatigued. What then becomes apparent is that the non-fatigued group remain virtually unaffected from baseline (see Figure 5.2). This categorisation represents a homogenous subgroup with relatively little variation in fatigue scores. No clinically or statistically significant changes occurred at any time-point for the non-fatigued group. In other words, the participants who were not fatigued before treatment tended to remain so. In fact, the non-fatigued group members tended to become marginally less fatigued during the early part of treatment – probably due to a concurrent decrease in anxiety – before experiencing a slight increase in fatigue by the end of treatment and retaining pre-treatment levels at four weeks follow-up. Approximately one quarter of the cohort actually improved overall from baseline to the end of treatment. A strong trend existed for such participants to belong to the non-fatigued group, and to record a small clinically non-significant decrease in fatigue. Four of the cohort recorded an improvement in fatigue of more than eight points. All these participants were in the non-fatigued group.

Compared to the non-fatigued group, the fatigued patients were significantly more fatigued before radiotherapy, and continued to become steadily more fatigued during treatment. The group difference in median scores was 13 at baseline, 23 at week three before decreasing to 16 four weeks later. Highly significant changes were evident within the fatigued group between baseline and on-treatment time-points. The magnitude and the large associated effect sizes signified the substantive nature of these changes. A clear recovery of dose-time response was discernable in these participants after the completion of treatment, although the IQR spread was widest at four-week follow-up indicating variance in post-treatment trajectory. Overall, the course of fatigue suggests the radiotherapy may exacerbate a pre-morbid state in the fatigued subgroup of participants.

Both the proportion of non-fatigued participants and the associated fatigue course is broadly in accordance with findings by Wratten et al. (2004), who reported 43% of participants as experiencing significant fatigue. The slightly higher proportion reported by Wratten et al. may be related to the longer treatment schedule. Additionally, their estimate was always likely to be slightly higher than the current study as it was derived using a FACIT-F cut-off of < 37, (although the exact criteria for classification was not wholly explicit). Notwithstanding minor methodological discrepancies, considering the close congruence of the findings, it is reasonable to estimate that the proportion of DCIS and EBC patients suffering significant fatigue during radiotherapy to be 40%.

Vis-à-vis the fatigued group, the trajectory of the fatigue response in relation to the chronology of the treatment is suggestive of a causative effect of the radiotherapy. Whilst only an RCT can truly establish a cause-effect relationship, it is useful to interpret the study findings with reference to the classic Bradford Hills (1963) criteria for causality, namely: strength of the relationship, consistency in different populations and under different circumstances, specificity (cause leads to a single effect), temporality (cause precedes effect in time), biological gradient (dose-response relationship), biological plausibility and experimental evidence (Breslow and Day 1987, Rothman and Greenland 1998). RRF is almost certainly not attributable to a single cause, but the increase in fatigue reported in this study, and many others, is to a greater or lesser degree consistent with these criteria. The specificity criteria are

questionable as radiotherapy may induce a symptom cluster including fatigue, however, the underlying aetiology may (or may not) share common mechanisms.

The careful framing of the study eligibility criteria would suggest that the increase in fatigue reported in the current study is attributable to direct or indirect effects of the radiotherapy treatment. Concomitant comorbidities and a history of pathologies that theoretically could confound the fatigue and/or inflammatory response were excluded. The composition of the exclusion criteria also provided a homogenous cohort regarding disease and treatment-related characteristics. Approximately 40% of breast radiotherapy patients were excluded as a consequence of the prescription of systemic poly-chemotherapies. It is salient to recognise that this (desirable) narrowing of the set of risk factors for fatigue inherently renders the results less universal. A further limitation was the potential confounding effect of prescription and over-the-counter drugs. A proportion of the pharmacopeia lists fatigue or drowsiness as a side effect. Regularly taken medication was recorded at baseline, but no attempt was made at control. A number of study participants took medicines that can cause fatigue – statins, anti-hypertensive medication, diuretic or gastric medication and a range of analgesics – throughout the study duration.

The next finding to account for is why only a minority of participants suffered significant fatigue? At a group level, the sharply divergent course of fatigue suggests baseline fatigue is a significant determinant, whilst the radiotherapy treatment exacerbates/amplifies a pre-existing difference. The factors that affect baseline fatigue will now be considered.

6.2 Risk factors for baseline fatigue

Psychological mood

Compared to 'healthy' populations, the average study participant self-reported moderately elevated levels of anxiety, as measured by the HADS anxiety scale. The mean cohort anxiety score at baseline (5.6) was 25% greater than the equivalent normative data reported from large north European populations (Mykletun et al. 2001, Spinhoven et al. 1997). 75% of the study participants were within the normal range (0

to 7), a further 12% in the mild range (8 to 10) and the remaining 13% in the probable case range (11 to 21). A minority of participants were therefore experiencing levels of anxiety that warranted clinical monitoring.

Comparing the study data to equivalent EBC samples, 2,208 women participating in the START QoL sub-study, recorded a comparable mean anxiety score of 6.0 (Hopwood et al. 2007), whereas Geinitz et al. (2001) reported a slighter lower pre-treatment score of 4.8. Approximately one third of the patients in these two studies would have previously undergone chemotherapy: a treatment that has the potential to affect individuals self-reporting of psychological mood in an unpredictable manner via phenomena such as response shift. Considering the equivalency of the scores at a group level, such effects are not obvious.

The baseline depression scores for the cohort were comparable to both the EBC data (Geinitz et al. 2001, Hopwood et al. 2007, Mills et al. 2003) and the available normative population data (Mykletun et al. 2001, Spinhoven et al. 1997). Surprisingly, study participants reported similar baseline levels of depression as non-cancerous populations. HADS categorical data confirmed that study patients were highly unlikely to actually be depressed, with 92 (%) of participants falling into the normal range, 4 (%) in the mild range and only a further 4 (%) at the lower bounds of the 'probable case' range. This study finding replicated the 3.1% of probable depression cases in the much larger START trial. The fact that only six participants' GPs were notified of high cumulative HADS scores – the threshold for which was deliberately set at a conservative level – reflects this state. The relationship between psychological mood and fatigue therefore appears to be a subtle one, with small variations in relatively low HADS scores being strongly associated with fatigue. Wider variation was evident in the anxiety scores compared to the depression scores.

The numerically larger non-fatigued group was a relatively homogenous subgroup, with considerably less variability evident in both anxiety and depression data relative to the fatigued group. The non-fatigued participants self-reported a significantly lesser intensity of both anxiety and depression than the fatigued group. The median anxiety level of four for the non-fatigued group is identical to the normative population score. In contrast, the equivalent score of eight for the fatigued group was at the lower end of

the mild classification. The depression scores for the fatigued group were significantly higher than for the non-fatigued group, but levels still tended to be relatively low. For example, the 75th percentile for the fatigued group (6.25) was within the normal range.

Convergent test results consistently indicated the strong relationship between psychological mood and baseline fatigue. Firstly, the ANOVA main effect for the cumulative HADS group was large, significantly different for all HADS levels and in the direction such that participants with higher baseline HADS scores were more fatigued. The absence of a discernable interaction effect between BMI and HADS group indicated that BMI did not have a mediating effect of depression on fatigue in these patients. In other words, low psychological mood does not appear to influence fatigue through inherent associations with BMI, as speculated by Geinitz et al. (2001). Presumably, depression levels are either inherent/pre-existing or predominately influenced by other factors centred on the disease, diagnosis and surgery. Secondly, the strongest bivariate relationship with baseline fatigue was depression. The correlation was strongly negative and highly significant. Bearing in mind the inverse nature of the FACIT-F scale, the correct interpretation of this finding is that more intense depression was strongly associated with increased fatigue. Thirdly, in multivariable analysis, baseline depression uniquely explained approximately a third of variance in baseline fatigue. This meant that depression was by some distance the strongest multivariable predictor of baseline fatigue. In contrast, anxiety was not a strong multivariable risk factor. This is probably due to the two variables sharing a proportion of the variance in fatigue explained. However, the finding does suggest a more proximal relationship between depression and fatigue compared to anxiety.

In comparison to the depression correlation, the relationship between anxiety and baseline fatigue was highly statistically significant, but approximately half the strength (see Table 5.4 for bivariate baseline correlations). In accordance with START trial data, older age was significantly associated with lower anxiety but did not influence depression level. As younger breast cancer patients with poorer prognosis were effectively excluded from the current study due to the receipt of chemotherapy, the negative correlation between anxiety and age cannot be explained by more aggressive treatment regimes or concerns regarding differential prognoses. Interestingly, participants with a histological diagnosis of DCIS recorded both a

clinically significant elevated median fatigue score at baseline (38) compared to all other diagnoses (46), and a greater intensity of anxiety and depression. The lower psychological mood in the participants diagnosed with DCIS – which was not related to lesser age – seems somewhat paradoxical as the prognosis for this patient group is excellent. So why might patients with a DCIS diagnosis have a lower psychological mood? DCIS is usually an asymptomatic pathology, diagnosed through radiographic screening. This leads to a rapid transformation from person to patient (and back to person). Whilst not typical of diary entries from participants with a DCIS diagnosis, two quotes from this group illustrate a problematic transition:

> *'Still feels unreal – as if it is happening to someone else.'* (participant 083JE, week one)

> *'Here is the frightening part. I didn't know I had breast cancer until my first mammogram on the 13th Feb. What a rollercoaster ride since then but thinking about being away from it all, I feel like I am going to be out on a limb, my safety net removed'.* (participant 040SH, week three)

However, this scenario also applies to many early invasive cancers. It may be uncertainty regarding the natural history of this pre-cancerous pathology, and therefore the necessity of treatment, has the potential to cause additional shock and anxiety. Whilst this study subgroup only comprised 13 participants, in-depth (quantitative and qualitative) investigation of the impacts of a DCIS diagnosis may prove an illuminating research area.

The relationship between depression and baseline fatigue

The strength of the association between baseline fatigue and depression is striking and demands explanation. The psychometric properties of the HADS scale have been validated in diverse settings (Herrmann 1997), including cancer patients (Moorey et al. 1990). Despite this, a prosaic reason for the strong correlation could be a degree of overlap between the operalisation of concepts, and therefore content of the two measurement tools. For example, one of the HADS depression items states 'I feel as if I am slowed down'. To assess the sensitivity of the correlation coefficient between fatigue and depression to this item, the statistic was re-calculated after its removal.

The result was a marginal reduction, from ρ = -.71 to -.70. This sensitivity analysis replicates an action conducted by Smets et al. (1996) in a study of mixed-site radiotherapy patients. They reported strong positive correlations, of between r = .56 to .67, between the HADS scale and the Multidimensional Fatigue Inventory (MFI-20) after removing the same item. The two findings suggest that substantive associations exist between the two variables, beyond an overlap in the operalisation of concepts.

A number of possibilities exist as regards the nature of the relationships between fatigue and depression. Broadly, the association may be causal or not. Fatigue may be an antecedent of depression, or vice versa. Alternatively, the two symptoms may simply coexist; possibly as constituent parts of a symptom cluster involving an inflammatory aetiology. The aetiological possibility that a profound immunological state involving cytokines is a risk factor for both breast cancer and fatigue and depression offers a further level of complexity. In the context of the treatment of CRF, if a common pathological pathway exists that underlies fatigue and depression then modulation of cytokine production and/or inflammatory pathways may provide the basis for novel treatments. If pre-existing depression has a causative association with fatigue, then focussing on anti-depressive interventions and/or psychosocial support may be more productive.

The data relevant to the theoretical inflammatory link will now be evaluated. Moderate but significant bivariate correlations were evinced between baseline IL-6sR concentration and a greater intensity of baseline fatigue, depression and anxiety. A low to moderate significant correlation was also found with BMI. To ensure significant relationships were not overlooked, theoretically relevant data was re-analysed using the parametric Pearson's product-moment correlation. Where indicated, data were transformed to improve normality of distribution prior to re-analysis. The results were almost identical, which increased confidence in the chosen non-parametric approach (data not shown). A further finding of note was a significant moderate positive correlation between IL-6sR and haemoglobin. The reason for this association is obscure. Certainly, there was no bivariate relationship between baseline haemoglobin level and fatigue. Similarly, no other baseline blood counts exhibited statistically significant associations with either baseline IL-6sR concentration or fatigue score.

Wratten et al. (2004) reported a correlation between baseline fatigue and IL-6 of r = .32, but after controlling for BMI this relationship was no longer significant. In contrast, in the current study, partial correlations controlling for BMI had little effect on the bivariate relationships between IL-6sR and both fatigue and depression, suggesting no relational role for BMI. However, the relationship between IL-6sR and fatigue was rendered non-significant when depression was controlled for (and the relationship between IL-6sR and depression when fatigue is controlled for). These results suggest that shared associations with depression level influence the association between IL-6sR and baseline fatigue.

Given the 'partialling' effect of depression, it is possible that the participants recording the most elevated HADS depression scores were subject to a depression-related fatigue aetiology, distinct from a more generalised cytokine-related mechanism. The fact that the removal of the most depressed fifth of patients from correlational analysis only slightly reduced the association between IL-6sR and fatigue is not supportive of this thesis. In light of the study aims, the apparent importance of depression instigated a further exploration of the relationship between pre-treatment depression and IL-6sR. The resultant data indicated that participants with elevated baseline depression had statistically significantly higher IL-6sR concentrations compared to participants with the lowest depression scores. No equivalent significant effect was discernable for any level of anxiety. Depression scores, but not anxiety scores, appeared to have a direct relationship to inflammation. These data raise the possibility of distinct pathological mechanisms for the anxiety and depression reported by the study participants.

As might be expected, anxiety and depression exhibited moderate to strong correlations at baseline. The two variables are clearly related. Studies conducted by behavioural scientists investigating symptomology during cytokine therapy for cancer (Capuron et al. 2000, Capuron et al. 2002) may elucidate the nature of this relationship. They make a distinction between a cytokine-induced neurovegetative dimension involving fatigue, impaired sleep, loss of appetites, etc. and a psychological dimension affecting mood and anxiety. Comparable divisions have been made in breast cancer studies between psychoneurological clusters including fatigue and depression and an emotional cluster including anxiety (Kim et al. 2008).

The pleiotropy and myriad physiological and psychological effects that IL-6/IL-6sR transsignalling can induce complicates the interpretation of the relational cytokine and anxiety and depression data. For example, elevated IL-6 levels have been linked with depressive states in normal populations (Maes et al. 1997, Lanquillon et al. 2000) and cancer patients (Musselman et al. 2001). Furthermore, research has documented that psychological stress and states of anxiety are associated with elevated IL-6 and IL-6sR in non-cancerous populations (Gaab et al. 2005, Maes et al. 1999). This work was extended to cancer patients by Miller et al. (2008) and breast cancer survivors by Bower et al. (2007), in an effort to provide mechanistic insight into depressive and associated behavioural symptoms. The body of work broadly explores the mechanisms that connect psychological stress with behavioural symptoms through bi-directional regulation of inflammatory cytokines by the HPA axis (Miller et al. 2008). A focus has been the glucocorticoid cortisol, commonly referred to as the stress hormone. As the appellation implies, cortisol is a central biological player in the response to stress and acts to dampen the immune/inflammatory response.

Under normal physiological conditions, the adrenal glands secrete cortisol in a circadian rhythm. Hypocortisolism is associated with fatigue, poor sleep hygiene and mood disorders (Jager et al. 2008). It has been demonstrated that fatigued breast cancer survivors have reduced levels of circadian cortisol production (Bower et al. 2002), flattened cortisol response curves (Bower et al. 2005b), and a blunted cortisol response to acute psychological stress (Bower et al. 2005a). As cortisol is a potent hormonal suppressor of the inflammatory response it would be expected decreased cortisol production would be associated with an augmented pro-inflammatory response. Indeed, Bower et al. (2007) reported that cortisol production was both negatively and linearly correlated with the IL-6 response to experimental stress in patients with breast cancer. A recent review of the biological effects of psychological interventions in breast cancer patients identified psychological stress-related dysregulation of cortisol production as a principal mediator of relevant biological processes (McGregor and Antoni 2009). Recent authoritative evidence has further demonstrated that psychological stress and depression can sensitise the response to subsequent immunological challenge (Glaser and Kiecolt-Glaser 2005, Seruga et al. 2008).

In the current study, the relatively low level of depression reported before treatment is arguably unlikely to precipitate the levels of self-reported fatigue. More plausible is the idea that the two symptoms may coexist as part of a neuro-immunological cluster. Considering the stress aspect, the psychological stress associated with a breast cancer diagnosis should not be underestimated: the shock, the psychosocial and physiological impact and ultimately a confrontation with mortality. Layered uncertainties regarding the course of treatments and the individual response to them must be assimilated in a relatively short span of time. The degree and quality of psychosocial support available is likely to be a specific influence on the anxiety response to breast cancer (Burgess et al. 2005), and broader socioeconomic factors may also be relevant here (Macleod et al. 2004).

One mechanistic explanation that is at least consistent with the inter-related FACIT-F, HADS anxiety and depression and IL-6sR study data, and extant theory and empirical data, is that patients who are pre-disposed to become fatigued during radiotherapy have a distinct response to the psychological stress of the cancer diagnosis and surgery. This response may involve a reduced HPA response. In these patients, biological responses to the psychological stress of diagnosis favours elevated circulating IL-6 concentrations. Consequential signalling of CNS pathways may potentate neurovegetative symptoms such as fatigue and depression. In this scenario, anxiety would largely be due to psychological or non-somatic mechanisms. The anxiety and depression responses would therefore be closely related phenomena, but the level of inflammatory markers would influence the latter more directly.

The clinical implications of this speculative scenario are three-fold. Firstly, patients with sensitised stress response pathways inhere an immunological landscape that is susceptible to a heightened inflammatory response during the prospective immunological stress of radiotherapy. It would be expected that sickness behaviour symptoms such as depression and fatigue would be more apparent in this patient subgroup, as reasoned by Bower et al. (2002), Bower et al. (2007), Dantzer et al. (2008), Jager et al. (2008), Miller et al. (2008), Myers (2008). The basis of the distinct response to stress is uncertain. Genetic polymorphisms (Collado-Hidalgo et al. 2008), inherent personality traits (De Vries et al. 2009), socio-demographic factors (Macleod et al. 2004) or simply a direct psychological reaction to the cancer and scheduled

treatments may all be influences. It is conceivable that ongoing investigations regarding the genetics of cancer progression and the role of the immune system (Apetoh et al. 2007, Coussens and Werb 2002) may provide valuable translational insights for CRF. In retrospect, it would have been sensible to request ethical approval to retain a small sample of whole blood that would have enabled the future genotyping of leukocyte DNA signalling via polymerase chain reaction primers. Essentially, this procedure would move the enquiry one step back up the biological chain. It is possible that polymorphisms in a Toll-like receptor or cytokine response genes (Apetoh et al. 2007) affects the immune response to radiotherapy and hence fatigue.

Trait anxiety is a more readily accessible concept than genetics. According to psychologists (De Vries et al. 2009), trait anxiety is a relatively stable characteristic of an individual that influences the stress response when confronted by a traumatic event: an event such as a breast cancer diagnosis. In a psychological study of EBC patients and women with a benign abnormality in the breast, trait anxiety was the only significant predictor of depression. Furthermore, Smets et al. (1998a) found no evidence for bivariate or multivariable associations between neuroticism and fatigue in radiotherapy patients. Whilst the placement of too much importance on single study findings is inadvisable, the results are suggestive of a (psychological) personality trait basis for anxiety but not (neurovegetative) fatigue. Anxiety would however act as a trigger for both depression and fatigue.

The second implication of the pre-destined anxiety related fatigue RRF hypothesis is that the strong association between mood and fatigue in breast cancer patients highlights the need for closer monitoring of anxiety and depression levels in breast patients before treatment. Younger patients and those from lower socioeconomic groups may benefit most from a service provision that extends to increased psychosocial support and talking therapies where indicated (Macleod et al. 2004).

The third implication is that RRF research and treatment approaches can be targeted at two complimentary dimensions: the psychological and the neurovegetative. A recent review of RCTs demonstrated the efficacy of psychological interventions in reducing anxiety in breast cancer patients (McGregor and Antoni 2009). Standard pre-treatment familiarisation with the treatment environment through written and verbal

information remains important (Macleod et al. 2004), but in reality may be rushed and inconsistent. As trait anxiety is a stable characteristic early interventions should focus on aiding successful coping techniques rather than fundamental change. Such adaptations may prevent the subsequent movement from a normal to a fatigued state. Innovations such as the radiotherapy open evening pioneered by Smith and Butters (2009) offers an ideal opportunity for patients to anticipate the reality of their forthcoming treatment and consider appropriate adaptations. This process may be aided by the interactions with those present; both experts (therapeutic radiographers), and an instant peer group.

For a (sizeable) minority, the neurovegetative dimension may be treated most profitably through neuroimmunological antagonists and possibly graded exercise. The current study indicated that the 40% of participants recording the most intense baseline fatigue had significantly more elevated concentrations of IL-6sR compared to the least fatigued 20%. More evidence is required to establish proof of principle, however, the associated effect size was relatively large. RCT methodology provides the most efficient way to address the viability of such approaches. NSAIDs and cytokine antagonists such as the naturally occurring IL-6 antagonist soluble gp130 or blockers of signalling pathways may provide novel targets for treatment.

The current study did not measure the levels of any marker of HPA function. The validity of extrapolating the body of the Bower et al. data from breast cancer survivors (one to five years post treatment) to the acute phase is uncertain. Therefore, further work is needed to elicit the relationships between cortisol concentrations and both cytokine data and behavioural symptoms before and during treatment. The proliferation of small-scale studies, with a diversity of populations, biological agents assayed and outcome measures present problems when pooling samples. This situation accentuates the importance of standardised methods and established inflammatory markers.

The question of whether depression antecedes baseline fatigue is impossible to discern definitively from the current data: the temporal relationships between the two variables will be discussed in section 6.3. Clarification of the relationships between symptoms proximal to the initial diagnosis warrants further research. Intervention

studies that modulate one specific component of anxiety or depression form the most pragmatic way forward. Further testing of drugs such as methylphenidate, modafinil and paroxetine could generate both aetiological and treatment-effect information (Carroll et al. 2007).

The relationships between BMI, physical activity and baseline fatigue

The mean BMI of the participants in the fatigued group was approximately 5% greater when compared to the non-fatigued group. This difference was not statistically significant. The finding that baseline fatigue was not significantly different for low, medium or high BMI participants also suggests a lack of substantive association between BMI and baseline fatigue. Consistent with these findings, no significant bivariate correlation was found between the two variables. These findings are contrary to previous studies (Kilmurray et al. 2004, Wratten et al. 2004), which have reported significant positive associations between BMI and baseline fatigue in breast radiotherapy patients. The Wratten et al. study reported a moderate correlation between BMI and pre-treatment FACIT-F score of $\rho = .4$, $p = 0.01$, compared to $\rho = .10$ in the current study. The mean BMI (and variability) reported in the former study, 28.9 kg/m^2 (SD = 5.6) is comparable to that recorded in the current study.

BMI is conspicuously an imperfect measure of body composition, which does not account well for extremes; for example, the smaller frames of Chino-Asian ethnicities. Estimation of body-fat percentage through diverse techniques is in many respects a superior metric for body composition. A number of methodological issues may also account for the difference in findings. In this study, BMI was calculated using the average weight at baseline and week three to incorporate weight changes during treatment. However, height was not measured at a consistent time of day in order to account for progressive spinal disc compression during the day. A methodological comparison is not possible, as the precise methods used in the Wratten et al. study are not detailed. The relatively tighter exclusion criteria of the current study may influence associations between BMI and fatigue in unpredictable ways. Additionally, it is always possible that significant associations are Type II errors. That is, a spurious finding that is an artefact of multiple comparisons.

The current data also revealed a lack of significant interaction effects between BMI and psychological mood, as measured by the cumulative HADS score, or physical activity level, as measured by the total IPAQ score. BMI does not appear to influence fatigue directly through inherent associations with depressed mood and decreased activity levels, as speculated by Geinitz et al. (2001) and Wratten et al. (2004). Despite the lack of evidence for a central role for BMI in baseline fatigue level, it is relevant to consider the contribution of adipocytes to IL-6 release (Mohamed-Ali 1997), and hence the indirect stimulus for IL-6sR upregulation. The Spearman's correlation between BMI and baseline IL-6sR concentration here was modest but statistically significant. Therefore, when theoretically relevant, the evaluation of correlative relationships between IL-6sR and appropriate variables were supplemented by partial correlations controlling for the effect of BMI. The relationship between BMI and irradiated volumes of tissues will be addressed in the longitudinal variable section 6.3.

The aforementioned two-way between groups ANOVA results did reveal a significant main effect for physical activity, as measured by the IPAQ. The effect for physical activity level was moderate, and suggested that participants who recorded a high level of activity – as defined by the IPAQ scoring protocol in Appendix 4 – were partially insulated from the fatiguing effects of radiotherapy. Furthermore, despite the lack of interaction between BMI and fatigue revealed in the preceding analysis, the benefit of high activity levels was most marked for participants in the highest BMI group. The high activity classification is a level of activity that equates to at least 12,500 steps per day. One combination of activity that fulfils the criteria for the 'high' classification is an hour of vigorous-intensity activity – for example heavy digging, running or swimming – over and above the basal level of activity at least three days a week. An alternate activity combination is an hour of more moderate exercise seven days a week. The latter activity regime would be realistic for the majority of study participants with good performance status. Indeed, approximately 20% of participants recorded a variety of vigorous-intensity activities in their IPAQ measurements. This subgroup was typically involved in structured exercise activities such as going to the gym, running or swimming. Although the non-fatigued and fatigued groups reported virtually identical baseline median (and mean) physical activity levels, 29% of the non-fatigued group were sufficiently active to be classified in the high activity category compared to only 13% in the fatigued group.

Overall, the IPAQ data reveals a surprisingly active cohort. The median score at baseline (1692 MET-min/week) was greater than the normative data for a number of countries. The normative data was established for a sample of 16,230, drawn from across the European Union (Rütten and Abu-Omar 2004). For comparison purposes, the Netherlands's sample was the most active national population (2366 MET-min/week): at the lower end of spectrum Northern Ireland (693 MET-min/week), Sweden (1119 MET-min/week) and France (1173 MET-min/week) were all less active than the study cohort. Participants in the population study were aged 15 years and older, which may tend to elevate the normative estimates, although median data should remain insensitive to outliers and extreme values.

The population study used the short-form IPAQ, whereas the current study used the long-form. Johnson-Kozlow et al. (2006) have suggested that the long-form may be susceptible to over-estimates of cumulative scores through 'double counting' of activities. To counter this threat to validity, the researcher provided participants with a careful and consistent explanation regarding the correct completion of the questionnaire. However, erroneous interpretation remains a possibility. Ankle-worn devices called accelerometers, measuring say steps per day/week, can provide an easily understood, objective measure of activity. This study chose to use the IPAQ to capture dynamic changes in activity domains, but where logistically feasible their use should be adopted.

The current baseline data for the individual domain-specific activities were very similar for the two fatigue groups. Similarly, the cumulative time spent sitting was almost identical. The elevated fatigue experienced by the fatigued patients does not appear to be sufficient to impact significantly on activity levels before treatment. Neither does the data support a directional relationship whereby decrement in physical functioning (and a consequent decrease in activity) antedates fatigue. However, it is noteworthy that the non-fatigued group had more than twice the proportion of participants compared to the fatigued group classified as attaining the high level of activity. This high activity classification is associated with lower fatigue and appears to constitute a substantively important threshold. Moderate strength bivariate correlations were revealed between higher baseline physical activity and both lower fatigue and lower levels of depression,

again indicating potential benefits from being active prior to treatment. Of course an association is not evidence of a causal relationship. It is plausible that participants who are very active are less fatigued for many inter-related lifestyle reasons. For example, only two of the participants classified in the high activity group were current smokers. Interestingly, anxiety level was not significantly correlated with physical activity.

The general benefits of aerobic and resistance exercise as a treatment for CRF have been established in a series of reviews (McNeely et al. 2006, Knols et al. 2005, Cramp and Daniel 2008), although a notable Cochrane Review specific to adjuvant breast cancer patients was equivocal (Markes et al. 2006). The evidence suggests more benefit is accrued after the completion of adjuvant treatment compared to before or during treatment (McNeely et al. 2006, Cramp and Daniel 2008). Whilst the favourable physiological effects such as cardiorespiratory fitness are well established, the associations between physical activity and CRF are uncertain. Logic suggests that physical activity may serve to impede the negative feedback loop between fatigue and physical de-conditioning identified in CRF models (Figure 3.8). In addition to favourable physiological changes are the potential psychological benefits of exercise – which may be maximised when conducted as a group activity (Samarel et al. 1998) – for patients experiencing low psychological mood. The strength of evidence for the positive effects of exercise on anxiety and depression is weaker than for fatigue (Cramp and Daniel 2008). As previously mentioned, no relationships were discernible between anxiety and activity level in the current study.

The association between fatigue and physical activity prior to treatment implies that active patients may benefit from maintaining an activity program. A number of study participants were aware of potential links between exercise and reduced fatigue, which had provided a motivation to change lifestyle. A minority had designed quite ambitious exercise programmes at the outset of radiotherapy. For less active participants, there may be benefits of a change in behaviour at the earliest stage after diagnosis, although this benefit may only be accrued in the short-term if a reasonably high activity threshold is broken. Of course, exercise affords multiple potential health benefits beyond the narrow outcome of CRF: notably reduced relapse rates (Holmes et al. 2005, Pierce et al. 2007), although confounding factors may account for this relationship. The range of patients' performance and fatigue status will always

determine that activity advice will need to be tailored to the individual. Early patient-specific advice regarding activity and exercise could be provided at the same time as information regarding post-surgical exercises.

The identification of the optimal approach, timing and duration of exercise programmes in breast cancer patients remain priorities for the research community. Further interventional research is required to clarify the most efficacious mode for administrating exercise in breast radiotherapy patients. Qualitative research exploring the acceptability of different activity programmes and barriers and motivators to behaviour change in this patient group should inform the interventional approach.

The impact of patient-related, disease-related and haematological characteristics on baseline fatigue

The only pre-treatment patient-related characteristic exhibiting (marginal) statistical significance (and a moderate effect size) for fatigue was age. The associated moderate effect size suggests that this effect is substantive. As might be expected, the oldest participants (62 or older) were the most fatigued before radiotherapy. This effect is reflected in the normal population data for women (Cella et al. 2002a). However, there was no clear trend for the age groups, with the middle group (55 to 61) being significantly different from the other two groups, and recording scores that reflected the least fatigue. The positive relationship between age and fatigue exists despite a negative relationship to anxiety. No relationship exists between age and depression. These findings concur with the pattern of results reported from the larger START trial QoL data (Hopwood et al. 2007).

Bower et al. (2000) reported fatigue was most severe amongst menopausal breast cancer survivors. Subgroup analysis indicated no significant differences between fatigue and the menopausal status or HRT history of the current study participants. The sample was predominately post-menopausal, with only 11 pre-menopausal and 16 peri-menopausal participants. However, these data replicate a finding in a larger sample of 212 EBC patients that was more balanced as regards menopausal status (Goldstein et al. 2006).

None of the disease-related or surgical characteristics, including time elapsed from surgery to commencing radiotherapy, appears to have had a significant effect on baseline fatigue.

Relative to the fatigued group, the non-fatigued group had elevated total and differential white blood counts. The difference was statistically non-significant. It is noteworthy that whilst the differences are small in absolute terms, a comparable pattern is replicated across all leukocyte sub-types. In addition, the pre-treatment difference tended to be sustained at all time-points. The substantive importance of these differences is unclear, but it is conceivable that the pattern may be indicative of a sub-optimal or at least distinct immune state. No equivalent differences were evident for any of the study erythrocyte parameters. In contrast to the current results, Wratten et al. (2004) found positive associations between baseline red blood cell counts and baseline fatigue. The discrepancy in findings may be partly attributable to the fact that 15 of 52 subjects in that study had received chemotherapy prior to radiotherapy treatment.

Multivariable relationships at baseline

The multivariable model comprising depression, physical activity and IL-6sR accounted for 52% of the variance in baseline fatigue. The associated effect size was large, indicating that the model had high statistical power. Despite the careful framing of eligibility criteria, expert clinical advice and a consideration of the published evidence of fatigue covariates, just less than half the variance in baseline fatigue was explained by obscure factors. This fact serves to highlight the complexity of analysing toxicity endpoints. A panoply of factors including pain, comorbidities, coping strategies, use of prescription drugs, and contextual issues exist that may affect fatigue status and confound the relationships between variables.

Multivariable analysis itself may reveal interaction effects, which may have the effect of modifying the bivariate relationships between exposure factors and fatigue, sometimes in unexpected directions (Katz 2006, p. 6–13). Given the strength of the bivariate relationship between anxiety and fatigue, the lack of a statistically significant

model contribution from anxiety was surprising. The fact that anxiety shares a large proportion of variance with the stronger predictor depression probably accounts for this apparent anomaly. The calculation of semi-partial (squared) correlation coefficients indicates the unique contribution of the variable to the DV with no shared variance with other variables (Tabachnick and Fidell 2007, p. 145). This statistic revealed depression uniquely accounts for more than a third of the variance in baseline fatigue. In contrast, physical activity and IL-6sR concentration did not make statistically unique contributions to the model, when other factors were controlled for. Relative to depression, IL-6sR concentration is a weak factor in determining baseline fatigue levels. Again, this may be due to shared variance with other IVs. As previously suggested, it is possible that IL-6sR influences fatigue through secondary associations with depression. Semi-partial (squared) correlation coefficient data implied that approximately 15% of the variance in fatigue was shared between depression and the two other IVs. These data also suggested IL-6sR shared a larger proportion with depression, compared to physical activity. The latter appeared to act largely as a discrete factor. No significant multivariable role was discernable for white blood counts or any other haematological variable.

6.3 Change in longitudinal variables from baseline, and the impact on fatigue

Anxiety and depression

Mean anxiety for the whole cohort, as measured by the HADS, decreased only very slightly from 5.6 scale points at baseline to 5.3 at week three of radiotherapy. This slight improvement in anxiety during radiotherapy was common across fatigue categories and age groups. Notwithstanding a degree of cross-study variation in the pre-existing level, this finding has been replicated across studies (Geinitz et al. 2001, Hopwood et al. 2007). Presumably, it is attributable to an increasing familiarity with the treatment, staff and treatment environment.

Anxiety scores for the fatigued group were higher at baseline than for the non-fatigued group, median scores being eight and four respectively. By week three of treatment,

both groups had recorded a median decrease of one point. Baseline anxiety level was a strong determinant of anxiety during radiotherapy. However, the parallel longitudinal course for the two fatigue groups indicated that anxiety appears to affect baseline fatigue level, rather than the change in fatigue during treatment. Thus, the increase in fatigue reported by the fatigued group was not attributable to the change in anxiety during treatment.

Only two (outlier) cases of the 62-strong non-fatigued group recorded sufficiently intense anxiety scores to be classified as 'probable cases'. In contrast, approximately one third of the fatigued group retained this classification throughout treatment. For a significant minority it appears that if not addressed prior to the start of radiotherapy, elevated levels of anxiety are likely to persist throughout treatment. Younger patients (aged less than 54) were particularly at risk. During treatment, the younger patients became disproportionately more fatigued. This effect may be partially related to additional demands of dependents and jobs but appears predominately to be related to significant relationships with a greater intensity of anxiety at baseline. Age did not appear to influence depression levels during treatment.

Mean cohort depression scores increased slightly during treatment from 3.0 at baseline, to 4.1 at week three. These data are comparable to the scores recorded in the START trial (Hopwood et al. 2007), and represent a more intense symptomology than for normal populations (Mykletun et al. 2001, Spinhoven et al. 1997). None of the non-fatigued group was classified as a probable case of depression, whereas six of the 38 fatigued group participants were. Even within this subgroup the maximum HADS depression score recorded at any time-point was 13; a scale score that signifies the lower reaches of the probable diagnostic classification. The prevalence of clinically substantive depression was therefore very low. It is known that otherwise healthy depressed people invariably experience fatigue: the depression levels recorded here do not seem sufficiently intense to explain the corresponding fatigue levels. Certainly, the widespread use of any anti-depressant measures in this patient group is not indicated. Any consideration of an interventional use of anti-depressants in a clinical trial setting should be solely as a putative CRF treatment.

A number of studies have dismissed the link between depression and fatigue due to a low prevalence of depression that fulfils diagnostic criteria. Moreover, Jacobsen and Weitzner (2004, p. 225) suggest that the use of diagnostic fatigue criteria, such as the ICD-10, which specifically excludes cases where fatigue is a 'primary consequence of a co-morbid psychiatric disorder', may be useful in discriminating between the two symptoms. In the current study, the levels of depression recorded were not sufficiently elevated to be classified as such, but remain highly associated with fatigue.

Distinguishing longitudinal fatigue from depression is not straightforward, as fatigue is a symptom of depression and the two symptoms are common in cancer patients. A crude 'average' correlation coefficient across eight studies that recorded both fatigue and depression (Andrykowski et al. 1998, Hann et al. 1998, Geinitz et al. 2001, Smets et al. 1996, Smets et al. 1998a, Smets et al. 1998b, Stone et al. 2001, Visser and Smets 1998) was $r = .54$. This figure was based on 1039 patients, but was unweighted for study sample sizes. Broadly, fatigue may reduce mood, fatigue may be a symptom of depression or the symptoms may be related to the interaction effect of a third agent related to the cancer or treatment, for example cytokines.

A study that specifically addressed the directional nature of the relationship between fatigue/depression was Visser and Smets (1998). They found that pre-treatment fatigue explained 11% of the variability in post-treatment depression level, whereas pre-treatment depression level explained 4% of the variability in post-treatment fatigue. These data do not strongly support the theory that fatigue is secondary to depression. In the current study, the high degree of the correlation between measurements of the two symptoms at all time-points suggests that concurrent levels may be more important. Furthermore, the longitudinal consistency of the measures supports the theory that the symptoms coexist. If this was the case, it is intuitive to expect that feedback loops are likely to exist where one symptom feeds into another.

Unfortunately, as HADS data was not recorded at the four-week follow-up, the course of depression after treatment cannot be addressed by this study. At the study design stage it was felt little would be gained from post-treatment HADS measurements as fatigue was the primary endpoint. In retrospect, given the apparent importance of

depression, it would have been interesting to compare the post-radiotherapy course of the HADS and the fatigue data.

Studies that have shown a divergence of depression and fatigue contradict the concept that the two symptoms share a common aetiology. Either such that fatigue increases during radiotherapy whilst depression does not (Geinitz et al. 2001, Greenberg et al. 1992, Smets et al. 1998a, Visser et al. 1998), or that the two symptoms exhibit alternate longitudinal courses (Bennett et al. 2004, Goldstein et al. 2006). The current study data does not bear such observation out. What the depression scores for the aggregated cohort data obscure is that the fatigued group tend to record increasingly intense depression scores over the course of treatment, whereas the non-fatigued group remains stable and relatively low throughout treatment. Median depression scores for the non-fatigued group remained at a constant and low level of one scale score (see Figure 5.21), a lower score than the normal population average. In contrast, the fatigued group recorded an increase in depression from a median score of four at baseline, six and a half at week two and seven at week three. The median depression scores recorded for the fatigued group are therefore comparable to normative data at baseline, but increase during treatment into the 'borderline' classification of Zigmond and Snaiths' (1983) categorisation. The upper end of the IQR was nine, which is at the threshold of the 'probable case' classification. The divergent course of the depression scores for the fatigue groups indicates that depression level is an important factor in fatigue both at baseline and during treatment. Furthermore, the courses of the two HADS components for the fatigue groups are consistent with the theory of a group of patients at a high risk of exacerbating neurovegatative symptoms based on the immune response to tissue damage and inflammation.

Contrary to the concept that the increase in depression was attributable to an associated increase in IL-6sR was the lack of a significant bivariate correlation between the two variables during treatment. Inflammation is not a stable state. It is therefore conceivable that fatigue, scored over the previous week, did not correlate well with a single IL-6sR sample. Nonetheless, the lack of statistical association was surprising. Morrow et al. (2003) tested the effect of the selective serotonin re-uptake inhibitor anti-depressant paroxetine in cancer patients. The resultant findings provide

further empirical evidence that weighs against a close causal connection between the two variables. As might be expected, depression was reduced, but recorded fatigue was unaffected. This would suggest that these two symptoms coexist, but are discrete pathological entities. The importance of distinguishing between symptoms may be lessened by the availability of psychostimulant agents that have concomitant anti-depressive properties, or anti-depressants with energising effects (e.g. methylphenidate).

Further clinical trials are indicated to clarify the efficacy of different psychological interventions to treat fatigue in breast cancer patients. Cognitive-behavioural therapy is likely to be expensive. The use of psychosocial support, relaxation exercises and mindfulness or hypnotherapy techniques may be used more efficiently to modulate anxiety and stress responses. The front-line position of treatment and review radiographers means they are well placed to research, deliver and assess such clinical initiatives.

Two reports of survival analysis in Scandinavian patients provide a further level of evidence that point to the importance of depression in breast cancer diagnosis and treatment (Hjerl et al. 2002, Hjerl et al. 2003). They have reported that the risk of mortality remains significantly higher in female breast cancer patients with depressive symptoms, after controlling for suicide and accidental death.

Physical activity

The median and mean cumulative IPAQ data highlighted differing aspects of the respective activity levels of the fatigued and non-fatigued groups. The two groups reported comparable median physical activity levels at baseline. By week three of treatment, the median activity levels of the fatigued group was 70% of what it was at baseline, with the non-fatigued group reporting no change in median activity levels. The two groups reported virtually identical mean cumulative IPAQ score at baseline. However, the fatigued group reported a proportional decrease of 30% in mean activity levels from baseline to week three. In contrast, the non-fatigued group recorded an increase of 341 MET-min/wk in the same period, which corresponds to a proportional

increase of 12% on baseline levels. This elevation of the mean was attributable to a number of participants undertaking a (considerably) higher than usual level of activity during radiotherapy. The median values arguably provide a more representative statistic as they remained insensitive to such changes. The fatigue experienced by the fatigued group was apparently sufficiently intense to reduce activity levels by a third. The corollary of this was an increase in the median time spent sitting: by more than an hour a day by week three of radiotherapy. In contrast, the median amount of time spent sitting was unchanged from baseline to week three of treatment for the non-fatigued group.

Although many causal relationships are conceivable, the lack of significant bivariate correlations between IPAQ scores and all other variables except fatigue scores was suggestive of a relatively direct relationship between activity and fatigue. Indeed, measures of physical activity can arguably be considered a proxy for fatigue levels. In animal studies this is often the only way to gauge fatigue. The most plausible direction of the relationship is such that an increase in fatigue impacts on lower activity levels. It is possible that a decrease in activity caused the increase in fatigue, but many diary quotes from the fatigued group suggest otherwise:

> *' ...unable to do anything except basic chores.'* (participant 047EN, week three)

> *' ...made myself get to nearby shop was going to go to local park but got part way and had to turn back.'* (participant 030JH, week two)

> *'Trying to work & carry on as usual, wish I could take time off work.'* (participant 016AC, week one)

> *'Felt tired and exhausted coming home after final radiotherapy treatment, sleeping in the car on the way home, wanted to go to bed but didn't, went to purchase paint for my daughter's bedroom came back and had to go to bed for a few hours.'* (participant 064PN, week three)

A strong emergent theme from the fatigued group diaries is a tension between the desire to reduce activities and the need to maintain the architecture of normal life. The reduction – of 581 MET-min/wk – in cumulative median activity for the fatigued group was largely due to a decrease in domestic activities (washing, cleaning, garden work,

etc.) and particularly a near cessation of social, sport and leisure-type activities. It is noticeable that the median score for leisure-type activities was zero before and during radiotherapy. Together these data are reflective of the motivational adaptive nature of the sickness behaviour framework, whereby the consequences of behaviour render the change more or less likely. Consistent with this framework, these patients will maintain the basic necessary activities. The scope of the basics of life will vary depending on individual circumstances. Essential activities ranged from simply attending daily treatment, to continuing full-time work and looking after dependents. Other routine activities may be designated a lower priority and become curtailed. Considered together, the diary and quantitative data form a consistent body of self-reported evidence that activity is reduced in response to fatigue.

As previously mentioned, the mean activity data highlighted the fact that a minority of participants recorded very high levels of activity. It may not be surprising that those who were active before treatment tend to maintain activity levels during treatment. In fact, the percentage of participants recording a high level of activity remained constant before and during treatment. This raises the question of whether increasing exercise is appropriate for fatigued patients during treatment. The sickness behaviour model would suggest that patients experiencing fatigue based on activation of the immune system might be better served by reducing activity. The advice commonly given to patients to 'do what you can, but rest if you need to' appears vague but reasonable; particularly in light of the diary quotes. In the CFS setting, this self-management approach is sometimes referred to as pacing. The aim of pacing is to maintain activities while avoiding overexertion through self-awareness of an individual's limits.

Applying the sickness behaviour theory to the findings suggests an adaptive approach, which reflects reorganised priorities, may prevent a progression along the energy continuum to a state of fatigue. Pressure to adopt a non-adaptive approach, may take a variety of forms, both internal and external. The need to maintain employment and family life activities are often overt. A counter-pressure to be 'ill' and exhibit appropriate behaviour is more subtle. Certainly, a number of participants' described feelings of guilt or fraudulence, at being so active during breast cancer therapy.

A consistent evidence-based message regarding physical exercise may currently be an unrealistic aim. A number of participants had designed quite ambitious exercise programmes at the outset of radiotherapy. Whilst such initiatives should not be discouraged, the benefit may depend partly on the motivation for the change. During treatment, exercise may serve to disrupt a potential de-conditioning feedback loop but not greatly alleviate fatigue. Sustained lifestyle change may serve to improve health-related QoL and even improve relapse probabilities.

Interleukin-6 soluble receptor

Considering the cohort as a whole, the median concentration of IL-6sR increased modestly during radiotherapy before returning towards baseline concentration at four-week follow-up (Figure 5.14). A significant effect for time was evident, represented by a large effect size. The only time-point when IL-6sR concentration was statistically significantly different to other points was at week three of radiotherapy, suggesting a substantive but cumulative effect. No comparative results for IL-6sR concentrations during radiotherapy could be identified; the levels reported by (Collado-Hidalgo et al. 2006) for breast cancer survivors' one to five years post-radiotherapy results are, however, available. They reported mean plasma concentrations of 40.1 ng/mL and 30.6 ng/mL for fatigued and non-fatigued participants respectively. The current study recorded mean sera concentrations that were 3% and 10% higher than for the fatigued survivors in the Collado-Hidalgo study, at baseline and week three respectively.

The samples from prostate cancer patients assayed pre-experimentally also provide a scientifically interesting comparison for the experimental breast cancer participants. The median concentration for the prostate was relatively elevated before radiotherapy, 54.5 ng/mL decreasing to 36.8 ng/mL at the twentieth and final fraction of radiotherapy treatment. This pattern of data may be indicative of the paraneoplastic effects of the macroscopic tumour on immunological pathways. That is, as the tumourcidal effects of the radiotherapy shrink the tumour, the associated release of bioactive inflammatory agents will tend to reduce the shedding of membrane bound IL-6R into the soluble isoform. It is signal that the field sizes for radical prostate treatment are much smaller

than for breast radiotherapy. This factor may partly explain the different pattern in results, although not the magnitude of decrease in the prostate group.

Normal serum ranges quoted for healthy populations are 14 to 46 ng/mL with a mean of 31 ng/mL (R&D Systems 2007), and 15.2 to 45.0 ng/mL, mean 25.5 ng/mL (Dugué and Leppänen 1998). Additional comparative data was generated pre-experimentally for six healthy female volunteers. No age matching was undertaken. The measured median (IQR) concentration for these subjects of 30.6 ng/mL (25.5–38.5 ng/mL) was of the same order as the published normative data. The measures of central tendency for the whole breast cancer cohort are therefore at the upper limit, but still within normal ranges. Individual concentrations displayed a high degree of heterogeneity (and to make this manifest median data and IQR were reported for the experimental data). The range of extreme values was 19.9 to 70.6 ng/mL at baseline and 23.62 to 72.4 ng/mL at week three. At baseline, 30% of subjects had an IL-6sR concentration above the upper normal limit of 46 ng/m, rising to 40% at week three. A wider analytical point is that results exhibiting wide variations commonly complicate the evaluation of biological samples (Dugué and Leppänen 1998). For example, the heterogeneity of the baseline data obfuscates an interpretation of the influence of baseline IL-6sR concentration on subsequent changes.

Evidence suggests that levels of IL-6sR concentrations are reflective of the circulating levels of IL-6 (Chalaris et al. 2007, Collado-Hidalgo et al. 2006, Jones 2005). The strong positive correlation between the two variables for a subgroup of 24 participants extends this body of literature. When activated, IL-6 may increase by many factors. Changes in the two cytokines are likely to be non-linear, with potentially large changes in IL-6 reflected in much smaller relative changes in IL-6sR. The degree of correlation at week three of radiotherapy increases confidence that the partial elevation of IL-6sR during radiotherapy evinced in Figures 5.14 is a real dose effect, related to the radiotherapy as opposed to a random fluctuation. In accordance with this concept, the increase in IL-6sR during radiotherapy is reversed after the completion of treatment.

The pattern of the data suggests a probable, but weak causal link between radiation and peripheral serum IL-6sR concentration. However, the individual variability within this data is large. Normal tissue reactions are subject to individual tolerances, with a

minority of patients suffering disproportionately. If a proportion is genetically determined, a sufficiently sensitive laboratory assay may render high-risk individuals identifiable. Interestingly, Collado-Hidalgo et al. (2008) have recently provided preliminary evidence for variation in cytokine gene polymorphisms and a potential link to CRF. The next consideration was whether IL-6sR concentrations related to fatigue at the behavioural level.

Relationships between interleukin-6 soluble receptor and fatigue

At baseline, there was no significant difference in IL-6sR concentrations between fatigued and non-fatigued groups. By week three, the IL-6sR concentration of the fatigued group was significantly higher than the non-fatigued group. The upregulation of IL-6sR was significantly elevated within the fatigued group, but not in the non-fatigued group. Considering the extremes of fatigue, a subgroup of participants recording fatigue scores below the bottom quintile recorded virtually no change in concentration (37.1 ng/mL to 37.0 ng/mL) from baseline to week three, compared to (41.9 ng/mL to 51.3 ng/mL) for the most fatigued fifth. Both findings are consistent with the concept of a subgroup of participants, defined by pre-existing factors that are susceptible to an elevated inflammatory response during radiotherapy.

Apart from the problem of wide variability, an inherent problem with the interpretation of relatively small IL-6sR increases is the issue of inter-assay variation. At physiological concentrations, the coefficient of inter-assay variation was quantified at less than 3.9%. A reference sample assayed on eight separate occasions provided the most conservative estimate of inter-assay variation, of 7%. Arguably, therefore, only relatively large changes, of say 10% or more could be reliably detected. The magnitude of difference between fatigued and non-fatigued groups at week three was greater than this figure and can therefore reasonably be attributable to factors other than random error.

In accordance with the Collado-Hidalgo et al. (2006) findings, no significant correlation was found between IL-6 and fatigue during radiotherapy level at week three ($r = .08$, $p = 0.7$). A contrary finding from Wratten et al. (2004) reported that IL-6 correlated with

fatigue at the last week of radiotherapy (week five), but this correlation was not significant after controlling for BMI.

With reference to section 5.2.5, it was clear that, at baseline, a significant correlation between IL-6sR and fatigue no longer existed after controlling for depression. In marked contrast, a highly significant zero order Pearson's correlation between IL-6sR and fatigue at week three was almost unchanged when controlling for week three depression level. This finding indicates that during radiotherapy, the mediating effect of depression on the relationship between IL-6sR and fatigue is lessened. Additional partial correlation analyses indicated age, BMI or physical activity levels (data not shown) did not significantly influence associations between IL-6sR and fatigue. These results are consistent with a direct upregulating effect of radiation on IL-6sR levels, and a concomitant increase in fatigue.

Before discussing the effect of irradiated volumes on both IL-6sR and fatigue, three additional points are salient to the interpretation of the cytokine data. The bivariate associations between the variables are of a low to moderate order. A relevant consideration (that the current study cannot address) is how closely the peripheral concentration of IL-6sR reflects the local tissue concentration at the site of irradiation/inflammation. This is relevant, as relatively low levels of IL-6 can initiate profound CNS changes via paracrine signalling. Secondly, if sickness behaviour pathways are involved, the influence of the cytokine could be modified at many points in the chain from induction to behavioural action, for example, abnormal vagal afferent nerve or HPA axis activation. Furthermore, the effect of cytokines may be subtle and dependent on broader social, economic and demographic factors. In accordance with sickness behaviour theory, behaviour change may be a motivational state. Thirdly, acute phase proteins such as CRP and SAA (released in response to IL-6 activation) may provide improved non-specific biomarkers of inflammation.

Volumes of tissue irradiated

The heterogeneity of body shape and anatomical topography dictates that adequate PTV coverage yields a wide range of total volume of tissues irradiated within the

primary beam. For example, the volume of tissue irradiated within the 50% isodose varied between 582 cm^3 to 4956 cm^3, with a mean value of 1748. These parameters remain virtually unchanged after the removal of the two mastectomy cases. Maximum dose data reveals a range from 110 to 138% (M = 113%, SD = 4.1) of the applied dose. It important to note that this statistic represents a point dose and that the frequency distribution is skewed left with a mean value much nearer the lower end of the range. However, the retrospective evaluation of a 2D plan using 3D software reveals dose levels consistently higher than the 95 to 107% range stipulated by the guidelines ICRU 50 (1993) and 62 (1999). This finding indicates the dosimetric benefits of full off-axis 3D planning. Full dose compensation should act to reduce normal tissue doses without compromising PTV coverage.

Volumes of individual organs irradiated

Between 0.6% and 13.5% of the ipsilateral lung was irradiated within the 50% isodose with a mean value of 7.6%. This data indicates superior dose-volume characteristics as compared to historically reported data. Reported figures include 15.3% (7.2) for a parallel-opposed pair technique, 11.5% (7.2) for a non-divergent back border technique and 13.13% (6.5) for a half-beam block technique (Law et al. 2000). This comparative data also suggests the order of dose-volumetric impact of commonly used techniques. The paper also supported the use of differing techniques for different breast sizes. This may be important when both the volume of lung irradiated and the dose are strong determinants of early and late radiation-induced lung sequelae (Kahán et al. 2007).

Cardiac irradiation within the 50% isodose was between 0% and 4.7%, with a low mean value of 0.7%. For the 52 participants with right-sided tumours cardiac irradiation was negligible. The mean cardiac volume irradiated within the 50% isodose was 1.4% for participants with left-sided tumours. This figure compares well with the 5.7% (4.5) reported for 100 breast patients with left-sided tumours from a 12-year-old study (Gyenes et al. 1998). An earlier RCT had reported a mean (SD) cardiac volume of 25% (11.9), a figure that was found to be associated with excess cardiac morbidity and mortality (Rutqvist et al. 1992). This progression is reassuring and reflects the technical refinement in patient-beam anatomy in response to increasing recognition of

radiation-induced cardiac toxicity. Limited cardiac dose data using current techniques has been reported by the START trial (Venables et al. 2004). Using central slice data, 39 of 62 patients had no cardiac dose greater than 50% of the prescribed dose. Utilising 3D data, a comparable 56% of the current study participants received cardiac irradiation within this range. When considering participants with left-sided tumours, the mean (SD) maximum dose recorded was 90.7% (26.2) of the prescribed dose. Whilst this is a point dose, such irradiation is in excess of the 30Gy that has been advanced as a threshold dose for significant myocardial effects (EBCTCG 2000). The advent of 3D planning has provided the means to assess realistically the cardiac dose-volume data. Extant data then creates the challenge to minimise the iatrogenic effects, whether through cardiac shielding, prone irradiation, IMRT or partial breast irradiation.

Between 0 and 92 cm^3 of hepatic tissue was irradiated within the 50% isodose with a mean (SD) value of 11.7 cm^3 (1.1). As the CT planning scan acquiring the body data did not consistently extend beyond the inferior extent of the liver, only absolute values were consistently available. The female liver volume will vary – with body size and alcohol consumption – but has been estimated to be 1350cc (Andersen et al. 2000). A crude estimate of the volume of the liver irradiated during the study would be up to 7%, with a mean of approximately 1.7% for right-sided tumours. This finding refines previous unpublished data compiled by the author that detailed a mean of 1.6%, and range 0 to 5% (Courtier 2006). Only one reference was identified that addressed the irradiation of the liver during breast radiotherapy (Hoffman 1977). The use of non-current radiotherapy techniques severely limits the relevance of the study.

Tangential separation did not correlate well with the dose-volume parameters, and no other 2D variables were identified that were indicative of the volume of tissue irradiated.

Relationships between volumes of tissue irradiated and IL-6sR concentrations

The first query relates to the extent to which the dose-volumetric data impacts on a discernable increase in peripheral IL-6sR concentration? Results from the repeated measures analysis suggested that the volume of tissue irradiated did have a significant impact on IL-6sR concentrations. The relationship of the variables is such

that increasing volumes of tissue irradiated at all dose levels are associated with increasing IL-6sR concentration. The (moderate) effect size was comparable when considering the volume of tissue within the 10, 50 and 90% isodoses, indicating that low dose effects were not impressive. That is, a lower dose over a larger volume of tissue.

The extent to which the increased impact of irradiated volumes on IL-6sR concentrations could be attributed to the direct effects of irradiation and how much is secondary to associations between irradiated volumes and BMI is difficult to establish, as the latter two variables were strongly correlated. At baseline, BMI was not associated with fatigue, but it was with IL-6sR concentration. Presumably, secondary associations with BMI account for any association between irradiated volumes and IL-6sR at baseline. The moderate strength significant positive correlation between the volume of tissue irradiated within the primary beam and IL-6sR remained virtually unchanged during treatment, strengthening slightly at four weeks post-treatment. When a partial correlation analysis controls for BMI, the latter time-point is the only one that retains statistical significance. It is conspicuous that inflammation is intrinsically not a stable state. Over emphasis on cross-sectional correlations may not reflect the wave-like release of cytokines in response to radiation characterised by Herskind (1998). Indeed Bower et al. (2007) utilised a within-subjects design to relate cumulative cytokine concentrations at longitudinal time-points to fatigue levels to circumvent this problem.

Relationships between volumes of organs irradiated and IL-6sR concentrations

In a further attempt to discriminate between the effects of BMI and irradiated volumes of tissue, the dose-volumetric data for the individual organs were considered. Spearman's correlations revealed no statistically significant associations between IL-6sR concentration and any of the cardiac or pulmonary dose-volumetric parameters at any time-point (data not shown). Interestingly, correlations between the volume of liver irradiated within the 10% isodose and IL-6sR concentration were non-significant at baseline for subjects with right-sided tumours (n = 52), but consistently significant at week two, week three and four weeks' follow-up (n = 49). The medium strength correlations suggested, the irradiation of a sufficiently large volume of liver may be

associated with a peripherally detectable increase in IL-6sR concentration. However, the volume of liver irradiated was also positively correlated with BMI rendering interpretation ambiguous. No correlations existed for left-sided tumours confirming the radiation dose effect to be a substantive factor. What is clear is that higher BMI was associated with both larger volumes of hepatic irradiation (for the right-sided participants) and elevated peripheral IL-6sR.

The clinical significance of the hepatic data is uncertain. Hepatocytes are one of the few cells, other than leukocytes, to express the membrane bound IL-6 receptor. As the liver plays a central role in metabolising cytotoxic agents, the relevance of the finding may be increased when considering the scheduling of chemotherapy and radiotherapy treatments. A further point is that 3D data reveals an off-axis effect that would be missed with 2D planning protocols. Whilst the volume of liver irradiated is not a principal treatment planning issue, the 'as low as reasonably achievable' principle indicates that normal tissue doses should be minimised. A simple solution where indicated could be a half-beam block technique that attenuates divergent X-rays at the inferior border. Radiotherapy techniques that reduce the volumes of normal tissue irradiated may broadly be of most benefit to larger patients.

Relationships between the volumes of tissue irradiated and fatigue

The only published study identified that attempted to correlate the volume of tissue irradiated to fatigue (Geinitz et al. 2001) concluded that the association between the two variables was secondary to the close correlation between BMI and irradiated volumes. The two variables are closely correlated, but given the lack of association between BMI and fatigue in this study, it is conceivable that any correlation between irradiated volumes and fatigue may be attributable to the effects of irradiation. However, the data from the repeated measures analysis indicated that the total volumes of tissue irradiated were not closely associated with the fatigue scores. Furthermore, Spearman's correlations between the two variables were only significant at the four-week follow-up.

Considering individual organs, no significant associations were evident between any cardiac dose-volumetric parameter and fatigue. Cardiac irradiation does not appear to

contribute to either IL-6sR concentration or fatigue during the acute period. The study findings were in accordance with an ASCO conference abstract (Rucinska and Langkjer 2007) that found no relationship between cardiac irradiated volumes and fatigue in 48 EBC patients. They did report significant correlations between the volume of lung irradiated and fatigue. In the current study, the volume of lung irradiated within the 10% and 50% isodose levels, and the maximum lung dose, all correlated negatively with fatigue score at week three and four weeks post-treatment. Correlation coefficients suggested a small to moderate association between larger volumes of lung irradiated and increased fatigue. These correlations remain significant when BMI is controlled for. Finally, at four weeks' follow-up the maximum liver dose data revealed a small but statistically significant relationship fatigue (ρ = - .23, p = 0.02). Arguably, multiple comparisons will yield a number of statistically significant results with little or no clinical significance.

Considering the paucity of data relating irradiated volumes to fatigue, the establishment of a novel dataset and limited corroboration of existing organ data is an advance. The lack of an association between irradiated lung volumes and circulating IL-6sR did not support the concept that irradiation to the lung causes an elevation in IL-6sR that in turn causes an increase in fatigue. As previously stated, it is possible that the peripheral IL-6sR concentration is not reflective of the local inflammatory state, levels of IL-6 may act to mask levels of the soluble receptor and/or the activation of alternate biological pathways is involved. Regardless of biological mechanisms, the IMPORT study provides a unique opportunity to evaluate the role of – three levels of – irradiated volume on fatigue in a comparable low-risk EBC patient group. The framework of a well-designed randomised trial would yield the ideal context in which to isolate the dose-volume from extraneous clinical factors. More widely, it is conceivable that complex multi-beam IMRT radiotherapy techniques may serve to modulate the fatigue response, and as such, this outcome should be considered in clinical trials.

White blood counts

The rapid reproductive rate of leukocytes determines that leukocytes are highly radiosensitive. Leukocyte precursors are particularly vulnerable to radiation damage.

It would thus be expected that if sufficient leukopoetic tissue (ribs, sternum) is irradiated, that myeloblasts and peripheral leukocyte counts would decrease. Indeed, lymphocyte counts were reduced from baseline levels by approximately 50%, even at four weeks' follow-up. The current study did not record the volume of haemopoetic tissue irradiated due to technical issues affecting the reliability of the data. Geinitz et al. (2001) reported an equivalent reduction in leukocytes, and further speculated that the volume of haemopoetic tissue irradiated was insufficiently large to account for the pronounced haematological effects. The irradiation of circulating lymphoid stem cells may be an additive explanatory mechanism (Geinitz et al. 2001, Kleinburg et al. 1999). An alternate explanation may be the preferential recruitment of specific blood cells from the periphery to a local site of inflammation (Collado-Hidalgo et al. 2006).

Relationships between blood counts and fatigue

The data revealed no significant relationships at any time-points between composite, differential or ratios of differential WBC and fatigue. The recruitment and clearance of leukocytes involved in the initiation and resolution of an inflammatory episode (Collado-Hidalgo et al. 2006, Jones 2005) were not discernable here. More sophisticated analysis of leukocyte subsets, involving flow cytometry techniques as used by Collado-Hidalgo et al. (2006), may be useful in characterising the leukocytic response to radiotherapy and its relationship to fatigue.

The lymphocyte counts for the two fatigue groups revealed that the non-fatigued participants had elevated mean lymphocyte counts at all time-points, compared to the non-fatigued group. By week three of treatment, 10% of participants had a lymphocyte count that was below the lower bound of the normal range. Of this subgroup, four were in the non-fatigued group and the remainder in the fatigued group. These data were somewhat surprising as it might be expected that the upregulated cytokine response in these participants would be associated with increased levels of circulating white blood counts. The pattern may be indicative of a sub-optimal immune function or response to the breast cancer episode in the fatigued group. The substantive significance of the leukocyte data as regards RRF is uncertain as blood counts explained negligible amounts of the variance in fatigue in the multivariable analyses. Furthermore, the fatigued patients did not experience a disproportional change during

radiotherapy treatment, suggesting any affect of lymphocytes on fatigue is due to pre-existing levels. The role of baseline leukocyte counts to fatigue status during radiotherapy will be considered in section 6.5.

Anaemia is a well-known cause of fatigue that is common in cancer patients receiving chemotherapy. Congruent with previous findings (Geinitz et al. 2001, Irvine et al. 1994, Monga et al. 1999), haematocrit, haemaoglobin and all red blood parameters displayed no significance, statistical or substantive, for breast RRF. This is largely due to the much slower cycling of red blood cells and therefore relative radio-resistance of erythrocytes. Only one of the study participants recorded an abnormal haemoglobin level (10.5 g/dL) below the WHO threshold for a diagnosis of anaemia. This result was transient result and not repeated at any other time-point.

6.4 Factors that contribute to fatigue during radiotherapy treatment

Before discussing the factors that contribute to fatigue during radiotherapy treatment two general points salient to the analysis thereof are observed. Multiple regression analysis relies on between-subject variation in the IVs. If variability in an IV is small then a high probability exists that a non-significant (p-value) result will be returned for that variable. In the current study, where radiotherapy is a ubiquitous exposure, meaningful analysis is reliant on a degree of naturally occurring variation. Where, say, the variation in cardiac volumes is minimal, multiple regression will be unlikely to discern a unique contribution towards fatigue.

The second point is related to the use of the summary outcome measure – the average of the fatigue score at week two and week three. This accounts for the fact that longitudinal measurements are correlated, but the statistical price paid for this action is an associated loss in power (information), as raw data is not used (Ghosh et al. 1999). Statistical techniques – generalised estimating equations and mixed-effects models – are available which may be more powerful to detect results. That is, a gain in power by utilising all the measurements (Gueorguieva and Krystal 2004). These techniques were considered overly complex for use in this study, especially as time-points were uniform and missing data was not a major problem. By adopting a simpler

approach, assumptions regarding the correlation structure between time-points were reduced and interpretation of results enhanced.

The multiple regression data revealed that baseline fatigue explained 37% of the variation of fatigue during treatment. As a comparison, Smets et al. (1998a) reported that for a mixed-site sample of 250 radiotherapy patients, baseline fatigue accounted for 27% of the variation in fatigue during radiotherapy. The implications of the study findings are that patients at risk from fatigue may be identifiable preceding radiotherapy and interventions to ameliorate fatigue are best initiated early. The foci for such endeavours will be discussed in section 6.5. Depression level during treatment explained approximately the same proportion of fatigue as baseline fatigue (36%). The strength of this estimate is noteworthy, as it exists after controlling for baseline fatigue. Concurrent anxiety was not a strong predictor of fatigue during treatment. Physical activity level during treatment makes a small but statistically significant unique contribution to fatigue, with increased exercise associated with lower fatigue. As discussed previously, the implication of this finding may depend on which stage of the fatigue continuum an individual occupies. The more intensely fatigued may derive increased benefit from acute cognitive adjustments and psychosocial support.

The total volume of tissue irradiated by the primary beam uniquely explained less than 1% of the variance in fatigue. The close correlation of this variable with BMI again determined it was difficult to discriminate between the variables. As the unique contribution was substantively and statistically non-significant, neither variable had a strong influence on the overall model. IL-6sR concentration explained only approximately 0.5% of the variance in fatigue. As a lone variable IL-6sR explained approximately 8% of the variance in fatigue, suggesting it shares a degree of variance with other model variables. Considering these findings, and the previous longitudinal data, it would appear increased irradiated volumes have an upregulating effect on peripheral IL-6sR concentrations, but the concomitant increase in fatigue cannot be directly attributed to this effect. Relationships between inflammation and fatigue during treatment may exist, possibly via pathways that are more complex or mediated through depression. It is also possible that other factors that initiate IL-6 signalling were not recorded. For example, hormonal fluctuations related to menstrual changes

and the point in the menstrual cycle. A simple cause and effect relationship with RRF was always unlikely, and whilst alternative aetiological mechanisms remain obscure, further exploration of the role of cytokines in RRF should not be discounted.

Considering patient-related characteristics, increasing age was associated with lower anxiety, but age itself did not make a significant multivariable contribution. Experienced health care professionals, breast cancer survivors at focus groups, Wratten et al. (2004) and a small minority of fatigue diary entries all speculated that travelling for daily treatment could be a component of on-treatment tiredness. This postulation was not supported by the data, which revealed no bivariate association between either travel time or mode and fatigue during radiotherapy. All three participants who had a journey of more than one hour were solidly within the non-fatigued classification. Reassuringly, daily use, by 13 participants, of the hospital transport system throughout treatment was also not a contributing factor to fatigue.

Overall, three-quarters of the variance in fatigue could be explained by the simple measures of baseline fatigue, depression score at week three and physical activity at week three.

6.5 Baseline factors predictive of fatigue group status during radiotherapy treatment

Pre-treatment factors associated with fatigue during radiotherapy were: younger age, larger BMI, a history of smoking, a diagnosis of DCIS, higher anxiety and depression, higher IL-6sR concentration, lower levels of physical activity and increased baseline fatigue. No effect was discernable for menopausal status or HRT history.

The third of participants who had the most elevated IL-6sR concentration at baseline (greater than 45ng/mL) were more fatigued at baseline, and remained more fatigued during treatment.

Smokers and non-smokers were equally fatigued at baseline and at four-week follow-up. During treatment, participants who never smoked were less fatigued than the other

two categories. There may be associations between life-long non-smokers and healthy lifestyles that account for this effect. For example, the 18 smokers were less active than other participants during treatment, recording median IPAQ scores of 1251 MET/min/wk and 1695 MET/min/wk, respectively. Elevated IL-6sR responses to radiation cannot account for the differences in fatigue. As a group, smokers had lower mean IL-6sR concentration (41.3 ng/mL) than past smokers (42.5) and non-smokers (47.3) during radiotherapy. This finding may indicate a smoking-based dampening of the immune response to pulmonary irradiation as detailed by Bjermer et al. (1990).

Surgical characteristics did not relate to fatigue risk. Of all the disease-related characteristics under investigation, diagnosis was the only variable to indicate a statistically significant difference between fatigue groups. The DCIS patient group tended to be more anxious, as opposed to any disease-specific mechanisms.

Participants who continued to work during treatment were less fatigued before and during treatment, but a trend for increasing fatigue continued after treatment. During treatment, the normal routines of work may serve as a useful distraction for some, but potentially at the cost of a poor recovery. This pattern is consistent with the motivational adaptive theory of sickness behaviour, whereby subjects who cannot adapt routines move from tired to fatigued states. Participants who postponed work during treatment were more fatigued during the treatment, but returned towards baseline levels at follow-up. This pattern was similar to the participants who did not work. Whether patients should be advised to adopt flexible working practices is a moot point.

A number of studies have previously considered the ability of pre-treatment factors to explain later fatigue in radiotherapy patients. The Wratten et al. (2004) study reported that baseline FACIT-F score, neutrophil count and red blood were predictive of fatigue status during radiotherapy. In contrast, the current study found little evidence for relationships between haematological variables and fatigue. It may be relevant that 15 of the 52 participants in the Wratten et al. study had received chemotherapy prior to radiotherapy. Stone et al. (2001) reported that baseline fatigue and anxiety scores explained 54% of the variation in fatigue at the end of radiotherapy for a mixed sample of breast and prostate patients. Smets et al. (1998a) reported that pre-treatment

fatigue explained 27% of the variance in post-treatment fatigue for a mixed sample of patients. Collado-Hidalgo et al. (2006) developed a biomarker for fatigue in breast cancer survivors with estimated 87% classification accuracy and associated sensitivity of 0.83 and specificity of 0.83. The biomarker comprised of the ratio of IL-6sR to membrane expressed IL-6R and decreased peripheral $CD69^{+}$ lymphocytes. Primarily, this model extends the basis for an inflammatory and specifically transsignalling-mediated aetiology of breast cancer fatigue. Though the context is different, it also serves as a useful comparator in terms of accuracy for the current prognostic model. Thirdly, it is too complex to translate to the clinical setting. The current study sought to extend this body of findings and to develop an exploratory prognostic model with potential for both clinical and research applications.

Towards a prognostic model

Two seminal citations regarding scientific model building preface this final chapter section. The first is a quote normally attributed to Box and Draper (1987, p. 424): 'There are models. All models are wrong. Some models are useful.' Aside from the general caveat about models, the implication is that the context of the model is an important determinant of usefulness, rather than say consistency with the real-life phenomena. So, the model here is not concerned with explaining mechanistic aetiology or causal relationships, but simply strength of statistical association. The second (related) point is that when comparing models, the 'best' one was, in accordance with 'Occam's razor' (Gauch 2003). That is, the selected model should introduce the fewest assumptions and postulate the least number of variables to predict the outcome.

Prognostic models depend on knowledge of risk factors. The set of factors established in this study were used to generate the model. The three pre-treatment variables that, in combination, were most predictive of fatigue group during radiotherapy were fatigue, anxiety and physical activity scores at baseline. The model was significantly better than would be expected by chance at predicting outcomes. Overall, the model correctly classified 82% of patients to the correct fatigue group. The positive predictive value of 80% indicated that the proportion of participants predicted to be fatigued who

were classified correctly. Whilst this is a useful measure of model precision, a disadvantage is that this statistic varies with the prevalence of the outcome. Together these data demonstrate that it is possible to predict the fatigue response to radiotherapy for breast cancer based on three simple self-reported screening parameters. Concerning the ability of the model to predict the outcome for individual subjects, the sensitivity of the model was 71.1%. That is, 71.1% of participants who were actually in the fatigued group were correctly predicted. The specificity of the model was 88.7%. This is the proportion of participants who were not fatigued being correctly classified as such.

The logistic regression output in the current study indicated that for every point decrease in baseline fatigue score the likelihood of the participant being in the fatigued group increased by between nine and 27%. The actual value is likely to be nearer the point estimate of 19%. Similarly, an increase baseline HADS anxiety score by one point is associated with an increased likelihood of being in the fatigued group of between two and 38% with the point estimate being the mid-point of this range. At baseline, anxiety was not a statistically significant IV for fatigue, presumably, as much of its contribution was shared with depression. When baseline fatigue was included in the current predictive model the shared contribution between depression and fatigue rendered anxiety a significant contributor to fatigue during treatment. The scale of the IPAQ renders an interpretation of an associated odds ratio difficult, but the Wald statistic indicates a similar individual contribution to the model as the variable anxiety. The inclusion of anxiety and physical activity enhances the ability of the model to discriminate fatigued from non-fatigued cases.

The model performance was good, as it fitted the data well. Four outlier cases were conspicuous that did not fit the model well. Two of the cases were incorrectly predicted to be in the fatigued group. A further inspection of these cases revealed that one case was suffering from a bacterial infection over the two weeks preceding the baseline measurements. With the aid of antibiotics, the participant was recovered by the occasion of the week two measurements. The second case had experienced hot flushes and pain attributed to a three-month cessation from long-term HRT use. These symptoms, and fatigue and depression scores, improved markedly during the period of radiotherapy upon the GP prescription of the anti-depressant Mirtazapine.

Conversely, two cases were incorrectly predicted to be in the non-fatigued group. One case involved a lone foster mother of two young children who commenced treatment using the hospital transport system. This participant experienced great logistical difficulty in balancing parental commitments with the disruption of daily radiotherapy. This woman reported high levels of fatigue during radiotherapy, but recovered back to the low baseline level at four-week follow-up. The second case in this category recorded suffering from a heavy cold and cough in the second half of radiotherapy treatment.

The weakness of a single study dataset is that the model fits that particular dataset but suffers a large decrement in predictive ability when applied to a second dataset. This is referred to as 'over-fitting' of the data. Ideally, the performance of the model would be tested in an external dataset. The jackknife procedure utilised here is the closest equivalent to an external dataset as the confirmatory case is not included in the derivation dataset. This procedure suggested excellent cross-validity properties. Firstly, the discriminative ability of the confirmatory set, and the sensitivity and specificity were only marginally reduced. These data infer that the model was not disproportionately influenced by any individual case, indicating stability and validity. Secondly, the ability of the model to predict the individual validation cases was 80%. This represents a small (2%) decrement discriminative ability, and suggests that the model should perform well in an internal split-sample validation set.

Where the end-point of a study is a QoL outcome, as opposed to a setting where a very high sensitivity is crucial such as a prediction of diagnosis, then the need for validation is arguably lessened. Nevertheless, for the robustness of the model to be clinically established, the validity of the model should be tested using an external validation set. This validation sample would ideally be drawn from an alternate radiotherapy setting than the original study sample, possibly multiple settings. The sample would need to share similar disease and patient-related characteristics to the confirmatory sample. A random subsample drawn from an ongoing multi-centre study such as the IMPORT trial could provide a pragmatic dataset.

Utility of the prognostic model

The logistic regression output is still overly complex for use in a clinical setting. To extend the clinical utility of the model and draw inferences at the individual level, a patient at a high risk of significant fatigue during radiotherapy was characterised. This endeavour revealed that a fatigued subject during radiotherapy was likely to have a FACIT-F fatigue score of less than 40, a HADS anxiety score of greater than five and an IPAQ score that did not meet the criteria for a high level of physical activity. To illustrate the prognostic model; a subject with the mean (SD) cohort baseline FACIT score, 41.0 (9.8) and the mean baseline HADS anxiety score, 5.5 (3.9) had a 30% predicted probability of being in the fatigued group. Whereas, a subject with a one SD difference in baseline values, in the poorer prognosis direction, i.e. fatigue = 31.2 and anxiety = 9.4, has a 78% probability of being classified as fatigued.

If the model proves to have the ability to predict the outcome for an external sample then the prognostic model could be extended to create a simple (risk-scoring) prognostic index. Ranges of index scores can then be defined that equate to low, medium and high-risk classifications. Vincent et al. (2007) generated a comparable index for chemotherapy-induced anaemia risk in patients with non-small cell lung cancer. In general terms, a prognostic index can be used to minimise under and over treatment of fatigue. Prophylactic treatment can be targeted at high-risk patients most likely to benefit. The current lack of assessment of fatigue coupled to a general resistance of clinicians to use prognostic algorithms (Wasson and Sox 1996) suggests the most realistic use is in research settings. A number of potential uses can be envisaged including informing study inclusion/exclusion criteria or for stratification purposes. Women could be recruited or randomised prior to treatment based on risk status.

CHAPTER SEVEN **Concluding remarks**

This chapter aims to distil the key findings of the study. The studies position is briefly considered in relation to extant work. The principal findings will then be summarised and relevant assumptions and limitations detailed. A comparison of pre-contribution and post-contribution serves to highlight this studies' original contribution to the science of RRF and proposes of new directions for research. Finally, implications of the findings for theory and practice are summarised.

Position of the study

The rationale of this work was to apply a radiotherapy-led perspective to the problem of fatigue during adjuvant breast radiotherapy. The study was designed to address aetiological and prognostic uncertainties in the science of RRF and generate hypotheses. The greater body of CRF work informs the study, but is positioned somewhat separately in terms of specificity. Whilst the work can rightly be placed within the broad QoL paradigm, a more ambitious range of analytical objectives has been incorporated than is common in such studies. A further distinction of the current study is the extent to which it draws theoretically and empirically on bordering disciplines. For example, parallel work from the CFS setting is integrated. Fundamental to the integrated approach is the application of the sickness behaviour framework. The majority of CRF studies have not explicitly used a conceptual framework, or have adopted a framework that could be considered to be fragmented and overly complex to sustain conceptual coherency.

7.1 Summary of principal findings

The study data reveals that just over 60% of the cohort reports no significant change in fatigue intensity. This non-fatigued group experience an intensity of fatigue that is comparable to general population data before, during and after treatment. A distinct fatigued group are more fatigued prior to radiotherapy and experience clinically significant increases in fatigue. The stability and divergence of the two groups suggests that patients at a high risk of fatigue may be identifiable pre-radiotherapy. Based on this data, the prevalence of fatigue in patients undergoing curative

radiotherapy is approximately 40%. This finding (which addresses the first study aim) is important as it establishes the acute fatigue response that reflects the contemporary UK radiotherapy protocols. The current three week schedule appears to attenuate fatigue as compared to longer schedules. Three limiting aspects of the finding are noteworthy. One, compared to previous studies the sample is extremely homogenous as regards disease and treatment-related characteristics. The exclusion of patients receiving chemotherapy determined that the patients recruited did not have macroscopic nodal disease and were classified as between TNM stage groups 0 and IIA. Therefore, the study findings should strictly only be generalised back to this patient group. Two, the fatigued groups were defined, based on the assumption of a FACIT-F scale cut-off score of ≤ 34. Three, the available normative data is derived from the US population. The evaluation of the clinical relevance of the level of fatigue evident in this study (and future studies) would be enhanced by the availability of directly comparable UK healthy population data.

That just under 40% of participants' experienced significant fatigue during radiotherapy indicates that RRF is currently under-assessed. Crucially for this patient group, the magnitude of the evident fatigue intensification has profound impacts on health-related QoL. A further indicator of the impact of RRF was provided by the fatigue diaries. Although not reported fully in this thesis, a considerable volume of rich qualitative data has been accrued. In the future, an interpretative phenomenological analysis will thematically explore this data. This approach examines how individuals perceive and make sense of events they are facing. The diary entries will be cross-correlated to quantitative changes over time in the three questionnaire scores.

The second study aim was to determine the contribution of multiple factors to fatigue. Psychological mood is the strongest factor. Researchers have highlighted the link between psychological mood and CRF in patients with breast cancer, but the nature of this relationship was a matter of debate. Evidence was especially conflicted as to the extent to which the respective variables shared a common dynamic course. A better understanding of this matter would help shape the content and timing of potential fatigue treatments. The current study demonstrates that these relationships are more tractable when considered at a fatigue group level. It is then apparent that the respective courses of fatigue and depression are virtually super-imposed. Depression

intensifies during treatment for the fatigued group, whilst levels comparable to population norms remain unchanged in the non-fatigued group. Additional data indicates a positive relationship between fatigue and pro-inflammatory IL-6sR before treatment. This finding is important evidence supporting the concept of neuro-immunological symptom clustering.

On further evaluation of the fatigue group data it is apparent that anxiety affects fatigue level before but not during radiotherapy. Levels of anxiety that indicate a need for augmented support are thus sustained throughout treatment for a significant minority of women. Contrary to this need is the scenario where the service demands on a radiotherapy centre mean new patients are often provided rather rushed pre-treatment information. This may be adequate for many, but leaves a minority anxious. Younger patients and those with a diagnosis of DCIS or affected by adverse socioeconomic factors may be particularly vulnerable.

The study has not yet provided definitive evidence of the inter-relationships between psychological variables and fatigue, however, the data is consistent with the theory that psychological distress can sensitise the behavioural response to subsequent immunological challenges (Bower 2007, Glaser and Kiecolt-Glaser 2005, Miller et al. 2008, Seruga et al. 2008). According to this theory, a psychological anxiety response antecedes neuro-immunological symptoms, possibly via HPA axis modulation. The implication of this scenario is that interventions to address fatigue should focus on anxiety reduction, which should be instigated prior to treatment.

As pharmacological approaches are inevitably subject to toxicities, psychological support should be prioritised. Interventions under consideration by the researcher include psychosocial support via a telecare service, peer support, provided in person or via a DVD, and a cognitive behavioural therapy-based programme. The latter is likely to be expensive and should therefore be reserved for those likely to benefit most. Interventions would be developed and evaluated in accordance with the Medical Research Framework for complex interventions (MRC 2000). The current findings, which correspond to the preliminary modelling phase, suggest the active ingredients of a successful support programme. This work feeds directly into exploratory trials, designed to optimise the content and nature of an intervention. A further initiative

worthy of systematic evaluation is the 'open evening' initiative at VCC. The aim of the programme is to familiarise prospective patients with the reality of forthcoming treatment, and as such may plausibly reduce anxiety, and consequently fatigue. This evaluation could be via both qualitative and quantitative methods, and allow comparison with patients not attending the open evening.

The HADS data suggests anxiety does not relate directly with IL-6sR. However, the hypothesis that early dysfunction of the cortisol response is related to an elevated cytokine profile and a subsequent increase in fatigue during radiotherapy, represents a fundamental area for future research. Ideally, measurements would commence contemporaneously to the initial diagnosis, and project into the chronic phase. Healthy women and women with a benign breast abnormality would provide valuable comparison groups. Based on indications that coordinated immuno-neuro-endocrine fatigue responses in breast cancer patients may be partially pre-determined (Collado-Hidalgo et al. 2008), the retention of translational biological samples for future analysis of the gene environment variation should be considered an integral component of investigations.

The current study revealed an acute elevation in IL-6sR as a response to irradiation, which is of greater magnitude in more fatigued participants. The respective courses of fatigue and IL-6sR again suggest that radiotherapy exacerbates a pre-morbid state in the fatigued participants. With reference to the third study aim, the cumulative volume of tissue irradiated has a moderate effect on the IL-6sR concentration. Low dose effects are not discernable, except for the volume of liver irradiated. The liver is the only individual organ that has any relevance to IL-6sR release. With respect to current literature, this is the first time the effect of liver irradiation has been considered in a breast CRF study. Together these data establish a positive relationship between irradiation, IL-6sR and fatigue. The substantive significance of the relationships is less clear. Arguably, what the findings most clearly indicates is the increased use of 3D planning data, and an increased awareness of all the normal structures within the radiation portal? An evaluation of significance of the partial elevation in IL-6sR is compounded by large individual variations in cytokine concentration. A number of related assumptions and limitations may affect this data. The degree to which peripheral cytokine concentrations reflect local concentrations is at issue. Cytokine

release is known to be affected by circadian, diurnal and menstrual rhythms; none of which were controlled for. However, evidence suggests that the time of day and fasting have no effect on short-term variability of IL-6sR (Dugué and Leppänen 1998). The use of NSAID medication was also not excluded. However carefully ELISA assays are conducted, inter-assay variation is inevitable. Bearing in mind these limitations, the cumulative levels of cytokines may provide a more reliable marker of IL-6sR activity (and objective fatigue biomarker) than a one-off measurement. Therefore, a future secondary analysis of the cytokine data will be conducted, and the resultant parameter related to behavioural outcomes.

This study refines and extends the (very) limited previous data evaluating the link between irradiated volumes and fatigue. The total volumes of tissue irradiated are not closely associated with fatigue, despite limited evidence for an effect for the volume of lung irradiated. This may be partly due to insufficient variation in irradiated volumes. Hepatic and cardiac irradiation had no relationship with fatigue. A confounding issue related to the DVH-derived irradiated volume data is the dynamic nature of thoracic-irradiation. Despite this limitation, these data represent a reliable starting point. The characterisation of normal tissue responses is as important as increasingly sophisticated methods of tumour analysis. The IMPORT Low trial could provide a unique opportunity to test the hypothesis that partial breast irradiation is associated with a decrease in peripheral inflammation, and a lower intensity of fatigue. A speculative relationship between BMI and fatigue (Geinitz et al. 2001, Wratten et al. 2004) is not supported by the current data. Although mean BMI is slightly higher in fatigued patients, the difference was not significant. Furthermore, associations with depression or activity level do not affect the relationship between BMI and fatigue.

Research suggests that physical activity interventions can reduce CRF; however, the dynamic changes in activity during adjuvant treatment were not well defined. The current study shows that activity in the fatigued group declines in accordance with sickness behaviour theory. That is, a desire to reduce activity/energy expenditure exists, but behaviour change is dependent on the outcome of the change: effectively a re-prioritising of activities.

Implications for theory 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. During radiotherapy, review radiographers are vital to patient monitoring. As we approach the threshold of an era when breast fractionation schedules may be subject to change, pressures to reduce monitoring should be resisted. Weekly appointments should remain a minimum standard. Collaborative involvement with patients should however be encouraged, with 'well' women given the option of reducing contact.

The relative stability of the fatigue groups implies that standardised risk groups are tangible when selecting participants for research. Not incorporating fatigue status as an eligibility criteria renders studies that cannot discriminate between an intervention that reduces fatigue and one that prevents fatigue occurring. 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 (cytokine-induced) sickness behaviour framework successfully defined the study and provided a coherent plan of related concepts. Resultant data was consistent with the theories underlying the framework, which in turn was capable of generating scientifically robust hypotheses. Based on the study data, a hypothesis can be formulated that anxiety acts as a trigger for subsequent heightened fatigue, depression and inflammatory response. A future research strategy will therefore concentrate on anxiety/stress reduction strategies. 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.

The utility of diagnostic depression criteria is questionable in a breast RRF context. This is because the intensity or pattern of depression is likely to be insufficient to meet the criteria whilst remaining strongly related to fatigue. Conversely, patient diaries can provide a useful means of making sense of an individual's own personal and social world. The tracking of symptoms and the expression of emotions may potentially lead to an increased internal locus of control.

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 CFS research, provide a self-management strategy 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.

Final words

The prognostic model developed, in accordance with the fourth aim of this study, reliably identified 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. Considering the multiple issues that have the potential to affect the fatigue status, the prognostic model displayed good accuracy. Multiple confounding factors that may have reduced the accuracy of the model are: fitness prior to surgery, pain (surgical or otherwise), use of analgesics/opioids, sleep patterns, transient illness, transient family issues, patient's expectations of treatment and the information provided prior to radiotherapy.

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.

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Appendicies

Appendix 1 Search strategy

# ▲	Searches	Results
1	breast neoplasms.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	92483
2	radiotherapy.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	68005
3	inflammatory cytokines.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	12223
4	fatigue.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	28433
5	1 and 2	6112
6	3 or 5	18333
7	6 and 4	135

Adaptation
Breast neoplasms [surgery, radiotherapy, psychological, rehabilitation, immunology]
Cardiac Irradiation
Cytokines
Exercise therapy
Fatigue [diagnosis, etiology, prevention and control, physiopathology, drug therapy, rehabilitation, psychology]
Immune system [immune effects]
Interleukin-6/bl [radiation effects]
Liver Irradiation
Lung irradiation
Neoplasms
Radiation Injuries
Radiotherapy [adverse effects, psychology]
Radiotherapy Planning
Radiotherapy Computer-Assisted
Radiotherapy Dosage
Sickness Behaviour
Quality of Life

Appendix 2 Ethical and Recruitment documents

- Ethical confirmation
- Participant invitation letter
- Participant information sheet
- Study consent form
- Letter informing general practitioner of study participation

Canolfan Gwasanaethau Busnes
Business Services Centre

South East Wales Research Ethics Committee - Panel D

Telephone: 02920 376822/6823
Facsimile: 02920 376835

08 October 2007

Mr Nicholas Courtier
PhD student and therapeutic radiographer
Cardiff University
Department of Radiography, School of Healthcare Studies,
Room GF3, Ty Dewi Sant,
Heath Park, Cardiff
CF14 4XN

Dear Mr Courtier

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

REC reference number: **07/WSE04/82**

Thank you for your letter of 26 September 2007, responding to the South East Wales Research Ethics Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair, Dr DEB Powell.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The Committee has designated this study as exempt from site-specific assessment (SSA. There is no requirement for [other] Local Research Ethics Committees to be informed or for site-specific assessment to be carried out at each site.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application	5.3	11 July 2007
Investigator CV	N. Courtier	20 September 2007
Investigator CV	Dr T Gambling	08 July 2007
Protocol	3	26 April 2007
Covering Letter		09 July 2007
Letter from Sponsor		12 April 2007
Peer Review	Velindre NHS Trust	28 June 2007
Compensation Arrangements	Cardiff University	01 August 2006
Questionnaire: Hospital Anxiety and Depression Scale (HADS)	1	07 May 2007
Questionnaire: International Physical Activity Questionnaire	1	07 May 2007
Questionnaire: Functional Assessment of Cancer Therapies Fatigue Subscale	1	07 May 2007
Sample Diary/Patient Card	Patient Fatigue Diary	24 May 2007
Letter of invitation to participant	2	20 September 2007
GP/Consultant Information Sheets	1	03 July 2007
Participant Information Sheet	2	20 September 2007
Participant Consent Form	1	07 April 2007
Response to Request for Further Information		26 September 2007
Summary of Measures	1	03 July 2007
Study Flowplan	2	02 July 2007
Letter re Funding	rcbcwales	05 June 2007
Letter re Funding	The College of Radiographers	04 May 2007

R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly.

Guidance on applying for R&D approval is available from http://www.rdforum.nhs.uk/rdform.htm.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

Feedback on the application process

Now that you have completed the application process you are invited to give your view of the service you received from the National Research Ethics Service. If you wish to make your views known please use the feedback form available on the NRES website at:

https://www.nresform.org.uk/AppForm/Modules/Feedback/EthicalReview.aspx

We value your views and comments and will use them to inform the operational process and further improve our service.

07/WSE04/82	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

p.p.

Dr D E B Powell
Chair

Email: jagit.sidhu@bsc.wales.nhs.uk

Enclosures: *Standard approval conditions – Non CTIMP*

Copy to: R&D Department for Cardiff University

YMDDIRIEDOLAETH GIG
FELINDRE
VELINDRE
NHS TRUST

CARDIFF
UNIVERSITY
PRIFYSGOL
CAERDYDD

Department of Radiography

Cardiff University
GF3, Tŷ Dewi Sant
Cardiff CF14 4XN

Dear __/__/__

You are invited to take part in a study investigating fatigue during breast radiotherapy treatment. We are looking for 100 women to take part in the study. Patients such as yourself, who have had some form of surgery for breast cancer and who will soon receive radiotherapy treatment at Velindre Cancer Centre.

If you do take part in the study your treatment will be completely unaffected.

Taking part is entirely voluntary. It is up to you to decide whether or not to take part. Before you decide it is important for you to understand why the research is being done and what it will involve.

If you are interested to take part in the study could you please complete and return the prepaid postcard included with this information within seven days.

In the meantime if you wish to take part in the study, ask any questions or for any other reason, please feel free to contact me on the telephone numbers or email address below.

Yours sincerely,

Nick Courtier
Research Radiographer

Work: (029) 2031 6262
Mobile: 07914 722 791
Email: CourtierN@cardiff.ac.uk

Participant information sheet

Study title: A predictive model of fatigue in breast radiotherapy patients

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others, including your GP, if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Your doctor has advised you to have a course of radiotherapy as part of your treatment for breast cancer. We know that one of the side-effects of radiotherapy treatment can be fatigue. Fatigue may mean feeling more tired than usual, having less energy or feeling weak. Fewer than half the patients who receive radiotherapy to the breast become significantly more fatigued than they were before the treatment. The other patients maintain their usual energy levels throughout treatment. We aren't sure why this is the case. Evidence exists suggesting a variety of factors affect fatigue development whilst having breast radiotherapy treatment, some of which we will be testing in this research study.

The aim of the study is to try and determine the effect on fatigue of body size, levels of various parts of the blood, mood, activity levels and travelling for your treatment.

Why am I being invited to take part?

Because you are due to have radiotherapy as part of your breast cancer treatment, and we are interested in the effects of radiotherapy treatment on fatigue in breast cancer patients.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. You will also be given a copy of the consent form to keep. We will ask for your permission to inform your GP about the study and your participation in it.

If you agree to join you are still free to withdraw at any time without giving a reason. If you withdraw from the study this will not affect the standard of care you receive. If this were to happen, we would like permission to keep any measurements already collected as this information ensures that the overall quality of the research study is not impaired.

What will happen to me if I take part?

As part of your normal care you will be asked to attend Velindre Cancer Centre for a standard appointment in the radiotherapy planning department. If you decide to take part in this study the following will happen,

- You will be met by the researcher after the planning appointment and asked to fill in three brief questionnaires. The questionnaires will take about 10 to 15 minutes in total to complete.
- You will be asked to give a small quantity of blood (2-3 teaspoons full).
- At the end of each of the second and third weeks of radiotherapy treatment you will be asked to fill in the same three questionnaires and also asked to give blood on these two occasions.
- Four weeks after your treatment has finished you will be asked to attend the hospital for a final blood sample and to complete one final questionnaire.
- During the three weeks of radiotherapy treatment you will also be given a diary to record your experiences during the previous week. You only need to use the diary if you feel it is beneficial for you but it would be very helpful to the study if you do. The same three questions are asked, about how fatigue affects you and you life. Space is provided for brief answers that only need to be completed once a week. Full instructions and examples to guide you are included with the diary.

What are the side effects?

If you agree to participate in the study your radiotherapy treatment will be unchanged and hence identical to the current standard practice at this cancer centre. The only side effect that you may possibly expect from the study is any pain or bruising from having blood taken.

What are the possible disadvantages of taking part?

Blood will have to be taken at four time points. This is extra to what normally would happen for breast radiotherapy patients. Three of these blood samples will be taken during your normal treatment visits, and one extra hospital visit may be required four weeks after your radiotherapy treatment.

What are the possible benefits of taking part?
You may also find it helpful describing your feelings about the treatment in the diary. Otherwise, there are no direct benefits for you, but the study results may help us treat fatigue in women like yourself in the future.

What if new information becomes available?
Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. Although this unlikely in a study of this nature we will tell you about it and discuss with you whether you want to continue in the study. If the study is stopped for any other reason you will be told why.

What is the expense of volunteering?
None

Will I be paid for taking part in this study?
No. However, travel expenses will be offered to cover the extra visit hospital.

Are there any restrictions on what I might eat or do?
None.

What if there is a problem?
We do not believe you will suffer any injury from participating in this study. If you are concerned about any aspect of this study, you should ask to speak to the researchers, who will do their best to answer your questions. Contact Dr Tina Gambling, Tel: (029) 20 742785. Your progress will be watched closely during your treatment and you will be offered whatever is available to help with any side effects. In the event that something goes wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed due to someone's negligence then you may have grounds for legal action against Cardiff University, but you may have to pay your own legal costs. If you have any cause to complain about any aspect of the way you have been approached or treated, the normal NHS complaints mechanism is open to you. Your hospital will have a formal complaints procedure that is available to you.

Will my taking part in this study be kept confidential?
Your medical records will need to be seen by authorised members of the research team at your hospital, so that they can collect information needed for this research study and also to check that it is correct. Your name, date of birth and Velindre radiotherapy number will be held in a securely locked cabinet during the study and your data will then be referenced with a unique anonymous coded number. All information which is collected about you during the course of the research will be kept

strictly confidential and nothing that might identify you will be revealed to any third party. Data will be kept for 15 years to inform further research and treatment of fatigue.

GP notification

With your permission, your GP will be informed of your participation in the trial. We would also seek your permission to notify your GP if at any time your score for depression on the HADS scale was above a certain clinically significant point (score more than 19).

What will happen to the results of the research study?

Independent experts will review the progress of the research, and the results will be published in a respected medical journal as soon as there is enough information to be sure the results are reliable. You will not be identified in any report or publication. The results may help to decide how best to identify and treat patients who become fatigued during breast radiotherapy in the future. When the results are known we will provide you with a summary sheet of study findings with an individual fatigue report.

Who is organising this study?

Dr Tina Gambling, a researcher and senior radiography lecturer at Cardiff University, together with Nick Courtier, a qualified radiographer and PhD student at Cardiff University and Professor Malcolm Mason, a consultant oncologist at Velindre Hospital and Head of the Department of Oncology and Palliative Medicine at Cardiff University.

Who has reviewed this study?

We have approval for the study from both the Velindre Trust Research & Development Committee and a South Wales NHS Research Ethics Committee. Approval means that the Committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits, and that you have been given sufficient information on which to make an informed decision to take part or not.

Contact for further information

Nick Courtier (lead researcher) Tel: (029) 20 748156
Dr Tina Gambling (research coordinator) Tel: (029) 20 742785

Thank you very much for your help

STUDY CONSENT FORM

Short title of the study:

A predictive model of fatigue in breast radiotherapy patients

Name of the researcher:

Nick Courtier

Please initial box

1. I confirm that I have read and understand the information sheet dated 20/09/07(version 2) for the above study. I have had the opportunity to ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by the researcher or individuals from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP being informed of my participation in the study. If I score more than 19 on the Hospital Anxiety & Depression Scale I give permission for my GP to be informed. ☐

5. I agree to take part in the above study. ☐

Name of Patient	Date	Signature
Name of Person taking consent	Date	Signature

[1 copy given to patient, 1 copy retained by researcher, 1 copy retained by research office]

Department of Radiography

Cardiff University
GF3, Tŷ Dewi Sant
Cardiff CF14 4XN

Dear Dr

__ / __ / __

Re:

Your above named patient has agreed to take part in a research study being conducted at Velindre Cancer Centre, investigating fatigue during breast radiotherapy treatment. The study is observational in nature, leaving their treatment entirely unaffected.

Participants are required to self complete three brief questionnaires - the Functional Assessment of Cancer Therapies Fatigue subscale (FACT-F), the Hospital Anxiety and Depression Scale (HADS) and the International Physical Activity Questionnaire (IPAQ) - three times during their radiotherapy. At four time points, a 14ml blood sample will be taken at Velindre Phlebotomy Department. The blood will be used to generate a full differential blood count and to determine activity levels of a circulating inflammatory cytokine. The first measurement will be two weeks prior to radiotherapy treatment and the final measurement at four weeks after completion of radiotherapy.

The study is being organised by Nick Courtier, as part fulfilment of a PhD at Cardiff University together with supervisor Dr Tina Gambling (Cardiff University) and guided by Professor Malcolm Mason (Cancer Research Wales at Velindre Cancer Centre).

If you require any further information about the study please contact me.

Yours sincerely,

Nick Courtier
Research Radiographer
(029) 2031 6262
CourtierN@cardiff.ac.uk

Appendix 3 Study questionnaires and fatigue diary

- Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F)
- Hospital Anxiety and Depression Scale (HADS)
- International Physical Activity Questionnaire (IPAQ)
- Patient fatigue diary
- Baseline proforma

Functional Assessment of Chronic Illness Therapy Fatigue Subscale (FACIT-F)

Instructions:
Below is a list of statements that other people with your illness have said are important. By *circling* one number per line, please indicate how true each statement has been for you **during the past 7 days.**

	not at all	a little bit	some-what	quite a bit	very much
1. I feel fatigued	0	1	2	3	4
2. I feel weak all over	0	1	2	3	4
3. I feel listless ('washed out')	0	1	2	3	4
4. I feel tired	0	1	2	3	4
5. I have trouble starting things because I am tired	0	1	2	3	4
6. I have trouble finishing things because I am tired	0	1	2	3	4
7. I have energy	0	1	2	3	4
8. I am unable to do my usual activities	0	1	2	3	4
9. I need to sleep during the day	0	1	2	3	4
10. I am too tired to eat	0	1	2	3	4
11. I need help to do my usual activities	0	1	2	3	4
12. I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
13. I have to limit my social activity because I am tired	0	1	2	3	4

Hospital Anxiety and Depression Scale (HADS)

Instructions: Doctors are aware that emotions play an important part in most illnesses. This questionnaire is designed to help your doctor know how you feel.

Read each item and circle the number opposite the reply which comes closest to how you have been feeling in **the past week**. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

I feel tense or 'wound up'
- Most of the time..... 3
- A lot of the time..... 2
- Time to time, occasionally..... 1
- Not at all..... 0

I still enjoy the things I used to enjoy
- Definitely as much.....0
- Not quite so much.....1
- Only a little.....2
- Not at all.....3

I get a sort of frightened feeling like something awful is about to happen
- Very definitely and quite badly.....3
- Yes, but not too badly.....2
- A little, but it doesn't worry me.....1
- Not at all.....0

I can laugh and see the funny side of things
- As much as I always could.....0
- Not quite so much now.....1
- Definitely not so much now.....2
- Not at all.....3

Worrying thoughts go through my mind
- A great deal of the time.....3
- A lot of the time.....2
- From time to time but not too often.....1
- Only occasionally.....0

I feel cheerful
- Not at all.....3
- Not often.....2
- Sometimes.....1
- Most of the time.....0

I can sit at ease and feel relaxed
- Definitely.....0
- Usually.....1
- Not often.....2
- Not at all.....3

I feel as if I am slowed down
- Nearly all of the time.....3
- Very often.....2
- Sometimes.....1
- Not at all.....0

I get a frightened feeling like 'butterflies in the stomach'
- Not at all.....0
- Occasionally.....1
- Quite often.....2
- Very often.....3

I have lost interest in my appearance
- Definitely.....3
- I don't take as much care as I should.....2
- I may not take quite as much care.....1
- I take just as much care as ever.....0

I feel restless as if I have to be on the move
- Very much indeed.....3
- Quite a lot.....2
- Not very much.....1
- Not at all.....0

I look forward with enjoyment to things
- As much as I ever did.....0
- Rather less than I used to.....1
- Definitely less than I used to.....2
- Hardly at all.....3

I get sudden feelings of panic
- Very often indeed.....3
- Quite often.....2
- Not very often.....1
- Not at all.....0

I can enjoy a good book or radio or TV programme
- Often.....0
- Sometimes.....1
- Not often.....2
- Very seldom.....3

International Physical Activity Questionnaire (IPAQ)

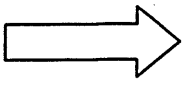
Instructions:
We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. They include questions about activities you do at work, as part of your house and garden work, to get from place to place, and in your spare time for recreation, exercise or sport.

In answering the following questions,

- **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal.

- **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

Please answer each question even if you do not consider yourself to be an active person.
Your answers are important

PTO


PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, volunteer work and any other unpaid work that you did **outside your home**. Do not include unpaid work you might do around your home, like housework, gardening, general maintenance, and caring for your family. These are asked about in Part3.

1. Do you currently have a job or do any unpaid work outside your home?

☐ Yes

☐ No → ***Skip to PART 2: TRANSPORTATION***

The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include travelling to and from work.

2. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, or climbing up stairs **as part of your work**? Only think about those physical activities that you did for at least 10 minutes at a time.

_____ **days per week**

☐ No vigorous job-related physical activity → ***Skip to question 4***

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

_____ **hours per day** _____ **minutes per day**

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

_____ **days per week**

☐ No moderate job-related physical activity → ***Skip to question 6***

5. How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?

_____ **hours per day** _____ **minutes per day**

6. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you did to travel to or from work.

_____ **days per week**

☐ No job-related walking → ***Skip to PART 2: TRANSPORTATION***

7. How much time did you usually spend on one of those days **walking** as part of your work?

_____ **hours per day** _____ **minutes per day**

PART 2: TRANSPORTATION

These questions are about how you travelled from place to place, including to places like work, shops, restaurants, and so on.

8. During the **last 7 days**, on how many days did you **travel in a motor vehicle** like a car, train or bus?

_____ **days per week**

☐ No travelling in a motor vehicle → ***Skip to question 10***

9. How much time did you usually spend on one of those days travelling in a car, train, bus, or other kind of motor vehicle?

_____ **hours per day**

_____ **minutes per day**

Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the **last 7 days**, on how many days did you **bicycle** for at least 10 minutes at a time to go from place to place?

_____ **days per week**

☐ No bicycling from place to place → ***Skip to question 12***

11. How much time did you usually spend on one of those days to **bicycle** from place to place?

_____ **hours per day**

_____ **minutes per day**

12. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time to go from place to place?

_____ **days per week**

☐ No walking from place to place → ***Skip to PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY***

13. How much time did you usually spend on one of those days **walking** from place to place?

_____ **hours per day**

_____ **minutes per day**

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the **last 7 days in and around your home**, like housework, gardening, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, or digging **in the garden or yard**?

_____ **days per week**

☐ No vigorous activity in garden or yard → ***Skip to question 16***

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in **the garden or yard**?

_____ **hours per day**

_____ **minutes per day**

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

_____ **days per week**

☐ No moderate activity in garden or yard → ***Skip to question 18***

17. How much time did you usually spend on one of those days doing **moderate** physical activities in **the garden or yard**?

_____ **hours per day**

_____ **minutes per day**

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

_____ **days per week**

☐ No moderate activity inside home → ***Skip to PART 4: RECREATION, SPORT AND LEISURE-TIME PHYSICAL ACTIVITY***

19. How much time did you usually spend on one of those days doing **moderate** physical activities **inside your home**?

_____ **hours per day**

_____ **minutes per day**

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the **last 7 days** solely for recreation, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?

_____ **days per week**

☐ No walking in leisure time → ***Skip to question 22***

21. How much time did you usually spend on one of those days **walking** in your leisure time?

_____ **hours per day**

_____ **minutes per day**

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like aerobics, running, bicycling, or swimming **in your leisure time**?

_____ **days per week**

☐ No vigorous activity in leisure time → ***Skip to question 24***

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ **hours per day**

_____ **minutes per day**

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a slow pace, swimming at a slow pace or dancing, **in your leisure time**?

_____ **days per week**

☐ No moderate activity in leisure time → ***Skip to PART 5: TIME SPENT SITTING***

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?

_____ **hours per day**

_____ **minutes per day**

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting while at work, at home and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

_____ **hours per day**

_____ **minutes per day**

27. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend day**?

_____ **hours per day**

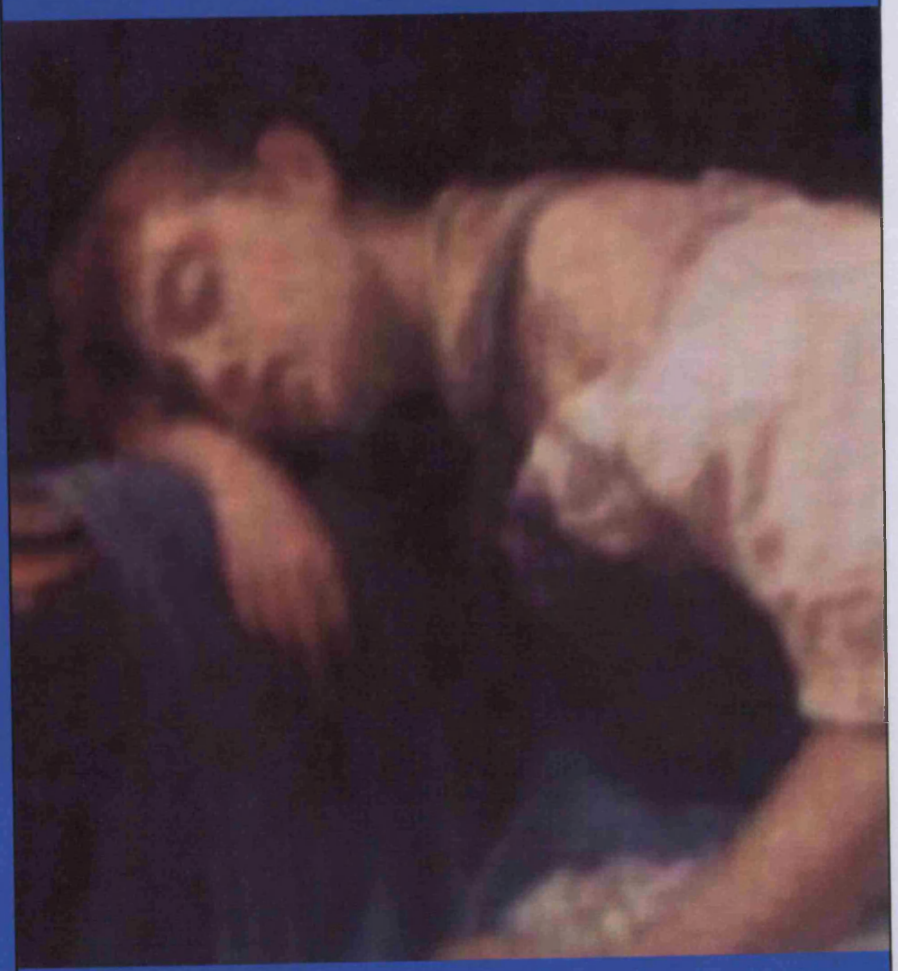
_____ **minutes per day**

This is the end of the questionnaires, thank you for participating.

Please return to:-

Nick Courtier
Department of Radiography
Cardiff University
GF3, Ty Dewi Sant,
Heath Park,
Cardiff,
CF14 4XN.

PATIENT FATIGUE DIARY



CONTENTS

3. Introduction

4. Diary questions

5. Examples of diary entries

6. Weekly diaries

12. Extra space

18. Questions for doctors

18. Useful phone numbers

19. Appointments

INTRODUCTION

This fatigue diary is designed to help you record your experiences whilst undergoing your radiotherapy treatment. Fatigue can be thought of as being more tired than usual or feeling weak and lacking energy.

It is entirely up to you if you fill in any of this diary, but it would be very helpful for the research if you do. You may find using the diary beneficial as it allows you to express your feelings about the impact of fatigue on your life, and may reveal any patterns in your symptoms.

For each week of your radiotherapy there is a page to record your responses to three questions about fatigue. The three questions are explained on the next page, and examples of diary entries are provided to guide you. Extra space is then provided if you need it.

At the end of the diary there is space for you to write down questions that you may want to ask your doctor or radiographers.There is also a list of useful contacts for further information or support, should you require them.

Feel free to use the diary in the way that best suits your needs; for example, recording sleep patterns or making daily diary entries. Each person's experience of cancer and its treatment is different, so please record **your** experiences.

QUESTIONS & ENTRY EXAMPLES

How do you feel physically?

Describe how your body feels and the kind of fatigue feelings you experience.

When do you feel better or worse?

- *'Week three Tuesday: the last few days I have had no energy whatsoever and feel weak all over'.*
- *'...I could have stayed in bed for days, but that doesn't make me feel less tired. Even though I'm tired I can't sleep.'*
- *'I noticed I tend to feel a bit tired in the afternoon, after going for my radiotherapy. I went to the gym as usual today and felt I had more energy after'.*
- *'I got breathless and dizzy climbing the stairs yesterday.'*
- *'halfway through the treatment and no problems!'*

Commencing: *02 September 2007*

How does fatigue affect the way you think?

Do you have difficulty thinking or concentrating?

Are you more forgetful than normal?

- *'...I can't seem to make decisions and have trouble just speaking in the morning!'*
- *'I'm really happy I continued to work part-time as it keeps a bit of normality and my concentration has been fine so far.'*

How does fatigue affect your mood and emotions?

Do you feel you should be doing more at home or work?

Are you more up and down than normal?

Does fatigue make you impatient with the people around you?

- *'Friday week 2 - Was feeling very emotional earlier this week, and I don't really know why'.*
- *'Beginning to feel a bit isolated as I've temporarily stopped going to my usual wed pm choir practice'.*
- *'...really positive as Week 3 and I still feel fine...'*

WEEK 1

Commencing:

How do you feel physically?

How does fatigue affect the way you think?

How does fatigue affect your mood and emotions?

WEEK 2

Commencing:

How do you feel physically?

How does fatigue affect the way you think?

How does fatigue affect your mood and emotions?

WEEK 3

Commencing:

How do you feel physically?

How does fatigue affect the way you think?

How does fatigue affect your mood and emotions?

EXTRA SPACE

How do you feel physically?

Commencing:

How does fatigue affect the way you think?

How does fatigue affect your mood and emotions?

EXTRA SPACE

How do you feel physically?

Commencing:

How does fatigue affect the way you think?

How does fatigue affect your mood and emotions?

EXTRA SPACE

How do you feel physically?

Commencing:

How does fatigue affect the way you think?

How does fatigue affect your mood and emotions?

QUESTIONS

to ask radiographers & doctors

USEFUL PHONE NUMBERS

Velindre Hospital (029) 2061 5888
Linac 1 extension 6261
Linac 2 extension 6940
Macmillan Information & Support Radiographer, **Joyce** extension 6428

Breast cancer support groups
Cardiff & Penarth, **Lynn Abel** (029) 2089 2481
South Gwent **Glenda** (01633) 872 221
North Gwent & Powys, **Lesley** (01873) 858 973
Rhondda, **Dianne** (01443) 683 220
Breast Cancer Care Cymru (0845) 077 1894
Tenovus Cancer Information Centre (029) 2019 6100

Nick Courtier (researcher) (029) 2074 8156

APPOINTMENTS

Socio-demographics

Name..... V..... Code.....

DOB..... ... Age..... ..... . Tel .....

Diagnosis..... Date..... Surgery..... Date.....

Laterality..... TNM..... Stage group..... Grade..... Tumour size.....(mm)

Treatment .....

GP.....

Medication.....

.....

Menopausal: pre / peri / post Years since menopause..... .

HRT: current user / previous / never

Work: Continued / postponed / changed / housewife / retired Occupation.....

Travel mode: Self drive / driven / ambulance / public transp. Travel Time.....hrs

Smoking History: Current / past / never ..... packs/day for .....yrs Years since quit.....

No. of dependants cared for .....

Measurements

Anthropometric: Height ..... (m) Weight ..... (kg)

Blood samples: FBC ☐ -80° Sample ☐

Questionnaires: FACT given ☐ IPAQ given ☐ HADS given ☐

completed ☐ completed ☐ completed ☐

Notes........

.....

RT data

Ist course? ☐ Energy.....

Medial: Field size..... Image x..... y..... lung..... wedge ..... MU.....

Lateral: Field size..... Image x..... y..... lung..... wedge ..... MU.....

Appendix 4 Data and statistical details

- Data processing rules
- Conversion table to transpose raw FACIT-F scores to interval scores
- Tests of normality and skewness for study variables
- Partial regression scatterplots for transformed baseline variables
- Dose-volume data descriptive statistics for the 10% and 90% isodoses
- Distribution, normality and skewness data for the mean of week 2 and week 3 FACIT-F scores
- Partial regression scatterplots for transformed on-treatment variables

Data processing rules

1. When multiple surgeries have been undertaken, the time from surgery to RT is calculated from the latest surgery.
2. If two histologically distinct tumours are present then the tumour size is taken as the aggregate of the two masses.
3. Continued in work category includes subjects who have a modified work pattern for the duration eg. Part time, changed hours etc.
4. Travel time for ambulance transport is taken as average time of 60 minutes (one way journey door to door).
5. Field area is the multiplication of the X and Y jaw radiation field sizes, not the area formed on the patients' skin by the light field.
6. Where FACIT-F scores answers are missing, a total score is prorated from the score of the answered items, so long as more than 50% of the items were answered.
7. An average is to be taken of any ranged responses for time spent on activities in the IPAQ form eg. 5-6 hours is converted to 5.5hours.
8. All cases in which the sum total of all the timed activities exceeded an average of 16 hours/day to be excluded from analysis. This assumes that on average an individual spends eight hours/day sleeping.
9. Only values of 10 or more minutes of activity should be included in the calculation of summary scores. Responses of less than 10 minutes to be re-coded as 'zero'.
10. Categorical IPAQ activity scores were defined as follows
    - **Low**
      No activity reported *OR* some activity is reported but not enough to meet the moderate or high categories
    - **Moderate**
      Either,
      a. Three or more days of vigorous-intensity activity of at least 20 minutes per day *OR*
      b. Five or more days of moderate-intensity activity and/or walking of at least 30 minutes per day *OR*

c. Five or more days of any combination of activities achieving a minimum of at least 600 MET-min/week

- **High**

  Either,

  a. Vigorous-intensity activity on at least three days and accumulating at least 1500 MET-minutes/week *OR*

  b. Seven or more days of any combination of activities achieving a minimum of at least 3000 MET-min/week

Conversion table to transpose raw FACIT-F scores to interval scores

Raw score	Interval measure	SE	Raw score	Interval measure	SE	Raw score	Interval measure	SE
0	0	17.0	18	46	3.0	36	61	2.8
1	11	9.5	19	47	2.9	37	62	2.9
2	18	6.9	20	48	2.9	38	63	2.9
3	23	5.8	21	49	2.9	39	64	3.0
4	26	5.1	22	49	2.8	40	65	3.1
5	28	4.6	23	50	2.8	41	66	3.1
6	31	4.3	24	51	2.8	42	67	3.2
7	32	4.0	25	52	2.8	43	68	3.4
8	34	3.8	26	53	2.8	44	69	3.5
9	36	3.7	27	54	2.8	45	71	3.7
10	37	3.5	28	54	2.7	46	72	3.9
11	38	3.4	29	55	2.7	47	74	4.2
12	40	3.3	30	56	2.7	48	76	4.7
13	41	3.2	31	57	2.8	49	79	5.4
14	42	3.2	32	58	2.8	50	83	6.5
15	43	3.1	33	59	2.8	51	89	9.2
16	44	3.0	34	60	2.8	52	100	16.8
17	45	3.0	35	60	2.8	-	-	-

Raw score to interval measure conversion table (based on 2292 anaemic cancer patients and 1010 general population (Cella et al. 2002c)) (SE = standard error)

Tests of normality and skewness for study variables

Tests of Normality & Skewness for patient characteristics

	Kolmogorov-Smirnov*			Skewness		
	Statistic	df	Sig.	Statistic	SE	Z-value
age	.071	100	.200*	0.272	0.241	1.13
tumour size (mm)	.155	100	.000	1.083	0.241	4.49
time form surg to RT (days)	.069	100	.200*	0.115	0.241	0.48
travel time for RT (min)	.214	100	.000	5.043	0.241	20.93
Pack years total	.252	100	.000	1.743	0.241	7.23
BMI	.064	100	.200*	0.544	0.241	2.25

Tests of Normality & Skewness for Baseline questionnaire data

	Kolmogorov-Smirnov*			Skewness		
	Statistic	df	Sig.	Statistic	SE	Z-value
FACIT-F raw	.158	100	.000	-1.145	.241	-4.75
FACIT-F interval	.069	100	.200	.098	.241	0.41
HADS anxiety	.188	100	.000	1.146	.241	4.76
HADS depression	.201	100	.000	1.256	.241	5.21
HADS sum (A+D)	.141	100	.000	1.168	.241	4.85
IPAQ sum	.144	100	.000	2.708	.241	11.2

Tests of Normality & Skewness for Baseline haematological variables

	Kolmogorov-Smirnov*			Skewness		
	Statistic	df	Sig.	Statistic	SE	Z-value
sIL6R conc. (ng/dL)	.086	100	.067	.503	.241	2.08
haemoglobin (g/dL)	.055	98	.200*	-.264	.244	-1.01
red blood cell count (10*12/L)	.068	98	.200*	-.245	.244	-1.00
haematocrit	.083	98	.090	.072	.244	0.3
mean corpuscular volume	.091	98	.044	-.325	.244	-1.34
MCH	.083	98	.096	-.689	.244	-1.01
Platelets (10*9/L)	.089	98	.056	.963	.244	4.00
white blood count	.117	98	.002	.570	.244	2.36
neutrophils (10*9/L)	.091	98	.043	.384	.244	1.59
lymphocytes (10*9/L)	.103	98	.012	.693	.244	2.88
monocytes (10*9/L)	.120	98	.001	.722	.244	3.00
eosinophils (10*9/L)	.161	98	.000	1.460	.244	6.06
basophils (10*9/L)	.218	98	.000	2.173	.244	9.01

Tests of Normality & Skewness for Week 2 questionnaire data

	Kolmogorov-Smirnov*			Skewness		
	Statistic	df	Sig.	Statistic	SE	Z-value
FACIT-F raw	.170	100	.000	-0.727	.241	-3.016
FACIT-F interval	.078	100	.133	0.296	.241	1.228
HADS anxiety	.150	100	.000	1.111	.241	4.609
HADS depression	.186	100	.000	0.905	.241	3.755
HADS sum (A+D)	.153	100	.000	1.014	.241	4.207
IPAQ sum	.150	100	.000	1.77	.241	7.344

Tests of Normality & Skewness for Week 2 haematological variables

	Kolmogorov-Smirnov*			Skewness		
	Statistic	df	Sig.	Statistic	SE	Z-value
sIL6R conc. (ng/dL)	.107	100	.007	.524	.241	2.17
haemoglobin (g/dL)	.069	100	.200*	-.532	.241	-2.2
red blood cell count (10*12/L)	.055	100	.200*	-.056	.241	-.23
haematocrit	.091	100	.040	-.036	.241	0.149
mean corpuscular volume	.097	100	.021	-.565	.241	-2.34
MCH	.079	100	.121	.353	.241	1.464
Platelets (10*9/L)	.066	100	.200*	.455	.241	1.887
white blood count	.065	100	.200*	.323	.241	1.34
neutrophils (10*9/L)	.099	100	.018	.6	.241	2.48
lymphocytes (10*9/L)	.094	100	.029	1.04	.241	4.31
monocytes (10*9/L)	.084	100	.078	.886	.241	3.67
eosinophils (10*9/L)	.198	100	.000	2.958	.241	12.27
basophils (10*9/L)	.259	100	.000	1.997	.241	8.28

Tests of Normality & Skewness for Week 3 questionnaire data

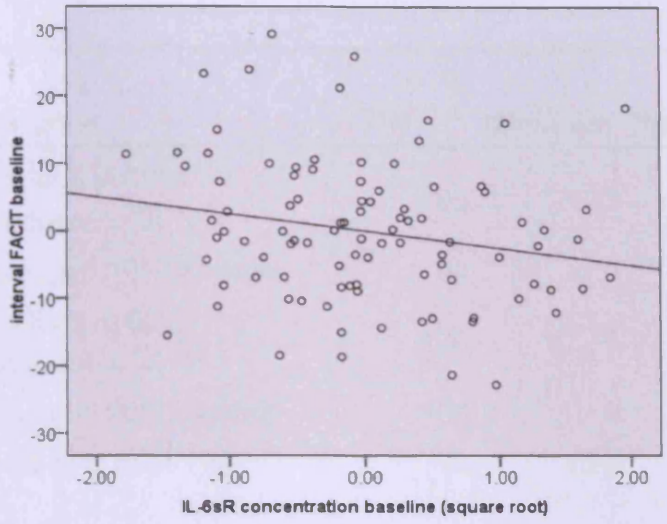
	Kolmogorov-Smirnov*			Skewness		
	Statistic	df	Sig.	Statistic	SE	Z-value
FACIT-F raw	.117	100	.002	.505	.241	2.09
FACIT-F interval	.079	100	.124	.439	.241	1.82
HADS anxiety	.146	100	.000	1.006	.241	4.17
HADS depression	.156	100	.000	0.770	.241	3.19
HADS sum (A+D)	.133	100	.000	.950	.241	3.94
IPAQ sum	.194	100	.000	1.77	.241	7.34

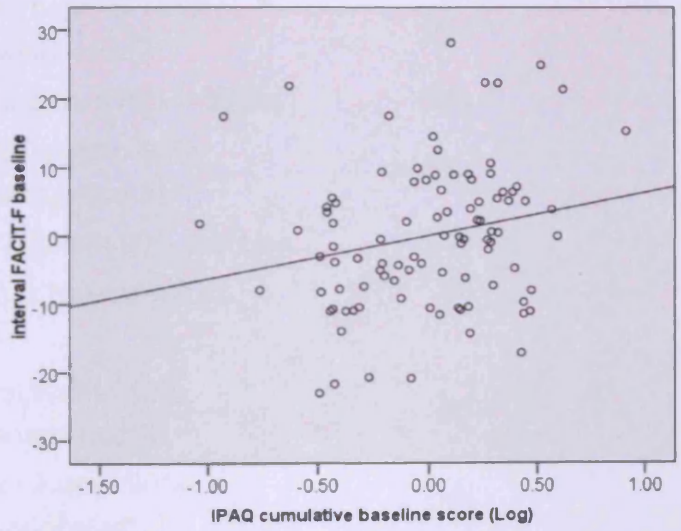
Tests of Normality & Skewness for Week 3 haematological variables

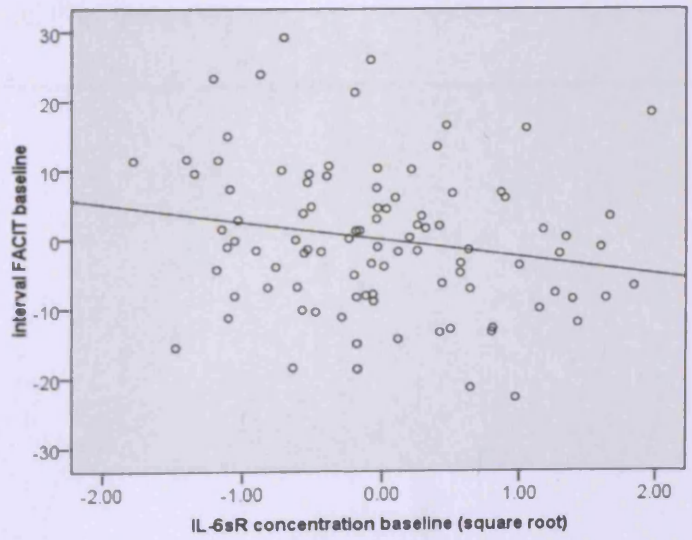
	Kolmogorov-Smirnov*			Skewness		
	Statistic	df	Sig.	Statistic	SE	Z-value
sIL6R conc. (ng/dL)	.056	100	.200*	.524	.241	2.17
haemoglobin (g/dL)	.056	100	.200*	-.532	.241	-2.2
red blood cell count (10*12/L)	.042	100	.200*	-.056	.241	-.23
haematocrit	.100	100	.016	-.036	.241	0.149
mean corpuscular volume	.099	100	.016	-.565	.241	-2.34
MCH	.094	100	.030	.353	.241	1.464
Platelets (10*9/L)	.072	100	.200*	.455	.241	1.887
white blood count	.083	100	.087*	.323	.241	1.34
neutrophils (10*9/L)	.085	100	.074	.6	.241	2.48
lymphocytes (10*9/L)	.084	100	.077	1.04	.241	4.31
monocytes (10*9/L)	.094	100	.03	.886	.241	3.67
eosinophils (10*9/L)	.145	100	.000	2.958	.241	12.27
basophils (10*9/L)	.249	100	.000	1.997	.241	8.28

*. This is a lower bound of the true significance.

Partial regression scatterplots for transformed baseline variables



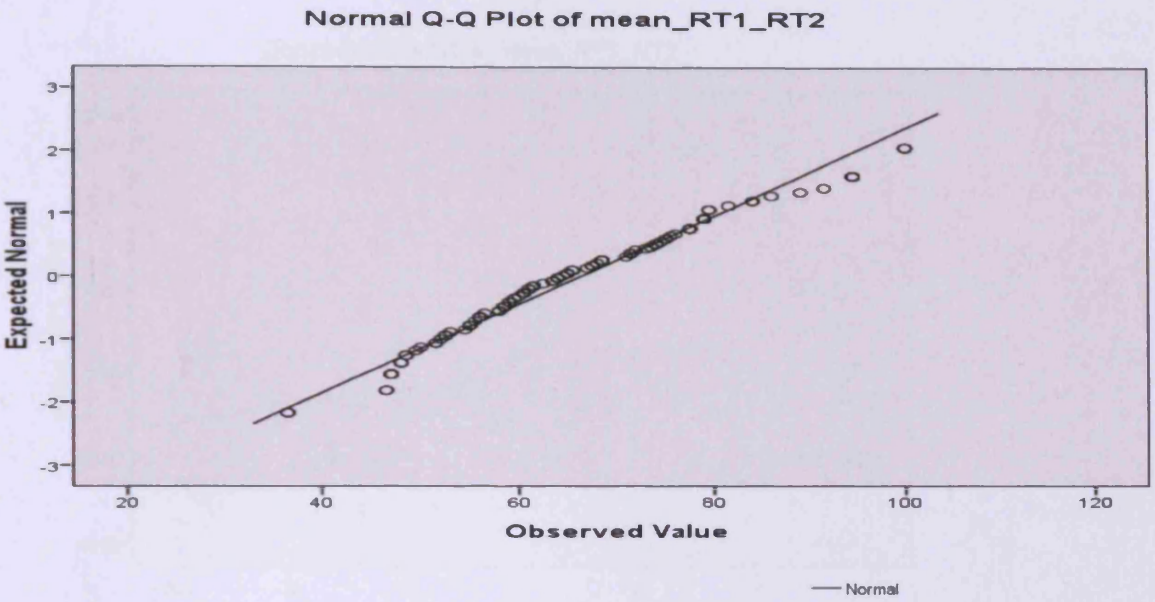


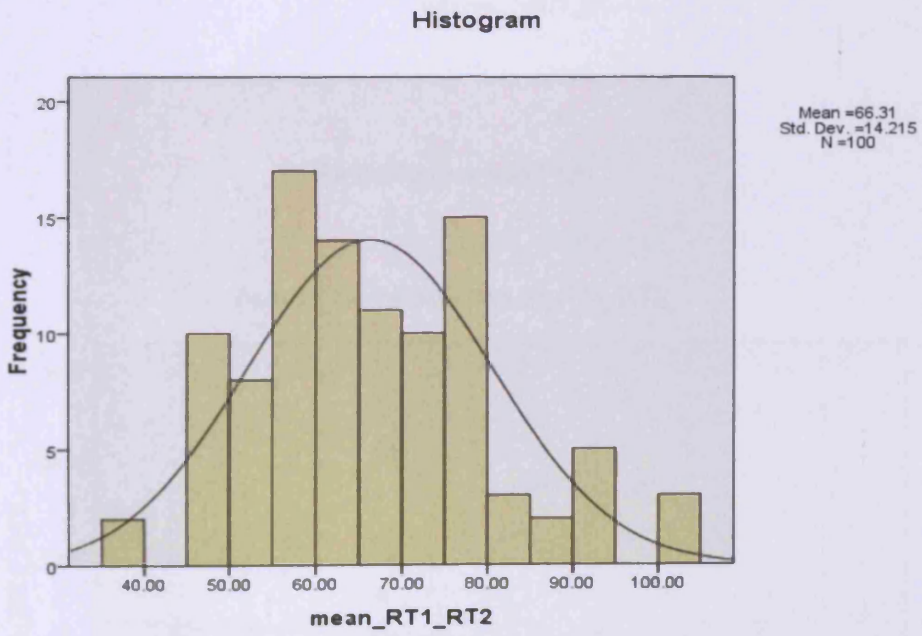


Dose-volume data descriptive statistics for the 10% and 90% isodoses

Variable	N	Minimum	Maximum	Mean	Std. Deviation
vol lung in 10% isodose(cc*3)	99	33	303	173.98	54.03
%lung in 10% isodose	99	2.0	139.0	14.47	13.09
vol lung in 90% isodose(cc*3)	100	0	183	68.88	37.01
%lung in 90% isodose	100	0	14.2	5.26	2.50
max lung dose (%)	99	13.0	121.0	106.33	12.11
vol heart in 10% isodose(cc*3)	100	-	353	18.78	40.25
%heart in10% isodose	100	-	64.0	2.88	6.93
vol heart in 90% isodose(cc*3)	100	-	44	2.28	5.70
%heart in 90% isodose	100	-	8.3	0.36	1.00
max heart dose (%)	97	2.5	110.7	46.74	46.59
vol liver in 10% isodose(cc*3)	100	-	226	29.98	47.38
vol liver in 90% isodose(cc*3)	100	-	62	5.98	12.07
max liver dose (%)	97	0.8	113.1	49.05	47.39

Distribution, normality and skewness data for the mean of week 2 and week 3 FACIT-F scores

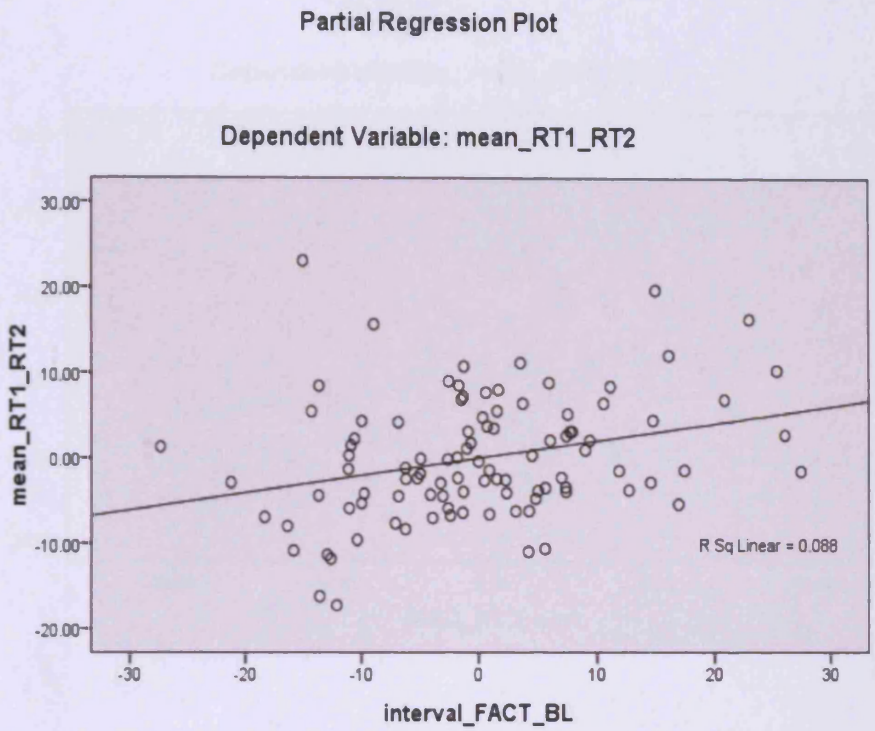


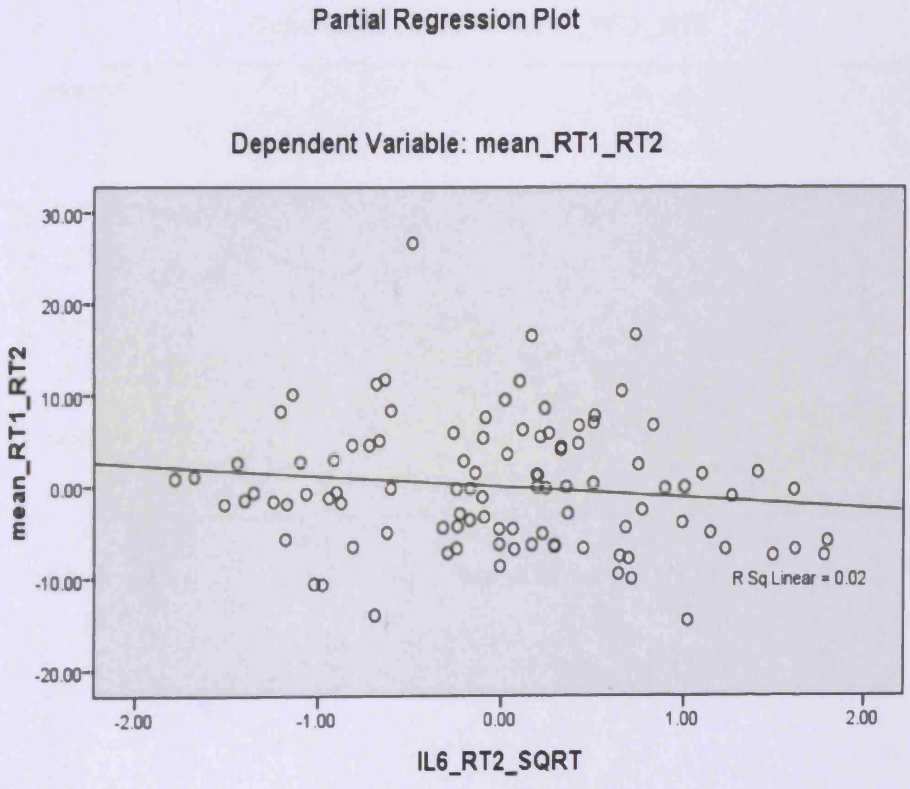


	Kolmogorov-Smirnov*			Skewness		
	Statistic	df	Sig.	Statistic	SE	Z-value
FACIT-F interval change (BL –RT2)	.083	100	.089	.443	.241	1.84

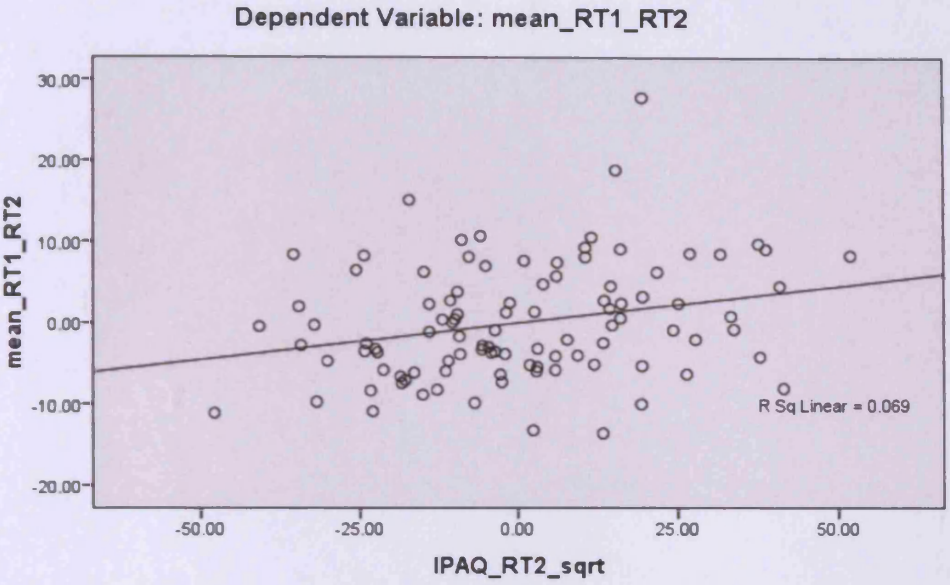
*. This is a lower bound of the true significance.

Partial regression scatterplots for transformed on-treatment variables





Partial Regression Plot



Partial Regression Plot

